CLAIMS

1. An oral prolonged release pharmaceutical composition comprising at least:
   a) at least one prolonged release material;
   b) at least hydromorphone or a pharmaceutically acceptable salt or derivative thereof and naloxone or a pharmaceutically acceptable salt or derivative thereof with hydromorphone or a pharmaceutically acceptable salt or derivative thereof and naloxone or a pharmaceutically acceptable salt or derivative thereof being present in the pharmaceutical composition in a weight ratio of about 2:1, about 1:1, about 1:2 or about 1:3.

2. Pharmaceutical composition according to claim 1, wherein the at least one prolonged release material and hydromorphone or a pharmaceutically acceptable salt or derivative thereof and naloxone or a pharmaceutically acceptable salt or derivative thereof are combined such that a prolonged release matrix is formed.

3. Pharmaceutical composition according to claim 2, wherein the prolonged release material is selected from the group comprising hydrophobic or hydrophilic polymers, protein-derived material, gums, substituted or unsubstituted hydrocarbons, digestible carbohydrates, fatty acids, fatty alcohols, glyceryl esters of fatty acids, natural and synthetic oils and natural and synthetic waxes.

4. Pharmaceutical composition according to claim 3, wherein the prolonged release material is a cellulose ether, a (meth)acrylic based (co)polymer and/or a fatty alcohol.

5. Pharmaceutical composition according to claim 4, wherein prolonged release material is a neutral (meth)acrylic based (co)polymer, a hydrophobic cellulose ether and/or a fatty alcohol.

6. Pharmaceutical composition according to any of claims 2, 3, 4, or 5, wherein the pharmaceutical composition comprises additionally at least one filler, at least one lubricant, at least one binder, at least one release rate modifiers, at least one spheronising agent and/or at least one anti-tacking agent

7. Pharmaceutical composition according to claim 6, wherein said filler is anhydrous lactose.

8. Pharmaceutical composition according to claim 6 or 7, wherein magnesium stearate and/or talc are used as lubricants.

9. Pharmaceutical composition according to claim 6, 7, or 8, wherein hydroxypropyl cellulose is used as binder.

10. Pharmaceutical composition according to any of claims 2, 3, 4, 5, 6, 7, 8 or 9, wherein the prolonged release matrix is heat treated.

11. Pharmaceutical composition according to any of claims 2, 3, 4, 5, 6, 7, 8, 9 or 10, wherein heat treatment takes place at a temperature in the range of about 30°C to about 95°C and for a time in the range of about 10 min to about 3 hours.

12. Pharmaceutical composition according to any of claims 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, wherein a prolonged release coating is disposed on the prolonged release matrix.

13. Pharmaceutical composition according to any of to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, wherein the composition releases the pharmaceutically active agents with the following in vitro release rate when measured using the Ph. Eur. paddle method in 500 or 900 ml of Simulated Gastric Fluid at 75 or 100 rpm at 37 degrees C° is:

at 1 h: 25 to 55% by weight of the pharmaceutically active agents,
at 2 h: 45 to 75% by weight of the pharmaceutically active agents,
at 3 h: 55 to 85% by weight of the pharmaceutically active agents,
at 4 h: 60 to 90% by weight of the pharmaceutically active agents,
at 6 h: 70 to 100% by weight of the pharmaceutically active agents,
at 8 h: more than 85% by weight of the pharmaceutically active agents,
at 10 h: more than 90% by weight of the pharmaceutically active agents.

14. Pharmaceutical composition according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, wherein the ratio of the amount of the pharmaceutically active agents released after 0.5, 1 or 2 hours of in vitro dissolution of the dosage form in 500 or 900 ml of Simulated Gastric Fluid with up to 40% ethanol using the Ph. Eur. paddle method at 75 or 100 rpm at 37 degrees C° compared to the amount of the active agents released after 0.5, 1 or 2 hours of in vitro dissolution of the dosage form in 500 or 900 ml of Simulated Gastric Fluid with 0% ethanol using the Ph. Eur. paddle method at 75 or 100 rpm at 37 degrees C° is about 2:1 or less, is about 1.5:1 or less, is about 1:1 or less, about 1:1.2 or less, about 1:1.4 or less, about 1:1.6 or less, about 1:1.8 or less, about 1:2 or less, about 1:2.5 or less about 1:3 or less or about 1:5 or less.

15. Pharmaceutical composition according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14, wherein the pharmaceutical composition after storage under stressed conditions releases the pharmaceutically active agents with substantially the same release rate as before subjecting the pharmaceutical composition to stressed conditions.

16. Pharmaceutical composition according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, wherein the pharmaceutical composition after storage under stressed conditions has less than 4% of total substances related to hydromorphone or a pharmaceutically acceptable salt or derivative thereof and/or related to naloxone or a pharmaceutically acceptable salt or derivative thereof.

17. Pharmaceutical composition according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, wherein the pharmaceutical composition is a multiparticulate formulation.

