

Biodegradable Implants for Sustained Drug Release in the Eye

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ABSTRACT The safety and effectiveness of systemic and topical medical therapies for ocular disorders are limited due to poor ocular drug uptake, nonspecificity to target tissues, systemic side effects, and poor adherence to therapy. Intravitreal injections can enhance ocular drug delivery, but the need for frequent retreatment and potential injection-related side effects limit the utility of this technique. Sustained-release drug delivery systems have been developed to overcome these limitations; such systems can achieve prolonged therapeutic drug concentrations in ocular target tissues while limiting systemic exposure and side effects and improving patient adherence to therapy. A critical factor in the development of safe and effective drug delivery systems has been the development of biocompatible polymers, which offer the versatility to tailor drug release kinetics for specific drugs and ocular diseases. Ocular implants include nonbiodegradable and biodegradable designs, with the latter offering several advantages. The polymers most commonly used in biodegradable delivery systems are synthetic aliphatic polyesters of the poly- α -hydroxy acid family including polylactic acid, polyglycolic acid, and polylactic-co-glycolic acid. The characteristics of these polymers for medical applications as well as the pharmacological properties, safety, and clinical effectiveness of biodegradable drug implants for the treatment of ocular diseases are reviewed herein.

KEY WORDS biodegradable polymer · ocular implant · polylactic acid · polylactic-co-glycolic acid · sustained release

INTRODUCTION

Topical drug therapy is the primary form of treatment for front-of-the-eye diseases, such as ocular surface diseases (e.g., conjunctivitis, dry eye), for elevated intraocular pressure, and for anterior uveitis (1–3). Anatomical and physiological barriers in the eye, including the corneal epithelium and conjunctival clearance mechanisms, afford protection against the entry of xenobiotics. These barriers also greatly impede the entry of drugs to the posterior segment, making it difficult to achieve therapeutic drug concentrations (1–4). Treatment of back-of-the-eye diseases such as diabetic retinopathy, neovascular age-related macular degeneration, and retinal venous occlusive disease is especially challenging with topical therapy given the greater diffusional distance (5). Although successful in rodent models (6,7), topical therapy for retinal diseases has yet to be proven successful in clinical trials. Systemically administered drugs can be used for treating front- and back-of-the-eye diseases. However, the accessibility of ocular tissues is greatly limited by the blood-aqueous and blood-retinal barriers. As a result, high systemic doses must be administered, which increases drug exposure in non-ocular tissues and, consequently, the risk of adverse systemic side effects (2,8).

Intravitreal drug injections have been used to deliver high drug concentrations to target tissues in the eye. However, the half-life of many intravitreally administered, low molecular-weight drugs, such as corticosteroids, ranges from 2 to 6 h (9), which results in transient efficacy and the need for frequent re-injections to maintain therapeutic drug

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concentrations (10). Larger molecular-weight compounds, such as vascular endothelial growth factor (VEGF) antibodies and antigen-binding fragments, have longer half-lives but still require monthly injections to maximize patient visual acuity potential (11–14). Frequent intravitreal injections increase the risk of serious adverse events including retinal detachment, endophthalmitis, and vitreous hemorrhage, as well as adverse manifestations in the anterior segment, such as cataract formation and intraocular pressure (IOP) elevation with corticosteroid use (15,16). Although the incidence rates of these serious side effects may be relatively low, they can be sight-threatening. Due to the anatomic and physiologic barriers to both topical and systemic drug therapy and the relatively short half-life of compounds administered by intravitreal injection (Table I), sustained drug delivery systems have evolved over the past decade to become an important approach for treating a variety of ocular diseases.

Sustained-release intrascleral and intravitreal drug implants and inserts have been developed for the treatment of ocular diseases. These polymer-based drug delivery systems are designed to achieve prolonged therapeutic drug concentrations in ocular target tissues that are not readily accessible by conventional means while limiting the side effects from systemic drug exposure, frequent intraocular injections, and high peak drug concentrations associated with pulsed dosing, as well as improving patient compliance (5,8,17,18).

Polymeric ocular drug delivery systems are classified as two basic types: nonbiodegradable and biodegradable (Table II) (5,10,19). The two most common nonbiodegradable device types include reservoir-type devices, in which a drug core is slowly released across a nonbiodegradable semipermeable polymer or is released from a nonbiode-

gradable polymer with an opening of fixed area, and implant-type devices, in which a nonbiodegradable free-floating pellet is injected intravitreally or a nonbiodegradable plug is anchored to the sclera. In a reservoir-type system, release kinetics can achieve a near-zero-order rate after establishing a steady-state concentration gradient across the nonbiodegradable semipermeable membrane. As long as solid drug remains within the core, the drug release will be relatively constant. Biodegradable systems are typically the matrix (monolithic) type, consisting of a homogeneous resin pellet made from drug and a biodegradable polymer; however, biodegradable core-shell and microcapsule systems have also been studied (20,21). Most of the clinically available ocular implants to date have been of the nonbiodegradable type, typically consisting of a combination of polyvinyl alcohol (PVA) and ethylene vinyl acetate (EVA) (21).

