Claims

1. A method of making a dry powder formulation, the method comprising co-jet milling unmicronised glycopyrrolate and magnesium stearate with milling gas having a humidity below 20% Relative Humidity to produce micronized composite particles, wherein the micronized composite particles are then subjected to a conditioning step which includes exposure of the micronized composite particles to humidity in the range of 10%-95% Relative Humidity at temperatures between 5°C to 88°C for at least 60 minutes.

2. The method according to claim 1, wherein the conditioning is initiated within 30 minutes of completing the milling, within 25 minutes, within 20 minutes, within 15 minutes, preferably within 10 minutes, more preferably within 5 minutes, most preferably immediately after completing the co-jet milling of the glycopyrrolate and magnesium stearate.

3. The method according to claims 1 to 2, wherein the fraction of the conditioned co-jet milled formulation which is greater than 10 µm is less than 20% by volume or mass, preferably wherein the fraction which is greater than 10 µm is less than 15% by volume or mass, more preferably wherein the fraction which is greater than 10 µm is less than 10% by volume or mass, or more preferably wherein the fraction which is greater than 10 µm is less than 5% by volume or mass, immediately after the co-jet milling and after the conditioning process as suitably determined by a Malvern Mastersizer or similar laser diffraction equipment.

4. The method according to claims 1 to 3, wherein the magnesium stearate is co-jet milled in an amount of from 1 to 25 % (w/w), more preferably from 2 to 20 % (w/w), more preferably 3 to 15 % (w/w), more preferably 4 to 10 % (w/w) but most preferably from 5 to 7.5 % (w/w) magnesium stearate by weight of the co-jet milled combination of glycopyrrolate and magnesium stearate.

5. The method according to claims 1 to 4, wherein the conditioning humidity is in the range of 30-90% RH, 45-90% RH or 50-88% RH or more preferably 60-87% RH.

6. The method according to claim 5, wherein the method further comprises subjecting the micronized composite particles to a ventilating atmosphere having relative humidity in

the range of 10%-95% RH, preferably 30-90% RH, 45-90% RH or 50-88% RH or more preferably 60-87%, preferably wherein the atmosphere is air.

7. The method according to claim 6, wherein ventilating atmosphere passes over and through a powder bed comprising micronized composite particles at a rate of less than 100 cm^3 /s, less than 10 cm^3 /s, less than 5 cm^3 /s, less than 2 cm^3 /s, less than 1 cm^3 /s, preferably less than 0.8 cm^3 /s, preferably less than 0.6 cm^3 /s, preferably less than 0.4 cm^3 /s, preferably less than 0.2 cm^3 /s, preferably less than 0.1 cm^3 /s, more preferably about 0.001 cm^3 /s.

8. The method according to claim 7, wherein the volume ratio of ventilating atmosphere to poured bulk powder is more than 1:1, preferably more than 10:1, preferably more than 100:1, preferably more than 1,000:1, preferably more than 10,000:1, preferably more than 100,000:1, preferably more than 1,000,000:1, more preferably more than 10,000,000:1.

9. The method according to claims 1 to 8, wherein the conditioning step is carried out for at least 75 minutes, preferably for at least 85 minutes, preferably for at least 1.5 hours, at least 2 hours, at least 3 hours, at least 5 hours, at least 6 hours, at least 12 hours, at least 18 hours, preferably at least 24 hours, preferably for at least 36 hours or more preferably for at least 48 hours.

10. The method according to claims 1 to 9, wherein the conditioning step includes exposing the micronized composite particles to a temperature in the range from 10°C to 50°C, more preferably 24°C to 50°C.

11. The method according to claims 1 to 10, wherein the micronized composite particles are blended with a carrier, preferably lactose, more preferably anhydrous lactose, more preferably alpha-lactose monohydrate, optionally after the conditioning step.

12. The method according to claim 11, wherein the micronized composite particles are present in an amount of less than 5%, less than 4%, less than 3%, preferably less than 2%, preferably less than 1%, preferably less than 0.75%, preferably less than 0.5% by weight of the formulation.

13. The method according to claims 1 to 12, wherein the conditioning step takes place by distributing the micronized composite particles on a surface, optionally wherein the conditioning step takes place on a tray.

14. The method according to claims 1 to 13, wherein the conditioning step involves exposing the micronized composite particles to the humidity for sufficient time for amorphous glycopyrrolate to re-crystallise after co-jet milling, as determined by dynamic vapour sorption.

15. The method according to claims 1 to 14, wherein the conditioning step involves powder agitation, optionally wherein the agitation is intermittent powder agitation.

16. The method according to claim 15, wherein the powder agitation takes place within 30 minutes of completing the milling, within 25 minutes, within 20 minutes, within 15 minutes, preferably within 10 minutes, more preferably within 5 minutes, most preferably immediately after completing the milling of the glycopyrrolate and magnesium stearate.

