

CLAIMS

1. A process for the preparation of sterile topical ophthalmic aqueous nanosuspensions containing fluticasone propionate Form A nanocrystals having a mean particle size from 100 nm to 1000 nm and a concentration of fluticasone propionate from 0.001% w/w to 1% w/w, said process comprises:
- 5 100 nm to 1000 nm and a concentration of fluticasone propionate from 0.001% w/w to 1% w/w, said process comprises:
- a) preparing an aqueous vehicle 1 containing: 0.5 % w/w methylcellulose 4000 cp, 1.0% w/w boric acid, 0.1% w/w edetate disodium dihydrate, 0.055% w/w sodium chloride, 0.01% w/w benzalkonium chloride, 0.2% w/w polysorbate 80,
10 hydrochloric acid 1N and / or sodium hydroxide 1N to adjust the pH at 7.3 – 7.5 and water to 100% w/w;
 - b) mixing an amount of fluticasone propionate Form A nanocrystals having a mean particle size from 100 nm to 1000 nm with an amount of aqueous vehicle 1 to obtain a slurry containing a concentration of fluticasone propionate of 2% w/w;
 - 15 c) applying high-shear, high-speed mixing to the slurry of step b) for at least 10 minutes;
 - d) preparing an aqueous vehicle 2 containing: 1.8% w/w glycerin, 0.5 % w/w methylcellulose 4000 cp, 1.0% w/w boric acid, 0.1% w/w edetate disodium dihydrate, 0.055% w/w sodium chloride, 0.01% w/w benzalkonium chloride, 0.2% w/w polysorbate 80, hydrochloric acid 1N and / or sodium hydroxide 1N to adjust
20 the pH at 7.3 – 7.5 and water q.s. to 100% w/w;
 - e) adding an aliquot of the aqueous vehicle 2 to the slurry of step c) to obtain a concentration of fluticasone propionate of about 1% w/w;
 - f) applying high-shear, high-speed mixing to the slurry of step e) till to obtain the
25 targeted mean particle size;
 - g) sterilizing the nanosuspension of step f) by autoclaving;
 - h) preparing an aqueous vehicle 3 containing: 0.9% w/w glycerin, 0.5 % w/w methylcellulose 4000 cp, 1.0% w/w boric acid, 0.1% w/w edetate disodium

dihydrate, 0.055% w/w sodium chloride, 0.01% w/w benzalkonium chloride, 0.2% w/w polysorbate 80, hydrochloric acid 1N and / or sodium hydroxide (1N) to adjust the pH at 7.3 – 7.5 and water to 100% w/w; and sterilizing the aqueous vehicle 3 by filtration;

- 5 i) aseptically adding an aliquot of the sterile aqueous vehicle 3 to the sterilized nanosuspension of step g) to prepare a sterile topical ophthalmic aqueous nanosuspensions containing the targeted concentration of fluticasone propionate nanocrystals Form A;

wherein the nanocrystals of fluticasone propionate Form A have a X-ray powder diffraction
10 pattern of said nanocrystals including peaks at about 7.8, 15.7, 20.8, 23.7, 24.5, and 32.5 degrees 2 Θ , further including peaks at about 9.9, 13.0, 14.6, 16.0, 16.9, 18.1, and 34.3 degrees 2 Θ , and wherein the nanocrystals are nanoplates having the [001] crystallographic axis substantially normal to the surfaces that define the thickness of the nanoplates.

2. The process according to claim 1 wherein the concentration of fluticasone
15 propionate in the final sterile topical ophthalmic aqueous nanosuspensions is from 0.001% to 0.5% w/w.

3. The process according to claim 1 wherein the concentration of fluticasone propionate in the final sterile topical ophthalmic aqueous nanosuspensions is 0.5% w/w, 0.25% w/w, 0.2% w/w, 0.1% w/w, 0.05% w/w, 0.03% w/w, 0.01% w/w or 0.005% w/w.

20 4. The process according to any of claims 1 to 3 wherein the high-shear, high-speed mixing of steps c) and f) is performed at 6000 RPM.

