REDUCED VOLUME FORMULATIONS INCLUDING AMINO ACID ENTITIES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Serial Nos. 62/913,515 and 62/913,524, the disclosures of which are hereby incorporated herein by reference in their entirety for all purposes.

BACKGROUND

Mixtures of amino acids have a number of uses relating to human health and disease treatment. Some amino acids have limited solubility and/or dispersion when added to aqueous mixtures at higher concentrations. Inefficient/limited dispersion or solubilization can lead to problems with aqueous suspensions of amino acids, including uneven distribution of amino acids in aqueous suspensions and partial dose delivery. For applications where large dose oral delivery of amino acids may be desirable, previous approaches have used high volumes to disperse the amino acids, or spray drying or spray coating to promote wetting of the amino acids. These approaches may add cost and complexity to the manufacture and use of large dose amino acid compositions. The above problems can be exacerbated by aqueous suspensions having low volumes. There is a need for techniques and compositions to improve the solubilization and/or dispersion of amino acids in aqueous suspensions.

SUMMARY ~~OF THE INVENTION~~

Provided herein are methods for improving the dispersion of an amino acid, e.g., a hydrophobic amino acid, in an aqueous suspension using a wetting agent. Uses of a wetting agent as described herein provide an improved approach to manufacturing of compositions capable of delivering large doses of amino acids in small volumes. Without wishing to be bound by theory, the present invention is directed, in part, to aqueous suspensions comprising wetting agents, and methods of providing and/or combining the same to produce aqueous suspensions that have high concentrations of amino acids (e.g., a hydrophobic amino acid), low volumes, and improved dispersion of said amino acids (e.g., a hydrophobic amino acid). Such aqueous suspensions may evenly distribute component amino acids, exhibiting characteristics such as improved mouthfeel, taste, appearance, preparation time (e.g., constitution time), and/or dose delivery. In some ~~embodiments~~examples, an aqueous suspension

has a volume less than or equal to 8, 7, 6, 5, 4, 3, 2, 1, or 0.5 ounces, and an overall amino acid concentration of at least 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, or 15 g/ounce or a hydrophobic amino acid concentration of at least 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.2, 2.4, 2.6, 2.8, 3, 3.2, 3.4, 3.6, 3.8, 4, 4.2, 4.4, 4.6, 4.8, or 5 g/ounce. In some ~~embodiments~~examples, a wetting agent for use in an aqueous suspension has an HLB value of either 8-9 or 2-3.

In an aspect, there is provided a method of manufacturing, making, or formulating an aqueous suspension, the method comprising:

providing a dry blended preparation comprising at least one hydrophobic amino acid entity, and a wetting agent; and

combining the dry blended preparation, the wetting agent, and water to form an aqueous suspension that achieves a standard for suspension uniformity,

wherein the aqueous suspension has a volume less than or equal to 8, 7, 6, 5, 4, 3, 2, 1, or 0.5 ounces, and one or both of:

i) an overall amino acid concentration of at least 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, or 15 g/ounce; or

ii) a hydrophobic amino acid concentration of at least 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.2, 2.4, 2.6, 2.8, 3, 3.2, 3.4, 3.6, 3.8, 4, 4.2, 4.4, 4.6, 4.8, or 5 g/ounce, and/or

wherein the wetting agent has an HLB value of 8-9 or 2-3,

thereby manufacturing, making, or formulating an aqueous suspension.

In another aspect, there is provided an aqueous suspension comprising:

a plurality of amino acid entities, including at least one hydrophobic amino acid entity;

a wetting agent; and

water,

wherein the aqueous suspension achieves a standard for suspension uniformity, and one or both of:

a) wherein the aqueous suspension has a volume less than or equal to 8, 7, 6, 5, 4, 3, 2, 1, or 0.5 ounces, and one or both of:

i) an overall amino acid concentration of at least 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, or 15 g/ounce; or

ii) a hydrophobic amino acid concentration of at least 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.2, 2.4, 2.6, 2.8, 3, 3.2, 3.4, 3.6, 3.8, 4, 4.2, 4.4, 4.6, 4.8, or 5 g/ounce, or

b) wherein the wetting agent has an HLB value of either 8-9 or 2-3.

