REVIEW

A Review of Implantable Intravitreal Drug Delivery Technologies for the Treatment of Posterior Segment Eye Diseases

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ABSTRACT: Intravitreal implantable device technology utilizes engineered materials or devices that could revolutionize the treatment of posterior segment eye diseases by affording localized drug delivery, responding to and interacting with target sites to induce physiological responses while minimizing side-effects. Conventional ophthalmic drug delivery systems such as topical eye-drops, systemic drug administration or direct intravitreal injections do not provide adequate therapeutic drug concentrations that are essential for efficient recovery in posterior segment eye disease, due to limitations posed by the restrictive blood-ocular barriers. This review focuses on various aspects of intravitreal drug delivery such as the impediment of the blood-ocular barriers, the potential sites or intraocular drug delivery device implantation, the various approaches employed for ophthalmic drug delivery and includes a concise critical incursion into specialized intravitreal implantable technologies for the treatment of anterior and posterior segment eye disease. In addition, pertinent future challenges and opportunities in the development of intravitreal implantable devices is discussed and explores their application in clinical ophthalmic science to develop innovative therapeutic modalities for the treatment of various posterior segment eye diseases. The inherent structural and functional properties, the potential for providing rate-modulated drug delivery to the posterior segment of the eye and specific development issues relating to various intravitreal implantable drug delivery devices are also expressed in this review. J Pharm Sci 99:2219–2239, 2010

Keywords: intravitreal implants; device technology; posterior segment eye disease; blood-ocular barriers; localized drug delivery; biomaterials; biodegradable polymers; vitreous humor

INTRODUCTION

The design of ophthalmic drug delivery systems is a unique challenge that is restricted by the anatomical position of the eye as well as the functional physiology of the eye tissues. The eye is a relatively isolated organ divided into an anterior and posterior segment with numerous avascular structures.[1] In this regard, the efficacy of topical drug delivery via eye-drops is only limited to the treatment of anterior segment eye diseases. The anterior segment includes the cornea, iris, crystalline lens, ciliary body and aqueous humor while the posterior segment comprises the vitreous body, retina, and choroid. Historically, the bulk of ophthalmic research focused on drug delivery to the anterior segment of the eye.[2] Due to the number of protective anterior segment barriers, typically less than 5% of an applied dose via an eye-drop will be delivered to the ocular tissues of the anterior segment and almost negligible quantities to none may enter the posterior segment if required.[3–7]

Various attempts have focused on trying to improve the bioavailability of eye-drop formulations. These

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include the addition of viscosity and penetration enhancers such as hydrogel-based polymers,[8] chelating agents,[9] preservatives,[10] surfactants,[11] bile salts,[12] the use of prodrugs and liposomal carriers,[13] mucoadhesives,[14] thermoreponsive gels,[15] and colloidal particulate formulations.[16] These approaches have the ability to prolong the precorneal residence time and improve the bioavailability of drugs within the anterior segment.[17,18] However they have no bearing on improving the delivery of drugs to the posterior segment of the eye where the majority of sight-threatening diseases are likely to emanate and prevail.

Systemic drug administration has been used to treat a few vitreo-retinal diseases.[19–21] However, previous studies reported that only minimal quantities of drug could reach the eye and hence large doses are required to obtain therapeutic drug levels in the posterior segment of the eye due to the restrictive blood-ocular barriers. Studies have revealed that the systemic route of drug administration for the treatment of posterior segment eye disease results in increased peripheral side-effects due to the large doses required for penetrating the blood-ocular barriers. Thus diseases affecting the posterior segment of the eye are difficult to treat and take longer to combat by employing conventional topical or systemic drug delivery.[22] Therefore research has been directed at specialized drug delivery technologies to the tissues of the posterior segment of the eye.[23–33]

THE BLOOD-OCULAR BARRIERS: AN IMPEDIMENT TO INTRAOCULAR DRUG DELIVERY

The blood-ocular barriers located at the level of the retinal vascular endothelial cells and retinal pigment epithelium inhibits the entry of drugs from the systemic circulation into the retinal tissue. The circumstances at the blood-ocular barriers are better understood considering two main barrier systems present. The *blood-aqueous barrier* regulates the exchange between the blood and intraocular fluid and concerns primarily the ciliary body where inward movements from the blood into the eye predominate. Aqueous humor is secreted into the posterior segment by the ciliary processes through the pupil into the anterior segment and leaves the eye by bulk flow at the segment angle by the trabecular or uveoscleral routes. Diffusional solute exchange between the aqueous humor and surrounding tissue, the posterior segment, and the vitreous compartment exists.[34] The other well defined barrier is the *blood-retinal barrier* responsible for homeostasis of the neuroretina and involves the outward movement of substances from the eye into the blood while the penetration of only a few important metabolic products is allowed into the eye. Hence the vitreous humor is located between the blood-aqueous barrier anteriorly and the blood-retinal barrier posteriorly. The extent of drug absorption intended to be delivered to the posterior segment of the eye is therefore severely hampered by these physiological barriers (Fig. 1).[6,7]

POTENTIAL SITES FOR INTRAOCULAR DRUG DELIVERY DEVICE IMPLANTATION AND MECHANISMS OF DRUG RELEASE

Currently, commercialized ocular drug delivery systems have been limited to the administration by topical and intravitreal routes. However, both clinical and nonclinical studies are ongoing to evaluate systems administered by subconjunctival, subtenon's capsule, intrascleral, subretinal, and suprachoroidal routes as well as improvements to topical application by using unique fornix devices or punctual placement (Fig. 2).[35] Systemic delivery using oral tablets is still a viable alternative to ocular administration, although unique delivery systems may not be preferred as it is usually easier for patients to comply with normal oral medication schedules, even if given more than once a day, instead of undergoing a surgical implantation procedure.

An intraocular device can be designed as either a reservoir or matrix system. Reservoir systems are noneroding devices that provide superior control of drug release by virtue of a specific physical rate control feature linked with the internal drug reservoir. This feature may be an opening in the device, a porous membrane or a coating through which drug diffusion is retarded. It is easier to achieve zero-order drug release kinetics using a reservoir system as

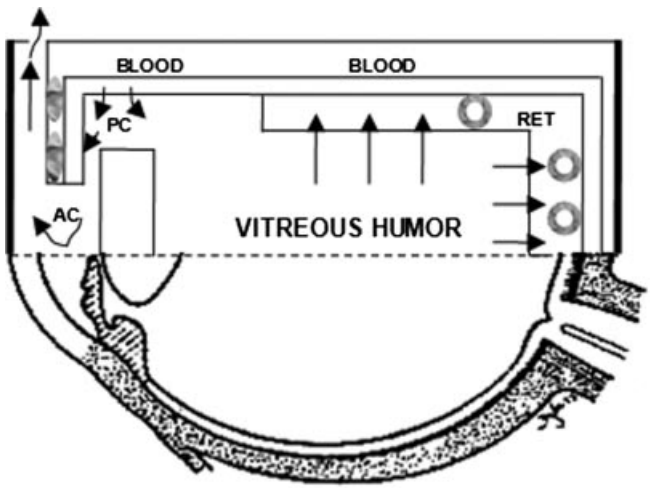

Figure 1. Schematic of the blood-ocular barriers. RET, retina; PC, posterior chamber; AC, anterior chamber (reproduced with permission from Ref. [6]).

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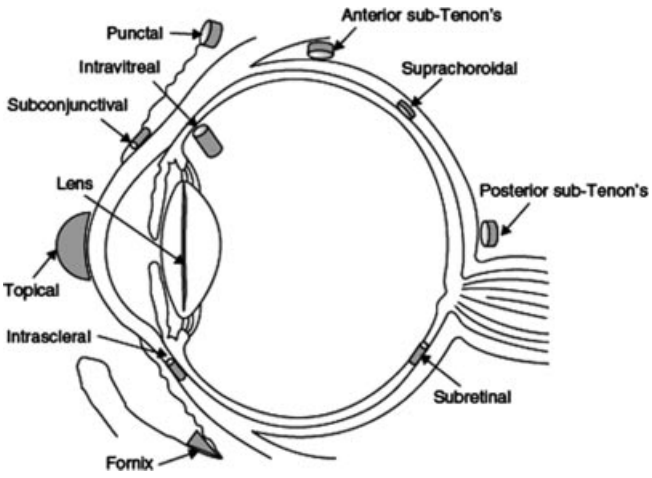

Figure 2. Potential sites for ocular drug delivery device administration (reproduced with permission from Ref. [35]).

there is only a single rate controlling variable that may impact drug delivery. In order to engineer noneroding intraocular devices, there are a number of useful biocompatible biomaterials such as the polyimides, polysulfones, polyvinyl alcohols, polyvinylidine fluorides, ethylene vinyl acetates, siloxane polymers, and various methacrylate and ethylacrylate polymers.

Alternatively, in a matrix system, drug is comixed with the rate controlling polymer. A matrix device can be engineered to produce zero-order drug release kinetics, for example, if the polymer is noneroding and the release is then governed by polymeric chain relaxation and the dissolution rate of the drug. However, in such a device, the drug concentration must be high enough such that, when erosion occurs from the matrix, it produces sufficient fenestrated channels in the device for aqueous diffusion media to reach the internally located drug particles. In a noneroding matrix system, the strength or resilience of the device could be compromised as diffused drug produces a series of interconnected voids through the device.

