SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a particulate plug for removing a preservative from a solution, suspension, or emulsion comprising a drug, the particulate plug comprising microparticles of a hydrophobic polymer/fatty acid blend, wherein the microparticles form a particulate plug capable of being fitted to an outlet of a container for the solution, emulsion, or suspension, wherein the particulate plug rapidly and selectively removes a preservative from the solution, emulsion, or suspension.

[0003b] In another aspect of the present disclosure, there is provided a hydrophobic polymer/fatty acid blend comprising a hydrophobic polymer and a fatty acid in a ratio from about 1:1 to about 1:20.

[0003c] In a further aspect of the present disclosure, there is provided a particulate plug disclosed herein, wherein the hydrophobic polymer/fatty acid blend comprises a hydrophobic polymer and a fatty acid in a ratio from about 1:1 to about 1:20.

[0003d] In another aspect of the present disclosure, there is provided a particulate plug for removing a preservative from a solution, suspension, or emulsion comprising a drug, the particulate plug comprising microparticles of a fatty acid, wherein the microparticles form a particulate plug capable of being fitted an outlet of a container for the solution, emulsion, or suspension, wherein the particulate plug rapidly and selectively removes a preservative from the solution, emulsion, or suspension.

[0004] Examples of the disclosure are directed to particulate plugs comprising hydrophobic polymer/fatty acid blend comprising a hydrophobic polymer and a fatty acid in a ratio from about 1:1 to about 1:20 for selectively removing a large fraction of the preservative without significantly removing the drug and specifically directed to achieving this for each eluting drop. The material of the plug may be designed to minimize drug binding. The material of the plug may depend on the properties of the drug whose binding is to be minimized. The binding may depend on the structure of the drug and/or the detailed structure of the matrix materials of the particles of the tip. Broadly, ophthalmic drugs can be divided into hydrophobic and hydrophilic categories depending of the affinity of the drug for water. Hydrophilic drugs are more soluble in water while hydrophobic drugs are less soluble.

[0005] Examples of the disclosure are directed to particulate plugs for removing a preservative from a drug solution where microparticles comprising the plug are hydrophobic polymer/fatty acid blend comprising a hydrophobic polymer and a fatty acid in a ratio from about 1:1 to about 1:20.

[0006] The drug can be a hydrophilic drug selected from Tables 1-4 such as, for example, Timolol Maleate, Levofloxacin, Dorzolamide, Brimonidine Tartrate, and/or hydrophobic drugs,

for example, latanoprost or bimatoprost, and/or a combination of drugs, for example, Combigan. The preservative may be Benzalkonium chloride (BAK).

[0007] One example provides a particulate plug for removing a preservative from a solution, suspension, or emulsion comprising a drug, the particulate plug comprising microparticles of a hydrophobic polymer/fatty acid blend, wherein the microparticles form a particulate plug capable of being fitted to an outlet of a container for the solution, emulsion, or suspension, wherein the particulate plug rapidly and selectively removes a preservative from the solution, emulsion, or suspension.

[0008] Another example provides the particulate plug wherein the microparticles have a dimension of 5 μM to about 10,000 μM.

[0009] Another example provides the particulate plug wherein the preservative comprises benzalkonium chloride (BAK).

[0010] Another example provides the particulate plug wherein the drug is selected from Table 1, Table 2, Table 3, or Table 4.

[0011] Another example provides the particulate plug wherein the hydrophobic polymer/fatty acid blend comprises a hydrophobic polymer selected from isotactic polypropylene, low density polyethylene, or high density polyethylene. Another example provides the particulate plug wherein the isotactic polypropylene has an average MW of about

250,000. Another example provides the particulate plug wherein the hydrophobic polymer/fatty acid blend comprises a hydrophobic polymer that is a thermoplastic. Another example provides the particulate plug wherein the hydrophobic polymer/fatty acid blend comprises a hydrophobic polymer that is a thermoset. Another example provides the particulate plug wherein the hydrophobic polymer/fatty acid blend comprises a product of a melt blend. Another example provides the particulate plug wherein the hydrophobic polymer/fatty acid blend comprises a product of a solution blend. Another example provides the particulate plug wherein the hydrophobic polymer/fatty acid blend comprises a product of a spray-dry blend.

[0012] Another example provides the particulate plug wherein the hydrophobic polymer/fatty acid blend comprises a fatty acid selected from a fatty acid having the structure of $CH_3(CH_2)_nCO_2H$, wherein n is 2 to 24. Another example provides the particulate plug wherein n is 6 to 24. Another example provides the particulate plug wherein n is 8 to 24. Another example provides the particulate plug wherein n is 8 to 20. Another example provides the particulate plug wherein n is 10 to 20. Another example provides the particulate plug wherein n is 12 to 20. Another example provides the particulate plug wherein n is 14 to 20. Another example provides the particulate plug wherein n is 14 to 18. Another example provides the particulate plug wherein n is 14 or 16. Another example provides the particulate plug wherein n is 16. Another example provides the particulate plug wherein the fatty acid is selected from caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, or cerotic acid. Another example provides the particulate plug wherein the fatty acid is selected from Myristoleic acid, Palmitoleic acid, Sapienic acid, Oleic acid, Elaidic acid, Vaccenic acid, Linoleic acid, Linoelaidic acid, α-Linolenic acid, Arachidonic acid, Eicosapentaenoic acid, Erucic acid, or Docosahexaenoic acid. Another example provides the particulate plug wherein the fatty acid is selected from a fatty acid having a melting point greater than 70 ^oC.

