

CLAIMS

WHAT IS CLAIMED IS:

1. A nozzle for removing a preservative from a fluid comprising a therapeutic agent to treat an eye, the nozzle comprising:
 - a fluid inlet configured to receive fluid from a container;
 - a fluid outlet coupled to the inlet, the outlet configured to deliver the fluid comprising the therapeutic agent to the eye;
 - a distance extending along an axis from the fluid inlet to the fluid outlet;
 - a fluid flow path extending from the fluid inlet to the fluid outlet, a porous material along the flow path to selectively remove the preservative; and
 - a flow diverter to divert regions of the fluid flow path in a plurality of different directions, a total distance along the fluid flow path through the porous material from the inlet to the outlet greater than the distance from the fluid inlet to the fluid outlet along the axis.
2. The nozzle of claim 1, wherein the flow diverter comprises a plurality of elongate structures to divert the fluid in the plurality of different directions and optionally wherein each of the plurality of flow diverters comprises a resistance to flow greater than the porous material located along the flow path
3. The nozzle of claim 2, wherein said each of the plurality of elongate structures comprises a length oriented in a direction corresponding to at least one of the plurality of directions, a width oriented transversely to said length and at least one of the plurality of directions, and a thickness oriented transversely to said length and said width and optionally wherein said length, width and thickness are oriented perpendicularly to each other and optionally wherein said length of said each of the plurality of elongate structures extends a distance of within a range from about 0.5 mm to about 10 mm.
4. The nozzle of claim 1, wherein the flow path comprises a circumferential distance about an axis extending between the fluid inlet and the fluid outlet, the nozzle comprising an outer circumference along an outer surface of the nozzle, the circumferential distance corresponding to at least half of the circumference of the nozzle.
5. The nozzle of claim 1, wherein the flow path substantially reverses direction at least once and optionally wherein the flow path substantially reverses direction at least twice.
6. The nozzle of claim 1, wherein the flow diverter increases the flow path by a factor of at least 1.5 compared to the distance from the fluid inlet to the outlet and optionally wherein the flow diverter increases the flow path by a factor of at least 2.0 and optionally wherein the flow diverter increases the flow path by a factor of at least 2.5 and optionally

wherein the flow diverter increases the flow path by a factor of at least 3.0 and optionally wherein the flow diverter increases the flow path by a factor of at least 5.0 and optionally wherein the factor is within a range from 2.0 to 10, 2.5 to 9, 3 to 8, or 5 to 7 and optionally wherein said factor comprises a multiplicative factor.

7. The nozzle of claim 6, wherein the porous material comprises a tortuosity and wherein the tortuosity of the porous material combined with the flow diverter increase the flow path in accordance with a multiplicative factor of a first flow path length corresponding to flow defined by the flow diverter and a second flow path length corresponding to the tortuosity of the porous material.

8. The nozzle of claim 1, wherein the flow path changes from a first direction along a first flow path to a second direction along a second flow path, an angle extending between the first flow path in the first direction and the second flow path in the second direction, the angle comprising at least 90 degrees, and optionally wherein the angle is within a range from 90 to 180 degrees and optionally wherein the flow path substantially reverses direction at least once and optionally wherein the flow path substantially reverses direction at least twice.

9. The nozzle of claim 1, wherein the fluid inlet comprises an inlet aperture, and the fluid outlet comprises an outlet aperture with the fluid path extending therebetween.

10. The nozzle of claim 9, wherein the inlet aperture, the outlet aperture and the plurality of flow diverters are arranged to allow fluid flow through the porous material while retaining the porous material with the flow diverters and optionally wherein the porous material comprises a porous polymer matrix.

11. The nozzle of claim 9, wherein the outlet aperture is configured to allow fluid flow while retaining the porous material.

12. The nozzle of claim 9, wherein the flow diverter extends between a first volume of the porous material and a second volume of the porous material in order to selectively direct flow from the first volume to the second volume.

13. The nozzle of claim 12, wherein the flow diverter comprises at least one interior aperture between the first volume and the second volume.

14. The nozzle of claim 12, wherein the first volume is fluidically coupled to the inlet aperture and the second volume is fluidically coupled to the outlet aperture, the second volume downstream from the first volume.

15. The nozzle of claim 1, further comprising an insert configured to fit into a commercially available eyedropper nozzle.

