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.

[0017] Methods are provided herein for preparing concentrated, low-viscosity liquid formulations of high-molecular-weight polysaccharides or nucleic acids, as well as methods for storing the low-viscosity, high-concentration polysaccharide or nucleic acid formulations, and for administration thereof to patients. In another embodiment, the viscosity-lowering agent (e.g., viscosity-lowering compounds of formulae A-I, A-II, A-III and variations thereof, ionic liquids, organophosphates, water-soluble organic dyes, and other viscosity-lowering compounds described herein) is added to facilitate processing (e.g., pumping, concentration, and/or filtration) by reducing the viscosity of the polysaccharide/nucleic acid solutions.

[0017a] In one aspect, there is provided a liquid pharmaceutical formulation for injection comprising one or more polysaccharides, one or more viscosity-lowering agents, wherein the one or more viscosity lowering agents comprise ammonium sulfate, creatinine, Yellow 5, 4-aminopyridine, 1-butyl-1-methylpyrrolidinium chloride (BMP-Cl), or combinations thereof; and 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 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 lower than an absolute viscosity of a control composition comprising the one or more polysaccharides and the pharmaceutically acceptable solvent, but without the one or more viscosity-lowering agents, wherein the absolute viscosity is an extrapolated zero-shear viscosity.

[0017b] In another aspect, there is provided the liquid pharmaceutical formulation as described herein which is to be administered by subcutaneous (SC) or intramuscular (IM) injections.

[0017c] In another aspect, there is a method of preparing the liquid pharmaceutical formulation as described herein, comprising the step of combining the one or more polysaccharides, the pharmaceutically acceptable solvent, and the one or more viscosity-lowering agents.

[0017d] In a further aspect, there is provided a liquid pharmaceutical formulation prepared by the method described herein.

[0017e] In another aspect, there is provided a lyophilized composition comprising one or more polysaccharides comprising heparin or dextran; and one or more viscosity-lowering

agents, wherein the one or more viscosity lowering agents comprise ammonium sulfate, creatinine, Yellow 5, 4-aminopyridine, 1-butyl-1-methylpyrrolidinium chloride (BMP-Cl), or combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. 1 depicts the viscosity in cP as a function of the flow rate for aqueous solutions of "medium-viscosity" sodium alginate in water (8.2 mg/mL, pH 7.4, diamonds), Dextran in phosphate buffer (approximately 200 mg/mL, squares), and Heparin sodium in phosphate buffer (approximately 300 mg/mL, pH 7.1, triangles).

[0019] FIG. 2 depicts the viscosity in cP as a function of flow rate for aqueous solutions of Dextran (400 mg/mL) in the presence of various viscosity-lowering excipients.

[0020] FIG. 3 depicts the viscosity in cP as a function of flow rate for aqueous solutions of DEAE-Dextran (340 mg/mL) in the presence of various viscosity-lowering excipients.

DETAILED DESCRIPTION OF THE INVENTION

I. DEFINITIONS

[0021] The term "polysaccharide," as used herein, refers to a compound made from at least two monosaccharide units which are linked via a glycosylic (or glycosidic) bond. Unless otherwise specified, a polysaccharide may contain only sugar components, or may contain non-sugar components as well, such as amino acids and small molecule aglycones. Polysaccharides having a molecular weight (expressed in kDa wherein "Da" stands for "Daltons" and 1 kDa = 1,000 Da) greater than about 10,000 Da may be designated "high-molecular-weight polysaccharides," whereas polysaccharides having a molecular weight less than about 10,000 Da may be designated "low-molecular-weight polysaccharides."

CLAIMS

We claim:

1. A liquid pharmaceutical formulation for injection comprising

(i) one or more polysaccharides;

(ii) one or more viscosity-lowering agents, wherein the one or more viscosity lowering agents comprise:

ammonium sulfate,

creatinine,

Yellow 5,

4-aminopyridine,

1-butyl-1-methylpyrrolidinium chloride (BMP-Cl),

or combinations thereof; 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 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 lower than an absolute viscosity of a control composition comprising the one or more polysaccharides and the pharmaceutically acceptable solvent, but without the one or more viscosity-lowering agents;

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

2. The liquid pharmaceutical formulation of claim 1, wherein the one or more polysaccharides are present in an amount of from 200 mg/ml to 400 mg/ml.

3. The liquid pharmaceutical formulation of claim 1 or 2, wherein the one or more polysaccharides is heparin.

4. The liquid pharmaceutical formulation of claim 1 or 2, wherein the one or more polysaccharides is dextran.

5. The liquid pharmaceutical formulation of any one of the previous claims, wherein the liquid pharmaceutical formulation is aqueous having a pH between about 4.0 and about 8.0.

