CLAIMS

1. A pharmaceutical composition comprising a plurality of timed pulsatile release and rapid release particles, wherein:

the timed pulsatile release particles each comprise a core coated with a timed pulsatile release layer;

the core comprises a weakly basic, poorly soluble drug and a pharmaceutically acceptable organic acid wherein the weakly basic drug is disposed over the organic acid and wherein a sustained release layer comprising a water insoluble polymer optionally in combination with a water soluble polymer or an enteric polymer, is disposed between the weakly basic drug and the organic acid;

the rapid release particles each comprise the weakly basic, poorly soluble drug, and release at least about 80 wt.% of the weakly basic, poorly soluble drug in about 15 minutes when dissolution tested using United States Pharmacopoeia (USP) dissolution methodology (Apparatus 2 - paddles@ 50 RPM and a two-stage dissolution medium at 37°C (first 2 hours in 0.1N HCl followed by testing in a buffer at pH 6.8).

2. The pharmaceutical composition of claim 1, wherein the core comprises a first inert bead, an organic acid layer, the sustained release layer, and a drug layer;
wherein:

the organic acid layer comprises the pharmaceutically acceptable organic acid and a first pharmaceutically acceptable polymeric binder;

the sustained release layer comprises a first pharmaceutically acceptable water insoluble polymer; and

the drug layer comprises the weakly basic, poorly soluble drug and a second pharmaceutically acceptable polymeric binder.

3. The pharmaceutical composition of claim 1, wherein the timed pulsatile release layer comprises a pharmaceutically acceptable water insoluble polymer and an enteric polymer.

4. The pharmaceutical composition of claim 1, wherein the rapid release particles each comprise an inert bead and a drug layer comprising the weakly basic, poorly soluble drug and a pharmaceutically acceptable polymeric binder; or the rapid release particles each comprise a granulate comprising the weakly basic, poorly soluble drug, a pharmaceutically acceptable polymeric binder, at least one excipient, and at least one disintegrant.

5. The pharmaceutical composition of claim 2, wherein the rapid release particles each comprise a second inert bead and a drug layer comprising the weakly basic, poorly soluble drug and a pharmaceutically acceptable polymeric binder.

6. The pharmaceutical composition of claim 2, wherein the rapid release particles each comprise a granulate comprising the weakly basic, poorly soluble drug, a pharmaceutically acceptable organic acid, a pharmaceutically acceptable polymeric binder, and at least one excipient.

7. The pharmaceutical composition of claim 2, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of citric acid, lactic acid, fumaric acid, malic acid, maleic acid, tartaric acid, succinic acid, oxalic acid, aspartic acid, and glutamic acid.

8. The pharmaceutical composition of claim 2, wherein the first and second pharmaceutically acceptable polymeric binders are each independently selected from the group consisting of polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone and vinyl alcohol, copolymers of polyvinylpyrrolidone and vinyl acetate, copolymers of polyvinylpyrrolidone with vinyl chloride, copolymers of polyvinylpyrrolidone with vinyl butyrate, copolymers of polyvinylpyrrolidone with vinyl laurate, copolymers of polyvinylpyrrolidone with vinyl stearate, hydroxypropylcellulose, hydroxypropylmethyl cellulose, carboxyalkylcelluloses, polyethylene oxide, sodium carboxymethyl cellulose, dextran, acacia, starch, and gelatin.

9. The pharmaceutical composition of claim 1, wherein the weakly basic, poorly soluble drug comprises a serotonin 5-HT_3 receptor antagonist.

10. The pharmaceutical composition of claim 9, wherein the serotonin 5-HT_3 receptor antagonist is selected from the group consisting of ondansetron, tropisetron, granisetron, dolasetron, and palonosetron.

11. The pharmaceutical composition of claim 2, wherein the weakly basic, poorly soluble drug comprises a serotonin 5-HT_3 receptor antagonist.

12. The pharmaceutical composition of claim 11, wherein the serotonin 5-HT_3 receptor antagonist is selected from the group consisting of ondansetron, tropisetron, granisetron, dolasetron, and palonosetron.

13. The pharmaceutical composition of claim 2, wherein the pharmaceutically acceptable water insoluble polymer selected from the group consisting of ethyl cellulose, cellulose acetate, polyvinyl acetate, neutral copolymers of ethyl acrylate and methylmethacrylate, copolymers of acrylic and methacrylic esters containing quaternary ammonium groups, and waxes.

