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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente 11-096-469

TÍTULO SOLICITADO: SUMINISTRO LIBERADO SOSTENIDO DE UNO O MÁS AGENTES.

PUBLICACIÓN: Gaceta 640 de 15/03/2012 número de publicación 201.

SOLICITANTE: QLT INC.

APODERADO: DILIA MARIA RODRIGUEZ D' ALEMAN

TRÁMITE: SUSTENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 15 de Junio de 2012, en los siguientes términos:

I. RATIFICACIÓN.

La solicitud en curso, que se refiere a implantes lagrimales de entrega y los métodos descritos en este documento proporcionan una liberación controlada de un agente terapéutico para el tratamiento de enfermedades, incluyendo tratamiento de glaucoma, hipertensión ocular o presión intraocular elevada, con latanoprost u otros agentes anti-glaucoma. También se suministra el tratamiento de la enfermedad, incluyendo glaucoma, hipertensión ocular o presión intraocular elevada, con latanoprost u otros agentes anti-glaucoma en conjunto con

intensificador de la penetración, tal como cloruro de benzalconio, y/o lágrimas artificiales. También se proporcionan implantes que contienen un núcleo de drogas emplacable en un punto lagrimal junto a un ojo de un paciente para la liberación controlada de un agente terapéutico, tal como latanoprost para el tratamiento del glaucoma, una droga principal que contiene un polímero tal como silicona reticulada, un agente terapéutico y un excipiente, en donde el excipiente puede aumentar la tasa de liberación del agente del núcleo de drogas, o puede aumentar la carga de fármaco en el núcleo, sin pérdida de homogeneidad deseable del agente dentro del núcleo, o se puede mejorar la retención del agente en el ojo o en el fluido lagrimal, o puede aumentar la penetración en la córnea del agente en el ojo; carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención.

II. COMPLEMENTO DE INFORMACIÓN.

En primer lugar, es indispensable indicar que cualquier persona medianamente versada en la formulación de productos farmacéuticos debe reconocer que un mismo principio activo se puede presentar en diferentes formas, por ejemplo, como comprimido, cápsula o solución acuosa y/o para su administración parenteral, y que así mismo, se puede formular utilizando diferentes excipientes farmacéuticamente aceptables. Reivindicar presentaciones farmacéuticas (SENFs) descritas con anterioridad en el estado de la técnica¹, en especial cuando dichas formulaciones comprenden fármacos igualmente descritos en el estado de la técnica²; así como reivindicar unas característica técnicas particulares que se asocian con ciertos efectos, como la liberación controlada por ejemplo, no pueden sustentar nivel inventivo alguno, dado que ensayar dichos principios activos junto a dichos excipientes para conseguir dichos efectos técnicos, por lo general, forma parte de la capacidad habitual de dicha persona versada en formulación de productos farmacéuticos.

Lo anterior se hace mucho más evidente a la luz de documentos como la patente americana US 2004-0071761 de título "NON-INVASIVE OCULAR DRUG DELIVERY" publicada el 15 de abril de 2004 la cual revela:

¹ Patente Británica GB1359198 (A) - OCULAR INSERT, publicada el 10 de julio de 1974

² La patente Americana US2003149294 - Process for the preparation of latanoprost publicada el 07 de agosto de 2003.

The present invention is drawn to a pharmaceutical compound for the treatment of posterior retinal diseases through topical application of the compound. The compound includes an effective amount of a therapeutic compound, and at least one additional agent that helps to prolong the residence time of the therapeutic compound within the extraocular space, or increase the transport of the therapeutic compound across a tissue of an eye toward and into a posterior ocular region, or both. The invention is additionally drawn to a device and method for delivering the compound.

(...)

[0073] Fluid retaining member 12 is shown in FIG. 1 in one preferred embodiment as a gauze pad having pharmaceutical compound 13 impregnated thereon. Alternatively, fluid retaining member 12 could comprise a patch, a sponge, a hydrogel, a porous ceramic, a silicone based membrane, or other materials familiar to one with ordinary skill in the art.

(...)

[0077] The rate limiting membranes can be either "hydrophobic" or "hydrophilic polymers". As used herein, the term "hydrophobic polymer" refers to polymers having equilibrium water content of less than about 10%. Suitable hydrophobic polymeric materials for use in the control membrane of the present invention include without limitation, polycarbonates, i.e., linear polyesters of carbonic acids in which

(...)

as those described in U.S. Pat. No. 4,144,317, incorporated herein by reference, polyamides, and polyurethanes. This list is merely exemplary of the materials suited for use in this invention. A more extensive list can be found in J. R. Scott & W. J. Roff, Handbook of Common Polymers (CRC Press, 1971) and in patents disclosing suitable materials for use in manufacturing microporous membranes such as U.S. Pat. No. 3,797,494, incorporated herein by reference.

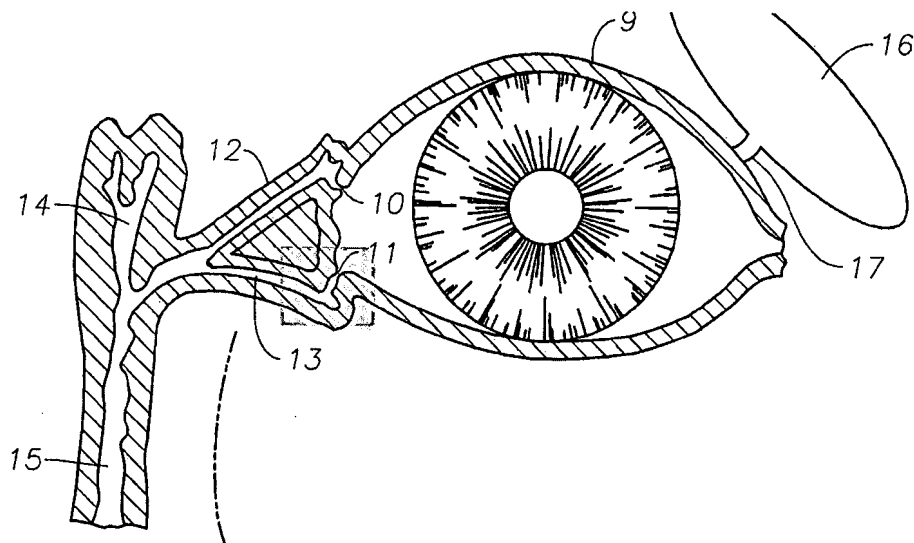
(...)

Como se puede observar claramente, en esta anterioridad se anticipa el uso de polímeros tales como silicona, poliamidas y poliuretano en la elaboración de dispositivos que permiten la aplicación de fármacos a nivel ocular, polímeros que también son usados en la solicitud colombiana en trámite.

Por su parte la patente americana US 2008-0181930 de título "PUNCTAL PLUGS AND METHODS OF DELIVERING THERAPEUTIC AGENTS" publicada el 31 de julio de 2008, revela lo siguiente:

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.

(...)



(...)

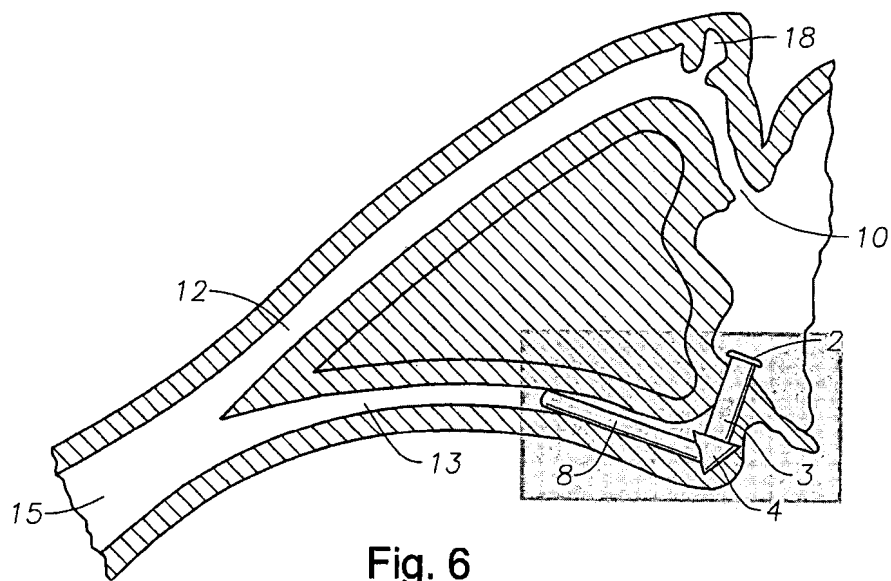


Fig. 6

(...)

[0009] 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 bromonidine), 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,

(...)

[0023] 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.

(...)

[0024] 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 commer-

(...)

[0062] 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.

(...)

What is claimed is:

1. A drug-delivery device comprising:

- (a) a body comprising a matrix of a silicone and an ophthalmic drug, the body having 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.

(...)

5. The drug-delivery device of claim 4 wherein the prostaglandin is cloprostenol, fluprostenol, latanoprost, travoprost, or unoprostone.

(...)

Como se puede observar claramente, en esta anterioridad se anticipan varios aspectos técnicos que para cualquier persona versada en la formulación de productos farmacéuticos resultaría ser una fuente de información suficiente como para guiar el desarrollo de formulaciones como las descritas en la solicitud en trámite. Específicamente se hace mención de un dispositivo que se puede instalar en el canal lacrimal interno del ojo, que comprende polímeros tales como siliconas o poliuretanos, que a manera de matriz contiene y controla la liberación de un principio activo (como latanoprost, entre otros) a través del ojo.

Esto demuestra que, existen en el estado del arte documentos que revelan dispositivos y/o implantes capaces de liberar agente activos análogos de prostaglandina tal como Latanoprost útiles en el tratamiento de glaucoma, hipertensión ocular o presión intraocular elevada, y que emplean polímeros comunes en su matriz, por lo tanto, el nivel inventivo de la solicitud colombiana en trámite se encuentra afectado de manera significativa.

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados tanto en este complemento de información como en el escrito de oposición presentado en su momento, con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

III. **ANEXOS.**

- ❖ Copia de todos los documentos mencionados en el acápite de Complemento de información.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A. 44.655 del C.S.J.

- 1 359 198 (21) Application No. 37792/71 (22) Filed 11 Aug. 1971
(44) Complete Specification published 10 July 1974
(51) International Classification A61K 9/00
(52) Index at acceptance
A5B 734 736 73Y 751 757
(72) Inventor RICHARD A. NESS



(54) OCULAR INSERT

- (71) We, ALZA CORPORATION, 950 Page Mill Road, Palo Alto, California, United States of America, a Corporation organized and existing under the laws of the State of California, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—
- This invention relates to inserts for dispensing drugs and has particular reference to an ocular insert for dispensing drugs to the eye over a prolonged period of time.
- At the present time, diseases of the eye are treated by applying ophthalmic drugs in liquid or ointment form. To be effective in many cases, the application of drug should be substantially continuous. Such continuous delivery of drug is not obtained through the use of liquid or ointment dosage forms, even though they be applied at intervals during the day and night. Periodic application of these dosage forms results in the eye receiving a massive, but unpredictable, amount of drug at the time of application but the drug is washed away rapidly by tears, leaving the eye substantially without medication until the next application. Ointment dosage forms are presently available only in unsterilized form and this too presents a problem.
- At a very early time, drugs were dissolved or dispensed in a water soluble gel of glycerinated gelatin that was shaped to the form of a lamella or eye disk. These lamellae were applied to the inner surface of the eyelid to supply drug to the eye. In use, the glycerinated gelatin vehicle dissolved rapidly in tear liquid, producing the same type of effect as liquid dosage forms. Lamellae are not a sustained release dosage form.
- The present invention resides in a medication dispensing ocular insert for a human eyeball, said tablet comprising a quantity of a drug confined within an interior chamber of a flexible, imperforate and continuous surfaced sealed container of non-allergenic polymeric material which is insoluble in tear liquid, said container being formed of a drug release rate controlling polymer which continuously permits said drug to flow therethrough by molecular diffusion to the eye at a sustained, predetermined and reproducible rate over a prolonged period of time, said rate being independent of the rate of flow of tear liquid over said insert, said container being adapted for insertion into the cul-de-sac of the conjunctiva between the sclera of the eyeball and the eyelid, to be held in place against the eyeball by the pressure of the lid by having a shape adapted to assume essentially the configuration of the sclera curvature; said drug being capable of transport through the unbroken walls of said container by diffusion and said container being so constructed and arranged that, when applied to the eyeball, to gradually release said drug thereto, drug or drug solution leaving said container by diffusion is transported to the eyeball by the flow of tears and by the blinking action of the eyelids.
- Polymeric materials used in forming the ocular insert are flexible, biologically inert, insoluble in tear liquid, and non-allergenic. It is important that the polymeric material be capable of transferring the drug through its unbroken walls by the diffusion of drug or drug solution therethrough. By utilizing the mechanism of molecular diffusion to dispense drug to the eye, the drug release can be sustained at a predetermined and reproducible rate which is independent of the rate of flow of tear liquid over the insert. In each case, selection of the polymeric material is dependent on the par-

