Claims

1. A method for making a pharmaceutical composition for pulmonary administration, the method comprising a step in which an inhalable pharmaceutically active material is acoustically blended in a resonant acoustic blender, wherein the pharmaceutical composition is for localised pulmonary administration, preferably wherein the active is for localised effect, alternatively wherein the active is for systemic effect.

2. A method according to claim 1 wherein the acoustic blending is conducted at from 5 Hz to about 1,000 Hz, preferably 15 Hz to about 1,000 Hz, more preferably 20 Hz to about 800 Hz, more preferably 30 Hz to 700 Hz, more preferably 40 Hz to 600 Hz, more preferably 50 Hz to 500 Hz, more preferably 55 Hz to 400 Hz, more preferably 60 Hz to 300 Hz, more preferably 60 Hz to 200 Hz, more preferably 60 Hz to 100 Hz, more preferably 60 Hz to 80 Hz, more preferably 60 Hz to 75 Hz, most preferably from about 60 to 61 Hz.

3. A method according to any preceding claim wherein the acoustic blending is conducted for at least 1 minute, for at least 2 minutes, for at least 3 minutes, for at least 4 minutes, for at least 5 minutes, for at least 6 minutes, for at least 7 minutes, for at least 8 minutes, for at least 9 minutes, for at least 10 minutes, for at least 11 minutes, for at least 12 minutes, for at least 13 minutes, for at least 14 minutes, for at least 15 minutes, for at least 16 minutes, for at least 17 minutes, for at least 18 minutes, for at least 19 minutes, for at least 20 minutes, for at least 21 minutes, for at least 22 minutes, for at least 23 minutes, for at least 24 minutes, for at least 25 minutes, for at least 26 minutes, for at least 27 minutes, for at least 28 minutes, for at least 29 minutes or for up to 30 minutes, or for up to 60 minutes.

~~4. A method according to any preceding claim wherein the pharmaceutical composition is for localised pulmonary administration, preferably wherein the active is for localised effect, alternatively wherein the active is for systemic effect.~~

~~5~~4. A method according to any preceding claim wherein the pharmaceutical composition comprises an excipient material.

~~6~~5. A method according to any preceding claim wherein the pharmaceutical composition further comprises additive material.

~~7~~6. A method according to any preceding claim wherein the pharmaceutically active material is particulate.

~~8~~7. A method according to any preceding claim, wherein the pharmaceutically active material is selected from a long-acting muscarinic antagonist and/or long-acting beta-adrenoceptor agonist and/or an inhaled corticosteroid.

~~9~~8. A method according to claim ~~9~~7, wherein the pharmaceutically active material is selected from budesonide, formoterol fumarate, glycopyrronium bromide, indacaterol maleate, umeclidinium bromide, vilanterol trifenatate, tiotropium bromide, salmeterol xinafoate~~, fluticasone propionate~~ or fluticasone propionate.

~~10~~9. A method according to claim ~~8~~7, wherein the pharmaceutically active material is glycopyrronium bromide and indacaterol maleate

~~11~~10. A method according to claim ~~8~~7, wherein the pharmaceutically active material is fluticasone furoate and vilanterol trifenatate.

~~12~~11. A method according to claim ~~8~~7, wherein the pharmaceutically active material is tiotropium bromide.

~~13~~12. A method according to claim ~~8~~7, wherein the pharmaceutically active material is umeclidinium bromide and vilanterol trifenatate.

~~14~~13. A method according to claim ~~8~~7, wherein the pharmaceutically active material is glycopyrronium bromide.

~~15~~14. A method as claimed in any of claims ~~5~~ 4 to ~~14~~ 13 wherein the excipient material is particulate.

~~16~~15. A method according to ~~according to~~ claim ~~15~~ 14 in which the excipient is lactose.

~~17~~16. A method according to ~~according to~~ claim ~~16~~ 15 wherein the excipient is alpha-lactose monohydrate, preferably wherein in the $D_{10} \leq 250$ µm, $D_{50} \leq 500$ µm and $D_{90} \leq 800$µm, more preferably wherein in the $D_{10} \leq 5$-15 µm, $D_{50} \leq 60$-80 µm and $D_{90} \leq 120$-160 µm, most preferably $D_{10} \leq 15$ µm, $D_{50} \leq 80$ µm and $D_{90} \leq 160$ µm.

~~18~~17. A method as claimed in claim ~~6~~ 5 wherein the additive material is particulate.

~~19~~18. A method as claimed in claim ~~18~~17, in which the additive material comprises an amino acid.

~~20~~19. A method as claimed in claim ~~18~~17, in which the additive material comprises a phospholipid.

~~21~~20. A method as claimed in claim ~~18~~17, in which the additive material comprises a metal stearate.

~~22~~21. A method as claimed in claim ~~21~~20, wherein the metal stearate is either magnesium stearate or calcium stearate, preferably wherein the additive is magnesium stearate.

~~23~~22. A method according to any preceding claim, wherein the acoustic blending step is carried out in the presence of a liquid.

~~24~~23. A method as claimed in claim ~~23~~22, wherein the liquid comprises a propellant suitable for use in a pressurised metered dose inhaler device.

~~25~~24. A method according to any proceeding claim, wherein the composition is conditioned during the acoustic blending.

~~26~~25. A method of claim ~~25~~24, wherein the active is conditioned during the acoustic blending.

