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(54) **SUSTAINED RELEASE LATANOPROST IMPLANT**

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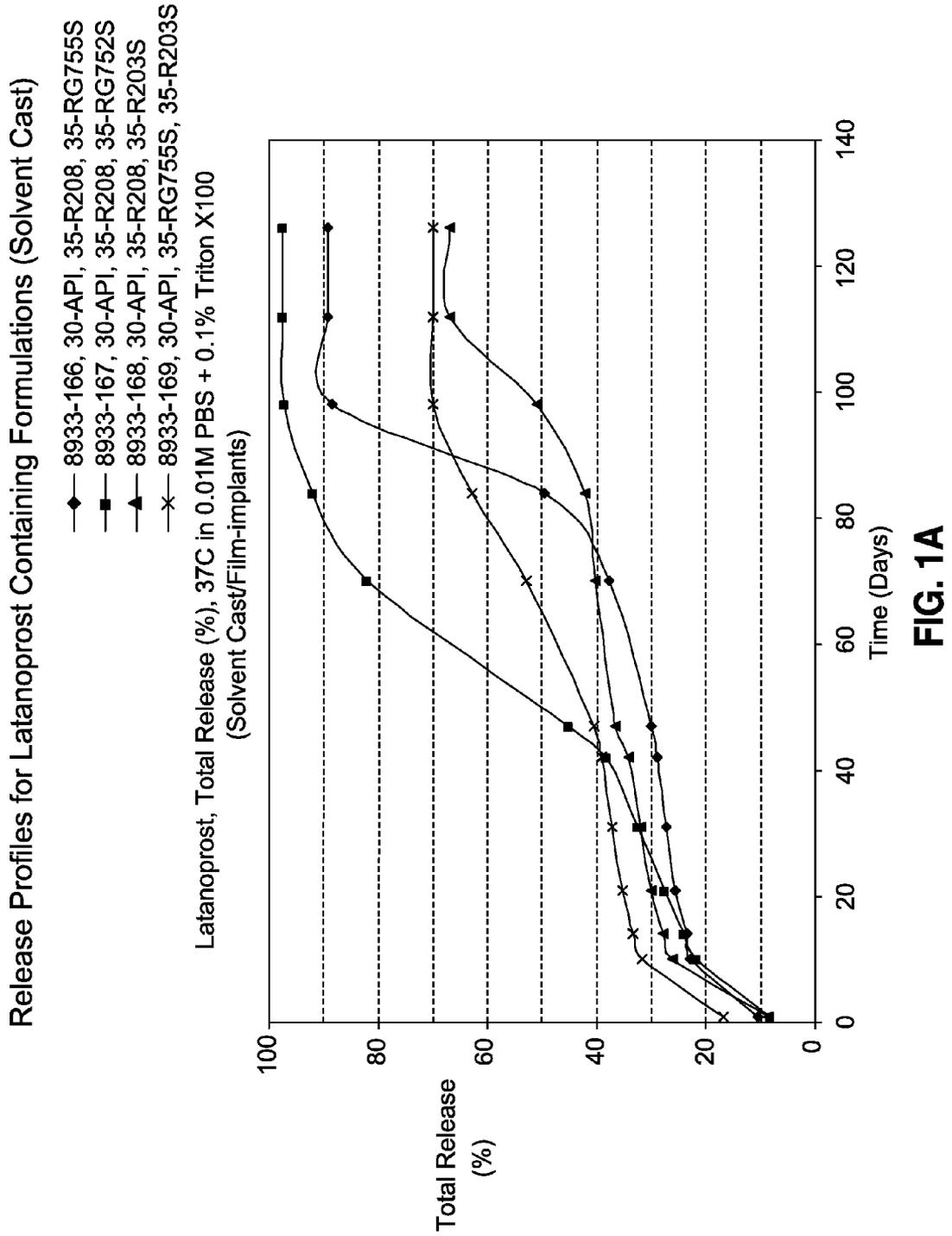
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(57) **ABSTRACT**

**Related U.S. Application Data**

(60) Provisional application No. 61/480,657, filed on Apr. 29, 2011, provisional application No. 61/480,630, filed on Apr. 29, 2011.

The present invention provides a sustained release, biodegradable intraocular latanoprost implant for reducing elevated intraocular pressure in an individual in need thereof. The implant can be configured as a film (e.g., a rolled film) or extruded filament, either of which can be inserted into the eye of the individual to provide for extended release of latanoprost for several days. Upon insertion into the eye, a rolled film may unroll to provide a film having a high surface area to volume ratio for drug diffusion.



Release Profiles for Latanoprost Containing Formulations (Solvent Cast)

- ◆ 9606-014, 30-API, 20-R208, 50-RG752S
- 9606-015, 30-API, 35-R208, 35-RG752S
- ▲ 9606-016, 30-API, 50-R208, 20-RG752S
- × 9606-017, 30-API, 60-R208, 10-RG752S

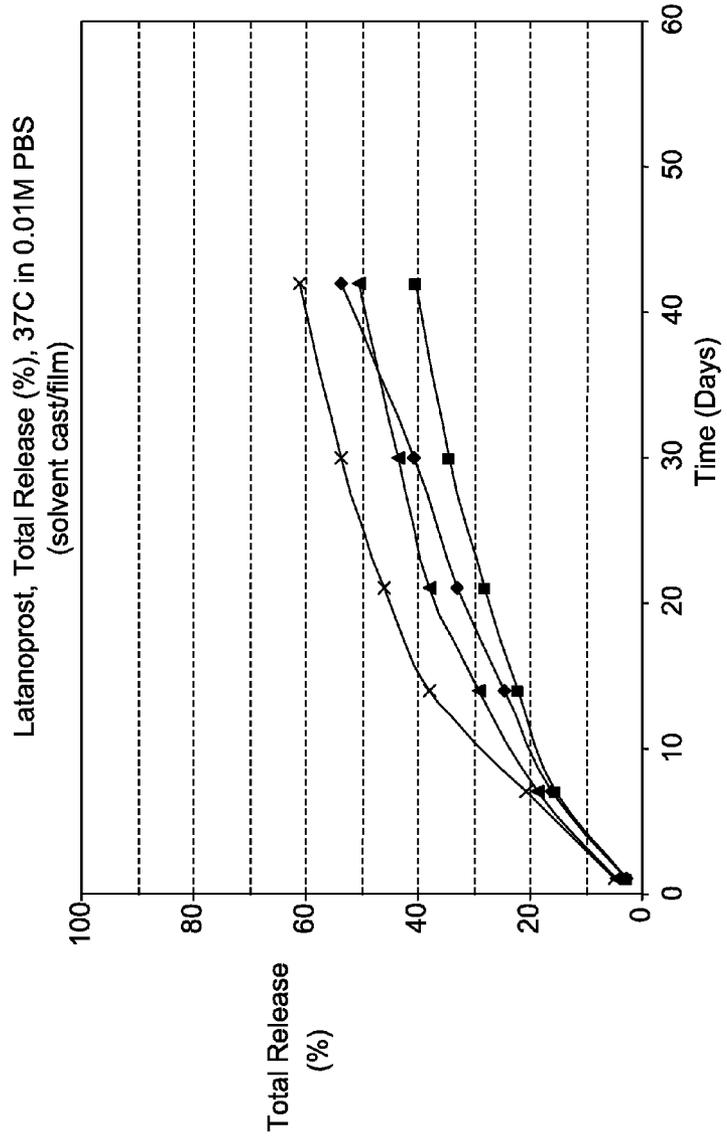


FIG. 1B

Release Profiles for Latanoprost Containing Formulations (Solvent Cast)

- ◆ 9606-014, 30-API, 20-R208, 50-RG752S
- 9606-015, 30-API, 35-R208, 35-RG752S
- ▲ 9606-016, 30-API, 50-R208, 20-RG752S
- ✱ 9606-017, 30-API, 60-R208, 10-RG752S

