Challenges and obstacles of ocular pharmacokinetics and drug delivery. Adv. Drug Del. Rev. 58, 1131-1135).

Recently, applicants have described preparation and testing of cyclodextrin-based eye drops containing dexamethasone (WO2018/100434, Johannesson, G., Moya-Ortega, M.D., Asgrimsdottir, G.M., Lund, S.H., Thorsteinsdottir, M., Loftsson, T., Stefansson, E., 2014. Kinetics of y-cyclodextrin nanoparticle suspension eye drops in tear fluid. Acta Ophthalmologica 92, 550-556; Thorsteinn Loftsson and Einar Stefansson, Cyclodextrin nanotechnology for ophthalmic drug delivery, US Pat. No. 7,893,040 (Feb. 22, 2011); Thorsteinn Loftsson and Einar Stefansson, Cyclodextrin nanotechnology for ophthalmic drug delivery, US Pat. No. 8,633, 172 (Jan. 21, 2014); Thorsteinn Loftsson and Einar Stefansson, Cyclodextrin nanotechnology for ophthalmic drug delivery US Pat. No. 8,999,953 (Apr. 7, 2015)).

These studies show that cyclodextrin-based eye drops containing active principle ingredient are promising for the treatment of ocular conditions.

However, under some storage conditions, for example when stored in low-density polyethylene (LDPE) vials for several months, the pH of cyclodextrin-based eye drops with active principle ingredient is not stable and decreases overtime. Thus, it is desirable to develop a method for stabilizing the pH of these aqueous compositions, in order to prevent the pH drop.

Brief description

In one aspect, the present disclosure refers to a method for stabilizing the pH of an aqueous composition comprising a corticosteroid, said method comprising the addition of an additive to prevent oxidation of the drug selected from the group consisting of sodium thiosulfate, methionine, 3,4-dihydroxybenzoic acid, sodium citrate, malic acid, sodium ascorbate, tartaric acid, α-monothioglycerol, butylated hyroxyanisole, lauryl gallate, lactic acid, tert-butylhydroquinone, and their salts or derivatives.

In another aspect, the present disclosure refers to an aqueous composition comprising a corticosteroid, cyclodextrin, preferably gamma-cyclodextrin, and an additive to prevent oxidation of the corticosteroid, wherein the additive to prevent oxidation is selected from the group consisting of sodium thiosulfate, methionine, 3,4-dihydroxybenzoic acid, sodium citrate, malic acid, sodium ascorbate, tartaric acid, α-monothioglycerol, butylated hyroxyanisole, lauryl gallate, lactic acid, tert-butylhydroquinone, and their salts or derivatives.

In yet another aspect, the present disclosure refers to use of a composition as disclosed herein in the manufacture of a medicament for treating an ocular condition, in particular an anterior ocular condition or a posterior ocular condition.

In another aspect, the present disclosure refers to use of a composition as disclosed herein in the manufacture of a medicament for treating central retinal vein occlusion or eye inflammations, wherein said corticosteroid is dexamethasone.

In yet another aspect, the present disclosure refers to use of a composition as disclosed herein, in the manufacture of a medicament for treating

- diabetic macular edema ; or
- inflammation following ocular surgery, typically following cataract surgery,

wherein said corticosteroid is dexamethasone.

In another aspect, the present disclosure refers to use of an additive to prevent oxidation of a corticosteroid for stabilizing the pH of an aqueous composition comprising a corticosteroid, in particular an aqueous composition comprising dexamethasone/gamma-cyclodextrin complexes.

In yet another aspect, the present disclosure refers to an aqueous composition as disclosed herein comprising:

a. 1% to 4% of dexamethasone,
b. 1% to 35% of gamma-cyclodextrin, and
c. sodium thiosulfate

wherein the % are % by weight based on the volume of the composition.

In another aspect, the present disclosure refers to an aqueous composition as disclosed herein comprising:

a. 1.5% of dexamethasone,
b. 5% to 25% of gamma-cyclodextrin, and
c. sodium thiosulfate

wherein the % are % by weight based on the volume of the composition.

