

active ingredient or a combination of active ingredients of a medicine. This device does however not guarantee sustained and controlled release of the medicine(s).

SUMMARY

- 5 Accordingly, it is the object of the present application to provide an improved sustained release intraocular drug delivery device, which solves at least some of the problems mentioned above.

The present inventors have designed an insoluble and inert sustained release intraocular drug delivery device, for insertion in the sulcus of the eye. The insertion of the device in
10 the sulcus of the eye does not initiate fibrotic processes and due to its inert nature in ocular fluids, the device can be removed after it has been depleted from its drug or earlier, in case of unwanted side-effect to the drug. Moreover, using the sulcus of the eye as insertion site allows the dimensions of the device to be such that sustained release of the therapeutic agent of choice can be attained for up to two years. In addition, the inventors
15 have discerned a simple method of manufacture of said intraocular device, allowing attaining product uniformity by standard manufacturing techniques.

According to the present application, a sustained release intraocular drug delivery device is provided comprising:

- (a) a polymeric matrix core into which at least one therapeutic agent is mixed, and;
20 (b) a polymeric coating completely surrounding said polymeric matrix material;

wherein said polymeric matrix core and polymeric coating are insoluble and inert in ocular fluids, and wherein said sustained release intraocular drug delivery device has an annular shape. Preferably, said device comprises an annular compliant segment, wherein said segment can range from 90 to 360°. More preferably, said device is configured for
25 insertion into the sulcus of the eye, even more preferably, said device has a cross sectional diameter ranging from 0.10 to 0.80 mm.

In a first aspect of the present application, there is provided a sustained release intraocular drug delivery device configured for the sulcus of the eye, comprising:

- (a) a polymeric rod-shaped matrix core into which at least one therapeutic agent is mixed,
30 and;
(b) a polymeric coating completely surrounding said polymeric matrix material;

wherein said polymeric matrix core and polymeric coating are insoluble and inert in ocular fluids, and wherein said sustained release intraocular drug delivery device is formed of a

compliant annular segment, having a cross sectional diameter ranging from 0.10 to 0.80 mm and having an external or outer diameter ranging from 5.0 to 15.0 mm, and wherein the degree of cross-linking in the polymer regulates the drug release rates from the polymeric coating.

- 5 According to a preferred embodiment, said sustained release intraocular drug delivery device contains a therapeutic agent for treating an eye-related disorder, which may be selected from the group consisting of antibiotic agents, antibacterial agents, antiviral agents, prostaglandin analogues, anti-glaucoma agents, antiallergenic agents, anti-inflammatory agents, anti-angiogenesis agents, immune system modifying agents, anti-
- 10 cancer agents, antisense agents, antifungal agents, myotic and anticholinesterase agents, mydriatic agents, differentiation modulator agents, sympathomimetic agents, anaesthetic

agents, vasoconstrictive agents, vasodilatory agents, decongestants, cell transport/mobility impeding agents, polypeptides and protein agents, steroidal agents, carbonic anhydrase inhibitor agents, polycations, polyanions, and lubricating agents.

In a preferred embodiment, said sustained release intraocular drug delivery device
5 contains a therapeutic agent which may be selected from the group consisting of bevacizumab, ranibizumab, aflibercept, timolol, latanoprost, dorzolamide, triamcinolone, dexamethasone or cyclosporin.

The present application also relates to a therapeutic agent for use in the treatment of
10 ocular diseases, wherein said therapeutic agent is administered in a sustained release intraocular drug delivery device according to the first aspect of the present application, and wherein said sustained release intraocular drug delivery device is inserted into the sulcus of the eye. In a preferred embodiment, said therapeutic agent for use is selected from the group comprising antibiotic agents, antibacterial agents, antiviral agents,
15 prostaglandin analogues, anti-glaucoma agents, antiallergenic agents, anti-inflammatory agents, anti-angiogenesis agents, immune system modifying agents, anti-cancer agents, antisense agents, antifungal agents, myotic and anticholinesterase agents, mydriatic agents, differentiation modulator agents, sympathomimetic agents, anaesthetic agents, vasoconstrictive agents, vasodilatory agents, decongestants, cell transport/mobility
20 impeding agents, polypeptides and protein agents, steroidal agents, carbonic anhydrase inhibitor agents, polycations, polyanions, and lubricating agents.