5 ticular drug and drug form to be used in the device. Exemplary materials for fabricating the ocular insert include hydrophobic polymers such as plasticized or un-
10 plasticized polyvinylchloride, plasticized nylon, unplasticized soft nylon, plasticized polyethylene terephthalate, and silicone rubber, and hydrophilic polymers such as
15 the hydrophilic hydrogels of esters of acrylic and methacrylic acid (as described in U.S. Patent Nos. 2,976,576 and 3,220,960 and Belgian Patent No. 701, 813), modified
20 collagen, cross-linked hydrophilic polyether gels (as described in U.S. Patent No. 3,419,006), cross-linked polyvinylalcohol, and cross-linked partially hydrolyzed polyvinylacetate. When plasticizers are used to impart flexibility to the polymer, various plasticizers known to the art can be employed, such as long-chain fatty amides, higher alcohols, and dioctyl phthalate.
25 Those skilled in the art will appreciate that many of the hydrophilic polymers suitable for use in this invention absorb tear liquid, forming a hydrogel therewith. Tear liquid entering the polymeric structure to form the swollen hydrogel molecules dissolves the drug within the polymeric insert, and the resulting drug
30 solution then diffuses outwardly from the hydrogel structure. Therefore, as used in this specification and the appended claims, the term "molecular diffusion" refers to the movement of molecules of a drug
35 through an imperforate polymeric body, as well as to the movement of a drug solution through an imperforate body. Use of the expression "insoluble in tear liquid" to refer to suitable polymeric materials means
40 that the polymeric materials do not dissolve and erode as a result of the action of tear liquid, but may absorb tear liquid, forming a swollen hydrogel.
45 Any of the drugs used to treat the eye and surrounding tissues can be incorporated in the ocular insert of this invention. Also, it is practical to use the eye and surrounding tissues as a point of entry for systemic drugs that enter circulation in
50 the blood stream and produce a pharmacologic response at a site remote from the point of application of the ocular insert. Thus, drugs which will pass through the eye or the tissue surrounding the eye
55 to the blood stream, but which are not used in therapy of the eye itself, can be incorporated in the ocular insert.
60 Suitable drugs for use in therapy of the eye with the ocular insert include, without limitation: anti-infectives: such as antibiotics, including tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, and erythromycin; sulfonamides,
65 including sulfacetamide, sulfamethizole and

sulfisoxazole; anti-virals, including idoxuridine; and other anti-infectives including nitrofurazone and sodium propionate; anti-allergens such as antazoline, methapyrilene, chlorpheniramine, pyrilamine and propenpyridamine; anti-inflammatories such as hydrocortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate, fluocinolone medrysone, prednisolone, prednisolone 21-phosphate and prednisolone acetate; decongestants such as phenylephrine, naphazoline, and tetrahydrazolone; miotics and anticholinesterases such as pilocarpine, eserine salicylate, carbachol, di-isopropyl fluorophosphate, phospholine iodide, and demecarium bromide; mydriatics such as atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, and hydroxyamphetamine; and sympathomimetics such as epinephrine. Drugs can be in various forms, such as uncharged molecules, components of molecular complexes, or non-irritating, pharmacologically acceptable salts, such as hydrochloride, hydrobromide, sulphate, phosphate, nitrate, borate, acetate, maleate and tartrate, salicylate. Furthermore, simple derivatives of the drugs (such as ethers, esters, amides, etc.) which have desirable retention and release characteristics but which are easily hydrolyzed by body pH and enzymes can be employed. The amount of drug incorporated in the ocular insert varies widely, depending on the particular drug, the desired therapeutic effect, and the time span for which the ocular insert will be used. Since the ocular insert is intended to provide the complete dosage regime for eye therapy for but a particular time span, such as 24 hours, there is no critical upper limit on the amount of drug incorporated in the device. For when the device is removed and disposed of it makes little difference whether any drug remains in the device. The lower limit will depend on the activity of the drug and its capability of being released from the device. Thus it is not practical to define a range for the therapeutically effective amount of drug incorporated into the device. However, typically, from 1 microgram to 1 milligram of drug is incorporated in the ocular insert.
120 In each case, the polymeric material used to form the ocular insert is chosen for its compatibility with a particular drug and its capability of releasing that drug by diffusion at an appropriate rate over a prolonged period of time. Specific, but non-limiting, examples of combinations of drugs and polymers for use in forming the ocular insert are: (1) chloramphenicol, incorporated into polyethylene terephthalate plasticized with higher alcohols; (2)
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promethazine trichloroacetate incorporated into polyvinylchloride plasticized with dioctylphthalate; (3) chloramphenicol dispersed throughout polydimethylsiloxane rubber; (4) pilocarpine or pilocarpine perfluorobutyrate incorporated into polyvinylchloride plasticized with dioctylsebacate; and (5) dexamethasone incorporated into nylon-66 plasticized with higher alcohols.

The ocular insert can be fabricated in any convenient shape for comfortable retention in the cul-de-sac. It is important, however, that the device have no sharp jagged or rough edges which can irritate the sensitive tissues of the eye. Thus the marginal outline of the ocular insert can be ellipsoid, bean-shaped, rectangular, etc. In cross-section, it can be concavo-convex, rectangular, etc. As the ocular insert is flexible and, in use, will assume essentially the configuration of the scleral curvature, the original shape of the device is not of controlling importance. Dimensions of the device can vary widely. The lower limit on the size of the device is governed by the amount of the particular drug to be applied to the eye and surrounding tissues to elicit the desired pharmacologic response, as well as by the smallest-sized device which conveniently can be inserted and removed from the eye. The upper limit on the size of the device is governed by the limited space within the cul-de-sac that conveniently and comfortably can be filled with an ocular insert. Typically, the ocular insert is 4 to 20 millimeters in length, 1 to 12 millimeters in width, and 0.1 to 1 millimeter in thickness. Preferably it is ellipsoidal in shape and about $6 \times 4 \times 0.5$ mm in size.

The ocular insert is a sealed container with walls of polymeric material and having the drug or the drug dispersed in a carrier in an interior chamber thereof. One such container has a circular or ellipsoidal cross-section and is tapered at the ends. Drug can be incorporated in the ocular insert in many ways. Any of the encapsulation, bonding, and coating techniques conventionally used in the art can be employed to form the outer flexible layer.

Following is a description by way of example only and with reference to the accompanying drawings of methods of carrying the invention into effect:—

In the drawings:—

Figure 1 is the front view of an eye showing the insertion of an insert in accordance with the invention.

Figure 2 is a section of Figure 1.

Referring particularly to Figures 1 and 2, to use the ocular insert 10 (shown by dot and dash lines in Fig. 1), it is placed in the

cul-de-sac 11 of the conjunctiva 12 between sclera 13 of the eyeball 14 and the lower lid 15. The pressure of the lower lid 15 maintains the ocular insert 10 in place. With the ocular insert 10 under the lower lid 15, the device is comfortable to the wearer and does not contact the cornea 16 during sleeping nor during normal ocular motion. Once in place, the ocular insert 10 functions as a drug reservoir gradually releasing drug to the eye and surrounding tissue. Drug 17 leaving the ocular insert by diffusion is transported to the eyeball 14 by the flow of tear liquid and by the blinking action of the eyelids. By use of the ocular insert, the eye is continuously bathed with drug 17 over a particular time span. Normally, the ocular insert 10 will be retained in place for a period of 24 hours, thereby supplying the complete dosage regime for eye therapy over that period of time. During the course of use, the polymeric body 18 of the ocular insert does not dissolve or erode into tear liquid and a predictable and reproducible dosage regime is provided.

Thus, the improved ocular insert of this invention offers many advantages. As it is formed of a polymeric material, insoluble in tear liquid, the ocular insert does not dissolve or erode in tear liquid during the course of therapeutic program. This permits the therapeutic program to be precisely controlled and the release of drug predicted with accuracy. That the ocular insert releases drug by diffusion is most important, since this too provides for close control over the rate of drug release from the polymer.

WHAT WE CLAIM IS:—

1. A medication dispensing ocular insert for a human eyeball, said insert comprising a quantity of a drug confined within an interior chamber of a flexible, impermeated and continuous surfaced sealed container of non-allergenic polymeric material which is insoluble in tear liquid, said container being formed of a drug release rate controlling polymer which continuously permits said drug to flow there-through by molecular diffusion to the eye at a sustained predetermined and reproducible rate over a prolonged period of time, said rate being independent of the rate of flow of tear liquid over said insert, said container being adapted for insertion into the cul-de-sac of the conjunctiva between the sclera of the eyeball and eyelid, to be held in place against the eyeball by the pressure of the lid, by having a shape adapted to assume essentially the configuration of the sclera curvature; said drug being capable of transport through the unbroken walls of said container by

diffusion and said container being so constructed and arranged that, when applied to the eyeball, to gradually release said drug thereto, drug or drug solution leaving said container by diffusion is transported to the eyeball by the flow of tears and by the blinking action of the eyelids.

2. An insert as claimed in claim 1 wherein the polymeric material is selected from plasticised polyvinyl chloride, plasticised nylon, unplasticised soft nylon, plasticised polyethylene terephthalate silicone rubber, hydrophilic hydrogel of an ester of acrylic or methacrylic acid, modified collagen, cross-linked hydrophilic polyether gel, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

3. An insert as claimed in either of the preceding claims wherein said drug is a preparation for heating the eye.

4. An insert as claimed in claim 1 wherein said drug is a systemically active drug which will pass through the eye to the bloodstream and produce a pharmacologic response at a site remote from the eye.

5. An insert as claimed in any one of the preceding claims wherein the container is an elongate body circular in cross-section about its major axis and tapered towards its ends.

6. An insert as claimed in any one of claims 1 to 4 wherein the container is an elongate body ellipsoidal in cross-section about its major axis and tapered towards its ends.

7. An insert as claimed in any preceding claim wherein the containers range from 4 to 20 millimeters in length, 1 to 12 millimeters in width, and 0.1 to 1 millimeter in thickness.

8. An insert as claimed in any one of the preceding claims wherein the said polymer forms a hydrogel with tear liquid whereby tear liquid entering the polymeric structure to form the hydrogel dissolves the drug and the resulting solution diffuses outwardly from the hydrogel structure.

9. An insert as claimed in any one of claims 1 to 7 wherein the drug is disposed in a carrier.

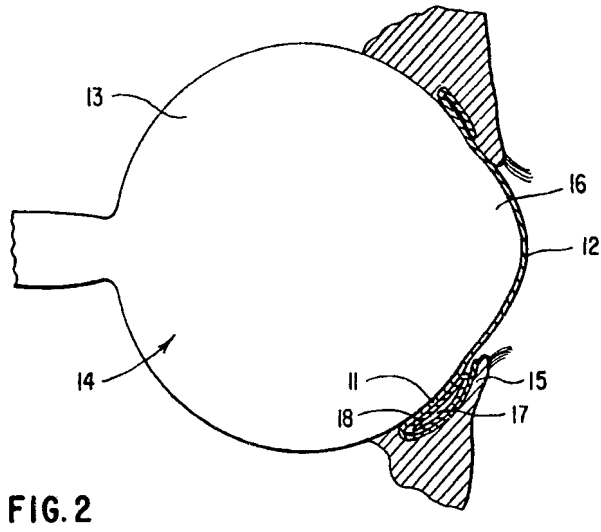
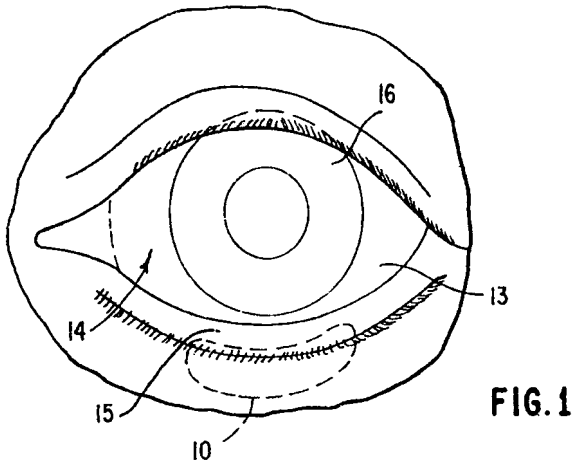
10. A drug dispensing insert substantially as herein described with reference to, and as illustrated in, Figures 1 and 2 of the accompanying drawings.

For the Applicants:—

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London W.C.2.





US 20030149294A1

13

(19) **United States**

(12) **Patent Application Publication**

Gutman et al.

(10) **Pub. No.: US 2003/0149294 A1**

(43) **Pub. Date: Aug. 7, 2003**

(54) **PROCESS FOR THE PREPARATION OF LATANOPROST**

(76) **Inventors: Arie Gutman, Haifa (IL); Gennadiy Nisnevich, Haifa (IL); Marina Etinger, Nesher (IL); Igor Zaltzman, Haifa (IL); Lev Judovich, Haifa (IL); Boris Pertsikov, Nesher (IL)**

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(21) **Appl. No.: 10/181,523**

(22) **PCT Filed: Jan. 26, 2001**

(86) **PCT No.: PCT/IL01/00076**

(30) **Foreign Application Priority Data**

Jan. 27, 2000 (IL) 134241

Publication Classification

(51) **Int. Cl.⁷ C07C 69/612; C07D 307/78**

(52) **U.S. Cl. 560/55; 549/305**

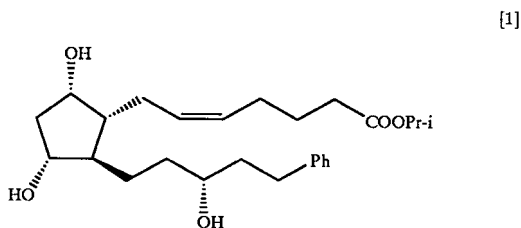
(57) **ABSTRACT**

Disclosed is a novel process for the preparation of the anti-glaucoma drug Latanoprost, in good yield, in large amounts and with desired purity. Also disclosed are novel intermediates for the above process.

PROCESS FOR THE PREPARATION OF LATANOPROST

FIELD OF THE INVENTION

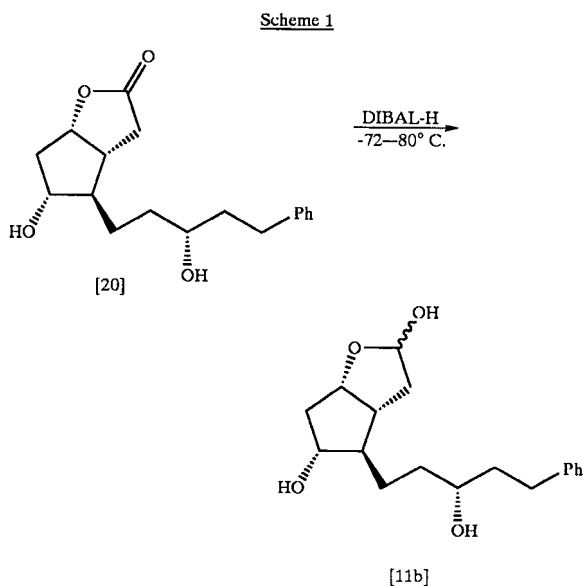
[0001] This invention relates to a novel process for the preparation of 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF_{2α} isopropyl ester (Latanoprost) of the formula [1]:



[0002] drug for treating glaucoma (Merck Index, 12th Ed., 5787).

