described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[0012] Other features and advantages of the invention will be apparent from the following detailed description and claims.

SUMMARY OF THE DISCLOSURE

[0013] In one aspect the present invention refers to a stable ophthalmic pharmaceutical formulation comprising (i) 30 mg/mL to 70 mg/mL of a pharmaceutically acceptable salt of an ophthalmic therapeutic agent having a solubility of less than 1 mg/mL in water, wherein the ophthalmic therapeutic agent is in solution in the formulation; and (ii) a cyclodextrin. In another aspect, the present invention refers to the use of a stable pharmaceutical formulation of the present invention, from an intravitreal delivery device comprising a reservoir chamber coupled to a porous structure, in the manufacture of a medicament for treating and/or ameliorating an ophthalmic disease or disorder of the posterior segment of the eye, wherein the formulation is contained in the reservoir of the device and is released into the eye through the porous structure. In yet another aspect, the present invention refers to a method of preparing a stable ophthalmic pharmaceutical formulation, the method comprising (a) preparing an organic solution of a pharmaceutically acceptable salt of an ophthalmic therapeutic agent in an organic solvent, wherein the ophthalmic therapeutic agent has a solubility of less than 1 mg/mL in water; (b) lyophilizing the organic solution, thereby preparing a lyophilized salt of the ophthalmic therapeutic agent; (c) dissolving a solubilizing agent and a buffering agent in water, thereby preparing a solution; (d) dissolving a cyclodextrin in the solution thereby preparing a low viscosity solution; and (e) adding, mixing, and dissolving the salt of the ophthalmic therapeutic agent in the low viscosity solution at a temperature from about 37°C to about 50°C, thereby preparing the stable ophthalmic pharmaceutical formulation comprising from 30 mg/mL to 70 mg/mL of the pharmaceutically acceptable salt of an ophthalmic therapeutic agent. The present disclosure relates generally to formulations of a therapeutic agent having low solubility in water. Receptor tyrosine

kinase inhibitor, *e.g.*, pazopanib, formulations and methods of preparation and use in treating and ameliorating ophthalmic diseases and/or disorders are disclosed herein.

[0014] The present disclosure provides stable pharmaceutical formulation(s) of a pharmaceutically acceptable salt of a therapeutic agent having low aqueous solubility, and one or more formulation agents, wherein the pharmaceutically acceptable salt is a monovalent or a divalent salt, and the one or more formulation agents comprise a complexing agent, a solubilizing agent, and optionally a buffering agent; wherein the salt of the therapeutic agent is in solution in the formulation. The therapeutic agent is pazopanib.

[0015] The present disclosure provides stable pharmaceutical formulation(s) of a pharmaceutically acceptable salt of a therapeutic agent having low aqueous solubility, and one or more formulation agents, wherein the pharmaceutically acceptable salt is a monovalent or a divalent salt, and the one or more formulation agents comprise a complexing agent, a solubilizing agent, and a buffering agent; wherein the salt of the therapeutic agent is in solution in the formulation. The therapeutic agent is pazopanib.

[0016] The present disclosure provides stable pharmaceutical formulation(s) of a pharmaceutically acceptable salt of a therapeutic agent having low aqueous solubility, and one or more formulation agents, wherein the pharmaceutically acceptable salt is a monovalent or a divalent salt, and the one or more formulation agents comprise a complexing agent, a solubilizing agent, but without a buffering agent; wherein the salt of the therapeutic agent is in solution in the formulation. The therapeutic agent is pazopanib.

[0017] The pharmaceutically acceptable salt is a monovalent or a divalent halide salt. The salt is a chloride salt. The monovalent salt is stable in formulation up to a

disclosure provides a method of converting a crystal form of pazopanib to a material containing crystal Form G of pazopanib, the method comprising dissolving the crystal form in DMSO and lyophilizing the resulting solution; in which the about 100% Form G of pazopanib is formed. The present disclosure provides a method of converting a crystal form of pazopanib to a material containing crystal Form G of pazopanib, the method comprising dissolving the crystal form in DMSO and lyophilizing the resulting solution; in which between about 70% to about 100% (*e.g.*, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, about 100%) Form G of pazopanib is formed.

[0036] The present disclosure provides a method of converting crystal Form A of pazopanib, *e.g.*, pazopanib 1HCl, to a material containing crystal Form G of pazopanib, the method comprising dissolving Form A in DMSO and lyophilizing the resulting solution; in which the at least about 70% Form G of pazopanib is formed. The present disclosure provides a method of converting crystal Form A of pazopanib to a material containing crystal Form G of pazopanib, the method comprising dissolving the crystal Form A in DMSO and lyophilizing the resulting solution; in which the about 100% Form G of pazopanib is formed. The present disclosure provides a method of converting crystal Form A of pazopanib to a material containing crystal Form G of pazopanib, the method comprising dissolving the crystal Form A in DMSO and lyophilizing the resulting solution; in which between about 70% to about 100% (*e.g.*, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, about 100%) Form G of pazopanib is formed.

