[0004] 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.

[0005] US Patent No. 5,080,800 teaches a process for removing components from solutions, including preservatives from eye-drops. The process involves the use of ion exchange resins to selectively remove ocular preservatives. Ion exchange resins have not been tested extensively for biocompatibility and cytotoxicity, and inherently are non-selective for molecules of same charge, adsorb ionic drugs as readily as any ionic preservative such as BAK. The hydraulic permeability of these resins is not addressed although this characteristic is critical for devices that allow formation of drops without excessive pressure. US Patent No. 5,080,800 does not teach on the importance of ensuring that the filters are designed to resist growth of microorganisms that may remain trapped. US Patent No. 5,080,800 does not teach on the necessary requirements to ensure that the concentration of the active drug in the drops coming out of the device do not fall below the minimum requirements based. Hence a practical way of retaining the beneficial behavior of preservatives while avoiding their toxic effects in the eye remains a need.

SUMMARY

[0005a] 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 polymer comprising oxidized polyolefin (OxPO) wherein the microparticles are irregular-shaped rigid aggregates and form a particulate plug having a hydraulic permeability greater than 0.01 Darcy and fits an outlet of a container for the solution, emulsion, or suspension, wherein the microparticles of OxPO further comprises absorbed portions of a preservative to be removed and/or a drug for delivery in the solution, emulsion or suspension, wherein the particulate plug has a partition coefficient for the preservative that is greater than a partition coefficient for the drug.

[0005b] In another aspect of the present disclosure, there is provided a method of removing a preservative from a drug solution, suspension, or emulsion, comprising:

providing a container having an extended outlet and a chamber for holding the drug solution, suspension, or emulsion comprising at least one drug and a preservative; the container comprising a particulate plug disclosed herein within the extended outlet; and

forcing the drug solution, suspension, or emulsion through the particulate plug.

[0005c] In a further aspect of the present disclosure, there is provided a device for delivery of a pharmaceutical formulation, the device comprising the particulate plug disclosed herein and a pharmaceutical formulation comprising one or more active therapeutic components and a preservative, wherein when the pharmaceutical formulation is forced through the particulate plug at least 90% of the preservative is removed, while at least 90% of the one or more active components are retained in the delivered pharmaceutical formulation.

[0005d] In another aspect of the present disclosure, there is provided a preservative removing device, comprising

microparticles of oxidized high density polyethylene (OxHDPE), wherein the microparticles are irregular-shaped rigid aggregates,

wherein the microparticles form a particulate plug having a hydraulic permeability greater than 0.01 Darcy,

wherein the plug fits an outlet of a container for a solution, emulsion, or suspension,

wherein the OxHDPE further comprises absorbed portions of a preservative to be removed and a therapeutic agent for delivery, wherein the particulate plug has a partition coefficient for the preservative that is greater than a partition coefficient for the drug.

[0005e] In a further aspect of the present disclosure, there is provided a preservative removing device, comprising

microparticles of oxidized polyolefin (OxPO), wherein the microparticles are irregular-shaped rigid aggregates

wherein the microparticles form a particulate plug having a hydraulic permeability greater than 0.01 Darcy,

wherein the plug fits an outlet of a container for a solution, emulsion, or suspension,

wherein the microparticles of OxPO optionally comprises absorbed portions of a preservative to be removed and a therapeutic agent for delivery, wherein the particulate plug has a partition coefficient for the preservative that is greater than a partition coefficient for the drug.

[0005f] In another aspect of the present disclosure, there is provided a method of removing a preservative from a drug solution, suspension, or emulsion, using a preservative removing device disclosed herein, comprising:

providing a container having an extended outlet and a chamber for holding the drug solution, suspension, or emulsion, the drug solution, suspension, or emulsion comprising at least one drug and a preservative; wherein the container comprises a particulate plug for removing the preservative from the solution, suspension, or emulsion, the particulate plug within the extended outlet; and

forcing the drug solution, suspension, or emulsion through the particulate plug.