BIODEGRADABLE OCULAR DRUG DELIVERY SYSTEMS

Biodegradable ocular drug delivery devices are composed of biocompatible polymers, which degrade into nontoxic byproducts, or polymers that solubilize *in vivo* and can be eliminated safely by the human body. Devices made from these polymers do not elicit permanent chronic foreign-body reactions (22) and do not require removal after the drug supply has been exhausted (1,23), which represents a distinct advantage over nonbiodegradable drug delivery systems. Biodegradable devices are typically constructed from synthetic aliphatic polyesters of the poly- α -hydroxy acid family, which include polyglycolic acid (PGA), polylactic acid (PLA), and the PGA/PLA copolymer, poly(lactic-co-glycolic acid) (PLGA).

PLGA is synthesized by means of random ring-opening copolymerization of the cyclic dimers of glycolic acid and lactic acid. Successive monomeric units of glycolic or lactic acid are linked together in PLGA during polymerization by ester linkages. The ratio of lactide to glycolide used for the polymerization can be varied, and this will alter the biodegradation characteristics of the product (Fig. 1). The possibility to tailor the polymer degradation time by altering the ratio of the lactic acid and glycolic acid used during synthesis has made PLGA attractive for use in the production of a variety of biomedical devices since the 1970s. PLGA is relatively easy to construct into various shapes, such as rods, screws, plates, and pins for orthopedic and dental surgery; resorbable suture materials; vascular grafts and stents; and surgical meshes and scaffolding for tissue regeneration (22,24). Importantly, the rate of PLGA biodegradation, molecular weight and degree of crystallinity affects the drug release characteristics of drug delivery

Table I Limitations of Ocular Drug Delivery Methods

Method	Limitations
Topical administration	<ul style="list-style-type: none"> Limited uptake Tear dilution/washout Short acting Poor adherence to therapy
Intravitreal injection	<ul style="list-style-type: none"> Targeted delivery Invasive/inconvenient/short lasting Adverse events related to injection
Systemic administration	<ul style="list-style-type: none"> Limited ocular penetration Systemic toxicity
Nonbiodegradable implants	<ul style="list-style-type: none"> Invasive surgery Require removal Adverse events related to implantation or removal surgery

systems, thus giving polymer composition a significant role in the customization of implant characteristics.

The rate of drug release from biodegradable devices depends on the total surface area of the device, the percentage of loaded drug, the water solubility of drug, and the speed of polymer degradation (25). An advantage of PLGA-based delivery systems is that the rate and degree of drug release can be manipulated by altering the polymer composition to influence the degradation characteristics (24). The three main factors that determine the degradation rate of PLGA copolymers are the lactide:glycolide ratio (Fig. 1), lactide stereoisomeric composition (i.e., the amount of L- vs. DL-lactide), and molecular weight (22,24). The lactide:glycolide ratio and stereoisomeric composition are most important for PLGA degradation, as they determine polymer hydrophilicity and crystallinity. PLGA with a 1:1 ratio of lactic acid to glycolic acid degrades faster than PLA or PGA (5), and the degradation rate can be decreased by increasing the content of either lactide or glycolide (Fig. 1) (21). Polymers with degradation times ranging from weeks to years can be manufactured simply by customizing the lactide:glycolide ratio and lactide stereoisomeric composition (24). The versatility of PGA and PLA has enabled the construction of delivery systems to tailor drug release for treating a variety of front- and back-of-the-eye diseases.

Drug release from PLA- and PLGA-based matrix drug delivery systems generally follows pseudo first-order or square-root kinetics. Release is influenced by many factors, including polymer, drug load, implant morphology, and porosity. In general, drug release occurs in three phases (Fig. 2):

- 1: Burst release: Drug release from the implant surface occurs, creating a short period of high drug release.
- 2: Diffusion and chain scission: Diffusional drug release, which is governed by the inherent solubility of the drug in the surrounding media, occurs. Random chain scission of polymers occurs by hydrolytic cleavage, which increases the porosity and surface area for drug diffusion
- 3: Biodegradation and mass loss: Drug release is associated with biodegradation of the polymer matrix, mass loss initially occurring in the central core of the implant, and a final burst in some delivery systems (Fig. 2) (1,3,5,19). The rapid achievement of high drug concentrations followed by a longer period of continuous lower-dose release makes such delivery systems ideally suited for acute-onset diseases that require a loading dose of drug followed by tapering doses over several months (20). More recent advancements in PLGA-based drug delivery systems have allowed for biphasic release characteristics with an initial high

(burst) rate of drug release followed by sustained zero-order kinetic release; i.e. drug release rate from matrix is steady and independent of the drug concentration in the surrounding milieu over longer periods (10).

