Known pMDI formulation strategies can involve the use of a wide range of different propellants, excipients, co-solvents and surfactants, and may take the form of suspensions, solutions or mixtures thereof. For instance, pMDI formulations may include one or more propellants such as alkanes (for instance propane, *n*-butane, isobutane, *n*-pentane, isopentane, neopentane), hydrofluoroalkanes (HFAs, for instance HFA-227, HFA-134a and HFA 152a), ethers (for instance dimethylether) and hydrofluoro-olefins (HFOs, for instance HFO-1234ze and HFO-1234yf). Co-solvents such as ethanol and water are commonly included in pMDI formulations. Excipients which are commonly included in pMDI formulations include antioxidants, preservatives, wetting agents, chelating agents, emulsifiers, flavourings, buffers, lubricants, suspending agents and tonicity adjusting agents.

Drugs which have low solubility in diluents are often formulated as suspensions. In such suspension formulations, an important consideration is uniform dispersion of the drug particles. Agglomeration, phase separation and flocculation can lead to variability in the metered dose. Additional excipients such as surfactants and co-solvents are therefore commonly used in suspension formulations to improve suspension properties. A further consideration for suspension formulations is that of particle size distribution. The particle size distribution of the drug is usually maintained in the respirable range (typically less than 5 μm).

Each of the components included in pMDI can have a number of effects on formulation stability and efficacy which are highly dependent on the identity of the drug to be formulated. Such effects cannot reliably be predicted in advance. Correct formulation of a drug for use in a pMDI is critical to ensure that the formulation can be used successfully in a clinical setting.

SUMMARY

In an aspect of the present disclosure, there is provided a use of a liquid pharmaceutical composition in the manufacture of a medicament for the treatment or prevention of a respiratory disorder,
which liquid pharmaceutical composition is suitable for administration by inhalation and comprises:

(i) a suspension of particles comprising 9,10-dimethoxy-2-(2,4,6-trimethylphenylimino)-3-(N-carbamoyl-2-aminoethyl)-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one (RPL554); and

(ii) a diluent which is 1,1,1,2-tetrafluoroethane (HFA-134a),

wherein the liquid pharmaceutical composition contains less than 0.05 % by weight of a surfactant relative to the total weight of the composition.

It is a surprising finding of the present disclosure that a liquid pharmaceutical composition comprising particles of RPL554 and HFA-134a (1,1,1,2-tetrafluoroethane) as a diluent/propellant and which is substantially free of a surfactant is particularly advantageous for delivery of RPL554 by a pressurised metered dose inhaler. A number of benefits have been found to be associated with the liquid pharmaceutical composition. The specific combination of RPL554 and

HFA-134a has been found to lead to a suspension pMDI formulation which has favourable suspension characteristics and reduced flocculation. It has also been found that a chemically and physically stable formulation may be achieved without requiring the presence of surfactants.

The ability to omit surfactants from the composition of the present disclosure is highly advantageous. That is because RPL554 is likely to be used in patients suffering from conditions such as COPD and asthma, who are at increased risk of an allergic inflammatory reaction to excipients such as surfactants. Further, given the teaching in WO 2014/140648 which suggests that a surfactant is necessary to achieve an adequate pMDI, it is surprising that adequate long term stability, without aggregation or flocculation of the particles of active ingredient, can be achieved without a surfactant.

It has also unexpectedly been found that particles of RPL554 are vulnerable to Ostwald ripening (growth of particles during suspension) in the presence of co-solvents such as ethanol. It is important to avoid Ostwald ripening as an increase in particle size can reduce the respirable fraction of particles present in the formulation. The liquid pharmaceutical formulations of the present disclosure are found to avoid Ostwald ripening of the RPL554 particles.

The present disclosure provides a liquid pharmaceutical composition suitable for administration by inhalation comprising: (i) a suspension of particles comprising 9,10-dimethoxy-2-(2,4,6-trimethylphenylimino)-3-(N-carbamoyl-2-aminoethyl)-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one (RPL554); and (ii) a diluent which is 1,1,1,2-tetrafluoroethane (HFA-134a), wherein the liquid pharmaceutical composition is substantially free of surfactant.

The present disclosure further provides a pressurised metered dose inhaler comprising a liquid pharmaceutical composition according to the invention.

The present disclosure also provides a liquid pharmaceutical composition according to the present disclosure for use in the treatment of the human or animal body. A liquid pharmaceutical composition according to the present disclosure may be used in the treatment or prevention of a disease or condition selected from asthma, allergic asthma, hay fever, allergic rhinitis, bronchitis, emphysema, bronchiectasis, chronic obstructive

pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), steroid resistant asthma, severe asthma, paediatric asthma, cystic fibrosis, lung fibrosis, pulmonary fibrosis, interstitial lung disease, skin disorders, atopic dermatitis, psoriasis, ocular inflammation, cerebral ischaemia, inflammatory diseases and auto-immune diseases.

