blister pack serves as both the mold and the package in which the pharmaceutical composition can be stored.

SUMMARY

[0008a] In an aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

65-85 % w/w coated active pharmaceutical ingredient (API);

15-30 % w/w first coating material coating the API; and

3-15 % w/w matrix former.

[0008b] In another aspect of the present disclosure, there is provided a method of preparing a pharmaceutical composition comprising:

coating an active pharmaceutical ingredient (API) with a first coating material to form coated API, wherein the first coating material comprises one or more deformable components;

applying mechanical stress to the coated Ibuprofen to deform the one or more deformable components;

coating the coated API with a second coating material comprising silica;

applying mechanical stress to embed the second coating material onto the first coating material of the coated API;

after embedding the second coating material onto the first coating material of the coated API, sieving the coated API to remove excess first coating material, wherein the excess first coating material comprises first coating material not bound to the coated API;

forming a pharmaceutical suspension comprising the twice coated API and a matrix solution or suspension;

dosing the pharmaceutical suspension into a mold; and

freeze drying the dosed pharmaceutical suspension in the mold to form a pharmaceutical composition.

[0008c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition prepared by a process comprising the steps of:

coating an active pharmaceutical ingredient (API) with a first coating material to form coated API, wherein the first coating material comprises one or more deformable components;

applying mechanical stress to the coated API to deform the one or more deformable components;

coating the coated API with a second coating material comprising silica;

applying mechanical stress to embed the second coating material onto the first coating material of the coated API;

after embedding the second coating material onto the first coating material of the coated API, sieving the coated API to remove excess first coating material, wherein the excess first coating material comprises first coating material not bound to the coated API;

forming a pharmaceutical suspension comprising the twice coated API and a matrix solution or suspension;

dosing the pharmaceutical suspension into a mold; and

freeze drying the dosed pharmaceutical suspension in the mold to form a pharmaceutical composition.

[0009] Provided are methods for minimizing agglomeration of coating material for coated Ibuprofen produced using various mixing processes. Agglomeration of coating material can decrease the stability of the pharmaceutical product over time. For example, a pharmaceutical product's disintegration time may increase over time if it comprises agglomerated coating material. An increased disintegration times and/or a decreased dissolution rate implies an unstable pharmaceutical product. An unstable pharmaceutical product can lead to a shorter shelf life than desired. Accordingly, examples provided may help minimize agglomeration of coating material for coated Ibuprofen to improve the stability of the pharmaceutical product during storage and to increase its shelf life.

[0010] For example, methods described include removing excess coating material from the coated Ibuprofen to minimize the possibility of agglomeration of the coating material particles. Particularly, methods provided include sieving the coated Ibuprofen such that the final pharmaceutical product is adequately surrounded by dry matrix, minimizing any agglomeration of coating material particles upon storage. Pharmaceutical compositions described provide for a disintegration time and a dissolution rate that remain relatively stable over time.

[0011] Also provided are compositions and methods for preparing compositions that can minimize aeration of hydrophobic coated Ibuprofen in suspension. For example, hydrophobic coated Ibuprofen may be mixed into a matrix solution/suspension to form a pharmaceutical

suspension to accurately dose into molds to form solid pharmaceutical compositions (e.g., article, tablet, etc.) for administering to a patient. However, the hydrophobicity of the coated Ibuprofen causes the coated Ibuprofen to resist dispersing into the solution/suspension. Consequently, this can cause air to become entrained with the pharmaceutical suspension, also known as aeration. Entrained air, or aeration of the pharmaceutical suspension, can cause phase separation of the coated Ibuprofen in the pharmaceutical suspension, causing a non-homogenous pharmaceutical suspension. Aeration and non-homogeneous pharmaceutical suspensions can lead to poor dose weight accuracy of the pharmaceutical suspension comprising the hydrophobic Ibuprofen dosed into preformed blister packs and poor content uniformity in the finished product (i.e., pharmaceutical composition).

[0012] Traditional mechanical means of anti-aeration and/or minimizing aeration have not been found to be successful due to the high viscosity of the pharmaceutical suspension. For example, minimizing aeration may be achieved by applying vacuum to a pharmaceutical suspension, but depending on the composition and further processing requirements this approach may not be suitable. In particular, applying a vacuum to the pharmaceutical suspension can cause the suspension to rise because the viscous suspension "holds onto" the entrained air. Volatile formulation components may also be lost during vacuum processing. Further, traditional anti-aerating agents, such as ethanol or simethicone emulsion are similarly ineffective at anti-aerating the suspension.

