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.

[0008a] In one aspect, the present disclosure refers to a pharmaceutical dosage unit tablet core, the tablet core comprising:

(1) 5 wt.% or more of a particulate pharmaceutical active drug which is cobimetinib hemifumarate polymorph Form A, wherein the particulate pharmaceutical active drug has a particle size D[v, 0.5] of from 25 µm to 65 µm, from 25 µm to 50 µm, or from 30 µm to 40 µm;

(2) a lubricant at a content based on the pharmaceutical dosage unit tablet core weight of from 0.5 wt.% to 5 wt.%, from 0.5 wt.% to 3 wt.%, from 1 wt.% to 3 wt.%, from 1 wt.% to 2.5 wt.%, or from 1.5 wt.% to 2 wt.%;

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

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

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

wherein a pre-blend of the particulate pharmaceutical active drug, lubricant, disintegrant, filler, and optionally the binder is compacted by application of a roller compaction force of from 1 kN/cm to 8 kN/cm, from 2 kN/cm to 5 kN/cm, or from 2 kN/cm to 4 kN/cm.

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 another aspect, the present disclosure refers to 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 cobimetinib hemifumarate polymorph Form A which has a particle size D[v, 0.5] of from 25 µm to 65 µm, from 25 µm to 50 µm, or from 30 µm to 40 µm 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 preblend; (3) dry granulating the finished pre-blend by application of a roller compaction force of from 1 kN/cm to 8 kN/cm, from 2 kN/cm to 5 kN/cm, or from 2 kN/cm to 4 kN/cm 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 finished final blend to form tablet cores; and (7) coating the tablet cores. In some examples 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] In still other examples of the disclosure, a pharmaceutical product is provided. 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. In another aspect, the present disclosure refers to a pharmaceutical product comprising: (1) a first tablet comprising the coated pharmaceutical dosage unit tablet core as disclosed herein; 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 another aspect, the present disclosure refers to use of a pharmaceutical product as disclosed herein in the manufacture of a medicament for treating BRAFV600 mutation-positive unresectable or metastatic melanoma.

[0013] In yet other examples 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 another aspect, the present disclosure refers to a pharmaceutical dosage unit tablet core, the tablet core comprising:
(1) 18.5 wt. % cobimetinib hemifumarate polymorph Form A, wherein the cobimetinib hemifumarate polymorph Form A has a particle size D[v, 0.5] of from 25 µm to 65 µm, from 25 µm to 50 µm, or from 30 µm to 40 µm;
(2) 45.6 wt. % microcrystalline cellulose;
(3) 30.4 wt. % lactose monohydrate;
(4) 4 wt. % croscarmellose sodium; and
(5) 1.5 wt. % magnesium stearate
wherein the tablet core is obtainable by application of a roller compaction force of from 1 kN/cm to 8 kN/cm, from 2 kN/cm to 5 kN/cm, or from 2 kN/cm to 4 kN/cm.

[0013b] In another aspect, the present disclosure refers to a coated pharmaceutical dosage unit tablet core, the coated tablet comprising: (1) 17.79 wt. % cobimetinib hemifumarate polymorph Form A, wherein the cobimetinib hemifumarate polymorph Form A has a particle size D[v, 0.5] of from 25 µm to 65 µm, from 25 µm to 50 µm, or from 30 µm to 40 µm;
(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
wherein the tablet core is obtainable by application of a roller compaction force of from 1 kN/cm to 8 kN/cm, from 2 kN/cm to 5 kN/cm, or from 2 kN/cm to 4 kN/cm.

[0013c] In another aspect, the present disclosure refers to a pharmaceutical product comprising:
(1) a first tablet comprising the coated tablet as disclosed herein; 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.

[0014] In other examples 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.

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 pharmaceutical dosage unit tablet core, the tablet core comprising:

(1) 5 wt.% or more of a particulate pharmaceutical active drug which is cobimetinib hemifumarate polymorph Form A, wherein the particulate pharmaceutical active drug has a particle size D[v, 0.5] of from 25 µm to 65 µm, from 25 µm to 50 µm, or from 30 µm to 40 µm;

(2) a lubricant at a content based on the pharmaceutical dosage unit tablet core weight of from 0.5 wt.% to 5 wt.%, from 0.5 wt.% to 3 wt.%, from 1 wt.% to 3 wt.%, from 1 wt.% to 2.5 wt.%, or from 1.5 wt.% to 2 wt.%;

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

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

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

wherein a pre-blend of the particulate pharmaceutical active drug, lubricant, disintegrant, filler, and optionally the binder is compacted by application of a roller compaction force of from 1 kN/cm to 8 kN/cm, from 2 kN/cm to 5 kN/cm, or from 2 kN/cm to 4 kN/cm.