16. The nozzle of claim 15, wherein the insert is configured to press fit into the commercially available eyedropper nozzle.
17. The nozzle of claim 15, wherein the insert comprises the flow diverter to separate regions of the flow path, a first cap, and a second cap.
18. The nozzle of claim 17, wherein the first cap comprises an inlet aperture configured to allow fluid flow while retaining the porous material.
19. The nozzle of claim 17, wherein the first cap is operably connected to the fluid inlet.
20. The nozzle of claim 17, wherein the second cap comprises an outlet aperture configured to allow fluid flow while retaining the porous material.
21. The nozzle of claim 17, wherein the second cap is operably connected to the fluid outlet.
22. The nozzle of claim 17, wherein the flow diverter is configured to separate regions of the flow path and comprises at least one flow diverter between a first volume of a porous polymer matrix and a second volume of a porous polymer matrix.
23. The nozzle of claim 22, wherein the flow diverter comprises at least one interior aperture between the first volume and the second volume.
24. The nozzle of claim 22, wherein a first volume is operably connected to the inlet aperture.
25. The nozzle of claim 22, wherein a second volume is operably connected to the outlet aperture.
26. The nozzle of claim 1, wherein the fluid comprises a solution, emulsion, or suspension comprising a preservative and a therapeutic agent.
27. The nozzle of claim 26, wherein the preservative comprises BAK.
28. The nozzle of claim 1, wherein the therapeutic agent comprises timolol, dorzolamide, dexamethasone phosphate, dexamethasone, or latanoprost.
29. The nozzle of claim 1, wherein the fluid is forced through the nozzle via the flow path.
30. The nozzle of claim 29, wherein forcing the fluid through the nozzle removes a preservative from the fluid.
31. The nozzle of claim 30, wherein at least 50 percent of the preservative is removed from the fluid and wherein at least 50 percent of the therapeutic agent is retained.
32. The nozzle of claim 29, wherein a squeeze pressure is exerted by a user to form a drop.

33. The nozzle of claim 32, wherein the squeeze pressure comprises at least 0.01 Atm.
34. The nozzle of claim 32, wherein the squeeze pressure is within a range from 0.01 Atm to 0.5 Atm.
35. The nozzle of claim 32, wherein the container has an internal pressure which increases with increasing squeeze pressure.
36. The nozzle of claim 35, wherein the internal pressure comprises a pressure within a range from 1 Atm to 5 Atm.
37. The nozzle of claim 32, wherein the drop is formed within a time defined by a range between 0.1 seconds and 10 seconds.
38. The nozzle of claim 32, wherein the drop comprises a volume defined by a range between 1 μL and 100 μL .
39. The nozzle of claim 32, wherein the drop comprises a flow rate defined by a range between 1 $\mu\text{L}/\text{min}$ and 1000 $\mu\text{L}/\text{min}$.
40. The nozzle of claim 1, wherein the container is a compressible bottle.
41. The nozzle of claim 1, wherein the nozzle is configured to provide multiple doses of a therapeutic agent.
42. The nozzle of claim 1, wherein the inlet is configured to decrease bacterial growth.
43. The nozzle of claim 1, wherein the porous material comprises a porous hydrophilic polymeric matrix disposed within the nozzle.
44. The nozzle of claim 43, wherein the matrix comprises a hydraulic permeability of at least 0.01 Darcy.
45. The nozzle of claim 43, wherein the matrix comprises a hydraulic permeability of at least 1 Darcy.
46. The nozzle of claim 43, wherein the matrix is configured to remove a preservative from a solution, emulsion, or suspension.
47. The nozzle of claim 43, wherein the matrix comprises a partition coefficient for the preservative from the solution, emulsion, or suspension of at least 100.
48. The nozzle of claim 43, wherein the matrix comprises PHEMA, poly hydroxyl ethyl methacrylate-co-methacrylic acid, or a combination thereof.
49. The nozzle of claim 43, wherein the matrix is preloaded with a preservative.
50. The nozzle of claim 43, wherein the porous polymeric matrix comprises a tortuosity of at least 1.5 to increase the flow path by a multiplicative factor of at least 1.5.

51. The nozzle of claim 43, wherein the porous polymeric matrix comprises a tortuosity of at least 2.0 to increase the flow path by a multiplicative factor of at least 2.0.