14. The pharmaceutical composition of claim 3, wherein the enteric polymer is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, pH-sensitive copolymers of methacrylic acid and methylmethacrylate, and shellac.

15. The pharmaceutical composition of claim 5, wherein the first inert bead has an average particle size of about 25-30 mesh, and the second inert bead has an average particle size selected from the group consisting of about 45-60 mesh, about 60-80 mesh, and about 80-200 mesh.

16. The pharmaceutical composition of claim 15, wherein the first and second inert beads comprise sugar or microcrystalline cellulose.

17. The pharmaceutical composition of claim 6, wherein the timed pulsatile release particles each comprise a 25-30 mesh sugar bead sequentially coated with the organic acid layer, a first sustained release layer; the drug layer; an optional sealing layer; and an optional second sustained release layer.

18. The pharmaceutical composition of claim 17, wherein the organic acid layer comprises fumaric acid and hydroxypropyl cellulose.

19. The pharmaceutical composition of claim 17, wherein the first sustained release layer comprises ethylcellulose and a pharmaceutically acceptable plasticizer.

20. The pharmaceutical composition of claim 17, wherein the second sustained release layer is present and comprises ethylcellulose and a pharmaceutically acceptable plasticizer.

21. The pharmaceutical composition of claim 20, wherein the first and second sustained release layers comprise ethylcellulose and a pharmaceutically acceptable plasticizer.

22. The pharmaceutical composition of claim 17, wherein the first sustained release layer comprises ethylcellulose and a pharmaceutically acceptable plasticizer, and the second sustained release layer is not present.

23. The pharmaceutical composition of claim 17, wherein the optional sealing layer is present and comprises hydroxypropylmethyl cellulose.

24. The pharmaceutical composition of claim 17, wherein the weakly basic, poorly soluble drug in the timed pulsatile release and rapid release beads comprises ondansetron, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

25. The pharmaceutical composition of claim 17, wherein:
the timed pulsatile release particles each comprise:
the organic acid layer comprises fumaric acid and hydroxypropyl cellulose;
the first sustained release layer comprises ethylcellulose and a first pharmaceutically acceptable plasticizer;
the drug layer comprises hydroxypropyl cellulose, and ondansetron or a pharmaceutically acceptable salt, solvate and/or ester thereof;
the optional sealing layer is present and comprises hydroxypropylmethyl cellulose;
the timed pulsatile release layer comprises ethylcellulose, hydroxypropylmethylcellulose phthalate, and a second pharmaceutically acceptable plasticizer;
the rapid release particles each comprise a granulate comprising:
ondansetron or a pharmaceutically acceptable salt, solvate and/or ester thereof;
fumaric acid;

lactose;
microcrystalline cellulose; and
crospovidone.

26. The pharmaceutical composition of claim 25, wherein the first and second pharmaceutically acceptable plasticizers are independently selected from the group consisting of triacetin, tributyl citrate, triethyl citrate, acetyl tri-n-butyl citrate, diethyl phthalate, dibutyl sebacate, polyethylene glycol, polypropylene glycol, castor oil, acetylated mono- and di-glycerides and mixtures thereof.

27. The pharmaceutical composition of claim 26, wherein the first and second pharmaceutically acceptable plasticizers are both triethyl citrate, and the second sustained release layer is not present.

28. A capsule comprising the pharmaceutical composition of claim 1.

29. A capsule comprising the pharmaceutical composition of claim 27.

30. Use of the pharmaceutical composition of claim 1 for the preparation of a medicament for treating emesis.

31. The use of claim 30, wherein the medicament is for administering once-a-day to a patient in need thereof.

32. Use of the pharmaceutical composition of claim 27 for the preparation of a medicament for treating emesis.

33. The use of claim 32, wherein the medicament is for administering once-a-day to a patient in need thereof.

34. The pharmaceutical composition of claim 24 wherein the weakly basic, poorly soluble drug in the timed pulsatile release and rapid release beads comprises ondansetron hydrochloride.

35. The pharmaceutical composition of claim 25 wherein the rapid release particles each comprise a granulate comprising:

ondansetron hydrochloride;

fumaric acid;

lactose;

microcrystalline cellulose; and

crospovidone.

