therapeutically effective amounts of protein due to problems with high viscosity and other properties of concentrated solutions of large proteins. For example, to provide a therapeutically effective amount of many high-molecular-weight proteins, such as mAbs, in volumes less than about 2 mL, protein concentrations greater than 150 mg/mL are often required.

It is, therefore, an object of the present invention to provide concentrated, low-viscosity liquid formulations of pharmaceutically important proteins, especially high-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 (SC) or intramuscular (IM) injection, rather than by lengthy intravenous infusion. These formulations include low-molecular-weight and/or high-molecular-weight proteins, such as mAbs, and viscosity-lowering agents that are

typically bulky polar organic compounds, such as many of the GRAS (US Food and Drug Administration's list of compounds generally regarded as safe), inactive injectable ingredients and FDA-approved therapeutics.

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

(i) an antibody;

(ii) procaine; 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 50 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 procaine; and

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

In one aspect, there is provided a lyophilized composition comprising:

(i) an antibody;

(ii) procaine; 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-lowering agents 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. In some embodiments, the viscosity is less than about 15 cP or even less than or about 10 cP at about 25° C. In certain embodiments, the viscosity of the formulation is about 10 cP. Formulations containing proteins and viscosity-lowering agents typically are measured at shear rates from about 0.6 s^{-1} to about 450 s^{-1}, and preferably from about 2 s^{-1} to about 400 s^{-1}, when measured using a cone and plate viscometer. Formulations containing proteins and viscosity-lowering agents typically are measured at shear rates from about 3 s^{-1} to about 55,000 s^{-1}, and preferably from about 20 s^{-1} to about 2,000s^{-1},when measured using a microfluidic viscometer.

The viscosity of the protein formulation is reduced by the presence of one or more viscosity-lowering agents. Unless specifically stated otherwise, the term "viscosity-lowering agent" includes both single compounds and mixtures of two or more compounds. It is preferred that the viscosity-lowering agent is present in the formulation at a concentration less than about 1.0 M, preferably less than about 0.50 M, more preferably less than about 0.30 M, and most preferably less than about 0.15 M. In some embodiments, the viscosity-lowering agent is present in the formulation in concentrations as low as 0.01 M. The formulations can have a viscosity that is at least about 30% less, preferably at least about 50% less, most preferably at least about 75% less, than the viscosity of the corresponding formulation under the same conditions except for replacement of the viscosity-lowering agent with an appropriate buffer or salt of about the same concentration. In

some embodiments, a low-viscosity formulation is provided where the viscosity of the corresponding formulation without the viscosity-lowering agent is greater than about 200 cP, greater than about 500 cP, or even above about 1,000 cP. In a preferred embodiment, the shear rate of the formulation is at least about 0.5 s^{-1}, when measured using a cone and plate viscometer or at least about 1.0 s^{-1}, when measured using a microfluidic viscometer.

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-lowering agent 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-lowering agent(s) facilitates and/or accelerates the reconstitution of the lyophilized dosage unit compared to a lyophilized dosage unit not containing a viscosity-lowering agent.

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-lowering agent 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 described herein comprising the step of combining the antibody, the pharmaceutically acceptable solvent, and the procaine.

We claim:

1. A liquid pharmaceutical formulation for injection comprising:

(i) an antibody;

(ii) procaine; 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 50 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 procaine; 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, comprising from about 174 mg/ml to about 230 mg/ml of the antibody.

4. The liquid pharmaceutical formulation of any one of claims 1-3, wherein the pharmaceutically acceptable solvent is aqueous.

5. The liquid pharmaceutical formulation of any one of claims 1-4, 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.

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

7. The liquid pharmaceutical formulation of any one of claims 1-6 in a unit-dose vial, multi-

dose vial, cartridge, or pre-filled syringe.

8. The liquid pharmaceutical formulation of any one of claims 1-7, wherein the liquid pharmaceutical formulation is isotonic to human blood serum.

9. The liquid pharmaceutical formulation of any one of claims 1-8, wherein the absolute viscosity is measured at a shear rate of at least about 0.5 s^{-1}, when measured using a cone and plate viscometer.

10. The liquid pharmaceutical formulation of any one of claims 1-9, wherein the absolute viscosity is measured at a shear rate of at least about 1.0 s^{-1}, when measured using a microfluidic viscometer.

11. A method of preparing the liquid pharmaceutical formulation of any one of claims 1-10 comprising the step of combining the antibody, the pharmaceutically acceptable solvent, and the procaine.

12. The liquid pharmaceutical formulation of any one of claims 1-10, wherein the antibody is a monoclonal antibody.

13. The liquid pharmaceutical formulation of claim 5, wherein the sugar alcohol is sorbitol or mannitol.

14. The liquid pharmaceutical formulation of any one of claims 1-10, wherein the liquid pharmaceutical formulation is reconstituted from a lyophilized composition.

15. A lyophilized composition comprising:
(i) an antibody;
(ii) procaine; and
(iii) a pharmaceutically acceptable excipient.

16. The lyophilized composition of claim 15, wherein, once reconstituted, the antibody has a concentration of at least 100 mg/ml.