ANTIBODY FORMULATIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application No. 63/232,299, filed on August 12, 2021, and U.S. Provisional Patent Application No. 63/316,604, filed on March 4, 2022, is hereby claimed, and the disclosure thereof is hereby incorporated by reference herein

INCORPORATION BY REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0002] Incorporated by reference in its entirety is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: 99.1 KB file named "A-2756-WO01-SEC_SeqListing.xml"; created on July 19, 2022.

BACKGROUND

[0003] Increasing the concentration of therapeutic proteins in drug formulations can cause problems. For example, formulations comprising high concentrations of protein may lead to aggregation resulting in the formation of high molecular weight (HMW) species. HMW species, can be of concern in some protein formulations. Aggregation can also potentially affect the subcutaneous bioavailability and pharmacokinetics of a therapeutic protein and can cause a loss of bioactivity and increase in immunogenicity of the protein. High concentration protein formulations may result in elevated viscosity that can adversely impact drug product filling and administration.

[0004] Thus, there is a need in the art for high concentration formulations of antibodies with reduced viscosity, high stability and low levels of aggregation.

SUMMARY

[0005] Presented herein are data demonstrating the initial stability, storage stability, and reduced viscosity of high concentration antibody liquid compositions comprising arginine glutamate or proline. Advantageously, the liquid compositions are isotonic and thus suitable for administration to subjects by injection or infusion. Surprisingly, the formulations presented herein comprise lower amounts of arginine glutamate or proline, compared to prior art formulations, and still retain the desired properties relating to initial aggregation, stability and viscosity. Accordingly, the present disclosure provides a liquid composition, e.g., an isotonic liquid composition, comprising a monoclonal antibody at a concentration greater than about 100 mg/mL, arginine glutamate, and a surfactant, wherein the pH of the liquid composition is about 4.5 to about 5.5. Also provided is a liquid composition, e.g., an isotonic liquid composition, comprising a monoclonal antibody at a concentration greater than about 100 mg/mL, proline, a buffer, and a surfactant, wherein the pH of the liquid composition is about 4.5 to about 5.5. In

various examples, the concentration of the monoclonal antibody is less than about 300 mg/mL or less than about 250 mg/mL. In exemplary examples, the presently disclosed liquid composition comprises about 110 mg/mL to about 250 mg/mL

