at the respective time points and analysed on HPLC using UV detector. The in-vitro release data is indicated as percentage dissolved based on the label content of actives tested.

[0179] The impurities of various formulations were determined using gradient HPLC method. The samples were extracted with methanol and water and separated on a reverse phase column using mobile phase consisting of potassium phosphate monobasic buffer and methanol. The actives and impurities were detected with UV detector. The results are reported in % for known degradation products and individual unknown degradation products and total impurities.

[0180] All publications, patents and patent applications referred to herein are incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

What is claimed is:

1. A prolonged release pharmaceutical dosage form comprising a plurality of coated beads, each of the coated beads comprising:

(a) a granule;

(b) a first layer coated on the granule, the first layer comprising: (i) hydromorphone or a pharmaceutically acceptable salt thereof, (ii) naloxone or a pharmaceutically acceptable salt thereof, (iii) an antioxidant compound, and (iii) a chelating compound; and

(c) a second layer coated on the first layer, the second layer comprising a prolonged release agent.

2. The prolonged release pharmaceutical dosage form defined in Claim 1, wherein (i) and (ii) are present in a weight ratio of from about 2:1 to about 1:2.

3. The prolonged release pharmaceutical dosage form defined in Claims 1-2, wherein (i) is a pharmaceutically acceptable salt of hydromorphone.

4. The prolonged release pharmaceutical dosage form defined in Claims 1-2, wherein (i) is hydromorphone hydrochloride.

5. The prolonged release pharmaceutical dosage form defined in Claims 1-4, wherein (ii) is a pharmaceutically acceptable salt of naloxone.

6. The prolonged release pharmaceutical dosage form defined in Claims 1-4, wherein (i) is naloxone hydrochloride.

7. The prolonged release pharmaceutical dosage form defined in Claims 1-6, wherein the antioxidant compound comprises sodium metabisulfite.

8. The prolonged release pharmaceutical dosage form defined in Claims 1-7, wherein the chelating agent comprises ethylenediaminetetraacetic acid (EDTA).

9. The prolonged release pharmaceutical dosage form defined in Claims 1-7, wherein the chelating agent comprises ethylenediaminetetraacetic acid (EDTA) disodium salt.

10. The prolonged release pharmaceutical dosage form defined in Claims 1-9, wherein the prolonged release compound is selected from the group consisting of a hydrophobic polymer, a hydrophilic polymer, a protein-derived material, a gum, a substituted or unsubstituted hydrocarbon, a digestible carbohydrate, a fatty acid, a fatty alcohol, a glyceryl ester of a fatty acid, a natural oil, a synthetic oil, a natural wax, a synthetic wax and any mixture of two or more of any of these.

11. The prolonged release pharmaceutical dosage form defined in Claims 1-9, wherein the prolonged release compound is selected from the group consisting of a cellulose ether, an acrylic based polymer, an acrylic based copolymer, a methacrylic based polymer, a methacrylic based copolymer, a fatty alcohol and any mixture of two or more of any of these.

12. The prolonged release pharmaceutical dosage form defined in Claims 1-9, wherein the prolonged release compound is selected from the group consisting of a neutral acrylic based polymer, a neutral acrylic based copolymer, a neutral methacrylic based polymer, a neutral methacrylic based copolymer, a hydrophobic cellulose ether, a fatty alcohol and any mixture of two or more of any of these.

13. The prolonged release pharmaceutical dosage form defined in Claims 1-9, wherein the prolonged release compound is ethyl cellulose.

14. The prolonged release pharmaceutical dosage form defined in Claims 1-13, wherein the granule is selected from an uncoated microcrystalline cellulose granule and a mannitol-polyvinylpyrrolidone granule.

15. The prolonged release pharmaceutical dosage form defined in Claims 1-14, further comprising:

(d) a third layer coated on the second layer, the third layer comprising a moisture barrier agent.

16. The prolonged release pharmaceutical dosage form defined in Claim 15, wherein the moisture barrier agent comprises a polyvinyl alcohol-polyethylene glycol graft copolymer.

17. The prolonged release pharmaceutical dosage form defined in Claims 1-16 in the form of a capsule.

18. The prolonged release pharmaceutical dosage form defined in Claim 17, wherein the capsule containing the plurality of coated beads.

19. The prolonged release pharmaceutical dosage form defined in Claims 17-18, wherein the capsule is a hydroxypropyl methyl cellulose capsule.

20. A coated bead comprising:

(a) a granule;

(b) a first layer coated on the granule, the first layer comprising: (i) hydromorphone or a pharmaceutically acceptable salt thereof, (ii) naloxone or a pharmaceutically acceptable salt thereof, (iii) an antioxidant compound, and (iii) a chelating compound; and

(c) a second layer coated on the first layer, the second layer comprising a prolonged release agent.

