

CLAIMS

WHAT IS CLAIMED IS:

1. A drug applicator for a system for ultrasound-enhanced delivery of at least one drug to a target site in an intraocular space, the system comprising a signal generating unit operationally connected to an ultrasound transducer,

wherein the drug applicator:

- (a) comprises at least one space holding the drug,
- (b) is made from a low ultrasound attenuation material,
- (c) is configured to provide low ultrasound loss coupling of the system to the

sclera or cornea, and

(d) is configured to be mechanically coupled to the system and further configured to be coupled to the ultrasound transducer with low ultrasound loss; and

wherein the signal generating unit and/or the ultrasound transducer are configured to emit an ultrasound wave form in at least one application cycle, the application cycle comprising at least one ultrasound emitting event with a time duration TA and a waiting period with a time duration TW.

2. A system for ultrasound-enhanced transscleral delivery of at least one drug to a target site in an intraocular space, the system comprising a signal generating unit operationally connected to an ultrasound transducer and a drug applicator,

wherein the drug applicator:

- (a) comprises at least one space hold the drug,
- (b) is made from a low ultrasound attenuation material,
- (c) is configured to provide low ultrasound loss coupling of the system to the

sclera or cornea, and

(d) is configured to be mechanically coupled to the system and further configured to be coupled to the ultrasound transducer with low ultrasound loss; and

wherein the signal generating unit and/or the ultrasound transducer are configured to emit an ultrasound wave form in at least one application cycle, the application cycle comprising at least one ultrasound emitting event with a time duration TA and a waiting period with a time duration TW.

3. The applicator according to claim 1 or the system according to claim 2, wherein the drug applicator is configured to be exchangeable and/or designed for a single use application.

4. The applicator according to claim 1 or 3 or the system according to claim 2 or 3, wherein the drug receiving space is substantially sealed at a surface designated for coupling with the sclera and the seal is configured to allow for drug permeation.

5. The applicator according to claim 1 or 3 or the system according to claim 2 or 3, wherein the drug receiving space is substantially open at a surface designated for coupling with the sclera.

6. The applicator according to any one of claims 1 and 3 to 5 or the system according to any one of claims 2 to 5, wherein the drug applicator is configured to be filled and/or refilled, and wherein the drug applicator receives between 10 μ L and 1 mL of the drug and optionally at least one additional substance.

7. The applicator according to any one of claims 1 and 3 to 6 or the system according to any one of claims 2 to 6, wherein the drug applicator is made from an elastic material having Young's Modulus of less than 10 GPa.

8. The applicator according to any one of claims 1 and 3 to 7 or the system according to any one of claims 2 to 7, wherein the drug applicator is made from at least one of the following materials:

epoxy resin, polyurethane rubber, polycarbonate, nylon 6 – 6, polyvinyl chloride, polyester, ultra-high molecular weight polyethylene, polypropylene, teflon, polystyrene, neoprene rubber, polyvinyl alcohol, polydimethylsiloxane, silicone-containing rubber, silicon hydrogel, silicone rubber, and

silicon rubber doped with at least one of the following materials: nickel, silver, palladium, tungsten, gold, platinum, silicon oxide, titanium oxide, aluminum oxide, barium sulphate, iron oxide, zirconium dioxide, cerium oxide, bismuth oxide, ytterbium oxide, lutetium oxide, hafnium oxide.

9. The applicator according to any one of claims 1 and 3 to 8 or the system according to any one of claims 2 to 8, further comprising a controller, wherein the controller is configured to

control at least one of a plurality of parameters of the application cycle, the plurality parameters of the application cycle are selected from the following:

- (a) the time duration TA of the ultrasound emitting event,
- (b) the time duration TW of the wait period after the ultrasound emitting event,
- (c) the number of application cycles,
- (d) the intensity of the ultrasound emitting event,
- (e) the central frequency of the ultrasound emitting event,
- (f) the mechanical index of the ultrasound emitting system, and
in case of a pulsed ultrasound emitting event:
- (g) the repetition rate of the ultrasound emitting event and
- (h) the duty cycle of the ultrasound emitting event.

10. The applicator according to any one of claims 1 and 3 to 9 or the system according to any one of claims 2 to 9, further comprising an information receiving and/or sending unit,
wherein the information receiving and/or sending unit is configured to receive and/or send an information related to the drug; and

wherein the information receiving and/or sending unit is operationally connected to the signal generating unit and/or the controller, or wherein the information receiving and/or sending unit is operationally connected to the signal generating unit and/or the controller and the controller configured to control at least one of a plurality of parameters of the application cycle based on the information related to the drug; and

preferably the information related to the drug being stored on the drug applicator.