BACKGROUND OF THE INVENTION

[0003] The known methods for synthesis of Latanoprost (see B. Resul et al., J. Med. Chem., 1993, 36, 243) include the stage of reducing of lactone-group of the compound [20] with excess of diisobutylaluminum hydride (DIBAL-H) at -72--80° C. to give the compound [11b] (Scheme 1):



[0004] However, this method is problematic as it is difficult to scale-up this highly exothermic reaction at such low temperature conditions. Furthermore, it was feared that increasing of temperature during DIBAL-H addition may lead to undesired processes in reduction of product [11b].

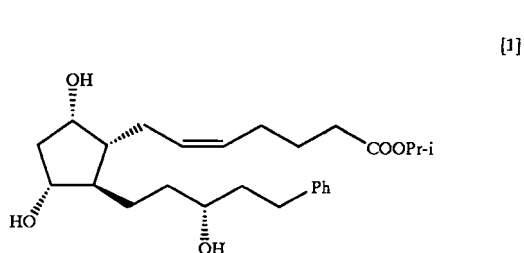
OBJECTS OF THE INVENTION

[0005] It is an object of this invention to provide a novel process for the preparation of Latanoprost in good yield, in large amounts and with desired purity.

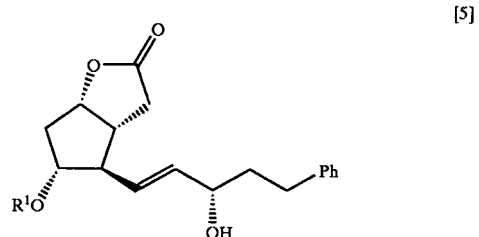
[0006] It is a further object of this invention to provide novel intermediates for the above process.

SUMMARY OF THE INVENTION

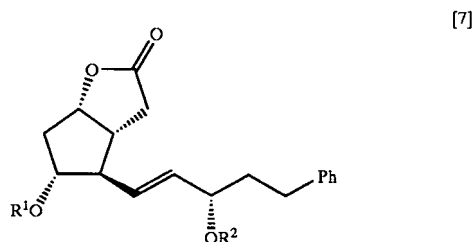
[0007] The above objects are achieved by present invention, which provides a process for the preparation of Latanoprost [1]



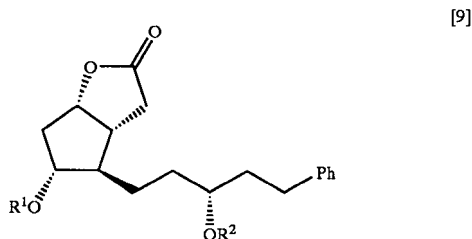
[0008] which comprises deriving the compound [5]



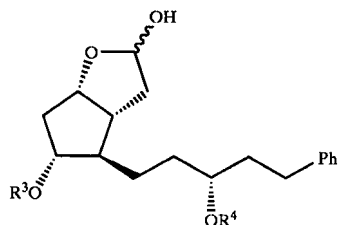
[0009] to give the compound [7]



[0010] which is hydrogenated in the presence of catalyst to give the compound of the Formula [9]



[0011] which is reduced with diisobutylaluminum hydride at temperature range from -50 to $+50^{\circ}$ C. followed by hydrolysis of the obtained reaction mixture under basic conditions to give compound [11], which is converted into latanoprost [1]



[11]

[0012] wherein one of R^1 and R^2 is an aryl carbonyl and the other one is selected from the group consisting of aryl carbonyl, acyl, trialkylsilyl, dialkylarylsilyl, 1-alkoxyalkyl, unsubstituted and alkyl-substituted tetrahydro-2H-pyran-2-yl and tetrahydrofuran-2-yl groups;

[0013] R^3 is hydrogen when R^1 is acyl and is equal to R^1 when it is trialkylsilyl, dialkylarylsilyl, 1-alkoxyalkyl, unsubstituted or alkyl-substituted tetrahydro-2H-pyran-2-yl or tetrahydrofuran-2-yl groups; and

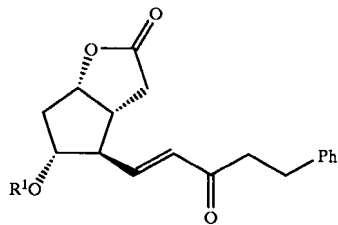
[0014] R^4 is hydrogen when R^2 is acyl and is equal to R^2 when it is trialkylsilyl, dialkylarylsilyl, 1-alkoxyalkyl, unsubstituted or alkyl-substituted tetrahydro-2H-pyran-2-yl or tetrahydrofuran-2-yl groups.

[0015] Some of the new compounds [7] and [9] which are obtained as intermediates in the process of the present invention may be purified by crystallization from organic solvents. This fact represent a further aspect of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0016] An advantage of the present invention is the fact that the highly selective reduction of lactone-group of the compound [9] with diisobutylaluminum hydride may proceed at industrially acceptable temperature range from -50 to $+50^{\circ}$ C., preferably from -20 to $+20^{\circ}$ C. On the basis of this we developed a new effective process for synthesis of Latanoprost [1] which process comprises the steps of:

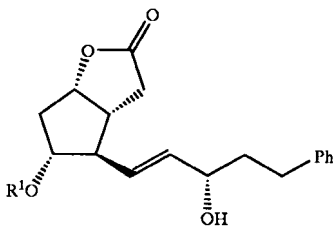
[0017] a) stereoselective reduction of oxo-group of compound of the Formula [4]:



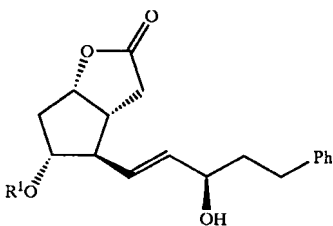
[4]

[0018] wherein R^1 is defined as above,

[0019] to yield a mixture of compounds of the Formula [5] (main product) and [6] (minor product):



[5]

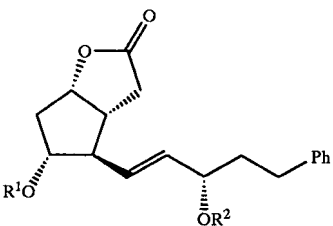


[6]

[0020] wherein R^1 is defined as above;

[0021] b) separating the desired compound [5] from the by-product [6] by column chromatography followed by oxidation of the hydroxy-group of the compound [6] for regeneration of compound [4].

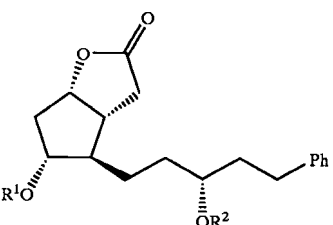
[0022] c) deriving compound [5] to give compound [7]:



[7]

[0023] wherein R^1 and R^2 are as defined above;

[0024] d) hydrogenating compound [7] in the presence of a catalyst to yield compound [9]:

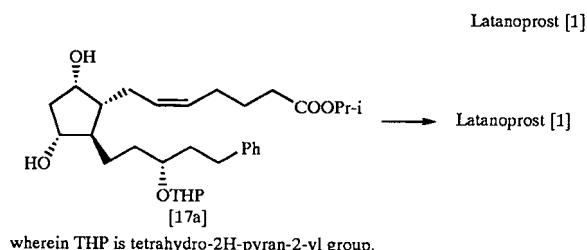


[9]

EXAMPLE 15

[0087]

Scheme 22

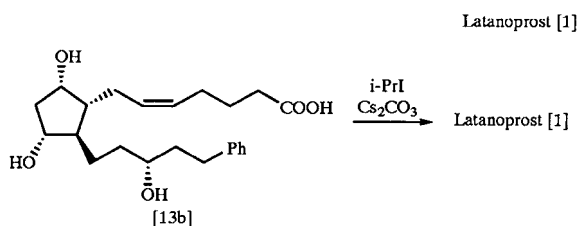


[0088] Pyridinium p-toluenesulfonate (16 mg) was added to a stirred solution of the compound [17a] (0.7 g) in ethanol (20 mL) at room temperature. The mixture was stirred at 50° C. over a period of 3 hours, by which time the reaction was complete (TLC monitoring). The mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane (40 mL). The solution was washed with water (10 mL) and brine (10 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate 1:1 v/v) to obtain Latanoprost. ¹H NMR (CDCl₃) is compatible with literature data.

EXAMPLE 16

[0089]

Scheme 23

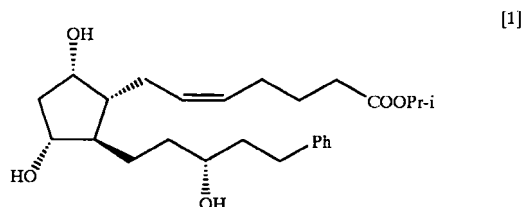


[0090] A mixture of Latanoprost acid [13b] (0.95 g, 2.4 mmol), isopropyl iodide (0.83 g, 4.8 mmol), cesium carbonate (1.20 g, 3.6 mmol) and DMF (20 mL) was stirred for 2-3 hours at 40-50° C. (TMC monitoring) and poured into a stirred mixture of 2 M aqueous NaHSO₄ (2.5 mL, 5 mmol), ice (50 mL) and ether (50 mL). The organic layer was separated and the water phase was extracted with ether (2x50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure to give 1.05 g (100% yield) of crude product. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 1:1 v/v) to give Latanoprost. ¹H NMR (CDCl₃) is compatible with literature data.

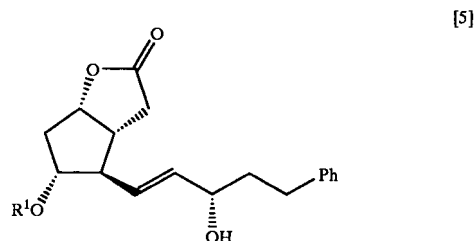
[0091] Although certain presently preferred embodiments of the invention have been described herein, it will be

apparent to those skilled in the art to which the invention pertains that variations and modifications of the described embodiments may be made without departing from the spirit and scope of the invention. Accordingly, it is intended that the invention be limited only to the extent required by the appended claims and the applicable rules of law.

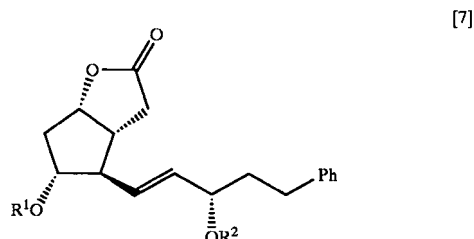
1. A process for the preparation of Latanoprost [1]



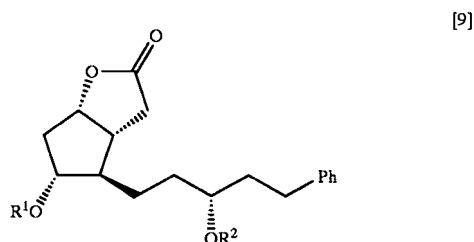
which comprises deriving the compound [5]



to give the compound [7]



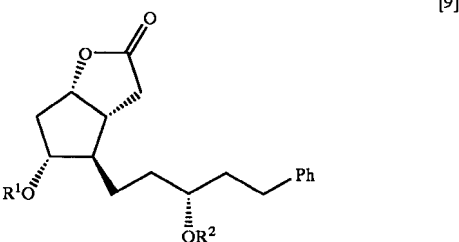
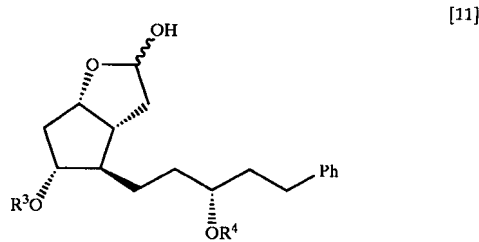
which is hydrogenated in the presence of catalyst to give the compound of the Formula [9]



which is reduced with diisobutylaluminum hydride at temperature range from -50 to +50° C. followed by hydrolysis

of the obtained reaction mixture under basic conditions to give compound [11], which is converted into latanoprost [1]

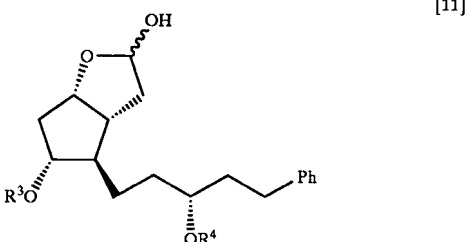
8. Compound of the formula [9]:



wherein one of R¹ and R² is an aryl carbonyl and the other one is selected from the group consisting of aryl carbonyl, acyl, trialkylsilyl, dialkylarylsilyl, 1-alkoxyalkyl, unsubstituted and alkyl-substituted tetrahydro-2H-pyran-2-yl and tetrahydrofuran-2-yl groups, and R³ is hydrogen when R¹ is acyl and is equal to R¹ when it is trialkylsilyl, dialkylarylsilyl, 1-alkoxyalkyl, unsubstituted or alkyl-substituted tetrahydro-2H-pyran-2-yl or tetrahydrofuran-2-yl groups; R⁴ is hydrogen when R² is acyl and is equal to R² when it is trialkylsilyl, dialkylarylsilyl, 1-alkoxyalkyl, unsubstituted or alkyl-substituted tetrahydro-2H-pyran-2-yl or tetrahydrofuran-2-yl groups.

wherein one of R¹ and R² is an aryl carbonyl group and the other one is selected from the group consisting of aryl carbonyl, acyl, trialkylsilyl, dialkylarylsilyl, 1-alkoxyalkyl, unsubstituted and alkyl-substituted tetrahydro-2H-pyran-2-yl and tetrahydrofuran-2-yl groups.

9. Compound of the formula [11]:



2. A process according to claim 1 wherein the said reduction of the compound [9] with diisobutylaluminum hydride is provided at temperature range from -20 to +20° C.

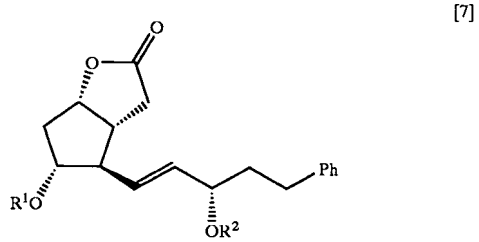
3. A process according to claim 1 wherein the said catalyst contains palladium, platinum or nickel.

4. A process according to claim 1 wherein the said catalyst is palladium on carbon.

5. A process according to claim 1 wherein the said hydrogenation of the compound [7] is carried out in the presence of bases and/or salts.

