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(54) **Title**: SUSTAINED-RELEASE RESERVOIR IMPLANTS FOR INTRACAMERAL DRUG DELIVERY

FIGURE 3: Hypotensive Lipid Release from a Reservoir Implant

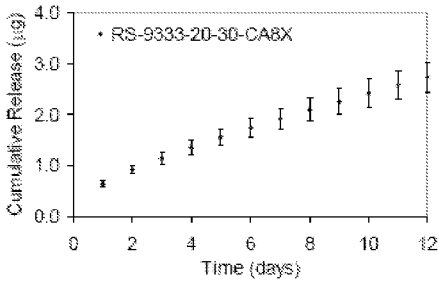

FIGURE 3 LEGEND: Implant described in Example 1, releasing the API, isopropyl 5-{3-[(2S)-1-{4-[(1S)-1-hydroxyhexyl] phenyl}-5-oxypyrrolidin-2-yl]propyl}thiophene-2-carboxylate at an in vitro release of 0.2ug/day.

(57) **Abstract**: The present invention provides a sustained release implant for intraocular use to treat elevated intraocular pressure, which implant is configured for intracameral or anterior vitreal administration to a patient with elevated intraocular pressure (IOP), said implant comprising a core of an antihypertensive agent surrounded by a polymer, which limits the rate of passage of the antihypertensive agent from the implant into the eye of said patient and said implant provides a linear rate of release of therapeutically effective amounts of said anti-hypertensive agent into the eye for a period of time of between 14 days and 365 days.

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SUSTAINED-RELEASE RESERVOIR IMPLANTS FOR INTRACAMERAL DRUG DELIVERY

CROSS REFERENCE TO RELATED APPLICATIONS

[1] This Application is related to, and claims the benefit of, US provisional Patent Application 61/321,422, filed on April 6, 2010, in the names of Michael R. Robinson, et al., which said provisional Patent Application is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[2] The present invention relates to sustained release implants for intraocular use, which implants are configured for primarily intracameral administration but also intrascleral, intracorneal, anterior vitreal administration to a patient suffering from an intraocular condition, said implant comprising a core of a drug, for treating said condition, surrounded by a polymer, which limits the rate of passage of the drug from the implant into the eye of said patient.

[3] United States Patent Application Serial No. 12/411,250 describes sustained release matrix drug delivery systems, such as microspheres and implants, where the active pharmaceutical ingredient (API) is mixed homogenously with the polymer (See Figure 1). These matrix systems can be placed in the eye, such as in the anterior chamber (i.e. intracameral) or intravitreal, to release ocular anti-hypertensive drugs. The rate of drug released depends on the total surface area of the implant, the percentage of drug loaded, the water solubility of the API, and the speed of polymer degradation.

[4] The present invention provides a sustained release implant for intraocular use and, in particular, to treat elevated intraocular pressure, which implant is configured for intracameral or anterior vitreal administration to a patient with an ocular condition, e.g. elevated intraocular pressure (IOP), said implant comprising a core of an ocular drug. e.g. an antihypertensive agent, surrounded by a polymer, which limits the rate of passage of the drug or antihypertensive agent from the implant into the eye of said patient and said implant provides a linear rate of release of therapeutically effective amounts of said anti-hypertensive agent into the eye for a period of time of between approximately 14 days and 365 days.

[5] In one aspect of the invention, there is provided a reservoir implant suitable for releasing a hypotensive lipid, comprising a core made with a mixture of a hypotensive lipid and a biodegradable polymer, e.g. a polycaprolactone, or a nonbiodegradible polymer, e.g. a silicone elastomer, and/or an excipient, e.g. a surfactant such as a tri block copolymers of ethylene oxide and propylene oxide or an ethylene oxide adduct of a fatty acid or alcohol, extruded into thin

filaments and coated with the rate limiting polymer, e.g. cellulose acetate, wherein said reservoir implant provides a linear release rate of hypotensive lipid over a period of 12 days or more.

[6] In another aspect of the invention, there is provided a reservoir implant suitable for releasing a hypotensive lipid, said implant comprising a core of said hypotensive lipid centrally located in a silicone tube having the ends closed by an impermeable ethylene vinyl acetate polymer, wherein the drug elutes from the sides of the silicone tube to provide a linear release over a period of 21 days or more.

[7]

Brief Description of the Drawings

[8] Figure 1 shows a matrix drug delivery system, as formed, and during the initial dissolving stage after placement in the eye.

[9] Figure 2 shows the reservoir drug delivery system, as formed, and during the initial dissolving stage after placement in the eye.

[10] Figure 3 shows the implant, described in Example 1, releasing the API, isopropyl 5-{3-[(2S)-1-{4-[(1S)-1-hydroxyhexyl] phenyl}-5-oxypyrrolidin-2-yl]propyl}thiophene-2-carboxylate at an in vitro release of 0.2ug/day.

[11] Figure 4 shows a reservoir implant, as described in Example 1, releases a hypotensive lipid after being placed intracamerally in a dog to reduce the intraocular pressure approximately 30 to 45% below baseline for at least 5 weeks.

[12] Figure 5 shows, a reservoir implant, as described in Example 1, releases a hypotensive lipid after being placed intravitreally in a dog to reduce the intraocular pressure to approximately a maximum of 15 to 20% below baseline over the initial 3 weeks.

[13] Figure 6 shows the Implants described in Example 2, releasing the API, isopropyl 5-{3-[(2S)-1-{4-[(1S)-1-hydroxyhexyl] phenyl}-5-oxypyrrolidin-2-yl]propyl}thiophene-2-carboxylate at an in vitro release of 6.3ug/day and 9.3 ug/day.

[14] Figure 7 shows, a reservoir implant, as described in example 2, releases a hypotensive lipid after being placed intracamerally in a dog to reduce the intraocular pressure to approximately 60% below baseline over a 2 week time frame.

[15] Figure 8 shows an intracameral reservoir implant releasing an EP2 agonist as described in Example 2.

[16] Figure 9 shows three reservoir implants, as described in example 2, release a hypotensive lipid after being placed sub-Tenon's in a dog to reduce the intraocular pressure to approximately a maximum of 18 to 20% below baseline over the initial 2 weeks.

[17] Figure 10 shows sub-Tenon's reservoir implants (arrow) releasing an EP2 agonist as described in Example 2.

[18] Figure 11 shows an implant, as described in Example 3, releases the API, isopropyl 5-{3-[(2S)-1-{4-[(1S)-1-hydroxyhexyl] phenyl}-5-oxypyrrolidin-2-yl]propyl}thiophene-2-carboxylate at an in vitro release rate of 46 ug/day and 66 ug/day.

Figure 12 describes certain implants of the invention comprising varying amounts of bimatoprost in the core surrounded by a polycaprolactone hollow tube of varying wall thicknesses.

Figure 13 shows the release rates of certain of the implants of Figure 12.

Figure 14 shows the release rates of certain of the implants of Figure 12.

Figure 15 shows the release rates of certain of the implants of Figure 12.

Detailed Description

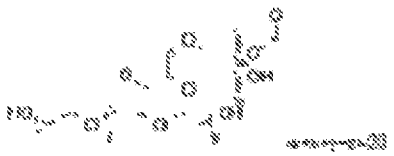
[19] The present invention provides sustained release reservoir drug delivery systems for intracameral or intravitreal application. Said reservoir systems comprise a drug reservoir surrounded by bioerodible or non-bioerodible polymers that control the drug release (See Figure 2).