If the polymer in the matrix device is bioerodible then the device may exhibit more complex drug release kinetics due to the erosion factor of the polymer which may contribute independently to the drug dissolution or diffusion behavior, unless the geometry of the device is considered to produce a constantly eroding drug releasing surface. In addition, biodegradable polymers may erode, either by bulk and/or surface erosion. Poly-lactides, polyglycolides, and polycaprolactone polymers are the most common biocompatible polymers employed for the design of biodegradable intraocular drug delivery matrices. Surface eroding biodegradable polymers include certain polyanhydrides and polyorthoesters. Generally, for intraocular drug delivery, the selection of a particular system depends on the duration that is anticipated for treatment of the disease site. It is also critical to have drugs with potencies in the μg/day range, to accommodate the limited space in the human eye. Other aspects of ophthalmic drug delivery systems have been presented elsewhere.[35–44]

VARIOUS APPROACHES EMPLOYED FOR OPHTHALMIC DRUG DELIVERY TO OVERCOME THE BLOOD–OCULAR BARRIERS

A number of approaches for drug delivery to the posterior segment of the eye have been explored over the last few decades.[45] These approaches include direct intravitreal injection of drug solutions, drug-loaded microparticle carriers such as microspheres, nanospheres,[46] and liposomes,[47,48] transscleral drug delivery devices,[49] targeting of drugs via the systemic circulation,[50] and intravitreal devices using polymers.[51–53]

Direct Intravitreal Injection

Direct intravitreal injection of drugs into the vitreous cavity is employed to achieve higher drug concentrations in the vitreous and the retina.[54–57] However, repeated injections are needed to maintain drug concentrations at an effective therapeutic level over a certain period of time since the half-life of drugs in the vitreous is relatively short. Intravitreal injections, providing more efficient drug delivery to the back of the eye, are effective for a wide range of drugs including low molecular mass drugs as well as macromolecules such as oligonucleotides and monoclonal antibodies or their fragments. The duration of effects of an intravitreally administered drug depends on the retention of the injected drug at the site of administration. The higher the intravitreal half-life of a drug injected in the vitreous cavity, the greater is the anticipated duration of the pharmacological response. Longer half-life of a drug makes it amenable for less frequent dosing. However, the half-life of most drugs used for the treatment of posterior segment eye diseases are short and therefore alternative approaches for drug delivery are required that ensures more effective long-term treatment. A scientific understanding of the relationship between physicochemical properties such as molecular weight, lipophilicity, and solubility and drug elimination is essential for the development of intravitreal drug delivery technologies with desired intravitreal pharmacokinetic properties. Repeated intravitreal injections results in extreme patient discomfort and may lead to complications such as vitreous hemorrhage, infection, and lens or retinal

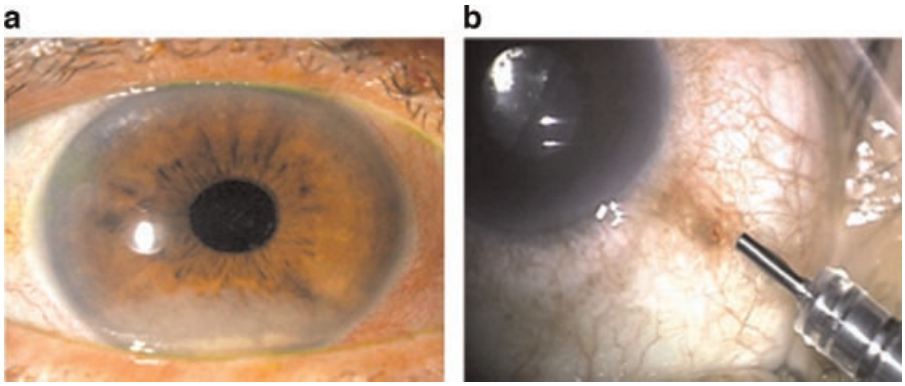

Figure 3. Digital images of (a) a human eye showing a case of endophthalmitis and (b) an intravitreal injection made at the ora serrate (reproduced with permission from Ref. [59]).

injury. The direct intravitreal injection route of drug administration is able to reduce the systemic side-effects and depending on the formulation approach it may be capable of retarding drug release. However intravitreal injections introduce further challenges, such as the progression of endophthalmitis and cataract due to repeated injections[58] (Fig. 3a and b).

Intravitreal injection of sustained-release drug delivery systems such as microspheres,[60] lipospheres[61,62] and nanospheres[63–67] offer attractive options. Colloidal-based systems are capable of delivering drug over a longer period of time than conventional intravitreal formulations used for injection into the vitreous cavity. Microparticles like microspheres or liposomes can be injected into the vitreous cavity with a fine needle and are able to release drug in the vitreous and maintain concentrations at a therapeutic level for a certain period of time.[68,69] Microspheres of biodegradable polymers such as poly(lactic acid) (PLA) or poly(lactide-*co*-glycolide) (PLGA) have shown to effectively deliver drugs to the vitreous and retina and can be tolerated by the ocular tissues.[70,71] Microspheres consist of a polymer matrix, which erodes over time releasing drug that is dispersed within the matrix. Drug release kinetics from polymeric microspheres could be controlled by changing the molecular mass of the polymers or the copolymerization ratio of PLA and PLGA. Bioerodible polymeric microspheres were shown to be effective in the treatment of ocular infections such as cytomegalovirus retinitis (CMV-R).[48,56,72] Figure 4 depicts scanning electron microscopy (SEM) images of PLGA microspheres developed by Hickey et al.[73]

The pharmaceutical world is becoming more and more aware of intraocular drug delivery challenges, and revolutionary therapeutic advances are being invented and implemented which may have the potential to vastly improve patient care and quality of life. Among these most promising developments are intravitreal drug delivery devices designed to deliver drugs with precision directly to the vitreous, retina, and choroid.[74,75]

Intravitreal Implantable Device Technology

Implantable sustained-release intravitreal device technology has being given much impetus due to the perceptible benefits afforded over the use of topical eye-drops, systemic drug administration and direct intravitreal injections as modes of drug delivery to the posterior segment of the eye as described earlier.[64,76] Solid biocompatible implantable devices for sustained or controlled intravitreal drug delivery to the posterior segment of the eye have been developed employing diverse approaches and includes the use of implantable devices such as osmotic mini-pumps, nonbioerodible and bioerodible drug-loaded pellets, configured capillary fibers, biodegradable scleral plugs, scleral discs, polymeric matrices and scaffolds of various geometries providing unique mechanisms of drug release for the delivery of drugs to the posterior segment of the eye.[32,33,77] The intraocular structures are easily (and visually) accessible and are confined and isolated from the systemic circulation by the inner and outer blood-ocular barriers that allow for the local delivery of drugs. Furthermore, the eye benefits from an "immune privilege" particularly observed in the anterior segment and in the sub-retinal space, limiting the risk of an exaggerated inflammatory reaction to foreign antigens and cell graft rejection.[78] In a study by Danckwerts and Fassihi,[78] the advantages offered by intravitreal implantable delivery systems have been published and are listed in Table 1. However, such systems are not without their risks. These are highlighted throughout the course of this review article.

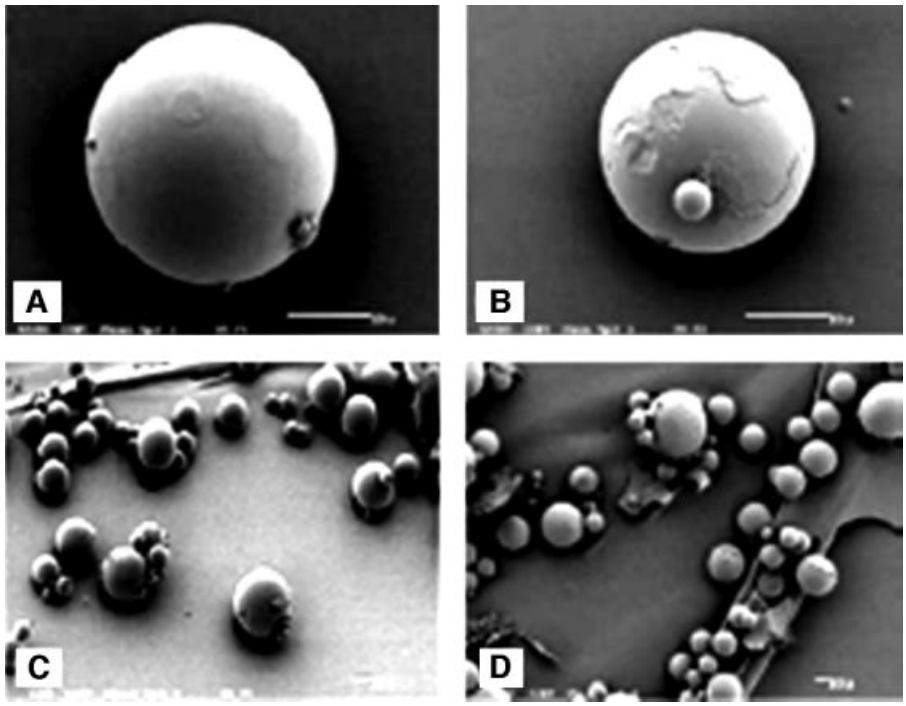

Figure 4. SEM images of poly(lactide-*co*-glycolide) microspheres for intravitreal administration (reproduced with permission from Ref. [73]).