[0005g] In a further aspect of the present disclosure, there is provided a device for delivery of a pharmaceutical formulation, comprising the particulate plug disclosed herein and a pharmaceutical formulation comprising one or more active components and a preservative, wherein when the pharmaceutical formulation is forced through the particulate plug at least 90% of the preservative is selectively removed while at least 90% of all active components are retained in the delivered pharmaceutical formulation.

[0005h] In another aspect of the present disclosure, there is provided a device for removing a preservative from an ophthalmic formulation, the device comprising:

a polymeric matrix disposed within an outlet of a reservoir, the reservoir comprising a solution, emulsion, or suspension disposed within the reservoir, wherein the solution, emulsion, or suspension comprises the preservative to be removed and an ophthalmic agent;

wherein the polymeric matrix comprises a wax which is permeable to the solution, emulsion, or suspension, wherein the polymeric matrix comprises microparticles of oxidized high density polyethylene (OxHDPE), wherein the polymeric matrix has a partition coefficient for the preservative that is greater than a partition coefficient the ophthalmic agent, and wherein a time scale for removal of the preservative is shorter than a timescale for flow of the solution, emulsion, or suspension through the polymeric matrix to an exterior of the reservoir.

[0005i] In a further aspect of the present disclosure, there is provided a device for removing a preservative from an ophthalmic formulation, the device comprising:

a reservoir comprising solution, emulsion, or suspension disposed therein, the solution, emulsion, or suspension comprising the preservative to be removed and an ophthalmic agent;

a polymeric matrix disposed within an outlet of a reservoir, wherein the polymeric matrix comprises a wax which is permeable to the solution, emulsion, or suspension, wherein the polymeric matrix comprises microparticles of oxidized polyolefin (OxPO); wherein the polymeric matrix absorbs greater than 50% of the preservative for a 200 microliter volume of the solution, emulsion, or suspension passed through the polymeric matrix.

[0006] ~~Embodiment~~Examples of the disclosure are directed to particulate plugs 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. By combining one or more different monomers into the formulation for making the particles, the material may selectively remove a preservative while minimizing binding of the drug.

[0007] ~~Embodiment~~Examples of the disclosure are directed to particulate plugs for removing a preservative from a drug solution where microparticles comprising the plug are oxidized polyolefins (OxPO). In some ~~embodiment~~examples the OxPO is an oxidized polyethylene. In some ~~embodiment~~examples the OxPO is an oxidized high density polyethylene (OxHDPE). The microparticles can be round, ovoid, smooth

surfaced or irregular-shaped rigid aggregates that form a particulate plug having a hydraulic permeability greater than 0.01 Da and where the plug fits an outlet of a container for a solution, emulsion, or suspension. In some ~~embodiment~~example~~s~~, the OxPO-comprising plugs further comprise absorbed portions of a preservative to be removed and/or a drug for delivery in solution, wherein the particulate plug rapidly and selectively removes a preservative from the solution, emulsion, or suspension.

[0008] The drug can be a hydrophilic drug, for example, Timolol Maleate, Levofloxacin, Dorzolamide, Brimonidine Tartrate, or and/or hydrophobic drugs, for example, latanoprost or bimatoprost, and/or a combination of hydrophilic drugs, for example, brimonidine and timolol (aka Combigan). The preservative may be Benzalkonium chloride (BAK).

[0009] Another ~~embodiment~~example of the disclosure is directed to a method of removing a preservative from a drug solution, where a container has an extended outlet and a chamber for holding a drug solution comprising at least one drug and a preservative where the extended outlet is packed with a particulate plug and the drug solution is forced through the particulate plug. The particulate plug can be preloaded with the drug or with the preservative.

[0010] In an ~~aspect~~example, the present disclosure provides a particulate plug for removing a preservative from a solution comprising a drug. The plug may comprise microparticles of OxPO, wherein the microparticles are of any shape and form a particulate plug having a hydraulic permeability greater than 0.01 Da and fits an outlet of a container for a solution, emulsion, or suspension, wherein the OxPO optionally further comprises absorbed portions of a preservative to be removed and/or a drug for delivery in solution, wherein the particulate plug rapidly and selectively removes a preservative from the solution, emulsion, or suspension.