PLA, PGA, and PLGA are cleaved predominantly by nonenzymatic hydrolysis of their ester linkages throughout the matrix, in the presence of water in the surrounding tissues. This process, referred to as bulk erosion, is distinguished from surface erosion of the drug/polymer matrix surface (5) occurring with polymers such as polyanhydrides (PAH) and polyorthoesters (POE). PLA, PGA, and 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 (23,24).

Safety of Biodegradable Polymers

The safety and biocompatibility of PLGA polymers was first demonstrated through their use in the production of the biodegradable sutures Dexon® (PGA; Covidien AG, Switzerland) and Vicryl® (L-PLGA; Johnson & Johnson Corp., New Brunswick, NJ), which have been used successfully in the clinical setting for more than 30 years (24). The biocompatibility of PLA and PLGA polymers has been further examined in both non-ocular and ocular tissues of animals and humans. The findings indicate that the polymers are generally well tolerated. In a long-term follow-up study of patients who had received PLA- and PLGA-containing resorbable-plate osteosyntheses for maxillary and mandibular fracture/reconstruction, radiographic imaging and histopathological assessments showed reliable biocompatibility and disintegration for both polymers: 85:15 PLGA degraded within 12 months and 70:30 PLA within 24 months (26). Acceptable biocompatibility of PLA and/or PLGA polymers has been demonstrated based on *in vitro* studies in dura, spinal cord, Schwann cells, brain tissue, and peripheral nerves (27).

The host response to polymeric implants is multifactorial and is affected by the physical and chemical properties of the polymer and by the physical properties of the implant (volume, shape, and surface characteristics). The response can be categorized to be tissue-dependent, organ-dependent, and species-dependent (25). Implantation of PLGA in bone or soft tissue of animals causes no inflammatory response, or only a mild response that diminishes with time, and is not associated with toxicity or allergy. In addition, the biocompatibility of PLGA-containing sutures and fracture fixation devices (rods, pins, screws, and plates) has been confirmed in human clinical

Table II Pharmacological Therapies and Drug Delivery Systems for the Treatment of Chronic Ocular Diseases

Brand name	Manufacturer	Materials	Active agent	Duration of drug release	Characteristics	Eye diseases
Biodegradable implants						
Surodex™ (18,20,33–36,57)	Allergan, Inc.	PLGA, HPMC	Dexamethasone (60 µg)	7–10 days	Biodegradable pellet	Investigational in the USA: Postoperative inflammation following cataract surgery (phase 3). Regulatory approvals in Singapore, China, Mexico
Ozurdex® (DEX PS DDS®) (37,38)	Allergan, Inc.	PLGA	Dexamethasone (0.7 mg)	6 months	Biodegradable, rod-shaped intravitreal implant	FDA approved for the treatment of macular edema following branch RVO or central RVO ^a . Investigational: DME, uveitis (Clinicaltrials.gov ID# NCT00168337; NCT00168389; NCT00333814)
Lacrisert® (32)	Aton Pharma	HPC	HPC (5 mg)	1 day	Biodegradable, translucent, rod-shaped, water-soluble insert	FDA approved for the treatment of moderate to severe dry eye syndrome, including keratitis sicca ^a
IBI 20089/Verisome™ (39,40,58)	ICON Bioscience, Inc.	Proprietary	Triamcinolone acetonide (6.9–13.8 mg)	Up to 1 year	Biodegradable	Investigational: CME associated with retinal vein occlusion and postoperative cataract surgery
Nonbiodegradable implants						
Ocusert® Pilo (1–3,8,59–61)	Alza Corp.	EVA, alginate acid	Pilocarpine (Ocusert Pilo-20, 20 µg/h; Ocusert Pilo-40, 40 µg/h)	Up to 7 days	Nonbiodegradable	FDA approved for the treatment of glaucoma (no longer marketed)
I-vation™ (1,3,10)	SurModics	Drug-polymer-coated nonferrous alloy helix (PBMA/PVA; Bravo Drug Delivery Polymer Matrix) EVA/PVA	Triamcinolone acetonide (1–3 µg/day)	2 years	Nonbiodegradable intravitreal implant	Investigational: DME phase 2b trial suspended in 2008 (Clinicaltrials.gov ID# NCT00692614)
Vitrasert® (62)	Bausch & Lomb	Silicone/PVA	Ganciclovir (4.5 mg)	5 to 8 months	Implantable reservoir system	FDA approved for the treatment of AIDS-related CMV retinitis ^a
Retisert® (1,10,56,63)	Bausch & Lomb/psSivida Ltd.	Silicone/PVA	Fluocinolone acetonide (0.59 mg)	Up to 3 years	Nonbiodegradable disc-shaped (3 × 2 × 5 mm) intravitreal implant	FDA approved for the treatment of uveitis. Investigational: DME, RVO
Lumitect™	NEI and NIH/Lux BioSciences	Silicone matrix	Cyclosporin (15–25 µg/day)	≈3 years	Episcleral implant (0.75–inch and 0.5 inch) versions	Investigational: GVHD (clinicaltrials.gov identifier NCT00102583); corneal allograft rejection (clinicaltrials.gov identifier NCT00447642)

