[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] In some examples of the disclosure, a process for preparing a pharmaceutical dosage unit tablet core is provided. 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 25µ to about 50 µm, or from about 30µ 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 examples 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.

[0008] In some other examples of the disclosure, a pharmaceutical dosage unit tablet core is provided. The tablet core comprises: (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.

[0008a] In one aspect, the present disclosure refers to 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, wherein the particulate pharmaceutical active drug is cobimetinib hemifumarate polymorph Form A.

[0009] In other examples of the disclosure, a pharmaceutical dosage unit tablet core is provided. The tablet core comprises: (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] In other examples of the disclosure, a coated pharmaceutical dosage unit tablet core is provided. The coated table comprises: (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] In other examples of the disclosure, a process for preparing a coated pharmaceutical dosage unit tablet is provided. The process comprises 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 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 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 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;
(2) 45.6 wt. % microcrystalline cellulose;
(3) 30.4 wt. % lactose monohydrate;
(4) 4 wt. % croscarmellose sodium; and
(5) 1.5 wt. % magnesium stearate.

[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;
(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.

[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) 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, wherein the particulate pharmaceutical active drug is cobimetinib hemifumarate polymorph Form A.

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 about 15 wt.% to about 25 wt.%, or about 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 about 25 µm to about 65 µm, from about 25 µm to about 50 µm, or from about 30 µm to about 40 µm.

4. 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 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.

5. 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 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.%.

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

7. 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 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.%.

8. The pharmaceutical dosage unit tablet core of claim 7, 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.

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

10. 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 about 1:1.5 to about 4:1, from about 1:1.25 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.

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 about 25 µm to about 40 µm.

12. 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 about 40 µm to about 65 µm.

13. 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 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.%.

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

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

16. 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%.

17. The pharmaceutical dosage unit tablet core of claim 16, 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.

18. A pharmaceutical product comprising:

(1) a first tablet comprising the coated pharmaceutical dosage unit tablet core of claim 16; 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.

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

20. Use of a pharmaceutical product of claim 18 in the manufacture of a medicament for treating BRAFV600 mutation-positive unresectable or metastatic melanoma.

21. The use of claim 20, 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.

22. The use of claim 20, wherein the first tablet is to be administered sequentially with the second tablet.

23. The use of claim 20, wherein the first tablet is to be administered concurrently with the second tablet.

24. The use of claim 20, wherein the unresectable or metastatic melanoma is BRAFV600E mutation-positive melanoma.

25. The use of claim 20, wherein the unresectable or metastatic melanoma is metastatic melanoma.

26. The use of claim 20, wherein the BRAFV600 mutation-positive unresectable or metastatic melanoma has not been previously treated.

27. 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.

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

29. The pharmaceutical dosage unit tablet core of claim 27, 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).

30. 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.

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

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

33. A pharmaceutical product comprising:
(1) a first tablet comprising the coated tablet of claim 30; 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.

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

35. Use of a pharmaceutical product of claim 33 in the manufacture of a medicament for treating BRAFV600 mutation-positive unresectable or metastatic melanoma.

36. The use of claim 35, 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.

37. The use of claim 35, wherein the first tablet is to be administered sequentially with the second tablet.

38. The use of claim 35, wherein the first tablet is to be administered concurrently with the second tablet.

39. The use of claim 35, wherein the unresectable or metastatic melanoma is BRAFV600E mutation-positive melanoma.

40. The use of claim 35, wherein the unresectable or metastatic melanoma is metastatic melanoma.

41. The use of claim 35, wherein the BRAFV600 mutation-positive unresectable or metastatic melanoma has not been previously treated.

42. 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 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 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.

43. The process of claim 42, 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.

44. The process of claim 42, 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.