Claims

1. A stable nanostructured Sildenafil composition comprising:

(a) nanostructured Sildenafil base or its pharmaceutically acceptable salts or co-crystals having an average particle size of less than 500 nm;

(b) at least one anionic polyelectrolyte or a non-ionic stabilizer or a mixture thereof or any additional stabilizer,

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

2. A composition according to claim 1, wherein the average particle size is between 500 nm and 50 nm, preferably 350 nm and 50 nm, preferably 100 nm and 50.

3. The composition according to claim 1 or 2 wherein the polyelectrolyte is selected from the group of nucleic acids, proteins, teichoic acids, polypeptides and polysaccharides and poly(sodium styrene sulfonate) and poly(meth)acrylate-based polymers and copolymers (synthetic), poly (acrylic-acid) and its derivatives cross-linked with allyl esters or sucrose or pentaerythriol.

4. The composition according to claim 1 or 2 wherein the non-ionic stabilizer is selected from the group of poly(vinyl-pyrrolidone), poly(2-ethyl-2-oxazoline), poly(methyl vinyl ether), polyvinyl alcohol, acetic acid ethenyl ester polymers with 1-ethenyl-2-pyrrolidinone (PVP/VA copolymers), poly(ethylene-glycol) and its derivatives (e.g.: PEG 2000, 6000, 35 000), ethylene oxide and propylene oxide block copolymers and its derivatives (e.g.: Pluronic 10 500, 6100, 6800), and polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tween® products).

5. The composition according to any of claims 1 to 4, where the composition contains additional stabilizer which is hydroxyl-propyl-cellulose derivatives, sodium lauryl sulfate, sodium dodecyl benzene sulfonate, tocopheryl polyethylene glycol succinates, polyethoxylated castor oils and its derivatives, any cationic stabilizers, preferably lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkylbenzyl dimethyl ammonium bromide, benzyl trimethylammonium bromide, benzalkonium chloride, hexadecyltrimethylammonium bromide.

6. Process for the preparation of nanostructured Sildenafil composition according to any of claims 1 to 5, comprising precipitating nanostructured Sildenafil base or its pharmaceutically acceptable salts or co-crystals from a solution of Sildenafil base or its

pharmaceutically acceptable salt comprising optionally one or more stabilizer or additional stabilizer, if desired, in the presence of a pharmaceutically acceptable acid or base, in a continuous flow reactor, preferably in a microfluidic based continuous flow reactor.

7. Process according to 6, comprising (1) dissolving Sildenafil base or its pharmaceutically acceptable salt and optionally one or more stabilizer or a mixture thereof in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising one or more polyelectrolytes or stabilizers or a mixture thereof, if desired in the presence of a pharmaceutically acceptable acid or base; and (3) precipitating the formulation from step (2).

8. Process according to claim 7, comprising (1) dissolving Sildenafil base or its pharmaceutically acceptable salt and one or more stabilizer(s) in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising a pharmaceutically acceptable acid or base; and (3) precipitating the formulation from step (2).

9. Process according to any of claims 6 to 8, comprising (a) the use of two different solvents miscible with each other, where Sildenafil base or its pharmaceutically acceptable salt or co- crystal is soluble only in one of them, or (b) using the same solvent in the two steps, where the polyelectrolyte complex of Sildenafil base or its pharmaceutically acceptable salt or co-crystal forms nanostructured particles, practically, with the restriction that the applied polyelectrolyte, stabilizer is soluble in the solvents used.

10. A pharmaceutical composition comprising a nanostructured composition according to any of claims 1 to 5 together with pharmaceutically acceptable auxiliary materials.

11. A pharmaceutical composition according to claim 10, wherein the composition is formulated into a dosage form of a buccal administration.

12. Use of nanostructured composition according to any of claims 1 to 5 for preparation of a medicament.

13. Use of nanostructured composition according to any of claims 1 to 5 or a pharmaceutical composition according to claim 10 or 11 in the manufacture of a medicament for the treatment of male or female sexual dysfunction and pulmonary arterial hypertension.

14. The use according to claim 13, wherein the composition has at least one property from the following group:

- a solubility of 24.5 mg/ml in water,
- instantaneous redispersibility in physiological mediums,
- enhanced transdermal permeability,
- increased absorption in human gastrointestinal tract,
- faster onset of action,

for decreasing the dosage used.

Claims

1. A stable nanostructured Sildenafil composition comprising:

(a) nanostructured Sildenafil base or its citrate salt having an average particle size of less than 500 nm;

(b) a stabilizer selected from the group consisting of poly(acrylic-acid) cross-linked with allyl esters and sodium dodecyl benzene sulfonate,

wherein the composition is prepared in a microfluidic based continuous flow reactor by the following process:

(1) dissolving Sildenafil citrate in water;

(2) adding to the solution of step (1) an aqueous solution of poly(acrylic-acid) cross-linked with allyl esters or sodium dodecyl benzene sulfonate stabilizer, and

(3) precipitating the formulation from step (2);

wherein the prepared stable nanostructured Sildenafil composition has partially amorphous structure.

2. The composition according to claim 1, wherein the average particle size is between 500 nm and 50 nm.

3. The composition according to claim 1, wherein the average particle size is between 350 nm and 50 nm.

4. The composition according to claim 1, wherein the average particle size is between 100 nm and 50 nm.

5. The composition according to any one of claims 1 to 4, wherein the poly(acrylic-acid) cross-linked with allyl esters as stabilizer is Carbopol 971.

6. Process for the preparation of a stable nanostructured Sildenafil composition according to any one of claims 1 to 4, comprising

(1) dissolving Sildenafil citrate in water;

(2) adding to the solution of step (1) an aqueous solution of poly(acrylic-acid) cross-linked with allyl esters or sodium dodecyl benzene sulfonate stabilizer, and

(3) precipitating the formulation from step (2).

7. A pharmaceutical composition comprising the composition according to any one of claims 1 to 5, together with pharmaceutically acceptable auxiliary materials.

8. The pharmaceutical composition according to claim 7, wherein the composition is formulated into a dosage form of a buccal administration.

9. The use of the composition according to any one of claims 1 to 5, in the manufacture of a medicament for the treatment of male or female sexual dysfunction.

10. The use of the composition according to any one of claims 1 to 5, in the manufacture of a medicament for the treatment of pulmonary arterial hypertension.

11. The use of the composition according to any one of claims 1 to 5, or the pharmaceutical composition according to claim 7 or claim 8, in the manufacture of a medicament for the treatment of male or female sexual dysfunction.

12. The use of the composition according to any one of claims 1 to 5, or the pharmaceutical composition according to claim 7 or claim 8, in the manufacture of a medicament for the treatment of pulmonary arterial hypertension.

13. The use according to claim 9 or claim 10, wherein the composition has at least one property from the following group:

- a solubility 24.5 mg/ml in water,
- instantaneous redispersibility in physiological mediums,
- enhanced transdermal permeability,
- increased absorption in human gastrointestinal tract,
- faster onset of action,

for decreasing the dosage used.