[0011] In another ~~aspect~~example, the present disclosure provides a method of removing a preservative from a drug solution, suspension, or emulsion. The method may comprise providing a container having an extended outlet and a chamber for holding the drug solution, suspension, or emulsion comprising at least one drug and a preservative; the container comprising a particulate plug comprising OxPO within the extended outlet; and forcing the drug solution, suspension, or emulsion through the particulate plug.

[0012] In some ~~embodiment~~example~~s~~, the method further comprises preloading the particulate plug with the drug and/or with the preservative. In some ~~embodiment~~example~~s~~, the drug comprises Timolol Maleate, Levofloxacin, Dorzolamide, Brimonidine Tartrate, or a combination thereof, such as brimonidine and timolol (aka Combigan). In some ~~embodiment~~example~~s~~, the preservative is Benzalkonium chloride (BAK). In some ~~embodiment~~example~~s~~, the plug comprises OxPO. In some ~~embodiment~~example~~s~~, the plug comprises an OxPO selected from an OxHDPE.

[0013] In another ~~aspect~~example, the present disclosure provides a device for delivery of a pharmaceutical formulation, the device comprising the particulate plug any ~~embodiment~~example and a pharmaceutical formulation comprising one or more active components and a preservative, wherein when the pharmaceutical formulation is forced through the particulate plug at least 90% of the preservative is selectively removed, while at least 90% of the one or more active components are retained in the delivered pharmaceutical formulation.

[0014] In some ~~embodiment~~examples, the device is an eye drop bottle for dispensing drops of the pharmaceutical formulation and wherein the concentration of the one or more active components in a dispensed drop is at least 90% of that of the formulation inside the eye drop bottle, for every drop of the formulation forced through the plug. In some ~~embodiment~~examples, the particulate plug comprises a packed bed of particles. In some ~~embodiment~~examples, the device has a holder assembly to retain the particulate plug while forcing the formulation through the plug. In some ~~embodiment~~examples, the particulate plug comprises a formulation entry face and a formulation exit face, and the holder assembly comprises filters on the solutions entry and exit faces of the particulate plug. In some ~~embodiment~~examples, the holder assembly comprises a solution permeable bag around the particulate plug. In some ~~embodiment~~examples, the particulate plug is sintered to fuse the particulate plug as a porous monolith. In some ~~embodiment~~examples, the particulate plug has a partition coefficient for the preservative that is at least 100 and a partition coefficient for each active component that is less than 1. In some ~~embodiment~~examples, the particulate plug is pre-equilibrated with the drug. In some ~~embodiment~~examples, the device further comprises packaging that holds the device in a position for forcing the formulation through the particulate plug from manufacture until the device is received by a patient for use.

[0015] In another ~~aspect~~example, the present disclosure provides a preservative removing device. The preservative removing device may comprise microparticles of OxPO, wherein the microparticles are of any shape, wherein the microparticles form a particulate plug having a hydraulic permeability greater than 0.01 Da, wherein the plug fits an outlet of a container for a solution, emulsion, or suspension, wherein the OxPO further comprises absorbed portions of a preservative to be removed and a therapeutic agent for delivery, wherein the particulate plug rapidly and selectively removes a preservative from the solution, emulsion, or suspension.

[0016] In another ~~aspect~~example, the present disclosure provides a method of removing a preservative from a drug solution, suspension, or emulsion, according to any ~~embodiment~~example. The method may comprise providing a container having an extended outlet and a chamber for holding the drug solution, suspension, or emulsion, the drug solution, suspension, or emulsion comprising at least one drug and a preservative; wherein the container comprises a particulate plug for removing the preservative from the solution, suspension, or emulsion, the particulate plug within the extended

outlet; and forcing the drug solution, suspension, or emulsion through the particulate plug. In some ~~embodiment~~examples, the method further comprises preloading the particulate plug with the drug or with the preservative.