17. The method according to claims 15 to 16, wherein the powder agitation involves a fluidised bed.

18. The method according to claims 15 to 16, wherein the powder agitation is provided by a Resonance Acoustic Mixer.

19. The method according to claims 1 to 18, wherein the milling gas has a humidity preferably below 15% Relative Humidity, preferably below 10% Relative Humidity, preferably below 5% Relative Humidity, more preferably below 2.5% Relative Humidity.

20. The method according to claims 1 to 19, wherein the milling gas is preferably air, nitrogen or helium or combination thereof.

21. The method according to claim 1 to 20, wherein the co-jet milling is carried out at an averaged powder feed rate of between 0.1 and 50 g/min, preferably at a feed rate of between 0.5 and 40 g/min, preferably at a feed rate of between 1 and 30 g/min, preferably at a feed rate of between 1.5 and 25 g/min, preferably at a feed rate of between 0.1 and 20 g/min, preferably at a feed rate of between 0.5 and 15 g/min, preferably at a feed rate of between 1 and 10 g/min, preferably at a feed rate of between 1.5 and 5 g/min.

22. The method according to claim 1 to 21, wherein the co-jet milling is carried out at an inlet pressure of between 3 and 12 bar, preferably at an inlet pressure of between 4 and 10 bar, or more preferably at an inlet pressure of between 5 and 9 bar.

23. The method according to claim 1 to 22, wherein the co-jet milling is carried out at a grinding pressure of more than 2 bar below the inlet pressure.

24. The method according to claim 23, wherein the grinding pressure is carried out at between 1 and 10 bar, preferably at a pressure of between 2 and 8 bar, or more preferably at a pressure of between 3 and 7 bar.

25. The method according to any preceding claims, wherein the formulation further comprises a beta-2 adrenoceptor agonist, preferably wherein the beta-2 adrenoceptor agonist is albuterol (salbutamol), metaproterenol, terbutaline, salmeterol, fenoterol, procaterol, preferably, formoterol, carmoterol and pharmaceutically acceptable salts thereof, more preferably wherein the beta-2 adrenoceptor agonist is (R)-5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]- 8-hydroxy-1H-quinolin-2-one maleate.

26. The method according to any preceding claims, wherein the formulation comprises glycopyrrolate, indacaterol and mometasone, preferably glycopyrronium bromide, indacaterol maleate and mometasone furoate.

27. A method of making a dry powder formulation, the method comprising co-jet milling unmicronised glycopyrrolate and magnesium stearate with milling gas having a humidity below 20% Relative Humidity to produce micronized composite particles, wherein the micronized composite particles are then subjected to a conditioning step which includes exposure of the micronized composite particles to humidity in the range of 10%-95% RH at temperatures between 5°C to 88°C for at least 10 minutes.

28. A formulation comprising co-jet milled and then co-conditioned particles comprising glycopyrrolate and magnesium stearate obtained or obtainable by a method according to any preceding claim, optionally for use in a treatment of a respiratory disease, or for use in the preparation of a medicament for the treatment of a respiratory disease.

29. A formulation according to claim 28 or a method according to any one of claims 1 to 27 wherein the glycopyrrolate is a racemate.

30. A formulation according to claim 28 or 29 or a method according to any one of claims 1 to 27 wherein the glycopyrrolate is a single enantiomer.

31. A formulation according to any one of claims 28 to 30 or a method according to any one of claims 1 to 27, wherein the magnesium stearate forms a coating on the surface of the glycopyrrolate particles as measured by energy-dispersive X-ray spectroscopy.

32. A formulation according to any one of claims 28 to 31 or a method according to any one of claims 1 to 27, wherein the formulation is for use in treatment of a respiratory condition.

33. A formulation according to claim 28 to 32, further comprising carrier particles, wherein the span of the co-jet milled and co-conditioned glycopyrrolate and magnesium stearate particles is less than 150, more preferably less than 125, more preferably less than 100, or more preferably less than 50 prior to blending with the carrier particles.

34. A dry powder inhaler containing a formulation comprising co-jet milled and then co-conditioned particles comprising glycopyrrolate and magnesium stearate as claimed in any one of claims 28 to 33.

35. Use of co-jet milled and co-conditioned particles according to any claims 28-34 in the manufacture of a medicament for the treatment of a respiratory disease, preferably wherein the respiratory disease is chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis (CF) and related airway diseases.

36. A pharmaceutical kit comprising micronized composite particles made by a method according to claims 1-24 and a further active according to claim 25, in combined or separate unit dosage forms, said forms being suitable for administration of the co-jet milled glycopyrrolate and the further active in effective amounts, optionally together with one or more inhalation devices for administration of both actives.