52. The nozzle of claim 43, wherein the porous polymeric matrix comprises a tortuosity of at least 2.5 to increase the flow path by a multiplicative factor of at least 2.5.

53. The nozzle of claim 43, wherein the porous polymeric matrix comprises a tortuosity of at least 3.0 to increase the flow path by a multiplicative factor of at least 3.0.

54. A device for compacting a polymer matrix within a nozzle for removing a preservative from a fluid comprising a therapeutic agent to an eye, the compaction device comprising: a handle comprising a proximal end and a distal end, wherein the proximal end is configured to be held by a press, wherein the distal end comprises one or a plurality of protrusions and wherein the protrusions are configured to fit within the nozzle of any one of the preceding claims.

55. A method of removing preservative from a therapeutic agent, the method comprising:

receiving a solution comprising the therapeutic agent and a preservative;

squeezing a compressible bottle comprising a nozzle for removing a preservative from a fluid comprising the therapeutic agent to an eye, wherein the nozzle comprises a fluid inlet, a fluid outlet, and a flow path extending from the fluid inlet to the fluid outlet; and

wherein a flow diverter directs flow of the solution in a plurality of different directions, the flow path greater than the distance from the inlet to the outlet.

56. An apparatus for removing a preservative from a fluid comprising a therapeutic agent to treat an eye, the apparatus comprising:

a fluid inlet configured to receive fluid from a container;

a fluid outlet coupled to the inlet, the outlet configured to deliver the fluid comprising the therapeutic agent to the eye;

a distance extending along an axis from the fluid inlet to the fluid outlet;

a fluid flow path extending from the fluid inlet to the fluid outlet, a porous material along the flow path to selectively remove the preservative; and

a flow diverter to divert regions of the fluid flow path in a plurality of different directions, a total distance along the fluid flow path through the porous material from the inlet to the outlet greater than the distance from the fluid inlet to the fluid outlet along the axis.

57. A preservative filtering device, comprising:

a nozzle of a multi-dose eye drop solution bottle comprising an opening at a first end configured to permit flow of eye drop solution from within the bottle to a subject, and a second end proximate to the eye drop solution contained within the bottle, and wherein the nozzle comprises positioned therein:

- a removal agent comprising a zinc-removal agent or a chlorine-removal agent,
- an inert material, and
- a screen,

wherein the inert material is positioned between the removal agent and the screen, and wherein the removal agent is positioned proximate the opening.

58. The device of claim 57, wherein the zinc-removal agent comprises EDTA.

59. The device of claim 58, wherein the EDTA is coated onto a plurality of polystyrene beads and the plurality of polystyrene beads are positioned within the nozzle.

60. The device of claim 58, wherein the EDTA is in crystalline form.

61. The device of claim 57, wherein the chlorine-removal agent comprises activated charcoal.

62. The device of claim 57, wherein the inert material comprises cellulose.

63. The device of claim 57, wherein the inert material comprises polystyrene beads.

64. The device of claim 57, wherein the removal agent is positioned adjacent the opening.

65. A multi-dose eye drop solution bottle comprising the preservative filtering device of any one of claims 57-65.

66. A device for removing a preservative from a formulation comprising a therapeutic agent, the device comprising:

- a nozzle comprising:

- a fluid outlet;

- an inlet cap comprising one or more apertures, the one or more apertures comprising a fluid inlet, wherein the inlet cap has a hydraulic permeability less than 10 Darcy;
- and

- a matrix disposed within the nozzle, wherein the matrix comprises absorbed particles of the preservative and wherein the hydraulic permeability of the inlet cap is less than a hydraulic permeability of the matrix.

67. The device of claim 66, further comprising an outlet cap comprising one or more apertures, the one or more apertures comprising the fluid outlet, wherein the outlet cap has a hydraulic permeability less than 10 Darcy.

68. The device of claim 67, wherein either of the inlet cap or the outlet cap comprises a screen.

69. The device of claim 67, wherein either of the inlet cap or the outlet cap comprises a mesh.

70. The device of claim 67, wherein either of the inlet cap or the outlet cap comprises a filter, wherein the filter comprise a pore size of about 0.2 microns.