6. The liquid pharmaceutical formulation of any one of the previous claims, wherein the one or more viscosity-lowering agents are present at a concentration of from about 0.01 M to about 1.0 M or from about 0.01 M to about 0.25 M.

7. The liquid pharmaceutical formulation of any one of the previous claims further comprising 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.

8. The liquid pharmaceutical formulation of claim 7, wherein the sugar alcohol comprises mannitol or sorbitol.

9. The liquid pharmaceutical formulation of claim 7, wherein the one or more pharmaceutically acceptable excipients comprises a polysorbate, poloxamer 188, sodium lauryl sulfate, a polyol, a poly(ethylene glycol), glycerol, a propylene glycol, or a poly(vinyl alcohol).

10. The liquid pharmaceutical formulation of any one of the previous claims in a unit-dose vial, multi-dose vial, cartridge or pre-filled syringe.

11. The liquid pharmaceutical formulation of any one of the previous claims wherein the liquid pharmaceutical formulation is reconstituted from a lyophilized composition.

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

13. The liquid pharmaceutical formulation of any one of the previous claims, 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, or a shear rate of at least about 1.0 s^{-1}, when measured using a microfluidic viscometer.

14. The liquid pharmaceutical formulation of any one of the previous claims, wherein the one or more viscosity lowering agents comprises ammonium sulfate.

15. The liquid pharmaceutical formulation of any one of claims 1 to 13, wherein the one or more viscosity lowering agents comprises creatinine.

16. The liquid pharmaceutical formulation of any one of claims 1 to 13, wherein the one or more viscosity lowering agents comprises Yellow 5.

17. The liquid pharmaceutical formulation of any one of claims 1 to 13, wherein the one or more viscosity lowering agents comprises 4-aminopyridine.

18. The liquid pharmaceutical formulation of any one of claims 1 to 13, wherein the one or more viscosity lowering agents comprises 1-butyl-1-methylpyrrolidinium chloride (BMP Cl).

19. The liquid pharmaceutical formulation of any one of claims 1-18 which is to be administered by subcutaneous (SC) or intramuscular (IM) injections. .

20. The liquid pharmaceutical formulation of claim 19, wherein the injections are to be performed with a heated syringe, a self-mixing syringe, an auto-injector, a pre-filled syringe,

or combinations thereof.

21. The liquid pharmaceutical formulation of claim 19 or 20, wherein the syringe is a heated syringe and the liquid pharmaceutical formulation has a temperature between 25°C and 40°C.

22. The liquid pharmaceutical formulation of any one of claims 19 to 21, wherein the liquid pharmaceutical formulation produces a primary irritation index of less than 3 when evaluated using a Draize scoring system.

23. The liquid pharmaceutical formulation of any one of claims 19 to 22, wherein the injection force of the injection is at least 10% less or at least 20% less than an injection force for a control composition comprising the one or more polysaccharides and the pharmaceutically acceptable solvent, but without the one or more viscosity-lowering, when administered in the same way.

24. The liquid pharmaceutical formulation of any one of claims 19 to 23, wherein the injection is to be administered with a needle between 27 and 31 gauge in diameter and the injection force is less than 30 N with the 27 gauge needle.

25. A method of preparing the liquid pharmaceutical formulation of any one of claims 1 to 18, comprising the step of combining the one or more polysaccharides, the pharmaceutically acceptable solvent, and the one or more viscosity-lowering agents.

26. A liquid pharmaceutical formulation prepared by the method of claim 25.

27. A lyophilized composition comprising:

(i) one or more polysaccharides comprising heparin or dextran; and

(ii) one or more viscosity-lowering agents, wherein the one or more viscosity lowering agents comprise:

ammonium sulfate,

creatinine,

Yellow 5,

4-aminopyridine,

1-butyl-1-methylpyrrolidinium chloride (BMP-Cl),

or combinations thereof.

28. The lyophilized composition of claim 27, wherein the one or more polysaccharides is heparin.

29. The lyophilized composition of claim 27, wherein the one or more polysaccharides is dextran.

30. The lyophilized composition of any one of claims 27-29, wherein the one or more viscosity lowering agents comprises ammonium sulfate.

31. The lyophilized composition of any one of claims 27-29, wherein the one or more viscosity lowering agents comprises creatinine.

32. The lyophilized composition of any one of claims 27-29, wherein the one or more viscosity lowering agents comprises Yellow 5.

33. The lyophilized composition of any one of claims 27-29, wherein the one or more viscosity lowering agents comprises 4-aminopyridine.

34. The lyophilized composition of any one of claims 27-29, wherein the one or more viscosity lowering agents comprises 1-butyl-1-methylpyrrolidinium chloride (BMP-Cl).