In another aspect, there is provided a method of making a dry blended preparation with improved hydrophobic amino acid dispersion, the method comprising:

providing a dry blended preparation comprising at least one hydrophobic amino acid entity and a wetting agent,

wherein, when the dry blended preparation is combined with water to form an aqueous suspension, the aqueous suspension achieves a standard for suspension uniformity, and

wherein one or both of:

a) the aqueous suspension has a volume less than or equal to 8, 7, 6, 5, 4, 3, 2, 1, or 0.5 ounces, and one or both of:

i) an overall amino acid concentration of at least 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, or 15 g/ounce; or

ii) a hydrophobic amino acid concentration of at least 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.2, 2.4, 2.6, 2.8, 3, 3.2, 3.4, 3.6, 3.8, 4, 4.2, 4.4, 4.6, 4.8, or 5 g/ounce, or

b) the wetting agent has an HLB value of 8-9 or 2-3,

thereby making a dry blended preparation with improved hydrophobic amino acid dispersion.

In another aspect, there is provided a dry blended preparation comprising:

a plurality of amino acid entities, including at least one hydrophobic amino acid entity; and

a wetting agent with an HLB value of 8-9 or 2-3,

wherein, when the dry blended preparation is combined with water to form an aqueous suspension with volume less than or equal to 8, 7, 6, 5, 4, 3, 2, 1, or 0.5 ounces, and one or both of:

i) an overall amino acid concentration of at least 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, or 15 g/ounce; or

ii) a hydrophobic amino acid concentration of at least 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.2, 2.4, 2.6, 2.8, 3, 3.2, 3.4, 3.6, 3.8, 4, 4.2, 4.4, 4.6, 4.8, or 5 g/ounce,

the aqueous suspension achieves a standard for suspension uniformity

In another aspect, there is provided a method of stabilizing N-acetylcysteine (NAC), e.g., in the presence of carnitine (CAR), the method comprising:

forming a dry blended preparation comprising NAC and CAR, under conditions such that deacetylation of NAC in the dry blended preparation is decreased compared to the deacetylation in a reference mixture,

wherein the dry blended preparation comprises less than 5, 4, 3, 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1% (w/w) water,

thereby stabilizing NAC.

In another aspect, there is provided a method of making a dry blended preparation comprising N-acetylcysteine (NAC) and carnitine (CAR), the method comprising:

forming a dry blended preparation comprising NAC and CAR, under conditions such that deacetylation of NAC in the dry blended preparation is decreased compared to the deacetylation in a reference mixture,

wherein the dry blended preparation comprises less than 5, 4, 3, 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1% (w/w) water,

thereby making an dry blended preparation comprising NAC and an CAR.

In another aspect, there is provided a dry blended preparation comprising:

N-acetylcysteine (NAC), carnitine (CAR) and an adsorbent (e.g., SiO_2),

wherein the dry blended preparation comprises less than 5, 4, 3, 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1% (w/w) water, and

wherein the adsorbent (e.g., SiO_2) is present at a weight percentage (w/w) of at least 0.05, 0.075, 0.1, 0.125, 0.15, 0.175, 0.2, 0.225, 0.25, 0.275, 0.3, 0.325, 0.35, 0.4, 0.425, 0.45, 0.475, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, or 5%, e.g., at least 0.3%, (and

optionally at less than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1.5, 1, 0.9, 0.8, 0.7, 0.6, 0.575, 0.55, 0.525, 0.5, 0.475, 0.45, 0.425, 0.4, 0.375, 0.35, or 0.325%).

In another aspect, there is provided a dry blended preparation comprising:

N-acetylcysteine (NAC) and an adsorbent (e.g., SiO_2),

wherein the dry blended preparation comprises less than 5, 4, 3, 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1% (w/w) water, and

wherein the adsorbent (e.g., SiO_2) is present at a weight percentage (w/w) of at least 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, or 40% (and optionally at less than 40, 35, 30, 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, or 6.5%).

Accordingly, in one ~~aspect~~example, the ~~invention~~disclosure features a method of improving the dispersion of a hydrophobic amino acid in an aqueous suspension, the method comprising providing a dry blended preparation comprising a hydrophobic amino acid entity, and a wetting agent; and combining the dry blended preparation, the wetting agent, and water to form an aqueous suspension that achieves a standard for suspension uniformity, thereby improving the dispersion of a hydrophobic amino acid in the aqueous suspension.

In another ~~aspect~~example, the ~~invention~~disclosure features a method of manufacturing, making, or formulating an aqueous suspension, the method comprising: providing a dry blended preparation comprising at least one hydrophobic amino acid entity, and a wetting agent; and combining the dry blended preparation, the wetting agent, and water to form an aqueous suspension that achieves a standard for suspension uniformity, thereby manufacturing, making, or formulating an aqueous suspension.

