extended period of time (Yellepeddi, V.K. and S. Palakurthi, Recent Advances in Topical Ocular Drug Delivery. Journal of Ocular Pharmacology and Therapeutics, 2015. 32(2): p. 67-82).

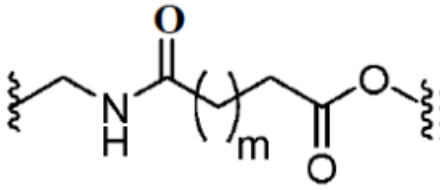
[00010] DURYSTA®, a bimatoprost intracameral implant approved by the FDA, is indicated for the reduction of intraocular pressure in patients with open angle glaucoma or ocular hypertension. The implant is limited to a single implant per eye without retreatment due to possible corneal endothelial cell loss and corneal adverse reactions and should be used with caution in patients with narrow angles or anatomical angle obstructions. Efficacy was evaluated in two multicenter, randomized, parallel-group, controlled 20-month (including 8-month extended follow-up) studies of DURYSTA compared to twice daily topical timolol 0.5% drops, in patients with open angel glaucoma or ocular hypertension. DURYSTA demonstrated an intraocular pressure reduction of approximately 5-8 mmHg in patients with a mean baseline intraocular pressure of 24.5 mmHg. The data show a raise in intraocular pressure for the DURYSTA group above the timolol group after week 12. DURYSTA® is an intracameral implant containing 10 µg of bimatoprost, in a solid polymer sustained-release drug delivery system. The drug delivery system consists of poly (D,Llactide), poly (D,L-lactide-co-glycolide), poly (D,L-lactide) acid end, and polyethylene glycol 3350. (Prescribing information revised 11/2020).

OBJECTS AND SUMMARY OF THE DISCLOSURE

[00010a] In one aspect of the present disclosure, there is provided a travoprost sustained release biodegradable intracameral implant comprising:

- a biodegradable hydrogel, wherein the hydrogel comprises a polymer network comprising one or more units of multi-arm polyalkylene glycol having a mass average molecular weight in the range from about 10,000 to about 20,000 Daltons that are crosslinked, and travoprost particles,
- the travoprost particles being in the form of travoprost intermixed with a biodegradable polymer comprising a polyactide, and
- the travoprost particles being dispersed within the hydrogel,

wherein the polyalkylene glycol units are cross-linked via a hydrolysable linker having the formula



wherein m is an integer from 0 to 10,wherein the implant has a length of about 1.00 mm to about 2.50 mm and a diameter of not more than 0.30 mm in its dried state,

wherein the travoprost particles have an average diameter ranging from 1 to 75 µm determined by laser diffraction,

and wherein the implant contains a dose of about 2 µg to about 30 µg of travoprost.

[00010b] In another aspect, there is provided a use of a travoprost sustained release biodegradable intracameral implant as defined above in the manufacture of a medicament for the treatment of intraocular pressure in a human subject with ocular hypertension and/or glaucoma for a period ranging from about 1 to about 24 months such as from about 3 to about 9 months with one single intracameral implant per eye in need of treating.

[00011] It is an object of certain examples of the present disclosure to provide an implant suitable for being inserted into the anterior chamber of the eye (intracameral implant) with dimensions small enough to fit into the iridocorneal angle of the eye when inserted. In particular the implant should have a size small enough to fit a wide range of iridocorneal angle sizes including narrow angels.

[00012] It is an object of certain examples of the present disclosure to provide an implant suitable for being inserted into the anterior chamber of the eye (intracameral implant) with dimensions small enough to fit into the iridocorneal angle of the eye and gets fixated in the iridocorneal angle during the period of treatment and/or until it is biodegraded.

[00013] It is an object of certain examples of the present disclosure to provide an implant suitable for being inserted into the anterior chamber of the eye (intracameral implant) which after insertion swells due to the uptake of aqueous humor and becomes increasingly soft before it dissolves and fully degrades.

[00014] Another object of certain examples of the present disclosure is to provide a travoprost sustained release biodegradable intracameral implant and corresponding method of treatment with limited movement of the implant.

[00015] Another object of certain examples of the present disclosure is to provide a travoprost sustained release biodegradable intracameral implant which is gentle to the endothelium.

[00016] It is an object of certain examples of the present disclosure to provide a method and corresponding use of treating ocular diseases in human subjects for an extended period of time, e.g. ranging from about 1 to about 24 months.