[0013] Accordingly, compositions and methods provided herein minimize the aeration of a pharmaceutical suspension comprising hydrophobic coated Ibuprofen to improve the homogeneity of the suspension and increase the dose weight accuracy. Specifically, examples provided can include matrix solutions/suspensions comprising chemical compounds comprising terpene and/or terpinol. In some examples, a matrix solution/suspension may comprise the terpene limonene. By introducing a terpene-comprising chemical compound such as limonene, the hydrophobic coated Ibuprofen may more readily incorporate into the matrix solution/suspension, minimizing the overall aeration of the pharmaceutical suspension.

[0014] Also provided herein are pharmaceutical compositions and methods for preparing pharmaceutical compositions that are formulated to preserve the functional coating of functionally-coated Ibuprofen during the manufacture process. Functionally-coated Ibuprofen are often mixed to form a pharmaceutical suspension. A pharmaceutical suspension allows for accurate dosing to form an administrable pharmaceutical product. Typically, shear forces required to incorporate the functionally-coated Ibuprofen into a pharmaceutical suspension can cause the functional coating to erode. Erosion of this coating can destroy or damage the properties of the functional coating. Accordingly, functionally-coated Ibuprofen with an eroded coating can experience an increased dissolution rate and decreased taste-masking properties when orally administered to a patient.

[0015] However, pharmaceutical compositions and methods for preparing pharmaceutical compositions provided herein include preserving the coating of functionally-coated Ibuprofen in the pharmaceutical suspension with hydrophobic fumed silica. Specifically, the hydrophobic fumed silica can provide a protective layer surrounding and/or embedded into

the functionally-coated Ibuprofen particle. In some examples, solventless processes for producing functionally-coated Ibuprofen may produce Ibuprofen comprising a first coating. According to some examples, hydrophobic fumed silica can be added during the solventless mixing process to produce a second, protective coating surrounding and/or partially or fully embedded into the functionally-coated Ibuprofen.

[0016] Additionally, the second, protective coating may limit the interaction between the functionally-coated Ibuprofen and the matrix solution/suspension such that impact of the functionally-coated Ibuprofen on the performance characteristics of the matrix is minimized.

[0017] In some examples, a pharmaceutical composition comprises: 65-85 % w/w Ibuprofen; 15-30 % w/w coating material coating the Ibuprofen; and 3-15 % w/w matrix surrounding the Ibuprofen. In some examples, the pharmaceutical composition comprises 50-400 mg Ibuprofen. In some examples, the coating material comprises a first coating material and a second coating material and the pharmaceutical composition comprises 10-30 % w/w the first coating material and 0.5-10 % w/w the second coating material. In some examples, the first coating material comprises a wax. In some examples, the second coating material comprises silica. In some examples, the pharmaceutical composition comprises 1-5% w/w anti-aerating agent. In some examples, the first coating material comprises one or more of carnauba wax, synthetic wax, or candelilla wax. In some examples, the matrix comprises a matrix former and a structure former. In some examples, the matrix former comprises one or more of a water soluble material, a water dispersible material, a polypeptide, a polysaccharide, a polyvinyl alcohol, a polyvinylpyrrolidone, and an acacia. In some examples, the matrix former comprises a polypeptide. In some examples, the polypeptide comprises gelatin. In some examples, the structure former comprises one or more of mannitol, dextrose, lactose, galactose, and cyclodextrin In some examples, the structure former comprises mannitol. In some examples, the pharmaceutical composition has a disintegration time of 4 seconds or less for at least one month under storage conditions of at least 25ºC and at least 60% relative humidity. In some examples, the pharmaceutical composition has a disintegration time of 4 seconds or less for at least two months under storage conditions of at least 25ºC and at least 60% relative humidity. In some examples, the pharmaceutical composition has a disintegration time of 3 seconds or less for at least two months under storage conditions of at least 25ºC and at least 60% relative humidity. In some examples, the pharmaceutical composition has a disintegration time of 4 seconds or less for at least one

