

METHODS OF PREPARING DRUG DELIVERY SYSTEMS FOR THE TREATMENT OF OCULAR DISEASES

CROSS REFERENCE TO RELATED APPLICATION

[001] This application claims the benefit of and priority to U.S. Application No. 63/612,918, filed December 20, 2023, the content of which is incorporated by reference herein in its entirety.

BACKGROUND

[002] Examples of debilitating ocular diseases include glaucoma, diabetic retinopathy (DR), retinal vein occlusion (RVO), retinopathy of prematurity (ROP), geographic atrophy (GA), and age-related macular degeneration (AMD). These ocular diseases can variously cause long-term damage to the eye and, ultimately, blindness. While neonates, the young, adults of all ages and the elderly are affected, only a handful of treatments exist. These treatments are only for a subset of ocular diseases and slow, but do not prevent, blindness. The annual economic burden on the U.S. alone is over \$100 billion.

[003] Options for treating the ocular diseases are still very limited largely due to lack of therapeutic efficacy. Efforts have been devoted to enhancing drug therapeutic effectiveness while minimizing side effects in the treatment or amelioration of ocular diseases. One such effort involves development of novel biodegradable ocular implants providing better permeability, treatability, and controlled release at target site.

[004] Edonentan is a highly selective and very potent endothelin A receptor antagonist. Edonentan was developed as a second-generation analog following the discontinuation of the first clinical candidate, BMS-193884, which was being developed for the treatment of congestive heart failure (CHF). Edonentan was in phase I trials by April 2002, but its development was discontinued.

[005] There remains a need to more effectively reduce the incidence of, treat or otherwise ameliorate glaucoma, DR, GA, AMD, RVO, and ROP.

SUMMARY

[006] The present disclosure provides biodegradable ocular implants designed to deliver an effective amount of edonentan to an ocular tissue. Such biodegradable ocular implants can be useful for treating an ocular disease (e.g., glaucoma, diabetic retinopathy (DR), retinal vein occlusion (RVO), retinopathy of prematurity (ROP), geographic atrophy (GA), and age-

related macular degeneration (AMD)). Also provided herein are methods of making a biodegradable ocular implant comprising an effective amount of edonentan.

[007] In one aspect, provided herein is a biodegradable ocular implant comprising:

- (i) edonentan, or a pharmaceutically acceptable salt thereof; and
- (ii) a biodegradable polymer,

wherein the edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 9 μm to about 250 μm .

[008] In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 9 μm to about 125 μm . In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 10 μm to about 15 μm . In some embodiments, the particle size distribution of the edonentan, or a pharmaceutically acceptable salt thereof, is further characterized by D50 of about 2.5 μm to about 150 μm . In some embodiments, the particle size distribution of the edonentan, or a pharmaceutically acceptable salt thereof, is further characterized by D50 of about 2.5 μm to about 40 μm . In some embodiments, the particle size distribution of the edonentan, or a pharmaceutically acceptable salt thereof, is further characterized by D50 of about 2.5 μm to about 6 μm . In some embodiments, the particle size distribution of the edonentan, or a pharmaceutically acceptable salt thereof, is further characterized by D10 of about 0.5 μm to about 90 μm . In some embodiments, the particle size distribution of the edonentan, or a pharmaceutically acceptable salt thereof, is further characterized by D10 of about 0.5 μm to about 10 μm . In some embodiments, the particle size distribution of the edonentan, or a pharmaceutically acceptable salt thereof, is further characterized by D10 of about 0.5 μm to about 2 μm .

[009] In some embodiments, the biodegradable ocular implant comprises about 20% w/w to about 60% w/w edonentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the biodegradable ocular implant comprises about 40% w/w to about 50% w/w edonentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the biodegradable ocular implant comprises about 45% w/w edonentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the edonentan is present in its free base form as a crystalline anhydrate.

[0010] In some embodiments, the biodegradable ocular implant comprises about 40% w/w to about 80% w/w of the biodegradable polymer. In some embodiments, the biodegradable ocular implant comprises about 50% w/w to about 60% w/w of the biodegradable polymer.

In some embodiments, the biodegradable ocular implant comprises about 55% w/w of the biodegradable polymer.

[0011] In some embodiments, the biodegradable polymer comprises one or more poly(lactic-co-glycolic acid) (PLGA) polymers. In some embodiments, the one or more PLGA polymers is selected from the group consisting of RG502, RG503, RG753S, DLG5002E, DLG5003E, DLG7505E, and combinations thereof. In some embodiments, the biodegradable polymer comprises PLGA RG503 and PLGA RG753S. In some embodiments, the biodegradable ocular implant comprises about 16.5% w/w of PLGA RG503 and about 38.5% w/w of PLGA RG753S. In some embodiments, the biodegradable polymer comprises PLGA RG502, PLGA RG503, and PLGA RG753S. In some embodiments, the biodegradable ocular implant comprises about 5.5% w/w of PLGA RG502, about 27.5% w/w of PLGA RG503, and about 22% w/w of PLGA RG753S. In some embodiments, the biodegradable polymer comprises PLGA DLG5002E, PLGA DLG5003E, and PLGA DLG7505E. In some embodiments, about 5.5% w/w of PLGA DLG5002E, about 27.5% w/w of PLGA DLG5003E, and about 22% w/w of PLGA DLG7505E. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 0.5% w/w of residual monomer.

[0012] In some embodiments, the biodegradable ocular implant has a length of about 4 mm. In some embodiments, the biodegradable ocular implant has a diameter of about 300 μm to about 360 μm . In some embodiments, the biodegradable ocular implant comprises about 180 μg to about 250 μg edonentan.

[0013] In another aspect, provided herein is a method of preparing a biodegradable ocular implant comprising edonentan, or a pharmaceutically acceptable salt thereof, and a biodegradable polymer, the method comprising;

- (a) milling the biodegradable polymer;
- (b) reducing the particle size of the edonentan, or a pharmaceutically acceptable salt thereof, to form a processed edonentan, or a pharmaceutically acceptable salt thereof;
- (c) mixing the milled biodegradable polymer and the processed edonentan, or a pharmaceutically acceptable salt thereof, to form a blend;
- (d) hot melt extruding the blend to form the biodegradable ocular implant.

[0014] In some embodiments, in step (a), the biodegradable polymer is cryomilled. In some embodiments, in step (a), the biodegradable polymer comprises one or more PLGA polymers. In some embodiments, the one or more PLGA polymers is selected from the group consisting of RG502, RG503, RG753S, DLG5002E, DLG5003E, DLG7505E, and combinations

thereof. In some embodiments, in step (a), the biodegradable polymer comprises PLGA RG503 and PLGA RG753S. In some embodiments, in step (a), the biodegradable polymer comprises about 30% w/w of PLGA RG503 and about 70% w/w of PLGA RG753S. In some embodiments, in step (a), the biodegradable polymer comprises PLGA RG502, PLGA RG503, and PLGA RG753S. In some embodiments, in step (a), the biodegradable polymer comprises about 10% w/w of PLGA RG502, about 50% w/w of PLGA RG503, and about 40% w/w of PLGA RG753S. In some embodiments, in step (a), the biodegradable polymer comprises PLGA DLG5002E, PLGA DLG5003E, and PLGA DLG7505E. In some embodiments, in step (a), the biodegradable polymer comprises about 10% w/w of PLGA DLG5002E, about 50% w/w of PLGA DLG5003E, and about 40% w/w of PLGA DLG7505E.

[0015] In some embodiments, in step (b), reducing the particle size of the edonentan, or a pharmaceutically acceptable salt thereof, comprises passing the edonentan, or a pharmaceutically acceptable salt thereof, through a 100-mesh screen. In some embodiments, in step (b), reducing the particle size of the edonentan, or a pharmaceutically acceptable salt thereof, comprises milling the edonentan, or a pharmaceutically acceptable salt thereof. In some embodiments, in step (b), reducing the particle size of the edonentan, or a pharmaceutically acceptable salt thereof, comprises micronizing the edonentan, or a pharmaceutically acceptable salt thereof. In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 10 μm to about 250 μm . In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D50 of about 2.5 μm to about 150 μm . In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of about 0.5 μm to about 90 μm . In some embodiments, in step (b), the edonentan, before and after milling, is present in its free base form as a crystalline anhydrate.

[0016] In some embodiments, in step (d), hot melting extruding the blend comprises:

- (i) hot melt extruding the blend at a temperature of about 95 °C to form a first extrudate;
- (ii) hot melt extruding the first extrudate at a temperature of about 100 °C to about 120 °C to an extruded filament; and
- (iii) cutting the extruded filament to form the biodegradable ocular implant.

[0017] In some embodiments, in step (d), hot melting extruding the blend comprises:

(i) hot melt extruding the blend at a temperature of about 85 °C to about 90 °C form a first extrudate;

(ii) hot melt extruding the first extrudate at a temperature of about 88 °C to about 90 °C form a second extrudate;

(iii) hot melt extruding the second extrudate at a temperature of about 71 °C to about 74 °C form an extruded filament; and

(iv) cutting the extruded filament to form the biodegradable ocular implant.

[0018] In another aspect, provided herein is a method of treating an ocular disease in a subject in need thereof, comprising contacting an ocular tissue of the subject with the biodegradable ocular implant disclosed herein.

[0019] In some embodiments, the ocular disease is selected from the group consisting of glaucoma, DR, GA, AMD, RVO, and ROP.

[0020] The details of one or more embodiments of the disclosure are set forth in the description below. Other features, objects, and advantages of the disclosure will be apparent from the below drawings, description and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] **FIG. 1** depicts the impact of particle size on the release rate of edonentan from implant formulations 2, 3 and 5.

[0022] **FIG. 2** depicts the impact of %w/w residual monomer remaining in the polymer to the release rate of edonentan from the PLGA matrix for implant formulations 1-4.

[0023] **FIG. 3** depicts the *in vitro* drug release profile of implant formulations 1-5.

[0024] **FIG. 4** depicts the daily elution rate of implant formulations 1-5.

[0025] **FIG. 5** depicts comparative *in vivo* edonentan release profile of implant formulations 1-3, 5, 6, and an implant formulation prepared using the solvent process described in Example 4.

[0026] **FIG. 6** and **FIG. 7** depict therapeutic target tissue levels of edonentan in the retina (**FIG. 6**) and retinal pigment epithelium/choroid (**FIG. 7**) of rabbits for IVT sustained release delivery of 45% edonentan in the viatelTM and RESOMER® implants.

[0027] **FIG. 8** and **FIG. 9** depict therapeutic target tissue levels of edonentan in the retina (**FIG. 8**) and retinal pigment epithelium/choroid (**FIG. 9**) of rabbits for IVT sustained release delivery of 45% edonentan micronized and milled implants.

[0028] FIG. 10 and FIG. 11 depict therapeutic target tissue levels of edonentan through 10 weeks in the retina (FIG. 10) and retinal pigment epithelium/choroid (FIG. 11) for IVT sustained release delivery of 45% edonentan 50/10/40 twin screw extrusion implants.

[0029] FIG. 12 depicts an exemplary overlay of XRPD pattern of Forms 1-4.

[0030] FIG. 13 depicts an exemplary XRPD pattern of Form 1.

[0031] FIG. 14 depicts an exemplary XRPD pattern of Form 2.

[0032] FIG. 15 depicts an exemplary XRPD pattern of Form 3.

[0033] FIG. 16 depicts an exemplary XRPD pattern of Form 4.

[0034] FIG. 17 depicts an exemplary DSC curve of Form 1.

[0035] FIG. 18 depicts an exemplary DSC curve of Form 2.

[0036] FIG. 19 depicts an exemplary DSC curve of Form 3.

[0037] FIG. 20 depicts an exemplary DSC curve of Form 4.

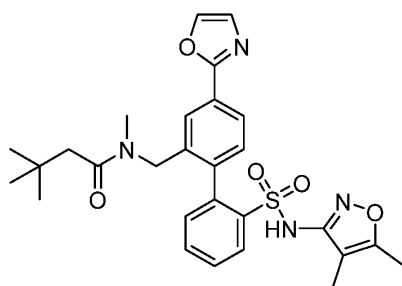
DETAILED DESCRIPTION

[0038] The present disclosure arises from the discovery that certain biodegradable ocular implants comprising edonentan, or a pharmaceutically acceptable salt thereof, are suitable for the prevention, treatment, or otherwise amelioration of ocular diseases including, but not limited to, glaucoma, diabetic retinopathy (DR), retinal vein occlusion (RVO), retinopathy of prematurity (ROP), geographic atrophy (GA), and age-related macular degeneration (AMD). Provided herein are biodegradable ocular implants generally comprising edonentan, or a pharmaceutically acceptable salt thereof, and a biodegradable polymer. Also provided herein are methods of preparing a biodegradable ocular implant described herein. The disclosure is further described below.

Compounds

[0039] The biodegradable ocular implants described herein comprise a compound useful for the treatment of an ocular disease (e.g., glaucoma, DR, RVO, ROP, GA, and AMD). It can be appreciated that compounds contemplated to be useful in the treatment of ocular diseases include, but are not limited to, endothelin receptor agonists (e.g., an endothelin-A receptor agonist).

[0040] In certain embodiments, the compound useful for the treatment of an ocular disease is a compound of Formula I:



(I), or a pharmaceutically acceptable salt thereof.

[0041] The compound of Formula I may also be referred to herein as Edonentan. Edonentan has the chemical name of N-[[2'-[[4,5-dimethyl-3-isoxazolyl]amino]sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide (molecular weight of 536.6 g/mol). Methods of preparing Edonentan are well known to a person of skill in the art. Suitable methods are disclosed, for example, in U.S. Patent No. 6,043,265.

[0042] In some embodiments, a biodegradable ocular implant described herein comprises about 20% w/w to about 60% w/w (e.g., about 20% w/w, about 25% w/w, about 30% w/w, about 35% w/w, about 40% w/w, about 45% w/w, about 50% w/w, about 55% w/w, or 60% w/w) edonentan, or a pharmaceutically acceptable salt thereof. In some embodiments, a biodegradable ocular implant described herein comprises about 35% w/w to about 55% w/w (e.g., about 35% w/w, about 40% w/w, about 45% w/w, about 50% w/w, or about 55% w/w) edonentan, or a pharmaceutically acceptable salt thereof. In some embodiments, a biodegradable ocular implant described herein comprises about 40% w/w to about 50% w/w (e.g., about 40% w/w, about 41% w/w, about 42% w/w, about 43% w/w, about 44% w/w, about 45% w/w, about 46% w/w, about 47% w/w, about 48% w/w, about 49% w/w, and about 50% w/w) edonentan, or a pharmaceutically acceptable salt thereof. In some embodiments, a biodegradable ocular implant described herein comprises about 45% w/w edonentan, or a pharmaceutically acceptable salt thereof.

[0043] In some embodiments, a biodegradable ocular implant described herein comprises about 150 µg to about 300 µg (e.g., about 150 µg, about 160 µg, about 170 µg, about 180 µg, about 190 µg, about 200 µg, about 210 µg, about 220 µg, about 230 µg, about 240 µg, about 250 µg, about 260 µg, about 270 µg, about 280 µg, about 290 µg, and about 300 µg) edonentan, or a pharmaceutically acceptable salt thereof. In some embodiments, a biodegradable ocular implant described herein comprises about 150 µg to about 250 µg (e.g., about 150 µg, about 155 µg, about 160 µg, about 165 µg, about 170 µg, about 175 µg, about 180 µg, about 185 µg, about 190 µg, about 195 µg, about 200 µg, about 205 µg, about 210 µg, about 215 µg, about 220 µg, about 225 µg, about 230 µg, about 235 µg, about 240 µg,

about 245 μg , and about 250 μg) edonentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the amount of the compound of Formula I in the biodegradable ocular implant is from about 180 μg to about 250 μg (e.g., about 180 μg , about 185 μg , about 190 μg , about 195 μg , about 200 μg , about 205 μg , about 210 μg , about 215 μg , about 220 μg , about 225 μg , about 230 μg , about 235 μg , about 240 μg , about 245 μg , and about 250 μg). In certain embodiments, a biodegradable ocular implant described herein comprises about 185 μg to about 225 μg edonentan, or a pharmaceutically acceptable salt thereof. In certain embodiments, a biodegradable ocular implant described herein comprises about 210 μg to about 240 μg edonentan, or a pharmaceutically acceptable salt thereof.

