IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VECTURA LIMITED,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 16-638-RGA
	)	
GLAXOSMITHKLINE LLC and GLAXO GROUP LIMITED,	)	
	)	
	)	**JURY TRIAL DEMANDED**
Defendants.	)	

THIRD AMENDED COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Vectura Limited ("Vectura"), for its Third Amended Complaint against Defendants GlaxoSmithKline LLC ("GSK") and Glaxo Group Limited ("GGL") (collectively, "Glaxo"), hereby alleges as follows:

THE PARTIES

1. Vectura is a corporation organized and existing under the laws of the United Kingdom, having its principal place of business at One Prospect West, Chippenham, Wiltshire SN14 6FH, United Kingdom.

2. On information and belief, GlaxoSmithKline LLC is a Delaware limited liability company and has headquarters in Philadelphia, Pennsylvania and Research Triangle Park, North Carolina. GlaxoSmithKline LLC operates as a subsidiary of GlaxoSmithKline plc.

3. On information and belief, Glaxo Group Limited is a corporation organized under the laws of Great Britain, having a principal place of business at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB06 0NN, United Kingdom. Glaxo Group Limited operates as a subsidiary of GlaxoSmithKline plc.

4. On information and belief, Glaxo is in the business of, among other things, manufacturing, marketing, importing, preparing, and selling pharmaceutical products that it distributes in the State of Delaware and throughout the United States.

NATURE OF ACTION

5. This is an action for infringement of United States Patent No. 8,303,991 ("the '991 Patent"), United States Patent No. 8,435,567 ("the '567 Patent"), and United States Patent No. 8,956,661 ("the '661 Patent") under the Patent Laws of the United States, 35 U.S.C. §§ 100 *et seq.*, including 35 U.S.C. § 271(a). A true and correct copy of the '991 Patent is attached as Exhibit A. A true and correct copy of the '567 Patent is attached as Exhibit B. A true and correct copy of the '661 Patent is attached as Exhibit C.

JURISDICTION AND VENUE

6. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338.

7. This Court has personal jurisdiction over GSK because it is a corporation organized and existing under the laws of the State of Delaware, has systematic and continuous contacts with this judicial district, and has committed acts of patent infringement giving rise to this action within this judicial district, including by placing and/or by inducing GGL to place BREO® ELLIPTA® 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder), BREO® ELLIPTA® 200/25 (fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder) (collectively, **"Breo®"**), ANORO® ELLIPTA® (umeclidinium and vilanterol inhalation powder) (**"Anoro®"**), and INCRUSE® ELLIPTA® (umeclidinium inhalation powder) (**"Incruse®"**) products into the stream of commerce in this district, such that GSK reasonably should have anticipated being subject to suit in this judicial district.

8. This Court has personal jurisdiction over GGL because it has committed acts of patent infringement giving rise to this action within this judicial district, including by placing and/or by inducing GSK to place Breo®, Anoro®, and Incruse® products into the stream of commerce in this district, such that GGL reasonably should have anticipated being subject to suit in this judicial district.

9. In the alternative, to the extent that GGL is otherwise not subject to the jurisdiction of this Court or of any other United States District Court, this Court has personal jurisdiction over GGL pursuant to Federal Rule of Civil Procedure 4(k)(2). This complaint arises under federal law and GGL has sufficient contacts with the U.S. as a whole to satisfy due process standards and justify application of federal law because, *inter alia*, GGL (a) directly, or through its subsidiaries, including GSK, manufactures, offers for sale, sells, and/or imports pharmaceutical drug products, including Breo®, Anoro®, and Incruse®, throughout the U.S.; (b) prioritizes investment in the growth of core therapeutic areas in the U.S. as part of its global business plan; (c) carries out global drug development and research in a closely integrated network including the U.S.; and (d) earns substantial revenues from the sales of its products, including Breo®, Anoro®, and Incruse®, in the U.S. On information and belief, GGL purposefully directs, directly or through its subsidiaries, including GSK, marketing and sales of pharmaceutical drug products, including Breo®, Anoro®, and Incruse®, throughout the U.S. Therefore, on information and belief, GGL has contacts with the U.S. sufficient to justify the application of U.S. law and to satisfy federal standards of forum selection.

10. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

FACTUAL BACKGROUND

A. General Background

11. Vectura is the owner of the ’991 Patent, which issued on November 6, 2012 from United States Patent Application No. 12/767,530.

12. Vectura is the owner of the ’567 Patent, which issued on May 7, 2013 from United States Patent Application No. 13/269,025.

13. Vectura is the owner of the ’661 Patent, which issued on February 17, 2015 from United States Patent Application No. 13/623,326.

14. GGL is identified in the Federal Food and Drug Administration (“FDA”) “Orange Book” as the New Drug Application (“NDA”) applicant for Breo®.

15. GSK is identified in the FDA Orange Book as the NDA applicant for Anoro®.

16. “Glaxo Grp England” is identified in the FDA Orange Book as the NDA applicant for Incruse®.

17. On information and belief, “Glaxo Grp England” is GGL.

18. Correspondence between the FDA and Glaxo concerning Breo®, Anoro®, and Incruse® is directed to and from GSK.

19. On information and belief, GSK and GGL have cooperated together in obtaining FDA approval of Breo®, Anoro®, and Incruse® and cooperate together to market and sell Breo®, Anoro®, and Incruse®.

20. Glaxo makes, uses, offers to sell, sells, and/or imports Breo®, Anoro®, and Incruse® within or into the United States, thereby infringing at least claims 1-5, 7, and 9 of the ’991 Patent; at least claims 1-3, 6, and 10-16 of the ’567 Patent; and at least claims 1, 15, 20, 21,

23-24, and 26-27 of the '661 Patent.

21. In 2010, Vectura and GGL (along with another Glaxo entity, GlaxoSmithKline Research & Development Ltd.) entered into a Patent License Agreement (the "Vectura-Glaxo License Agreement") under which Glaxo had the option to identify or "nominate" (on or before July 31, 2016) additional Vectura patents or pending patent applications for inclusion within the scope of the license. On July 26, 2016, Glaxo formally gave notice to Vectura that it would not be nominating any additional patents for inclusion in the license. On July 27, 2016, Vectura filed the initial complaint in this action.

B. Breo®, Anoro®, and Incruse® Infringe the '991 Patent

1. The '991 Patent

22. The '991 Patent is titled *Method of Making Particles for Use in a Pharmaceutical Composition*. The Abstract of the '991 Patent states that:

> The invention relates to a method for making composite active particles for use in a pharmaceutical composition for pulmonary administration, the method comprising a milling step in which particles of active material are milled 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. The invention also relates to compositions for inhalation prepared by the method.

(Ex. A, '991 Patent, Abstract.)

23. The '991 Patent discloses and claims such compositions, with claim 1 reading as follows:

> 1. Composite active particles for use in a pharmaceutical composition for pulmonary administration, each composite active particle comprising
>
> > a particle of active material and particulate additive material on the surface of that particle of active material,

> wherein the composite active particles have a mass median aerodynamic diameter of not more than 10 μm,
>
> and wherein the additive material promotes the dispersion of the composite active particles upon actuation of a delivery device.

(Ex. A, '991 Patent, claim 1, line breaks added for readability.)

24. The remaining claims of the '991 Patent are dependent claims further specifying the identity of the "additive material" (claims 2 and 3), the "mass median aerodynamic diameter" of the active particles (claim 4), the identity of the "active material" and "active particles" (claims 5-6), and claiming pharmaceutical compositions comprising the "composite active particles" of claim 1 (claims 7-10).

25. Upon information and belief, Glaxo was aware of the '991 Patent shortly after it issued and engaged in conversations with Vectura concerning the '991 Patent prior to the filing of this lawsuit. For example, on February 8-9, April 8, and July 2, 2016, the Director of Intellectual Property at Vectura exchanged emails and had discussions with individuals from the Intellectual Property and Business Development departments of Glaxo, discussing potential extension of the Vectura-Glaxo License Agreement to include additional patents. An additional teleconference between Vectura and Glaxo was held on July 25, 2016. These discussions concerned the licensing of U.S. patents infringed by the marketing and sale of Glaxo's FDA-approved drug products in the United States, and upon information and belief the content of these discussions was relayed to relevant persons within Glaxo, including at GSK and GGL. In these discussions Vectura specifically identified the '991 Patent, communicated to Glaxo that its Breo®, Anoro®, and Incruse® products fall within the scope of the '991 Patent claims, provided experimental data to support Vectura's views that those products infringe the '991 Patent, and offered to license the '991 Patent.

2. Breo®

26. On information and belief, Breo® satisfies each and every limitation of at least claims 1-5, 7, and 9 of the ’991 Patent either literally or under the doctrine of equivalents.

27. On information and belief, as specified in all of claims 1-5, 7, and 9 of the ’991 Patent, Breo® contains “[c]omposite active particles for use in a pharmaceutical composition for pulmonary administration, each composite active particle comprising a particle of active material and particulate additive material on the surface of that particle of active material, wherein the composite active particles have a mass median aerodynamic diameter of not more than 10 μm, and wherein the additive material promotes the dispersion of the composite active particles upon actuation of a delivery device.”

28. Specifically, Breo® contains composite active particles comprising particles of vilanterol, an active material, and magnesium stearate, a particulate additive material, on the surface of the vilanterol particles. Claims 1, 4, 5, 7, and 9 specify an “additive material” generally, while claim 2 specifies that the “additive material” includes a “metal stearate,” and claim 3 specifies that the metal stearate is magnesium stearate.

29. On information and belief, as specified in claims 1-5, 7, and 9 of the ’991 Patent, Breo® contains composite active particles having a mass median aerodynamic diameter of not more than 10 μm (claims 1-3, 5, 7, and 9) and not more than 5 μm (claim 4). Specifically, Breo® contains composite active particles having a mass median aerodynamic diameter of between 3 and 4 μm.

30. On information and belief, as specified in claims 1-5, 7, and 9 of the ’991 Patent, the “additive material” in Breo® “promotes the dispersion of the composite active particles upon actuation of a delivery device.” Specifically, magnesium stearate in Breo® promotes dispersion of vilanterol/magnesium stearate composite active particles upon actuation of a delivery device,

namely the Ellipta® delivery device, which is a dry powder inhaler (claim 9). Breo® is a pharmaceutical composition, as specified in claim 7.

31. On information and belief, as specified in claim 5, the active material in Breo® comprises a β_2-agonist, vilanterol.

3. Anoro®

32. On information and belief, Anoro® satisfies each and every limitation of claims 1-5, 7, and 9 of the '991 Patent either literally or under the doctrine of equivalents.

33. On information and belief, as specified in all of claims 1-5, 7, and 9 of the '991 Patent, Anoro® contains "[c]omposite active particles for use in a pharmaceutical composition for pulmonary administration, each composite active particle comprising a particle of active material and particulate additive material on the surface of that particle of active material, wherein the composite active particles have a mass median aerodynamic diameter of not more than 10 μm, and wherein the additive material promotes the dispersion of the composite active particles upon actuation of a delivery device."

34. Specifically, Anoro® contains composite active particles comprising particles of vilanterol and particles of umeclidinium, which are active materials, and magnesium stearate, a particulate additive material, on the surface of the vilanterol and umeclidinium particles. Claims 1, 4, 5, 7, and 9 specify an "additive material" generally, while claim 2 specifies that the "additive material" includes a "metal stearate," and claim 3 specifies that the metal stearate is magnesium stearate.

35. On information and belief, as specified in all of claims 1-5, 7, and 9 of the '991 Patent, Anoro® contains composite active particles having a mass median aerodynamic diameter of not more than 10 μm (claims 1-3, 5, 7, and 9) and not more than 5 μm (claim 4). Specifically,

Anoro® contains composite active particles having a mass median aerodynamic diameter of between 3 and 4 μm.

36. On information and belief, as specified in all of claims 1-5, 7, and 9 of the '991 Patent, the "additive material" in Anoro® "promotes the dispersion of the composite active particles upon actuation of a delivery device." Specifically, magnesium stearate in Anoro® promotes dispersion of vilanterol/magnesium stearate composite active particles and/or umeclidinium/magnesium stearate composite active particles upon actuation of a delivery device, namely the Ellipta® delivery device, which is a dry powder inhaler (claim 9). Anoro® is a pharmaceutical composition, as specified in claim 7.

37. On information and belief, as specified in claim 5, the active material in Anoro® comprises a β_2-agonist, vilanterol.

4. Incruse®

38. On information and belief, Incruse® satisfies each and every limitation of claims 1-4, 7, and 9 of the '991 Patent either literally or under the doctrine of equivalents.

39. On information and belief, as specified in all of claims 1-4, 7, and 9 of the '991 Patent, Incruse® contains "[c]omposite active particles for use in a pharmaceutical composition for pulmonary administration, each composite active particle comprising a particle of active material and particulate additive material on the surface of that particle of active material, wherein the composite active particles have a mass median aerodynamic diameter of not more than 10 μm, and wherein the additive material promotes the dispersion of the composite active particles upon actuation of a delivery device."

40. Specifically, Incruse® contains composite active particles comprising particles of umeclidinium, an active material, and magnesium stearate, a particulate additive material, on the

surface of the umeclidinium particles. Claims 1, 4, 7, and 9 specify an "additive material" generally, while claim 2 specifies that the "additive material" includes a "metal stearate," and claim 3 specifies that the metal stearate is magnesium stearate.

41. On information and belief, as specified in all of claims 1-4, 7, and 9 of the '991 Patent, Incruse® contains composite active particles having a mass median aerodynamic diameter of not more than 10 μm (claims 1-3, 7, and 9) and not more than 5 μm (claim 4). Specifically, Incruse® contains composite active particles having a mass median aerodynamic diameter of between 3 and 4 μm.

42. On information and belief, as specified in all of claims 1-4, 7, and 9 of the '991 Patent, the "additive material" in Incruse® "promotes the dispersion of the composite active particles upon actuation of a delivery device." Specifically, magnesium stearate in Incruse® promotes dispersion of umeclidinium/magnesium stearate composite active particles upon actuation of a delivery device, namely the Ellipta® delivery device, which is a dry powder inhaler (claim 9). Incruse® is a pharmaceutical composition, as specified in claim 7.

C. Breo®, Anoro®, and Incruse® Infringe the '567 Patent

1. The '567 Patent

43. The '567 Patent is titled *Pharmaceutical Compositions of Hydrophobic Surface-Modified Active Substance Microparticles for Inhalation*. The Abstract of the '567 Patent states that:

> The invention provides microparticles for use in a pharmaceutical composition for Pulmonary administration, each microparticle comprising a particle of an active substance having, on its surface, particles of a hydrophobic material suitable for delaying the dissolution of the active substance. The invention also provides a method for making the microparticles.

(Ex. B, '567 Patent, Abstract.)

44. The ’567 Patent discloses and claims such microparticles, with claim 1 reading as follows:

> 1. Microparticles for use in a pharmaceutical composition for pulmonary administration, comprising
>
> particles of an active substance having, on their surfaces,
>
> particles of a hydrophobic material suitable for promoting the dispersal of the active particles on actuation of an inhaler and suitable for delaying the dissolution of the active substance,
>
> wherein the hydrophobic material comprises one or more materials selected from the group consisting of hydrophobic amino acids, metal stearates, a C_{10} to C_{22} carboxylic acid, phospholipids, and derivatives thereof.

(Ex. B, ’567 Patent, claim 1, line breaks added for readability.)

45. The remaining claims of the ’567 Patent are dependent claims further specifying, *inter alia*, the identity of the “hydrophobic material” (claims 2-3), the “mass median aerodynamic diameter” of the microparticles (claim 6), the rate of dissolution of the microparticles (claim 10), the identity of the active substance (claim 11), the manner in which and the extent to which the hydrophobic material coats the surface of the active substance (claims 12-13), that the microparticles are suitable for use in a dry powder inhaler (claim 14), and compositions for inhalation comprising the microparticles of claim 1 (claims 15-16).

46. Upon information and belief, Glaxo was aware of the ’567 Patent shortly after it issued and engaged in conversations with Vectura concerning the ’567 Patent prior to the filing of this lawsuit. For example, on February 8-9, April 8, and July 2, 2016, the Director of Intellectual Property at Vectura exchanged emails and had discussions with individuals from the Intellectual Property and Business Development departments of Glaxo, discussing potential extension of the Vectura-Glaxo License Agreement to include additional patents. An additional

teleconference between Vectura and Glaxo was held on July 25, 2016. These discussions concerned the licensing of U.S. patents infringed by the marketing and sale of Glaxo's FDA-approved drug products in the United States, and upon information and belief the content of these discussions was relayed to relevant persons within Glaxo, including at GSK and GGL. During the July 25, 2016 teleconference , Vectura specifically identified the '567 Patent, communicated to Glaxo that its Breo®, Anoro®, and Incruse® products fall within the scope of the '567 Patent claims, and offered to license the '567 Patent.

2. Breo®

47. On information and belief, Breo® satisfies each and every limitation of at least claims 1-3, 6, and 10-16 of the '567 Patent either literally or under the doctrine of equivalents.

48. On information and belief, as specified in all of claims 1-3, 6, and 10-16 of the '567 Patent, Breo® contains "[m]icroparticles for use in a pharmaceutical composition for pulmonary administration, comprising particles of an active substance having, on their surfaces, particles of a hydrophobic material suitable for promoting the dispersal of the active particles on actuation of an inhaler and suitable for delaying the dissolution of the active substance, wherein the hydrophobic material comprises one or more materials selected from the group consisting of hydrophobic amino acids, metal stearates, a C_{10} to C_{22} carboxylic acid, phospholipids, and derivatives thereof."

49. Specifically, Breo® contains microparticles comprising particles of vilanterol, an active substance, and magnesium stearate, a hydrophobic material, on the surface of the vilanterol particles. Claims 1, 2, 6, and 10-16 specify a hydrophobic material that includes a "metal stearate" and a "C_{10} to C_{22} carboxylic acid," both of which encompass magnesium stearate. Magnesium stearate is a metal stearate, and comprises stearic acid, a C_{18} carboxylic

acid. Claim 3 further specifies that the metal stearate is magnesium stearate.

50. On information and belief, as specified in claims 1-3, 6, and 10-16 of the '567 Patent, the "hydrophobic material" in Breo® is "suitable for promoting the dispersal of the active particles on actuation of an inhaler and suitable for delaying the dissolution of the active substance." Specifically, magnesium stearate in Breo® promotes dispersion and delays the dissolution of vilanterol active particles.

51. On information and belief, as specified in claim 6 of the '567 Patent, Breo® contains microparticles "having a mass median aerodynamic diameter of not more than 10 μm." Specifically, Breo® contains microparticles having a mass median aerodynamic diameter of between 3 and 4 μm.

52. On information and belief, as specified in claim 10 of the '567 Patent, Breo® contains microparticles "having a rate of dissolution no greater than 80% of the rate of dissolution of particles of the active substance."

53. On information and belief, as specified in claim 11 of the '567 Patent, the active substance in Breo® comprises a β-agonist, vilanterol.

54. On information and belief, as specified in claim 12 of the '567 Patent, in Breo® "particles of hydrophobic material are present as a coating on the surface of the particles of active substance," and more specifically, are present as a "discontinuous coating" (claim 13). Specifically, in Breo®, particles of the hydrophobic material magnesium stearate are present as a discontinuous coating on the surface of particles of the active substance vilanterol.

55. On information and belief, as specified in claim 14 of the '567 Patent, Breo® contains microparticles "which are suitable for use in a powder for use in a dry powder inhaler," and as specified in claim 15 of the '567 Patent, Breo® is a composition that is suitable for

inhalation, and more specifically, is a dry powder "suitable for use in a dry powder inhaler" (claim 16). Specifically, Breo® is a composition comprising microparticles of vilanterol/magnesium stearate in powder form that is dispersed from the Ellipta® delivery device, a dry powder inhaler.

3. Anoro®

56. On information and belief, Anoro® satisfies each and every limitation of at least claims 1-3, 6, and 10-16 of the '567 Patent either literally or under the doctrine of equivalents.

57. On information and belief, as specified in all of claims 1-3, 6, and 10-16 of the '567 Patent, Anoro® contains "[m]icroparticles for use in a pharmaceutical composition for pulmonary administration, comprising particles of an active substance having, on their surfaces, particles of a hydrophobic material suitable for promoting the dispersal of the active particles on actuation of an inhaler and suitable for delaying the dissolution of the active substance, wherein the hydrophobic material comprises one or more materials selected from the group consisting of hydrophobic amino acids, metal stearates, a C_{10} to C_{22} carboxylic acid, phospholipids, and derivatives thereof."

58. Specifically, Anoro® contains microparticles comprising particles of vilanterol and particles of umeclidinium, which are active substances, and magnesium stearate, a hydrophobic material, on the surface of the vilanterol and umeclidinium particles. Claims 1, 2, 6, and 10-16 specify a hydrophobic material that includes a "metal stearate" and a "C_{10} to C_{22} carboxylic acid," both of which encompass magnesium stearate. Magnesium stearate is a metal stearate, and comprises stearic acid, a C_{18} carboxylic acid. Claim 3 further specifies that the metal stearate is magnesium stearate.

59. On information and belief, as specified in claims 1-3, 6, and 10-16 of the '567

Patent, the "hydrophobic material" in Anoro® is "suitable for promoting the dispersal of the active particles on actuation of an inhaler and suitable for delaying the dissolution of the active substance." Specifically, magnesium stearate in Anoro® promotes dispersion and delays the dissolution of vilanterol active particles, and on information and belief promotes dispersion and delays the dissolution of umeclidinium active particles.

60. On information and belief, as specified in claim 6 of the '567 Patent, Anoro® contains microparticles "having a mass median aerodynamic diameter of not more than 10 μm." Specifically, Anoro® contains microparticles having a mass median aerodynamic diameter of between 3 and 4 μm.

61. On information and belief, as specified in claim 10 of the '567 Patent, Anoro® contains microparticles "having a rate of dissolution no greater than 80% of the rate of dissolution of particles of the active substance."

62. On information and belief, as specified in claim 11 of the '567 Patent, the active substance in Anoro® comprises a β-agonist, vilanterol, and an antimuscarinic agent, umeclidinium.

63. On information and belief, as specified in claim 12 of the '567 Patent, in Anoro® "particles of hydrophobic material are present as a coating on the surface of the particles of active substance," and more specifically, are present as a "discontinuous coating" (claim 13). Specifically, in Anoro®, particles of the hydrophobic material magnesium stearate are present as a discontinuous coating on the surface of particles of the active substance vilanterol and on the surface of particles of the active substance umeclidinium.

64. On information and belief, as specified in claim 14 of the '567 Patent, Anoro® contains microparticles "which are suitable for use in a powder for use in a dry powder inhaler,"

and as specified in claim 15 of the ’567 Patent, Anoro® is a composition that is suitable for inhalation, and more specifically, is a dry powder “suitable for use in a dry powder inhaler” (claim 16). Specifically, Anoro® is a composition comprising microparticles of vilanterol and magnesium stearate, and microparticles of umeclidinium and magnesium stearate, in powder form that is dispersed from the Ellipta® delivery device, a dry powder inhaler.

4. Incruse®

65. On information and belief, Incruse® satisfies each and every limitation of at least claims 1-3, 6, and 11-16 of the ’567 Patent either literally or under the doctrine of equivalents.

66. On information and belief, as specified in all of claims 1-3, 6, and 11-16 of the ’567 Patent, Incruse® contains “[m]icroparticles for use in a pharmaceutical composition for pulmonary administration, comprising particles of an active substance having, on their surfaces, particles of a hydrophobic material suitable for promoting the dispersal of the active particles on actuation of an inhaler and suitable for delaying the dissolution of the active substance, wherein the hydrophobic material comprises one or more materials selected from the group consisting of hydrophobic amino acids, metal stearates, a C_{10} to C_{22} carboxylic acid, phospholipids, and derivatives thereof.”

67. Specifically, Incruse® contains microparticles comprising particles of umeclidinium, an active substance, and magnesium stearate, a hydrophobic material, on the surface of the umeclidinium particles. Claims 1, 2, 6, and 11-16 specify a hydrophobic material that includes a “metal stearate” and a “C_{10} to C_{22} carboxylic acid,” both of which encompass magnesium stearate. Magnesium stearate is a metal stearate, and comprises stearic acid, a C_{18} carboxylic acid. Claim 3 further specifies that the metal stearate is magnesium stearate.

68. On information and belief, as specified in claims 1-3, 6, and 11-16 of the ’567

Patent, the "hydrophobic material" in Incruse® is "suitable for promoting the dispersal of the active particles on actuation of an inhaler and suitable for delaying the dissolution of the active substance." Specifically, on information and belief, magnesium stearate in Incruse® promotes dispersion and delays the dissolution of umeclidinium active particles.

69. On information and belief, as specified in claim 6 of the '567 Patent, Incruse® contains microparticles "having a mass median aerodynamic diameter of not more than 10 μm." Specifically, Incruse® contains microparticles having a mass median aerodynamic diameter of between 3 and 4 μm.

70. On information and belief, as specified in claim 11 of the '567 Patent, the active substance in Incruse® comprises an antimuscarinic agent, umeclidinium.

71. On information and belief, as specified in claim 12 of the '567 Patent, in Incruse® "particles of hydrophobic material are present as a coating on the surface of the particles of active substance," and more specifically, are present as a "discontinuous coating" (claim 13). Specifically, in Incruse®, particles of the hydrophobic material magnesium stearate are present as a discontinuous coating on the surface of particles of the active substance umeclidinium.

72. On information and belief, as specified in claim 14 of the '567 Patent, Incruse® contains microparticles "which are suitable for use in a powder for use in a dry powder inhaler," and as specified in claim 15 of the '567 Patent, Incruse® is a composition that is suitable for inhalation, and more specifically, is a dry powder "suitable for use in a dry powder inhaler" (claim 16). Specifically, Incruse® is a composition comprising microparticles of umeclidinium and magnesium stearate in powder form that is dispersed from the Ellipta® delivery device, a dry powder inhaler.

D. Breo®, Anoro®, and Incruse® Infringe the '661 Patent

1. The '661 Patent

73. The '661 Patent is titled *Method of Making Composite Particles for Use in Pharmaceutical Compositions and Composite Particles and Compositions Thereof*. The Abstract of the '661 Patent states that:

> The invention relates to a method for making composite active particles for use in a pharmaceutical composition for pulmonary administration, the method comprising a milling step in which particles of active material are milled 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. The invention also relates to compositions for inhalation prepared by the method.

(Ex. C, '661 Patent, Abstract.)

74. The '661 Patent discloses and claims a method for making composite active particles, with independent claim 1 reading as follows:

> 1. A method for making composite active particles for use in a pharmaceutical composition for pulmonary administration, the method comprising a milling step in which particles of active material are milled 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 wherein the mass median aerodynamic diameter of the composite active particles is not more than 10 μm after milling.

(Ex. C, '661 Patent, claim 1.)

75. Dependent claims of the '661 Patent further specify that the additive material comprises a metal stearate (claim 15), composite active particles for use in a pharmaceutical composition as made by the method of claim 1 (claim 20), a pharmaceutical composition comprising composite active particles as made by a method according to claim 1 (claim 26), and

such a pharmaceutical composition which is a dry powder and is suitable for use in a dry powder inhaler (claim 27).

76. The ’661 Patent also discloses and claims composite active particles, with independent claim 21 reading as follows:

> 21. Composite active particles for use in a pharmaceutical composition for pulmonary administration, each composite active particle comprising a particle of active material and particulate additive material on the surface of that particle of active material, the composite active particles having a mass median aerodynamic diameter of not more than 9 μm and the additive material being suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device.

(Ex. C, ’661 Patent, claim 21.)

77. Dependent claims of the ’661 Patent further specify that the additive particles form a coating on the surfaces of the particles of active material (claim 23) and that the coating is a discontinuous coating (claim 24).

2. Breo®

78. On information and belief, Breo® satisfies each and every limitation of at least claims 1, 15, 20, 21, 23-24, and 26-27 of the ’661 Patent either literally or under the doctrine of equivalents.

79. On information and belief, as specified in all of claims 1, 15, 20, and 26-27 of the ’661 Patent, Breo® contains “composite active particles for use in a pharmaceutical composition for pulmonary administration,” made by a “method comprising a milling step in which particles of active material are milled 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

wherein the mass median aerodynamic diameter of the composite active particles is not more than 10 μm after milling."

80. Specifically, Breo® contains composite active particles made by milling particles of vilanterol, an active material, in the presence of magnesium stearate, an additive material. Claim 15 specifies an additive material comprising a "metal stearate," which encompasses magnesium stearate.

81. On information and belief, as specified in claims 1, 15, 20, and 26-27 of the '661 Patent, the "additive material" in Breo® is "suitable for the promotion of the dispersal of the composite active particles upon actuation of an inhaler." Specifically, magnesium stearate in Breo® is suitable for promoting dispersal.

82. On information and belief, as specified in claims 1, 15, 20, and 26-27 of the '661 Patent, Breo® contains composite active particles "wherein the mass median aerodynamic diameter of the composite active particles is not more than 10 μm after milling." Specifically, Breo® contains composite active particles having a mass median aerodynamic diameter of between 3 and 4 μm.

83. On information and belief, as specified in claims 20 and 26-27 of the '661 Patent, Breo® contains composite active particles for use in a pharmaceutical composition which is a dry powder and is suitable for use in a dry powder inhaler. Specifically, Breo® is a composition comprising composite active particles of vilanterol/magnesium stearate in powder form that is dispersed from the Ellipta® delivery device, a dry powder inhaler.

84. On information and belief, as specified in claim 21 of the '661 Patent, Breo® contains "[c]omposite active particles for use in a pharmaceutical composition for pulmonary administration, each composite active particle comprising a particle of active material and

particulate additive material on the surface of that particle of active material, the composite active particles having a mass median aerodynamic diameter of not more than 9 μm and the additive material being suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device."

85. Specifically, Breo® contains composite active particles comprising particles of vilanterol, an active material, and magnesium stearate, an additive material, on the surface of the vilanterol particles.

86. On information and belief, as specified in claim 21 of the '661 Patent, the "additive material" in Breo® is "suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device." Specifically, magnesium stearate in Breo® is suitable for promoting dispersal.

87. On information and belief, as specified in claim 21 of the '661 Patent, Breo® contains composite active particles "having a mass median aerodynamic diameter of not more than 9 μm."

