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

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, there is provided a liquid pharmaceutical formulation for injection comprising:

(i) an antibody;

(ii) about 0.4 M to about 0.5 M of 1-butyl-3-methylimidazolium methanesulfonate (BMI-Mes); and

(iii) a pharmaceutically acceptable solvent;

wherein the liquid pharmaceutical formulation, when in a volume suitable for injection, has an absolute viscosity 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 the absolute viscosity of a liquid pharmaceutical formulation comprising the antibody and the pharmaceutically acceptable solvent, but with an equivalent amount of sodium phosphate in place of the BMI-Mes; and

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

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.

For embodiments in which the protein is a "high-molecular-weight protein", the "high-molecular-weight protein," may have a molecular weight between about 100 kDa and about 1,000 kDa, preferably between about 120 kDa and about 500 kDa, and most preferably between about 120 kDa and about 250 kDa. The high-molecular-weight protein can be an antibody, such as a mAb, or a PEGylated or otherwise a derivatized form thereof. Preferred mAbs include natalizumab (TYSABRI®), cetuximab (ERBITUX®), bevacizumab (AVASTIN®), trastuzumab (HERCEPTIN®), infliximab (REMICADE®), rituximab (RITUXAN®), panitumumab (VECTIBIX®), ofatumumab (ARZERRA®), and biosimilars thereof. The high-molecular weight protein, optionally PEGylated, can be an enzyme. Other proteins and mixtures of proteins may also be formulated to reduce their viscosity.

In some embodiments, the protein and viscosity-reducing ionic liquid(s) are provided in a lyophilized dosage unit, sized for reconstitution with a sterile aqueous pharmaceutically acceptable vehicle, to yield the concentrated low-viscosity liquid formulations. The presence of the viscosity-reducing ionic liquid(s) facilitates and/or accelerates the reconstitution of the lyophilized dosage unit compared to a lyophilized dosage unit not containing a viscosity-reducing ionic liquid.

Methods are provided herein for preparing concentrated, low-viscosity liquid formulations of high-molecular-weight proteins such as mAbs, as well as methods for storing the low-viscosity, high-concentration protein formulations, and for administration thereof to patients. In another embodiment, the viscosity-reducing ionic liquid is added to facilitate processing (e.g., pumping, concentration, and/or filtration) by reducing the viscosity of the protein solutions.

In one aspect, there is provided a method of preparing any of the liquid pharmaceutical formulations as described herein comprising the step of combining the antibody, the pharmaceutically acceptable solvent, and the BMI-Mes.

DETAILED DESCRIPTION OF THE INVENTION

I. DEFINITIONS

The term "protein," as generally used herein, refers to a polymer of amino acids linked to each other by peptide bonds to form a polypeptide for which the chain length is sufficient to produce at least a detectable tertiary structure. Proteins having a molecular weight (expressed in kDa wherein "Da" stands for "Daltons" and 1 kDa = 1,000 Da) greater than about 100 kDa may be designated "high-molecular-weight proteins," whereas proteins having a molecular weight less than about 100 kDa may be designated "low-molecular-weight proteins." The term "low-molecular-weight

We claim:

1. A liquid pharmaceutical formulation for injection comprising:

(i) an antibody;

(ii) about 0.4 M to about 0.5 M of 1-butyl-3-methylimidazolium methanesulfonate (BMI-Mes); and

(iii) a pharmaceutically acceptable solvent;

wherein the liquid pharmaceutical formulation, when in a volume suitable for injection, has an absolute viscosity 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 the absolute viscosity of a liquid pharmaceutical formulation comprising the antibody and the pharmaceutically acceptable solvent, but with an equivalent amount of sodium phosphate in place of the BMI-Mes; and

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

2. The liquid pharmaceutical formulation of claim 1, wherein the antibody has a molecular weight of from about 120 kDa to about 250 kDa.

3. The liquid pharmaceutical formulation of claim 1 or 2, wherein the antibody is present in an amount of from about 180 mg to about 232 mg per 1 mL (mg/mL).

4. The liquid pharmaceutical formulation of any one of claims 1-3, wherein the liquid pharmaceutical formulation is aqueous having a pH between about 5.0 and about 8.0.

5. The liquid pharmaceutical formulation of any one of claims 1-4, comprising one or more pharmaceutically acceptable excipients for subcutaneous or intramuscular injection 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.

6. The liquid pharmaceutical formulation of claim 5, wherein one or more of the excipients is a polysorbate, poloxamer 188, sodium lauryl sulfate, a polyol, a poly(ethylene glycol), glycerol, a propylene glycol, or a poly(vinyl alcohol).

7. The liquid pharmaceutical formulation of claim 5, wherein the surfactant is present in an amount less than about 10 mg/mL.

8. The liquid pharmaceutical formulation of claim 6, wherein the polyol is present in an amount from about 2 mg/mL to about 900 mg/mL.

9. The liquid pharmaceutical formulation of any one of claims 1-8, wherein the absolute viscosity of the liquid pharmaceutical formulation is at least about 30% less than the absolute viscosity of a formulation comprising the antibody, the pharmaceutically acceptable solvent, and an appropriate buffer in place of the BMI-Mes, wherein the buffer is present at about the same concentration as the BMI-Mes.

10. The liquid pharmaceutical formulation of any one of claims 1-9 in a unit-dose vial, cartridge, container, or pre-filled syringe.

11. The liquid pharmaceutical formulation of any one of claims 1-10, having a volume of less than about 1.5 mL for subcutaneous (SC) injection, or less than about 3 mL for intramuscular (IM) injection.

12. The liquid pharmaceutical formulation of any one of claims 1-11, wherein the liquid pharmaceutical formulation is isotonic to human blood serum.

13. The liquid pharmaceutical formulation of any one of claims 1-12, wherein the absolute viscosity of the liquid pharmaceutical formulation is measured at a shear rate of at least about 0.5 s^{-1}, when measured using a cone and plate viscometer.

14. The liquid pharmaceutical formulation of any one of claims 1-12, wherein the absolute viscosity of the liquid pharmaceutical formulation is measured at a shear rate of at least about 1.0 s^{-1}, when measured using a microfluidic viscometer.

15. A method of preparing the liquid pharmaceutical formulation of any one of claims 1-14 comprising the step of combining the antibody, the pharmaceutically acceptable solvent, and the BMI-Mes.

16. The liquid pharmaceutical formulation of any one of claims 1-14, wherein the antibody is a monoclonal antibody.

17. The liquid pharmaceutical formulation of claim 6, wherein the polyol is a sugar alcohol.

18. The liquid pharmaceutical formulation of claim 17, wherein the sugar alcohol is sorbitol or mannitol.