Bioerodible and Nonbioerodible Intravitreal Implantable Devices

Bioerodible and nonbioerodible implantable devices have been developed with the drug release kinetics dependant on both the solubility and diffusion coefficient of the drug in the polymer, the drug-loading capacity, the device configuration and the *in vivo* degradation rate of the polymer. There are several major factors to consider during the development of implantable intravitreal drug delivery devices. Biocompatibility is essential and all components are required to be chemically inert, noncarcinogenic, hypoallergenic, and mechanically stable at the implantation site. Furthermore, the material should not be physically or chemically modified by local tissue nor cause any unexpected immune or inflammatory response at the site of implantation.[80,81] The overall development of these devices can be both time-consuming and complex, and may consist of various stability and biocompatibility tests.

Nonbioerodible devices are able to offer the advantages of sustained release and reduced host response. However, bioerodible intravitreal drug delivery devices have gained much popularity over nonbioerodible devices due to the fact that they are eventually absorbed or excreted by the body eliminating the need for surgical removal of the device after the drug-load has been depleted thereby increasing patient acceptance and compliance.[82,83] However, developing bioerodible devices is a more complicated task as numerous variables such as the *in vivo* erosion kinetics of the polymer is required to remain at a constant rate in order to maintain sustained-release of the drug, yet their benefits far supersede these challenges.

Furthermore, numerous factors may affect the rate of *in vivo* polymer erosion. Alterations in body pH or temperature may cause a transient increase or

Table 1. Advantages Offered by Implantable Intravitreal Drug Delivery Systems

Drugs are delivered close to their target sites of action and undesirable effects on other sites in the body are minimized
For drugs that cannot be administered by other routes and where compliance is likely to be a major challenge
In cases of extreme allergies or side-effects to drugs already administered, immediate removal of implantable devices is possible in contrast to injectable drug delivery systems
Less drug is required to treat the disease state, minimizing possible side-effects and enhanced efficacy of treatment
Capable of protecting drugs which are unstable *in vivo* and that would normally require frequent dosing intervals
The improved sustained release action offers better patient compliance
They bypasses the blood-ocular barriers allowing higher intraocular drug levels than could be achieved by systemic administration

Danckwerts and Fassihi[78] and Musch et al.[79]

decrease in the erosion rate of the device. The surface area of the drug delivery device also plays a significant role in its erosion. As erosion proceeds the surface area of the device decreases. Thus, changes in the shape of the device need to be taken into account during the formulation design. In order to attain uniform and constant release kinetics it is therefore necessary to use geometrical shapes with surface areas that do not drastically change as a function of time during erosion.[84] Another challenge with bioerodible devices is the extremely slow diffusion of drug from the polymeric matrix.[78] Diffusion of drug usually occurs at a slower rate than the bioerosion of the device and is dependent upon the chemical nature of the polymeric substance utilized in the formulation of the device. This poses a significant challenge to overcome in situations where the drug has a narrow therapeutic index.[85]

SPECIALIZED INTRAVITREAL IMPLANTABLE TECHNOLOGIES FOR THE TREATMENT OF ANTERIOR AND POSTERIOR SEGMENT EYE DISEASE

A Mucoadhesive Hydrogel-Based Thin Coiled Metallic Wire Device (OphthaCoil)

Pijls et al.[86,87] have developed an intraocular drug delivery device called "OphthaCoil" that is implanted in the conjunctival fornix after ethylene-oxide gas sterilization (Fig. 5). The device consists of a drug-loaded mucoadhesive hydrogel on a thin coiled metallic wire providing the device with flexibility and integrity. The ends of the coil are capped using a photo-curable cyanoacrylate adhesive. On contact with tear fluid the hydrogel coating swells and drug is released into the tear film. The OphthaCoil device has been shown to be well tolerated in the eyes of Beagle dogs and results have shown that the device is able to release ciprofloxacin for the treatment of bacterial infections in the posterior segment of the eye as well as for conjunctivitis or keratitis over a period of 16 h.[86–88] In order to improve the drug-loading capacity and the drug release kinetics two further approaches were explored where the interior of the coil was used as an additional drug reservoir and poly(2-hydroxyethyl methacrylate) and poly(2-hydroxyethyl methacrylate-*co*-1-vinyl-2-pyrrolidone) polymeric microspheres were incorporated as drug carriers.[89] *In vitro* drug release profiles revealed a six-fold increase of the drug-loading capacity. Preliminary *in vivo* evaluation of the OphthaCoil device was performed over a 2 h period to assess the tolerance of the device in the human eye. Ophthalmologic examinations of the eye indicated no signs of irritation. An OphthaCoil device with a drug bioavailability of 50% can be compared to 8–12 eye drops and the researchers foresee several potential applications of the device such as for the treatment of corneal ulcers, severe bacterial conjunctivitis, fungal keratitis and controlled delivery of drugs to the posterior segment of the eye, prior to cataract surgery.[90] Depending on the potency of the antibiotic agent, sustained delivery over a minimum of 5 h could be achieved.[86,87,91] It is not surprising that the use of an intraocular device that consists of a metallic core may cause concern even though the wire may be thin (76 μm in diameter) and the coil is extremely flexible. However, according to Pijls et al.[86,87] who have developed the OphthaCoil device, there is no contact between the metal wire and the ocular epithelium due to the hydrogel coating and the polymer caps. The essential role of the coiled metallic wire is to ensure device integrity throughout the application time window. Further proposed advantages of the OphthaCoil device (owing to the use of a metallic substrate) are the possible removal of the device with a magnet (instead of tweezers) and the enhanced X-ray visibility of the metallic coil, which is a purported safety issue. A disadvantage of the OphthaCoil device is the fact that removal of the device is required after the drug-load is depleted. However, the insertion and removal of the insert could be combined with control clinical examinations.[87] Reminiscent designs are discussed later in this review, such as the I-vation™ triamcinolone-coated screw that was developed by SurModics (Pty) Ltd. (Eden Prairie, MN), as a vehicle for drug delivery to the posterior segment of the eye.

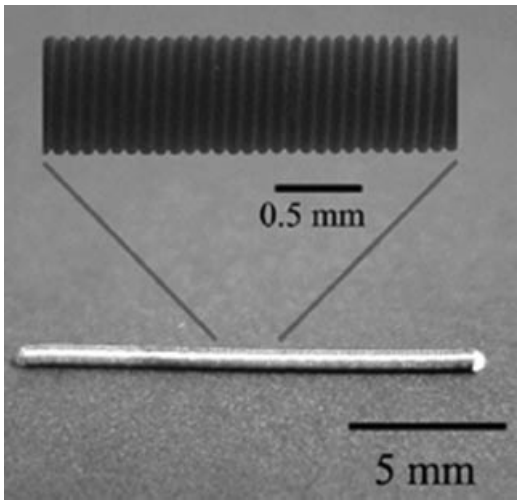

Figure 5. Image of the OphthaCoil drug delivery device (reproduced with permission from Ref. [87]).

An Imprinted Hydrogel Contact Lens Device

Ali et al.[92] have demonstrated zero-order release of low molecular mass, ketotifen fumarate ($M_w = 425$ g/

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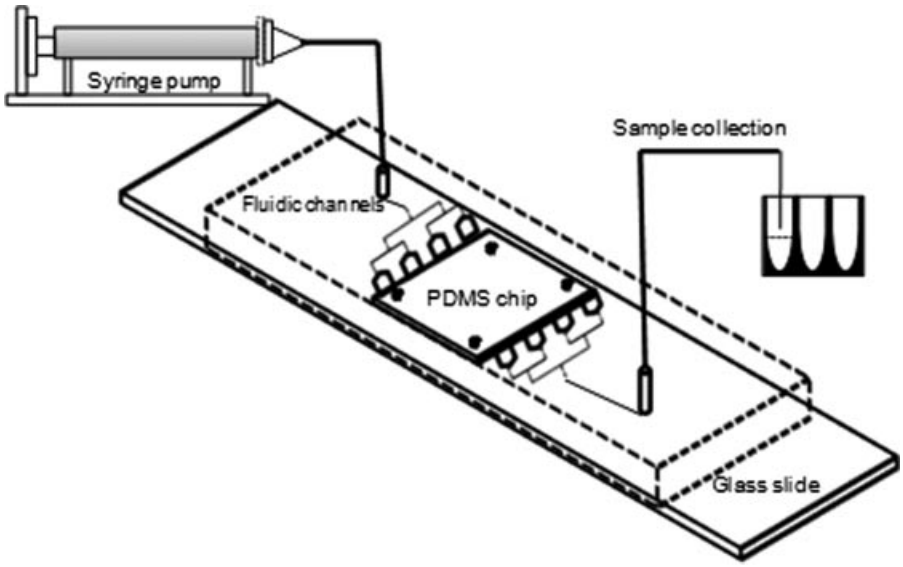

