

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 OF THE INVENTION

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 ~~a first aspect of~~ 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 matrix core into which at least one therapeutic agent is mixed, and;
- 30 (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, preferably having a cross sectional diameter ranging from 0.10 to 0.80 mm.

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-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.

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

10 In a second aspect of the present application relates to a therapeutic agent for use in the treatment of 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, 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 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.

25 ~~A third aspect of the~~ The present application further deals with a method of treating ocular diseases comprising 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 group consisting of bevacizumab, ranibizumab, aflibercept, timolol, latanoprost, dorzolamide, triamcinolone, dexamethasone or cyclosporine. The ~~invention~~ present disclosure further provides for a surgical method comprising the step of inserting the intraocular drug delivery device according to the ~~invention~~ present disclosure into the sulcus of the eye.

In a third 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.

A fourth aspect of the present application provides a process for preparing a sustained release intraocular drug delivery device according to the first aspect of the present application, comprising:

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

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

A fifth 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 comprising the steps of partially straightening the device by applying force, inserting the device in the sulcus of the eye, and releasing said device.

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.

Figure 5 shows a schematic representation of the mold used to form the polymeric matrix core of the intraocular sustained release drug delivery device, according to an embodiment of the present application.

5 **Figure 6** shows a schematic representation of the mold used to completely surround the polymeric matrix core, with the polymeric coating, to produce the intraocular drug delivery device, according to an embodiment of the present application.

Figure 7 shows a micrograph of a human eye, showing the site of insertion of the intraocular drug delivery device into the sulcus (Petermeier K. et al; J Cataract Refract. Surg. Vol. 38:986-991, 2012)

10 **Figure 8** shows the tensile curves of implants according to embodiments of the present invention prepared by molding and composed of (2) an EVA (18% vinyl acetate) + timolol core and EVA (18% vinyl acetate) shell; (3) an EVA (10% vinyl acetate) + timolol core and

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. A therapeutic agent for use in the treatment of ocular diseases, wherein said therapeutic agent is administered in a sustained release intraocular drug delivery device according to any one of claims 1 to 15, and wherein said sustained release intraocular drug delivery device is inserted into the sulcus of the eye.

17. The therapeutic agent for use according to claim 16, selected from the group consisting of: bevacizumab, ranibizumab, aflibercept, timolol, latanoprost, dorzolamide, triamcinolone, dexamethasone and cyclosporine.

20 18. Use of a compound in the manufacture of a medicament for A method of treating ocular diseases comprising administering a therapeutically effective amount of a compound for use in the treatment of ocular diseases, wherein said compound 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.

19. The ~~method use~~ according to claim 18, wherein said compound is selected from the group consisting of: bevacizumab, ranibizumab, aflibercept, timolol, latanoprost, dorzolamide, triamcinolone, dexamethasone and cyclosporine.

30 20. A process for preparing a sustained release intraocular drug delivery device according to claims 1 to 15, comprising:

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

- providing the resulting polymeric matrix core with a polymeric coating.

21. The process of claim 20, 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 20. The process according to claim 20 or 21, for use in manufacturing an intraocular device for the treatment of ocular diseases by inserting said device in the sulcus of the eye.

- 10 21. 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 aA surgical method for inserting or implanting the device according to any one of claims 1 to 15, comprising the steps of partially straightening the device by applying force, inserting the device in the sulcus of the eye, and releasing said device.