and 3 minutes (Sugrue, M.F., 1989. The pharmacology of antiglaucoma drugs. Pharmacology & Therapeutics 43, 91-138).

[0008] The third major obstacle is slow drug permeation through the membrane barrier, i.e. cornea and/or conjunctiva/sclera. The drug molecules must partition from the aqueous exterior into the membrane before they can passively permeate the membrane barrier. The result is that generally only few percentages of applied drug dose are delivered into the ocular tissues. The major part (50-100%) of the administered dose will be absorbed from the nasal cavity into the systemic drug circulation which can cause various side effects.

[0009] The present disclosure seeks to assist with the WHO's plan for reducing avoidable visual impairments by providing an ophthalmic composition and a method of making an ophthalmic composition that overcomes the obstacles of passive drug diffusion in the eye. In these efforts, Applicants provide a method for preparing an ophthalmic composition, which overcomes the major obstacles of passive drug diffusion by (1) increasing the solubility of poorly soluble drugs, (2) increasing the precorneal half-life of topically applied drugs, and (3) partitioning drug molecules from the aqueous exterior into the membrane to enable passive permeation of the membrane barrier. In exemplary embodiments, ophthalmic compositions comprising a combination of such features are provided.

SUMMARY

[0009a] In one aspect, the present invention refers to an ophthalmic composition comprising, in an ophthalmically acceptable medium: a solid complex comprising dexamethasone and γ-cyclodextrin, wherein the composition comprises less than 0.5%, in particular less than 0.3%, more particularly less than 0.2%, by weight of dexamethasone enol aldehyde based on the weight of the composition. In another aspect, the present invention refers to a method of preparing an ophthalmic composition, comprising the steps of:

a) suspending dexamethasone and γ-cyclodextrin in an ophthalmically acceptable medium to form a suspension; b) heating the suspension at temperature T1 lower than 120°C for a time t until the dexamethasone and the γ-cyclodextrin are substantially dissolved in the ophthalmically acceptable medium; and c)cooling the

resulting solution to a temperature T2 to obtain an ophthalmic composition comprising a solid complex of dexamethasone and γ-cyclodextrin, wherein the ophthalmic composition comprises less than 0.5%, in particular less than 0.3%, more particularly less than 0.2%, by weight of dexamethasone enol aldehyde based on the weight of the microsuspension. In another aspect, the present invention also refers to a method of preparing an ophthalmic composition, comprising the steps of: a) suspending γ-cyclodextrin in an ophthalmically acceptable medium to form a suspension; b) heating the suspension until the γ-cyclodextrin is dissolved in the ophthalmically acceptable medium; c) adding dexamethasone in solid form in the heated solution of step b) at a temperature T1 lower than 120°C for a time t until the dexamethasone is substantially dissolved in the ophthalmically acceptable medium; and d) cooling the resulting solution to a temperature T2 to obtain an ophthalmic composition comprising a solid complex of dexamethasone and γ-cyclodextrin, wherein the ophthalmic composition comprises less than 0.5%, in particular less than 0.3%, more particularly less than 0.2%, by weight of dexamethasone enol aldehyde based on the weight of the microsuspension. In yet another aspect, the present invention refers to a method of preparing an ophthalmic composition, comprising the steps of:a) suspending γ-cyclodextrin in an ophthalmically acceptable medium to form a suspension and sterilizing said suspension in an autoclave; b) suspending dexamethasone in an ophthalmically acceptable medium to form a suspension and sterilizing said suspension in an autoclave; c) mixing the compositions of steps a) and b) and heating the mixture at a temperature T1 lower than 120°C for a time t; d) cooling the resulting solution to a temperature T2 to obtain an ophthalmic composition comprising a solid complex of dexamethasone and γ-cyclodextrin. In another aspect, the present invention refers to an ophthalmic composition obtainable by the methods of the present invention. In yet another aspect, the present invention refers a use of the ophthalmic composition of the present invention in the manufacture of a medicament for the treatment of an ocular condition, in particular an anterior ocular condition or a posterior ocular condition, more particularly uveitis and macular edema. In a final aspect, the present invention refers the ophthalmic compositions of the present invention for use as a medicament as an eye drop solution.

[00010] Cyclodextrins are well-known to enhance the solubility and bioavailability of hydrophobic compounds. In aqueous solutions, cyclodextrins form inclusion complexes with many active pharmaceutical ingredients. The bottom-up preparation of active pharmaceutical ingredient/cyclodextrin complexes involves suspending an active pharmaceutical ingredient and a cyclodextrin in an aqueous medium and heating the resulting suspension. Upon dissolution of the active pharmaceutical ingredient and the cyclodextrin, complexes of active pharmaceutical ingredient and cyclodextrin are formed. The hot solution is subsequently cooled to precipitate the solid complexes of active pharmaceutical ingredient and cyclodextrin.

[00011] Applicants have surprisingly found that the diameter of the particles and the viscosity of the composition can be tailored with the heating and cooling steps and the presence of stabilizing polymers in the aqueous medium. To prevent

WHAT IS CLAIMED IS:

1. An ophthalmic composition comprising, in an ophthalmically acceptable medium:

a solid complex comprising dexamethasone and γ-cyclodextrin,

wherein the composition comprises less than 0.5%, in particular less than 0.3%, more particularly less than 0.2%, by weight of dexamethasone enol aldehyde based on the weight of the composition.

2. The ophthalmic composition according to Claim 1, wherein the composition further comprises a polymer, for example poloxamer.

