[0005] Accordingly, there is a need to develop stable and effective pharmaceutical compositions that allow for a formulation of Bempedoic acid and Ezetimibe hat have improved, desirable PK and bulk physical properties.

[0006] The present disclosure overcomes difficulties associated with co-formulating Bempedoic acid and Ezetimibe, as described in detail below.

SUMMARY

[0007] Herein disclosed is the development of novel combination formulations for a drug product comprising Bempedoic acid (ETC- 1002) and Ezetimibe. Also disclosed herein are granulated compositions of Bempedoic acid.

[0008] Two formulation options for the combination are identified as improved and compatible for both Bempedoic acid (ETC- 1002) and Ezetimibe from a bioavailability study conducted and disclosed herein: a monolayer and a bilayer tablet formulation. The monolayer tablet is manufactured with granulated mixtures from both compounds blended together into a single layer. The bilayer tablet is manufactured with granulated mixtures from each compound compressed into two (2) separate layers.

[0009] The inventors have found that surface treatment of ETC- 1002 with colloidal silicon dioxide reduces or eliminates the stickiness problem. This treatment involves blending ETC-1002 with colloidal silicon dioxide first, and then mixing the blend with hydroxypropyl cellulose (HPC-L) and microcrystalline cellulose in rapid mixer granulator; prior to granulation. Granulation is also carried with a binder solution comprising colloidal silicon dioxide and hydroxypropyl cellulose (HPC-L). The treatment of ETC- 1002 and the preparation of the premix for granulation is carried out in such a way that: 1) excessive hydrophobicity is not imparted to the active, 2) the dissolution and release profile of ETC-1002 is not adversely impacted, 3) the stability of ETC- 1002 is not adversely affected, and 4) incompatibility from any of the excipients does not arise in the fixed dose combination formulation containing Ezetimibe, particularly in the monolayer formulation.

[0009a] In one aspect of the present disclosure, there is provided a pharmaceutical composition comprising Bempedoic acid granules, wherein the Bempedoic acid granules comprise:

180 mg Bempedoic acid;

3.5 mg colloidal silicon dioxide; and

12 mg hydroxypropyl cellulose.

[0009b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising Bempedoic acid granules and Ezetimibe granules, wherein the Bempedoic acid granules comprise 180 mg Bempedoic acid, 3.5 mg colloidal silicon dioxide, and 12 mg hydroxypropyl cellulose, and the

Ezetimibe granules comprise 10 mg Ezetimibe, 1 mg povidone, and 2 mg sodium lauryl sulfate.

[0009c] In a further aspect of the present disclosure, there is provided a process of granulating Bempedoic acid, the process comprising:

mixing Bempedoic acid with colloidal silicon dioxide to obtain a dry mixture;

blending the dry mixture with hydroxypropyl cellulose and microcrystalline cellulose to obtain a blend; and

granulating the blend with a binder solution comprising colloidal silicon dioxide.

[0009d] In another aspect of the present disclosure, there is provided a process of manufacturing a tablet comprising Ezetimibe granules and Bempedoic acid granules, the process comprising:

mixing Bempedoic acid with colloidal silicon dioxide to obtain a dry mixture;

blending the dry mixture with hydroxypropyl cellulose and microcrystalline cellulose to obtain a blend;

granulating the blend with a binder solution comprising colloidal silicon dioxide to obtain the Bempedoic acid granules;

granulating Ezetimibe with povidone, sodium lauryl sulfate, and a pharmaceutically acceptable excipient to obtain the Ezetimibe granules;

blending the Ezetimibe granules and Bempedoic acid granules together to form a granulated mixture;

compressing the granulated mixture into a tablet; and

coating the tablet.

[0009e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein for use in treating or reducing the risk of cardiovascular disease.

[0009f] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating familial hypercholesterolemia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 shows the Zetia dissolution profile for Ezetimibe in 500mL of dissolution medium using a USP Apparatus-II at 50 rpm.

[0011] FIG. 2 shows the dissolution profile of Bempedoic Acid tablet in different media with 2.0% w/v sodium lauryl sulfate (SLS).