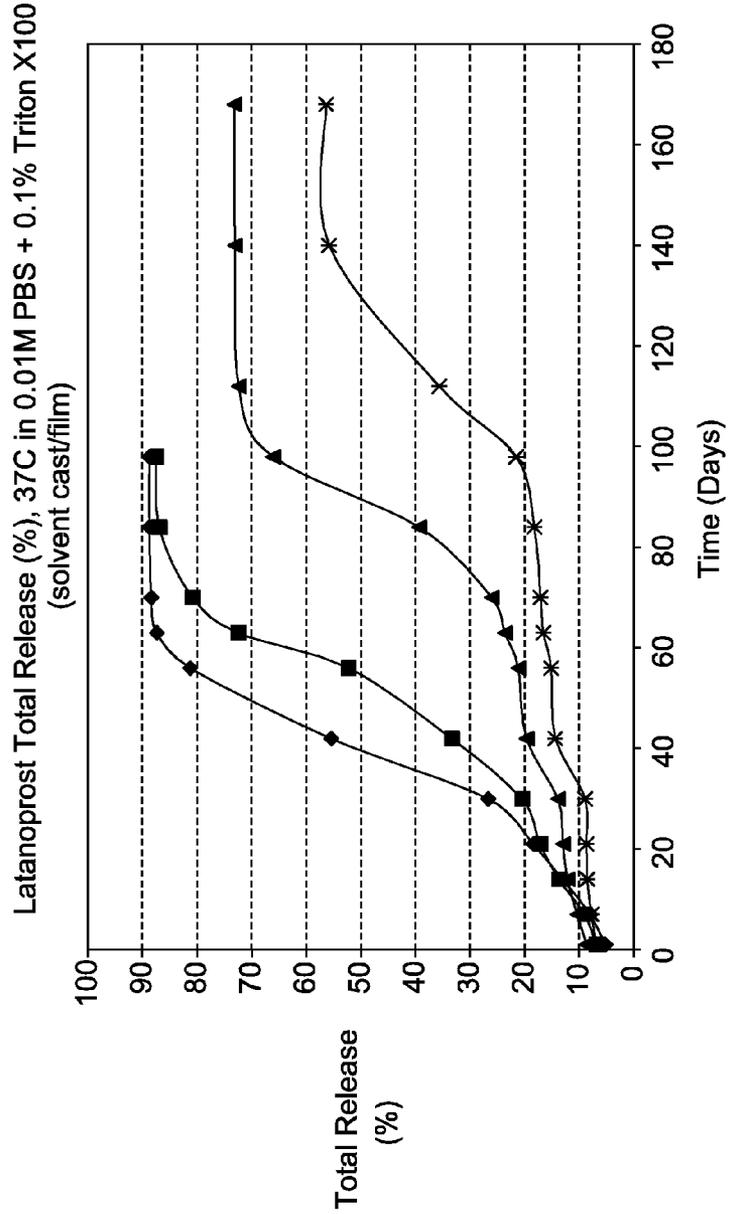


FIG. 1C

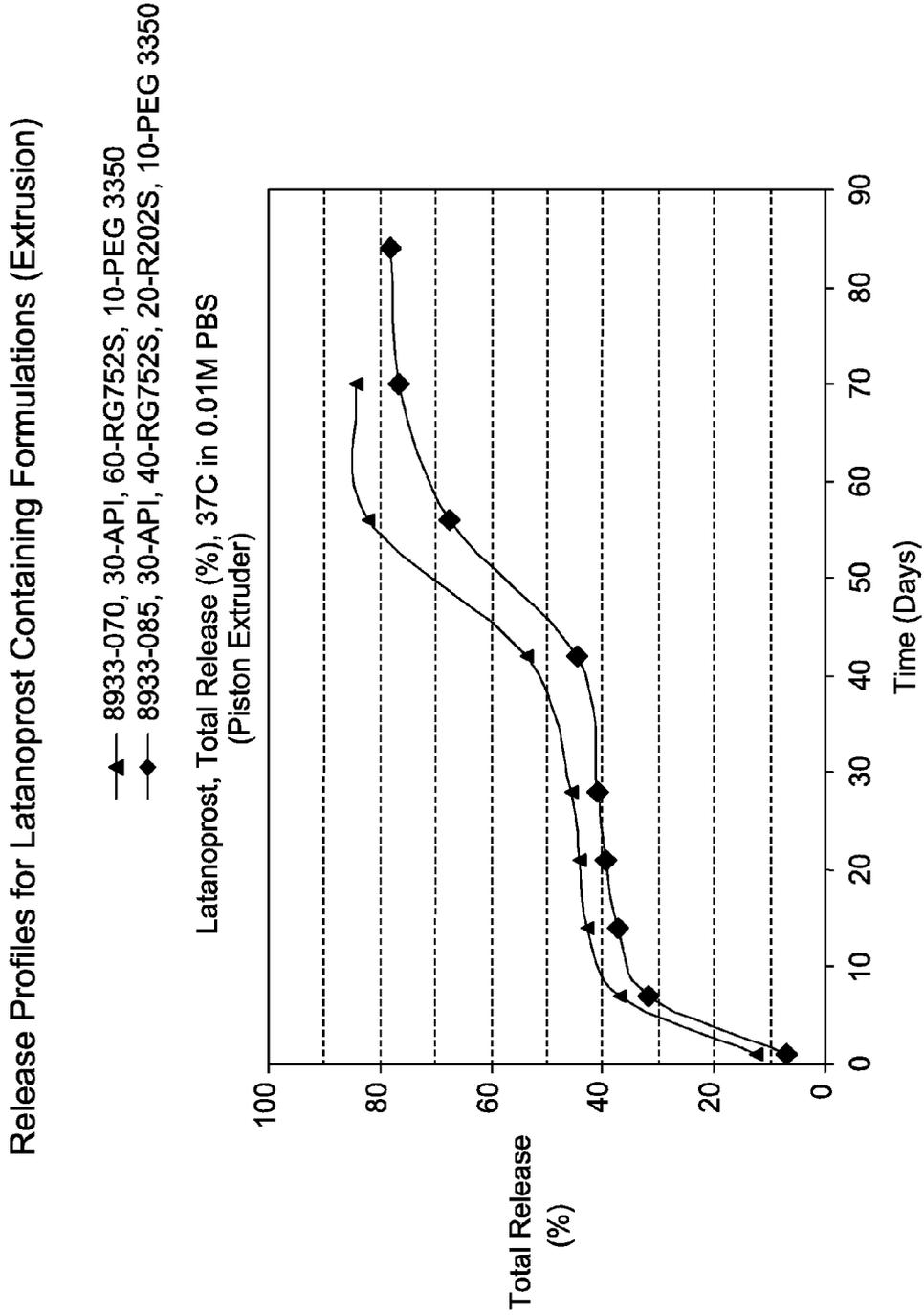


FIG. 2A

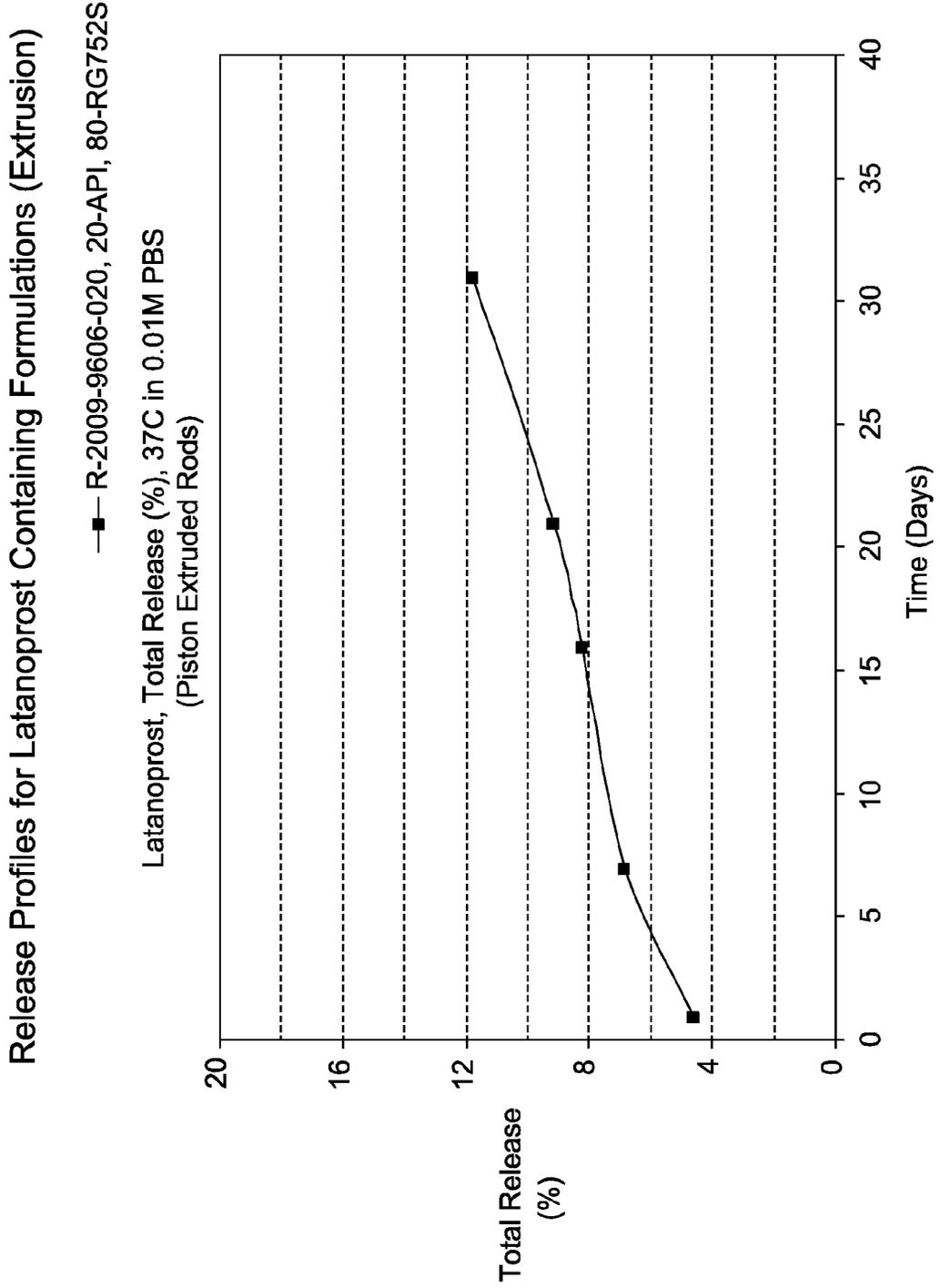


FIG. 2B

Release Profiles for Latanoprost Containing Formulations (Extrusion)

- ◆ 9606-030, 20-API, 40-RG752S, 40-R202S
- ▲ 9606-032, 20-API, 40-R202S, 40-R202H

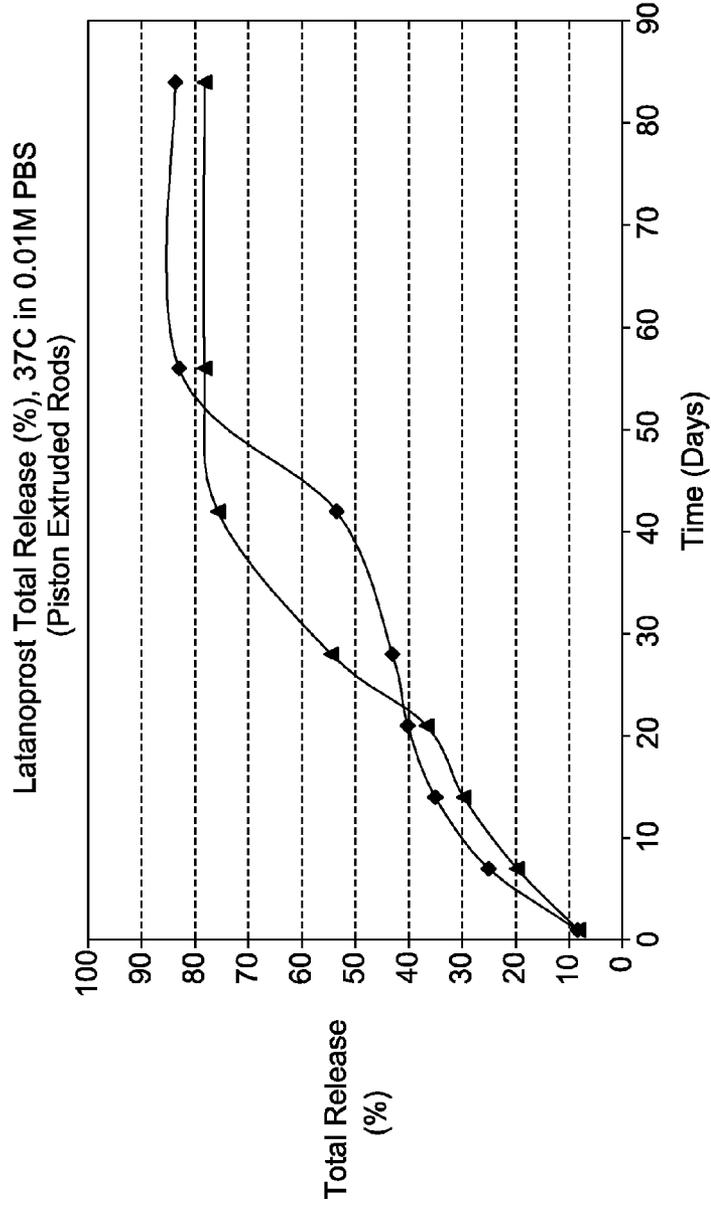


FIG. 2C

## SUSTAINED RELEASE LATANOPROST IMPLANT

### CROSS REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims the benefit of U.S. Provisional Application No. 61/480,657, filed Apr. 29, 2011, and U.S. Provisional Application 61/480,630, filed Apr. 29, 2011. The contents of each of these provisional applications are hereby incorporated by reference.

### BACKGROUND OF THE INVENTION

**[0002]** 1. Field of the Invention

**[0003]** The present invention relates to biodegradable intraocular implants that provide for the sustained release of latanoprost, and to methods of making these implants, and to methods of using these implants to reduce elevated intraocular pressure in individuals in need thereof.

**[0004]** 2. Summary of the Related Art

**[0005]** Latanoprost is a prostaglandin  $F_{2\alpha}$  analogue which is indicated in the treatment of open-angle glaucoma or ocular hypertension in patients who are intolerant of other intraocular pressure (IOP)—lowering medications or insufficiently responsive (i.e., failed to achieve target IOP after multiple measurements over time) to another IOP-lowering medication. Latanoprost may be used alone or in combination with other antiglaucoma agents.

**[0006]** Latanoprost is an isopropyl ester prodrug of an analog of prostaglandin  $F_{2\alpha}$ . It is hydrolyzed by esterases in the cornea to latanoprost acid, which is biologically active. The elimination of latanoprost acid from plasma is rapid (half-life 17 minutes) after either ophthalmic or intravenous administration. Latanoprost's pharmacology makes it a candidate for formulation as an IOP lowering sustained release polymer implant. However, its physicochemical properties make it an extremely challenging molecule to incorporate into a biodegradable implant. That is, Latanoprost (MW 432.58) is a colorless to slightly yellow oil that is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol and octanol. It is practically insoluble in water.

**[0007]** It is believed that a latanoprost sustained release implant would be an effective treatment for long-term reduction of intraocular pressure associated with glaucoma or other ocular diseases.

