CONCENTRATED PROTEIN FORMULATIONS AND USES THEREOF

RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119 of United States provisional application 61/339191, filed March 1, 2010, the entire contents of which are incorporated herein by reference.

TECHNICAL FIELD

The present disclosure is directed to stable protein formulations, specifically, formulations of a concentrated protein and methods of use thereof.

BACKGROUND

The development of concentrated protein formulations comprising proteins at a concentration of greater than 100 mg/mL presents many challenges. At such high concentrations, these proteins are restricted by solubility, administration volume and manufacturing limitations, stability issues, and delivery obstacles exist. Developing formulations in which the component protein is at present in high concentration may also present aggregation problems. Concentrated protein formulations specific for injectable administration present a particular complication in that they tend to be highly viscous. Not only do these formulations present potential difficulties during subcutaneous administration to an individual, but also during preparation and manufacture.

There is a need for highly concentrated protein formulations having low viscosity, particularly for the ready administration of protein-based drugs and biologics to subjects via parenteral routes. The present invention provides a solution to this need.

SUMMARY

In one aspect, there is disclosed herein a formulation comprising a concentrated protein in an amount greater than 100 mg/mL and less than 200 mg/mL, a tonicifier of a salt and a buffer present in a combined amount of 110 mM to 120 mM and a surfactant, wherein the formulation has an osmolality of less than 290 mOsm and has a viscosity of less than 40 cps.

In one of its ~~aspects~~examples, the present ~~invention~~disclosure provides a low viscosity, concentrated protein formulation, composition, or preparation which is hypotonic and can be readily administered to a subject, including humans, and readily manufactured and stored.

1) The ~~invention~~disclosure further encompasses a formulation comprising a concentrated protein, a tonicifier comprising a salt and a buffer present in a combined amount of from about 110 mM to about 120 mM and a surfactant, wherein the formulation is hypotonic. In an ~~embodiment~~example, the concentrated protein is in an amount greater than about or equal to 100 mg/mL and less than about or equal to 200 mg/mL or in an amount of about 162 mg/mL to about 175 mg/mL. In an ~~embodiment~~example, the concentrated protein is an enzyme, a polypeptide, a peptide, an antibody or a fragment of an antibody, a monoclonal antibody, a

polyclonal antibody, a nanobody, or a hybrid antibody. In an ~~embodiment~~example, the concentrated protein is a monoclonal antibody that is humanized or a fragment of the humanized antibody.

In another aspect, there is disclosed herein a formulation comprising:
a concentrated protein in an amount greater than 100 mg/mL and less than 200 mg/mL;
a salt in an amount greater than 90 mM and less than 100 mM;
a buffer comprising a nonpolar neutral amino acid in an amount greater than 5 mM and less than 25 mM;
a surfactant in an amount greater than 0.001 % w/v and less than 0.2 % w/v; and, optionally,
a stabilizing agent or non-salt tonicifier in an amount of 0.05% w/v to 1.8% w/v;
wherein the formulation has an osmolality of 222 to 265 mOsm.

2) Formulations ~~of the invention~~disclosed herein comprise a salt in an amount of less than 100 mM or in an amount that is about 90 mM, about 95 mM, equal to 90 mM, or equal to 95 mM. The salt may be one or more of ammonium chloride, ammonium sulfate, ammonium thiocyanate, arginine hydrochloride, calcium chloride, magnesium chloride, sodium acetate, sodium chloride, sodium gluconate, sodium lactate, sodium thiocyanate, zinc chloride, or any combination thereof. The buffer in the formulations is present in an amount of about or equal to 5 mM to about or equal to 25 mM, or about or equal to 5 mM to about or equal to 20 mM and may comprise one or more amino acids, or a derivative or L-molecular form thereof. The one or more amino acids may be histidine, glycine, or a combination of histidine and glycine. Other suitable buffer reagents include tartaric acid, maleic acid, succinic acid, citric acid and acetate acid.

3) The formulations may contain a surfactant, which is present in an amount of about or equal to 0.001% w/v to about or equal to 0.2% w/v, in an amount of about or equal to 0.005% to about or equal to 0.2%, or in an amount of about or equal to 0.05% to about or equal to 0.2%. The surfactant may be a detergent, pluronic, polysorbate, polysorbate 20 (e.g., Tween®20), polyethylene glycol, or a combination thereof.

4) The formulations may further contain a stabilizing agent, which may be in an amount from about or equal to 0.05 % w/v to about or equal to1.8 % w/v, or from about or equal to 0.2% to about or equal to 1.8% w/v, or from about or equal to 0.3% to about or equal to 1.5% w/v of the total formulation. The stabilizing agent may be a monosaccharide, a disaccharide, or a combination thereof. The stabilizing agent may also be a sugar, a sugar alcohol, or a derivative thereof.