[20] As shown in Figure 2, the drug delivery system comprises an implant (10) configured for implantation in the anterior vitreal, space which implant comprises a core (11), which, in the embodiment shown in this figure, is fabricated as a bundle of individual fibers (15), said fibers comprising a drug for treating an ocular condition. Said drug may be combined with one or more excipients to form a mixture and the mixture extruded into fibers, which fibers are bundled to form a contiguous body to provide the core of the implant. The core is surrounded by a polymer (15) which is permeable to the drug and controls the passage of the drug from the core into the eye in which the implant is placed. In this embodiment, the rate limiting polymer completely surrounds the drug-containing core. However, the rate limiting polymer may not be the sole means of surrounding the core to isolate the core. As shown in Figure 2a the drug-containing core (19) may be centrally located in a tube (21) which tube may be a polymer which is permeable to the drug and controls the passage of the drug from the core into the eye in which the implant is placed. The tube heat sealed at one or both ends (23) or capped (25) at one or both ends with a drug impermeable polymer.

[21] As further shown in Figure 2, water from the anterior chamber of the eye diffuses through the rate controlling polymers to the drug reservoir, dissolves the drug at the contact site of the drug reservoir, and the drug diffuses outwards from the polymer into the ocular tissues. The advantage of a reservoir drug delivery system over matrix drug delivery systems is that the reservoir delivers a smaller initial drug burst followed by a steady-state release rate that persists until the majority of the drug reservoir is depleted. The release rate is directly proportional to both the surface area of the implant, the diffusivity (i.e. the diffusion coefficient of the drug through the rate-limiting polymers), and indirectly proportional to the thickness of the surrounding polymers. The drug release from the reservoir implant can be tuned to the desired release rate by altering the surface area of drug diffusion, changing the polymer, and/or varying the thickness of the polymer coating. Another advantage of a reservoir implant is the ability to harbor large drug loads so that the implant can release for a minimum of 3 months and up to 5 years. In addition, the drug reservoirs and the rate-controlling polymer membranes can be fabricated using separate processes then assembled together to form implants. Mild fabrication process can be selected for making the drug reservoirs so that the activity and/or chemical integrity of the drugs or pharmaceutical agents in the reservoirs are protected from harsh conditions (high temperature and high shearing force) that may be needed for melt extrusion. Therefore, drug degradation is minimized. This is particularly useful for delivery of heat-labile drug compounds. The rate-controlling membranes can also shield the drugs in the reservoirs from enzymatic degradation.

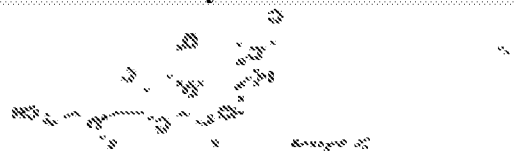
[22] The drug reservoirs can contain drug, only, or a mixture of drug and excipients. A variety of excipients can be incorporated in the formulations of the said drug reservoirs. These include, but are not limited to, surfactants, e.g. tri block copolymers of ethylene oxide and propylene oxide and ethylene oxide adducts of fatty acids or alcohols; anti-oxidants; pH modulating agents; bulking agents; osmotic agents; tonicity agents; disintegrating agents; binders, gliding agents; etc. For example, the said excipients can be selected from the following: Pluronic F68, Pluronic F127 (Polyoxamer 407), polysorbate 80, polysorbate 20, sodium dodecyl sulfate, hydroxypropyl-beta-cyclodextrin, poly(ethylene oxide), poly(ethylene glycol), polyvinylpyrrolidone, hydroxypropyl methylcellulose, carboxymethylcellulose, sodium phosphate, sodium chloride. The drug reservoirs can be fabricated using a various methods including compression, packing, and/or extrusion. The preferred surfactants are further described below:

Polysorbate 80



Polyoxyethylene (20) sorbitan monooleate

Polysorbate 20



Polyoxyethylene (20) sorbitan monolaurate
Polysorbate 20
PEG(20)sorbitan monolaurate

[23] Poloxamer 407 is a hydrophilic non-ionic surfactant of the more general class of copolymers known as poloxamers. Poloxamer 407 is a triblock copolymer consisting of a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol. The approximate lengths of the two PEG blocks is 101 repeat units while the approximate length of the propylene glycol block is 56 repeat units. This particular compound is also known by the BASF trade name Pluronic F127.

[24] Poloxamer 188, also known as Pluronic F68, is also a triblock copolymer with a similar chemical structure to Poloxamer 407 containing a center block of polypropylene glycol (PPG) flanked by a poly(ethylene glycol) (PEG) block on each side. The molecular weight of Poloxamer 188 is lower than Poloxamer 407.

[25] The rate-controlling membranes surrounding the drug reservoirs can be made of non-degradable polymers including, but not limited to, silicone elastomers, poly(ethylene-co-vinylacetate), polyurethane, or biodegradable polymers such as aliphatic polyesters. The membranes can be fabricated by solution casting, spray coating, or melt extrusion.

[26] The implants can be fabricated in the following ways:

[27] -Coating a pre-formed drug reservoir using conventional coating methods including dip coating, spray coating, etc.

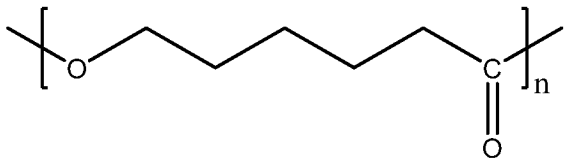
[28] -Inserting / filling a pre-formed drug reservoir into a pre-formed capsule made of said rate-controlling polymers.

[29] -Co-extruding the drug reservoir formulation and the rate-controlling polymer.

[30] In one embodiment of the invention, the rate-controlling membranes are made of degradable aliphatic polyesters such as, but not limited to, poly(ε-caprolactone), poly(D,L-

lactide), poly(L-lactide), copolymers of lactones such as poly(D,L-lactide-co-glycolide), and mixtures of two or more of these polymers. The polymers can be melt-extruded or molded into capsules with one of the ends open. Drug reservoirs in their solid or liquid forms are then filled into the open-ended capsules and the open ends are subsequently sealed. The drug load can be released over time and the polymer structure bioerodes within ~6 to 12 months of drug release. The reservoir delivery systems can be also placed in the sub-Tenon's, subconjunctival, episcleral, intrascleral, suprachoroidal, intrachoroidal, and sub-retinal spaces.

[31] Poly(ε-caprolactone) (PCL) is a biodegradable aliphatic polyester. It is usually prepared by ring-opening polymerization of ε-caprolactone using a catalyst such as stannous octoate. The chemical structure of PCL is as follows:



[32] Examples of drugs that can be used with the reservoir delivery systems include the following:

[33] -Hypotensive lipids (e.g. bimatoprost and compounds set forth in U.S. Pat. No. 5,352,708), and other prostaglandin analogues like latanoprost (Xalatan), bimatoprost (Lumigan), travoprost (Travatan), unoprostone, EP2/EP4 receptor agonists, and Asterand compounds. The prostaglandin analogues increase uveoscleral outflow of aqueous humor and bimatoprost also increases trabecular outflow.

[34] -Topical beta-adrenergic receptor antagonists such as timolol, betaxolol, levobetaxolol, carteolol, levobunolol, and propranolol decrease aqueous humor production by the ciliary body.