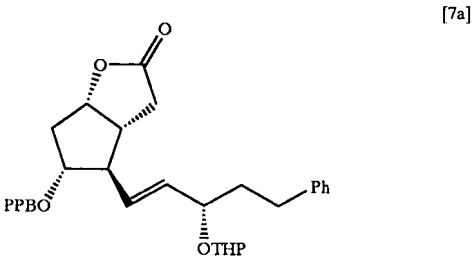
6. The process defined in claim 1, which comprises isolating the compounds of Formulae [7] and [9] in the course of the synthesis and, if desired, purifying them by re-crystallization.

7. Compound of the formula [7]:



wherein R³ and R⁴ are selected from the group consisting of hydrogen, trialkylsilyl, dialkylarylsilyl, 1-alkoxyalkyl, unsubstituted and alkyl-substituted tetrahydro-2H-pyran-2-yl and tetrahydrofuran-2-yl groups, and one of the R³ and R⁴ is hydrogen group.

10. (3aR,4R,5R,6aS)-Hexahydro-5-(p-phenylbenzoyloxy)-4-[(3S)-5-phenyl-3-[(tetrahydro-2H-pyran-2-yl)oxy]-1E-pentenyl]-2H-cyclopenta[b]furan-2-one [7a]:

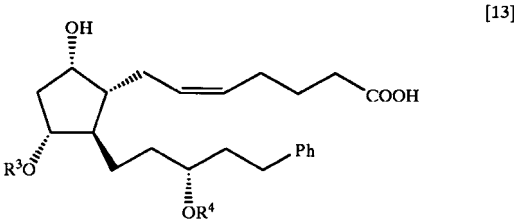
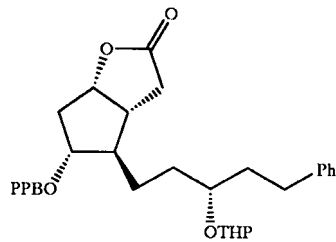


wherein one of R¹ and R² is an aryl carbonyl group and the other one is selected from the group consisting of aryl carbonyl, acyl, trialkylsilyl, dialkylarylsilyl, 1-alkoxyalkyl, unsubstituted and alkyl-substituted tetrahydro-2H-pyran-2-yl and tetrahydrofuran-2-yl groups.

wherein PPB is p-phenylbenzoyl group and THP is tetrahydro-2H-pyran-2-yl group.

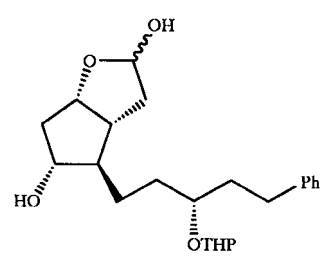
11. (3aR,4R,5R,6aS)-Hexahydro-5-(p-phenylbenzoyloxy)-4-[(3R)-5-phenyl-3-[(tetrahydro-2H-pyran-2-yl)oxy]pentyl]-2H-cyclopenta[b]furan-2-one [9a]:

a metal salt of 5-(triphenylphosphoranylidene)pentanoic acid to form a compound of formula [13]

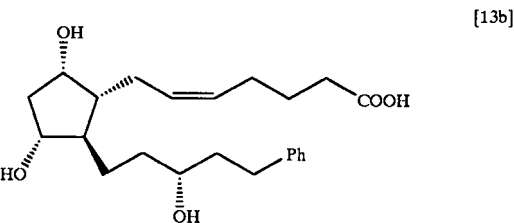


wherein PPB is p-phenylbenzoyl group and THP is tetrahydro-2H-pyran-2-yl group.

12. (3aR,4R,5R,6aS)-Hexahydro-5-hydroxy-4-[(3R)-5-phenyl-3-[(tetrahydro-2H-pyran-2-yl)oxy]pentyl]-2H-cyclopenta[b]furan-2-ol [11a]:



wherein R³ and R⁴ are as defined above; and when R³ and/or R⁴ in compound [13] is other than hydrogen, removing the protecting group to yield latanoprost acid [13b]



following esterification of compound [13b] with compound [16]:



wherein X is a leaving group, in the presence of a base to obtain latanoprost [1].

15. A process according to claim 14, wherein said base is cesium carbonate.

* * * * *

wherein THP is tetrahydro-2H-pyran-2-yl group.

13. A process according to claim 1 wherein R¹ and R² are selected from the group consisting of benzoyl, p-toluoyl, p-phenylbenzoyl and tetrahydro-2H-pyran-2-yl groups, and at least one of the R¹ and R² is arylcarbonyl group.

14. A process according to claim 1, wherein compound [11] is converted into latanoprost [1] by reacting [11] with



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(19) **United States**

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(54) **NON-INVASIVE OCULAR DRUG DELIVERY**

Publication Classification

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(51) **Int. Cl.⁷** **A61K 31/137; A61K 9/70**
(52) **U.S. Cl.** **424/449; 514/649**

(57) **ABSTRACT**

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The present invention is drawn to a pharmaceutical compound for the treatment of posterior retinal diseases through topical application of the compound. The compound includes an effective amount of a therapeutic compound, and at least one additional agent that helps to prolong the residence time of the therapeutic compound within the extraocular space, or increase the transport of the therapeutic compound across a tissue of an eye toward and into a posterior ocular region, or both. The invention is additionally drawn to a device and method for delivering the compound.

(21) Appl. No.: **10/269,911**

(22) Filed: **Oct. 11, 2002**

NON-INVASIVE OCULAR DRUG DELIVERY

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] The present invention generally applies to the treatment of ocular conditions, and specifically applies to improved methods, materials and devices for the non-invasive treatment of intermediate and posterior eye pathologies.

[0003] 2. Background Art

[0004] Numerous sight-threatening maladies result from diseases in the posterior portion of the eye. Posterior and intermediate uveitis, HSV retinitis, age related macular degeneration, diabetic retinopathy, bacterial, fungal, or viral endophthalmitis, eye cancers, glioblastomas, and glaucomatous degradation of the optic nerve are but a few of the diseases that will result in blindness if left untreated.

[0005] A plethora of conventional pharmacological agents currently exist to treat these conditions. Delivery of the agents to the site of action, however, has heretofore proven difficult. In order to exert a sufficient pharmaceutical effect on the intermediate and posterior eye tissues, the compound must be delivered to these tissues in pharmacologically relevant concentrations. Delivering therapeutic concentration of drug to the intermediate and posterior ocular region via conventional delivery methods has proven difficult in practice, as the methods are fraught with drawbacks.

[0006] Currently, there are four known methods of delivering the compounds to the posterior ocular chamber including: direct injection into the vitreous, systemic administration with subsequent distribution into the eye through optic blood flow, injection into the areas surrounding the globe with subsequent passive diffusion through the sclera into the globe, and topical application to the cornea and/or sclera with subsequent passive diffusion posteriorly into the globe's interior. Each of the above-mentioned methods has its shortcomings.

[0007] The preferred delivery method for drug administration into any body tissue is by oral administration due to its simplicity, non-invasiveness, and patient acceptance. Less acceptable, but effective methods of reaching body tissues by way of the systemic vasculature include invasive transcutaneous injections of compounds through the skin. Yet other methods involve non-invasive transport by percutaneous absorption. Generally, however, delivery of a drug into the eye via systemic methods is difficult because the eye is an immunoprivileged organ. The blood vessels supplying the eye have tight junctions between their endothelial cells, thus preventing the transfer of most non-endogenous compounds from the blood to the eye. In this way, the blood-retinal barrier's function is very similar to the protection afforded the central nervous system by the blood-brain barrier. The blood-retinal barrier inhibits entry of most systemically circulating drugs into the eye itself. In order to achieve therapeutic concentrations in the eye following systemic delivery, therefore, large quantities of the drug must be administered to overcome the barrier. The excessive quantities of the drug in the systemic circulation, of course, expose the entire body to the negative effects and potential toxicity of the drugs. For example, if a steroid is administered in large doses to a patient, such as for the treatment of uveitis, the entire body experiences the steroidal effects.

These effects include fluid retention, electrolyte imbalance, immunosuppression, myopathy, cataract formation, behavior changes and bone demineralization, among others. Similarly, if large doses of a vascular endothelial growth factor (VEGF) antagonist are administered, systemic effects include the delayed healing of injuries and decreased blood perfusion to body tissues. As such, whole body toxicity precludes systemic delivery of medicaments as a way to achieve therapeutic concentration in the globe's interior.

[0008] More targeted, non-systemic delivery methods are similarly known in the art. As early as the 1920's, clinicians administered drugs to the eye by retrobulbar injection. Other methods have developed through the years, including subtenon's capsule, peribulbar, and subconjunctival injections, all of which comprise invasive delivery methods for injecting large amounts of a drug into a periorbital space. Through injection to areas surrounding the globe, these methods achieve a high local concentration of the drug, allowing for transcleral drug delivery to the posterior chamber by passive, Fickian driven diffusion. The injections, however, carry significant risks, including pain, risk of infection, tissue scarring, retrobulbar hemorrhage, ecchymosis, elevated intraocular pressure, accidental perforation of the globe, and eye proptosis. Further, despite their relatively targeted nature, periorbital injections can result in high systemic drug concentrations because the drug does not diffuse unidirectionally into the globe, but diffuses radially into the capillaries and vasculature surrounding the globe. In fact, some researchers found systemic levels of 60 ng/ml plasma following a 5 mg peribulbar injection of dexamethasone; a plasma concentration they concluded was comparable to a "high oral dose" (approximately 7.5 mg). Weijtens O, Van Der Sluijs F A, Schoemaker R C, Lentjes EGWM, Choen A F, Romijn FPHTM, and Van Meurs J C (1997). *Peribulbar corticosteroid injection: vitreal and serum concentrations after dexamethasone disodium phosphate injection*. Am J Ophthalmol, 123:358-63.

[0009] Another method for the introduction of medication into the eye includes direct injection of the drug into the vitreous. Intravitreal injections have been used to deliver antibacterial and antifungal agents for the treatment of bacterial and fungal endophthalmitis, antivirals for treatment of viral retinitis, and steroids for the treatment of uveitis. The half-life of most compounds in the vitreous, however, is relatively short, usually on the scale of just a few hours. Therefore, the intravitreal injections must be repeated, often multiple times a week. The repeated injections can cause pain, discomfort, intraocular pressure increases, intraocular bleeding, increased chances for infection, and the possibility of retinal detachment.

[0010] A similar method to the intravitreal injections requires the implantation of drug containment matrices into the vitreal compartment or the surgical implantation of a sustained release drug delivery device into the vitreal compartment. Such devices may be bioerodible, or non-erodible. They often must be, however, surgically implanted into the interior of the globe to be effective. Once the drug payload is exhausted, a new matrix may be inserted to replace the old, or the old device left in place and a new matrix inserted nearby. Although effective, such devices carry with them significant risks, separate and apart from the risks associated with major implantation surgery. The problems include pain, discomfort, intraocular bleeding, intraocular pressure

increases, chance of infection, and the possibility of retinal detachment. Lastly, if ocular drug toxicity is observed, such as increased intraocular pressure or cataractogenesis during implantation therapy, the toxicity has to be managed or the device removed.

[0011] One final category of drug delivery includes the introduction of materials into the interior of the ocular globe by diffusion through the sclera into the globe's interior. Such diffusion can be passive or active, wherein drug may be driven by an external driving force, such as iontophoresis, into the eye.

[0012] For passive delivery of drugs to the eye, a sustained release drug delivery device, a matrix saturated with the drug, a polymer containing the drug, or a collagen shield containing the drug can all be placed adjacent to the episclera. The drug, once in contact with the eye, diffuses into the ocular tissue by a process that is governed by Fick's law. Fick's law reads:

$$J=PA\Delta C$$

[0013] Where

[0014] J=drug flux into the eye

[0015] P=permeability of drug through the sclera

[0016] A=area of device in contact with the eye

[0017] ΔC =concentration gradient across the sclera

[0018] Despite the well-known nature of Fickian transport, it has not as of yet been recognized that passive delivery through the conjunctiva and sclera could yield therapeutic concentrations of medicament in the posterior portion of the eye. The inability to deliver effective amounts of drug to the eye runs contrary to empirically determined information on the transport of those drugs.

[0019] Geroski and Edelhauser investigated the in vitro passive scleral permeability of numerous compounds. Geroski, D. H. and H. F. Edelhauser, *Transscleral drug delivery for posterior segment disease*, Adv. Drug. Del. Rev. 52:37-48 (2001). Through their results, Geroski and Edelhauser found that permeability of the compounds was inversely related to molecular weight, with smaller compounds having higher transport rates than larger compounds. Regardless of molecular size, however, the transport rates of all compounds remained relatively high, with small compounds having transport rates on the order of 1×10^{-5} cm/s, and large compounds having transport rates on the order of 1×10^{-6} cm/s. Yet despite finding such high permeabilities, Geroski and Edelhauser failed to recognize the reasonable utility of in vivo passive, transscleral drug delivery to achieve therapeutic drug concentrations within the eye.

[0020] Thus, the inability to deliver drugs effectively through topical administration must be due to environmental conditions in the drug delivery pathway or within the eye itself that degrade or eliminate the drug. Two particular conditions have been postulated as being responsible for the loss of topically administered drug. Topically administered drugs are exposed directly to lacrimal fluids within the eye, which contain enzymes and proteins that can attack the drug. It is postulated that, once applied, enzymes, which break the drug down from its effective form, attack the drugs. Alternately, the lacrimal proteins can bind with the active form of the drug, thereby inactivating it or preventing its transport.

In any case, the environmental conditions in the extrascleral space, within the transport pathways, and within the eye tend to create a harsh environment for the transport and viability of the effective form of the drug.

[0021] As mentioned, one reason why conventional topical administration of drugs to the eye has heretofore not achieved effective concentrations of drug in the posterior of the eye is because of the effectiveness of the vasculature in clearing the drug. In order for topically administered compounds to be reach the back of the eye, the drug must pass through several layers of ocular tissues before reaching the vitreous. Several of these tissues, more specifically the conjunctiva and the choroid, have extensive blood supplies. In addition to delivering nutrients and oxygen to the tissues, these vascular beds are also responsible for removing waste byproducts of metabolism. Further, these vascular beds serve a protective function by removing exogenous and potentially noxious stimuli before they can reach the visual pathways of the eye's interior. These tissues contain the clearing vasculature of the eye, which can shunt the drug from the ocular region to the systemic vasculature, thus not allowing the drug to be exposed to the back of the eye. Combined with enzymatic degradation and protein binding elucidated above, these environmental conditions create a particularly formidable barrier for delivery to the posterior portion of the eye following passive, topical delivery.

