


A combination of ensifentrine and glycopyrrolate useful for treating respiratory disorders is described in WO 2014/140648 A.

The formulation of pharmaceutical compounds is complex and unpredictable. This is particularly the case for liquid pharmaceutical compositions for administration by inhalation. For instance, such inhalable liquid pharmaceutical compositions must be sufficiently stable so that a suitably consistent dose is delivered during inhalation, even after storage for a period of time. The difficulties associated with preparation of an inhalable pharmaceutical composition are compounded when that composition comprises two active agents, for instance as for the combination of ensifentrine and glycopyrrolate. For such combination formulations, stability of both pharmaceutical compounds must be controlled.

There is a need to develop a liquid pharmaceutical composition comprising ensifentrine and glycopyrrolate in which both compounds are stable. It is also desirable to prepare a liquid pharmaceutical composition which is suitable for administration by inhalation.

**SUMMARY**

In one aspect of the present disclosure, there is provided a liquid pharmaceutical composition suitable for administration by inhalation comprising:

(i) ensifentrine particles;

(ii) glycopyrrolate; and

(iii) a diluent, which diluent comprises water,

wherein:

the concentration of ensifentrine particles is from 0.1 to 5.0 mg/mL;

the glycopyrrolate is dissolved in the diluent;

the concentration of glycopyrrolate is less than or equal to 5.0 mg/mL; and

the pH of the liquid pharmaceutical composition is from 3.0 to 6.0.

In another aspect of the present disclosure, there is provided a nebuliser comprising a liquid pharmaceutical composition disclosed herein.

In a further aspect of the present disclosure, there is provided a liquid pharmaceutical composition disclosed herein for use in the treatment of the human or animal body.

In another aspect of the present disclosure, there is provided a use of a liquid pharmaceutical composition disclosed herein in the manufacture of a medicament for the treatment or prevention of a disease or condition selected from chronic obstructive pulmonary disease (COPD), asthma, allergic asthma, hay fever, allergic rhinitis, bronchitis, emphysema, bronchiectasis, adult respiratory distress syndrome (ARDS), steroid resistant asthma, severe asthma, paediatric asthma, cystic fibrosis, lung fibrosis, pulmonary fibrosis, interstitial lung disease, atopic dermatitis, psoriasis, ocular inflammation, and cerebral ischaemia.

It is a surprising finding of the present disclosure that a pharmaceutical composition in which both ensifentrine and glycopyrrolate are stable can be produced by formulating ensifentrine as a suspension of particles and glycopyrrolate as a solution in an aqueous diluent at a low pH and in which the concentration of glycopyrrolate is low relative to the concentration of ensifentrine. This specific formulation in which ensifentrine is suspended and glycopyrrolate is dissolved has been shown to be stable with respect to chemical degradation of both active agents after storage for at least three months.

## CLAIMS

1. A liquid pharmaceutical composition suitable for administration by inhalation comprising:

(i) ensifentrine particles;

(ii) glycopyrrolate; and

(iii) a diluent, which diluent comprises water,

wherein:

the concentration of ensifentrine particles is from 0.1 to 5.0 mg/mL;

the glycopyrrolate is dissolved in the diluent;

the concentration of glycopyrrolate is less than or equal to 5.0 mg/mL; and

the pH of the liquid pharmaceutical composition is from 3.0 to 6.0.

2. A liquid pharmaceutical composition according to claim 1, wherein the pH of the liquid pharmaceutical composition is from 3.5 to 5.0.

3. A liquid pharmaceutical composition according to claim 1 or claim 2, wherein the liquid pharmaceutical composition further comprises a buffer, preferably wherein the buffer is a citrate buffer.

4. A liquid pharmaceutical composition according to any one of claims 1 to 3, wherein the concentration of the buffer is from 10.0 to 40.0 mg/mL, preferably from 20.0 to 30.0 mg/mL.

5. A liquid pharmaceutical composition according to any one of the preceding claims, wherein the concentration of glycopyrrolate is from 0.01 mg/mL to 2.0 mg/mL, preferably from 0.02 mg/mL to 0.25 mg/mL.

6. A liquid pharmaceutical composition according to any one of the preceding claims, wherein the weight ratio ensifentrine:glycopyrrolate in the liquid pharmaceutical composition is from 1:5 to 200:1, preferably from 15:1 to 120:1.

7. A liquid pharmaceutical composition according to any one of the preceding claims, wherein the concentration of ensifentrine particles is from 0.15 to 2.5 mg/mL.

8. A liquid pharmaceutical composition according to any one of the preceding claims, wherein the ensifentrine particles have a Dv50 of from 0.5 to 5.0 μm.