[35] -Alpha-adrenergic agonists such as brimonidine (Alphagan) and apraclonidine (iopidine) work by a dual mechanism, decreasing aqueous production and increasing uveoscleral outflow. Less-selective sympathomimetics like epinephrine and dipivefrin (Propine) increase outflow of aqueous humor through trabecular meshwork and possibly through uveoscleral outflow pathway, probably by a beta 2-agonist action.

[36] -Miotic agents (parasympathomimetics) like pilocarpine work by contraction of the ciliary muscle, tightening the trabecular meshwork and allowing increased outflow of the aqueous humor.

[37] -Carbonic anhydrase inhibitors like dorzolamide (Trusopt), brinzolamide (Azopt), acetazolamide (Diamox) lower secretion of aqueous humor by inhibiting carbonic anhydrase in the ciliary body.

[38] -Other drugs that lower IOP can be used in the delivery system such as Rho-kinase inhibitors (e.g. INS117548) designed to lower IOP by disrupting the actin cytoskeleton of the trabecular meshwork, Latrunculin B compound (e.g. INS115644), PF-04217329, PF-03187207, AR-102, AL-6221, AL-3789, calcium channel blockers, vaptans (vasopressin-receptor antagonists), anecortave acetate and analogues, ethacrynic acid, and cannabinoids.

[39] Combinations of ocular anti-hypertensives, such as a beta blocker and a prostaglandin analogue, can also be used in the delivery systems. These include Ganfort (bimatoprost/timolol), Extravan or Duotrav (travoprost/timolol), Xalcom (latanoprost/timolol, Combigan (brimonidine/timolol, and Cosopt (dorzolamide/timolol).

[40] In combination with an IOP lowering drug, an agent that confers neuroprotection can also be placed in the delivery system and includes memantine and serotonergics [e.g., 5-HT.sub.2 agonists, such as S-(+)-1-(2-aminopropyl)-indazole-6-ol)].

[41] Non-antihypertensive agents can also be used, such as anti-VEGF compounds to treat anterior or posterior segment neovascularization, or corticosteroids to treat uveitis, macular edema, and neovascular diseases.

[42] The following examples are intended to illustrate the present invention.

[43] Example 1:

[44]

[45] A reservoir implant releasing the hypotensive lipid, isopropyl 5-{3-[(2S)-1-{4-[(1S)-1-hydroxyhexyl] phenyl}-5-oxypyrrolidin-2-yl]propyl}thiophene-2-carboxylate (an EP2 agonist), was formulated into a reservoir implant for intracameral and intravitreal application. The reservoir cores were made with a formulation comprising the hypotensive lipid, a poly(ε-caprolactone) and a poloxamer at a weight ratio of 2:6:2, e.g., Poloxamer 407 a triblock copolymer consisting of a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol, which was extruded into thin filaments and the cores were coated with cellulose acetate. The total drug loading was 200 ug and the in vitro release rates were 0.2ug/day (See Figure 3). The release rate was linear over a 12-day period. An intracameral injection of the implant was performed in a dog. The intraocular pressure was reduced approximately 30 to 45% below baseline for a minimum of 5 weeks (See Figure 4). A similar reservoir implant was placed intravitreally in a dog. The intraocular pressure was

reduced to approximately a maximum of 15 to 20% below baseline over the initial 3 weeks (See Figure 5).

[46]

[47] Example 2

[48]

[49] A reservoir implant releasing, isopropyl 5-{3-[(2S)-1-{4-[(1S)-1-hydroxyhexyl] phenyl}-5-oxypyrrolidin-2-yl]propyl}thiophene-2-carboxylate was formulated into a reservoir implant using a silicone tube, 1 mm in diameter. The drug reservoir was the API centrally located in tube and the ends were closed using ethylene vinyl acetate polymer. Implants with two effective lengths, 2 mm and 3 mm, were made. The drug loading was 563 μg in the 2 mm implants and 997 μg in the 3 mm implants. In vitro release rates of these implants were 6.3 μg/day and 9.3 ug/day for the 2 mm and 3 mm implants, respectively (See Figure 6). The drug elutes from the sides of the silicone tube with a linear release observed over a 21 day time period. Implantation of an implant was performed in the anterior chamber of a dog. An intracameral injection of an implant releasing at 6.3 ug/day was performed in a dog. There was a profound reduction in the intraocular pressure compared with the baseline (See Figure 7). The intracameral implant was well tolerated and biocompatible (See Figure 8). Three implants were placed in the sub-Tenon's space in a dog and the intraocular pressure was reduced to approximately a maximum of 18 to 20% below baseline over the initial 2 weeks (See Figure 9). The sub-Tenon's implants were well tolerated with no clinical signs of inflammation (See Figure 10).

[50]

[51] Example 3

[52]

[53] Poly(ε-caprolactone) (PCL) tubes with an inner diameter (ID) of 790 μm and outer diameters (OD) of 1090 μm and 1350 μm were cut into 6 mm in length. One of the open ends of the tubes was heat sealed, 1.5 mg of isopropyl 5-{3-[(2S)-1-{4-[(1S)-1-hydroxyhexyl] phenyl}-5-oxypyrrolidin-2-yl]propyl}thiophene-2-carboxylate, an EP2 agonist, was filled into each of the tubes using a syringe. The open end was then heat sealed to form a capsule-like implant. In vitro release profiles are shown in Figure 11. The drug release rate was 46 μg/day for the implants with the outer diameter of 1090 μm and 66 μg/day for the ones with the outer diameter of 1350 μm.

[54]

[55] Example 4

[56]

[57] A sustained release implant comprising a core of an antihypertensive agent surrounded by a polymer, and configured for intracameral or anterior vitreal administration to a patient, is used to treat a patient with elevated intraocular pressure (IOP). The polymer utilized in said implant limits the rate of passage of the antihypertensive agent from the implant into the eye of the patient and provides a linear rate of release of therapeutically effective amounts of the anti-hypertensive into the eye for from 12 days to 365 days. The implant comprises a nonbiodegradable polymer, selected from the group consisting of silicone elastomers, poly(ethylene-co-vinylacetate)and polyurethane. or the implant comprises a biodegradable polymer, i.e., an aliphatic polyester.

[58] The antihypertensive agent is selected from the group consisting of hypotensive lipids, i.e. bimatoprost, latanoprost, travoprost, unoprostone, EP2 receptor agonists EP2/EP4 receptor agonists; beta-adrenergic receptor antagonists, i.e. timolol, betaxolol, levobetaxolol, carteolol, levobunolol and propranolol; alpha-adrenergic agonists, i.e. brimonidine and apraclonidine; sympathomimetics, i.e. epinephrine and dipivefrin; miotic agents, i.e. pilocarpine; carbonic anhydrase inhibitors, i.e. dorzolamide, brinzolamide and acetazolamide; Rho-kinase inhibitors, i.e. Latrunculin B compound, PF-04217329, PF-03187207, AR-102, AL-6221, and AL-3789, calcium channel blockers, vasopressin-receptor antagonists, i.e. vaptans, anecortave acetate and analogues and ethacrynic acid and cannabinoids. Alternatively, the antihypertensive agent is a combination of ocular anti-hypertensives, and the combination is selected from the group

consisting of bimatoprost/timolol, travoprost/timolol, latanoprost/timolol, brimonidine/timolol, and dorzolamide/timolol.

[59] Alternatively, the implant is a reservoir implant releasing a drug for treating an ocular condition, suitable for intracameral and intravitreal application to treat an ocular condition and comprises a core made with a formulation comprising the drug, a polycaprolactone and a polyoxamer, which formulation is extruded into thin filaments, assembled into a bundle and coated with cellulose acetate, wherein the reservoir implant provides a linear release rate of the drug over a 12 day period.