In another ~~aspect~~example, the ~~invention~~disclosure features a method of reducing foaming of an aqueous suspension comprising a hydrophobic amino acid, the method comprising: providing a dry blended preparation comprising at least one hydrophobic amino acid entity, and a wetting agent; and combining the dry blended preparation, the wetting agent, and water to form an aqueous suspension that achieves a standard for suspension uniformity, thereby reducing foaming of an aqueous suspension comprising a hydrophobic amino acid.

In another ~~aspect~~example, the ~~invention~~disclosure features a method of increasing the solubilization rate of an amino acid (e.g., hydrophobic amino acid) in an aqueous suspension, the method comprising: providing a dry blended preparation comprising at least one hydrophobic amino acid entity, and a wetting agent; and combining the dry blended preparation, the wetting agent, and water to form an aqueous suspension that achieves a

standard for suspension uniformity, thereby increasing the solubilization rate of an amino acid (e.g., hydrophobic amino acid) in an aqueous suspension.

In another ~~aspect~~example, the ~~invention~~disclosure features an aqueous suspension comprising: a plurality of amino acid entities, including at least one hydrophobic amino acid entity; a wetting agent; and water, wherein the aqueous suspension achieves a standard for suspension uniformity.

In another ~~aspect~~example, the ~~invention~~disclosure features a method of making a dry blended preparation with improved hydrophobic amino acid dispersion, the method comprising: providing a dry blended preparation comprising at least one hydrophobic amino acid entity and a wetting agent, wherein, when the dry blended preparation is combined with water to form an aqueous suspension the aqueous suspension achieves a standard for suspension uniformity, thereby making a dry blended preparation with improved hydrophobic amino acid dispersion.

In another ~~aspect~~example, the ~~invention~~disclosure features a dry blended preparation comprising: a plurality of amino acid entities, including at least one hydrophobic amino acid entity; and a wetting agent, e.g., with an HLB value of 8-9 or 2-3, wherein, when the dry blended preparation is combined with water to form an aqueous suspension, the aqueous suspension achieves a standard for suspension uniformity.

In another ~~aspect~~example, the ~~invention~~ disclosure features a kit comprising: a plurality of amino acid entities, including at least one hydrophobic amino acid entity; a wetting agent; and instructions for combining the plurality of amino acid entities and the wetting agent into an aqueous suspension that achieves a standard for suspension uniformity.

In another ~~aspect~~example, the ~~invention~~disclosure features a method of directing provision of an aqueous suspension, the method comprising: providing a dry blended preparation comprising at least one hydrophobic amino acid entity, and a wetting agent; and providing instructions for combining the dry blended preparation, the wetting agent, and water to form an aqueous suspension that achieves a standard for suspension uniformity, thereby directing provision of an aqueous suspension.

In another ~~aspect~~example, the ~~invention~~disclosure features a method of evaluating the dispersion of a dry blended preparation comprising at least one hydrophobic amino acid entity, the method comprising: providing a dry blended preparation comprising at least one hydrophobic amino acid entity, and a wetting agent; combining the dry blended preparation, wetting agent, and water to form an aqueous suspension; and evaluating whether the aqueous suspension achieves a standard for suspension uniformity (e.g., as defined by a government regulatory agency or by standard industry practice) by acquiring a value for the amount of an amino acid entity (e.g., a hydrophobic amino acid entity) at a sampling point (e.g., in weight % of total

amino acid entities or weight % of the total mixture), and optionally comparing said value to a reference value,

thereby evaluating the dispersion of the dry blended preparation.

In some ~~embodiments~~examples, the aqueous suspension has a volume less than or equal to 8, 7, 6, 5, 4, 3, 2, 1, or 0.5 ounces, and one or both of: i) an overall amino acid concentration of at least 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, or 15 g/ounce; or ii) a hydrophobic amino acid concentration of at least 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.2, 2.4, 2.6, 2.8, 3, 3.2, 3.4, 3.6, 3.8, 4, 4.2, 4.4, 4.6, 4.8, or 5 g/ounce. In some ~~embodiments~~examples, the wetting agent has an HLB value of either 8-9 or 2-3. In some examples~~embodiments~~, the wetting agent has an HLB value of either 8-9 or 2-3, and the aqueous suspension has a volume less than or equal to 8, 7, 6, 5, 4, 3, 2, 1, or 0.5 ounces, and one or both of: i) an overall amino acid concentration of at least 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, or 15 g/ounce; or ii) a hydrophobic amino acid concentration of at least 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.2, 2.4, 2.6, 2.8, 3, 3.2, 3.4, 3.6, 3.8, 4, 4.2, 4.4, 4.6, 4.8, or 5 g/ounce.