CLAIMS

1. A pharmaceutical composition comprising a plurality of timed pulsatile release and rapid release particles, wherein:

the timed pulsatile release particles each comprise a core coated with a timed pulsatile release layer;

the core comprises a weakly basic, poorly soluble drug and a pharmaceutically acceptable organic acid wherein the weakly basic drug is disposed over the organic acid and wherein a sustained release layer comprising a water insoluble polymer optionally in combination with a water soluble polymer or an enteric polymer, is disposed between the weakly basic drug and the organic acid;

the rapid release particles each comprise the weakly basic, poorly soluble drug, and release at least about 80 wt. % of the weakly basic, poorly soluble drug in about 15 minutes when dissolution tested using United States Pharmacopoeia (USP) dissolution methodology (Apparatus 2--paddles@50 RPM and a two-stage dissolution medium at 37° C. (first 2 hours in 0.1N HCl followed by testing in a buffer at pH 6.8).

2. The pharmaceutical composition of claim 1, wherein the core comprises a first inert bead, an organic acid layer, the sustained release layer, and a drug layer;

wherein:

the organic acid layer comprises the pharmaceutically acceptable organic acid and a first pharmaceutically acceptable polymeric binder;

the sustained release layer comprises a first pharmaceutically acceptable water insoluble polymer; and

the drug layer comprises the weakly basic, poorly soluble drug and a second pharmaceutically acceptable polymeric binder.

3. The pharmaceutical composition of claim 1, wherein the timed pulsatile release layer comprises a pharmaceutically acceptable water insoluble polymer and an enteric polymer.

4. The pharmaceutical composition of claim 1, wherein the rapid release particles each comprise an inert bead and a drug layer comprising the weakly basic, poorly soluble drug and a pharmaceutically acceptable polymeric binder; or the rapid release particles each comprise a granulate comprising the weakly basic, poorly soluble drug, a pharmaceutically acceptable polymeric binder, at least one excipient, and at least one disintegrant.

5. The pharmaceutical composition of claim 2, wherein the rapid release particles each comprise a second inert bead and a drug layer comprising the weakly basic, poorly soluble drug and a pharmaceutically acceptable polymeric binder.

6. The pharmaceutical composition of claim 2, wherein the rapid release particles each comprise a granulate comprising the weakly basic, poorly soluble drug, a pharmaceutically acceptable organic acid, a pharmaceutically acceptable polymeric binder, and at least one excipient.

7. The pharmaceutical composition of claim 2, wherein the pharmaceutically acceptable organic acid is selected from the group consisting of citric acid, lactic acid, fumaric acid, malic acid, maleic acid, tartaric acid, succinic acid, oxalic acid, aspartic acid, and glutamic acid.

8. The pharmaceutical composition of claim 2, wherein the first and second pharmaceutically acceptable polymeric binders are each independently selected from the group consisting of polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone and vinyl alcohol, copolymers of polyvinylpyrrolidone and vinyl acetate, copolymers of polyvinylpyrrolidone with vinyl chloride, copolymers of polyvinylpyrrolidone with vinyl butyrate, copolymers of polyvinylpyrrolidone with vinyl laurate, copolymers of polyvinylpyrrolidone with vinyl stearate, hydroxypropylcellulose, hydroxypropylmethyl cellulose, carboxyalkylcelluloses, polyethylene oxide, sodium carboxymethyl cellulose, dextran, acacia, starch, and gelatin.

9. The pharmaceutical composition of claim 1, wherein the weakly basic, poorly soluble drug comprises a serotonin 5-HT_3 receptor antagonist.

10. The pharmaceutical composition of claim 9, wherein the serotonin 5-HT_3 receptor antagonist is selected from the group consisting of ondansetron, tropisetron, granisetron, dolasetron, and palonosetron.

11. The pharmaceutical composition of claim 2, wherein the weakly basic, poorly soluble drug comprises a serotonin 5-HT_3 receptor antagonist.

12. The pharmaceutical composition of claim 11, wherein the serotonin 5-HT_3 receptor antagonist is selected from the group consisting of ondansetron, tropisetron, granisetron, dolasetron, and palonosetron.

13. The pharmaceutical composition of claim 2, wherein the pharmaceutically acceptable water insoluble polymer selected from the group consisting of ethyl cellulose, cellulose acetate, polyvinyl acetate, neutral copolymers of ethyl acrylate and methylmethacrylate, copolymers of acrylic and methacrylic esters containing quaternary ammonium groups, and waxes.