[0044] In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D90 of about 9 μm to about 250 μm (e.g., about 9 μm , about 10 μm , about 20 μm , about 30 μm , about 40 μm , about 50 μm , about 60 μm , about 70 μm , about 80 μm , about 90 μm , about 100 μm , about 110 μm , about 120 μm , about 130 μm , about 140 μm , about 150 μm , about 160 μm , about 170 μm , about 180 μm , about 190 μm , about 200 μm , about 210 μm , about 220 μm , about 230 μm , about 240 μm , or about 250 μm). In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D90 of about 9 μm to about 125 μm (e.g., about 9 μm , about 10 μm , about 15 μm , about 20 μm , about 25 μm , about 30 μm , about 35 μm , about 40 μm , about 45 μm , about 50 μm , about 55 μm , about 60 μm , about 65 μm , about 70 μm , about 75 μm , about 80 μm , about 85 μm , about 90 μm , about 95 μm , about 100 μm , about 105 μm , about 110 μm , about 115 μm , about 120 μm , or about 125 μm). In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D90 of about 9 μm to about 15 μm (e.g., about 9 μm , about 9.25 μm , about 9.5 μm , about 9.75 μm , about 10 μm , about 10.25 μm , about 10.5 μm , about 10.75 μm , about 11 μm , about 11.25 μm , about 11.5 μm , about 11.75 μm , about 12 μm , about 12.25 μm , about 12.5 μm , about 12.75 μm , about 13 μm , about 13.25 μm , about 13.5 μm , about 13.75 μm , about 14 μm , about 14.25 μm , about 14.5 μm , about 14.75 μm , or about 15 μm).

[0045] In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D50 of about 2.5 μm to about 150 μm (e.g., about 2.5 μm , about 10 μm , about 20 μm , about 30 μm , about 40 μm , about 50 μm , about 60 μm , about 70 μm , about 80 μm , about 90 μm , about 100 μm , about 110 μm , about 120 μm , about 130 μm , about 140 μm , or about 150

μm). In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D50 of about 2.5 μm to about 40 μm (e.g., about 2.5 μm, about 5 μm, about 7.5 μm, about 10 μm, about 12.5 μm, about 15 μm, about 17.5 μm, about 20 μm, about 22.5 μm, about 25 μm, about 27.5 μm, about 30 μm, about 32.5 μm, about 35 μm, about 37.5 μm, or about 40 μm). In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D50 of about 2.5 μm to about 6 μm (e.g., about 2.5 μm, about 2.75 μm, about 3 μm, about 3.25 μm, about 3.5 μm, about 3.75 μm, about 4 μm, about 4.25 μm, about 4.5 μm, about 4.75 μm, about 5 μm, about 5.25 μm, about 5.5 μm, about 5.75 μm, or about 6 μm).

[0046] In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D10 of about 0.5 μm to about 90 μm (e.g., about 0.5 μm, about 5 μm, about 10 μm, about 15 μm, about 20 μm, about 25 μm, about 30 μm, about 35 μm, about 40 μm, about 45 μm, about 50 μm, about 55 μm, about 60 μm, about 65 μm, about 70 μm, about 75 μm, about 80 μm, about 85 μm, or about 90 μm). In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D10 of about 0.5 μm to about 10 μm (e.g., about 0.5 μm, about 1 μm, about 1.5 μm, about 2 μm, about 2.5 μm, about 3 μm, about 3.5 μm, about 4 μm, about 4.5 μm, about 5 μm, about 5.5 μm, about 6 μm, about 6.5 μm, about 7 μm, about 7.5 μm, about 8 μm, about 8.5 μm, about 9 μm, about 9.5 μm, or about 10 μm). In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D10 of about 0.5 μm to about 2 μm (e.g., about 0.5 μm, about 0.6 μm, about 0.7 μm, about 0.8 μm, about 0.9 μm, about 1 μm, about 1.1 μm, about 1.2 μm, about 1.3 μm, about 1.4 μm, about 1.5 μm, about 1.6 μm, about 1.7 μm, about 1.8 μm, about 1.9 μm, or about 2 μm).

[0047] In certain embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by one or more of the following: (i) a D10 of about 0.5 μm to about 90 μm; (ii) a D50 of about 2.5 μm to about 150 μm; and (iii) a D90 of about 9 μm to about 250 μm. In certain embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by one or more of the following: (i) a D10 of about 0.5 μm to about 10 μm; (ii) a D50 of about 2.5 μm to about 40 μm; and (iii) a D90 of about 9 μm to about 125 μm. In certain embodiments, the

edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by one or more of the following: (i) a D10 of about 0.5 μm to about 2 μm ; (ii) a D50 of about 2.5 μm to about 6 μm ; and (iii) a D90 of about 9 μm to about 15 μm .

[0048] In certain embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D10 of about 0.5 μm to about 90 μm , a D50 of about 2.5 μm to about 150 μm , and a D90 of about 9 μm to about 250 μm . In certain embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D10 of about 0.5 μm to about 10 μm , a D50 of about 2.5 μm to about 40 μm , and a D90 of about 9 μm to about 125 μm . In certain embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D10 of about 0.5 μm to about 2 μm , a D50 of about 2.5 μm to about 6 μm , and a D90 of about 9 μm to about 15 μm .

[0049] In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D90 of less than about 250 μm (e.g., about 9 μm , about 10 μm , about 20 μm , about 30 μm , about 40 μm , about 50 μm , about 60 μm , about 70 μm , about 80 μm , about 90 μm , about 100 μm , about 110 μm , about 120 μm , about 130 μm , about 140 μm , about 150 μm , about 160 μm , about 170 μm , about 180 μm , about 190 μm , about 200 μm , about 210 μm , about 220 μm , about 230 μm , or about 240 μm). In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D90 of less than about 125 μm (e.g., about 9 μm , about 10 μm , about 15 μm , about 20 μm , about 25 μm , about 30 μm , about 35 μm , about 40 μm , about 45 μm , about 50 μm , about 55 μm , about 60 μm , about 65 μm , about 70 μm , about 75 μm , about 80 μm , about 85 μm , about 90 μm , about 95 μm , about 100 μm , about 105 μm , about 110 μm , about 115 μm , or about 120 μm). In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D90 of less than about 15 μm (e.g., about 9 μm , about 9.25 μm , about 9.5 μm , about 9.75 μm , about 10 μm , about 10.25 μm , about 10.5 μm , about 10.75 μm , about 11 μm , about 11.25 μm , about 11.5 μm , about 11.75 μm , about 12 μm , about 12.25 μm , about 12.5 μm , about 12.75 μm , about 13 μm , about 13.25 μm , about 13.5 μm , about 13.75 μm , about 14 μm , about 14.25 μm , about 14.5 μm , or about 14.75 μm).

[0050] In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D50 of less than about 150 μm (e.g., about 2.5 μm , about 10 μm , about 20 μm , about 30 μm , about 40 μm , about 50 μm , about 60 μm , about 70 μm , about 80 μm , about 90 μm , about 100 μm , about 110 μm , about 120 μm , about 130 μm , or about 140 μm). In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D50 of less than about 40 μm (e.g., about 2.5 μm , about 5 μm , about 7.5 μm , about 10 μm , about 12.5 μm , about 15 μm , about 17.5 μm , about 20 μm , about 22.5 μm , about 25 μm , about 27.5 μm , about 30 μm , about 32.5 μm , about 35 μm , or about 37.5 μm). In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D50 of less than about 6 μm (e.g., about 2.5 μm , about 2.75 μm , about 3 μm , about 3.25 μm , about 3.5 μm , about 3.75 μm , about 4 μm , about 4.25 μm , about 4.5 μm , about 4.75 μm , about 5 μm , about 5.25 μm , about 5.5 μm , or about 5.75 μm).

[0051] In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D10 of less than about 90 μm (e.g., about 0.5 μm , about 5 μm , about 10 μm , about 15 μm , about 20 μm , about 25 μm , about 30 μm , about 35 μm , about 40 μm , about 45 μm , about 50 μm , about 55 μm , about 60 μm , about 65 μm , about 70 μm , about 75 μm , about 80 μm , or about 85 μm). In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D10 of less than about 10 μm (e.g., about 0.5 μm , about 1 μm , about 1.5 μm , about 2 μm , about 2.5 μm , about 3 μm , about 3.5 μm , about 4 μm , about 4.5 μm , about 5 μm , about 5.5 μm , about 6 μm , about 6.5 μm , about 7 μm , about 7.5 μm , about 8 μm , about 8.5 μm , about 9 μm , or about 9.5 μm). In some embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D10 of less than about 2 μm (e.g., about 0.5 μm , about 0.6 μm , about 0.7 μm , about 0.8 μm , about 0.9 μm , about 1 μm , about 1.1 μm , about 1.2 μm , about 1.3 μm , about 1.4 μm , about 1.5 μm , about 1.6 μm , about 1.7 μm , about 1.8 μm , or about 1.9 μm).

[0052] In certain embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by one or more of the following: (i) a D10 of less than about 90 μm ; (ii) a D50 of less than about

150 μm ; and (iii) a D90 of less than about 250 μm . In certain embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by one or more of the following: (i) a D10 of less than about 10 μm ; (ii) a D50 of less than about 40 μm ; and (iii) a D90 of less than about 125 μm . In certain embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by one or more of the following: (i) a D10 of less than about 2 μm ; (ii) a D50 of less than about 6 μm ; and (iii) a D90 of less than about 15 μm .

[0053] In certain embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D10 of less than about 90 μm , a D50 of less than about 150 μm , and a D90 of less than about 250 μm . In certain embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D10 of less than about 10 μm , a D50 of less than about 40 μm , and a D90 of less than about 125 μm . In certain embodiments, the edonentan, or a pharmaceutically acceptable salt thereof, present in the biodegradable ocular implant has a particle size distribution characterized by a D10 of less than about 2 μm , a D50 of less than about 6 μm , and a D90 of less than about 15 μm .

[0054] In some embodiments, the particle size distributions described herein are measured using a laser diffraction technique. In some embodiments, the instrument used to measure the particle size distributions described herein is a Malvern Mastersizer (e.g., a Mastersizer 3000), a HELOS particle size analyzer, or a LS-909 laser particle size analyzer.

[0055] In some embodiments, the edonentan is present in the biodegradable ocular implant in its free base form. In some embodiments, the edonentan is present in the biodegradable ocular implant in its free base form as a crystalline solid. In some embodiments, the crystalline solid is a crystalline form described herein. In some embodiments, the edonentan is present in the biodegradable ocular implant in its free base form as a crystalline anhydrate. In some embodiments, the edonentan is present in the biodegradable ocular implant as edonentan anhydrous crystalline Form 4.

Biodegradable Polymers

[0056] Suitable polymeric materials or compositions for use in the biodegradable ocular implants described herein include those materials which are compatible, that is biocompatible, with the eye so as to cause no substantial interference with the functioning or

physiology of the eye. Such polymeric materials may be biodegradable, bioerodible or both biodegradable and bioerodible.

[0057] The term "biodegrade" or "biodegradable" as used herein generally refers to a biologically assisted degradation process that the polymer making-up the implant undergoes in a biological environment, such as within the body of a subject. It would be appreciated that biodegradation encompasses within its scope the processes of absorption, dissolution, breaking down, degradation, assimilation, or otherwise removal of the implant from the body, a biological environment.

[0058] The term "polymer" as used herein encompasses both homopolymers (polymers having only one type of repeating unit) and copolymers (a polymer having more than one type of repeating unit).

[0059] The term "biodegradable polymer" as used herein refers to a polymer or polymers, which degrade *in vivo*, under physiological conditions. The release of the therapeutic agent occurs concurrent with, or subsequent to, the degradation of a biodegradable polymer over time.

[0060] In preferable embodiments, the biodegradable polymer is a PLGA (poly(lactic-co-glycolic acid)). PLGA polymers are known to degrade via backbone hydrolysis (bulk erosion) and the final degradation products are lactic and glycolic acids, which are non-toxic and considered natural metabolic compounds. Lactic and glycolic acids are eliminated safely via the Krebs cycle by conversion to carbon dioxide and water.

[0061] PLGA is synthesized through random ring-opening co-polymerization of the cyclic dimers of glycolic acid and lactic acid. Successive monomeric units of glycolic or lactic acid are linked together by ester linkages. The ratio of lactide to glycolide can be varied, altering the biodegradation characteristics of the product. By altering the ratio, it is possible to tailor the polymer degradation time. Importantly, drug release characteristics are affected by the rate of biodegradation, molecular weight, and degree of crystallinity in drug delivery systems. By altering and customizing the biodegradable polymer matrix, the drug delivery profile can be changed.

[0062] PLGA is cleaved predominantly by non-enzymatic hydrolysis of its ester linkages throughout the polymer matrix, in the presence of water in the surrounding tissues. PLGA polymers are biocompatible, because they undergo hydrolysis in the body to produce the original monomers, lactic acid and/or glycolic acid. Lactic and glycolic acids are nontoxic and eliminated safely via the Krebs cycle by conversion to carbon dioxide and water. The biocompatibility of PLGA polymers have been further examined in both non-ocular and

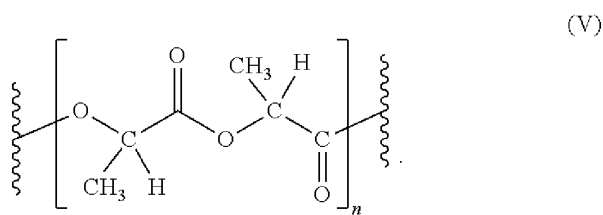
ocular tissues of animals and humans. The findings indicate that the polymers are well tolerated.

[0063] Examples of PLGA polymers, which may be utilized in an embodiment of the disclosure, include the RESOMER® Product line from Evonik Industries and VIATEL™ Product line from Ashland Inc. identified as, but are not limited to, RG502, RG502H, RG503, RG503H, RG504, RG504H, RG505, RG653H, RG750S, RG752H, RG752S, RG753H, RG753S, RG755S, RG756S, RG757S, RG858S, DLG 5003E, DLG 5002E, and DLG 7505E.

[0064] Such PLGA polymers include both acid and ester terminated polymers with inherent viscosities ranging from approximately 0.14 to approximately 1.7 dL/g when measured at 0.1% w/v in CHCl₃ at 25 °C. with an Ubbelohde size 0c glass capillary viscometer. Example polymers used in various embodiments of the disclosure may include variation in the mole ratio of D,L-lactide to glycolide from approximately 50:50 to approximately 85:15, including, but not limited to, 50:50, 65:35, 75:25, and 85:15.

[0065] Other examples of PLGA polymers which may be utilized in an embodiment of the disclosure include those produced by Lakeshore Biomaterials identified as, but are not limited to, DLG 1A, DLG 3 A, or DLG 4A. Such DLG polymers include both acid (A) and ester (E) terminated polymers with inherent viscosities ranging from approximately 0.05 to approximately 1.0 dL/g when measured at 0.1% w/v in CHCl₃ at 25° C. with an Ubbelohde size 0c glass capillary viscometer. Example polymers used in various embodiments of the disclosure may include variation in the mole ratio of D,L-lactide to glycolide from approximately 1:99 to approximately 99:1, including, but not limited to, 50:50, 65:35, 75:25, and 85:15.