[0017] In another ~~aspect~~example, the present disclosure provides a device for delivery of a pharmaceutical formulation, comprising the particulate plug of any ~~embodiment~~example and a pharmaceutical formulation comprising one or more active components and a preservative, wherein when the pharmaceutical formulation is forced through the particulate plug at least 90% of the preservative is selectively removed while at least 90% of all active components are retained in the delivered pharmaceutical formulation.

[0018] In some ~~embodiment~~examples, the device is an eye drop bottle for dispensing drops of the pharmaceutical formulation and wherein the concentration of the active components in a dispensed drop is at least 90% of that of the formulation inside the eye drop bottle for every drop of the solution forced through the plug. In some ~~embodiment~~examples, the device has a holder assembly to retain the particulate plug while forcing the solution through the particulate plug. In some ~~embodiment~~examples, the particulate plug comprises a formulation entry face and a formulation exit face, and the holder assembly comprises filters on the entry and exit faces of the particulate plug. In some ~~embodiment~~examples, the device further comprises packaging that holds the device in a position for forcing the solution, suspension, or emulsion through the particulate plug from manufacture until the device is received by a patient for use.

[0019] Additional ~~aspect~~examples and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative ~~embodiment~~examples of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different ~~embodiment~~examples, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0020] 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.

CLAIMS

WHAT IS CLAIMED IS:

1. A particulate plug for removing a preservative from a solution, suspension, or emulsion comprising a drug, the particulate plug comprising microparticles of a polymer comprising oxidized polyolefin (OxPO) wherein the microparticles are irregular-shaped rigid aggregates and form a particulate plug having a hydraulic permeability greater than 0.01 Darcy~~Da~~ and fits an outlet of a container for the solution, emulsion, or suspension, wherein the microparticles of OxPO further comprises absorbed portions of a preservative to be removed and/or a drug for delivery in the solution, emulsion or suspension, wherein the particulate plug has a partition coefficient for the preservative that is greater than a partition coefficient for the drug~~rapidly and selectively removes a preservative from the solution, emulsion, or suspension~~.

2. The particulate plug of claim 1, wherein the oxidized polyolefin (OxPO) is selected from a homopolymer or copolymer of ethylene, propylene, 1-butene, 4-methyl-1-pentene, 3-methyl-1-butene, 4,4-dimethyl-1-pentene, 3-methyl-1-pentene, 4-methyl-1-hexene, 5-ethyl-1-hexene, 6-methyl-1-heptene, 1-hexene, 1-heptene, 1-octene, 1-nonene, or 1-decene.

3. The particulate plug of claim 1, wherein the oxidized polyolefin (OxPO) is selected from a homopolymer or copolymer of ethylene.

4. The particulate plug of claim 3, wherein the oxidized polyolefin (OxPO) is an oxidized high density polyethylene (OxHDPE).

5. The particulate plug of claim 1, wherein the oxidized polyolefin (OxPO) is selected from a polymer formed by the Fischer-Tropsch process.

6. The particulate plug of claim 1, wherein the drug is selected from timolol maleate, levofloxacin, dorzolamide, brimonidine tartrate, or a combination thereof.

7. The particulate plug of claim 1, wherein the preservative comprises benzalkonium chloride (BAK).

8. A method of removing a preservative from a drug solution, suspension, or emulsion, comprising:

providing a container having an extended outlet and a chamber for holding the drug solution, suspension, or emulsion comprising at least one drug and a preservative; the container comprising a particulate plug according to claim 1 within the extended outlet; and

forcing the drug solution, suspension, or emulsion through the particulate plug.

9. The method according to claim 8, further comprising:

preloading the particulate plug with the drug and/or with the preservative.

10. The method according to claim 8, wherein the drug comprises timolol maleate, levofloxacin, dorzolamide, brimonidine tartrate, or a combination thereof.

11. The method according to claim 8, wherein the preservative is benzalkonium chloride (BAK).

12. A device for delivery of a pharmaceutical formulation, the device comprising the particulate plug of claim 1 and a pharmaceutical formulation comprising one or more active therapeutic components and a preservative, wherein when the pharmaceutical formulation is forced through the particulate plug at least 90% of the preservative is ~~selectively~~ removed, while at least 90% of the one or more active components are retained in the delivered pharmaceutical formulation.