5) The formulations have a viscosity of about 25 cps to about 60 cps, or a viscosity of about 40 cps to about 50 cps. The formulations have a pH of from about 5.4 to about 6.4, or a pH of from about 5.4 to about 6, or a pH of 5.4 to 5.6. The formulations have an osmolality of less than about 290 mOs/kg, or an osmolality of about 250 mOs/kg to about 280 mOs/kg, or an osmolality of about 260 mOs/kg.

6) The formulations ~~of the invention~~ may comprise a therapeutic protein, such as any type of antibody, or a fragment thereof, for administration to a subject in need thereof. In an ~~embodiment~~example, the formulation is a liquid or solution formulation.

7) The ~~invention~~disclosure further encompasses a liquid or solution formulation that includes a concentrated protein in an amount greater than or equal to 100 mg/mL and less than or

equal to 200 mg/mL; a salt in an amount greater than or equal to 90 mM or 95 mM and less than or equal to 100 mM; a buffer in an amount greater than or equal to 5 mM and less than or equal to 25 mM; a surfactant in an amount greater than or equal to 0.001 % w/v and less than or equal to 0.2 % w/v; and, optionally, a stabilizing agent in an amount of about 0.05 % w/v to about 1.8 % w/v; wherein the formulation has an osmolality of about 250 to about 280 mOsm; a viscosity of about 25 cP to about 60 cP, a pH of from 5.4 to 6.4 and an osmolality of about 240 mOs/kg to about 280 mOs/kg.

In yet another aspect, there is disclosed herein a low viscosity, hypotonic formulation, comprising:

(a) a concentrated protein in an amount greater than 100 mg/mL and less than 200 mg/mL, wherein the concentrated protein is an antibody or a fragment thereof;

(b) a salt in an amount selected from 90 mM or 95 mM;

(c) a buffer comprising a neutral nonpolar amino acid and in an amount of 20 mM;

(d) a surfactant in an amount of 0.005% - 0.2% w/v; and optionally

(e) a stabilizing agent or non-salt tonicifier in an amount sufficient to provide an osmolality of 222 to 265 mOs/kg, wherein the formulation has a viscosity of less than 40 cps.

In a further aspect, there is disclosed herein a low viscosity hypotonic formulation, comprising:

(a) a concentrated antibody or fragment thereof in an amount greater than 100 mg/mL and less than 200 mg/mL, wherein the antibody is selected from a monoclonal antibody, a human antibody, or a humanized monoclonal antibody;

(b) a salt in an amount selected from 90 mM or 95 mM, wherein the salt is sodium chloride;

(c) a buffer in an amount of 20 mM, wherein the buffer comprises histidine, glycine, or a combination thereof;

(d) a surfactant in an amount of 0.005% - 0.2% w/v, wherein the surfactant is a polysorbate or poloxamer; and optionally,

(e) a stabilizing agent or non-salt tonicifier in an amount of 0.2% - 1.8% w/v, wherein the stabilizing agent or non-salt tonicifier is selected from a sugar alcohol, a monosaccharide, a disaccharide, or a combination thereof.

In a further aspect, there is disclosed herein a low viscosity hypotonic formulation, comprising:

(a) a concentrated antibody or fragment thereof in an amount greater than 100 mg/mL and less than 200 mg/mL;

(b) a salt in an amount selected from 90 mM or 95 mM, wherein the salt is selected from sodium chloride, sodium gluconate, or sodium lactate;

(c) a buffer in an amount of 20 mM, wherein the buffer is selected from histidine, glycine, or a combination of histidine and glycine;

(d) a surfactant in an amount of 0.005 % -0.2% w/v, wherein the surfactant is a polysorbate or a pluronic; and

(e) a stabilizing agent or non-salt tonicifier in an amount sufficient to provide an osmolality of the formulation of 230 mOs/kg to 280 mOs/kg, wherein the stabilizing agent or non-salt tonicifier is selected from a sugar alcohol, a monosaccharide, a disaccharide, or a combination thereof.

In a further aspect, there is disclosed herein a composition comprising a protein in an amount greater than 100 mg/mL and less than 200 mg/mL, a tonicifier comprising a salt and a buffer present in a combined amount of from 110 mM to 120 mM and a surfactant present in an amount of from 0.001% to 0.2% w/v, wherein the formulation has an osmolality of 230 to 290 mOs/kg and the buffer includes a neutral nonpolar amino acid.

