As such, there are regulatory and technical barriers to the industrial use of caprate as an excipient in drug product formulations.

SUMMARY

The instant disclosure provides processes that generate solids that are agglomerates of adjustable particle size, with powder flow properties and compression behavior superior to those of commercially available alternatives. The instant process is cost-effective and generates material with excellent flow and compaction properties, making it suitable for use as an excipient in manufacturing processes and finished drug products. The instant process is also scalable, as it is capable of generating large volumes of solid material. In various examples, the instant process comprises a method of producing medium chain fatty acid sodium salts, such as sodium caprate.

Further provided herein are products generated by the instant process. These products—which are solid crystalline powders that may serve as excipients in drug formulations—have superior flow properties and compaction properties relative to commercial medium chain fatty acid sodium salts. These products may be substantially free of gelling or fiber- or needle-like dispersions of crystals.

The present disclosure, in one aspect, relates to a process for preparing agglomerated crystals of a sodium salt of a medium chain fatty acid comprising the steps of:

a) dissolving a medium chain fatty acid in a first solvent to produce a first solution, wherein the first solvent comprises an aprotic polar solvent;

b) adding to the first solution (i) a second solvent, wherein the second solvent comprises a medium chain aliphatic hydrocarbon solvent, and (ii) a solution comprising a sodium salt of a short chain alcohol to create a resulting slurry; and

c) isolating agglomerated crystals from the resulting slurry.

In various examples, the first solvent comprises or is an aprotic polar solvent. Without wishing to be bound by theory, an aprotic polar solvent is particularly suitable for dissolving a medium chain fatty acid (e.g., capric acid) while avoiding excessive solubilization of the crystalline product (e.g., sodium caprate). In some examples, the first solvent comprises an aprotic polar solvent selected from acetonitrile, dimethylformamide (DMF), dimethylacetamide (DMAC), and n-methyl-2-pyrolidone (NMP). In some examples, the second solvent comprises a medium chain aliphatic hydrocarbon solvent selected from heptane, hexane, and octane. In some

examples, the second solvent comprises a solvent selected from heptane and hexane. As such, in some examples, the present process comprises the steps of:

a) dissolving a medium chain fatty acid in an aprotic polar solvent selected from acetonitrile, DMF, DMAC, and NMP to produce a first solution;

b) adding to the first solution an aliphatic hydrocarbon solvent selected from heptane and hexane, and about 1 molar equivalent of a solution comprising a sodium salt of a short chain alcohol to create a resulting slurry; and

c) isolating the agglomerated crystals from the resulting slurry.

In another aspect, the present disclosure relates to a process for preparing agglomerated crystals of a sodium salt of a medium chain fatty acid comprising the steps of:

a) dissolving a medium chain fatty acid in acetonitrile to produce a first solution;

b) adding to the first solution heptane and about 1 molar equivalent of a solution comprising a sodium salt of a short chain alcohol to create a resulting slurry; and

c) isolating the agglomerated crystals from the resulting slurry.

In some examples, the sodium salt of a short chain alcohol is sodium methoxide. In some examples, the solution comprising a sodium salt of a short chain alcohol comprises methanol or ethanol. In particular examples, the solution contains methanol. In particular examples, the solution comprising a sodium salt of a short chain alcohol comprises methanol and sodium methoxide.

In various examples, the second solvent and solution comprising a sodium salt of a short chain alcohol are added separately, to the first solution. This is referred to in the present disclosure as addition by “separate feed line.”

In various examples, the agglomerated crystals in the resulting slurry comprises sodium caprate. This agglomerated crystalline product may be referred to herein as “Product A.”

In another aspect, the present disclosure relates to a process for preparing agglomerated crystals of sodium caprate comprising the steps of:

a) dissolving capric acid in acetonitrile to produce a first solution;

b) adding to the first solution heptane and about 1 molar equivalent of a solution comprising sodium methoxide to create a resulting slurry; and

c) isolating agglomerated crystals of sodium caprate from the resulting slurry.

In another aspect, the present disclosure relates to a composition comprising a sodium salt of a medium chain fatty acid generated using the process as defined herein.

Other examples, aspects and features of the present disclosure are further described in or will be apparent from the ensuing description, examples and appended claims.

BRIEF DESCRIPTIONS OF THE DRAWINGS

FIG. 1 shows the X-Ray Powder Diffraction data for Product A using the instant invention, as compared to commercially available alternatives of sodium caprate.

FIG. 2 is a differential scanning calorimeter (DSC) scan of Product A.

