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(71) Applicant(s)
Alcon Research, Ltd.

(72) Inventor(s)
Tian, Youqin;Weiner, Alan L.;Rodstrom, Theron R.;Bakshi, Shivalik;Marsh, David Allen;Smith II, Larry

(74) Agent / Attorney
Phillips Ormonde Fitzpatrick, 367 Collins Street, Melbourne, VIC, 3000

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(71) Applicant (for all designated States except US): **ALCON RESEARCH, LTD.** [US/US]; 6201 South Freeway, IP Legal TB4-8, Fort Worth, TX 76134-2099 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **RODSTROM, Theron, R.** [US/US]; P. O. Box 212, Cranfills Gap, TX 76637 (US). **SMITH, II, Larry** [US/US]; County Road 302 Box 2119, Glen Rose, TX 76043 (US). **TIAN, Youqin** [US/US]; 5605 Poplar Court, Colleyville, TX 76034 (US). **MARSH, David, Allen** [US/US]; 7856 Skylake Drive, Fort Worth, TX 76179 (US). **WEINER, Alan, L.** [US/US]; 7211 Riverbrook Court, Arlington, TX 76001 (US). **BAKSHI, Shivalik** [CA/US]; 70 S. Huntington Avenue, Apartment 22, Boston, MA 02130 (US).

(74) Agents: **RYAN, Patrick, M.** et al.; Alcon Research, Ltd., IP Legal TB4-8, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

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(57) Abstract: The present invention concerns implantable ocular devices for the sustained release of medication to the eye, and methods for manufacturing and using such devices. In one embodiment, the present invention provides a device comprising: (a) a body comprising a matrix of a prostaglandin and a silicone; (b) a parylene coating on the outer surface of the body; and (c) one or more pores extending from the outer surface of the parylene coating to the outer surface of the body.



WO 2008/094989 A3

PUNCTAL PLUGS AND METHODS OF DELIVERING THERAPEUTIC AGENTS

5 BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to the fields of implantable ocular devices, pharmaceuticals, and methods of drug delivery to the eye. More particularly, it
10 concerns implantable ocular devices for the sustained delivery of a therapeutic compound to the eye.

2. Description of Related Art

Glaucoma is the leading cause of blindness worldwide. It is the most common cause of optic neuropathy.

15 One major risk factor for developing glaucoma is family history. Several different inherited forms of glaucoma have been described. Primary congenital or infantile glaucoma is an inherited disorder that is characterized by an improper development of the aqueous outflow system of the eye, which leads to elevated intraocular pressure and damage to the optic nerve.

20 Open angle glaucoma is a common disorder characterized by atrophy of the optic nerve resulting in visual field loss and eventual blindness. Open angle glaucoma has been divided into two major groups, based on age of onset and differences in clinical presentation. Juvenile-onset open angle glaucoma (JOAG) usually manifests itself in late childhood or early adulthood. Adult- or late-onset primary open angle
25 glaucoma (POAG) is the most common type of glaucoma. It is milder and develops more gradually than JOAG, with variable onset usually after the age of 40. POAG is associated with slight to moderate elevation of intraocular pressure, and often responds satisfactorily to regularly monitored medical treatment. Unfortunately, this disease may not be detected until after irreversible damage to the optic nerve has
30 already occurred because it progresses gradually and painlessly.

Ocular hypertension is a condition wherein intraocular pressure is elevated but no apparent loss of visual function has occurred; such patients are considered to be at high risk for the eventual development of the visual loss associated with glaucoma. If glaucoma or ocular hypertension is detected early and treated promptly with medications that effectively reduce elevated intraocular pressure, loss of visual function or its progressive deterioration can generally be ameliorated. Drug therapies that have proven useful for the reduction of intraocular pressure include both agents that decrease aqueous humor production and agents that increase the outflow facility. Such therapies are in general administered by one of two possible routes, topically (direct application to the eye) or orally.

Examples of agents used for treating glaucoma include β -blockers (*e.g.*, timolol, betaxolol, levobetaxolol, carteolol, levobunolol, propranolol), carbonic anhydrase inhibitors (*e.g.*, brinzolamide and dorzolamide), α_1 antagonists (*e.g.*, nipradolol), α_2 agonists (*e.g.* iopidine and brimonidine), miotics (*e.g.*, pilocarpine and epinephrine), prostaglandin analogs (*e.g.*, latanoprost, travoprost, unoprostone, and compounds set forth in U.S. Pat. Nos. 5,889,052; 5,296,504; 5,422,368; and 5,151,444), "hypotensive lipids" (*e.g.*, bimatoprost and compounds set forth in U.S. Pat. No. 5,352,708), and neuroprotectants (*e.g.*, compounds from U.S. Pat. No. 4,690,931, particularly eliprodil and R-eliprodil, as set forth in a pending application U.S. Ser. No. 60/203,350, and appropriate compounds from WO 94/13275, including memantine.

One of the limitations of topical therapy is inadequate and irregular delivery of the therapeutic agent to the eye. For example, when an eye drop is applied to the eye, a substantial portion of the drop may be lost due to overflow of the lid margin onto the cheek.

Various ocular drug delivery implants have been described in an effort to improve and prolong drug delivery. For example, U.S. Pat. No. 3,949,750 discloses a punctal plug made of a tissue-tolerable, readily sterilizable material, such as Teflon, HEMA, hydrophilic polymer, methyl methacrylate, silicone, stainless steel or other inert metal material. It is stated that the punctal plug may be impregnated with ophthalmic medication or that the punctal plug may contain a reservoir of the ophthalmic drug.

U.S. Pat. No. 5,053,030 discloses an intracanalicular implant that can be used as a carrier or medium for distributing medications throughout the body. U.S. Pat. No. 5,469,867 discloses a method of blocking a channel, such as the lacrimal canaliculus by injecting a heated flowable polymer into the channel and allowing it to cool and solidify. The polymer may be combined with a biologically active substance that could leach out of the solid occluder once it has formed in the channel.

WO 99/37260 discloses a punctal plug made of a moisture absorbing material, which is not soluble in water, such as a modified HEMA. It is also disclosed that an inflammation inhibitor, such as heparin, may be added to the material from which the punctal plug is made.

U.S. Pat. No. 6,196,993 discloses a punctal plug containing glaucoma medication. The medication is contained in a reservoir within the plug. The reservoir is in fluid communication with a pore through which the medication is released onto the eye.

U.S. Pub. No. 2003/0143280 discloses the use of biodegradable polymer capsules for treating ophthalmic disorder including dry eye and glaucoma. The capsules are made of any biodegradable, biocompatible polymer and may contain a treating agent.

U.S. Pub. No. 2004/0013704 discloses solid or semi-solid implant compositions lacking polymeric ingredients. These implant compositions are made of lipophilic compounds and may be implanted anywhere in the eye including the punctum or lacrimal canaliculus. It is stated that the implants may contain any ophthalmic drug, including anti-glaucoma drugs.

WO 2004/066980 discloses a device for delivering a carbonic anhydrase inhibitor (CAI) to the eye over an extended period of time. In one embodiment, the device has an inner CAI-containing core and an outer polymeric layer. The outer layer may be permeable, semi-permeable, or impermeable to the drug. Where the outer layer is impermeable to the drug, it may have one or more openings to permit diffusion of the CAI.

U.S. Pub. No. 2005/0232972 discloses ocular implants to which active agents have been applied to at least one surface. In one embodiment, the implant may contain a hollow core filled with medication. In another embodiment, the medication may be applied to one or more bands of polymer material. Alternatively, a porous or absorbent material can be used to make up the entire plug or implant which can be saturated with the active agent.

WO 2006/031658 discloses lacrimal canalicular inserts including a polymer component and a therapeutic component. The polymer component may include one or more non-biodegradable polymers, one or more biodegradable polymers, or combinations thereof. The insert may comprise a matrix of a polymer component and a therapeutic component. The inserts may be coated with a substantially impermeable coating.

