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(54) **DRUG DELIVERY DEVICE**

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(57) **ABSTRACT**

Drug delivery devices, and methods of delivering pharmaceutically active agents to a target tissue within a body using such devices, are disclosed. One drug delivery device includes a body having an internal surface for placement proximate a target tissue and a well having an opening to the internal surface. An inner core comprising a pharmaceutically active agent is disposed in the well.

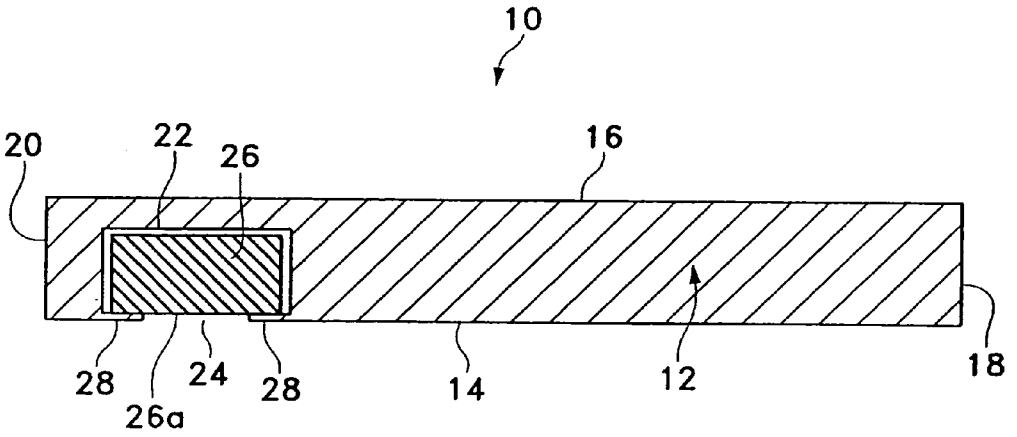
10
20
22
26
16
28
26a
24
28
14
12
18

FIG. 1

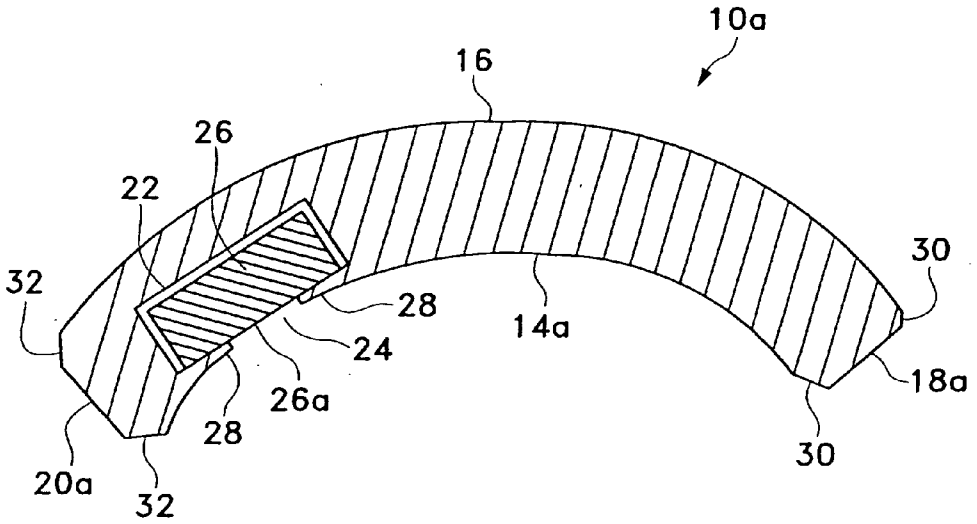
10a
16
26
22
32
28
24
26a
14a
30
18a
28
20a
32
30