[60] In this example, the intraocular pressure is reduced approximately 30 to 45% below baseline for a minimum of 5 weeks, or the intraocular pressure is reduced to approximately a maximum of 15 to 20% below baseline over the initial 3 weeks. The total drug loading is 200 μg. The drug release rate is 0.2 μg/day.

[61] Alternatively, a reservoir implant releasing a hypotensive lipid, the implant and suitable for intracameral and intravitreal application is used to treat an ocular condition. Said implant comprises a core of the hypotensive lipid centrally located in a silicone tube having the ends closed by an impermeable ethylene vinyl acetate polymer, wherein the drug elutes from the sides of the silicone tube to provide a linear release over a 21 day time period. The silicone tube has a diameter of 1 mm. The hypotensive lipid is an EP2 agonist. The intraocular pressure is reduced approximately 18 to 20% below baseline for a minimum of 2 weeks when placed in the sub-Tenon's space.

[62] Alternatively, a reservoir implant releasing a hypotensive lipid, the implant and suitable for intracameral and intravitreal application is used to treat an ocular condition. Said implant comprises a core of the hypotensive lipid centrally located in a polycaprolactone tube having the ends heat sealed wherein the drug elutes from the sides of the silicone tube to provide a linear release observed over a 14 day time period. The tube has an inner diameter of 790 μm. The tube may has an outer diameter of 1090 μm and releases drug at a rate of 46 μg/day or the tube has an outer diameter of 1350 μm and releases drug at a rate of 66 μg/day.

[63] Alternatively the implant comprises from about 10 to about 50 weight percent of the anti-hypertensive agent and from about 50 to about 90 weight percent of the polymer.

[64] Example 5

[65]

[66] Poly(ε-caprolactone) (PCL) tubes with inner diameters (ID) of 800 μm and 1000 and an outer diameters (OD) of 980, 1150, 1170 and 1180 μm were cut into 8 mm lengths. One of the open ends of the tubes was heat sealed and varying amounts, i.e. from about 0.08 to 0.4 mg., of

bimatoprost were filled into each of the tubes using a syringe. (See Figure 12.) The open end was then heat sealed to form a capsule-like implant. In-vitro release profiles are shown in Figures 13 through 15.

[67] As a result of said experiment, the following conclusions were drawn:

PCL wall thickness affects permeability

With relatively thin walls, dissolution rate in the tubing is rate-determining step, as diffusion through the wall is fast and the release rate can be increased by increasing the filling.

With thick walls, both dissolution rate and wall thickness control release rate.

Hydrophilic additives (e.g. PEG 3350) significantly increase release rates.

The present invention is not to be limited in scope by the exemplified embodiments, which are only intended as illustrations of specific aspects of the invention. It will be appreciated that the invention is not limited thereto. Accordingly, any and all variations and modifications which may occur to those skilled in the art are to be considered to be within the scope and spirit of the invention as defined in the appended claims.

What is claimed is:

1. A sustained release implant for intraocular use to treat elevated intraocular pressure, configured for intracameral or anterior vitreal administration to a patient with elevated intraocular pressure (IOP), said implant comprising a core of an antihypertensive agent surrounded by a polymer, which limits the rate of passage of the antihypertensive agent from the implant into the eye of said patient, wherein said implant provides a linear rate of release of therapeutically effective amounts of said anti-hypertensive into said eye for a period of time of between 12 days and 365 days.

2. The implant of Claim 1 wherein said polymer is a nonbiodegradable polymer.

3. The implant of Claim 2 wherein said polymer is selected from the group consisting of silicone elastomers, poly(ethylene-co-vinylacetate)and polyurethane.

4. The implant of Claim 1 wherein said polymer is a biodegradable polymer.

5. The implant of claim 4 wherein said polymer is an aliphatic polyester.

6. The implant of Claim 1 wherein antihypertensive agent is selected from the group consisting of hypotensive lipids, beta-adrenergic receptor antagonists, alpha-adrenergic agonists, sympathomimetics, miotic agents, carbonic anhydrase inhibitors, Rho-kinase inhibitors, calcium channel blockers, vaptans (vasopressin-receptor antagonists,) and cannabinoids.

7. The implant of Claim 6 wherein antihypertensive agent is selected from the group consisting of bimatoprost, latanoprost, travoprost, unoprostone, EP2/EP4 receptor agonists, timolol, betaxolol, levobetaxolol, carteolol, levobunolol, propranolol, brimonidine, apraclonidine, epinephrine, dipivefrin, pilocarpine, dorzolamide, brinzolamide, acetazolamide, Rho-kinase inhibitors, Latrunculin B compound, PF-04217329, PF-03187207, AR-102, AL-6221, AL-3789, calcium channel blockers, vaptans, anecortave acetate and analogues, ethacrynic acid and cannabinoids.

8. The implant of Claim 6 wherein antihypertensive agent is a combination of ocular anti-hypertensives.

9. The implant of claim 8 wherein said combination is selected from the group consisting of bimatoprost/timolol, travoprost/timolol), latanoprost/timolol, brimonidine/timolol, and dorzolamide/timolol.

10. The implant of claim 1, wherein said antihypertensive agent is an EP2 agonist.

11. A reservoir implant releasing a hypotensive lipid, said implant being suitable for intracameral and intravitreal application to treat an ocular condition and comprising a core made with API/PCL/Pluronics extruded into thin filaments and coated with cellulose acetate, wherein said reservoir implant provides a linear release rate of hypotensive lipid over a 12 day period.

12. The reservoir implant of claim 11 wherein said hypotensive lipid is an EP2 agonist.

13. The reservoir implant of claim 12 wherein said ocular condition is ocular hypertension.

14. A intracameral reservoir implant according to claim 13 wherein the intraocular pressure was reduced approximately 30 to 45% below baseline for a minimum of 5 weeks.

15. An intravitreal reservoir implant according to claim 13 wherein the intraocular pressure was reduced to approximately a maximum of 15 to 20% below baseline over the initial 3 weeks

16. The reservoir implant of claim 12 wherein the total drug loading was 200 ug.

17. The reservoir implant of claim 12 wherein the drug release rate is 0.2 ug/day.

18. A reservoir implant releasing a hypotensive lipid, said implant being suitable for intracameral and intravitreal application to treat an ocular condition and comprising a core of said hypotensive lipid centrally located in a silicone tube having the ends closed by an impermeable ethylene vinyl acetate polymer, wherein the drug elutes from the sides of the silicone tube to provide a linear release over a 21 day time period.

19. The reservoir implant of claim 18, wherein said silicone tube has a diameter of 1 mm.

20. The reservoir implant of claim 18 wherein said hypotensive lipid is an EP2 agonist.

21. The reservoir implant of claim 18 wherein said ocular condition is ocular hypertension.

22. A intracameral reservoir implant according to claim 21 wherein the intraocular pressure was reduced approximately 18 to 20% below baseline for a minimum of 2 weeks when placed in the sub-Tenon's space.

23. A reservoir implant releasing a hypotensive lipid, said implant being suitable for intracameral and intravitreal application to treat an ocular condition and comprising a core of said hypotensive lipid centrally located in a polycaprolactone tube having the ends heat sealed wherein the drug elutes from the sides of the silicone tube to provide a linear release observed over a 14 day time period.