U.S. Pub. No. 2006/0020248 discloses an ophthalmological device for lacrimal insertion that includes a reservoir for a medication, such as a glaucoma, antimicrobial, anti-inflammatory, or dry-eye syndrome medication.

A reservoir drug-delivery device is a device that contains a receptacle or chamber for storing the drug. There are drawbacks to reservoir drug delivery devices in that they are difficult to manufacture, difficult to achieve drug content uniformity (*i.e.*, device to device reproducibility, particularly with small ocular devices), and they carry the risk of a “dose dump” if they are punctured. In matrix drug delivery devices the drug is dispersed throughout a polymeric matrix and is released as it dissolves or diffuses out of the matrix. Matrix devices have an advantage over reservoir devices in that they are not subject to a dose dump if punctured. A disadvantage of matrix devices is that it can be difficult to achieve zero-order drug release kinetics. Zero-order drug release or near zero-order drug release is desirable because the rate of drug release is independent of the initial concentration of the drug, thus the drug can be released at therapeutic levels over a sustained period of time. The manufacture of matrix devices can also present difficulties when the drug and the polymer are processed and extruded at elevated temperature and/or pressure as this may reduce the activity of the drug.

The devices of the present invention address these deficiencies in the art by providing matrix devices that achieve zero-order or near zero-order drug-release kinetics typically associated with reservoir devices, but without the risk of dose dumping and the manufacturing difficulties of reservoir devices.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a drug-delivery device comprising:

- (a) a body comprising a matrix of a silicone and an ophthalmic drug, the body having a head portion and a shaft portion defining an outer surface and being configured to be inserted through a punctal aperture and positioned in a punctum or lacrimal canaliculus;
- (b) a parylene coating on a portion of the outer surface of the body; and
- (c) at least one pore in the parylene coating, wherein the at least one pore extends from an outer surface of the parylene coating to the surface of the head portion of the body.

In another aspect, the present invention provides a method of manufacturing a drug-delivery device, comprising:

- (a) extruding a matrix of a silicone and an ophthalmic drug to form a drug-delivery device comprising a body having:
 - (i) a shaft portion having a first end and a second end, wherein the shaft portion is configured for insertion through a punctal aperture and positioning in a punctum or lacrimal canaliculus;
 - (ii) a head portion attached to the first end of the main portion, wherein the head portion is configured to rest on the exterior of the punctum; and
 - (iii) a distal tip portion attached to the second end of the shaft portion;
- (b) depositing a parylene coating on the surface of the body; and
- (c) etching at least one pore in the parylene coating on the surface of the head portion of the body, wherein the at least one pore extends from an outer surface of the parylene coating to the surface of the head portion of the body.

In another aspect, the present invention provides a method of treating glaucoma or ocular hypertension in a subject, comprising:

- (a) obtaining a drug-delivery device comprising:
 - (i) a body comprised of a matrix of a silicone and a prostaglandin, the body having: a shaft portion having a first end and a second end, wherein the shaft portion is

configured for insertion through a punctal aperture and positioning in a punctum or lacrimal canaliculus; a head portion attached to the first end of the main portion, wherein the head portion is configured to rest on the exterior of the punctum; and a distal tip portion attached to the second end of the shaft portion;

- (ii) a parylene coating on the surface of the body;
 - (iii) at least one pore in the parylene coating, wherein the at least one pore extends from an outer surface of the parylene coating to the surface of the head portion of the body;
- (b) implanting the drug-delivery device in the punctum of a subject with glaucoma or ocular hypertension.

In one embodiment, the present invention provides a drug-delivery device comprising: (a) a body comprising a matrix of a hydrophobic flexible polymer and a therapeutic compound; (b) a coating located on the outer surface of the first member, the coating comprising a second non-biodegradable polymer that is substantially impermeable to the therapeutic compound; and (c) at least one pore extending from the outer surface of the coating to the outer surface of the body. The devices of the present invention may be configured for implantation at any location within the body of a subject. In particular embodiments, the device is configured for implantation in the punctum, lacrimal canaliculus, sub-conjunctiva space, anterior sub-Tenon space, or any other location suitable for release of medication on to the eye of the subject. For example, for delivering a therapeutic compound to the eye, a device of the present invention may be configured as a punctal plug, lacrimal insert, or fornix device.

The hydrophobic flexible polymer may be, for example, a silicone, a polyacrylate, polyurethane, or a combination of two or more of these polymers. The silicone may be any unrestricted silicone suitable for injection, compression, or transfer molding. Non-limiting examples of commercially available, unrestricted silicones that may be used in making the devices of the present invention include MED-4870, MED-4830, MED-4840, MED-4850, MED-4860, or MED-4880 (NuSil Technology LLC). Non-limiting examples of polyacrylates include polymers of 2-hydroxyethylmethacrylate (HEMA), methacrylic acid (MA), methyl methacrylate (MMA). The therapeutic compound may be any therapeutic compound, so long as the therapeutic compound is dispersible or miscible in the polymer matrix (*e.g.*, a silicone matrix). The dispersion may be of solid particles or oil. In particular embodiments, the therapeutic compound is a compound that can be applied for the treatment of an ophthalmic disorder. For example, the therapeutic compound may be a glaucoma medication, an antimicrobial medication, an anti-inflammatory medication, or a dry-eye syndrome medication, or a therapeutic

compound that can be applied in the treatment of diabetic retinopathy or age-related macular degeneration. Highly potent ophthalmic drugs, such as prostaglandins, triamcinolone, 15-HETE (Icomucet), and rimexolone, are well suited for delivery with the devices of the present invention. The prostaglandin may be a natural or a
5 synthetic prostaglandin. Non-limiting examples of prostaglandins include cloprostenol, fluprostenol, latanoprost, travoprost, and unoprostone.

In certain aspects of the invention, the concentration of the prostaglandin in the matrix is between about 0.5% to about 15%, about 1% to about 10%, about 1% to about 9%, about 1% to about 8%, about 1% to about 7%, about 3% to about 7%,
10 about 1% to about 6%, about 1% to about 5%, about 5% to about 10%, or about 2.5% to about 7.5% by weight.

The coating located on the outer surface of the body of the device comprises a second non-biodegradable polymer that is substantially impermeable to the therapeutic compound, or is at least less permeable to the therapeutic compound than
15 the therapeutic compound is to the first non-biodegradable polymer. In one embodiment, the coating has a thickness of between about 0.5 nanometers (nm) to about 100 micrometers (μm), about 100 nm to about 50 μm , about 1 μm to about 20 μm , about 5 μm to about 15 μm , or about 1 μm to about 10 μm . In certain aspects of the invention the coating is a parylene coating.

One or more pores are etched in the coating to permit the release of the therapeutic compound from the matrix. The pore size and/or the pore number may be adjusted to achieve the desired release rate for the particular therapeutic agent in the matrix. In certain embodiments of the invention, the pore has a diameter, as measured at the outer surface of the coating, of between about 1 μm to about 100 μm , about 1
25 μm to about 50 μm , or about 5 μm to about 50 μm . In certain embodiments, the number of pores is between 1 to about 100,000; 1 to about 20,000; 1 to about 10,000; 1 to about 2,000; 1 to about 1,000; 1 to about 100; 1 to about 50; 1 to about 10; 1 to about 8; 1 to about 5; about 5 to about 100; about 5 to about 10; about 10 to about 100,000; about 10 to about 10,000; about 10 to about 2,000; about 10 to about 1,000;
30 about 10 to about 100; about 100 to about 100,000; about 100 to about 10,000; about 100 to about 2,000; or about 100 to about 1,000. In certain aspects, the pores are located only on the surface of the device that is adjacent to the eye such that the

therapeutic compound is released unidirectionally onto the eye. For example, where the device is a punctal plug the pore or pores would be located only on the end of the punctal plug that is closest to the front of the eye and exposed to the tears.