monoclonal antibody. In various examples, the concentration of the monoclonal antibody is the concentration of the monoclonal antibody is about 120 mg/mL to about 180 mg/mL. Optionally, the liquid composition comprises about 120 mg/mL monoclonal antibody. In alternative examples, the liquid composition comprises about 135 mg/mL to about 165 mg/mL monoclonal antibody, or about 140 mg/mL to about 160 mg/mL monoclonal antibody. In exemplary instances, the liquid composition comprises about 140 mg/mL or about 150 mg/mL monoclonal antibody. The monoclonal antibody of the presently disclosed liquid compositions is, in various examples, an IgG_1 antibody. Alternatively, in various instances, the monoclonal antibody of the presently disclosed liquid compositions is an IgG_2 antibody. The monoclonal antibody, in exemplary examples, is an anti-IL-15 antibody, an anti-PD-1 antibody, an anti-RANKL antibody, or an anti-GITR antibody. Exemplary antibodies are described herein. In one aspect, the present disclosure refers to a liquid composition comprising (a) an anti-IL-15 antibody at a concentration greater than about 100 mg/mL, (b) about 70 mM to about 210 mM arginine base, (c) about 80 mM to about 240 mM glutamate, and (d) a surfactant, wherein the pH of the liquid composition is about 4.5 to about 5.5. In another aspect, the present disclosure refers to a liquid composition comprising (a) an anti-IL-15 antibody at a concentration greater than about 100 mg/mL, (b) about 115 mM to about 345 mM proline, (c) a buffer, and (d) a surfactant, wherein the pH of the liquid composition is about 4.5 to about 5.5. In another aspect, the present disclosure refers to a liquid composition comprising, per mL of the liquid composition, (i) about 135 mg to about 165 mg of an anti-IL-15 antibody comprising a Heavy Chain (HC) Complementarity-Determining Region (CDR) 1 of SEQ ID NO: 1, a HC CDR2 of SEQ ID NO: 2, a HC CDR3 of SEQ ID NO: 3, a Light Chain (LC) Complementarity-Determining Region (CDR) 1 of SEQ ID NO: 4, a LC CDR2 of SEQ ID NO: 5, and a LC CDR3 of SEQ ID NO: 6, (ii) about 21 mg to about 26 mg arginine base, (iii) about 21 mg to about 26 mg glutamate, and (iv) about 0.01% (w/v) polysorbate 80 (PS80), wherein the liquid composition has a pH of about 4.5 to about 5.5. In yet another aspect, the present disclosure refers to a liquid composition comprising, per mL of the liquid composition, (i) about 135 mg to about 165 mg of an anti-IL-15 antibody comprising a Heavy Chain (HC) Complementarity-Determining Region (CDR) 1 of SEQ ID NO: 1, a HC CDR2 of SEQ ID NO: 2, a HC CDR3 of SEQ ID NO: 3, a Light Chain (LC) Complementarity-Determining Region (CDR) 1 of SEQ ID NO: 4, a LC CDR2 of SEQ ID NO: 5, and a LC CDR3 of SEQ ID NO: 6, (ii) about 23 mg to about 30 mg proline, (iii) about 0.5 mg to about 2 mg acetate, and (iv) about 0.01% (w/v) polysorbate 80 (PS80), wherein the liquid composition has a pH of about 4.5 to about 5.5. In another aspect, the present disclosure refers to a method of preparing a liquid composition comprising greater than about 100 mg/mL of an anti-IL-15 antibody, said method comprising (a) combining the antibody with a diafiltration (DF) buffer comprising about 70 mM to about 210 mM arginine base and about 80 mM to about 240 mM glutamic acid, and (b) adding a surfactant. In

various examples, the liquid composition comprises about 200 mM to about 400 mM arginine glutamate. Optionally, the liquid composition comprises about 225 mM to about 350 mM arginine glutamate. In various instances, the liquid composition comprises about 250 mM to about 325 mM arginine glutamate, or about 200 mM to about 300 mM or about 200 mM arginine glutamate. In various examples, the monoclonal antibody is formulated with about 50 mM to about 300 mM arginine base, optionally, about 85 mM to about 190 mM L-arginine. In various examples, the monoclonal antibody is formulated with about 135 mM to about 165 mM arginine base. In various instances, the monoclonal antibody is formulated with about 155 mM to about 185 mM glutamic acid. In exemplary instances, the monoclonal antibody is formulated with about 150 mM arginine base and about 170 mM glutamic acid. In various instances, the monoclonal antibody is formulated with about 136 mM arginine base and about 159 mM glutamic acid. In various instances, the liquid composition comprises a molar ratio of arginine to glutamate of about 0.7:1.0 to about 1.1:1.0. For example, the molar ratio of arginine to glutamate is about 0.8:1.0 to about 1.1: 1.0. In various examples, arginine and glutamate are the only amino acids present in the liquid composition. In exemplary instances, the liquid composition comprises (a) about 150 mg to about 165 mg monoclonal antibody, (b) about 22 mg to about 26 mg L-arginine (e.g., about 24 mg to about 25 mg), (c) about 22 mg to about 26 mg glutamate (e.g., about 23 mg to about 24 mg), and (d) about 0.01 mg PS80, wherein the liquid composition has a pH of about 4.7 to about 5.3. In various instances, the liquid composition consists essentially of or consists of only (a) to (d). For example, the liquid composition does not comprise any additional buffer or any sugar. In alternative exemplary examples, the liquid composition of the present disclosure comprises proline and a buffer, instead of arginine glutamate. In various examples, the liquid composition comprises about 200 mM to about 300 mM proline, optionally, about 225 mM to about 275 mM proline or about 235 mM to about 265 mM. In various instances, the liquid composition comprises about 240 mM to about 260 mM proline. In various examples, the proline is L-proline and/or proline is the only amino acid present in the liquid composition. In various instances, the buffer is selected from the group consisting of: succinate, glutamate, histidine, and acetate. Preferably, the buffer is acetate, e.g., acetate prepared with glacial

