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 ~~and/or nucleic acids~~;

~~—~~(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 ~~when the polysaccharides and/or nucleic acid is combined with the solvent and viscosity lowering agent~~the liquid pharmaceutical formulation, when in a volume suitable for injection, ~~the formulation~~ has an absolute viscosity from about 1 cP to about 50 cP at 25°C, as measured~~, for example,~~ using a cone and plate viscometer or a microfluidic viscometer; and the absolute viscosity of the liquid pharmaceutical formulation is lower than ~~the~~ an absolute viscosity of a control composition comprising the one or more polysaccharides and the pharmaceutically acceptable solvent, ~~otherwise substantially the same formulation~~ but without the one or more viscosity-lowering agents;

wherein the absolute viscosity ~~in each case~~ 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.

~~2. The formulation of claim 1, wherein the polysaccharide has a molecular weight of between about 0.5 kDa and about 2,000 kDa, and the nucleic acid has a molecular weight of between about 1 kDa and about 5,000 kDa.~~

~~3. The formulation of any one of claims 1 and 2, wherein the polysaccharide has a molecular weight from about 1 kDa and about 1,000 kDa, preferably from about 2 kDa and about 500 kDa.~~

~~4~~3. The liquid pharmaceutical formulation of ~~any of claims 1-3~~ claim 1 or 2, wherein the one or more polysaccharides is ~~selected from the group consisting of heparins~~ heparin. ~~of different molecular weights and their derivatives, polysaccharide vaccines, hyaluronic acids,~~

~~dermatan sulfate, chondroitin 4 sulfate, chondroitin 6 sulfate, keratan sulfate, heparan sulfate, curdlan sulfate, cyclodextrins, alginate, chitosan; and the nucleic acid is selected from the group consisting of linear and circular DNA, single stranded and double stranded DNA, DNA aptamers, DNAzymes, RNA, RNAi, siRNA, shRNA, miRNA, mRNA, lincRNA, ribozymes, morpholinos, and combinations thereof.~~

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

~~5. The formulation of any one of claims 1-4, wherein the polysaccharides or nucleic acids are present in a combined amount from about 100 mg to about 2,000 mg per 1 mL (mg/mL); optionally greater than about 150 mg/mL.~~

~~6. The formulation of any one of claims 1-5, wherein the formulation comprises at least two different polysaccharides, preferably wherein both of the polysaccharides have a molecular weight of at least about 50 kDa.~~

~~7. The formulation of any one of claims 1-6, wherein the initial absolute viscosity at the same polysaccharide or nucleic acid concentration prior to adding a viscosity lowering agent exceeds about 60 cP, exceeds about 80cP, or exceeds about 100 cP.~~

~~8~~5. The liquid pharmaceutical formulation of any one of the previous claims ~~1-7~~, wherein the liquid pharmaceutical formulation is aqueous having a pH between about 4.0 and about 8.0.

~~9~~6. The liquid pharmaceutical formulation of any one of the previous claims ~~1-8~~, wherein the ~~comprising~~ one or more viscosity-lowering agents are present ~~in~~ 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.

~~10. The formulation of any one of claims 1-9, comprising a viscosity lowering agent present in a concentration less than about 0.15 M or less than about 0.10 M.~~

~~11~~7. The liquid pharmaceutical formulation of any one of the previous claims ~~1-10~~ further comprising one or more pharmaceutically acceptable excipients ~~for subcutaneous (SC) or intramuscular (IM) injection selected from the group consisting of~~comprising a sugar~~s or~~, sugar alcohol~~s~~, buffering agent~~s~~, preservative~~s~~, carrier~~s~~, antioxidant~~s~~, chelating agent~~s~~, natural polymer, ~~or~~ synthetic polymer~~s~~, cryoprotectant~~s~~, lyoprotectant~~s~~, surfactant~~s~~, bulking agent~~s~~, ~~and~~ stabilizing agent~~s~~ or any combination thereof.

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

~~12~~9. The liquid pharmaceutical formulation of claim ~~11~~7, wherein the one or more ~~of the~~ pharmaceutically acceptable excipients ~~is selected from the group consisting of~~ comprises a

polysorbate~~s~~, poloxamer 188, sodium lauryl sulfate, a polyol, ~~selected from the group consisting of sugar alcohols such as mannitol and sorbitol,~~ a poly(ethylene glycol~~s~~), glycerol, a propylene glycol~~s~~, ~~and~~ or a poly(vinyl alcohol~~s~~).

