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.

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.

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

10. 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.