Figure 6. Schematic of the micro-fluidic chip design with physiological ocular flow from contact lens drug delivery evaluation (reproduced with permission from Ref. [92]).

mol), from a molecularly imprinted hydrogel device used as therapeutic contact lenses. Zero-order or concentration-independent release kinetics is highly desirable from drug delivery devices. *In vitro* drug release studies were performed within a novel microfluidic device that was able to simulate the volumetric flow rates, tear volume and tear composition of the eye (Fig. 6). Imprinted gels with multiple functional monomers and complexation points to the drug demonstrated delayed drug release kinetics compared to less functionalized systems. Under infinite sink conditions, the imprinted contact lenses demonstrated Fickian release kinetics with diffusion coefficients ranging from 4.04×10^{-9} to 5.57×10^{-10} cm^2/s.[92] The authors reported the highest functionalized gel to exhibit a diffusion coefficient averaging <10 times than minimally functionalized hydrogels and released ketotifen over 5 days with three distinct rates of release. Under physiological volumetric flow rates, the release rate was constant for a duration of 3.5 days delivering a therapeutic dose and was fitted to a Power Law model indicating zero-order release with $n = 0.981 \pm 0.006$ ($R^2 = 0.99$). The device has the potential for molecular imprinting to further tailor the drug release kinetics via the imprinting process. However, it is rather complicated to produce and requires several intricate design processes to affect the reproducibility of the molecular imprinting technology employed. In addition, the device has shown to release drug only up to 5 days with three distinct rates of drug release. This may not be suitable for posterior segment eye diseases that require chronic suppressive maintenance therapy over several weeks to months.

A Cyclosporine-Loaded Discoid Device

Gilger and coworkers[93] reported on a discoid intravitreal device developed for the constant release of cyclosporine (CsA) in inflammatory episodes of uveitis in horses. This was accomplished by measuring clinical signs, intraocular damage, cellular infiltrates, and T-lymphocyte counts in conjunction with the associated level of transcribed cytokine specific mRNA. The effects of the device on recurrent inflammatory episodes in experimental uveitis were determined. Nine healthy horses were immunized peripherally with H37RA-mTB antigen twice, and then received 25 mg of H37RA-mTB antigen intravitreally in the right eye and an equal volume of balanced salt solution intravitreally in the left eye. Two weeks later, the animals randomly received either the CsA-loaded device or a placebo in both eyes. One week after implantation of the devices, 25 mg of H37RA-mTB antigen was re-injected into the right eye of each animal. Clinical signs of ophthalmic inflammation were graded following injections and implantation. Aqueous and vitreous humor protein levels, infiltrating cell counts, total number of T-lymphocytes, and levels of IL-2 and IFNg-mRNA were significantly less in eyes containing the CsA device compared to the eyes with the placebo. CsA devices did not completely eliminate the development of a recurrent experimental inflammatory episode in the horse model. However, the duration and severity of inflammation, cellular infiltration, tissue destruction, and pro-inflammatory cytokines RNA transcript levels were significantly less in eyes implanted with the CsA devices.[93,94] Results from the study were

rather focused on demonstrating the effectiveness of delivering CsA via an intraocular device for the treatment of immune-mediated intraocular inflammation in the equine eye model. However the flexibility of the device for delivering other drug molecules and the efficacy of the device in other animal models or human subjects is yet to be reported.

A Gelfoam®-Based Device for the Delivery of Insulin

Lee and coworkers,[95,96] have delivered insulin employing an acidified absorbable gelatin sponge-based (Gelfoam®) (Pharmacia & Upjohn Company, Division of Pfizer Inc., New York, NY) intraocular device that can be efficiently absorbed into the systemic circulation without the aid of an absorption enhancer. The Gelfoam® device is soft and pliable and may be worn with contact lenses. A Gelfoam® device is approximately 6mm in diameter with a 2 mm thickness and is excised from a slab of Gelfoam® sponge comprising 0.2 mg of Zn-insulin dissolved in a 30 mL solution of 10% (v/v) acetic acid in water. The Gelfoam® insulin-loaded device was evaluated in the rabbit eye model. Results suggested that a change in the Gelfoam® upon treatment with acid was responsible for the systemic absorption of insulin from the device. Generally an absorption enhancer is required for the systemic absorption of insulin delivered by the ocular route.[97–111] Lee and coworkers[96] showed that the device could provide a uniform blood glucose reduction over 8 h with the aid of Brij-78 as an absorption enhancer. Furthermore, this group also showed that similar results could be obtained from enhancer-free devices to which acetic acid had been added and removed by evaporation.[97] They have shown that acetic acid enhances the systemic absorption of insulin from the gelatin-based devices by the intraocular route. The pH of tear fluid changed from a pH value of 7 to 5 immediately after the instillation of the acid-treated device and returned to pH 7 within 5 min while absorption continued for over 8 h (Fig. 7a). This indicated that tear pH was not

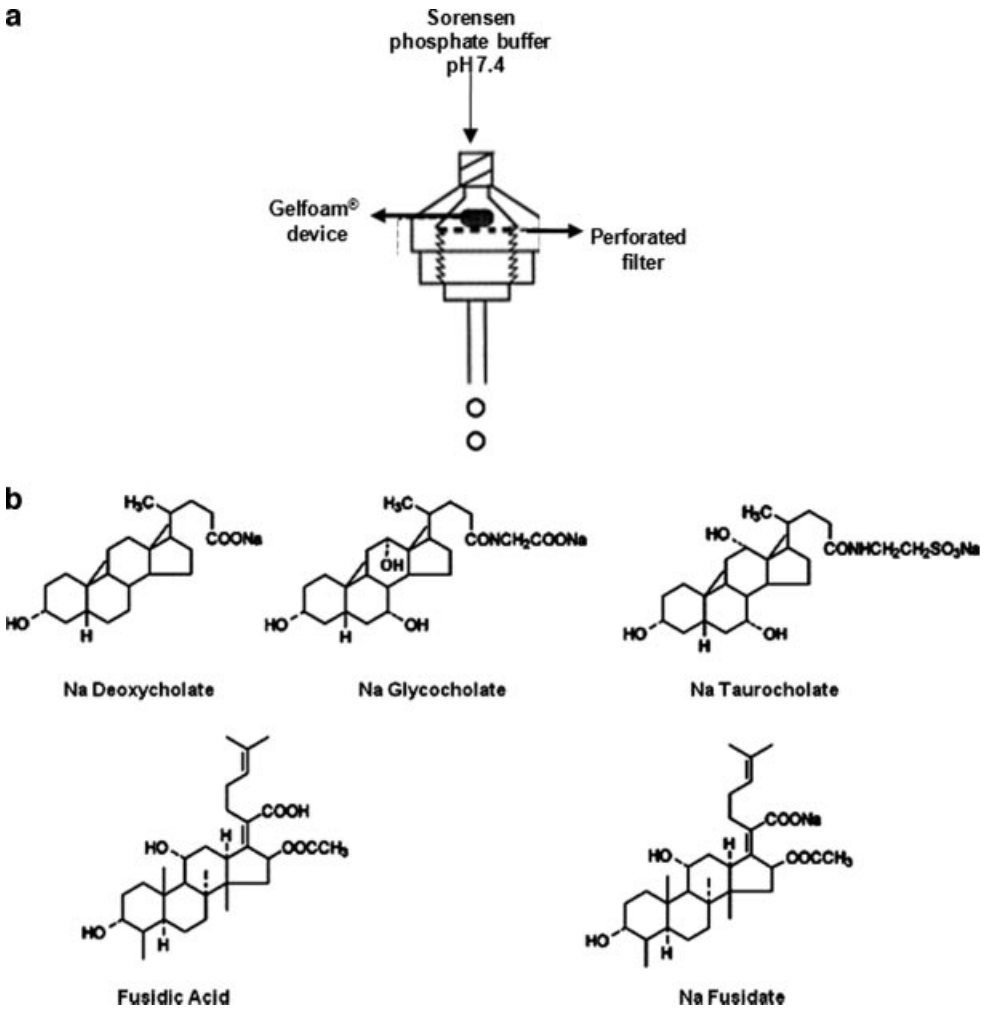

Figure 7. (a) Experimental set-up for the determination of Zn-insulin concentrations released from the Gelfoam® device and (b) chemical structures of the various compounds comprising the Gelfoam®-based device (reproduced with permission from Ref. [112]).

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responsible for enhancing the absorption of insulin.[112] Overall, the data suggested that the enhancement of the absorption of insulin is due to a change in the Gelfoam® upon acid treatment. This was confirmed by the devices that were not treated by acid and were inactive whereas those that were acid treated were active. While neither the chemical composition nor the mechanism by which the device functions are clearly understood, it is clear that the interaction of gelatin with dilute acetic acid produces a potent enhancer which promotes the systemic absorption of insulin delivered via the intraocular route. Although the Gelfoam® device is currently employed for the systemic delivery of drugs via the ocular route, future research into the applications of this device may realize its potential for the intraocular delivery of drugs to the posterior segment of the eye. However significant modifications would be required in order to produce a device that would be able to provide intravitreal drug release that can provide efficacy over a longer period than 8 h that has been achieved.