11. The applicator according to any one of claims 1 and 3 to 10 or the system according to any one of claims 2 to 10, wherein,

when the drug comprises molecules with a size of 70 kDa or less, the controller is configured to control the time duration TA to be between 30s and 300 s and the drug applicator is configured such that the drug transit through the sclera during the time duration TA; and/or

when the drug comprises molecules with a size of more than 70 kDa, the controller is configured to control the time duration TW to be between 60s and 600 s and the drug applicator is configured such that the molecules drug transit through the sclera during the time duration TW.

12. The applicator according to any one of claims 1 and 3 to 11 or the system according to any one of claims 2 to 11, wherein the system further comprises display and/or manual input unit

configured to display and/or manually set at least one of the plurality parameters of the application cycle.

13. The applicator according to any one of claims 1 and 3 to 12 or the system according to any one of claims 2 to 12, wherein the system further comprises a temperature sensor configured to sense the temperature of the surface of the sclera or cornea, preferably a thermocouple and/or an infrared thermometer, and

wherein the controller is configured to control the ultrasound emission event such that during the time T_A the temperature of the surface of the sclera or cornea does not increase by more than 1°C .

14. A method for the delivery of a drug to a target site in an intraocular space, wherein the method comprises the steps of:

- (a) providing a drug applicator and/or a system according any one of claims 1 to 13,
- (b) coupling the drug applicator to a surface of the sclera, and
- (c) applying at least one ultrasound application cycle, wherein the application cycle comprises a ultrasound application with a time duration T_A and a waiting period with a time duration T_W .

15. A method for operating the applicator and/or the system according to any one of claims 1 to 13.

16. A device for delivery of at least one drug to a target side in an intraocular space of an eye, wherein the device comprises:

an ultrasound-generating device configured to generate ultrasound that is delivered to a desired site of the eye; and

an interface configured to couple the device, without the use of tools, to a drug applicator comprising the at least one drug, wherein the drug applicator is configured to aid in the delivery of the ultrasound to the desired site of the eye,

wherein the device has a volume of less than 2500 cm^3 .

17. The device of claim 16, wherein the device and drug applicator, when the drug applicator is coupled via the interface, has a volume of less than 3000 cm^3 .

18. The device of claim 16, wherein the device has a volume of less than 1000 cm³.
19. The device of claim 16, wherein the device has a maximum dimension of less than 25 cm.
20. The device of claim 16, wherein the device and drug applicator, when the drug applicator is coupled via the interface, has a maximum dimension of less than 30 cm.
21. The device of claim 16, wherein the device has a maximum dimension of less than 15 cm.
22. The device of claim 16, wherein the device has a weight of less than 9 kg.
23. The device of claim 16, wherein the device and drug applicator have a collective weight of less than 10 kg.
24. The device of claim 16, further comprising a housing that at least partially encloses the ultra-sound generating device.
25. The device of claim 16, further comprising a signal generating unit in communication with the ultrasound-generating unit.
26. The device of claim 25, wherein the signal generating unit comprises a controller configured to control the signal generating unit and an amplifier configured to generate an ultrasound signal.
27. The device of claim 16, wherein the device is a handheld device.
28. The device of claim 16, wherein the device is a wearable device.
29. The device of claim 28, wherein the device is configured to be worn on a user's head at least partially over an eye of the user.
30. The device of claim 16, wherein the ultrasound-generating device is configured to operate at a frequency between 20 kHz and 100 kHz.
31. The device of claim 30, wherein the ultrasound-generating device operates at an excitation voltage of less than 30 V_{RMS}.

32. The device of claim 16, wherein the ultrasound-generating device comprises a flexural transducer.

33. The device of claim 16, wherein the ultrasound-generating device weighs less than 200 g.

34. The device of claim 16, wherein the ultrasound-generating device has a maximum dimension less than 3 cm.

35. The device of claim 16, wherein the interface permits repeatable coupling and decoupling of the drug applicator with the device.