month under storage conditions of at least 30ºC and at least 65% relative humidity. In some examples, the pharmaceutical composition has a disintegration time of 4 seconds or less for at least two months under storage conditions of at least 30ºC and at least 65% relative humidity. In some examples, the pharmaceutical composition has a disintegration time of 4 seconds or less for at least one month under storage conditions of at least 40ºC and at least 75% relative humidity. In some examples, the pharmaceutical composition has a disintegration time of 4 seconds or less for at least two months under storage conditions of at least 40ºC and at least 75% relative humidity. In some examples, the pharmaceutical composition has a disintegration time of 4 seconds or less for at least three months under storage conditions of at least 25ºC and at least 60% relative humidity. In some examples, the pharmaceutical composition has a disintegration time of 4 seconds or less for at least three months under storage conditions of at least 30ºC and at least 65% relative humidity. In some examples, the pharmaceutical composition has a disintegration time of 4 seconds or less for at least three months under storage conditions of at least 40ºC and at least 75% relative humidity. In some examples, the pharmaceutical composition has a disintegration time of 4 seconds or less for at least six months under storage conditions of at least 25ºC and at least 60% relative humidity. In some examples, the pharmaceutical composition has a disintegration time of 4 seconds or less for at least six months under storage conditions of at least 30ºC and at least 65% relative humidity. In some examples, the pharmaceutical composition has a disintegration time of 4 seconds or less for at least six months under storage conditions of at least 40ºC and at least 75% relative humidity. In some examples, the pharmaceutical composition has a dissolution test result of 10%, 5%, 3% or less after 5 minutes. In some examples, the matrix comprises a viscosity modifier. In some examples, the viscosity modifier comprises xanthan gum. In some examples, the anti-aerating agent comprises one or more of a terpene or a terpinol. In some examples, the anti-aerating agent comprises a liquid flavor. In some examples, wherein the anti-aerating agent comprises a liquid flavor comprising limonene. In some examples, the anti-aerating agent comprises one or more of orange flavor, lemon flavor, grapefruit flavor, lime flavor, strawberry flavor, or peppermint flavor. In some examples, the pharmaceutical composition comprises from 3-10% w/w matrix former. In some examples, the pharmaceutical composition comprises from 3-10 % w/w structure former.

[0018] In some examples, a pharmaceutical composition can be prepared by a process comprising steps of: coating Ibuprofen with a first coating material to form coated Ibuprofen,

wherein the first coating material comprises one or more deformable components; applying mechanical stress to the coated Ibuprofen to deform the one or more deformable components; coating the coated Ibuprofen with a second coating material comprising silica; applying mechanical stress to embed the second coating material onto the first coating material of the coated Ibuprofen; sieving the coated Ibuprofen to remove excess first coating material, wherein the excess first coating material comprises first coating material not bound to the coated Ibuprofen; forming a pharmaceutical suspension comprising the twice coated Ibuprofen and a matrix solution or suspension; dosing the pharmaceutical suspension into a mold; and freeze drying the dosed pharmaceutical suspension in the mold to form a pharmaceutical composition. In some examples, sieving the coated Ibuprofen comprises passing the coated Ibuprofen through a device comprising two or more sieves. In some examples, sieving the coated Ibuprofen comprises sieving the coated Ibuprofen to an average particle size of 75 μm or greater. In some examples, sieving the coated Ibuprofen comprises sieving the coated Ibuprofen to an average particle size of 200 μm or less. In some examples, the weight of dosed pharmaceutical suspension is within 10 percent of a target dose weight . In some examples, the weight of dosed pharmaceutical suspension has a consistency within 5 percent of a target dose weight. In some examples, the weight of dosed pharmaceutical suspension has a consistency within 2.5 percent of a target dose weight. In some examples, the weight of dosed pharmaceutical suspension has a consistency within 1 percent of a target dose weight. In some examples, mixing the coated Ibuprofen into a matrix solution or suspension comprises in-line mixing at 15-20°C degrees Celsius. In some examples, the coated Ibuprofen experiences less than 40% loss in particle size within the first 2 hours after mixing into the solution matrix. In some examples, the coated Ibuprofen experiences less than 30% loss in particle size within the first 2 hours after mixing into the solution matrix. In some examples, the coated Ibuprofen experiences less than 20% loss in particle size within the first 2 hours after mixing into the solution matrix.

[0019] In some examples, a method of treating a patient comprises administering to a patient the pharmaceutical composition of any disclosed herein. In some examples, the patient is human.

[0020] In some examples, a method of preparing a pharmaceutical composition comprises: coating Ibuprofen with a first coating material to form coated Ibuprofen, wherein the first coating material comprises one or more deformable components; applying

CLAIMS

1. A pharmaceutical composition comprising:
   65-85 % w/w coated active pharmaceutical ingredient (API);
   15-30 % w/w first coating material coating the API; and
   3-15 % w/w matrix former.

2. The pharmaceutical composition of claim 1, wherein the first coating material comprises 10-30 % w/w of the coated API.