An Ethylene Vinyl Acetate and Poly(Vinyl) Alcohol Reservoir Device (Vitrasert®)

Nonbiodegradable polymers were first used clinically for intraocular sustained release of ganciclovir in the treatment of cytomegalovirus retinitis (CMV-R).[51,79] The Vitrasert® reservoir-type device (Chiron Vision Inc., Irvine, CA), composed of drug and polymeric coats of polyvinyl alcohol (PVA) and ethylene vinyl acetate (EVA). The device is implanted in patients requiring the treatment of CMV-R. PVA, a permeable polymer regulates the rate of ganciclovir permeation through the device (Fig. 8). EVA, an impermeable polymer, limits the surface area of the device through which ganciclovir can be released. The device has shown to have no initial burst effect. The commercially used device is relatively large and requires a 4–5 mm sclerotomy at the pars plana for implantation. Furthermore, because the device is nonbiodegradable, the drug depleted device needs to be removed during a second surgery in order to implant another device if required. The complications related to multiple implantations are vitreous hemorrhage, rhegmatogenous retinal detachment, endophthalmitis, and cystoid macular oedema with epi-retinal membrane, which occurred in 12% of eyes in one study.[113] Currently, the same type of implant containing dexamethasone, fluocinolone acetonide, or cyclosporine is being tested to treat severe uveitis.[94,114,115] The sustained release of triamcinolone and 5-fluorouracil (5-FU) was studied in the treatment of experimental proliferative vitreoretinopathy (PVR).[116] However, the sustained release of these steroids may cause secondary glaucoma and cataract. Numerous candidate drugs tested for the treatment of age-related macular degeneration (AMD) may be applicable using the sustained release Vitrasert® device. Furthermore, occasional endophthalmitis and an increased rate of retinal detachments have been reported after implantation of the Vitrasert® device.[1] Most patients are expected to experience an immediate and temporary decrease in visual acuity which lasts for approximately 2–4 weeks postoperatively that is attributed to the surgical procedure. Nevertheless, the Vitrasert® device has witnessed the most clinical success to date as an intraocular device and has been extensively used for the treatment of CMV-retinitis. Other devices such as the Retisert® and Medidur® devices have since been developed and refined based on the clinical success of the Vitrasert® device.

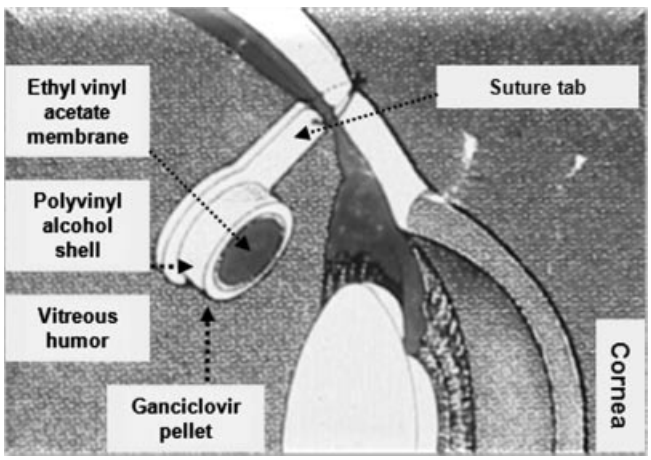

Figure 8. Schematic of the nonbiodegradable Vitrasert® device implanted in the human eye.

The Retisert® and Medidur® Devices

Retisert® (Bausch & Lomb Inc., Rochester, NY) is a reservoir-based fluocinolone-loaded implant designed to provide drug release over a period of approximately 1000 days (Fig. 9). The implant contains 0.59 mg of drug, and it delivers 0.5 μg/day of the corticosteroid, fluocinolone.[117] In addition, there have been uveitis and diabetic macular edema (DME) trials undertaken with the Retisert® technology, but currently the device is indicated for uveitis only. While a benefit is seen in both conditions, the ocular side-effects of the device are significant enough that limits its indication to uveitis. The device has shown significant efficacy with 1 year postimplantation (the recurrence rate for uveitis was 5.4% compared with 46% in the control eye). In the case of DME with an extensive cystoid component, complete resolution of fluid was noted 6 weeks after implantation and the preexisting laser spots that were previously invisible with edema were

Figure 9. Comparison of the sizes of the Medidur®, Retisert®, and Vitrasert® implants (reproduced with permission from Ref. [117]).

visible. The challenge is the ocular side-effects of steroids, where a 50% rate of glaucoma was observed which is unacceptable in DME patients. Additionally, cataracts are almost ubiquitous after 3 years of implantation and 93% of eyes require cataract surgery compared to 20% in a control group.[117] In addition, reported surgical complications of the device have included choroidal detachment, endophthalmitis, hypotony, retinal detachment, vitreous hemorrhage, vitreous loss, exacerbation of intraocular inflammation and wound dehiscence. When considering such devices, cognizance must be taken of the ultimate risk–benefit ratio. In a recent National Institutes of Health (NIH) sponsored 5-year clinical trial the effectiveness of the Retisert® device as compared with conventional therapy (oral corticosteroids) in the management of posterior uveitis is being evaluated in 400 patients at 20 sites throughout North America. The Medidur® device (Alimera Sciences Inc., Atlanta, GA and pSivida Inc., Watertown, MA) also contains fluocinolone, but it is a much smaller device (Fig. 9). The device is easy to surgically implant and is performed through a 3.5 mm incision with a 25G needle into the back of the eye during an outpatient visit, which enables self-sealing of the wound. The insertion procedure is similar to an intravitreal injection that is commonly employed by retinal specialists. It is a reservoir-type nonbiodegradable implant that is not sutured to the eye wall and floats freely in the vitreous space. The device has shown to release the drug betamethasone constantly for at least 3 months without detectable drug concentrations in the aqueous humor of the rabbit eye model. Betamethasone concentrations in the retina-choroid after implantation were maintained above the concentrations effective for suppressing inflammatory reactions for at least 4 weeks. The betamethasone concentration was greater in the posterior half of the retina-choroid than in the vitreous. Interestingly, the implant showed more effective delivery to the macular region. Medidur® is a promising device for the treatment of the retinal and choroidal diseases. A Phase 3 clinical trial is underway for the treatment of uveitis with limited safety data acquired from 20 patients with 900 patients in a larger Phase 3 clinical trial for the treatment of DME.[117] There are two separate studies under evaluation—one device that releases fluocinolone for 18 months and another for 36 months. Medidur® may thus hold some advantage over Retisert®. It has been shown to have a more favorable ocular hypertension side-effect profile. This may have to do with the positioning of the device relative to the ciliary body and/or the trabecular meshwork (anteroposterior implant localization in the eye). The manufacturers are undertaking investigations to evaluate the validity of this statement.

A Micro-Electromechanical Device

A micro-electromechanical (MEM) intraocular drug delivery device was investigated by Li et al.,[118] for the treatment of incurable ocular diseases (Fig. 10). Unlike conventional ocular drug delivery devices, the MEM device is capable of being refilled, features electronic control of drug delivery, and enables

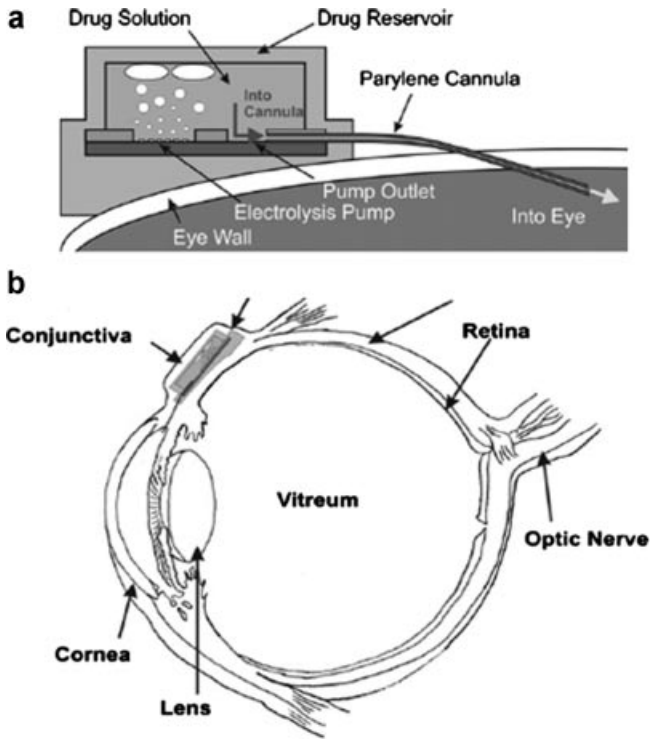

Figure 10. Schematic diagrams of (a) A cross-section of the micro-electrochemical drug delivery device depicting electrochemical pumping of drug into the eye, and (b) illustration of the implanted device under the conjunctiva in the anterior chamber of the human eye (reproduced with permission from Ref. [118]).