88. On information and belief, as specified in claims 23-24 of the '661 Patent, Breo® contains composite active particles "in which the additive particles form a coating on the surfaces of the particles of active material" (claim 23), and "in which the coating is a discontinuous coating" (claim 24). Specifically, in Breo®, particles of the additive material magnesium stearate are present as a discontinuous coating on the surface of particles of the active material vilanterol.

3. Anoro®

89. On information and belief, Anoro® satisfies each and every limitation of at least claims 1, 15, 20, 21, 23-24, and 26-27 of the '661 Patent either literally or under the doctrine of

equivalents.

90. On information and belief, as specified in all of claims 1, 15, 20, and 26-27 of the '661 Patent, Anoro® contains "composite active particles for use in a pharmaceutical composition for pulmonary administration," made by a "method comprising a milling step in which particles of active material are milled 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 wherein the mass median aerodynamic diameter of the composite active particles is not more than 10 μm after milling."

91. Specifically, Anoro® contains composite active particles made by milling particles of vilanterol and umeclidinium, which are active materials, in the presence of magnesium stearate, an additive material. Claim 15 specifies an additive material comprising a "metal stearate," which encompasses magnesium stearate.

92. On information and belief, as specified in claims 1, 15, 20, and 26-27 of the '661 Patent, the "additive material" in Anoro® is "suitable for the promotion of the dispersal of the composite active particles upon actuation of an inhaler." Specifically, magnesium stearate in Anoro® is suitable for promoting dispersal.

93. On information and belief, as specified in claims 1, 15, 20, and 26-27 of the '661 Patent, Anoro® contains composite active particles "wherein the mass median aerodynamic diameter of the composite active particles is not more than 10 μm after milling." Specifically, Anoro® contains composite active particles having a mass median aerodynamic diameter of between 3 and 4 μm.

94. On information and belief, as specified in claims 20 and 26-27 of the '661 Patent, Anoro® contains composite active particles for use in a pharmaceutical composition which is a

dry powder and is suitable for use in a dry powder inhaler. Specifically, Anoro® is a composition comprising composite active particles of vilanterol and magnesium stearate, and composite active particles of umeclidinium and magnesium stearate, in powder form that is dispersed from the Ellipta® delivery device, a dry powder inhaler.

95. On information and belief, as specified in claim 21 of the '661 Patent, Anoro® contains "[c]omposite active particles for use in a pharmaceutical composition for pulmonary administration, each composite active particle comprising a particle of active material and particulate additive material on the surface of that particle of active material, the composite active particles having a mass median aerodynamic diameter of not more than 9 μm and the additive material being suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device."

96. Specifically, Anoro® contains composite active particles comprising particles of magnesium stearate, an additive material, on the surface of particles of the active material vilanterol and on the surface of particles of the active material umeclidinium.

97. On information and belief, as specified in claim 21 of the '661 Patent, the "additive material" in Anoro® is "suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device." Specifically, magnesium stearate in Anoro® is suitable for promoting dispersal.

98. On information and belief, as specified in claim 21 of the '661 Patent, Anoro® contains composite active particles "having a mass median aerodynamic diameter of not more than 9 μm."

99. On information and belief, as specified in claims 23-24 of the '661 Patent, Anoro® contains composite active particles "in which the additive particles form a coating on

the surfaces of the particles of active material" (claim 23), and "in which the coating is a discontinuous coating" (claim 24). Specifically, in Anoro®, particles of the additive material magnesium stearate are present as a discontinuous coating on the surface of particles of the active material vilanterol and on the surface of particles of the active material umeclidinium.

4. Incruse®

100. On information and belief, Incruse® satisfies each and every limitation of at least claims 1, 15, 20, 21, 23-24, and 26-27 of the '661 Patent either literally or under the doctrine of equivalents.

101. On information and belief, as specified in all of claims 1, 15, 20, and 26-27 of the '661 Patent, Incruse® contains "composite active particles for use in a pharmaceutical composition for pulmonary administration," made by a "method comprising a milling step in which particles of active material are milled 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 wherein the mass median aerodynamic diameter of the composite active particles is not more than 10 μm after milling."

102. Specifically, Incruse® contains composite active particles made by milling particles of umeclidinium, an active material, in the presence of magnesium stearate, an additive material. Claim 15 specifies an additive material comprising a "metal stearate," which encompasses magnesium stearate.

103. On information and belief, as specified in claims 1, 15, 20, and 26-27 of the '661 Patent, the "additive material" in Incruse® is "suitable for the promotion of the dispersal of the composite active particles upon actuation of an inhaler." Specifically, magnesium stearate in Incruse® is suitable for promoting dispersal.

104. On information and belief, as specified in claims 1, 15, 20, and 26-27 of the '661 Patent, Incruse® contains composite active particles "wherein the mass median aerodynamic diameter of the composite active particles is not more than 10 μm after milling." Specifically, Incruse® contains composite active particles having a mass median aerodynamic diameter of between 3 and 4 μm.

105. On information and belief, as specified in claims 20 and 26-27 of the '661 Patent, Incruse® contains composite active particles for use in a pharmaceutical composition which is a dry powder and is suitable for use in a dry powder inhaler. Specifically, Incruse® is a composition comprising composite active particles of umeclidinium/magnesium stearate in powder form that is dispersed from the Ellipta® delivery device, a dry powder inhaler.

106. On information and belief, as specified in all of claim 21 of the '661 Patent, Incruse® contains "[c]omposite active particles for use in a pharmaceutical composition for pulmonary administration, each composite active particle comprising a particle of active material and particulate additive material on the surface of that particle of active material, the composite active particles having a mass median aerodynamic diameter of not more than 9 μm and the additive material being suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device."

107. Specifically, Incruse® contains composite active particles comprising particles of umeclidinium, an active material, and magnesium stearate, an additive material, on the surface of the umeclidinium particles.

108. On information and belief, as specified in claim 21 of the '661 Patent, the "additive material" in Incruse® is "suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device." Specifically, magnesium stearate in

Incruse® is suitable for promoting dispersal.

109. On information and belief, as specified in claim 21 of the ’661 Patent, Incruse® contains composite active particles “having a mass median aerodynamic diameter of not more than 9 μm.”

110. On information and belief, as specified in claims 23-24 of the ’661 Patent, Incruse® contains composite active particles “in which the additive particles form a coating on the surfaces of the particles of active material” (claim 23), and “in which the coating is a discontinuous coating” (claim 24). Specifically, in Incruse®, particles of the additive material magnesium stearate are present as a discontinuous coating on the surface of particles of the active material umeclidinium.

COUNT I

Infringement of the ’991 Patent – Breo®

111. Plaintiffs incorporate each of the preceding paragraphs 11 to 31 as if fully set forth herein.

112. For the reasons set forth in detail above, Glaxo’s manufacture, use, offer for sale, sale, and/or importation of Breo® constitutes infringement of at least claims 1-5, 7, and 9 of the ’991 Patent under 35 U.S.C. § 271(a).

113. Glaxo’s infringement is willful. As set forth above in paragraph 25, prior to the filing of the complaint Glaxo had knowledge of the existence of the ’991 Patent and knowledge that its manufacture, use, offer for sale, sale, and/or importation of Breo® without a license infringes one or more claims of the ’991 Patent. This is an exceptional case.

COUNT II

Infringement of the ’991 Patent – Anoro®

114. Plaintiffs incorporate each of the preceding paragraphs 11 to 25 and 32 to 37 as if fully set forth herein.

115. For the reasons set forth in detail above, Glaxo’s manufacture, use, offer for sale, sale, and/or importation of Anoro® constitutes infringement of at least claims 1-5, 7, and 9 of the ’991 Patent under 35 U.S.C. § 271(a).

116. Glaxo’s infringement is willful. As set forth above in paragraph 25, prior to the filing of the complaint Glaxo had knowledge of the existence of the ’991 Patent and knowledge that its manufacture, use, offer for sale, sale, and/or importation of Anoro® without a license infringes one or more claims of the ’991 Patent. This is an exceptional case.

COUNT III

Infringement of the ’991 Patent – Incruse®

117. Plaintiffs incorporate each of the preceding paragraphs 11 to 25 and 38 to 42 as if fully set forth herein.

118. For the reasons set forth in detail above, Glaxo’s manufacture, use, offer for sale, sale, and/or importation of Incruse® constitutes infringement of at least claims 1-4, 7, and 9 of the ’991 Patent under 35 U.S.C. § 271(a).

119. Glaxo’s infringement is willful. As set forth above in paragraph 25, prior to the filing of the complaint Glaxo had knowledge of the existence of the ’991 Patent and knowledge that its manufacture, use, offer for sale, sale, and/or importation of Incruse® without a license infringes one or more claims of the ’991 Patent. This is an exceptional case.

COUNT IV

Infringement of the ’567 Patent – Breo®

120. Plaintiffs incorporate each of the preceding paragraphs 11 to 21 and 43 to 55 as if fully set forth herein.

121. For the reasons set forth in detail above, Glaxo’s manufacture, use, offer for sale, sale, and/or importation of Breo® constitutes infringement of at least claims 1-3, 6, and 10-16 of the ’567 Patent under 35 U.S.C. § 271(a).

122. Glaxo’s infringement is willful. As set forth above in paragraph 46, prior to the filing of the complaint Glaxo had knowledge of the existence of the ’567 Patent and knowledge that its manufacture, use, offer for sale, sale, and/or importation of Breo® without a license infringes one or more claims of the ’567 Patent. This is an exceptional case.

COUNT V

Infringement of the ’567 Patent – Anoro®

123. Plaintiffs incorporate each of the preceding paragraphs 11 to 21, 43 to 46, and 56 to 64 as if fully set forth herein.

124. For the reasons set forth in detail above, Glaxo’s manufacture, use, offer for sale, sale, and/or importation of Anoro® constitutes infringement of at least claims 1-3, 6, and 10-16 of the ’567 Patent under 35 U.S.C. § 271(a).

125. Glaxo’s infringement is willful. As set forth above in paragraph 46, prior to the filing of the complaint Glaxo had knowledge of the existence of the ’567 Patent and knowledge that its manufacture, use, offer for sale, sale, and/or importation of Anoro® without a license infringes one or more claims of the ’567 Patent. This is an exceptional case.

COUNT VI

Infringement of the ’567 Patent – Incruse®

126. Plaintiffs incorporate each of the preceding paragraphs 11 to 21, 43 to 46, and 65 to 72 as if fully set forth herein.

127. For the reasons set forth in detail above, Glaxo’s manufacture, use, offer for sale, sale, and/or importation of Incruse® constitutes infringement of at least claims 1-3, 6, and 11-16 of the ’567 Patent under 35 U.S.C. § 271(a).

128. Glaxo’s infringement is willful. As set forth above in paragraph 46, prior to the filing of the complaint Glaxo had knowledge of the existence of the ’567 Patent and knowledge that its manufacture, use, offer for sale, sale, and/or importation of Incruse® without a license infringes one or more claims of the ’567 Patent. This is an exceptional case.

COUNT VII

Infringement of the ’661 Patent – Breo®

129. Plaintiffs incorporate each of the preceding paragraphs 11 to 21 and 73 to 88 as if fully set forth herein.

130. For the reasons set forth in detail above, Glaxo’s manufacture, use, offer for sale, sale, and/or importation of Breo® constitutes infringement of at least claims 1, 15, 20, 21, 23-24, and 26-27 of the ’661 Patent under 35 U.S.C. § 271(a).

COUNT VIII

Infringement of the ’661 Patent – Anoro®

131. Plaintiffs incorporate each of the preceding paragraphs 11 to 21, 73 to 77, and 89 to 99 as if fully set forth herein.

132. For the reasons set forth in detail above, Glaxo’s manufacture, use, offer for sale,

sale, and/or importation of Anoro® constitutes infringement of at least claims 1, 15, 20, 21, 23-24, and 26-27 of the '661 Patent under 35 U.S.C. § 271(a).

COUNT IX

Infringement of the '661 Patent – Incruse®

133. Plaintiffs incorporate each of the preceding paragraphs 11 to 21, 73 to 77, and 100 to 110 as if fully set forth herein.

134. For the reasons set forth in detail above, Glaxo's manufacture, use, offer for sale, sale, and/or importation of Incruse® constitutes infringement of at least claims 1, 15, 20, 21, 23-24, and 26-27 of the '661 Patent under 35 U.S.C. § 271(a).

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully requests the following relief:

A. that judgment be entered that Glaxo has infringed and is infringing the '991 Patent through the manufacture, use, offer for sale, sale, and/or importation of Breo®;

B. that judgment be entered that Glaxo has infringed and is infringing the '991 Patent through the manufacture, use, offer for sale, sale, and/or importation of Anoro®;

C. that judgment be entered that Glaxo has infringed and is infringing the '991 Patent through the manufacture, use, offer for sale, sale, and/or importation of Incruse®;

D. that judgment be entered that Glaxo's infringement of the '991 Patent has been willful;

E. that damages or other monetary relief be awarded to Vectura as appropriate with respect to Glaxo's past infringement and any continuing or future infringement of the '991 Patent;

F. that judgment be entered that Glaxo has infringed and is infringing the ’567 Patent through the manufacture, use, offer for sale, sale, and/or importation of Breo®;

G. that judgment be entered that Glaxo has infringed and is infringing the ’567 Patent through the manufacture, use, offer for sale, sale, and/or importation of Anoro®;

H. that judgment be entered that Glaxo has infringed and is infringing the ’567 Patent through the manufacture, use, offer for sale, sale, and/or importation of Incruse®;

I. that judgment be entered that Glaxo’s infringement of the ’567 Patent has been willful;

J. that damages or other monetary relief be awarded to Vectura as appropriate with respect to Glaxo’s past infringement and any continuing or future infringement of the ’567 Patent;

K. that judgment be entered that Glaxo has infringed and is infringing the ’661 Patent through the manufacture, use, offer for sale, sale, and/or importation of Breo®;

L. that judgment be entered that Glaxo has infringed and is infringing the ’661 Patent through the manufacture, use, offer for sale, sale, and/or importation of Anoro®;

M. that judgment be entered that Glaxo has infringed and is infringing the ’661 Patent through the manufacture, use, offer for sale, sale, and/or importation of Incruse®;

N. that damages or other monetary relief be awarded to Vectura as appropriate with respect to Glaxo’s past infringement and any continuing or future infringement of the ’661 Patent;

O. that a declaration be issued that this is an exceptional case and an award of reasonable attorneys’ fees pursuant to 35 U.S.C. § 285;

P. costs and expenses in this action; and

Q. such other and further relief as the Court may deem just and proper.

DEMAND FOR JURY TRIAL

Vectura hereby demands trial by jury on all claims and issues so triable.

/s/ Kelly E. Farnan

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Dated: June 19, 2017

EXHIBIT A

US008303991B2

(12) **United States Patent**
Staniforth et al.

(10) **Patent No.: US 8,303,991 B2**
(45) **Date of Patent: *Nov. 6, 2012**

(54) **METHOD OF MAKING PARTICLES FOR USE IN A PHARMACEUTICAL COMPOSITION**

(75) Inventors: **John Staniforth**, Bath (GB); **Matthew Michael James Green**, Surrey (GB); **David Alexander Vodden Morton**, Bath (GB)

(73) Assignee: **Vectura Limited**, Wiltshire (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/767,530**

(22) Filed: **Apr. 26, 2010**

(65) **Prior Publication Data**

US 2010/0209358 A1 Aug. 19, 2010

Related U.S. Application Data

(63) Continuation of application No. 10/433,072, filed as application No. PCT/GB01/05315 on Nov. 30, 2001, now Pat. No. 7,736,670.

(30) **Foreign Application Priority Data**

Nov. 30, 2000	(GB)	0029261.5
Dec. 19, 2000	(GB)	0030946.8
Apr. 9, 2001	(WO)	PCT/GB01/01606
Oct. 5, 2001	(GB)	0124010.0

(51) **Int. Cl.**

A61K 9/14	(2006.01)
A61K 31/04	(2006.01)
A61K 31/045	(2006.01)
A61K 31/40	(2006.01)
A61K 47/00	(2006.01)

(52) **U.S. Cl.** **424/489**; 514/408; 514/728; 514/741; 514/784; 514/785; 514/788

(58) **Field of Classification Search** 424/489; 514/408, 728, 741, 784, 785, 788

See application file for complete search history.

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Primary Examiner — James H. Alstrum-Acevedo

(74) *Attorney, Agent, or Firm* — Reed Smith LLP; William J. McNichol, Jr.; Maryellen Feehery Hank

(57) **ABSTRACT**

The invention relates to a method for making composite active particles for use in a pharmaceutical composition for pulmonary administration, the method comprising a milling step in which particles of active material are milled 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. The invention also relates to compositions for inhalation prepared by the method.

10 Claims, 6 Drawing Sheets

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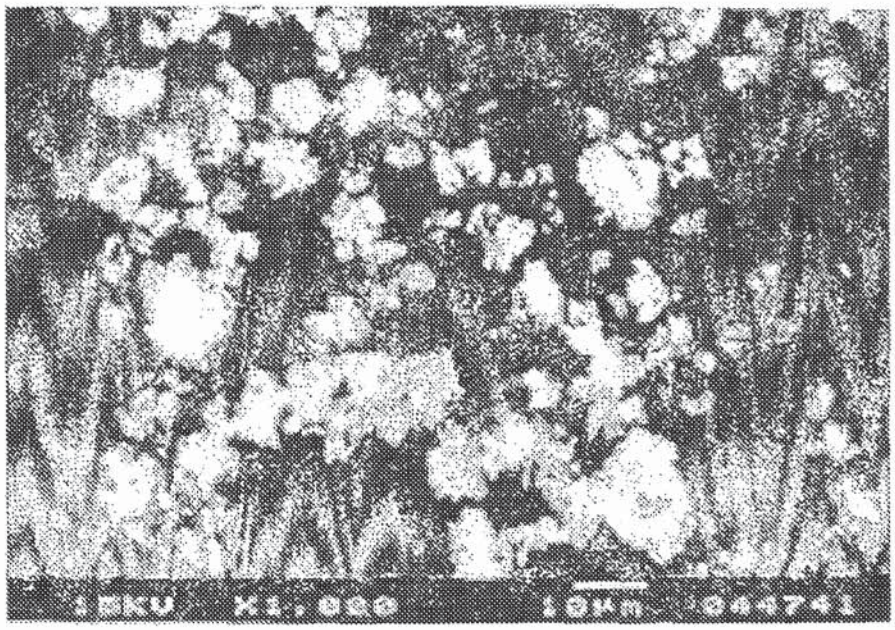


Fig 1

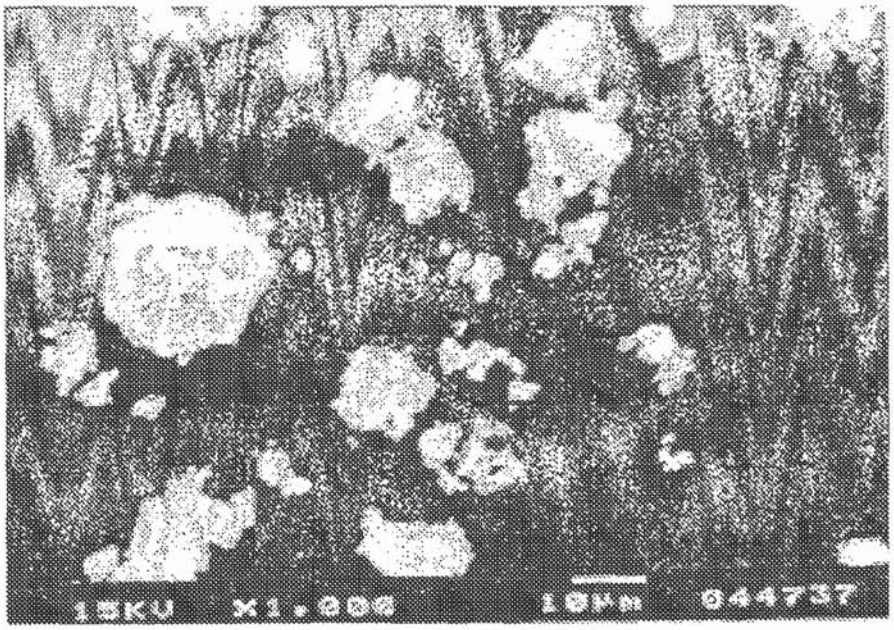


Fig 2

Fig 3

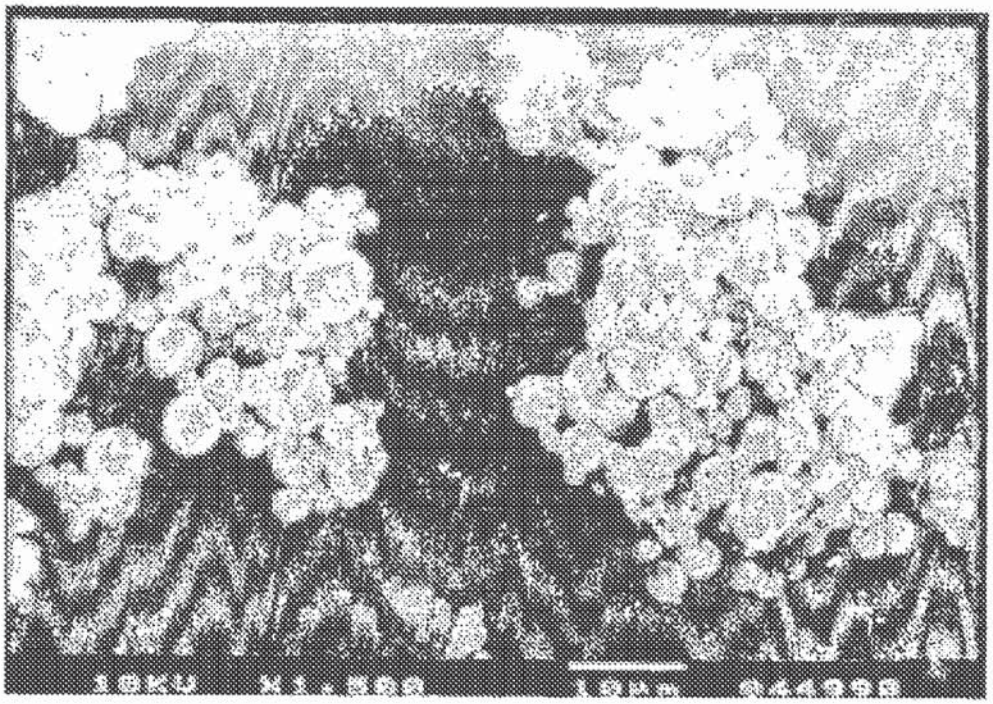


Fig 4

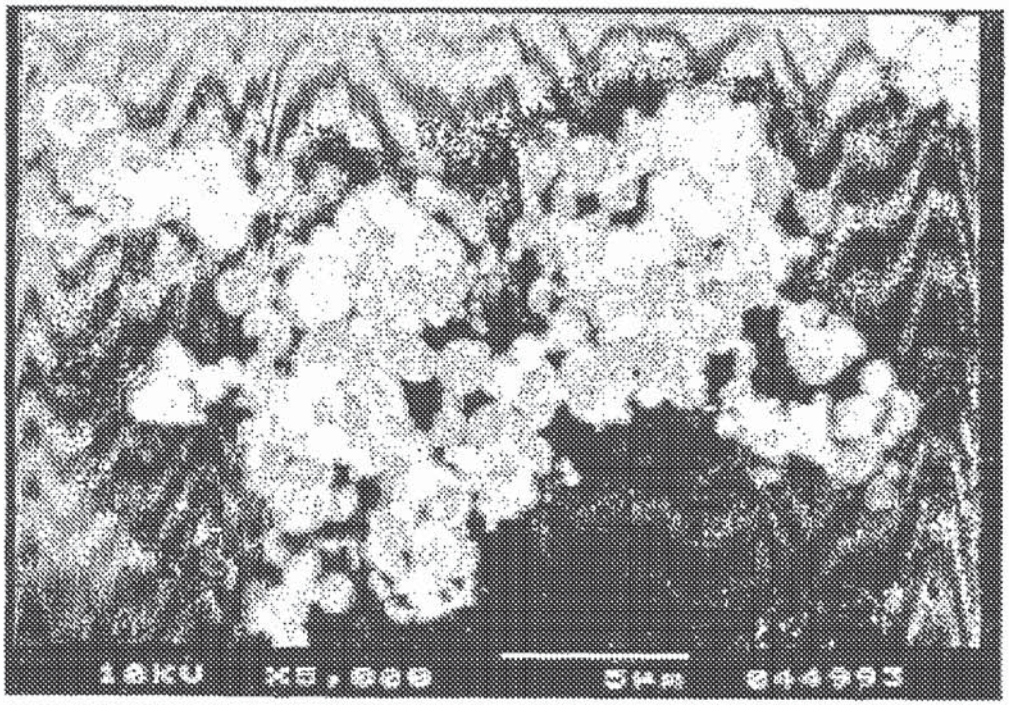


Fig 5

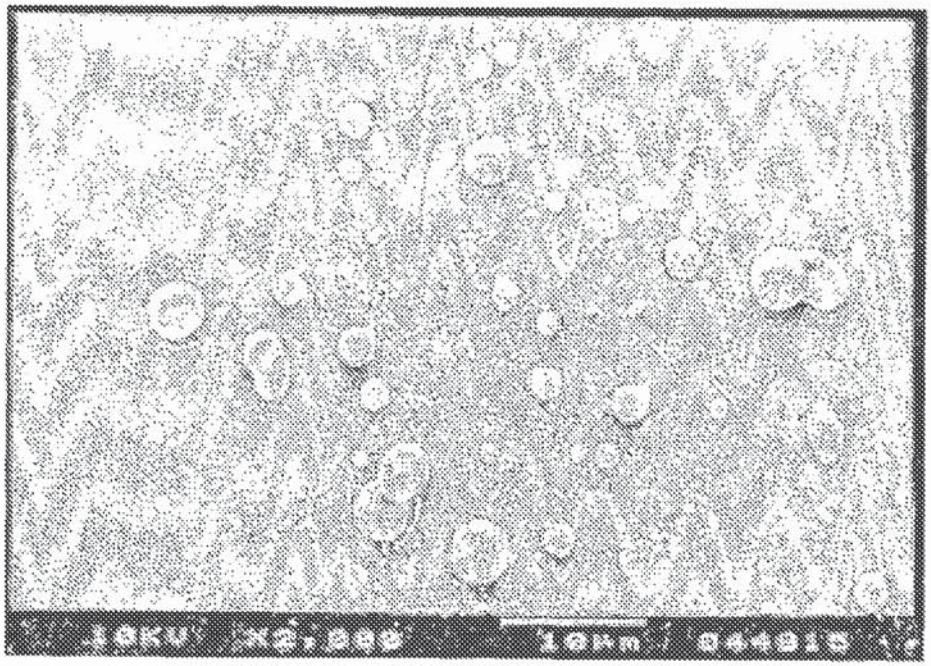


Fig 6

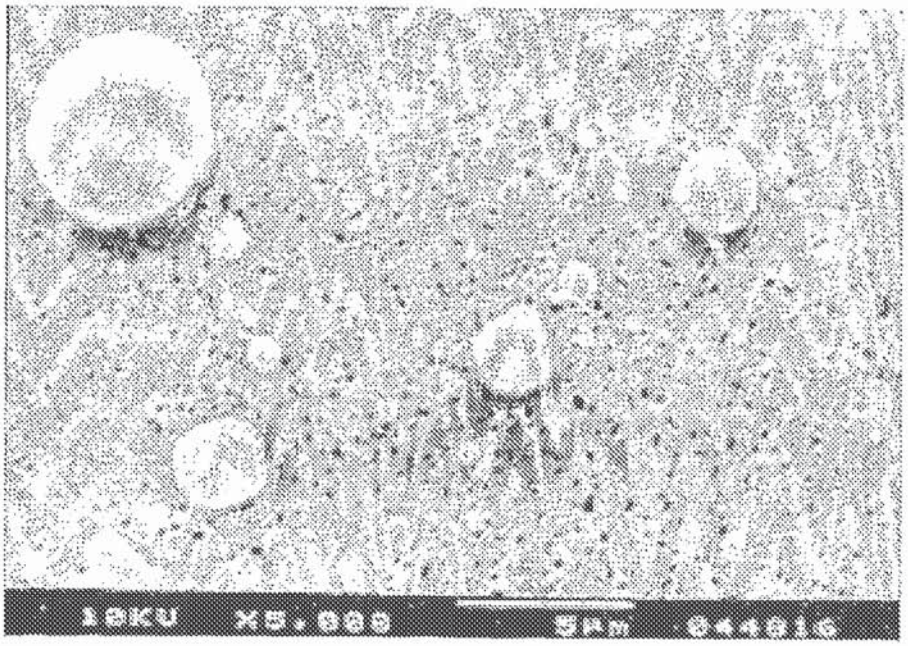
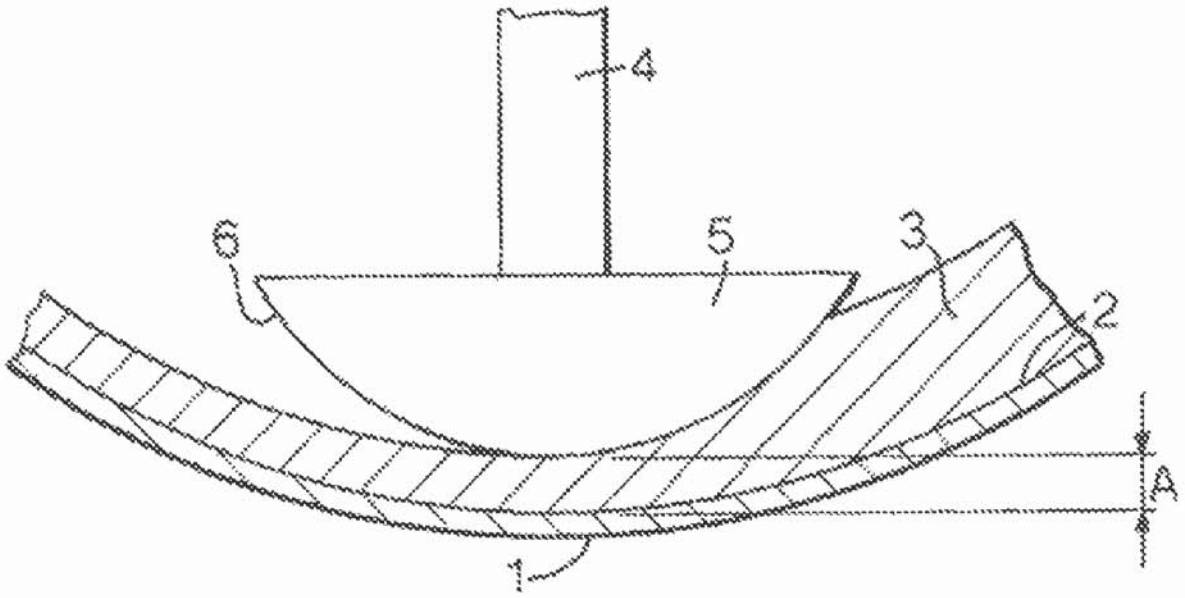


Fig 7

Fig.8.