13. The device of claim 12, wherein the device is an eye drop bottle for dispensing drops of the pharmaceutical formulation and wherein the concentration of the one or more active components in a dispensed drop is at least 90% of that of the formulation inside the eye drop bottle, for every drop of the formulation forced through the plug.

14. The device of claim 12, wherein the particulate plug comprises a packed bed of particles.

15. The device of claim 12, wherein the device has a holder assembly to retain the particulate plug while forcing the formulation through the plug.

16. The device of claim 15, wherein the particulate plug comprises a formulation entry face and a formulation exit face, and the holder assembly comprises filters on the solutions entry and exit faces of the particulate plug.

17. The device of claim 15, wherein the holder assembly comprises a solution permeable bag around the particulate plug.

18. The device of claim 12, wherein the particulate plug is sintered to fuse the particulate plug as a porous monolith.

19. The device of claim 12, wherein the particulate plug has a partition coefficient for the preservative that is at least 100 and a partition coefficient for each active component that is less than 1.

20. The device of claim 12, wherein the particulate plug is pre-equilibrated with the drug.

21. The device of claim 12, wherein the device further comprises packaging that holds the device in a position for forcing the formulation through the particulate plug from manufacture until the device is received by a patient for use.

22. A preservative removing device, comprising

microparticles of oxidized high density polyethylene (OxHDPE), wherein the microparticles are irregular-shaped rigid aggregates,

wherein the microparticles form a particulate plug having a hydraulic permeability greater than 0.01 Darcy,~~Da~~

wherein the plug fits an outlet of a container for a solution, emulsion, or suspension,

wherein the OxHDPE further comprises absorbed portions of a preservative to be removed and a therapeutic agent for delivery, wherein the particulate plug has a partition coefficient for the preservative that is greater than a partition coefficient for the drug~~rapidly and selectively removes a preservative from the solution, emulsion, or suspension~~.

23. A preservative removing device, comprising

microparticles of oxidized polyolefin (OxPO), wherein the microparticles are irregular-shaped rigid aggregates

wherein the microparticles form a particulate plug having a hydraulic permeability greater than 0.01 Darcy,~~Da~~

wherein the plug fits an outlet of a container for a solution, emulsion, or suspension,

wherein the microparticles of OxPO optionally comprises absorbed portions of a preservative to be removed and a therapeutic agent for delivery, wherein the particulate plug has a partition coefficient for the preservative that is greater than a partition coefficient for the drug~~rapidly and selectively removes the preservative from the solution, emulsion, or suspension~~.

24. The particulate plug of claim 23, wherein the oxidized polyolefin (OxPO) is selected from a homopolymer or copolymer of ethylene, propylene, 1-butene, 4-methyl-1-pentene, 3-methyl-1-butene, 4,4-dimethyl-1-pentene, 3-methyl-1-pentene, 4-methyl-1-hexene, 5-ethyl-1-hexene, 6-methyl-1-heptene, 1-hexene, 1-heptene, 1-octene, 1-nonene, or 1-decene.

25. The particulate plug of claim 23, wherein the oxidized polyolefin (OxPO) is selected from a homopolymer or copolymer of ethylene.

26. The particulate plug of claim 25, wherein the oxidized polyolefin (OxPO) is an oxidized high density polyethylene (OxHDPE).

27. The particulate plug of claim 23, wherein the oxidized polyolefin (OxPO) is selected from a polymer formed by the Fischer-Tropsch process.

28. The preservative removing device of claim 22, wherein the irregular-shaped rigid aggregates are rough edged particles and the rough edged particles comprise a diameter less than 250 microns.

29. The preservative removing device of claim 28, wherein the rough edged particles comprise a diameter less than 150 microns.

30. The preservative removing device of any one of claims 22 to 29, wherein the preservative comprises benzalkonium chloride.

31. The preservative removing device of any one of claims 22 to 30, wherein the preservative is SofZia or Purite.

32. The preservative removing device of any one of claims 22 to 31, wherein the therapeutic agent comprises at least one of timolol maleate, levofloxacin, dorzolamide, brimonidine tartrate, bimatoprost, tetrahydrozoline, or olopatadine.

