[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 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.

[0007a] In one aspect, there is provided a process for preparing a pharmaceutical dosage unit tablet core, the process comprising: (1) blending a particulate pharmaceutical drug active which is cobimetinib hemifumarate polymorph Form A, an intragranular filler comprising (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, an intragranular disintegrant comprising sodium starch glycolate, croscarmellose sodium, and combinations thereof, and an intragranular lubricant comprising magnesium stearate, sodium stearyl fumarate, and combinations thereof, to form a pre-blend, wherein the particulate pharmaceutical drug active 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) compacting the pre-blend by application of a 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; (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 5 kN to 20 kN, from 14 kN to 19 kN, from 14 kN to 18 kN, or from 8 kN to 13 kN to form the pharmaceutical dosage unit tablet core.

[0008] Disclosed is a pharmaceutical dosage unit tablet core. In one example, 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 one example, 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 one example, 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 one example, 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 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] 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 one example, there is provided a pharmaceutical product comprising: (1) a first tablet of the examples disclosed above; 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 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 one example, 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 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.

[0014a] In one example, there is provided a kit comprising: (1) a first tablet as described in the examples above; 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 which is cobimetinib hemifumarate polymorph Form A, an intragranular filler comprising (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, an intragranular disintegrant comprising sodium starch glycolate, croscarmellose sodium, and combinations thereof, and an intragranular lubricant comprising magnesium stearate, sodium stearyl fumarate, and combinations thereof, to form a pre-blend, wherein the particulate pharmaceutical drug active 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) compacting the pre-blend by application of a 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;

   (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 5 kN to 20 kN, from 14 kN to 19 kN, from 14 kN to 18 kN, or from 8 kN to 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 2 mm to 5 mm, from 2 mm to 4 mm, from 3 mm to 5 mm or from 4 mm to 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 45 µm to 500 µm, from 45 µm to 400 µm, from 45 µm to 300 µm, from 45 µm to 200 µm, from 45 µm to 100 µm, from 50 µm to 60 µm, from 65 µm to 100 µm, from 45 µm to 80 µm, or from 75 µm to 100 µm.

4. The process of any one of the preceding claims 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 0.85 g/mL to 0.95 g/mL and from 0.9 g/mL to 0.95 g/mL;

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

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

6. The process of any one of the preceding claims 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 one of the preceding claims, wherein the total lubricant content based on pharmaceutical dosage unit tablet core weight is 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.%.

8. The process of claim 6 or claim 7, wherein

   (1) the intragranular lubricant content based on 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 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.%.

9. The process of any one of the preceding claims, wherein the total disintegrant content based on pharmaceutical dosage unit tablet core weight is 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.%.

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 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 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.%.

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 one of the preceding claims, wherein the total filler content based on pharmaceutical dosage unit tablet core weight is 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.%.

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

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

15. The process of any one of claims 2 to 14, wherein:

(a) the particulate pharmaceutical active drug has a particle size D[v, 0.5] of from 27 μm to 37 μm, the roller compaction gap force is about 2 kN/cm, and the gap width is about 5 mm; or

(b) the particulate pharmaceutical active drug has a particle size D[v, 0.5] of from 38 μm to 65 μm, the roller compaction gap force is from 2 kN/cm to 4 kN/cm, and the gap width is from 4 mm to 5 mm.

16. The process of any one of the preceding claims, wherein the filler comprises (1) lactose or (2) lactose and microcrystalline cellulose wherein the weight ratio of lactose to microcrystalline cellulose is from 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.

17. The process of any one of the preceding claims, wherein the pre-blend further comprises a binder at a total binder content based on pharmaceutical dosage unit 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.%, optionally wherein the binder comprises povidone, copovidone, pregelatinized starch, hydroxypropyl methylcellulose, and combinations thereof.

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

19. The process of any one of the preceding claims, 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.