In certain aspects, the devices of the present invention deliver a therapeutically effective dose of the therapeutic compound to the subject for about 20 days, about 30 days, about 60 days, about 90 days, about 120 days, about 180 days about 240 days, about 300 days, about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, about 6 years, about 7 years, or about 8 years, or any range derivable therein. In particular embodiments, the devices of the present invention deliver a therapeutically effective dose of the therapeutic compound for at least 90 days.

In certain embodiments, the present invention provides a drug-delivery device comprising: a body comprised of a matrix of a silicone and a prostaglandin, the body having: a shaft portion having a first end and a second end, wherein the shaft portion is configured for insertion through a punctal aperture and positioning in a punctum or lacrimal canaliculus; a head portion attached to the first end of the main portion, wherein the head portion is configured to rest on the exterior of the punctum; and a distal tip portion attached to the second end of the shaft portion; a parylene coating on the surface of the body; at least one pore in the parylene coating, wherein the at least one pore extends from an outer surface of the parylene coating to the surface of the head portion of the body.

In some embodiments, the body further comprises a canalicular extension attached to the distal tip portion, wherein the canalicular extension is configured for insertion through the punctal aperture and the punctum and positioning in the lacrimal canaliculus. A canalicular extension may serve at least two purposes: (1) to improve retention of the plug; and (2) to serve as an additional source of the therapeutic compound. In certain embodiments of the invention, the canalicular extension extends into the nasolacrimal duct and is positioned in both the lacrimal canaliculus and the nasolacrimal duct. In certain aspects of the invention, the canalicular extension has a length L1 and the body has a length L2. The ratio of the length L1 to the length L2 can be about 0.5:1, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, 15:1, 16:1, 17:1, 18:1, 19:1, 20:1, 21:1, 22:1, 23:1, 24:1, 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 50:1, or 100:1, or any range derivable therein. In some

embodiments, the length of the canalicular extension is between about 1 millimeter (mm) to 30 mm, 1.5 mm to 20 mm, 2 mm to 15 mm, 2 mm to 10 mm, 2 mm to 5 mm, 5 mm to 15 mm, or 5 mm to 10 mm. In three preferred embodiments, the lengths of the canalicular extensions are 8 mm, 15 mm, and 30 mm, respectively. In certain
5 embodiments, the canalicular extension further comprises an integral stylus. The integral stylus may be made of any biocompatible material that provides increased stiffness to the canalicular extension. For example, the integral stylus may be made from stainless steel or a PEEK (oxy-1, 4-phenyleneoxy-1, 4-phenylene-carbonyl-1, 4-phenylene) polymer.

10 In certain embodiments, the body further comprises a band or a coating of a bio-expandable polymer on all or a portion of the shaft, distal tip, and/or canalicular extension. The band or coating of bio-expandable polymer will aid in the retention of the implanted device.

15 In another embodiment, the present invention provides a method of manufacturing an implantable ocular device, comprising: (a) extruding a matrix of a silicone and a prostaglandin to form a body configured for implantation in the punctum, lacrimal canaliculus, sub-conjunctiva space, or anterior sub-Tenon space; (b) depositing a parylene coating on the outer surface of the body; and (c) etching at
20 least one pore in the parylene coating, the pore extending through the parylene coating to the outer surface of the body. In certain aspects, the matrix is extruded to form a punctal plug or a fornix device.

25 In one embodiment, the present invention provides a method of manufacturing a drug-delivery device, comprising: (a) extruding a matrix of a silicone and a prostaglandin to form a drug-delivery device comprising a body having: (i) a shaft portion having a first end and a second end, wherein the shaft portion is configured for insertion through a punctal aperture and positioning in a punctum or lacrimal
30 canaliculus; (ii) a head portion attached to the first end of the shaft portion, wherein the head portion is configured to rest on the exterior of the punctum; and (iii) a distal tip portion attached to the second end of the shaft portion; (b) depositing a parylene coating on the surface of the body; and (c) etching at least one pore in the parylene coating on the surface of the head portion of the body, wherein the at least one pore

extends from an outer surface of the parylene coating to the surface of the head portion of the body.

In certain aspects of the invention the parylene coating is deposited using vapor deposition. In particular embodiments, the pore is etched using oxygen plasma etching or focused ion beam etching. In certain embodiments, the parylene coating is deposited at a thickness of between about 0.5 nanometers (nm) to about 100 micrometers (μm), about 100 nm to about 50 μm , or about 1 μm to about 10 μm . The pore or pores may be etched in the parylene coating using, for example, oxygen plasma etching or focused ion beam etching. In certain aspects of the invention, the opening of the pore is substantially circular. The number of pores and the size of the pores etched in the parylene may be adjusted to achieve the desired release rate for the prostaglandin. In certain aspects, the pores are etched only on the surface of the device that will be adjacent to the eye once the device is implanted. In certain embodiments, the pore has a diameter, as measured at the outer surface of the coating, of between about 1 μm to about 100 μm , about 1 μm to about 50 μm , or about 5 μm to about 50 μm . . In some embodiments, 1 to about 100,000; 1 to about 10,000; 1 to about 1,000; 1 to about 100; 1 to about 50; 1 to about 10; 1 to about 8; 1 to about 5; about 5 to about 100; about 5 to about 10; about 10 to about 100,000; about 10 to about 10,000; about 10 to about 1,000; or about 10 to about 100 are etched.

In one embodiment, the present invention provides a method of treating an ocular disorder in a subject comprising: (a) obtaining an implantable ocular device for the sustained release of medication to the eye, the device comprising: (i) a body comprising a matrix of a therapeutic agent and a silicone; (ii) a parylene coating on the outer surface of the body; and (iii) one or more pores extending from the outer surface of the parylene coating to the outer surface of the body; and (b) implanting the device in the punctum, lacrimal canaliculus, sub-conjunctiva space, or anterior sub-Tenon space of the subject. The implantable ophthalmic device may be, for example, a punctal plug, a lacrimal canalicular insert, or a fornix device.

In particular embodiments, the present invention provides a method of treating glaucoma or ocular hypertension in a subject, comprising: (a) obtaining a drug-delivery device comprising: (i) a body comprised of a matrix of a silicone and a prostaglandin, the body having: a shaft portion having a first end and a second end,

wherein the shaft portion is configured for insertion through a punctal aperture and positioning in a punctum or lacrimal canaliculus; a head portion attached to the first end of the shaft portion, wherein the head portion is configured to rest on the exterior of the punctum; and a distal tip portion attached to the second end of the shaft portion;

5 (ii) a parylene coating on the surface of the body; (iii) at least one pore in the parylene coating, wherein the at least one pore extends from an outer surface of the parylene coating to the surface of the head portion of the body; (b) implanting the drug-delivery device in the punctum of a subject with glaucoma or ocular hypertension.

10 In some embodiments, biodegradable microspheres of the drug are formed first and then incorporated into a silicone to form a matrix. Microspheres, microcapsules and nanospheres (collectively, "microspheres") are generally accepted as spherical particles with diameters ranging from approximately 50 nm to 1000 micrometers. They are reservoir devices that come in a variety of different forms,

15 including, but not limited to, porous, hollow, coated, or uncoated forms with a pharmaceutically active agent either incorporated into or encapsulated by polymeric material via numerous known methods. Such known methods include, but are not limited to, spray drying, spinning disk and emulsification methods. Microspheres may be formed from a myriad of polymeric materials selected from, but not limited to,

20 to, polylactic acids, polyglycolic acids, polylactic-glycolic acids, poly caprolactones, triglycerides, polyethylene glycols, poly orthoesters, poly anhydrides, polyesters, cellulose and combinations thereof. The amount of drug incorporated or encapsulated in the microsphere is generally between 0.001% and about 50%. In this embodiment, preformed microspheres are incorporated into the drug-delivery device

25 body such that the body comprises a matrix of a silicone and drug-loaded microspheres. The microsphere content incorporated into the drug-delivery device body is generally between 1% and 50%.