Iluvien™/Medidur™ (10.63)	Alimera Sciences	PVA (with silicone bioadhesive in low-dose version)	Fluocinolone acetonide (0.59 mg; 0.2–0.5 µg/day)	18–30 months	Nonbiodegradable rod-shaped (3.5 mm length × 0.37 mm diameter) intravitreal implant	Investigational: DME (phase 3)
NT-501 (64–66)	Neurotech	Hollow-fiber membrane supported by a PETP scaffold	Ciliary neurotrophic factor (up to 15 ng/day)		Nonbiodegradable, polymer encapsulated drug-secreting cells	Investigational: ARMD, retinitis pigmentosa

^a See individual product labels for complete information

ARMD age-related macular degeneration. CME cystoid macular edema. DME diabetic macular edema. EVA ethylene vinyl acetate. FDA Food and Drug Administration. GVDH graft-versus-host diseases. HPC hydroxypropyl cellulose. HPMC hydroxypropyl methylcellulose. ME macular edema. NEI National Eye Institute. NIH National Institutes of Health. PBMA polybutyl methacrylate. PETP polyethylene terephthalate. PLGA polylactic-co-glycolic acid. PVA polyvinyl alcohol. RVO retinal vein occlusion. $t_{1/2}$ half-life.

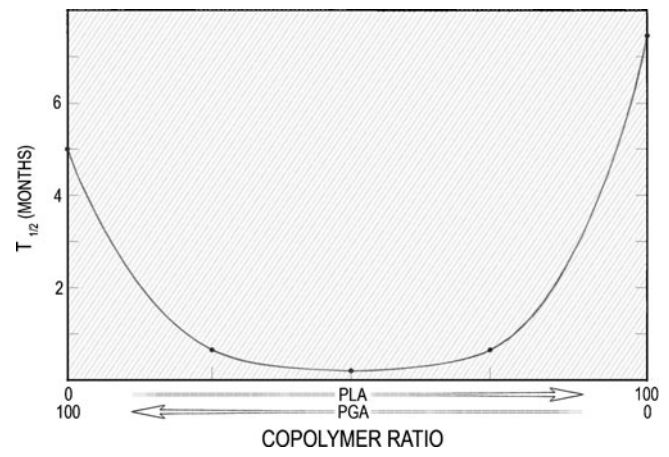
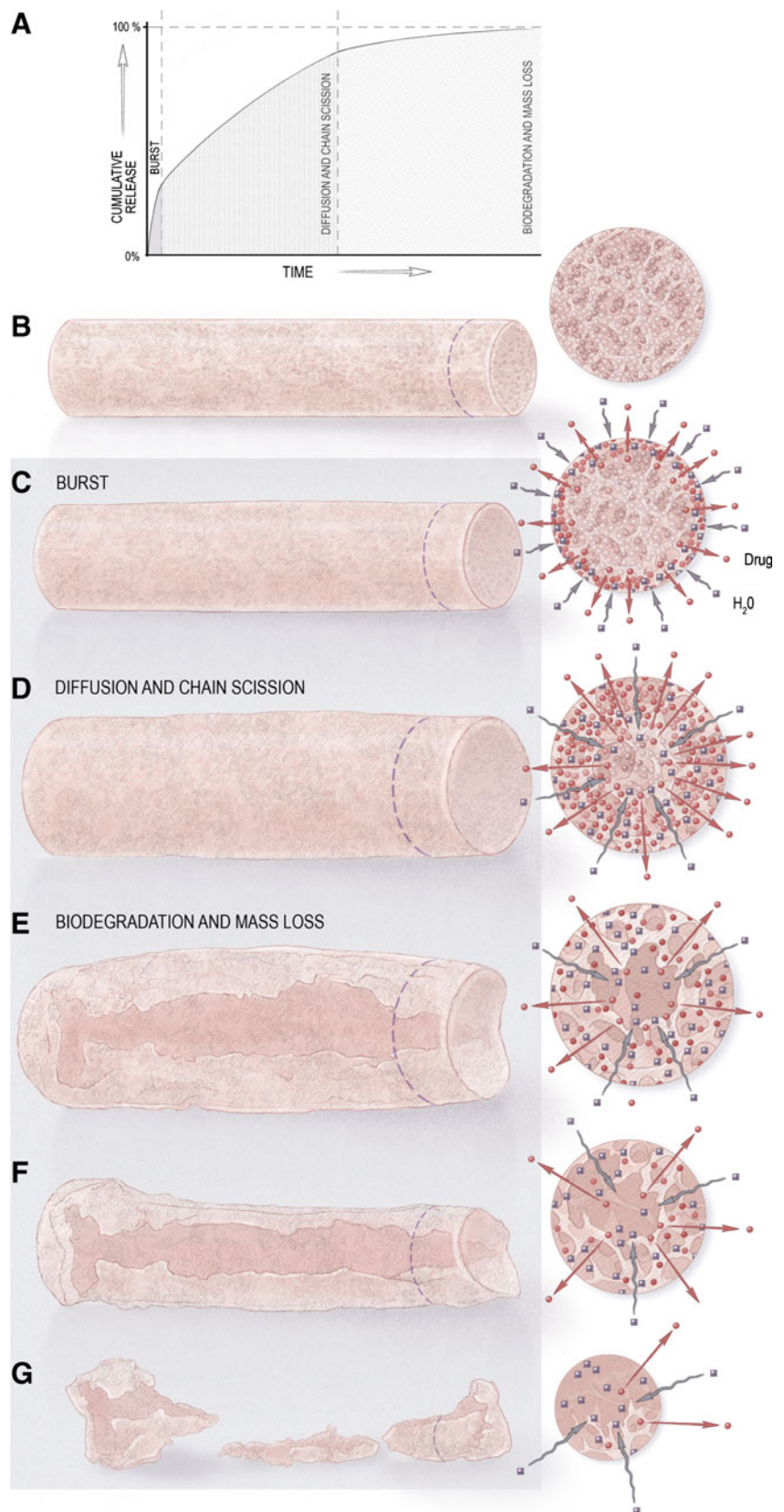