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targeted intraocular drug delivery. The refillable design permits long-term drug therapy and avoids repetitive surgeries. Electronic control of dosing is achieved by using electrolysis-actuated pumping to deliver drugs directly to the posterior segment of the eye. A flexible transscleral cannula allows targeted delivery to tissues in both the anterior and posterior segments of the eye. The device has demonstrated to provide flow rates suitable for ocular drug therapy from pL/min to L/min. Both continuous and bolus drug delivery modes may be used to achieve accurate delivery of a target volume of 250 nL of drug. An encapsulation packaging technique was developed for acute surgical studies and preliminary *ex vivo* drug delivery experiments in porcine eyes were performed. To deliver drug into the eye, the device is actuated by manually depressing the drug reservoir. This action generates an overpressure in the reservoir which in turn causes a check valve in the cannula to open and allow drug to enter the intraocular space (Fig. 10). Upon depletion of drug, the drug reservoir is refilled by puncturing the reservoir wall with a syringe needle and emptying the syringe into the reservoir. To achieve variable delivery rates and the ability to select either bolus or continuous delivery, an active device having electrochemically driven drug delivery was also investigated.[118] The electrolysis pump consists of two inter-digitated platinum electrodes immersed in an electrolyte. The electrode geometry improves the pumping efficiency by reducing the current path through the solution which also serves to lower the heat generation.[119] When current or voltage is applied, with the drug as an electrolyte, electrolysis of water in the drug at the electrodes produces oxygen and hydrogen gases. The gases generated result in an internal pressure increase in the sealed reservoir which causes drug to be released through the cannula and into the eye. Electrolysis is a reversible process and ceases when the applied current or voltage is switched off. This allows the gradual recombination of hydrogen and oxygen to water. Drug is stored in a reservoir integrated on top of the electrolysis pump. Preliminary *ex vivo* testing was performed demonstrating the feasibility of the MEM device for intraocular drug delivery.[118] However, the device is extremely difficult to produce and requires significant patient intervention to achieve the required therapeutic efficacy. Although somewhat ingenious this device may not be entirely suitable for chronic intraocular drug delivery to the posterior segment of the eye.

Poly(Lactic) Acid Scleral Plug Devices

Vitreoretinal drug delivery with biodegradable scleral plug devices has been investigated[120] (Fig. 11). The drug-loaded scleral plugs of various dimensions comprise biodegradable polymers and can be implanted at the pars plana and gradually release effective doses of drugs with polymer biodegradation over several months. For instance, the biodegradable scleral implant (Fig. 11a and b) (mass = 8.5 mg; length = 5 mm) is prepared from poly(DL-lactide) (PLA) or poly(DL-lactide-*co*-glycolide) (PLGA) and contains various quantities of ganciclovir (GCV). The release profiles of GCV were dependent on the type of polymers used, the polymer molecular mass, and the quantity GCV loaded. Once implanted the implantation site is replaced with connective tissue. Electroretinography and histological studies revealed minimal retinal toxicity. The implantable scleral plug may be advantageous for diseases such as cytomegalovirus retinitis that respond to repeated intravitreal injections and for vitreoretinal disorders such as proliferative vitreoretinopathy that require vitrectomy. Other scleral devices such as the nonerodible, refillable reservoir device and coated coil matrix (Fig. 11c and d) have also been developed. The devices can be implanted at the pars plana without a suture through a scleral incision. Since it comprises biodegradable polymers or is refillable it does not need to be removed once the drug-load is depleted. Release profiles obtained from the scleral plug devices generally have a tri-phasic release pattern depicted by (i) an initial burst effect, (ii) a diffusional release phase, and (iii) a final burst phase. The duration and the rate of GCV release is affected by the molecular mass and the copolymeric ratio, the total surface and volume of the matrices, and the drug loading. Blending of PLA with various molecular masses prolonged the linear release of GCV.[120] A 10% GCV-loaded scleral implant prepared from PLA (M_w = 130,000 g/mol) released GCV *in vitro* over a period of 6 months.[121] The *in vivo* release and biodegradation were studied using 25% GCV-loaded plugs comprising PLGA (75/25; M_w = 121,000 g/mol) in pigmented rabbits. The GCV concentration in the range of ED_{50} for human CMV was maintained in the vitreous for over 3 months and in the retina/choroid for over 5 months. The GCV concentration was greater in the retina/choroid than in the vitreous throughout the study. The scleral plugs showed two distinct phases of biodegradation, a lag-time followed by erosion. During the erosional phase, the mass of PLGA was significantly reduced with the plugs being separated into two pieces at the site of scleral penetration and displaced into the vitreous ten weeks after implantation. The fragments disappeared from the vitreous and the sub-conjunctival space 5 months after implantation.[122] However, scleral plug devices do bring their own disadvantages, such as a second burst in the late phase of drug release. Therefore researchers have explored different geometrical

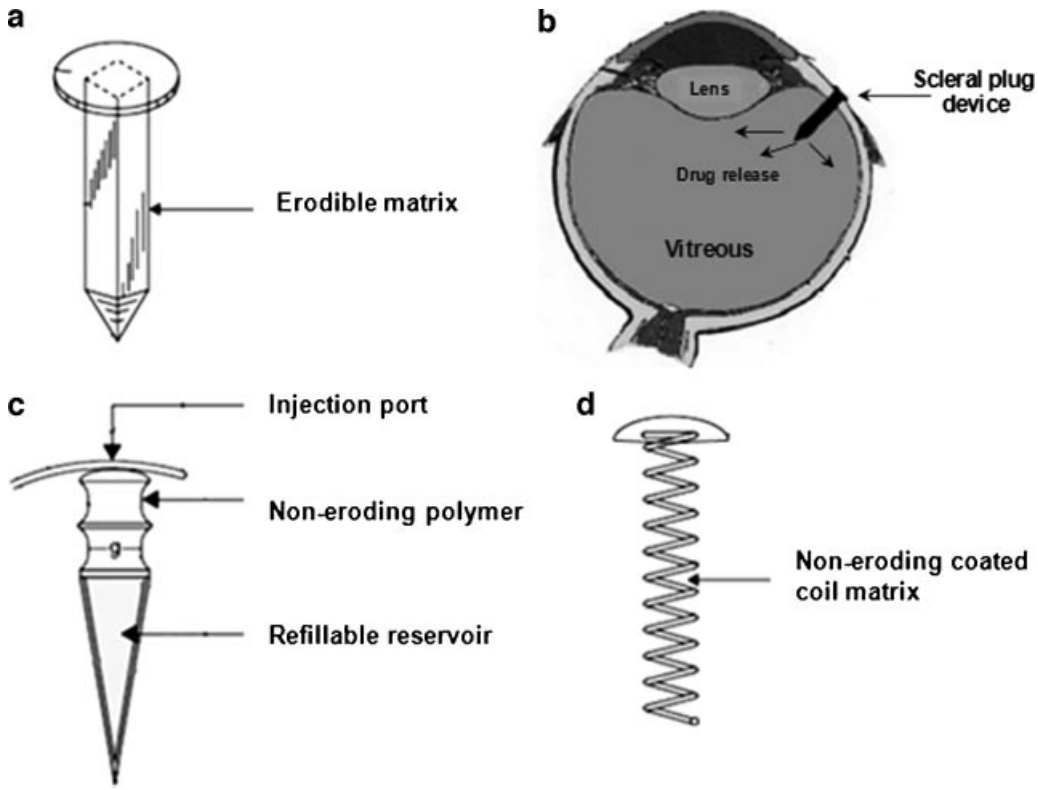

Figure 11. Images of (a) the scleral plug drug delivery device, (b) illustration of the device implanted through the scleral in the human eye, (c) noneroding reservoir device allowing for re-injection of depleted bioactive, and (d) noneroding metal coil with a matrix coating (reproduced with permission from Refs. [121,123,124]).

designs in order to circumvent the undesirable drug release kinetics obtained and have therefore investigated the use of scleral discoid-shaped and donut-shaped devices for more controlled drug release kinetics.

A Scleral Discoid Device

A scleral discoid device was developed to release triamcinolone acetonide (TA) over several months.[125,126] Scleral disks were manufactured by a compression-molding method using a new synthetic polymer, poly(methylidenemalonate) (PMM2.1.2), as the matrix (Fig. 12). PMM2.1.2 is a synthetic polymer that has been mainly used for the manufacture of particulates systems.[127] Its use for the development of intraocular implants has been advocated since it has been demonstrated to be nontoxic and biodegradable leading to the formation of nontoxic products including ethanol and glycolic acid.[128,129] The scleral discoid device displayed superior physicomechanical properties adapted for *in vivo* intraocular implantation when high molecular mass PMM2.1.2 (100–150 kDa) associated with ethoxylated derivatives of stearic acid

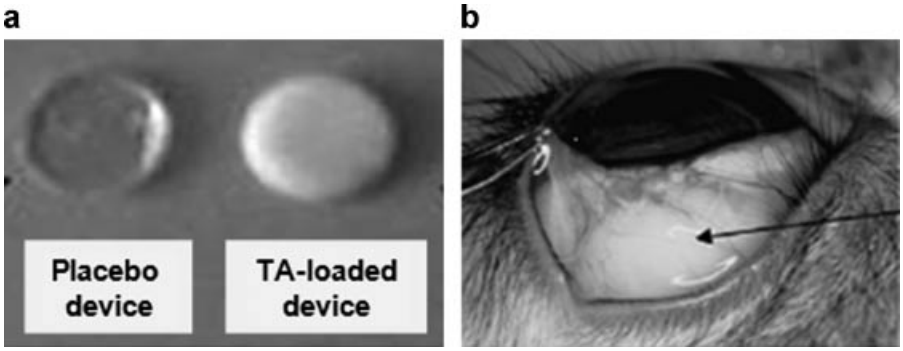

Figure 12. Images of a scleral device (a) drug-loaded and unloaded, and (b) implanted into the peribulbar space at the sclera of a beagle dog eye model (reproduced with permission from Ref. [130]).

