

Ocular Implants in the Clinic and Under Clinical Investigation for Ocular Disorders

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Abstract

The human eye is protected with many anatomical and physiological barriers which not only exclude the entry of xenobiotics but also lower the bioavailability of therapeutic agents. A frequent administration of topical eye drop formulations and intravitreal injections is necessary for anterior and posterior segment ocular disorders respectively, to maintain effective tissue drug levels. This potential problem can be narrowed by the use of sustained release ocular implants. Drug loaded ocular implants can sustain the release of the active therapeutic agents and uninterruptedly maintain drug concentrations at the desired site of action. This mini review article discusses about biodegradable and non-biodegradable ocular implants that are present in the clinic and the ones under clinical investigation for anterior and posterior segment ocular disorders.

Keywords: *Encapsulated cell technology; Punctum plugs; Retisert; Iluvian; Anterior and posterior segment ocular disorders*

Introduction

The human eye is considered as a window to the brain and similar to the brain it is protected by various ocular barriers [1]. Topically administered ophthalmic formulations have a bioavailability less than 5% due the presence of various dynamic and static ocular barriers. Dynamic factors like tear dilutions, aqueous humor turn over, retinal-blood barrier and conjunctival-blood barrier causes drug drainage into the systemic circulation. While static barriers like corneal and conjunctival epithelia retard the passive absorption of the drug molecules in the ocular tissues. Along with ocular barriers, precorneal factors such as blinking can reduce the absorption of topically applied eye drop formulations [2]. Ocular implants implanted either surgically or inserted in the anterior segment of the eye can provide controlled drug delivery to the affected ocular tissues over a prolonged period of time. Such novel drug delivery technology can prove to be efficacious over traditional eye drops for improving drug bioavailability and reducing dosing frequency.

Ocular barriers in the posterior segment of the eye like retinal, scleral and choroidal epithelia, and blood retinal barrier limits the entry of systemically administered drugs to reach the back of the eye in therapeutic concentrations. The sclera is a tough layer of collagen fibers limits the permeation of hydrophobic and hydrophilic compounds administered topically to reach to the back of the eye. Macromolecules are practically impermeable through the scleral barrier. This is the reason why many anti-VEGF monoclonal antibodies like Lucentis® and Eylea® are administered through intravitreal injections [3]. Ocular implants can also be advantageous to treat the back-of-the-eye disorders in a similar way to the anterior segment ocular disorders. Intravitreal or posterior ocular segment implants can sustain drug delivery and reduce the frequency of painful intravitreal injections. This mini review attempts to give an insight to the readers about the ocular implants (Figure 1) currently used in the clinic and implants under clinical investigation (Table 1 and 2) for majority of the ocular disorders.

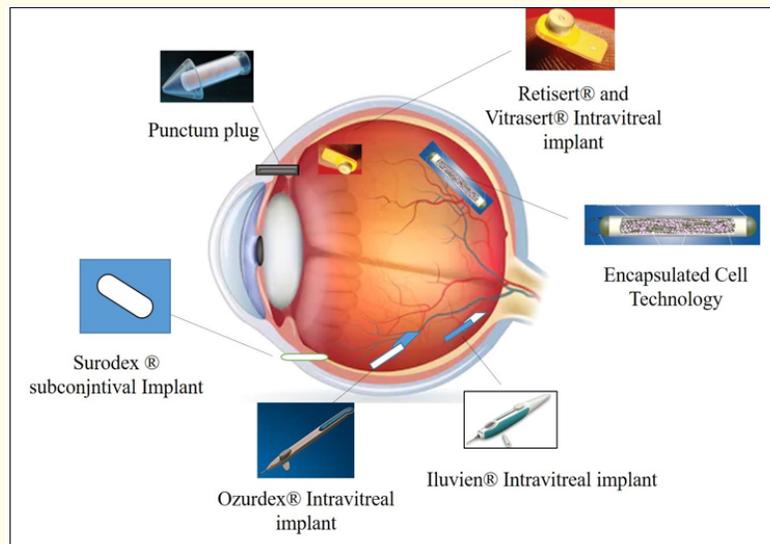


Figure 1: Anterior and posterior segments ocular implants.