Fig. 1 Relationship between lactide/glycolide content and degradation half-life of PLGA. Graph illustrates how PLA and PGA polymer ratios can be adjusted to result in a specific biodegradation half-life and drug release from the implant.

trials (24). Examples of implantable PLGA-containing products marketed to date include Vicryl® (Ethicon) and Polysorb® (U.S. Surgical, North Haven, CT) sutures; Biologically Quiet (Instrument Makar, Okemos, MI) and SD sorb (Surgical Dynamics, Norwalk, CT) suture anchors; orthopedic fixation devices such as Lactosorb® (Biomet, Warsaw, IN) and BiosorbPDX (Bionx Implants, Bluebell, PA) screws for craniomaxillofacial fixation, Biologically Quiet staples (Instrument Makar) for ACL reconstruction, SD sorb meniscal staples (Surgical Dynamics) for meniscus repair, and SmartPinPDX pins (Bionx) for fracture fixation; and non-ocular drug delivery implants such as Zoladex (goserelin acetate, AstraZeneca UK Ltd., UK) for prostate cancer, Nutropin® Depot (human growth hormone; Genentech, Inc., South San Francisco, CA) for growth deficiencies, Trelstar® Depot (triptorelin pamoate) for prostate cancer, and Sandostatin LAR® (octreotide; Novartis AG, Switzerland) for acromegaly (24).

PLA and PLGA biocompatibility has also been studied in ocular tissues, and the polymers have been suggested to display even better tolerability than when placed in nonocular tissues. The anterior chamber, vitreous cavity, and subretinal space are known to display immune privilege. The features that account for the immune privilege of the eye include the blood-ocular barrier as well as the absence of lymphatic drainage pathways, soluble immunomodulatory factors in aqueous humor, immunomodulatory ligands on the surface of ocular parenchymal cells, and indigenous tolerance-promoting antigen-presenting cells (28). Based on these features, it has been speculated that polymers implanted into the vitreous cavity would provoke less of an inflammatory reaction than in other tissues. Biodegradable PLA/PLGA polymers have been experimentally implanted in various tissues of the eye and have been shown to be well tolerated (5,29–31).