[0066] RESOMERS® and/or viatel™ identified by an “RG” or “DLG” in the product name, such as RG752S, is a poly(D,L-lactide-co-glycolide) or PLGA having the general structure (V):



[0067] The synthesis of various molecular weights of DLG with various D,L-lactide-glycolide ratios is possible. In one embodiment, DLG, such as 1A, with an inherent viscosity of approximately 0.05 to approximately 0.15 dL/g can be used. In another embodiment,

DLG, such as 2A, with an inherent viscosity of approximately 0.15 to approximately 0.25 dL/g can be used.

[0068] Poly(D,L-lactide-co-glycolide) or PLGA copolymers can be synthesized at different ratios of lactide to glycolide, such as a lactide: glycolide ratio of 75:25. These copolymers can be an ester-terminated PLGA copolymer, as identified by the terminal “S” in the product name, or an acid-terminated PLGA copolymer, as identified by the terminal “H” in the product name.

[0069] “RG502” as used herein as used herein refers to a poly(D,L-lactide-co-glycolide) developed by Evonik (RESOMER®) having a lactide to glycolide ratio of about 50:50 and having a molecular weight (M_w) of about 7000 to about 17000.

[0070] “RG503” as used herein as used herein refers to a poly(D,L-lactide-co-glycolide) developed by Evonik (RESOMER®) having a lactide to glycolide ratio of about 50:50 and having a M_w of about 24000 to about 38000.

[0071] “RG753S” as used herein as used herein refers to a poly(D,L-lactide-co-glycolide) developed by Evonik (RESOMER®) having a lactide to glycolide ratio of about 75:25.

[0072] “DLG 5002E” as used herein as used herein refers to a poly(D,L-lactide-co-glycolide) developed by Ashland (viatel™) having a lactide to glycolide ratio of about 50:50 and an inherent viscosity (dl/g) of about 0.10 – 0.30.

[0073] “DLG 5003E” as used herein as used herein refers to a poly(D,L-lactide-co-glycolide) developed by Ashland (viatel™) having a lactide to glycolide ratio of about about 50:50 and an inherent viscosity (dl/g) of about 0.20 – 0.40.

[0074] “DLG 7505E” as used herein as used herein refers to a poly(D,L-lactide-co-glycolide) developed by Ashland (viatel™) having a lactide to glycolide ratio of about 75:25 and an inherent viscosity (dl/g) of about 0.40 – 0.60.

[0075] In some embodiments, a biodegradable ocular implant described herein comprises about 40% w/w to about 80% w/w (e.g., about 40% w/w, about 45% w/w, about 50% w/w, about 55% w/w, about 60% w/w, about 65% w/w, about 70% w/w, about 75% w/w, or about 80% w/w) of the biodegradable polymer. In some embodiments, a biodegradable ocular implant described herein comprises about 45% w/w to about 65% w/w (e.g., about 45% w/w, about 50% w/w, about 55% w/w, about 60% w/w, or about 65% w/w) of the biodegradable polymer. In some embodiments, a biodegradable ocular implant described herein comprises about 50% w/w to about 60% w/w (e.g., about 50% w/w, about 51% w/w, about 52% w/w, about 53% w/w, about 54% w/w, about 55% w/w, about 56% w/w, about 57% w/w, about 58% w/w, about 59% w/w, or about 60% w/w) of the biodegradable polymer. In some

embodiments, a biodegradable ocular implant described herein comprises about 55% w/w of the biodegradable polymer.

[0076] In some embodiments, the biodegradable polymer comprises one or more PLGA polymers. In some embodiments, the biodegradable polymer comprises two or more PLGA polymers. In some embodiments, the biodegradable polymer comprises three or more PLGA polymers.

[0077] In some embodiments, the one or more PLGA polymers is selected from the group consisting of RG502, RG503, RG753S, DLG5002E, DLG5003E, DLG7505E, and combinations thereof. In some embodiments, the two or more PLGA polymers is selected from the group consisting of RG502, RG503, RG753S, DLG5002E, DLG5003E, DLG7505E, and combinations thereof. In some embodiments, the three or more PLGA polymers is selected from the group consisting of RG502, RG503, RG753S, DLG5002E, DLG5003E, DLG7505E, and combinations thereof.

[0078] In some embodiments, the biodegradable polymer comprises PLGA RG503 and PLGA RG753S. In some embodiments, a biodegradable ocular implant described herein comprises about 16.5% w/w of PLGA RG503 and about 38.5% w/w of PLGA RG753S.

[0079] In some embodiments, the biodegradable polymer comprises PLGA RG502, PLGA RG503, and PLGA RG753S. In some embodiments, a biodegradable ocular implant described herein comprises about 5.5% w/w of PLGA RG502, about 27.5% w/w of PLGA RG503, and about 22% w/w of PLGA RG753S.

[0080] In some embodiments, the biodegradable polymer comprises PLGA DLG5002E, PLGA DLG5003E, and PLGA DLG7505E. In some embodiments, a biodegradable ocular implant described herein comprises about 5.5% w/w of PLGA DLG5002E, about 27.5% w/w of PLGA DLG5003E, and about 22% w/w of PLGA DLG7505E.

[0081] In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises about 0.2% w/w to about 2.5% w/w (e.g., about 0.2% w/w, about 0.3% w/w, about 0.4% w/w, about 0.5% w/w, about 0.6% w/w, about 0.7% w/w, about 0.8% w/w, about 0.9% w/w, about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, or about 2.5% w/w) of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises about 0.2% w/w to about 2.2% w/w. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises about 1.3% w/w

to about 2.2% w/w. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises about 0.2% w/w to about 0.4% w/w.

[0082] In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 2.5% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 2.4% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 2.3% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 2.2% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 2.1% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 2% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 1.5% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 1.4% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 1.3% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 1.2% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 1.1% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 0.5% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 0.4% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 0.35% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 0.3% w/w of residual monomer. In some embodiments, each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 0.25% w/w of residual monomer.

[0083] In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 1 month to about 12 months (e.g., about 1 month to about 11 months, about 1 month to about 10 months, about 1 month to about 9 months, about 1 month to about 8 months, about 1 month to about 7 months, about 1 month to about 6 months, about 1 month to about 5 months, about 1 month to about 4 months, about 1 month to about 3 months, and about 1 month to about 2 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 1, about 2, about 3, about 4, about 5, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months or about 12 months. In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 1 month. In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 2 months. In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 3 months. In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 4 months. In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 5 months. In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 6 months.

Biodegradable Ocular Implant

[0084] A biodegradable ocular implant described herein generally comprises edonentan, or a pharmaceutically acceptable salt thereof and a biodegradable polymer. In preferable embodiments, the compound is a compound of Formula I.

[0085] In one aspect, provided herein is a biodegradable ocular implant comprising:

- (i) edonentan, or a pharmaceutically acceptable salt thereof; and
- (ii) a biodegradable polymer,

wherein the edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 10 μm to about 250 μm .

[0086] In another aspect, provided herein is a biodegradable ocular implant comprising:

- (i) edonentan, or a pharmaceutically acceptable salt thereof; and
- (ii) one or more poly(lactic-co-glycolic acid) (PLGA) polymers,

wherein each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 0.5% w/w of residual monomer.

[0087] In various embodiments, the biodegradable ocular implant has a diameter of about 200 μm to about 500 μm (e.g., about 200 μm , about 225 μm , about 250 μm , about 275 μm , about 300 μm , about 325 μm , about 350 μm , about 375 μm , about 400 μm , about 425 μm ,

about 450 μm , about 475 μm , and about 500 μm). In various embodiments, the biodegradable ocular implant has a diameter of about 300 μm to about 400 μm (e.g., about 300 μm , about 305 μm , about 310 μm , about 315 μm , about 320 μm , about 325 μm , about 330 μm , about 335 μm , about 340 μm , about 345 μm , about 350 μm , about 355 μm , about 360 μm , about 365 μm , about 370 μm , about 375 μm , 380 μm , 385 μm , 390 μm , 395 μm , and 400 μm). In various embodiments, the biodegradable ocular implant has a diameter of about 300 μm to about 360 μm . In certain embodiments, the biodegradable ocular implant has a diameter of about 310 μm , about 321 μm , about 325 μm , about 330 μm , about 345 μm , or about 356 μm .

[0088] In various embodiments, the implant has a length of about 3 mm to about 6 mm (e.g., 3 mm, 3.1 mm, 3.2 mm, 3.3 mm, 3.4 mm, 3.5 mm, 3.6 mm, 3.7 mm, 3.8 mm, 3.9 mm, 4.0 mm, 4.1 mm, 4.2 mm, 4.3 mm, 4.4 mm, 4.5 mm, 4.6 mm, 4.7 mm, 4.8 mm, 4.9 mm, 5 mm, 5.1 mm, 5.2 mm, 5.3 mm, 5.4 mm, 5.5 mm, 5.6 mm, 5.7 mm, 5.8 mm, 5.9 mm, 6.0 mm). In various embodiments, the implant has a length of about 4 mm to about 5 mm (e.g., about 4.1 mm, about 4.2 mm, about 4.3 mm, about 4.4 mm, about 4.5 mm, about 4.6 mm, about 4.7 mm, about 4.8 mm, about 4.9 mm, and about 5 mm). In certain embodiments, the implant has a length of about 4 mm.

[0089] In various embodiments, the implant has a total weight of about 300 μg to about 600 μg (e.g., about 300 μg , about 325 μg , about 350 μg , about 375 μg , about 400 μg , about 425 μg , about 450 μg , about 475 μg , about 500 μg , about 525 μg , about 550 μg , about 575 μg , and 600 μg). In various embodiments, the implant has a total weight of about 400 μg to about 600 μg (e.g., about 400 μg , about 405 μg , about 410 μg , about 415 μg , about 420 μg , about 425 μg , about 430 μg , about 435 μg , about 440 μg , about 445 μg , about 450 μg , about 455 μg , about 460 μg , about 465 μg , about 470 μg , about 475 μg , about 480 μg , about 485 μg , about 490 μg , about 495 μg , about 500 μg , about 505 μg , about 510 μg , about 515 μg , about 520 μg , about 525 μg , about 530 μg , about 535 μg , about 540 μg , about 545 μg , about 550 μg , about 555 μg , about 560 μg , about 565 μg , about 570 μg , about 575 μg , about 580 μg , about 585 μg , about 590 μg , about 595 μg , and about 600 μg). In certain embodiments, the implant has a total weight of about 415 μg , about 440 μg , about 501 μg , about 523 μg , about 526 μg , or about 529 μg .

[0090] The rate of therapeutic agent (e.g., edonentan) release from an intravitreal implant or particle suspension (for example, a biodegradable ocular implant of the present disclosure) may depend on several factors, including but not limited to the surface area of the implant,

therapeutic agent content, and water solubility of the therapeutic agent, and speed of polymer degradation.

[0091] In some embodiments, about 5% to about 40% (e.g., about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, or about 40%) of the edonentan is released from the biodegradable ocular implant after being incubated in 3 mL of phosphate-buffered saline (PBS) at pH 7.4 with 0.1% Tween in a shaking incubator set at 39 °C and 50 rpm for 28 days. In some embodiments, about 40% or less of the edonentan is released from the biodegradable ocular implant after being incubated in 3 mL of phosphate-buffered saline (PBS) at pH 7.4 with 0.1% Tween in a shaking incubator set at 39 °C and 50 rpm for 28 days.

[0092] In some embodiments, about 20% to about 60% (e.g., about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%) of the edonentan is released from the biodegradable ocular implant after being incubated in 3 mL of phosphate-buffered saline (PBS) at pH 7.4 with 0.1% Tween in a shaking incubator set at 39 °C and 50 rpm for 42 days. In some embodiments, about 60% or less of the edonentan is released from the biodegradable ocular implant after being incubated in 3 mL of phosphate-buffered saline (PBS) at pH 7.4 with 0.1% Tween in a shaking incubator set at 39 °C and 50 rpm for 42 days.

[0093] In some embodiments, about 35% to about 80% (e.g., about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, or about 80%) of the edonentan is released from the biodegradable ocular implant after being incubated in 3 mL of phosphate-buffered saline (PBS) at pH 7.4 with 0.1% Tween in a shaking incubator set at 39 °C and 50 rpm for 70 days. In some embodiments, about 80% or less of the edonentan is released from the biodegradable ocular implant after being incubated in 3 mL of phosphate-buffered saline (PBS) at pH 7.4 with 0.1% Tween in a shaking incubator set at 39 °C and 50 rpm for 70 days.

[0094] In various embodiments, the implant is administered as an intravitreal administration. An intravitreal administration refers to drug administration into the vitreous humor of the eye. In some embodiments, the implant is administered locally to the back of the eye. In some embodiments, the implant is injected into the intravitreal space using a needle and applicator.

[0095] In some embodiments, the biodegradable ocular implant is a sterile biodegradable ocular implant. As used herein, "sterile" refers to the composition meeting the requirements of sterility enforced by medicine regulatory authorities, such as the MCA in the UK or the FDA in the US. Tests are included in current versions of the compendia, such as the British Pharmacopoeia and the US Pharmacopoeia. In some embodiments, the biodegradable ocular

implant is a substantially pure biodegradable ocular implant. In some embodiments, the biodegradable ocular implant is a medical-grade biodegradable ocular implant. In some embodiments, the biodegradable ocular implant is administered into the intravitreal space every 3 to 12 months.

Method of Making

[0096] Provided herein are methods for preparing a biodegradable ocular implant described herein. The methods generally comprise hot melt extruding a blend of edonentan, or a pharmaceutically acceptable salt thereof, and a biodegradable polymer to form the biodegradable ocular implant.

[0097] In one aspect, provided herein is a method of preparing a biodegradable ocular implant comprising edonentan, or a pharmaceutically acceptable salt thereof, and a biodegradable polymer, the method comprising;

- (a) milling the biodegradable polymer;
- (b) reducing the particle size of the edonentan, or a pharmaceutically acceptable salt thereof, to form a processed edonentan, or a pharmaceutically acceptable salt thereof;
- (c) mixing the milled biodegradable polymer and the processed edonentan, or a pharmaceutically acceptable salt thereof, to form a blend;
- (d) hot melt extruding the blend to form the biodegradable ocular implant.

[0098] In some embodiments, in step (a), the biodegradable polymer is cryomilled.

[0099] In some embodiments, in step (a), the biodegradable polymer comprises one or more PLGA polymers. In some embodiments, the one or more PLGA polymers is selected from the group consisting of RG502, RG503, RG753S, DLG5002E, DLG5003E, DLG7505E, and combinations thereof.

[00100] In some embodiments, in step (a), the biodegradable polymer comprises PLGA RG503 and PLGA RG753S. In some embodiments, in step (a), the biodegradable polymer comprises about 30% w/w of PLGA RG503 and about 70% w/w of PLGA RG753S.

[00101] In some embodiments, in step (a), the biodegradable polymer comprises PLGA RG502, PLGA RG503, and PLGA RG753S. In some embodiments, in step (a), the biodegradable polymer comprises about 10% w/w of PLGA RG502, about 50% w/w of PLGA RG503, and about 40% w/w of PLGA RG753S.

[00102] In some embodiments, in step (a), the biodegradable polymer comprises PLGA DLG5002E, PLGA DLG5003E, and PLGA DLG7505E. In some embodiments, in step (a), the biodegradable polymer comprises about 10% w/w of PLGA DLG5002E, about 50% w/w of PLGA DLG5003E, and about 40% w/w of PLGA DLG7505E.