Table 1: Anterior segment ocular implants currently under clinical investigation [26].

Drug delivery system	Clinical trial description	Sponsor/Collaborator	Clinical trial number	Phase
Latanoprost punctal plug delivery system (L-PPDS)	1. A Study of the L-PPDS With Adjunctive Xalatan® Eye Drops in Subjects With Ocular Hypertension or Open-Angle Glaucoma. 2. Comparison of Latanoprost PPDS With Timolol Maleate GFS in Subjects With Ocular Hypertension or Open-Angle Glaucoma. 3.A Safety Study of the Latanoprost Punctal Plug Delivery System (L-PPDS) in Subjects With Ocular Hypertension or Open Angle Glaucoma.	Mati Therapeutics Inc.; QLT Inc.	NCT01037036; NCT02014142 NCT00820300	
Punctum plug	Safety and Efficacy of Punctum Plug Insertion in Patients With Dry Eye	Allergan	NCT01684436	
Perforated Punctum Plugs	Perforated Punctum Plugs for Treatment of Papillary Conjunctivitis in Otherwise Healthy Patients	Rabin Medical Center; Alpha Net Co. Ltd.	NCT02503956	
Sirolimus	Subconjunctival Sirolimus for the Treatment of Autoimmune Active Anterior Uveiti.	National Eye Institute (NEI)	NCT02042027	I
Timolol; Bimatoprost Ocular Insert	Dose-Ranging Study of the Bimatoprost Ocular Insert	ForSight Vision5, Inc.	NCT02358369	II
Gamunex-C	Subconjunctival IVIg (Gamunex-C) Injection for Corneal Neovascularization and Inflammatory Conditions	University of Utah	NCT02042027	II
DiscoVisc®; Healon®; Amvisc® Plus	To Compare the Ability of DiscoVisc® OVD to Protect the Corneal Endothelium and Maintain Anterior Chamber Space With Healon® and Amvisc® PLUS During Cataract Surgery	Alcon Research	NCT00763360	IV

Table 2: Posterior segment ocular implants in the clinic and under clinical investigation [25].