The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually

30 exclusive.

Throughout this application, the term "about" is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value.

Following long-standing patent law, the words "a" and "an," when used in conjunction with the word "comprising" in the claims or specification, denotes one or more, unless specifically noted.

In this document (including the claims), the terms "comprise" (and any form of comprise, such as "comprises" and "comprising"), "have" (and any form of have, such as "has" and "having"), and "include" (and any form of include, such as "includes" and "including") are open-ended linking verbs.

The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Other aspects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention in combination with the detailed description of illustrative embodiments presented below.

5 **FIG. 1** is a front view of a punctal plug.

FIG. 2 is a cross-sectional view of a punctal plug.

FIGS. 3A and 3B are top views of punctal plugs.

FIG. 4 is an illustration of a punctal plug with a canalicular extension.

FIG. 5 is an illustration of the lacrimal duct system of a mammalian eye.

10 **FIG. 6** is an illustration of one of the present medical devices positioned in the lacrimal duct system of a mammalian eye.

FIG. 7 is a partial cross-section of a punctal plug with a canalicular extension.

FIG. 8 shows the effect of surface area on AL-6598 release from silicone devices in PBS at 37°C.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

A matrix of silicone and a therapeutic compound may be molded and cured into devices of various shapes that can be useful as drug delivery systems. Such devices can be molded into shapes configured for implantation at essentially any location in the body of a subject. In particular embodiments, a matrix of silicone and prostaglandin is molded into a device for ocular drug delivery for the treatment of glaucoma. In one embodiment, the device is molded by extrusion in which the drug/silicone mixture is pushed through a die with heat such that the cured form takes on the profile of the die.

In vitro and *in vivo* studies demonstrated that release of prostaglandin from silicone monolithic devices is controlled by the surface area of the device exposed to the environment, although there is a slight drug concentration contribution to the release profile. *In vivo* studies also demonstrated that the release of prostaglandin from silicone monolithic devices is several times faster than that expected from *in vitro* results, and that the duration of efficacy of such a device would be too short to be clinically practical unless a major modification of the drug release rate could be achieved. To provide a therapeutic compound/silicone matrix with a drug release profile that is practical as an implantable ocular device, the present invention provides a device comprising: a first member comprising a matrix of a therapeutic compound and a silicone; a parylene coating on the outer surface of the first member; and one or more pores extending from the outer surface of the parylene coating to the outer surface of the first member. Increasing the pore size and/or the number of pores will increase the exposed surface area of the matrix and thus increase the rate at which the therapeutic compound is released. The matrix optionally includes biodegradable microspheres containing the drug in order to provide additional control of the drug release rate from the matrix.

Preferably, devices of the present invention yield zero-order or near zero-order drug release profiles. In a zero-order reaction, the rate of reaction is a constant. When the limiting reactant is completely consumed, the reaction abruptly stops. (Differential Rate Law: $r = k$; the rate constant, k , has units of $\text{mole L}^{-1} \text{sec}^{-1}$.) This is distinguished from first-order and second-order reactions. A first-order reaction is

where the rate of reaction is directly proportional to the concentration of only one of the reactants and as the reactant is consumed during the reaction, the concentration drops and so does the rate of reaction. (Differential Rate Law: $r = k [A]$; the rate constant, k , has units of sec^{-1}). A second-order reaction is where the rate of reaction is directly proportional to the square of the concentration of one of the reactants (or to the concentration of two first order reactants) and decreases rapidly (faster than linear) as the concentration of the reactant decreases (Differential Rate Law: $r = k [A]^2$ or $r = k [A][B]$; the rate constant, k , has units of $\text{L mole}^{-1} \text{sec}^{-1}$.) Near zero-order describes a situation where there may be an initial brief period where the reaction appears to follow more complex kinetics, but then reverts to zero-order for the majority of the lifetime of the drug release. This is usually the case with devices that have an initial burst of drug – the reaction has an initial rate that appears to change but then maintains a constant rate for the majority of the release.

In one embodiment, the present devices and systems comprise an implantable ocular device configured as a plug for insertion into the punctum and/or lacrimal canaliculus of the eye. FIG. 5 illustrates the lacrimal duct system of a mammalian eye 9. The system includes a lower punctum 11 connected to a lower lacrimal canaliculus 13, and an upper punctum 10 connected to an upper lacrimal canaliculus 12. Canaliculli 12 and 13 are connected to a lacrimal sac 14 and a nasolacrimal duct 15. A lacrimal gland 16 is connected to eye 9 via a lacrimal duct 17. In general, tears are produced by lacrimal gland 16 and are provided to eye 9 via lacrimal duct 17, and tears are drained from eye 9 via punctum 10 and canaliculus 12, punctum 11 and canaliculus 13, and nasolacrimal duct 15.

A variety of plugs for insertion into puncta 10 and 11 and/or canaliculli 12 and 13 are known in the art. Punctal plugs are described in, for example, U.S. Pat. Nos. 3,949,750; 5,283,063; 4,915,684; 4,959,048; 5,723,005; 6,149,684; 6,290,684; 5,417,651; 5,423,777; 5,741,292; 6,027,470; 5,830,171; 6,016,806; 6,041,785; 6,234,175; 6,306,114; and 6,344,047; each of which is incorporated by reference.

One of the drug-delivery devices of the present invention is shown in FIGs. 1-3. The drug-delivery device comprises: a body 1 comprising a matrix of a silicone and a prostaglandin, the body having an outer surface and being configured to be inserted through a punctal aperture and positioned in a punctum 10 or 11 or lacrimal

canaliculus **12** or **13**; (b) a parylene coating **5** on a portion of the outer surface of body **1**; and (c) at least one pore **6** in parylene coating **5**, wherein pore **6** extends from an outer surface of parylene coating **5** to the outer surface of body **1**.

In one embodiment, the matrix comprises a silicone and drug-loaded
5 biodegradable microspheres.

A punctal plug typically includes a body **1** having a proximal head portion **2**, a distal tip portion **4**, and a shaft portion **3** connecting proximal head portion **2** and distal tip portion **4**. Shaft portion **3** is often smaller in cross-sectional size than proximal head portion **2** and the widest part of distal tip portion **4**. A punctal plug is
10 usually inserted, distal tip first, in a punctal aperture and advanced distally in punctum **10** or **11** until proximal head portion **2** is seated on the punctal opening. Punctal plugs may be made available in different sizes corresponding to anatomical puncta and canaliculi of different cross-sectional sizes. Proximal head portion **2** is normally
15 larger than the punctal aperture such that proximal head portion **2** does not pass through the punctal opening and remains exposed in eye **9**. Distal tip portion **4** typically has a cross-sectional size to fill punctum **10** or **11** and to anchor punctal plug **1** in place. The occlusion presented by punctal plug **1** deters tear fluid from draining from eye **9** through the punctal opening and the corresponding canalicular canal. Punctal plug **1** may partially or fully occlude punctum **10** or **11**. Punctal plugs are
20 typically implanted in the eye using insertion tools (*e.g.*, cannula), and punctal plugs may therefore have an axial passage **7** for releasably engaging the insertion tools to facilitate or guide implantation.

A drug delivery device of the present invention may also be formed as an intracanalicular implant. Intracanalicular implants, which are disposed entirely within
25 the canalicular canal without exposure or protrusion thereof in the eye, are described in, for example, U.S. Pat. Nos. 4,660,546; 5,049,142; and 5,053,030; 5,163,959; and 5,171,270, each of which is incorporated by reference.