3. The ophthalmic composition according to Claim 2, in which the amount of polymer is 0.5 to 5%, in particular 1 to 4%, more particularly 2 to 3%, more particularly 2.2 to 2.8%, by weight of polymer based on the weight of the composition.

4. The ophthalmic composition according to Claim 3, wherein the viscosity of the composition is from 4 to 14 cP, preferably 5 to 13 cP, more preferably 6 to 12 cP.

5. An ophthalmic composition according to any one of claims 1 to 4, in which the dexamethasone is present in the composition at a concentration of 10 mg/mL to 20 mg/mL.

6. An ophthalmic composition according to any one of claims 1 to 5, in which 60 to 95% by weight, in particular 70 to 90% by weight, of the dexamethasone in the composition is in the form of solid complexes.

7. An ophthalmic composition according to claim 6, in which about 40% to about 80% by weight of the dexamethasone in the composition is in the form of solid complexes with a diameter of greater than about 1 μm and about 20% to about 60% by weight of the dexamethasone in the composition is in the form of solid complexes with a diameter of less than about 1 μm.

8. An ophthalmic composition according to any one of claims 1 to 7, in which the amount of γ-cyclodextrin is from 1 to 25%, in particular 5 to 20%, more particularly 10 to 18%, even more particularly 12 to 16%, by weight of γ-cyclodextrin based on the weight of the composition.

9. An ophthalmic composition according to any one of claims 1 to 8, in which the solid complex has a diameter D_{50} of less than 100 μm, in particular 1 to 25 μm, more particularly 2 to 10 μm, even more particularly 3 to 8 μm.

10. An ophthalmic composition according to any one of claims 1 to 9, wherein the composition comprises:

- 1 to 2% of dexamethasone, for example 1.5% of dexamethasone;
- 12 to 16% of γ-cyclodextrin, for example 14% of γ-cyclodextrin;
- 2.2 to 2.8% of polymer, for example 2.5% of poloxamer;
- 0 to 0.04% of preservatives, for example 0.02% of benzalkonium chloride;
- 0 to 0.2% of stabilizing agent, for example 0.1% of disodium edetate;
- 0 to 1% of electrolyte, for example 0.57% of sodium chloride; and
- water;

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

11. A method of preparing an ophthalmic composition, comprising the steps of:

a) suspending dexamethasone and γ-cyclodextrin in an ophthalmically acceptable medium to form a suspension;

b) heating the suspension at temperature T1 lower than 120°C for a time t until the dexamethasone and the γ-cyclodextrin are substantially dissolved in the ophthalmically acceptable medium; and

c) cooling the resulting solution to a temperature T2 to obtain an ophthalmic composition comprising a solid complex of dexamethasone and γ-cyclodextrin, wherein the ophthalmic composition comprises less than 0.5%, in particular less than 0.3%, more particularly less than 0.2%, by weight of dexamethasone enol aldehyde based on the weight of the microsuspension.

12. A method of preparing an ophthalmic composition, comprising the steps of:

a) suspending γ-cyclodextrin in an ophthalmically acceptable medium to form a suspension;

b) heating the suspension until the γ-cyclodextrin is dissolved in the ophthalmically acceptable medium;

c) adding dexamethasone in solid form in the heated solution of step b) at a temperature T1 lower than 120°C for a time t until the dexamethasone is substantially dissolved in the ophthalmically acceptable medium; and

d) cooling the resulting solution to a temperature T2 to obtain an ophthalmic composition comprising a solid complex of dexamethasone and γ-cyclodextrin, wherein the ophthalmic composition comprises less than 0.5%, in particular less than 0.3%, more particularly less than 0.2%, by weight of dexamethasone enol aldehyde based on the weight of the microsuspension.

13. A method of preparing an ophthalmic composition, comprising the steps of:

a) suspending γ-cyclodextrin in an ophthalmically acceptable medium to form a suspension and sterilizing said suspension in an autoclave;

b) suspending dexamethasone in an ophthalmically acceptable medium to form a suspension and sterilizing said suspension in an autoclave;

c) mixing the compositions of steps a) and b) and heating the mixture at a temperature T1 lower than 120°C for a time t;

d) cooling the resulting solution to a temperature T2 to obtain an ophthalmic composition comprising a solid complex of dexamethasone and γ-cyclodextrin.

14. A method according to any one of claims 11 to 13, wherein temperature T1 is 80 to 110°C, in particular 80 to 105°C, more particularly 80 to 100°C.

15. A method according to any one of claims 11 to 14, wherein temperature T2 is 10 to 40°C, in particular 15 to 35°C, more particularly 20 to 30°C.

16. A method according to any one of claims 11 to 16, wherein temperature T1 is cooled to temperature T2 with a rate of 1 to 25°C/min, in particular 2 to 20°C/min, more particularly 5 to 18°C/min.

17. An ophthalmic composition obtainable by the method according to any one of claims 11 to 16, wherein the ophthalmic composition comprises less than 0.5%, in particular less than 0.3%, more particularly less than 0.2%, by weight of dexamethasone enol aldehyde based on the weight of the microsuspension.

18. Use of the ophthalmic composition according to any one of claims 1 to 10 and 17 in the manufacture of a medicament, for the treatment of an ocular condition, in particular an anterior ocular condition or a posterior ocular condition, more particularly uveitis and macular edema.

19. The ophthalmic composition according to any one of claims 1 to 10 or 17 for use as a medicament as an eye drop solution.