24. The reservoir implant of claim 23 wherein said tube has an inner diameter of 790μm.

25. The reservoir implant of claim 24 wherein said tube has an outer diameter of 1090 μm and releases drug at a rate of 46 μg/day.

26. The reservoir implant of claim 25 wherein said tube has an outer diameter of 1350 μm and releases drug at a rate of 66 μg/day

27. A method for treating elevated intraocular pressure, the method comprising the step of intracameral or anterior vitreal administration, to a patient with elevated intraocular pressure (IOP), of a sustained release implant comprising an antihypertensive agent and a polymer, said implant being suitable for intracameral and intravitreal application and comprising a core of said antihypertensive agent, surrounded by a polymer which limits the rate of passage of the antihypertensive agent from the implant into the eye of said patient, wherein said implant provides a linear rate of release of therapeutically effective amounts of said anti-hypertensive agent into said eye for a period of time of between 12 days and 365 days.

28. The method of claim 27 wherein said implant comprises from about 10 to about 50 weight percent of said anti-hypertensive agent and from about 50 to about 90 weight percent of said polymer.

29. The method of claim 28, wherein the implant can reduce IOP from about 20% to about 70% of baseline IOP.

30. The method of claim 29 wherein said core comprises an API/PCL/Pluronics formulation extruded into thin filaments and coated with cellulose acetate.

31. A reservoir implant releasing a hypotensive lipid, said implant being suitable for intracameral, posterior chamber (i.e. behind the iris in the ciliary sulcus) and intravitreal application to treat an ocular condition and comprising a core of said hypotensive lipid centrally located in a hollow tube, wherein said tube comprises an aliphatic polyester polymer selected from the group consisting of polycaprolactone, polylactic acid, polyglycolic acid, and polylactic-co-glycolic acid and having an inner diameter and an outer diameter and heat sealed ends, wherein said inner diameter and an outer diameter are sized to provide a wall having a thickness sufficient to control the release rate of said hypotensive lipid.

32. The reservoir implant of claim 31 wherein said hypotensive lipid is a prostaglandin analogue, prostamide, or EP2 or EP4 agonist,

33. The reservoir implant of claim 31 wherein said tube has an inner diameter of from 75 to 1000 μm.

34. The reservoir implant of claim 31 wherein said tube has an outer diameter of from 150 to 1180 μm

35. The reservoir implant of claim 31 wherein said tube has a wall thickness of 20 to 150 μm and the release rate of said hypotensive lipid is independent of the amount of said hypotensive lipid in said core.

36. The reservoir implant of claim 31 wherein said wall comprises a PEG and the release rate of said hypotensive lipid is independent of the amount of said hypotensive lipid in said core.

FIGURE 1: MATRIX DRUG DELIVERY SYSTEM

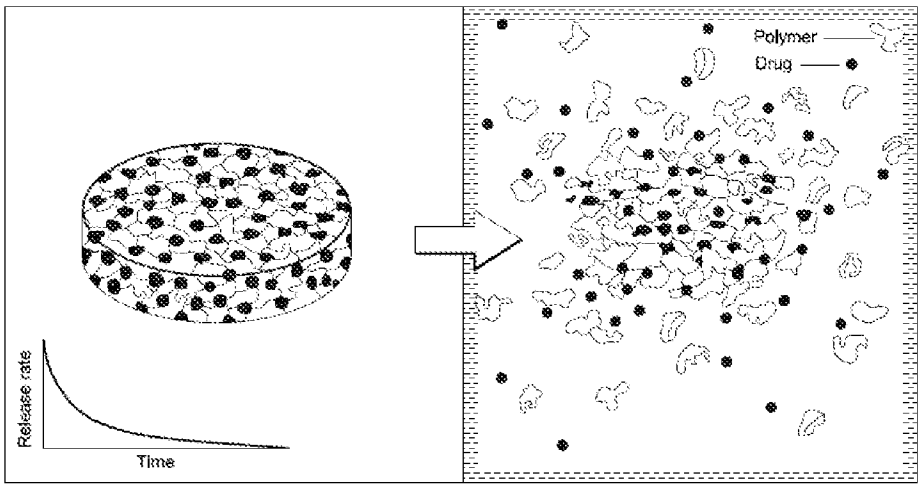
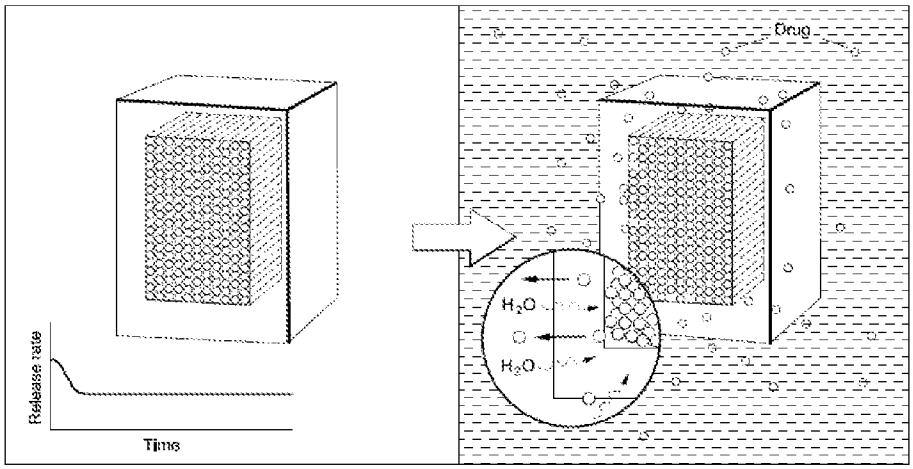
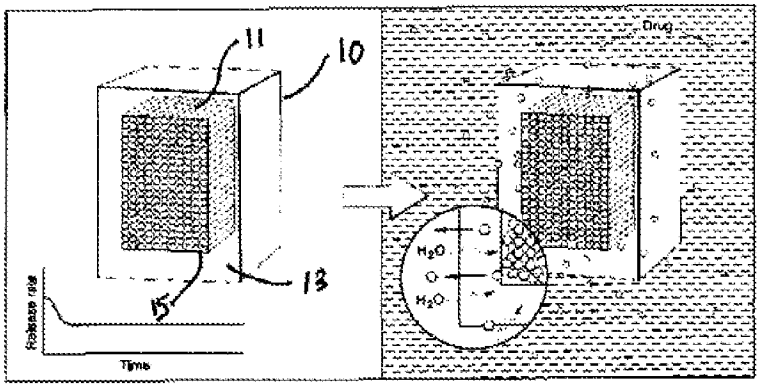