[00103] In some embodiments, in step (b), reducing the particle size of the edonentan, or a pharmaceutically acceptable salt thereof, comprises passing the edonentan, or a pharmaceutically acceptable salt thereof, through a 100-mesh screen. In some embodiments, in step (b), reducing the particle size of the edonentan, or a pharmaceutically acceptable salt

thereof, comprises milling the edonentan, or a pharmaceutically acceptable salt thereof. In some embodiments, in step (b), reducing the particle size of the edonentan, or a pharmaceutically acceptable salt thereof, comprises micronizing the edonentan, or a pharmaceutically acceptable salt thereof.

[00104] In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 10 μm to about 250 μm .

[00105] In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 9 μm to about 250 μm (e.g., about 9 μm , about 10 μm , about 20 μm , about 30 μm , about 40 μm , about 50 μm , about 60 μm , about 70 μm , about 80 μm , about 90 μm , about 100 μm , about 110 μm , about 120 μm , about 130 μm , about 140 μm , about 150 μm , about 160 μm , about 170 μm , about 180 μm , about 190 μm , about 200 μm , about 210 μm , about 220 μm , about 230 μm , about 240 μm , or about 250 μm). In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 9 μm to about 125 μm (e.g., about 9 μm , about 10 μm , about 15 μm , about 20 μm , about 25 μm , about 30 μm , about 35 μm , about 40 μm , about 45 μm , about 50 μm , about 55 μm , about 60 μm , about 65 μm , about 70 μm , about 75 μm , about 80 μm , about 85 μm , about 90 μm , about 95 μm , about 100 μm , about 105 μm , about 110 μm , about 115 μm , about 120 μm , or about 125 μm). In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 9 μm to about 15 μm (e.g., about 9 μm , about 9.25 μm , about 9.5 μm , about 9.75 μm , about 10 μm , about 10.25 μm , about 10.5 μm , about 10.75 μm , about 11 μm , about 11.25 μm , about 11.5 μm , about 11.75 μm , about 12 μm , about 12.25 μm , about 12.5 μm , about 12.75 μm , about 13 μm , about 13.25 μm , about 13.5 μm , about 13.75 μm , about 14 μm , about 14.25 μm , about 14.5 μm , about 14.75 μm , or about 15 μm).

[00106] In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D50 of about 2.5 μm to about 150 μm (e.g., about 2.5 μm , about 10 μm , about 20 μm , about 30 μm , about 40 μm , about 50 μm , about 60 μm , about 70 μm , about 80 μm , about 90 μm , about 100 μm , about 110 μm , about 120 μm , about 130 μm , about 140 μm , or about 150 μm). In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D50 of about 2.5 μm to about 40

μm (e.g., about 2.5 μm, about 5 μm, about 7.5 μm, about 10 μm, about 12.5 μm, about 15 μm, about 17.5 μm, about 20 μm, about 22.5 μm, about 25 μm, about 27.5 μm, about 30 μm, about 32.5 μm, about 35 μm, about 37.5 μm, or about 40 μm). In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D50 of about 2.5 μm to about 6 μm (e.g., about 2.5 μm, about 2.75 μm, about 3 μm, about 3.25 μm, about 3.5 μm, about 3.75 μm, about 4 μm, about 4.25 μm, about 4.5 μm, about 4.75 μm, about 5 μm, about 5.25 μm, about 5.5 μm, about 5.75 μm, or about 6 μm).

[00107] In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of about 0.5 μm to about 90 μm (e.g., about 0.5 μm, about 5 μm, about 10 μm, about 15 μm, about 20 μm, about 25 μm, about 30 μm, about 35 μm, about 40 μm, about 45 μm, about 50 μm, about 55 μm, about 60 μm, about 65 μm, about 70 μm, about 75 μm, about 80 μm, about 85 μm, or about 90 μm). In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of about 0.5 μm to about 10 μm (e.g., about 0.5 μm, about 1 μm, about 1.5 μm, about 2 μm, about 2.5 μm, about 3 μm, about 3.5 μm, about 4 μm, about 4.5 μm, about 5 μm, about 5.5 μm, about 6 μm, about 6.5 μm, about 7 μm, about 7.5 μm, about 8 μm, about 8.5 μm, about 9 μm, about 9.5 μm, or about 10 μm). In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of about 0.5 μm to about 2 μm (e.g., about 0.5 μm, about 0.6 μm, about 0.7 μm, about 0.8 μm, about 0.9 μm, about 1 μm, about 1.1 μm, about 1.2 μm, about 1.3 μm, about 1.4 μm, about 1.5 μm, about 1.6 μm, about 1.7 μm, about 1.8 μm, about 1.9 μm, or about 2 μm).

[00108] In certain embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by one or more of the following: (i) a D10 of about 0.5 μm to about 90 μm; (ii) a D50 of about 2.5 μm to about 150 μm; and (iii) a D90 of about 9 μm to about 250 μm. In certain embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by one or more of the following: (i) a D10 of about 0.5 μm to about 10 μm; (ii) a D50 of about 2.5 μm to about 40 μm; and (iii) a D90 of about 9 μm to about 125 μm. In certain embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by one or more of the

following: (i) a D10 of about 0.5 μm to about 2 μm ; (ii) a D50 of about 2.5 μm to about 6 μm ; and (iii) a D90 of about 9 μm to about 15 μm .

[00109] In certain embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of about 0.5 μm to about 90 μm , a D50 of about 2.5 μm to about 150 μm , and a D90 of about 9 μm to about 250 μm . In certain embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of about 0.5 μm to about 10 μm , a D50 of about 2.5 μm to about 40 μm , and a D90 of about 9 μm to about 125 μm . In certain embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of about 0.5 μm to about 2 μm , a D50 of about 2.5 μm to about 6 μm , and a D90 of about 9 μm to about 15 μm .

[00110] In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of less than about 250 μm (e.g., about 9 μm , about 10 μm , about 20 μm , about 30 μm , about 40 μm , about 50 μm , about 60 μm , about 70 μm , about 80 μm , about 90 μm , about 100 μm , about 110 μm , about 120 μm , about 130 μm , about 140 μm , about 150 μm , about 160 μm , about 170 μm , about 180 μm , about 190 μm , about 200 μm , about 210 μm , about 220 μm , about 230 μm , or about 240 μm). In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of less than about 125 μm (e.g., about 9 μm , about 10 μm , about 15 μm , about 20 μm , about 25 μm , about 30 μm , about 35 μm , about 40 μm , about 45 μm , about 50 μm , about 55 μm , about 60 μm , about 65 μm , about 70 μm , about 75 μm , about 80 μm , about 85 μm , about 90 μm , about 95 μm , about 100 μm , about 105 μm , about 110 μm , about 115 μm , or about 120 μm). In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of less than about 15 μm (e.g., about 9 μm , about 9.25 μm , about 9.5 μm , about 9.75 μm , about 10 μm , about 10.25 μm , about 10.5 μm , about 10.75 μm , about 11 μm , about 11.25 μm , about 11.5 μm , about 11.75 μm , about 12 μm , about 12.25 μm , about 12.5 μm , about 12.75 μm , about 13 μm , about 13.25 μm , about 13.5 μm , about 13.75 μm , about 14 μm , about 14.25 μm , about 14.5 μm , or about 14.75 μm).

[00111] In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D50 of less than about 150 μm (e.g., about 2.5 μm , about 10 μm , about 20 μm , about 30 μm , about 40 μm ,

about 50 μm , about 60 μm , about 70 μm , about 80 μm , about 90 μm , about 100 μm , about 110 μm , about 120 μm , about 130 μm , or about 140 μm). in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D50 of less than about 40 μm (e.g., about 2.5 μm , about 5 μm , about 7.5 μm , about 10 μm , about 12.5 μm , about 15 μm , about 17.5 μm , about 20 μm , about 22.5 μm , about 25 μm , about 27.5 μm , about 30 μm , about 32.5 μm , about 35 μm , or about 37.5 μm). In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D50 of less than about 6 μm (e.g., about 2.5 μm , about 2.75 μm , about 3 μm , about 3.25 μm , about 3.5 μm , about 3.75 μm , about 4 μm , about 4.25 μm , about 4.5 μm , about 4.75 μm , about 5 μm , about 5.25 μm , about 5.5 μm , or about 5.75 μm).

[00112] In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of less than about 90 μm (e.g., about 0.5 μm , about 5 μm , about 10 μm , about 15 μm , about 20 μm , about 25 μm , about 30 μm , about 35 μm , about 40 μm , about 45 μm , about 50 μm , about 55 μm , about 60 μm , about 65 μm , about 70 μm , about 75 μm , about 80 μm , or about 85 μm). In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of less than about 10 μm (e.g., about 0.5 μm , about 1 μm , about 1.5 μm , about 2 μm , about 2.5 μm , about 3 μm , about 3.5 μm , about 4 μm , about 4.5 μm , about 5 μm , about 5.5 μm , about 6 μm , about 6.5 μm , about 7 μm , about 7.5 μm , about 8 μm , about 8.5 μm , about 9 μm , or about 9.5 μm). In some embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of less than about 2 μm (e.g., about 0.5 μm , about 0.6 μm , about 0.7 μm , about 0.8 μm , about 0.9 μm , about 1 μm , about 1.1 μm , about 1.2 μm , about 1.3 μm , about 1.4 μm , about 1.5 μm , about 1.6 μm , about 1.7 μm , about 1.8 μm , or about 1.9 μm).

[00113] In certain embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by one or more of the following: (i) a D10 of less than about 90 μm ; (ii) a D50 of less than about 150 μm ; and (iii) a D90 of less than about 250 μm . In certain embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by one or more of the following: (i) a D10 of less than about 10 μm ; (ii) a D50 of less than about 40 μm ; and (iii) a D90 of less than about 125 μm . In certain embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a

particle size distribution characterized by one or more of the following: (i) a D10 of less than about 2 μm ; (ii) a D50 of less than about 6 μm ; and (iii) a D90 of less than about 15 μm .

[00114] In certain embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of less than about 90 μm , a D50 of less than about 150 μm , and a D90 of less than about 250 μm . In certain embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of less than about 10 μm , a D50 of less than about 40 μm , and a D90 of less than about 125 μm . In certain embodiments, in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of less than about 2 μm , a D50 of less than about 6 μm , and a D90 of less than about 15 μm .

[00115] In some embodiments, in step (b), the particle size distributions described herein are measured using a laser diffraction technique. In some embodiments, in step (b), the instrument used to measure the particle size distributions described herein is a Malvern Mastersizer (e.g., a Mastersizer 3000), a HELOS particle size analyzer, or a LS-909 laser particle size analyzer.

[00116] In some embodiments, in step (b), the edonentan, before and after milling, is present in its free base form as a crystalline anhydrate. In some embodiments, in step (b), the edonentan, before and after milling, is present in its free base form as an anhydrous crystalline form described herein. In some embodiments, in step (b), the edonentan, before and after milling, is present in its free base form as an anhydrous crystalline Form 4.

[00117] In some embodiments, in step (d), hot melting extruding the blend comprises:

- (i) hot melt extruding the blend at a temperature of about 95 $^{\circ}\text{C}$ to form a first extrudate;
- (ii) hot melt extruding the first extrudate at a temperature of about 100 $^{\circ}\text{C}$ to about 120 $^{\circ}\text{C}$ to an extruded filament; and
- (iii) cutting the extruded filament to form the biodegradable ocular implant.

[00118] In some embodiments, in step (i), hot melt extruding the blend is performed using a Thermo Haake Conical Twin Screw Extruder with a 1.96 mm die. In certain embodiments, in step (i), hot melt extruding the blend is performed using a screw speed of about 10 rpm.

[00119] In some embodiments, in step (ii), hot melt extruding the first extrudate is performed using a Thermo Haake Conical Twin Screw Extruder with a 0.31 mm – 0.33 mm die. In certain embodiments, in step (i), hot melt extruding the blend is performed using a screw speed of about 4 to about 10 rpm.

[00120] In some embodiments, in step (d), hot melting extruding the blend comprises:

(i) hot melt extruding the blend at a temperature of about 85 °C to about 90 °C form a first extrudate;

(ii) hot melt extruding the first extrudate at a temperature of about 88 °C to about 90 °C form a second extrudate;

(iii) hot melt extruding the second extrudate at a temperature of about 71 °C to about 74 °C form an extruded filament; and

(iv) cutting the extruded filament to form the biodegradable ocular implant.

[00121] In some embodiments, in step (i), hot melt extruding the blend is performed using a Thermo Haake Conical Twin Screw Extruder with a 3 mm die.

[00122] In some embodiments, in step (ii), hot melt extruding the first extrudate is performed using a Thermo Haake Conical Twin Screw Extruder with a 1.54 mm die.

[00123] In some embodiments, in step (iii), hot melt extruding the second extrudate is performed using a Barrell custom ram extruder with a 0.325 mm die.

Crystalline Forms of Edonentan

[00124] In one aspect, the biodegradable ocular implants described herein comprise one or more solid forms of edonentan, or a pharmaceutically acceptable salt thereof.

[00125] In another aspect, the biodegradable ocular implants described herein comprise one or more solid forms of edonentan.

[00126] In certain embodiments, the solid form of edonentan is an anhydrous crystalline form (Form 4), having an X-ray powder diffraction (XRPD) pattern comprising at least three characterization peaks, in terms of 2θ , selected from peaks at $5.6\pm0.2^\circ$, $11.4\pm0.2^\circ$, $17.7\pm0.2^\circ$, $19.3\pm0.2^\circ$, $21.1\pm0.2^\circ$, and $21.9\pm0.2^\circ$.

[00127] In some embodiments of the solid form, the anhydrous crystalline Form 4 has the following XRPD pattern expressed in terms of diffraction angles (2θ): $5.6\pm0.2^\circ$, $11.4\pm0.2^\circ$, $17.7\pm0.2^\circ$, $19.3\pm0.2^\circ$, and $21.9\pm0.2^\circ$. In some embodiments of the solid form, the anhydrous crystalline Form 4 has the following XRPD pattern expressed in terms of diffraction angles (2θ): $11.4\pm0.2^\circ$, $17.7\pm0.2^\circ$, and $19.3\pm0.2^\circ$.

[00128] In some embodiments of the solid form, the anhydrous crystalline Form 4 is characterized by an XRPD pattern comprising one or more diffraction angles (2θ) selected from: $5.6\pm0.2^\circ$, $11.4\pm0.2^\circ$, $17.7\pm0.2^\circ$, $19.3\pm0.2^\circ$, and $21.9\pm0.2^\circ$. In some embodiments of the solid form, the anhydrous crystalline Form 4 is characterized by an XRPD pattern comprising one or more diffraction angles (2θ) selected from: $11.4\pm0.2^\circ$, $17.7\pm0.2^\circ$, and $19.3\pm0.2^\circ$.

[00129] In some embodiments of the solid form, the anhydrous crystalline Form 4 shows a temperature of melting (T_m) of about 163 °C, as determined by differential scanning calorimetry (DSC) analysis.

[00130] In some embodiments of the solid form, the anhydrous crystalline Form 4 is characterized by an XRPD pattern comprising one or more diffraction angles (2θ) selected from: $5.6\pm0.2^\circ$, $11.4\pm0.2^\circ$, $17.7\pm0.2^\circ$, $19.3\pm0.2^\circ$, and $21.9\pm0.2^\circ$; and a T_m of about 163 °C, as determined by DSC analysis. In some embodiments of the solid form, the anhydrous crystalline Form 4 is characterized by an XRPD pattern comprising one or more diffraction angles (2θ) selected from: $11.4\pm0.2^\circ$, $17.7\pm0.2^\circ$, and $19.3\pm0.2^\circ$; and a T_m of about 163 °C, as determined by DSC analysis.

