REDUCING VISCOSITY OF PHARMACEUTICAL FORMULATIONS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/067,637 filed October 23, 2014, which is incorporated in its entirety by reference herein.

BACKGROUND

Pharmaceutically active proteins, such as antibodies, are frequently formulated in liquid solutions, particularly for parenteral injection. For products that need to be administered via a subcutaneous route, for example use in self administration; formulations in delivery volumes greater than 1-2 milliliters are not well tolerated. In such cases highly concentrated protein formulations are desirable to meet the limited dose volume. The high dose and small volume requirements such administration means that the protein therapeutic can reach concentrations of upwards of 100 mg/ml or more. Highly concentrated protein formulations can pose many challenges to the manufacturability and administration of protein therapeutics. One challenge posed by some highly concentrated protein formulations is increased viscosity. High viscosity formulations are difficult to handle during manufacturing, including at the bulk and filling stages. High viscosity formulations are also difficult to draw into a syringe and inject, making administration to the patient difficult and unpleasant. The need to identify compounds that are useful for reducing viscosity of highly concentrated protein formulations, to develop methods of reducing the viscosity of such formulations, and to provide pharmaceutical formulations with reduced viscosity are well known in the pharmaceutical industry. The present invention provides such compounds, methods and formulations.

SUMMARY

In one aspect, the present invention refers to the use of an excipient selected from the group consisting of n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof for reducing the viscosity of a liquid pharmaceutical formulation comprising a therapeutic protein at a concentration of at least 70 mg/ml, comprising the step of combining the therapeutic protein with a viscosity-reducing concentration of the excipient. In another aspect, the present invention refers to a pharmaceutical formulation produced by the use of the present invention. In another aspect, the present invention refers to a pharmaceutical composition comprising a therapeutic protein at a concentration of at least 70 mg/mL having a reduced viscosity, and an excipient selected from the group consisting of the n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof at a viscosity-reducing concentration, wherein the concentration of the excipient is from 50 mM to 300 mM and wherein the viscosity is reduced by at least 5% when compared to a control formulation lacking the excipient, wherein the control formulation lacking the excipient has a viscosity of at least 6 cP. In another aspect, the present invention refers to a method of preparing a

lyophilized powder comprising the step of lyophilizing a pharmaceutical composition of the present invention. In another aspect, the present invention refers to a lyophilized powder comprising a therapeutic protein and an excipient selected from the group consisting of the n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof, wherein the excipient is present at a weight:weight concentration effective to reduce viscosity upon reconstitution with a diluent. In still another aspect, the present invention refers to a method for reconstituting a lyophilized powder of the present invention, comprising the step of adding a sterile aqueous diluent. Also disclosed herein is an excipient selected from the group consisting of n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof at selected concentrations for use in reducing the viscosity of protein formulations. Methods for reducing the viscosity of protein formulations by combining a high concentration therapeutic protein with a viscosity-reducing concentration of an excipient selected from the group consisting of n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof are disclosed herein. Also disclosed herein is lyophilized powder comprising a therapeutic protein and an excipient selected from the group consisting of n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof wherein the excipient is present at a weight: weight concentration effective to reduce viscosity upon reconstitution with a diluent. Also disclosed herein is a lyophilized powder comprising a therapeutic protein and a diluent for reconsititution that contains an excipient selected from the group consisting of n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof.

Disclosed herein is a method for reducing the viscosity of a liquid pharmaceutical formulation comprising a therapeutic protein at a concentration of at least 70 mg/ml, comprising the step of combining the therapeutic protein with a viscosity-reducing concentration of an excipient selected from the group consisting of n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof. In one example the viscosity of the formulation is reduced by at least 5%. In another example the viscosity of the formulation is reduced by at least 10%. In another example the viscosity of the formulation is reduced by at least 20%. In another example the viscosity of the formulation is reduced by at least 30%. In another example the viscosity of the formulation is reduced by at least 40%. In another example the viscosity of the formulation is reduced by at least 50%. In another example the viscosity of the formulation is reduced by at least 60%. In another example the viscosity of the formulation is reduced by at least 70%. In another example the viscosity of the formulation is reduced by at least 80%. In a related example, pharmaceutical formulations produced by such methods are disclosed.