[00017] It is an object of certain examples of the present disclosure to provide a method and corresponding use of treating ocular diseases in human subjects for an unlimited period of time.

[00018] It is an object of certain examples of the present disclosure to provide a method and corresponding use for safely and effectively treating the intraocular pressure in human subjects for an extended period of time, e.g. ranging from about 2 to about 12 months or 3 to about 9 months, e.g. for about 3 to about 4 months or for about 3 to about 6 months or for about 6 to about 9 months.

[00019] It is an object of certain examples of the present disclosure to provide a method and corresponding use for safely and effectively treating the intraocular pressure in human subjects for an unlimited period of time.

[00020] It is an object of certain examples of the present disclosure to provide a method and corresponding use for safely and effectively treating the intraocular pressure in human subjects with ocular hypertension or glaucoma, e.g. open angle glaucoma, for an extended period of time, e.g. ranging from about 2 to about 12 months or from about 3 to about 9 months, e.g. for about 3 to about 4 months or about 3 to about 9 months for about 6 to about 9 months.

[00021] It is an object of certain examples of the present disclosure to provide a method and corresponding use for safely and effectively treating the intraocular pressure in human subjects with ocular hypertension or glaucoma, e.g. open angle glaucoma, for an unlimited period of time.

[00022] Another object of certain examples of the present disclosure to provide a prostaglandin antagonist (e.g., travoprost) sustained release biodegradable intracameral implant which provides a constant or substantially constant prostaglandin antagonist release with limited burst at the beginning for safely and effectively treating the intraocular pressure in human subjects with ocular hypertension or glaucoma, e.g. open angle glaucoma.

[00023] Another object of certain examples of the present disclosure is to provide a prostaglandin antagonist (e.g., travoprost) sustained release biodegradable intracameral implant and corresponding method of treatment which do not cause inconvenience or discomfort once implanted into the anterior chamber of the human subject's eye, such as a sensation of having a foreign object in the eye or eye pain.

[00024] Another object of certain examples of the present disclosure is to provide a method for preservative free treating the intraocular pressure in human subjects.

[00025] Another object of certain examples of the present disclosure is to provide a travoprost sustained release biodegradable intracameral implant and corresponding method of treatment and wherein the implant is cosmetically invisible.

[00026] Another object of certain examples of the present disclosure is to provide a travoprost sustained release biodegradable intracameral implant and corresponding method of treatment wherein the implant can be monitored in the eye.

[00027] Another object of certain examples of the disclosure is to provide a prostaglandin antagonist (e.g., travoprost) release biodegradable intracameral implant which is easily insertable into the human subject's eye, such as the anterior chamber or the posterior chamber of the human subject's eye.

[00028] Another object of certain examples of the present disclosure is to provide a prostaglandin antagonist (e.g., travoprost) sustained release biodegradable intracameral implant which is sufficiently small to be inserted into the human subject's eye, such as the anterior chamber or the posterior chamber of the human subject's eye.

[00029] Another object of certain examples of the present disclosure is to provide a travoprost sustained release biodegradable intracameral implant and corresponding method of treatment which is biodegradable in a residual-free manner once inserted into the anterior chamber of the human subject's eye and does not need to be removed by a surgery, i.e. the implant is fully biodegradable.

[00030] Another object of certain examples of the present disclosure is to provide a travoprost sustained release biodegradable intracameral implant and corresponding method of treatment which can be used for a continuous treatment of the intraocular pressure associated with open angle glaucoma and/or ocular hypertension in a human subject.

[00031] Another object of certain examples of the present disclosure is to provide a travoprost sustained release biodegradable intracameral implant and corresponding method of treatment, wherein said implant provides a long-term treatment effect.

[00032] Another object of certain examples of the present disclosure is to provide a travoprost sustained release biodegradable intracameral implant and corresponding method of treatment, wherein said implant provides a long-term treatment effect and causes no change of pachymetry and endothelial cell count. One or more of these objects of the present disclosure and others are solved by one or more examples as disclosed and claimed herein.

[00033] The individual examples of the present disclosure are disclosed in the specification and claimed in the independent claims, while the dependent claims claim particular examples and variations of these exmaples of the disclosure. Details of the various examples of the present disclosure are provided in the detailed description below.

BRIEF DESCRIPTION OF THE DRAWINGS

[00034] **Figure 1a** An illustration of in vitro releases of formulations 1a, 1b, 2 and 3 measured at 37 °C.