Drug, dosage form	Brand, manufacturer or stage of development	Clinical indication	Main excipient/device
Betamethasone Sub-Tenon injection of sustained release microspheres	DE-102; Santen Pharmaceutical Co. Ltd. And Oakwood Laboratories	Macular edema associated with diabetes and branch retinal vein occlusion	Biodegradable microspheres
Sirolimus Intravitreal injections	DE-109; Santen Pharmaceutical Co. Ltd. And Oakwood Laboratories	Non-infectious uveitis of the posterior eye	A slowly dissolving depot
Biosilicon DDS for small molecules and macromolecules	Thethadur; pSivida Corp.	Intraocular diseases	Honeycomblike nanostructured bioerodible/non-erodible porous silicon
Ganciclovir ophthalmic implant	Vitrasert™, Zirgan™; pSivida Corp.	Cytomegalovirus (CMV) ocular infection	Sustained-release silicon implant
Fuocinolone-loaded ophthalmic implant	Retisert™; pSivida Corp.	Chronic non-infectious posterior uveitis	Sustained-release silicon implant
Fuocinolone-loaded ophthalmic implant	Iluvien™; pSivida Corp.	Chronic non-infectious posterior uveitis	Sustained-release silicon implant
Lntanoprost ophthalmic implant	Durasert™; pSivida Corp.	Ocular hypertension and glaucoma	Sustained-release biodegradable implant
Dexamethasone Intravitreal implant	Ozurdex™; Allergan, Inc.	Diabetic macular edema (DME)	Sustained-release silicon implant
Dexamethasone Injectable ophthalmic emulsion	Cortiject™; Santen Pharmaceutical Co. Ltd.	DME; noninfectious inflammation of the uvea; central retinal vein occlusion (CRVO)	Injectable ophthalmic emulsion containing a corticosteroid prodrug
Triamcinolone ophthalmic injection	IBI-20089 Verisome™; Icon Bioscience	Cystoid macular edema (CME)	Sustained-release intravitreal lipid-based DDS as verisome (translucent liquid to form gel in the eye)
BioSilicon-based protein delivery system	Tethadur; pSivida Corp.	Neuroprotective agents	Sustained-release biodegradable (PLGA)/ biosilicon implant
Brimonidine Intravitreal implant	NCT02087085; Allergan Inc.	Geographic atrophy, Macular degeneration	Intravitreal Implant
Bimatoprost Sustained-release DDS	NCT02250651; Allergan Inc.	Glaucoma, Open-Angle Ocular Hypertension	Sustained-release DDS
triamcinolone acetonide Sustained-release implant	I-vation™; Surmodics Inc.	DME	Sustained-release DDS poly(methyl methacrylate), ethylene-vinyl acetate copolymer
Laser activated injectable DDS	ODTx	Different diseases in posterior segment of the eye	Controlled drug delivery by activating specific reservoirs
Ciliary neurotrophic factor (CNTF) producing cells Semipermeable hollow fiber membrane	Renexus (NT-501); Renexus Group & Noah Group	Atrophic age-relate macular degeneration (AMD)	Semipermeable hollow fiber membrane with ciliary neurotrophic factor (CNTF) producing cells [retinal pigment epithelium (RPE)]
VEGF receptor Fc-fusion protein (VEGFR-Fc)-releasing cells	NT-503; Neurotech	AMD	Semipermeable hollow fiber membrane with ciliary neurotrophic factor (CNTF) producing cells [retinal pigment epithelium (RPE)]
Triamcinolone acetonide (TA) Injection device for DDS	iTrack microcatheter; iScience Interventional	Neovascular AMD	Injection device for suprachoroidal delivery of TA
Ranibizumab Refillable port drug delivery system (PDS)	Genentech, ForSight Vision 4 Inc.	ADM	Ranibizumab controlled-release PDS

Anterior segment ocular implants

Drug loaded ocular implants can be inserted or implanted into the anterior segment of the eye for controlled drug delivery which can sustain for a prolonged period. Anterior segment ocular implants can be either inserted into the tear ducts called as punctum plugs or be inserted in the *cul-de-sac* pocket of the eye lids. Anterior ocular implants can also be surgically inserted into the conjunctival region for uninterrupted and prolonged drug delivery. The following section discusses in brief about various anterior segment implants [4].

Punctum plugs

Punctum plugs, also known as lacrimal plugs are biocompatible and noninvasive anterior segment ocular implants inserted into the tear ducts. Punctum plug delivery system (PPDS) provides sustained and controlled drug release up to 180 days. SmartPlug® is a recently developed PPDS constructed from a thermosensitive hydrophobic acrylic polymer for dry eye disease. SmartPlug® absorbs surrounding fluids and forms a soft gel like structure [5]. Ocular Therapeutix™ (Bedford, MA, USA) has developed three PPDS. (i) OTX-TP (travoprost PPDS) for the controlled delivery of travoprost for 90 days to treat ocular hypertension is in a Phase III clinical trial (NCT02914509), (ii) OTX-DP (dexamethasone PPDS) in a Phase III clinical trial for the treatment of chronic allergic conjunctivitis and inflammation after cataract surgery (NCT02988882, NCT02736175), (iii) OTX-TP2 (travoprost PPDS) has completed Phase I clinical trial for open angle glaucoma (NCT01845038) [6].