In yet another aspect, the present disclosure refers to an aqueous composition as disclosed herein comprising:

a. 1 to 4% of dexamethasone,
b. 1 to 35% of γ-cyclodextrin,
c. 2.2 to 2.8% of poloxamer,
d. 0 to 0.2% of disodium edetate,
e. 0.05 to 0.45% of sodium thiosulfate,

f. 0 to 1 % of sodium chloride; and

g. water;

wherein the % are % by weight based on the volume of the composition.

A first example of the present disclosure is a method for stabilizing the pH of an aqueous composition comprising a drug, said method comprising the addition of an additive to prevent oxidation of the drug.

The inventors have surprisingly found that the addition of an additive to prevent oxidation of the drug to the aqueous solution can prevent the drop of pH, especially during long storage periods.

A second example of the present disclosure is an aqueous composition comprising a corticosteroid, cyclodextrin and an additive to prevent oxidation of the corticosteroid, wherein said additive is present in the composition at a concentration between 0.15% (w/v) and 0.6% (w/v), for example between 0.15% (w/v) and 0.45% (w/v), and preferably at a concentration between 0.2% (w/v) and 0.4% (w/v).

A third example of the present disclosure is the use of an additive to prevent oxidation of a corticosteroid for stabilizing the pH of an aqueous composition comprising a corticosteroid.

A fourth example of the present disclosure is a method for stabilizing the pH of an aqueous composition comprising a drug, said method comprising the use of an oxygen absorber to prevent oxidation of the drug.

Detailed description

Definitions

As used herein the term "% by weight of a compound X based on the volume of the composition", also abbreviated as"% w/v", corresponds to the amount of compound X in grams that is introduced in 100 mL of the composition.

As used herein an "ocular condition" is a disease, ailment or other condition which affects or involves the eye, one of the parts or regions of the eye, or the surrounding tissues such as the lacrimal glands. Broadly speaking, the eye includes the eyeball and the tissues and fluids which constitute the eyeball, the periocular muscles (such as the oblique and rectus muscles), the portion of the optic nerve which is within or adjacent to the eyeball and surrounding tissues such as the lacrimal glands and the eye lids.

As used herein an "anterior ocular condition" is a disease, ailment or condition which affects or which involves an anterior (i.e. front of the eye) ocular region or site, such as a periocular muscle, an eye lid, lacrimal gland or an eye ball tissue or fluid which is located anterior to the posterior wall of the lens capsule or ciliary muscles.

Thus, an anterior ocular condition primarily affects or involves one or more of the following: the conjunctiva, the cornea, the anterior chamber, the iris, the lens, or the lens capsule, and blood vessels and nerves which vascularize or innervate an anterior ocular region or site. An anterior ocular condition is also considered herein as extending to the lacrimal apparatus. In particular, the lacrimal glands which secrete tears, and their excretory ducts which convey tear fluid to the surface of the eye.

Moreover, an anterior ocular condition affects or involves the posterior chamber, which is behind the retina but in front of the posterior wall of the lens capsule.

An anterior ocular condition includes a disease, ailment or condition such as, for example, aphakia; pseudophakia; astigmatism; blepharospasm; cataract; conjunctival diseases; conjunctivitis; corneal diseases; corneal ulcer; dry eye syndromes; eyelid diseases; lacrimal apparatus diseases; lacrimal duct obstruction; myopia; presbyopia; pupil disorders; refractive disorders and strabismus. Glaucoma can also be considered to be an anterior ocular condition because a clinical goal of glaucoma treatment can be to reduce a hypertension of aqueous fluid in the anterior chamber of the eye (i.e. reduce intraocular pressure).

CLAIMS

1. Method for stabilizing the pH of an aqueous composition comprising a corticosteroid, said method comprising the addition of an additive to prevent oxidation of the drug selected from the group consisting of sodium thiosulfate, methionine, 3,4-dihydroxybenzoic acid, sodium citrate, malic acid, sodium ascorbate, tartaric acid, α-monothioglycerol, butylated hyroxyanisole, lauryl gallate, lactic acid, tert-butylhydroquinone, and their salts or derivatives.

2. Method according to claim 1, wherein the aqueous composition comprises cyclodextrin, preferably gamma-cyclodextrin.

3. Method according to claim 1 or 2, wherein the drug is dexamethasone.

4. Method according to any of the preceding claims, wherein the additive to prevent oxidation is selected from the group consisting of sodium thiosulfate, L-methionine, 3,4-dihydroxybenzoic acid, sodium citrate tribasic dehydrate, DL-malic acid, (+)-sodium L-ascorbate, DL-tartaric acid, α-monothioglycerol, and butylated hyroxyanisole.