[0037] In one example the present disclosure provides a stable pharmaceutical formulation of pazopanib 1HCl for intravitreal delivery from a delivery device including a complexing agent, a solubilizing agent, and optionally a buffering agent. Before dissolving, pazopanib 1HCl is lyophilized in DMSO, which converts at least about 70% crystalline phase form A of pazopanib 1HCl to crystalline phase form G and increases

stability. Pazopanib 1HCl in the formulation thus formed does not precipitate when diluted and/or during or upon delivery into the vitreous for at least 50 days.

[0038] In one example the present disclosure provides a stable pharmaceutical formulation of pazopanib 1HCl for intravitreal delivery from a delivery device including a complexing agent, a solubilizing agent, and optionally a buffering agent. Before dissolving, pazopanib 1HCl is lyophilized in trifluoro ethanol (TFE), which converts crystalline phase form A of pazopanib 1HCl to partially or completely amorphous and/or microcrystalline phase. Pazopanib 1HCl in the formulation thus formed does not precipitate when diluted and/or during or upon delivery into the vitreous for at least 50 days.

[0039] The present disclosure provides a method of converting a crystal form of pazopanib to an amorphous form of pazopanib, the method comprising dissolving the crystal form in TFE and lyophilizing the resulting solution; in which up to or at least 96% amorphous pazopanib is formed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] In order to understand the invention and to demonstrate how it may be carried out in practice, embodiments now described, by way of non-limiting example only, with reference to the accompanying drawing in which:

[0041] FIG. 1 shows line graphs of in vitro drug release from implants (4.5 sccm gas flow) filled with various forms of pazopanib formulated with CAPTISOL®. The measured release data is shown together with the predicted release from the diffusion model.

[0042] FIG. 2A shows a therapeutic device implanted under the conjunctiva and extending through the sclera to release a therapeutic agent into vitreous humor of the eye so as to treat the retina, in accordance with variations described herein.

[0043] FIG. 2B shows structures of a therapeutic device configured for placement in an eye as in FIG. 2A, in accordance with variations described herein.

[0044] FIG. 2C shows a therapeutic device loaded into an insertion cannula, in which the device comprises an elongate narrow shape for insertion into the sclera, and in which the device is configured to expand to a second elongate wide shape for retention at least partially in the sclera, in accordance with variations described herein.

[0045] FIG. 2D shows a therapeutic device comprising a reservoir suitable for loading in a cannula, in accordance with variations described herein.

CLAIMS

WHAT IS CLAIMED IS:

1. A stable ophthalmic pharmaceutical formulation comprising:
   (i) 30 mg/mL to 70 mg/mL of a pharmaceutically acceptable salt of an ophthalmic therapeutic agent having a solubility of less than 1 mg/mL in water, wherein the ophthalmic therapeutic agent is in solution in the formulation; and
   (ii) a cyclodextrin.

2. The formulation of claim 1, comprising from 40 mg/mL to 60 mg/mL of the pharmaceutically acceptable salt of the ophthalmic therapeutic agent.

3. The formulation of claim 1, wherein the ophthalmic therapeutic agent has a solubility of less than 0.01 mg/mL in water.

4. The formulation of claim 1, wherein the ophthalmic therapeutic agent is a tyrosine kinase inhibitor.

5. The formulation of claim 4, wherein the tyrosine kinase inhibitor is pazopanib.

6. The formulation of claim 1, wherein the pharmaceutically acceptable salt is a monovalent salt or a divalent salt.

7. The formulation of claim 6, wherein the monovalent salt or the divalent salt is a chloride salt.

8. The formulation of claim 1, wherein the pharmaceutically acceptable salt of the ophthalmic therapeutic agent is lyophilized.

9. The formulation of claim 8, wherein the salt is lyophilized with dimethyl sulfoxide, trifluoroethanol, or a trifluoroethanol-water mixture.

10. The formulation of claim 1, wherein the cyclodextrin is 2-hydroxypropyl-β-cyclodextrin, methyl-β-cyclodextrin, randomly methylated-β-cyclodextrin, ethylated-β-cyclodextrin, triacetyl-β-cyclodextrin, peracetylated-β-cyclodextrin, carboxymethyl-β-

cyclodextrin, hydroxyethyl -β-cyclodextrin, 2-hydroxy-3-(trimethylammonio)propyl-β-cyclodextrin, glucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin, sulfobutyl ether-β-cyclodextrin, branched-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated-γ-cyclodextrin, trimethyl-γ-cyclodextrin, or a combination of two or more of the foregoing.

11. The formulation of claim 1, wherein the cyclodextrin is sulfobutyl ether-β-cyclodextrin, hydroxypropyl β-cyclodextrin, or a combination thereof.