5. The process according to claim 4 wherein in step f) the high-shear, high-speed mixing is applied for at least 10 minutes.

6. The process according to any of claims 1 to 5 wherein the aqueous vehicles 1 and 2
25 are filtered through 0.2 μ m filter before their use.

7. The process according to any of claims 1 to 6 wherein the sterilization of step g) is performed by autoclaving the nanosuspension of step f) at about 122 °C for about 40 minutes.

8. A process for the preparation of sterile topical ophthalmic aqueous nanosuspensions containing fluticasone propionate Form A nanocrystals having a mean particle size from 100 nm to 1000 nm and a concentration of fluticasone propionate from 0.001% w/w to 1% w/w, said process comprises:

- 5 a-1) sterilizing fluticasone propionate Form A nanocrystals having a mean particle size from 100 nm to 1000 nm;
- b-1) preparing an aqueous vehicle 1 containing: 0.5 % w/w methylcellulose 4000 cp, 1.0% w/w boric acid, 0.1% w/w edetate disodium dihydrate, 0.055% w/w sodium chloride, 0.01% w/w benzalkonium chloride, 0.2% w/w polysorbate 80,
10 hydrochloric acid 1N and / or sodium hydroxide 1N to adjust the pH at 7.3 – 7.5 and water q.s. to 100% w/w; and sterilizing said aqueous vehicle 1 by filtration;
- c-1) aseptically mixing an amount of sterilized fluticasone propionate nanocrystals form A with an amount of the sterilized aqueous vehicle 1 to obtain a slurry containing a concentration of fluticasone propionate of 2% w/w;
- 15 d-1) applying high-shear, high-speed mixing to the slurry of step c-1) for at least 10 minutes;
- e-1) preparing an aqueous vehicle 2 containing: 1.8% w/w glycerin, 0.5 % w/w methylcellulose 4000 cp, 1.0% w/w boric acid, 0.1% w/w edetate disodium dihydrate, 0.055% w/w sodium chloride, 0.01% w/w benzalkonium chloride, 0.2%
20 w/w polysorbate 80, hydrochloric acid 1N / sodium hydroxide 1N to adjust the pH at 7.3 – 7.5 and water q.s. to 100% w/w; and sterilizing said aqueous vehicle 2 by filtration;
- f-1) aseptically adding an aliquot of the sterilized aqueous vehicle 2 to the slurry of step d-1) to obtain a concentration of fluticasone propionate of about 1% w/w;
- 25 g-1) applying high-shear, high-speed mixing to the slurry of step f-1) till to obtain the targeted mean particle size;
- h-1) preparing an aqueous vehicle 3 containing: 0.9% w/w glycerin, 0.5 % w/w methylcellulose 4000 cp, 1.0% w/w boric acid, 0.1% w/w edetate disodium

dihydrate, 0.055% w/w sodium chloride, 0.01% w/w benzalkonium chloride, 0.2% w/w polysorbate 80, hydrochloric acid 1N and / or sodium hydroxide 1N to adjust the pH at 7.3 – 7.5 and water to 100% w/w; and sterilizing said aqueous vehicle 3 by filtration;

- 5 i-1) aseptically adding an aliquot of the sterilized aqueous vehicle 3 to the nanosuspension of step g-1) to prepare a sterile topical ophthalmic aqueous nanosuspension containing the final concentration of fluticasone propionate nanocrystals Form A;

wherein the nanocrystals of fluticasone propionate Form A have a X-ray powder diffraction
10 pattern including peaks at about 7.8, 15.7, 20.8, 23.7, 24.5, and 32.5 degrees 2Θ , further including peaks at about 9.9, 13.0, 14.6, 16.0, 16.9, 18.1, and 34.3 degrees 2Θ , and wherein the nanocrystals are nanoplates having the [001] crystallographic axis substantially normal to the surfaces that define the thickness of the nanoplates.

9. The process according to claim 8 wherein the concentration of fluticasone
15 propionate in the final sterile topical ophthalmic aqueous nanosuspensions is from 0.001% to 0.5% w/w.

