OCULAR IMPLANT CONTAINING AN ACTIVE AGENT

TECHNICAL FIELD

[0001] The present invention relates to the treatment of ocular diseases. According to the present invention, ocular diseases are treated by administering an implant that is biodegradable and provides sustained release of an active agent suitable for ocular therapy.

BACKGROUND

[0002] There are many ocular diseases that can be treated with pharmacotheraopy. The problem with pharmacotherapy is that systemic administration is not ideal because high levels of systemic dosing is required to achieve effective intraocular concentrations. This leads to the increased incidence of unacceptable side effects. Similarly, ocular instillation of active agents (e.g. eye drops) is often ineffective because therapeutic levels of drug in the middle or back portions of the eye are often not achieved and drug concentration is difficult to control due to wash out, user error, and other factors. Other local therapy routes such as intravitreal injection have failed because such delivery routes tend to result in short half-life and rapid clearance, without sustained release capability being attained. Additionally, daily injections are frequently required to maintain therapeutic ocular drug levels, which is not tolerable to many patients. Some active agents are poorly soluble and are injected as a suspension. These solid particulates, however, can settle onto the retina or migrate to contact the lens or even move into the anterior chamber and lead to localized toxic effects.

[0003] The use of ocular implants for drug delivery offers many advantages over traditional drops or injections. These devices are typically placed in or adjacent to the eye tissues and offer better drug release and treatment duration potential. Although ocular implant devices have improved over the years, there are still many deficiencies. First, not all ocular implants are biodegradable, leaving a permanent foreign object or requiring tedious removal procedures following drug administration. Additionally, most biodegradable implants do not completely dissolve until long after their useful lifespan. The user is therefore left with implant residues that may accumulate with repeat treatment and/or interfere with vision. Next, some ocular implants consist of complicated multiple layers requiring extensive manufacturing processes. This leads to increased production costs and time, and raises the likelihood of contamination from additional handling. Also, formulations containing hydrophobic drugs with biodegradable matrices can result in very little or no release of active agent until erosion of the network occurs. This can lead to drug-dumping, which provides little benefit and causes toxicity issues. Finally, in instances where the drug has low solubility the use of ocular implants have proven less successful because of the delicate balance between long term sustained release and the risk of unwanted particle suspension and migration in the middle or back of the eye.

[0004] There continues to exist a need in the art for ocular implants to treat ocular disease.

[0005] All references disclosed herein are hereby incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY OF THE INVENTION

[0005a] In an aspect of the present disclosure, there is provided a sustained release biodegradable ocular implant comprising a hydrogel and an active agent, wherein the active agent is not a tyrosine kinase inhibitor, wherein the hydrogel comprises a polymer network comprising polyethylene glycol (PEG) units, wherein active agent particles are dispersed within the hydrogel, and wherein the implant is cylindrical and in its dry state has a length of less than 17 mm.

[0005b] In another aspect, there is provided a sustained release biodegradable ocular implant as defined above for the treatment of age-related macular degeneration.

[0005c] In another aspect, there is provided a use of a sustained release biodegradable ocular implant as defined above in the preparation of a medicament for the treatment of neovascular age-related macular degeneration.

[0006] It is an object of certain examples of the present disclosure to provide an ocular implant comprising an active agent that is effective for treating ocular diseases such as neovascular age-related macular degeneration (AMD), DME, and RVO in a patient for an extended period of time.

[0007] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that provides for sustained release of the active agent into the eye.

[0008] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that is pre-loaded into a syringe, thereby avoiding contamination of the implant prior to injection as no further preparation steps are needed.

[0009] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that is sufficiently biodegradable, i.e., cleared from the eye within a time coinciding with the active agent release, avoiding floaters within the patient's eye (empty implant vehicle residues) and/or avoiding the need for removal of the empty implant from the eye after the treatment period.

[00010] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that is biodegradable, wherein decomposition of the implant into smaller particles that may e.g. impact vision are avoided during implant degradation.

[00011] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent, wherein the stability of the ocular implant is less affected by varying environments in the eye such as vitreous humor viscosity, pH of the vitreous humor, composition of the vitreous humor and/or intraocular pressure (IOP) when compared to hydrogels formed *in situ* after injection.

[00012] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that is biocompatible and non-immunogenic due to the implant being free or substantially free of animal- or human-derived components.

[00013] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that is free of preservatives, such as antimicrobial preservatives.

[00014] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that is easy to inject, in particular intravitreally.

[00015] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that contains a therapeutically effective amount of the active agent but is relatively small in length and/or diameter.

[00016] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that is dimensionally stable when in a dry state but changes its dimensions upon hydration, e.g. after administration to the eye.

[00017] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that has a small diameter when in a dry state to fit into the lumen of a fine-diameter needle (such as a 22- to 30-gauge needle) and increases in diameter but decreases in length upon hydration, e.g. after administration to the eye; thus, providing a minimally invasive method of administration.

[00018] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that is injected in a dry form and hydrates *in situ* (i.e. in the eye) when injected.