71. The device of claim 67, wherein either of the inlet cap or the outlet cap is prewetted with a preservative.

72. The device of claim 66, wherein the nozzle further comprises a flow diverter to divert regions of the fluid flow path in a plurality of different directions, a total distance along the fluid flow path through the matrix from the fluid inlet to the fluid outlet being longer than a distance along an axis from the fluid inlet to the fluid outlet.

73. The device of claim 66, wherein the hydraulic permeability of the inlet cap is about 0.1 Darcy.

74. The device of claim 67, wherein the hydraulic permeability of the outlet cap is about 0.1 Darcy.

75. The device of claim 67, wherein a pore size of the one or more apertures in the inlet cap or the outlet cap is less than a particle size of the matrix.

76. The device of claim 75, wherein a pore size of the one or more apertures in the inlet cap or the outlet cap is about 0.2 microns.

77. The device of claim 66, wherein a first drop of the formulation from the device and a tenth drop of the formulation from the device comprise equal concentrations of the preservative to within 10%.

78. The device of claim 66, wherein a drop of the formulation from the device dispensed on a first day and a second drop dispensed on a seventh day comprise equal concentrations of the preservative to within 10% at a drop rate of at least one drop per day.

79. The device of claim 66, wherein the formulation is forced through the nozzle from the fluid inlet to the fluid outlet.

80. The device of claim 79, wherein forcing the fluid through the nozzle removes a preservative from the formulation.

81. The device of claim 80, wherein at least 50 percent of the preservative is removed from the fluid and wherein at least 50 percent of the therapeutic agent is retained.

82. The device of claim 80, wherein a squeeze pressure is exerted by a user to form a drop.

83. The device of claim 82, wherein the squeeze pressure comprises at least 0.01 Atm.
84. The device of claim 82, wherein the squeeze pressure is within a range from 0.01 Atm to 0.5 Atm.
85. The device of claim 82, wherein the device further comprises a reservoir containing the formulation and wherein the reservoir has an internal pressure which increases with increasing squeeze pressure.
86. The device of claim 85, wherein the internal pressure comprises a pressure within a range from 1 Atm to 5 Atm.
87. The device of claim 82, wherein the drop is formed within a time defined by a range between 0.1 seconds and 10 seconds.
88. The device of claim 82, wherein the drop comprises a volume defined by a range between 1 μ L and 100 μ L.
89. The device of claim 82, wherein the drop comprises a flow rate defined by a range between 1 μ L/min and 1000 μ L/min.
90. A flow diverter comprising:
a fluid inlet, a fluid outlet, and a flow path connecting the fluid inlet to the fluid outlet;
wherein the flow diverter comprises at least two interior apertures, wherein the interior apertures connect at least three regions of the flow path, and wherein the flow path substantially changes direction at each of the at least two interior apertures;
wherein a matrix is disposed within an interior volume of the flow diverter such that a fluid traversing the flow path flows through the matrix, wherein the fluid comprises a solution, emulsion, or suspension comprising a preservative and a therapeutic agent, wherein the matrix comprises absorbed particles of the preservative from the solution, emulsion or suspension.
91. The flow diverter of claim 90, wherein the flow diverter is a part of a nozzle system for delivery of an ophthalmic agent and wherein the nozzle system comprises a nozzle cap.
92. The flow diverter of claim 91, wherein the flow diverter is removably coupled to an interior of a nozzle of the nozzle system and wherein the flow diverter is secured within the nozzle with a nozzle cap.
93. The flow diverter of claim 91, wherein the flow diverter is coupled to an interior of a nozzle of the nozzle system and wherein the flow diverter is not removable.

94. The flow diverter of claim 91, wherein the flow diverter is coupled to an insert and wherein the insert is removably coupled to the interior of a nozzle of the system.

95. The flow diverter of claim 91, wherein a mesh, a screen, or a filter is disposed between a nozzle cap and a flow diverter.

96. The flow diverter of claim 91, wherein a mesh, a screen, or a filter is disposed between an outlet of the nozzle and the fluid outlet of the flow diverter.

97. The flow diverter of claim 90, wherein the at least three regions of the flow path are separated from one another by one or more barriers, wherein the one or more barriers comprise the interior apertures.