~~13. The formulation of claim 11, wherein the surfactant is present in a concentration less than about 10 mg/mL.~~

~~14. The formulation of claim 12, comprising a polyol present in a concentration from about 2 mg/mL to about 900 mg/mL.~~

~~15. The formulation of any one of claims 1-14, wherein the absolute viscosity is from about 5 cP to about 50 cP at 25°C.~~

~~16. The formulation of any one of claims 1-15, wherein the absolute viscosity is at least about 30% lower than the absolute viscosity of a formulation without the viscosity lowering agent when measured under the same conditions except for replacement of the viscosity-lowering agent with an appropriate buffer of about the same concentration.~~

~~17. The formulation of any one of claims 1-16, wherein the absolute viscosity is at least about 2-fold or about 4-fold less than the absolute viscosity of a formulation without the viscosity lowering agent when measured under the same conditions except for replacement of the viscosity lowering agent with an appropriate buffer of about the same concentration.~~

~~18~~10. The liquid pharmaceutical formulation of any one of ~~claims 1-17~~the previous claims in a unit-dose vial, multi-dose vial, cartridge ~~container,~~ or pre-filled syringe.

~~19~~11. The liquid pharmaceutical formulation of any one of the previous claim~~s~~ ~~18~~ wherein the ~~polysaccharide or nucleic acid, the viscosity-lowering agent and/or excipients are in dry form, preferably~~ liquid pharmaceutical formulation is reconstituted from a lyophilized composition.

~~20. The formulation of any of claims 1-19, wherein the volume of the formulation when the viscosity lowering agent, polysaccharide or nucleic acid, and solvent are combined is less than about 1.5 mL for SC injections, and less than about 3 mL for IM injections.~~

~~21~~12. The liquid pharmaceutical formulation of any one of the previous claims ~~1-20~~, wherein the liquid pharmaceutical formulation is isotonic to human blood serum.

~~22. The formulation of any one of claims 1-21 which behaves rheologically essentially as a Newtonian liquid at conditions under which it would be administered to a person in need thereof.~~

~~23. The formulation of any one of claims 1-22 achieving a therapeutically effective dosage as compared to the same dose of the polysaccharide or nucleic acid administered by intravenous infusion.~~

~~24. The formulation of any one of claims 1-23 wherein the viscosity lowering agent is present at a concentration that causes no significant signs of toxicity or injection site irritation when administered via SC or IM injection.~~

~~25~~13. The liquid pharmaceutical formulation of any one of the previous claims ~~1-24~~, 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 ~~.~~

~~26. The formulation of any of claims 1-24, wherein the absolute viscosity of the formulation is measured at 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).

~~27~~19. ~~A method of administering a therapeutically effective amount of a polysaccharide or nucleic acid comprising SC or IM injections of t~~The liquid pharmaceutical formulation of any one of claims 1-~~26~~18 which is to be administered by subcutaneous (SC) or intramuscular (IM) injections. .

~~28~~20. The liquid pharmaceutical formulation ~~method~~ of claim ~~27~~19, wherein the ~~SC or IM~~ injections are to be performed with a ~~syringe selected from the group consisting of~~ heated syringe~~s~~, a self-mixing syringe~~s~~, an auto-injector~~s~~, a pre-filled syringe~~s~~, ~~and~~ or combinations thereof.

~~29~~21. The liquid pharmaceutical formulation ~~method~~ of claim ~~28~~19 or 20, wherein the syringe is a heated syringe and the liquid pharmaceutical formulation ~~is administered at~~has a temperature between 25°C and 40°C.

~~30~~22. The liquid pharmaceutical formulation ~~method~~ of any one of claims ~~27-29~~19 to 21, wherein the liquid pharmaceutical formulation produces a primary irritation index of less than 3 when evaluated using a Draize scoring system.

~~31~~23. The liquid pharmaceutical formulation ~~method~~ of any one of claims ~~27-30~~19 to 22, wherein the injection force of the injection is at least 10% less or at least 20% less than ~~the~~ an injection force for ~~the otherwise same formulation~~ a control composition comprising the one or more polysaccharides and the pharmaceutically acceptable solvent, but without the one or more viscosity-lowering, ~~agent~~ when administered in the same way.

~~32~~24. The liquid pharmaceutical formulation ~~method~~ of any one of claims ~~27-31~~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.

~~33~~25. A method of preparing ~~a~~ the liquid pharmaceutical formulation of any one of claims 1 to 18, comprising the step of combining the one or more polysaccharide~~s and/or nucleic acid~~, the pharmaceutically acceptable solvent, and the one or more viscosity-lowering agent~~s of any of claims 1-26~~.

~~34. The method of claim 33, wherein the formulation is in a pre-filled syringe or cartridge.~~

~~35. A method of facilitating purification of a polysaccharide or nucleic acid comprising adding to a polysaccharide and/or nucleic acid solution an effective amount of the viscosity-lowering agent of any of claims 1 or 7-10 to reduce the viscosity of the polysaccharide and/or nucleic acid solution.~~

~~36. The method of claim 35 wherein the polysaccharide and/or nucleic acid viscosity-lowering agent solution is purified or concentrated using a method selected from the group consisting of ultrafiltration/diafiltration, tangential flow filtration, centrifugal concentration, and dialysis.~~

~~37. A method of preparing a polysaccharide or nucleic acid, comprising fermenting an appropriate organism in the presence of the viscosity lowering agent of any of claims 1 or 7-10 in an amount sufficient to maintain a low viscosity of the fermentation mixture.~~

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).