[0012] FIG. 3 depicts the dissolution profile for Reference Product combinations at various dissolution conditions.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising Bempedoic acid granules, wherein the Bempedoic acid granules comprise:

180 mg Bempedoic acid;

3.5 mg colloidal silicon dioxide; and

12 mg hydroxypropyl cellulose.

2. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition has a bulk density of at least 0.25 gm/ml and no more than 0.55 gm/ml.

3. The pharmaceutical composition of claim 1 or 2, wherein the pharmaceutical composition has a Carr's Index of at least 10 and no more than 30.

4. The pharmaceutical composition of any one of claims 1-3, wherein the Bempedoic acid granules have an angle of repose of at least 20° and no more than 45°.

5. The pharmaceutical composition of any one of claims 1-4, wherein Bempedoic acid is present in an amount of at least 50% and no more than 95% by weight of the total pharmaceutical composition.

6. The pharmaceutical composition of any one of claims 1-5, wherein the Bempedoic acid granules further comprise microcrystalline cellulose.

7. A pharmaceutical composition comprising Bempedoic acid granules and Ezetimibe granules, wherein
the Bempedoic acid granules comprise 180 mg Bempedoic acid, 3.5 mg colloidal silicon dioxide, and 12 mg hydroxypropyl cellulose, and the
Ezetimibe granules comprise 10 mg Ezetimibe, 1 mg povidone, and 2 mg sodium lauryl sulfate.

8. The pharmaceutical composition of claim 7, wherein the pharmaceutical composition comprises at least 50% and no more than 95% Bempedoic acid by weight of the total pharmaceutical composition and at least 0.5% and no more than 20% Ezetimibe by weight of the total pharmaceutical composition.

9. The pharmaceutical composition of claim 7 or 8, wherein the bempedoic acid granules further comprise microcrystalline cellulose.

10. The pharmaceutical composition of any one of claims 7-9, wherein the Ezetimibe granules further comprise one or more of microcrystalline cellulose, sodium starch glycolate, and lactose monohydrate.

11. The pharmaceutical composition of claim 9 or 10, wherein the microcrystalline cellulose has an average particle size of at least 100 μm and comprises a moisture content at least 3% and no more than 5% by weight of the microcrystalline cellulose.

12. The pharmaceutical composition of any one of claims 7-11, wherein the pharmaceutical composition is in the form of a tablet.

13. A process of granulating Bempedoic acid, the process comprising:

mixing Bempedoic acid with colloidal silicon dioxide to obtain a dry mixture;

blending the dry mixture with hydroxypropyl cellulose and microcrystalline cellulose to obtain a blend; and

granulating the blend with a binder solution comprising colloidal silicon dioxide.

14. A process of manufacturing a tablet comprising Ezetimibe granules and Bempedoic acid granules, the process comprising:

mixing Bempedoic acid with colloidal silicon dioxide to obtain a dry mixture;

blending the dry mixture with hydroxypropyl cellulose and microcrystalline cellulose to obtain a blend;

granulating the blend with a binder solution comprising colloidal silicon dioxide to obtain the Bempedoic acid granules;

granulating Ezetimibe with povidone, sodium lauryl sulfate, and a pharmaceutically acceptable excipient to obtain the Ezetimibe granules;

blending the Ezetimibe granules and Bempedoic acid granules together to form a granulated mixture;

compressing the granulated mixture into a tablet; and

coating the tablet.

15. The process of claim 14, wherein the coating comprises one or more of: PVA, glycerol monocaprylocaprate type 1, sodium lauryl sulfate, titanium dioxide and talc.

16. The process of claim 14, wherein the coating comprises each one of: PVA, glycerol monocaprylocaprate type 1, sodium lauryl sulfate, titanium dioxide and talc.

17. A pharmaceutical composition of any one of claims 1-12 for use in treating or reducing the risk of cardiovascular disease.

18. Use of a pharmaceutical composition of any one of claims 1-12 in the manufacture of a medicament for treating familial hypercholesterolemia.

19. The process of claim 13, wherein the binder solution further comprises hydroxypropyl cellulose.

20. The process of claim 14, wherein the binder solution further comprises hydroxypropyl cellulose.

21. The process of claim 14, wherein the pharmaceutically acceptable excipient is selected from lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, and combinations thereof.