18. Pharmaceutical composition according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17, wherein hydromorphone hydrochloride and naloxone hydrochloride are used.

19. Pharmaceutical composition according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18, wherein hydromorphone hydrochloride is used at amounts equivalent to about 1 mg, about 2 mg, about 4 mg, about 8 mg, about 12 mg, about 16 mg, about 24 mg, about 32 mg, about 40 mg, about 48 mg or about 64 mg of anhydrous hydromorphone hydrochloride.

20. Pharmaceutical composition according to any of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19, wherein naloxone hydrochloride is used at amounts equivalent to about 1 mg, about 2 mg, about 4 mg, about 8 mg, about 12 mg, about 16 mg, about 24 mg, about 32 mg, about 48 mg, about 64 mg, about 96 mg, about 128 or about 256 mg of anhydrous naloxone hydrochloride.

21. Method of manufacturing an oral prolonged release pharmaceutical composition according to any of claim 1 to 20 comprising at least the steps of:

a) producing granules comprising at least one prolonged release material, at least hydromorphone or a pharmaceutically acceptable salt or derivative thereof and at least naloxone or a pharmaceutically acceptable salt or derivative thereof,
b) optionally selecting granules of step a) of substantially uniform size;
c) optionally adding additional prolonged release material;
d) optionally compressing said granules of step a), b) or c) to obtain an oral prolonged release pharmaceutical composition in the form of a tablet;
e) optionally heat treating said compressed granules of steps a), b), c) or d);
f) optionally coating with a prolonged releasing coating;
g) optionally curing the composition.

22. Method according to claim 20, wherein step a) comprises the following steps:

aa) blending a prolonged release material with at least hydromorphone or a pharmaceutically acceptable salt or derivative thereof and at least naloxone or a pharmaceutically acceptable salt or derivative thereof and optionally with at least one filler, at least one lubricant,

at least one binder, at least one release rate modifier, at least one spheronising agent and/or at least one anti-tacking agent;

ab) dry granulating or extruding said blend of step aa) to obtain granules;

ac) optionally drying said granules of step ab).

23. Method according to any of claims 21 or 22, wherein heat treatment takes place at a ambient humidity at a temperature in the range of about 40° C to about 90° C and for a time in the range of about 15 min to about 90 min.

24. Oral prolonged release pharmaceutical composition obtainable by a method according to any of claims 21 to 23.

CLAIMS

1. An oral prolonged release pharmaceutical composition comprising at least:

   a) at least one prolonged release material;

   b) at least hydromorphone or a pharmaceutically acceptable salt or derivative thereof and naloxone or a pharmaceutically acceptable salt or derivative thereof with hydromorphone or a pharmaceutically acceptable salt or derivative thereof and naloxone or a pharmaceutically acceptable salt or derivative thereof being present in the pharmaceutical composition in a weight ratio range of 2:1 to 1:3,

   wherein the at least one prolonged release material and hydromorphone or a pharmaceutically acceptable salt or derivative thereof and naloxone or a pharmaceutically acceptable salt or derivative thereof are combined such that a prolonged release matrix is formed, and

   wherein a prolonged release coating is disposed on the prolonged release matrix.

2. Use of an oral prolonged release pharmaceutical composition comprising at least:

   a) at least one prolonged release material;

   b) at least hydromorphone or a pharmaceutically acceptable salt or derivative thereof and naloxone or a pharmaceutically acceptable salt or derivative thereof with hydromorphone or a pharmaceutically acceptable salt or derivative thereof and naloxone or a pharmaceutically acceptable salt or derivative thereof being present in the pharmaceutical composition in a weight ratio range of 2:1 to 1:3

for the preparation of a medicament for the treatment of pain, thereby beneficially influencing hydromorphone-induced constipation.

3. Use according to claim 2, wherein the at least one prolonged release material and hydromorphone or a pharmaceutically acceptable salt or derivative thereof and naloxone or a pharmaceutically acceptable salt or derivative thereof are combined such that a prolonged release matrix is formed.

4. Use according to claim 3, wherein a prolonged release coating is disposed on the prolonged release matrix.

5. Pharmaceutical composition according to claim 1, or use according to claim 2, 3 or 4, wherein hydromorphone or a pharmaceutically acceptable salt or derivative thereof and naloxone or a pharmaceutically acceptable salt or derivative thereof are present in the pharmaceutical composition in a weight ratio of about 2:1, about 1:1, about 1:2 or about 1:3.

6. Pharmaceutical composition according to claim 1 or 5, or use according to claim 3, 4 or 5, wherein the prolonged release material is selected from the group comprising hydrophobic or hydrophilic polymers, protein-derived material, gums, substituted or unsubstituted hydrocarbons, digestible carbohydrates, fatty acids, fatty alcohols, glyceryl esters of fatty acids, natural and synthetic oils and natural and synthetic waxes.