Fig. 2 Drug-release mechanisms and biodegradation of matrix implant. **a** Schematic graph illustrating the cumulative release of drug from a PLGA implant at each phase of drug release and biodegradation. **b** Dry implant prior to implantation shows porous structure of PLGA. Magnified view (right) shows drug molecules (red spheres) interspersed in the pores and skeleton of the PLGA polymer. **c** Burst phase of drug release is the short phase occurring immediately after implantation. Magnified view (right) shows water penetrating the pores of PLGA (black curved arrows and squares) on the surface and drug molecules diffusing out of the implant on the surface (red arrows and red spheres). **d** Diffusion and random chain scission phase of drug release. Implant swells slightly as water molecules penetrate deeper into the core of the implant. The polymer is undergoing random chain scission, where the long PLGA chains are cleaved at random locations. Magnified view (right) shows water molecules (black curved arrows and squares) and drug molecules (red arrows and spheres) entering and exiting the implant from the core, respectively. **e** Biodegradation and mass loss phase is when the polymer begins to structurally break down from internal cavitation. Magnified view (right) shows that much of the drug molecules have diffused out from the cavity. **f** Continued biodegradation causes structural changes that alter the shape of the implant. Magnified view (right) shows that water is still passing through the polymer and less drug is available for release. **g** Implant fragments towards the end of biodegradation. Magnified view (right) shows that water is still passing through the smaller polymer skeleton and even less drug is available for release.



Examples of Biodegradable Ocular Drug Delivery Systems

Lacrisert® (Aton Pharma, Inc., Lawrenceville, NJ), introduced in 1981, is a sterile, translucent, rod-shaped, water-soluble, biodegradable ophthalmic insert made of hydroxypropyl cellulose (HPC), a physiologically inert substance, for daily administration into the inferior cul-de-sac of the eye. The sustained release of HPC (5 mg) stabilizes and thickens the precorneal tear film and prolongs tear breakup time. The implant is approved to relieve the signs and symptoms of moderate to severe dry eye syndrome, including keratitis sicca, and is indicated especially for patients who remain symptomatic after therapy with artificial tears (32). Once-daily treatment with Lacrisert was shown to be more effective in relieving dry eye symptoms than 4-times-daily treatments with topical artificial tears (32). The implant, which can be self-administered up to twice daily using a specially designed applicator, is generally well tolerated. Side effects, which are typically mild and transient, include blurred vision, ocular discomfort/irritation, matting/stickiness of eyelashes, photophobia, hypersensitivity, eyelid edema, and hyperemia. The results of patient surveys regarding comfort and product preference favored Lacrisert over artificial tears (32).

Surodex™ (Allergan, Inc., Irvine, CA) is a rod-shaped biodegradable matrix implant (1.0×0.5 mm) consisting of dexamethasone and PLGA with hydroxypropyl methylcellulose (HPMC) which provides sustained drug release at a constant rate (60 µg over 7–10 days) (20). The implant is inserted in the anterior chamber following cataract surgery to control postoperative inflammation (33–36). Surodex does not require suture fixation and is well tolerated (18,20). In cataract patients, Surodex was shown to reduce anterior chamber cells and flare in the postoperative period and to have an anti-inflammatory effect at least as good as that of topical steroids (33–35).

A dexamethasone posterior-segment drug delivery system (Ozurdex®, formerly Posurdex, Allergan Inc, Irvine, CA) has recently been introduced into clinical practice.



Fig. 3 Ozurdex sustained-release drug delivery system. The dexamethasone drug pellet at a dose of 350 µg or 700 µg is inserted using a 22-gauge microinjector.

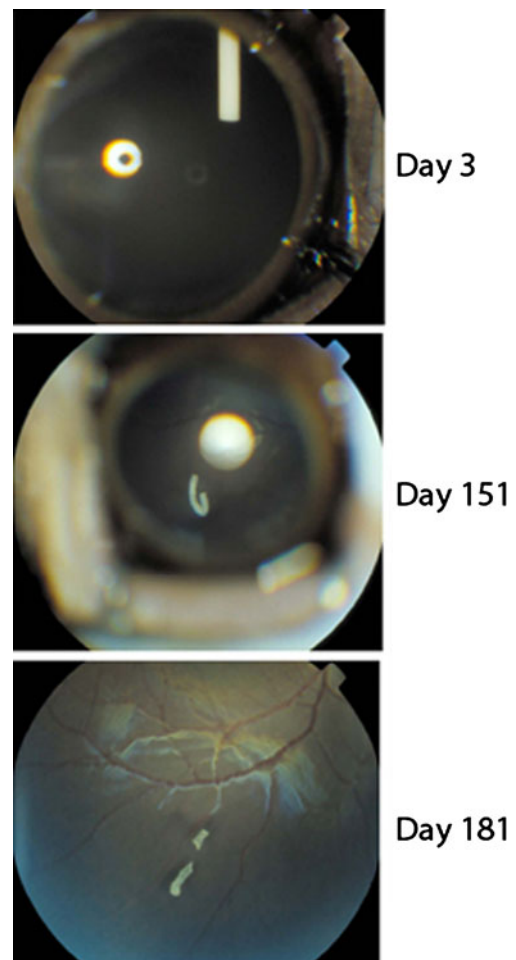


Fig. 4 Photographic images showing biodegradation of PLGA dexamethasone 700-ug implant (Ozurdex) in a monkey eye over a 6-month period (Allergan, data on file).