[0022] As such, it is an object of the present invention to effectively and safely deliver medicament to a posterior retinal portion of an eye, without the potential risks and side effects associated with systemic and injectable delivery methods.

[0023] It is another object of the present invention to provide for an enhanced pharmaceutical preparation that improves the effective delivery concentration of a medicament to the intermediate and posterior retinal region.

[0024] These and other objects will become apparent to one of ordinary skill in the art given the specification, claims and drawings appended hereto.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] FIG. 1 comprises a perspective view of the device of the present invention;

[0026] FIG. 2 comprises a perspective view of an alternative embodiment of the device; and

[0027] FIG. 3 comprises a perspective view of yet another alternative embodiment of the present invention.

SUMMARY OF THE INVENTION

[0028] The present invention consists of a pharmaceutical compound for the treatment of posterior retinal conditions, a device for administering the compound, and a method for using both. The pharmaceutical compound generally consists of an effective amount of a therapeutic compound and at least one means for prolonging the residence time of the therapeutic compound's contact with the eye. Further, the formulation will be sufficient for increasing the transport of the therapeutic compound across the sclera of an eye toward and into a posterior retinal region, wherein the drug formulation increases the efficiency and efficacy of delivery of the compound to the back of an eye.

[0029] Common therapeutic agents that can be utilized with the present invention include steroids, antibacterials, antivirals, antifungals, antimetabolites, VEGF inhibitors, ICAM inhibitors, antibodies, protein kinase C inhibitors, chemotherapeutic agents, neuroprotective agents, nucleic acid derivatives, aptamers, proteins, enzymes, peptides, polypeptides, immunosuppressive agents, mast cell stabilizing agents, and mycophenolate mofetil, among others or any combination thereof.

[0030] In one preferred embodiment, the compound will exhibit enhanced flux over pure topical administration because of decreased pre-scleral clearance or binding and decreased shunting into the systemic vasculature. A second preferred embodiment is one that increases the retention in the globe's interior by decreasing clearance through humor dynamics or clearance into the choroidal and retinal vasculature. For example, because pre-retinal clearance is a function of conjunctival and choroidal blood flow, a vasoconstrictor can be administered to the eye to, in turn, reduce the vascular blood flow of the conjunctiva and therefore enhance drug transport into the eye. Vasoconstrictors are well known in the art and can include α -agonists such as naphazoline and tetrahydrozoline, sympathomimetics, and sympathomimetic amines selected from the group consisting of phynylethylamine, epinephrine, norepinephrine, dopamine, dobutamine, colterol, ethylnorepinephrine, isoproterenol, isoeutharine, metaproterenol, terbutaline, metaraminol, phenylephrine, tyramine, hydroxyamphetamine, ritrodrene, prenalterol, methoxamine, albuterol, amphetamine, methamphetamine, benzphetamine, ephedrine, phenylpropanolamine, methentermine, phentermine, fenfluramine, propylhexedrine, diethylpropion, phenmetrazine, and phendimetrazine or any combination thereof.

[0031] Alternatively, the pharmaceutical compound can be retained within the eye by combining it with an encapsulating agent that encapsulates the therapeutic agent so as to retard the clearance of the therapeutic agent. Common encapsulating agents include liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins. Another effect of these encapsulating agents is to decrease degradation of the therapeutic agent in the extraocular space by inhibiting metabolism by lacrimal enzymes and binding to lacrimal proteins. Still another effect of these agents are to help sustain the therapeutic agent within a portion of the eye, as they help to form an intimate contact with at least a portion of an ocular tissue. Still another effect of these agents is to extend the absorption time of the therapeutic agent within an eye by providing a biochemical shell for controlling the exposure of the therapeutic agent to ocular fluids. Finally, encapsulating the therapeutic compound in an encapsulating agent additionally increases transscleral and transconjunctival transport.

[0032] Preferably, the above-discussed pharmaceutical composition is delivered to the eye in an ophthalmic device for the topical delivery of a therapeutic compound. Such a device preferably includes a fluid retaining member that contains a pharmaceutical formulation containing a releasable therapeutic drug for treating posterior ocular pathologies. Such a device preferably includes at least one means for prolonging the residence time of the therapeutic compound within the eye and a means for increasing the transport of the therapeutic compound across the conjunctiva and

sclera toward and into a posterior ocular region. The pharmaceutical formulation preferably comprises the same compound discussed above.

[0033] In a preferred embodiment, the fluid retaining member additionally comprises a rate-limiting membrane that controls the rate of delivery of the therapeutic agent out of the housing and into an eye. Additionally, it is preferred that the fluid retaining member comprises a flexible seal circumferentially surrounding a reservoir for retaining the therapeutic compound, wherein the flexible seal creates a fluid-tight barrier when placed into contact with a surface of an eye.

[0034] In an alternative, but preferred, embodiment, the ophthalmic device additionally includes a means for decreasing the lag-time of molecular transport through the use of an active driving force. An active driving force provides an additional motivation for driving molecules across the ocular tissues and into the posterior retinal area. Such an active driving force could comprise ultra sound or iontophoresis, for example. If iontophoresis is used, it may be used with either direct or alternating iontophoretic current. The active driving force may be applied in a constant manner, or intermittently, as needed. If intermittent application is chosen, the active driving force may be applied at regular intervals, or irregular intervals.

[0035] The application of the active driving force may further be applied solely at specific times, or for specific lengths. For example, the active driving force may be applied only at the beginning of the treatment. Alternatively, the active driving force may be applied for less than 60 minutes, less than 20 minutes, or less than 5 minutes, depending upon the desired application.

[0036] The present invention is also directed to a method for increasing the concentration of a therapeutic compound in a posterior eye region, including the steps of administering to a patient an effective amount of a therapeutic compound, at least one means for prolonging the residence time of the therapeutic compound within the extraocular space, and means for increasing the transscleral transport of the therapeutic compound into the globe's interior. Preferably, the therapeutic compound and the flux enhancer are administered concurrently, but may additionally be administered one after the other. In that case it is preferred that the therapeutic compound is administered second.

[0037] Preferably, the method further includes the step of applying a means for decreasing the lag-time of molecular transport across the tissue, wherein the lag-time decreasing means comprises the application of an active driving force.

[0038] Through the administration of a pharmaceutical compound in the above manner, several positive effects can be achieved. One preferred effect is increased concentration of the therapeutic compound in a posterior region of the patient's eye. Another preferred effect is the increased efficiency and efficacy of the treatment of intermediate and posterior ocular conditions.

DETAILED DESCRIPTION OF THE INVENTION

[0039] I. Definitions

[0040] Before describing the present invention in detail, it is to be understood that this invention is not limited to

member 12 so that, upon application of fluid retaining member 12 to an ocular surface, an effective amount of therapeutic compound 14 is released from fluid retaining member 12 and delivered to a posterior region of the patient's eye.

[0073] Fluid retaining member 12 is shown in FIG. 1 in one preferred embodiment as a gauze pad having pharmaceutical compound 13 impregnated thereon. Alternatively, fluid retaining member 12 could comprise a patch, a sponge, a hydrogel, a porous ceramic, a silicone based membrane, or other materials familiar to one with ordinary skill in the art.

[0074] In one preferred embodiment of the invention shown in FIG. 2, fluid retaining member 12 comprises a housing 20 having fluid reservoir 22 for retaining pharmaceutical compound 13, and seal 26 circumferentially surrounding reservoir 22. Housing 20 comprises a retention space, namely fluid reservoir 22, for retaining pharmaceutical compound 13 therein. Additionally, housing 20 can include sponge, gauze, or other similar member for the releasable retention of pharmaceutical compound 13 within fluid reservoir 22.

[0075] Surrounding reservoir 22 is seal 26, which helps to efficiently and effectively deliver medicament out of device 10 and to the posterior retinal region of an eye. Seal 26 comprises a smooth, flexible material capable of forming a fluid-tight seal against an eye of a patient upon operative placement of device 10 thereon. Preferred materials for seal 26 include silicone of varying degrees of softness. For example, Dow Q7-2218 two-part soft silicone gel, silicone and elastomer equivalents from Nusil, low durometer urethanes, and similar materials are useful in the construction of barrier element 26. It is preferred that barrier element 26 be composed of low-durometer silicone elastomeric gels. Both housing 20 and seal 26 are preferably constructed from the same materials. Alternatively, however, housing 20 may comprise a rigid or semi-rigid material to enhance secure containment of the pharmaceutical compound.

[0076] In another preferred embodiment shown in FIG. 3, fluid retaining member 12 is associated with rate limiting membrane 28 for controlling the delivery rate of medicament out of fluid retaining member 12. As will be described further below, generally medicament that is delivered through topical application to an eye is absorbed into the eye via standard Fickian transport. Occasionally, however, a medicament will have a transport rate that is unnecessarily high, causing an overabundance of medicament to be introduced into the eye, which is wasteful and even dangerous. Rate limiting membrane 28 is associated between the medicament on fluid retaining member 12 and the eye of the patient so as to slow the transport of the medicament into the eye.

[0077] The rate limiting membranes can be either "hydrophobic" or "hydrophilic polymers". As used herein, the term "hydrophobic polymer" refers to polymers having equilibrium water content of less than about 10%. Suitable hydrophobic polymeric materials for use in the control membrane of the present invention include without limitation, polycarbonates, i.e., linear polyesters of carbonic acids in which carbonate groups recur in the polymer chain by phosgenation of a dihydroxy aromatic such as bisphenol A, polyvinylchlorides, polyamides such as polyhexamethylene adipamide and other such polyamides commonly known as

"nylon", modacrylic copolymers such as those formed of polyvinylchloride and acrylonitrile, and styreneacrylic acid copolymers, polysulfones such as those characterized by diphenylene sulfone groups in the linear chain thereof, halogenated polymers such as polyvinylidene fluoride and polyvinylfluoride, polychloroethers and thermoplastic polyethers, acetal polymers such as polyformaldehyde, acrylic resins such as polyacrylonitrile, polymethyl methacrylate and poly n-butyl methacrylate, polyurethanes, polyimides, polybenzimidazoles, polyvinyl acetate, aromatic and aliphatic polyethers, cellulose esters such as cellulose triacetate, epoxy resins, olefins such as polyethylene and polypropylene, porous rubber, poly(ethylene oxides) which are sufficiently cross-linked to have an equilibrium water content of less than about 10%, polyvinylpyrrolidones which are sufficiently cross-linked to have an equilibrium water content of less than about 10%, poly(vinyl alcohols) which are sufficiently cross-linked to have an equilibrium water content of less than about 10%; derivatives of polystyrene such as poly(sodium styrenesulfonate) and polyvinylbenzyltrimethyl-ammonium chloride, poly(hydroxyethyl methacrylate), poly(isobutyl vinyl ether), polyisoprenes, polyalkenes, ethylene vinyl acetate copolymers, particularly those having 1-40 weight percent vinyl acetate content, such as those described in U.S. Pat. No. 4,144,317, incorporated herein by reference, polyamides, and polyurethanes. This list is merely exemplary of the materials suited for use in this invention. A more extensive list can be found in J. R. Scott & W. J. Roff, Handbook of Common Polymers (CRC Press, 1971) and in patents disclosing suitable materials for use in manufacturing microporous membranes such as U.S. Pat. No. 3,797,494, incorporated herein by reference.

[0078] As used herein, the term "hydrophilic resin" refers to resins which are at least water wettable but not necessarily water soluble and having an equilibrium water content of greater than about 10% and preferably greater than about 20%. Suitable hydrophilic resins for use in the control membrane of the present invention include materials such as polyvinylpyrrolidone, polyethylene oxides, polyox, polyox blended with polyacrylic acid or Carbopol, cellulose derivatives such as hydroxypropyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, pectin, starch, guar gum, locust bean gum, and the like, along with blends thereof. Particularly suitable hydrophilic materials are ion exchange resins having a degree of crosslinking providing equilibrium water content greater than about 10%. Ion exchange resins and their properties are described in The Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Edition, Volume 13, pps. 678 to 705, John Wiley & Sons (1981).

[0079] Preferably, the above-described ophthalmic device 10 may be beneficially associated with a means for decreasing the lag-time of molecular transport. While the above pharmaceutical compounds are capable of prolonging the residence time, and/or enhancing the transport of the therapeutic compound, the transport of the molecules across the ocular tissues is still dictated by the laws of Fickian diffusion. Therefore, it may be beneficial in some cases to add an active delivery component to the device 10. By combining the passive delivery disclosed above with an additional, active drug delivery component, the lag time of the molecule within the first several layers of the ocular tissue can be decreased, thus improving the delivery of the molecules to the posterior retinal area.

[0080] Typically, such an active delivery component comprises an iontophoretic delivery mechanism, or an ultra sonic delivery mechanism. Iontophoresis is the use of an electric current, either alternating or direct current, to drive charged compounds from a device into the tissues of a patient. Ultra sonic delivery is the use of ultra sound waves to drive molecules into and through the tissues of a patient. Such devices are well known in the art.

[0081] The active driving force is preferably used either before or in conjunction with the normal, passive delivery operations of the device. Typically, it is beneficial to utilize the active driving force at specific times, for specific lengths of time, to enhance and benefit the passive delivery operations. For example, an active driving force could be beneficially provided at the beginning of the application of the ophthalmic device 10. By doing so, initial barriers to the normal, Fickian transport can be reduced, allowing for increased passive drug delivery throughout operation. Preferably, for example, the active driving force can be applied for a period of 1-5 minutes before the passive delivery operations have started. Additionally, applying the active driving force for limited periods of time throughout operation, such as, for example, for a period of less than 60 minutes, less than 20 minutes, or even less than 5 minutes can provide similar benefits.

[0082] In another preferred embodiment, it is contemplated that the application of the active driving force for these limited periods of time can be done in intervals also, either regularly or intermittently as may be needed. For example, an active driving force can be applied initially for 1-5 minutes, and then halted completely for a period of passive drug delivery lasting for between 1-3 hours. After the passive delivery operations, an active driving force can be applied again, and passive operations repeated. The application of the active driving force, followed by passive delivery may then be cycled continuously until treatment is completed. Alternatively, the active driving force may be used in conjunction with the passive delivery of the therapeutic agent. In any case, the combination of active and passive delivery mechanisms may improve the overall delivery of the beneficial pharmaceutical agent to the posterior retinal region of the eye.