More preferably, said therapeutic agent for use is selected from the group consisting of bevacizumab, ranibizumab, aflibercept, timolol, latanoprost dorzolamide, triamcinolone, dexamethasone or cyclosporine.

The present application further deals with a method of treating ocular diseases comprising
25 administering a therapeutically effective amount of a therapeutic agent for treating eye-related disorders, wherein said agent is administered in a sustained release intraocular drug delivery device according to the first aspect of the present application, and wherein said sustained release intraocular drug delivery device is inserted into the sulcus of the eye, such that the ocular disease is treated. Preferably, said agent is selected from the
30 group consisting of bevacizumab, ranibizumab, aflibercept, timolol, latanoprost dorzolamide, triamcinolone, dexamethasone or cyclosporine. The present disclosure further provides for a surgical method comprising the step of inserting the intraocular drug delivery device according to the present disclosure into the sulcus of the eye.

In a second aspect of the present application, there is provided a use of a compound in the manufacture of a medicament for treating ocular diseases, wherein said medicament is to be administered in a sustained release intraocular drug delivery device as defined herein, and wherein said sustained release intraocular drug delivery device is to be inserted into the sulcus of the eye, such that the ocular disease is treated, wherein said compound is selected from the group consisting of: bevacizumab, ranibizumab, aflibercept, timolol, latanoprost, dorzolamide, triamcinolone, dexamethasone and cyclosporine.

A third aspect of the present application provides a process when used to prepare a sustained release intraocular drug delivery device according to the first aspect of the present application, which comprises:

- mixing the at least one therapeutic agent with an insoluble and inert polymer disclosed herein;
- molding and/ or extruding said mixture to afford a polymeric matrix core; and,
- providing the resulting polymeric matrix core with a polymeric coating disclosed herein.

The present disclosure hence provides for a method of manufacturing an intraocular drug delivery device according to the present disclosure for use in treating eye-related disorders.

A fourth aspect of the present disclosure provides a use of a compound in the manufacture of a medicament for treating ocular diseases, wherein said medicament is to be administered in a device as defined herein, and wherein said device is to be inserted or implanted into the sulcus of the eye by a surgical method, wherein the device is to be partially straightened by applying force, the device is to be inserted in the sulcus of the eye, and the device is to be released.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1A, shows a three-dimensional representation of the polymeric matrix of the intraocular drug delivery device, according to an embodiment of the present application. **Figure 1B**, shows a side view of the polymeric matrix of the intraocular drug delivery device, according to an embodiment of the present application.

Figure 2A, shows a three-dimensional representation of the sustained release intraocular drug delivery device, according to an embodiment of the present application. **Figure 2B**, shows a side view of the polymeric matrix of the sustained release intraocular drug delivery device, according to an embodiment of the present application.

Figure 3 shows a calibration curve of timolol.

Figure 4 shows a calibration curve of dorzolamide.

CLAIMS

1. A sustained release intraocular drug delivery device configured for the sulcus of the eye, comprising:

5 (a) a polymeric rod-shaped matrix core into which at least one therapeutic agent is mixed, and;

(b) a polymeric coating completely surrounding said polymeric matrix material;

10 wherein said polymeric matrix core and polymeric coating are insoluble and inert in ocular fluids, and wherein said sustained release intraocular drug delivery device is formed of a compliant annular segment, having a cross sectional diameter ranging from 0.10 to 0.80 mm and having an external or outer diameter ranging from 5.0 to 15.0 mm, and wherein the degree of cross-linking in the polymer regulates the drug release rates from the polymeric coating.

15 2. The device according to claim 1, wherein said polymeric matrix core has a cross-sectional diameter of 0.05 mm to 0.48 mm.

3. The device according to claims 1 or 2, wherein said polymeric coating is a polymeric membrane with a thickness ranging from 0.05 to 0.32 mm.

