molecular-weight proteins, such as mAbs.

It is a further object of the present invention to provide concentrated low-viscosity liquid formulations of proteins, especially high-molecular-weight proteins, such as mAbs, capable of delivering therapeutically effective amounts of these proteins in volumes useful for SC and IM injections.

It is a further object of the present invention to provide the concentrated liquid formulations of proteins, especially high-molecular-weight proteins, such as mAbs, with low viscosities that can improve injectability and/or patient compliance, convenience, and comfort.

It is also an object of the present invention to provide methods for making and storing concentrated, low-viscosity formulations of proteins, especially high-molecular-weight proteins, such as mAbs.

It is an additional object of the present invention to provide methods of administering low-viscosity, concentrated liquid formulations of proteins, especially high-molecular-weight proteins, such as mAbs.

It is an additional object of the present invention to provide methods for processing reduced-viscosity, high-concentration biologics with concentration and filtration techniques known to those skilled in the art.

SUMMARY OF THE INVENTION

Concentrated, low-viscosity, low-volume liquid pharmaceutical formulations of proteins have been developed. Such formulations can be rapidly and conveniently administered by subcutaneous or intramuscular injection, rather than by lengthy intravenous infusion. These formulations include low-molecular-weight and/or high-molecular-weight proteins, such as mAbs, and viscosity-reducing ionic liquids.

In one aspect, provided herein is a liquid pharmaceutical formulation for injection comprising: (i) an antibody; (ii) one or more viscosity-reducing ionic liquids, wherein the one or more viscosity-reducing ionic liquids comprise: 4-(3-butyl-1-imidazolio)-1-butane sulfonate (BIM) or a pharmaceutically acceptable salt thereof; 1-butyl-3-methylimidazolium methanesulfonate (BMI Mes) or a pharmaceutically acceptable salt thereof; 1-butyl-1-methylpyrrolidinium chloride (BMP Chloride) or a pharmaceutically acceptable salt thereof; or 4-ethyl-4-methylmorpholinium methylcarbonate (EMMC) or a pharmaceutically acceptable salt thereof; and (iii) a

pharmaceutically acceptable solvent; wherein the liquid pharmaceutical formulation, when in a volume suitable for injection, has an absolute viscosity of from about 1 cP to about 100 cP at 25°C as measured using a cone and plate viscometer or a microfluidic viscometer; and the absolute viscosity of the liquid pharmaceutical formulation is less than an absolute viscosity of a control composition comprising the antibody and the pharmaceutically acceptable solvent but without the one or more viscosity-reducing ionic liquids; wherein the absolute viscosity is an extrapolated zero-shear viscosity.

In one aspect, provided herein is a liquid pharmaceutical formulation as described herein for use in the administration of a therapeutically effective amount of the antibody to a subject by subcutaneous or intramuscular injection.

In one aspect, provided herein is a method of preparing the liquid pharmaceutical formulation as described herein, comprising the step of combining the antibody, the pharmaceutically acceptable solvent, and the one or more viscosity-reducing ionic liquids.

In one aspect, provided herein is a lyophilized composition comprising: (i) an antibody; (ii) one or more viscosity-reducing ionic liquids, wherein the one or more viscosity-reducing ionic liquids comprise: 4-(3-butyl-1-imidazolio)-1-butane sulfonate (BIM) or a pharmaceutically acceptable salt thereof; 1-butyl-3-methylimidazolium methanesulfonate (BMI Mes) or a pharmaceutically acceptable salt thereof; 1-butyl-1-methylpyrrolidinium chloride (BMP Chloride) or a pharmaceutically acceptable salt thereof; or 4-ethyl-4-methylmorpholinium methylcarbonate (EMMC) or a pharmaceutically acceptable salt thereof; and; (iii) a pharmaceutically acceptable excipient.

The concentration of proteins is between about 10 mg/mL and about 5,000 mg/mL, more preferably from about 100 mg/mL to about 2,000 mg/mL. In some embodiments, the concentration of proteins is between about 100 mg/mL to about 500 mg/mL, more preferably from about 300 mg/mL to about 500 mg/mL. Formulations containing proteins and viscosity-reducing ionic liquids are stable when stored at a temperature of 4° C, for a period of at least one month, preferably at least two months, and most preferably at least three months. The viscosity of the formulation is less than about 75 cP, preferably below 50 cP, and most preferably below 20 cP at about 25° C.