Also disclosed herein is a pharmaceutical composition comprising a therapeutic protein at a concentration of at least 70 mg/mL, and an excipient selected from the group consisting of n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof. In one example the concentration of the excipient is from about 5 mM to about 700 mM. In a related example the concentration of the excipient is from about 100 mM to about 400 mM. In another related example the concentration of the excipient is from about 200 mM to about 300 mM. In still another related example the concentration of the excipient is from about 140 mM to about 170 mM. Also disclosed herein are such pharmaceutical compositions having a pH between about 4.0 to about 8.0. In a related example the pH is about 4.0 to about 6.0. In a further related example the pH is about 4.8 to about 5.4.

Also disclosed herein is a method of preparing a lyophilized powder comprising the step of lyophilizing a pharmaceutical formulation as described above.

Disclosed herein is a lyophilized powder comprising a therapeutic protein and an excipient selected from the group consisting of n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof wherein the excipient is present at a weight:weight concentration effective to reduce viscosity upon reconstitution with a diluent. In one example the excipient is present at a concentration of between about 100 μg per mg therapeutic protein to about 1 mg per mg therapeutic protein. In a related example the excipient is present at a concentration between about 200 μg to about 500 μg per mg therapeutic protein. In a further related example the excipient is present at a concentration between about 150 μg to about 250 μg per mg therapeutic protein. Also disclosed herein is a method for reconstituting a lyophilized powder as described above comprising the step of adding a sterile aqueous diluent.

Also disclosed herein are therapeutic proteins that are antibodies. Also disclosed herein are formulations or compositions as described above wherein the therapeutic protein is an antibody. In addition, also

disclosed herein is a lyophilized powder as described above wherein the therapeutic protein is an antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a bar graph showing the effects of various excipients on the viscosity of an antibody solution.

Figure 2 is a bar graph showing the effects of various excipients on the viscosity of an antibody solution.

DETAILED DESCRIPTION

Reducing the viscosity of high concentration therapeutic protein formulations is of interest to the pharmaceutical industry. The excipients, n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof, were discovered to reduce the viscosity of such formulations. The invention provides the excipient at selected concentrations for use in reducing the viscosity of protein formulations. Methods for reducing the viscosity of protein formulations by combining the therapeutic protein with a viscosity-reducing concentration of an excipient selected from the group consisting of n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof is provided herein. Also provided is lyophilized powder comprising a therapeutic protein and an excipient selected from the group consisting of n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof, wherein the excipient is present at a weight:weight concentration effective to reduce viscosity upon reconstitution with a diluent.

Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, *e.g.*, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001) and Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates (1992), and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The terminology used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well

CLAIMS

WHAT IS CLAIMED IS:

1. Use of an excipient selected from the group consisting of n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof for reducing the viscosity of a liquid pharmaceutical formulation comprising a therapeutic protein at a concentration of at least 70 mg/ml having a viscosity of at least 6 cP, comprising the step of combining the therapeutic protein with a viscosity-reducing concentration of the excipient, wherein the concentration of the excipient is from 50 mM to 300 mM and wherein the viscosity is reduced by at least 5% when compared to a control formulation lacking the excipient.

2. The use of claim 1 wherein the excipient is n-acetyl arginine.

3. The use of claim 1 wherein the excipient is n-acetyl lysine.

4. The use of claim 1 wherein the excipient is n-acetyl histidine.

5. The use of claim 1 wherein the excipient is n-acetyl proline.

6. The use of claim 1 wherein viscosity of the formulation is reduced by at least 25% when compared to the control formulation lacking the excipient.