The present disclosure also provides a method of treating or preventing a disease or condition as defined herein in a subject, which method comprises administering to said subject an effective amount of a liquid pharmaceutical composition according according to the present disclosure.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a schematic of visual assessment of suspension performance in pressure rated glass vials.

Figure 2 shows the sedimentation score against propellant mixtures for each product strength.

Figure 3 shows a diagrammatic representation of a test canister after 24 hours with the dip tube location into the liquid phase.

Figure 4 shows a RPL554 solubility graph with increasing ethanol concentrations, with or without oleic acid.

Figure 5 shows mean fine particle dose against product strength of the pMDI formulations.

DETAILED DESCRIPTION OF THE INVENTION

The liquid pharmaceutical composition of the invention comprises a suspension of particles of 9,10-dimethoxy-2-(2,4,6-trimethylphenylimino)-3-(N-carbamoyl-2-aminoethyl)-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one (RPL554). For the avoidance of doubt, the RPL554 is in free-base form. While the majority of the particles present in the liquid pharmaceutical composition are typically in suspension in the diluent, it is also the case that some or all of the particles in the liquid pharmaceutical composition according to the invention may have settled to the

CLAIMS

1. Use of a liquid pharmaceutical composition in the manufacture of a medicament for the treatment or prevention of a respiratory disorder, which liquid pharmaceutical composition is suitable for administration by inhalation and comprises:

(i) a suspension of particles comprising 9,10-dimethoxy-2-(2,4,6-trimethylphenylimino)-3-(N-carbamoyl-2-aminoethyl)-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one (RPL554); and

(ii) a diluent which is 1,1,1,2-tetrafluoroethane (HFA-134a),

wherein the liquid pharmaceutical composition contains less than 0.05 % by weight of a surfactant relative to the total weight of the composition.

2. The use according to claim 1, wherein the liquid pharmaceutical composition contains less than 0.05 % by weight of any additional excipient selected from a co-solvent and a surfactant relative to the total weight of the composition.

3. The use according to claim 1 or claim 2, wherein the liquid pharmaceutical composition contains less than 0.05 % by weight of any additional excipient relative to the total weight of the composition.

4. The use according to any one of the preceding claims, wherein the liquid pharmaceutical composition contains less than 0.01 % by weight of said surfactant or said additional excipient, relative to the total weight of the composition.

5. The use according to any one of the preceding claims, wherein the liquid pharmaceutical composition contains less than 0.001 % by weight of said surfactant or said additional excipient, relative to the total weight of the composition.

6. The use according to any one of the preceding claims, wherein the particles comprise at least 50% by weight of RPL554 relative to the total weight of the particles.

7. The use according to any one of the preceding claims, wherein the particles comprise at least 99% by weight of RPL554 relative to the total weight of the particles.

8. The use according to any one of the preceding claims, wherein RPL554 is the sole active agent in the liquid pharmaceutical composition.

9. The use according to any one of the preceding claims, wherein the liquid pharmaceutical composition consists essentially of (i) RPL554 and (ii) 1,1,1,2-tetrafluoroethane.

10. The use according to any one of the preceding claims, wherein the liquid pharmaceutical composition comprises at least 99.5 % by weight of (i) RPL554 and (ii) 1,1,1,2-tetrafluoroethane relative to the total weight of the composition.

11. The use according to any one of the preceding claims, wherein the particles comprising RPL554 have a particle size distribution with a Dv50 (median particle size by volume) value of from 0.2 μm to 5 μm.

12. The use according to any one of the preceding claims, wherein the concentration of particles comprising RPL554 in the liquid pharmaceutical composition is from 0.1 mg/mL to 200 mg/mL.

13. The use according to any one of the preceding claims, wherein the liquid pharmaceutical formulation is suitable for administration by pressurised metered dose inhaler.

14. The use according to any one of the preceding claims, wherein the liquid pharmaceutical composition is in a pressurised metered dose inhaler.

15. The use according to any one of claims 1 to 13, wherein the respiratory disorder is selected from asthma, allergic asthma, hay fever, allergic rhinitis, bronchitis, emphysema, bronchiectasis, chronic obstructive pulmonary disease

(COPD), adult respiratory distress syndrome (ARDS), steroid resistant asthma, severe asthma, paediatric asthma, cystic fibrosis, lung fibrosis, pulmonary fibrosis and interstitial lung disease.

16. The use according claim 15 wherein the disease or condition is chronic obstructive pulmonary disease (COPD).