[00131] In some embodiments, the edonentan comprises at least about 90% by weight of anhydrous crystalline Form 4, based on the total weight of edonentan present in the biodegradable ocular implant. In some embodiments, the edonentan comprises at least about 95% by weight of anhydrous crystalline Form 4, based on the total weight of edonentan present in the biodegradable ocular implant. In some embodiments, the edonentan comprises at least about 96% by weight of anhydrous crystalline Form 4, based on the total weight of edonentan present in the biodegradable ocular implant. In some embodiments, the edonentan comprises at least about 97% by weight of anhydrous crystalline Form 4, based on the total weight of edonentan present in the biodegradable ocular implant. In some embodiments, the edonentan comprises at least about 98% by weight of anhydrous crystalline Form 4, based on the total weight of edonentan present in the biodegradable ocular implant. In some embodiments, the edonentan comprises at least about 99% by weight of anhydrous crystalline Form 4, based on the total weight of edonentan present in the biodegradable ocular implant.

[00132] In some embodiments, the solid form of edonentan is an anhydrous crystalline form (Form 1), wherein the anhydrous crystalline Form 1 has an XRPD pattern comprising at least three diffraction peaks, in terms of 2θ , selected from peaks at $6.3\pm0.2^\circ$, $7.5\pm0.2^\circ$, $11.7\pm0.2^\circ$, $15.1\pm0.2^\circ$, and $17.3\pm0.2^\circ$; and the edonentan comprises at least about 90% by weight of the anhydrous crystalline Form 1, based on the total weight of edonentan present in the biodegradable ocular implant.

[00133] In some embodiments, the solid form of edonentan is a monohydrate crystalline form (Form 2), wherein the monohydrate crystalline Form 2 has an XRPD pattern comprising at least three diffraction peaks, in terms of 2θ , selected from peaks at $9.6\pm0.2^\circ$, $10.4\pm0.2^\circ$, $19.6\pm0.2^\circ$, $19.7\pm0.2^\circ$, $22.0\pm0.2^\circ$, $22.9\pm0.2^\circ$, and $23.7\pm0.2^\circ$; and the edonentan comprises at

least about 90% by weight of the monohydrate crystalline Form 2, based on the total weight of edonentan present in the biodegradable ocular implant.

[00134] In certain embodiments, the solid form of edonentan is an anhydrous crystalline (Form 3), wherein the anhydrous crystalline Form 3 has an XRPD pattern comprising at least three diffraction peaks, in terms of 2θ , selected from peaks at $7.8\pm 0.2^\circ$, $9.0\pm 0.2^\circ$, $11.6\pm 0.2^\circ$, $15.8\pm 0.2^\circ$, and $19.1\pm 0.2^\circ$; and the edonentan comprises at least about 90% by weight of the anhydrous crystalline Form 3, based on the total weight of edonentan present in the biodegradable ocular implant.

[00135] In some embodiments, the solid form of edonentan is an amorphous solid form. As used herein, the term “amorphous” refers to a solid material having no long-range order in the position of its molecules. Amorphous solids are generally supercooled liquids in which the molecules are arranged in a random manner so that there is no well-defined arrangement, e.g., molecular packing, and no long-range order. Amorphous solids are generally isotropic, i.e., exhibit similar properties in all directions and do not have definite melting points. For example, an amorphous material is a solid material having no sharp characteristic crystalline peak(s) in its XRPD pattern (i.e., is not crystalline as determined by XRPD). Instead, one or several broad peaks (e.g., halos) appear in its XRPD pattern.

Ocular Diseases

[00136] The methods of the present disclosure generally comprise the use of a biodegradable ocular implant comprising edonentan described herein for the treatment and amelioration of an ocular disease selected from glaucoma, diabetic retinopathy (DR), retinal vein occlusion (RVO), retinopathy of prematurity (ROP), geographic atrophy (GA), and age-related macular degeneration (AMD), which are described below.

Glaucoma

[00137] In the treatment of glaucoma using a biodegradable ocular implant comprising edonentan described herein, a “therapeutically effective amount” can be determined by assessing an improvement in retinal blood flow (RBF) over what could be achieved by the standard of care (lowering of intra-ocular pressure (IOP)). For a glaucoma indication, the improvement in blood flow in the healthy rabbit ocular model can be used as predictive of pharmacodynamic response (PD) in humans. Rabbits are commonly used to assess ocular PK/PD relationship for compounds targeting human ocular diseases due to the anatomic and functional similarities of the rabbit and human eye. Previously, intravitreal administration of

ET-1 into the rabbit eye has been shown to induce significant vasoconstriction and optic nerve damage (Sasaoka M. et al, Exp Eye Res 2006; Sugiyama T. et al, Arch Ophthalmol. 2009). Efficacy in this model is benchmarked to the reversal of perfusion impairment induced by intravitreal ET-1 administration at a concentration equivalent to the levels observed in human glaucoma patients' plasma and aqueous humor (Li S. et al, Journal of Ophthalmology 2016).

[00138] Other examples of relevant animal glaucoma models are Morrison's rat model of acutely elevated IOP and the laser-induced non-human primate (NHP) glaucoma model. Glaucoma in Morrison's rat model is induced by sustained elevation of IOP through hypertonic saline administration via episcleral veins. In the laser-induced NHP glaucoma model, after sustained elevation of IOP, optic nerve head blood flow has been shown to be reduced (Wang L. et al., Invest Ophthalmol. Vis Sci 2012). Furthermore, the reduction in optic nerve head blood flow has been shown to correlate with long-term structural changes in the optic nerve (Cull G. et al., Invest Ophthalmol. Vis Sci 2013).

[00139] Efficacy in the above-described glaucoma models is defined as reduction in IOP, improvement in optic nerve head or retinal blood flow from baseline, prevention or slowing of the progression of structural neurodegenerative changes such as retinal nerve fiber layer thickness as measured by optical coherence tomography (OCT) or retinal ganglion cell counts on flat mount as well as functional changes such as electroretinography (ERG) or contrast sensitivity after treatment with edonentan.

[00140] It is believed that the effect of compositions comprising edonentan on retinal blood flow can be assessed by the *blood vessel radius* (r) in Poiseuille's Law. An increase in (r) with an endothelin antagonist, would induce a more pronounced increase in blood flow than what can be achieved by an increase in perfusion pressure through IOP reduction:

$$\text{Blood flow} = (\text{perfusion pressure} \times \pi r^4) / (8\eta l)$$

where

l : blood vessel length

r : blood vessel radius

η : blood viscosity

perfusion pressure: mean arterial pressure – IOP

[00141] Furthermore, a biodegradable ocular implant comprising edonentan described herein may reduce IOP and/or prevent RGC death through mechanisms independent of improvement in retinal/optic nerve head tissue perfusion. Accordingly, by using certain specific edonentan, one (*r*) or more (IOP) of the above parameters can be altered to improve the RBF, thereby achieving therapeutic efficacy in treating glaucoma.

[00142] In some embodiments, the glaucoma patients are started on treatment as soon as they are diagnosed. In some embodiments, a biodegradable ocular implant comprising edonentan described herein is administered locally to the back of the eye using (e.g., using an intravitreal biodegradable ocular implant), with a frequency of every 3 to 12 months (e.g., every 4 to 12 months, every 5 to 12 months, every 6 to 12 months, every 7 to 12 months, every 8 to 12 months, every 9 to 12 months, every 10 to 12 months, every 11 to 12 months, every 3 to 4 months, every 3 to 5 months, every 3 to 6 months, every 3 to 7 months, every 3 to 8 months, every 3 to 9 months, every 3 to 10 months, or every 3 to 11 months).

[00143] In some embodiments, a biodegradable ocular implant described herein for treating glaucoma in a subject in need thereof comprises a biodegradable polymer (e.g., PLGA) that biodegrades substantially from about 1 month to about 24 months (e.g., about 2 months to about 24 months, about 5 months to 24 months, about 7 months to about 10 months, about 10 months to about 24 months, about 12 months to about 24 months, about 15 months to about 24 months, about 17 months to about 24 months, about 20 months to about 24 months, and about 22 months to about 24 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 3 months to about 12 months (e.g., about 4 months to about 12 months, 5 months to about 12 months, about 5 months to about 12 months, about 6 months to about 12 months, about 7 months to about 12 months, about 8 months to about 12 months, about 9 months to about 12 months, about 10 months to about 12 months, and about 11 months to about 12 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 12 months to about 18 months (e.g., about 13 months to about 18 months, about 14 months to about 18 months, about 15 months to about 18 months, about 16 months to about 18 months, about 17 months to about 18 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months.

Diabetic Retinopathy (DR)

[00144] Diabetes can cause serious late complications which are classified as microangiopathic (retinopathy, neuropathy, and diabetic nephropathy) and macroangiopathic

(cardiovascular disease). DR is the result of damage to the small blood vessels and neurons of the retina. The earliest changes leading to DR include narrowing of the retinal arteries associated with reduced retinal blood flow; dysfunction of the neurons of the inner retina, followed in later stages by changes in the function of the outer retina, associated with subtle changes in visual function; dysfunction of the blood-retinal barrier, which protects the retina from many substances in the blood (including toxins and immune cells), leading to the leakage of blood constituents into the retinal neuropile. Later, the basement membrane of the retinal blood vessels thickens, capillaries degenerate and lose cells, particularly pericytes and vascular smooth muscle cells. This leads to loss of blood flow and progressive ischemia, and microscopic aneurysms which appear as balloon-like structures jutting out from the capillary walls, which recruit inflammatory cells; and lead to advanced dysfunction and degeneration of the neurons and glial cells of the retina.

[00145] Ischemia and oxidant injury observed in DR compromises blood flow and tissue ischemia, which can be reversed by the biodegradable ocular implants comprising edonentan described herein. For DR indication, the improvement in retinal perfusion is anticipated to reduce hypoxia and suppress vascular endothelial growth factor (VEGF) upregulation with a resultant benefit of slowing vascular proliferative changes, neovascularization and/or macular edema complications.

[00146] As a surrogate model for the ischemic retinopathy changes observed in DR, a preclinical mouse model of retinopathy of prematurity (ROP) can be used. Oxygen-induced retinopathy in the mouse is a reproducible and quantifiable proliferative retinal neovascularization model suitable for examining pathogenesis and therapeutic intervention for retinal neovascularization in ROP and other vasculopathologies including DR. The model is induced by exposure of one-week-old C57BL/6J mice to 75% oxygen for 5 days and then to room air as previously described (Smith LEH et al., Invest Ophthalmol Vis Sci 1994). Efficacy in this preclinical model of ROP can be assessed by studying retinal hypoxia and neovascularization. The current standard of care in DR includes anti-VEGF therapies which only address advanced vascular complications of disease.

[00147] In some embodiments, the patients with DR are started on this treatment during the non-proliferative stages of the disease. In some embodiments, a biodegradable ocular implant comprising edonentan described herein is administered locally to the back of the eye (e.g., using an intravitreal biodegradable ocular implant), with a frequency of every 3 to 12 months (e.g., every 4 to 12 months, every 5 to 12 months, every 6 to 12 months, every 7 to 12 months, every 8 to 12 months, every 9 to 12 months, every 10 to 12 months, every 11 to 12

months, every 3 to 4 months, every 3 to 5 months, every 3 to 6 months, every 3 to 7 months, every 3 to 8 months, every 3 to 9 months, every 3 to 10 months, or every 3 to 11 months).

[00148] In some embodiments, a biodegradable ocular implant described herein for treating DR in a subject in need thereof comprises a biodegradable polymer (e.g., PLGA) that biodegrades substantially from about 1 month to about 24 months (e.g., about 2 months to about 24 months, about 5 months to 24 months, about 7 months to about 10 months, about 10 months to about 24 months, about 12 months to about 24 months, about 15 months to about 24 months, about 17 months to about 24 months, about 20 months to about 24 months, and about 22 months to about 24 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 3 months to about 12 months (e.g., about 4 months to about 12 months, 5 months to about 12 months, about 5 months to about 12 months, about 6 months to about 12 months, about 7 months to about 12 months, about 8 months to about 12 months, about 9 months to about 12 months, about 10 months to about 12 months, and about 11 months to about 12 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 12 months to about 18 months (e.g., about 13 months to about 18 months, about 14 months to about 18 months, about 15 months to about 18 months, about 16 months to about 18 months, about 17 months to about 18 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months.

Retinal Vein Occlusion (RVO)

[00149] Retinal vein occlusion (RVO), a vascular disorder of the retina, is currently treated with intravitreal injection of anti-VEGF drugs to inhibit the growth factor that causes macular edema and corticosteroids to combat the inflammatory components which lead to edema. It is highly desirable to use the biodegradable ocular implants comprising edonentan described herein for treating RVO by improving tissue perfusion and reducing inflammation while avoiding the unwanted effects of systemic immunosuppression and/or local adverse effects of steroids.

[00150] RVO is currently treated with intravitreal steroids and anti-VEGF agents. We hypothesize that improving perfusion of existing vessels will reduce the degree of macular edema and VEGF upregulation and the downstream maladaptive changes that manifests as RVO. To test efficacy, a preclinical mouse model of ischemic retinopathy can be used. Oxygen-induced retinopathy in the mouse is a reproducible and quantifiable proliferative retinal neovascularization model suitable for examining pathogenesis and therapeutic

intervention for retinal neovascularization in many ischemic retinopathies including RVO. The model is induced by exposure of one-week-old C57BL/6J mice to 75% oxygen for 5 days and then to room air as previously described (Smith LEH et al., Invest Ophthalmol Vis Sci 1994). The efficacy in this preclinical model of ischemic retinopathy can be assessed by studying retinal hypoxia and neovascularization. A biodegradable ocular implant described herein comprising a “therapeutically effective amount” of edonentan can be additive to the current standard of care by improving tissue perfusion and reducing inflammation mediated by ET-1 while avoiding the unwanted effects of local steroids. In some embodiments of treating RVO, the biodegradable ocular implant comprising edonentan described herein is administered locally to the back of the eye using an intravitreal biodegradable ocular implant. The frequency of administration will vary based on a patient’s disease course and response to therapy.

[00151] In some embodiments, a biodegradable ocular implant comprising edonentan described herein is administered locally to the back of the eye (e.g., using an intravitreal biodegradable ocular implant), with a frequency of every 3 to 12 months (e.g., every 4 to 12 months, every 5 to 12 months, every 6 to 12 months, every 7 to 12 months, every 8 to 12 months, every 9 to 12 months, every 10 to 12 months, every 11 to 12 months, every 3 to 4 months, every 3 to 5 months, every 3 to 6 months, every 3 to 7 months, every 3 to 8 months, every 3 to 9 months, every 3 to 10 months, or every 3 to 11 months).

[00152] In some embodiments, a biodegradable ocular implant described herein for treating RVO in a subject in need thereof comprises a biodegradable polymer (e.g., PLGA) that biodegrades substantially from about 1 month to about 24 months (e.g., about 2 months to about 24 months, about 5 months to about 24 months, about 7 months to about 10 months, about 10 months to about 24 months, about 12 months to about 24 months, about 15 months to about 24 months, about 17 months to about 24 months, about 20 months to about 24 months, and about 22 months to about 24 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 3 months to about 12 months (e.g., about 4 months to about 12 months, 5 months to about 12 months, about 5 months to about 12 months, about 6 months to about 12 months, about 7 months to about 12 months, about 8 months to about 12 months, about 9 months to about 12 months, about 10 months to about 12 months, and about 11 months to about 12 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 12 months to about 18 months (e.g., about 13 months to about 18 months, about 14 months to about 18 months, about 15 months to about 18 months, about 16 months to about 18 months, about 17 months to about

18 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months.