9. A liquid pharmaceutical composition according to any one of the preceding claims, wherein the glycopyrrolate is a pharmaceutically acceptable salt of glycopyrronium,

preferably wherein the glycopyrrolate is glycopyrronium bromide or glycopyrronium chloride,

more preferably wherein the glycopyrrolate is glycopyrronium bromide.

10. A liquid pharmaceutical composition according to any one of the preceding claims, wherein the diluent is water and the liquid pharmaceutical composition comprises at least 80 % by weight of the diluent based on the total weight of the liquid pharmaceutical composition.

11. A liquid pharmaceutical composition according to any one of the preceding claims, wherein the liquid pharmaceutical composition further comprises a tonicity adjuster, preferably wherein the tonicity adjuster is sodium chloride.

12. A liquid pharmaceutical composition according to claim 11, wherein the concentration of the tonicity adjuster is greater than or equal to 1.0 mg/mL, preferably from 4.0 to 20.0 mg/mL, more preferably from 6.0 to 12.0 mg/mL.

13. A liquid pharmaceutical composition according to any one of the preceding claims, wherein the liquid pharmaceutical composition further comprises one or more surfactants, preferably wherein the one or more surfactants are selected from a polysorbate and a sorbitan alkyl ester.

14. A liquid pharmaceutical composition according to claim 13, wherein the total concentration of the one or more surfactants is from 0.01 to 2.0 mg/mL, preferably from 0.1 to 1.0 mg/mL.

15. A liquid pharmaceutical composition according to any one of the preceding claims, wherein the liquid pharmaceutical composition comprises:

(i) ensifentrine particles;

(ii) glycopyrrolate;

(iii) the diluent;

(iv) a polysorbate surfactant;

(v) optionally a sorbitan alkyl ester surfactant;

(vi) a citrate buffer; and

(vii) sodium chloride.

16. A liquid pharmaceutical composition according to any one of the preceding claims, wherein the liquid pharmaceutical composition comprises:

(i) ensifentrine particles;

(ii) glycopyrrolate; and

(iii) a diluent, which diluent comprises water,

wherein:

the concentration of ensifentrine particles is from 0.1 to 2.5 mg/mL;

the glycopyrrolate is dissolved in the diluent;

the concentration of glycopyrrolate is less than or equal to 0.25 mg/mL;

the pH of the liquid pharmaceutical composition is from 4.3 to 4.7; and

the weight ratio of ensifentrine:glycopyrrolate in the liquid pharmaceutical composition is from 5:1 to 150:1

17. A liquid pharmaceutical composition according to any one of the preceding claims, wherein the liquid pharmaceutical composition comprises:

(i) ensifentrine particles;

(ii) glycopyrrolate;

(iii) a diluent, which diluent comprises water;

(iv) a polysorbate surfactant;

(v) a sorbitan alkyl ester surfactant;

(vi) a citrate buffer; and

(vii) sodium chloride,

wherein:

the concentration of ensifentrine particles is from 0.1 to 2.5 mg/mL;
the glycopyrrolate is dissolved in the diluent;
the concentration of glycopyrrolate is less than or equal to 0.25 mg/mL;
the pH of the liquid pharmaceutical composition is from 4.3 to 4.7;
the total concentration of the surfactants is from 0.01 to 2.0 mg/mL;
the concentration of the sodium chloride is from 6.0 to 12.0 mg/mL; and
the weight ratio of ensifentrine:glycopyrrolate in the liquid pharmaceutical composition is from 15:1 to 120:1.

18. A liquid pharmaceutical composition according to any one of the preceding claims, which liquid pharmaceutical composition is stable with respect to chemical degradation of ensifentrine and glycopyrrolate for at least 1 month when stored at a temperature of 25°C and a relative humidity of 60 %.

19. A liquid pharmaceutical composition according to any one of the preceding claims, which liquid pharmaceutical composition is suitable for administration by a nebuliser.

20. A nebuliser comprising a liquid pharmaceutical composition according to any one of the preceding claims.

21. A liquid pharmaceutical composition according to any one of claims 1 to 19 for use in the treatment of the human or animal body.

22. Use of a liquid pharmaceutical composition according to any one of claims 1 to 19 in the manufacture of a medicament for the treatment or prevention of a disease or condition selected from chronic obstructive pulmonary disease (COPD), asthma, allergic asthma, hay fever, allergic rhinitis, bronchitis, emphysema, bronchiectasis, adult respiratory distress syndrome (ARDS), steroid resistant asthma, severe asthma, paediatric asthma, cystic fibrosis, lung fibrosis, pulmonary fibrosis, interstitial lung disease, atopic dermatitis, psoriasis, ocular inflammation, and cerebral ischaemia.

23. The use according to claim 22, wherein the disease or condition is chronic obstructive pulmonary disease (COPD).