Cul-de-sac implants

Cul-de-sac is a depression where the palpebral and the bulbar conjunctiva meet in the lower or the upper eyelids. Lacrisert® and Ocuser® are examples of *cul-de-sac* implants. Ocuser® delivers pilocarpine over a period of seven days and indicated for the treatment of glaucoma. Pilocarpine in the insert caused unwanted side effects like miosis and eyebrow ache which resulted in its removal from the market [7]. Lacrisert® is a hydroxypropyl cellulose implant indicated for the treatment of dry eye disease [8]. It acts as a lubricant releasing cellulose which helps to maintain the tear film integrity. However, Lacrisert® can cause ocular irritation, foreign body sensation, hyperemia, blurry vision and hypersensitivity [9].

Subconjunctival implants

Ocular implants are surgically inserted into the sub-conjunctival region and the episcleral region for prolonged drug delivery to the anterior ocular tissues. Surodex® is inserted into the sub-conjunctival region following cataract surgery to relieve post-surgery inflammation. Surodex® releases drug (dexamethasone) for a period of 7 - 10 days [10]. LX201 is a conjunctival implant developed by Lux Biosciences for the delivery of Cyclosporine-A to the conjunctiva and cornea for period of one year. The effectiveness of LX201 is being evaluated in a Phase III clinical trial for the treatment of corneal graft rejection (NCT00447642).

Posterior segment ocular implants

Drug delivery for posterior segment ocular diseases remains challenging due to various barriers. Ocular implants inserted surgically in the back-of-the eye, which can help to cure disorders like age related macular degeneration (AMD), diabetic retinopathy (DR), diabetic macular edema (DME), posterior uveitis and retinal vein occlusion (RVO). Posterior ocular segment implants or intravitreal implants can sustain drug release and reduce the need of frequent intravitreal injections and associated pain. This can greatly help in overcoming the disadvantages of intravitreal injections like retinal hemorrhage, retinal detachment and low patient compliance due to frequent injections. The following section gives an overview about intravitreal implants currently used in the clinic.

Vitrasert® intravitreal implant

Vitrasert® (Bausch and Lomb, Inc, USA) releases antiviral drug ganciclovir (4.5 mg) for a period of 6 - 8 months. It is used for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) [11]. It utilizes Durasert™ technology and releases the active therapeutic agent for a prolonged period. Durasert™ consists of a drug core surrounded by layers of polymers encapsulated in a cylindrical device with a small orifice. The drug release into the surrounding aqueous media depends upon the polymer concentration and the types of polymers used.

Retisert® intravitreal implant

Retisert® (Bausch and Lomb, Inc., USA) is an intravitreal fluocinolone acetonide eluting implant, which is surgically implanted into the vitreous humor through the pars plana and anchored to the sclera by a suture [12]. Retisert® contains fluocinolone acetonide, which is surrounded by a silicon elastomer cup containing an orifice for drug elution. The intraocular steroid implant can release the drug up to three years and maintain the anti-inflammatory effect after a single implantation [13,14]. The implant received a fast track FDA approval as an orphan drug for treatment of posterior uveitis [15].

Iluvien® intravitreal implant

Iluvien® (Alimera Sciences) an intravitreal implant, contains steroid drug fluocinolone acetonide (0.19 mg) indicated for the treatment of DME. It is the most recent FDA approved intravitreal implant approved in 2014 and the first long term acting treatment for DME [16]. Iluvien® can release sub microgram levels of fluocinolone acetonide for a prolonged period of 36 months [17]. Iluvien® demonstrated improved signs and symptom of DME with lower and higher dose of fluocinolone acetonide in a Phase II clinical trial. The lower dose implant released 0.2 µg/day while the higher dose released 0.5 µg/day of fluocinolone acetonide. The onset of action after insertion of Iluvien® implant was very rapid and the effectiveness of the implant lasted for a period of three years [18]. Currently Iluvien® is being evaluated for the treatment of wet AMD (NCT00605423), dry AMD (NCT00695318) and macular edema secondary to RVO (NCT00770770) as compared to standard anti-VEGF therapy (Leucentis®).