### BRIEF SUMMARY OF THE INVENTION

**[0008]** The present invention provides a sustained release biodegradable polymer implant containing latanoprost. In one embodiment, latanoprost is incorporated into a solid biodegradable implant, wherein said implant comprises a mixture of a polylactide (PLA) and a lactide-glycolide copolymer (PLGA). The implant is fabricated by combining latanoprost, PLA and PLGA polymers by melt extrusion or by dissolving the components in a solvent and removing the solvent to recover a solid composite, e.g. a polymeric film or fiber, which may be fabricated into a sustained release polymer implant containing latanoprost. The composite, in the form of a thin film, can be cut to any shape and dimension. For example, a disc shaped implant that is about 100  $\mu\text{m}$  to about 500  $\mu\text{m}$  thick and about 2 to about 6 mm in diameter may be formed from a thin film comprising latanoprost. In ophthalmic use, this thin implant may be rolled-up and inserted

into the subTenon's space through a small opening. Once inserted, it may unfurl either partially or completely to its original disc shape providing a large surface for drug diffusion through the sclera.

**[0009]** Accordingly, one embodiment is an intraocular implant comprising or consisting of latanoprost and a biodegradable polymer matrix. The latanoprost can be incorporated in the polymer matrix. In certain embodiments the latanoprost is homogeneously distributed throughout the polymer matrix.

**[0010]** The implant can be prepared in the form of a film (e.g. a thin polymeric film) or an extruded filament (i.e. fiber). The film can be prepared by a solvent casting method, and the extruded filament by a hot-melt extrusion method or by direct compression, as described herein.

**[0011]** The biodegradable polymer matrix in the film or extruded filament (i.e., fiber) can comprise or consist of a poly(D-lactide), a poly(L-lactide), a poly(D,L-lactide), a polyglycolide, a poly(D,L-lactide-co-glycolide) (PLGA), or a combination thereof.

**[0012]** The percent of D,L-lactide in the PLGA can be about 0 to less than about 100%, about 15-85%, or about 35-65%. In specific embodiments the molar ratio of D,L-lactide to glycolide in the PLGA copolymer is about 75:25 or about 50:50.

**[0013]** In certain embodiments, the film is about 2 to about 100  $\mu\text{m}$  to about 500  $\mu\text{m}$  thick and may be about 2 to about 6 mm in diameter. In a particular embodiment the intraocular implant is configured as a rolled film.

**[0014]** The film can be made by a solvent casting method and may contain about 30% (w/w) latanoprost, 20-60% (w/w) of a poly(D,L-lactide), and about 10-50% (w/w) of a poly(D,L-lactide-co-glycolide).

**[0015]** The filament (or fiber) can be made by a hot-melt extrusion method and may comprise about 20-30% (w/w) latanoprost, about 40-80% (w/w) of a poly(D,L-lactide-co-glycolide), and about 0-20% of a poly(D,L-lactide).

**[0016]** In another embodiment, the filament comprises about 20-30% w/w latanoprost, 40-60% (w/w) of a poly(D,L-lactide-co-glycolide), 0-20% of a poly(D,L-lactide), and 0-10% w/w PEG 3350.

**[0017]** In another embodiment, the fiber comprises a mixture of poly(D,L-lactide) (PLA) and poly(D,L-lactide-co-glycolide) (PLGA) polymers. In a more specific embodiment, the fiber comprises from about 20 to about 60 percent w/w PLA and from about 10 to about 50 percent w/w PLGA.

**[0018]** In one embodiment, the film comprises a poly(D,L-lactide) (PLA) selected from the group consisting of RESOMER® R208 and RESOMER® R203S, and a poly(D,L-lactide-co-glycolide) (PLGA) selected from the group consisting of RESOMER® RG752S and RESOMER® RG755S.

**[0019]** In one embodiment, the extruded fiber comprises poly(D,L-lactide) (PLA) RESOMER® R202S, and poly(D,L-lactide-co-glycolide) (PLGA) RESOMER® RG752S.

**[0020]** RESOMER® R202H is an acid terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g, as measured for a 0.1% solution in chloroform at 25° C.

**[0021]** RESOMER® R208 is an ester terminated poly(D,L-lactide) having an inherent viscosity of about 1.8-2.2 dl/g, as measured for a 0.1% solution in chloroform at 25° C.

**[0022]** RESOMER® R202S is an ester terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g, as measured for a 0.1% solution in chloroform at 25° C.

**[0023]** RESOMER® R203S is an ester terminated poly(D, L-lactide) having an inherent viscosity of about 0.25-0.35 dl/g, as measured for a 0.1% solution in chloroform at 25° C.

**[0024]** RESOMER® RG752S is an ester terminated poly(D,L-lactide-co-glycolide) having an inherent viscosity of about 0.16-0.24 dl/g (as measured for a 0.1% solution in chloroform at 25° C.), and a D,L-lactide:glycolide ratio of about 75:25.

**[0025]** RESOMER® RG755S is an ester terminated poly(D,L-lactide-co-glycolide) having an inherent viscosity of about 0.50-0.70 dl/g (as measured for a 0.1% solution in chloroform at 25° C.), and a D,L-lactide:glycolide ratio of about 75:25.

**[0026]** In one embodiment, the film comprises or consists of 30% w/w latanoprost, 35% w/w R208, and 35% w/w RG755S.

**[0027]** In another embodiment, the film comprises or consists of 30% w/w/latanoprost, 35% w/w R208, and 35% w/w RG752S.

**[0028]** In another embodiment, the film comprises or consists of 30% w/w latanoprost, 35% w/w R208, and 35% w/w R203S 35%.

**[0029]** In another embodiment, the film comprises or consists of 30% w/w latanoprost, 35% w/w R203S, and 35% w/w RG755S.

**[0030]** In another embodiment, the film comprises or consists of 30% w/w latanoprost, 20% w/w R208, and 50% w/w RG752S.

**[0031]** In another embodiment, the film comprises or consists of 30% w/w latanoprost, 35% w/w R208, and 35% w/w RG752S.

**[0032]** In another embodiment, the film comprises or consists of 30% w/w latanoprost, 50% w/w R208, and 20% w/w RG752S.

**[0033]** In another embodiment, the film comprises or consists of 30% latanoprost, 60% w/w R208, and 10% w/w RG752S.

**[0034]** In another embodiment, the intraocular implant is in the form of an extruded fiber comprising latanoprost incorporated in a biodegradable polymer matrix.

**[0035]** The extruded intraocular implant (i.e., fiber) may further comprise a polyethylene glycol (PEG). The PEG can act as a plasticizing agent, making it possible to extrude the implant (i.e., to form the fiber) at temperatures lower than might otherwise be possible in the absence of the PEG. Lower extrusion temperatures are desirable to preserve latanoprost activity.

**[0036]** In one embodiment the PEG plasticizer is PEG 3350.

**[0037]** One embodiment provides for a biodegradable intraocular implant for reducing intraocular pressure in an eye of an individual in need thereof, the implant comprising latanoprost and a biodegradable polymer, wherein:

**[0038]** a) the implant does not contain bimatoprost;

**[0039]** b) the implant is in the form of a film or an extruded filament;

**[0040]** c) said filament optionally further comprises a polyethylene glycol (PEG);

**[0041]** d) said film is about 100  $\mu$ m to about 500  $\mu$ m thick and about 2 to about 6 mm in diameter;

**[0042]** e) said biodegradable polymer is

**[0043]** i) an ester terminated poly(D,L-lactide) having an inherent viscosity of about 1.8-2.2 dl/g (R208);

**[0044]** ii) an ester terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g (R202S);

**[0045]** iii) an acid terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g (R202H);

**[0046]** iv) an ester terminated poly(D,L-lactide) having an inherent viscosity of about 0.25-0.35 dl/g (R203S);

**[0047]** v) an ester terminated poly(D,L-lactide-co-glycolide) having an inherent viscosity of about 0.16-0.24 dl/g and a D,L-lactide to glycolide ratio of about 75:25 (RG752S); or

**[0048]** vi) an ester terminated poly(D,L-lactide-co-glycolide) having an inherent viscosity of about 0.50-0.70 dl/g and a D,L-lactide to glycolide ratio of about 75:25 (RG755S); or

**[0049]** vii) a combination of any two or more of i, ii, iii, iv, v, or vi;

**[0050]** f) wherein the solubility parameters for each of the latanoprost, the biodegradable polymer(s), and the PEG differ one from the other by no more than 10 MPa<sup>1/2</sup>; and wherein

**[0051]** g) the implant releases latanoprost continuously for at least 30 days after placement in the eye of the individual.