FIGURE 2: RESERVOIR DRUG DELIVERY SYSTEM





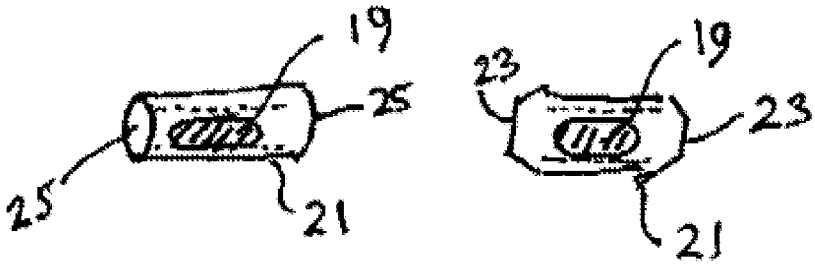


Figure 2a

FIGURE 3: Hypotensive Lipid Release from a Reservoir Implant

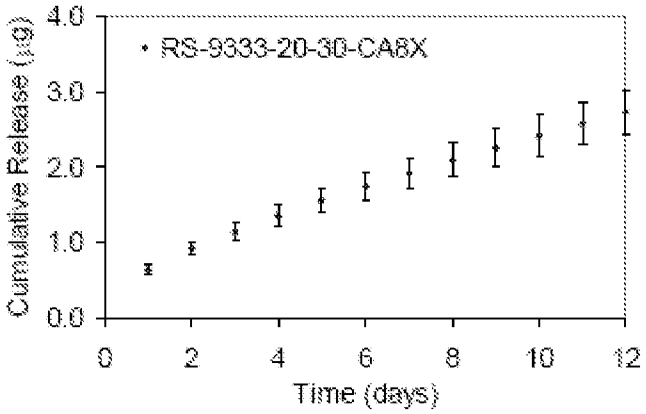


FIGURE 3 LEGEND: Implant described in Example 1, releasing the API, isopropyl 5-{3-[(2S)-1-{4-[(1S)-1-hydroxyhexyl] phenyl}-5-oxypyrrolidin-2-yl]propyl}thiophene-2-carboxylate at an in vitro release of 0.2ug/day.

FIGURE 4: Intraocular Pressure Reduction with an Intracameral Reservoir Implant

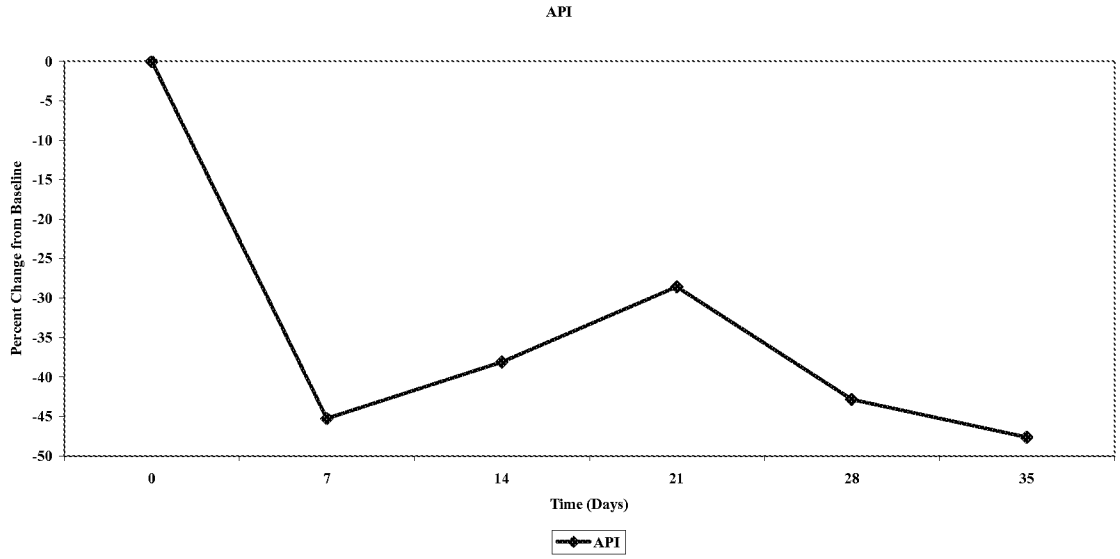


FIGURE 4 LEGEND: As described in example 1, a reservoir implant releasing a hypotensive lipid (0.2ug/day release) was placed intracamerally in a dog. The intraocular pressure was reduced approximately 30 to 45% below baseline for at least 5 weeks.

FIGURE 5: Intraocular Pressure Reduction with an Intravitreal Reservoir Implant

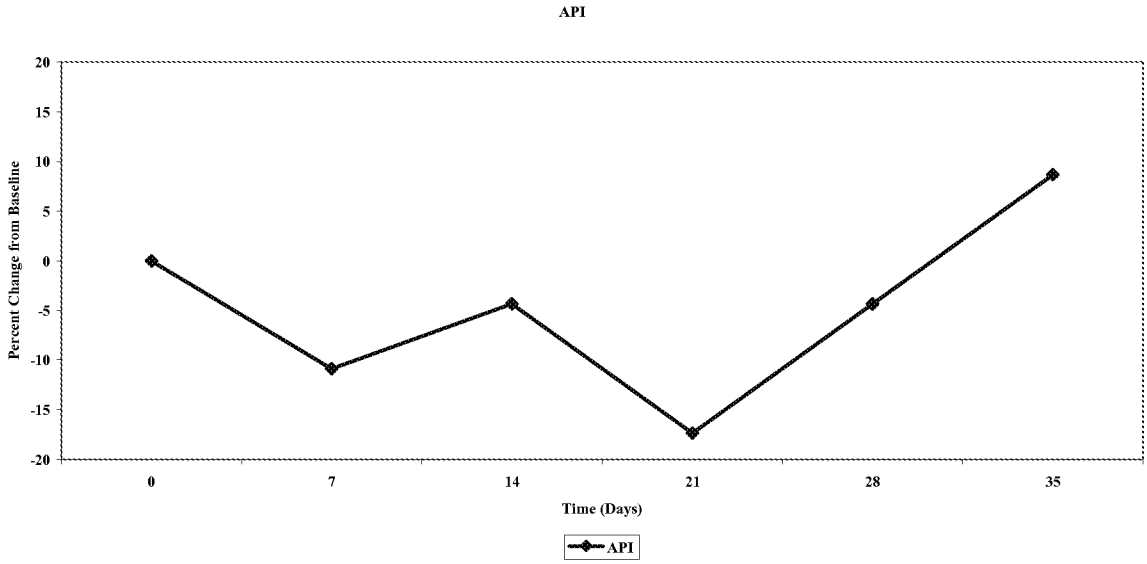


FIGURE 5 LEGEND: As described in example 1, a reservoir implant releasing a hypotensive lipid (0.2ug/day release) was placed intravitreally in a dog. The intraocular pressure was reduced to approximately a maximum of 15 to 20% below baseline over the initial 3 weeks.

FIGURE 6 Hypotensive Lipid Release from a Reservoir Implant

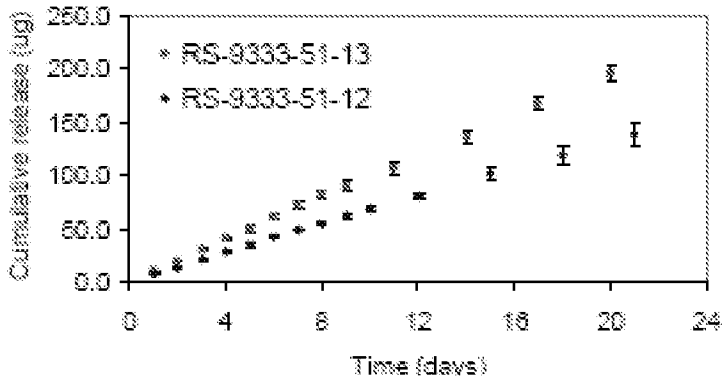


FIGURE 6 LEGEND: Implants described in Example 2, releasing the API, isopropyl 5-{3-[(2S)-1-{4-[(1S)-1-hydroxyhexyl] phenyl}-5-oxypyrrolidin-2-yl]propyl}thiophene-2-carboxylate at an in vitro release of 6.3ug/day and 9.3 ug/day.