CLAIMS:

1. A liquid pharmaceutical formulation for injection comprising:

(i) an antibody;

(ii) one or more viscosity-reducing ionic liquids, wherein the one or more viscosity-reducing ionic liquids comprise:

4-(3-butyl-1-imidazolio)-1-butane sulfonate (BIM) or a pharmaceutically acceptable salt thereof;

1-butyl-3-methylimidazolium methanesulfonate (BMI Mes) or a pharmaceutically acceptable salt thereof;

1-butyl-1-methylpyrrolidinium chloride (BMP Chloride) or a pharmaceutically acceptable salt thereof; or

4-ethyl-4-methylmorpholinium methylcarbonate (EMMC) or a pharmaceutically acceptable salt thereof; and

(iii) a pharmaceutically acceptable solvent;

wherein the liquid pharmaceutical formulation, when in a volume suitable for injection, has an absolute viscosity of from about 1 cP to about 100 cP at 25°C as measured using a cone and plate viscometer or a microfluidic viscometer; and the absolute viscosity of the liquid pharmaceutical formulation is less than an absolute viscosity of a control composition comprising the antibody and the pharmaceutically acceptable solvent but without the one or more viscosity-reducing ionic liquids;

wherein the absolute viscosity is an extrapolated zero-shear viscosity.

2. The liquid pharmaceutical formulation of claim 1, wherein the viscosity-reducing ionic liquid is 4-(3-butyl-1-imidazolio)-1-butane sulfonate (BIM) or a pharmaceutically acceptable salt thereof.

3. The liquid pharmaceutical formulation of claim 1, wherein the viscosity-reducing ionic liquid is 1-butyl-3-methylimidazolium methanesulfonate (BMI Mes) or a pharmaceutically acceptable salt thereof.

4. The liquid pharmaceutical formulation of claim 1, wherein the viscosity-reducing ionic liquid is 1-butyl-1-methylpyrrolidinium chloride (BMP Chloride) or a pharmaceutically acceptable salt thereof.

5. The liquid pharmaceutical formulation of claim 1, wherein the viscosity reducing ionic liquid is 4-ethyl-4-methylmorpholinium methylcarbonate (EMMC) or a pharmaceutically acceptable salt thereof.

6. The liquid pharmaceutical formulation of any one of claims 1-5, wherein the antibody has a molecular weight of from about 120 kDa to about 250 kDa.

7. The liquid pharmaceutical formulation of any one of claims 1-6, wherein the antibody is a monoclonal antibody.

8. The liquid pharmaceutical formulation of any one of claims 1-7, comprising from about 100 mg/ml to about 500 mg/ml of the antibody.

9. The liquid pharmaceutical formulation of any one of claims 1-8, comprising from about 191 mg/ml to about 270 mg/ml of the antibody.

10. The liquid pharmaceutical formulation of any one of claims 1-9, wherein the pharmaceutically acceptable solvent is aqueous.

11. The liquid pharmaceutical formulation of any one of claims 1-10, wherein the one or more viscosity-reducing ionic liquids are present at a concentration of from about 0.01 M to about 1.0 M.

12. The liquid pharmaceutical formulation of any one of claims 1-11, wherein the one or more viscosity-reducing ionic liquids are present at a concentration of from about 0.20 M to about 0.50 M.

13. The liquid pharmaceutical formulation of any one of claims 1-12, further comprising one or more pharmaceutically acceptable excipients, the one or more pharmaceutically acceptable excipients comprising a sugar, sugar alcohol, buffering agent, preservative, carrier, antioxidant, chelating agent, natural polymer, synthetic polymer, cryoprotectant, lyoprotectant, surfactant, bulking agent, stabilizing agent, or any combination thereof.

14. The liquid pharmaceutical formulation of claim 13, wherein the one or more pharmaceutically acceptable excipients comprise a polysorbate, poloxamer 188, sodium lauryl sulfate, a polyol, a poly(ethylene glycol), glycerol, a propylene glycol, or a poly(vinyl alcohol).

