[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, the present disclosure refers to a granulated composition comprising:

Bempedoic acid admixed with a lubricant selected from the group consisting of: colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate.

[0009a] In another aspect, the present disclosure refers to a pharmaceutical composition comprising:

Bempedoic acid admixed with a lubricant selected from the group consisting of: colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate;

Ezetimibe; and
a pharmaceutically acceptable excipient.

[0009b] In a further aspect, the present disclosure refers to a process of granulating Bempedoic acid, the process comprising:
dry mixing: Bempedoic acid, a lubricant and a pharmaceutically acceptable excipient, wherein the lubricant is selected from the group consisting of: colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate;
separately mixing an aqueous preparation of HPC-L;
blending the dry mixture and aqueous preparation; and
granulating the blend.

[0009c] In another aspect, the present disclosure refers to a bilayer tablet comprising Bempedoic acid and Ezetimibe, wherein the first layer comprises:
Ezetimibe granulated with a pharmaceutically acceptable excipient;
and wherein the second layer comprises:
Bempedoic acid granulated with a lubricant and a pharmaceutically acceptable excipient, wherein the lubricant is selected from the group consisting of: colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate.

[0009d] In a further aspect, the present disclosure refers to a process of manufacturing a monolayer tablet comprising Ezetimibe and Bempedoic acid, the process comprising:
granulating a composition comprising Ezetimibe and granulating a composition comprising Bempedoic acid, where each composition is granulated separately;
blending the Ezetimibe and Bempedoic acid granulations together;
compressing the blend into a single layer; and
coating the single layer.

[0009e] In another aspect, the present disclosure refers to a process of manufacturing a bilayer tablet comprising Ezetimibe and Bempedoic acid, the process comprising:
granulating a composition comprising Ezetimibe and granulating a composition comprising Bempedoic acid, where each composition is granulated separately;
blending the Ezetimibe granules with a pharmaceutically acceptable excipient;
blending the Bempedoic acid granules with a pharmaceutically acceptable excipient;
compressing the Ezetimibe and Bempedoic acid blends into a single composition containing two (2) separate layers; and
coating the composition.

[0009f] In a further aspect, the present disclosure refers to a kit comprising one or more of the granulated compositions or pharmaceutical compositions or one or more tablets of any one of the above claims and instructions for use.

[0009g] In another aspect, the present disclosure refers to a pharmaceutical composition comprising: Bempedoic acid admixed with a lubricant selected from the group consisting of: colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate; Ezetimibe; and a pharmaceutically acceptable excipient, for use in treating or reducing the risk of cardiovascular disease.

[0009h] In a further aspect, the present disclosure refers to a use of a pharmaceutical composition comprising: Bempedoic acid admixed with a lubricant selected from the group consisting of: colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate; Ezetimibe; and a pharmaceutically acceptable excipient, in the manufacture of a medicament for treating or reducing the risk of cardiovascular disease.

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 granulated composition comprising: Bempedoic acid admixed with a lubricant selected from the group consisting of: colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate.

2. The granulated composition of claim 1, wherein the composition further comprises a pharmaceutically acceptable excipient.

3. The granulated composition of claim 1 or claim 2, wherein the lubricant is colloidal silicon dioxide.

4. The granulated composition of any one of claims 1-3, wherein the composition has a bulk density of at least 0.25 gm/ml and no more than 0.55 gm/ml.

5. The granulated composition of any one of claims 1-4, wherein the composition has a Carr's Index of at least 10 and no more than 30.

6. The granulated composition of any one of claims 1-5, wherein the granules of the composition have an angle of repose of at least 20° and no more than 45°.

7. The granulated composition of any one of claims 1-6, wherein the Bempedoic acid is present in an amount of at least 50% and no more than 95% by weight of the total formulation.

8. The granulated composition of any one of claims 1-7, wherein the composition further comprises hydroxypropyl cellulose (HPC-L).

