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 the polymeric shell is heat treated within a temperature range of 210-230°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 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 to be injected 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,

wherein the polymeric shell is heat treated within a temperature range of 210-230°C.

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 for at least one hour.

27. A pharmaceutical composition for use in decreasing inflammation or managing pain in a patient in need thereof comprising 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, and wherein the polymeric shell is heat treated within a temperature range of 210-230 ℃.

28. The pharmaceutical composition 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 pharmaceutical composition 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 pharmaceutical composition of any one of claims 27-29, wherein the crystalline drug core comprises fluticasone propionate.

31. The pharmaceutical composition of any one of claims 27-30 wherein the pharmaceutical composition is to be administered by injecting, intra-articularly, to an affected joint of said patient.

32. The pharmaceutical composition 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 pharmaceutical composition of any one of claims 27-30 wherein the pharmaceutical composition is to be administered by injecting the pharmaceutical composition into an epidural space of said patient.

34. The pharmaceutical composition 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 pharmaceutical composition of any one of claims 27-30 wherein the pharmaceutical composition is to be administered by injecting the pharmaceutical composition into an vitreous humour of the patient.

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

37. The pharmaceutical composition of any one of claims 27-30 wherein the pharmaceutical composition is to be administered by injecting the pharmaceutical composition into a space adjacent to an implant having scar tissue.

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

39. The pharmaceutical composition 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 pharmaceutical composition of 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 pharmaceutical composition 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 pharmaceutical composition of any one of claims 27-41 wherein the sustained release of the corticosteroid lasts for 2-12 months.

43. The pharmaceutical composition in any one of claims 27-42 where the microparticles of the pharmaceutical composition are mixed with the vehicle immediately prior to injection.

44. 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.

45. The method of claim 44 wherein heating the coated microparticles does not extend beyond 2 hours.

46. The method of claim 44 or claim 45 wherein the crystalline drug core is substantially pure fluticasone or a pharmaceutically acceptable ester thereof.

47. The method of any one of claims 44-46 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).

48. A unit dosage form of any one of claims 20-26 for use in decreasing inflammation or managing pain in a patient in need thereof.