[0083] Alternatively, it may be possible to utilize the active driving force, alone, to deliver sufficient quantities of the pharmaceutical agent to the posterior retinal regions. Preferably, such an application of active driving force would include a single, 1-5 minute application of active driving force.

[0084] In operation, the above-described device 10 is first impregnated with a sufficient amount of pharmaceutical compound 13 so as to deliver an effective amount of a therapeutic compound 14 contained within the pharmaceutical compound to a posterior region of an eye. Thereafter, device 10 is placed in operative position upon an ocular surface of a patient, whereafter the pharmaceutical compound 13 is delivered to the surface of the eye, passing through at least one of the scleral and conjunctival tissues into the interior region of the eye for effective and efficient delivery of the therapeutic compound 14 to a posterior region of the eye.

[0085] If the device 10 comprises, for example, a simple impregnated gauze pad, placement of the device 10 upon an

ocular surface may be accomplished by simply placing the gauze pad upon an eye, or by securing the pad through medical tape, an eye patch, or the like. Alternatively, if device 10 instead comprises a housing 20 having a seal 26 thereon, it may be placed on the eye in any way that allows for a substantially fluid-tight seal between device 10 and the eye. Preferably, device 10 with seal 26 is placed between the eyelid and the eye of the patient, securing device 10 in place. Other surface applications, however, are similarly contemplated.

[0086] Once the seal 26 is in operative position upon an eye, it immediately provides for improved delivery of the pharmaceutical compound 13 to the eye. Initially, once seal 26 is in operative placement, a fluid-tight barrier between device 10 and the eye is formed, sealing pharmaceutical compound 13 in, and the surrounding lacrimal fluids out. As such, by merely placing the device 10 upon the eye, pharmaceutical compound 13 can be secured within device 10, ensuring concentrated delivery, and damaging enzymes and lacrimal proteins can, for the most part, be removed from the equation. Further, by focusing the topical application of the drug to a single, specific area, the underlying vasculature to which the pharmaceutical compound 13 can be exposed is limited. Therefore, there is less of a clearing vasculature to be overcome in delivery of the compound 13 to the rear of the eye.

[0087] Either of the above embodiments may additionally include rate-limiting membrane 28. If the selected pharmaceutical compound 13 comprises an excessive rate of transport, rate-limiting membrane 28 will help to slow the Fickian transport of the compound 13 out of the device 10. Once device 10 is placed upon the eye, pharmaceutical compound 13 is passed across membrane and into an ocular tissue. As the compound 13 passes across membrane, however, the rate of transport is slowed to an acceptable rate.

[0088] Through the use of the above pharmaceutical formulations, either in combination with a delivery device or alone, the efficacy and efficiency of medicament delivery to the posterior regions of an eye is increased.

[0089] The foregoing description merely explains and illustrates the invention and the invention is not limited thereto except insofar as the appended claims are so limited, as those skilled in the art who have the disclosure before them will be able to make modifications without departing from the scope of the invention.

What is claimed is:

1. A pharmaceutical formulation for the treatment of posterior ocular conditions, comprising:

an effective amount of a therapeutic compound; and

at least one of means for enhancing the transport of the therapeutic compound across the sclera of an eye toward and into at least one of an intermediate and a posterior portion of the eye, and means for prolonging the residence time of the therapeutic compound within the intermediate and posterior portions of the eye.

2. The formulation according to claim 1, wherein the transport enhancing means comprises means for reducing the vascular clearance of the therapeutic compound during administration of an effective amount of the therapeutic compound to the eye.

3. The formulation according to claim 2, wherein the enhancing means comprises a vasoconstrictor that may be administered to the eye to, in turn, reduce the vascular blood flow in tissues of the eye.

4. The formulation according to claim 3, wherein the vasoconstrictor comprises an α -agonist.

5. The formulation according to claim 4, wherein the vasoconstrictor is selected from one of the group consisting of naphazoline, tetrahydrozoline, and sympathomimetics.

6. The formulation according to claim 3, wherein the vasoconstrictor comprises a sympathomimetic amine selected from one of the group consisting of phenylethylamine, epinephrine, norepinephrine, dopamine, dobutamine, colterol, ethylnorepinephrine, isoproterenol, isoetharine, metaproterenol, terbutaline, metaraminol, phenylephrine, tyramine, hydroxyamphetamine, ritrodine, prenalterol, methoxamine, albuterol, amphetamine, methamphetamine, benzphetamine, ephedrine, phenylpropanolamine, methamphetamine, phentermine, fenfluramine, propylhexedrine, diethylpropion, phenmetrazine, and phendimetrazine.

7. The formulation according to claim 2, wherein the enhancing means comprises an encapsulating agent that encapsulates the therapeutic compound.

8. The formulation according to claim 7, wherein the encapsulating agent inhibits the vascular clearance of the therapeutic agent during its transport across the sclera.

9. The formulation according to claim 7, wherein the encapsulating agent increases the rate and amount of transport of the therapeutic agent across the sclera.

10. The formulation according to claim 7, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.

11. The formulation according to claim 1, wherein the transport enhancing means comprises means for decreasing degradation of the therapeutic agent before transscleral delivery.

12. The formulation according to claim 11, wherein the degradation decreasing means comprises an encapsulating agent that encapsulates the therapeutic agent, wherein the encapsulating agent inhibits metabolism of the therapeutic agent by lacrimal enzymes.

13. The formulation according to claim 11, wherein the degradation decreasing means comprises an encapsulating agent that encapsulates the therapeutic agent, wherein the encapsulating agent inhibits binding of the therapeutic agent to extraocular lacrimal proteins or intraocular pigments.

14. The formulation according to claim 1, wherein the transport enhancing means comprises means for extending the absorption time of the therapeutic agent into an eye, the extending means comprising an encapsulating agent that encapsulates the therapeutic agent, wherein the encapsulating agent provides a biochemical shell for controlling the exposure of the therapeutic agent to ocular fluids.

15. The formulation according to claim 14, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.

16. The formulation according to claim 1, wherein the transport enhancing means comprises encapsulating the therapeutic compound in an encapsulating agent, wherein the encapsulating agent increases transscleral transport.

17. The formulation according to claim 16, wherein the encapsulating agent is selected from the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.

18. The formulation according to claim 1, wherein the transport enhancing means comprises an encapsulating agent that encapsulates the therapeutic agent, wherein the encapsulating agent forms an intimate contact with at least a portion of an ocular tissue.

19. The formulation according to claim 18, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.

20. The formulation according to claim 1, wherein the prolonging means comprises encapsulating the therapeutic compound in an encapsulating agent, wherein the encapsulating agent decreases the removal of the therapeutic agent through at least one of vitreous humor fluid dynamics and globe clearance.

21. The formulation according to claim 20, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.

22. The formulation according to claim 1, wherein the therapeutic compound is selected from the group consisting of steroids, antibacterials, antivirals, antifungals, antimetabolites, VEGF inhibitors, ICAM inhibitors, antibodies, protein kinase C inhibitors, chemotherapeutic agents, neuroprotective agents, nucleic acid derivatives, aptamers, proteins, enzymes, peptides, polypeptides, immunosuppressive agents, mast cell stabilizing agents, and mycophenolate mofetil.

23. An ophthalmic device for the topical delivery of a therapeutic compound to a posterior region of an eye, comprising:

a fluid retaining member;

a therapeutic compound for treating posterior retinal conditions releasably associated with the fluid retaining member; and

at least one of means for enhancing the transport of the therapeutic compound across the sclera of an eye toward and into at least one of an intermediate and a posterior portion of the eye, and means for prolonging the residence time of the therapeutic compound within the intermediate and posterior portions of the eye.

24. The device according to claim 23, wherein the transport enhancing means comprises means for reducing the vascular clearance of the therapeutic compound during administration of an effective amount of the therapeutic compound to the eye.

25. The device according to claim 24, wherein the reducing means comprises a vasoconstrictor that may be administered to the eye to, in turn, reduce the vascular blood flow in tissues of the eye.

26. The device according to claim 25, wherein the vasoconstrictor comprises an α -agonist.

27. The device according to claim 26, wherein the vasoconstrictor is selected from one of the group consisting of naphazoline, tetrahydrozoline, and sympathomimetics.

28. The device according to claim 26, wherein the vasoconstrictor comprises a sympathomimetic amine selected from one of the group consisting of phenylethylamine, epinephrine, norepinephrine, dopamine, dobutamine, col-

terol, ethylnorepinephrine, isoproterenol, isoetharine, metaproterenol, terbutaline, metaraminol, phenylephrine, tyramine, hydroxyamphetamine, ritrodine, prenalterol, methoxamine, albuterol, amphetamine, methamphetamine, benzphetamine, ephedrine, phenylpropanolamine, methentermine, phentermine, fenfluramine, propylhexedrine, diethylpropion, phenmetrazine, and phendimetrazine.

29. The device according to claim 24, wherein the enhancing means comprises an encapsulating agent that encapsulates the therapeutic compound.

30. The device according to claim 29, wherein the encapsulating agent inhibits the vascular clearance of the therapeutic agent during its transport across the sclera.

31. The device according to claim 29, wherein the encapsulating agent increases the rate and amount of transport of the therapeutic agent across the sclera.

32. The device according to claim 29, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.

33. The device according to claim 23, wherein the transport enhancing means comprises means for decreasing degradation of the therapeutic agent before transscleral delivery.

34. The device according to claim 33, wherein the decreasing means comprises an encapsulating agent that encapsulates the therapeutic agent, wherein the encapsulating agent inhibits metabolism of the therapeutic agent by lacrimal enzymes.

35. The device according to claim 33, wherein the decreasing means comprises an encapsulating agent that encapsulates the therapeutic agent, wherein the encapsulating agent inhibits binding of the therapeutic agent to extraocular lacrimal proteins or intraocular pigments.

36. The device according to claim 23, wherein the transport enhancing means comprises means for extending the absorption time of the therapeutic agent into an eye, the extending means comprising an encapsulating agent that encapsulates the therapeutic agent, wherein the encapsulating agent provides a biochemical shell for controlling the exposure of the therapeutic agent to ocular fluids.

37. The device according to claim 36, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.

38. The device according to claim 23, wherein the transport enhancing means comprises encapsulating the therapeutic compound in an encapsulating agent, wherein the encapsulating agent increases transscleral transport.

39. The device according to claim 38, wherein the encapsulating agent is selected from the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.

40. The device according to claim 23, wherein the transport enhancing means comprises an encapsulating agent that encapsulates the therapeutic agent, wherein the encapsulating agent forms an intimate contact with at least a portion of an ocular tissue.

41. The device according to claim 40, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.

42. The device according to claim 23, wherein the prolonging means comprises encapsulating the therapeutic compound in an encapsulating agent, wherein the encapsu-

lating agent decreases the removal of the therapeutic agent through at least one of vitreous humor fluid dynamics and globe clearance.

43. The device according to claim 42, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.

44. The device according to claim 23, wherein the therapeutic compound is selected from the group consisting of steroids, antibacterials, antivirals, antifungals, antimetabolites, VEGF inhibitors, ICAM inhibitors, antibodies, protein kinase C inhibitors, chemotherapeutic agents, neuroprotective agents, nucleic acid derivatives, aptamers, proteins, enzymes, peptides, polypeptides, immunosuppressive agents, mast cell stabilizing agents, and mycophenolate mofetil.

45. The device according to claim 23, wherein the means comprises a rate-limiting membrane that controls the rate of delivery of the therapeutic agent out of the housing and into the eye.

46. The device according to claim 23, wherein the housing comprises a flexible seal circumferentially surrounding a reservoir for retaining the therapeutic compound, wherein the flexible seal creates a fluid-tight barrier when placed into contact with a surface of an eye.

47. The device according to claim 23, further comprising means for decreasing the lag time of molecular transport, wherein the lag-time decreasing means comprises an active driving force.

48. The device according to claim 47 wherein the active driving force is ultra sound.

49. The device according to claim 47 wherein the active driving force is iontophoresis.

50. The device according to claim 47 wherein the active driving force is applied constantly.

51. The device according to claim 47 wherein the active driving force is applied intermittently.

52. The device according to claim 49 wherein the active driving force is applied at regular intervals.

53. The device according to claim 49 wherein the active driving force is applied at irregular intervals.

54. The device according to claim 47 wherein the active driving force is applied only at the beginning of the treatment.

55. The device according to claim 54 wherein the length of application of the active driving force is less than 60 minutes.

56. The device according to claim 55 wherein the length of application of the active driving force is less than 20 minutes.

57. The device according to claim 56 wherein the length of application of the active driving force is less than 5 minutes.

