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).

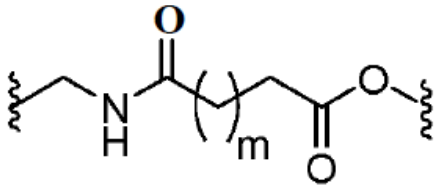
[00010] DURYSTA®, a bimatoprost intracameral implant approved by the FDA, is indicated for the reduction of intraocular pressure in patients with open angle glaucoma or ocular hypertension. The implant is limited to a single implant per eye without retreatment due to possible corneal endothelial cell 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 10,000 to 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 polylactide, and
- the travoprost particles being dispersed within the hydrogel,

wherein the polymer network is formed by reacting an electrophilic group-containing multi-arm precursor with a nucleophilic group-containing cross-linking agent, wherein the electrophilic group is selected from the group consisting of a succinimidylglutarate (SG) group and a succinimidylazelate (SAZ) group, 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, and wherein the polyalkylene glycol units are cross-linked via a hydrolysable linker having the formula



wherein m is 2 or 6, wherein the implant has a length of 1.00 mm to 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 2 µg to 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 1 to 24 months such as from 3 to 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.

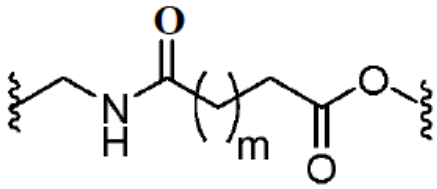
[00014] Another object of certain examples of the present disclosure is to provide a travoprost sustained release biodegradable intracameral implant and corresponding method of treatment with limited movement of the implant.

[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.

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 10,000 to 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 polylactide, and
    - the travoprost particles being dispersed within the hydrogel,

    wherein the polymer network is formed by reacting an electrophilic group-containing multi-arm precursor with a nucleophilic group-containing cross-linking agent, wherein the electrophilic group is selected from the group consisting of a succinimidylglutarate (SG) group and a succinimidylazelate (SAZ) group, 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, and wherein the polyalkylene glycol units are cross-linked via a hydrolysable linker having the formula



    wherein m is 2 or 6, wherein the implant has a length of 1.00 mm to 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 2 µg to 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 0.30 mm to 0.49 mm, or from 0.40 mm to 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 20 µg to 110 µg, or of 30 µg to 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, or 21 µg to 30 µg, or 11 µg to 20 µg, or 2 µg to 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 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 0.05 to less than 0.5 dl/g, such as from 0.35 to 0.45 dl/g, such as wherein the first type of particles contains from 40 wt.-% to 50 wt.-%, such as from 43 wt.-% to 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 0.5 to less than 0.80 dl/g, such as ranging from 0.6 to less than 0.80 dl/g,

such as wherein the second type of particles contains from 40 wt.-% to 50 wt.-%, such as from more than 45 wt.-% to 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 0.8 to 1.7 dl/g, such as ranging from 0.8 to 1.0 dl/g, such as wherein the third type of particles contains from 40 wt.-% to 50 wt.-%, such as from 41 wt.-% to 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 0.05 to 1.7 dl/g, such as ranging from 0.55 to 0.75 dl/g, such as wherein the fourth type of particles contains from 40 wt.-% to 50 wt.-%, such as from 41 wt.-% to 43 wt.-% travoprost based on the total mass of the fourth type of particles.