Ozurdex® intravitreal implant

Ozurdex® (Allergan, CA, USA) is a dexamethasone-implant approved by FDA for the management of macular edema following branched retinal vein occlusion or central retinal vein occlusion [19]. The implant contains 0.7 mg dexamethasone in a poly lactide-co-glycolide (PLGA) matrix which can provide sustained drug release for 90 days. Ozurdex® consists of Novadur™ system which is biodegradable and biocompatible system made from a matrix of PLGA. PLGA polymer hydrolyses in vitreous humor to release lactic acid and glycolic acid making the PLGA matrix biodegradable. Ozurdex® is currently being evaluated as a mono therapy in a Phase III clinical trial for its efficacy in treating DME (NCT00168389). Allergan has developed another PLGA intravitreal implant containing brimonidine tartrate which is a α 2 adrenergic agonist. The implant releases neurotrophic factors like brain derived neurotrophic factor and ciliary neurotrophic factor [20]. The implant is being evaluated in clinical trials for its safety and efficacy for the treatment of retinitis pigmentosa (NCT00661479) and dry AMD (NCT00658619). The neurotrophic factors released from the brimonidine implant can rescue the cell death of retinal cell layers like retinal pigment epithelium, photoreceptors and ganglion cells [21].

Encapsulated cell technology

Ocular implants made from Encapsulated Cell Technology (ECT) contain a capsule consisting of genetically modified cells confined in a polymeric biocompatible matrix. Biocompatible and biodegradable polymers like hyaluronic acid and collagen are utilized for this matrix formation. ECT intravitreal ocular implant has an outer semipermeable membrane, which allows the transport of neurotrophic factors from the implant but does not allow the entry of immune cells into the implant from the surrounding tissue. ECT implant absorbs nutrients from the surrounding vitreous humor and tissue matrix, which aids the growth of transfected cells. These implants are inserted into the pars plana and attached to the sclera of the posterior segment of the eye [22]. Renexus® (NT-501) is an example of ECT intravitreal implant which contains transfected human retinal pigment epithelium cells with a plasmid encoding for neurotrophic growth factor like ciliary neurotrophic factor (CNTF). Renexus® is currently under a Phase III clinical trial for glaucoma, dry AMD and retinitis pigmentosa (NCT03316300). ECT ocular implants produce and release active biological molecules for a prolonged period, thus helping in ocular tissue regeneration. Scientists have also demonstrated that genetically modified RPE can also produce soluble VEGF-1 receptor for a period of 50 days [23]. Although the investigators reported a modest VEGF inhibition *in-vivo* model, this technology can be used to treat back-of-the-eye disorders like AMD, DR, DME and macular edema [24].

Conclusion and Future Directions

This mini review illustrates in brief ocular implants currently under development and used in the clinic for various ocular disorders. The traditional ocular drug delivery systems like eye drops for the anterior segment ocular disorders and intravitreal injections for the posterior segment ocular disorders require frequent dosing. This is primarily due to the rigid ocular barriers which discourages active absorption of the therapeutic molecules to a great extent. Drug eluting ocular implants can be a very useful novel ocular drug delivery platform to overcome the problems associated with the use of above mentioned traditional ocular drug delivery systems. Ocular implants not only increase drug bioavailability but also sustain from months to years depending on the end use. Although ocular implants seems as an attractive and convenient alternative to traditional ocular drug delivery systems, they also cause ocular irritation, foreign body sensation, possible immunological resection and the possible problem of floaters for posterior segment implants. Hence, while developing ocular implants, the surface characters and the biomaterials used in the preparation of such devices should also be of importance. Bio-inspired drug delivery systems [25] and components can result in superior performing ocular implants. Use of appropriate preclinical disease model can go a long way in predicting the performance of the ocular implants at an early stage. Ocular implants is an innovative way of ocular drug delivery and its success in the clinic demands further research and development for higher performing ocular implants.

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