15. The liquid pharmaceutical formulation of claim 13, wherein the sugar alcohol is sorbitol or mannitol.

16. The liquid pharmaceutical formulation of any one of claims 1-15, in a unit-dose vial, multi-dose vial, cartridge, or pre-filled syringe.

17. The liquid pharmaceutical formulation of any one of claims 1-16, wherein the liquid pharmaceutical formulation is reconstituted from a lyophilized composition.

18. The liquid pharmaceutical formulation of any one of claims 1-17, wherein the liquid pharmaceutical formulation is isotonic to human blood serum.

19. The liquid pharmaceutical formulation of any one of claims 1-18, wherein the absolute viscosity is measured at a shear rate of about 0.5 s^{-1} when measured using a cone and plate viscometer, or a shear rate of about 1.0 s^{-1} when measured using a microfluidic viscometer.

20. A liquid pharmaceutical formulation of any one of claims 1-19 for use in the administration of a therapeutically effective amount of the antibody to a subject by subcutaneous or intramuscular injection.

21. The liquid pharmaceutical formulation of claim 20, wherein the injection is to be performed with a syringe.

22. The liquid pharmaceutical formulation of claim 21, wherein the syringe is a heated syringe, a self-mixing syringe, an auto-injector, a prefilled syringe, or combinations thereof.

23. The liquid pharmaceutical formulation of claim 22, wherein the liquid pharmaceutical formulation in the heated syringe has a temperature between 25°C and 40°C.

24. The liquid pharmaceutical formulation of any one of claims 20-23, wherein the liquid pharmaceutical formulation produces a primary irritation index of less than 3 when evaluated using a Draize scoring system.

25. The liquid pharmaceutical formulation of any one of claims 20-24, wherein the injection has an injection force that is at least 10% less than an injection force for a control composition comprising the antibody and the pharmaceutically acceptable solvent but without the one or more viscosity-reducing ionic liquids, when used for administration in the same way.

26. The liquid pharmaceutical formulation of any one of claims 20-24, wherein the injection has an injection force that is at least 20% less than an injection force for a control composition comprising the antibody and the pharmaceutically acceptable solvent but without the one or more viscosity-reducing ionic liquids, when used for administration in the same way.

27. The liquid pharmaceutical formulation of any one of claims 20-26, wherein the injection is to be performed with a needle between 27 and 31 gauge in diameter and the injection force is less than 30 N with the 27 gauge needle.

28. A method of preparing the liquid pharmaceutical formulation of any one of claims 1-19, comprising the step of combining the antibody, the pharmaceutically acceptable solvent, and the one or more viscosity-reducing ionic liquids.

29. A lyophilized composition comprising:

(i) an antibody;

(ii) one or more viscosity-reducing ionic liquids, wherein the one or more viscosity-reducing ionic liquids comprise:

4-(3-butyl-1-imidazolio)-1-butane sulfonate (BIM) or a pharmaceutically acceptable salt thereof;

1-butyl-3-methylimidazolium methanesulfonate (BMI Mes) or a pharmaceutically acceptable salt thereof;

1-butyl-1-methylpyrrolidinium chloride (BMP Chloride) or a pharmaceutically acceptable salt thereof; or

4-ethyl-4-methylmorpholinium methylcarbonate (EMMC) or a pharmaceutically acceptable salt thereof; and;

(iii) a pharmaceutically acceptable excipient.

30. The lyophilized composition of claim 29, wherein the viscosity-reducing ionic liquid is 4-(3-buty1-1-imidazolio)-1-butane sulfonate (BIM) or a pharmaceutically acceptable salt thereof.

31. The lyophilized composition of claim 29, wherein the viscosity-reducing ionic liquid is 1-butyl-3-methylimidazolium methanesulfonate (BMI Mes) or a pharmaceutically acceptable salt thereof.

32. The lyophilized composition of claim 29, wherein the viscosity-reducing ionic liquid is 1-butyl-l-methylpyrrolidinium chloride (BMP Chloride) or a pharmaceutically acceptable salt thereof.

33. The lyophilized composition of claim 29, wherein the viscosity reducing ionic liquid is 4-ethyl-4-methylmorpholinium methylcarbonate (EMMC) or a pharmaceutically acceptable salt thereof.

34. The lyophilized composition of any one of claims 29-33, wherein, once reconstituted, the antibody has a concentration of at least 100 mg/ml.