21. The coated bead defined in Claim 20, wherein (i) and (ii) are present in a weight ratio of from about 2:1 to about 1:2.

22. The coated bead defined in Claims 20-21, wherein (i) is a pharmaceutically acceptable salt of hydromorphone.

23. The coated bead defined in Claims 20-21, wherein (i) is hydromorphone hydrochloride.

24. The coated bead defined in Claims 20-23, wherein (ii) is a pharmaceutically acceptable salt of naloxone.

25. The coated bead defined in Claims 20-23, wherein (i) is naloxone hydrochloride.

26. The coated bead defined in Claims 20-25, wherein the antioxidant compound comprises sodium metabisulfite.

27. The coated bead defined in Claims 20-26, wherein the chelating agent comprises ethylenediaminetetraacetic acid (EDTA).

28. The coated bead defined in Claims 20-26, wherein the chelating agent comprises ethylenediaminetetraacetic acid (EDTA) disodium salt.

29. The coated bead defined in Claims 20-28, wherein the prolonged release compound is selected from the group consisting of a hydrophobic polymer, a hydrophilic polymer, a protein-derived material, a gum, a substituted or unsubstituted hydrocarbon, a digestible carbohydrate, a fatty acid, a fatty alcohol, a glyceryl ester of a fatty acid, a natural oil, a synthetic oil, a natural wax, a synthetic wax and any mixture of two or more of any of these.

30. The coated bead defined in Claims 20-28, wherein the prolonged release compound is selected from the group consisting of a cellulose ether, an acrylic based polymer, an acrylic based copolymer, a methacrylic based polymer, a methacrylic based copolymer, a fatty alcohol and any mixture of two or more of any of these.

31. The coated bead defined in Claims 20-28, wherein the prolonged release compound is selected from the group consisting of a neutral acrylic based polymer, a neutral acrylic based copolymer, a neutral methacrylic based polymer, a neutral methacrylic based copolymer, a hydrophobic cellulose ether, a fatty alcohol and any mixture of two or more or of any of these.

32. The coated bead defined in Claims 20-28, wherein the prolonged release compound is ethyl cellulose.

33. The coated bead defined in Claims 20-32, wherein the granule is selected from an uncoated microcrystalline cellulose granule and a mannitol-polyvinylpyrrolidone granule.

34. The coated bead defined in Claims 30-33, further comprising:

(d) a third layer coated on the second layer, the third layer comprising a moisture barrier agent.

35. The coated bead defined in Claim 34, wherein the moisture barrier agent comprises a polyvinyl alcohol-polyethylene glycol graft copolymer.

36. A prolonged release pharmaceutical dosage form comprising a plurality of coated beads disposed in a hydroxypropyl methyl cellulose capsule, each of the coated beads comprising:

(a) a granule;

(b) a first layer coated on the granule, the first layer comprising: (i) hydromorphone hydrochloride, (ii) naloxone hydrochloride, (iii) an antioxidant compound, and (iii) a chelating compound, wherein (i) and (ii) are present in a weight ratio of about 2:1;

(c) a second layer coated on the first layer, the second layer comprising ethyl cellulose; and

(d) a third layer coated on the second layer, the third layer comprising a polyvinyl alcohol-polyethylene glycol graft copolymer.

37. The coated bead defined in Claim 36, wherein the granule is an uncoated microcrystalline cellulose granule.

38. The coated bead defined in Claim 36, wherein the granule is a mannitol-polyvinylpyrrolidone granule.

39. Use of a combination of an antioxidant (such as sodium metabisulfite) and a chelating agent (such as ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate) to improve the stability and/or dissolution properties of a prolonged release dosage form comprising (i) hydromorphone or a pharmaceutically acceptable salt thereof and (ii) naloxone or a pharmaceutically acceptable salt thereof.

40. The use defined in Claim 39, wherein the dosage form is a matrix dosage form.

41. The use defined in Claim 39, wherein the dosage form is coated bead dosage form.

42. The use defined in Claim 39, wherein the dosage form is a coated granule dosage form.

43. The use defined in Claims 39-42, wherein (i) and (ii) are present in a weight ratio of from about 2:1 to about 1:2.

44. The use defined in Claims 39-43, wherein (i) is a pharmaceutically acceptable salt of hydromorphone.

45. The use defined in Claims 39-43, wherein (i) is hydromorphone hydrochloride.

46. The use defined in Claims 39-45, wherein (ii) is a pharmaceutically acceptable salt of naloxone.

47. The use defined in Claims 39-45, wherein (i) is naloxone hydrochloride.

48. The use defined in Claims 39-47, wherein the antioxidant compound comprises sodium metabisulfite.

49. The use defined in Claims 39-48, wherein the chelating agent comprises ethylenediaminetetraacetic acid (EDTA).

50. The use defined in Claims 39-48, wherein the chelating agent comprises ethylenediaminetetraacetic acid (EDTA) disodium salt.