**[0052]** In another embodiment, the implant does not contain a prostamide.

**[0053]** The film can be in the form of a rolled film that can partially or completely unfurl upon insertion into the eye.

**[0054]** The filament can comprise about 5 to about 10% by weight PEG 3350.

**[0055]** In one embodiment the extruded latanoprost-containing filament does not contain polyethylene glycol.

**[0056]** In one embodiment the film comprises or consists of about 30% by weight latanoprost, about 35% by weight of an ester terminated poly(D,L-lactide) having an inherent viscosity of about 1.8-2.2 dl/g (R208), and about 35% by weight of an ester terminated poly(D,L-lactide-co-glycolide) having an inherent viscosity of about 0.50-0.70 dl/g and a D,L-lactide:glycolide ratio of about 75:25 (RG755S).

**[0057]** In one embodiment the film comprises or consists of about 30% by weight latanoprost, about 35% by weight of an ester terminated poly(D,L-lactide) having an inherent viscosity of about 1.8-2.2 dl/g (R208), and about 35% by weight of an ester terminated poly(D,L-lactide) having an inherent viscosity of about 0.25-0.35 dl/g (R203S).

**[0058]** In one embodiment the extruded filament comprises or consists of about 20% by weight latanoprost, about 75% by weight of an ester terminated poly(D,L-lactide-co-glycolide) having an inherent viscosity of about 0.16-0.24 dl/g and a D,L-lactide:glycolide ratio of about 75:25 (RG752S); and about 5% by weight of PEG 3350.

**[0059]** In one embodiment the extruded filament comprises or consists of about 30% by weight latanoprost, about 40% by weight of an ester terminated poly(D,L-lactide-co-glycolide) having an inherent viscosity of about 0.16-0.24 dl/g and a D,L-lactide:glycolide ratio of about 75:25 (RG752S), about 20% by weight of an ester terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g (R202S), and about 10% by weight of PEG 3350.

**[0060]** In one embodiment the extruded filament comprises or consists of about 20% by weight latanoprost, about 40% by weight of an ester terminated poly(D,L-lactide-co-glycolide)

having an inherent viscosity of about 0.16-0.24 dl/g and a D,L-lactide:glycolide ratio of about 75:25 (RG752S); and about 40% by weight of an ester terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g (R202S).

**[0061]** In one embodiment the extruded filament comprises or consists of about 20% by weight latanoprost, about 40% by weight of an ester terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g (RG202S), and about 40% by weight of an acid terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g (R202H).

**[0062]** Another embodiment is a method of providing an ocular implant to a person in need thereof, the method comprising rolling a film comprising latanoprost and a biodegradable polymer or combination of polymers into a cylindrical shape, inserting said rolled film into the eye of a patient and allowing said film to unroll or partially unroll to provide a large surface for drug diffusion. In certain embodiments the unrolled film is about 25  $\mu\text{M}$  to about 500  $\mu\text{M}$  thick, or about 100  $\mu\text{m}$  to about 500  $\mu\text{m}$  thick and about 2 mm to about 6 mm in diameter. The person in need can be a person suffering from elevated intraocular pressure, such as a patient that has glaucoma.

**[0063]** In certain embodiments the rolled film is inserted into the subTenon's space through a small opening and allowed to partially unfurl or unfurl to its original shape thereby providing a large surface for drug diffusion through the sclera.

**[0064]** Another embodiment provides for a method of reducing intraocular pressure (i.e., treating ocular hypertension) in a subject in need, the method comprising placing an ocular implant into an eye of the subject, the implant comprising latanoprost and a biodegradable polymer. The ocular implant can be a film (e.g., a rolled film) or an extruded filament as described herein. The implant can be placed into the vitreous body, subconjunctival space, subTenon's space, or anterior chamber of the eye, for example.

**[0065]** Another embodiment is a method of fabricating an intraocular implant comprising a thin film of latanoprost in a biodegradable polymer matrix by solvent casting, the method comprising dissolving one or more biodegradable polymers and latanoprost in an appropriate organic solvent, casting said solution onto a suitable substrate and removing said solvent to recover a thin film of latanoprost in a biodegradable polymer matrix. In certain embodiments the solvent is selected from the group consisting of dichloromethane, ethanol, octanol, chloroform, acetone and acetonitrile. In certain embodiments the solution comprises from 10 to 75% solids, wherein said solids comprise latanoprost, polymer and other components which are useful for modifying the release of latanoprost from the resulting film and/or plasticizers of said polymer which contribute to the flexibility of the film.

**[0066]** One embodiment provides for a method of making a biodegradable intraocular implant comprising:

**[0067]** a) dissolving the biodegradable polymer(s) in an organic solvent under constant stirring to form a first solution;

**[0068]** b) adding latanoprost to the first solution under constant stirring to form a second solution;

**[0069]** c) sonicating the second solution to remove air bubbles;

**[0070]** d) casting the second solution into a glass dish;

**[0071]** e) evaporating the solvent to form a dry film; and

**[0072]** f) cutting the film into circular portions of about 2 to about 6 mm in diameter each.

**[0073]** Useful solvents include dichloromethane.

**[0074]** The method can further comprise rolling the circular portions to form a rolled film implant that can partially or completely unfurl upon placement in the eye of an individual suffering from elevated intraocular pressure.

**[0075]** Another embodiment provides for a method of making a biodegradable intraocular implant, the method comprising: mixing PEG 3350, the latanoprost, and the biodegradable polymer(s), to form a mixture; and extruding the mixture at a temperature of less than about 80° C. to form a filament that will release latanoprost continuously for at least 30 days after placement in the eye of the individual.

#### Definitions

**[0076]** "About" means that the number, range, value or parameter so qualified encompasses ten percent more and ten percent less of the number, range, value or parameter.

**[0077]** A "patient in need" can be a human or non-human mammal suffering from an ocular condition. The ocular condition may be a condition treatable with a latanoprost-containing implant. Examples of an ocular conditions treatable with a latanoprost-containing implant include glaucoma and elevated intraocular pressure (or ocular hypertension).

**[0078]** "Treat", "treating", or "treatment" means a reduction or resolution or prevention of an ocular condition. A treatment is usually effective to reduce at least one symptom of an ocular condition.

**[0079]** "Therapeutically effective amount" means the level or amount of agent needed to treat an ocular condition, or reduce a symptom associated with the condition without causing significant negative or adverse side effects to the eye or a region of the eye. In view of the above, a therapeutically effective amount of latanoprost is an amount that is effective in reducing intraocular pressure in an eye of an individual.

**[0080]** "Therapeutic component" means that portion of an implant other than the polymer matrix comprising one therapeutic agent used to treat an ocular condition. The therapeutic component can be a discrete region of an implant, or it may be homogeneously distributed throughout the implant.

**[0081]** "Biodegradable polymer" means a polymer or polymers which degrade in vivo, and wherein erosion of the polymer or polymers over time occurs concurrent with or subsequent to release of the therapeutic agent, e.g. the latanoprost. The terms "biodegradable" and "bioerodible" are equivalent and are used interchangeably herein. A biodegradable polymer may be a homopolymer, a copolymer, or a polymer comprising more than two different polymeric units. The polymer can be a gel or hydrogel type polymer. Examples include PLA or PLGA polymers or mixtures or derivatives thereof.