FIGURE 7: Intraocular Pressure Reduction with an Intracameral Reservoir Implant

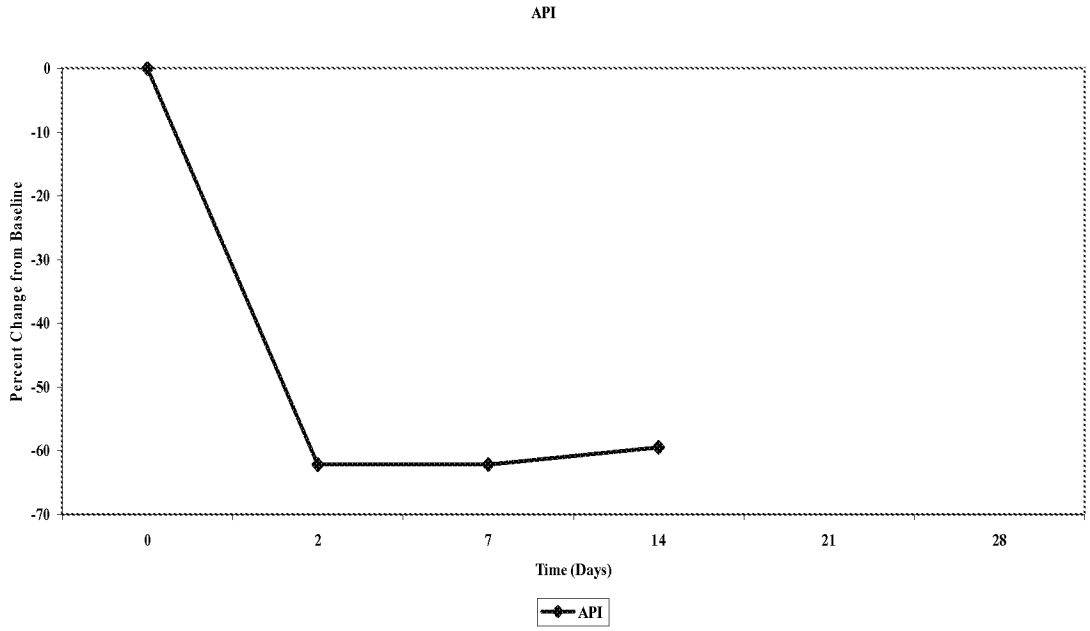


FIGURE 7 LEGEND: As described in example 2, a reservoir implant releasing a hypotensive lipid (6.3ug/day release) was placed intracamerally in a dog. The intraocular pressure was reduced to approximately 60% below baseline over a 2 week time frame.

FIGURE 8: External photograph of a dog with an Intracameral Reservoir Implant

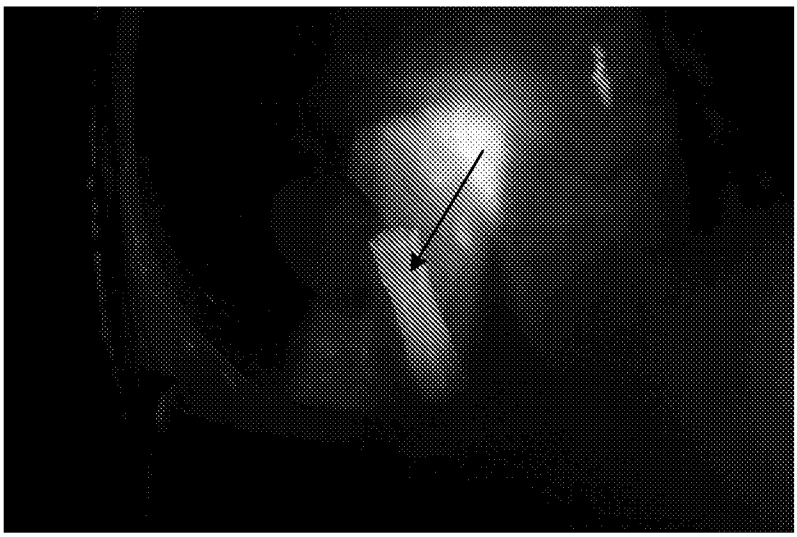


FIGURE 8 LEGEND: An intracameral reservoir implant releasing an EP2 agonist as described in Example 2

FIGURE 9: Intraocular Pressure Reduction with a Sub-Tenon's Reservoir Implant

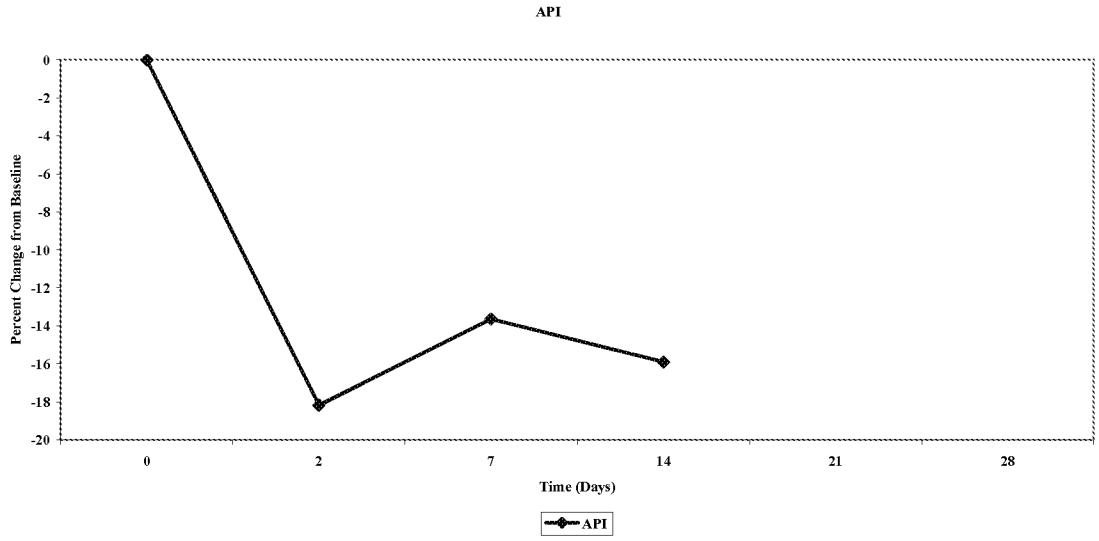


FIGURE 9 LEGEND: As described in example 2, three reservoir implants releasing a hypotensive lipid (6.3ug/day release per implant) were placed sub-Tenon's in a dog. The intraocular pressure was reduced to approximately a maximum of 18 to 20% below baseline over the initial 2 weeks.

FIGURE 10: External photograph of a dog with sub-Tenon's Reservoir Implants

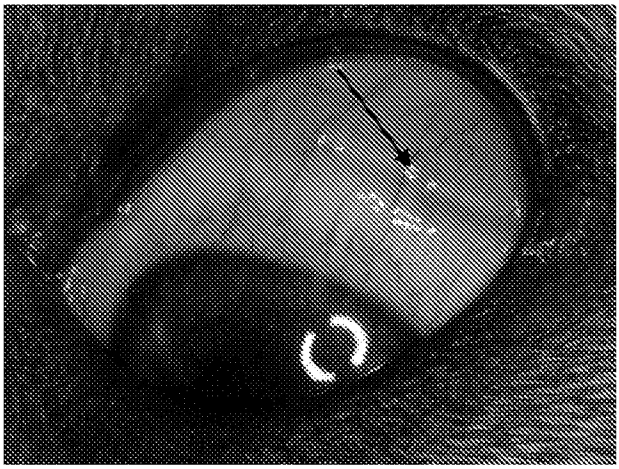


FIGURE 10 LEGEND: Sub-Tenon's reservoir implants (arrow) releasing an EP2 agonist as described in Example 2. The implants were well tolerated and biocompatible.

