Inhalation therapy offers the best potential for optimal delivery to the lungs with reduction in systemic side effects. Inhalation treatment targets the airways, lowering the dose of the drug required for optimal efficacy. Also, a low incidence of systemic side effects normally occurs with a rapid onset of drug action. Nebulizers are a very suitable method of treatment for lung infestations of fungi or bacteria as they fill the air with a very fine mist of respirable droplets capable of depositing in all regions of the lung.

However, protein formulation as a liquid for inhalation therapy is a highly complex process as it requires the product to be ready for addition to a nebulizer and remain stable during aerosol generation. The formulation must maintain stability upon long term storage, minimize the effect of nebulization on the integrity of the protein and have appropriate tonicity for pulmonary delivery. Thus, a fine balance between stability, tolerability in the lungs, including potential toxicity, and isotonicity is key to achieve an efficient formulation of protein for inhalation therapy.

The same challenges do not arise when proteins are formulated as a lyophilized product for resuspension, as isotonicity can be achieved upon resuspension and long term stability is ensured only for the dried lyophilate. Thus, the same excipient composition is not always applicable for two different formulations

A liquid formulation of GM-CSF (LEUKINE®) has previously been disclosed for i.v. administration (US2002141970A1). US2002141970A1 suggest addition of a chelating agent as an excipient to increase stability of the compound.

The formulation of drug solution for nebulization is designed to optimize drug solubility and stability; small changes in formulation may also affect inhaled mass, particle size distribution, and treatment time.

Nebulization carries an inherent risk of destabilizing proteins. The main reason for protein instability upon nebulization is unfolding and aggregation at the air-liquid interface, and thus the use of GM-CSF for nebulization requires a stable liquid formulation, which is ready for use for inhalation and does not result in significant changes upon nebulization.

Summary

In a first aspect, the present disclosure refers to a formulation of recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF), comprising

a. rhGM-CSF at a concentration of from 150 µg/mL to 500 µg/mL;

b. recombinant human albumin (rHA) at a concentration of from 0.5 mg/mL to 1.50 mg/mL;

c. polyethylene glycol-4000 (PEG-4000) at a concentration of from 0.05 mg/mL to 0.15 mg/mL; and

d. mannitol at a concentration of from 45 mg/mL to 100 mg/mL.

In another aspect, the present disclosure refers to an inhaler comprising the formulation as disclosed herein.

In yet another aspect, the present disclosure refers to a use of the formulation as disclosed herein, in the manufacture of a medicament for pulmonary disease.

In a further aspect, the present disclosure refers to a use of the formulation as disclosed herein, in the manufacture of a medicament for treatment of a lung infection.

In another aspect, the present disclosure refers to a method of manufacturing a formulation of rhGM-CSF, the method comprising:

a. preparing a buffer comprising one or more stabilizers, citric acid monohydrate, Na_2HPO_4, recombinant human serum albumin (rHSA), and PEG-4000;

b. combining the buffer of step a. with rhGM-CSF; and

c. filtering the combination of step b. to generate the formulation of rhGM-CSF, wherein the formulation of rhGM-CSF comprises:

i. rhGM-CSF at a concentration of from 150 µg/mL to 500 µg/mL;

ii. rHSA at a concentration of from 0.5 mg/mL to 1.50 mg/mL;

iii. PEG-4000 at a concentration of from 0.05 mg/mL to 0.15 mg/mL; and

iv. mannitol at a concentration of from 45 mg/mL to 100 mg/mL.

In yet another aspect, the present disclosure refers to the formulation as disclosed herein, for use in therapy.

The present disclosure discloses a stable liquid formulation of rhGM-CSF, which is ready for use for inhalation and does not experience relevant instability upon nebulization.

In one example of the present disclosure the combination of a sugar alcohol or a sugar, albumin and polyethylene glycol (PEG) and water provides a highly stable liquid formulation of rhGM-CSF.

Claims

1. A formulation of recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF), comprising:
a. rhGM-CSF at a concentration of from 150 µg/mL to 500 µg/mL;
b. recombinant human albumin (rHA) at a concentration of from 0.5 mg/mL to 1.50 mg/mL;
c. polyethylene glycol-4000 (PEG-4000) at a concentration of from 0.05 mg/mL to 0.15 mg/mL; and
d. mannitol at a concentration of from 45 mg/mL to 100 mg/mL.

2. The formulation of claim 1, wherein:
the concentration of the rhGM-CSF is from 200 µg/mL to 300 µg/mL;
the concentration of the rHA is from 0.5 mg/mL to 1.50 mg/mL;
the concentration of the PEG-4000 is from 0.05 mg/mL to 0.15 mg/mL; and
the concentration of the mannitol is from 45 mg/mL to 100 mg/mL.

3. The formulation of claim 1, wherein the rhGM-CSF is molgramostim (SEQ ID NO: 1), sargramostim (SEQ ID NO: 2), or regramostim.

4. The formulation of claim 3, wherein the rhGM-CSF is molgramostim (SEQ ID NO: 1).

5. The formulation of claim 1, wherein less than 5% of impurity is formed in the formulation after 6 months of storage at 25 °C.

6. The formulation of claim 5, wherein the impurity is determined using high-performance liquid chromatography (HPLC).

7. The formulation of claim 1, further comprising a buffer.

8. The formulation of claim 7, wherein the buffer is citric acid monohydrate or Na_2HPO_4.

9. The formulation of claim 8, wherein the rhGM-CSF is molgramostim (SEQ ID NO: 1) and wherein the liquid formulation further comprises one or more of:
Tween 80 at a concentration of from 0 mg/mL to 0.1 mg/ml;
Na_2HPO_4 at a concentration of from 2.6 mg/mL to 15.5 mg/mL; and

citric acid monohydrate at a concentration of from 0.28 mg/mL to 1.7 mg/mL.

10. The formulation of claim 1, wherein an osmolality of the formulation is from 250 mOsm/L to 375 mOsm/L.

11. The formulation of claim 1, wherein a percentage of the rhGM-CSF remaining after 3 months storage is more than 60% and/or wherein less than 5% of impurity is formed in the formulation after 6 months of storage at 25 °C.

12. The formulation of claim 11, wherein the impurity is determined using HPLC.

13. The formulation of claim 1, wherein the formulation is a liquid formulation.

14. The formulation of claim 1, wherein the formulation is nebulized.

15. The formulation of claim 14, wherein at least 90% of a biologic potency of rhGM-CSF is retained after nebulization.

16. The formulation of claim 1, wherein the formulation is to be administered to the lungs.

17. An inhaler comprising the formulation of claim 1.

18. Use of the formulation of claim 1, in the manufacture of a medicament for pulmonary disease.

19. Use of the formulation of claim 1, in the manufacture of a medicament for treatment of a lung infection.

20. A method of manufacturing a formulation of rhGM-CSF, the method comprising:
a. preparing a buffer comprising one or more stabilizers, citric acid monohydrate, Na_2HPO_4, recombinant human serum albumin (rHSA), and PEG-4000;
b. combining the buffer of step a. with rhGM-CSF; and
c. filtering the combination of step b. to generate the formulation of rhGM-CSF, wherein the formulation of rhGM-CSF comprises:
i. rhGM-CSF at a concentration of from 150 µg/mL to 500 µg/mL;
ii. rHSA at a concentration of from 0.5 mg/mL to 1.50 mg/mL;
iii. PEG-4000 at a concentration of from 0.05 mg/mL to 0.15 mg/mL; and

iv. mannitol at a concentration of from 45 mg/mL to 100 mg/mL.

21. The formulation of claim 1, for use in therapy.