9. The granulated composition of any one of claims 1-8, wherein the composition further comprises microcrystalline cellulose.

10. The granulated composition of claim 9, wherein the amount of the HPC-L is at least 3%) and no more than 10% by weight of the total formulation; the amount of the Bempedoic acid is at least 50% and no more than 95% by weight of the total formulation; and the amount of the microcrystalline cellulose is at least 1% and no more than 20% by weight of the total formulation.

11. A pharmaceutical composition comprising:

Bempedoic acid admixed with a lubricant selected from the group consisting of: colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate;

Ezetimibe; and

a pharmaceutically acceptable excipient.

12. The pharmaceutical composition of claim 11, wherein the composition comprises at least 40% and nor more than 95% Bempedoic acid by weight of the total composition and at least 0.5% and no more than 20% Ezetimibe by weight of the total composition.

13. The pharmaceutical composition of any one of claims 11-12, wherein the composition further comprises one or more of: magnesium stearate, hydroxypropyl cellulose (HPC-L), a pyrrolidone compound, a saccharide, an anionic surfactant, microcrystalline cellulose and a starch.

14. The pharmaceutical composition of any one of claims 11-12, wherein the composition further comprises each one of: magnesium stearate, hydroxypropyl cellulose (HPC-L), a pyrrolidone compound, a saccharide, an anionic surfactant, microcrystalline cellulose and a starch.

15. The pharmaceutical composition of any one of claims 13-14, wherein the microcrystalline cellulose, when present, comprises an average particle size of at least 100 μιη and comprises a moisture content at least 3% and no more than 5% by weight of the microcrystalline cellulose.

16. The pharmaceutical composition of any one of claims 13-15, wherein the anionic surfactant, when present, is sodium lauryl sulfate.

17. The pharmaceutical composition of any one of claims 13-16, wherein the pyrrolidone compound, when present, is Povidone.

18. The pharmaceutical composition of any one of claims 13-17, wherein the saccharide, when present, is lactose monohydrate.

19. The pharmaceutical composition of any one of claims 13-18, wherein 1.03% by weight of the total magnesium stearate when present, has a particle size at least 45 μιη and no more than 150 μιη.

20. The pharmaceutical composition of any one of claims 11-19, wherein the composition is in the form of a tablet and further comprises a polyvinyl alcohol (PVA) based coating; and wherein the coating comprises: polyvinyl alcohol (PVA), glycerol monocaprylocaprate type 1, sodium lauryl sulfate, titanium dioxide and talc.

21. The pharmaceutical composition of any one of claims 11-20, wherein the amount of magnesium stearate is between 1 mg and 10 mg, the amount of hydroxypropyl cellulose (HPC-L) is between 5 mg and 25 mg, the amount of pyrrolidone compound is between 0.5 mg and 5 mg, the amount of saccharide is between 50 mg and 100 mg, the amount of anionic surfactant is between 0.5 mg and 5 mg, the amount of microcrystalline cellulose is between 25 mg and 100 mg and the amount of sodium starch glycolate is between 5 mg and 50 mg.

22. The pharmaceutical composition of any one of claims 11-21, wherein the amount of Bempedoic acid is between 80 mg and 250 mg; and the amount of Ezetimibe is between 5 mg and 25 mg.

23. The pharmaceutical composition of any one of claims 11-21, wherein the amount of Bempedoic acid is 180 mg and the amount of Ezetimibe is 10 mg.

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

dry mixing: Bempedoic acid, a lubricant and a pharmaceutically acceptable excipient, wherein the lubricant is selected from the group consisting of: colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate;

separately mixing an aqueous preparation of HPC-L;

blending the dry mixture and aqueous preparation; and

granulating the blend.