20 4. The device according to any one of claims 1 to 3, wherein said annular segment ranges from 90 to 360° of the ring, preferably from 180 to 360°, more preferably from 300 to 360° of the ring.

5. The device according to any one of claims 1 to 4, wherein said polymeric matrix core comprises a polymer selected from the group consisting of ethylene-co-vinylacetate, poly(dimethylsiloxane), polypropylene, polyethylene, preferably high density polyethylene, plasticized polyethylene terephthalate, poly(methyl methacrylate), polyvinyl acetate, cross-linked polyvinyl alcohol, cross-linked polyvinyl butyrate, ethylene ethylacrylate copolymer, polyethyl hexylacrylate, polyvinyl chloride, polyvinyl acetals, polyvinyl alcohol, polyvinyl acetate, ethylene vinylchloride copolymer, polyvinyl esters, polyvinylbutyrate, polyvinylformal, polyamides, polymethylmethacrylate, polybutylmethacrylate, plasticized polyvinyl chloride, plasticized nylon, plasticized soft nylon, natural rubber, polyisoprene, 30 polyisobutylene, polybutadiene, polyethylene, polytetrafluoroethylene, polyvinylidene chloride, polyacrylonitrile, cross-linked polyvinylpyrrolidone, polytrifluorochloroethylene, chlorinated polyethylene, poly(1,4-isopropylidene diphenylene carbonate), vinylidene chloride, acrylonitrile copolymer, vinyl chloride-diethyl fumarate copolymer, silicone rubbers, ethylene-propylene rubber, silicone-carbonate copolymers, vinylidene chloride-vinyl chloride copolymer, vinyl chloride-acrylonitrile copolymer and vinylidene chloride-acrylonitrile copolymer, polycarbonate, polyurethane, thermoplastic elastomers (TPE)

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12. The device according to any one of claims 1 to 11, wherein said at least one therapeutic agent is selected from the group consisting of bevacizumab, ranibizumab, aflibercept, timolol, latanoprost, dorzolamide, triamcinolone, dexamethasone or cyclosporin.

5 13. The device according to any one of claims 1 to 12, wherein said polymeric matrix core comprises polyethylene, preferably high density polyethylene, and wherein said polymeric coating comprises polyethylene, preferably high density polyethylene, or poly(methyl methacrylate).

10 14. The device according to any one of claims 1 to 12, wherein said polymeric matrix core comprises poly(methyl methacrylate), and wherein said polymeric coating comprises polyethylene, preferably high density polyethylene, or poly(methyl methacrylate).

15. The device according to claim 13 or 14, wherein said at least one therapeutic agent comprises timolol.

15 16. Use of a compound in the manufacture of a medicament for treating ocular diseases, wherein said medicament is to be administered in a sustained release intraocular drug delivery device according to claims 1 to 15, and wherein said sustained release intraocular drug delivery device is to be inserted into the sulcus of the eye, such that the ocular disease is treated, wherein said compound is selected from the group consisting of: bevacizumab, ranibizumab, aflibercept, timolol, latanoprost, dorzolamide, triamcinolone, dexamethasone
20 and cyclosporine.

17. A process when used to prepare a sustained release intraocular drug delivery device according to claims 1 to 15, which comprises:

- mixing the at least one therapeutic agent with an insoluble and inert polymer of claim 5;

25 - molding and/ or extruding said mixture to afford a polymeric matrix core; and,

- providing the resulting polymeric matrix core with a polymeric coating of claim 8.

18. The process of claim 17, wherein the step of providing the resulting polymer matrix core with a polymeric coating is performed by covering said resulting polymeric matrix core with a polymeric membrane in a mold, and heating said mold.

- 5 19. The process according to claim 17 or 18, when used to manufacture an intraocular device for insertion in the sulcus of the eye, for the treatment of ocular diseases .

20. Use of a compound in the manufacture of a medicament for treating ocular diseases, wherein said medicament is to be administered in a device according to claims 1 to 15, and wherein said device is to be inserted or implanted into the sulcus of the eye by a surgical
10 method, wherein the device is to be partially straightened by applying force, he device is to be inserted in the sulcus of the eye, and the device is to be released.