[00035] **Figure 1b** An in vitro release of formulations 1a, 1b, 2 and 3 measured at 40 °C.

[00036] **Figure 1c** Implant Integrity Rating vs Time (Weeks)

[00037] **Figure 1d** typical Karl Fischer plot of the blank obtained using the method disclosed herein.

[00038] **Figure 1e** typical Karl Fischer plot of the water standard obtained using the method disclosed herein.

[00039] **Figure 1f** typical Karl Fischer plot of an OTX-TP sample obtained using the method disclosed herein.

[00040] **Figure 2** An illustration of the clinical phase 1 study design.

[00041] **Figure 3a** Average pachymetry for cohort 1 of the clinical phase 1 study from baseline to month 22.

[00042] **Figure 3b** Average pachymetry for cohort 2 of the clinical phase 1 study from baseline to month 9.

[00043] **Figure 3c** Average pachymetry for cohort 3 of the clinical phase 1 study from baseline to month 9.

[00044] **Figure 3d** Average pachymetry for cohort 4 of the clinical phase 1 study from baseline to month 6.

[00045] **Figure 4a** Average ECC for cohort 1 of the clinical phase 1 study from baseline to month 9.

[00046] **Figure 4b** Average ECC for cohort 2 of the clinical phase 1 study from baseline to month 9.

[00047] **Figure 4c** Average ECC for cohort 3 of the clinical phase 1 study from baseline to month 6.

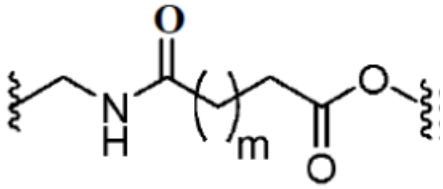
[00048] **Figure 5a** Mean IOP change from baseline in cohort 1 of the clinical phase 1 study.

[00049] **Figure 5b** Mean IOP change from baseline in cohort 2 of the clinical phase 1 study.

Claims

1. A travoprost sustained release biodegradable intracameral implant comprising:
    - a biodegradable hydrogel, wherein the hydrogel comprises a polymer network comprising one or more units of multi-arm polyalkylene glycol having a mass average molecular weight in the range from about 10,000 to about 20,000 Daltons that are crosslinked, and travoprost particles,
    - the travoprost particles being in the form of travoprost intermixed with a biodegradable polymer comprising a polyactide, and
    - the travoprost particles being dispersed within the hydrogel,

    wherein the polyalkylene glycol units are cross-linked via a hydrolysable linker having the formula



    wherein m is an integer from 0 to 10,wherein the implant has a length of about 1.00 mm to about 2.50 mm and a diameter of not more than 0.30 mm in its dried state,
    wherein the travoprost particles have an average diameter ranging from 1 to 75 µm determined by laser diffraction,
    and wherein the implant contains a dose of about 2 µg to about 30 µg of travoprost.

2. The travoprost sustained release biodegradable intracameral implant according to claim 1, wherein the implant has a diameter of less than 0.50 mm after 24 hours of hydration in vitro in phosphate-buffered saline at a pH of 7.4 at 37 °C.

3. The travoprost sustained release biodegradable intracameral implant according to claim 2, wherein the implant has a diameter ranging from about 0.30 mm to 0.49 mm, or from about 0.40 mm to about 0.49 mm, after 24 hours of hydration in vitro in phosphate-buffered saline at a pH of 7.4 at 37 °C.

4. The travoprost sustained release biodegradable intracameral implant according to any one of claims 1 to 3, wherein a ratio of the diameter of the implant after 24 hours of hydration in vitro in phosphate-buffered saline at a pH of 7.4 at 37 °C to the diameter of the implant in its dried state is less than 2.5.
5. The travoprost sustained release biodegradable intracameral implant according to any one of the preceding claims, wherein the implant is in the form of a fiber.

6. The travoprost sustained release biodegradable intracameral implant according to any one of the preceding claims, wherein the implant has a total weight of about 20 µg to about 110 µg, or of about 30 µg to about 105 µg in its dried state.

7. The travoprost sustained release biodegradable intracameral implant according to any one of the preceding claims, wherein the implant shows a burst of less than 15%, based on the total weight of

travoprost in the implant, on day 1 measured in vitro under simulated physiological sink conditions in 50 mL of 1x PBS, 0.5% castor oil, 0.01% sodium fluoride buffer at pH 7.2-7.4 at 37 °C.