Ozurdex is a biodegradable implant consisting of 0.7 mg dexamethasone within a solid, rod-shaped PLGA copolymer (Novadur™, Allergan, Inc.) matrix (Figs. 3 and 4). The implant is designed to release dexamethasone biphasically, with peak doses for the initial 2 months, followed by lower therapeutic doses for up to 6 months. A novel single-use applicator is used to insert the drug pellet (6.5 mm×0.45 mm) into the vitreous through a 22-gauge pars plana injection (Fig. 3). The procedure is performed in-office rather than in a surgical setting and does not require sutures for wound closure. Ozurdex was approved by the FDA in June 2009 for the treatment of macular edema (ME) associated with retinal vein occlusion, and it is currently being evaluated in clinical trials for the treatment of macular edema secondary to diabetic retinopathy (Clinicaltrials.gov ID# NCT00168337; NCT00168389) and for the treatment of uveitis (NCT00333814). In a phase 2 clinical trial, patients treated with the 700-µg implant showed marked improvement in vision—up to a 3-line increase in visual acuity as compared with a control

group, with therapeutic effects persisting up to 180 days in some eyes. The treatment was not associated with sterile endophthalmitis or an increased incidence of retinal detachment (37). A clinical safety evaluation of Ozurdex following intravitreal insertion by sclerotomy in a 6-month phase 2 study in patients with persistent ME showed a mild increase in the incidence of adverse events in the treatment groups relative to the observation groups on day 8, which was expected as a result of the surgical procedure (i.e., hyperemia, pruritus, vitreous hemorrhage, and anterior chamber cells and flare) (38). As of October 2009, more than 2,500 patients have been enrolled in Ozurdex studies.

A Novadur-based implant for the delivery of brimonidine tartrate is in the early stages of development. It is currently being evaluated in clinical trials of patients with retinitis pigmentosa (phase 1 and 2; ID NCT00661479), glaucomatous optic neuropathy (phase 2; NCT00693485), age-related macular degeneration (phase 2; NCT00658619), and rhegmatogenous macula-off retinal detachment (phase 2; ID NCT00972374).

Verisome™ (Ramscor, Inc., Menlo Park, CA) is a zero-order sustained-release, intraocular drug delivery technology for the formulation of drugs as long-acting biodegradable solids, gels, or liquids that can be administered intravitreally via a standard 30-gauge injection. The technology is nonpolymer-based and proprietary. It can be adapted for a variety of drugs, including small molecules, peptides, proteins, and monoclonal antibodies, to allow custom tailoring of the duration of action (<http://www.iconbioscience.com/Technology-Overview.html>). An investigational triamcinolone acetonide (TA) formulation using the Verisome system (IBI 20089) was shown in rabbits to provide sustained delivery of TA at a mean daily dose of 1.1 µg/mL for up to 1 year from a single injection (39). IBI 20089 was also recently evaluated for safety and efficacy in a phase 1 trial in 10 patients with cystoid macular edema associated with retinal vein occlusion (40). A formulation of IBI 20089 that delivers 13.8 mg TA was found to significantly reduce macular thickness at 120 days post-treatment and was more effective than a 6.9-mg formulation. The delivery system visibly reduced in size as the drug was released, and it was well tolerated, with the exception of one case of IOP elevation that required surgery.

Other biodegradable polymers, such as glycolide-co-lactide-co-caprolactone copolymers (PGLC), polycaprolactones (PCL), polyorthoesters (POE), and polyanhydrides (PAH), have been explored for ocular drug delivery systems (1,5,17,19), but these technologies are still in the early stages of development, and none have yet been marketed commercially. PGLC has been used in combination with cyclosporine to treat experimental uveitis (41), in an intracameral dexamethasone implant to prevent corneal

graft rejection in an animal model (42), and with FK506 to prolong corneal allograft survival (43). Polymers that degrade by surface erosion, such as POE and PAH (e.g. 1,3-bis-carboxyphenoxypropane), are biocompatible and may reduce drug burst effects when they are not required clinically (1). POE, which is hydrophobic and degrades by surface erosion, has been used to deliver 5-fluorouracil (44). PAH, which also undergoes surface erosion, has been used in implants to deliver 5-fluorouracil, 5-fluorouridine, mitomycin C, taxol, and etoposide as adjuncts in glaucoma-filtration surgery in animals (5,23).

The naturally occurring biopolymers chitosan and gelatin have been used in ocular inserts to deliver levofloxacin and gatifloxacin for the treatment of conjunctivitis. These systems provide prolonged drug release with zero-order kinetics (45).