acetic acid. In exemplary examples, the buffer is prepared with about 1 mM to about 50 mM buffer, optionally, glacial acetic acid. In exemplary instances, the buffer is prepared with about 18 mM to about 22 mM buffer, optionally, 20 mM glacial acetic acid. Optionally, the liquid composition comprises about 30 mM to about 38 mM buffer, e.g., about 34 mM acetate. The pH of the buffer in various examples is titrated with sodium hydroxide. In exemplary examples, the surfactant is amphipathic and/or nonionic, optionally, a polysorbate. In exemplary instances, the surfactant is polysorbate 20 (PS20) or polysorbate 80 (PS80) or a mixture thereof. The liquid composition in exemplary examples comprises a surfactant at a concentration of about 0.001% (w/v) to about 0.050% (w/v). Optionally, the surfactant is present at a concentration of about 0.005% (w/v) to about 0.025% (w/v) or about 0.01% (w/v) ± 0.001% (w/v) surfactant. In preferred examples, the liquid composition comprises about 0.01% (w/v) polysorbate 80 (PS80). The pH of the presently disclosed liquid composition is about 4.70 to about 5.30, optionally, about 5.0. In exemplary examples, the liquid composition comprises, per mL liquid composition, (a) about 150 mg to about 165 mg monoclonal antibody, (b) about 22 mg to about 26 mg L-arginine, (c) about 22 mg to about 26 mg glutamate, and (d) about 0.01 mg PS80, wherein the liquid composition has a pH of about 4.7 to about 5.3. In various examples, the liquid composition comprises, per mL liquid composition, about 150 mg to about 165 mg monoclonal antibody in about 180 mM to about 220 mM proline, about 30 mM to about 38 mM acetate, and about 0.01% (w/v) PS80, wherein the liquid composition has a pH of about 4.7 to about 5.3. In exemplary examples, the liquid composition is an isotonic liquid composition wherein less than about 5% of the antibody is degraded after storage at 2ºC to 8ºC for about 20 months to about 26 months, as determined by Size Exclusion Chromatography (SEC) and the liquid composition has a viscosity less than less than 30 cP at 25 °C, $1000s^{-1}$.

[0006] Methods of preparing a liquid composition comprising a target concentration of a monoclonal antibody, wherein the target concentration is greater than about 100 mg/mL are further provided herein. In exemplary examples, the liquid composition is an isotonic liquid composition wherein less than about 5% of the antibody is degraded after storage at 2ºC to 8ºC for about 20 months to about 26 months, as determined by Size Exclusion Chromatography (SEC) and the liquid composition has a viscosity less than less than 30 cP at 25 °C, $1000s^{-1}$. In exemplary examples, the method comprises (a) combining the monoclonal antibody with a diafiltration (DF) buffer comprising (i) about 50 mM to about 300 mM arginine base and (ii) an amount of glutamate to achieve a molar ratio of arginine to glutamate of about 0.7:1.0 to about 1.1:1.0 (e.g., about 0.8:1.0 to about 1.1:1.0), and (b) adding a surfactant. Optionally, the DF buffer comprises about 85 mM to about 190 mM arginine. Optionally, the DF buffer comprises about 135 mM to about 165 mM arginine base. In preferred examples, the DF buffer comprises about 155 mM to about 185 mM glutamate, e.g., about 150 mM arginine base and about 170 mM glutamate. In various

instances, the pH of the DF buffer is about the same as the final pH of the prepared liquid composition. Optionally,

the final pH of the prepared liquid composition is about 4.5 to about 5.5, optionally, about 4.7 to about 5.3. In various instances, the surfactant is PS80 and/or is present at a final concentration of about 0.01% (w/v). A liquid composition prepared by the presently disclosed method is provided herein. In another aspect, the present disclosure refers to a liquid composition prepared by the method as described herein.