FIG. 2

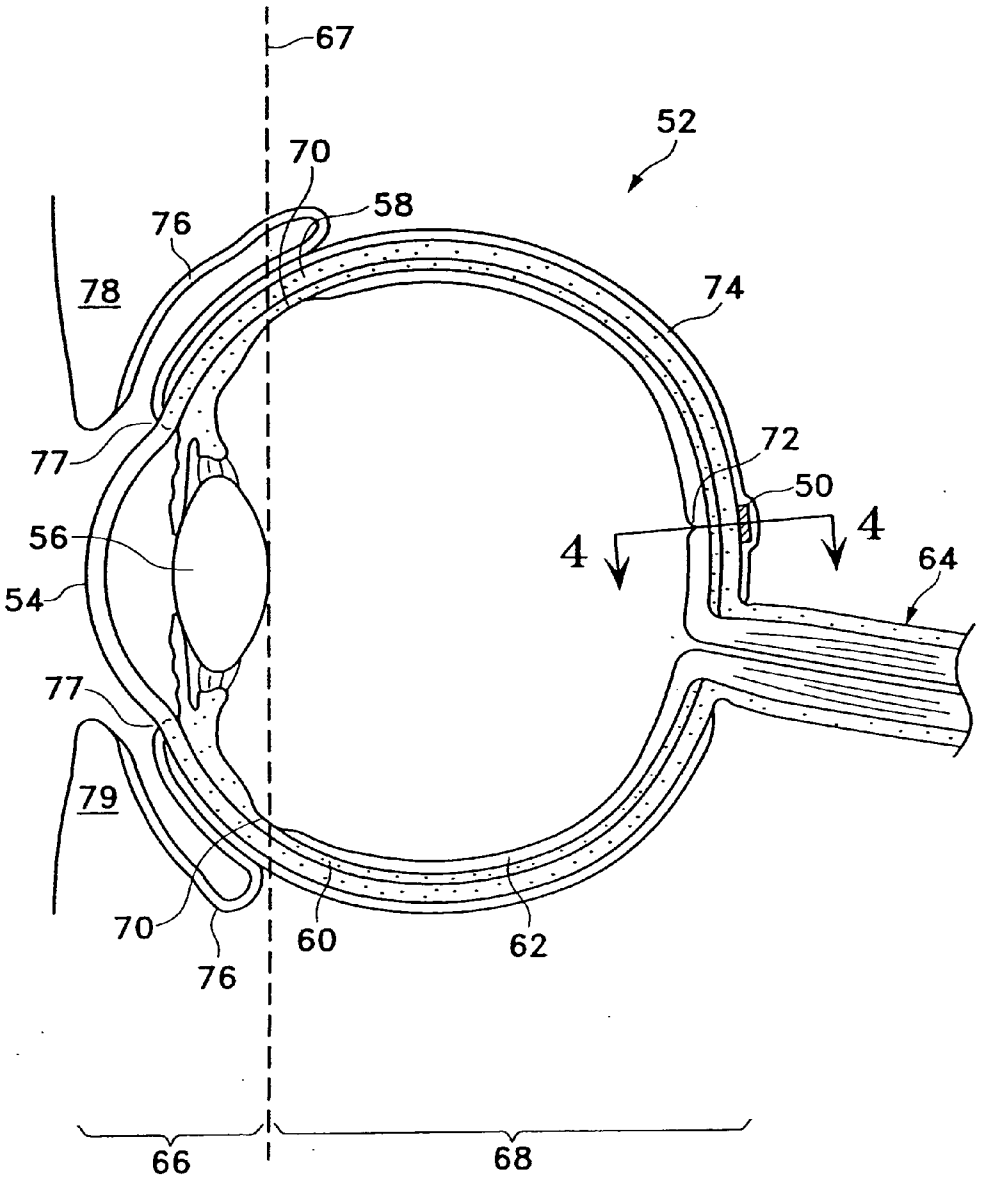

FIG. 3

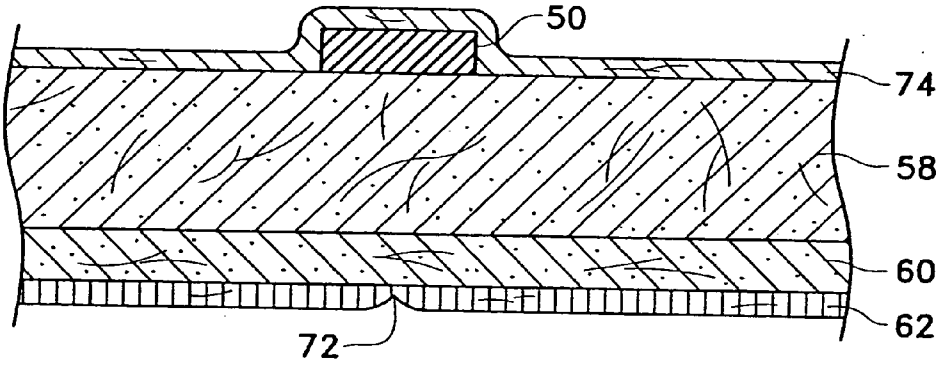

FIG. 4

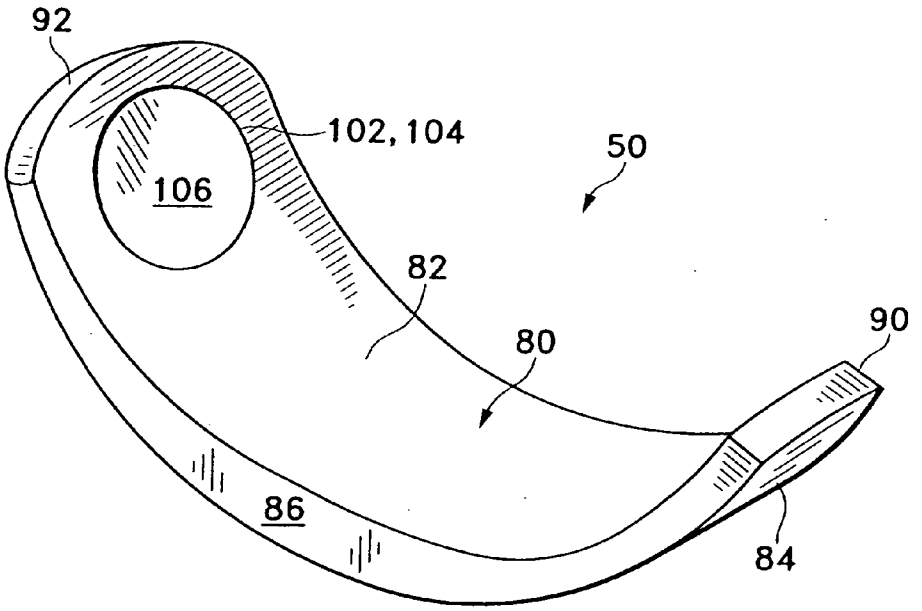

FIG. 5

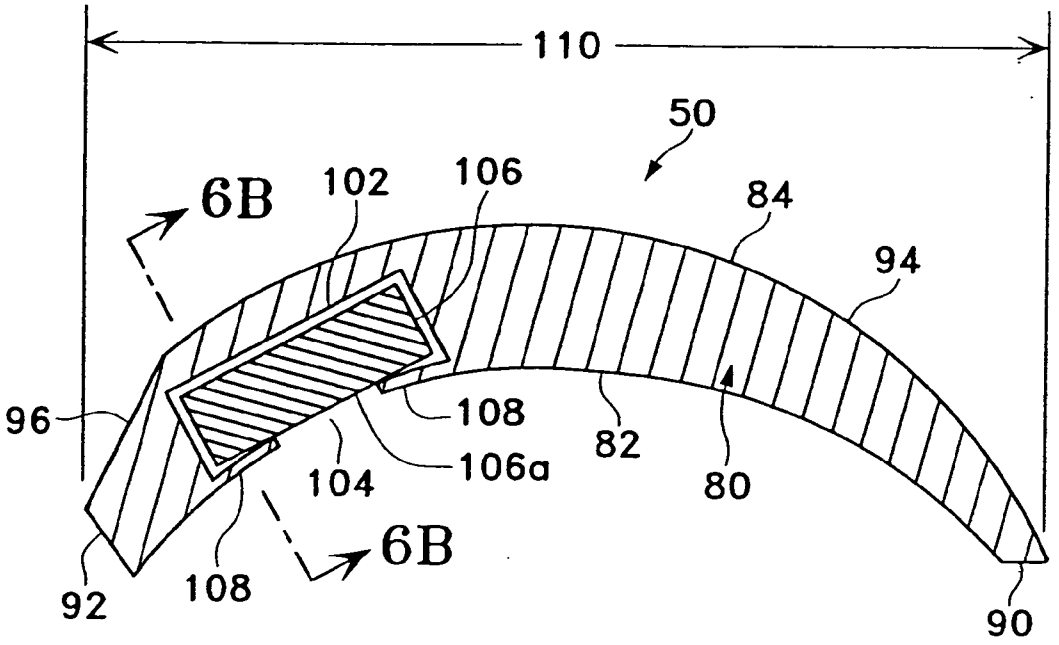
110
50
6B
102
106
84
94
96
108
82
80
104
106a
6B
92
108
90