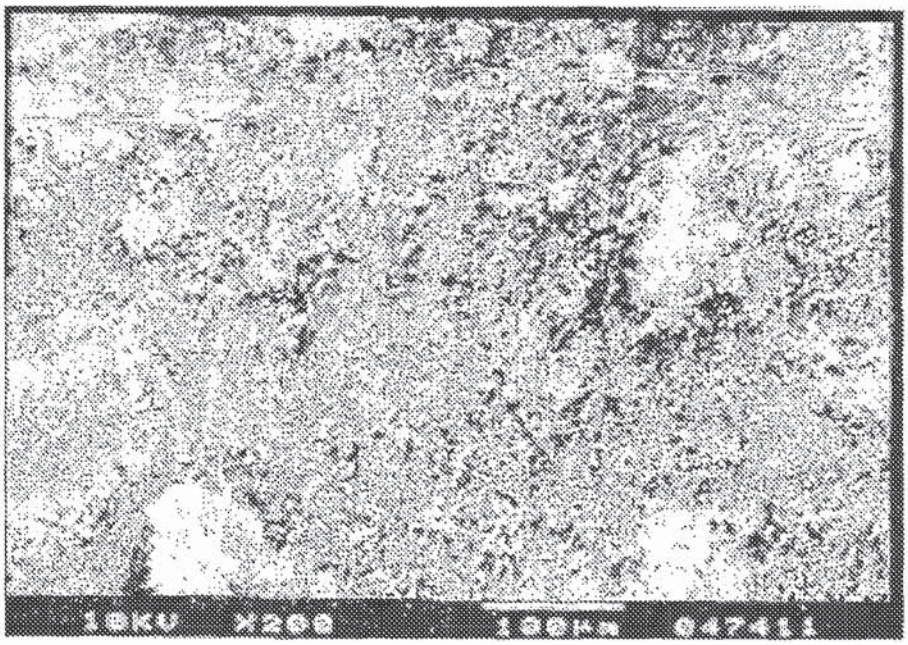


Fig 9

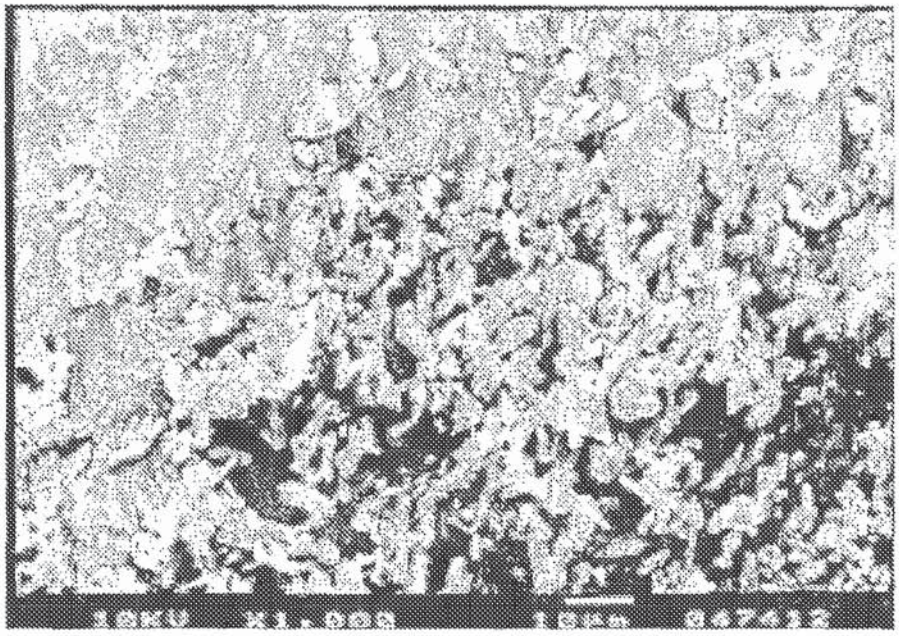


Fig 10

METHOD OF MAKING PARTICLES FOR USE IN A PHARMACEUTICAL COMPOSITION

This application is a continuation application of U.S. patent application Ser. No. 10/433,072, filed Sep. 12, 2003, which is a national stage application of PCT/GB01/05315, filed Nov. 30, 2001, the disclosures of which are hereby incorporated by reference in their entireties.

The present invention relates to particles and to methods of making particles. In particular, the invention relates to methods of making composite active particles comprising a pharmaceutically active material for inhalation.

It is known to administer to patients drugs in the form of fine particles (active particles). For example, in pulmonary administration a particulate medicament composition is inhaled by the patient. Pulmonary administration is particularly suitable for medicaments which are intended to cure or alleviate respiratory conditions such as asthma and for medicaments which are not suitable for oral ingestion such as certain biological macromolecules. Known devices for the administration of drugs to the respiratory system include pressurised metered dose inhalers (pMDI's) and dry powder inhalers (DPI's).

The size of the active particles is of great importance in determining the site of the absorption. In order that the particles be carried deep into the lungs, the particles must be very fine, for example having a mass median aerodynamic diameter of less than 10 μm. Particles having aerodynamic diameters greater than 10 μm are likely to impact the walls of the throat and generally do not reach the lung. Particles having aerodynamic diameters in the range of 5 μm to 0.5 μm will generally be deposited in the respiratory bronchioles whereas smaller particles having aerodynamic diameters in the range of 2 to 0.05 μm are likely to be deposited in the alveoli.

Such small particles are, however, thermodynamically unstable due to their high surface area to volume ratio, which provides significant excess surface free energy and encourages particles to agglomerate. In the inhaler, agglomeration of small particles and adherence of particles to the walls of the inhaler are problems that result in the active particles leaving the inhaler as large agglomerates or being unable to leave the inhaler and remaining adhered to the interior of the inhaler.

In an attempt to improve that situation, dry powders for use in dry powder inhalers often include particles of an excipient material mixed with the fine particles of active material. Such particles of excipient material may be coarse, for example, having mass median aerodynamic diameters greater than 90μ, (such coarse particles are referred to as carrier particles) or they may be fine.

The step of dispersing the active particles from other active particles and from particles of excipient material, if present, to form an aerosol of fine active particles for inhalation is significant in determining the proportion of the dose of active material which reaches the desired site of absorption in the lungs. In order to improve the efficiency of that dispersal it is known to include in the composition additive materials. Such additive materials are thought to reduce the attractive forces between the particles thereby promoting their dispersal. Compositions comprising fine active particles and additive materials are disclosed in WO 97/03649.

Fine particles of active material suitable for pulmonary administration have often been prepared by milling, for example, jet milling. However, once the particles reach a minimum size referred to as the critical size, they re-combine at the same rate as being fractured, or do not fracture effectively and therefore do not reduce further in size. Thus, manufacture of fine particles by milling can require much effort and

there are factors which consequently place limits on the minimum size of particles of active material which can be achieved, in practice, by such milling processes.

The present invention provides in a first aspect a method for making composite active particles for use in a pharmaceutical composition for pulmonary administration, the method comprising a milling step in which particles of active material are milled 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.

The method of the invention will, in general, produce composite active particles. The composite active particles are very fine particles of active material which have, upon their surfaces, an amount of the additive material. The additive material is preferably in the form of a coating on the surfaces of the particles of active material. The coating may be a discontinuous coating. The additive material may be in the form of particles adhering to the surfaces of the particles of active material. As explained below, at least some of the composite active particles may be in the form of agglomerates.

When the composite active particles are included in a pharmaceutical composition the additive material promotes the dispersal of the composite active particles on administration of that composition to a patient, via actuation of an inhaler. ("Actuation of an inhaler" refers to the process during which a dose of the powder is removed from its rest position in the inhaler. That step takes place after the powder has been loaded into the inhaler ready for use.) The effectiveness of that promotion of dispersal has been found to be enhanced in comparison to a composition made by simple blending of similarly sized particles of active material with additive material.

The presence of the additive material on the surfaces of the particles of active material may confer controlled or delayed release properties and may provide a barrier to moisture.

It has also been found that the milling of the particles of active material in the presence of an additive material produces significantly smaller particles and/or requires less time and less energy than the equivalent process carried out in the absence of the additive material. Using the method of the invention, it has been possible to produce composite active particles which have a mass median aerodynamic diameter (MMAD) or a volume median diameter (VMD) of less than 1 μm. It is often not possible to make such small particles by other milling methods.

It is known that a milling process will tend to generate and increase the level of amorphous material on the surfaces of the milled particles thereby making them more cohesive. In contrast, the composite active particles of the invention will often be found to be less cohesive after the milling treatment.

The word "milling" as used herein refers to any mechanical process which applies sufficient force to the particles of active material that it is capable of breaking coarse particles (for example, particles of mass medium aerodynamic diameter greater than 100 μm) down to fine particles of mass median aerodynamic diameter not more than 50 μm or which applies a relatively controlled compressive force as described below in relation to the Mechano-Fusion and Cyclomix methods. It has been found that processes such as blending which do not apply a high degree of force are not effective in the method of the invention. It is believed that is because a high degree of force is required to separate the individual particles of active material and to break up tightly bound agglomerates of the active particles such that effective mixing and effective application of the additive material to the surfaces of those particles is achieved. It is believed that an especially desirable aspect of the milling process is that the additive material may become deformed in the milling and may be smeared over or

fused to the surfaces of the active particles. It should be understood, however, that in the case where the particles of active material are already fine, for example, having a mass median aerodynamic diameter below 20μ prior to the milling step, the size of those particles may not be significantly reduced. The important thing is that the milling process applies a sufficiently high degree of force or energy to the particles.

The method of the invention generally involves bringing the additive particles into close contact with the surfaces of the active particles. In order to achieve coated particles, a degree of intensive mixing is required to ensure a sufficient break-up of agglomerates of both constituents, dispersal and even distribution of additive over the host active particles.

Where the additive particles are very small (typically <1 micron), generally less work is required, firstly as it is not required to break or deform but only to deagglomerate, distribute and embed the additive particles onto the active particle and secondly because of the naturally high surface energies of such small additive particles. It is known that where two powder components are mixed and the two components differ in size, there is a tendency for the small particles to adhere to the large particles (to form so called 'ordered mixes'). The short range Van der Waals interactions for such very fine components may be sufficient to ensure adhesion. However, where both additive and active particles are very fine (for example less than 5 microns) a substantial degree of mixing will be required to ensure a sufficient break-up of agglomerates of both constituents, dispersal and even distribution of additive particles over the active particles as noted above. In some cases a simple contact adhesion may be insufficient and a stronger embedding or fusion of additive particles onto active particles is required to prevent segregation, or to enhance the structure and functionality of the coating.

Where the additive particles are not so small as to be sufficiently adhered by Van der Waals forces alone, or where there are advantages to distorting and/or embedding the additive particles substantially onto the host active particle, a greater degree of energy is required from the milling. In this case, the additive particles should experience sufficient force to soften and/or break, to distort and to flatten them. These processes are enhanced by the presence of the relatively harder active particles which act as a milling media as well as a de-agglomerating media for such processes. As a consequence of this process the additive particles may become wrapped around the core active particle to form a coating. These processes are also enhanced by the application of a compressive force as mentioned above.

As a consequence of the milling step, complete or partial, continuous or discontinuous, porous or non-porous coatings may be formed. The coatings originate from a combination of active and additive particles. They are not coatings such as those formed by wet processes that require dissolution of one or both components. In general, such wet coating processes are likely to be more costly and more time consuming than the milling process of the invention and also suffer from the disadvantage that it is less easy to control the location and structure of the coating.

A wide range of milling devices and conditions are suitable for use in the method of the invention. The milling conditions, for example, intensity of milling and duration, should be selected to provide the required degree of force. Ball milling is a preferred method. Centrifugal and planetary ball milling are especially preferred methods. Alternatively, a high pressure homogeniser may be used in which a fluid containing the particles is forced through a valve at high pressure producing conditions of high shear and turbulence. Shear forces on the particles, impacts between the particles and machine surfaces or other particles and cavitation due to acceleration of the fluid may all contribute to the fracture of the particles and may also provide a compressive force. Such homogenisers may be more suitable than ball mills for use in large scale preparations of the composite active particles. Suitable homogensiers include EmulsiFlex high pressure homogenisers which are capable of pressures up to 4000 Bar, Niro Soavi high pressure homogenisers (capable of pressures up to 2000 Bar), and Microfluidics Microfluidisers (maximum pressure 2750 Bar). The milling step may, alternatively, involve a high energy media mill or an agitator bead mill, for example, the Netzch high energy media mill, or the DYNO-mill (Willy A. Bachofen AG, Switzerland). Alternatively the milling may be a dry coating high energy process such as a Mechano-Fusion system (Hosokawa Micron Ltd) or a Hybridizer (Nara). Other possible milling devices include air jet mills, pin mills, hammer mills, knife mills, ultracentrifugal mills and pestle and mortar mills.

Especially preferred methods are those involving the Mechano-Fusion, Hybridiser and Cyclomix instruments.

Preferably, the milling step involves the compression of the mixture of active and additive particles in a gap (or nip) of fixed, predetermined width (for example, as in the Mechano-Fusion and Cyclomix methods described below).

Some preferred milling methods will now be described in greater detail.

Mechano-Fusion:

As the name suggests, this dry coating process is designed to mechanically fuse a first material onto a second material. The first material is generally smaller and/or softer than the second. The Mechano-Fusion and Cyclomix working principles are distinct from alternative milling techniques in having a particular interaction between inner element and vessel wall, and are based on providing energy by a controlled and substantial compressive force.

The fine active particles and the additive particles are fed into the Mechano-Fusion driven vessel, where they are subject to a centrifugal force and are pressed against the vessel inner wall. The powder is compressed between the fixed clearance of the drum wall and a curved inner element with high relative speed between drum and element. The inner wall and the curved element together form a gap or nip in which the particles are pressed together. As a result the particles experience very high shear forces and very strong compressive stresses as they are trapped between the inner drum wall and the inner element (which has a greater curvature than the inner drum wall). The particles violently collide against each other with enough energy to locally heat and soften, break, distort, flatten and wrap the additive particles around the core particle to form a coating. The energy is generally sufficient to break up agglomerates and some degree of size reduction of both components may occur. Embedding and fusion of additive particles onto the active particles may occur, and may be facilitated by the relative differences in hardness (and optionally size) of the two components. Either the outer vessel or the inner element may rotate to provide the relative movement. The gap between these surfaces is relatively small, and is typically less than 10 mm and is preferably less than 5 mm, more preferably less than 3 mm. This gap is fixed, and consequently leads to a better control of the compressive energy than is provided in some other forms of mill such as ball and media mills. Also, in general, no impaction of milling media surfaces is present so that wear and consequently contamination are minimised. The speed of rotation may be in the range of 200 to 10,000 rpm. A scraper may also be present to break up any caked material building up on the vessel surface. This

is particularly advantageous when using fine cohesive starting materials. The local temperature may be controlled by use of a heating/cooling jacked built into the drum vessel walls. The powder may be re-circulated through the vessel.

Cyclomix Method (Hosokawa Micron):

The Cyclomix comprises a stationary conical vessel with a fast rotating shaft with paddles which move close to the wall. Due to the high rotational speed of the paddles, the powder is propelled towards the wall, and as a result the mixture experiences very high shear forces and compressive stresses between wall and paddle. Such effects are similar to the Mechano-Fusion as described above and may be sufficient to locally heat and soften, to break, distort, flatten and wrap the additive particles around the active particles to form a coating. The energy is sufficient to break up agglomerates and some degree of size reduction of both components may also occur depending on the conditions and upon the size and nature of the particles.

Hybridiser Method:

This is a dry process which can be described as a product embedding or filming of one powder onto another. The fine active particles and fine or ultra fine additive particles are fed into a conventional high shear mixer pre-mix system to form an ordered mixture. This powder is then fed into the Hybridiser. The powder is subjected to ultra-high speed impact, compression and shear as it is impacted by blades on a high speed rotor inside a stator vessel, and is re-circulated within the vessel. The active and additive particles collide with each other. Typical speeds of rotation are in the range of 5,000 to 20,000 rpm. The relatively soft fine additive particles experience sufficient impact force to soften, break, distort, flatten and wrap around the active particle to form a coating. There may also be some degree of embedding into the surface of the active particles.

Other preferred methods include ball and high energy media mills which are also capable of providing the desired high shear force and compressive stresses between surfaces, although as the clearance gap is not controlled, the coating process may be less well controlled than for Mechano-Fusion milling and some problems such as a degree of undesired re-agglomeration may occur. These media mills may be rotational, vibrational, agitational, centrifugal or planetary in nature.

It has been observed in some cases that when ball milling active particles with additive material, a fine powder is not produced. Instead the powder was compacted on the walls of the mill by the action of the mill. That has inhibited the milling action and prevented the preparation of the composite active particles. That problem occurred particularly when certain additive materials were used, in cases where the additive material was present in small proportions (typically <2%), in cases where the milling balls were relatively small (typically <3 mm), in cases where the milling speed was too slow and where the starting particles were too fine. To prevent this occurring it is advantageous to ball mill in a liquid medium. The liquid medium reduces the tendency to compaction, assists the dispersal of additive material and improves any milling action.

It has been found to be preferable to use a large number of fine milling balls, rather than fewer heavy balls. The finer balls perform a more efficient co-milling action. Preferably the balls have a diameter of less than 5 mm, advantageously less than 2 mm. Liquid media are preferred which do not dissolve the active material and which evaporate rapidly and fully, for example non-aqueous liquids such as diethylether, acetone, cyclohexane, ethanol, isopropanol or dichloromethane. Liquid media are preferred which are non flammable, for example dichloromethane and fluorinated hydrocarbons, especially fluorinated hydrocarbons which are suitable for use as propellants in inhalers.

Pestle and mortar mills are other mills which also provide a very high shear force and compressive stresses between surfaces.

Mechano-Micros and Micros mills made by Nara (where particles are compressed by rotating grinding rings) may also be used. Mills referred to impact mixers, attrition mills, pin mills and disc mills may also be used.

The mass median aerodynamic diameter of the particles of active material may be substantially reduced during the milling step especially when the active material is in the form of coarse particles prior to the milling step. The mass median aerodynamic diameter (MMAD) of the particles of active material may be reduced by at least 10%, by at least 50%, or by at least 70% during the milling step depending on the milling conditions and the MMAD of the active particles prior to the milling step.

Advantageously, after the milling step, the MMAD of the active particles is less than 9 μm, preferably less then 4 μm and more preferably less then 2 μm.

In a similar way, where the additive material is in the form of coarse particles prior to the milling step, their MMAD will be substantially reduced during the milling step. The MMAD of the particles of additive material may be reduced by at least 10%, at least 50% or at least 70% during the milling step, depending on the milling conditions and on the MMAD of the particles of additive material before the milling step. The size of the additive particles after the milling step is preferably significantly less than the size of the active particles, to enable the additive materials to more effectively coat the surfaces of the active particles. In practice, that difference in size between the active particles and additive particles is likely to be achieved as a consequence of the milling because the additive material will usually be more easily fractured or deformed than the active material and so will be broken into smaller particles than the active material. As noted above, the particles of additive material preferably become smeared over or fused to the surfaces of the particles of active material, thereby forming a coating which may be substantially continuous or discontinuous. Where the coating is discontinuous, it preferably covers, on average, at least 50% (that is, at least 50% of the total surface area of the active particles will be covered by additive material), more advantageously at least 70% and most preferably at least 90% of the surfaces of the active particles. The coating is preferably on average less than 1 μm, more preferably less than 0.5 μm and most preferably less than 200 nm thick.

The milling step may be carried out in a closed vessel, for example in a ball mill or a Mechano-Fusion device. The use of a closed vessel prevents loss of ultrafine particles or vapour of the additive material which has been found to occur in jet milling or other open processes. Preferably, the milling is not jet milling (micronisation).

The milling may be wet milling, that is, the milling step may be carried out in the presence of a liquid. That liquid medium may be high or low volatility and of any solid content as long as it does not dissolve the active particles to any significant degree and its viscosity is not so high that it prevents effective milling. The liquid medium preferably is not aqueous. The liquid is preferably one in which the additive material is substantially insoluble but some degree of solubility may be acceptable as long as there is sufficient additive material present that undissolved particles of additive material remain. The presence of a liquid medium helps to prevent compacting of the particles of active material on the walls of

the vessel and may also allow the more even spreading of the additive material on the surface of the particles of active material as compared to dry milling.

It has been found that the Mechano-Fusion and Cyclomix techniques referred to above often provide the composite active particles as individual, that is, unagglomerated composite active particles. That is in contrast to less controlled methods such as ball milling, which have been found to often produce the composite active particles in the form of agglomerated composite active particles.

The mass median aerodynamic diameter of the composite active particles is preferably not more than 10 μm, and advantageously it is not more than 5 μm, more preferably not more than 3 μm and most preferably not more than 1 μm. Accordingly, advantageously at least 90% by weight of the composite active particles have a diameter of not more than 10 μm, advantageously not more than 5 μm, preferably not more than 3 μm and more preferably not more than 1 μm. Advantageously, after the milling step, the active particles will be of a suitable size for inhalation to the desired part of the lung, for example, having an MMAD in the range of 3 to 0.1 μm for absorption in the deep lung, 5 to 0.5 μm for absorption in the respiratory bronchioles, 10 to 2 μm for delivery to the higher respiratory system and 2 to 0.05 μm for delivery to the alveoli. Accordingly, advantageously the diameter of at least 90% by weight of the composite active particles have an aerodynamic diameter in the range of 3 to 0.1 μm, preferably 5 to 0.5 μm, advantageously 10 to 2 μm, and especially advantageously 2 to 0.05 μm. The MMAD of the active particles will not normally be lower than 0.01 μm.

As mentioned above, the composite active particles produced after the milling step may be of a suitable size for delivery to the desired part of the respiratory system.

However, the composite active particles may be smaller than that suitable size or at least some of the composite active particles may, after the milling step, be in the form of agglomerates which are larger than the suitable size. The method therefore preferably also comprises, after the milling step, a processing step in which the degree of agglomeration of the composite active particles is changed. The processing step may be an agglomeration step in which the particles of active material agglomerate to form agglomerated composite active particles. In that way agglomerates of a size tailored to the requirement may be produced. Whilst any method of agglomeration can be used, for example, granulation, preferably, the composite active particles are agglomerated in a drying step (as described below) to form agglomerated composite active particles. Preferably, the agglomeration step is a spray drying step. The spray drying conditions may be selected to produce droplets having a desired size in the range of 1000 μm to 0.5 μm. The size of the agglomerates produced will depend largely on the concentration of the composite active particles in the spray feed and the droplet size. Other materials, for example, binders may be included in the spray feed. Where the milling step involves wet milling, the suspension or slurry may be spray dried directly after the milling step. Agglomeration may also be conducted in a fluid bed dryer or granulator.

Where, after the milling step, at least some of the composite active particles are in the form of agglomerates and it is desired to break those agglomerates down or to reduce their size, the processing step may be a deagglomeration step. The deagglomeration step may involve mechanical breaking up of the unwanted agglomerates, for example, by forcing them through a sieve or by subjecting them to a treatment in a dry fluidised bed, a jet mill, a ball mill or other form of milling device. The intensity and/or duration of that treatment step will, in general, be less that of the milling step. The deagglomeration step may also be a spray drying step because, whilst spray drying as a drying step is particularly useful in preparing agglomerated composite active particles, by appropriate control of the conditions it is possible to produce the composite active particles largely as single particles rather than as agglomerates.

The term "agglomerated composite active particles" refers to particles which consist of more than one composite active particle, those composite active particles being adhered to each other. Where the agglomerated particles are for inhalation they will preferably have a MMAD which renders them suitable for deposition in the desired part of the lung.

Preferably, the method comprises, after the milling step, a drying step in which a mixture of the composite active particles and a liquid is dried to remove the liquid. The mixture may be in the form of a slurry or suspension. During the drying step, especially when spray drying is used, the degree of agglomeration of the composite active particles may change, in which case the drying step is the same step as the processing step mentioned above. However, the drying step may be included for other reasons, for example, when the milling is wet milling, and it is desired to produce the composite active particles as a dry powder.

The drying step may involve filtration followed by drying, or evaporation of the liquid. Preferably, the drying step is a spray drying step. Alternatively, the liquid may be evaporated slowly or the drying step may be a freeze drying step.

The milling is preferably dry, that is to say, there is no liquid present during the milling and the mixture to be milled is in the form of a dry particulate. In that case, liquid may be added after the milling step, usually in order that a drying step be used to form agglomerated composite active particles, as described above.

Advantageously, the milling step is carried out at a reduced temperature, for example, below 10° C. and preferably below 0° C. Such low temperature conditions may increase the efficiency of the milling step and/or reduce decomposition of the active material.

The optimum amount of additive material will depend on the chemical composition and other properties of the additive material and upon the nature of the active material and/or excipient material. In general, the amount of additive material in the composite particles will be not more than 60% by weight, based on the weight of the active material and/or excipient material. However, it is thought that for most additive materials the amount of additive material should be in the range of 40% to 0.25%, preferably 30% to 0.5%, more preferably 20% to 2%, based on the total weight of the additive material and the active material being milled. In general, the amount of additive material is at least 0.01% by weight based on the weight of the active material.

The terms "additive particles" and "particles of additive material" are used interchangeably herein. The additive particles comprise one or more additive materials. Preferably, the additive particles consist essentially of the additive material.

Advantageously the additive material is an anti-adherent material and will tend to decrease the cohesion between the composite active particles and between the composite active particles and any other particles present in the pharmaceutical composition.

Advantageously the additive material is an anti-friction agent (glidant) and will give better flow of the pharmaceutical composition in, for example, a dry powder inhaler which will lead to a better dose reproducibility.

Where reference is made to an anti-adherent material, or to an anti-friction agent, the reference is to include those mate-

rials which are able to decrease the cohesion between the particles, or which will tend to improve the flow of powder in an inhaler, even though they may not usually be referred to as anti-adherent material or an anti-friction agent. For example, leucine is an anti-adherent material as herein defined and is generally thought of as an anti-adherent, material but lecithin is also an anti-adherent material as herein defined, even though it is not generally thought of as being anti-adherent, because it will tend to decrease the cohesion between the composite active particles and between the composite active particles and any other particles present in the pharmaceutical composition.

The additive material may include a combination of one or more materials.

It will be appreciated that the chemical composition of the additive material is of particular importance. Preferably, the additive material is a naturally occurring animal or plant substance.

Advantageously, the additive material includes one or more compounds selected from amino acids and derivatives thereof, and peptides and derivatives thereof. Amino acids, peptides and derivatives of peptides are physiologically acceptable and give acceptable release of the active particles on inhalation.

It is particularly advantageous for the additive material to comprise an amino acid. The additive material may comprise one or more of any of the following amino acids: leucine, isoleucine, lysine, valine, methionine, phenylalanine. The additive may be a salt or a derivative of an amino acid, for example aspartame or acesulfame K. Preferably, the additive particles consist substantially of an amino acid, more preferably of leucine, advantageously L-leucine. The D- and DL-forms may also be used. As indicated above, leucine has been found to give particularly efficient dispersal of the active particles on inhalation.

The additive material may include one or more water soluble substances. This helps absorption of the substance by the body if the additive reaches the lower lung. The additive material may include dipolar ions, which may be zwitterions.

Alternatively, the additive material may comprise a phospholipid or a derivative thereof. Lecithin has been found to be a good material for the additive material.

Preferably, the additive material comprises a metal stearate, or a derivative thereof, for example, sodium stearyl fumarate or sodium stearyl lactylate. Advantageously, the additive material comprises a metal stearate. For example, zinc stearate, magnesium stearate, calcium stearate, sodium stearate or lithium stearate. Preferably, the additive material comprises magnesium stearate.

The additive material may include or consist of one or more surface active materials, in particular materials that are surface active in the solid state, which may be water soluble, for example lecithin, in particular soya lecithin, or substantially water insoluble, for example solid state fatty acids such as oleic acid, lauric acid, palmitic acid, stearic acid, erucic acid, behenic acid, or derivatives (such as esters and salts) thereof such as glyceryl behenate. Specific examples of such materials are: phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols and other examples of natural and synthetic lung surfactants; lauric acid and its salts, for example, sodium lauryl sulphate, magnesium lauryl sulphate; triglycerides such as Dynsan 118 and Cutina HR; and sugar esters in general.

Other possible additive materials include sodium benzoate, hydrogenated oils which are solid at room temperature, talc, titanium dioxide, aluminium dioxide, silicon dioxide and starch.

The additive material preferably comprises one or more materials selected from the group consisting of amino acids, lecithins, phospholipids, sodium stearyl fumarate, glyceryl behenate and metal stearates (especially magnesium stearate).

The terms "active particles" and "particles of active material" are used interchangeably herein. The active particles referred to throughout the specification will comprise one or more pharmacologically active agents. The active particles advantageously consist essentially of one or more pharmacologically active agents. Suitable pharmacologically active agents may be materials for therapeutic and/or prophylactic use. Active agents which may be included in the formulation include those products which are usually administered orally by inhalation for the treatment of disease such as respiratory disease, for example, β-agonists.

The active particles may comprise at least one β_2-agonist, for example one or more compounds selected from terbutaline, salbutamol, salmeterol and formetorol. If desired, the active particles may comprise more than one of those active agents, provided that they are compatible with one another under conditions of storage and use. Preferably, the active particles are particles of salbutamol sulphate. References herein to any active agent is to be understood to include any physiologically acceptable derivative. In the case of the B_2-agonists mentioned above, physiologically acceptable derivatives include especially salts, including sulphates.