14. The pharmaceutical composition of claim 3, wherein the enteric polymer is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, pH-sensitive copolymers of methacrylic acid and methylmethacrylate, and shellac.

15. The pharmaceutical composition of claim 5, wherein the first inert bead has an average particle size of about 25-30 mesh, and the second inert bead has an average particle size selected from the group consisting of about 45-60 mesh, about 60-80 mesh, and about 80-200 mesh.

16. The pharmaceutical composition of claim 15, wherein the first and second inert beads comprise sugar or microcrystalline cellulose.

17. The pharmaceutical composition of claim 6, wherein the timed pulsatile release particles each comprise a 25-30 mesh sugar bead sequentially coated with the organic acid layer, a first sustained release layer; the drug layer; an optional sealing layer; and an optional

second sustained release layer.

18. The pharmaceutical composition of claim 17, wherein the organic acid layer comprises fumaric acid and hydroxypropyl cellulose.

19. The pharmaceutical composition of claim 17, wherein the first sustained release layer comprises ethylcellulose and a pharmaceutically acceptable plasticizer.

20. The pharmaceutical composition of claim 17, wherein the second sustained release layer is present and comprises ethylcellulose and a pharmaceutically acceptable plasticizer.

21. The pharmaceutical composition of claim 20, wherein the first and second sustained release layers comprise ethylcellulose and a pharmaceutically acceptable plasticizer.

22. The pharmaceutical composition of claim 17, wherein the first sustained release layer comprises ethylcellulose and a pharmaceutically acceptable plasticizer, and the second sustained release layer is not present.

23. The pharmaceutical composition of claim 17, wherein the optional sealing layer is present and comprises hydroxypropylmethyl cellulose.

24. The pharmaceutical composition of claim 17, wherein the weakly basic, poorly soluble drug in the timed pulsatile release and rapid release beads comprises ondansetron, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

25. The pharmaceutical composition of claim 17, wherein: the timed pulsatile release particles each comprise:

the organic acid layer comprises fumaric acid and hydroxypropyl cellulose;

the first sustained release layer comprises ethylcellulose and a first pharmaceutically acceptable plasticizer;

the drug layer comprises hydroxypropyl cellulose, and ondansetron or a pharmaceutically acceptable salt, solvate and/or ester thereof;

the optional sealing layer is present and comprises hydroxypropylmethyl cellulose;

the timed pulsatile release layer comprises ethylcellulose, hydroxypropylmethylcellulose phthalate, and a second pharmaceutically acceptable plasticizer;

the rapid release particles each comprise a granulate comprising:

ondansetron or a pharmaceutically acceptable salt, solvate and/or ester thereof;

fumaric acid;

lactose;

microcrystalline cellulose; and

crospovidone.

26. The pharmaceutical composition of claim 25, wherein the first and second pharmaceutically acceptable plasticizers are independently selected from the group consisting of triacetin, tributyl citrate, triethyl citrate, acetyl tri-n-butyl citrate, diethyl phthalate, dibutyl sebacate, polyethylene glycol, polypropylene glycol, castor oil, acetylated mono- and di-glycerides and mixtures thereof.

27. The pharmaceutical composition of claim 26, wherein the first and second pharmaceutically acceptable plasticizers are both triethyl citrate, and the second sustained release layer is not present.

28. A capsule comprising the pharmaceutical composition of claim 1.

29. A capsule comprising the pharmaceutical composition of claim 27.

30. The pharmaceutical composition of claim 1 for use in a method of treating emesis, wherein the pharmaceutical composition is for administering to a patient in need thereof.

31. The pharmaceutical composition for the use of claim 30, wherein said administering is once-a-day.

32. The pharmaceutical composition of claim 27 for use in a method of treating emesis, wherein the pharmaceutical composition is for administering to a patient in need thereof.

33. The pharmaceutical composition for the use of claim 32, wherein said administering is once-a-day.

34. The pharmaceutical composition of claim 24 wherein the weakly basic, poorly soluble drug in the timed pulsatile release and rapid release beads comprises ondansetron hydrochloride.

35. The pharmaceutical composition of claim 25 wherein the rapid release particles each comprise a granulate comprising:

ondansetron hydrochloride;

fumaric acid;

lactose;

microcrystalline cellulose; and

crospovidone.