FIG. 6A

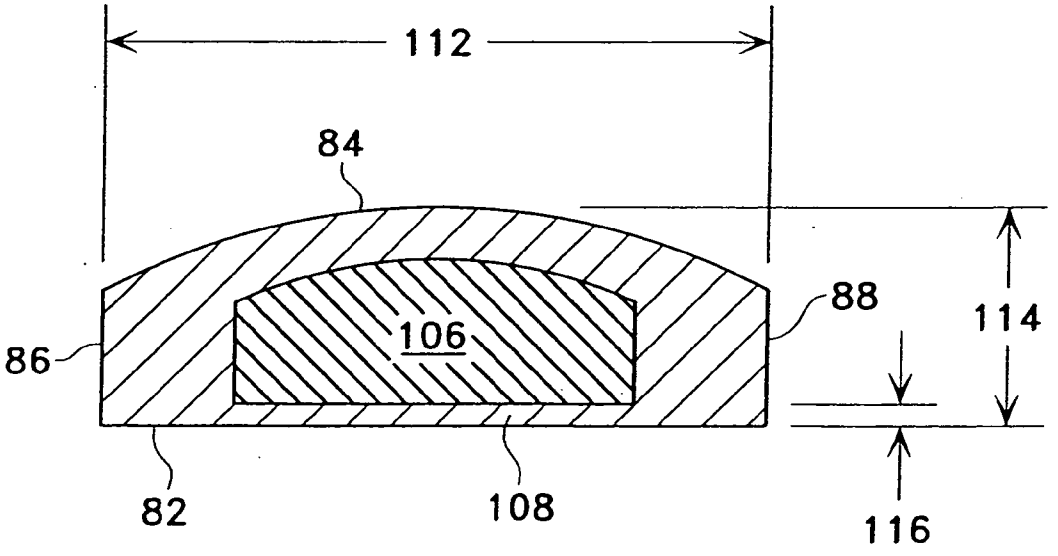
112
84
88
114
86
106
82
108
116

FIG. 6B

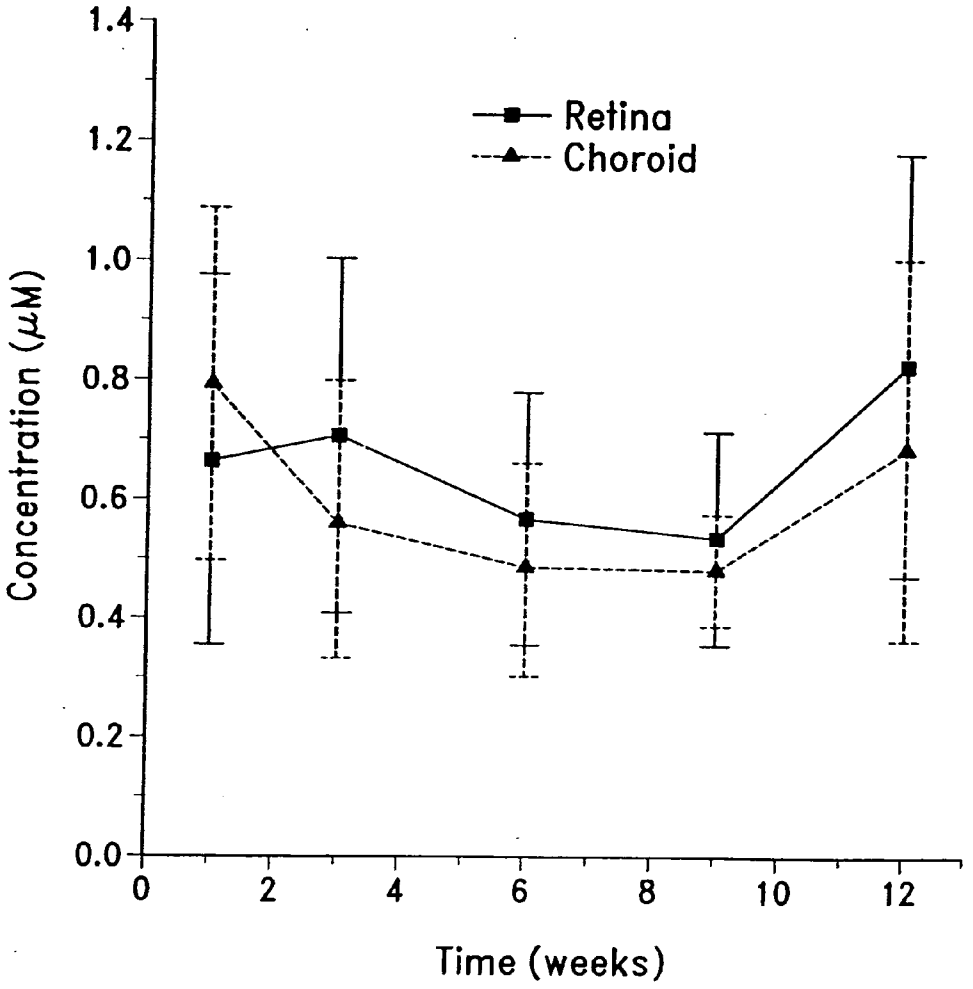
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Concentration (μM)
Retina
Choroid
0
2
4
6
8
10
12
Time (weeks)

FIG. 7

DRUG DELIVERY DEVICE

[0001] This application is a continuation of U.S. application Ser. No. 10/186,960, filed Jul. 1, 2002, which is a continuation of U.S. application Ser. No. 09/660,000, filed Sep. 12, 2000, now U.S. Pat. No. 6,413,540, which claims priority from U.S. Provisional Application No. 60/160,673, filed Oct. 21, 1999.

FIELD OF THE INVENTION

[0002] The present invention generally pertains to biocompatible implants for localized delivery of pharmaceutically active agents to body tissue. More particularly, but not by way of limitation, the present invention pertains to biocompatible implants for localized delivery of pharmaceutically active agents to the posterior segment of the eye.

DESCRIPTION OF THE RELATED ART

[0003] Several diseases and conditions of the posterior segment of the eye threaten vision. Age related macular degeneration (ARMD), choroidal neovascularization (CNV), retinopathies (i.e. diabetic retinopathy, vitreoretinopathy), retinitis (i.e. cytomegalovirus (CMV) retinitis), uveitis, macular edema, and glaucoma are several examples.

[0004] Age related macular degeneration (ARMD) is the leading cause of blindness in the elderly. ARMD attacks the center of vision and blurs it, making reading, driving, and other detailed tasks difficult or impossible. About 200,000 new cases of ARMD occur each year in the United States alone. Current estimates reveal that approximately forty percent of the population over age **75**, and approximately twenty percent of the population over age **60**, suffer from some degree of macular degeneration. "Wet" ARMD is the type of ARMD that most often causes blindness. In wet ARMD, newly formed choroidal blood vessels (choroidal neovascularization (CNV)) leak fluid and cause progressive damage to the retina.