A punctal plug or intracanalicular implant according to the present invention may also comprise a canalicular extension **8**, which extends into the canaliculus **12**
30 or **13**. The length of the canalicular extension may be such that it also extends into the nasolacrimal duct **15**. The canalicular extension increases the volume of matrix,

and thereby the amount of therapeutic compound, in the device. The canalicular extension **8** also serves to increase the retention of the implanted device. In addition, the increased size of a device with the canalicular extension increases the likelihood that the patient will notice if the device becomes dislodged from the punctum. One of the drug delivery devices including a canalicular extensions is shown in FIG. 4. FIG. 6 shows a drug-delivery with a canalicular extension positioned in the lacrimal duct system. In certain embodiments, the canalicular extension comprises an integral stylus **19** as shown in the partial cross-section view in FIG. 7.

The implantable ocular devices of the present invention may be used for the topical delivery of eye medications including, for example, glaucoma medication, ocular hypertension medications, antimicrobial medication, anti-inflammatory medication, or dry-eye syndrome medication. In one embodiment, the therapeutic compound is a prostaglandin. The prostaglandin may be a natural or a synthetic prostaglandin. Prostaglandins are metabolite derivatives of arachidonic acid. Arachidonic acid in the body is converted to prostaglandin G₂, which is subsequently converted to prostaglandin H₂. Other naturally occurring prostaglandins are derivatives of prostaglandin H₂. A number of different types of prostaglandins are known in the art including A, B, C, D, E, F, G, I and J-Series prostaglandins (EP 0 561 073 A1). Non-limiting examples of prostaglandins include cloprostenol, fluprostenol, latanoprost, travoprost, and unoprostone.

The devices of the present invention are coated with a non-biodegradable polymer **5** to reduce the exposed surface area of the matrix. In some embodiments of the present invention, the coating is parylene. Parylene is flexible, hydrophobic, substantially impermeable to prostaglandins, highly resistant to chemicals, and can be applied to surfaces by vapor deposition with high conformity and consistency. Parylene also meets FDA Class VI requirements, and has been used in medical device applications to cover implants like pacemakers and shunts. Parylene is the generic name for members of a unique polymer series. The basic member of the series, called Parylene N, is poly-para-xylylene, a linear, highly crystalline material. Other members of the series include Parylene C, Parylene D, and Parylene F.

Methods for depositing parylene coatings on silicone are known in the art. For example, a parylene coating may be vapor deposited on a silicone device of the

present invention by placing the device in a vacuum deposition chamber and drawing a vacuum in the chamber to approximately 0.1 torr. A parylene dimer (di-para-xylylene) is vaporized at approximately 150°C. A pyrolysis of the monomer (para-xylylene) is then affected at approximately 680°C and 0.5 torr. The monomer then
5 enters the deposition chamber at approximately room temperature (approximately 25°C) and is adsorbed and polymerizes onto the silicone device. The resultant coating is conformal, covering all exposed surfaces equally.

Parylene coatings may be deposited in layers with thicknesses of as little as about 0.5 nanometers up to several millimeters. Once the coating has been applied to
10 the implantable ocular device, one or more pores may be etched in the coating to permit the release of the therapeutic compound from the matrix by providing an opening in the coating through which the therapeutic compound can diffuse. Alternatively, the pores may be created during the parylene deposition process by masking the surface of the device at positions where there pores are desired. The pore
15 size and/or the pore number may be adjusted to achieve the desired release rate for the particular therapeutic agent in the matrix. As mentioned above, the release of therapeutic compound from the silicone matrix was controlled by the exposed surface area of the matrix. Thus, increasing the pore size and/or the number of pores will increase the exposed surface area of the matrix and thus increase the rate at which the
20 therapeutic compound is released from the matrix. Furthermore, the pores may be positioned on the device such that the therapeutic compound is released unidirectionally onto the eye. For example, where the device is a punctal plug the pore or pores would be located on the head portion of the punctal plug that is exposed to the tears.

25 The pores may be etched into the coating of the device using, for example, a focused ion beam (FIB) or an oxygen plasma etching process (*see e.g.*, Meng and Tai, 2005; incorporated by reference). It is preferable to etch the pores on a substantially flat surface of the device as it makes the etching process more consistent. FIB uses a focused beam of gallium ions to sputter atoms from the surface of the material being
30 etched. Because parylene is not conductive, the impinging gallium ions tend to “charge up” the parylene layer over time, which may eventually inhibit milling. To overcome this charging effect, the parylene surface may be coated with a thin layer of

conductive material (*e.g.*, metal or carbon) or provided with a temporary contact to a conductive material. Focused ion beams have a Gaussian profile. As a result, the milled holes have sloping sidewalls (*i.e.*, the holes get smaller as they go deeper). Based on studies of FIB etching through a 5 μm layer of parylene deposited on a
5 silicone die, it was determined that an aspect ratio of under about 5:1 (*e.g.*, a 1 μm diameter pore, as measured at the outer surface of the parylene coating, through a 5 μm thick layer of parylene) is needed to form a pore that extends completely through the parylene layer.

Oxygen plasma etching is a dry-etching process that takes place in an oxygen
10 plasma environment where oxygen radicals are formed. Typical conditions for oxygen plasma etching include: an oxygen pressure of from about 10 to about 500 millitorr, and an RF power of from about 100 to about 200 watts. Another way to etch pores in the coating of the device is with a scanning electron microscope probe.

The following examples are included to demonstrate preferred embodiments
15 of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be
20 made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

The Release of Prostaglandin from a Silicone Matrix is Controlled by the Surface Area of the Matrix Exposed to the Environment

25 To study the effect of surface area on the release of prostaglandin from a silicone matrix, prostaglandin release from silicone dies of three different sizes was measured. The largest silicone die measured 10mm x 10mm x 1mm. A $\frac{1}{2}$ size device (10mm x 5mm x 1mm) and a $\frac{1}{4}$ size device (5mm x 5mm x 1mm) were also used in this study. Each silicone die contained 10% AL-6598, which is a DP class
30 prostaglandin analogue. The silicone die were placed in phosphate buffered saline (PBS) at 37°C and the amount of AL-6598 released was measured. As shown in FIG.

8, the release of AL-6598 was dependent on the size of the silicone die with the larger surface area resulting in the more rapid drug release.

EXAMPLE 2

Parylene Coating and Etching

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Two silicone die (10mm x 10mm x 1mm) were coated with 5 μm of parylene using a vapor deposition process. To coat the silicone die, the die were placed in a vacuum deposition chamber and a vacuum was drawn in the chamber to approximately 0.1 torr. A parylene dimer (di-para-xylylene) was vaporized at
10 approximately 150°C. Then pyrolysis of the monomer (para-xylylene) was affected at approximately 680°C and 0.5 torr. The monomer then entered the deposition chamber at approximately room temperature (approximately 25°C) and was adsorbed and polymerized onto the silicone die.

The parylene coated silicone die were then milled using FIB. Pores of 1 μm
15 and 1.5 μm were milled through the 5 μm thick layer of parylene on one of the silicone die. Each pore was milled within 30 seconds. 1000 Angstroms of metal were deposited on the surface of the parylene to prevent the “charging up” of the parylene layer by the impinging gallium ions during the FIB etching process. Focused ion beams have a Gaussian profile. As a result, the pores have sloping sidewalls. To
20 determine the smallest feature size that can be etched through the parylene, multiple pores with diameters of 0.5 μm , 1 μm , 1.5 μm , 3 μm , and 5 μm were milled in the 5 μm parylene layer of the other silicone die. The 0.5 μm pore did not extend completely through the parylene layer because of the sloping sidewalls, whereas the 1 μm and larger pores did extend completely through the parylene layer. From this
25 study it can be seen that pores with an aspect ratio under 5:1 can be milled through the parylene layer using the FIB process.