(Simulsol™, Seppic Inc., Fairfield, NJ) or oligomers of methylidenemalonate as a plasticizer was used. After implantation in rabbit eyes, the scleral discoid device displayed ocular biocompatibility. Clinical follow-up and ocular inflammation parameters, such as inflammatory cell counts and protein content in the aqueous humor demonstrated that the devices did not provoke abnormal inflammation. The scleral device was able to release TA in the vitreous and the sclera over a period of 5 weeks. The study also supported the fact that the scleral route is promising for the treatment of posterior segment eye disease, allowing higher concentrations of drug with minimal side-effects.[130] Okabe et al.[131] also developed an intrascleral implant prepared from PVA and EVA containing betamethasone in the form of a disk (4 mg in mass, 1 mm thick, and 4 mm in diameter). This implantable disk was able to release betamethasone at a therapeutic level over a period of 4 weeks without an initial burst-effect. Since intrascleral implantation does not require perforation of the eye wall, the device may reduce several complications noted with other devices that require surgical imposition into the vitreous compartment. However the device has been shown to only deliver drug over a period of 4 weeks.

An Osmotic Minipump Device

A posterior segment implantable osmotic minipump device was first developed by Michelson and Nozik.[132] The osmotic minipump was implanted subcutaneously in the ear region of a rabbit eye model of endophthalmitis. The device had connective tubing directly infusing into the vitreous cavity through a pars plana incision and maintained a calculated dose of the antibiotic gentamicin (0.01 mg/h) over 4 days. Other investigators attempted similar pump models,[133,134] but none of these approaches reached clinical acceptance due to the vehemently irreproducible results obtained. More recently, much interest has been focused on uncomplicated slow-release intravitreal implantable devices to treat CMV-retinitis and PVR.

A Hyaluronic Acid Plug Device

A hyaluronic acid (HA) intravitreal plug device was developed comprising three different HA esters namely, 100% ethyl ester, 100% benzyl ester and 75% benzyl ester (Fig. 13). The plugs were implanted through a sclerotomy at 3.5 mm from the limbus of rabbit eyes in order to study the biocompatibility and the biodegradation rate *in vivo*.[135] The shaft diameter of the plugs was measured by ultrasound biomicroscopy to assess the *in vivo* biodegradation of the device. Slit lamp microscopy, indirect ophthalmoscopy and electroretinography were performed periodically. The effects of the device on ocular tissues were also evaluated histologically. All the plugs displayed biocompatibility with plugs of both the total esters found to undergo slow erosion kinetics. The partial benzyl ester was completely reabsorbed after 15 days. Analysis of variance showed a high correlation between the biodegradation rate and the time of resorption. The biodegradation rate of each device was related to the chemical structure of the three types of HA. The study suggested that the intravitreal plug devices based on HA esters may provide useful biocompatible and biodegradable devices for potential drug delivery in the treatment of posterior segment eye diseases.

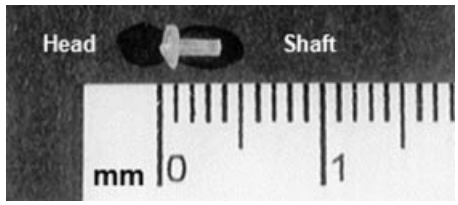

Figure 13. Digital image depicting the head and shaft configuration of the hyaluronic acid scleral plug delivery device (≈5 mm in length) (reproduced with permission from Ref. [135]).

A Novel Helical Device

The I-vation® technology (SurModics (Pty) Ltd., Eden Prairie, MN) consists of a helical coil with an eluting polymer containing triamcinolone. The device provides a way of obtaining controlled release of the common ocular corticosteroid, triamcinolone. The device is implanted through a 25G needle-stick and it is self-anchoring within the sclera (Fig. 14). Initially, there were concerns regarding conjunctival exposure with the metallic screw. However, these challenges were overcome ensuring that the hub of the screw was flush with the scleral surface and not seated at an angle. A prospective, randomized, double-masked multicenter trial is underway to evaluate the technology, using two formulations in 30 patients with DME.[117]

A Micro-Machined Drug Delivery Device

The Ocular Drug Delivery Group at the University of California (Irvine, USA) developed a micro-machined intraocular drug delivery device (Fig. 15). The goal of the project is to use micromachining technology to engineer a passive, programmable, pulsatile drug delivery device, with numerous pulses, yet small enough to be used as an ocular implantable device. The device is designed with null zones in the polymer and drug-loaded zones. This enables drug levels to

Figure 14. Digital image depicting (a) the I-vation technology from SurModics® (Eden Prairie, MN) consisting of a helical coil with an eluting triamcinolone-loaded polymer, (b) the device implanted through a 25G needle stick and is self-anchoring within the sclera and (c) the relative size of the device (reproduced with permission from Ref. [117]).

cycle up and down in a preprogrammed manner, also allowing native expression of endogenous cytokines and growth factors.[117] A pulsatile system is of considerable interest for intraocular drug delivery as the programmed release of a specific dose of drug at a specific time could potentially minimize drug-related side-effects. The overall safety and efficacy of this device is yet to be established.

Encapsulated Cell Technology for Intraocular Delivery

Encapsulated Cell Technology (Neurotech (Pty) Ltd., Lincoln, RI) ophthalmic device is rather controversial (Fig. 16). The technology uses ARPE-19 cells, a human retinal pigment epithelium (RPE) cell-line. The cells are commercially available and have been modified to produce ciliary neurotrophic factor (CNTF) and can be designed to produce various growth factors. Neurotech (Pty) Ltd. claims that the cells can produce rhuFab V2, a ranibizumab-like (Lucentis®; Genentech (Pty) Ltd., San Francisco, CA) compound. The controversy is that the RPE cells produce other compounds as well and the question is whether these are being disproportionately stimulated. RPE cells that are present in the human eye are able to naturally produce growth factors on a continual basis.[117]

The Visulex® Noninvasive Iontophoretic Ocular Drug Delivery Device

The Visulex® (Aciont Inc., Salt Lake City, UT) is a noninvasive, iontophoretic ocular drug delivery device that can deliver therapeutically relevant doses of triamcinolone acetonide (TA) (Fig. 17). Researchers performed iontophoresis of triamcinolone acetonide phosphate (TAP) on the eyes of healthy New Zealand White rabbits.[136,137] An electrical current of 3 mA for 20 min using a Visulex® sustained-release formulation of TAP, *in vivo* was employed. Li and coworkers[136] conducted an *in vivo* study in the rabbit eye model in order to examine the quantity of TAP delivered into the eye. They dissected the enucleated

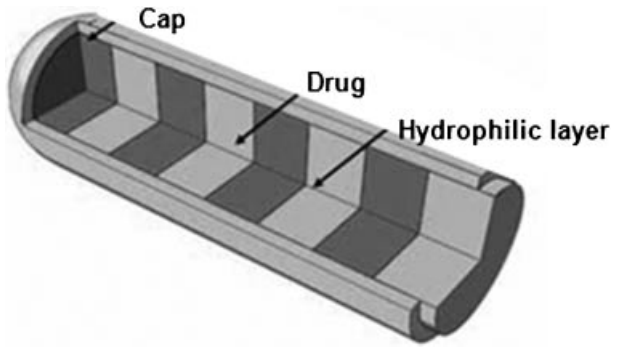

Figure 15. A Schematic of the micromachined drug delivery device developed by the Ocular Drug Delivery Group at the University of California (Irvine, USA) (reproduced with permission from Ref. [117]).

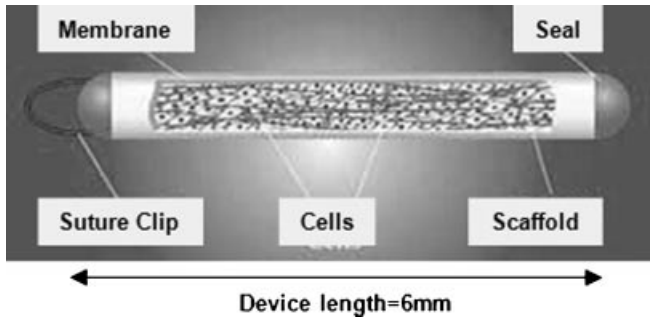

Figure 16. The Encapsulated Cell Technology implant is 6 mm long and is surgically placed inside the eye. The CNTG elutes over time and the explants continue to secrete CNTF (reproduced with permission from Ref. [117]).