8) The ~~invention~~disclosure further encompasses a low viscosity, hypotonic, liquid formulation, which includes a concentrated protein in an amount greater than about or equal to 100 mg/mL and less than about or equal to 200 mg/mL, wherein the concentrated protein is any type of antibody, or a fragment thereof; a salt in an amount of about or equal to 90 mM or 95 mM; a buffer in an amount of about or equal to 20 mM; a surfactant in an amount of about 0.005 % w/v; and optionally a stabilizing agent in an amount of about 0.05%-0.5% w/v.

9) The ~~invention~~disclosure further encompasses a low viscosity hypotonic formulation, which includes a concentrated antibody or fragment thereof in an amount greater than about or equal to 100 mg/mL and less than about or equal to 200 mg/mL; a salt in an amount of about 90mM or 95 mM, wherein the salt is sodium chloride; a buffer in an amount of about 20 mM, wherein the buffer is histidine; a surfactant in an amount of about 0.005 % w/v, wherein the surfactant is polysorbate; and a stabilizing agent in an amount of about 0.3% w/v or about 0.6% w/v, wherein the stabilizing agent is sorbitol or sucrose, respectively. The formulation may be a liquid or solution formulation.

10) The ~~invention~~disclosure further encompasses a low viscosity hypotonic formulation, which includes a concentrated antibody or fragment thereof in an amount greater than about or equal to 100 mg/mL and less than about or equal to 200 mg/mL; a salt in an amount of about or equal to 95 mM, wherein the salt is sodium chloride; a buffer in an amount of about or equal to 20 mM, wherein the buffer is a combination of glycine and histidine; and a surfactant in an amount of about or equal to 0.005 % w/v, wherein the surfactant is a polysorbate. The formulation may further include a stabilizing agent in an amount of about 0.001% to 1.5 % w/v, wherein the stabilizing agent is sorbitol or sucrose.

In one aspect, there is disclosed herein an article of manufacture comprising a container and a formulation having a viscosity of less than 40 cps comprising a protein in a concentration of greater than 100 mg/mL and less than 200 mg/mL, a tonicifier of a salt and a buffer present in a combined amount of from 110 mM to 120 mM, a surfactant in an amount of from 0.005% to 0.2% and instructions for use.

The ~~invention~~disclosure further embraces an article of manufacture, which includes a container and a formulation comprising a protein in a concentration of greater than 100 mg/mL and less than 200 mg/mL, a tonicifier of a salt and a buffer present in an amount of from about 110 mM to about 120 mM, a surfactant and instructions for use. In an ~~embodiment~~example, the formulation in the article of manufacture further comprises a stabilizing agent in an amount of about 0.001% to

1.5 % w/v. In an ~~embodiment~~example, the container is selected from a bottle, a vial, a syringe, a pen, a pump, a multidose needle syringe, a multidose pen, a jet injector, a syrette, an autoinjector, a pre-filled syringe, or a combination thereof. In an ~~embodiment~~example, the formulation is included in the container of the article of manufacture.

These and other aspects of the present disclosure will become apparent to those skilled in the art after a reading of the following detailed description, including the illustrative embodiments and examples.

DETAILED DESCRIPTION OF THE EMBODIMENTS

The present invention is directed to stable, low viscosity formulations, compositions, or preparations, which are hypotonic and comprise one or more proteins present in a high concentration, i.e. greater than 100 mg/mL and less than 200 mg/mL. The formulations, compositions, or preparations of the invention are useful in the delivery of a therapeutic or prophylactic medicament, biologic, drug, and the like, to a subject in need thereof. Throughout this disclosure, the terms formulation, composition and preparation are used interchangeably.

More specifically, the stable formulations containing a highly concentrated protein have a low viscosity, which is beneficial for parenteral and subcutaneous administration. In an embodiment, the formulation is pharmaceutically and/or physiologically acceptable and provides a stable vehicle for a protein that is in high concentration. The formulations may be presented in a kit or article of manufacture for commercial distribution and use.

It is noted that the percent amounts of components of the formulations described herein are present in w/v of the total formulation.

In one embodiment, a formulation of the invention comprises a protein in an amount greater than about 100 mg/ml to about 200 mg/ml; a salt in an amount less than about 100 mM, from about 50 mM to about 90 mM, from about 50 mM to about 95 mM, about or equal to 90 mM, or about or equal to 95 mM, a buffer in an amount of from about or equal to 5 mM to about or equal to 20 mM; less than about 20 mM, or equal to 20 mM; and a surfactant in an amount of about 0.001% to about 0.2%. In an embodiment, the formulation is hypotonic. In an embodiment, the formulation has low viscosity. In an embodiment, the formulation is in the form of a liquid or solution. In some embodiments, the formulation also comprises, in addition to a salt as a first tonicifier, a second non-salt tonicifying agent, such as a sugar, sugar alcohol, a monosaccharide, a disaccharide, or a combination thereof, such that the osmolality of the formulation is less than about 290 mOs/kg, or about 260 mOs/kg.