12. The formulation of claim 1, further comprising a solubilizing agent, a buffering agent, or a combination thereof.

13. The formulation of claim 12, wherein the solubilizing agent is poly(vinyl pyrrolidone); and wherein the buffering agent is Histidine HCl.

14. The use of a stable pharmaceutical formulation of any one of claims 1 to 13, from an intravitreal delivery device comprising a reservoir chamber coupled to a porous structure, in the manufacture of a medicament for treating and/or ameliorating an ophthalmic disease or disorder of the posterior segment of the eye, wherein the formulation is contained in the reservoir of the device and is released into the eye through the porous structure.

15. The use of claim 14, wherein the disease or disorder is diabetic retinopathy, age-related macular degeneration, pathologic choroidal neovascularization, pathologic retinal neovascularization, uveitis, retinal vein occlusion, ocular trauma, surgery induced edema, surgery induced neovascularization, cystoid macular edema, ocular ischemia, retinopathy of prematurity, Coat's disease, sickle cell retinopathy, or neovascular glaucoma.

16. The use of claim 14, wherein the reservoir chamber is re-fillable and is re-filled with the formulation after the device is inserted into the eye.

17. The use of claim 16, wherein the reservoir chamber is re-filled with the formulation after the device has been in the eye for between 30 and 90 days, or up to 6 months.

18. A method of preparing a stable ophthalmic pharmaceutical formulation, the method comprising:

(a) preparing an organic solution of a pharmaceutically acceptable salt of an

ophthalmic therapeutic agent in an organic solvent, wherein the ophthalmic therapeutic agent has a solubility of less than 1 mg/mL in water;

(b) lyophilizing the organic solution, thereby preparing a lyophilized salt of the ophthalmic therapeutic agent;

(c) dissolving a solubilizing agent and a buffering agent in water, thereby preparing a solution;

(d) dissolving a cyclodextrin in the solution thereby preparing a low viscosity solution; and

(e) adding, mixing, and dissolving the salt of the ophthalmic therapeutic agent in the low viscosity solution at a temperature from about 37°C to about 50°C, thereby preparing the stable ophthalmic pharmaceutical formulation comprising from 30 mg/mL to 70 mg/mL of the pharmaceutically acceptable salt of an ophthalmic therapeutic agent.

19. The method of claim 18, wherein the method further comprises adding and dissolving about two times more of the amount of the cyclodextrin after step (e).

20. The method of claim 18, wherein the organic solvent is dimethyl sulfoxide, trifluoroethanol, or a trifluoroethanol-water mixture.

21. The method of claim 18, wherein the organic solvent is dimethyl sulfoxide; and wherein lyophilizing the organic solution converts one crystalline form of the salt of the ophthalmic therapeutic agent to a different crystalline form of the salt of the ophthalmic therapeutic agent.

22. The method of claim 18, further comprising adjusting the pH.

23. The method of claim 22, wherein the pH of the formulation is adjusted from about 6 to about 7 with a base.

24. The method of claim 18, wherein the lyophilized salt is dissolved in the solution at step (e) at a temperature between about 37°C to about 50°C.

25. The method of claim 18, wherein the method further comprises continuously mixing at least the solubilizing agent, the buffering agent, the cyclodextrin, and the lyophilized salt, while adding water, at a temperature from about 37°C to about 50°C.

26. The method of claim 18, wherein the formulation comprises from 40 mg/mL to 60 mg/mL of the pharmaceutically acceptable salt of the ophthalmic therapeutic agent.

27. The method of claim 18, wherein the ophthalmic therapeutic agent has a solubility of less than 0.01 mg/mL in water.

28. The method of claim 18, wherein the ophthalmic therapeutic agent is a tyrosine kinase inhibitor.

29. The method of claim 28, wherein the tyrosine kinase inhibitor is pazopanib.

30. The method of claim 18, wherein the pharmaceutically acceptable salt is a monovalent salt or a divalent salt.

31. The method of claim 30, wherein the monovalent salt or the divalent salt is a chloride salt.

32. The method of claim 18, wherein the cyclodextrin is 2-hydroxypropyl-β-cyclodextrin, methyl-β-cyclodextrin, randomly methylated-β-cyclodextrin, ethylated-β-cyclodextrin, triacetyl-β-cyclodextrin, peracetylated-β-cyclodextrin, carboxymethyl-β-cyclodextrin, hydroxyethyl -β-cyclodextrin, 2-hydroxy-3-(trimethylammonio)propyl-β-cyclodextrin, glucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin, sulfobutyl ether-β-cyclodextrin, branched-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated-γ-cyclodextrin, trimethyl-γ-cyclodextrin, or a combination of two or more of the foregoing.

33. The method of claim 18, wherein the cyclodextrin is sulfobutyl ether-β-cyclodextrin, hydroxypropyl β-cyclodextrin, or a combination thereof.

34. The method of claim 18, wherein the solubilizing agent is poly(vinyl pyrrolidone); and wherein the buffering agent is Histidine HCl.