7. The use of claim 1 wherein viscosity of the formulation is reduced by at least 50% when compared to the control formulation lacking the excipient.

8. The use of claim 1 wherein viscosity of the formulation is reduced by at least 80% when compared to the control formulation lacking the excipient.

9. A pharmaceutical composition comprising a therapeutic protein at a concentration of at least 70 mg/mL having a reduced viscosity, and an excipient selected from the group consisting of the n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof, wherein the concentration of the excipient is from 50 mM to 300 mM and wherein the viscosity is reduced by at least 5% when compared to a control formulation lacking the excipient, wherein the control formulation lacking the excipient has a viscosity of at least 6 cP.

10. The pharmaceutical composition of claim 9, wherein the excipient is n-acetyl arginine.

11. The pharmaceutical composition of claim 9, wherein the excipient is n-acetyl lysine.

12. The pharmaceutical composition of claim 9, wherein the excipient is n-acetyl histidine.

13. The pharmaceutical composition of claim 9, wherein the excipient is n-acetyl proline.

14. The pharmaceutical composition of claim 9, wherein the concentration of the excipient is from 100 mM to 250 mM.

15. The pharmaceutical composition of any of claims 9-14, having a pH between 4.0 to 8.0.

16. The pharmaceutical composition of claim 15, having a pH of 4.6 to 5.4.

17. A method of preparing a lyophilized powder comprising the step of lyophilizing a pharmaceutical composition of any of claims 9-16.

18. A lyophilized powder comprising a therapeutic protein and an excipient selected from the group consisting of the n-acetyl arginine, n-acetyl lysine, n-acetyl histidine, n-acetyl proline and mixtures thereof, wherein the excipient is present at a weight:weight concentration effective to reduce viscosity upon reconstitution with a diluent, wherein the concentration of the excipient is from 50 mM to 300 mM upon reconstitution of the lyophilized powder, and wherein a control comprising the lyophilized powder comprising the therapeutic protein but lacking the excipient when reconstituted has a viscosity of at least 6 cP, and viscosity of the reconstituted lyophilized powder with the excipient is reduced by at least 5% when compared to the reconstituted control.

19. The lyophilized powder of claim 18, wherein the excipient is present at a concentration of between 100 µg per mg therapeutic protein to 1 mg per mg therapeutic protein.

20. The lyophilized powder of claim 18, wherein the excipient is present at a concentration of between 200 µg to 500 µg per mg therapeutic protein to 1 mg per mg therapeutic protein.

21. A method for reconstituting a lyophilized powder of any of claims 18-20, comprising the step of adding a sterile aqueous diluent.

22. The method of claims 18 or 21, wherein the therapeutic protein is an antibody.

23. The pharmaceutical formulation or pharmaceutical composition of any of claims 9-16, wherein the therapeutic protein is an antibody.

24. The lyophilized powder of any of claims 18-20, wherein the therapeutic protein is an antibody.

25. The use of any of claims 1-8, wherein the therapeutic protein is an antibody.

26. The pharmaceutical composition of claim 9, wherein the concentration of the excipient is from 100 mM to 250 mM.

27. The pharmaceutical composition of claim 9, wherein the concentration of the excipient is from 140 mM to 200 mM.

28. The pharmaceutical composition of claim 9, wherein the concentration of the excipient is selected from the group consisting of from 50, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 250, and 300 mM.

29. The use of claim 1, wherein the liquid pharmaceutical formulation comprising a therapeutic protein has a viscosity of at least 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 100, 125, 150, 175, or 200 cP.

30. The pharmaceutical composition of claim 9, wherein the pharmaceutical composition has a viscosity of at least 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 100, 125, 150, 175, or 200 cP.

31. The lyophilized powder of claim 18, wherein the lyophilized powder comprising the therapeutic protein but lacking the excipient when reconstituted has a viscosity of at least 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 100, 125, 150, 175, and 200 cP.