[0007] The present disclosure additionally provides an article of manufacture comprising any one of the presently disclosed isotonic liquid compositions. Optionally, the article comprises about 1 mL to about 5 mL of the isotonic liquid composition. In another aspect, the present disclosure refers to an article of manufacture comprising the liquid composition as described herein, optionally, comprising about 1 mL to about 5 mL of the liquid composition.

[0008] Also provided is a pre-filled syringe comprising any one of the presently disclosed isotonic liquid compositions, optionally, comprising about 1 mL to about 5 mL of the isotonic liquid composition. In another aspect, the present disclosure refers to a pre-filled syringe comprising the liquid composition as described herein, optionally, comprising about 1 mL to about 5 mL of the liquid composition.

[0009] A vial comprising any one of the presently disclosed isotonic liquid compositions is further provided by the present disclosure. Optionally, the vial comprises about 1 mL to about 5 mL of the isotonic liquid composition. In another aspect, the present disclosure refers to a vial comprising the liquid composition as described herein, optionally, comprising about 1 mL to about 5 mL of the liquid composition.

[0010] The present disclosure also provides an autoinjector comprising any one of the presently disclosed isotonic liquid compositions. In yet another aspect, the present disclosure refers to an autoinjector comprising the liquid composition as described herein.

[0011] Methods of treating a disease in a subject are provided by the present disclosure. In exemplary examples, the method comprises administering to the subject an isotonic liquid composition of any one of the preceding claims in an amount effective to treat the disease. Additionally, use of the isotonic liquid composition of the present disclosure for treating a disease is provided. In another aspect, the present disclosure refers to a liquid composition as described herein for use in therapy. In yet another aspect, the present disclosure refers to the use of the liquid composition as described herein in the manufacture of a medicament for treating a celiac disease.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 is a graph of the % HMW species formed in the indicated antibody formulations having the indicated target antibody concentrations.

DETAILED DESCRIPTION

[0013] The present disclosure provides liquid compositions comprising high concentrations of an antibody, e.g., a monoclonal antibody. Collectively, antibodies form a family of plasma proteins known as immunoglobulins and comprise of immunoglobulin domains. (Janeway et al., Immunobiology: The Immune System in Health and Disease, 4th ed., Elsevier Science Ltd./Garland Publishing, 1999. As used herein, the term "antibody" refers to a protein having a conventional immunoglobulin format, comprising heavy and light chains, and comprising variable and constant regions. For example, an antibody may be an IgG which is a "Y-shaped" structure of two identical pairs of polypeptide chains, each pair having one "light" (typically having a molecular weight of about 25 kDa) and one "heavy" chain (typically having a molecular weight of about 50-70 kDa). An antibody has a variable region and a constant region. In IgG formats, the variable region is generally about 100-110 or more amino acids, comprises three complementarity determining regions (CDRs), is

WHAT IS CLAIMED:

1. A liquid composition comprising (a) an anti-IL-15 antibody at a concentration greater than about 100 mg/mL, (b) about 70 mM to about 210 mM arginine base, (c) about 80 mM to about 240 mM glutamate, and (d) a surfactant, wherein the pH of the liquid composition is about 4.5 to about 5.5.

2. The liquid composition of claim 1, comprising:
about 100 mM to about 170 mM arginine base; and/or

about 120 mM to about 200 mM glutamate.

3. The liquid composition of claim 2, comprising:
about 120 mM to about 150 mM arginine base; and/or

about 140 mM to about 175 mM glutamate.

4. The liquid composition of claim 3, comprising:
about 136 mM arginine base; and/or

about 159 mM glutamate.

5. The liquid composition of any one of claims 1-4, wherein arginine and glutamate are the only amino acids present in the liquid composition.

6. The liquid composition of any one of claims 1-5, comprising less than about 0.001% (w/v) a buffer other than glutamate.

7. A liquid composition comprising (a) an anti-IL-15 antibody at a concentration greater than about 100 mg/mL, (b) about 115 mM to about 345 mM proline, (c) a buffer, and (d) a surfactant, wherein the pH of the liquid composition is about 4.5 to about 5.5.

8. The liquid composition of claim 7, comprising:

about 170 mM to about 290 mM proline; and/or

about 1 mM to about 100 mM buffer, optionally, about 1 mM to about 50 mM buffer.