WHAT IS CLAIMED IS:

1. A process for preparing agglomerated crystals of a sodium salt of a medium chain fatty acid comprising the steps of:

a) dissolving a medium chain fatty acid in a first solvent to produce a first solution, wherein the first solvent comprises an aprotic polar solvent;

b) adding to the first solution (i) a second solvent, wherein the second solvent comprises a medium chain aliphatic hydrocarbon solvent, and (ii) a solution comprising a sodium salt of a short chain alcohol to create a resulting slurry; and

c) isolating agglomerated crystals from the resulting slurry.

2. The process of Claim 1, wherein the first solvent is selected from acetonitrile, DMF, DMAC, and NMP.

3. The process of Claim 1 or 2, wherein the second solvent is selected from heptane and hexane.

4. The process of any one of Claims 1-3, wherein the medium chain fatty acid comprises capric acid, and the first solvent comprises acetonitrile.

5. The process of any one of Claims 1-3, wherein the second solvent is heptane.

6. A process for preparing agglomerated crystals of a sodium salt of a medium chain fatty acid comprising the steps of:

a) dissolving a medium chain fatty acid in acetonitrile to produce a first solution;

b) adding to the first solution heptane and about 1 molar equivalent of a solution comprising a sodium salt of a short chain alcohol to create a resulting slurry; and

c) isolating agglomerated crystals from the resulting slurry.

7. The process of Claim 6, wherein, in step b, the heptane and the solution comprising a sodium salt of a short chain alcohol are added to the first solution at a temperature below about 40°C.

8. The process of Claim 6 or 7, wherein in step b, the heptane is added over about 3.5 to about 4.5 hours at a controlled rate, with constant stirring.

9. The process of any one of Claims 6-8, wherein, after step b, the resulting slurry is stirred for at least one hour.

10. The process of any one of Claims 6-9, wherein, after step b, the resulting slurry is stirred for 15 hours to 25 hours.

11. A process for preparing agglomerated crystals of sodium caprate comprising the steps of:

a) dissolving capric acid in acetonitrile to produce a first solution;

b) adding to the first solution heptane and about 1 molar equivalent of a solution comprising sodium methoxide to create a resulting slurry; and

c) isolating agglomerated crystals of sodium caprate from the resulting slurry.

12. The process of Claim 11, wherein, in step b, the heptane and the solution comprising sodium methoxide are added to the first solution at a temperature below about 40°C to induce a liquid-liquid phase separation.

13. The process of Claim 11 or 12, wherein, after step b, the resulting slurry is stirred for at least one hour.

14. The process of any one of Claims 6-13, wherein 6 L/kg to 8 L/kg of acetonitrile is added in step a.

15. The process of any one of Claims 6-14, wherein 1.7 L/kg to 2.1 L/kg of heptane is added in step b.

16. The process of any one of Claims 6-15, wherein in step b, the heptane is added over about 3.5 to about 4.5 hours.

17. The process of any one of Claims 11-13, comprising the steps of:

a) dissolving capric acid in 6 L/kg to 30 L/kg of acetonitrile to produce a first solution;

b) adding to the first solution 1.5 L/kg to 5 L/kg of heptane and 0.75 to 1.5 molar equivalent of a solution comprising about 20 to about 40 wt% of sodium methoxide at a temperature below about 40°C to induce a liquid-liquid phase separation and create a resulting slurry;

c) stirring the resulting slurry for at least one hour; and

d) filtering the resulting slurry to provide agglomerated sodium caprate crystals.

18. The process of any one of Claims 11-13, comprising the steps of:

a) dissolving capric acid in 6 L/kg to 30 L/kg of acetonitrile, to produce a first solution;

b) adding to the first solution about 1 molar equivalent of a solution comprising about 30 wt% sodium methoxide, over about 4.5 to about 5.5 hours, at a temperature of about 20°C to about 30°C, with constant stirring;

c) about 1 hour after adding the solution comprising sodium methoxide in step b, adding about 1.5 L/kg to about 4 L/kg of heptane to produce resulting slurry;

d) stirring the resulting slurry for 15 hours to 25 hours; and

e) filtering the resulting slurry to separate resulting solids and drying said resulting solids to provide agglomerated crystals of sodium caprate.

19. The process of Claim 18, wherein in step c, the heptane is added over about 3.5 to about 4.5 hours at a controlled rate, with constant stirring.

20. A composition comprising a sodium salt of a medium chain fatty acid generated using the process of any one of Claims 1-19.