Figure 11: Hypotensive lipid release from reservoir implants

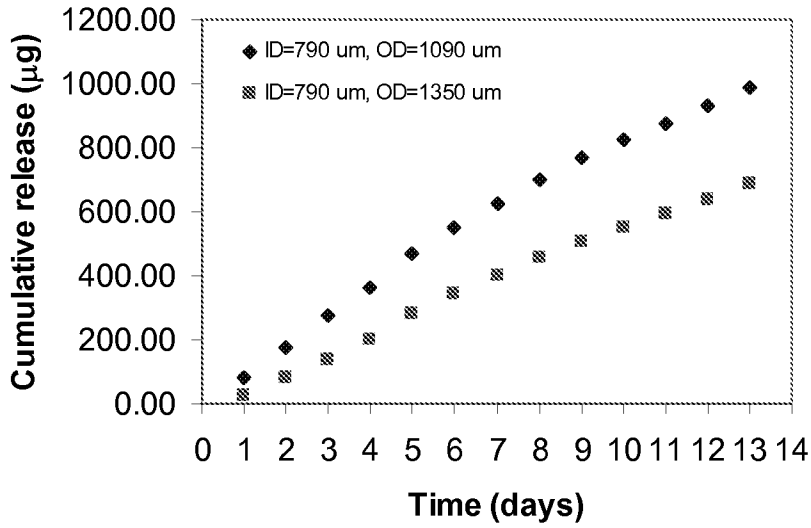


FIGURE 11 LEGEND. Implant described in Example 3, release the API, isopropyl 5-{3-[(2S)-1-{4-[(1S)-1-hydroxyhexyl] phenyl}-5-oxypyrrolidin-2-yl]propyl}thiophene-2-carboxylate at an in vitro release rate of 46 ug/day and 66 ug/day.

FIGURE 12

PCL hollow tubing

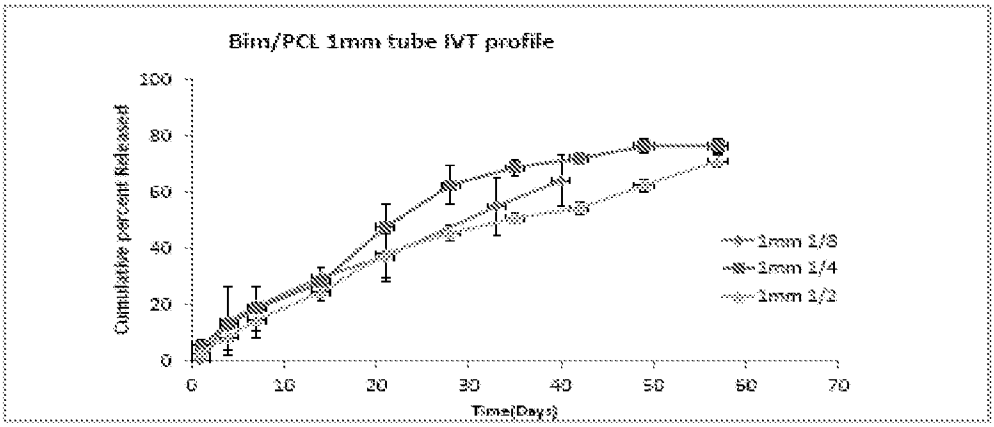
Lot	T1P3	T1P1	T1P2	T2P1
Polymer	PCL	PCL	PCL	PCL/PEG (85/15)
OD ID Length	1150 um 1000 um 8 mm	1180 um 800 um 8 mm	980 um 800 um 8 mm	1170 um 1000 um 8 mm
Drug fill in hollow tubing	¼ fill: 0.329mg ½ fill: 0.175 mg 1/8 fill: 0.09mg mg	¼ fill: 0.360 mg 1/2 fill: 0.192 mg		¼ fill: 0.385 mg

Objectives:

1. To figure out if the absolute amounts of drug release depend on drug loading.
2. To measure release rate with different wall thickness and permeabilities.

FIGURE 13

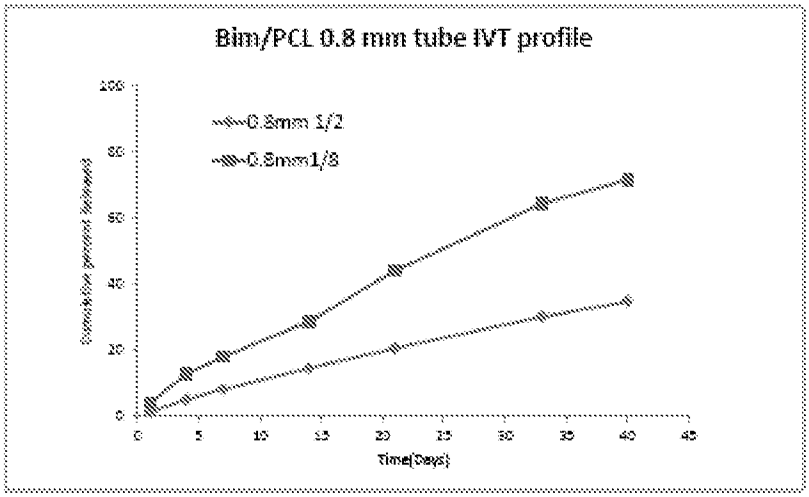
Bimatoprost release from T1P3: 150 um wall



- Dissolution rate in stagnant water in tube is RDS
- Diffusion through thin wall is fast.
- Release is proportional to surface area, i.e. % releases independent on% fill.

FIGURE 14

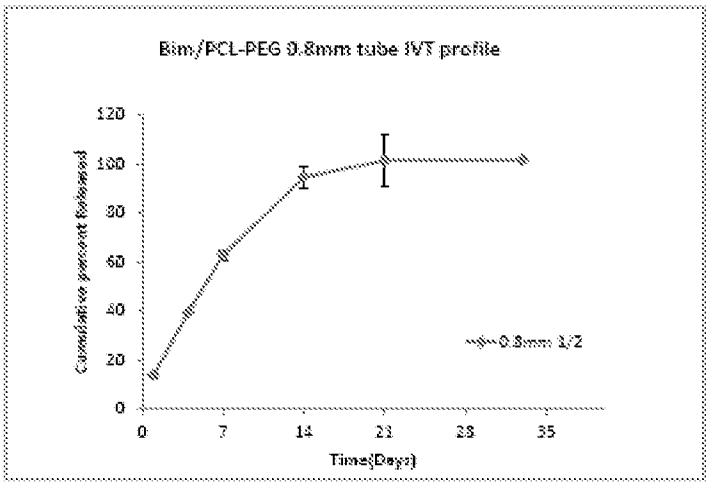
Bimatoprost release from T1P1: 380 um wall



- Dissolution rate in stagnant water in tube is slow
- Diffusion through thick wall is slow.
- Release is determined by both, % release slows down with high % fill.

FIGURE 15

Bimatoprost release from T2P1: 170 um wall with 15% PEG



- Dissolution rate in less stagnant water in tube is RDS.
- Diffusion through porous wall is very fast.
- Release should be close to its dissolution rate.
- Predict to be independent on % fill.