8. The travoprost sustained release biodegradable intracameral implant according to any one of the preceding claims, wherein the total mass of the biodegradable polymer in the implant is less than 34 µg, less than 30 µg, less than 20 µg, or less than 10 µg.

9. The travoprost sustained release biodegradable intracameral implant according to any one of the preceding claims, wherein the travoprost in the implant is less than 25 µg, or less than 20 µg, or less than 10 µg.

10. The travoprost sustained release biodegradable intracameral implant according to any one of the preceding claims, wherein the total mass of the implant in its dried state is less than 103 µg, less than 80 µg or less than 50 µg.

11. The travoprost sustained release biodegradable intracameral implant according to any one of the preceding claims, wherein the travoprost particles have an average diameter ranging from 20 to 75 µm, or 20 to 55 µm determined by laser diffraction.

12. The travoprost sustained release biodegradable intracameral implant according to any one of the preceding claims, wherein the one or more multi-arm polyethylene glycol unit(s) have from 4 to 8 arms.

13. The travoprost sustained release biodegradable intracameral implant according to any one of the preceding claims, wherein m in the formula of the hydrolyzable linker is 1, 2, 3 or 6.

14. The travoprost sustained release biodegradable intracameral implant according to any of the preceding claims, wherein the polymer network is formed by reacting an electrophilic group-containing multi-arm-polymer precursor with a nucleophilic group-containing cross-linking agent.

15. The travoprost sustained release biodegradable intracameral implant according to claim 14, wherein the electrophilic group is a succinimidylglutarate (SG) group, a succinimidylazelate (SAZ) group, a succinimidyladipate (SAP) group or a succinimidylsuccinate (SS) group, and the nucleophilic group-containing crosslinking agent is an amine.

16. The travoprost sustained release biodegradable intracameral implant according to any of claims 12 to 15, wherein the multi-arm polymer precursor is selected from the group consisting of 8-arm-15K-SG polyethylene glycol or 8-arm-15K-SAZ polyethylene glycol; and the nucleophilic group-containing cross-linking agent is a trilysine.

17. The travoprost sustained release biodegradable intracameral implant according to any one of the preceding claims, wherein the travoprost particles are a blend of at least two types of travoprost particles selected from the group consisting of

1) a first type of travoprost particles made of a mixture of:

- travoprost and

- a biodegradable polymer consisting of a polylactide or polylactides having an acid end group and an inherent viscosity specification ranging from about 0.05 to less than about 0.5 dl/g, such as from about 0.35 to about 0.45 dl/g,

such as wherein the first type of particles contains from about 40 wt.-% to about 50 wt.-%, such as from about 43 wt.-% to about 45 wt.-% travoprost, based on the total mass of the first type of particles;

2) a second type of travoprost particles made of a mixture of:

- travoprost and

- a biodegradable polymer consisting of a polylactide or polylactides having an acid end group and an inherent viscosity specification ranging from about 0.5 to less than about 0.80 dl/g, such as ranging from about 0.6 to less than about 0.80 dl/g,

such as wherein the second type of particles contains from about 40 wt.-% to about 50 wt.-%, such as from more than about 45 wt.-% to about 47 wt.-% travoprost, based on the total mass of the second type of particles;

3) a third type of travoprost particles made of a mixture of:

- travoprost and

- a biodegradable polymer consisting of a polylactide or polylactides having an acid end group and an inherent viscosity specification ranging from about 0.8 to about 1.7 dl/g, such as ranging from about 0.8 to about 1.0 dl/g,

such as wherein the third type of particles contains from about 40 wt.-% to about 50 wt.-%, such as from about 41 wt.-% to about 43 wt.-% travoprost based on the total mass of third type of particles;

4) a fourth type of travoprost particles made of a mixture of:

- travoprost and

- a biodegradable polymer consisting of a polylactide or polylactides having an ester end group and an inherent viscosity specification ranging from about 0.05 to about 1.7 dl/g, such as ranging from about 0.55 to about 0.75 dl/g,

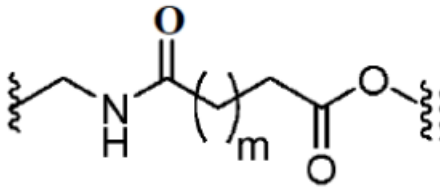
such as wherein the fourth type of particles contains from about 40 wt.-% to about 50 wt.-%, such as from about 41 wt.-% to about 43 wt.-% travoprost based on the total mass of the fourth type of particles.