In certain ~~embodiments~~examples, provided herein is a dry blended compostion including a) a leucine amino acid entity, b) an isoleucine amino acid entity, c) a valine amino acid entity, d) an arginine amino acid entity, e) a glutamine amino acid entity, and f) an N-acetylcysteine (NAC) entity, wherein the wetting agent is lecithin, e.g., a lecithin having an HLB value of 8-9 and/or 20 to 40% amphiphilic phospholipid (e.g., phosphatidylcholine), e.g., Alcolec 40P or a substantially equivalent lecithin.

In certain ~~embodiments~~examples, provided herein is a dry blended compostion including a) a leucine amino acid entity, b) an isoleucine amino acid entity, c) a valine amino acid entity, d) a histidine amino acid entity, e) a lysine amino acid entity, f) a threonine amino acid entity, g) an ornithine amino acid entity, and h) an aspartate amino acid entity, wherein the wetting agent is lecithin, e.g., a lecithin having an HLB value of 8-9 and/or 20 to 40% amphiphilic phospholipid (e.g., phosphatidylcholine), e.g., Alcolec 40P or a substantially equivalent lecithin.

In further ~~embodiments~~examples, the dry blended compostion includes one or more pharmecutically acceptable excipients. In further examples~~embodiments~~, the dry blended compostion includes an adsorbent, e.g., SiO_2.

Provided herein are methods of stabilizing N-acetylcysteine (NAC) in the presence of an acetyl acceptor, e.g., carnitine (CAR), comprising forming a dry blended preparation comprising NAC and the acetyl acceptor (e.g., CAR) under conditions such that deacetylation of NAC in the dry blended preparation is decreased compared to the deacetylation in a reference mixture (e.g., a dry blended preparation not formed under the conditions that decrease deacetylation of NAC). In some ~~embodiments~~examples, the conditions comprise including an adsorbent in the dry blended preparation. Without wishing to be bound by theory, an adsorbent may bind the water present in a dry blended preparation, e.g., preventing the water from facilitating the deacetylation of NAC, e.g., by CAR or water associated with CAR. A dry blended preparation formed under conditions that decrease deacetylation of NAC may have improved stability and longevity (e.g., shelf life) compared to dry blended preparations comprising NAC and not formed under conditions decreasing deacetylation.

Accordingly, in one ~~aspect~~example, the ~~invention~~disclosure features a method of stabilizing NAC, e.g., in the presence of an acetyl acceptor, e.g., CAR, the method comprising: forming a dry blended preparation comprising NAC and CAR, under conditions such that deacetylation of NAC in the dry blended preparation is decreased compared to the deacetylation in a reference mixture, wherein the dry blended preparation comprises less than 5, 4, 3, 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1% (w/w) water, thereby stabilizing NAC.

In another ~~aspect~~example, the ~~invention~~disclosure features a method of decreasing the deacetylation of NAC in the presence of an acetyl acceptor (e.g., (CAR)), the method comprising: forming a dry blended preparation comprising NAC and CAR, under conditions such that deacetylation of NAC in the dry blended preparation is decreased compared to the deacetylation in a reference mixture, wherein the dry blended preparation comprises less than 5, 4, 3, 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1% (w/w) water, thereby decreasing the deacetylation of NAC in the presence of an acetyl acceptor (e.g., CAR).

In another ~~aspect~~example, the ~~invention~~disclosure features a method of making a dry blended preparation comprising NAC and an acetyl acceptor, e.g., (CAR), the method comprising: forming a dry blended preparation comprising NAC and the acetyl acceptor, e.g. CAR, under conditions such that deacetylation of NAC in the dry blended preparation is decreased

compared to the deacetylation in a reference mixture, wherein the dry blended preparation comprises less than 5, 4, 3, 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1% (w/w) water, thereby making a dry blended preparation comprising NAC and an acetyl acceptor (e.g., CAR).