58. The device according to claim 49 wherein the iontophoretic current is direct current.

59. The device according to claim 49 wherein the iontophoretic current is alternating current.

60. A method for increasing the concentration of a therapeutic compound in a posterior region of the eye, comprising the steps of:

administering to a patient an effective amount of a therapeutic compound; and

- additionally administering a pharmaceutical compound with the therapeutic compound, wherein the pharmaceutical compound comprises at least one of means for enhancing the transport of the therapeutic compound across the sclera of an eye toward and into at least one of an intermediate and a posterior portion of the eye, and means for prolonging the residence time of the therapeutic compound within the intermediate and posterior portions of the eye.
61. The method according to claim 60, wherein the step of administering and the step of additionally administering are undertaken concurrently.
62. The method according to claim 60, wherein the step of administering is undertaken prior to the step of additionally administering.
63. The method according to claim 60, wherein the transport enhancing means comprises means for reducing the clearance of the therapeutic compound during administration of the effective amount of the therapeutic compound to the eye.
64. The method according to claim 63, wherein the reducing means comprises a vasoconstrictor that may be administered to the eye with the therapeutic agent to, in turn, reduce the vascular blood flow within the tissues of the eye.
65. The method according to claim 64, wherein the vasoconstrictor comprises an α -agonist.
66. The method according to claim 65, wherein the vasoconstrictor is selected from one of the group consisting of, naphazoline, tetrahydrozoline, and sympathomimetics.
67. The method according to claim 65, wherein the vasoconstrictor comprises a sympathomimetic amine selected from one of the group consisting of phenylethylamine, epinephrine, norepinephrine, dopamine, dobutamine, colterol, ethylnorepinephrine, isoproterenol, isoetharine, metaproterenol, terbutaline, metaraminol, phenylephrine, tyramine, hydroxyamphetamine, ritrodrene, prenalterol, methoxamine, albuterol, amphetamine, methamphetamine, benzphetamine, ephedrine, phenylpropanolamine, methamphetamine, phentermine, fenfluramine, propylhexedrine, diethylpropion, phenmetrazine, and phendimetrazine.
68. The method according to claim 63, wherein the enhancing means comprises an encapsulating agent that encapsulates the therapeutic agent.
69. The method according to claim 68, wherein the encapsulating agent inhibits the vascular clearance of the therapeutic agent during its transport across the sclera.
70. The method according to claim 68, wherein the encapsulating agent increases the rate and amount of transport of the therapeutic agent across the sclera.
71. The method according to claim 68, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, and microemulsions.
72. The method according to claim 60, wherein the transport enhancing means comprises means for decreasing degradation of the therapeutic prior to delivery.
73. The method according to claim 72, wherein the degradation decreasing means comprises an encapsulating agent that encapsulates the therapeutic agent, wherein the encapsulating agent inhibits metabolism of the therapeutic agent by lacrimal enzymes.
74. The method according to claim 73, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.
75. The method according to claim 72, wherein the degradation decreasing means comprises an encapsulating agent that encapsulates the therapeutic agent, wherein the encapsulating agent inhibits binding of the therapeutic agent to extraocular lacrimal proteins and intraocular pigments.
76. The method according to claim 75, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.
77. The method according to claim 60, wherein the transport enhancing means comprises means for extending the absorption time of the therapeutic agent into an eye, the extending means comprising an encapsulating agent that encapsulates the therapeutic agent, wherein the encapsulating agent provides a biochemical shell for controlling the exposure of the therapeutic agent to ocular fluids.
78. The method according to claim 77, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.
79. The method according to claim 60, wherein the enhancing means comprises encapsulating the therapeutic compound in an encapsulating agent, wherein the encapsulating agent increases the rate and or the extent of transscleral transport.
80. The method according to claim 79, wherein the encapsulating agent is selected from the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.
81. The method according to claim 60, wherein the prolonging means comprises encapsulating the therapeutic compound in an encapsulating agent, wherein the encapsulating agent decreases the removal of the therapeutic agent through at least one of vitreous humor fluid dynamics and globe clearance.
82. The method according to claim 81, wherein the encapsulating agent is selected from one of the group consisting of liposomes, micelles, microemulsions, nanoparticles, and cyclodextrins.
83. The method according to claim 60, wherein the therapeutic compound is selected from the group consisting of steroids, antibacterials, antivirals, antifungals, antimetabolites, VEGF inhibitors, ICAM inhibitors, antibodies, protein kinase C inhibitors, chemotherapeutic agents, neuroprotective agents, nucleic acid derivatives, aptamers, proteins, enzymes, peptides, polypeptides, immunosuppressive agents, mast cell stabilizing agents, and mycophenolate mofetil.
84. The method according to claim 60, further comprising the step of applying a means to decrease the lag-time of molecular transport across the tissue, wherein the lag-time decreasing means comprises an active driving force.
85. The method according to claim 60 wherein the active driving force is ultra sound.
86. The method according to claim 60 wherein the active driving force is iontophoresis.
87. The method according to claim 58 wherein the active driving force is applied constantly.
88. The method according to claim 60 wherein the active driving force is applied intermittently.
89. The method according to claim 86 wherein the active driving force is applied at regular intervals.
90. The method according to claim 86 wherein the active driving force is applied at irregular intervals.

91. The method according to claim 60 wherein the active driving force is applied only at the beginning of the treatment.

92. The method according to claim 91 wherein the length of application of the active driving force is less than 60 minutes.

93. The method according to claim 92 wherein the length of application of the active driving force is less than 20 minutes.

94. The method according to claim 93 wherein the length of application of the active driving force is less than 5 minutes.

95. The method according to claim 86 wherein the iontophoretic current is direct current.

96. The device according to claim 86 wherein the iontophoretic current is alternating current.

97. A method for achieving an effect in a patient comprising administering an effective amount of a compound of claim 1 to the patient, wherein the effect is increased concentration of the therapeutic compound in a posterior retinal region of the patient.

98. A method for achieving an effect in a posterior retinal region of a living subject, comprising:

administering an effective amount of a therapeutic agent selected from one of the group consisting of steroids, antibacterials, antivirals, antifungals, antimetabolites, VEGF inhibitors, ICAM inhibitors, antibodies, protein kinase C inhibitors, chemotherapeutic agents, neuroprotective agents, nucleic acid derivatives, aptamers, proteins, enzymes, peptides, polypeptides, immunosuppressive agents, mast cell stabilizing agents, and mycophenolate mofetil to a surface region of an ocular tissue of the living subject; and

additionally administering an effective amount of a pharmaceutical compound along with the therapeutic agent, wherein the pharmaceutical compound comprises at least one of means for prolonging the residence time of the therapeutic compound within the eye, and means

for increasing the transport of the therapeutic compound across a tissue of an eye toward and into a posterior retinal region;

wherein the effect is to treat at least one posterior ocular condition.

99. A method for achieving an effect in a patient comprising administering an effective amount of a compound of claim 23 to the patient by application of the device of claim 23, wherein the effect is increased concentration of the therapeutic compound in a posterior ocular region of the patient.

100. A method for achieving an effect in a posterior retinal region of a living subject, comprising:

placing a drug delivery device comprising a fluid-retaining member on an eye of a patient, wherein the fluid-retaining member releasably contains:

an effective amount of a therapeutic agent selected from one of the group consisting of steroids, antibacterials, antivirals, antifungals, antimetabolites, VEGF inhibitors, ICAM inhibitors, antibodies, protein kinase C inhibitors, chemotherapeutic agents, neuroprotective agents, nucleic acid derivatives, aptamers, proteins, enzymes, peptides, polypeptides, immunosuppressive agents, mast cell stabilizing agents, and mycophenolate mofetil to a surface region of an ocular tissue of the living subject; and

an effective amount of a pharmaceutical compound, wherein the pharmaceutical compound comprises at least one of means for prolonging the residence time of the therapeutic compound within the eye, and means for increasing the transport of the therapeutic compound across a tissue of an eye toward and into a posterior retinal region; and

administering the therapeutic agent and the pharmaceutical compound to the eye, wherein the effect is to treat at least one posterior ocular pathology.

* * * * *

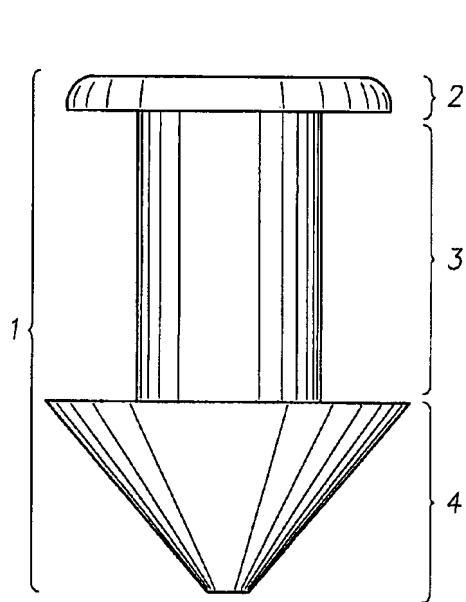


Fig. 1

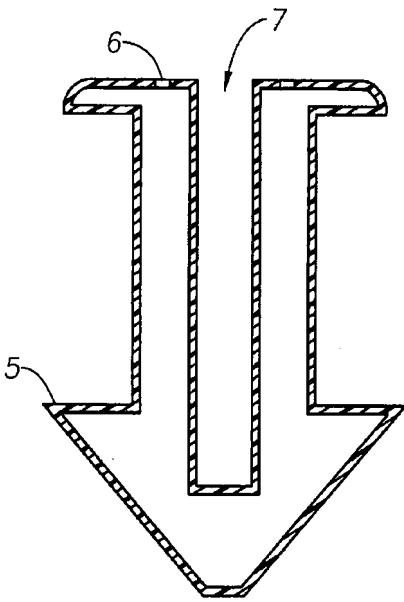


Fig. 2

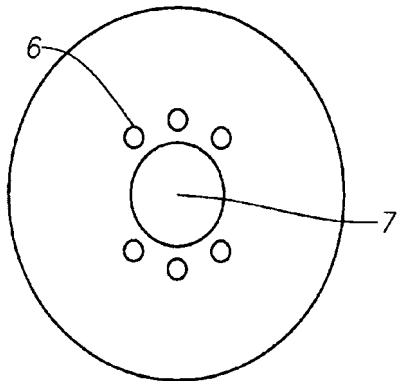


Fig. 3A

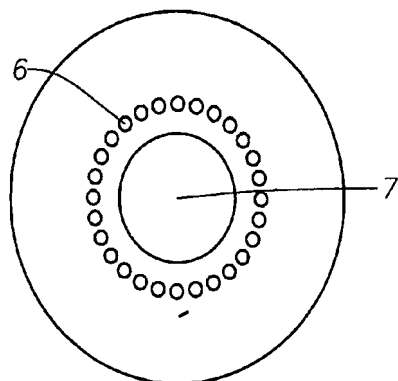


Fig. 3B

Fig. 4

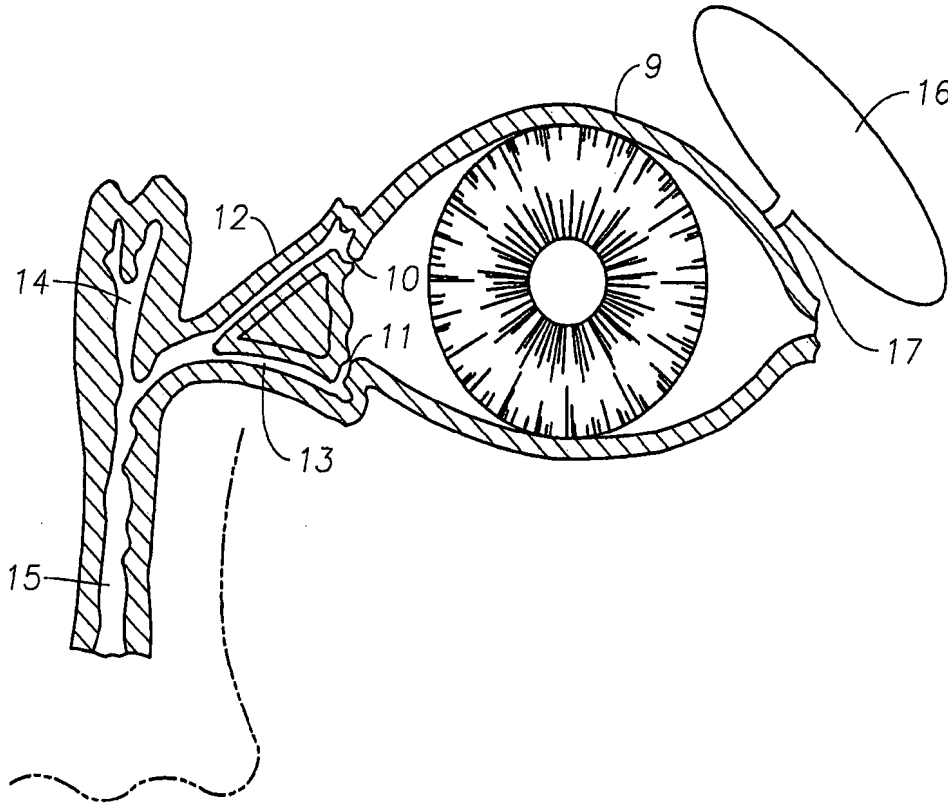
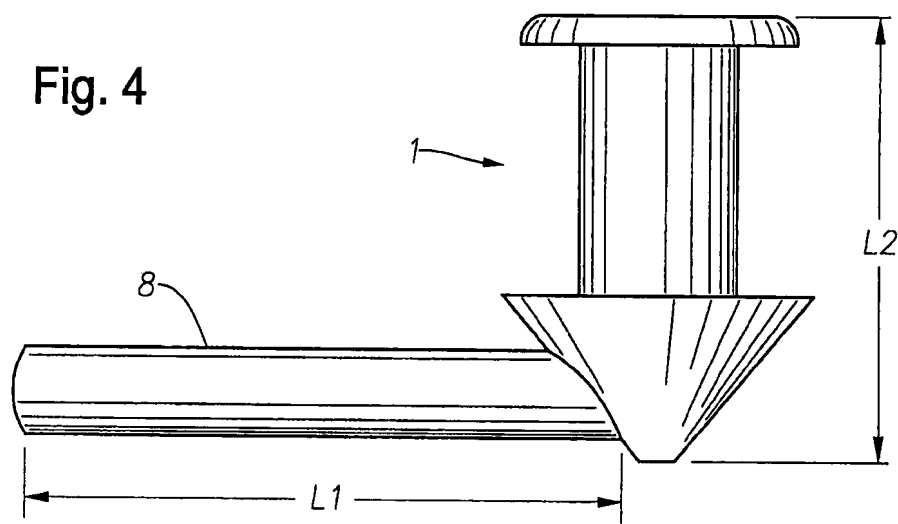
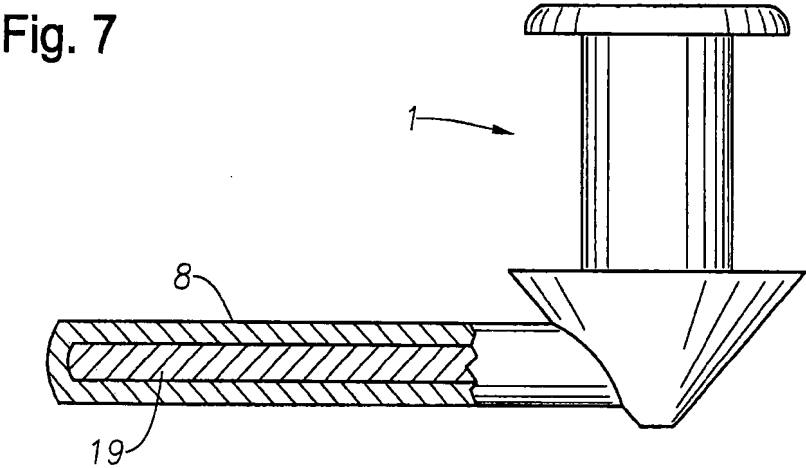
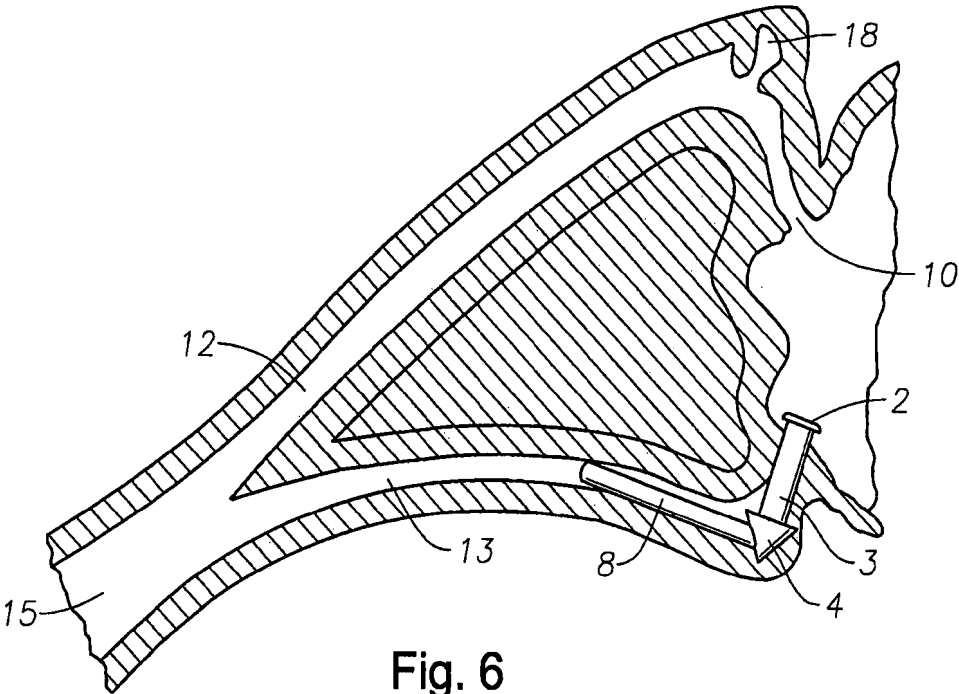