[0005] In the particular case of CNV in ARMD, two main methods of treatment are currently being developed, (a) photocoagulation and (b) the use of angiogenesis inhibitors. However, photocoagulation can be harmful to the retina and is impractical when the CNV is near the fovea. Furthermore, photocoagulation often results in recurrent CNV over time. Oral or parenteral (non-ocular) administration of anti-angiogenic compounds is also being tested as a systemic treatment for ARMD. However, due to drug-specific metabolic restrictions, systemic administration usually provides sub-therapeutic drug levels to the eye. Therefore, to achieve effective intraocular drug concentrations, either an unacceptably high dose or repetitive conventional doses are required. Periocular injections of these compounds often result in the drug being quickly washed out and depleted from the eye, via periocular vasculature and soft tissue, into the general circulation. Repetitive intraocular injections may result in severe, often blinding, complications such as retinal detachment and endophthalmitis.

[0006] In order to prevent complications related to the above-described treatments and to provide better ocular treatment, researchers have suggested various implants aimed at localized delivery of anti-angiogenic compounds to the eye. U.S. Pat. No. 5,824,072 to Wong discloses a non-biodegradable polymeric implant with a pharmaceutically active agent disposed therein. The pharmaceutically active agent diffuses through the polymer body of the implant into the target tissue. The pharmaceutically active agent may include drugs for the treatment of macular degeneration and diabetic retinopathy. The implant is placed substantially within the tear fluid upon the outer surface of the eye over an avascular region, and may be anchored in the conjunctiva or sclera; episclerally or intrasclerally over an avascular region; substantially within the suprachoroidial space over an avascular region such as the pars plana or a surgically induced avascular region; or in direct communication with the vitreous.

[0007] U.S. Pat. No. 5,476,511 to Gwon et al. discloses a polymer implant for placement under the conjunctiva of the eye. The implant may be used to deliver neovascular inhibitors for the treatment of ARMD and drugs for the treatment of retinopathies, retinitis, and CMV retinitis. The pharmaceutically active agent diffuses through the polymer body of the implant.

[0008] U.S. Pat. No. 5,773,019 to Ashton et al. discloses a non-bioerodable polymer implant for delivery of certain drugs including angiostatic steroids and drugs such as cyclosporine for the treatment of uveitis. Once again, the pharmaceutically active agent diffuses through the polymer body of the implant.

[0009] All of the above-described implants require careful design and manufacture to permit controlled diffusion of the pharmaceutically active agent through a polymer body (matrix devices) or polymer membrane (reservoir devices) to the desired site of therapy. Drug release from these devices depends on the porosity and diffusion characteristics of the matrix or membrane, respectively. These parameters must be tailored for each drug moiety to be used with these devices. Consequently, these requirements generally increase the complexity and cost of such implants.

[0010] U.S. Pat. No. 5,824,073 to Peyman discloses an indentor for positioning in the eye. The indentor has a raised portion that is used to indent or apply pressure to the sclera over the macular area of the eye. This patent discloses that such pressure decreases choroidal congestion and blood flow through the subretinal neovascular membrane, which, in turn, decreases bleeding and subretinal fluid accumulation.

[0011] Therefore, a need exists in the biocompatible implant field for a surgically implantable drug delivery device capable of safe, effective, rate-controlled, localized delivery of a wide variety of pharmaceutically active agents to any body tissue. The surgical procedure for implanting such a device should be safe, simple, quick, and capable of being performed in an outpatient setting. Ideally, such a device should be easy and economical to manufacture. Furthermore, because of its versatility and capability to deliver a wide variety of pharmaceutically active agents, such an implant should be capable of use in clinical studies to deliver various agents that create a specific physical condition in a patient or animal subject. In the particular field of ophthalmic drug delivery, such an implantable drug delivery device is especially needed for localized delivery of pharmaceutically active agents to the posterior segment of the eye to combat ARMD, CNV, retinopathies, retinitis, uveitis, macular edema, and glaucoma.

SUMMARY OF THE INVENTION

[0012] One aspect of the present invention comprises a drug delivery device including a body having an internal surface for placement proximate a target tissue and a well having an opening to the internal surface. An inner core comprising a pharmaceutically active agent is disposed in the well.

[0013] In another aspect, the present invention comprises a method of delivering a pharmaceutically active agent to a target tissue within a body. A drug delivery device is provided. The drug delivery device includes a body having an internal surface and a well having an opening to the internal surface, and an inner core disposed in the well comprising a pharmaceutically active agent. The device is disposed within the body so that the pharmaceutically active agent is in communication with the target tissue through the opening.

[0014] In a further aspect, the present invention comprises an ophthalmic drug delivery device including a body having a scleral surface for placement proximate a sclera and a well or cavity having an opening to the scleral surface. An inner core comprising a pharmaceutically active agent is disposed in the well.

[0015] In a further aspect, the present invention comprises a method of delivering a pharmaceutically active agent to an eye having a sclera. A drug delivery device is provided. The drug delivery device includes a body having a scleral surface and a well having an opening to the scleral surface, and an inner core disposed in the well comprising a pharmaceutically active agent. The device is disposed within the eye so that the pharmaceutically active agent is in communication with the sclera through the opening.

[0016] In a further aspect, the present invention comprises a method of delivering a pharmaceutically active agent to an eye having a sclera, a Tenon's capsule, and a macula. A drug delivery device comprising a body having a pharmaceutically active agent disposed therein is provided. The device is disposed on an outer surface of the sclera, below the Tenon's capsule, and proximate the macula.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] For a more complete understanding of the present invention, and for further objects and advantages thereof, reference is made to the following description taken in conjunction with the accompanying drawings in which:

[0018] **FIG. 1** is a side sectional view of a drug delivery device according to a preferred embodiment of the present invention;

[0019] **FIG. 2** is a side sectional view of a second drug delivery device according to a preferred embodiment of the present invention;

[0020] **FIG. 3** is a side sectional view schematically illustrating the human eye;

[0021] **FIG. 4** is detailed cross-sectional view of the eye of **FIG. 3** along line **4-4**;

[0022] **FIG. 5** is a perspective view of an ophthalmic drug delivery device according to a preferred embodiment of the present invention;

[0023] **FIG. 6A** is a side sectional view of the ophthalmic drug delivery device of **FIG. 5**;

[0024] **FIG. 6B** is an enlarged cross-sectional view of the ophthalmic drug delivery device of **FIG. 6A** taken along line **6B-6B**; and

[0025] **FIG. 7** is a graphical illustration of the results of a pharmacokinetic study with New Zealand White rabbits implanted with the ophthalmic drug delivery device of **FIGS. 5 through 6B** showing the mean concentration of a pharmaceutically active agent at a target site in the retina and choroid of the rabbits as a function of time.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0026] The preferred embodiments of the present invention and their advantages are best understood by referring to **FIGS. 1 through 7** of the drawings, like numerals being used for like and corresponding parts of the various drawings.