**[0082]** Prostaglandin synthase inhibitors (prostaglandin synthase inhibitors) have been described by, for example, Woodward et al. (2007) *British Journal of Pharmacology* 150:342-352. Prostaglandin synthase inhibitors have been disclosed in, for example, U.S. Pat. Nos. 6,395,787 and 6,403,649.

**[0083]** The solubility parameter for a substance is a numerical value which indicates the relative solvency behavior of that substance. The concept is discussed and defined in US 2008/0145403.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0084]** FIGS. 1A-C show release profiles for latanoprost-containing formulations of Example 1.

[0085] FIGS. 2A-C show release profiles for latanoprost-containing formulations of Example 2.

#### DETAILED DESCRIPTION OF THE INVENTION

[0086] Latanoprost is very difficult to incorporate into biodegradable polymer matrices, because it is an oil. It has now been discovered, that this problem can be overcome by using a combination of high molecular weight PLA and PLGA polymers and fabricating the implant by melt extrusion or casting in an appropriate solvent. The oily drug substance (DS), i.e. latanoprost, helps plasticize the polymer and allows the production of a homogeneous polymer film. The appropriate combination of solvent and polymer is based on the solubility parameters of the solvent and polymers, e.g. the solubility parameter of dichloromethane is  $19.8 \text{ MPa}^{0.5}$ . It has been determined that dichloromethane is a good solvent for PLA and PLGA, which have solubility parameters of about  $21.1 \text{ MPa}^{0.5}$  and about  $22.1 \text{ MPa}^{0.5}$ , respectively. Thus, a solvent having a solubility parameter of from  $17.1$  to  $26.1 \text{ MPa}^{0.5}$ , preferably from  $17.6$  to  $25.6$ , e.g.  $21.1$  or  $22.1 \text{ MPa}^{0.5}$  may be used in the practice of this invention. Such solvents may include dichloromethane, isopropanol, ethanol, acetonitrile and octanol.

[0087] For purposes of forming a film or an extruded filament that will provide for a long-lasting extended and perhaps nearly linear rate of latanoprost release, the solubility parameters of the latanoprost, biodegradable polymer(s), co-solvent (e.g., PEG 3350), and organic solvent preferably differ by no more than about  $10 \text{ MPa}^{0.5}$  from one another. In one embodiment, the solubility parameters of the components chosen for inclusion in the extruded implant or film differ by no more than about  $7 \text{ MPa}^{0.5}$ , one from the other.

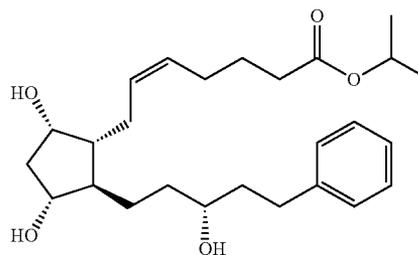
[0088] The solubility parameter of PEG 3350 is about  $20 \text{ MPa}^{0.5}$ .

[0089] When preparing an extruded filament with latanoprost, it is important to keep the extrusion temperature as low as possible to avoid loss and degradation of the latanoprost. The temperatures ordinarily needed to extrude drug-containing biodegradable polymer implants can cause the latanoprost to degrade and/or bubble out of the mixture, thereby causing undesirable loss of the oily drug. This can be overcome by using a select combination of low molecular weight polymers and a plasticizer such as a polyethylene glycol (PEG) that are compatible with the drug substance. The oily DS (e.g. latanoprost) and PEG plasticize the polymers to a degree that allows the mixture to be extruded at a temperature where the DS is not degraded or lost. In some embodiments, the latanoprost-containing polymer mixture is extruded at a temperature of about  $50^\circ \text{C}$ ., from about  $50^\circ \text{C}$ . to about  $55^\circ \text{C}$ ., less than about  $60^\circ \text{C}$ ., less than about  $70^\circ \text{C}$ ., less than about  $80^\circ \text{C}$ ., or at a temperature from about  $50^\circ \text{C}$ . to less than about  $80^\circ \text{C}$ .

[0090] An extruded filament may be cut to implant lengths of from about  $5 \mu\text{m}$  to about  $10 \text{ mm}$ , e.g. about  $1$ ,  $2$ , or  $3 \text{ mm}$ , or from about  $10 \mu\text{m}$  to about  $1 \text{ mm}$ . The implants may have any appropriate length so long as the diameter of the implant permits the implant to move through a needle. The filament can have a diameter of less than about  $500 \mu\text{m}$ , or from about  $500 \mu\text{m}$  to about  $1.5 \text{ mm}$ .

[0091] The total weight of an implant can be less than about  $250 \mu\text{g}$  or from about  $250$ - $5000 \mu\text{g}$  or more. For example, an extruded implant may weigh about  $500 \mu\text{g}$ , about  $1000 \mu\text{g}$ , or about  $2000 \mu\text{g}$ .

[0092] Latanoprost (CAS Registry No. 130209-82-4) is disclosed in U.S. Pat. Nos. 6,429,226; 6,417,230; 6,187,813; 6,030,999; 5,849,791; 5,627,208; 5,578,618; 5,422,368 and 5,296,504 and has the following structure:



[0093] In the present invention, latanoprost is incorporated into a biodegradable polymer composite by melt extrusion, direct compression, or by dissolving latanoprost in a solvent for latanoprost and the polymer to form a solution of latanoprost and the polymer and removing said solvent to provide a solid composite of latanoprost and said biodegradable polymer. Said solid composite is preferably formed by casting a film of said solution of latanoprost and the polymer and removing said solvent to recover a thin film. The solubility parameter for latanoprost is about  $22$  to about  $24 \text{ MPa}^{0.5}$ .

[0094] The thickness of said film is controlled by adjusting the thickness of said cast solution and/or the solids content of the latanoprost/polymer solution. Preferably said thickness is from about  $25$  to about  $500 \mu\text{m}$ , e.g. from about  $25$  to about  $75 \mu\text{m}$ .

[0095] Suitable polymeric materials or compositions for use in the implant include those materials, which are compatible, i.e. biocompatible, with the eye so as to cause no substantial interference with the functioning or physiology of the eye. Such materials preferably are at least partially and more preferably substantially completely biodegradable or bioerodible or bioabsorbable.

[0096] Of interest for use in the implants of this invention are polymers of hydroxyaliphatic carboxylic acids, either homopolymers or copolymers. Polyesters of interest include polymers of D-lactic acid, L-lactic acid, racemic lactic acid and glycolic acid, and combinations thereof. Generally, by employing the L-lactate or D-lactate, a slowly eroding polymer or polymeric material is achieved, while erosion is substantially enhanced with the lactate racemate.

[0097] Some preferred characteristics of the polymers or polymeric materials for use in the present invention may include biocompatibility, compatibility, ease of use of the polymer in making the implant of the present invention, a half-life in the physiological environment of at least about  $6$  hours, preferably greater than about one day, and not significantly increasing the viscosity of the vitreous.

[0098] The biodegradable polymeric materials, which are included to form the implant, are desirably subject to enzymatic or hydrolytic instability. Water-soluble polymers may be cross-linked with hydrolytic or biodegradable unstable cross-links to provide useful water insoluble polymers. The degree of stability can be varied widely, depending upon the choice of monomer, whether a homopolymer or copolymer is employed, employing mixtures of polymers, and whether the polymer includes terminal acid groups.

**[0099]** Equally important to controlling the biodegradation of the polymer is the relative average molecular weight of the polymeric composition employed in the implant. Different molecular weights of the same or different polymeric compositions may be included in the implant to modulate the release profile. In certain implants, the relative average molecular weight of the polymer will range from about 9 to about 200 kD, usually from about 10 to about 54 kD, and more usually from about 12 to about 45 kD.