10. The process according to claim 8 wherein the concentration of fluticasone propionate in the final sterile topical ophthalmic aqueous nanosuspensions is 0.5% w/w, 0.25% w/w, 0.2% w/w, 0.1% w/w, 0.05% w/w, 0.03% w/w, 0.01% w/w or 0.005% w/w.

20 11. The process according to any of claims 8 to 10 wherein in step a-1) the fluticasone propionate Form A nanocrystals are sterilized by autoclaving a suspension of fluticasone propionate Form A nanocrystals in water for injection having a concentration of fluticasone propionate between 2 % to 20 % w/w.

12. The process according to claim 11 wherein the suspension of fluticasone propionate
25 Form A nanocrystals in water is autoclaved at about 122 °C for about 30 minutes.

13. The process according to any of claims 8 to 12 wherein in step d-1) and step g-1) the high-shear, high-speed mixing is performed at 6000 RPM.

14. The process according to claim 13 wherein in step g-1) the high-shear, high-speed

mixing is applied for at least 10 minutes.

15. The process according to anyone of claims 1 to 14 wherein fluticasone propionate nanocrystals form A are prepared according to the following steps:

- 5 1) preparing a phase I solution comprising 0.45% w/w fluticasone propionate polymorph 1, 23,2% w/w polyethylene glycol 400 (PEG 400), 68.8% w/w polypropylene glycol 400 (PPG 400), 7.6% w/w polysorbate 80 (Tween 80); and filtering the phase I solution through 0.8/0.2 μm Polyethersulfone (PES) filter;
- 10 2) preparing a phase II solution comprising 0.01% w/w benzalkonium chloride, 0.40% (w/w) methyl cellulose 15 cP, 0.1% w/w polyethylene glycol 40 stearate (PEG-40 stearate), citrate buffer to pH 3.4 to 3.8 and water q.s. to 100% w/w; and filtering the phase II solution through 0.8/0.2 μm Polyethersulfone (PES) filter;
- 3) cooling the filtered phase I and phase II solutions to a temperature from 0 to 4°C;
- 15 4) mixing the phase I and the phase II solutions in a reactor equipped with ultrasonic transducer (QSonica Q2000 Ultrasonic transducer) to obtain a phase III suspension of nanocrystals, wherein:
 - the phase I solution and the phase II solution are pumped continuously into the reactor at flow rates of 600 ml/min (phase I solution) and 2400 ml/min (phase II solution) respectively to obtain a phase III suspension;
 - 20 - the volumes ratio phase I and phase II is 1:4;
 - the sonication is applied during the mixing with an output power of 60%;
 - the average temperature of phase III suspension is about 11°C; and
- 5) low shear mixing phase III suspension of step 4) at sufficient speed to create a vortex, at room temperature for a minimum of 30 minutes in absence of sonication;
- 25 6) annealing the phase III suspension at 40°C over a period of time not less than 16 hours;
- 7) preparing a buffer solution comprising 0.2% w/w polyethylene glycol 40 stearate (PEG-40 stearate), 0.2% w/w polysorbate 80 (Tween 80), 0.001% w/w

benzalkonium chloride, 0.05% w/w sodium phosphate monobasic monohydrate, 0.02% w/w sodium phosphate dibasic dihydrate and water q.s. to 100% w/w, having a pH 6.3 ± 0.2 ; and filtering the buffer solution through 0.8/0.2 μm Polyethersulfone (PES) filter;

- 5 8) diluting the phase III suspension of step 6) with the filtered buffer solution wherein the volumes ratio buffer solution and phase III is 1:1;
- 9) centrifuging the diluted phase III suspension to recover the fluticasone propionate nanocrystals Form A and washing the recovered nanocrystals;
- 10) washing the collected nanocrystals with water for injection.