Retinopathy of prematurity (ROP)

[00153] ROP is a retinal vasoproliferative disease that affects premature infants. ROP continues to be a major preventable cause of blindness and visual handicaps globally. With improved perinatal care, improved survival of moderately preterm infants, and limited resources for oxygen delivery and monitoring, more mature preterm infants are developing severe ROP in developing countries.

[00154] The pathophysiology of ROP is characterized by two phases. Phase I ROP is due to vaso-obliteration beginning immediately after birth secondary to a marked decrease in vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1). Phase II begins around 33 weeks' postmenstrual age (PMA). During this phase, VEGF levels increase, especially if there is retinal hypoxia with increasing retinal metabolism and demand for oxygen leading to abnormal vasoproliferation. For advanced stages of ROP, laser ablation of avascular retina, early treatment of ROP (ETROP) protocol, intravitreal injection of anti-VEGF antibodies (e.g. bevacizumab) and vitrectomy are used to protect central vision and prevent retinal detachment. Long-term complications such as refractory errors, recurrence of ROP and risk of retinal detachment require continued follow-up with an ophthalmologist through adolescence and beyond.

[00155] ROP is induced by severe ischemia due to underdevelopment of retinal vessels secondary to premature birth. Therefore, as an aspect of the disclosure, we believe that improving perfusion of existing vessels with a biodegradable ocular implant comprising edonentan described herein will reduce the degree of ischemia and VEGF upregulation and the downstream maladaptive changes that manifests as ROP. To test efficacy, a preclinical mouse model of ROP can be used. Oxygen-induced retinopathy in the mouse is a reproducible and quantifiable proliferative retinal neovascularization model suitable for examining pathogenesis and therapeutic intervention for retinal neovascularization in ROP. The model is induced by exposure of one-week-old C57BL/6J mice to 75% oxygen for 5 days and then to room air as previously described (Smith LEH et al., Invest Ophthalmol Vis Sci 1994). The efficacy in this preclinical model of ROP can be assessed by studying retinal hypoxia and neovascularization. A biodegradable ocular implant described herein comprising a "therapeutically effective amount" of edonentan will be additive to the current standard of care by improving tissue perfusion and reducing pathologic neovascularization

induced by VEGF. In some embodiments, the medication is administered locally to the back of the eye using an intravitreal biodegradable ocular implant with a frequency of every 4 to 6 weeks as needed based on patient's disease course and response to therapy. For example, the intravitreal biodegradable ocular implant is administered locally to the back of the eye using an intravitreal injection with a frequency of every 5 weeks as needed based on patient's disease course and response to therapy.

[00156] In some embodiments, the patients with ROP are started on this treatment during the non-proliferative stages of the disease. In some embodiments, a biodegradable ocular implant comprising edonentan described herein is administered locally to the back of the eye using (e.g., an intravitreal biodegradable ocular implant), with a frequency of every 3 to 12 months (e.g., every 4 to 12 months, every 5 to 12 months, every 6 to 12 months, every 7 to 12 months, every 8 to 12 months, every 9 to 12 months, every 10 to 12 months, every 11 to 12 months, every 3 to 4 months, every 3 to 5 months, every 3 to 6 months, every 3 to 7 months, every 3 to 8 months, every 3 to 9 months, every 3 to 10 months, or every 3 to 11 months).

[00157] In some embodiments, a biodegradable ocular implant described herein for treating ROP in a subject in need thereof comprises a biodegradable polymer (e.g., PLGA) that biodegrades substantially from about 1 month to about 24 months (e.g., about 2 months to about 24 months, about 5 months to about 24 months, about 7 months to about 10 months, about 10 months to about 24 months, about 12 months to about 24 months, about 15 months to about 24 months, about 17 months to about 24 months, about 20 months to about 24 months, and about 22 months to about 24 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 3 months to about 12 months (e.g., about 4 months to about 12 months, 5 months to about 12 months, about 5 months to about 12 months, about 6 months to about 12 months, about 7 months to about 12 months, about 8 months to about 12 months, about 9 months to about 12 months, about 10 months to about 12 months, and about 11 months to about 12 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 12 months to about 18 months (e.g., about 13 months to about 18 months, about 14 months to about 18 months, about 15 months to about 18 months, about 16 months to about 18 months, about 17 months to about 18 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months.

Age-related macular degeneration (AMD)

[00158] Age-related macular degeneration (AMD), also known as macular degeneration, is a deterioration of the central portion of the retina, causing severe and irreversible loss of vision. AMD is a common cause of visual loss in the elderly, with increasing prevalence due to increasing life expectancy. Clinically, it is classified as early-stage (medium-sized drusen and retinal pigmentary changes) to late-stage (neovascular and atrophic). AMD is a multifactorial disease encompassing a complex interplay between ageing, environmental risk factors and genetic susceptibility. Chronic inflammation, lipid deposition, oxidative stress and impaired extracellular matrix maintenance are strongly implicated in AMD pathogenesis. However, the exact interactions of pathophysiological events that culminate in drusen formation and the associated degeneration processes remain to be elucidated. Despite tremendous advances in clinical care and in unravelling pathophysiological mechanisms, the unmet medical need related to AMD remains substantial.

[00159] In some embodiments, the AMD is wet AMD. In some embodiments, the AMD is dry AMD.

[00160] Wet AMD is characterized by the presence of neovascularization within the macula. It occurs when abnormal blood vessels develop under retina and macula. The blood vessels leak blood and fluid. Vision loss with the wet form of macular degeneration tends to occur more rapidly than with the dry form. It can cause rapid and severe loss of central vision.

[00161] Dry AMD accounts for nearly 90% of cases. It occurs when tiny yellow protein deposits called drusen form under macula. The built-up deposits dry and thin macula. Vision loss with the dry form of macular degeneration tends to occur gradually.

[00162] Drusen is characteristic of macular degeneration. Drusen are tiny yellow or white accumulations of extracellular material that build up between Bruch's membrane and the retinal pigment epithelium (RPE) of the eye. The drusen contain proteins and lipids (naturally occurring molecules that include fats). Patients with drusen deposits or other protein exudates in the eye are at risk of developing AMD. The deposition of drusen reduces the effectiveness of the exchange of oxygen, nutrients and waste products between the RPE and the retinal choroid plexus. Given that the retina and the photoreceptors have a very high energy consumption and a need for effective oxygenation, any reduction in the RPE's ability to support the photoreceptors and neuronal tissue can result in stress of the retinal tissues and increased risk of developing AMD.

[00163] In some embodiments, the patients with AMD are started on this treatment during the non-proliferative stages of the disease. In some embodiments, a biodegradable ocular

implant comprising edonentan described herein is administered locally to the back of the eye using (e.g., an intravitreal biodegradable ocular implant), with a frequency of every 3 to 12 months (e.g., every 4 to 12 months, every 5 to 12 months, every 6 to 12 months, every 7 to 12 months, every 8 to 12 months, every 9 to 12 months, every 10 to 12 months, every 11 to 12 months, every 3 to 4 months, every 3 to 5 months, every 3 to 6 months, every 3 to 7 months, every 3 to 8 months, every 3 to 9 months, every 3 to 10 months, or every 3 to 11 months).

[00164] In some embodiments, a biodegradable ocular implant described herein for treating age-related macular degeneration in a subject in need thereof comprises a biodegradable polymer (e.g., PLGA) that biodegrades substantially from about 1 month to about 24 months (e.g., about 2 months to about 24 months, about 5 months to 24 months, about 7 months to about 10 months, about 10 months to about 24 months, about 12 months to about 24 months, about 15 months to about 24 months, about 17 months to about 24 months, about 20 months to about 24 months, and about 22 months to about 24 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 3 months to about 12 months (e.g., about 4 months to about 12 months, 5 months to about 12 months, about 5 months to about 12 months, about 6 months to about 12 months, about 7 months to about 12 months, about 8 months to about 12 months, about 9 months to about 12 months, about 10 months to about 12 months, and about 11 months to about 12 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 12 months to about 18 months (e.g., about 13 months to about 18 months, about 14 months to about 18 months, about 15 months to about 18 months, about 16 months to about 18 months, about 17 months to about 18 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months.

Geographic atrophy (GA)

[00165] Geographic atrophy (GA) is a medical term that refers to later-stage cases of dry AMD. Symptoms of GA include, but are not limited to: loss of visual acuity (sharpness of vision), difficulty reading, driving, doing crafts or any other activity that relies on central vision, a dark spot, or blind spot, in central vision, difficulty seeing in dim light, and colors becoming drab or less vibrant.

[00166] GA is easily recognized clinically, as it appears as a well-demarcated area of decreased retinal thickness, compared to the surrounding retina, with a relative change in color that allows an increased visualization of the underlying choroidal vessels. Pigmentary

alteration may be present, either hypopigmentation or hyperpigmentation, surrounding the macular atrophy.

[00167] In some embodiments, the patients with GA are started on this treatment during the non-proliferative stages of the disease. In some embodiments, a biodegradable ocular implant comprising edonentan described herein is administered locally to the back of the eye using (e.g., an intravitreal biodegradable ocular implant), with a frequency of every 3 to 12 months (e.g., every 4 to 12 months, every 5 to 12 months, every 6 to 12 months, every 7 to 12 months, every 8 to 12 months, every 9 to 12 months, every 10 to 12 months, every 11 to 12 months, every 3 to 4 months, every 3 to 5 months, every 3 to 6 months, every 3 to 7 months, every 3 to 8 months, every 3 to 9 months, every 3 to 10 months, or every 3 to 11 months).

[00168] In some embodiments, a biodegradable ocular implant described herein for treating geographic atrophy in a subject in need thereof comprises a biodegradable polymer (e.g., PLGA) that biodegrades substantially from about 1 month to about 24 months (e.g., about 2 months to about 24 months, about 5 months to 24 months, about 7 months to about 10 months, about 10 months to about 24 months, about 12 months to about 24 months, about 15 months to about 24 months, about 17 months to about 24 months, about 20 months to about 24 months, and about 22 months to about 24 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 3 months to about 12 months (e.g., about 4 months to about 12 months, 5 months to about 12 months, about 5 months to about 12 months, about 6 months to about 12 months, about 7 months to about 12 months, about 8 months to about 12 months, about 9 months to about 12 months, about 10 months to about 12 months, and about 11 months to about 12 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially from about 12 months to about 18 months (e.g., about 13 months to about 18 months, about 14 months to about 18 months, about 15 months to about 18 months, about 16 months to about 18 months, about 17 months to about 18 months). In some embodiments, the biodegradable polymer (e.g., PLGA) biodegrades substantially in about 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months.

Definitions

[00169] As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent depending upon the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art, given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

[00170] As used herein, the term “effective amount” refers to the amount of a compound sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. As used herein, the term “treating” includes any effect, e.g., lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[00171] “Individual,” “patient,” or “subject” are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds of the disclosure can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like). “Modulation” includes antagonism (*e.g.*, inhibition), agonism, partial antagonism and/or partial agonism.

[00172] The term “pharmaceutically acceptable salt(s)” as used herein refers to salts of acidic or basic groups that may be present in compounds used in the compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts, particularly calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one

carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

[00173] “Therapeutically effective amount” includes an amount of a compound of the disclosure that is effective when administered alone or in combination to treat the desired condition or disorder. “Therapeutically effective amount” includes an amount of the combination of compounds claimed that is effective to treat the desired condition or disorder. The combination of compounds can be additive and is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* 1984, 22:27-55, occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower incidence of adverse side effects and/or toxicity, increased efficacy, or some other beneficial effect of the combination compared with the individual components.

[00174] As used herein, the term "substantially" refers to the complete or nearly complete extent or degree of an action, characteristic, property, state, structure, or result. For example, a polymer that is "substantially" biodegraded would mean that the object is either completely biodegraded or nearly completely biodegraded.

EXAMPLES

[00175] In order that the disclosure described herein may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

[00176] Abbreviations: D: distribution; DSC: differential scanning calorimetry; LC: label claim; w/w: weight-by-weight; HPLC: high-performance liquid chromatography; PBS: phosphate buffer saline; rpm: revolutions per minute; DR: diabetic retinopathy; GLP: good laboratory practice; IVT: intravitreal; IPA: isopropyl alcohol; LC-MS: liquid chromatograph mass spectrometer; MS: mass spectrometer; PLGA: poly(D,L-lactide-co-glycolide); RPE: retinal pigment epithelium; THF: tetrahydrofuran; UPLC: ultra-performance liquid chromatography; XRPD: X-ray powder diffraction.

Example 1. Preparation of Edonentan Implants I

[00177] Polymers (PLGA) were cryomilled to reduce the particle size and achieve uniformity. Edonentan was prepared by using methods disclosed, for example, in U.S. Patent No. 6,043,265. Form 4 of edonentan was then prepared as described herein in Example 6. The edonentan was further screened, milled, or micronized to adjust the particle size. A ratio of the polymers and edonentan were mixed and the resulting powder blend was then fed into a heated Thermo Haake Conical Twin Screw Extruder (85 – 88 °C) with a 3-mm die and the extrudate was collected. The specific ratios of polymers and edonentan are shown in **Table 1**. The extrudate was broken up into approximately 0.5-inch pieces and placed into a jar. The pieces in the jar were manually mixed and then fed back into the heated Thermo Haake Conical Twin Screw Extruder (88 – 90 °C) for the second time and extruded through a 1.54-mm die. The resulting extrudate was pelletized and blended. The blended material was fed into the cylinder of a Barrell custom ram extruder, heated to the appropriate temperature (71 – 74 °C), and then extruded through a 0.325-mm die (actual filament diameter 0.345 mm). The diameter of die may be adjusted based on the processing conditions to achieve the target diameter of filament. The extruded filament was then cut into 4-mm implants containing approximately 210 µg to 240 µg of edonentan per implant.

Table 1. Edonentan formulations 1-5

Edonentan Containing Implant Formulations (1 – 5)							
Formulation No.	Edonentan % w/w	Polymer % w/w ¹					
		RG502	RG503	RG753S	DLG 5002E	DLG 5003E	DLG 7505E
1	45	10	50	40			
2	45				10	50	40
3	45	10	50	40			
4	45				10	50	40
5	45	10	50	40			

¹ Total weight of polymer in the implant is 55% w/w.

Edonentan Particle Size

[00178] The impact of edonentan particle size on the release rate of the implants, prepared with process described above, including twin screw compounding and ram extrusion process, was investigated. Three distinct particle size ranges were investigated: (1) edonentan passed through a 100-mesh screen (150 μm), (2) milled edonentan, and (3) micronized edonentan.

Table 2a, **Table 2b**, and **Table 2c** summarize the particle size ranges. **FIG. 1** depicts the impact of particle size on the release rate of edonentan from implant formulations 2, 3 and 5. The effect of edonentan particle size on release rate was consistent for each of the different PLGA compositions tested.

Table 2a.^a Particle size distribution of edonentan particles prepared by screening

	Edonentan particle size distribution ^b		
	D10	D50	D90
Screened	84 μm	146 μm	226 μm ^c

^a “D” refers to distribution.

^b Particle size distribution analyzed using a Mastersizer 3000 medium-volume cell. 80 mg edonentan was added to 120 mL of dispersant (0.1% Span 80 in hexanes) and calculated as an average of 5 measurements.

^c Only material that passed through a 100-mesh screen was used in manufacturing the biodegradable ocular implants.

Table 2b.^a Particle size distribution of edonentan particles prepared by milling

	Edonentan particle size distribution ^b		
	D ₁₀	D ₅₀	D ₉₀
Milled	9 μm	40 μm	112 μm

^a “D” refers to distribution.