2. The pharmaceutical dosage unit tablet core of claim 1, wherein the particulate pharmaceutical active drug content based on the weight of the tablet core is from 15 wt.% to 25 wt.%, or 20 wt.%.

3. The pharmaceutical dosage unit tablet core of claim 1, wherein the particulate pharmaceutical active drug has a particle size D[v, 0.5] of from 50 μm to 60 μm.

4. The pharmaceutical dosage unit tablet core of claim 1, wherein said tablet core comprises intragranular lubricant and extragranular lubricant, wherein:

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

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

5. The pharmaceutical dosage unit tablet core of claim 1, wherein the lubricant comprises magnesium stearate, sodium stearyl fumarate, or a combination thereof.

6. The pharmaceutical dosage unit tablet core of claim 1, wherein said tablet core comprises intragranular disintegrant and extragranular disintegrant, wherein:

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

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

7. The pharmaceutical dosage unit tablet core of claim 6, wherein the weight ratio of the intragranular disintegrant to the extragranular disintegrant is 1:5, 1:3, 1:1, or 2:1.

8. The pharmaceutical dosage unit tablet core of claim 1, wherein the disintegrant comprises sodium starch glycolate, croscarmellose sodium, or a combination thereof.

9. The pharmaceutical dosage unit tablet core of claim 1, wherein the filler comprises (1) lactose or (2) lactose and microcrystalline cellulose, wherein the weight ratio of lactose to microcrystalline cellulose is from 1:1.5 to 4:1, from 1:1.25 to 4:1, from 1:1 to 4:1 from 1:1 to 3:1, from 1.5:1 to 3:1, or from 2:1 to 2.5:1.

10. The pharmaceutical dosage unit tablet core of claim 1, wherein the particulate pharmaceutical active drug has a particle size D[v, 0.5] of from 25 µm to 40 µm.

11. The pharmaceutical dosage unit tablet core of claim 1, wherein the particulate pharmaceutical active drug has a particle size D[v, 0.5] of from 40 µm to 65 µm.

12. The pharmaceutical dosage unit tablet core of claim 1, wherein the tablet core further comprises a binder at a total binder content based on said tablet core weight of from 1 wt.% to 10 wt.%, from 1 wt.% to 7 wt.%, from 1 wt.% to 6 wt.%, or from 1 wt.% to 5 wt.%.

13. The pharmaceutical dosage unit tablet core of claim 12, wherein the binder comprises povidone, copovidone, pregelatinized starch, hydroxypropyl methylcellulose, or a combination thereof.

14. The pharmaceutical dosage unit tablet core of claim 1, wherein said 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.

15. The pharmaceutical dosage unit tablet core of claim 1, 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%.

16. The pharmaceutical dosage unit tablet core of claim 15, wherein the coated pharmaceutical dosage unit tablet core comprises from 2 wt.% to 6 wt.% or from 3 wt.% to 5 wt.% of the film-coating based on the weight of said tablet core, and wherein the film-coating comprises:

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

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

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

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

17. A pharmaceutical product comprising:

(1) a first tablet comprising the coated pharmaceutical dosage unit tablet core of claim 15; 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.

18. The pharmaceutical product of claim 17, wherein the first tablet comprises 20 mg cobimetinib, 40 mg cobimetinib, or 60 mg cobimetinib.

19. Use of a pharmaceutical product of claim 17 in the manufacture of a medicament for treating BRAFV600 mutation-positive unresectable or metastatic melanoma.

20. The use of claim 19, wherein one or more first tablets are to be 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 to be administered to provide a total dose of 960 mg vemurafenib, twice daily each day of the 28 day cycle.

21. The use of claim 19, wherein the first tablet is to be administered sequentially with the second tablet.

22. The use of claim 19, wherein the first tablet is to be administered concurrently with the second tablet.

23. The use of claim 19, wherein the unresectable or metastatic melanoma is BRAFV600E mutation-positive melanoma.

24. The use of claim 19, wherein the unresectable or metastatic melanoma is metastatic melanoma.

25. The use of claim 19, wherein the BRAFV600 mutation-positive unresectable or metastatic melanoma has not been previously treated.