[0013] Another example provides the particulate plug wherein the weight-to-weight ratio of the hydrophobic polymer-to-fatty acid is from about 1:1 to about 1:20. Another example provides the particulate plug wherein the weight-to-weight ratio of the hydrophobic polymer-to-fatty acid is about 1:1. Another example provides the particulate plug wherein the weight-to-weight ratio of the hydrophobic polymer-to-fatty acid is about 1:2. Another example provides the particulate plug wherein the weight-to-weight ratio of the hydrophobic polymer-to-fatty acid is about 1:3. Another example provides the particulate plug wherein the weight-to-weight ratio of the hydrophobic polymer-to-fatty acid is about 1:4. Another example provides the particulate plug wherein the weight-to-weight ratio of the hydrophobic polymer-to-

fatty acid is about 1:5. Another example provides the particulate plug wherein the weight-to-weight ratio of the hydrophobic polymer-to-fatty acid is about 1:6. Another example provides the particulate plug wherein the weight-to-weight ratio of the hydrophobic polymer-to-fatty acid is about 1:7. Another example provides the particulate plug wherein the weight-to-weight ratio of the hydrophobic polymer-to-fatty acid is about 1:8. Another example provides the particulate plug wherein the weight-to-weight ratio of the hydrophobic polymer-to-fatty acid is about 1:9. Another example provides the particulate plug wherein the weight-to-weight ratio of the hydrophobic polymer-to-fatty acid is about 1:10.

[0014] Another example provides the particulate plug wherein the microparticles have a dimension of 5 μM to about 50 μM. Another example provides the particulate plug wherein the microparticles have a dimension of 50 μM to about 100 μM. Another example provides the particulate plug wherein the microparticles have a dimension of 100 μM to about 500 μM. Another example provides the particulate plug wherein the microparticles have a dimension of 500 μM to about 1000 μM. Another example provides the particulate plug wherein the microparticles have a dimension of 1,000 μM to about 10,000 μM.

[0015] One example provides a hydrophobic polymer/fatty acid blend comprising a hydrophobic polymer and a fatty acid in a ratio from about 1:1 to about 1:20. Another example provides the blend wherein the hydrophobic polymer and the fatty are combined in a vessel suitable for chemical reaction; heated to above the melting point of each component forming a homogenous composition; and poured into cool water.

[0016] One example provides a particulate plug, for removing a preservative from a solution, suspension, or emulsion comprising a drug, the particulate plug comprising microparticles of a hydrophobic polymer/fatty acid blend, wherein the microparticles form a particulate plug capable of being fitted to an outlet of a container for the solution, emulsion, or suspension, wherein the particulate plug rapidly and selectively removes a preservative from the solution, emulsion, or suspension, wherein the hydrophobic polymer/fatty acid blend comprises a hydrophobic polymer and a fatty acid in a ratio from about 1:1 to about 1:20. Another example provides the particulate plug wherein the blend is prepared by the process of the hydrophobic polymer and the fatty are combined in a vessel suitable for chemical reaction; heated to above the melting point of each component forming a homogenous composition; and poured into cool water.

[0017] One example provides a particulate plug for removing a preservative from a solution, suspension, or emulsion comprising a drug, the particulate plug comprising microparticles of a fatty acid, wherein the microparticles form a particulate plug capable of being fitted an outlet of a container for the solution, emulsion, or suspension, wherein the particulate plug rapidly and

selectively removes a preservative from the solution, emulsion, or suspension. Another example provides the particulate plug wherein the fatty acid is stearic acid.

[0018] One example provides a particulate plug for removing a preservative from a solution, suspension, or emulsion comprising a drug, the particulate plug consisting essentially of microparticles of a fatty acid, wherein the microparticles form a particulate plug capable of being fitted an outlet of a container for the solution, emulsion, or suspension, wherein the particulate plug rapidly and selectively removes a preservative from the solution, emulsion, or suspension. Another example provides the particulate plug wherein the fatty acid is stearic acid.

INCORPORATION BY REFERENCE

[0019] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

DETAILED DESCRIPTION

[0020] The present disclosure provides a preservative removal agent. A preservative removal agent may rapidly and selectively remove preservatives of the present disclosure from a solution, emulsion, or suspension comprising a therapeutic agent. The preservative removal agent may rapidly and selectively extract the preservative, allowing the eye drop formulation to flow through the plug with minimal pressure drop, yet with sufficient time to remove the preservative and with sufficient surface area to adsorb the preservative. The matrix may comprise a material with a high affinity for the preservative, such as for example benzalkonium chloride (BAK), and low affinity for a therapeutic agent, such as a drug or other ophthalmological agent.

[0021] In 2009, the European Medicines Agency's Committee for Medicinal Products for Human Use concluded that unpreserved formulations "are needed for patients with lower tolerance to preservatives," and "for long-term treatment, formulations without preservatives are valuable alternatives." Considering the adverse effects of preservatives, the development of safe eye drop dispensing devices to deliver preservative-free formulations has been pursued for more than a decade. Preservative-free formulations are available in single-dose containers to eliminate the need for preservatives; however, these are not convenient and too expensive for wide public use.