[0027] **FIG. 1** schematically illustrates a drug delivery device **10** according to a preferred embodiment of the present invention. Device **10** may be used in any case where localized delivery of a pharmaceutically active agent to body tissue is required. By way of example, device **10** may be used to treat a medical disorder of the eye, ear, nose, throat, skin, subcutaneous tissue, or bone. Device **10** may be used in humans or animals.

[0028] Device **10** generally includes a body **12** having an internal surface **14** and an external surface **16**. As shown in **FIG. 1**, body **12** preferably has a generally rectangular three-dimensional geometry with a proximal end **18** and a distal end **20**. Body **12** may have any other geometry that has an internal surface **14** for placement proximate a target tissue in the body of a patient. By way of example, body **12** may have a cylindrical, an oval, a square, or other polygonal three-dimensional geometry.

[0029] Body **12** includes a well or cavity **22** having an opening **24** to internal surface **14**. An inner core **26** is preferably disposed in well **22**. Inner core **26** is preferably a tablet comprising one or more pharmaceutically active agents. Alternatively, inner core **26** may comprise a conventional hydrogel having one or more pharmaceutically active agents disposed therein. A retaining member **28** is preferably disposed proximate opening **24**. Retaining member **28** prevents inner core **26** from falling out of well **22**. When inner core **26** is a cylindrical tablet, retaining member **28** is preferably a continuous rim or lip disposed circumferentially around opening **24** having a diameter slightly less than the diameter of tablet **26**. Alternatively, retaining member **26** may comprise one or more members that extend from body **12** into opening **24**. Although not shown in **FIG. 1**, inner core **26** may alternatively comprise a suspension, solution, powder, or combination thereof containing one or more pharmaceutically active agents. In this embodiment, internal surface **14** is formed without opening **24**, and the suspension, solution, powder, or combination thereof diffuses through the relatively thin portion of internal surface **14** below inner core **26**. Still further in the alternative, device **10** may be formed without well **22** or inner core **26**, and the pharmaceutically active agent(s) in the form of a suspension, solution, powder, or combination thereof may be dispersed

throughout body **12** of device **10**. In this embodiment, the pharmaceutically active agent diffuses through body **12** into the target tissue.

[**0030**] The geometry of device **10** maximizes communication between the pharmaceutically active agent of inner core **26** and the tissue underlying internal surface **14**. Internal surface **14** preferably physically contacts the target tissue. By way of example, if the target tissue has a generally flat surface, device **10** would be appropriate for the delivery of a pharmaceutically active agent. As another example, if the target tissue has a generally convex surface, a device **10***a* shown in **FIG. 2** having a generally concave internal surface **14***a* designed to mate with such a target surface may be utilized. Corners **30** of proximal end **18***a*, and corners **32** of distal end **20***a*, may be slanted and/or rounded off to facilitate surgical placement of device **10***a* and to maximize comfort to the patient. Retaining member **28** is preferably designed with a minimum thickness necessary to retain inner core **26** so as to dispose a surface **26***a* of inner core **26** in close proximity to the target tissue. Although not shown in **FIG. 1** or **2**, inner core **26** may be formed so that surface **26***a* physically contacts the target tissue.

[**0031**] Alternatively, device **10** or **10***a* may be disposed in the body of a patient so that internal surface **14** or **14***a* is disposed proximate the target tissue. In this case, internal surface **14** or **14***a* physically contacts intermediate tissue disposed between it and the target tissue. The pharmaceutically active agent of inner core **26** communicates with the target tissue through opening **24** and this intermediate tissue.

[**0032**] Referring again to **FIG. 1**, body **12** preferably comprises a biocompatible, non-bioerodable material. Body **12** more preferably comprises a biocompatible, non-bioerodable polymeric composition. Said polymeric composition may be a homopolymer, a copolymer, straight, branched, cross-linked, or a blend. Examples of polymers suitable for use in said polymeric composition include silicone, polyvinyl alcohol, ethylene vinyl acetate, polylactic acid, nylon, polypropylene, polycarbonate, cellulose, cellulose acetate, polyglycolic acid, polylactic-glycolic acid, cellulose esters, polyethersulfone, acrylics, their derivatives, and combinations thereof. Examples of suitable soft acrylics are more fully disclosed in U.S. Pat. No. 5,403,901, which is incorporated herein in its entirety by reference. Said polymeric composition most preferably comprises silicone. Of course, said polymeric composition may also comprise other conventional materials that affect its physical properties, including, but not limited to, porosity, tortuosity, permeability, rigidity, hardness, and smoothness. Exemplary materials affecting certain ones of these physical properties include conventional plasticizers, fillers, and lubricants. Said polymeric composition may comprise other conventional materials that affect its chemical properties, including, but not limited to, toxicity, hydrophobicity, and body **12**—inner core **26** interaction. Body **12** is preferably impermeable to the pharmaceutically active agent of inner core **26**. When body **12** is made from a generally elastic polymeric composition, the diameter of well **22** may be slightly less than the diameter of inner core **26**. This frictional fit secures inner core **26** within well **22**. In this embodiment, body **12** may be formed without retaining member **28**, if desired.

[**0033**] Inner core **26** may comprise any pharmaceutically active agents suitable for localized delivery to a target tissue. Examples of pharmaceutically active agents suitable for inner core **26** are anti-infectives, including, without limitation, antibiotics, antivirals, and antifungals; antiallergenic agents and mast cell stabilizers; steroidal and non-steroidal anti-inflammatory agents; combinations of anti-infective and anti-inflammatory agents; decongestants; anti-glaucoma agents, including, without limitation, adrenergics, β-adrenergic blocking agents, α-adrenergic agonists, parasypathomimetic agents, cholinesterase inhibitors, carbonic anhydrase inhibitors, and prostaglandins; combinations of anti-glaucoma agents; antioxidants; nutritional supplements; drugs for the treatment of cystoid macular edema including, without limitation, non-steroidal anti-inflammatory agents; drugs for the treatment of ARMD, including, without limitation, angiogenesis inhibitors and nutritional supplements; drugs for the treatment of herpetic infections and CMV ocular infections; drugs for the treatment of proliferative vitreoretinopathy including, without limitation, antimetabolites and fibrinolytics; wound modulating agents, including, without limitation, growth factors; antimetabolites; neuroprotective drugs, including, without limitation, eliprodil; and angiostatic steroids for the treatment of diseases or conditions of the posterior segment of the eye, including, without limitation, ARMD, CNV, retinopathies, retinitis, uveitis, macular edema, and glaucoma. Such angiostatic steroids are more fully disclosed in U.S. Pat. Nos. 5,679,666 and 5,770,592, which are incorporated herein in their entirety by reference. Preferred ones of such angiostatic steroids include 4,9(11)-Pregnadien-17α,21-diol-3,20-dione and 4,9(11)-Pregnadien-17α,21-diol-3,20-dione-21-acetate. Inner core **26** may also comprise conventional non-active excipients to enhance the stability, solubility, penetrability, or other properties of the active agent or the drug core.