The active particles may be particles of ipatropium bromide.

The active particles may include a steroid, which may be beclomethasone dipropionate or may be Fluticasone. The active principle may include a cromone which may be sodium cromoglycate or nedocromil. The active principle may include a leukotriene receptor antagonist.

The active particles may include a carbohydrate, for example heparin.

The active particles may advantageously comprise a pharmacologically active agent for systemic use and advantageously they are capable of being absorbed into the circulatory system via the lungs. For example, the active particles may comprise peptides or polypeptides such as Dnase, leukotrienes or insulin. The pharmaceutical compositions of the invention may in particular have application in the administration of insulin to diabetic patients, preferably avoiding the normally invasive administration techniques used for that agent. The composite active particles could also be used for the local administration of other agents for example for pain relief (e.g. analgesics such as Fentanyl or dihydroergotamine which is used for the treatment of migraine), anti cancer activity, anti-virals, antibiotics or the local delivery of vaccines to the respiratory tract.

Whilst it will often be desired to obtain the composite active particles in dry form, as described above, where the pharmaceutical composition is one comprising a liquid, for example, as propellant, it may be preferable for the active particles to be milled in the presence of that liquid and to omit the drying step, simply using the slurry or suspension of the composite active particles in the liquid as an ingredient in the pharmaceutical composition. Thus for example, where the pharmaceutical composition is for use in a pMDI, the active particles and the additive material may be milled in the presence of liquid propellant (under pressure or at below room temperature if necessary). The resulting slurry may be used directly in a pMDI or further materials may be added, for example, more propellant, surfactants, or co-solvents.

Accordingly, the invention also provides, in one embodiment, a method of making composite active particles for use

in a pharmaceutical composition, the method comprising a milling step in which particles of active material are milled in the presence of a liquid and an additive material which is suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device.

Preferably, the liquid comprises a propellant suitable for use in a pMDI. Suitable propellants include CFC-12, HFA-134a, HFA-227, HCFC-22 (difluorochlormethane), HCFC-123 (dicholorotrifluorethane), HCFC-124 (chlorotetrafluoroethane), dimethyl ether, propane, n-butane, isobutane, HFA-125 (pentafluoroethane) and HFA-152 (difluoroethane). If however, it is desired to isolate the dry composite active particles (or agglomerates thereof) the method may also include a drying step, preferably a spray drying step. Accordingly, in a further embodiment, the invention provides a method of making composite active particles for use in a pharmaceutical composition, the method comprising

a wet milling step in which the particles of active material are milled in the presence of a liquid and an additive material which is suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device; and

a drying step in which the liquid is removed.

As explained above, the conditions of the drying step, which is preferably a spray drying step, may be chosen either to provide agglomerated composite active particles of a desired size or to provide substantially unagglomerated particles, that is, individual composite active particles. In some cases it may be preferable to perform the milling step in the absence of liquid, (dry milling). The composite active particles may then be agglomerated by mixing with a liquid and drying to give agglomerated composite active particles. Accordingly, in a further embodiment, the invention provides a method of making agglomerated composite active particles for use in a pharmaceutical composition, the method comprising:

a dry milling step in which particles of active material are milled in the presence of an additive material which is suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device; and

an agglomeration step, in which the composite active particles are mixed with a liquid and the mixture is dried to remove the liquid.

The invention also provides composite active particles for use in a pharmaceutical composition, preferably a pharmaceutical composition for inhalation, more preferably a powder for a dry powder inhaler.

The invention also provides composite active particles for use in a pharmaceutical composition, each composite active particle comprising a particle of active material and additive material on the surface of that particle of active material, the composite active particles having a mass median aerodynamic diameter of not more than 2 μm, the additive material being suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device. Preferably, the composite active particles have a, MMAD of not more than 1 μm, especially advantageously not more than 0.5 μm. As noted above, the composite particles may be in the form of agglomerated composite particles.

MMAD may be determined using an impinger, for example, a multi-stage, liquid impinger. Volume median diameters and measurements of the proportion of particles having a diameter less than a certain value may be determined by the Malvern laser light scattering method.

Advantageously, the composite active particles do not comprise significant amounts (more then 10% by weight) of a polymer of a type which would result in the particles becoming sticky. Such polymers include polymers of a alpha-hydroxycarboxylic acid, for example, polylactic acid, copolymers of lactic acid and block copolymers such as ethylene oxide/propylene oxide block copolymers or poloxamines.

The invention further provides a pharmaceutical composition comprising composite active particles. Preferably, the pharmaceutical composition is a dry powder and is suitable for use in a dry powder inhaler. Such pharmaceutical compositions may comprise essentially only the composite active particles or they may comprise additional ingredients such as carrier particles and flavouring agents. Carrier particles may be of any acceptable excipient material or combination of materials. For example, the carrier particles may be composed of one or more materials selected from sugar alcohols, polyols and crystalline sugars. Other suitable carriers include inorganic salts such as sodium chloride and calcium carbonate, organic salts such as sodium lactate and other organic compounds such as polysaccharides and oligosaccharides. Advantageously the carrier particles are of a polyol. In particular the carrier particles may be particles of crystalline sugar, for example mannitol, dextrose or lactose. Preferably, the carrier particles are of lactose.

Advantageously, substantially all (by weight) of the carrier particles have a diameter which lies between 20 μm and 1000 μm, more preferably 50 μm and 1000 μm. Preferably, the diameter of substantially all (by weight) of the carrier particles is less than 355 μm and lies between 20 μm and 250 μm. Preferably at least 90% by weight of the carrier particles have a diameter between from 60 μm to 180 μm. The relatively large diameter of the carrier particles improves the opportunity for other, smaller particles to become attached to the surfaces of the carrier particles and to provide good flow and entrainment characteristics and improved release of the active particles in the airways to increase deposition of the active particles in the lower lung.

The ratio in which the carrier particles (if present) and composite active particles are mixed will, of course, depend on the type of inhaler device used, the type of active particles used and the required dose. The carrier particles may be present in an amount of at least 50%, more preferably 70%, advantageously 90% and most preferably 95% based on the combined weight of the composite active particles and the carrier particles.

Where carrier particles are included in the pharmaceutical composition, that composition preferably also includes small excipient particles having, for example, a particle size between 5 to 20 μm. Preferably the small excipient particles are present in an amount of from 1% to 40%, more preferably 5% to 20% based on the weight of the carrier particles.

Compositions for use in a dry powder inhaler which include carrier particles will preferably include at least 2%, more preferably at least 5% and most preferably at least 10% by weight of the composite active particles based on the total mass of the composition. The composite active particles are especially suitable for dry powder compositions which do not include significant amounts of carrier particles and in such compositions the composite active particles will preferably be present in a proportion of at least 60%, more preferably at least 80% by weight based on the total weight of the composition.

The pharmaceutical composition may comprise a propellant and be suitable for use in a pressurised metered dose inhaler.

The invention also provides the use of an additive material as a milling aid in the milling of particles of active material. The term milling aid should be understood to refer to a sub-

stance which reduces the amount of energy required to mill the particles of active material and/or excipient material.

Embodiments of the invention will now be described for the purposes of illustration only with reference to the Figures in which:

FIGS. **1** and **2** are scanning electron micrographs of the composite active particles of Example 1;

FIG. **3** is a scanning electron micrograph of the composite active particles of Example 1a;

FIG. **4** is a scanning electron micrograph of the composite particles of Example 2;

FIG. **5** is a scanning electron micrograph of the same sample of particle's shown in FIG. **4** but at a higher magnification;

FIG. **6** is a scanning electron micrograph of the composite particles of Example 3;

FIG. **7** is a scanning electron micrograph of the same sample of particles shown in FIG. **6** but at a higher magnification;

FIG. **8** is a schematic drawing of part of a Mechano-Fusion machine; and

FIGS. **9** and **10** are electromicrographs of composite active particles according to the invention comprising salbutamol sulphate and magnesium stearate in a ratio of 19:1 (Example 4).

All percentages are by weight unless indicated otherwise.

EXAMPLE 1

5 g of micronised salbutamol sulphate (particle size distribution: 1 to 5 μm) and 0.5 g of magnesium stearate were added to a 50 cm^3 stainless steel milling vessel together with 20 cm^3 dichloromethane and 124 g of 3 mm stainless steel balls. The mixture was milled at 550 rpm in a Retsch S100 Centrifugal Mill for 5 hours. The powder was recovered by drying and sieving to remove the mill balls. An electron micrograph of the powder is shown in FIG. **1**. This was repeated 3 times using leucine in place of the magnesium stearate and an electron micrograph of the powder is shown in FIG. **2**. The powders shown in FIGS. **1** and **2** appear to have particles in the size range 0.1 to 0.5 μm.

EXAMPLE 1a

Micronised salbutamol sulphate and magnesium stearate were combined as particles in a suspension in the ratio 10:1 in propanol. This suspension was processed in an Emulsiflex C50 high pressure homogeniser by 5 sequential passes through the system at 25,000 psi. This dry material was then recovered by evaporating the propanol. The particles are shown in FIG. **3**.

EXAMPLE 2

It was found that, on drying, the powder prepared in Example 1 including magnesium stearate as additive material formed assemblies of primary particles which were hard to deagglomerate. A sample of this powder was re-dispersed by ball milling for 90 minutes at 550 rpm in a mixture of ethanol, polyvinylpyrolidone (PVPK30) and HFA227 liquid propellant to give the following composition:

0.6% w/w	Salbutatmol sulphate/magnesium stearate composite particles
0.2% w/w	PVPK30
5.0% w/w	Ethanol
94.2% w/w	HFA 227

(The PVP was included to stabilise the suspension of the composite particles in the ethanol/HFA227).

The suspension could be used directly as in a pMDI. In this example, however, the composition was sprayed from a pressurised can through an orifice ~0.4 mm in diameter to produce dried composite active particles of salbutamol sulphate and magnesium stearate with PVP. Those particles (shown in FIGS. **4** and **5**) were collected and examined and were found to be in the aerodynamic size range 0.1 to 4 μm.

EXAMPLE 3

The process of Example 2 was repeated except that the composition was as follows:

3% w/w	Salbutamol sulphate/magnesium stearate composite particles
1% w/w	PVPK30
3% w/w	Ethanol
93% w/w	HFA 227

The particles produced are shown in FIGS. **6** and **7**.

EXAMPLE 4

Salbutamol Sulphate/Magnesium Stearate Blends

a) Homogenised Magnesium Stearate

240 g magnesium stearate (Riedel de Haen, particle size by Malvern laser diffraction:d_{50}=9.7 μm) was suspended in 2150 g dichloroethane. That suspension was then mixed for 5 minutes in a Silverson high shear mixer. The suspension was then processed in an Emulsiflex C50 high pressure homogeniser fitted with a heat exchanger at 10000 psi for 20 minutes in, circulation mode (300 cm^3/min) for 20 minutes. The suspension was then circulated at atmospheric pressure for 20 minutes allow it to cool. The next day, the suspension was processed in circulation mode (260 cm^3/min) at 20000 psi for 30 minutes. The dichloroethane was removed by rotary evaporation followed by drying in a vacuum over at 37° C. overnight. The resulting cake of material was broken up by ball milling for 1 minute. The homogenised magnesium stearate had a particle size of less than 2 μm.

b) A 9:1 by weight blend of salbutamol sulphate and homogenised magnesium stearate having a particle size of less than 2 μm was prepared by blending the two materials with a spatula. An electron micrograph of the blended material showed that the blend was mostly in the form of agglomerated particles, the agglomerates having diameters of 50 μm and above. The blend was then processed in a Mechano-Fusion mill (Hosokawa) as follows:

Machine data:	
Hosokawa Mechano-Fusion:	AMS-Mini
Drive:	2.2 kW
Housing:	stainless steel
Rotor:	stainless steel
Scraper:	None

-continued

Machine data:	
Cooling:	Water
Gas purge:	None

The Mechano-Fusion device (see FIG. **8**) comprises a cylindrical drum **1** having an inner wall **2**. In use, the drum rotates at high speed. The powder **3** of the active and additive particles is thrown by centrifugal force against the inner wall **2** of the drum **1**. A fixed arm **4** projects from the interior of the drum in a radial direction. At the end of the arm closest to the wall **2**, the arm is provided with a member **5** which presents an arcuate surface **6**, of radius of curvature less than that of inner wall **2**, toward that inner wall. As the drum **1** rotates, it carries powder **3** into the gap between arcuate surface **6** and inner wall **2** thereby compressing the powder. The gap is of a fixed, predetermined width A. A scraper (not shown in FIG. **8**) may be provided to scrape the compressed powder from the wall of the drum.

All samples were premixed for 5 minutes by running the machine at 1000 rpm. The machine speed was then increased to 5050 rpm for 30 minutes. The procedure was repeated for salbutamol sulphate/magnesium stearate in the following weight ratios: 19:1, 3:1, 1:1.

Electronmicrographs of the 19:1 processed material are shown in FIGS. **9** and **10** and indicate that the material was mostly in the form of simple small particles of diameter less than 5 μm or in very loose agglomerates of such particles with only one agglomerate of the original type being visible.

The 3:1 and the 19:1 blends were then each loaded into a 20 mg capsule and fired from a twin stage impinger. A sample of unprocessed salbutamol sulphate was also fired from the TSI to provide a comparison.

The fine particle fractions were then calculated and are given in table 1.

TABLE 1

Fine Particle Fraction results for salbutamol sulphate blends.

Composition	Fine Particle Fraction %
salbutamol sulphate	28
salbutamol sulphate/magnesium stearate 19:1	66
salbutamol sulphate/magnesium stearate 3:1	66

EXAMPLE 5

Micronised glycopyrrolate and homogenised magnesium stearate (as described in Example 4) were combined in a weight ratio of 75:25. This blend (−20 g) was then milled in the Mechano-Fusion AMS-Mini system as follows. The powder was pre-mixed for 5 minutes at −900 rpm. The machine speed was then increased to −4,800 rpm for 30 minutes. During the milling treatment the Mechano-Fusion machine was run with a 3 mm clearance between element and vessel wall, and with cooling water applied. The powder of composite active particles was then recovered from the drum vessel.

The experiment was repeated using the same procedure but the active particle and homogenised magnesium stearate were combined in the ratio 95:5, and milled for 60 minutes at 4,800 rpm.

This above process was repeated using the same procedure with a sample of sodium salicilate as a model drug and homogenised magnesium stearate in the ratio 90:10, where the sodium salicilate had been produced as approximately micron sized spheres by spray drying from a Buchi 191 spray dryer. It was believed that the spherical shape of these particles may be advantageous in the coating process. Milling was for 30 minutes at 4,800 rpm.

The invention claimed is:

1. Composite active particles for use in a pharmaceutical composition for pulmonary administration, each composite active particle comprising a particle of active material and particulate additive material on the surface of that particle of active material, wherein the composite active particles have a mass median aerodynamic diameter of not more than 10 μm, and wherein the additive material promotes the dispersion of the composite active particles upon actuation of a delivery device.

2. Composite active particles as claimed in claim **1**, wherein the additive material includes one or more of: an amino acid or derivative thereof; a peptide or derivative thereof; a phospholipid or derivative thereof, a surface active material; or a metal stearate or derivative thereof.

3. Composite active particles as claimed in claim **2**, wherein the additive material includes magnesium stearate.

4. Composite active particles as claimed in claim **1**, wherein the composite active particles have a mass median aerodynamic diameter of not more than 5 μm, not more than 3 μm or not more than 1 μm.

5. Composite active particles as claimed in claim **1**, wherein the active material comprises one or more of: a steroid, a cromone, a β_2 agonist, or a leukotriene receptor antagonist.

6. Composite active particles as claimed in claim **1**, wherein the active particles comprise terbutaline, salbutamol, salmeterol, formoterol or glycopyrrolate.

7. A pharmaceutical composition comprising composite active particles as claimed in claim **1**.

8. A pharmaceutical composition as claimed in claim **7**, consisting essentially of only the composite active particles.

9. A pharmaceutical composition as claimed in claim **7**, which is a dry powder and is suitable for use in a dry powder inhaler.

10. A pharmaceutical composition as claimed in claim **7**, which comprises a propellant and is suitable for use in a pressurized metered dose inhaler.

* * * * *

EXHIBIT B

US008435567B2

(12) **United States Patent**
Staniforth et al.

(10) **Patent No.: US 8,435,567 B2**
(45) **Date of Patent: *May 7, 2013**

(54) **PHARMACEUTICAL COMPOSITIONS OF HYDROPHOBIC SURFACE-MODIFIED ACTIVE SUBSTANCE MICROPARTICLES FOR INHALATION**

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(73) Assignee: **Vectura Limited**, Chippenham (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/269,025**

(22) Filed: **Oct. 7, 2011**

(65) **Prior Publication Data**

US 2012/0027863 A1 Feb. 2, 2012

Related U.S. Application Data

(63) Continuation of application No. 10/433,185, filed on Sep. 12, 2003, now Pat. No. 8,048,451.

(30) **Foreign Application Priority Data**

Nov. 30, 2000	(GB)	0029261.5
Dec. 19, 2000	(GB)	0030946.8
Oct. 5, 2001	(GB)	0124010.0

(51) **Int. Cl.**

A61K 9/00	(2006.01)
A61K 9/14	(2006.01)
A61K 9/16	(2006.01)

(52) **U.S. Cl.**
USPC **424/489**; 424/46

(58) **Field of Classification Search** 424/46, 424/489
See application file for complete search history.

(56) **References Cited**

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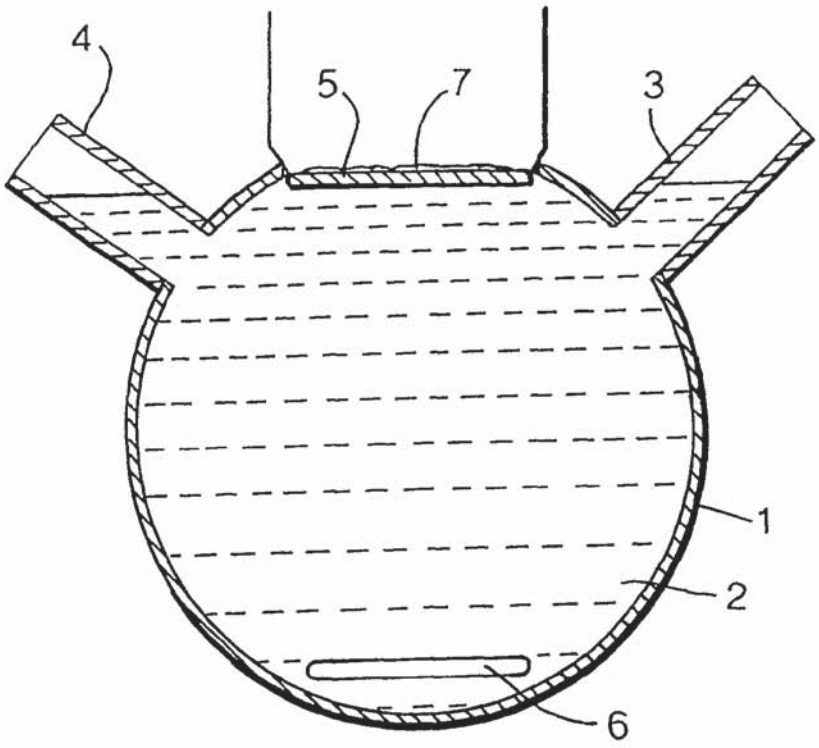
Primary Examiner — James H. Alstrum-Acevedo
(74) *Attorney, Agent, or Firm* — Reed Smith LLP; William J. McNichol, Jr.

(57) **ABSTRACT**

The invention provides microparticles for use in a pharmaceutical composition for Pulmonary administration, each microparticle comprising a particle of an active substance having, on its surface, particles of a hydrophobic material suitable for delaying the dissolution of the active substance. The invention also provides a method for making the microparticles.

17 Claims, 6 Drawing Sheets

Fig.1.



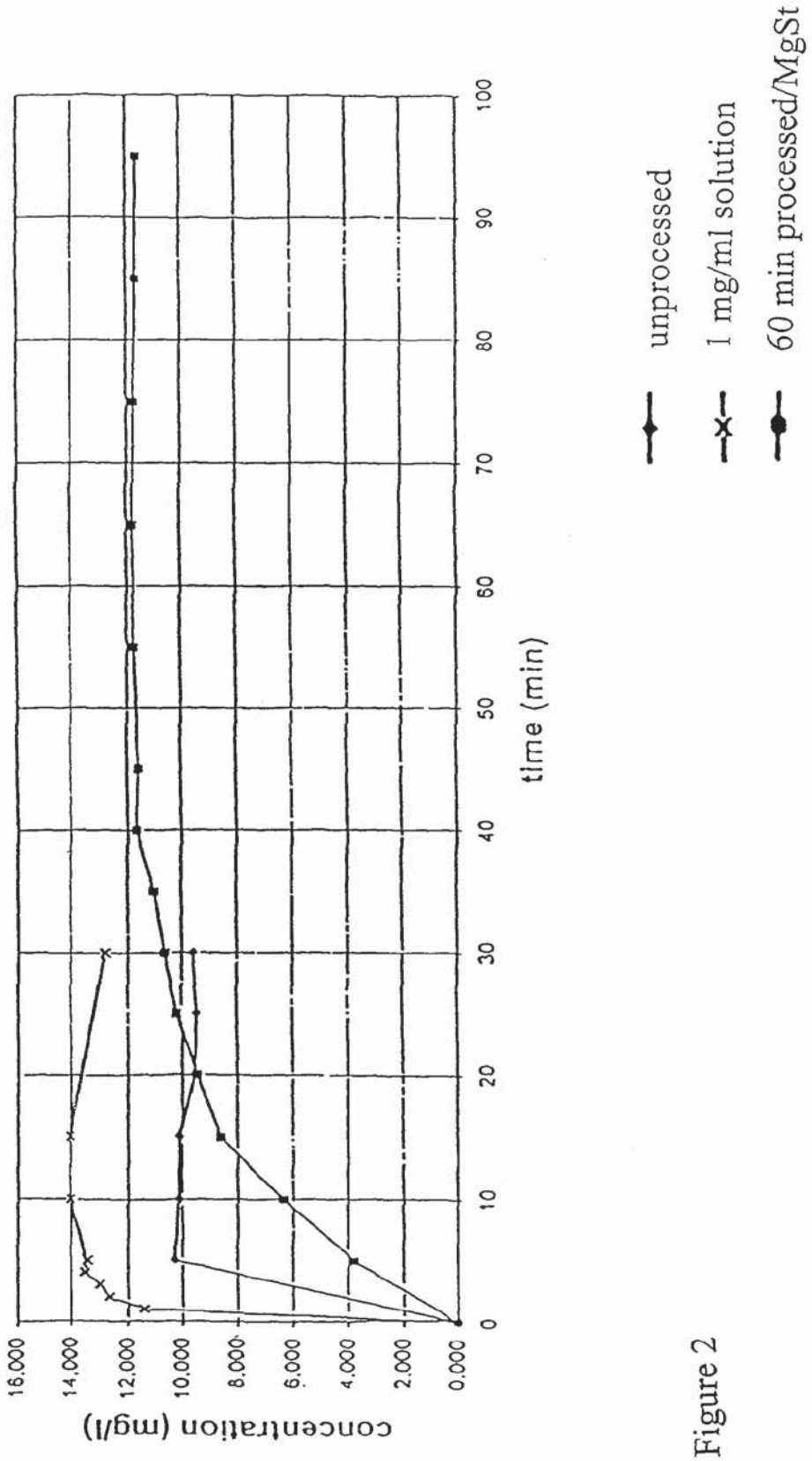

concentration (mg/l)
16,000
14,000
12,000
10,000
8,000
6,000
4,000
2,000
0,000
time (min)
0
10
20
30
40
50
60
70
80
90
100
unprocessed
1 mg/ml solution
60 min processed/MgSt

Figure 2

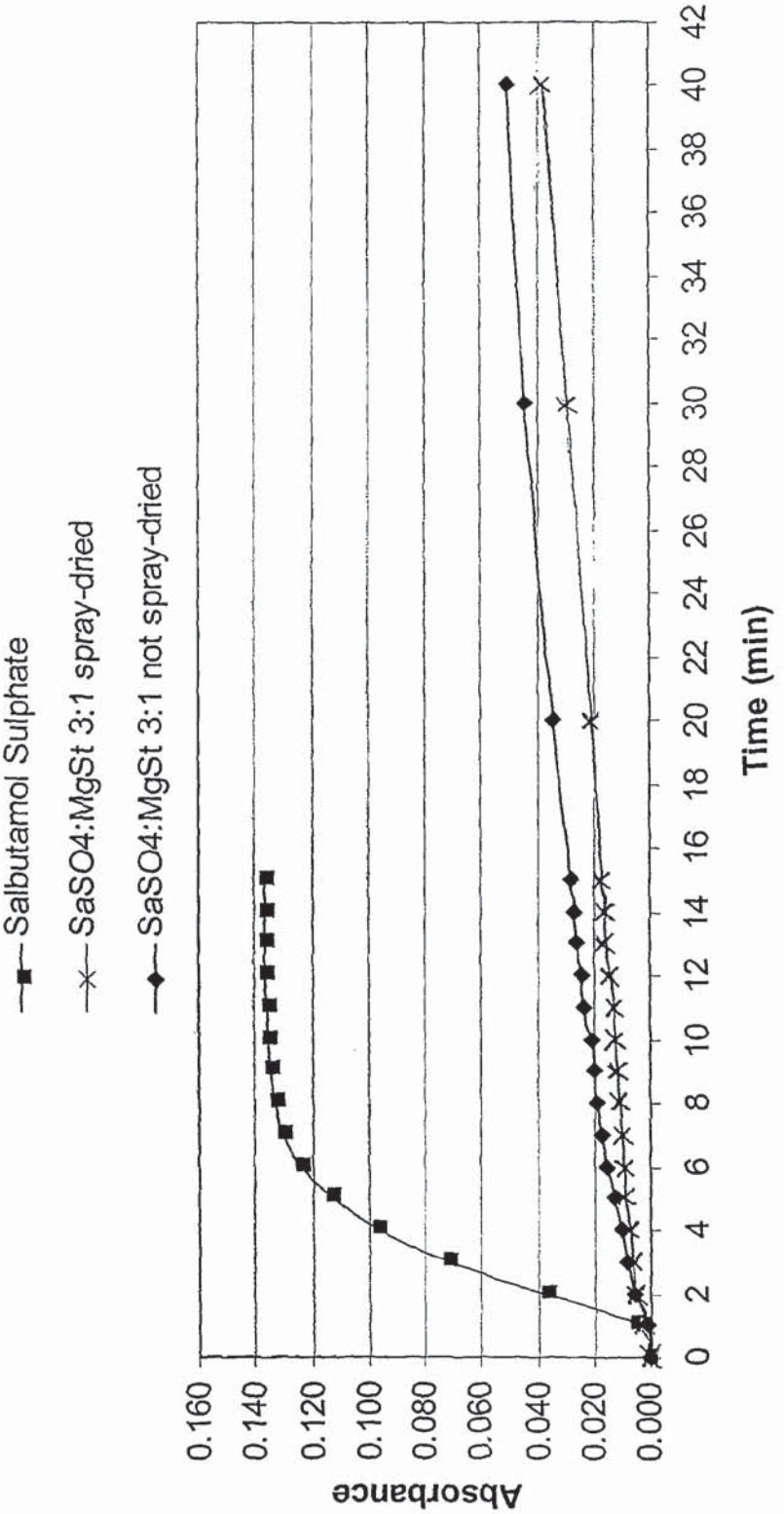

Salbutamol Sulphate
SaSO4:MgSt 3:1 spray-dried
SaSO4:MgSt 3:1 not spray-dried
Absorbance
0.160
0.140
0.120
0.100
0.080
0.060
0.040
0.020
0.000
Time (min)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42

Figure 3

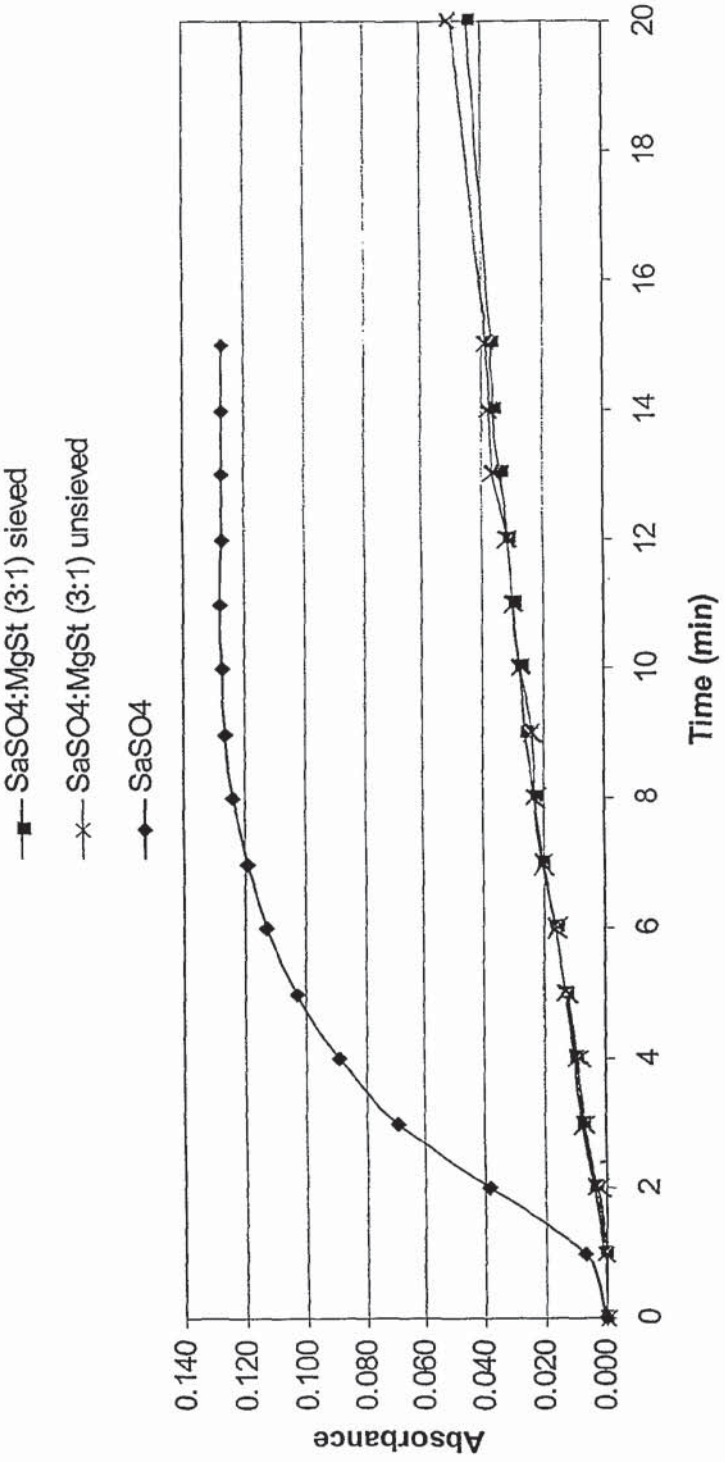

SaSO4:MgSt (3:1) sieved
SaSO4:MgSt (3:1) unsieved
SaSO4
Absorbance
0.140
0.120
0.100
0.080
0.060
0.040
0.020
0.000
Time (min)
0
2
4
6
8
10
12
14
16
18
20

Figure 4

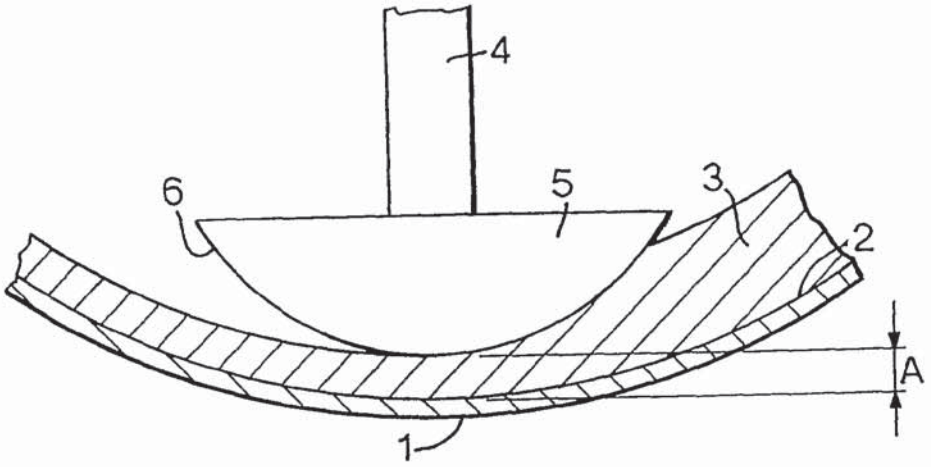


Figure 5

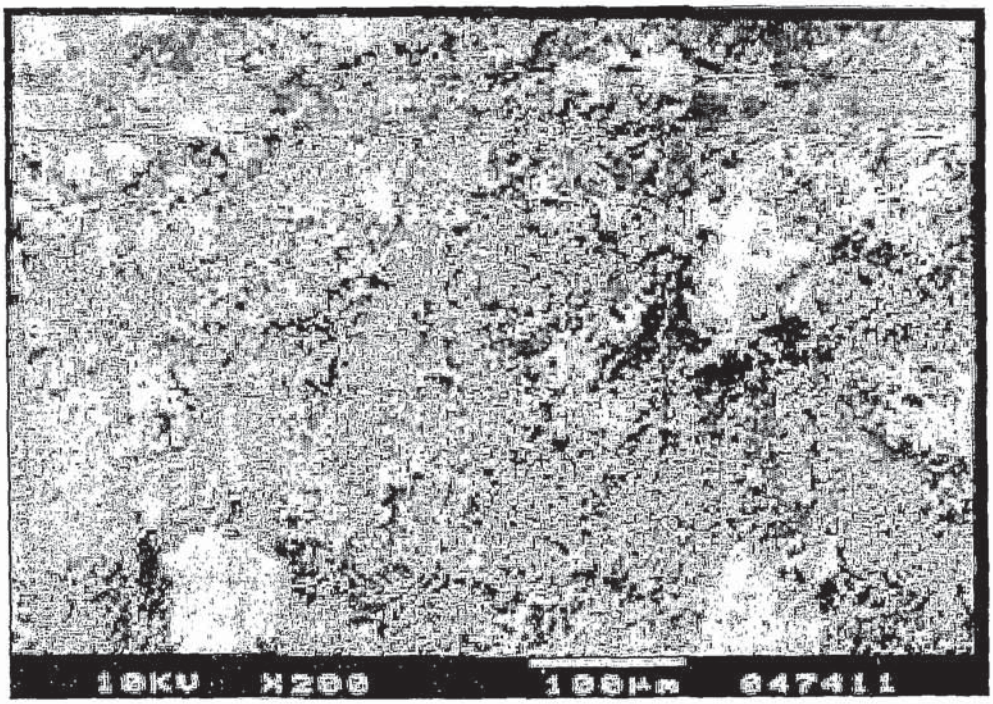


Fig 6

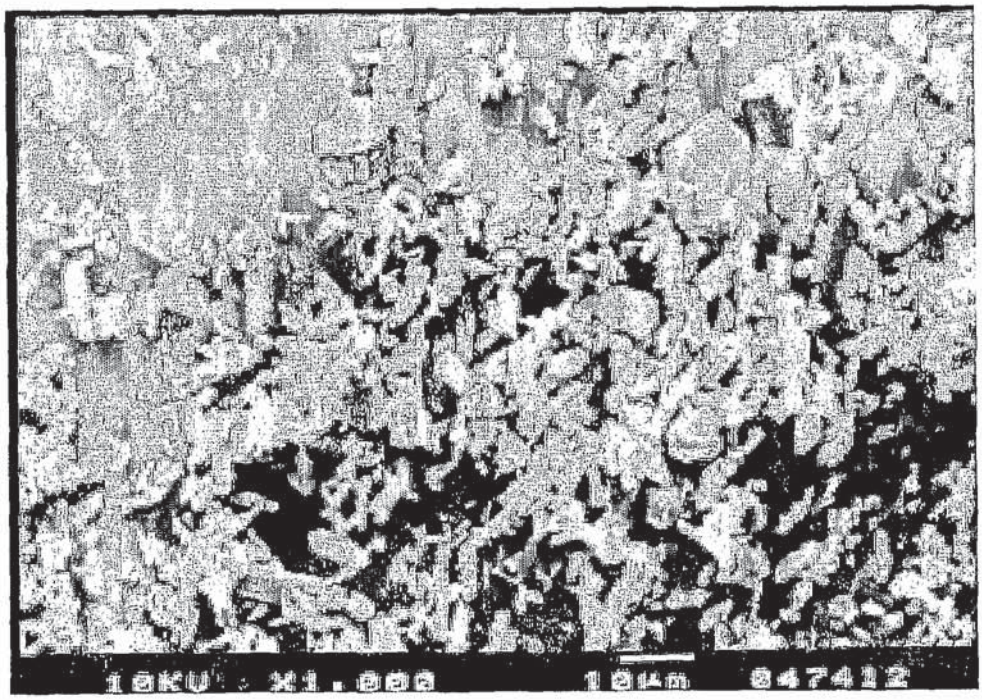


Fig 7

PHARMACEUTICAL COMPOSITIONS OF HYDROPHOBIC SURFACE-MODIFIED ACTIVE SUBSTANCE MICROPARTICLES FOR INHALATION

This application is a Continuation of application Ser. No. 10/433,185, filed Sep. 12, 2003, now U.S. Pat No. 8,048,451. The invention relates to pharmaceutical compositions for inhalation.

Pulmonary administration is known for the delivery of drugs for the treatment of respiratory conditions such as asthma and is receiving increasing attention as a route for the delivery of systemic drugs such as insulin. Known devices for the administration of drugs to the respiratory system include pressurised metered dose inhalers (pMDI's) and dry powder inhalers (DPI's).

In pulmonary administration, the size of the active particles is of great importance in determining the site of the absorption. In order that the particles be carried deep into the lungs, the particles must be very fine, for example having a mass median aerodynamic diameter of less than 10 μm. Particles having aerodynamic diameters greater than 10 μm are likely to impact the walls of the throat and generally do not reach the lung. Particles having aerodynamic diameters in the range of 5 μm to 0.5 μm will generally be deposited in the respiratory bronchioles whereas smaller particles having aerodynamic diameters in the range of 2 to 0.05 μm are likely to be deposited in the alveoli.

In an attempt to improve the flow of the powder, dry powders for use in dry powder inhalers often include particles of an excipient material mixed with the fine particles of active material. Such particles of excipient material may be coarse, for example having a mass median aerodynamic diameter greater than 90 μm, (such coarse particles are referred to as carrier particles) or they may be fine.

Propellant-based formulations for use with pressurized metered dose inhalers are also known and are widely used.

It has long been desired to develop pharmaceutical formulations in which the pharmaceutically active substance is released over a comparatively long period of time in order to maintain the concentration of the active substance in the blood at a desired level for a comparatively longer period of time. An associated benefit is an increase in patient compliance with the dosing regime brought about by reducing the number of, and/or the frequency of, the administrations necessary to maintain the concentration of the active substance in the blood at the desired level.

Delayed release compositions have been developed for delivery of drug to the gastrointestinal tract and some such compositions are commercially available. Systems for the controlled delivery of an active substance through the skin have also been developed.

Known techniques for preparing controlled release formulations can be categorised into one of two types. The first type involves the application of a barrier substance, in solution, to the active substance, for example, by spray drying or precipitation. The second type involves condensation of a barrier substance, from a vapour of the barrier substance, onto particles of active material.

However, there remains a need to develop a delayed release composition for pulmonary administration having satisfactory properties.

The present invention provides microparticles for use in a pharmaceutical composition for pulmonary administration, each microparticle comprising a particle of active substance having, on its surface, particles of a hydrophobic material suitable for delaying the dissolution of the active substance.

The term "microparticles" as used herein refers to particles of a size suitable for pulmonary administration or smaller, for example, having an MMAD of 10 μm or less.

The microparticles of the invention are able to release the active substance over a longer period than similarly-sized particles of the active substance alone and therefore a reduced frequency of administration, preferably only once a day or less, is possible. Furthermore, that delayed release of the active substance provides a lower initial peak of concentration of the active substance which may result in reduced side effects associated with the active substance.

The hydrophobic material will be suitable for delaying the dissolution of the active substance in an aqueous medium. A test method for determining whether a particular hydrophobic substance is suitable for delaying that dissolution is given below. The test may also be used for determining the extent of the reduction in the rate of dissolution and references herein to a reduction in that rate are to be understood as referring to the test given below. An alternative measure of hydrophobicity is the contact angle. The contact angle of a material is the angle between a liquid droplet and the surface of the material over which it spreads. The hydrophobic material preferably has a contact angle of more than 90°, more preferably more than 95° and most preferably more than 100°. The skilled person will be aware of suitable methods of measuring the contact angle for a particular substance.

The hydrophobic material will be pharmacologically acceptable for administration to the lungs in the amounts required according to the invention. Preferably, the hydrophobic material will not be sticky because sticky substances will tend to reduce dispersibility of the powder. Preferably, the hydrophobic material is a solid at room temperature.

Preferably, the hydrophobic material is one which is suitable for promoting the dispersal of the active particles on actuation of an inhaler.

The particles of hydrophobic material may include a combination of one or more substances. Preferably, all of those substances are hydrophobic materials but it is within the scope of the invention for the hydrophobic particles to include one or more substances which are not themselves hydrophobic, as long as the particles also contain materials which are hydrophobic in sufficient quantity that the mixture is hydrophobic as defined herein.

Preferably, the hydrophobic material is a naturally occurring animal or plant substance.

Advantageously, the hydrophobic material includes one or more compounds selected from hydrophobic amino acids and derivatives thereof, and hydrophobic peptides and polypeptides having a molecular weight from 0.25 to 1000 Kda, and derivatives thereof. Hydrophobic amino acids, peptides or polypeptides and derivatives of peptides or polypeptides are often physiologically acceptable.

It is advantageous for the hydrophobic material to comprise a hydrophobic amino acid. The additive material may comprise one or more of any of the following amino acids: tyrosine, tryptophan, glutamic acid, aspartic acid, leucine, isoleucine, lysine, valine, methionine, phenylalanine. The additive may be a salt or a derivative of an amino acid, for example, aspartame or acesulfame K. Preferred derivatives include salts, esters and amides. Preferably, the additive particles consist substantially of an amino acid, more preferably of leucine, advantageously L-leucine. The D- and DL-forms may also be used.

The hydrophobic material may have a limited degree of water solubility. This helps absorption of the hydrophobic substance by the body when the hydrophobic material reaches the lower lung. The hydrophobic material may, how-

ever, be insoluble in water, for example, the hydrophobic material may be magnesium stearate.

The hydrophobic material may comprise lecithin or a phospholipid or a derivative thereof such as an ester, amide or salt.

Preferably, the hydrophobic material comprises or consists of a C_{10} to C_{22} carboxylic acid which may be linear or branched, saturated or unsaturated or a derivative thereof such as an ester, amide or a salt.

Advantageously, the hydrophobic material comprises a metal stearate, or a derivative thereof, for example, sodium stearyl fumarate or sodium stearyl lactylate. Preferably, the hydrophobic material comprises a metal stearate. For example, magnesium stearate, calcium stearate, sodium stearate or lithium stearate. Preferably, the hydrophobic material comprises magnesium stearate.

The hydrophobic material may include or consist of one or more surface active materials, in particular materials that are surface active in the solid state, which may be water soluble to some degree, for example, lecithin, in particular soya lecithin, or substantially water insoluble, for example, solid state fatty acids such as oleic acid, behenic acid, or derivatives (such as esters and salts) thereof such as glyceryl behenate. Specific examples of such materials are: phosphatidylethanolamines, phosphatidylcholines, phosphatidylglycerols and other examples of natural synthetic lung surfactants; triglycerides such as DYNASAN 118 and CUTINA HR; and sugar esters in general, hydrogenated oils which are solid at room temperature, sorbitan esters which are solid at room temperature, cetyl stearyl alcohol and cetyl alcohol.

The hydrophobic material preferably comprises one or more materials selected from the group consisting of hydrophobic amino acids, lecithins, phospholipids, metal stearates (especially magnesium stearate), sodium stearyl fumarate, solid state fatty acids and glyceryl behenate.

The optimum amount of hydrophobic material will depend on, inter alia, the chemical composition and other properties of the hydrophobic material and upon the nature and particle size of the active material. In general, the amount of hydrophobic material in the composite particles will be not more than 90% by weight, based on the total weight of the microparticles.

Advantageously, the microparticles comprise not more than 80%, more preferably not more than 60%, more preferably not more than 40% by weight of the hydrophobic material, based on the total weight of the microparticles. The microparticles will usually comprise at least 0.01% by weight of the hydrophobic material and will preferably comprise at least 1%, more preferably at least 5% and optionally at least 15% by weight of the hydrophobic material, based on the total weight of the microparticles.

The microparticles advantageously comprise at least 0.1% by weight, preferably at least 1%, more preferably at least 10%, more advantageously at least 50% and especially advantageously at least 90% by weight of the active substance based on the total weight of the microparticles. The microparticles will, in general, not comprise more than 99.9% by weight of the active substance based on the total weight of the microparticles.

The mass median aerodynamic diameter of the microparticles is preferably not more than 10 μm, and advantageously not more than 5 μm, more preferably not more than 3 μm and may be less than 1 μm. Accordingly, advantageously at least 90% by weight of the microparticles have a diameter of not more than 10 μm, advantageously not more than 5 μm, preferably not more than 3 μm and optionally not more than 1 μm. Advantageously, the microparticles will be the size of a suitable size for inhalation to the desired part of the lung, for example, having an MMAD in the range of 3 to 0.1 μm for absorption in the deep lung, 5 to 0.5 μm for absorption in the respiratory bronchioles, 10 to 2 μm for delivery to the higher respiratory system and 2 to 0.05 μm for delivery to the alveoli. Accordingly, advantageously at least 90% by weight of the microparticles have an aerodynamic diameter in the range of 3 to 0.1 μm, preferably 5 to 0.5 μm, advantageously 10 to 2 μm, and especially advantageously 2 to 0.05 μm. The MMAD of the microparticles will not normally be lower than 0.1 μm.

Alternatively, the microparticles may have diameters lower than the preferred range but may be present in the form of agglomerated microparticles, those agglomerated microparticles having mass median aerodynamic diameters in one of the ranges described above. The term "agglomerated microparticles" refers to particles which consist of more than one microparticle, those microparticles being adhered to each other. For example, an agglomerated microparticle of diameter 5 μm may consist of a large number of microparticles each having a diameter of 1 μm or less, adhered together. The agglomerated microparticles will normally be sufficiently stable that they do not break up during administration to the patient. The microparticles may also have on their surfaces a film forming material which may help to bind them together in an agglomerate.

Advantageously, the microparticles have at least a partial coating of a film-forming material which acts as a further barrier to the release of the active substance. The film-forming material will be pharmaceutically acceptable for administration to the lungs in amounts required in accordance with the invention. Suitable film forming materials are disclosed in U.S. Pat. No. 5,738,865 and U.S. Pat. No. 5,612,053 and include polysaccharides such as xanthan gum. Other preferred polysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, the propylene glycol ester and the polyethylene glycol esters and galactomannan gums, which are polysaccharides composed solely of mannose and galactose. Locust bean gum, which has a higher ratio of mannose to the galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

Other naturally occurring polysaccharide gums known to those skilled in the food and pharmaceutical arts are also useful as the delayed release carrier of the invention. Such polysaccharides include alginic acid derivatives, carageenans, tragacanth, acacia, karaya, the polyethylene glycol esters of these gums, chitin, chitosan, mucopolysaccharides, konjac, starch, substituted starches, starch fragments, dextrins, British gums having a molecular weight of about 10,000 daltons, dextrans and the like. The starches can either be in native form i.e., ungelled starches such as potato, corn, rice, banana, etc., or gelled starches or semi-synthetic starches.

Starch and starch fragments are especially preferred polysaccharides and the combination of xanthan gum with locust bean gum is an especially preferred gum combination.

Other film-forming materials include pharmaceutically acceptable synthetic polymeric compounds such as polyvinylpyrrolidone (PVP) and protein materials such as albumin and gelatin.

The film-forming material may be present in an amount of from 99% to about 10%, preferably from 50% to about 10%, by weight based on the total weight of the microparticles, that is, the total weight of the active substance and the hydrophobic material.

Preferably, the microparticles are such that, when inhaled, the active substance exerts its pharmacological effect over a period significantly greater (for example, greater by at least 20%, more preferably at least 50%) than the period over

which the active substance exerts its pharmacological effect when inhaled alone (that is, when an equivalent quantity of the active substance is inhaled in the form of inhalable particles consisting of the active substance).

The invention will be of particular value where the active substance is one which exerts its pharmacological effect over a limited period and where, for therapeutic reasons, it is desired to extend that period. Preferably, the microparticles comprise an active substance that, when inhaled, exerts its pharmacological effect over a period of less than 12 hours, the microparticles being such that the active substance exerts its pharmacological effect over a period greater than 12 hours. The duration of the pharmacological effect for any particular active substance can be measured by methods known to the skilled person and will be based on the administration of the dose of that substance that is recognised as being optimal for that active substance in the circumstances. For example, where the active substance is salbutamol sulphate, the duration of the pharmacological effect will be measured by measuring the effect of administering a dose of the medically-recommended quantity of salbutamol upon the patients' respiratory volume. The means of measuring the duration of the period over which a particular active substance exerts its pharmacological effect will depend upon the nature of the active substance and may include, for example, the monitoring of variables relating to inhalation such as FEV_1 level where the active substance is one which exerts a pharmacological effect over the pulmonary system, for example, salbutamol. Further examples include the monitoring of blood sugar levels where the active substance is insulin or the subjective monitoring of pain relief by the patient where the active substance is an analgesic. Where it is not possible to unambiguously monitor the duration of the pharmacological effect of the active substance, for example, because that duration depends from instance to instance upon external factors beyond experimental control, the duration of the pharmacological effect may be assumed to be the same as the duration over which the active substance has the desired concentration in a relevant bodily fluid. Methods for measuring such concentrations are known to the skilled person. Advantageously, the microparticles are such that the active substance exerts its pharmacological effect over a period of at least 15 hours, preferably at least 24 hours.

Preferably, the microparticles are such that the rate of dissolution of the active substance (when tested according to the procedure given below) is no greater than 80%, more preferably no greater than 70%, advantageously no greater than 50% and most preferably no greater than 30%, of the rate of dissolution of particles of the active substance.

Optionally, the microparticles do not comprise an effective amount of an antimuscarinic substance. Optionally, the microparticles do not comprise an effective amount of glycopyrrolate. Optionally, the microparticles do not consist of a mixture of micronised glycopyrrolate and magnesium stearate in the ratio of 75:25 by mass. Suitable active substances include materials for therapeutic and/or prophylactic use. Active substances which may be included in the formulation include those products which are usually administered orally by inhalation for the treatment of disease such as respiratory disease, for example, β-agonists.

The active substance may be a β_2-agonist, for example, a compound selected from terbutaline, salbutamol, salmeterol and formetorol. If desired, the microparticles may comprise more than one of those active substances, provided they are compatible with one another under conditions of storage and use. Preferably, the active substance may be salbutamol sulphate. References herein to any active agent is to be understood to include any physiologically acceptable derivative. In the case of the β_2-agonists mentioned above, physiologically acceptable derivatives include especially salts, including sulphates.

The active substance may be a steroid, which may be beclomethasone dipropionate or may be fluticasone. The active substance may be a cromone which may be sodium cromoglycate or nedocromil. The active substance may be a leukotriene receptor antagonist.

The active substance may be a carbohydrate, for example heparin.

The active substance may advantageously comprise a pharmacologically active substance for systemic use and advantageously is capable of being absorbed into the circulatory system via the lungs. For example, the active substance may be a peptide or a polypeptide such as Dnase, leukotrienes or insulin. Preferably, the active substance is a biological macromolecule, for example, a polypeptide, a protein, or a DNA fragment. The active substance may be selected from the group consisting of insulin, human growth hormone, cytokines, cyclosporin, interferon, gonadotrophin agonists and antagonists, erythropoietin, leptin, antibodies, vaccines, antisense oligonucleotides, calcitonin, somotastatin, parathyroid hormone, alpha-1-antitrypsin, Factor 7, Factor 8, Factor 9, and estradiol. Advantageously the active substance is selected from the group consisting of insulin, human growth hormone, cytokines, cyclosporin, interferon, gonadotrophin agonists and antagonists, erythropoietin, leptin, antibodies, vaccines and antisense oligonucleotides. The microparticles of the invention may in particular have application in the administration of insulin to diabetic patients, preferably avoiding the normally invasive administration techniques used for that agent. The microparticles could also be used for pulmonary administration of other agents, for example, for pain relief (e.g. analgesics such as fentanyl or dihydroergotamine which is used for the treatment of migraine), anti-cancer activity, anti-virals, antibiotics or the local delivery of vaccines to the respiratory tract.

The active substance is present in the form of particles and at least some of the hydrophobic material is present on the surfaces of those particles of active substance. Such microparticles may be formed by dry mixing together particles of active substance and particles of hydrophobic substance or by combining particles of the hydrophobic substance with particles of active substance to form, in a liquid, a suspension, followed by the evaporation of the solvent to leave the particles of hydrophobic material on the surface of the particles of active substance.

The terms "active particles" and "particles of active substance" are used interchangeably herein. The active particles referred to throughout the specification will comprise one or more pharmacologically active substances. The active particles will advantageously consist essentially of one or more pharmacologically active substances.

The hydrophobic material may be in the form of a coating on the surfaces of the active particles. The coating may be a discontinuous coating. The hydrophobic material may be in the form of particles adhering to the surfaces of the particles of the active material. Furthermore, as explained above, at least some of the microparticles may be in the form of agglomerates.

The invention further provides a composition for inhalation comprising microparticles as described above. Preferably, the composition is a dry powder and is suitable for use in a dry powder inhaler. Such compositions may comprise essentially only the microparticles or they may comprise additional ingredients such as carrier particles and flavouring

agents. Carrier particles may be of any acceptable excipient material or combination of materials. For example, the carrier particles may consist substantially of one or more materials selected from sugar alcohols, polyols and crystalline sugars. Other suitable carriers include inorganic salts such as sodium chloride and calcium carbonate, organic salts such as sodium lactate and other organic compounds such as polysaccharides and oligosaccharides. Advantageously, the carrier particles are of a polyol. In particular the carrier particles may consist substantially of a crystalline sugar, for example mannitol, dextrose or lactose. Preferably, the carrier particles are of lactose.

Advantageously, substantially all (by weight) of the carrier particles have a diameter which lies between 20 μm and 1000 μm, more preferably 50 μm and 1000 μm. Preferably, the diameter of substantially all (by weight) of the carrier particles is less than 355 μm and lies between 20 μm and 250 μm. Preferably at least 90% by weight of the carrier particles have a diameter between from 60 μm to 180 μm. The relatively large diameter of the carrier particles improves the opportunity for other, smaller particles to become attached to the surfaces of the carrier particles and to provide good flow and entrainment characteristics and improved release of the active particles in the airways to increase deposition of the active particles in the lower lung.

The ratio in which the carrier particles (if present) and microparticles are mixed will, of course, depend on the type of inhaler device used, the active substance used and the required dose. The carrier particles are preferably present in an amount of at least 50%, more preferably 70%, advantageously 90% and most preferably 95% based on the combined weight of the microparticles and the carrier particles.

Where carrier particles are included in the pharmaceutical composition, that composition preferably also includes small excipient particles having, for example, a particle size between 5 to 20 μm. Preferably the small excipient particles are present in an amount of from 1% to 40%, more preferably 5% to 20% based on the weight of the carrier particles.

The pharmaceutical composition may comprise a propellant and be suitable for use in a pressurised metered dose inhaler. The microparticles will be present as a suspension in the propellant and the composition may include one or more surfactants known in the art for stabilising such suspensions.

The invention further provides a method of preparing microparticles for use in a pharmaceutical composition for pulmonary administration, each microparticle comprising an active substance and a hydrophobic material suitable for delaying the dissolution of the active substance, the method comprising the step of combining the active substance with the hydrophobic material.

Preferably, as noted above, particles comprising the active substance are combined with particles of the hydrophobic material. Preferably, the active substance is milled in the presence of the hydrophobic material.

The word "milling" as used herein refers to any mechanical process which applies sufficient force to the particles of active material that it is capable of breaking coarse particles (for example, particles of mass medium aerodynamic diameter greater than 100 μm) down to fine particles of mass median aerodynamic diameter not more than 50 μm or which applies a relatively controlled compressive force as described below in relation to the Mechano-Fusion and Cyclomix methods. It has been found that processes such as blending which do not apply a high degree of force are not effective in the method of the invention. It is believed that is because a high degree of force is required to separate the individual particles of active material and to break up tightly bound agglomerates of the active particles such that effective mixing and effective application of the hydrophobic material to the surfaces of those particles is achieved. It is believed that an especially desirable aspect of the milling process is that the hydrophobic material may become deformed in the milling and may be smeared over or fused to the surfaces of the active particles. It should be understood, however, that in the case where the particles of active material are already fine, for example, having a mass median aerodynamic diameter below 20μ prior to the milling step, the size of those particles may not be significantly reduced. The important thing is that the milling process applies a sufficiently high degree of force or energy to the particles.

The method of the invention generally involves bringing the particles of hydrophobic material into close contact with the surfaces of the active particles. In order to achieve coated particles, a degree of intensive mixing is required to ensure a sufficient break-up of agglomerates of both constituents, dispersal and even distribution of additive over the host active particles.

Where the particles of hydrophobic material are very small (typically <1 micron), generally less work is required, firstly, as it is not required to break or deform but only to deagglomerate, distribute and embed the additive particles onto the active particle and, secondly, because of the naturally high surface energies of such small particles of hydrophobic material. It is known that where two powder components are mixed and the two components differ in size, there is a tendency for the small particles to adhere to the large particles (to form so called 'ordered mixes'). The short range Van der Waals interactions for such very fine components may be sufficient to ensure adhesion. However, where both the particles of hydrophobic material and active particles are very fine (for example less than 5 microns) a substantial degree of mixing will be required to ensure a sufficient break-up of agglomerates of both constituents, dispersal and even distribution of additive particles over the active particles as noted above. In some cases a simple contact adhesion may be insufficient and a stronger embedding or fusion of particles of hydrophobic material onto active particles is required to prevent segregation, or to enhance the structure and functionality of the coating.

Where the particles of hydrophobic material are not so small as to be sufficiently adhered by Van der Waals forces alone, or where there are advantages to distorting and/or embedding the particles of hydrophobic material substantially onto the host active particle, a greater degree of energy is required from the milling. In this case, the particles of hydrophobic material should experience sufficient force to soften and/or break, to distort and to flatten them. These processes are enhanced by the presence of the relatively harder active particles which act as a milling media as well as a de-agglomerating media for such processes. As a consequence of this process the particles of hydrophobic material may become wrapped around the core active particle to form a coating. These processes are also enhanced by the application of a compression force as mentioned above.

As a consequence of the milling step, complete or partial, continuous or discontinuous, porous or non-porous coatings may be formed. The coatings originate from a combination of active particles and particles of hydrophobic material. They are not coatings such as those formed by wet processes that require dissolution of one or both components. In general, such wet coating processes are likely to be more costly and more time consuming than the milling process and also suffer from the disadvantage that it is less easy to control the location and structure of the coating.

A wide range of milling devices and conditions are suitable for use in the method of the invention. The milling conditions, for example, intensity of milling and duration, should be selected to provide the required degree of force. Ball milling is a preferred method. Centrifugal and planetary ball milling are especially preferred methods. Alternatively, a high pressure homogeniser may be used in which a fluid containing the particles is forced through a valve at high pressure producing conditions of high shear and turbulence. Shear forces on the particles, impacts between the particles and machine surfaces or other particles and cavitation due to acceleration of the fluid may all contribute to the fracture of the particles and may also provide a compressive force. Such homogenisers may be more suitable than ball mills for use in large scale preparations of the composite active particles. Suitable homogensiers include EMULSIFLEX® high pressure homogenisers which are capable of pressure up to 4000 Bar, Niro Soavi high pressure homogenisers (capable of pressures up to 2000 Bar), and Microfluidics Microfluidisers (maximum pressure 2750 Bar). The milling step may, alternatively, involve a high energy media mill or an agitator bead mill, for example, the Netzch high energy media mill, or the DYNO-mill (Willy A. Bachofen A G, Switzerland). Alternatively the milling may be a dry coating high energy process such as a Mechano-Fusion system (Hosokawa Micron Ltd) or a Hybridizer (Nara). Other possible milling devices include air jet mills, pin mills, hammer mills, knife mills, ultracentrifugal mills and pestle and mortar mills.

Especially preferred methods are those involving the Mechano-Fusion, Hybridiser and Cyclomix instruments.

Preferably, the milling step involves the compression of the mixture of active particles and particles of hydrophobic material in a gap (or nip) of fixed, predetermined width (for example, as in the Mechano-Fusion and Cyclomix methods described below).

Some preferred milling methods will now be described in greater detail.

Mechano-Fusion:

As the name suggests, this dry coating process is designed to mechanically fuse a first material onto a second. The first material is generally smaller and/or softer than the second. The Mechano-Fusion and Cyclomix working principles are distinct from alternative milling techniques in having a particular interaction between inner element and vessel wall, and are based on providing energy by a controlled and substantial compressive force.

The fine active particles and the particles of hydrophobic particles are fed into the Mechano-Fusion driven vessel, where they are subject to a centrifugal force and are pressed against the vessel inner wall. The powder is compressed between the fixed clearance of the drum wall and a curved inner element with high relative speed between drum and element. The inner wall and the curved element together form a gap or nip in which the particles are pressed together. As a result the particles experience very high shear forces and very strong compressive stresses as they are trapped between the inner drum wall and the inner element (which has a greater curvature than the inner drum wall). The particles violently collide against each other with enough energy to locally heat and soften, break, distort, flatten and wrap the particles of hydrophobic material around the core particle to form a coating. The energy is generally sufficient to break up agglomerates and some degree of size reduction of both components may occur. Embedding and fusion of particles of hydrophobic material onto the active particles may occur, facilitated by the relative differences in hardness (and optionally size) of the two components. Either the outer vessel or the inner element may rotate to provide the relative movement. The gap between these surfaces is relatively small, and is typically less than 10 mm and is preferably less than 5 mm, more preferably less than 3 mm. This gap is fixed, and consequently leads to a better control of the compressive energy than is provided in some other forms of mill such as ball and media mills. Also, preferably, no impaction of milling media surfaces is present so that wear and consequently contamination are minimised. The speed of rotation may be in the range of 200 to 10,000 rpm. A scraper may also be present to break up any caked material building up on the vessel surface. This is particularly advantageous when using fine cohesive starting materials. The local temperature may be controlled by use of a heating/cooling jacked built into the drum vessel walls. The powder may be re-circulated through the vessel.

Cyclomix Method (Hosokawa Micron):

The Cyclomix comprises a stationary conical vessel with a fast rotating shaft with paddles which move close to the wall. Due to the high rotational speed of the paddles, the powder is propelled towards the wall, and as a result the mixture experiences very high shear forces and compressive stresses between wall and paddle. Such effects are similar to the Mechano-Fusion as described above and may be sufficient to locally heat and soften, to break, distort, flatten and wrap the particles of hydrophobic material around the active particles to form a coating. The energy is sufficient to break up agglomerates and some degree of size reduction of both components may also occur depending on the conditions and upon the size and nature of the particles.

Hybridiser Method:

This is a dry process which can be described as a product embedding or filming of one powder onto another. The fine active particles and fine or ultra fine particles of hydrophobic material are fed into a conventional high shear mixer pre-mix system to form an ordered mixture. This powder is then fed into the Hybridiser. The powder is subjected to ultra-high speed impact, compression and shear as it is impacted by blades on a high speed rotor inside a stator vessel, and is re-circulated within the vessel. The active particles and particles of hydrophobic material collide with each other. Typical speeds of rotation are in the range of 5,000 to 20,000 rpm. The relatively soft fine additive particles experience sufficient impact force to soften, break, distort, flatten and wrap around the active particle to form a coating. There may also be some degree of embedding into the surface of the active particles.

Other preferred methods include ball and high energy media mills which are also capable of providing the desired high shear force and compressive stresses between surfaces, although as the clearance gap is not controlled, the coating process may be less well controlled than for Mechano-Fusion milling and some problems such as a degree of undesired re-agglomeration may occur. These media mills may be rotational, vibrational, agitational, centrifugal or planetary in nature.

It has been observed in some cases that when ball milling active particles with hydrophobic material, a fine powder is not produced. Instead the powder was compacted on the walls of the mill by the action of the mill. That has inhibited the milling action and prevented the preparation of the microparticles. That problem occurred particularly when certain hydrophobic materials were used, in cases where the hydrophobic material was present in small proportions (typically <2%), in cases where the milling balls were relatively small (typically <3 mm), in cases where the milling speed was too slow and where the starting particles were too fine. To prevent this occurring it is advantageous to ball mill in a liquid

medium. The liquid medium reduces the tendency to compaction, assists the dispersal of hydrophobic material and improves any milling action.

It has been found to be preferable to use a large number of fine milling balls, rather than fewer heavy balls. The finer balls perform a more efficient co-milling action. Preferably the balls have a diameter of less than 5 mm, advantageously less than 2 mm. Liquid media are preferred which do not dissolve the active material and which evaporate rapidly and fully, for example non-aqueous liquids such as diethylether, acetone, cyclohexane, ethanol, isopropanol or dichloromethane. Liquid media are preferred which are non flammable, for example dichloromethane and fluorinated hydrocarbons, especially fluorinated hydrocarbons which are suitable for use as propellants in inhalers.

Pestle and mortar mills are other mills which also provide a very high shear force and compressive stresses between surfaces.

Mechano-Micros and Micros mills made by Nara (where particles are compressed by rotating grinding rings) may also be used. Mills referred to as impact mixers, attrition mills, pin mills and disc mills may also be used.

The mass median aerodynamic diameter of the particles of active material may be substantially reduced during the milling step especially when the active material is in the form of coarse particles prior to the milling step. The mass median aerodynamic diameter (MMAD) of the particles of active material may be reduced by at least 10%, by at least 50%, or by at least 70% during the milling step depending on the milling conditions and the MMAD of the active particles prior to the milling step.

Advantageously, after the milling step, the MMAD of the active particles is less than 9 μm, preferably less then 4 μm and more preferably less then 2 μm.

In a similar way, where the hydrophobic material is in the form of coarse particles prior to the milling step, their MMAD will be substantially reduced during the milling step. The MMAD of the particles of hydrophobic material may be reduced by at least 10%, at least 50% or at least 70% during the milling step, depending on the milling conditions and on the MMAD of the particles of hydrophobic material before the milling step.

The size of the particles of hydrophobic material after the milling step is preferably significantly less than the size of the active particles, to enable the hydrophobic materials to more effectively coat the surfaces of the active particles. In practice, that difference in size between the active particles and particles of hydrophobic material will be achieved as a consequence of the milling because the hydrophobic material will usually be more easily fractured or deformed than the active material and so will be broken into smaller particles than the active material. As noted above, the particles of hydrophobic material preferably become smeared over or fused to the surfaces of the particles of active material, thereby forming a coating which may be substantially continuous or discontinuous. Where the coating is discontinuous, it preferably covers on average of at least 50% (that is, at least 50% of the total surface area of the active particles will be covered by additive material), more advantageously at least 70% and most preferably at least 90% of the surfaces of the active particles. The coating is preferably on average less than 1 μm, more preferably less than 0.5 μm and most preferably less than 200 nm thick.

The milling step may be carried out in a closed vessel, for example in a ball mill or a Mechano-Fusion device. The use of a closed vessel prevents loss of ultrafine particles or vapour of the hydrophobic material which has been found to occur in jet milling or other open processes. Preferably, the milling is not jet milling (micronisation).

The milling may be wet milling, that is, the milling step may be carried out in the presence of a liquid. That liquid medium may be high or low volatility and of any solid content as long as it does not dissolve the active particles to any significant degree and its viscosity is not so high that it prevents effective milling. The liquid medium preferably is not aqueous. The liquid is preferably one in which the hydrophobic material is substantially insoluble but some degree of solubility may be acceptable as long as there is sufficient hydrophobic material present that undissolved particles of hydrophobic material remain. The presence of a liquid medium helps to prevent compacting of the particles of active material on the walls of the vessel and may also allow the more even spreading of the hydrophobic material on the surface of the particles of active material as compared to dry milling.

It has been found that the Mechano-Fusion and Cyclomix techniques referred to above often provide the microparticles as individual, that is, unagglomerated microparticles. That is in contrast to less controlled methods such as ball milling, which have been found to often produce the microparticles in the form of agglomerated microparticles.

Alternatively, particles comprising the active substance are combined with the particles of hydrophobic material in a spray drying step, that is, by spray drying a suspension comprising the particles of active substance and particles of hydrophobic substances. The film forming material, if present, will be dissolved in the suspension. The skilled person will be able to select appropriate spray drying conditions. A number of commercially available spray drying machines can be used to prepare the microparticles of the invention, for example, suitable machines are manufactured by Buchi and Niro. In a typical spray drying machine the suspension to be dried is pumped from a stirred reservoir to an atomisation chamber where it is sprayed from a nozzle as fine droplets (preferably the droplets are in the range of 1 to 20 μm in diameter) into a stream of heated air, for example, inlet temperatures in the range of 50 to 150° C. (nitrogen can be used in place of air if there is a risk of undesirable oxidation of the active substance). The temperature of the heated air must be sufficient to evaporate the liquid and dry the microparticles to a free flowing powder but should not be so high as to degrade the active substance. The microparticles may be collected in a cyclone or a filter or a combination of cyclones and filters.

The invention also provides a method of pulmonary administration of an active substance comprising the step of administering microparticles as described above to a person in need thereof.

The invention also provides the use of a hydrophobic material in a pharmaceutical composition comprising an active substance for pulmonary administration, to delay the dissolution of the active substance in the lung. Preferably, the use of the hydrophobic substance reduces the rate of dissolution of the active substance by at least 20%, preferably at least 30% and more preferably by at least 50%.

According to a further aspect of the invention, a pharmaceutical composition for pulmonary delivery comprises an active substance that exerts a pharmacological effect over a period less than 12 hours, in a delayed release formulation, wherein, on administration, the formulation permits the active substance to exert its pharmacological effect over a period greater than 12 hours.

The delayed release formulation will preferably comprise or consist of microparticles as described above.

Embodiments of the invention will now be described for the purposes of illustration only with reference to the Figures in which:

FIG. **1** shows an apparatus used in the dissolution test;

FIG. **2** shows the results of the dissolution test on the formulations of Example 3;

FIG. **3** shows dissolution curves for salbutamol sulphate and salbutamol sulphate/magnesium stearate blends;

FIG. **4** shows dissolution curves for sieved and unsieved blends of salbutamol sulphate and magnesium stearate;

FIG. **5** is a schematic drawing of part of a Mechano-Fusion machine; and

FIGS. **6** and **7** are electron micrographs of composite active particles according to the invention comprising salbutamol sulphate and magnesium stearate in a ratio of 19:1.

EXAMPLE 1a

5 g of micronised salbutamol sulphate (particle size distribution: 1 to 5 μm) and 0.5 g of magnesium stearate were added to a 50 cm^3 stainless steel milling vessel together with 20 cm^3 dichloromethane and 124 g of 3 mm stainless steel balls. The mixture was milled at 550 rpm in a Retsch S100 Centrifugal Mill for 5 hours. The powder was recovered by drying and sieving to remove the mill balls. The powders were examined using a scanning electron microscope and were found to have particles in the size range 0.1 to 0.5 μm.

EXAMPLE 1b

Micronised salbutamol sulphate and magnesium stearate were combined as particles in a suspension in the ratio 10:1 in propanol. This suspension was processed in an Emulsiflex C50 high pressure homogeniser by 5 sequential passes through the system at 25,000 psi. This dry material was then recovered by evaporating the propanol.

EXAMPLE 1c

It was found that, on drying, the powder prepared in Example 1a including magnesium stearate as additive material formed assemblies of primary particles which were hard to deagglomerate. A sample of this powder was re-dispersed by ball milling for 90 minutes at 550 rpm in a mixture of ethanol, polyvinylpyrrolidone (PVPK30) and HFA227 liquid propellant to give the following composition:

0.6% w/w	Salbutamol sulphate/magnesium stearate microparticles
0.2% w/w	PVPK30
5.0% w/w	Ethanol
94.2% w/w	HFA 227

(The PVP was included to stabilise the suspension of the microparticles in the ethanol/HFA227).

The composition was sprayed from a pressurised can through an orifice ~0.4 mm in diameter to produce dried microparticles of salbutamol sulphate and magnesium stearate with PVP. Those particles were collected and examined and were found to be in the aerodynamic size range 0.1 to 4 μm.

EXAMPLE 2

The process of Example 1c was repeated except that the composition was as follows:

3% w/w	Salbutamol sulphate/magnesium stearate microparticles
1% w/w	PVPK30
3% w/w	Ethanol
93% w/w	HFA 227

Similarly, a sample was redispersed in dichloromethane and spray dried.

EXAMPLE 3

A mixture of micronised glycopyrrolate and magnesium stearate in the ratio 75:25 by mass (total mass of approximately 1 g) was placed in a ball mill on top of 100 g of 2 mm stainless steel balls. The mill volume was approximately 58.8 cm^3. 5 cm^3 of cyclohexane was added to wet the mixture. The mill was sealed and secured in a Retsch S100 centrifuge. Centrifugation was then carried out at 500 rpm for 240 minutes in total. Small samples (approximately 5-10 mg) of wet powder were then removed from the mill every 60 minutes. The samples were dried in an oven at 37° C. under a vacuum, prior to using the samples in the dissolution test.

The samples were analysed in a Cecil Aquarius CE7200 ultraviolet spectrophotometer at a wavelength of 200 nm. The concentration of the samples was calculated with a previously prepared calibration graph and the concentration versus time was plotted. To establish the base line diffusion characteristics of the system, 1 cm^3 aqueous solution containing 1 mg of glycopyrrolate was added to the system and the samples taken as above. The results are shown in FIG. **2**.

FIG. **2** shows that the sample containing only glycopyrrolate exhibited a quick release of the glycopyrrolate into the reservoir, with the first time point at 5 minutes showing a concentration of greater than 10 mg/l. In contrast, the glycopyrrolate/magnesium stearate composition showed the delayed release properties, with a concentration at 5 minutes of approximately 3.7 mg/l. The maximum concentration is achieved after 40 minutes in contrast to that of glycopyrrolate only, which achieves the maximum concentration at only 10 minutes.

EXAMPLE 4

Salbutamol Sulphate/Magnesium Stearate Blends

a) Homogenised Magnesium Stearate

240 g magnesium stearate (Riedel de Haen, particle size by Malvern laser diffraction:d_{50}=9.7 μm) was suspended in 2150 g dichloroethane. That suspension was then mixed for 5 minutes in a Silverson high shear mixer. The suspension was then processed in an Emulsiflex C50 high pressure homogeniser fitted with a heat exchanger at 10000 psi for 20 minutes in circulation mode (300 cm^3/min) for 20 minutes. The suspension was then circulated at atmospheric pressure for 20 minutes allow it to cool. The next day, the suspension was processed in circulation mode (260 cm^3/min) at 20000 psi for 30 minutes. The dichloroethane was removed by rotary evaporation followed by drying in a vacuum over at 37° C. overnight. The resulting cake of material was broken up by ball milling for 1 minute. The homogenised magnesium stearate had a particle size of less than 2 μm.

b) A 9:1 by weight blend of salbutamol sulphate and homogenised magnesium stearate having a particle size of less than 2 μm was prepared by blending the two materials with a spatula. An electron micrograph of the blended material showed that

the blend was mostly in the form of agglomerated particles, the agglomerates having diameters of 50 μm and above. The blend was then processed in a Mechano-Fusion mill (Hosokawa) as follows:

Machine data:	Hosokawa Mechano-Fusion:	AMS-Mini
	Drive:	2.2 kW
	Housing:	stainless steel
	Rotor:	stainless steel
	Scraper:	None
	Cooling:	Water
	Gas purge:	None

The Mechano-Fusion device (see FIG. **5**) comprises a cylindrical drum **1** having an inner wall **2**. In use, the drum rotates at high speed. The powder **3** of the active and additive particles is thrown by centrifugal force against the inner wall **2** of the drum **1**. A fixed arm **4** projects from the interior of the drum in a radial direction. At the end of the arm closest to the wall **2**, the arm is provided with a member **5** which presents an arcuate surface **6**, of radius of curvature less than that of inner wall **2**, toward that inner wall. As the drum **1** rotates, it carries powder **3** into the gap between arcuate surface **6** and inner wall **2** thereby compressing the powder. The gap is of a fixed, predetermined width A. A scraper (not shown in FIG. **5**) may be provided to scrape the compressed powder from the wall of the drum.

All samples were premixed for 5 minutes by running the machine at 1000 rpm. The machine speed was then increased to 5050 rpm for 30 minutes. The procedure was repeated for salbutamol sulphate/magnesium stearate in the following weight ratios: 19:1, 3:1, 1:1.

Electronmicrographs of the 19:1 processed material are shown in FIGS. **6** and **7** and indicate that the material was mostly in the form of simple small particles of diameter less than 5 μm or in very loose agglomerates of such particles with only one agglomerate of the original type being visible.

The 3:1 and the 19:1 blends were then each loaded into a 20 mg capsule and fired from a twin stage impinger. A sample of unprocessed salbutamol sulphate was also fired from the TSI to provide a comparison.

The fine particle fractions were then calculated and are given in table 1.

TABLE 1

Fine Particle Fraction results for salbutamol sulphate blends.

Composition	Fine Particle Fraction %
salbutamol sulphate	28
salbutamol sulphate/magnesium stearate 19:1	66
salbutamol sulphate/magnesium stearate 3:1	66

A 1 g sample of the 3:1 blend was suspended by ball milling in 10 cm^3 dichloromethane for 5 minutes. The suspension was then spray dried on a Buchi B191 spray dryer using the following conditions inlet T=50° C., aspirator 100%, liquid flow 10 cm^3/min nozzle air flow 800 cm^3/hr. The 3:1 blend, the spray dried 3:1 blend and a sample of salbutamol sulphate were then each tested for dissolution rate using the procedure outlined above. The results are shown in FIG. **3**. It is clear from FIG. **3** that the 3:1 blend of salbutamol sulphate:magnesium stearate dissolves at a significantly slower rate than the salbutamol sulphate with no magnesium stearate. That delayed dissolution effect is shown by the spray dried sample of the 3:1 blend. That contrasts to the results of similar experiments carried out using blends of drug and magnesium stearate where the magnesium stearate has not been homogenised (and does not have a particle size below 2 μm) in which spray drying of the blend has produced a significant decrease in the extent of the delayed dissolution effect.

To test the effect of any agglomeration in the blend upon the dissolution rate of the salbutamol sulphate in the blends a sample of the 3:1 salbutamol sulphate:magnesium stearate blend was brushed through a 45 μm sieve. FIG. **4** shows the dissolution curves for the sieved and unsieved blends and for salbutamol sulphate. It can be seen that the sieved and unsieved 3:1 blends had the same dissolution rate.

1) Standard Dissolution Test

This test is used as a model test for the length of time taken for a particular formulation to dissolve on the lung membrane.

The apparatus used is shown in FIG. **1** and comprises a 195 cm^3 reservoir (**1**) filled with deionised water (**2**) and having an inlet port (**3**) and an outlet port (**4**). A sintered glass disc (**5**) of approximately 50 mm diameter and 3 mm depth occupies an opening at the top of the reservoir (**1**) and sits horizontally in contact with the water (**2**). The water in the reservoir is stirred by a magnetic stirrer (**6**).

A known mass of approximately 1 mg of the formulation (**7**) to be tested is placed on the sinter and a timer is started. At various times, 1 cm^3 samples of the water are removed from the reservoir and are immediately replaced with 1 cm^3 deionised water to maintain the volume in the reservoir. The concentration of the active substance in the 1 cm^3 samples is determined by a suitable method. The particular method will, of course, depend on the nature of the active substance but such methods will be known to the skilled person.

A graph of concentration of the active substance in the reservoir of water versus time is then plotted.

2) Standard Formulation Test

In order to determine whether or not a particular hydrophobic material is suitable for delaying the dissolution of the active substance, the following test is carried out.

A standard test formulation is prepared in the following manner:

A mixture of salbutamol sulphate and the material to be tested in the ratio of 75:25 by mass (total mass of approximately 1 g) is placed in a ball mill chamber on top of 100 g of 2 mm diameter stainless steel balls. The mill chamber volume is approximately 58.8 cm^3. 5 cm^3 of an inert non-solvent is added to wet the mixture. The mill is sealed and secured in a Retsch S100 centrifuge. Centrifugation is then carried out at 500 rpm for 240 minutes in total. A small sample (approximately 5-10 mg) of wet powder is removed from the mill after 60 minutes. The sample is then dried in an oven at 37° C. under vacuum for 2 hours or as long as necessary to remove the inert non-solvent.

Where the hydrophobic material is such that no suitable non-solvent can be found, the mixture of salbutamol sulphate and the hydrophobic material is combined in a Mechano-Fusion apparatus as described above in example 4b).

The dry powder is then tested using the standard dissolution test given above.

The procedure is repeated using the active substance in the absence of the hydrophobic material in order to provide a basis for comparison. The resulting dried active substance is then tested using the standard dissolution test.

If the graph of concentration versus time for the active substance combined with the hydrophobic material shows

that that active substance in that combination has dissolved more slowly than the active substance alone, the hydrophobic material is regarded as being suitable for delaying the dissolution of the active substance.

The degree to which the hydrophobic material delays the dissolution of the active substance is a measure of the efficiency of the hydrophobic material. In particular, where it is desired to measure the delayed release performance of a particular formulation, that can be done by carrying out the standard dissolution test given above on a sample of the microparticles to be tested and upon a (control) sample of the active substance. For a true comparison the particle size distribution of the particles of the active substance must be the same or similar in the sample of formulation to be tested as in the (control) sample of active substance. The rate of dissolution of the active substance in the microparticles to be tested as a percentage of the rate of dissolution of the active substance alone can then be calculated by the following formula:

$$\%\ \text{rate of dissolution} = \frac{TA}{TF} \times 100$$

Where TA=time taken for the concentration of the active substance to reach a maximum for the sample of active substance alone.

Where TF=time taken for the concentration of the active substance to reach a maximum for the sample of the formulation to be tested.

Thus, for example, if the concentration of the active substance in the dissolution test on the formulation reached a maximum at 40 minutes and the concentration of the active substance alone reached a maximum at 10 minutes, the % rate of dissolution for the formulation would be 10/40×100=25%, corresponding to a decrease in the rate of dissolution of 75%.

An alternative method is to measure the contact angle. Additive materials having contact angles greater than 90° are also regarded as hydrophobic additive materials.

The invention claimed is:

1. Microparticles for use in a pharmaceutical composition for pulmonary administration, comprising particles of an active substance having, on their surfaces, particles of a hydrophobic material suitable for promoting the dispersal of the active particles on actuation of an inhaler and suitable for delaying the dissolution of the active substance, wherein the hydrophobic material comprises one or more materials selected from the group consisting of hydrophobic amino acids, metal stearates, a C_{10} to C_{22} carboxylic acid, phospholipids, and derivatives thereof.

2. The microparticles according to claim **1**, wherein the hydrophobic material comprises a C_{10} to C_{22} carboxylic acid, which may be linear or branched, saturated or unsaturated, or a derivative thereof.

3. The microparticles according to claim **1**, wherein the hydrophobic material comprises magnesium stearate.

4. The microparticles according to claim **1**, wherein the hydrophobic material comprises a phospholipid.

5. The microparticles according to claim **1**, which comprise not more than 90% of the hydrophobic material based on the total weight of the microparticles.

6. The microparticles according to claim **1**, having a mass median aerodynamic diameter of not more than 10 μm.

7. The microparticles as claimed in claim **1**, which are in the form of agglomerated microparticles.

8. The microparticles as claimed in claim **1**, which have at least a partial coating of a film-forming material.

9. The microparticles as claimed in claim **1**, being such that, upon inhalation of the microparticles, the active substance exerts its pharmaceutical effect over a period greater by at least 20% than the period over which the active substance exerts its pharmaceutical effect when inhaled alone.

10. The microparticles as claimed in claim l, having a rate of dissolution no greater than 80% of the rate of dissolution of particles of the active substance.

11. The microparticles as claimed in claim **1**, comprising an effective amount of an antimuscarinic agent, β-agonist, leukotriene receptor antagonist or steroid.

12. The microparticles as claimed in claim **1**, in which the particles of hydrophobic material are present as a coating on the surface of the particles of active substance.

13. The microparticles as claimed in claim **12**, in which the coating is a discontinuous coating.

14. The microparticles as claimed in claim **1**, which are suitable for use in a powder for use in a dry powder inhaler.

15. A composition for inhalation, comprising microparticles as claimed in claim **1**.

16. The composition as claimed in claim **15**, which is a dry powder and is suitable for use in a dry powder inhaler.

17. The composition as claimed in claim **15**, which comprises a propellant and is suitable for use in a pressurised metered dose inhaler.

* * * * *

EXHIBIT C

US008956661B2

(12) **United States Patent**
Staniforth et al.

(10) **Patent No.: US 8,956,661 B2**
(45) **Date of Patent: *Feb. 17, 2015**

(54) **METHOD OF MAKING COMPOSITE PARTICLES FOR USE IN PHARMACEUTICAL COMPOSITIONS AND COMPOSITE PARTICLES AND COMPOSITIONS THEREOF**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(63) Continuation of application No. 12/767,530, filed on Apr. 26, 2010, now Pat. No. 8,303,991, which is a continuation of application No. 10/433,072, filed as application No. PCT/GB01/05315 on Nov. 30, 2001, now Pat. No. 7,736,670.

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Oct. 5, 2001	(GB)	0124010.0

(51) **Int. Cl.**

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A61K 9/00	(2006.01)
A61K 9/14	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 9/50*** (2013.01); ***A61K 9/0075*** (2013.01); ***A61K 9/008*** (2013.01); ***A61K 9/145*** (2013.01); *A61K 9/1617* (2013.01)

USPC **424/490**

(58) **Field of Classification Search**

USPC 424/490

See application file for complete search history.

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Assistant Examiner — Daniel L Branson
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(57) **ABSTRACT**

The invention relates to a method for making composite active particles for use in a pharmaceutical composition for pulmonary administration, the method comprising a milling step in which particles of active material are milled 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. The invention also relates to compositions for inhalation prepared by the method.

32 Claims, 6 Drawing Sheets

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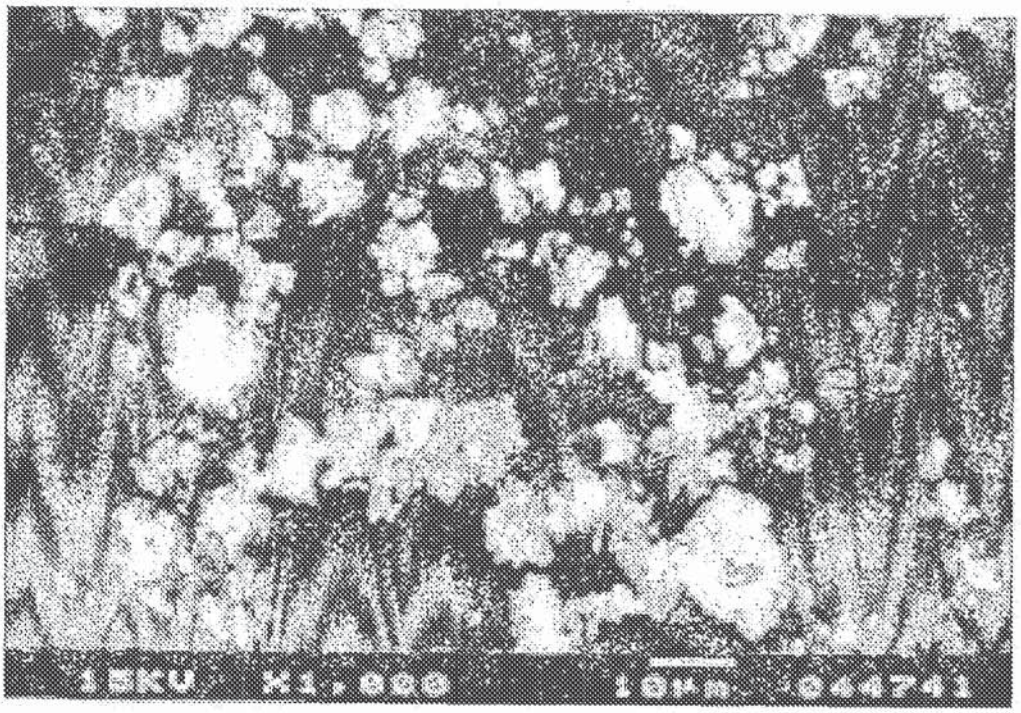


Fig 1

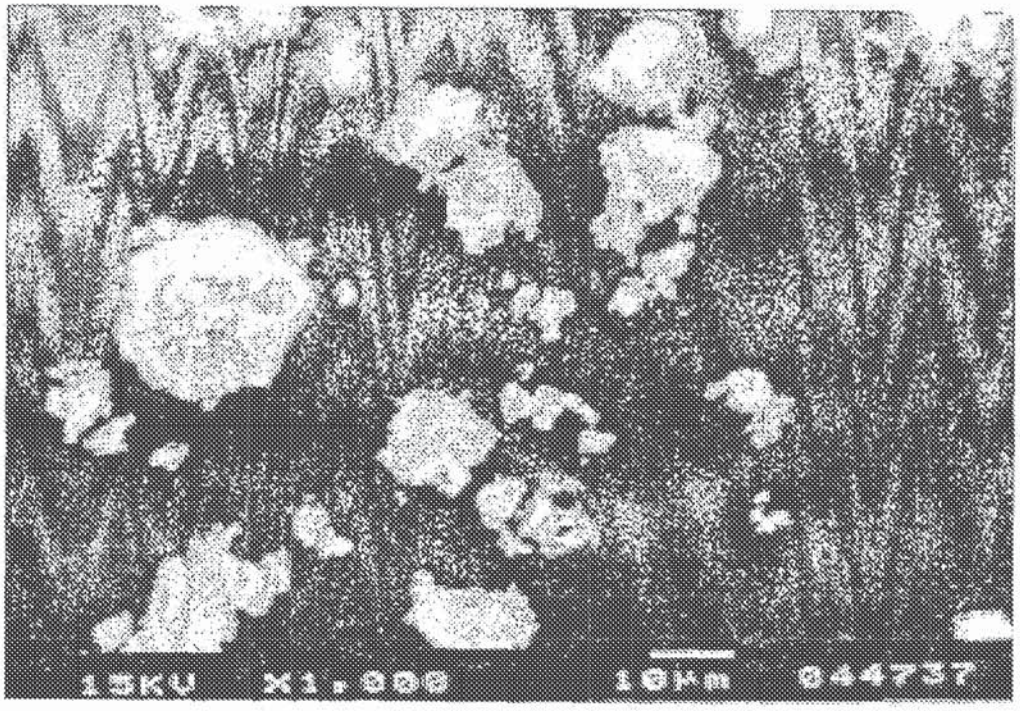


Fig 2

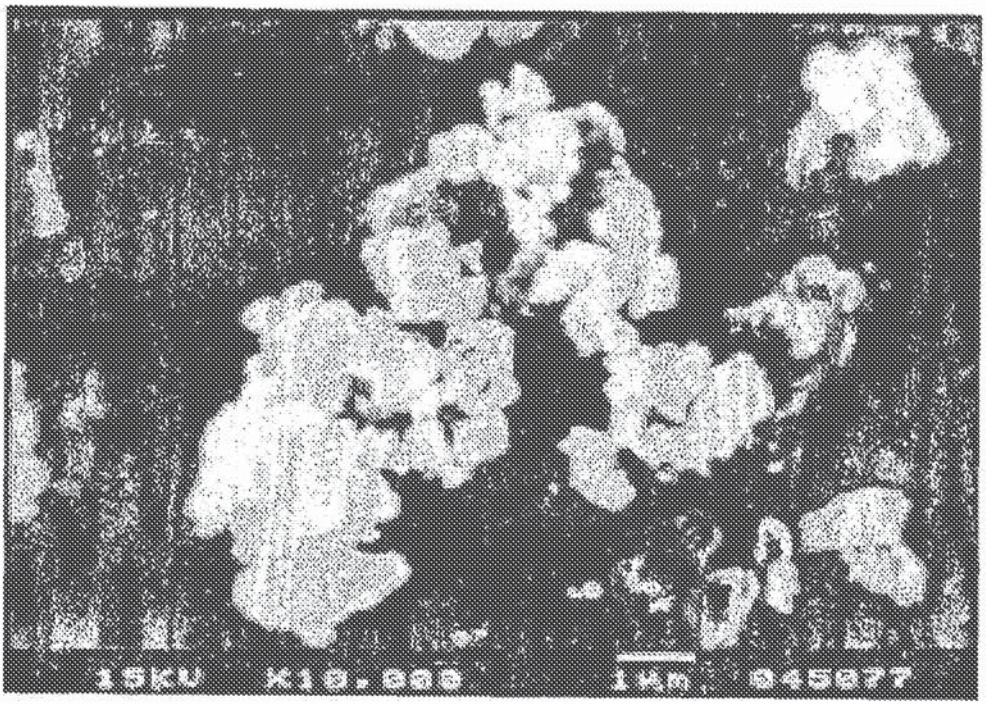


Fig 3

Fig 4

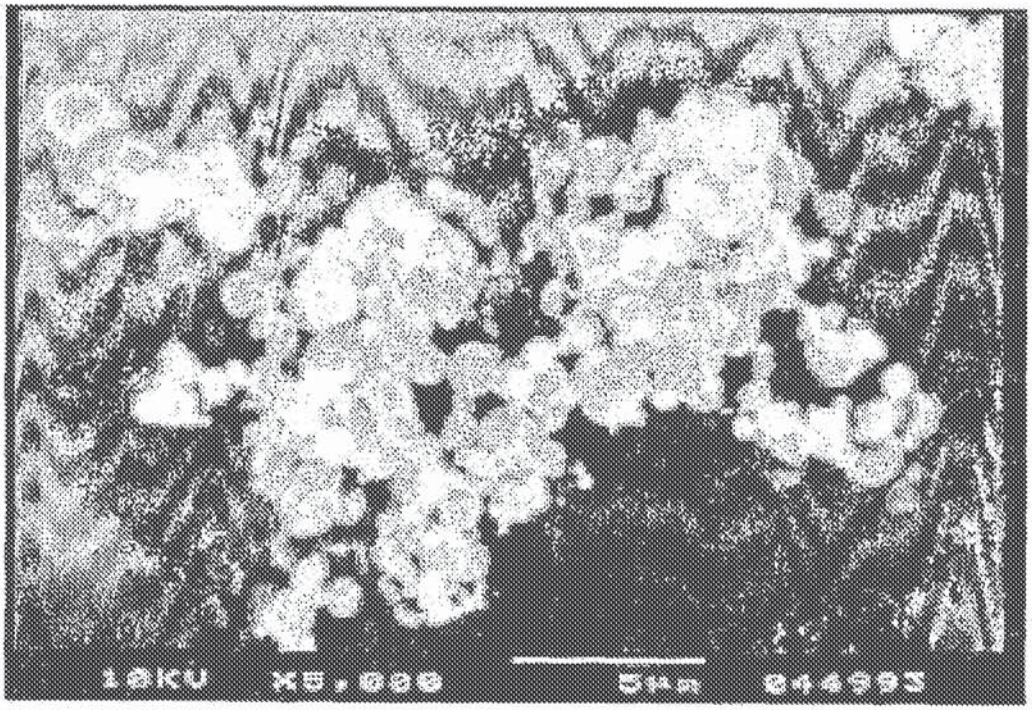


Fig 5

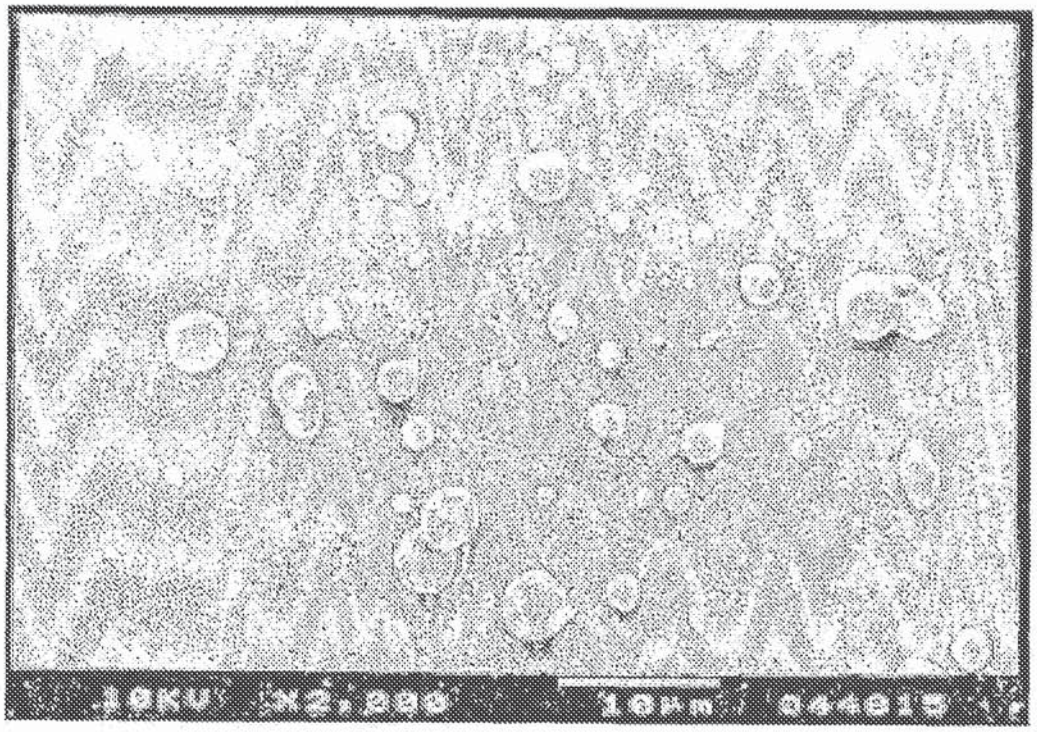


Fig 6

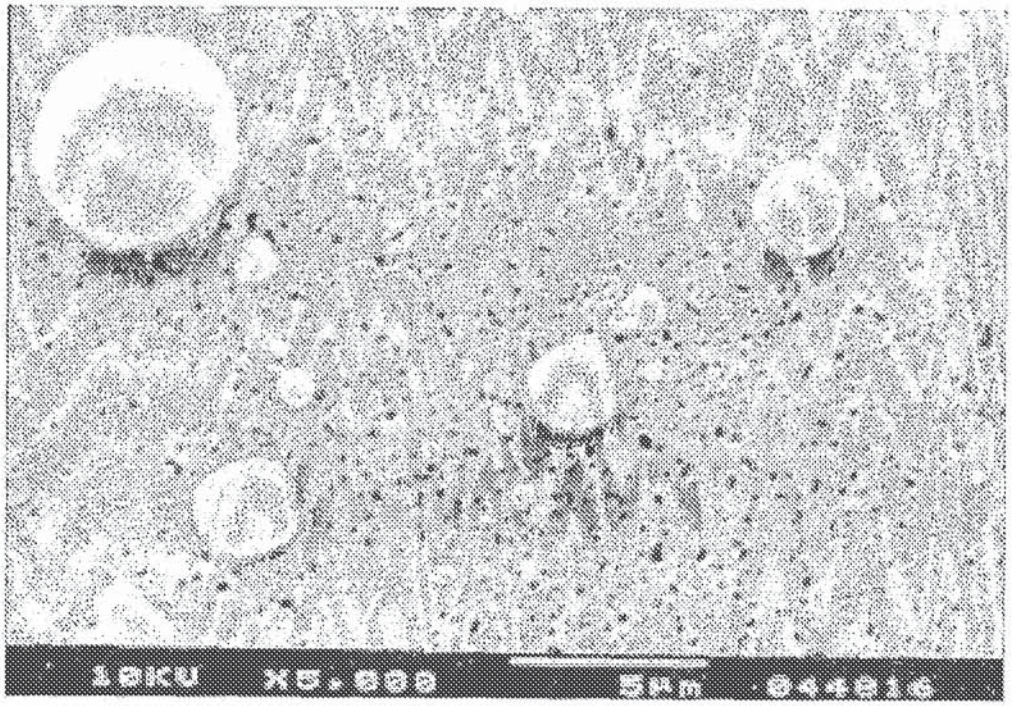
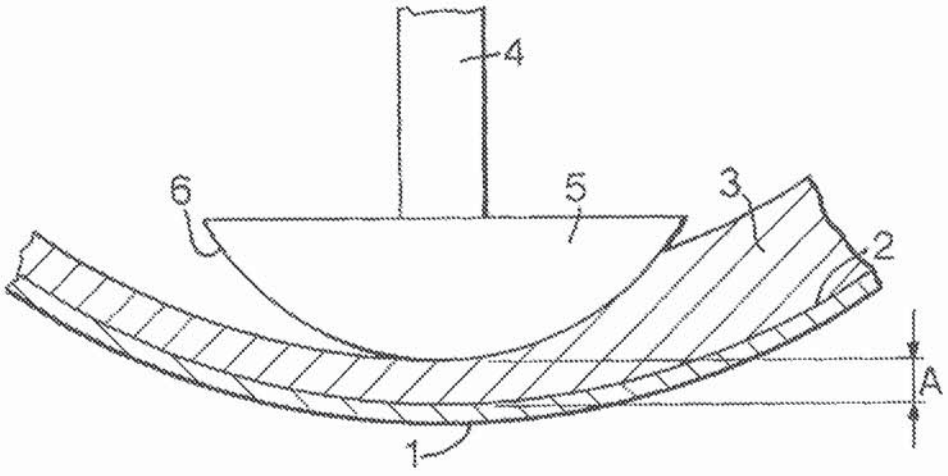


Fig 7

Fig.8.



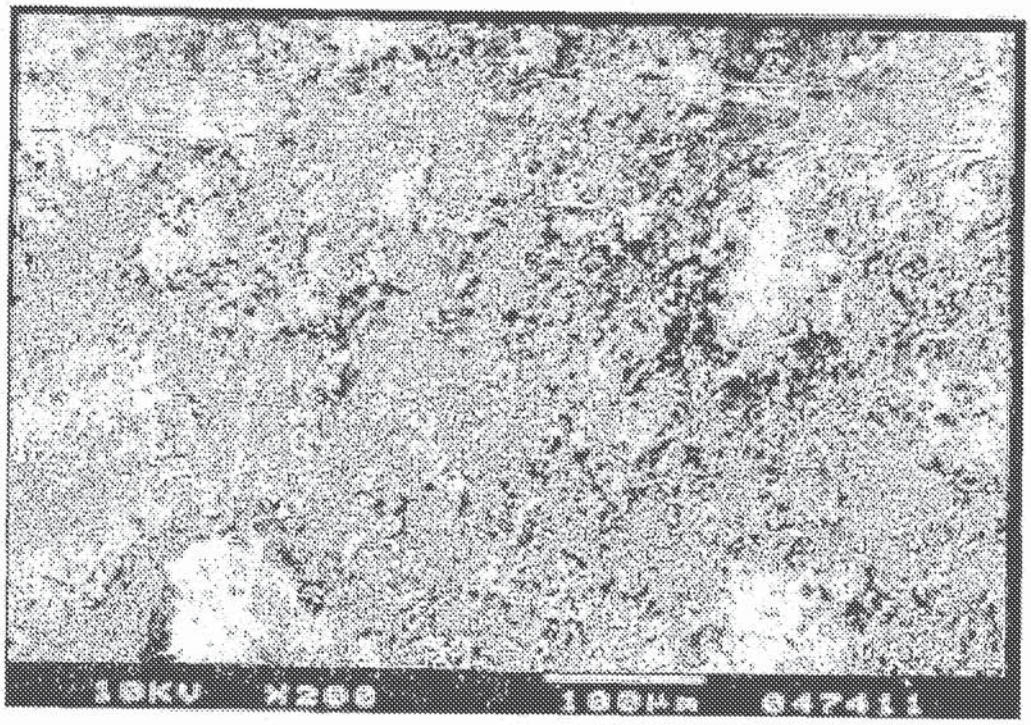


Fig 9

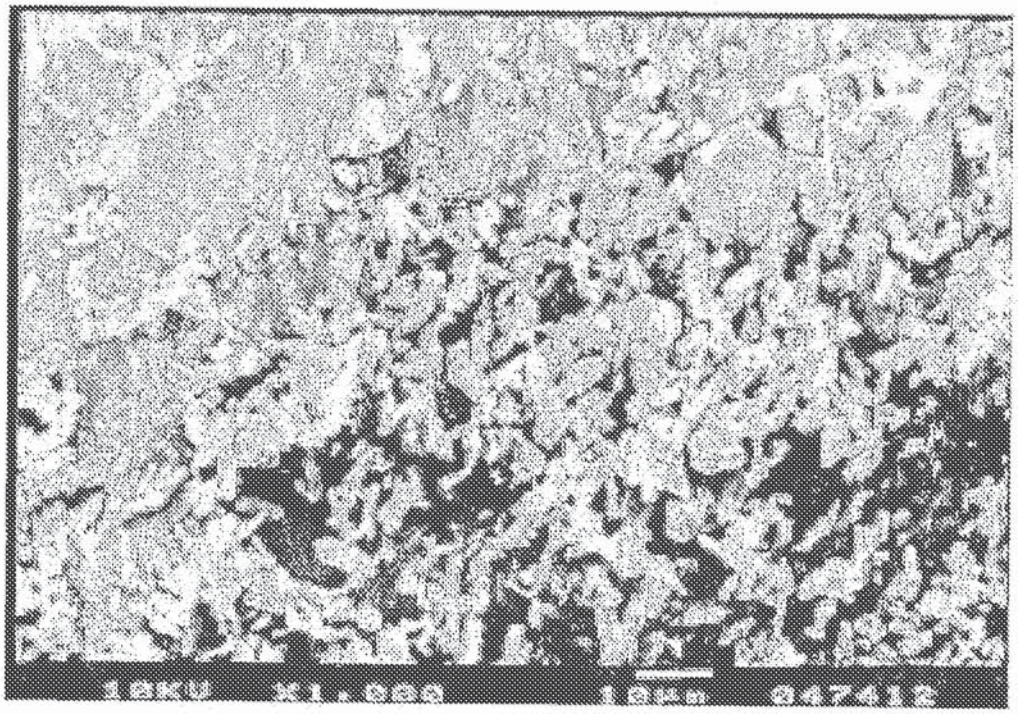


Fig 10

METHOD OF MAKING COMPOSITE PARTICLES FOR USE IN PHARMACEUTICAL COMPOSITIONS AND COMPOSITE PARTICLES AND COMPOSITIONS THEREOF

RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 12/767,530 filed Apr. 26, 2010 which is a continuation of U.S. application Ser. No. 10/433,072 filed Sep. 12, 2003, now U.S. Pat. No. 7,736,670 which is the United States national stage of International Application No. PCT/GB01/05315, filed Nov. 30, 2001, which was published under PCT Article 21 in English as International Publication No. WO 02/43701, and which claims benefit of British Application No. 0029261.5 filed, Nov. 30, 2000. British Application No. 0030946.8 filed Dec. 19, 2000, PCI Application No. PCT/GB01/01606 filed Apr. 9, 2001 and British Application No. 0124010.0 filed Oct. 5, 2001.

The present invention relates to particles and to methods of making particles. In particular, the invention relates to methods of making composite active particles comprising a pharmaceutically active material for inhalation.

It is known to administer to patients drugs in the form of fine particles (active particles). For example, in pulmonary administration, a particulate medicament composition is inhaled by the patient. Pulmonary administration is particularly suitable for medicaments which are intended to cure or alleviate respiratory conditions such as asthma and for medicaments which are not suitable for oral ingestion such as certain biological macro-molecules. Known devices for the administration of drugs to the respiratory system include pressurised metered dose inhalers (pMDI's) and dry powder inhalers (DPI's).

The size of the active particles is of great importance in determining the site of the absorption. In order that the particles be carried deep into the lungs, the particles must be very fine, for example having a mass median aerodynamic diameter of less than 10 μm. Particles having aerodynamic diameters greater than 10 μm are likely to impact the walls of the throat and generally do not reach the lung. Particles having aerodynamic diameters in the range of 5 μm to 0.5 μm will generally be deposited in the respiratory bronchioles whereas smaller particles having aerodynamic diameters in the range of 2 to 0.5 μm are likely to be deposited in the alveoli.

Such small particles are, however, thermodynamically unstable due to their high surface area to volume ratio, which provides significant excess surface free energy and encourages particles to agglomerate. In the inhaler, agglomeration of small particles and adherence of particles to the walls of the inhaler are problems that result in the active particles leaving the inhaler as large agglomerates or being unable to leave the inhaler and remaining adhered to the interior of the inhaler.

In an attempt to improve that situation, dry powders for use in dry powder inhalers often include particles of an excipient material mixed with the fine particles of active material. Such particles of excipient material may be coarse, for example, having mass median aerodynamic diameters greater than 90μ, (such coarse particles are referred to as carrier particles) or they may be fine.

The step of dispersing the active particles from other active particles and from particles of excipient material, if present, to form an aerosol of fine active particles for inhalation is significant in determining the proportion of the dose of active material which reaches the desired site of absorption in the lungs. In order to improve the efficiency of that dispersal it is known to include in the composition additive materials. Such additive materials are thought to reduce the attractive forces between the particles thereby promoting their dispersal. Compositions comprising fine active particles and additive materials are disclosed in WO 97/03649.

Fine particles of active material suitable for pulmonary administration have often been prepared by milling, for example, jet milling. However, once the particles reach a minimum size referred to as the critical size, they re-combine at the same rate as being fractured, or do not fracture effectively and therefore do not reduce further in size. Thus, manufacture of fine particles by milling can require much effort and there are factors which consequently place limits on the minimum size of particles of active material which can be achieved, in practice, by such milling processes.

The present invention provides in a first aspect a method for making composite active particles for use in a pharmaceutical composition for pulmonary administration, the method comprising a milling step in which particles of active material are milled 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.

The method of the invention will, in general, produce composite active particles. The composite active particles are very fine particles of active material which have, upon their surfaces, an amount of the additive material. The additive material is preferably in the form of a coating on the surfaces of the particles of active material. The coating may be a discontinuous coating. The additive material may be in the form of particles adhering to the surfaces of the particles of active material. As explained below, at least some of the composite active particles may be in the form of agglomerates.

When the composite active particles are included in a pharmaceutical composition the additive material promotes the dispersal of the composite active particles on administration of that composition to a patient, via actuation of an inhaler. ("Actuation of an inhaler" refers to the process during which a dose of the powder is removed from its rest position in the inhaler. That step takes place after the powder has been loaded into the inhaler ready for use.) The effectiveness of that promotion of dispersal has been found to be enhanced in comparison to a composition made by simple blending of similarly sized particles of active material with additive material.

The presence of the additive material on the surfaces of the particles of active material may confer controlled or delayed release properties and may provide a barrier to moisture.

It has also been found that the milling of the particles of active material in the presence of an additive material produces significantly smaller particles and/or requires less time and less energy than the equivalent process carried out in the absence of the additive material. Using the method of the invention, it has been possible to produce composite active particles which have a mass median aerodynamic diameter (MMAD) or a volume median diameter (VMD) of less than 1 μm. It is often not possible to make such small particles by other milling methods.

It is known that a milling process will tend to generate and increase the level of amorphous material on the surfaces of the milled particles thereby making them more cohesive. In contrast, the composite active particles of the invention will often be found to be less cohesive after the milling treatment.

The word "milling" as used herein refers to any mechanical process which applies sufficient force to the particles of active material that it is capable of breaking coarse particles (for example, particles of mass medium aerodynamic diameter greater than 100 μm) down to fine particles of mass median aerodynamic diameter not more than 50 μm or which applies

a relatively controlled compressive force as described below in relation to the Mechano-Fusion and Cyclomix methods. It has been found that processes such as blending which do not apply a high degree of force are not effective in the method of the invention. It is believed that is because a high degree of force is required to separate the individual particles of active material and to break up tightly bound agglomerates of the active particles such that effective mixing and effective application of the additive material to the surfaces of those particles is achieved. It is believed that an especially desirable aspect of the milling process is that the additive material may become deformed in the milling and may be smeared over or fused to the surfaces of the active particles. It should be understood, however, that in the case where the particles of active material are already fine, for example, having a mass median aerodynamic diameter below 20μ prior to the milling step, the size of those particles may not be significantly reduced. The important thing is that the milling process applies a sufficiently high degree of force or energy to the particles.

The method of the invention generally involves bringing the additive particles into close contact with the surfaces of the active particles. In order to achieve coated particles, a degree of intensive mixing is required to ensure a sufficient break-up of agglomerates of both constituents, dispersal and even distribution of additive over the host active particles.

Where the additive particles are very small (typically <1 micron), generally less work is required, firstly as it is not required to break or deform but only to deagglomerate, distribute and embed the additive particles onto the active particle and secondly because of the naturally high surface energies of such small additive particles. It is known that where two powder components are mixed and the two components differ in size, there is a tendency for the small particles to adhere to the large particles (to form so called 'ordered mixes'). The short range Van der Waals interactions for such very fine components may be sufficient to ensure adhesion. However, where both additive and active particles are very fine (for example less than 5 microns) a substantial degree of mixing will be required to ensure a sufficient break-up of agglomerates of both constituents, dispersal and even distribution of additive particles over the active particles as noted above. In some cases a simple contact adhesion may be insufficient and a stronger embedding or fusion of additive particles onto active particles is required to prevent segregation, or to enhance the structure and functionality of the coating.

Where the additive particles are not so small as to be sufficiently adhered by Van der Waals forces alone, or where there are advantages to distorting and/or embedding the additive particles substantially onto the host active particle, a greater degree of energy is required from the milling. In this case, the additive particles should experience sufficient force to soften and/or break, to distort and to flatten them. These processes are enhanced by the presence of the relatively harder active particles which act as a milling media as well as a de-agglomerating media for such processes. As a consequence of this process the additive particles may become wrapped around the core active particle to form a coating. These processes are also enhanced by the application of a compressive force as mentioned above.

As a consequence of the milling step, complete or partial, continuous or discontinuous, porous or non-porous coatings may be formed. The coatings originate from a combination of active and additive particles. They are not coatings such as those formed by wet processes that require dissolution of one or both components. In general, such wet coating processes are likely to be more costly and more time consuming than the milling process of the invention and also suffer from the disadvantage that it is less easy to control the location and structure of the coating.

A wide range of milling devices and conditions are suitable for use in the method of the invention. The milling conditions, for example, intensity of milling and duration, should be selected to provide the required degree of force. Ball milling is a preferred method. Centrifugal and planetary ball milling are especially preferred methods. Alternatively, a high pressure homogeniser may be used in which a fluid containing the particles is forced through a valve at high pressure producing conditions of high shear and turbulence. Shear forces on the particles, impacts between the particles and machine surfaces or other particles and cavitation due to acceleration of the fluid may all contribute to the fracture of the particles and may also provide a compressive force. Such homogenisers may be more suitable than ball mills for use in large scale preparations of the composite active particles. Suitable homogenisers include EmulsiFlex high pressure homogenisers which are capable of pressures up to 4000 Bar, Niro Soavi high pressure homogenisers (capable of pressures up to 2000 Bar), and Microfluidics Microfluidisers (maximum pressure 2750 Bar). The milling step may, alternatively, involve a high energy media mill or an agitator bead mill, for example, the Netzch high energy media mill, or the DYNO-mill (Willy A. Bachofen AG, Switzerland). Alternatively the milling may be a dry coating high energy process such as a Mechano-Fusion system (Hosokawa Micron Ltd) or a Hybridizer (Nara). Other possible milling devices include air jet mills, pin mills, hammer mills, knife mills, ultracentrifugal mills and pestle and mortar mills.

Especially preferred methods are those involving the Mechano-Fusion, Hybridiser and Cyclomix instruments.

Preferably, the milling step involves the compression of the mixture of active and additive particles in a gap (or nip) of fixed, predetermined width (for example, as in the Mechano-Fusion and Cyclomix methods described below).

Some preferred milling methods will now be described in greater detail.

Mechano-Fusion:

As the name suggests, this dry coating process is designed to mechanically fuse a first material onto a second material. The first material is generally smaller and/or softer than the second. The Mechano-Fusion and Cyclomix working principles are distinct from alternative milling techniques in having a particular interaction between inner element and vessel wall, and are based on providing energy by a controlled and substantial compressive force.

The fine active particles and the additive particles are fed into the Mechano-Fusion driven vessel, where they are subject to a centrifugal force and are pressed against the vessel inner wall. The powder is compressed between the fixed clearance of the drum wall and a curved inner element with high relative speed between drum and element. The inner wall and the curved element together form a gap or nip in which the particles are pressed together. As a result the particles experience very high shear forces and very strong compressive stresses as they are trapped between the inner drum wall and the inner element (which has a greater curvature than the inner drum wall). The particles violently collide against each other with enough energy to locally heat and soften, break, distort, flatten and wrap the additive particles around the core particle to form a coating. The energy is generally sufficient to break up agglomerates and some degree of size reduction of both components may occur. Embedding and fusion of additive particles onto the active particles may occur, and may be facilitated by the relative differences in hardness (and option-

ally size) of the two components. Either the outer vessel or the inner element may rotate to provide the relative movement. The gap between these surfaces is relatively small, and is typically less than 10 mm and is preferably less than 5 mm, more preferably less than 3 mm. This gap is fixed, and consequently leads to a better control of the compressive energy than is provided in some other forms of mill such as ball and media mills. Also, in general, no impaction of milling media surfaces is present so that wear and consequently contamination are minimised. The speed of rotation may be in the range of 200 to 10,000 rpm. A scraper may also be present to break up any caked material building up on the vessel surface. This is particularly advantageous when using fine cohesive starting materials. The local temperature may be controlled by use of a heating/cooling jacked built into the drum vessel walls. The powder may be re-circulated through the vessel.

Cyclomix Method (Hosokawa Micron):

The Cyclomix comprises a stationary conical vessel with a fast rotating shaft with paddles which move close to the wall. Due to the high rotational speed of the paddles, the powder is propelled towards the wall, and as a result the mixture experiences very high shear forces and compressive stresses between wall and paddle. Such effects are similar to the Mechano-Fusion as described above and may be sufficient to locally heat and soften, to break, distort, flatten and wrap the additive particles around, the active particles to form a coating. The energy is sufficient to break up agglomerates and some degree of size reduction of both components may also occur depending on the conditions and upon the size and nature of the particles.

Hybridiser Method:

This is a dry process which can be described as a product embedding or filming of one powder onto another. The fine active particles and fine or ultra fine additive particles are fed into a conventional high shear mixer pre-mix system to form an ordered mixture. This powder is then fed into the Hybridiser. The powder is subjected to ultra-high speed impact, compression and shear as it is impacted by blades on a high speed rotor inside a stator vessel, and is re-circulated within the vessel. The active and additive particles collide with each other. Typical speeds of rotation are in the range of 5,000 to 20,000 rpm. The relatively soft fine additive particles experience sufficient impact force to soften, break, distort, flatten and wrap around the active particle to form a coating. There may also be some degree of embedding into the surface of the active particles.

Other preferred methods include ball and high energy media mills which are also capable of providing the desired high shear force and compressive stresses between surfaces, although as the clearance gap is not controlled, the coating process may be less well controlled than for Mechano-Fusion milling and some problems such as a degree of undesired re-agglomeration may occur. These media mills may be rotational, vibrational, agitational, centrifugal or planetary in nature.

It has been observed in some cases that when ball milling active particles with additive material, a fine powder is not produced. Instead the powder was compacted, on the walls of the mill by the action of the mill. That has inhibited the milling action and prevented the preparation of the composite active particles. That problem, occurred particularly when certain additive materials were used, in cases where the additive material was present in small proportions (typically <2%), in cases where the milling balls were relatively small (typically <3 mm), in cases where the milling speed was too slow and where the starting particles were too fine. To prevent this occurring it is advantageous to ball mill in a liquid medium. The liquid medium reduces the tendency to compaction, assists the dispersal of additive material and improves any milling action.

