Claims

1. A stable nanostructured Aprepitant composition comprising:

(a) nanostructured Aprepitant having an average particle size of less than about 200 nm;

(b) at least one stabilizer;

wherein the composition is prepared in a continuous flow reactor, preferably in a microfluidic based continuous flow reactor.

2. A stable nanostructured Aprepitant composition according to Claim 1 further comprising an additional stabilizer for steric and electrostatical stabilization.

3. The composition according to Claim 1 or 2, wherein the stabilizer is selected from the group of non-ionic, anionic, cationic polymers/surfactants, and zwitterionic surfactants, or combinations thereof.

4. The composition according to Claim 1 or 3 wherein the stabilizer is selected from the group of cellulose and its derivatives, polyvinylpyrrolidone, graft copolymer comprised of polyethylene, glycol, polyvinylcaprolactam and polyvinylacetate (e.g. Soluplus), sodium lauryl sulfate, gelatin, cetostearyl alcohol, polyethylene glycols, acetic acid ethenyl ester polymer with l-ethenyl-2- pyrrolidinone (PVP/VA copolymers), sodium dodecyl benzene sulfonate, tocopheryl polyethylene glycol succinates, urea, citric acid, sodium-acetate, polyethoxylated castor oils and its derivateives, polyoxyethylene stearates, methylcellulose, hydroxyethylcellulose, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (e.g., Pluronics, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (e.g., Tetronic, also known as Poloxamine, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, D-alfa-Tocopherol polyethylene glycol 1000 succinate, poly(2-ethyl-2-oxazoline), poly (methyl vinyl ether), random copolymers of vinyl pyrrolidone and vinyl acetate, such as Plasdone S630.

5. The composition according to claim 1 or 4 wherein the stabilizer is selected from the group of a polyvinylcaprolactam-polyvinyl acetate-polyethylene glycol graft copolymer and/or poloxamers and/or polyvinylpyrrolidone and/or sodium lauryl sulfate.

6. A process for the preparation of nanostructured Aprepitant composition according to any of Claims 1 to 5, comprising mixing the solution of Aprepitant and at least one stabilizer preferably according to Claim 4 with an other solvent preferably water containing optionally at least one stabilizer preferably according to Claim 4 in a continuous flow reactor, preferably in a microfluidic based continuous flow reactor.

7. The process according to 6, comprising (1) dissolving Aprepitant and at least one stabilizer in a suitable solvent; (2) adding the formulation from step (1) to a solvent optionally comprising one or more stabilizers; and (3) precipitating the formulation from step (2).

8. A pharmaceutical composition comprising a nanostructured composition according to any of claims 1 to 5 together with pharmaceutically acceptable auxiliary materials, preferably in the form of oral, pulmonary, rectal, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal or topical administration.

9. Use of nanostructured composition according to any of claims 1 to 5 or the pharmaceutical composition according to Claim 8 for preparation of a medicament.

10. Use of nanostructured composition according to any of claims 1 to 5 or the pharmaceutical composition according to Claim 8 for prevention of acute and delayed chemotherapy-induced nausea and vomiting and for prevention of postoperative nausea and vomiting.

11. The use according to claim 10-11, wherein the composition has

- a solubility at least about 0.1 mg/ml in FassiF and 0.4 mg/mL in FessiF solution,
- in vitro permeability through artificial membrane at least $1*10^{-6}$ cm/s in FassiF condition and $1*10^{-6}$ cm/s in FessiF condition
- instantaneous redispersibility in a physiological medium,
- reduced or eliminated fed/fasted effect,
- at least bioequivalent absorption in human gastrointestinal tract compared to the reference or marketed compound,
- faster onset of action,

for decreasing the dosage used.

Claims

1. A stable nanostructured Aprepitant composition comprising:

(a) nanostructured Aprepitant having an average particle size of less than about 200 nm;

(b) at least one stabilizer;

wherein the composition is prepared in a continuous flow reactor, preferably in a microfluidic based continuous flow reactor.

2. A stable nanostructured Aprepitant composition according to Claim 1 further comprising an additional stabilizer for steric and electrostatical stabilization.

3. The composition according to Claim 1 or 2, wherein the stabilizer is selected from the group of non-ionic, anionic, cationic polymers/surfactants, and zwitterionic surfactants, or combinations thereof.

4. The composition according to Claim 1 or 3 wherein the stabilizer is selected from the group of cellulose and its derivatives, polyvinylpyrrolidone, graft copolymer comprised of polyethylene, glycol, polyvinylcaprolactam and polyvinylacetate (e.g. Soluplus), sodium lauryl sulfate, gelatin, cetostearyl alcohol, polyethylene glycols, acetic acid ethenyl ester polymer with l-ethenyl-2- pyrrolidinone (PVP/VA copolymers), sodium dodecyl benzene sulfonate, tocopheryl polyethylene glycol succinates, urea, citric acid, sodium-acetate, polyethoxylated castor oils and its derivateives, polyoxyethylene stearates, methylcellulose, hydroxyethylcellulose, polyvinyl alcohol (PVA), 4-(l,l,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (e.g., Pluronics, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (e.g., Tetronic, also known as Poloxamine, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, D-alfa-Tocopherol polyethylene glycol 1000 succinate, poly(2-ethyl-2-oxazoline), poly (methyl vinyl ether), random copolymers of vinyl pyrrolidone and vinyl acetate, such as Plasdone S630.

5. The composition according to claim 1 or 4 wherein the stabilizer is selected from the group of a polyvinylcaprolactam-polyvinyl acetate-polyethylene glycol graft copolymer and/or poloxamers and/or polyvinylpyrrolidone and/or sodium lauryl sulfate.

6. A process for the preparation of nanostructured Aprepitant composition according to any of Claims 1 to 5, comprising mixing the solution of Aprepitant and at least one

stabilizer preferably according to Claim 4 with an other solvent preferably water containing optionally at least one stabilizer preferably according to Claim 4 in a continuous flow reactor, preferably in a microfluidic based continuous flow reactor.

7. The process according to 6, comprising (1) dissolving Aprepitant and at least one stabilizer in a suitable solvent; (2) adding the formulation from step (1) to a solvent optionally comprising one or more stabilizers; and (3) precipitating the formulation from step (2).

8. A pharmaceutical composition comprising a nanostructured composition according to any of claims 1 to 5 together with pharmaceutically acceptable auxiliary materials, preferably in the form of oral, pulmonary, rectal, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal or topical administration.

9. Use of nanostructured composition according to any of claims 1 to 5 or the pharmaceutical composition according to Claim 8 for preparation of a medicament.

10. Use of nanostructured composition according to any of claims 1 to 5 or the pharmaceutical composition according to Claim 8 for prevention of acute and delayed chemotherapy-induced nausea and vomiting and for prevention of postoperative nausea and vomiting.

11. The use according to claim 9-10, wherein the composition has

- a solubility at least about 0.1 mg/ml in FassiF and 0.4 mg/mL in FessiF solution,
- in vitro permeability through artificial membrane at least $1*10^{-6}$ cm/s in FassiF condition and $1*10^{-6}$ cm/s in FessiF condition
- instantaneous redispersibility in a physiological medium,
- reduced or eliminated fed/fasted effect,
- at least bioequivalent absorption in human gastrointestinal tract compared to the reference or marketed compound,
- faster onset of action,

for decreasing the dosage used.