36. The device of claim 16, wherein the drug applicator is configured to hold at least 100 μ l of the at least one drug.

37. The device of claim 16, wherein the device is powered by an on-board power source.

38. The device of claim 37, wherein the power source comprises primary cell batteries.

39. A method for generating instructions for delivery of at least one drug to a target site in an intraocular space of an eye, said method comprising:

obtaining a signal indicative of an identity of the at least one drug to be delivered or an identity of a treatment plan for the eye; and

generating, with aid of one or more processors, instructions for operation of an ultrasound-generating device based on the signal indicative of the identity of the at least one drug to be delivered or the identity of a treatment plan for the eye.

40. The method of claim 39, further comprising applying ultrasound using the ultrasound-generating device in accordance with the instructions to effect delivery of the at least one drug to the target site in the intraocular space of the eye.

41. The method of claim 39, wherein the signal is provided in response to a user input of the identity of the at least one drug or the identity of the treatment plan for the eye.

42. The method of claim 39, wherein the at least one drug is contained in a drug applicator operably coupled to the ultrasound-generating device.

43. The method of claim 42, wherein the drug applicator is removably coupled to the ultrasound-generating device.

44. The method of claim 43, wherein the drug applicator is coupled to the ultrasound-generating device in a removable fashion.

45. The method of claim 42, wherein the signal is provided in response to a label on-board the drug applicator indicative of the at least one drug to be delivered or the identity of the treatment plan for the eye.

46. The method of claim 45, wherein the drug applicator is pre-loaded with the at least one drug.

47. The method of claim 39, wherein the determination of the instructions comprises selecting the instructions from a plurality of instruction options for various drugs or treatment plans.

48. The method of claim 39, wherein the one or more processors are on-board a device comprising the ultrasound-generating device.

49. The method of claim 39, wherein the instructions comprise a frequency of the ultrasound.

50. The method of claim 39, wherein the instructions comprise a mechanical index.

51. The method of claim 39, wherein the instructions comprise a number of cycles and timing of the generation of the ultrasound.

52. The method of claim 39, wherein the generation of ultrasound permits draining of fluid from within the eye to reduce pressure within the eye.

53. The method of claim 52, wherein the draining of fluid occurs concurrently with the delivery of the at least one drug.

54. The method of claim 52, wherein the draining of fluid occurs prior to the delivery of the at least one drug.

55. The method of claim 52, wherein the draining of fluid occurs subsequent to the delivery of the at least one drug.

56. The method of claim 52, wherein the ultrasound operates at a frequency below 1 MHz when draining the fluid from within the eye.

57. The method of claim 52, wherein a temperature of the eye is increased by no more than 2 degree C when draining the fluid from within the eye.

58. The method of claim 52, wherein the draining of fluid occurs during treatment of reducing intraocular pressure.

59. The method of claim 58, wherein the draining of the fluid occurs during treatment of glaucoma.

60. The method of claim 39, wherein the identity of the treatment plan for the eye comprises an identity of a disease being treated.

61. A device for delivery of at least one drug to a target site in an intraocular space of an eye, wherein the device comprises:

an ultrasound-generating device configured to generate ultrasound that is delivered to a desired site of the eye; and

an interface configured to repeatedly couple the device to a drug applicator comprising the at least one drug, wherein the drug applicator is configured to aid in the delivery of the ultrasound to the desired site of the eye,

wherein the interface comprises a coupling medium having a thickness that is a multiple of a propagation speed of the coupling medium over a resonance frequency.

62. The device of claim 61, wherein the coupling is effectuated without the use of a tool.

63. The device of claim 61, wherein the coupling medium has a thickness that is an odd multiple of a propagation speed of the coupling medium over four times a resonance frequency.

64. The device of claim 61, wherein the coupling medium is configured to optimize impedance matching of the ultrasound-generating device and the drug applicator.

65. The device of claim 61, wherein the coupling medium is a solid.

66. The device of claim 61, wherein the coupling medium is a liquid, suspension, or gel.

67. The device of claim 61, wherein the ultrasound-generating device is configured to be at least partially inserted into a drug applicator case.

68. The device of claim 67, wherein the ultrasound-generating device comprises a pin configured to slide through a slot of the case to permit the ultrasound-generating device to lock into the case.

69. The device of claim 61, wherein the drug applicator is configured to be at least partially inserted into an ultrasound-generating device case.

70. The device of claim 61, wherein the interface comprises a first fastener configured to mate with a second fastener on-board the drug applicator.

71. The device of claim 70, wherein the first fastener and the second fastener are configured to be screwed together.

72. The device of claim 70, wherein the first fastener and the second fastener are configured to snap together.

73. The device of claim 61, wherein the interface permits a magnetic connection between the ultrasound-generating device and the drug applicator.