[**0034**] If inner core **26** is a tablet, it may further comprise conventional excipients necessary for tableting, such as fillers and lubricants. Such tablets may be produced using conventional tableting methods. The pharmaceutically active agent is preferably distributed evenly throughout the tablet. In addition to conventional tablets, inner core **26** may comprise a special tablet that bioerodes at a controlled rate, releasing the pharmaceutically active agent. By way of example, such bioerosion may occur through hydrolosis or enzymatic cleavage. If inner core **26** is a hydrogel, the hydrogel may bioerode at a controlled rate, releasing the pharmaceutically active agent. Alternatively, the hydrogel may be non-bioerodable but allow diffusion of the pharmaceutically active agent.

[**0035**] Device **10** may be made by conventional polymer processing methods, including, but not limited to, injection molding, extrusion molding, transfer molding, and compression molding. Preferably, device **10** is formed using conventional injection molding techniques. Inner core **26** is preferably disposed in well **22** after the formation of body **12** of device **10**. Retaining member **28** is preferably resilient enough to allow inner core **26** to be inserted through opening **24** and then to return to its position as shown in **FIG. 1**.

[**0036**] Device **10** is preferably surgically placed proximate a target tissue. The surgeon first makes an incision proximate the target tissue. Next, the surgeon performs a blunt dissection to a level at or near the target tissue. Once the target tissue is located, the surgeon uses forceps to hold device **10** with internal surface **14** facing the target tissue and distal end **20** away from the surgeon. The surgeon then

introduces device **10** into the dissection tunnel, and positions device **10** with internal surface **14** facing the target tissue. Once in place, the surgeon may or may not use sutures to fix device **10** to the underlying tissue, depending on the specific tissue. After placement, the surgeon sutures the opening and places a strip of antibiotic ointment on the surgical wound.

[**0037**] The physical shape of body **12**, including the geometry of internal surface **14**, well **22**, opening **24**, and retaining member **28**, facilitate the unidirectional delivery of a pharmaceutically effective amount of the pharmaceutically active agent from inner core **26** to the target tissue. In particular, the absence of a polymer layer or membrane between inner core **26** and the underlying tissue greatly enhances and simplifies the delivery of an active agent to the target tissue.

[**0038**] Device **10** can be used to deliver a pharmaceutically effective amount of a pharmaceutically active agent to target tissue for many years, depending on the particular physicochemical properties of the pharmaceutically active agent employed. Important physicochemical properties include hydrophobicity, solubility, dissolution rate, diffusion coefficient, and tissue affinity. After inner core **26** no longer contains active agent, a surgeon may easily remove device **10**. In addition, the "preformed" tunnel facilitates the replacement of an old device **10** with a new device **10**.

[**0039**] **FIGS. 3 through 6**B schematically illustrate an ophthalmic drug delivery device **50** according to a preferred embodiment of the present invention. Device **50** may be used in any case where localized delivery of a pharmaceutically active agent to the eye is required. Device **50** is particularly useful for localized delivery of active agents to the posterior segment of the eye. A preferred use for device **50** is the delivery of pharmaceutically active agents to the retina proximate the macula for treating ARMD, choroidial neovascularization (CNV), retinopathies, retinitis, uveitis, macular edema, and glaucoma. Of course, device **50** may also be utilized for localized delivery of pharmaceutically active agents to body tissue other than the eye, if desired.

[**0040**] Referring first to **FIG. 3**, a human eye **52** is schematically illustrated. Eye **52** has a cornea **54**, a lens **56**, a sclera **58**, a choroid **60**, a retina **62**, and an optic nerve **64**. An anterior segment **66** of eye **52** generally includes the portions of eye **52** anterior of a line **67**. A posterior segment **68** of eye **52** generally includes the portions of eye **52** posterior of line **67**. Retina **62** is physically attached to choroid **60** in a circumferential manner proximate pars plana **70**. Retina **62** has a macula **72** located slightly lateral to its optic disk. As is well known in the ophthahnic art, macula **72** is comprised primarily of retinal cones and is the region of maximum visual acuity in retina **62**. A Tenon's capsule or Tenon's membrane **74** is disposed on sclera **58**. A conjunctiva **76** covers a short area of the globe of eye **52** posterior to limbus **77** (the bulbar conjunctiva) and folds up (the upper cul-de-sac) or down (the lower cul-de-sac) to cover the inner areas of upper eyelid **78** and lower eyelid **79**, respectively. Conjunctiva **76** is disposed on top of Tenon's capsule **74**. As is shown in **FIGS. 3 and 4**, and as is described in greater detail hereinbelow, device **50** is preferably disposed directly on the outer surface of sclera **58**, below Tenon's capsule **74** for treatment of most posterior segment diseases or conditions. In addition, for treatment of ARMD in humans, device **50** is preferably disposed directly on the outer surface of sclera **58**, below Tenon's capsule **74**, with an inner core of device **50** proximate macula **72**.

[**0041**] **FIGS. 5, 6A**, and 6B schematically illustrate drug delivery device **50** in greater detail. Device **50** generally includes a body **80** having a scleral surface **82** and an orbital surface **84**. Scleral surface **82** is preferably designed with a radius of curvature that facilitates direct contact with sclera **58**. Orbital surface **84** is preferably designed with a radius of curvature that facilitates implantation under Tenon's capsule **74**. Body **80** preferably has a curved, generally rectangular three-dimensional geometry with rounded sides **86** and **88**, proximal end **90**, and distal end **92**. As shown best in the side sectional view of **FIG. 6A**, orbital surface **84** preferably has tapered surfaces **94** and **96** proximate proximal end **90** and distal end **92**, respectively, that facilitate sub-Tenon implantation of device **50** and enhance the comfort of the patient. Body **80** may alternatively have a geometry similar to that of device **10***a* shown in **FIG. 2**. In addition, body **80** may have any other geometry that has a curved scleral surface **82** for contact with sclera **58**. By way of example, body **80** may have a generally cylindrical, oval, square, or other polygonal three-dimensional geometry.