9. The liquid composition of claim 8, comprising:

about 200 mM to about 255 mM proline; and/or

about 10 mM to about 30 mM buffer, optionally, about 15 mM to about 25 mM buffer.

10. The liquid composition of claim 9, comprising about 230 mM proline.

11. The liquid composition of any one of claims 7-10, wherein:

proline is the only amino acid present in the composition; and/or

the buffer is selected from the group consisting of succinate, glutamate, histidine, and acetate.

12. The liquid composition of claim 11, wherein the buffer is acetate.

13. The liquid composition of any one of claims 1-12, comprising:

not more than 0.001% (w/v) of a sugar, sugar alcohol, or citrate; and/or

not more than 0.001% (w/v) disaccharide.

14. The liquid composition of any one of claims 1-13, comprising not more than 0.001% (w/v) trehalose or sucrose.

15. The liquid composition of any one of claims 1-14, wherein the concentration of the anti-IL-15 antibody is less than about 300 mg/mL.

16. The liquid composition of any one of claims 1-15, comprising about 110 mg/mL to about 200 mg/mL anti-IL-15 antibody.

17. The liquid composition of claim 16, comprising about 150 mg/mL or about 165 mg/mL anti-IL-15 antibody.

18. The liquid composition of any one of claims 1-17, wherein the anti-IL-15 antibody is an IgG_1 antibody.

19. The liquid composition of claim 18, comprising a Heavy Chain (HC) Complementarity-Determining Region (CDR) 1 of SEQ ID NO: 1, a HC CDR2 of SEQ ID NO: 2, a HC CDR3 of SEQ ID NO: 3, a Light Chain (LC) Complementarity-Determining Region (CDR) 1 of SEQ ID NO: 4, a LC CDR2 of SEQ ID NO: 5, and a LC CDR3 of SEQ ID NO: 6.

20. The liquid composition of claim 18 or 19, comprising a HC variable region of SEQ ID NO: 7 and a LC variable region of SEQ ID NO: 8.

21. The liquid composition of any one of claims 18-20, comprising a HC of SEQ ID NO: 9 and a LC of SEQ ID NO: 10.

22. The liquid composition of any one of claims 1-21, comprising a surfactant at a concentration of about 0.001% (w/v) to about 0.050% (w/v), optionally wherein the surfactant is amphipathic and/or nonionic.

23. The liquid composition of claim 22, wherein the surfactant is polysorbate 20 (PS20) or polysorbate 80 (PS80) or a mixture thereof.

24. The liquid composition of claim 23, comprising about 0.01% (w/v) polysorbate 80 (PS80).

25. The liquid composition of any one of claims 1-24, wherein the surfactant does not significantly alter the viscosity of the composition.

26. The liquid composition of any one of claims 1-25, having a pH of about 4.6 to about 5.4.

27. The liquid composition of claim 26, having a pH of about 4.8 to about 5.2.

28. The liquid composition of claim 27, having a pH of about 5.0.

29. The liquid composition of any one of claims 1-28, wherein:

the viscosity of the liquid composition is less than 50 cP at 25 °C, $1000s^{-1}$; and/or

the composition has an osmolality in a range of about 200 mOsm/kg to about 500 mOsm/kg, optionally, about 225 mOsm/kg to about 400 mOsm/kg; and/or

less than 5% of the antibody is degraded after storage at 2ºC to 8ºC for at least or about 12 months or about 24 months to about 36 months, as determined by Size Exclusion Chromatography (SEC).

30. The liquid composition of claim 29, wherein:

the viscosity of the liquid composition is less than 30 cP at 25 °C, $1000s^{-1}$; and/or

the composition has an osmolality in a range of about 250 mOsm/kg to about 350 mOsm/kg; and/or

less than 5% of the antibody is degraded after storage at 2ºC to 8ºC for about 30 to about 40 months, as determined by SEC.

31. The liquid composition of claim 30, wherein:

the viscosity of the liquid composition is less than 20 cP at 25 °C, $1000s^{-1}$; and/or

the composition is isotonic; and/or

less than 5% of the antibody is degraded after storage at 2ºC to 8ºC for about 36 to about 40 months, as determined by SEC.