74. The device of claim 61, wherein the drug applicator has an attenuation coefficient of 5 dB/MHz/cm or lower.

75. The device of claim 61, wherein the interface provides a coupling loss of less than 10%.

76. The device of claim 61, wherein the ultrasound-generating device is configured to operate at a frequency between 20 kHz and 100 kHz.

77. The device of claim 76, wherein the ultrasound-generating device operates at an excitation voltage of less than 30 V_{RMS}.

78. The device of claim 61, wherein the ultrasound-generating device comprises a flexural transducer.

79. A device for delivery of at least one drug to a target side in an intraocular space of an eye, wherein the device comprises:

an ultrasound-generating device configured to generate ultrasound that is delivered to a desired site of the eye;

a light source configured to generate light that is delivered to the desired site of the eye; and

an interface configured to couple the device to a drug applicator comprising the at least one drug, wherein the drug applicator is configured to aid in the delivery of the ultrasound to the desired site of the eye and is configured to permit the light from the light source to be delivered to the desired site of the eye.

80. The device of claim 79, wherein the light source is configured to generate UV light.

81. The device of claim 80, wherein the light source is configured to emit light at UV-A wavelengths.

82. The device of claim 79, wherein the light from the light source is configured to cause cross-linking of the at least one drug upon exposure of the at least one drug to the light.

83. The device of claim 82, wherein the at least one drug comprises a light-sensitive molecule.

84. The device of claim 83, wherein the at least one drug comprises riboflavin.

85. The device of claim 79, wherein the ultrasound-generating device and the light source are enclosed within a housing.

86. The device of claim 79, wherein the light source is coupled to the ultrasound-generating device.

87. The device of claim 79, wherein the light source has a fixed position relative to the ultrasound-generating device.

88. The device of claim 79, wherein the ultrasound-generating device comprises an interior space within which the light source resides.

89. The device of claim 88, wherein the ultrasound-generating device has a circular cross-section with a free space in the middle that forms the interior space.

90. The device of claim 88, wherein the interior space further comprises an optical element that modifies light emitted by the light source.

91. The device of claim 79, wherein the ultrasound-generating device comprises an interior space within which a data collection device resides.

92. The device of claim 91, wherein the recording device is a camera or a microphone.

93. The device of claim 79, wherein the ultrasound-generating device weighs less than 200 g.

94. The device of claim 79, wherein the ultrasound-generating device has a maximum dimension of less than 3 cm.

95. The device of claim 79, wherein the light source is configured to direct light through the drug applicator when the drug applicator is coupled to the device.

96. A drug applicator for delivery of at least one drug to a target site in an intraocular space of an eye, wherein the drug applicator comprises:

a first portion formed from an opaque material configured to at least partially define at least one space configured to hold the at least one drug;

a second portion formed from a material that is at least partially transparent to light of selected wavelengths, configured to permit light of the selected wavelengths to pass from one side of the drug applicator to another side of the drug applicator; and

an interface configured to couple the drug applicator to an ultrasound-generating device configured to generate ultrasound that is delivered to a desired site of the eye via the drug applicator.

97. The applicator of claim 96, wherein the ultrasound-generating device is operably coupled to a light source configured to provide the light of selected wavelengths.

98. The applicator of claim 97, wherein the light source is configured to generate UV light.

99. The applicator of claim 97, wherein the light from the light source is configured to cause cross-linking of the at least one drug upon exposure of the at least one drug to the light.

100. The applicator of claim 99, wherein the at least one drug comprises riboflavin.

101. The applicator of claim 97, wherein the ultrasound-generating device and the light source are enclosed within a housing.

102. The applicator of claim 97, wherein the ultrasound-generating device comprises an interior space within which the light source resides.

103. The applicator of claim 96, wherein the at least one space is a single continuous space.

104. The applicator of claim 96, wherein the at least one space comprises multiple discontinuous spaces.

105. The applicator of claim 104, wherein the multiple discontinuous spaces comprises pores.

106. The applicator of claim 96, wherein the first portion comprises an outer surface that is coated with a material that reflects the light of selected wavelengths.

107. The applicator of claim 106, wherein the material is configured to reflect UV light to reduce any UV exposure to an outer environment.

108. The applicator of claim 96, wherein the first portion comprises a target side configured to contact a desired site of the eye.