[**0042**] Body **80** includes a well or cavity **102** having an opening **104** to scleral surface **82**. An inner core **106** is preferably disposed in well **102**. Inner core **106** is preferably a tablet comprising one or more pharmaceutically active agents. Alternatively, inner core **106** may comprise a conventional hydrogel having one or more pharmaceutically active agents disposed therein. A retaining member **108** is preferably disposed proximate opening **104**. Retaining member **108** prevents inner core **106** from falling out of well **102**. When inner core **106** is a cylindrical tablet, retaining member **108** is preferably a continuous rim or lip disposed circumferentially around opening **104** having a diameter slightly less than the diameter of tablet **106**. Alternatively, retaining member **108** may comprise one or more members that extend from body **80** into opening **104**. Although not shown in **FIG. 6A**, inner core **106** may alternatively comprise a suspension, solution, powder, or combination thereof containing one or more pharmaceutically active agents. In this embodiment, scleral surface **82** is formed without opening **104**, and the suspension, solution, powder, or combination thereof diffuses through the relatively thin portion of scleral surface **82** below inner core **26**. Still further in the alternative, device **50** may be formed without well **102** or inner core **106**, and the pharmaceutically active agent(s) in the form of a suspension, solution, powder, or combination thereof may be dispersed throughout body **80** of device **50**. In this embodiment, the pharmaceutically active agent diffuses through body **80** into the target tissue.

[**0043**] The geometry and dimensions of device **50** maximize communication between the pharmaceutically active agent of inner core **106** and the tissue underlying scleral surface **82**. Scleral surface **82** preferably physically contacts the outer surface of sclera **58**. Although not shown in **FIG. 6A** or 6B, inner core **106** may be formed so that surface **106***a* physically contacts the outer surface of sclera **58**. Alternatively, scleral surface **82** may be disposed proximate the outer surface of sclera **58**. By way of example, device **50** may be disposed in the periocular tissues just above the outer surface of sclera **58** or intra-lamellarly within sclera **58**.

[**0044**] Body **80** preferably comprises a biocompatible, non-bioerodable material. Body **80** more preferably com-

prises a biocompatible, non-bioerodable polymeric composition. The polymeric composition comprising body **80**, and the polymers suitable for use in the polymeric compositions of body **80**, may be any of the compositions and polymers described hereinabove for body **12** of device **10**. Body **80** most preferably is made from a polymeric composition comprising silicone. Body **80** is preferably impermeable to the pharmaceutically active agent of inner core **106**. When body **80** is made from a generally elastic polymeric composition, the diameter of well **102** may be slightly less than the diameter of inner core **106**. This frictional fit secures inner core **106** within well **102**. In this embodiment, body **80** may be formed without retaining member **108**, if desired.

[**0045**] Inner core **106** may comprise any ophthalmically acceptable pharmaceutically active agents suitable for localized delivery. Exemplary pharmaceutically active agents include the pharmaceutically active agents listed hereinabove for inner core **26** of device **10**. Inner core **106** may also comprise conventional non-active excipients to enhance the stability, solubility, penetrability, or other properties of the active agent.

[**0046**] If inner core **106** is a tablet, it may further comprise conventional excipients necessary for tableting, such as fillers and lubricants. Such tablets may be produced using conventional tableting methods. The pharmaceutically active agent is preferably distributed evenly throughout the tablet. In addition to conventional tablets, inner core **106** may comprise a special tablet that bioerodes at a controlled rate, releasing the pharmaceutically active agent. By way of example, such bioerosion may occur through hydrolosis or enzymatic cleavage. If inner core **106** is a hydrogel, the hydrogel may bioerode at a controlled rate, releasing the pharmaceutically active agent. Alternatively, the hydrogel may be non-bioerodable but allow diffusion of the pharmaceutically active agent.

[**0047**] Device **50** may be made by conventional polymer processing methods, including, but not limited to, injection molding, extrusion molding, transfer molding, and compression molding. Preferably, device **50** is formed using conventional injection molding techniques as described hereinabove for device **10**.

[**0048**] Device **50** is preferably surgically placed directly on the outer surface of sclera **58** below Tenon's capsule **74** using a simple surgical technique that is capable of being performed in an outpatient setting. The surgeon first performs a peritomy in one of the quadrants of eye **52**. Preferably, the surgeon performs the peritomy in the infra-temporal quadrant, about 3 mm posterior to limbus **77** of eye **52**. Once this incision is made, the surgeon performs a blunt dissection to separate Tenon's capsule **74** from sclera **58**, forming an antero-posterior tunnel. Once the tunnel is formed, the surgeon uses forceps to hold device **50** with scleral surface **82** facing sclera **58** and distal end **92** away from the surgeon. The surgeon then introduces device **50** into the tunnel in a generally circular motion to position inner core **106** of device **50** generally above the desired portion of retina **62**. The surgeon then closes the peritomy by suturing Tenon's capsule **74** and conjunctiva **76** to sclera **58**. After closing, the surgeon places a strip of antibiotic ointment on the surgical wound. Alternatively, the surgeon may suture proximal end **90** of device **50** to sclera **58** to hold device **50** in the desired location before closure of the tunnel.

[**0049**] In the case of ARMD in the human eye, the surgeon utilizes the above-described technique to position inner core **106** of device **50** in one of two preferred locations in the infra-temporal quadrant of eye **52**. One preferred location is directly on the outer surface of sclera **58**, below Tenon's capsule **74**, with inner core **106** positioned proximate to, but not directly above, macula **72**. A surgeon may position inner core **106** of device **50** at this location by moving distal end **92** of device **50** below the inferior oblique muscle in a direction generally parallel to the lateral rectus muscle. A second preferred location is directly on the outer surface of sclera **58**, below Tenon's capsule **74**, with inner core **106** positioned directly above macula **72**. A surgeon may position inner core **106** of device **50** at this location by moving distal end **92** of device **50** toward macula **72** along a path generally between the lateral and inferior rectus muscles and below the inferior oblique muscle. For ARMD, the pharmaceutically active agent of inner core **106** is preferably one of the angiostatic steroids disclosed in U.S. Pat. Nos. 5,679,666 and 5,770,592.

[**0050**] The physical shape of body **80** of device **50**, including the geometry of scleral surface **82**, well **102**, opening **104**, and retaining member **108**, facilitate the unidirectional delivery of a pharmaceutically effective amount of the pharmaceutically active agent from inner core **106** through sclera **58**, choroid **60**, and into retina **62**. In particular, the absence of a polymer layer or membrane between inner core **106** and sclera **58** greatly enhances and simplifies the delivery of an active agent to retina **62**.

[**0051**] It is believed that device **50** can be used to deliver a pharmaceutically effective amount of a pharmaceutically active agent to retina **62** for many years, depending on the particular physicochemical properties of the pharmaceutically active agent employed. Important physicochemical properties include hydrophobicity, solubility, dissolution rate, diffusion coefficient, and tissue affinity. After inner core **106** no longer contains active agent, a surgeon may easily remove device **50**. In addition, the "pre-formed" tunnel facilitates the replacement of an old device **50** with a new device **50**.