EXAMPLE 3**Punctal Plug Containing Microspheres**

Travoprost is prepared as a polylactic acid microsphere having an average size
5 of 100 nm – 1 μ m. The microspheres contain 10% travoprost by weight. 10 g of
drug-loaded microspheres are added to 45 g of silicone Part A in a first Semco press
tube and mixed on a Flack Tek mixer at 1500 RPM for 30 seconds. 45 g of silicone
Part B are added to a second Semco press tube. Both press tubes are placed on an
injection assembly of a premetered silicone press and injected into a steel mold to
10 make a silicone die having the desired punctal plug shape and dimensions. After
curing, the silicone device is coated with parylene and etched according to the
procedures described in Example 2.

* * * * *

15 All of the compositions and methods disclosed and claimed herein can be
made and executed without undue experimentation in light of the present disclosure.
While the devices and methods of this invention have been described in terms of
particular embodiments, it will be apparent to those of skill in the art that variations
may be applied to the devices and methods and in the steps or in the sequence of steps
20 of the methods described herein without departing from the concept, spirit and scope
of the invention. More specifically, it will be apparent that certain agents which are
both chemically and physiologically related may be substituted for the agents
described herein while the same or similar results would be achieved. All such
similar substitutes and modifications apparent to those skilled in the art are deemed to
25 be within the spirit, scope and concept of the invention as defined by the appended
claims. The appended claims are not to be interpreted as including means-plus-
function limitations, unless such a limitation is explicitly recited in a given claim
using the phrase(s) “means for” and/or “step for,” respectively.

REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated
5 herein by reference.

U.S. Patent 3,949,750
U.S. Patent 3,949,750
U.S. Patent 4,660,546
10 U.S. Patent 4,690,931
U.S. Patent 4,915,684
U.S. Patent 4,959,048
U.S. Patent 5,049,142;
U.S. Patent 5,053,030
15 U.S. Patent 5,053,030
U.S. Patent 5,151,444
U.S. Patent 5,163,959
U.S. Patent 5,171,270
U.S. Patent 5,283,063
20 U.S. Patent 5,296,504
U.S. Patent 5,352,708
U.S. Patent 5,417,651
U.S. Patent 5,422,368
U.S. Patent 5,423,777
25 U.S. Patent 5,469,867
U.S. Patent 5,723,005
U.S. Patent 5,741,292
U.S. Patent 5,830,171
U.S. Patent 5,889,052
30 U.S. Patent 6,016,806
U.S. Patent 6,027,470
U.S. Patent 6,041,785
U.S. Patent 6,149,684
U.S. Patent 6,196,993

- U.S. Patent 6,234,175
U.S. Patent 6,290,684
U.S. Patent 6,306,114
U.S. Patent 6,344,047
5 U.S. Patent 6,020,350
U.S. Patent Publn. 2003/0143280
U.S. Patent Publn. 2004/0013704
U.S. Patent Publn. 2005/0232972
U.S. Patent Publn. 2006/0020248
10 PCT Appln. WO 2004/066980
PCT Appln. WO 2006/031658
PCT Appln. WO 94/13275
PCT Appln. WO 99/37260
EP 0 561 073 A1
15
Meng and Tai, "Parylene Etching Techniques for Microfluidics and BioMEMS,"
Micro Electro Mechanical Systems, 30:568-571, 2005

The claims defining the invention are as follows:

1. A drug-delivery device comprising:
 - (a) a body comprising a matrix of a silicone and an ophthalmic drug, the body having a head portion and a shaft portion defining an outer surface and being configured to be inserted through a punctal aperture and positioned in a punctum or lacrimal canaliculus;
 - (b) a parylene coating on a portion of the outer surface of the body; and
 - (c) at least one pore in the parylene coating, wherein the at least one pore extends from an outer surface of the parylene coating to the surface of the head portion of the body.
2. The drug-delivery device of claim 1, wherein the body further comprises a distal tip portion attached to the second end of the shaft portion

wherein the shaft portion has a first end and a second end, and is configured for insertion through a punctal aperture and positioning in a punctum or lacrimal canaliculus; and

wherein the head portion is attached to the first end of the shaft portion and is configured to rest on the exterior of the punctum.
3. The drug-delivery device of claim 1 or claim 2, wherein the ophthalmic drug is a prostaglandin, triamcinolone, icomucet, or rimexolone.
4. The drug-delivery device of claim 3 wherein the ophthalmic drug is a prostaglandin.
5. The drug-delivery device of claim 4 wherein the prostaglandin is cloprostenol, fluprostenol, latanoprost, travoprost, or unoprostone.
6. The drug-delivery device of any one of claims 1 to 5, wherein the concentration of the prostaglandin in the matrix is between about 1% to about 10% by weight.
7. The drug-delivery device of any one of claims 1 to 5, wherein the concentration of the prostaglandin in the matrix is between about 3% to about 7% by weight.
8. The drug-delivery device of any one of claims 1 to 7, wherein the parylene coating is between about 1 μm to about 20 μm thick.
9. The drug-delivery device of any one of claims 1 to 7, wherein the parylene coating is between about 5 μm to about 15 μm thick.

10. The drug-delivery device of claim 2, wherein the body further comprises a canalicular extension attached to the distal tip portion of the body, wherein the canalicular extension is configured for insertion through the punctal aperture and the punctum and positioning in the lacrimal canaliculus.

11. The drug-delivery device of claim 10, wherein the canalicular extension has a length L1 and the body has a length L2, wherein the ratio of the length L1 to the length L2 is between about 2:1 to about 10:1.

12. The drug-delivery device of claim 10 or claim 11, wherein the canalicular extension is configured for positioning in both the lacrimal canaliculus and a nasolacrimal duct.

13. A method of manufacturing a drug-delivery device, comprising:

(a) extruding a matrix of a silicone and an ophthalmic drug to form a drug-delivery device comprising a body having:

(i) a shaft portion having a first end and a second end, wherein the shaft portion is configured for insertion through a punctal aperture and positioning in a punctum or lacrimal canaliculus;

(ii) a head portion attached to the first end of the main portion, wherein the head portion is configured to rest on the exterior of the punctum; and

(iii) a distal tip portion attached to the second end of the shaft portion;

(b) depositing a parylene coating on the surface of the body; and

(c) etching at least one pore in the parylene coating on the surface of the head portion of the body, wherein the at least one pore extends from an outer surface of the parylene coating to the surface of the head portion of the body.

14. The method of claim 13, wherein the depositing of the parylene coating comprises vapor deposition.

15. The method of claim 13 or claim 14, wherein the at least one pore is etched using oxygen plasma etching.

16. The method of any one of claims 13 to 15, wherein the parylene coating is deposited at a thickness about 1 μm to about 20 μm .

17. The method of any one of claims 13 to 15, wherein the parylene coating is deposited at a thickness about 5 μ m to about 15 μ m.

18. The method of any one of claims 13 to 17, wherein the at least one pore has a diameter of about 1 μ m to about 50 μ m.

19. The method of any one of claims 13 to 18, wherein 1 to about 1,000 pores are etched.

20. A method of treating glaucoma or ocular hypertension in a subject, comprising:

(a) obtaining a drug-delivery device comprising:

(i) a body comprised of a matrix of a silicone and a prostaglandin, the body having: a shaft portion having a first end and a second end, wherein the shaft portion is configured for insertion through a punctal aperture and positioning in a punctum or lacrimal canaliculus; a head portion attached to the first end of the main portion, wherein the head portion is configured to rest on the exterior of the punctum; and a distal tip portion attached to the second end of the shaft portion;

(ii) a parylene coating on the surface of the body;

(iii) at least one pore in the parylene coating, wherein the at least one pore extends from an outer surface of the parylene coating to the surface of the head portion of the body;

(b) implanting the drug-delivery device in the punctum of a subject with glaucoma or ocular hypertension.

21. The method of claim 20, wherein the prostaglandin is cloprostenol, fluprostenol, latanoprost, travoprost, or unoprostone.