5. Method according to any of Claims 1-3, wherein the additive to prevent oxidation is selected from the group consisting of sodium thiosulfate, methionine, and, 3,4-dihydroxybenzoic acid.

6. Method according to any of the preceding claims, wherein the additive to prevent oxidation is sodium thiosulfate.

7. Method according to any of the preceding claims, wherein the additive to prevent oxidation of the drug is added to the aqueous composition at a concentration of at least 0.05 % (w/v), for example at a concentration between 0.05% (w/v) and 1% (w/v).

8. Method according to any of the preceding claims, wherein the pH of the aqueous composition comprising a drug is between 4 and 8, preferably between 4.5 and 6.

9. Aqueous composition comprising a corticosteroid, cyclodextrin, preferably gamma-cyclodextrin, and an additive to prevent oxidation of the corticosteroid, wherein the additive to prevent oxidation is selected from the group consisting of sodium thiosulfate, methionine, 3,4-dihydroxybenzoic acid, sodium citrate, malic acid, sodium ascorbate, tartaric acid, α-monothioglycerol, butylated hyroxyanisole, lauryl gallate, lactic acid, tert-butylhydroquinone, and their salts or derivatives.

10. The composition according to claim 9, wherein the corticosteroid is dexamethasone, typically 1.5% (w.v) dexamethasone.

11. The composition according to any of claims 9 or 10, wherein the additive to prevent oxidation is selected from the group consisting of sodium thiosulfate, L-methionine, 3,4-dihydroxybenzoic acid, sodium citrate tribasic dehydrate, DL-malic acid, (+)-sodium L-ascorbate, DL-tartaric acid, α-monothioglycerol, and butylated hyroxyanisole.

12. The composition according to any of claims 9 to 11, wherein the additive to prevent oxidation is selected from the group consisting of sodium thiosulfate, methionine, and, 3,4-dihydroxybenzoic acid.

13. The composition according to any of claims 9 to 12, wherein the additive to prevent oxidation is sodium thiosulfate.

14. The composition according to any of claims 9 to 13, wherein the pH of the composition is between 4 and 8, preferably between 4.5 and 6.

15. The composition according to any of Claims 9 to 14, which is a microsuspension, preferably comprising 80% to 95% of the corticosteroid in microparticles having a diameter of 1 μm to 10 μm.

16. Use of the composition according to any of claims 9 to 15 in the manufacture of a medicament for treating an ocular condition, in particular an anterior ocular condition or a posterior ocular condition.

17. Use of the composition according to any of claims 9 to 16 in the manufacture of a medicament for treating central retinal vein occlusion or eye inflammations, wherein said corticosteroid is dexamethasone.

18. Use of the composition according to any of claims 9 to 17, in the manufacture of a medicament for treating

- diabetic macular edema ; or
- inflammation following ocular surgery, typically following cataract surgery, wherein said corticosteroid is dexamethasone.

19. Use of an additive to prevent oxidation of a corticosteroid for stabilizing the pH of an aqueous composition comprising a corticosteroid, in particular an aqueous composition comprising dexamethasone/gamma-cyclodextrin complexes.

20. Aqueous composition according to any of claims 9 to 15 comprising:

a. 1% to 4% of dexamethasone,
b. 1% to 35% of gamma-cyclodextrin, and
c. sodium thiosulfate

wherein the % are % by weight based on the volume of the composition.

21. Aqueous composition according to any of claims 9 to 15 comprising:

a. 1.5% of dexamethasone,

b. 5% to 25% of gamma-cyclodextrin, and

c. sodium thiosulfate

wherein the % are % by weight based on the volume of the composition.

22. Aqueous composition according to any of claims 9 to 15 comprising:

a. 1 to 4% of dexamethasone,

b. 1 to 35% of γ-cyclodextrin,

c. 2.2 to 2.8% of poloxamer,

d. 0 to 0.2% of disodium edetate,

e. 0.05 to 0.45% of sodium thiosulfate,

f. 0 to 1 % of sodium chloride; and

g. water;

wherein the % are % by weight based on the volume of the composition.