109. The applicator of claim 108, wherein the target side is formed from a soft biocompatible material.

110. The applicator of claim 108, wherein the target side is configured to deliver reagents that improves delivery of the at least one drug to the target site.

111. The applicator of claim 96, wherein the first portion is formed from an elastic material.

112. The applicator of claim 96, wherein the second portion is transparent to ultraviolet light.

113. The applicator of claim 96, wherein the second portion is surrounded by the first portion.

114. The applicator of claim 96, wherein the drug applicator is configured to be pre-loaded with the at least one drug.

115. The applicator of claim 96, wherein the drug applicator comprises a sealing material configured to prevent contamination.

116. The applicator of claim 96, wherein the drug applicator is configured to receive in situ loading of the at least one drug.

117. A method for delivery of at least one drug to a target site in an intraocular space of an eye, said method comprising:

applying a drug-holding overlay to a surface of the eye comprising the at least one drug, wherein the drug-holding overlay is configured to permit closure of the eye while the drug-holding overlay is applied to the surface;

positioning an ultrasound-generating device to a desired site of the eye; and
generating ultrasound using the ultra-sound generating device and applying the ultrasound to the desired site,

wherein the generation of the ultrasound delivers the at least one drug to the target site in the intraocular space of the eye without damaging tissue of the eye.

118. The method of claim 117, wherein the drug-holding overlay is a contact lens or a film.

119. The method of claim 117, wherein the drug-holding overlay is formed of a porous material.

120. The method of claim 117, wherein the drug-holding overlay is formed of a hydrophilic, hydrophobic, amphiphilic, and sterile material.

121. The method of claim 117, wherein the at least one drug is encapsulated in the drug-holding overlay.

122. The method of claim 117, wherein the at least one drug is adhered on a surface of the drug-holding overlay.

123. The method of claim 117, wherein drug-holding overlay has an attenuation coefficient of 5 dB/MHz/cm or lower.

124. The method of claim 117, wherein the ultrasound-generating device is positioned over an eyelid of the eye.

125. The method of claim 117, wherein the ultrasound-generating device is positioned on a sclera of the eye.

126. The method of claim 117, wherein the ultrasound-generating device is positioned on a cornea of the eye.

127. The method of claim 117, wherein the ultrasound-generating device comes into contact with the drug-holding overlay.

128. The method of claim 117, further comprising a drug applicator that is operably coupled to the ultrasound-generating device.

129. The method of claim 128, wherein the drug applicator is positioned over an eyelid of the eye.

130. The method of claim 128, wherein the drug applicator is positioned over a sclera of the eye.

131. The method of claim 128, wherein the drug applicator is positioned over a cornea of the eye.

132. A device for delivery of at least one drug to a target side in an intraocular space of an eye, said device comprising:

an eyewear frame comprising at least one extension configured to extend behind a wearer's ear when the device is worn by the wearer; and

one or more ultrasound-generating devices supported by the eyewear frame, wherein each ultrasound-generating device is configured to generate ultrasound that is delivered to a desired site of the eye when the device is worn by the wearer,

wherein the generation of the ultrasound delivers the at least one drug to the target site in the intraocular space of the eye without damaging tissue of the eye.

133. The device of claim 132, further comprising a drug applicator supported by the eyewear frame, said drug applicator comprising the at least one drug.

134. The device of claim 133, wherein the drug applicator is operably coupled to the one or more ultrasound-generating devices.

135. The device of claim 133, wherein the drug applicator is located to at least partially cover the eye when the device is worn by the wearer.

136. The device of claim 132, wherein the eyewear frame comprises a glasses frame.

137. The device of claim 132, wherein the eyewear frame forms goggles.

138. The device of claim 132, wherein the eyewear frame forms a helmet comprising a portion that covers at least one eye.

139. The device of claim 132, wherein the ultrasound-generating device is affixed to the eyewear frame.

140. The device of claim 132, wherein the ultrasound-generating device is removable from the eyewear frame.

141. The device of claim 132, wherein the ultrasound-generating device is movable from one portion of the eyewear frame to another portion of the eyewear frame.

142. The device of claim 132, wherein the ultrasound-generating device is located to at least partially cover the eye when the device is worn by the wearer.