98. The flow diverter of claim 91, wherein the flow path traverses an angular path about an axis of the nozzle.

99. A flow diverter comprising:
a fluid inlet, a fluid outlet, and a flow path connecting the fluid inlet to the fluid outlet;

wherein the flow diverter comprises a coiled barrier, wherein the flow path traverses an angular path about an axis of the flow diverter and around the coiled barrier, wherein one end of the flow path is at the interior of the coil and wherein an opposite end of the flow path is at the exterior of the coil;

wherein a matrix is disposed within an interior volume of the flow diverter such that a fluid traversing the flow path flows through the matrix, wherein the fluid comprises a solution, emulsion, or suspension comprising a preservative and a therapeutic agent, wherein the matrix comprises absorbed particles of the preservative from the solution, emulsion or suspension.

100. The flow diverter of claim 99, wherein the flow diverter is a part of a nozzle system for delivery of an ophthalmic agent and wherein the nozzle system comprises a nozzle cap.

101. The flow diverter of claim 100, wherein the flow diverter is removably coupled to an interior of a nozzle of the nozzle system and wherein the flow diverter is secured within the nozzle with a nozzle cap.

102. The flow diverter of claim 100, wherein the flow diverter is coupled to an interior of a nozzle of the nozzle system and wherein the flow diverter is not removable.

103. The flow diverter of claim 100, wherein the flow diverter is coupled to an insert and wherein the insert is removably coupled to the interior of a nozzle of the system.

104. The flow diverter of claim 100, wherein a mesh, a screen, or a filter is disposed between a nozzle cap and a flow diverter.

105. The flow diverter of claim 100, wherein a mesh, a screen, or a filter is disposed between an outlet of the nozzle and the fluid outlet of the flow diverter.

106. The flow diverter of claim 99, wherein the coiled barrier is supported by spacers, the spacers forming a plurality of interior apertures.

107. The flow diverter of claim 99, wherein the coiled barrier is supported by an interior column.

108. A flow diverter comprising:
a fluid inlet, a fluid outlet, and a flow path connecting the fluid inlet to the fluid outlet;

wherein the flow diverter comprises at least one inner region and at least one outer region, the at least one inner region being within the at least one outer region, and the at least one inner region and the at least one outer region being fluidically connected;

wherein a matrix is disposed within an interior volume of the flow diverter such that a fluid traversing the flow path flows through the matrix, wherein the fluid comprises a solution, emulsion, or suspension comprising a preservative and a therapeutic agent, wherein the matrix comprises absorbed particles of the preservative from the solution, emulsion or suspension.

109. The flow diverter of claim 108, wherein the flow diverter is a part of a nozzle system for delivery of an ophthalmic agent and wherein the nozzle system comprises a nozzle cap.

110. The flow diverter of claim 109, wherein the flow diverter is removably coupled to an interior of a nozzle of the nozzle system and wherein the flow diverter is secured within the nozzle with a nozzle cap.

111. The flow diverter of claim 109, wherein the flow diverter is coupled to an interior of a nozzle of the nozzle system and wherein the flow diverter is not removable.

112. The flow diverter of claim 109, wherein the flow diverter is coupled to an insert and wherein the insert is removably coupled to the interior of a nozzle of the system.

113. The flow diverter of claim 109, wherein a mesh, a screen, or a filter is disposed between a nozzle cap and a flow diverter.

114. The flow diverter of claim 109, wherein a mesh, a screen, or a filter is disposed between an outlet of the nozzle and the fluid outlet of the flow diverter.

115. The flow diverter of claim 108, wherein the at least one inner region and the at least one outer region are fluidically connected by a plurality of interior apertures.

116. The flow diverter of claim 108, wherein the at least one inner region and the at least one outer region are fluidically connected by a plurality of interior apertures.

117. The flow diverter of claim 116, wherein the apertures are circular or annular.

118. The flow diverter of any one of claims 90-117, wherein the preservative comprises BAK.

119. The nozzle of claim 90-117, wherein the therapeutic agent comprises timolol, dorzolamide, dexamethasone phosphate, dexamethasone, or latanoprost.

120. The flow diverter of any one of claims 90-117, wherein the matrix comprises absorbed particles of the preservative from the fluid.

121. The flow diverter of any one of claims 90-117, wherein a flow rate for the fluid through the flow diverter under human applied pressure is within a range between 1 $\mu\text{L}/\text{min}$ and 1000 $\mu\text{L}/\text{min}$.