18. The travoprost sustained release biodegradable intracameral implant according to any one of preceding claims, wherein the travoprost particles are a blend of particles made of

- a first type of travoprost particles made of a mixture of travoprost and the biodegradable polymer consisting of a polylactide or polylactides having an acid end group and an inherent viscosity specification ranging from about 0.05 to less than about 0.5 dl/g, such as from about 0.35 to about 0.45 dl/g, wherein the first type of particles contains from about 40 wt.-% to about 50 wt.-%, such as from about 43 wt.-% to about 45 wt.-% travoprost, based on the total mass of the first type of particles; and
- a second type of travoprost particles made of a mixture of travoprost and the biodegradable polymer consisting of a polylactide or polylactides having an acid end group and an inherent viscosity specification ranging from about 0.5 to less than about 0.80 dl/g, such as ranging from about 0.6 to less than about 0.80 dl/g, wherein the second type of particles contains from about 40 wt.-% to about 50 wt.-%, such as more than from about 45 wt.-% to about 47 wt.-% travoprost, based on the total mass of the second type of particles,

such as wherein the blend contains, based on the total amount of the blend, about 35 wt.-% to about 55 wt.-% particles of the first type of particles and about 35 wt.-% to about 55 wt.-% particles of the second type of particles; or

such as wherein about 35 wt.-% to about 55 wt.-% of the total amount of travoprost in the implant is present in the form of particles of the first type of particles and about 35 wt.-% to about 55 wt.-% of the total amount of travoprost in the implant is present in the form of particles of the second type of particles, wherein optionally the polymer network is formed by reacting an electrophilic group-containing multi-arm-polymer precursor with a nucleophilic group-containing cross-linking agent, the electrophilic group is a succinimidylglutarate (SG) group and the multi-arm polymer precursor an 8-arm-15K-SG polyethylene glycol; and the nucleophilic group-containing cross-linking agent is a trilysine, or the polymer network comprises an 8-arm-polyethylene glycols being cross-linked including a group represented by the following formula



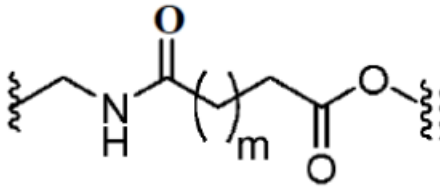
wherein m is 2.

19. The travoprost sustained release biodegradable intracameral implant according to any one of the preceding claims, wherein the travoprost particles are a blend of particles made of

- a first type of particles made of a mixture of travoprost and the biodegradable polymer consisting of a polylactide or polylactides having an acid end group and an inherent viscosity specification ranging from about 0.05 to less than about 0.5 dl/g, such as from about 0.35 to about 0.45 dl/g, wherein the first type of particles contains from about 40 wt.-% to about 50 wt.-%, such as from about 43 wt.-% to about 45 wt.-% travoprost, based on the total mass of the first type of particles,
- a second type of travoprost particles made of a mixture of travoprost and the biodegradable polymer consisting of a polylactide or polylactides having an acid end group and an inherent viscosity specification ranging from about 0.5 to less than about 0.80 dl/g, such as ranging from about 0.6 to less than about 0.80 dl/g, wherein the second type of particle contains from about 40 wt.-% to about 50 wt.-%, such as more than from about 45 wt.-% to about 47 wt.-% travoprost, based on the total mass of the second type of particles, and
- a third type of travoprost particles made of a mixture of travoprost and the biodegradable polymer consisting of a polylactide or polylactides having an acid end group and an inherent viscosity specification ranging from about 0.8 to about 1.7 dl/g, such as ranging from about 0.8 to about 1.0 dl/g, wherein the third type of particles contains from about 40 wt.-% to about 50 wt.-%, such as from about 41 wt.-% to about 43 wt.-% travoprost, based on the total mass of the third type of particles,

such as wherein the blend contains, based on the total amount of blend, about 20 wt.-% to about 35 wt.-% particles of the first type of particles and about 30 wt.-% to about 50 wt.-% particles of the second type of particles and about 25 wt.-% to about 45 wt.-% of particles of the third type of particles; or such as wherein about 20 wt.-% to about 35 wt.-% of the total amount of travoprost in the implant is present in the form of particles of the first type of particles and about 30 wt.-% to about 50 wt.-% of the total amount of travoprost in the implant is present in the form of particles of the second type of particles,