[00019] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that when placed in the eye has low cative agent concentration at the implant surface thereby avoiding toxicity of the active agent when the implant gets in contact with ocular cells or tissues such as the retina.

[00020] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that is stable and has a defined shape and surface area both in a dry state prior to as well as in a hydrated state after the injection (i.e. inside the eye).

[00021] Another object of certain examples of the present disclosure n is to provide an ocular implant comprising an active agent that is easy to handle, in particular that does not spill or fragment easily.

[00022] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that enables administration of an exact dose (within a broad dose range), thereby avoiding the risk of over- and under-dosing.

[00023] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that generally stays in the area of the eye to which it was administered.

[00024] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent wherein the implant causes minimal or no visual impairment after administration.

[00025] Another object of certain examples of the present disclosure is to provide an ocular implant comprising a TKI such as axitinib that is safe and well tolerated.

[00026] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that does not induce severe adverse events, such as severe ocular adverse events.

[00027] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that provides for sustained release of a therapeutically effective amount of the active agent over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months.

[00028] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that provides for sustained release of the active agent over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, thereby avoiding the need for frequent implant administrations.

[00029] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that provides for sustained release the active agent over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, thereby inhibiting angiogenesis over this period of time.

[00030] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that provides for sustained release of the TKI over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, wherein the catiev agent levels in ocular tissues such as the retina and the choroid, as well as the vitreous humor are consistently maintained at a therapeutically efficient level, in particular at a level sufficient for inhibition of angiogenesis, over this period of time.

[00031] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that provides for sustained release of the active agent over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, wherein no toxic concentrations of the active agent are observed in ocular tissues such as the retina and the choroid, as well as the vitreous humor over this period of time.

[00032] Another object of certain examples of the present disclosure is to provide an ocular implant comprising an active agent that provides for sustained release of the active agent over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, wherein the active agent is not accumulating in the anterior chamber of the eye.

[00033] Another object of certain examples of the present disclosure is to provide an ocular implant comprising ab active agent that provides sustained release of an active agent over an extended period of time, such as over a period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, wherein the active is not or is not substantially resorbed systemically thereby substantially avoiding systemic toxicity.

[00034] Another object of certain examples of the present disclosure is to provide a method of treating ocular diseases such as AMD, DME, and RVO in a patient in need thereof, for a treatment period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months.

[00035] Another object of certain examples of the present disclosure is to provide a method of treating ocular diseases such as AMD, DME, and RVO in a patient in need thereof, for a treatment period of up to 3 months or longer, such as at least 6, at least 9, at least 11 months, or at least 13 months, without the need for the administration of rescue medication during the treatment period, or wherein rescue medication is required to be administered only rarely, such as 1, 2 or 3 times, during the treatment period.

[00036] Another object of certain examples of the present disclosure is to provide a method of treating ocular diseases such as AMD, DME, and RVO in a patient in need thereof, such as a patient who has been treated with anti-VEGF before or a patient who is naïve for anti-VEGF treatment.

[00037] Another object of certain examples of the present disclosure is to provide a method of treating ocular diseases such as AMD, DME, and RVO in a patient in need thereof, such as a patient who has been treated with anti-VEGF before and has not responded to the previous anti-VEGF treatment.

[00038] Another object of certain examples of the present disclosure is to provide a method of treating ocular diseases such as AMD, DME, and RVO in a patient in need thereof, such as a patient with a diagnosis of primary subfoveal neovascularization (SFNV) secondary to AMD.

[00039] Another object of certain examples of the present disclosure is to provide a method of treating ocular diseases such as AMD, DME, and RVO in a patient in need thereof, such as a patient with a diagnosis of previously treated subfoveal neovascularization (SFNV) secondary to neovascular AMD with leakage involving the fovea, who has been previously treated with anti-VEGF.

[00040] Another object of certain examples of the present disclosure is to provide a method of manufacturing an ocular implant comprising an active agent.

[00041] Another object of certain examples of the present disclosure is to provide a method of protecting an ocular implant from premature hydration during storage and handling, wherein the ocular implant is sensitive to moisture such that it for instance changes its dimensions upon hydration.

[00042] Another object of certain examples of the present disclosure is to provide a method of minimizing potential tissue damage during injection of an ocular implant.

[00043] Another object of certain examples of the present disclosure is to provide a kit comprising one or more ocular implants comprising an active agent and optionally comprising a means for injecting the ocular implant.

[00044] Another object of certain examples of the present disclosure is to provide a method of reducing the central subfield thickness as measured by optical coherence tomography in a patient whose central subfield thickness is elevated due to an ocular disease involving angiogenesis by for instance reducing retinal fluid.

[00045] Another object of the present disclosure is to provide a method of essentially maintaining or preventing a clinically significant increase of the central subfield thickness as measured by optical coherence tomography in a patient whose central subfield thickness is elevated due to an ocular disease involving angiogenesis while not increasing retinal fluid.