In another ~~aspect~~exmaple, the ~~invention~~disclosure features a method of evaluating the stability of NAC in a dry blended preparation, the method comprising: providing a dry blended preparation comprising NAC; and determining the level of NAC, e.g., at a first time point and at a second time point; and optionally, comparing the level of NAC to a reference value, e.g., a NAC value between 90-110% of the original level of NAC in the mixture, wherein the dry blended preparation comprises less than 5, 4, 3, 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1% (w/w) water, thereby evaluating the stability of NAC in a dry blended preparation.

In another ~~aspect~~example, the ~~invention~~disclosure features a method of pre-treating NAC, the method comprising: providing a mixture of NAC and an adsorbent, thereby pre-treating NAC.

In another ~~aspect~~example, the ~~invention~~disclosure features a method of pre-treating CAR, the method comprising: providing a mixture of CAR and an adsorbent, thereby pre-treating CAR.

In another ~~aspect~~example, the ~~invention~~disclosure features a dry blended preparation comprising:

NAC; an acetyl acceptor (e.g., CAR); and an adsorbent (e.g., SiO_2), wherein the dry blended preparation comprises less than 5, 4, 3, 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1% (w/w) water, and wherein the adsorbent (e.g., SiO_2) is present at a weight percentage (w/w) of at least 0.05, 0.075, 0.1, 0.125, 0.15, 0.175, 0.2, 0.225, 0.25, 0.275, 0.3, 0.325, 0.35, 0.4, 0.425, 0.45, 0.475, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, or 5%, e.g., at least 0.3%, (and optionally at less than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1.5, 1, 0.9, 0.8, 0.7, 0.6, 0.575, 0.55, 0.525, 0.5, 0.475, 0.45, 0.425, 0.4, 0.375, 0.35, or 0.325%).

In another ~~aspect~~example, the ~~invention~~disclosure features a mixture, e.g., a dry blended preparation, comprising: NAC and an adsorbent (e.g., SiO_2), wherein the mixture, e.g., dry blended preparation, comprises less than 5, 4, 3, 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1% (w/w) water, and wherein the adsorbent (e.g., SiO_2) is present at a weight percentage (w/w) of at least 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.5, 8, 8.5, 9, 9.5, or 10% (and

optionally at less than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, or 6.5%). In some ~~embodiments~~examples, the mixture comprises no other amino acid entity besides NAC. In some ~~embodiments~~examples, the mixture is a

dry blended preparation. In some ~~embodiments~~examples, the mixture, e.g., dry blended preparation, does not comprise CAR.

In futher ~~rmbodiments~~examples, the dry blended preparation may include: a) a leucine (L)-amino acid entity, b) an arginine (R)-amino acid entity, and/or c) a glutamine (Q)-amino acid entity.

In futher examples~~rmbodiments~~, the dry blended preparation may include: a) a leucine (L)-amino acid entity, b) an arginine (R)-amino acid entity, and c) a glutamine (Q)-amino acid entity.

In futher examples~~rmbodiments~~, the dry blended preparation may include: a) a leucine (L)-amino acid entity, b) an arginine (R)-amino acid entity, c) a glutamine (Q)-amino acid entity, d) a citrulline amino acid entity, e) a serine (S)-amino acid entity, f) a valine (V)-amino acid entity, g) a histidine (H)-amino acid entity, and h) a lysine (K)-amino acid entity.

In futher examples~~rmbodiments~~, the dry blended preparation may include: a) a leucine (L)-amino acid entity, b) an arginine (R)-amino acid entity, c) a glutamine (Q)-amino acid entity, d) an isoleucine (I)-amino acid entity, and e) a serine (S)-amino acid entity.

Additional features of any of the aforesaid methods or compositions include one or more of the following enumerated embodiments.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific ~~embodiments~~ examples of the ~~invention~~ disclosure described herein. Such equivalents are intended to be encompassed by the following enumerated embodiments.

All publications, patent applications, patents, and other references (e.g., sequence database reference numbers) mentioned herein are incorporated by reference in their entirety.

ENUMERATED EMBODIMENTS

1. A method of improving the dispersion of a hydrophobic amino acid in an aqueous suspension, the method comprising:

providing a dry blended preparation comprising a hydrophobic amino acid entity, and a wetting agent; and

combining the dry blended preparation, the wetting agent, and water to form an aqueous suspension that achieves a standard for suspension uniformity,

wherein the aqueous suspension has a volume less than or equal to 8, 7, 6, 5, 4, 3, 2, 1, or 0.5 ounces, and one or both of: