CLAIMS

WE CLAIM:

1. A pharmaceutical composition, comprising:

a plurality of microparticles, the microparticle including:

(1) a crystalline drug core of more than 70% by weight of the microparticle, the crystalline drug core including one or more crystals of fluticasone or a pharmaceutically acceptable salt or ester thereof; and

(2) a polymeric shell encapsulating the crystalline drug core, the polymeric shell being in contact but immiscible with the crystalline drug core,

wherein said microparticles when dissolution tested using United States Pharmacopoeia Type II apparatus exhibit a dissolution half-life of 12-20 hours, wherein the dissolution conditions are: 3 milligrams of microparticles in 200 milliliters of dissolution medium of 70% v/v methanol and 30% v/v of water at 25°C.

2. The pharmaceutical composition of claim 1 wherein the plurality of microparticles have a mean diameter in the range of 80 μm to 150 μm and a standard deviation of less than 50% of the mean diameter.

3. The pharmaceutical composition of claim 2 wherein the plurality of microparticles have a mean diameter of 75μm and a standard deviation of less than 50% of the mean diameter.

4. The pharmaceutical composition of claim 2 wherein the plurality of microparticles have a mean diameter of 150 μm and a standard deviation of less than 50% of the mean diameter.

5. The pharmaceutical composition of claim 1 wherein more than 90% of the microparticles have diameters in the range of 100-300 μm.

6. The pharmaceutical composition of claim 1 wherein more than 90% of the microparticles have diameters in the range of 50-100 μm.

7. The pharmaceutical composition of any one of claims 1-6 wherein the crystalline drug core comprises fluticasone, fluticasone furoate, or fluticasone propionate, or a combination thereof.

8. The pharmaceutical composition of claim 7 wherein the crystalline drug core comprises 100% of fluticasone propionate.

9. The pharmaceutical composition of any one of claims 1-8 wherein the polymeric shell comprises one or more biodegradable polymers selected from the group consisting of polyvinyl alcohol (PVA), ethylene vinyl acetate(EVA), poly(p-xylylene) polymers, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), poly(valerolactone) (PVL), poly(ε-decalactone) (PDL), poly(1,4-dioxane-2,3-dione), poly(1,3-dioxane-2-one), poly(para-dioxanone) (PDS), poly(hydroxybutyric acid) (PHB), poly(hydroxyvaleric acid) (PHV), and poly(β-malic acid) (PMLA).

10. The pharmaceutical composition of any one of claims 1-9 wherein the microparticle comprises 90-98% w/w of crystalline drug core and 2-10% w/w of polymeric shell.

11. The pharmaceutical composition of any one of claims 1-10 wherein the polymeric shell is heat treated within a temperature range of 210-230°C for at least one hour.

12. The pharmaceutical composition of any one of claims 1-11, further comprising a pharmaceutically acceptable vehicle in which the plurality of microparticles is suspended.

13. A pharmaceutical composition, comprising:

a plurality of microparticles, the microparticle including:

(1) a crystalline drug core of more than 70% by weight of the microparticle, the crystalline drug core including one or more crystals of fluticasone or a pharmaceutically acceptable salt or ester thereof; and

(2) a polymeric shell encapsulating the crystalline drug core, the polymeric shell being in contact but immiscible with the crystalline drug core,

wherein the microparticles are heat treated within a temperature range of 210-230°C for at least one hour.

14. The pharmaceutical composition of claim 13 wherein more than 90% of the microparticles have diameters in the range of 100-300 μm.

15. The pharmaceutical composition of claim 13 wherein more than 90% of the microparticles have diameters in the range of 50-100 μm.

16. The pharmaceutical composition of any one of claims 13-15 wherein the crystalline drug core is fluticasone, fluticasone furoate, or fluticasone propionate.

17. The pharmaceutical composition of claim 16 wherein the crystalline drug core comprises 100% of fluticasone propionate.

18. The pharmaceutical composition of any one of claims 14-17 wherein the polymeric shell comprises one or more biodegradable polymers selected from the group consisting of polyvinyl alcohol (PVA), ethylene vinyl acetate (EVA), poly(p-xylylene) polymers, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), poly(valerolactone) (PVL), poly(ε-decalactone) (PDL), poly(1,4-dioxane-2,3-dione), poly(1,3-dioxane-2-one), poly(para-dioxanone) (PDS),

poly(hydroxybutyric acid) (PHB), poly(hydroxyvaleric acid) (PHV), and poly(β-malic acid) (PMLA).

19. The pharmaceutical composition of any one of claims 14-18 wherein the microparticle comprises 90-98% w/w of crystalline drug core and 2-10% w/w of polymeric shell.

20. A unit dosage form of a corticosteroid for injecting into a body compartment, comprising:

a plurality of microparticles, the microparticle including:

(1) a crystalline drug core of more than 70% by weight of the microparticle; and

(2) a polymeric shell encapsulating the crystalline drug core,

wherein the crystalline drug core includes one or more crystals of a corticosteroid selected from fluticasone, fluticasone furoate, and fluticasone propionate, and the polymeric shell is in contact but immiscible with the crystalline drug core,

wherein the unit dosage form is capable of sustained-release of the corticosteroid over a period of 2-12 months while maintaining a minimum therapeutically effective concentration of the corticosteroid within the body compartment.

21. The unit dosage form of claim 20 wherein the body compartment is a joint, an epidural space, intravitreal space, a surgically created space, or a space adjacent to an implant.

22. The unit dosage form of claim 20 or claim 21 wherein, within the sustained release period of 2-12 months, the corticosteroid is released locally within the body compartment and provides below a quantifiable limit of plasma corticosteroid 7 days after injection.

23. The unit dosage form of any one of claims 20-22 wherein the plurality of microparticles have a mean diameter in the range of 50 μm to 150 μm and a standard deviation of less than 50% of the mean diameter.

24. The unit dosage form of any one of claims 20-23 wherein the microparticle comprises 90-98% w/w of crystalline drug core and 2-10% w/w of polymeric shell.

25. The unit dosage form of any one of claims 20-24 wherein the polymeric shell comprises one or more biodegradable polymers selected from the group consisting of polyvinyl alcohol (PVA), ethylene vinyl acetate (EVA), poly(p-xylylene) polymers, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), poly(valerolactone) (PVL), poly(ε-decalactone) (PDL), poly(1,4-dioxane-2,3-dione), poly(1,3-dioxane-2-one), poly(para-dioxanone) (PDS), poly(hydroxybutyric acid) (PHB), poly(hydroxyvaleric acid) (PHV), and poly(β-malic acid) (PMLA).

26. The unit dosage form of any one of claims 20-25 wherein the polymeric shell is heat treated within a temperature range of 210-230°C for at least one hour.

27. A method of decreasing inflammation or managing pain in a patient in need thereof comprising administering to the patient, via injection to a body compartment, a therapeutically effective amount of a pharmaceutical composition for sustained release of a corticosteroid wherein the pharmaceutical composition comprises a plurality of microparticles and a pharmaceutically acceptable vehicle, the microparticle including:

(1) a crystalline drug core of more than 70% by weight of the microparticle; and

(2) a polymeric shell encapsulating the crystalline drug core,

and wherein the crystalline drug core includes one or more crystals of fluticasone or a pharmaceutically acceptable salt or ester thereof, and the polymeric shell is in contact but immiscible with the crystalline drug core.

28. The method of claim 27 wherein said microparticles have a mean diameter of between 50 μm and 400 μm, or between 50 μm and 250 μm, or between 80 μm and 150 μm.

29. The method of claim 27 or claim 28 wherein more than 90% of the microparticles have diameters in the range of 100-300 μm, or more than 90% of the microparticles have diameters in the range of 50-100 μm.

30. The method of claim any one of claims 27-29, wherein the crystalline drug core comprises fluticasone propionate.

31. The method of claim any one of claims 27-30 wherein administering the pharmaceutical composition comprises injecting, intra-articularly, to an affected joint of said patient.

32. The method of claim 31 wherein the inflammation or pain in a patient is due to at least one of osteoarthritis, rheumatoid arthritis or injury induced arthritis.

33. The method of any one of claims 27-30 wherein administering pharmaceutical composition comprises injecting the pharmaceutical composition into an epidural space of said patient.

34. The method of claim 33 wherein the inflammation or pain in a patient is due to at least one of spinal disc protrusion, spinal nerve inflammation in cervical, thoracic or lumbar, chronic low back pain from nerve root compression.

35. The method of any one of claims 27-30 wherein administering pharmaceutical composition comprises injecting the pharmaceutical composition into an vitreous humour of the patient.

36. The method of claim 35 wherein the inflammation or pain in a patient is due to diabetic macular edema or uveitis.

37. The method of any one of claims 27-30 wherein administering pharmaceutical composition comprises injecting the pharmaceutical composition into a space adjacent to an implant having scar tissue.

38. The method of claim 37 wherein the inflammation or pain in the patient is due to recurrent capsular contractions or keloid scarring.

39. The method of any one of claims 27-38, wherein said crystalline drug core of the pharmaceutical composition for sustained release comprises substantially pure corticosteroid and is at least 90% of the microparticle by weight.

40. The method claim any one of claims 27-39 wherein the polymeric shell comprises at least one of polylactic acid, polyvinyl alcohol, ethylene vinyl acetate and parylene.

41. The method of any one of claims 27-40 wherein said microparticles when dissolution tested using United States Pharmacopoeia

Type II apparatus exhibit a dissolution half-life of 12-20 hours, wherein the dissolution conditions are: 3 milligrams of microparticles in 200 milliliters of dissolution medium of 70% v/v methanol and 30% v/v of water at 25°C.

42. The method of any one of claims 27-40 wherein the microparticles are heat-treated at 210-230°C prior to being formulated into the pharmaceutical composition.

43. The method of any one of claims 27-42 wherein the sustained release of the corticosteroid lasts for 2-12 months.

44. The method in any one of claims 27-43 where the microparticles of the pharmaceutical composition are mixed with the vehicle immediately prior to injection.

45. A method for forming coated microparticles, comprising:

providing a crystalline drug core including one or more crystals of a corticosteroid,

forming a polymeric shell by coating one or more coats of a polymeric solution having a biodegradable polymer and a solvent;

allowing the solvent to dry to provide coated microparticles; and

heating the coated microparticles at 210-230°C for at least one hour.

46. The method of claim 45 wherein heating the coated microparticles does not extend beyond 2 hours.

47. The method of claim 45 or claim 46 wherein the crystalline drug core is substantially pure fluticasone or a pharmaceutically acceptable ester thereof.

48. The method of any one of claims 45-47 wherein the one or more biodegradable polymers are polyvinyl alcohol (PVA), ethylene vinyl acetate, poly(p-xylylene) polymers, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), poly(valerolactone) (PVL), poly(ε-decalactone) (PDL), poly(1,4-dioxane-2,3-dione), poly(1,3-dioxane-2-one), poly(para-dioxanone) (PDS), poly(hydroxybutyric acid) (PHB), poly(hydroxyvaleric acid) (PHV), or poly(β-malic acid) (PMLA).

49. A method of decreasing inflammation or managing pain in a patient in need thereof comprising:

administering to the patient, via a single injection to a body compartment, a unit dosage form for sustained release of a corticosteroid wherein the unit dosage form comprises a plurality of microparticles and a pharmaceutically acceptable vehicle,

wherein the crystalline drug core includes one or more crystals of a corticosteroid selected from fluticasone, fluticasone furoate, and fluticasone propionate, and the polymeric shell is in contact but immiscible with the crystalline drug core,

and wherein, following the single injection, the corticosteroid is released over a period of 2-12 months while maintaining a minimum therapeutically effective concentration of the corticosteroid within the body compartment.

50. The method of claim 49 wherein the body compartment is a joint, epidural space, intravitreal space, a surgically created space, or a space near an implant having scar tissue.

51. The method of claims 49 or 50 wherein, within the sustained release period of 2-12 months, the corticosteroid is released locally

within the body compartment and provides plasma corticosteroid below a quantifiable limit 7 days after injection.

52. The method of any one of claims 49-51 wherein the plurality of microparticles have a mean diameter in the range of 50 μm to 150 μm and a standard deviation of less than 50% of the mean diameter.

53. The method of any one of claims 49-52 wherein the polymeric shell comprises one or more biodegradable polymers selected from the group consisting of polyvinyl alcohol (PVA), ethylene vinyl acetate poly(p-xylylene) polymers, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), poly(valerolactone) (PVL), poly(ε-decalactone) (PDL), poly(1,4-dioxane-2,3-dione), poly(1,3-dioxane-2-one), poly(para-dioxanone) (PDS), poly(hydroxybutyric acid) (PHB), poly(hydroxyvaleric acid) (PHV), and poly(β-malic acid) (PMLA).

54. The method of any one of claims 49-53 wherein the polymeric shell is heat treated within a temperature range of 210-230°C for at least one hour.

55. The method of claim 49 wherein administering to the patient comprising administering the unit dosage form of any one of claims 20-26.

CLAIMS

WE CLAIM:

1. A pharmaceutical composition, comprising:

a plurality of microparticles, the microparticle including:

(1) a crystalline drug core of more than 70% by weight of the microparticle, the crystalline drug core including one or more crystals of fluticasone or a pharmaceutically acceptable salt or ester thereof; and

(2) a polymeric shell encapsulating the crystalline drug core, the polymeric shell being in contact but immiscible with the crystalline drug core,

wherein said microparticles when dissolution tested using United States Pharmacopoeia Type II apparatus exhibit a dissolution half-life of 12-20 hours, wherein the dissolution conditions are: 3 milligrams of microparticles in 200 milliliters of dissolution medium of 70% v/v methanol and 30% v/v of water at 25°C,

wherein the plurality of microparticles have a mean diameter in the range of 80 µm to 150 µm and a standard deviation of less than 50% of the mean diameter.

2. The pharmaceutical composition of claim 1 wherein the plurality of microparticles have a mean diameter of 75µm and a standard deviation of less than 50% of the mean diameter.

3. The pharmaceutical composition of claim 1 wherein the plurality of microparticles have a mean diameter of 150 µm and a standard deviation of less than 50% of the mean diameter.

4. A pharmaceutical composition, comprising:

a plurality of microparticles, the microparticle including:

(1) a crystalline drug core of more than 70% by weight of the microparticle, the crystalline drug core including one or more crystals of fluticasone or a pharmaceutically acceptable salt or ester thereof; and

(2) a polymeric shell encapsulating the crystalline drug core, the polymeric shell being in contact but immiscible with the crystalline drug core,

wherein said microparticles when dissolution tested using United States Pharmacopoeia Type II apparatus exhibit a dissolution half-life of 12-20 hours, wherein the dissolution conditions are: 3 milligrams of microparticles in 200 milliliters of dissolution medium of 70% v/v methanol and 30% v/v of water at 25°C,

wherein more than 90% of the microparticles have diameters in the range of 100-300 μm.

5. A pharmaceutical composition, comprising:

a plurality of microparticles, the microparticle including:

(1) a crystalline drug core of more than 70% by weight of the microparticle, the crystalline drug core including one or more crystals of fluticasone or a pharmaceutically acceptable salt or ester thereof; and

(2) a polymeric shell encapsulating the crystalline drug core, the polymeric shell being in contact but immiscible with the crystalline drug core,

wherein said microparticles when dissolution tested using United States Pharmacopoeia Type II apparatus exhibit a dissolution half-life of 12-20 hours, wherein the dissolution conditions are: 3 milligrams of microparticles in 200 milliliters of dissolution medium of 70% v/v methanol and 30% v/v of water at 25°C,

wherein more than 90% of the microparticles have diameters in the range of 50-100 μm.

6. The pharmaceutical composition of any one of claims 1-5 wherein the crystalline drug core comprises fluticasone, fluticasone furoate, or fluticasone propionate, or a combination thereof.

7. The pharmaceutical composition of claim 6 wherein the crystalline drug core comprises 100% of fluticasone propionate.

8. The pharmaceutical composition of any one of claims 1-7 wherein the polymeric shell comprises one or more biodegradable polymers selected from the group consisting of polyvinyl alcohol (PVA), ethylene vinyl acetate(EVA), poly(p-xylylene) polymers, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(ϵ-caprolactone) (PCL), poly(valerolactone) (PVL), poly(ϵ-decalactone) (PDL), poly(1,4-dioxane-2,3-dione), poly(1,3-dioxane-2-one), poly(para-dioxanone) (PDS), poly(hydroxybutyric acid) (PHB), poly(hydroxyvaleric acid) (PHV), and poly(β-malic acid) (PMLA).

9. The pharmaceutical composition of any one of claims 1-8 wherein the microparticle comprises 90-98% w/w of crystalline drug core and 2-10% w/w of polymeric shell.

10. The pharmaceutical composition of any one of claims 1-9 wherein the polymeric shell is heat treated within a temperature range of 210-230°C for at least one hour.

11. The pharmaceutical composition of any one of claims 1-10, further comprising a pharmaceutically acceptable vehicle in which the plurality of microparticles is suspended.