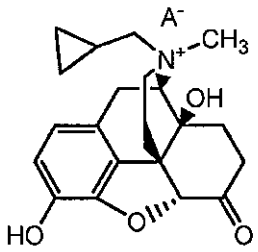
Claims

What is claimed is:

1. A salt of formula (**I**):



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wherein A^- is an anion of an amphiphilic pharmaceutically acceptable excipient.

2. The salt according to claim 1, wherein the pharmaceutically acceptable excipient has a pK_a of 3 or less.

3. The salt according to claims 1, wherein the pharmaceutically acceptable excipient comprises a sulfate ($-OSO_3^-$) group.

4. The salt according to any one of claims 1-3, wherein the pharmaceutically acceptable excipient comprises a saturated or unsaturated, branched or unbranched, cyclic or acyclic C_{4-30} aliphatic group that is optionally substituted.

5. The salt according to claim 1-3, wherein the pharmaceutically acceptable excipient comprises a saturated, unbranched, acyclic, unsubstituted C_{4-30} alkyl group.

6. The salt according to claim 1-3, wherein the pharmaceutically acceptable excipient comprises a saturated, unbranched, acyclic, unsubstituted C_{7-15} alkyl group.

7. The salt according to claim 1-3, wherein the pharmaceutically acceptable excipient comprises a C_{12} *n*-alkyl group.

8. The salt according to claim 1, wherein A^- is dodecyl sulfate.

9. A pharmaceutical composition for oral administration comprising the salt according to any one of claims 1-8.

10. A pharmaceutical composition for oral administration comprising a solid dosage of methylnaltrexone or a pharmaceutically acceptable salt thereof, and an amphiphilic pharmaceutically acceptable excipient.

11. The pharmaceutical composition of claim 10, wherein the methylnaltrexone or a pharmaceutically acceptable salt thereof, and the amphiphilic pharmaceutically acceptable excipientform an ion pair when dissolved in solution.

12. The pharmaceutical composition of claim 11, wherein the ion pair is formed when the methylnaltrexone or a pharmaceutically acceptable salt thereof and the amphiphilic pharmaceutically acceptable excipient are dissolved in solution at a pH of greater than about 1 and less than about 4.

13. The pharmaceutical composition of claim 12, further comprising a disintegrant.

14. The pharmaceutical composition of any one of claims 10-13, wherein at least 50% of the composition dissolves in a dissolution apparatus with paddles at 100 rpm in 900 mL of 0.1 N HCl at 37 °C within about 15 minutes.

15. The composition of claim 14, wherein at least 75% of the composition dissolves in a dissolution apparatus with paddles at 100 rpm in 900 mL of 0.1 N HCl at 37 °C within about 15 minutes.

16. The composition of claim 15, wherein at least 90% of the composition dissolves in a dissolution apparatus with paddles at 100 rpm in 900 mL of 0.1 N HCl at 37 °C within about 10 minutes.

17. The composition of any one of claims 10-16, wherein the composition in solution has an apparent octanol/water partition coefficient for methylnaltrexone of at least 0.25 at a pH between 1 and 4.

18. The composition according to claim 17, wherein the apparent partition coefficient is at least 1.

19. The composition according to claim 18, wherein the apparent partition coefficient is at least 10.

20. The composition according to claim 19, wherein the apparent partition coefficient is at least 20.

21. The composition according to claim 20, wherein the apparent partition coefficient is at least 30.

22. The composition according to any one of claims 10-21, wherein the pharmaceutically acceptable excipient has a pKa of 3 or less.

23. The composition according to any one of claims 10-22, wherein the pharmaceutically acceptable excipient comprises a sulfate ($-OSO_3^-$) group.

24. The composition according to any one of claims 10-22, wherein the pharmaceutically acceptable excipient comprises a saturated or unsaturated, branched or unbranched, cyclic or acyclic C_{4-30} aliphatic group that is optionally substituted.

25. The composition according to any one of claims 10-22, wherein the pharmaceutically acceptable excipient comprises a saturated, unbranched, acyclic, unsubstituted C_{4-30} alkyl group.

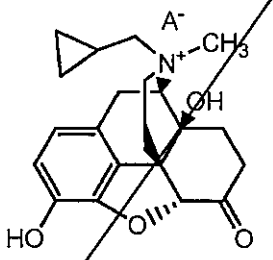
26. The composition according to any one of claims 10-22, wherein the pharmaceutically acceptable excipient comprises a saturated, unbranched, acyclic, unsubstituted C_{7-15} alkyl group.

27. The composition according to any one of claims 10-22, wherein the pharmaceutically acceptable excipient comprises a C_{12} *n*-alkyl group.