- 10 16. An ophthalmic aqueous nanosuspension administrable topically onto eyelids, eyelashes or eyelid margin consisting of:

(a) 0.001% to 1% w/w fluticasone propionate Form A nanocrystals;

(b) 0.50% w/w methylcellulose 4000 cp;

(c) 0.2% w/w polysorbate 80;

- 15 (d) 0.10% w/w edetate disodium dihydrate;

(e) 1.0 % w/w boric acid;

(f) 0.9% w/w glycerin;

(g) 0.01% w/w benzalkonium chloride;

(h) 0.055% w/w sodium chloride;

- 20 (i) hydrochloric acid 1N and/or sodium hydroxide 1N as adjusting agents in an amount sufficient to pH 7.3-7.5; and

(j) water q.s. to 100% w/w,

- wherein said nanocrystals of fluticasone propionate Form A have a mean particle size from 100 nm to 1000 nm and a X-ray powder diffraction pattern including peaks at about 7.8, 15.7, 20.8, 23.7, 24.5, and 32.5 degrees 2θ , further including peaks at about 9.9, 13.0, 14.6, 16.0, 16.9, 18.1, and 34.3 degrees 2θ , and wherein the nanocrystals are nanoplates having the [001] crystallographic axis substantially normal to the surfaces that define the thickness of the nanoplates.
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17. The ophthalmic aqueous nanosuspension according to claim 16 wherein the concentration of fluticasone propionate is from 0.001% to 0.5% w/w.
18. The ophthalmic aqueous nanosuspension according to claim 16 wherein the concentration of fluticasone propionate is 0.5% w/w, 0.25% w/w, 0.2% w/w, 0.1% w/w,
5 0.05% w/w, 0.03% w/w, 0.01% w/w or 0.005% w/w.
19. The ophthalmic aqueous nanosuspension according to claim 16 wherein the concentration of fluticasone propionate is 0.2% w/w or 0.1% w/w or 0.05% w/w.
20. An ophthalmic aqueous nanosuspension according to anyone of claims 16 to 19 for use in a method of treatment blepharitis, posterior blepharitis, Meibomian gland
10 dysfunction or dry eye disease wherein the method comprises topically applying to eyelids, eyelashes or eyelid margin an effective amount of the ophthalmic aqueous nanosuspension.
21. An ophthalmic aqueous nanosuspension according to anyone of claims 16 to 19 for use in a method of reducing the symptoms and / or clinical signs associated with blepharitis, posterior blepharitis, Meibomian gland dysfunction or dry eye disease wherein the method
15 comprises topically applying to eyelids, eyelashes or eyelid margin an effective amount of the ophthalmic aqueous nanosuspension.
22. The ophthalmic aqueous nanosuspension according to claim 16 for use in a method according to claim 20 or 21 wherein the ophthalmic aqueous nanosuspension consists of.
- (a) 0.1% w/w fluticasone propionate Form A nanocrystals;
 - 20 (b) 0.50% w/w methylcellulose 4000 cp;
 - (c) 0.2% w/w polysorbate 80;
 - (d) 0.10% w/w edetate disodium dihydrate;
 - (e) 1.0 % w/w boric acid;
 - (f) 0.9% w/w glycerin;
 - 25 (g) 0.01% w/w benzalkonium chloride;
 - (h) 0.055% w/w sodium chloride;
 - (i) hydrochloric acid 1N and/or sodium hydroxide 1N as adjusting agents in an amount sufficient to pH 7.3-7.5; and (j) water q.s. to 100% w/w,

wherein said nanocrystals of fluticasone propionate Form A have a mean particle size from 100 nm to 1000 nm and a X-ray powder diffraction pattern including peaks at about 7.8, 15.7, 20.8, 23.7, 24.5, and 32.5 degrees 2Θ , further including peaks at about 9.9, 13.0, 14.6, 16.0, 16.9, 18.1, and 34.3 degrees 2Θ , and wherein the nanocrystals are nanoplates having
5 the [001] crystallographic axis substantially normal to the surfaces that define the thickness of the nanoplates.

23. The ophthalmic aqueous nanosuspension for use in a method according to anyone of claims 20 to 22 wherein the method comprises topically applying to eyelids, eyelashes or eyelid margin the ophthalmic aqueous nanosuspension at least once a day for at least two
10 weeks.