[**0052**] The following example illustrates effective drug delivery to a rabbit retina using a preferred embodiment and surgical technique of the present invention, but are in no way limiting.

EXAMPLE

[**0053**] A device **50** was surgically implanted on the outer surface of the sclera, below the Tenon's capsule, generally along the inferior border of the lateral rectus muscle of the right eye of twenty (20) New Zealand White rabbits using a procedure similar to that described hereinabove for implantation of device **50** on sclera **58** of eye **52**. Device **50** was constructed as shown in **FIGS. 5 through 6**B, with the following dimensions. Body **80** had a length **110** of about 15 mm, a width **112** of about 7.0 mm, and a maximum thickness **114** of about 1.8 mm. Retaining member **108** had a thickness **116** of about 0.15 mm. Scleral surface **82** had a radius of curvature of about 8.5 mm and an arc length of about 18 mm. Inner core **106** was a cylindrical tablet with a diameter of about 5.0 mm and a thickness of about 1.5 mm. Opening **104** had a diameter of about 3.8 mm. Well **102** had a diameter of about 4.4 mm. The pharmaceutically active agent used in

tablet **106** was 4,9(11)-Pregnadien-17α,21-diol-3,20-dione, an angiostatic steroid sold by Steraloids, Inc. of Wilton, N.H., and which is more fully disclosed in U.S. Pat. Nos. 5,770,592 and 5,679,666. The formulation of tablet **106** consisted of 99.75 weight percent 4,9(11)-Pregnadien-17α, 21-diol-3,20-dione, and 0.25 weight percent magnesium stearate.

[**0054**] At one week after implantation, 4 rabbits were euthanized and their right eyes were enucleated. The device **50** was removed from the eyes, and the location of tablet **106** was marked on their sclerae. Following the removal of the anterior segment and the vitreous of each eye and inversion of the thus formed eye-cup, a 10 mm diameter circular zone of retinal tissue, concentric with and below the location of tablet **106** on the sclera, was harvested (the "target site"). A 10 mm diameter circular zone of retinal tissue was also harvested from a second site located remote from the target site and on the other side of the optic nerve. In addition, a 10 mm diameter circular zone of retinal tissue was harvested from a third site located between the second site and the target site. Similar 10 mm diameter circular zones of choroidal tissue were also harvested at the target site, second site, and third site. All these tissues were separately homogenized, and the concentration of angiostatic steroid in each of these tissues was determined via an ocular pharmacokinetic study using high performance liquid chromatography and mass spectrometry analysis (LC-MS/MS). This procedure was repeated at 3, 6, 9, and 12 weeks after implantation.

[**0055**] **FIG. 7** shows the mean concentration of 4,9(11)-Pregnadien-17α,21-diol-3,20-dione in the retina and the choroid at the target site as a function of time. The "error bars" surrounding each data point represent standard deviation. As shown in **FIG. 7**, device **50** delivered a pharmaceutically effective and generally constant amount of 4,9(11)-Pregnadien-17α,21-diol-3,20-dione to the retina and the choroid at the target site for a time period of up to twelve weeks. In contrast, the levels of 4,9(11)-Pregnadien-17α,21-diol-3,20-dione in the retina and the choroid at the second and third sites were at or near zero. Therefore, device **50** also delivered a localized dose of angiostatic steroid to the retina and the choroid at the target site.

[**0056**] From the above, it may be appreciated that the present invention provides improved devices and methods for safe, effective, rate-controlled, localized delivery of a variety of pharmaceutically active agents to any body tissue. The surgical procedure for implanting such devices is safe, simple, quick, and capable of being performed in an outpatient setting. Such devices are easy and economical to manufacture. Furthermore, because of their capability to deliver a wide variety of pharmaceutically active agents, such devices are useful in clinical studies to deliver various agents that create a specific physical condition in a patient or animal subject. In the particular field of ophthalmic drug delivery, such devices are especially useful for localized delivery of pharmaceutically active agents to the posterior segment of the eye to combat ARMD, CNV, retinopathies, retinitis, uveitis, macular edema, and glaucoma.

[**0057**] It is believed that the operation and construction of the present invention will be apparent from the foregoing description. While the apparatus and methods shown or described above have been characterized as being preferred, various changes and modifications may be made therein without departing from the spirit and scope of the invention as defined in the following claims.

What is claimed is:

1. An ophthalmic drug delivery device, comprising:

a body having:

a scleral surface having a radius of curvature that facilitates contact with a sclera of a human eye;

a well having an opening to said scleral surface; and

a geometry that facilitates disposing said device on an outer surface of said sclera, below a Tenon's capsule of said eye, and in a posterior segment of said eye; and

an inner core disposed in said well and comprising a pharmaceutically active agent.

2. The ophthalmic drug delivery device of claim 1, wherein said body has a geometry that facilitates disposing said device on said outer surface of said sclera, below said Tenon's capsule, and in said posterior segment so that said inner core is disposed proximate a macula of said eye.

3. The ophthalmic drug delivery device of claim 2, wherein said body has a geometry that facilitates disposing said device on said outer surface of said sclera, below said Tenon's capsule, and in said posterior segment so that said inner core is disposed generally above said macula.

4. The ophthalmic drug delivery device of claim 1, wherein said inner core is a tablet.

5. The ophthalmic drug delivery device of claim 4, wherein at least a portion of said body is made from a generally elastic material so that said generally elastic material, a geometry of said well, and a geometry of said tablet frictionally secure said tablet within said well.

6. The ophthalmic drug delivery device of claim 4, wherein said tablet is formulated to bioerode and release said pharmaceutically active agent at a controlled rate.

7. The ophthalmic drug delivery device of claim 1, wherein said inner core is a hydrogel.

8. The ophthalmic drug delivery device of claim 7, wherein said hydrogel is formulated to bioerode and release said pharmaceutically active agent at a controlled rate.

9. The ophthalmic drug delivery device of claim 7, wherein said pharmaceutically active agent diffuses through said hydrogel at a controlled rate.

10. The ophthalmic drug delivery device of claim 1, further comprising a retaining member extending from said body proximate said opening, and wherein said retaining member helps to retain said inner core in said well.

11. The ophthalmic drug delivery device of claim 10, wherein said retaining member comprises a rim at least partially disposed around said opening.

12. The ophthalmic drug delivery device of any one of claims **1-11**, wherein said pharmaceutically active agent comprises a compound selected from the group consisting of 4,9(11)-Pregnadien-17α,21-diol-3,20-dione and 4,9(11)-Pregnadien-17α,21-diol-3,20-dione-21-acetate.

13. The ophthalmic drug delivery device of any one of claims **1-11**, wherein said pharmaceutically active agent comprises eliprodil.

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