**[0100]** In some implants, copolymers of glycolic acid and lactic acid are used, where the rate of biodegradation is controlled by the ratio of glycolic acid to lactic acid. The most rapidly degraded copolymer has roughly equal amounts of glycolic acid and lactic acid. Homopolymers, or copolymers having ratios other than equal, are more resistant to degradation. The ratio of glycolic acid to lactic acid will also affect the brittleness of the implant, where a more flexible implant is desirable for larger geometries. The percent of polylactic acid in the polylactic acid polyglycolic acid (PLGA) copolymer can be 0-100%, preferably about 15-85%, more preferably about 35-65%. In some implants, a 50/50 PLGA copolymer is used.

**[0101]** The biodegradable polymer matrix of the intraocular implant comprises a mixture of two or more biodegradable polymers, selected from the group consisting of PLA, PLGA and mixtures thereof. For example, the implant may comprise a mixture of a first biodegradable polymer and a different second biodegradable polymer, wherein at least one or more of the biodegradable polymers may have terminal acid groups.

PLA/PLGA polymers from the RESOMER ® product line are available from Evonik Industries AG, Germany, and include the following:		
Resomer	Monomer ratio	i.v. dL/g
RG502	50:50 poly (D,L-lactide-co-glycolide)	0.2
RG502H	50:50 poly (D,L-lactide-co-glycolide), acid end	0.2
RG503	50:50 poly (D,L-lactide-co-glycolide)	0.3
RG504	50:50 poly (D,L-lactide-co-glycolide)	0.5
RG505	50:50 poly (D,L-lactide-co-glycolide)	0.7
RG506	50:50 poly (D,L-lactide-co-glycolide)	0.8
RG752	75:25 poly (D,L lactide-co-glycolide)	0.2
RG755	75:25 poly(D,L lactide-co-glycolide)	0.6
RG756	75:25 poly(D,L lactide-co-glycolide)	0.8
RG858	85:15 poly (D,L-lactide-co-glycolide)	1.4
R202H	poly (D,L-lactide), acid end	0.2
R203	poly (D,L-lactide)	0.3
R206	poly (D,L-lactide)	0.6
R104	poly (D,L-lactide)	(3500)

**[0102]** An intraocular implant comprising a thin film of latanoprost in a biodegradable polymer matrix may be made by solvent casting utilizing the following method: The polymers are dissolved in an appropriate solvent, like dichloromethane, with constant stirring. Latanoprost is added and stirring maintained. The solution is sonicated for 5 min to remove any air bubbles, and this solution is then cast onto a suitable substrate (e.g. glass culture dish), covered with weigh paper to ensure controlled evaporation of solvent, and placed in a fume cupboard overnight. After evaporation of the

solvent, the solid polymeric film containing drug substance, i.e. latanoprost, is removed and stored in a desiccator prior to use.

**[0103]** The solvent is selected for its ability to dissolve sufficient polymer and latanoprost to provide solutions, which may be cast and evaporated to form a thin flexible film of latanoprost surrounded by a matrix of said polymer.

**[0104]** The solvent may be dichloromethane, chloroform, acetone, acetonitrile, etc. For solvating properties and ease of solvent removal acetone or dichloromethane, e.g. dichloromethane, is preferred.

**[0105]** The solution may comprise from 10 to 75% solids, e.g. 30 to 50%, wherein said solids comprise latanoprost, polymer and other components which are useful for modifying the release of latanoprost from the resulting film and/or plasticizers of said polymer which contribute to the flexibility of the film.

**[0106]** The film-shaped implant made by solvent casting contains 30% Latanoprost, 0-70% of a biodegradable poly(D, L-lactide-co-glycolide) polymer (Resomer® RG755S or Resomer® RG752S) and 0-70% of a biodegradable poly(D, L-lactide) polymer (Resomer® 8208 or Resomer® R203S). The successful invention formulations are summarized in Table 1. As shown in Table 1, said preferred thin film implants comprise 30% latanoprost, 10-50% of a biodegradable poly (D,L-lactide-co-glycolide) polymer (Resomer® RG755S or Resomer® RG752s) and 20-60% of a biodegradable poly(D, L-lactide) polymer (Resomer® R208 and/or Resomer® R203S).

**[0107]** Examples of the most preferred thin film implant formulation of the invention are latanoprost 30%, R208 35% and RG752S 35%; latanoprost 30%, R208 35% and RG755S 35%; latanoprost 30%, R208 35% and R203S 35%; and latanoprost 30%, R203S 35% and R755S 35%.

**[0108]** Release of the drug (latanoprost) from an erodible polymer is the consequence of several mechanisms or combinations of mechanisms. Some of these mechanisms include desorption from the implant's surface, dissolution, diffusion through porous channels of the hydrated polymer and erosion. Erosion can be bulk or surface or a combination of both. The shell of the intraocular implant may release drug at a rate effective to sustain release of an amount of drug for more than one week after implantation into an eye. In certain implants, therapeutic amounts of drug are released for no more than about 30-35 days after implantation. For example, an implant may release the drug at a rate effective to sustain a therapeutically effective amount of drug for about one month (i.e., about 30 days) after being placed in an eye. As another example, the implant may release drug at a rate effective to sustain a therapeutically effective amount of drug for more than forty days, such as for about six months.

**[0109]** The following examples are intended to illustrate the present invention.

## EXAMPLE 1

[0110]

TABLE 1

Latanoprost Containing Film Formulations					
Formulation No	w/w, %				
	Latanoprost	Resomer R208	Resomer R203S	Resomer RG752S	Resomer RG755S
R-2007-8933-166	30	35	0	0	35
R-2007-8933-167	30	35	0	35	0
R-2007-8933-168	30	35	35	0	0
R-2007-8933-169	30	0	35	0	35
R-2009-9606-014	30	20	0	50	0
R-2009-9606-015	30	35	0	35	0
R-2009-9606-016	30	50	0	20	0
R-2009-9606-017	30	60	0	10	0

[0111] Release studies were performed in triplicates as follows. The dried film was cut using 4-mm biopsy punch (approximately 2.0-mg), and was placed into a 10-mL vial containing 0.01M phosphate buffered saline (pH 7.4)+0.1% Triton X100. The samples were then transferred into a shaking water bath set at 37° C. and 50 rpm. At various time-points, the solution was removed and analyzed by HPLC for the amount of released latanoprost. The removed solution is replaced with fresh phosphate buffered saline solution. Drug release profiles are shown in FIGS. 1A-C.

[0112] The film-shaped implants made by solvent casting can be cut to any shape and dimension. One example is a disc shaped implant 100  $\mu$ m to 500  $\mu$ m thick and 2 to 6 mm in diameter.

## EXAMPLE 2

[0113] This example prepares an extruded solid polymer implant containing latanoprost. While the above discussion relates mainly to the problems of incorporating latanoprost in a film oily drug substances (DS) are also very difficult to incorporate into hot-melt extruded implants because they exude the oily DS when heated. It is important to keep the extrusion temperature as low as possible to avoid loss and

be extruded at a temperature where the DS is not degraded or lost. Suitable formulations are shown in Table 2.

[0114] The polymer implants were made by hot-melt extrusion using a mechanically driven ram microextruder, but they can also be made by direct compression or solvent casting. The implants are rod-shaped, but they can be made into any geometric shape by changing the extrusion or compression die.

[0115] The samples were initially mixed using a spatula in a weigh-boat for 15 minutes. The samples were then transferred into a stainless steel container containing two ¼" stainless steel balls and mixing continued using a Turbula mixer for two separate 15-min cycles. The powder blend was mixed by hand using a spatula between each cycle and after the final cycle. The blended material was then compacted into an extruder barrel using a pellet compactor; then the extruder barrel was placed into the heated well of the piston extruder and extruded using a 500  $\mu$ m nozzle.