22. The method of claim 20 or claim 21, wherein the concentration of the prostaglandin in the matrix is between about 1% to about 10% by weight.

23. The method of claim 20 or claim 21, wherein the concentration of the prostaglandin in the matrix is between about 3% to about 7% by weight.

24. The drug-delivery device according to claim 1, substantially as herein described with reference to the Examples, and/or accompanying Figures.

25. The method of manufacturing a drug-delivery device according to claim 13, substantially as

herein described with reference to the Examples, and/or accompanying Figures.

26. The method of treating glaucoma or ocular hypertension in a subject according to claim 20, substantially as herein described with reference to the Examples, and/or accompanying Figures.

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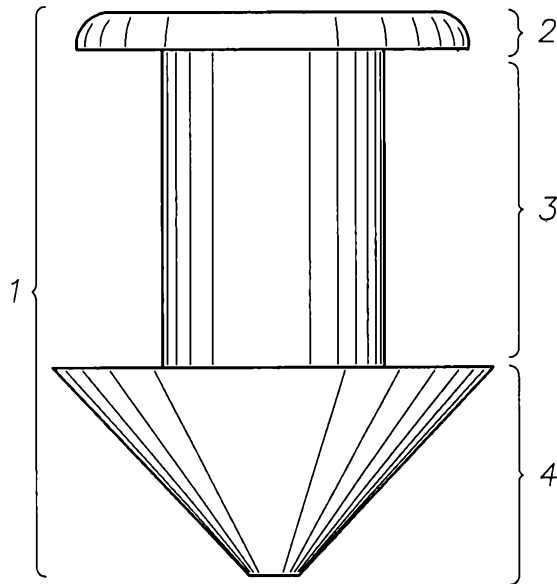


Fig. 1

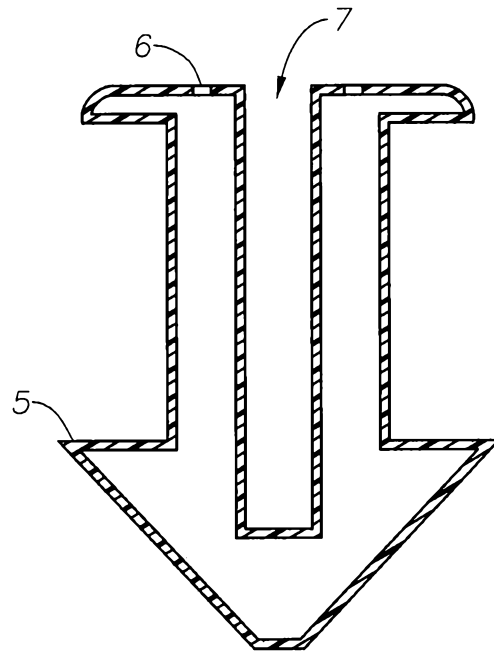


Fig. 2

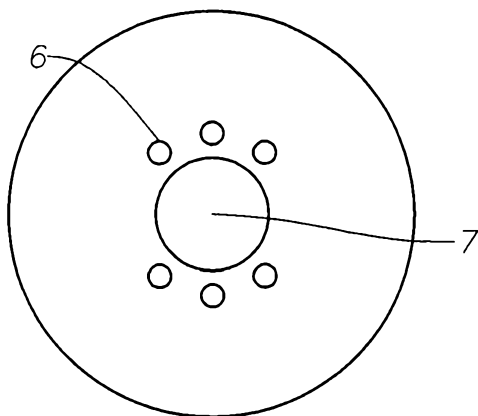


Fig. 3A

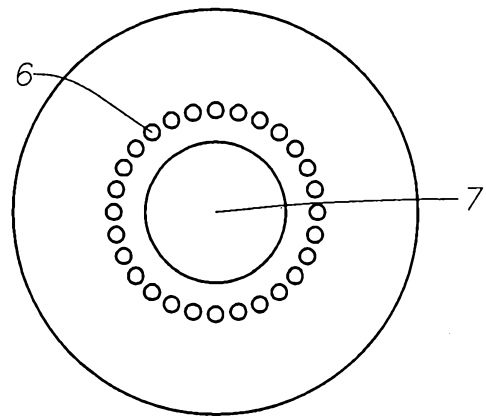


Fig. 3B

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Fig. 4

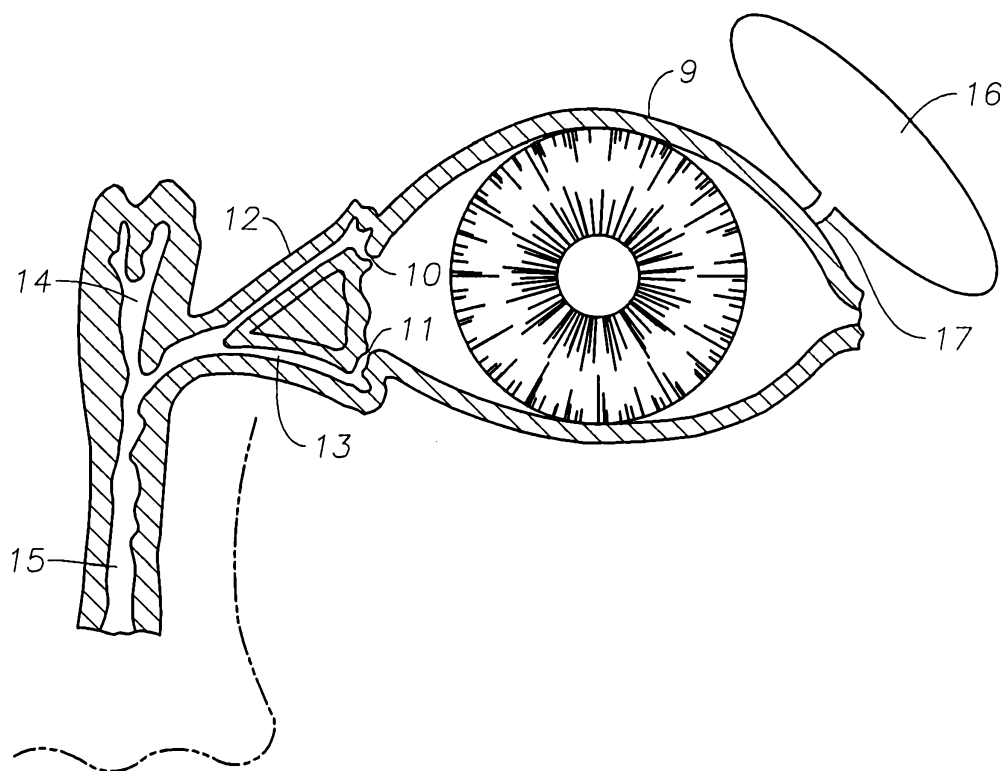
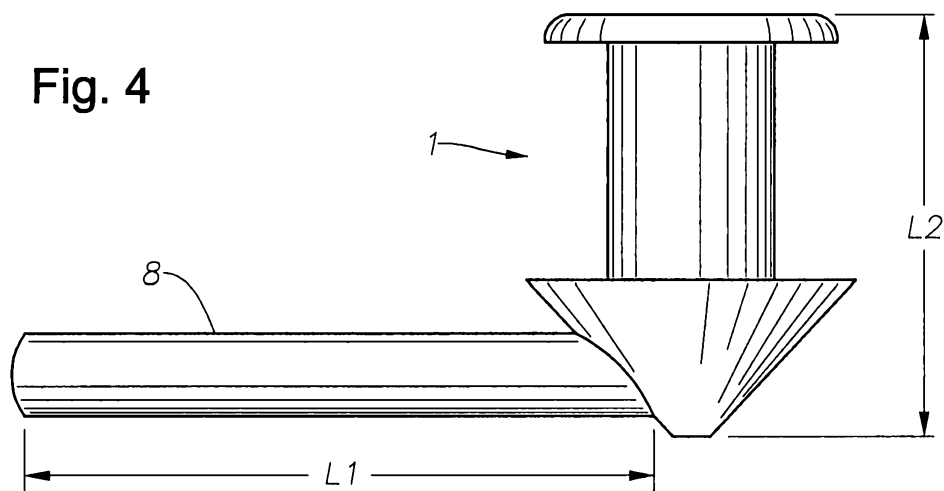