28 The composition according to any one of claims 10-22, wherein the pharmaceutically acceptable excipient is an anionic surfactant.

29. The composition according to any one of claims 10-22, wherein the pharmaceutically acceptable excipient is sodium dodecyl sulfate (SDS).

30. The composition according to any one of claims 10-29, wherein the composition comprises a compound of formula (**I**):



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wherein A^- is an anion of an amphiphilic pharmaceutically acceptable excipient.

31. The composition according to claims 10-30, wherein the disintegrant is an effervescent disintegrant.

32. The composition according to claim 10-30, wherein the disintegrant is a bicarbonate.

33. The composition according to claim 10-30 wherein the disintegrant is sodium bicarbonate.

34. The composition according to any one of claims 9-33, wherein the composition comprises from about 5% to about 80% pharmaceutically acceptable excipient, based upon the total weight of the composition.

35. The composition according to claim 9-33, wherein the formulation contains about 7% to about 75% methylnaltrexone, based upon total weight of the composition.

36. The composition according to any one of claims 9-33, wherein the composition is a tablet.

37. The composition according any one of claims 9-36, wherein the composition is a tablet comprising at least one or more of a binder, a chelating agent, a wetting agent, a lubricant, a non-functional coating, or an antioxidant, and combinations thereof.

38. The composition according to claim 37, wherein the composition comprises a chelating agent.

39. The composition according to claim 38, wherein the chelating agent is a salt of EDTA.

40. The composition according to claim 38, wherein the chelating agent is calcium EDTA disodium.

41. The composition according to claim 37, wherein the composition comprises a lubricant.

42. The composition according to claim 41, wherein the lubricant is magnesium stearate.

43. The composition according to claim 37, wherein the composition comprises an antioxidant.

44. The composition according to claim 43 wherein the antioxidant is ascorbic acid.

45. The composition according to claim 37, wherein the composition comprises:
(a) about 7% to about 75% of methylnaltrexone bromide, based upon total weight of the composition;

(b) about 5% to about 80% of an amphiphilic pharmaceutically acceptable excipient, based upon total weight of the composition;
(c) about 0.01%, to about 5% of a chelating agent, based upon total weight of the composition;
(d) about 1%, about 25% of a wetting agent, based upon total weight of the composition;
(e) about 5% to about 90% of a binder, based upon total weight of the composition;
(f) about 1%, to about 25% of a disintegrant, based upon total weight of the composition;
(g) about 0.1%, to about 7% of a lubricant, based upon total weight of the composition; and optionally
(h) about 0.01% to about 5% of an antioxidant, based upon the total weight of the composition.

46. The composition according to claim 45, wherein the binders are microcrystalline cellulose and silicified microcrystalline cellulose.

47. The composition according to claim 45, wherein the disintegrant is crospovidone.

48. The composition according to claim 45, wherein the chelating agent is calcium EDTA.

49. The composition according to claim 45, wherein the wetting agent is polysorbate 80.

50. The compositon according to claim 45, wherein the lubricant is magnesium stearate.

51. The composition according to claim 45, wherein and the antioxidant is ascorbic acid.

52. A method of reducing one or more side effects of opioid therapy in a subject receiving opioid treatment comprising administering to the subject the composition according to any one of claims 9-51.

53. The method according to claim 52, wherein the side effect is caused, mediated, or exacerbated by opioid receptor activity.

54. The method according to claim 52, wherein the side effect affected by treatment comprises at least one effect selected from inhibition of intestinal motility, gastrointestinal dysfunction, constipation, bowel hypomotility, impaction, gastric hypomotility, GI sphincter constriction, increased sphincter tone, inhibition of gastrointestinal motility, inhibition of gastric emptying, delayed gastric emptying, incomplete evacuation, nausea, emesis, cutaneous flushing, bloating, abdominal distension, sweating, dysphoria, pruritis, and urinary retention.

55. The method of claim 52, wherein the subject is a patient receiving opioid administration for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 3 months, at least 6 months, at least 12 months, or more.

56. The method according to claim 55, wherein the patient has chronic non-malignant pain.

57. The method according to claim 53-56, wherein the subject is administered an amount of the composition sufficient to achieve laxation within about 24 hours of administration.

58. The method according to claim 57, wherein the subject is administered an amount of the composition sufficient to achieve laxation within about 4 hours of administration.

59. The method according to any one of claims 57 and 4658 wherein the subject is in a fasted state at the time of administration.