33. The preservative removing device of claim 31, wherein the therapeutic agent comprises timolol maleate and brimonidine tartrate.

34. The preservative removing device of claim 31, wherein the therapeutic agent comprises timolol maleate.

35. A method of removing a preservative from a drug solution, suspension, or emulsion, using a preservative removing device according to any one of claims 22 to 34, comprising:

providing a container having an extended outlet and a chamber for holding the drug solution, suspension, or emulsion, the drug solution, suspension, or emulsion comprising at least one drug and a preservative; wherein the container comprises a particulate plug for removing the preservative from the solution, suspension, or emulsion, the particulate plug within the extended outlet; and

forcing the drug solution, suspension, or emulsion through the particulate plug.

36. The method according to claim 35, further comprising:

preloading the particulate plug with the drug or with the preservative.

37. A device for delivery of a pharmaceutical formulation, comprising the particulate plug of any one of claims 22-36 and a pharmaceutical formulation comprising one or more active components and a preservative, wherein when the pharmaceutical formulation is forced through the particulate plug at least 90% of the preservative is selectively removed while at least 90% of all active components are retained in the delivered pharmaceutical formulation.

38. The device of claim 37, wherein the device is an eye drop bottle for dispensing drops of the pharmaceutical formulation and wherein the concentration of the active components in a dispensed drop is at least 90% of that of the formulation inside the eye drop bottle for every drop of the solution forced through the plug.

39. The device of claim 37 or 38, wherein the device has a holder assembly to retain the particulate plug while forcing the solution through the particulate plug.

40. The device of any one of claims 37 to 39, wherein the particulate plug comprises a formulation entry face and a formulation exit face, and the holder assembly comprises filters on the entry and exit faces of the particulate plug.

41. The device of any one of claims 37 to 40, wherein the device further comprises packaging that holds the device in a position for forcing the solution, suspension, or emulsion through the particulate plug from manufacture until the device is received by a patient for use.

42. A device for removing a preservative from an ophthalmic formulation, the device comprising:

a polymeric matrix disposed within an outlet of a reservoir, the reservoir comprising a solution, emulsion, or suspension disposed within the reservoir, wherein the solution, emulsion, or suspension comprises the preservative to be removed and an ophthalmic agent;

wherein the polymeric matrix comprises a wax which is permeable to the solution, emulsion, or suspension, wherein the polymeric matrix comprises microparticles of oxidized high density polyethylene (OxHDPE), wherein the polymeric matrix has a partition coefficient for the preservative that is greater than a partition coefficient the ophthalmic agent, and wherein ~~the~~ a time scale for removal of the preservative is shorter than a timescale for flow of the solution, emulsion, or suspension through the polymeric matrix to an exterior of the reservoir.

43. The device of claim 42, wherein the OxHDPE comprises an acid value of about 30 mgKOH/g as measured by DIN EN ISO 2114.

44. The device of claim 42, wherein the OxHDPE comprises a drop point between 125 and 135 Celsius as measured by DGF M-III 3.

45. The device of claim 42, wherein the OxHDPE comprises a density of about 0.98 grams per cubic centimeter as measured by DIN 51579.

46. The device of claim 42, wherein the OxHDPE comprises a viscosity of 4.00 mPas at 190 Celsius as measured by DIN EN ISO3104.

47. The device of claim 42, wherein the OxHDPE comprise particles sized between 125 and 250 microns.

48. The device of claim 42, wherein the polymeric matrix is a homopolymer of OxHDPE.

49. The device of claim 42, wherein the preservative comprises benzalkonium chloride.

50. The device of claim 42, wherein the preservative is SofZia or Purite.

51. The device of claim 42, wherein the ophthalmic~~therapeutic~~ agent comprises at least one of timolol maleate, levofloxacin, dorzolamide, brimonidine tartrate, bimatoprost, tetrahydrozoline, or olopatadine.

52. The device of claim 42, wherein the ophthalmic~~therapeutic~~ agent comprises timolol maleate and brimonidine tartrate.