143. A method for delivery of at least one drug to a target site in an intraocular space of an eye, said method comprising:

positioning an ultrasound-generating device and a drug applicator relative to a desired site of a sclera of the eye, wherein the drug applicator comprises the at least one drug; and

generating ultrasound using the ultra-sound generating device and applying the ultrasound to the desired site of the sclera at a frequency of about 30 to 60 kHz and a mechanical index of between 0.1 and 0.3,

wherein the generation of the ultrasound delivers the drug to the target site in the intraocular space of the eye at a concentration of at least 1.3 $\mu\text{g/ml}$ at a speed of at least 90 $\mu\text{m}^2/\text{s}$ without damaging tissue of the eye.

144. The method of claim 143, further comprising at least partially enclosing the ultrasound generating device within a housing.

145. The method of claim 144, wherein the housing permits the ultrasound-generating device to be handheld.

146. The method of claim 144, wherein the housing permits the ultrasound-generating device to be worn.

147. The method of claim 143, further comprising providing communications from a signal generating unit to the ultrasound-generating unit.

148. The method of claim 147, wherein the signal generating unit comprises a controller configured to control the signal generating unit and an amplifier configured to generate an ultrasound signal.

149. The method of claim 143, wherein the ultrasound-generating device operates at an excitation voltage of less than 30 V_{RMS} .

150. The method of claim 143, wherein the ultrasound-generating device comprises a flexural transducer.

151. The method of claim 143, wherein the ultrasound-generating device weighs less than 200 g.

152. The method of claim 143, wherein the ultrasound-generating device has a maximum dimension less than 3 cm.

153. The method of claim 143, wherein the drug applicator and the ultrasound-generating device are configured to coupled and decoupled from one another.

154. The method of claim 143, wherein the drug applicator is positioned to contact the eye at the desired site.

155. The method of claim 143, wherein the drug applicator is positioned to contact a different portion of the eye than the desired site.

156. The method of claim 143, wherein the drug applicator is configured to hold at least 100 μl of the at least one drug.

157. The method of claim 143, wherein the drug delivered to the target site comprises molecules of at least 70 kDa.

158. The method of claim 143, wherein the ultrasound is generated for a time duration of less than 300 s.

159. A method for ultrasound-enhanced delivery of at least one drug to a target site in an intraocular space of an eye, said method comprising:

positioning an ultrasound-generating device and a drug applicator relative to a desired site of a sclera of the eye, wherein the drug applicator comprises the at least one drug; and

generating ultrasound using the ultra-sound generating device and applying the ultrasound to the desired site of the sclera with a mechanical index of between 0.1 and 0.3,

wherein the generation of the ultrasound delivers the drug to the target site in the intraocular space of the eye at a concentration of at least 1.3 $\mu\text{g/ml}$ at a speed of at least 90 $\mu\text{m}^2/\text{s}$ without damaging tissue of the eye and without increasing temperature of the tissue by more than 1 degree C.

160. The method of claim 159, further comprising at least partially enclosing the ultrasound generating device within a housing.

161. The method of claim 160, wherein the housing permits the ultrasound-generating device to be handheld.

162. The method of claim 160, wherein the housing permits the ultrasound-generating device to be worn

163. The method of claim 159, further comprising providing communications from a signal generating unit to the ultrasound-generating unit.

164. The method of claim 163, wherein the signal generating unit comprises a controller configured to control the signal generating unit and an amplifier configured to generate an ultrasound signal.

165. The method of claim 159, wherein the ultrasound-generating device operates at an excitation voltage of less than 30 V_{RMS}.

166. The method of claim 159, wherein the ultrasound-generating device comprises a flexural transducer.

167. The method of claim 159, wherein the ultrasound-generating device weighs less than 200 g.

168. The method of claim 159, wherein the ultrasound-generating device has a maximum dimension less than 3 cm.

169. The method of claim 159, wherein the drug applicator and the ultrasound-generating device are configured to coupled and decoupled from one another.

170. The method of claim 159, wherein the drug applicator is positioned to contact the eye at the desired site.

171. The method of claim 159, wherein the drug applicator is positioned to contact a different portion of the eye than the desired site.

172. The method of claim 159, wherein the drug applicator is configured to hold at least 100 µl of the at least one drug.

173. The method of claim 159, wherein the drug delivered to the target site comprises molecules of at least 70 kDa.

174. The method of claim 159, wherein the drug delivered to the target site comprises small molecules below 900 Da.

175. The method of claim 159, wherein the drug delivered to the target site comprises large molecules below 250 kDa.

176. The method of claim 159, wherein the ultrasound is generated for a time duration of less than 300 s.