7. Pharmaceutical composition according to claim 6, or use according to claim 6, wherein the prolonged release material is a cellulose ether, a (meth)acrylic based (co)polymer and/or a fatty alcohol.

8. Pharmaceutical composition according to claim 7, or use according to claim 7, wherein the prolonged release material is a neutral (meth)acrylic based (co)polymer, a hydrophobic cellulose ether and/or a fatty alcohol.

9. Pharmaceutical composition according to claim 1, 5, 6, 7 or 8, or use according to claim 3, 4, 5, 6, 7 or 8, wherein the pharmaceutical composition comprises additionally at least one filler, at least one lubricant, at least one binder, at least one release rate modifiers, at least one spheronising agent and/or at least one anti-tacking agent.

10. Pharmaceutical composition according to claim 9, or use according to claim 9, wherein said filler is anhydrous lactose, wherein magnesium stearate and/or talc are used as lubricants, and wherein hydroxypropyl cellulose is used as binder.

11. Pharmaceutical composition according to claim 1, 5, 6, 7, 8, 9, or 10, or use according to claim 3, 4, 5, 6, 7, 8, 9 or 10, wherein the prolonged release matrix is heat treated.

12. Pharmaceutical composition according to claim 1, 5, 6, 7, 8, 9, 10 or 11, or use according to claim 3, 4, 5, 6, 7, 8, 9, 10 or 11, wherein heat treatment takes place at a temperature in the range of about 30°C to about 95°C and for a time in the range of about 10 min to about 3 hours.

13. Pharmaceutical composition according to claim 1, 5, 6, 7, 8, 9, 10, 11 or 12, or use according to claim 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, wherein the composition releases the pharmaceutically active agents with the following in vitro release rate when measured using the Ph. Eur. paddle method in 500 or 900 ml of Simulated Gastric Fluid at 75 or 100 rpm at 37 degrees C° is:

at 1 h:	25 to 55% by weight of the pharmaceutically active agents,
at 2 h:	45 to 75% by weight of the pharmaceutically active agents,
at 3 h:	55 to 85% by weight of the pharmaceutically active agents,
at 4 h:	60 to 90% by weight of the pharmaceutically active agents,
at 6 h:	70 to 100% by weight of the pharmaceutically active agents,
at 8 h:	more than 85% by weight of the pharmaceutically active agents,
at 10 h:	more than 90% by weight of the pharmaceutically active agents.

14. Pharmaceutical composition according to claim 1, 5, 6, 7, 8, 9, 10, 11, 12 or 13, or use according to claim 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, wherein the ratio of the amount of the pharmaceutically active agents released after 0.5, 1 or 2 hours of in vitro dissolution of the dosage form in 500 or 900 ml of Simulated Gastric Fluid with up to 40% ethanol using the Ph. Eur. paddle method at 75 or 100 rpm at 37 degrees C° compared to the amount of the active agents released after 0.5, 1 or 2 hours of in vitro dissolution of the dosage form in 500 or 900 ml of Simulated Gastric Fluid with 0% ethanol using the Ph. Eur. paddle method at 75 or 100 rpm at 37 degrees C° is about 2:1 or less, is about 1.5:1 or less, is about 1:1 or less, about 1:1.2 or less, about 1:1.4 or less, about 1:1.6 or less, about 1:1.8 or less, about 1:2 or less, about 1:2.5 or less about 1:3 or less or about 1:5 or less.

15. Pharmaceutical composition according to claim 1, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14, or use according to claim 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14, wherein the pharmaceutical composition after storage under stressed conditions releases the pharmaceutically active agents with substantially the same release rate as before subjecting the pharmaceutical composition to stressed conditions and/or wherein the pharmaceutical composition after storage under stressed conditions has less than 4% of total substances related to hydromorphone or a pharmaceutically acceptable salt or derivative thereof and/or related to naloxone or a pharmaceutically acceptable salt or derivative thereof.

16. Pharmaceutical composition according to claim 1, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, or use according to claim 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, wherein the pharmaceutical composition is a multiparticulate formulation.

17. Pharmaceutical composition according to claim 1, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, or use according to claim 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, wherein hydromorphone hydrochloride and naloxone hydrochloride are used.

18. Pharmaceutical composition according to claim 1, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17, or use according to claim 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17, wherein hydromorphone hydrochloride is used at amounts equivalent to about 1 mg, about 2 mg, about 4 mg, about 8 mg, about 12 mg, about 16 mg, about 24 mg, about 32 mg, about 40 mg, about 48 mg or about 64 mg of anhydrous hydromorphone hydrochloride and wherein naloxone hydrochloride is used at amounts equivalent to about 1 mg, about 2 mg, about 4 mg, about 8 mg, about 12 mg, about 16 mg, about 24 mg, about 32 mg, about 48 mg, about 64 mg, about 96 mg, about 128 or about 256 mg of anhydrous naloxone hydrochloride.