26. A pharmaceutical dosage unit tablet core, the tablet core comprising:
(1) 18.5 wt. % cobimetinib hemifumarate polymorph Form A, wherein the cobimetinib hemifumarate polymorph Form A has a particle size D[v, 0.5] of from 25 µm to 65 µm, from 25 µm to 50 µm, or from 30 µm to 40 µm;

(2) 45.6 wt. % microcrystalline cellulose;
(3) 30.4 wt. % lactose monohydrate;
(4) 4 wt. % croscarmellose sodium; and
(5) 1.5 wt. % magnesium stearate;
wherein the tablet core is obtainable by application of a roller compaction force of from 1 kN/cm to 8 kN/cm, from 2 kN/cm to 5 kN/cm, or from 2 kN/cm to 4 kN/cm.

27. The pharmaceutical dosage unit tablet core of claim 26, 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.

28. The pharmaceutical dosage unit tablet core of claim 26, wherein the microcrystalline cellulose has a bulk density from 0.26 to 0.31 g/mL, a degree of polymerization of not more than 350, and a particle size measured by air jet of not more than 1 wt. %+60 mesh (250 microns) and not more than 30 wt. %+200 mesh (75 microns).

29. A coated pharmaceutical dosage unit tablet core, the coated tablet comprising:
(1) 17.79 wt. % cobimetinib hemifumarate polymorph Form A, wherein the cobimetinib hemifumarate polymorph Form A has a particle size D[v, 0.5] of from 25 µm to 65 µm, from 25 µm to 50 µm, or from 30 µm to 40 µm;
(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
wherein the tablet core is obtainable by application of a roller compaction force of from 1 kN/cm to 8 kN/cm, from 2 kN/cm to 5 kN/cm, or from 2 kN/cm to 4 kN/cm.

30. The coated pharmaceutical dosage unit tablet of claim 29, 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.

31. The coated pharmaceutical dosage unit tablet of claim 29, wherein the film coating comprises:
(1) 40 wt. % polyvinyl alcohol;
(2) 25 wt. % titanium dioxide;
(3) 20.2 wt. % macrogol/PEG 3350; and
(4) 14.8 wt. % talc.

32. A pharmaceutical product comprising:
(1) a first tablet comprising the coated tablet of claim 29; 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.

33. The pharmaceutical product of claim 32, wherein the first tablet comprises 20 mg cobimetinib, 40 mg cobimetinib, or 60 mg cobimetinib.

34. Use of a pharmaceutical product of claim 32 in the manufacture of a medicament for treating BRAFV600 mutation-positive unresectable or metastatic melanoma.

35. The use of claim 34, wherein one or more first tablets are to be 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 to be administered to provide a total dose of 960 mg vemurafenib, twice daily each day of the 28 day cycle.

36. The use of claim 34, wherein the first tablet is to be administered sequentially with the second tablet.

37. The use of claim 34, wherein the first tablet is to be administered concurrently with the second tablet.

38. The use of claim 34, wherein the unresectable or metastatic melanoma is BRAFV600E mutation-positive melanoma.

39. The use of claim 34, wherein the unresectable or metastatic melanoma is metastatic melanoma.

40. The use of claim 34, wherein the BRAFV600 mutation-positive unresectable or metastatic melanoma has not been previously treated.

41. 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 cobimetinib hemifumarate polymorph Form A which has a particle size D[v, 0.5] of from 25 µm to 65 µm, from 25 µm to 50 µm, or from 30 µm to 40 µm 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 preblend;
(3) dry granulating the finished pre-blend by application of a roller compaction force of from 1 kN/cm to 8 kN/cm, from 2 kN/cm to 5 kN/cm, or from 2 kN/cm to 4 kN/cm 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 finished final blend to form tablet cores; and
(7) coating the tablet cores.

42. The process of claim 41, further comprising suspending a film-coat solid mixture in water to form a coating slurry mixture and coating the tablet cores with the coating mixture slurry.

43. The process of claim 41, wherein:
(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; and
(3) first lubricant component and the second lubricant component are each selected from magnesium stearate, sodium stearyl fumarate, and combinations thereof.