It has been found, to be preferable to use a large number of fine milling balls, rather than fewer heavy balls. The finer balls perform a more efficient co-milling action. Preferably the balls have a diameter of less than 5 mm, advantageously less than 2 mm. Liquid media are preferred which do not dissolve the active material and which evaporate rapidly and fully, for example non-aqueous liquids such, as diethylether, acetone, cyclohexane, ethanol, isopropanol or dichloromethane. Liquid media are preferred which, are non flammable, for example dichloromethane and fluorinated hydrocarbons, especially fluorinated hydrocarbons which are suitable for use as propellants in inhalers.

Pestle and mortar mills are other mills which also provide a very high shear force and compressive stresses between surfaces.

Mechano-Micros and Micros mills made by Nara (where particles are compressed by rotating grinding rings) may also be used. Mills referred to impact mixers, attrition mills, pin mills and disc mills may also be used.

The mass median aerodynamic diameter of the particles of active material may be substantially reduced during the milling step especially when the active material is in the form of coarse particles prior to the milling step. The mass median aerodynamic diameter (MMAD) of the particles of active material may be reduced by at least 10%, by at least 50%, or by at least 70% during the milling step depending on the milling conditions and the MMAD of the active particles prior to the milling step.

Advantageously, after the milling step, the MMAD of the active particles is less than 9 μm, preferably less then 4 μm and more preferably less then 2 μm.

In a similar way, where the additive material is in the form of coarse particles prior to the milling step, their MMAD will be substantially reduced during the milling step. The MMAD of the particles of additive material may be reduced by at least 10%, at least 50% or at least 70% during the milling step, depending on the milling conditions and on the MMAD of the particles of additive material before the milling step. The size of the additive particles after the milling step is preferably significantly less than the size of the active particles, to enable the additive materials to more effectively coat the surfaces of the active particles. In practice, that difference in size between the active particles and additive particles is likely to be achieved as a consequence of the milling because the additive material will usually be more easily fractured or deformed than the active material and so will be broken into smaller particles than the active material. As noted above, the particles of additive material preferably become smeared over or fused to the surfaces of the particles of active material, thereby forming a coating which may be substantially continuous or discontinuous. Where the coating is discontinuous, it preferably covers, on average, at least 50% (that is, at least 50% of the total surface area of the active particles will be covered by additive material), more advantageously at least 70% and most preferably at least 90% of the surfaces of the active particles. The coating is preferably on average less than 1 μm, more preferably less than 0.5 μm and most preferably less than 200 nm thick.

The milling step may be carried out in a closed vessel, for example in a ball mill or a Mechano-Fusion device. The use of a closed vessel prevents loss of ultrafine particles or vapour of the additive material which has been found to occur in jet milling or other open processes. Preferably, the milling is not jet milling (micronisation).

The milling may be wet milling, that is, the milling step may be carried out in the presence of a liquid. That liquid medium may be high or low volatility and of any solid content as long as it does not dissolve the active particles to any significant degree and its viscosity is not so high that it prevents effective milling. The liquid medium preferably is not aqueous. The liquid is preferably one in which the additive material is substantially insoluble but some degree of solubility may be acceptable as long as there is sufficient additive material present that undissolved particles of additive material remain. The presence of a liquid medium helps to prevent compacting of the particles of active material on the wails of the vessel and may also allow the more even spreading of the additive material on the surface of the particles of active material as compared to dry milling.

It has been found that the Mechano-Fusion and Cyclomix techniques referred to above often provide the composite active particles as individual, that is, unagglomerated composite active particles. That is in contrast to less controlled methods such as ball milling, which have been found to often produce the composite active particles in the form of agglomerated composite active particles.

The mass median aerodynamic diameter of the composite active particles is preferably not more than 10 μm, and advantageously it is not more than 5 μm, more preferably not more than 3 μm and most preferably not more than 1 μm. Accordingly, advantageously at least 90% by weight of the composite active particles have a diameter of not more than 10 μm, advantageously not more than 5 μm, preferably not more than 3 μm and more preferably not more than 1 μm. Advantageously, after the milling step, the active particles will be of a suitable size for inhalation to the desired part of the lungs for example, having an MMAD in the range of 3 to 0.1 μm for absorption in the deep lung, 5 to 0.5 μm for absorption in the respiratory bronchioles, 10 to 2 μm for delivery to the higher respiratory system and 2 to 0.5 μm for delivery to the alveoli. Accordingly, advantageously the diameter of at least 90% by weight of the composite active particles have an aerodynamic diameter in the range of 3 to 0.1 μm, preferably 5 to 0.5 μm, advantageously 10 to 2 μm, and especially advantageously 2 to 0.05 μm. The MMAD of the active particles will not normally be lower than 0.01 μm.

As mentioned above, the composite active particles produced after the milling step may be of a suitable size for delivery to the desired part of the respiratory system.

However, the composite active particles may be smaller than that suitable size or at least some of the composite active particles may, after the milling step, be in the form of agglomerates which are larger than the suitable size. The method therefore preferably also comprises, after the milling step, a processing step in which the degree of agglomeration of the composite active particles is changed. The processing step may be an agglomeration step in which the particles of active material agglomerate to form agglomerated composite active particles. In that way agglomerates of a size tailored to the requirement may be produced. Whilst any method of agglomeration can be used, for example, granulation, preferably, the composite active particles are agglomerated in a drying step (as described below) to form agglomerated composite active particles. Preferably, the agglomeration step is a spray drying step. The spray drying conditions may be selected to produce droplets having a desired size in the range of 1000 μm to 0.5 μm. The size of the agglomerates produced will depend largely on the concentration of the composite active particles in the spray feed and the droplet size. Other materials, for example, binders may be included in the spray feed. Where the milling step involves wet milling, the suspension or slurry may be spray dried directly after the milling step. Agglomeration may also be conducted in a fluid bed dryer or granulator.

Where, after the milling step, at least some of the composite active particles are in the form of agglomerates and it is desired to break those agglomerates down or to reduce their size, the processing step may be a deagglomeration step. The deagglomeration step may involve mechanical breaking up of the unwanted agglomerates, for example, by forcing them through a sieve or by subjecting them to a treatment in a dry fluidised bed, a jet mill, a ball mill or other form of milling device. The intensity and/or duration of that treatment step will, in general, be less that of the milling step. The deagglomeration step may also be a spray drying step because, whilst spray drying as a drying step is particularly useful in preparing agglomerated composite active particles, by appropriate control of the conditions it is possible to produce the composite active particles largely as single particles rather than as agglomerates.

The term "agglomerated composite active particles" refers to particles which consist of more than one composite active particle, those composite active particles being adhered to each other. Where the agglomerated particles are for inhalation they will preferably have a MMAD which renders them suitable for deposition in the desired part of the lung.

Preferably, the method comprises, after the milling step, a drying step in which a mixture of the composite active particles and a liquid is dried to remove the liquid. The mixture may be in the form of a slurry or suspension. During the drying step, especially when spray drying is used, the degree of agglomeration of the composite active particles may change, in which case the drying step is the same step as the processing step mentioned above. However, the drying step may be included for other reasons, for example, when the milling is wet milling, and it is desired to produce the composite active particles as a dry powder.

The drying step may involve filtration followed by drying, or evaporation of the liquid. Preferably, the drying step is a spray drying step. Alternatively, the liquid may be evaporated slowly or the drying step may be a freeze drying step.

The milling is preferably dry, that is to say, there is no liquid present during the milling and the mixture to be milled is in the form of a dry particulate. In that case, liquid may be added after the milling step, usually in order that a drying step be used to form agglomerated composite active particles, as described above.

Advantageously, the milling step is carried out at a reduced temperature, for example, below 10° C. and preferably below 0° C. Such low temperature conditions may increase the efficiency of the milling step and/or reduce decomposition of the active material.

The optimum amount of additive material will depend on the chemical composition and other properties of the additive material and upon the nature of the active material and/or excipient material. In general, the amount of additive material in the composite particles will be not more than 60% by weight, based on the weight of the active material and/or excipient material. However, it is thought that for most additive materials the amount of additive material should be in the range of 40% to 0.25%, preferably 30% to 0.5%, more preferably 20% to 2%, based on the total weight of the additive material and the active material being milled. In general, the amount of additive material is at least 0.01% by weight based on the weight of the active material.

The terms "additive particles" and "particles of additive material" are used interchangeably herein. The additive par-

ticles comprise one or more additive materials. Preferably, the additive particles consist essentially of the additive material.

Advantageously the additive material is an anti-adherent material and will tend to decrease the cohesion between the composite active particles and between the composite active particles and any other particles present in the pharmaceutical composition.

Advantageously the additive material is an anti-friction agent (glidant) and will give better flow of the pharmaceutical composition in, for example, a dry powder inhaler which will lead to a better dose reproducibility.

Where reference is made to an anti-adherent material, or to an anti-friction agent, the reference is to include those materials which are able to decrease the cohesion between the particles, or which will tend to improve the flow of powder in an inhaler, even though they may not usually be referred to as anti-adherent material or an anti-friction agent. For example, leucine is an anti-adherent material as herein defined and is generally thought of as an anti-adherent material but lecithin is also an anti-adherent material as herein defined, even though it is not generally thought of as being anti-adherent, because it will tend to decrease the cohesion between the composite active particles and between the composite active particles and any other particles present in the pharmaceutical composition.

The additive material may include a combination of one or more materials.

It will be appreciated that the chemical composition of the additive material is of particular importance. Preferably, the additive material is a naturally occurring animal or plant substance.

Advantageously, the additive material includes one or more compounds selected from amino acids and derivatives thereof, and peptides and derivatives thereof. Amino acids, peptides and derivatives of peptides are physiologically acceptable and give acceptable release of the active particles on inhalation.

It is particularly advantageous for the additive material to comprise an amino acid. The additive material may comprise one or more of any of the following amino acids: leucine, isoleucine, lysine, valine, methionine, phenylalanine. The additive may be a salt or a derivative of an amino acid, for example aspartame or acesulfame K. Preferably, the additive particles consist substantially of an amino acid, more preferably of leucine, advantageously L-leucine. The D- and DL-forms may also be used. As indicated above, leucine has been found to give particularly efficient dispersal of the active particles on inhalation.

The additive material may include one or more water soluble substances. This helps absorption of the substance by the body if the additive reaches the lower lung. The additive material may include dipolar ions, which may be zwitterions.

Alternatively, the additive material may comprise a phospholipid or a derivative thereof. Lecithin has been found to be a good material for the additive material.

Preferably, the additive material comprises a metal stearate, or a derivative thereof, for example, sodium stearyl fumarate or sodium stearyl lactylate. Advantageously, the additive material comprises a metal stearate. For example, zinc stearate, magnesium stearate, calcium stearate, sodium stearate or lithium stearate. Preferably, the additive material comprises magnesium stearate.

The additive material may include or consist of one or more surface active materials, in particular materials that are surface active in the solid state, which may be water soluble, for example lecithin, in particular soya lecithin, or substantially water insoluble, for example solid state fatty acids such as oleic acid, lauric acid, palmitic acid, stearic acid, erucic acid, behenic acid, or derivatives (such as esters and salts) thereof such as glyceryl behenate. Specific examples of such materials are: phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols and other examples of natural and synthetic lung surfactants; lauric acid and its salts, for example, sodium lauryl sulphate, magnesium lauryl sulphate; triglycerides such as Dynsan 118 and Cutina HR; and sugar esters in general.

Other possible additive materials include sodium benzoate, hydrogenated oils which are solid at room temperature, talc, titanium dioxide, aluminium dioxide, silicon dioxide and starch.

The additive material preferably comprises one or more materials selected from the group consisting of amino acids, lecithins, phospholipids, sodium stearyl fumarate, glyceryl behenate and metal stearates (especially magnesium stearate).

The terms "active particles" and "particles of active material" are used interchangeably herein. The active particles referred to throughout the specification will comprise one or more pharmacologically active agents. The active particles advantageously consist essentially of one or more pharmacologically active agents. Suitable pharmacologically active agents may be materials for therapeutic and/or prophylactic use. Active agents which may be included in the formulation include those products which are usually administered orally by inhalation for the treatment of disease such as respiratory disease, for example, β-agonists.

The active particles may comprise at least one β_2-agonist, for example one or more compounds selected from terbutaline, salbutamol, salmeterol and formetorol. If desired, the active particles may comprise more than one of those active agents, provided that they are compatible with one another under conditions of storage and use. Preferably, the active particles are particles of salbutamol sulphate. References herein to any active agent is to be understood to include any physiologically acceptable derivative. In the case of the β_2-agonists mentioned above, physiologically acceptable derivatives include especially salts, including sulphates.

The active particles may be particles of ipatropium bromide.

The active particles may include a steroid, which may be beclomathasone dipropionate or may be fluticasone. The active principle may include a cromone which may be sodium cromoglycate or nedocromil. The active principle may include a leukotriene receptor antagonist.

The active particles may include a carbohydrate, for example heparin.

The active particles may advantageously comprise a pharmacologically active agent for systemic use and advantageously they are capable of being absorbed into the circulatory system via the lungs. For example, the active particles may comprise peptides or polypeptides such as DNAse, leukotrienes or insulin. The pharmaceutical compositions of the invention may in particular have application, in the administration of insulin to diabetic patients, preferably avoiding the normally invasive administration techniques used for that agent. The composite active particles could also be used for the local administration of other agents for example for pain relief (e.g. analgesics such as Fentanyl or dihydroergotamine which is used for the treatment of migraine), anti cancer activity, anti-virals, antibiotics or the local delivery of vaccines to the respiratory tract.

Whilst it will often be desired to obtain the composite active particles in dry form, as described above, where the pharmaceutical composition is one comprising a liquid, for

example, as propellant, it may be preferable for the active particles to be milled in the presence of that liquid and to omit the drying step, simply using the slurry or suspension of the composite active particles in the liquid as an ingredient in the pharmaceutical composition. Thus for example, where the pharmaceutical composition is for use in a pMDI, the active particles and the additive material may be milled in the presence of liquid propellant (under pressure or at below room, temperature if necessary). The resulting slurry may be used directly in a pMDI or further materials may be added, for example, more propellent, surfactants, or co-solvents.

Accordingly, the invention also provides, in one embodiment, a method of making composite active particles for use in a pharmaceutical composition, the method comprising a milling step in which particles of active material are milled in the presence of a liquid and an additive material which is suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device.

Preferably, the liquid comprises a propellant suitable for use in a pMDI. Suitable propellants include CFC-12, HFA-134a, HFA-227, HCFC-22 (difluorochlormethane), HCFC-123 (dicholorotrifluorethane), HCFC-124 (chlorotetrafluoroethane), dimethyl ether, propane, n-butane, isobutane, HFA-125 (pentafluoroethane) and HFA-152 (difluoroethane). If however, it is desired to isolate the dry composite active particles (or agglomerates thereof) the method may also include a drying step, preferably a spray drying step. Accordingly, in a further embodiment, the invention provides a method of making composite active particles for use in a pharmaceutical composition, the method comprising

a wet milling step in which the particles of active material are milled in the presence of a liquid and an additive material which is suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device; and

a drying step in which the liquid is removed.

As explained above, the conditions of the drying step, which is preferably a spray drying step, may be chosen either to provide agglomerated composite active particles of a desired size or to provide substantially unagglomerated particles, that is, individual composite active particles. In some cases it may be preferable to perform the milling step in the absence of liquid, (dry milling). The composite active particles may then be agglomerated by mixing with a liquid and drying to give agglomerated composite active particles. Accordingly, in a further embodiment, the invention provides a method of making agglomerated composite active particles for use in a pharmaceutical composition, the method comprising:

a dry milling step in which particles of active material are milled in the presence of an additive material which is suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device; and

an agglomeration step, in which the composite active particles are mixed with a liquid and the mixture is dried to remove the liquid.

The invention also provides composite active particles for use in a pharmaceutical composition, preferably a pharmaceutical composition for inhalation, more preferably a powder for a dry powder inhaler.

The invention also provides composite active particles for use in a pharmaceutical composition, each composite active particle comprising a particle of active material and additive material on the surface of that particle of active material, the composite active particles having a mass median aerodynamic diameter of not mere than 2 μm, the additive material being suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device. Preferably, the composite active particles have a MMAD of not more than 1 μm especially advantageously not more than 0.5 μm. As noted above, the composite particles may be in the form of agglomerated composite particles.

MMAD may be determined using an impinger, for example, a multi-stage liquid impinger. Volume median diameters and measurements of the proportion of particles having a diameter less than a certain value may be determined, by the Malvern laser light scattering method.

Advantageously, the composite active particles do not comprise significant amounts (more then 10% by weight) of a polymer of a type which would result in the particles becoming sticky. Such polymers include polymers of a alpha-hydroxycarboxylic acid, for example, polylactic acid, copolymers of lactic acid and block copolymers such as ethylene oxide/propylene oxide block copolymers or poloxamines.

The invention further provides a pharmaceutical composition comprising composite active particles. Preferably, the pharmaceutical composition is a dry powder and is suitable for use in a dry powder inhaler. Such pharmaceutical compositions may comprise essentially only the composite active particles or they may comprise additional ingredients such as carrier particles and flavouring agents. Carrier particles may be of any acceptable excipient material or combination of materials. For example, the carrier particles may be composed of one or more materials selected from sugar alcohols, polyols and crystalline sugars. Other suitable carriers include inorganic salts such as sodium chloride and calcium carbonate, organic salts such as sodium lactate and other organic compounds such as polysaccharides and oligosaccharides. Advantageously the carrier particles are of a polyol. In particular the carrier particles may be particles of crystalline sugar, for example mannitol, dextrose or lactose. Preferably, the carrier particles are of lactose.

Advantageously, substantially all (by weight) of the carrier particles have a diameter which lies between 20 μm and 1000 μm, more preferably 50 μm and 1000 μm. Preferably, the diameter of substantially all (by weight) of the carrier particles is less than 355 μm and lies between 20 μm and 250 μm. Preferably at least 90% by weight of the carrier particles have a diameter between from 60 μm to 180 μm. The relatively large diameter of the carrier particles improves the opportunity for other, smaller particles to become attached to the surfaces of the carrier particles and to provide good flow and entrainment characteristics and improved release of the active particles in the airways to increase deposition of the active particles in the lower lung.

The ratio in which the carrier particles (if present) and composite active particles are mixed will, of course, depend on the type of inhaler device used, the type of active particles used, and the required dose. The carrier particles may be present in an amount of at least 50%, more preferably 70%, advantageously 90% and most preferably 35% based on the combined weight of the composite active particles and the carrier particles.

Where carrier particles are included in the pharmaceutical composition, that composition preferably also includes small excipient particles having, for example, a particle size between 5 to 20 μm. Preferably the small excipient particles are present in an amount of from 1% to 40%, more preferably 5% to 20% based on the weight of the carrier particles.

Compositions for use in a dry powder inhaler which include carrier particles will preferably include at least 2%, more preferably at least 5% and most preferably at least 10% by weight of the composite active particles based on the total mass of the composition. The composite active particles are

especially suitable for dry powder compositions which do not include significant amounts of carrier particles and in such compositions the composite active particles will preferably be present in a proportion of at least 60%, more preferably at least 80% by weight based on the total weight of the composition.

The pharmaceutical composition may comprise a propellant and be suitable for use in a pressurised metered dose inhaler.

The invention also provides the use of an additive material as a milling aid in the milling of particles of active material. The term milling aid should be understood to refer to a substance which reduces the amount of energy required to mill the particles of active material and/or excipient material.

Embodiments of the invention will now be described for the purposes of illustration only with reference to the Figures in which:

BRIEF DESCRIPTIONS OF THE DRAWINGS

FIGS. **1** and **2** are scanning electron micrographs of the composite active particles of Example 1;

FIG. **3** is a scanning electron micrograph of the composite active particles of Example 1a;

FIG. **4** is a scanning electron micrograph of the composite particles of Example 2;

FIG. **5** is a scanning electron micrograph of the same sample of particles shown in FIG. **4** but at a higher magnification;

FIG. **6** is a scanning electron micrograph of the composite particles of Example 3;

FIG. **7** is a scanning electron micrograph of the same sample of particles shown in FIG. **6** but at a higher magnification;

FIG. **8** is a schematic drawing of part of a Mechano-Fusion machine; and

FIGS. **9** and **10** are electromicrographs of composite active particles according to the invention comprising salbutamol sulphate and magnesium stearate in a ratio of 19:1.

All percentages are by weight unless indicated otherwise.

Example 1

5 g of micronised salbutamol sulphate (particle size distribution: 1 to 5 μm) and 0.5 g of magnesium stearate were added to a 50 cm^3 stainless steel milling vessel together with 20 cm^3 dichloromethane and 124 g of 3 mm stainless steel balls. The mixture was milled at 550 rpm in a Retsch S100 Centrifugal Mill for 5 hours. The powder was recovered by drying and sieving to remove the mill balls. An electron micrograph of the powder is shown in FIG. **1**. This was repeated 3 times using leucine in place of the magnesium stearate and an electron, micrograph of the powder is shown in FIG. **2**. The powders shown in FIGS. **1** and **2** appear to have particles in the size range 0.1 to 0.5 μm.

Example 1a

Micronised salbutamol sulphate and magnesium stearate were combined as particles in a suspension in the ratio 10:1 in propanol. This suspension was processed in an Emulsiflex C50 high pressure homogeniser by 5 sequential passes through the system at 25,000 psi. This dry material was then recovered by evaporating the propanol. The particles are shown in FIG. **3**.

Example 2

It was found that, on drying, the powder prepared in Example 1 including magnesium stearate as additive material formed assemblies of primary particles which were hard to deagglomerate. A sample of this powder was re-dispersed by ball milling for 90 minutes at 550 rpm in a mixture of ethanol, polyvinylpyrolidone (PVPK30) and HFA227 liquid propellant to give the following composition:

0.6% w/w	Salbutamol sulphate/magnesium stearate composite particles
0.2% w/w	PVPK30
5.0% w/w	Ethanol
94.2% w/w	HFA 227

(The PVP was included to stabilise the suspension of the composite particles in the ethanol/HFA227).

The suspension could be used directly as in a pMDI. In this example, however, the composition was sprayed from a pressurised can through an orifice ~0.4 mm in diameter to produce dried composite active particles of salbutamol sulphate and magnesium stearate with PVP. Those particles (shown in FIGS. **4** and **5**) were collected and examined and were found to be in the aerodynamic size range 0.1 to 4 μm.

Example 3

The process of Example 2 was repeated except that the composition was as follows:

3% w/w	Salbutamol sulphate/magnesium stearate composite particles
1% w/w	PVPK30
3% w/w	Ethanol
93% w/w	HFA 227

The particles produced are shown in FIGS. **6** and **7**.

Example 4

Salbutamol Sulphate/Magnesium Stearate Blends

a) Homogenised Magnesium Stearate

240 g magnesium stearate (Riedel de Haen, particle size by Malvern laser diffraction: d_{50}=0.7 μm) was suspended in 2150 g dichloroethane. That suspension was then mixed for 5 minutes in a Silverson high shear mixer. The suspension was then processed in an Emulsiflex C50 high pressure homogeniser fitted with a heat exchanger at 10000 psi for 20 minutes in circulation mode (300 cm^3/min) for 20 minutes. The suspension was then circulated at atmospheric pressure for 20 minutes allow it to cool. The next day, the suspension was processed in circulation mode (260 cm^3/min) at 20000 psi for 30 minutes. The dichloroethane was removed by rotary evaporation followed by drying in a vacuum over at 37° C overnight. The resulting cake of material was broken up by ball milling for 1 minute. The homogenised magnesium stearate had a particle size of less than 2 μm.

b) A 9:1 by weight blend of salbutamol sulphate and homogenised magnesium stearate having a particle size of less than 2 μm was prepared by blending the two materials with a spatula. An electron micrograph of the blended material showed that the blend was mostly in the form of agglomerated particles, the agglomerates having diameters of 50 μm and above. The blend was then processed in a Mechano-Fusion mill (Hosokawa) as follows:

Machine Data:

Hosokawa Mechano-Fusion: AMS-Mini

Drive: 2.2 kW

Housing: stainless steel

Rotor: stainless steel
Scraper: None
Cooling: Water
Gas purge: None

The Mechano-Fusion device (see FIG. **8**) comprises a cylindrical drum **1** having an inner wall **2**. In use, the drum rotates at high speed. The powder **3** of the active and additive particles is thrown by centrifugal force against the inner wall **2** of the drum **1**. A fixed arm **4** projects from the interior of the drum in a radial direction. At the end of the arm closest to the wall **2**, the arm is provided with a member **5** which presents an arcuate surface **6**, of radius of curvature less than that of inner wall **2**, toward that inner wall. As the drum **1** rotates, it carries powder **3** into the gap between arcuate surface **6** and inner wall **2** thereby compressing the powder. The gap is of a fixed, predetermined width A. A scraper (not shown in FIG. **8**) may be provided to scrape the compressed powder from the wall of the drum.

All samples were prefixed for 5 minutes by running the machine at 1000 rpm. The machine speed was then increased to 5050 rpm for 30 minutes. The procedure was repeated for salbutamol sulphate/magnesium stearate in the following weight ratios: 19:1, 3:1, 1:1.

Electronmicrographs of the 19:1 processed material are shown in FIGS. **9** and **10** and indicate that the material was mostly in the form of simple small particles of diameter less than 5 μm or in very loose agglomerates of such particles with only one agglomerate of the original type being visible.

The 3:1 and the 19:1 blends were then each loaded into a 20 mg capsule and fired from a twin stage impinger. A sample of unprocessed salbutamol sulphate, was also fired from the TSI to provide a comparison.

The fine particle fractions were then calculated and are given in table 1.

TABLE 1

Fine Particle Fraction results for salbutamol sulphate blends.

Composition	Fine Particle Fraction %
salbutamol sulphate	28
salbutamol sulphate/magnesium stearate 19:1	66
salbutamol sulphate/magnesium stearate 3:1	66

Example 5

Micronised glycopyrrolate and homogenised magnesium stearate (as described in Example 4) were combined in a weight ratio of 75:25. This blend (~20 g) was then milled in the Mechano-Fusion AMS-Mini system as follows. The powder was pre-mixed for 5 minutes at ~900 rpm. The machine speed was then increased to ~4,800 rpm for 30 minutes. During the milling treatment the Mechano-Fusion machine was run with a 3 mm clearance between element and vessel wall, and with cooling water applied. The powder of composite active particles was then recovered from the drum vessel.

The experiment was repeated using the same procedure but the active particle and homogenised magnesium stearate were combined in the ratio 95:5, and milled for 60 minutes at 4,800 rpm.

This above process was repeated using the same procedure with a sample of sodium salicilate as a model drug and homogenised magnesium stearate in the ratio 90:10, where the sodium salicilate had been produced as approximately micron sized spheres by spray drying from a Buchi 191 spray dryer. It was believed that the spherical shape of these particles may be advantageous in the coating process. Milling was for 30 minutes at 4,800 rpm.

The invention claimed is:

1. A method for making composite active particles for use in a pharmaceutical composition for pulmonary administration, the method comprising a milling step in which particles of active material are milled 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 wherein the mass median aerodynamic diameter of the composite active particles is not more than 10 μm after milling.

2. A method as claimed in claim **1**, in which the milling step is carried out in the presence of a liquid.

3. A method as claimed in claim **2**, in which the liquid comprises a propellant suitable for use in a pressurised metered dose inhaler device.

4. A method as claimed in claim **2**, which also comprises, after the milling step, a processing step in which the degree of aggregation of the composite active particles is changed.

5. A method as claimed in claim **4**, in which the processing step is an agglomeration step.

6. A method as claimed in claim **4**, in which the processing step is a deagglomeration step.

7. A method as claimed in claim **1**, which comprises, after the milling step, a drying step in which a mixture of the composite active particles and a liquid is dried to remove the liquid.

8. A method as claimed in claim **7**, which the liquid is added after the milling step.

9. A method according to claim **7**, during which, in the drying step, the composite active particles agglomerate to form agglomerated composite active particles.

10. A method as claimed in claim **7**, in which the drying step is a spray drying step.

11. A method as claimed in claim **7**, in which in the drying step the liquid is evaporated slowly.

12. A method as claimed in claim **7**, in which the drying steep is a freeze drying step.

13. A method as claimed in claim **1**, in which the additive material comprises an amino acid.

14. A method as claimed in claim **1**, in which the additive material comprises a phospholipid.

15. A method as claimed in claim **1**, in which the additive material comprises a metal stearate.

16. A method according to claim **1** in which the milling step involves ball milling.

17. A method according to claim **1** in which the milling step involves passing a mixture of particles of additive material and particles of active material, in a liquid, through a constriction under pressure.

18. A method according to claim **1** in which the milling step involves compressing a mixture of the active particles and additive particles in a gap of predetermined width.

19. A method as claimed in claim **18** in which the gap is not more than 10 mm wide.

20. Composite active particles for use in a pharmaceutical composition as made by the method of claim **1**.

21. Composite active particles for use in a pharmaceutical composition for pulmonary administration, each composite active particle comprising a particle of active material and particulate additive material on the surface of that particle of active material, the composite active particles having a mass median aerodynamic diameter of not more than 9 μm and the

additive material being suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device.

22. Composite active particles as claimed in claim **21**, which are in the form of agglomerated composite active particles.

23. Composite particles as claimed in claim **21** in which the additive particles form a coating on the surfaces of the particles of active material.

24. Composite active particles as claimed in claim **23** in which the coating is a discontinuous coating.

25. Composite active particles as claimed in claim **23** in which the coating is not more than 1 μm thick.

26. A pharmaceutical composition comprising composite active particles as made by a method according to claim **1**.

27. A pharmaceutical composition as claimed in claim **26**, which is a dry powder and is suitable for use in a dry powder inhaler.

28. A pharmaceutical composition, as claimed in claim **26**, which comprises a propellant and is suitable for use in a pressurised metered dose inhaler.

29. A method for milling an active material using an additive material as a milling aid, comprising milling particles of active material 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 wherein the mass median aerodynamic diameter of the composite active particles is not more than 10 μm after milling.

30. A method as claimed in claim **1**, which also comprises, after the milling step, a processing step in which the degree of aggregation of the composite active particles is changed.

31. A method as claimed in claim **30**, in which the processing step is an agglomeration step.

32. A method as claimed in claim **30**, in which the processing step is a deagglomeration step.

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