[0116] The implants made by hot-melt extrusion contain 20-30% Latanoprost, 40-60% of a biodegradable poly(D,L-lactide-co-glycolide) polymer (Resomer® RG752s), 0-40% of a biodegradable poly(D,L-lactide) polymer (Resomer® R202s), 0-40% of a biodegradable poly(D,L-lactide) acid end capped polymer (Resomer® R20214), and 0-10% PEG-3350. The successful hot-melt extruded invention formulations are summarized in Table 2.

TABLE 2

Latanoprost Containing Extruded Filament Formulations					
Formulation No	w/w, %				
	Latanoprost	Resomer RG752S	Resomer R202S	Resomer 202H	PEG-3350
R-2008-8933-070	30	60	0	0	10
R-2008-8933-085	30	40	20	0	10
R-2009-9606-019	20	75	0	0	5
R-2009-9606-020	20	80	0	0	0
R-2009-9606-030	20	40	40	0	0
R-2009-9606-032	20	0	40	40	0

degradation of the DS. This can be overcome by using a select combination of polymers and a plasticizer like PEG that are compatible with the drug substance. The oily DS and PEG plasticize the polymers to a degree that allows the mixture to

[0117] Release studies were performed in triplicates as follows. The filaments were cut into one milligram implant (approximately 3-mm long), and was placed into a 10-mL vial containing 0.01M phosphate buffered saline (pH 7.4).

The samples were then transferred into a shaking water bath set at 37° C. and 50 rpm. At various time-points, the solution was removed and analyzed by HPLC for the amount of released latanoprost. The removed solution is replaced with fresh phosphate buffered saline solution. Drug release profiles are shown FIGS. 2A-C.

**[0118]** The present invention is not to be limited in scope by the exemplified embodiments, which are only intended as illustrations of specific aspects of the invention.

**[0119]** In general, considering both the solvent cast thin film and the extruded implants of this invention, latanoprost may comprise from 10 to 60%, more preferably from 20 to 50%, e.g. 30%, of the implant and the implant further comprising a mixture of two or more biodegradable polymers, selected from the group consisting of PLA, PLGA and mixtures thereof. The range of concentrations of the preferred polymer components that can be used in the implant of the invention are 10 to 60%, R208; 10 to 60%, R203S; 10 to 60%, RG752S, and 10 to 60%, 755S.

**[0120]** Unless otherwise specified the percentages of drug, polymer(s), and PEG (co-solvent) given above represent the mass of the component relative to the total mass of the composition or implant formulation, the ratio multiplied by 100 to give the weight/weight percentage of the component in the implant (i.e. the % w/w).

**[0121]** Various other modifications of the invention, in addition to those disclosed herein, will be apparent to those skilled in the art by a careful reading of the specification, including the claims, as originally filed. It is intended that all such modifications will fall within the scope of the appended claims.

What is claimed is:

1. A biodegradable intraocular implant for reducing intraocular pressure in an eye of an individual in need thereof, the implant comprising latanoprost and one or more biodegradable polymers, wherein:

- a) the implant does not contain bimatoprost;
- b) the implant is in the form of a film or an extruded filament;
- c) said filament optionally further comprises a polyethylene glycol (PEG);
- d) said film is about 100  $\mu\text{m}$  to about 500  $\mu\text{m}$  thick and about 2 to about 6 mm in diameter;
- e) the solubility parameters for each of the latanoprost, the biodegradable polymer(s), and the PEG differ one from the other by no more than 10 MPa<sup>42</sup>;
- f) the implant releases latanoprost continuously for at least 30 days after placement in the eye of the individual; and wherein
- g) the biodegradable polymer(s) is/are selected from the group consisting of
  - i) an ester terminated poly(D,L-lactide) having an inherent viscosity of about 1.8-2.2 dl/g (R208);
  - ii) an ester terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g (R2025);
  - iii) an acid terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g (R202H);
  - iv) an ester terminated poly(D,L-lactide) having an inherent viscosity of about 0.25-0.35 dl/g (R2035);
  - v) an ester terminated poly(D,L-lactide-co-glycolide) having an inherent viscosity of about 0.16-0.24 dl/g and a D,L-lactide to glycolide ratio of about 75:25 (RG7525); and

vi) an ester terminated poly(D,L-lactide-co-glycolide) having an inherent viscosity of about 0.50-0.70 dl/g and a D,L-lactide to glycolide ratio of about 75:25 (RG755S).

2. A biodegradable implant according to claim 1, wherein the implant does not contain a prostamide.

3. A film according to claim 1, wherein said film is in the form of a rolled film that can partially or completely unfurl upon insertion into the eye.

4. A biodegradable implant according to claim 1, wherein said extruded filament comprises about 5 to about 10% by weight PEG 3350.

5. A biodegradable implant according to claim 1, said implant in the form of a film and comprising about 30% by weight latanoprost, about 35% by weight of an ester terminated poly(D,L-lactide) having an inherent viscosity of about 1.8-2.2 dl/g (R208), and about 35% by weight of an ester terminated poly(D,L-lactide-co-glycolide) having an inherent viscosity of about 0.16-0.24 dl/g and a D,L-lactide:glycolide ratio of about 75:25 (RG752S).

6. A biodegradable implant according to claim 1, said implant in the form of a film and comprising about 30% by weight latanoprost, about 20% by weight of an ester terminated poly(D,L-lactide) having an inherent viscosity of about 1.8-2.2 dl/g (R208), and about 50% by weight of an ester terminated poly(D,L-lactide-co-glycolide) having an inherent viscosity of about 0.16-0.24 dl/g and a D,L-lactide:glycolide ratio of about 75:25 (RG752S).

7. A biodegradable implant according to claim 1, said implant in the form of an extruded filament and consisting of about 20% by weight latanoprost, about 40% by weight of an ester terminated poly(D,L-lactide-co-glycolide) having an inherent viscosity of about 0.16-0.24 dl/g and a D,L-lactide:glycolide ratio of about 75:25 (RG752S); and about 40% by weight of an ester terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g (R202S).

8. A biodegradable implant according to claim 1, said implant in the form of an extruded filament and consisting of about 20% by weight latanoprost, about 40% by weight of an ester terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g (RG202S), and about 40% by weight of an acid terminated poly(D,L-lactide) having an inherent viscosity of about 0.16-0.24 dl/g (R202H).

9. A method for making a biodegradable intraocular implant according to claim 1, the method comprising:

- a) dissolving the biodegradable polymer(s) in an organic solvent under constant stirring to form a first solution;
- b) adding latanoprost to the first solution under constant stirring to form a second solution;
- c) sonicating the second solution to remove air bubbles;
- d) casting the second solution into a glass dish;
- e) evaporating the solvent to form a dry film; and
- f) cutting the film into circular portions of about 2 to about 6 mm in diameter each.

10. The method of claim 9, wherein the solvent is dichloromethane.

11. The method of claim 9, further comprising rolling said circular portions to form a rolled film implant that can partially or completely unfurl upon placement in the eye of an individual suffering from elevated intraocular pressure.

12. A method for making a biodegradable intraocular implant according to claim 1, the method comprising:

- a) mixing the latanoprost, the biodegradable polymer(s), and optionally the PEG to form a mixture; and

b) extruding the mixture at a temperature of less than about 80° C. to form a filament that will release latanoprost continuously for at least 30 days after placement in the eye of the individual.

**13.** A method for providing an ocular implant to a patient in need thereof, wherein the implant is in the form of a film rolled into a cylindrical shape, the rolled film comprising latanoprost and a biodegradable polymer, the method comprising placing the rolled film in the eye of the patient, whereby said film can unroll or partially unroll to provide a

large surface for drug diffusion, and wherein the implant releases latanoprost continuously for at least 30 days after placement in the eye of the patient.

**14.** The method of claim **12**, wherein the unrolled film is circular, about 100  $\mu\text{m}$  to about 500  $\mu\text{m}$  thick, and about 2 mm to about 6 mm in diameter.

**15.** The method of claim **12**, wherein the patient in need is suffering from elevated intraocular pressure.

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