Fig. 5



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

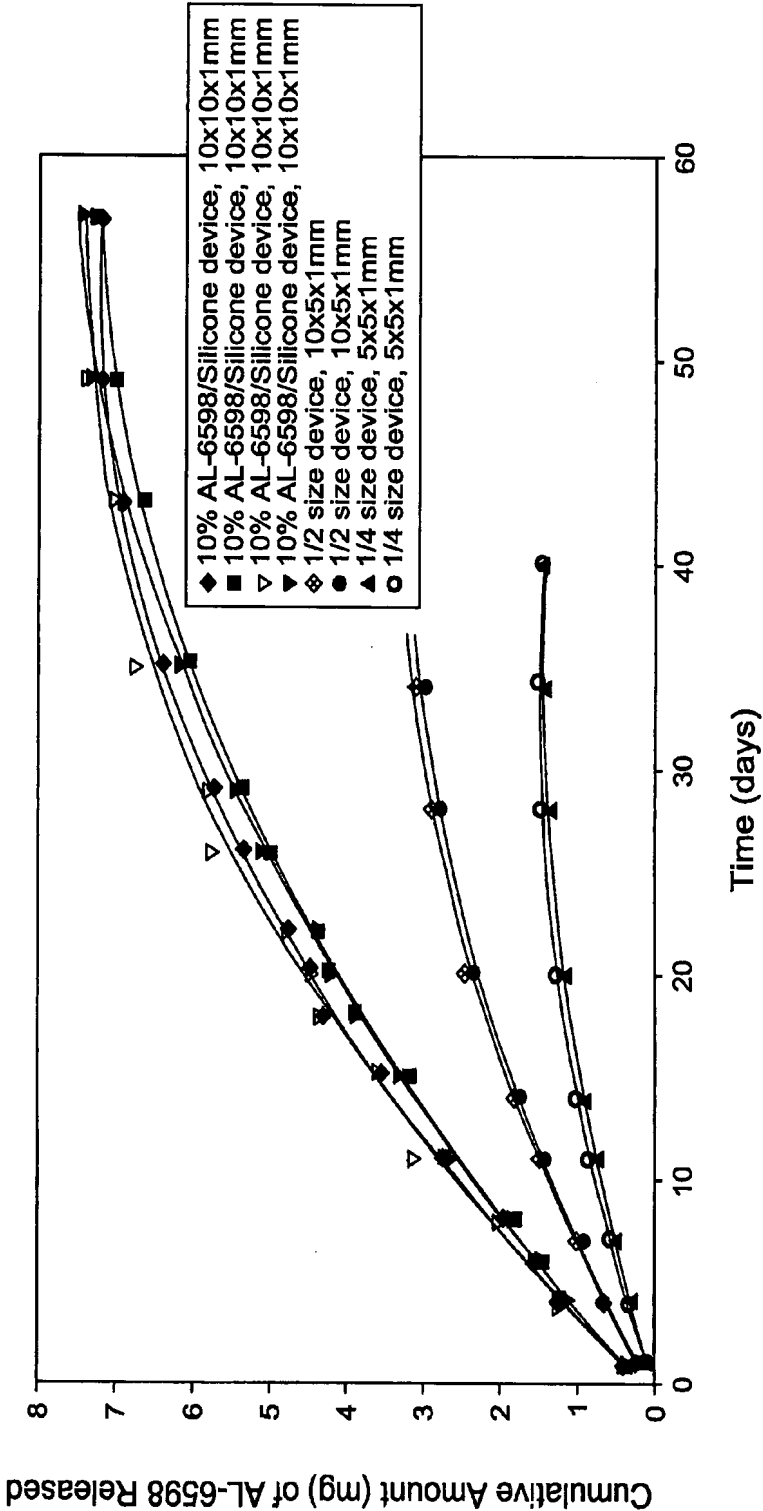


Fig. 8

PUNCTAL PLUGS AND METHODS OF DELIVERING THERAPEUTIC AGENTS

[0001] This application claims priority to U.S. Provisional Application, U.S. Ser. No. 60/898,599 filed Jan. 31, 2007.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention relates generally to the fields of implantable ocular devices, pharmaceuticals, and methods of drug delivery to the eye. More particularly, it concerns implantable ocular devices for the sustained delivery of a therapeutic compound to the eye.

[0004] 2. Description of Related Art

[0005] Glaucoma is the leading cause of blindness worldwide. It is the most common cause of optic neuropathy.

[0006] 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.

[0007] 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 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 already occurred because it progresses gradually and painlessly.

[0008] 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.

[0009] 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.

[0010] 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.

[0011] 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.

[0012] 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.

[0013] 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.

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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 mate-

rial can be used to make up the entire plug or implant which can be saturated with the active agent.

[0019] 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.

[0020] 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.

[0021] 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.

[0022] 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

[0023] 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.

[0024] 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 commer-

cially 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 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 synthetic prostaglandin. Non-limiting examples of prostaglandins include cloprostenol, fluprostenol, latanoprost, travoprost, and unoprostone.

[0025] 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%, 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.

[0026] 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 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.

[0027] 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 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; 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.

[0028] 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.

[0029] 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.

[0030] 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 embodiments, the canalicular extension further comprises an integral stylus. The integral stylus may be made of any bio-compatible 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-phenylene-oxy-1,4-phenylene-carbonyl-1,4-phenylene)polymer.

[0031] 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.

[0032] 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 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.

[0033] 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 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.

[0034] 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.

[0035] 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.

[0036] 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; (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.

[0037] 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, 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, polylactic acids, polyglycolic acids, polylactic-glycolic acids, poly caprolactones, triglycerides, polyethylene glycols, poly orthoesters, poly anhydrides, polyesters, cellulotics 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 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%.

[0038] 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 exclusive.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] Other objects, 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 modifica-

tions 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

[0043] 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.

[0044] FIG. 1 is a front view of a punctal plug.

[0045] FIG. 2 is a cross-sectional view of a punctal plug.

[0046] FIGS. 3A and 3B are top views of punctal plugs.

[0047] FIG. 4 is an illustration of a punctal plug with a canalicular extension.

[0048] FIG. 5 is an illustration of the lacrimal duct system of a mammalian eye.

[0049] FIG. 6 is an illustration of one of the present medical devices positioned in the lacrimal duct system of a mammalian eye.

[0050] FIG. 7 is a partial cross-section of a punctal plug with a canalicular extension.

[0051] FIG. 8 shows the effect of surface area on AL-6598 release from silicone devices in PBS at 37° C.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0052] 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.

[0053] 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.

[0054] 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 $\text{L mole}^{-1} \text{sec}^{-1}$.) 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.

[0055] 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. Canaliculi 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.

[0056] A variety of plugs for insertion into puncta 10 and 11 and/or canaliculi 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.

[0057] 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.

[0058] In one embodiment, the matrix comprises a silicone and drug-loaded biodegradable microspheres.

[0059] 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 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 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 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.

[0060] A drug delivery device of the present invention may also be formed as an intracanalicular implant. Intracanalicular implants, which are disposed entirely within 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.

[0061] A punctal plug or intracanalicular implant according to the present invention may also comprise a canalicular extension 8, which extends into the canaliculum 12 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.

[0062] 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 G_2 , which is subsequently converted to prostaglandin H_2 . Other naturally occurring prostaglandins are derivatives of prostaglandin H_2 . 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.

[0063] 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.

[0064] 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 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.

[0065] 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 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 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 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.

[0066] 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 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 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.

[0067] Oxygen plasma etching is a dry-etching process that takes place in an oxygen 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.

[0068] The following examples are included to demonstrate preferred embodiments 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 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

[0069] 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 10 mm×10 mm×1 mm. A ½ size device (10 mm×5 mm×1 mm) and a ¼ size device (5 mm×5 mm×1 mm) were also used in this study. Each silicone die contained 10% AL-6598, which is a DP class 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

[0070] Two silicone die (10 mm×10 mm×1 mm) 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 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.

[0071] The parylene coated silicone die were then milled using FIB. Pores of 1 µm 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 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

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

[0072] Travoprost is prepared as a polylactic acid microsphere having an average size of 100 nm-1 μm. 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 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.

[0073] 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 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 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

[0074] The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

[0075] U.S. Pat. No. 3,949,750
 [0076] U.S. Pat. No. 3,949,750
 [0077] U.S. Pat. No. 4,660,546
 [0078] U.S. Pat. No. 4,690,931
 [0079] U.S. Pat. No. 4,915,684
 [0080] U.S. Pat. No. 4,959,048
 [0081] U.S. Pat. No. 5,049,142;
 [0082] U.S. Pat. No. 5,053,030
 [0083] U.S. Pat. No. 5,053,030
 [0084] U.S. Pat. No. 5,151,444
 [0085] U.S. Pat. No. 5,163,959
 [0086] U.S. Pat. No. 5,171,270
 [0087] U.S. Pat. No. 5,283,063
 [0088] U.S. Pat. No. 5,296,504
 [0089] U.S. Pat. No. 5,352,708
 [0090] U.S. Pat. No. 5,417,651
 [0091] U.S. Pat. No. 5,422,368
 [0092] U.S. Pat. No. 5,423,777
 [0093] U.S. Pat. No. 5,469,867
 [0094] U.S. Pat. No. 5,723,005

[0095] U.S. Pat. No. 5,741,292
 [0096] U.S. Pat. No. 5,830,171
 [0097] U.S. Pat. No. 5,889,052
 [0098] U.S. Pat. No. 6,016,806
 [0099] U.S. Pat. No. 6,027,470
 [0100] U.S. Pat. No. 6,041,785
 [0101] U.S. Pat. No. 6,149,684
 [0102] U.S. Pat. No. 6,196,993
 [0103] U.S. Pat. No. 6,234,175
 [0104] U.S. Pat. No. 6,290,684
 [0105] U.S. Pat. No. 6,306,114
 [0106] U.S. Pat. No. 6,344,047
 [0107] U.S. Patent 60/203,350
 [0108] U.S. Patent Publn. 2003/0143280
 [0109] U.S. Patent Publn. 2004/0013704
 [0110] U.S. Patent Publn. 2005/0232972
 [0111] U.S. Patent Publn. 2006/0020248
 [0112] PCT Appln. WO 2004/066980
 [0113] PCT Appln. WO 2006/031658
 [0114] PCT Appln. WO 94/13275
 [0115] PCT Appln. WO 99/37260
 [0116] EP 0 561 073 A1
 [0117] Meng and Tai, "Parylene Etching Techniques for Microfluidics and BioMEMS," *Micro Electro Mechanical Systems*, 30:568-571, 2005

What is claimed is:

1. A drug-delivery device comprising:
 - (a) a body comprising a matrix of a silicone and an ophthalmic drug, the body having 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 comprises:
 - (a) 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;
 - (b) 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
 - (c) a distal tip portion attached to the second end of the shaft portion.
3. The drug-delivery device of claim 1, 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 claim 1, wherein the concentration of the prostaglandin in the matrix is between about 1% to about 10% by weight.
7. The drug-delivery device of claim 1, wherein the concentration of the prostaglandin in the matrix is between about 3% to about 7% by weight.
8. The drug-delivery device of claim 1, wherein the parylene coating is between about 1 μm to about 20 μm thick.

- 9. The drug-delivery device of claim 1, 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, 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, wherein the at least one pore is etched using oxygen plasma etching.

- 16. The method of claim 13, wherein the parylene coating is deposited at a thickness about 1 μm to about 20 μm .
- 17. The method of claim 13, wherein the parylene coating is deposited at a thickness about 5 μm to about 15 μm .
- 18. The method of claim 13, wherein the at least one pore has a diameter of about 1 μm to about 50 μm .
- 19. The method of claim 13, 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, wherein the concentration of the prostaglandin in the matrix is between about 1% to about 10% by weight.
- 23. The method of claim 20, wherein the concentration of the prostaglandin in the matrix is between about 3% to about 7% by weight.

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