Fig. 5

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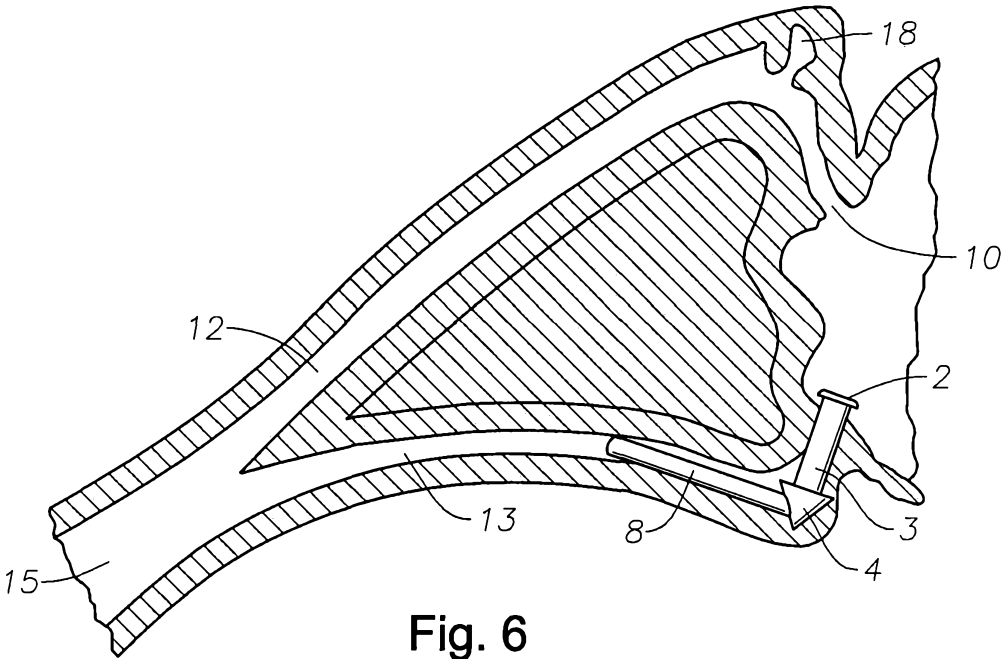
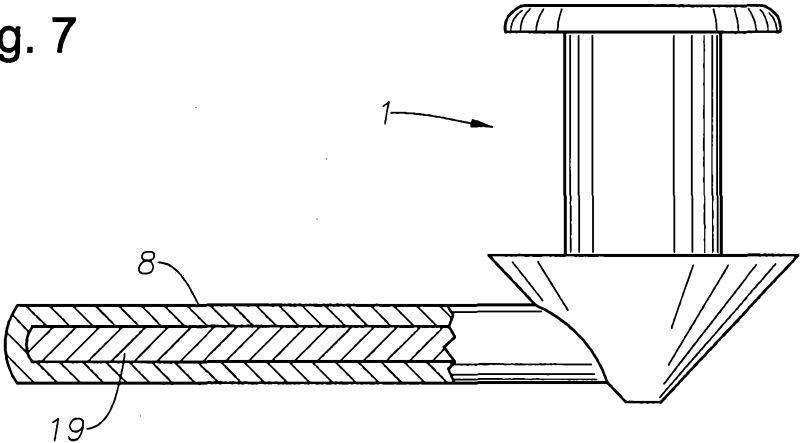


Fig. 7



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The Effect of Surface Area on AL-6598 Release
from Silicone Devices in PBS at 37°C

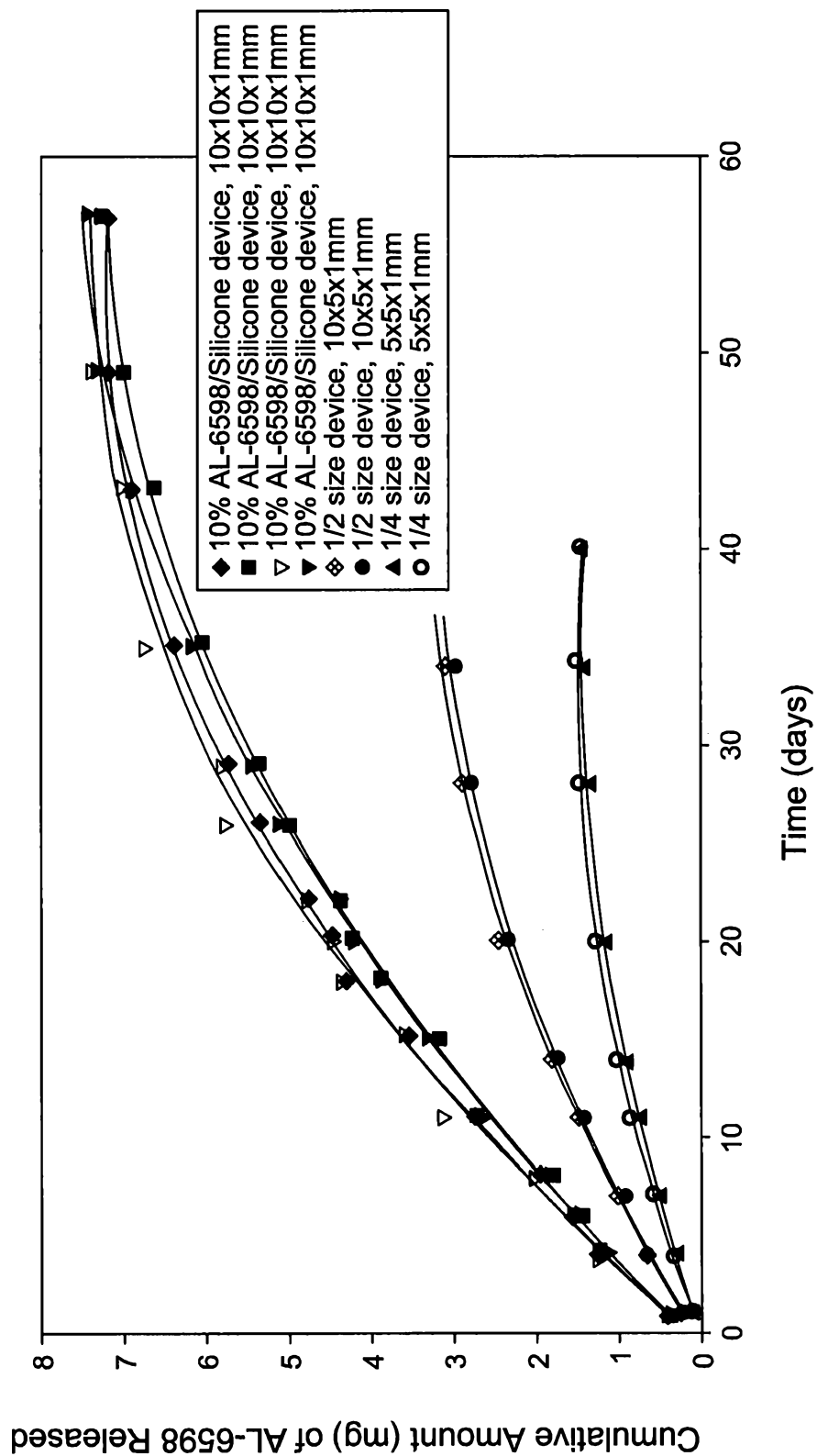


Fig. 8