25. The process of claim 24, wherein the process further comprises using a rapid mixer to granulate the blend.

26. The process of any one of claims 24-25, wherein the process further comprises drying the blend.

27. The process of any one of claims 24-26, wherein the process further comprises milling and co-sifting the blend.

28. The process of any one of claims 24-27, wherein the dry mixing is carried out for at least forty-five (45) minutes.

29. The process of claim 28, wherein the dry mixing is carried out for no more than twenty four (24) hours in duration.

30. A bilayer tablet comprising Bempedoic acid and Ezetimibe, wherein the first layer comprises:

Ezetimibe granulated with a pharmaceutically acceptable excipient;

and wherein the second layer comprises:

Bempedoic acid granulated with a lubricant and a pharmaceutically acceptable excipient, wherein the lubricant is selected from the group consisting of: colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate.

31. The bilayer tablet of claim 30, wherein the Bempedoic acid is at least 20% and no more than 64% by weight of the total tablet and Ezetimibe is at least 1% and no more than 7%) by weight of the total tablet.

32. The bilayer tablet of any one of claims 30-31, wherein the first layer is at least 0.1% and no more than 23% by weight of the total tablet and the second layer is at least 0.1% and no more than 74% by weight of the total tablet.

33. The bilayer tablet of any one of claims 30-32, wherein the Friability of the tablet is at least 0.01%) and no more than 0.1%.

34. A process of manufacturing a monolayer tablet comprising Ezetimibe and Bempedoic acid, the process comprising:

granulating a composition comprising Ezetimibe and granulating a composition comprising Bempedoic acid, where each composition is granulated separately;

blending the Ezetimibe and Bempedoic acid granulations together;

compressing the blend into a single layer; and

coating the single layer.

35. The process of claim 34, wherein the process further comprises drying the tablets.

36. The process of any one of claims 34-35, wherein the coating comprises one or more of: PVA, glycerol monocaprylocaprate type 1, sodium lauryl sulfate, titanium dioxide and talc.

37. The process of any one of claims 34-36, wherein the coating comprises each one of: PVA, glycerol monocaprylocaprate type 1, sodium lauryl sulfate, titanium dioxide and talc.

38. A process of manufacturing a bilayer tablet comprising Ezetimibe and Bempedoic acid, the process comprising:

granulating a composition comprising Ezetimibe and granulating a composition comprising Bempedoic acid, where each composition is granulated separately;

blending the Ezetimibe granules with a pharmaceutically acceptable excipient;

blending the Bempedoic acid granules with a pharmaceutically acceptable excipient;

compressing the Ezetimibe and Bempedoic acid blends into a single composition containing two (2) separate layers; and

coating the composition.

39. The process of claim 38, wherein the process further comprises drying the tablets.

40. The process of any one of claims 38-39, wherein the Bempedoic acid composition includes colloidal silicon dioxide, sodium stearyl fumarate, or magnesium stearate.

41. The process of any one of claims 38-40, wherein the Ezetimibe composition includes an anionic surfactant.

42. A kit comprising one or more of the granulated compositions or pharmaceutical compositions or one or more tablets of any one of the above claims and instructions for use.

43. The kit of claim 42, wherein the instructions for use recite a process or recite directions for mixing the one or more of the granulated compositions or pharmaceutical compositions or one or more tablets with one or more compositions.

44. A pharmaceutical composition comprising: Bempedoic acid admixed with a lubricant selected from the group consisting of: colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate; Ezetimibe; and a pharmaceutically acceptable excipient, for use in treating or reducing the risk of cardiovascular disease.

45. The pharmaceutical composition of claim 44, wherein the pharmaceutical composition comprises a fixed dose of Bempedoic acid and a fixed dose of Ezetimibe.

46. Use of a pharmaceutical composition comprising: Bempedoic acid admixed with a lubricant selected from the group consisting of: colloidal silicon dioxide, sodium stearyl fumarate, and magnesium stearate; Ezetimibe; and a pharmaceutically acceptable excipient, in the manufacture of a medicament for treating or reducing the risk of cardiovascular disease.

47. The use of claim 46, wherein the medicament comprises a fixed dose of Bempedoic acid and a fixed dose of Ezetimibe.