^b Particle size distribution analyzed using a Mastersizer 3000 small-volume cell. 1 mL of dispersant (0.1% Span 80 in hexanes) was added to 10 mg edonentan and calculated as an average of 5 measurements.

Table 2c.^a Particle size distribution of edonentan particles prepared by micronizing

	Edonentan particle size distribution ^b		
	D ₁₀	D ₅₀	D ₉₀
Micronized	2 µm	6 µm	14 µm

^a “D” refers to distribution.^b Particle size distribution analyzed using a LS-909 laser particle size analyzer.**PLGA % residual monomer**

[00179] The impact of % residual monomer in the PLGA was investigated across PLGAs having similar viscosity. The edonentan particle size, PLGAs, the ratio of PLGAs, and the amount of % residual monomer in each PLGA for formulations 1-5 are described in **Table 3a** and **Table 3b**. It was found that the difference in % residual monomer remaining in the polymer was found to impact the release rate of edonentan from the PLGA matrix. As shown in **FIG. 2**, maintaining the % residual monomer to $\leq 0.5\%$ is critical to maintaining the duration of the edonentan implant.

Table 3a. Edonentan particle size and PLGA in Formulations 1, 3, 5

Edonentan Containing Implant Formulations 1, 3, 5				
Formulation No.	Edonentan	Polymer % w/w ¹ (% w/w Total Residual Monomer ^a)		
		RG502 (0.22)	RG503 (0.25)	RG753S (0.33)
1	Screened	10	50	40
3	Milled	10	50	40
5	Micronized	10	50	40

¹ Total weight of polymer in the implant is 55% w/w.^a approximate monomer composition of D,L-Lactide + Glycolide.

Table 3b. Edonentan particle size and PLGA in Formulations 2, 4

Edonentan Containing Implant Formulations 2, 4				
Formulation No.	Edonentan	Polymer % w/w ¹ (% w/w Total Residual Monomer ^a)		
		DLG5002E (1.32)	DLG5003E (2.12)	DLG7505E (1.99)
2	Screened	10	50	40
4	Milled	10	50	40

¹ Total weight of polymer in the implant is 55% w/w.

^a approximate monomer composition of D,L-Lactide + Glycolide.

Example 2. In vitro drug release properties of Formulations 1-5

[00180] For *in vitro* drug release testing, six implants from each formulation in **Table 1** were randomly cut from extruded filaments and incubated in 3-mL of PBS at pH 7.4 with 0.1% Tween in a shaking incubator set at 39 °C and 50 rpm. The drug release profiles of the implants were sampled at designated time points, and the released edonentan content was analyzed by an HPLC assay described below. The release medium was completely replaced with fresh medium during each sampling time point. The *in vitro* drug release profile is depicted in **FIG. 3** and the daily elution rate is depicted in **FIG. 4**.

HPLC Assay

[00181] Samples were chromatographed using reverse phase chromatography which utilizes a Waters XBridge C18 column and 0.1% formic acid in water and 0.1% formic acid in acetonitrile as mobile phase. A linear gradient was used from 55% to 5% aqueous over 2.5 minutes with detection at 275 nm. Samples were evaluated against external standards prepared from the analytical reference material.

Example 3. Preparation of Edonentan Implants II

[00182] Polymers were cryomilled to reduce the particle size. Edonentan was prepared by using methods disclosed, for example, in U.S. Patent No. 6,043,265, and the edonentan was further micronized to adjust the particle size. A ratio of the polymers and edonentan were mixed and the resulting powder blend was then fed into a heated Thermo Haake Twin Screw Extruder (95 °C, 10 rpm screw speed) fitted with a 1.96 mm die and the extrudate collected.

The specific ratios of polymers and edonentan are shown in **Table 4**. The extrudate was broken up into approximately 1/8-inch pieces and placed into a jar. The pieces in the jar were manually mixed and then fed back into the heated twin screw extruder (110 °C) for the second time and extruded at 100 – 120 °C with screw speeds of 4 – 10 rpm through a 0.31-0.33-mm die (actual filament diameter from 0.321 – 0.356 mm). The diameter of the die may be adjusted based on the processing conditions to achieve the target diameter of filament. The extruded filament was then cut into 4-mm implants containing approximately 185 µg to 225 µg of edonentan per implant.

Table 4. Edonentan formulations 6-7

Edonentan Containing Implant Formulations (6 – 7)				
Formulation No.	Edonentan %w/w	Polymer % w/w ¹ (% w/w Total Residual Monomer ^a)		
		RG502 (0.22)	RG503 (0.25)	RG753S (0.33)
6	45 (Micronized)	10	50	40
7	45 (Micronized)		30	70

¹ Total weight of polymer in the implant is 55% w/w.

^a approximate monomer composition of D,L-Lactide + Glycolide.

Edonentan Particle Size

[00183] **Table 5** summarizes the particle size distribution of edonentan in Formulations 6-7.

Table 5.^a Particle size distribution of edonentan particles prepared by micronizing

	Edonentan particle size distribution ^b		
	D ₁₀	D ₅₀	D ₉₀
Micronized	0.57 µm	2.52 µm	9.25 µm

^a “D” refers to distribution.

^b Particle size distribution analyzed using a HELOS particle size analyzer.

Example 4. Comparative study

[00184] The *in vivo* edonentan release profile of a biodegradable ocular implant manufactured by the solvent casting procedure (a “solvent casted implant”) disclosed in U.S. Patent Application No. 18/060,503 (“503 application”) was compared against the release

profiles of the biodegradable implants prepared by the methods described in Examples 1 and 3 herein. In this study, solvent casted implants (referred to as “solvent process” in FIG. 5) consisted of 45% w/w edonentan in a polymer matrix consisting of 10% RG502, 50% RG 503 and 40% RG753S. These solvent casted implants were prepared using the solvent casting process, cryomilled, and injection molded as described in the '503 application. The implants were then implanted into the ocular tissues of rabbits (see Example 5 for the rabbit model tested). The implants were removed at various timepoints from the vitreous, soaked in acetonitrile overnight, and then analyzed for content by HPLC. Samples were chromatographed using reverse phase chromatography which utilizes a Waters XBridge C18 column and 0.1% formic acid in water and 0.1% formic acid in acetonitrile as mobile phase. A linear gradient was used from 55% to 5% aqueous over 2.5 minutes with detection at 275 nm. Samples are evaluated against external standards prepared from the analytical reference material. Comparative *in vivo* edonentan release profiles for the different implants are illustrated in FIG. 5.

Example 5. Pharmacokinetics studies

I. 10-week Ocular Pharmacokinetics of Edonentan Intravitreal Implants in Rabbits

[00185] In a non-GLP 10-week ocular pharmacokinetic study in rabbits, two edonentan Intravitreal implants manufactured via the process described in Example 1 using polymers from RESOMER or VIATEL (total implant weight RESOMER 526 µg/implant, 474 µg/2 implants, total implant weight VIATEL 489 µg/implant, 440 µg/2 implants) were administered as a single bilateral intravitreal (IVT) injections (2 animals and 4 eyes per timepoint). The implants contained 45% edonentan in a blend of either RESOMER® containing 50% RG503, 10% RG502, and 40% RG753S or VIATEL™ containing 50% DLG 5003E, 10% DLG 5002E, and 40% DLG 7505E. Rabbits were euthanized at weeks 4, 7, 8 and 10 (week 7 was only for the VIATEL group, week 10 was only for the RESOMER group) and drug concentrations in aqueous humor, lens, retina, and RPE/choroid were determined.

[00186] Ocular tissue was analyzed for edonentan content using an analytical method based on protein precipitation and liquid-liquid extraction followed by reverse-phase LC-MS/MS analysis. An Agilent 1290 UPLC coupled to an Agilent 6430 triple quadrupole mass spectrometer was used for analysis. The quantitation range for edonentan was 0.1 to 350 ng/mL. Tissue samples were homogenized and extracted with 0.1% formic acid in acetonitrile which was spiked with deuterated edonentan at approximately 10 ng/mL. The

extracts were analyzed using reversed-phase liquid chromatographic separation with tandem mass spectrometric detection in the positive ion mode following the quantitative transition m/z 537.2 to 439.1 for edonentan and m/z 540.2 to 442.1 for deuterated edonentan.

[00187] IVT sustained release delivery of 45% edonentan in the RESOMER® implants demonstrated achievement of sustainable therapeutic target tissue levels of edonentan for the duration of the study (**FIG. 6** and **FIG. 7**). The cumulative total edonentan released from implants was 99% at 10 weeks (**Table 6**). IVT sustained release delivery of 45% edonentan in the viatel™ implants demonstrated achievement of sustainable therapeutic target tissue levels of edonentan through 8 weeks (**FIG. 6** and **FIG. 7**). The cumulative total edonentan released from implants was 100% at 8 weeks (**Table 6**).

Table 6. Cumulative edonentan released from implants during 10-week ocular pharmacokinetic of edonentan intravitreal implant in rabbits

Timepoint	% Released	
	RESOMER Edonentan Implants	VIATEL Edonentan Implants
Day 28	16	35
Day 49	NT	90
Day 56	88	100
Day 70	99	NT
NT: not tested		

II. 12-week ocular pharmacokinetics of edonentan Intravitreal Implants in rabbits

[00188] In a non-GLP 12-week ocular pharmacokinetic study in rabbits, two edonentan Intravitreal implants manufactured via the process described in Example 1 using API of either milled or micronized particle size (total implant weight micronized 529 μ g/implant, 476 μ g Edonentan/2 implants, total implant weight milled 523 μ g/implant, 470 μ g Edonentan/2 implants) were administered as a single bilateral IVT injection (2 animals and 4 eyes per timepoint, week 10 of the micronized study used 4 animals 8 eyes). The implants contained 45% edonentan, either micronized or milled, in a blend of RESOMER® containing 50% RG503, 10% RG502 and 40% RG753S. Rabbits were euthanized at weeks 4, 8 and 12 and drug concentrations in aqueous humor, lens, retina, and RPE/choroid were determined.

[00189] Ocular tissue was analyzed for edonentan content using an analytical method based on protein precipitation and liquid-liquid extraction followed by reverse-phase LC-MS/MS analysis. An Agilent 1290 UPLC coupled to an Agilent 6430 triple quadrupole mass spectrometer was used for analysis. The quantitation range for edonentan was 0.1 to 350 ng/mL. Tissue samples were homogenized and extracted with 0.1% formic acid in acetonitrile which was spiked with deuterated edonentan at approximately 10 ng/mL. The extracts were analyzed using reversed-phase liquid chromatographic separation with tandem mass spectrometric detection in the positive ion mode following the quantitative transition m/z 537.2 to 439.1 for edonentan and m/z 540.2 to 442.1 for deuterated edonentan.

[00190] IVT sustained release delivery of 45% edonentan (micronized) implants demonstrated achievement of sustainable therapeutic target tissue levels of edonentan for the duration of the study (**FIG. 8** and **FIG. 9**). The cumulative total edonentan released from (micronized) implants was 100% at 11 weeks (**Table 7**). IVT sustained release delivery of 45% edonentan (milled) implants demonstrated achievement of sustainable therapeutic target tissue levels of edonentan through 10 weeks (**FIG. 8** and **FIG. 9**). The cumulative total edonentan released from (milled) implants was 100% at 10 weeks (**Table 7**).

Table 7. Cumulative edonentan released from implants during 12-week ocular pharmacokinetic of edonentan intravitreal implants in rabbits

Timepoint	% Released	
	Micronized Edonentan Implants	Milled Edonentan Implants
Day 28	6.1	12.6
Day 42	NT	67.3
Day 56	88.2	NT
Day 70	99.5	99.6
Day 77	100.0	NT
NT: not tested		

III. 12-week ocular pharmacokinetics of edonentan Intravitreal Implants in rabbits

[00191] In a non-GLP 12-week ocular pharmacokinetic study in rabbits, two edonentan intravitreal implants manufactured via the process described in Example 3 by twin screw extrusion containing a polymer ratio of either 50/10/40 RG503/RG502/RG753S or 30/70 RG503/RG753S (total implant weight 50/10/40 RG503/RG502/RG753S 415 µg/implant, 374

µg Edonentan/2 implants, total implant weight 30/70 RG503/RG753S 501 µg/implant, 451 µg Edonentan/2 implants) were administered as a single bilateral IVT injection (2 animals and 4 eyes per timepoint, week 10 of the 50/10/40 polymer ratio was 4 animals and 8 eyes). The implants contained 45% micronized edonentan, in a blend of RESOMER® containing either 50% RG503, 10% RG502 and 40% RG753S or 30% RG503 and 70% RG753S. Rabbits were euthanized at weeks 4, 6, 7, 8, 10 and 12 and drug concentrations in aqueous humor, lens, retina, and RPE/choroid were determined.

[00192] Ocular tissue was analyzed for edonentan content using an analytical method based on protein precipitation and liquid-liquid extraction followed by reverse-phase LC-MS/MS analysis. An Agilent 1290 UPLC coupled to an Agilent 6430 triple quadrupole mass spectrometer was used for analysis. The quantitation range for edonentan was 0.1 to 350 ng/mL. Tissue samples were homogenized and extracted with 0.1% formic acid in acetonitrile which was spiked with deuterated edonentan at approximately 10 ng/mL. The extracts were analyzed using reversed-phase liquid chromatographic separation with tandem mass spectrometric detection in the positive ion mode following the quantitative transition m/z 537.2 to 439.1 for edonentan and m/z 540.2 to 442.1 for deuterated edonentan.

[00193] IVT sustained release delivery of 45% edonentan (50/10/40 polymer ratio) implants demonstrated achievement of sustainable therapeutic target tissue levels of edonentan through 10 weeks (**FIG. 10** and **FIG. 11**). The cumulative total edonentan released from (50/10/40 polymer ratio) implants was 99.7% at 10 weeks (**Table 8**).

Table 8. Cumulative edonentan released from implants during 12-week ocular pharmacokinetic of edonentan intravitreal implants in rabbits

Timepoint	% Released
	50/10/40 RG503/RG502/RG753S Edonentan Implants
Week 4	
Week 6	57.5
Week 7	74.2
Week 8	91.9
Week 10	99.7
Week 12	NT
NT: not tested	

Example 6. Crystalline forms of edonentan

Exemplary method of preparing crystalline Form 1

[00194] Amorphous edonentan (840 mg) was dissolved in 12 mL of IPA. The resulting solution was filtered and the filter was washed with additional 2.5 mL of IPA. The filtrate was concentrated to dryness, dissolved in 11.8 mL of IPA and heated with stirring to 60 °C. Then, 18 mL of warm water was added dropwise at 60 °C while stirring vigorously and the solution was stirred at 60 °C for 1 h. The solution was slowly cooled to 25 °C, filtered and dried under vacuum at 25 °C to provide 660 mg of crystalline Form 1 (XRPD and DSC in **FIG. 13** and **FIG. 17**, respectively).

Exemplary method of preparing crystalline Form 2

[00195] Amorphous edonentan (250 mg) was dissolved in 3.5 mL of IPA. The resulting solution was filtered and the filter was washed with additional 0.25 mL of IPA. The solution was then heated to 60 °C whereupon 7.5 mL of warm water was added dropwise at 60 °C while stirring vigorously and then stirred at 60 °C for 1 h. After slowly cooling to 25 °C, the mixture was filtered to provide crystalline Form 2 (XRPD and DSC in **FIG. 14** and **FIG. 18** respectively). Alternatively, a preferred method of preparing crystalline Form 2 is as follows. Amorphous edonentan (1 g) was slurried in 20 mL of water at 25 °C for 15 hours. The

solution was then filtered to give the crystalline Form 2 (XRPD and DSC in **FIG. 14** and **FIG. 18**, respectively).

