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;
b. albumin; and
c. polyethylene glycol (PEG).

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 administration.

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, disodium hydrogen phosphate, 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.

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.

In one example the liquid formulation described above is for use as a medicament for nebulization.

In one example the liquid formulation of rhGM-CSF is for use in the treatment of aPAP or NTM infection.

In one example a method for pulmonary delivery of recombinant rhGM-CSF comprising nebulizing rhGM-CSF, a sugar alcohol, albumin and PEG is disclosed.

In a further example a nebulizer comprising the liquid formulation of rhGM-CSF is disclosed for use in the treatment of aPAP or NTM infection.

Description of Drawings

Figure 1: Impact of Mannitol on % rhGM-CSF remaining after 3 months at 40°C. The impact of mannitol concentration on stability of liquid formulation of rhGM-CSF was evaluated at accelerated conditions over 3 months. The concentration of mannitol was found to influence drug stability. Higher concentrations (50 mg/mL) of mannitol improved stability of rhGM-CSF. The y-axis is % rhGM-CSF content remaining compared to T0.

Figure 2: Impact of rhGM-CSF level within groupings of mannitol conc. on % GM-CSF remaining after 3 months at 40°C

The impact of rhGM-CSF concentration on stability of the liquid formulation was also evaluated at accelerated conditions over 3 months. The concentration of rhGM-CSF was found to influence drug stability. Higher concentrations of rhGM-CSF (400 µg/mL)

Claims

1. A formulation of recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF), comprising
   a. rhGM-CSF;
   b. albumin; and
   c. polyethylene glycol (PEG).

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

3. The formulation of claim 2, further comprising a sugar alcohol or a sugar.

4. The formulation of claim 3, wherein the sugar is maltose, trehalose, sucrose, mannose, lactose or galactose, or wherein the sugar alcohol is mannitol or sorbitol.

5. The formulation of claim 4, wherein the albumin is recombinant human albumin.

6. The formulation of claim 5, wherein the PEG is selected from the group consisting of PEG-1000, PEG-1550, PEG-2000, PEG-3000, PEG-3350, PEG-4000, or PEG-8000.

7. The formulation of claim 6, wherein the PEG is PEG-4000.

8. The formulation of claim 7, wherein:
   a concentration of the rhGM-CSF is from 150 µg/mL to 500 µg/mL;
   a concentration of the albumin is from 0.5 mg/mL to 1.50 mg/mL;
   a concentration of the PEG is from 0.05 mg/mL to 0.15 mg/mL; and
   a concentration of the sugar alcohol is from 45 mg/mL to 100 mg/mL.

9. The formulation of claim 8, wherein the formulation is a liquid formulation.

10. The formulation of claim 8, wherein the formulation is nebulized.

11. The formulation of claim 8, wherein the rhGM-CSF is molgramostim (SEQ ID NO: 1), the sugar alcohol is mannitol, the albumin is recombinant human albumin, and the PEG is PEG-4000.

12. The formulation of claim 11, wherein
a concentration of the rhGM-CSF is from 150 μg/mL to 500 μg/mL;
a concentration of the recombinant human albumin is from 0.5 mg/mL to 1.50 mg/mL;
a concentration of the PEG-4000 is from 0.05 mg/mL to 0.15 mg/mL; and
a concentration of the mannitol is from 45 mg/mL to 100 mg/mL.

13. The formulation of claim 12, wherein
a concentration of the rhGM-CSF is from 200 μg/mL to 300 μg/mL;
a concentration of the recombinant human albumin is from 0.5 mg/mL to 1.50 mg/mL;
a concentration of the PEG-4000 is from 0.05 mg/mL to 0.15 mg/mL; and
a concentration of the mannitol is 45 mg/mL to 100 mg/mL.

14. The formulation of claim 12, further comprising a buffer, wherein the buffer is citric acid monohydrate or Na_2HPO_4.

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

16. The formulation of claim 9 or claim 10, wherein a percentage of the rhGM-CSF remaining after 3 months storage is more than 60%.

17. An inhaler comprising the formulation of claim 12.

18. Use of the formulation of claim 12, in the manufacture of a medicament for pulmonary administration.

19. Use of the formulation of claim 12, 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, disodium hydrogen phosphate, 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.

21. The method of claim 20, wherein the formulation of rhGM-CSF comprises:
a concentration of the rhGM-CSF is from 200 µg/mL to 300 µg/mL;
a concentration of the rHSA is from 0.5 mg/mL to 1.50 mg/mL;
a concentration of the PEG-4000 is from 0.05 mg/mL to 0.15 mg/mL; and
a concentration of the mannitol is from 45 mg/mL to 100 mg/mL.

22. The formulation of claim 12, for use in therapy.