60. The method according to any one of claims 57 and 58, wherein the subject has fasted for at least 10 hours.

61. The method according to any one of claims 57 and 58, wherein the subject has fasted overnight.

62. The method according to any one of claims 57 and 58, wherein the subject has not fasted.

63. The method of any of claims 52-62, wherein the composition is administered orally to the subject.

64. The method of any one of claims 52-63, further comprising selecting the subject that is receiving opioid treatment.

65. The method of claim 64, wherein the subject has been receiving a daily dose of >50 mg of oral morphine equivalents for at least 14 days.

66. A method of preparing a methylnaltrexone formulation comprising the steps of:

preparing a wet granulation comprising methylnaltrexone or a pharmaceutically acceptable salt thereof, an amphiphilic pharmaceutically acceptable excipient, at least one disintegrant, at least one binder, at least one chelating agent, at least one wetting agent, and optionally at least one filler; and

forming a solid dosage unit.

67. The method of claim 66, wherein the wet granulation is formed by dry blending the methylnaltrexone, binder, amphiphilic pharmaceutically acceptable excipient, and optionally a disintegrant; and granulating the dry blend with a solution of a chelating agent and/or a wetting agent to form a wet granulation.

68. The method of claim 66, wherein the pharmaceutically acceptable excipient is sodium dodecyl sulfate.

69. The method of claim 66, wherein the pharmaceutically acceptable excipient has a pK_a of 3 or less.

70. The method of claim 66, wherein the pharmaceutically acceptable excipient comprises a sulfate ($-OSO_3^-$) group.

71. The method of claim 66, wherein the pharmaceutically acceptable excipient comprises a saturated or unsaturated, branched or unbranched, cyclic or acyclic C_{4-30} aliphatic group that is optionally substituted.

72. The method of claim 66, wherein the pharmaceutically acceptable excipient comprises a saturated, unbranched, acyclic, unsubstituted C_{4-30} alkyl group.

73. The method of claim 66, wherein the pharmaceutically acceptable excipient comprises a saturated, unbranched, acyclic, unsubstituted C_{7-15} alkyl group.

74. The method of claim 66, wherein the pharmaceutically acceptable excipient comprises a C_{12} *n*-alkyl group.

75. The method of claim 66, wherein the disintegrant is sodium bicarbonate.

76. The method of claim 66, wherein the disintegrant is crospovidone.

77. The method of claim 66, wherein the binder is microcrystalline cellulose.

78. The method of claim 66, wherein the chelating agent is calcium EDTA.

79. The method of claim 66, wherein the wetting agent is Polysorbate 80.

80. The method of claim 66, further comprising:
drying the wet granulation;
milling the dried granulation;
blending one or more additional disintegrants with the dried granulation; and

optionally adding a lubricant, a glidant, or a combination thereof to the dried granulation before the step of forming, wherein at least one disintegrant is an effervescent disintegrant.

81. The method of claim 80, wherein the effervescent disintegrant is selected from the group consisting of sodium bicarbonate, potassium bicarbonate, calcium carbonate, sodium carbonate, and combinations thereof.

82. The method of claim 80 wherein the effervescent disintegrant is sodium bicarbonate.

83. The method of claim 80, wherein a disintegrant is crospovidone.

84. The method of claim 80, wherein an additional disintegrant is crospovidone.

85. The method of claim 80, wherein the lubricant is magnesium stearate.

86. The method of claim 85, wherein the glidant is selected from the group consisting of talc, silicone dioxide, and combinations thereof.

87. The method of claim 80, wherein the binder is silicified microcrystalline cellulose.

88. The method of any one of claims 66-87, whereby the method provides a methylnaltrexone formulation which in solution yields an apparent octanol/water partition coefficient for methylnaltrexone of at least 0.25 at a pH between 1 and 4.

89. The method of any one of claims 66-87, whereby the method provides a methylnaltrexone formulation which in solution yields an apparent octanol/water partition coefficient for methylnaltrexone of at least 10 at a pH between 1 and 4.

90. The method of any one of claims 66-87, whereby the method provides a methylnaltrexone formulation which in solution yields an apparent octanol/water partition coefficient for methylnaltrexone of at least 20 at a pH between 1 and 4.

91. The method of any one of claims 66-87, whereby the method provides a methylnaltrexone formulation with a dissolution profile substantially as depicted in *Figure 1* in 900 ml 0.1 N HCl at 37 °C.

92. The method of any claims 66-91, wherein the solid dosage unit is a tablet.

93. A product produced by the method of any of claims 66-92.

94. A multi-day pack comprising multiple unit dosage compositions according to any one of claims 9-47.

95. The pack of claim 94, wherein the pack is a 7-day, 14-day, or 30 day pack.

96. The pack of claim 94, wherein the pack further comprises prescribing information.

Claims:

1. An invention not claimed in any divisional application.