3. The pharmaceutical composition of claim 1 or 2, wherein the first coating material comprises a wax.

4. The pharmaceutical composition of claim 3, wherein the first coating material comprises one or more of carnauba wax, synthetic wax, or candelilla wax.

5. The pharmaceutical composition of any of claims 1-4, wherein the matrix former comprises one or more of a water soluble material, a water dispersible material, a polypeptide, a polysaccharide, a polyvinyl alcohol, a polyvinylpyrrolidone, and an acacia.

6. The pharmaceutical composition of claim 5, wherein the matrix former comprises a polypeptide.

7. The pharmaceutical composition of claim 6, wherein the polypeptide comprises gelatin.

8. The pharmaceutical composition of any of claims 1-7, comprising a structure former comprising one or more of mannitol, dextrose, lactose, galactose, and cyclodextrin.

9. The pharmaceutical composition of any of claims 1-8, comprising 0.01-0.2 % w/w viscosity modifier.

10. The pharmaceutical composition of claim 9, wherein the viscosity modifier comprises xanthan gum.

11. The pharmaceutical composition of any of claims 1-10, comprising 0.1-2 % w/w anti-aerating agent.

12. The pharmaceutical composition of claim 11, wherein the anti-aerating agent comprises one or more of a terpene or a terpinol.

13. The pharmaceutical composition of claim 12, wherein the anti-aerating agent comprises limonene.

14. The pharmaceutical composition of claim 13, wherein the anti-aerating agent comprises one or more of orange flavor, lemon flavor, grapefruit flavor, lime flavor, strawberry flavor, or peppermint flavor.

15. The pharmaceutical composition of any of claims 1-14, comprising a sweetener.

16. The pharmaceutical composition of any of claims 1-15, comprising a second coating material, the second coating material surrounding the first coating material and comprising 0.5-5 % w/w silica.

17. The pharmaceutical composition of any of claims 1-16, wherein the pharmaceutical composition has a disintegration time of 4 seconds or less for at least six months under storage conditions of at least 25ºC and at least 60% relative humidity.

18. The pharmaceutical composition of any of claims 1-16, wherein the pharmaceutical composition has a disintegration time of 4 seconds or less for at least six months under storage conditions of at least 30ºC and at least 65% relative humidity.

19. The pharmaceutical composition of any of claims 1-16, wherein the pharmaceutical composition has a disintegration time of 4 seconds or less for at least six months under storage conditions of at least 40ºC and at least 75% relative humidity.

20. The pharmaceutical composition of any of claims 1-19, wherein the API comprises Ibuprofen.

21. A method of preparing a pharmaceutical composition comprising:

coating an active pharmaceutical ingredient (API) with a first coating material to form coated API, wherein the first coating material comprises one or more deformable components;

applying mechanical stress to the coated Ibuprofen to deform the one or more deformable components;

coating the coated API with a second coating material comprising silica;

applying mechanical stress to embed the second coating material onto the first coating material of the coated API;

after embedding the second coating material onto the first coating material of the coated API, sieving the coated API to remove excess first coating material, wherein the excess first coating material comprises first coating material not bound to the coated API;

forming a pharmaceutical suspension comprising the twice coated API and a matrix solution or suspension;

dosing the pharmaceutical suspension into a mold; and

freeze drying the dosed pharmaceutical suspension in the mold to form a pharmaceutical composition.

22. The method of claim 21, wherein sieving the coated API comprises passing the coated API through a device comprising two or more sieves.

23. The method of claim 21 or 22, wherein sieving the coated API comprises sieving the coated API to an average particle size of 75 μm of greater.

24. The method of any of claims 21-23, wherein sieving the coated API comprises sieving the coated API to an average particle size of 200 μm or less.

25. The method of any of claims 21-24, wherein the API comprises Ibuprofen.

26. A pharmaceutical composition prepared by a process comprising the steps of:

coating an active pharmaceutical ingredient (API) with a first coating material to form coated API, wherein the first coating material comprises one or more deformable components;

applying mechanical stress to the coated API to deform the one or more deformable components;

coating the coated API with a second coating material comprising silica;

applying mechanical stress to embed the second coating material onto the first coating material of the coated API;

after embedding the second coating material onto the first coating material of the coated API, sieving the coated API to remove excess first coating material, wherein the excess first coating material comprises first coating material not bound to the coated API;

forming a pharmaceutical suspension comprising the twice coated API and a matrix solution or suspension;

dosing the pharmaceutical suspension into a mold; and

freeze drying the dosed pharmaceutical suspension in the mold to form a pharmaceutical composition.

27. The pharmaceutical composition of claim 26, wherein the API comprises Ibuprofen.