53. The device of claim 42, wherein the ophthalmic~~therapeutic~~ agent comprises timolol maleate.

54. A device for removing a preservative from an ophthalmic formulation, the device comprising:

a reservoir comprising solution, emulsion, or suspension disposed therein, the solution, emulsion, or suspension comprising the preservative to be removed and an ophthalmic agent;

a polymeric matrix disposed within an outlet of a reservoir, wherein the polymeric matrix comprises a wax which is permeable to the solution, emulsion, or suspension, wherein the polymeric matrix comprises microparticles of oxidized polyolefin (OxPO); wherein the polymeric matrix absorbs greater than 50% of the preservative for a 200 microliter volume of the solution, emulsion, or suspension passed through the polymeric matrix.

55. The particulate plug of claim 54, wherein the oxidized polyolefin (OxPO) is selected from a homopolymer or copolymer of ethylene, propylene, 1-butene, 4-methyl-1-pentene, 3-methyl-1-butene, 4,4-dimethyl-1-pentene, 3-methyl-1-pentene, 4-methyl-1-hexene, 5-ethyl-1-hexene, 6-methyl-1-heptene, 1-hexene, 1-heptene, 1-octene, 1-nonene, or 1-decene.

56. The particulate plug of claim 54, wherein the oxidized polyolefin (OxPO) is selected from a homopolymer or copolymer of ethylene.

57. The particulate plug of claim 56, wherein the oxidized polyolefin (OxPO) is an oxidized high density polyethylene (OxHDPE).

58. The particulate plug of claim 23, wherein the oxidized polyolefin (OxPO) is selected from a polymer formed by the Fischer-Tropsch process.

59. The device of claim 54, wherein the reservoir is coupled to a nozzle for delivery of the ophthalmic formulation.

60. The device of claim 59, wherein the reservoir is compressible and wherein compression of the reservoir forms a drop at an outlet of the nozzle.

61. The device of claim 60, wherein the drop comprises a volume of about 200 microliters and wherein the drop is formed within about 2 seconds.

62. The device of claim 54, wherein the OxPO comprises an acid value of about 30 mgKOH/g as measured by DIN EN ISO 2114.

63. The device of claim 54, wherein the OxPO comprises a drop point between 125 and 135 Celsius as measured by DGF M-III 3.

64. The device of claim 54, wherein the OxPO comprises a density of about 0.98 grams per cubic centimeter as measured by DIN 51579.

65. The device of claim 54, wherein the OxPO comprises a viscosity of 4.00 mPas at 190 Celsius as measured by DIN EN ISO3104.

66. The device of claim 54, wherein the OxPO comprise particles sized between 125 and 250 microns.

67. The device of claim 54, wherein the polymeric matrix is a homopolymer of OxHDPE.

68. The device of claim 54, wherein the preservative comprises benzalkonium chloride.

69. The device of claim 54, wherein the preservative is SofZia or Purite.

70. The device of claim 54, wherein the ophthalmic~~therapeutic~~ agent comprises at least one of timolol maleate, levofloxacin, dorzolamide, brimonidine tartrate, bimatoprost, tetrahydrozoline, or olopatadine.

71. The device of claim 54, wherein the ophthalmic~~therapeutic~~ agent comprises timolol maleate and brimonidine tartrate.

72. The device of claim 54, wherein the ophthalmic~~therapeutic~~ agent comprises timolol maleate.

73. The device of claim 57, wherein the OxHDPE comprises an acid value of about 30 mgKOH/g as measured by DIN EN ISO 2114.

74. The device of claim 57, wherein the OxHDPE comprises a drop point between 125 and 135 Celsius as measured by DGF M-III 3.

75. The device of claim 57, wherein the OxHDPE comprises a density of about 0.98 grams per cubic centimeter as measured by DIN 51579.

76. The device of claim 57, wherein the OxHDPE comprises a viscosity of 4.00 mPas at 190 Celsius as measured by DIN EN ISO3104.

77. The device of claim 57, wherein the OxHDPE comprise particles sized between 125 and 250 microns.