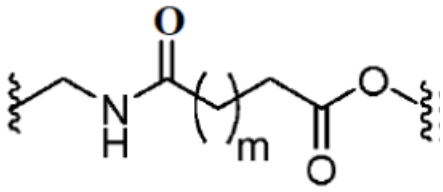
and about 25 wt.-% to about 45 wt.-% of the total amount of travoprost in the implant is present in the form of particles of the third type of particles,
wherein optionally the polymer network is formed by reacting an electrophilic group-containing multi-arm-polymer precursor with a nucleophilic group-containing cross-linking agent, the electrophilic group is a succinimidylglutarate (SG) group and the multi-arm polymer precursor an 8-arm-15K-SG polyethylene glycol; and the nucleophilic group-containing cross-linking agent is a trilysine or the polymer network comprises an 8-arm-polyethylene glycols being cross-linked including a group represented by the following formula



wherein m is 2.

20. The travoprost sustained release biodegradable intracameral implant according to any one of the preceding claims, wherein the travoprost particles are a blend of particles made of
- a first type of particles made of a mixture of travoprost and the biodegradable polymer consisting of a polylactide or polylactides having an acid end group and an inherent viscosity specification ranging from about 0.05 to less than about 0.5 dl/g, such as from about 0.35 to about 0.45 dl/g, wherein the first type of particles contains from about 40 wt.-% to about 50 wt.-%, such as from about 43 wt.-% to about 45 wt.-% travoprost, based on the total mass of the first type of particles,
- a second type of particles made of a mixture of travoprost and the biodegradable polymer consisting of a polylactide or polylactides having an acid end group and an inherent viscosity specification ranging from about 0.5 to less than about 0.80 dl/g, such as ranging from about 0.6 to less than about 0.80 dl/g, wherein the second type of particles contains from about 40 wt.-% to about 50 wt.-%, such as more than from about 45 wt.-% to about 47 wt.-% travoprost, based on the total mass of the second type of particles,
- a third type of particles made of travoprost and the biodegradable polymer consisting of a polylactide or polylactides having an acid end group and an inherent viscosity specification ranging from about 0.8 to about 1.7 dl/g, such as ranging from about 0.8 to about 1.0 dl/g, wherein the third type of particles contain from about 40 wt.-% to about 50 wt.-%, such as from about 41 wt.-% to about 43 wt.-% travoprost, based on the total mass of the third type of particles, and
- a fourth type of particles made of travoprost and the biodegradable polymer consisting of a polylactide or polylactides having an ester end group and an inherent viscosity specification ranging from about 0.05 to about 1.7 dl/g, such as ranging from about 0.55 to about 0.75 dl/g, wherein the fourth type of particles contains from about 40 wt.-% to about 50 wt.-% travoprost, based on the total mass of the fourth types of particles,
such as wherein the blend contains, based on the total amount of blend, about 15 wt.-% to about 25 wt.-% particles of the first type of particles and about 15 wt.-% to about 25 wt.-% particles of the second type of particles and about 5 wt.-% to about 15% of particles of the third type of particles and about 40 wt.-% to about 60 wt.-% of particles of the fourth type of particles; or

such as wherein about 15 wt.-% to about 25 wt.-% of the total amount of travoprost in the implant is present in the form of particles of the first type of particles and about 15 wt.-% to about 25 wt.-% of the total amount of travoprost in the implant is present in the form of particles of the second type of particles and about 5 wt.-% to about 15 wt.-% of the total amount of travoprost in the implant is present in the form of particles of the third type of particles and about 40 wt.-% to about 60 wt.-% of the total amount of travoprost in the implant is present in the form of particles of the fourth type of particles,
wherein optionally the polymer network is formed by reacting an electrophilic group-containing multi-arm-polymer precursor with a nucleophilic group-containing cross-linking agent, the electrophilic group is a succinimidylazelate (SAZ) group, and the multi-arm polymer precursor is a 8-arm-15K-SAZ polyethylene glycol; and the nucleophilic group-containing cross-linking agent is a trilysine, or the polymer network comprises an 8-arm-polyethylene glycols being cross-linked including a group represented by the following formula



wherein m is 6.

21. Use of a travoprost sustained release biodegradable intracameral implant according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of intraocular pressure in a human subject with ocular hypertension and/or glaucoma for a period ranging from about 1 to about 24 months such as from about 3 to about 9 months with one single intracameral implant per eye in need of treating.