[00046] Another object of certain examples of the present disclosure is to provide a method of reducing, essentially maintaining or preventing a clinically significant increase of the central subfield thickness as measured by optical coherence tomography in a patient whose central subfield thickness is elevated due to an ocular disease involving angiogenesis while improving or at least not impairing the patient's visual acuity as measured for instance by means of best corrected visual acuity.

[00047] Another object of certain examples of the present disclosure is to provide a method of improving the vision of a patient whose vision is impaired due to an ocular disease involving angiogenesis.

[00048] Another object of certain examples the present disclosure is to provide a method of improving the vision of a patient whose vision is impaired due to the presence of retinal fluid (caused for instance by an ocular disease involving angiogenesis) by means of reducing retinal fluid in the patient (as for instance evidenced by a reduction the central subfield thickness as measured by optical coherence tomography).

[00049] One or more of these objects of the present disclosure and others are solved by one or more examples as disclosed and claimed herein.

[00050] 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 examples of the disclosure. Details of the various examples of the present disclosure are provided in the detailed description below.

[00051] Throughout this application various references are cited. The disclosures of these references are hereby incorporated by reference into the present disclosure. In case of conflict, the disclosure in the present application prevails.

BRIEF DESCRIPTION OF THE DRAWINGS

[00052] **Figure 1** Schematic representation of one embodiment of the implant packaging. In this embodiment, implants are pre-loaded into thin-walled needles separately packaged from the injection device. An all-in-one device with needles already connected to the injection device is also possible.

[00053] **Figure 2** Schematic representation of one embodiment of implant localization. After injection the implant hydrates in situ while maintaining a cylindrical shape. The implant is localized in the posterior part of the eye.

[00054] **Figure 3** Schematic representation of hydrogel biodegradation over time. As the drug is released, a clearance zone is formed (black) as low solubility drug particles (white) gradually dissolve and drug diffuses from hydrogel to the aqueous surrounding (as for instance the vitreous humor). Over time, the gel degrades and is resorbed, while drug diffuses out. During the degradation process, the gel gradually swells until degradation is advanced to the point of shrinkage and distortion.

CLAIMS

1. A sustained release biodegradable ocular implant comprising a hydrogel and an active agent, wherein the active agent is not a tyrosine kinase inhibitor, wherein the hydrogel comprises a polymer network comprising polyethylene glycol (PEG) units, wherein active agent particles are dispersed within the hydrogel, and wherein the implant is cylindrical and in its dry state has a length of less than 17 mm.

2. The sustained release biodegradable ocular implant according to claim 1, wherein the implant is cylindrical and in its dry state has a diameter of 0.1 mm to 0.5 mm and a length of less than 17 mm.

3. The sustained release biodegradable ocular implant of claim 1 or 2, wherein the active agent is an active agent suitable for the treatment of age-related macular degeneration.

4. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the active agent is avacincaptad pegol.

5. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant in its dry state has a total weight of 0.2 mg to 1.5 mg.

6. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is cylindrical and in its hydrated state (after 24 hours in phosphate-buffered saline at a pH of 7.2 at 37°C) has a length of equal to or less than 10 mm and a diameter of equal to or less than 0.8 mm.

7. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant is an intravitreal implant.

8. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the implant provides for the release of the active agent for a period of at least 3 months after administration, at least 6 months after administration, at least 9 months after administration, or at least 12 months after administration.

9. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the polymer network is formed by reacting an electrophilic group-containing multi-arm PEG precursor with a nucleophilic group-containing multi-arm PEG precursor or another nucleophilic group-containing crosslinking agent.

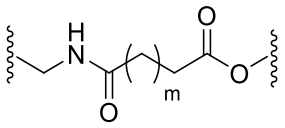
10. The sustained release biodegradable ocular implant of claim 9, wherein the electrophilic group is a N-hydroxysuccinimidyl (NHS) ester end group, preferably a succinimidylazelate (SAZ) end group, a succinimidyladipate (SAP) end group, a succinimidylglutarate (SG) end group, and/or a succinimidylsuccinate (SS) end group or a combination of any of these, and the nucleophilic group is an amine group.

11. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the hydrogel comprises multi-arm PEG units, preferably 4-arm and/or 8-arm PEG units that are the same or different, and that have a number average molecular weight of from about 10,000 to about 60,000 Daltons, preferably about 20,000 Daltons.

12. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the PEG units are 4a20k and/or 8a20k PEG units.

13. The sustained release biodegradable ocular implant of any of claims 9 to 12, wherein the polymer network is formed by reacting the electrophilic group-containing PEG precursor 4a20kPEG-SAZ with the nucleophilic group-containing PEG precursor 8a20kPEG-NH_2.

14. The sustained release biodegradable ocular implant of any of the preceding claims, wherein the hydrogel comprises crosslinked PEG units, and the crosslinks between the PEG units include a group represented by the following formula



wherein m is an integer from 0 to 10, preferably m is 6.

15. A sustained release biodegradable ocular implant according to any of the preceding claims for the treatment of age-related macular degeneration.

16. Use of a sustained release biodegradable ocular implant according to any of claims 1 to 14 in the preparation of a medicament for the treatment of neovascular age-related macular degeneration.