In another embodiment, a formulation of the invention comprises a concentrated protein, or a high concentration of protein, in an amount of greater than about 100 mg/mL to about 200

32. A formulation comprising:

a concentrated protein in an amount greater than 100 mg/mL and less than 200 mg/mL;

a salt in an amount greater than 90 mM and less than 100 mM;

a buffer comprising a nonpolar neutral amino acid in an amount greater than 5 mM and less than 25 mM;

a surfactant in an amount greater than 0.001 % w/v and less than 0.2 % w/v; and, optionally,

a stabilizing agent or non-salt tonicifier in an amount of 0.05% w/v to 1.8% w/v;, wherein the formulation has an osmolality of 222 to 265 mOsm.

33. The formulation of claim 32, wherein the concentrated protein is selected from an antibody or a fragment thereof, a blood clotting factor, an enzyme, a peptide, or a combination thereof.

34. The formulation of claim 32, wherein the salt is selected from sodium chloride, sodium gluconate, sodium lactate, or a combination thereof.

35. The formulation of claim 32, wherein the buffer includes a combination of glycine and histidine.

36. The formulation of claim 32, wherein the surfactant is selected from polysorbate-20, polysorbate-40, polysorbate-60, polysorbate-80, pluronic, or a combination thereof.

37. The formulation of claim 32, wherein the stabilizing agent or non-salt tonicifier is selected from one or more of sorbitol, mannitol, sucrose, trehalose, glycerol, maltose, lactose, or a combination thereof.

38. The formulation of claim 32, wherein the formulation has a viscosity selected from 10 cps to25 cps or 20 cps to 30 cps.

39. The formulation of claim 32, wherein the formulation has a pH of 5.4 – 6.4.

40. The formulation of claim 32, wherein the formulation has an osmolality of 240 mOs/kg.

41. A low viscosity, hypotonic formulation, comprising:

(a) a concentrated protein in an amount greater than 100 mg/mL and less than 200 mg/mL, wherein the concentrated protein is an antibody or a fragment thereof;

(b) a salt in an amount selected from 90 mM or 95 mM;

(c) a buffer comprising a neutral nonpolar amino acid and in an amount of 20 mM;

non-salt tonicifier is selected from a sugar alcohol, a monosaccharide, a disaccharide, or a combination thereof.

46. The formulation of claim 45, wherein the stabilizing agent or non-salt tonicifier is present in an amount of 0.2% to 1.8% w/v.

47. A composition comprising a protein in an amount greater than 100 mg/mL and less than 200 mg/mL, a tonicifier comprising a salt and a buffer present in a combined amount of from 110 mM to 120 mM and a surfactant present in an amount of from 0.001% to 0.2% w/v, wherein the formulation has an osmolality of 230 to 290 mOs/kg and the buffer includes a neutral nonpolar amino acid.

48. The composition of claim 47, wherein the protein is an enzyme, a polypeptide, a peptide, an antibody or a fragment of an antibody.

49. The composition of claim 48, wherein the antibody is a monoclonal antibody or a fragment thereof, a polyclonal antibody or a fragment thereof, a humanized monoclonal antibody or a fragment thereof, a human antibody or a fragment thereof, a nanobody, or a hybrid antibody or a fragment thereof.

50. The composition of claim 47, wherein the protein is present in an amount of 120 mg/mL to 185 mg/mL.

51. The composition of claim 47, wherein the salt is present in an amount of 90 mM or 95 mM.

52. The composition of claim 47, wherein the buffer is present in an amount of 20 mM.

53. The composition of claim 47, wherein the surfactant is present in an amount of 0.005% w/v.

54. The composition of claim 47, further comprising a non-salt tonicifier in an amount of from 0.05% to 1.5% w/v.

55. The composition of claim 47 or claim 51 wherein the salt is selected from one or more of sodium chloride, sodium gluconate, or sodium lactate.

56. The composition of claim 47 or claim 52, wherein the buffer comprises glycine.

57. The composition of claim 47 or claim 53, wherein the surfactant is selected from one or more of a polysorbate or a pluronic.

58. The composition of claim 57, wherein the polysorbate is polysorbate 20 (Tween® 20) or polysorbate 80 (Tween® 80).

59. The composition of claim 54, wherein the non-salt tonicifier is selected from one or more of sorbitol, mannitol, sucrose, trehalose, or glycerol.