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 use of 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; 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 wherein the reservoir chamber is re-fillable and is to be re-filled with the formulation after insertion of the device into the eye. In one example, there is disclosed 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 example, there is disclosed 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 example, there is disclosed 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. In 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 and mixing the lyophilized salt of the ophthalmic therapeutic agent in the low viscosity solution at a temperature from 37°C to 50°C until the opthalmic therapeutic agent is dissolved therein, thereby preparing the stable ophthalmic pharmaceutical formulation. In yet another aspect, the present invention refers to a method of preparing a stable ophthalmic pharmaceutical formulation, the method comprising: (a) mixing a monovalent salt of an ophthalmic therapeutic agent in an organic solvent comprising dimethylsulfoxide or trifluoroethanol, thereby forming an organic solution; (b) lyophilizing the organic solution, thereby forming a lyophilized monovalent salt of the ophthalmic therapeutic agent; (c) adding the lyophilized monovalent salt of the ophthalmic therapeutic agent to a solution comprising a solubilizing agent, a buffering agent, and a cyclodextrin; and (f) mixing the lyophilized monovalent salt of the ophthalmic therapeutic agent in the solution at a temperature from 37°C to 50°C until the opthalmic therapeutic agent is dissolved therein, thereby preparing the stable ophthalmic pharmaceutical formulation. 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

CLAIMS

WHAT IS CLAIMED IS:

1. Use of 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;

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 wherein the reservoir chamber is re-fillable and is to be re-filled with the formulation after insertion of the device into the eye.

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

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

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

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

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

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

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

9. The use of claim 8, wherein the salt is lyophilized with dimethyl sulfoxide,

trifluoroethanol, or a trifluoroethanol-water mixture.

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

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

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

14. The use of claim 1, 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.

15. The use of claim 1, 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.

16. 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 and mixing the lyophilized salt of the ophthalmic therapeutic agent in the low viscosity solution at a temperature from 37°C to 50°C until the opthalmic therapeutic agent is dissolved therein, thereby preparing the stable ophthalmic pharmaceutical formulation.

17. The method of claim 16, wherein the method further comprises adding and dissolving about two times more of the amount of the cyclodextrin after step (e).

18. The method of claim 16, wherein the organic solvent comprises dimethyl sulfoxide or trifluoroethanol.

19. The method of claim 16, wherein the organic solvent is dimethyl sulfoxide.

20. The method of claim 16, further comprising adjusting the pH with an acid to a pH equal to or less than 2.

21. The method of claim 16, further comprising adjusting the pH of the formulation with a base to a pH from 6 to 7.

22. The method of claim 16, 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 37°C to 50°C.

23. The method of claim 16, wherein the formulation comprises from 40 mg/mL to 60 mg/mL of the pharmaceutically acceptable salt of the ophthalmic therapeutic agent.

24. The method of claim 16, wherein the ophthalmic therapeutic agent has a solubility of less than 0.01 mg/mL in water.

25. The method of claim 16, wherein the ophthalmic therapeutic agent is a tyrosine kinase inhibitor.

26. The method of claim 25, wherein the tyrosine kinase inhibitor is pazopanib.

27. The method of claim 16, wherein the pharmaceutically acceptable salt is a monovalent salt or a divalent salt.

28. The method of claim 27, wherein the monovalent salt or the divalent salt is a chloride salt.

29. The method of claim 16, 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.

30. The method of claim 16, wherein the cyclodextrin is sulfobutyl ether-β-cyclodextrin, hydroxypropyl β-cyclodextrin, or a combination thereof.

31. The method of claim 16, wherein the solubilizing agent is poly(vinyl pyrrolidone); and wherein the buffering agent is Histidine HCl.

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

(a) mixing a monovalent salt of an ophthalmic therapeutic agent in an organic solvent comprising dimethylsulfoxide or trifluoroethanol, thereby forming an organic solution;

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

(c) adding the lyophilized monovalent salt of the ophthalmic therapeutic agent to a solution comprising a solubilizing agent, a buffering agent, and a cyclodextrin; and

(f) mixing the lyophilized monovalent salt of the ophthalmic therapeutic agent in the solution at a temperature from 37°C to 50°C until the opthalmic therapeutic agent is dissolved therein, thereby preparing the stable ophthalmic pharmaceutical formulation.

33. The method of claim 32, 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.

34. The method of claim 32, wherein the cyclodextrin is sulfobutyl ether-β-cyclodextrin, hydroxypropyl β-cyclodextrin, or a combination thereof.

35. The method of claim 32, wherein the solubilizing agent is trehalose, methylcellulose, ethylcellulose, sodium carboxymethylcellulose, sodium hyaluronate, sodium alginate, polyethylene glycol, glycerin, propylene glycol, triacetin, N,N-dimethylacetamide, poly(vinyl pyrrolidone), pyrrolidone, or a combination of two or more thereof.

36. The method of claim 35, wherein the solublizing agent is poly(vinyl pyrrolidone).

37. The method of claim 32, wherein the buffering agent is histidine HCl.