32. The liquid composition of claim 31, wherein the viscosity of the liquid composition is less than or about 10 cP at 25 °C, $1000s^{-1}$.

33. A liquid composition comprising, per mL of the liquid composition,

(i) about 135 mg to about 165 mg of an anti-IL-15 antibody comprising a Heavy Chain (HC) Complementarity-Determining Region (CDR) 1 of SEQ ID NO: 1, a HC CDR2 of SEQ ID NO: 2, a HC CDR3 of SEQ ID NO: 3, a Light Chain (LC) Complementarity-Determining Region (CDR) 1 of SEQ ID NO: 4, a LC CDR2 of SEQ ID NO: 5, and a LC CDR3 of SEQ ID NO: 6,

(ii) about 21 mg to about 26 mg arginine base,

(iii) about 21 mg to about 26 mg glutamate, and

(iv) about 0.01% (w/v) polysorbate 80 (PS80), wherein the liquid composition has a pH of about 4.5 to about 5.5.

34. A liquid composition comprising, per mL of the liquid composition,

(i) about 135 mg to about 165 mg of an anti-IL-15 antibody comprising a Heavy Chain (HC) Complementarity-Determining Region (CDR) 1 of SEQ ID NO: 1, a HC CDR2 of SEQ ID NO: 2, a HC CDR3 of SEQ ID NO: 3, a Light Chain (LC) Complementarity-Determining Region (CDR) 1 of SEQ ID NO: 4, a LC CDR2 of SEQ ID NO: 5, and a LC CDR3 of SEQ ID NO: 6,

(ii) about 23 mg to about 30 mg proline,

(iii) about 0.5 mg to about 2 mg acetate, and

(iv) about 0.01% (w/v) polysorbate 80 (PS80), wherein the liquid composition has a pH of about 4.5 to about 5.5.

35. A method of preparing a liquid composition comprising greater than about 100 mg/mL of an anti-IL-15 antibody, said method comprising (a) combining the antibody with a diafiltration (DF) buffer comprising about 70 mM to about 210 mM arginine base and about 80 mM to about 240 mM glutamic acid, and (b) adding a surfactant.

36. The method of claim 35, wherein the DF buffer comprises:
about 100 mM to about 170 mM arginine base; and/or

about 120 mM to about 200 mM glutamic acid.

37. The method of claim 36, wherein the DF buffer comprises:

about 120 mM to about 150 mM arginine base; and/or

about 140 mM to about 175 mM glutamic acid.

38. The method of claim 37, wherein the DF buffer comprises:

about 136 mM arginine base; and/or

about 159 mM glutamic acid.

39. The method of any one of claims 35-38, wherein arginine and glutamic acid are the only amino acids present in the DF buffer and/or glutamic acid.

40. The method of any one of claims 35-39, wherein the pH of the DF buffer is about the same as the pH of the liquid composition.

41. The method of any one of claims 35-40, wherein the pH of the liquid composition is about 4.5 to about 5.5, optionally, about 4.7 to about 5.3 or about 4.8 to about 5.2.

42. The method of any one of claims 35-41, wherein:

the surfactant is polysorbate 80; and/or

the concentration of the surfactant in the prepared liquid composition is about 0.01% (w/v).

43. A liquid composition prepared by the method of any one of claims 35-42.

44. An article of manufacture comprising the liquid composition of any one of claims 1-34, optionally, comprising about 1 mL to about 5 mL of the liquid composition.

45. A pre-filled syringe comprising the liquid composition of any one of claims 1-34, optionally, comprising about 1 mL to about 5 mL of the liquid composition.

46. A vial comprising the liquid composition of any one of claims 1-34, optionally, comprising about 1 mL to about 5 mL of the liquid composition.

47. An autoinjector comprising the liquid composition of any one of claims 1-34.

48. A liquid composition of any one of claims 1-34 for use in therapy.

49. Use of a liquid composition of any one of claims 1-34 in the manufacture of a medicament for treating a celiac disease.