~~27~~26. A method of claim ~~26~~25, wherein the active is conditioned by an elevated level of relative humidity as compared to ambient conditions.

2827. A method of claims ~~26~~ 25 to 2726, wherein the active is conditioned by increasing the relative humidity over time to about 60-80%RH, preferably to about 75%.

2928. A method of claim 2524, wherein the active is conditioned at a minimum temperature.

3029. The method of claim 2928, wherein the minimum temperature is at least 10 °C, at least 20 °C, at least 30 °C, at least ~~at least~~ 40 °C, at least 50°C, preferably at least 60 °C.

3130. A method of claim 2625, wherein the pharmaceutically active material is selected from a long-acting muscarinic antagonist, long-acting beta-adrenoceptor agonist and/or inhaled corticosteroid.

3231. A method according to claim 3130, wherein the pharmaceutically active material is selected from budesonide, formoterol fumarate, glycopyrronium bromide, indacaterol maleate, umeclidinium bromide, vilanterol trifenatate, tiotropium bromide, salmeterol xinafoate~~, fluticasone propionate~~ or fluticasone propionate.

3332. A method according to claim 3130, wherein the pharmaceutically active material is glycopyrronium bromide and indacaterol maleate

3433. A method according to claim 3130, wherein the pharmaceutically active material is fluticasone furoate and vilanterol trifenatate.

3534. A method according to claim 3130, wherein the pharmaceutically active material is tiotropium bromide.

3635. A method according to claim 3130, wherein the pharmaceutically active material is umeclidinium bromide and vilanterol trifenatate.

3736. A method according to claim 3130, wherein the pharmaceutically active material is glycopyrronium bromide.

3837. The method of any preceding claim, wherein the active is submitted to mechanofusion prior to acoustic blending.

~~39~~38. The method of any preceding claim, wherein the active is micronised prior to acoustic blending.

~~40~~39. The method of claim ~~39~~ 38 wherein the micronisation is by impact milling or jet milling, preferably air-jet milling.

~~41~~40. A method according to any preceding claim, wherein after acoustic blending the active ingredient is packaged into a receptacle or delivery device.

~~42~~41. A pharmaceutical composition comprising an active material, obtained using the method claimed in any preceding claim.

~~43~~42. A pharmaceutical composition according to claim ~~42~~ 41 further comprising an excipient material and optionally an additive ~~active~~ material.

~~44~~43. A pharmaceutical composition according to claim ~~43~~ 42 wherein the excipient is lactose, preferably alpha-lactose monohydrate.

~~45~~44. An inhaler device comprising a composition obtained using the method claimed in any one of claims 1 to ~~41~~40.

~~46~~45. A pharmaceutical composition obtained by the method of any one of claims 1 to ~~41~~40 for use in medicine.

~~47~~46 A method for preparing composite active particles for use in a pharmaceutical composition for pulmonary administration, the method comprising a step in which particles of active material are acoustically blended in the presence of particles of an additive material which is suitable for the promotion of the dispersal of the composite active particles upon actuation of an inhaler.

~~48~~47. A method for making a pharmaceutical composition for pulmonary administration, the method comprising a step in which particles of the pharmaceutical composition are acoustically blended together to create composite particles.

~~49. The method of claim 48,~~ wherein pharmaceutically active material is acoustically blended in the presence of particles of additive material so that the additive material coats the active particles, wherein the additive material comprises an amino acid, a metal stearate, or a phospholipid.

~~50~~48. A method for making a pharmaceutical composition, the method comprising a step in which an inhalable pharmaceutically active material is acoustically blended with excipient material, wherein the acoustic frequency operating range is from 5 Hz to about 1,000 Hz for a period ~~of at least~~ for at least 2 minutes, preferably, wherein the excipient material comprises lactose.

~~51~~49. Use of a resonant acoustic blender for the preparation of an inhalable pharmaceutical composition.

~~52~~50. The use according to claim ~~51~~ 49 in which the composition is an inhalable composition for treatment of respiratory diseases.

~~53~~51. Use of an additive material in a pharmaceutical composition for pulmonary administration, wherein the additive material is suitable for minimising an increase in blend temperature during blending as compared with the blend temperature exhibited by a blend in the absence of said additive material.

~~54. The use according to claim 53,~~ wherein the additive material is selected from amino acid, phospholipid or a metal stearate.

~~55~~52. The use according to claim ~~54~~ 51, wherein the additive material is a metal stearate.

~~56~~53. The use according to claim ~~55~~ 52, wherein the additive material is magnesium stearate or calcium stearate, preferably wherein the additive material is magnesium stearate.

~~57~~54. The use according to claim ~~53~~ 51, wherein the additive material is present in an amount of about 0.1 to about 5% (w/w), preferably from about 1 to about 5% (w/w), preferably about 0.1 to 4% (w/w), preferably about 0.1 to 3% (w/w), preferably about 0.1 to 2% (w/w), preferably about 0.1 to 1% (w/w), more preferably about 0.1 to 0.5% (w/w) of the pharmaceutical composition.

5855. The use according to claims 5351-5754, wherein the blending is performed in an apparatus selected from either a resonant acoustic mixer, a high shear mixer preferably a Diosna or more preferably a TRV high speed mixer, or a low shear mixer preferably a Turbula.

5956. The use according to claim 5855, wherein the blending is performed in a resonant acoustic mixer.