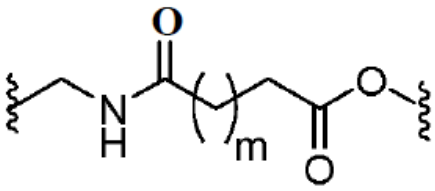
13. The travoprost sustained release biodegradable intracameral implant according to any one of claims 1 to 12, wherein the travoprost particles are a blend of particles made of

- 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 0.05 to less than 0.5 dl/g, such as from 0.35 to 0.45 dl/g, wherein the first type of particles contains from 40 wt.-% to 50 wt.-%, such as from 43 wt.-% to 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 0.5 to less than 0.80 dl/g, such as ranging from 0.6 to less than 0.80 dl/g, wherein the second type of particles contains from 40 wt.-% to 50 wt.-%, such as more than from 45 wt.-% to 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, 35 wt.-% to 55 wt.-% particles of the first type of particles and 35 wt.-% to 55 wt.-% particles of the second type of particles; or

such as wherein 35 wt.-% to 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 35 wt.-% to 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.

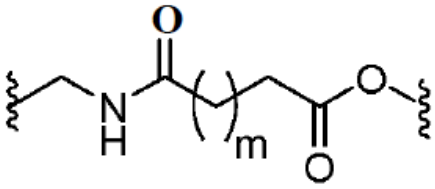
14. The travoprost sustained release biodegradable intracameral implant according to any one of claims 1 to 12, wherein the travoprost particles are a blend of particles made of

- 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 0.05 to less than 0.5 dl/g, such as from 0.35 to 0.45 dl/g, wherein the first type of particles contains from 40 wt.-% to 50 wt.-%, such as from 43 wt.-% to 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 0.5 to less than 0.80 dl/g, such as ranging from 0.6 to less than 0.80 dl/g, wherein the second type of particle contains from 40 wt.-% to 50 wt.-%, such as more than from 45 wt.-% to 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 0.8 to 1.7 dl/g, such as ranging from 0.8 to 1.0 dl/g, wherein the third type of particles contains from 40 wt.-% to 50 wt.-%, such as from 41 wt.-% to 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, 20 wt.-% to 35 wt.-% particles of the first type of particles and 30 wt.-% to 50 wt.-% particles of the second type of particles and 25 wt.-% to 45 wt.-% of particles of the third type of particles; or

such as wherein 20 wt.-% to 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 30 wt.-% to 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 25 wt.-% to 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.

15. The travoprost sustained release biodegradable intracameral implant according to any one of claims 1 to 12, 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

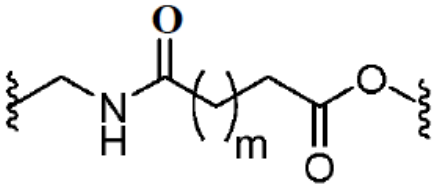
0.05 to less than 0.5 dl/g, such as from 0.35 to 0.45 dl/g, wherein the first type of particles contains from 40 wt.-% to 50 wt.-%, such as from 43 wt.-% to 45 wt.-% travoprost, based on the total mass of the first type of particles,

- 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 0.5 to less than 0.80 dl/g, such as ranging from 0.6 to less than 0.80 dl/g, wherein the second type of particles contains from 40 wt.-% to 50 wt.-%, such as more than from 45 wt.-% to 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 0.8 to 1.7 dl/g, such as ranging from 0.8 to 1.0 dl/g, wherein the third type of particles contain from 40 wt.-% to 50 wt.-%, such as from 41 wt.-% to 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 0.05 to 1.7 dl/g, such as ranging from 0.55 to 0.75 dl/g, wherein the fourth type of particles contains from 40 wt.-% to 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, 15 wt.-% to 25 wt.-% particles of the first type of particles and 15 wt.-% to 25 wt.-% particles of the second type of particles and 5 wt.-% to 15% of particles of the third type of particles and 40 wt.-% to 60 wt.-% of particles of the fourth type of particles; or

such as wherein 15 wt.-% to 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 15 wt.-% to 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 5 wt.-% to 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 40 wt.-% to 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.

16. Use of a travoprost sustained release biodegradable intracameral implant according to any one of claims 1 to 15 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 1 to 24 months such as from 3 to 9 months with one single intracameral implant per eye in need of treating.

17. The use of claim 16, wherein glaucoma is open angle glaucoma.