Exemplary method of preparing crystalline Form 3

[00196] Amorphous edonentan (250 mg) was dissolved in 0.5 mL of ethyl acetate. The resulting solution was filtered and heated to 60 °C, and 1.5 mL of hexane was added dropwise at 60 °C while stirring vigorously. To the resulting slightly cloudy solution, 0.1 mL of ethyl acetate was added, resulting in a clear solution which was then stirred at 60 °C for 1 h. The solution was slowly cooled to 25 °C and the resulting precipitate was filtered to provide crystalline Form 3 (XRPD and DSC in **FIG. 15** and **FIG. 19**, respectively).

Exemplary method of preparing crystalline Form 4

[00197] Amorphous edonentan (100 mg) was added to 2 mL of water containing 0.2 mL of tetrahydrofuran (THF). The resulting mixture was stirred at 50 °C for 24 hours, cooled and filtered to provide Form 4, which was confirmed by XRPD (**FIG. 16**) and DSC (**FIG. 20**) to be distinct from Forms 1, 2 and 3.

[00198] In an alternate method, 107 mg of amorphous edonentan was added to 1 mL of water followed by the addition of an equivalent of KOH in 1 mL of water. The resulting solution was heated to 60 °C for 20 minutes, filtered warm and acidified with 1 mL of 0.2 N HCl. The resulting mixture was stirred for 5 hours at 60 °C, cooled and filtered to give Form 4, which was confirmed by XRPD.

[00199] In an alternate method, 150 mg of edonentan (Form 3) was added to a mixture of isopropanol and water (1 mL and 2 mL, respectively). The resulting slurry was stirred at 15°C for 48 hours and then filtered. The sample was confirmed by an XRPD analysis to be Form 4, demonstrating that under these conditions, Form 4 is more thermodynamically stable than Form 3.

[00200] In an alternate method, 200 mg of edonentan (Form 1) was added to a mixture of isopropanol and water (1.3 mL and 2.6 mL, respectively). The resulting solution was heated to 80 °C and stirred for 24 h, then cooled and filtered. The sample thus obtained was confirmed by an XRPD analysis to be Form 4, demonstrating that under these conditions, Form 4 is more thermodynamically stable than Form 1.

[00201] In an alternate method, 100 mg of edonentan (amorphous) was scurried in 10 mL of water and heated to 100 °C for 40 hours. The resulting solution was cooled to ambient temperature and filtered to afford Form 4. In an alternate method, amorphous (crude)

Edonentan is dissolved in 8 volumes of isopropanol at 60 °C. The resulting solution is cooled to 57 °C, and then a small crystal of the crystalline Form 4 is added. After 2 hours, the solution is cooled to 5 °C, held for 15 hours, and filtered to afford the crystalline Form 4.

XRPD patterns of crystalline forms

[00202] The XRPD patterns of crystalline Forms 1-4 are shown in **FIGS 12-16**. The XRPD pattern of the crystalline form described herein was recorded using a Polycrystalline X-ray diffractometer (Bruker, D8 ADVANCE). The CuK α radiation was operating at a voltage of 40 kV and a current of 40 mA with a transmission slit of 1.0 mm and cable-stayed slit of 0.4°. A sample was placed in the center of sample holder groove and the surface of sample holder was leveled with the surface of sample holder. The data were collected over continuous scanning with a step size of 0.02 ° and a speed of 8°/min using the lynxeye detector.

[00203] The following **Tables 9-12** list certain XRPD characteristic peaks for crystalline Forms 1-4, respectively.

Table 9. Exemplary XRPD patterns of crystalline Form 1

2 θ	Intensity (counts)
6.3	1250
7.5	2750
11.7	1400
15.1	2200
17.3	900

Table 10. Exemplary XRPD patterns of crystalline Form 2

Angle [2 θ]	Intensity (counts)
9.6	2250
10.4	1500
11.1	600
12.3	750
14.6	1000
15.1	800
17.2	1000
19.6	3000
19.7	3000
22.0	1500
22.9	1500
23.7	2000

Table 11. Exemplary XRPD patterns of crystalline Form 3

2θ	Intensity (counts)
7.8	2000
9.0	2750
11.6	750
15.8	2500
19.1	900

Table 12. Exemplary XRPD patterns of crystalline Form 4

Angle [2θ]	Intensity (counts)
5.6	1800
11.4	12600
14.4	1400
15.7	1200
16.8	1400
17.7	4800
19.3	6700
21.1	2900
21.9	2400
23.9	2400
24.6	1900

Physiochemical properties of crystalline forms

[00204] Provided herein are exemplary physicochemical properties of crystalline forms.

The melting points described herein can be measured using the following procedure:

i. Melting Point Protocol

[00205] The maximal melting point peak (T_m) of each crystalline form was determined using DSC. The DSC of the crystalline form described herein was measured using the TA instrument DSC Q2000. A sample (1.3010 mg) was weighed in an aluminum crucible and heated from 30 °C to 300 °C at a heating rate of 10 °C/min. Temperatures at crystalline melting peak start, peak onset, peak max, and peak end were collected.

[00206] The solubility described herein can be measured using the following procedure:

ii. Solubility Analysis Protocol

1. No less than 2.0 mg samples are weighed into lower chamber of whatman miniuniprep vials (GE Healthcare). 450 µL of buffer was added into each chamber.
2. Filter pistons of miniuniprep vials are placed and compressed to the position of the liquid level to allow for contact of buffer and compound with the filter during incubation.

3. The samples are vortexed for 2 minutes followed by incubation at room temperature (about 25 ± 2 °C) for 24 hours with shaking at 500 rpm.
4. Miniunipreps are compressed to prepare the filtrates for injection into HPLC system. All vials are inspected for visible undissolved material before filtering and for leakage after filtering.
5. Dilute supernatant with buffer by a factor of 100 folds to make diluents which are analyzed with HPLC.

[00207] Provided in **Table 13** below are exemplary physicochemical properties of crystalline Forms 1-4. The physicochemical properties can be obtained using the methods described above.

Table 13. Exemplary physicochemical properties of crystalline Forms 1-4

Polymorph	Solvation	T _m (°C)	Solubility pH 7.0 Phosphate Buffer (µg/mL)
Form 1	anhydrate	151	264
Form 2	monohydrate	122	35
Form 3	anhydrate	162	251
Form 4	anhydrate	163	138

EQUIVALENTS AND SCOPE

[00208] In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[00209] Furthermore, the disclosure encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in

any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the disclosure, or aspects of the disclosure, is/are referred to as comprising particular elements and/or features, certain embodiments of the disclosure or aspects of the disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00210] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the disclosure can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[00211] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present disclosure, as defined in the following claims.

CLAIMS

WHAT IS CLAIMED:

1. A biodegradable ocular implant comprising:
(i) edonentan, or a pharmaceutically acceptable salt thereof; and
(ii) a biodegradable polymer,
wherein the edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 9 μm to about 250 μm .
2. The biodegradable ocular implant of claim 1, wherein the edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 9 μm to about 125 μm .
3. The biodegradable ocular implant of claim 1 or 2, wherein the edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 9 μm to about 15 μm .
4. The biodegradable ocular implant of any one of claims 1-3, wherein the particle size distribution of the edonentan, or a pharmaceutically acceptable salt thereof, is further characterized by D50 of about 2.5 μm to about 150 μm .
5. The biodegradable ocular implant of any one of claims 1-4, wherein the particle size distribution of the edonentan, or a pharmaceutically acceptable salt thereof, is further characterized by D50 of about 2.5 μm to about 40 μm .
6. The biodegradable ocular implant of any one of claims 1-5, wherein the particle size distribution of the edonentan, or a pharmaceutically acceptable salt thereof, is further characterized by D50 of about 2.5 μm to about 6 μm .
7. The biodegradable ocular implant of any one of claims 1-6, wherein the particle size distribution of the edonentan, or a pharmaceutically acceptable salt thereof, is further characterized by D10 of about 0.5 μm to about 90 μm .

8. The biodegradable ocular implant of any one of claims 1-7, wherein the particle size distribution of the edonentan, or a pharmaceutically acceptable salt thereof, is further characterized by D10 of about 0.5 μm to about 10 μm .
9. The biodegradable ocular implant of any one of claims 1-8, wherein the particle size distribution of the edonentan, or a pharmaceutically acceptable salt thereof, is further characterized by D10 of about 0.5 μm to about 2 μm .
10. The biodegradable ocular implant of any one of claims 1-9, comprising about 20% w/w to about 60% w/w edonentan, or a pharmaceutically acceptable salt thereof.
11. The biodegradable ocular implant of any one of claims 1-10, comprising about 40% w/w to about 50% w/w edonentan, or a pharmaceutically acceptable salt thereof.
12. The biodegradable ocular implant of any one of claims 1-11, comprising about 45% w/w edonentan, or a pharmaceutically acceptable salt thereof.
13. The biodegradable ocular implant of any one of claims 1-12, wherein the edonentan is present in its free base form as a crystalline anhydrate.
14. The biodegradable ocular implant of any one of claims 1-13, comprising about 40% w/w to about 80% w/w of the biodegradable polymer.
15. The biodegradable ocular implant of any one of claims 1-14, comprising about 50% w/w to about 60% w/w of the biodegradable polymer.
16. The biodegradable ocular implant of any one of claims 1-15, comprising about 55% w/w of the biodegradable polymer.
17. The biodegradable ocular implant of any one of claims 1-16, wherein the biodegradable polymer comprises one or more poly(lactic-co-glycolic acid) (PLGA) polymers.

18. The biodegradable ocular implant of claim 17, wherein the one or more PLGA polymers is selected from the group consisting of RG502, RG503, RG753S, DLG5002E, DLG5003E, DLG7505E, and combinations thereof.
19. The biodegradable ocular implant of any one of claims 1-18, wherein the biodegradable polymer comprises PLGA RG503 and PLGA RG753S.
20. The biodegradable ocular implant of claim 19, comprising about 16.5% w/w of PLGA RG503 and about 38.5% w/w of PLGA RG753S.
21. The biodegradable ocular implant of any one of claims 1-18, wherein the biodegradable polymer comprises PLGA RG502, PLGA RG503, and PLGA RG753S.
22. The biodegradable ocular implant of claim 21, comprising about 5.5% w/w of PLGA RG502, about 27.5% w/w of PLGA RG503, and about 22% w/w of PLGA RG753S.
23. The biodegradable ocular implant of any one of claims 1-18, wherein the biodegradable polymer comprises PLGA DLG5002E, PLGA DLG5003E, and PLGA DLG7505E.
24. The biodegradable ocular implant of claim 23, comprising about 5.5% w/w of PLGA DLG5002E, about 27.5% w/w of PLGA DLG5003E, and about 22% w/w of PLGA DLG7505E.
25. The biodegradable ocular implant of any one of claims 17-24, wherein each of the one or more PLGA polymers present in the biodegradable ocular implant comprises no greater than about 0.5% w/w of residual monomer.
26. The biodegradable ocular implant of any one of claims 1-25, wherein the biodegradable ocular implant has a length of about 4 mm.
27. The biodegradable ocular implant of any one of claims 1-26, wherein the biodegradable ocular implant has a diameter of about 300 μm to about 360 μm .

28. The biodegradable ocular implant of any one of claims 1-26, wherein the biodegradable ocular implant comprises about 180 µg to about 250 µg edonentan.
29. A method of preparing a biodegradable ocular implant comprising edonentan, or a pharmaceutically acceptable salt thereof, and a biodegradable polymer, the method comprising;
- (a) milling the biodegradable polymer;
 - (b) reducing the particle size of the edonentan, or a pharmaceutically acceptable salt thereof, to form a processed edonentan, or a pharmaceutically acceptable salt thereof;
 - (c) mixing the milled biodegradable polymer and the processed edonentan, or a pharmaceutically acceptable salt thereof, to form a blend;
 - (d) hot melt extruding the blend to form the biodegradable ocular implant.
30. The method of claim 29, wherein in step (a), the biodegradable polymer is cryomilled.
31. The method of claim 29 or 30, wherein in step (a), the biodegradable polymer comprises one or more PLGA polymers.
32. The method of claim 31, wherein the one or more PLGA polymers is selected from the group consisting of RG502, RG503, RG753S, DLG5002E, DLG5003E, DLG7505E, and combinations thereof.
33. The method of any one of claims 29-32, wherein in step (a), the biodegradable polymer comprises PLGA RG503 and PLGA RG753S.
34. The method of claim 33, wherein in step (a), the biodegradable polymer comprises about 30% w/w of PLGA RG503 and about 70% w/w of PLGA RG753S.
35. The method of any one of claims 29-32, wherein in step (a), the biodegradable polymer comprises PLGA RG502, PLGA RG503, and PLGA RG753S.
36. The method of claim 35, wherein in step (a), the biodegradable polymer comprises about 10% w/w of PLGA RG502, about 50% w/w of PLGA RG503, and about 40% w/w of PLGA RG753S.

37. The method of any one of claims 29-32, wherein in step (a), the biodegradable polymer comprises PLGA DLG5002E, PLGA DLG5003E, and PLGA DLG7505E.
38. The method of claim 37, wherein in step (a), the biodegradable polymer comprises about 10% w/w of PLGA DLG5002E, about 50% w/w of PLGA DLG5003E, and about 40% w/w of PLGA DLG7505E.
39. The method of any one of claims 29-38, wherein in step (b), reducing the particle size of the edonentan, or a pharmaceutically acceptable salt thereof, comprises passing the edonentan, or a pharmaceutically acceptable salt thereof, through a 100-mesh screen.
40. The method of any one of claims 29-38, wherein in step (b), reducing the particle size of the edonentan, or a pharmaceutically acceptable salt thereof, comprises milling the edonentan, or a pharmaceutically acceptable salt thereof.
41. The method of any one of claims 29-38, wherein in step (b), reducing the particle size of the edonentan, or a pharmaceutically acceptable salt thereof, comprises micronizing the edonentan, or a pharmaceutically acceptable salt thereof.
42. The method of any one of claims 29-41, wherein in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D90 of about 10 μm to about 250 μm .
43. The method of any one of claims 29-42, wherein in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D50 of about 2.5 μm to about 150 μm .
44. The method of any one of claims 29-43, wherein in step (b), the processed edonentan, or a pharmaceutically acceptable salt thereof, has a particle size distribution characterized by a D10 of about 0.5 μm to about 90 μm .
45. The method of any one of claims 29-44, wherein in step (b), the edonentan, before and after milling, is present in its free base form as a crystalline anhydrate.

46. The method of any one of claims 29-45, wherein in step (d), hot melting extruding the blend comprises:

- (i) hot melt extruding the blend at a temperature of about 95 °C to form a first extrudate;
- (ii) hot melt extruding the first extrudate at a temperature of about 100 °C to about 120 °C to an extruded filament; and
- (iii) cutting the extruded filament to form the biodegradable ocular implant.

47. The method of any one of claims 29-45, wherein in step (d), hot melting extruding the blend comprises:

- (i) hot melt extruding the blend at a temperature of about 85 °C to about 90 °C form a first extrudate;
- (ii) hot melt extruding the first extrudate at a temperature of about 88 °C to about 90 °C form a second extrudate;
- (iii) hot melt extruding the second extrudate at a temperature of about 71 °C to about 74 °C form an extruded filament; and
- (iv) cutting the extruded filament to form the biodegradable ocular implant.

48. A method of treating an ocular disease in a subject in need thereof, comprising contacting an ocular tissue of the subject with the biodegradable ocular implant of any one of claims 1-28.

49. The method of claim 48, wherein the ocular disease is selected from the group consisting of glaucoma, diabetic retinopathy, retinal vein occlusion, retinopathy of prematurity, geographic atrophy, and age-related macular degeneration.