In addition to their use in sustained-release implants and inserts, biodegradable polymers can be used in a variety of other ways to increase the residence time of drugs, slow drug clearance, and enhance drug absorption. Biodegradable polymers have been employed experimentally as viscosity enhancers, as mucoadhesive agents, in drug-releasing contact lenses, and in injectable formulations (e.g. hydrogels and liposomes as well as microemulsions, microsuspensions, microspheres, microcapsules and their nanoscale counterparts). These therapeutic strategies and examples of such ocular drug delivery systems have been discussed in depth in several recent reviews (1–3,17,19). Microsomes are spherical liposomal structures, ranging in size from roughly 0.01 to 10 µm that consist of vesicular lipid bilayers separated by water or an aqueous buffer compartment (1,2,8). Microsomes allow for the circumvention of cell membrane barriers and protection of the delivered drug from metabolic or immune attack, thereby reducing drug toxicity and enhancing the therapeutic effect. Several studies have examined the feasibility of using microspheres composed from PLGA, PLA, and other biodegradable polymers as biodegradable systems for the sustained ocular delivery of therapeutic drugs (29,31,46) including progesterone (47), adriamycin (30), and pegaptanib (48). Microspheres composed of the biodegradable biopolymer chitosan have been used to deliver acyclovir through the rabbit cornea (49) and have been shown to enhance ocular delivery of ofloxacin from erodible inserts constructed from polyethylene oxide (50). Smaller-sized particulate drug delivery systems include nanoparticles, which are polymeric colloidal particles (ranging in size from 10 to 1,000 nm) consisting of macromolecular materials in which the drug is dissolved, entrapped, encapsulated, and/or to which the drug is adsorbed or attached; nanospheres, which are solid spheres containing drug bound in a matrix or adsorbed on the surface of a colloidal carrier; and nanocapsules, which are small capsules with a central cavity surrounded by a

polymeric membrane (1,2,8). Biodegradable PLA nanoparticles (140 nm) administered intravitreally have been shown to localize in the retinal pigment epithelium (51), and coating nanoparticles with polyethylene glycol (PEG) has been reported to enhance the therapeutic efficacy of treatment for ocular diseases such as autoimmune uveoretinitis (52). Drug-impregnated contact lenses have been widely investigated for the sustained release of ocular drugs (53–55). Soft contact lenses are typically composed of nonbiodegradable hydrogels of poly(2-hydroxyethylmethacrylate) (PHEMA) or hydroxyethylmethacrylate (HEMA) copolymerized with other monomers such as methacrylic acid, acetone acrylamide, and vinyl pyrrolidone. Typically, the amount of drug that can be loaded into such systems is low, and release is usually rapid and poorly controlled; however, entrapping the drug in a biodegradable nanoparticle prior to incorporation into the contact lens can be used to sustain the release (1).

NONBIODEGRADABLE OCULAR DRUG DELIVERY SYSTEMS

In nonbiodegradable reservoir-type devices, PVA, a permeable polymer, is typically used as a structural element, while the device's drug-restricting membrane is composed of EVA, a hydrophobic polymer that is relatively impermeable to hydrophilic drugs (1,3,5). Drug release from reservoir-type devices occurs when water diffuses through the outer EVA coating and partially dissolves the enclosed drug, forming a saturated drug solution that is then released into the surrounding tissue via diffusion (1,3). Drug release occurs at a constant rate, and the duration of release is limited primarily by the rate of drug dissolution within the reservoir. The drug release rate can be slowed by increasing the surface area or thickness of the drug-restricting polymer, and drug delivery can be increased by maximizing the surface area available for drug diffusion or by using a more permeable membrane. Nonbiodegradable reservoir-type devices are typically designed to release drug over a span of months or years for the treatment of chronic conditions that require long-term drug therapy.

Nonbiodegradable implants, although useful in some clinical situations, have several distinct drawbacks (Table I). Some designs require relatively large incisions for implantation, may require sutures or some other form of anchoring, and require re-implantation once the drug is completely released to maintain efficacy and optional removal of the prior implant. The implantation and removal of nonbiodegradable implants can be associated with serious side effects such as retinal detachment, vitreous hemorrhage, and cataract formation (1,3,5,10,22,23,56).

CONCLUSIONS

Biodegradable polymer-based drug delivery systems show considerable promise for the treatment of ocular diseases. Such systems offer a potential solution to many of the limitations of conventional methods for the administration of ophthalmic drugs, especially for treating sight-threatening retinal diseases. Some polymers used in biodegradable drug delivery systems offer well-documented biocompatibility and an acceptable ocular safety profile, while other polymers are investigational and are in varying stages of development. The versatility of biodegradable polymers allows for construction of delivery systems to tailor the drug release for treating a variety of front- and back-of-the-eye diseases. In addition, biodegradable drug delivery systems can also be used to repurpose well-established drugs that may be ineffective by conventional administration routes and provide a sustained-release platform to be practical and effective for treating eye diseases. Clinical studies are in progress examining the efficacy and safety of such delivery systems in a variety of ocular diseases.

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