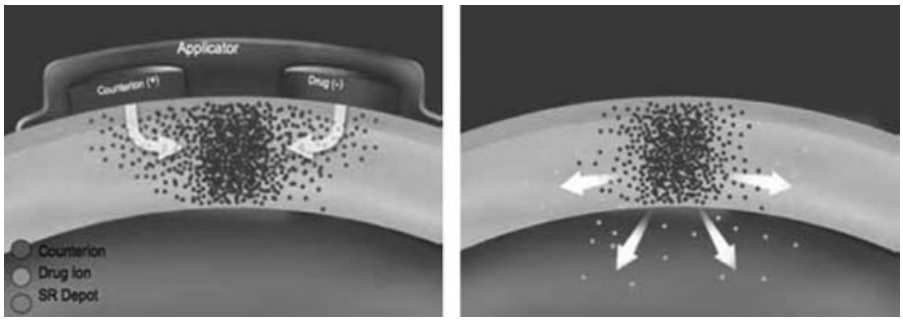

Figure 17. Schematic depicting the Visulex® depot-forming technology (reproduced with permission from Ref. [138]).

rabbit eyes and used a high performance liquid chromatography (HPLC) assay to determine the drug distribution in the rabbit ocular tissues. An efficacy study was also conducted to evaluate the Visulex® transscleral drug delivery system in an endotoxin-induced posterior uveitis rabbit model using direct ophthalmologic examination. A contrast agent was visually tracked as part of a precipitating sustained-release depot formed by the Visulex® device at various time intervals with magnetic resonance imaging (MRI) to determine the distribution of drug released from the device. In the pharmacokinetics study, the quantity of TAP delivered into the sclera and retina/choroid regions were approximately 0.03 mg using the Visulex® device. Significant levels were also found in similar tissue samples dissected from test eyes at later time intervals. The results of the efficacy study showed a significant improvement in the uveitis score of the eyes treated by the TAP-loaded Visulex® sustained release device.[138] The MRI study showed noticeable distribution of the contrast agent from the precipitating device toward the back of the eye. The Visulex® device can noninvasively deliver a therapeutic dose of TAP for the treatment of posterior segment eye diseases.[138] However, further studies are required to fully evaluate the distribution of drug released over time from the Visulex® device as drug depots within the eye. In addition, the duration of the drug action attained with the iontophoretic technique is less prolonged than with the controlled release drug delivery devices described.

A Pellet Device Comprising a Silicone Shell

Thalidomide is known to be a potent angiostatic agent. However, its systemic side-effects include peripheral neuropathy, central nervous system (CNS) depression, and embryo-toxicity which have resulted in the lowering of dosages administered to patients for the treatment of subretinal neovascularization. Systemic inhibition of angiogenesis in elderly patients may also interfere with the development of collateral circulation, which has a role in the prevention of CNS as well as cardiac ischemic events. Velez and Whitcup[139] have developed an implant that successfully releases therapeutic intraocular doses of thalidomide, and could be used for the treatment of subretinal neovascularization (Fig. 18). This system, however, has several disadvantages. The outer shell is nonbiodegradable. Therefore, after the drug has been released, minor surgery is necessary for the removal of the delivery device from the eye. There is also the possibility that shell rupture may potentially lead to "dose dumping" during therapy. Depending on the type of drug loaded into the reservoir, "dose dumping" may result in toxic side-effects from drug concentrations that exceed maximum safety levels.

A Donut-Shaped Minitablet Device

A novel donut-shaped minitablet (DSMT) was developed and evaluated as a biodegradable intraocular drug delivery system using poly(lactic-*co*-glycolic) acid polymer combinations for rate-modulated delivery of antiviral drugs[32,33] (Fig. 19). The DSMT device was manufactured using a special set of punches fitted with a central-rod in a Manesty tableting press. The erosion kinetics was assessed by gravimetric analysis and scanning electron microscopy. The device gradually eroded when immersed in simulated vitreous humor (SVH) (pH 7.4, 37°C) and released

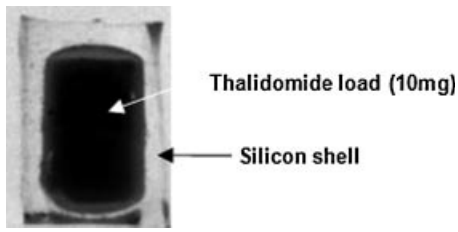

Figure 18. Experimental thalidomide implant, 10 mg pellet, with a silicone shell (reproduced with permission from Ref. [139]).

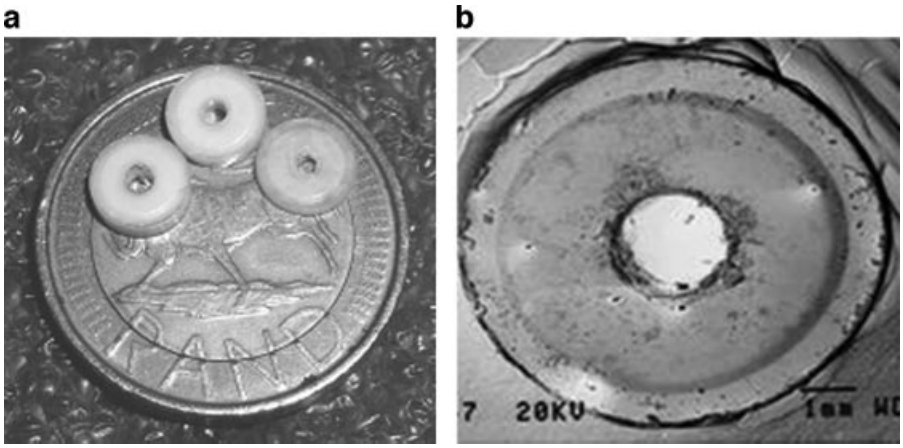

Figure 19. (a) A digital image depicting the DSMT device in relation to a typical South African five rand coin and (b) an SEM image showing the homogenous and semi-opaque surface of the DSMT device (reproduced with permission from Ref. [32]).

drugs in a sustained manner. Since the device is bioerodible, there will be no need to remove the device once it has released its entire drug load. The device is simple to manufacture, and is reproducible since it is produced on a conventional tableting press using novel tooling. A digital image of the DSMT device is depicted in Figure 19. The novel geometric design and veracity of the DSMT device was retained over 24 weeks of erosion indicating that the device was suitable as a biodegradable drug delivery system. When considering the duration of drug released from the DSMT device, it was found that by the careful selection of the type and concentration of polymer employed in formulating the DSMT device, it was possible to produce a device that could release drug for any period up to 12 months. In current *in vivo* studies by Choonara et al. 12 New Zealand White rabbits were used. The DSMT was implanted through the pars plana/peripheral retina of the right eye and sutured with 9-0 nylon. The possible adverse effects of the DSMT on ocular tissues were assessed clinically for changes in the vitreous (vitreous haze) and retina (oedema, chorio-retinal atrophy, vascular changes, exudative changes, and necrosis) adjacent to the implanted device, histological examination, slit lamp examination, measurement of intraocular pressure and indirect ophthalmoscopy. Two rabbits were euthanized on days 3, 7, 14, 28, 48, and 72. The residual devices, vitreous, plasma samples and ocular tissue were retrieved and stored at $-70^{\circ}C$ prior to GCV concentration analysis by ultra performance liquid chromatography (UPLC). Current results from the study has demonstrated that the DSMT was well tolerated up to a last time point reaching 72 days and was visible by indirect ophthalmoscopic analysis in the supero-temporal quadrant of the rabbit eye. Retinal detachments and significant vitreous hemorrhages were absent for the duration of the study and clinically no changes were observed in the vitreous, retina and choroid. The recovery of GCV spiked into placebo vitreous and serum samples was 97.4–105.0% indicating a valid evaluation of GCV concentration in the vitreous and serum. The DSMT devices displayed constant GCV release within the ED_{50} for human CMV-R (0.1–2.75 μg/mL). In comparison to *in vitro* release data *in vivo* release displayed a reduced initial burst with a steady phase of diffusional release of 40% by 28 days, 50% by day 48, and 69% after 72 days. The DSMT device is simple to manufacture as it is the only intraocular device known that is produced on a conventional tableting press and has proved to be a flexible and versatile biodegradable intraocular device (from *in vitro* studies and current *in vivo* animal investigations) that is able to provide rate-modulated release of drugs to the posterior segment of the eye. However the device is yet to be evaluated in human subjects.

Pertinent Future Challenges and Opportunities in the Development of Intravitreal Implantable Drug Delivery Technologies

Several implantable intravitreal drug delivery devices have been developed and many more are currently under design. However, none of the marketed products have yet proved to be an all encompassing device that is relatively safe and uncomplicated for patient use, allows for simple implantation procedures to secure the device in the posterior segment of the eye by ophthalmic surgeons, is fully biodegradable and provides zero-order drug release in the vitreal cavity over a period of several months to even years. In order to design an effective intravitreal drug delivery device, the challenges lining the pathway to success must be considered.

Firstly, local drug delivery intended for a single eye should not treat the contra-lateral eye. In addition, for certain diseases not limited to the eye, local drug delivery fails to treat the manifestations of extra-ocular disease. Cases in point are infectious diseases such as cytomegalovirus or ocular inflammatory diseases with systemic involvement, such as Behçet's disease, Vogt-Kayanagi-Harada disease, and sarcoidosis. Higher intravitreal concentrations of drug attained with intravitreal devices may offer a greater therapeutic effect, but may also be associated with increased ocular toxicity. Drugs that demonstrate safety in the eye over short durations may be toxic upon extended intraocular exposure. Furthermore, throughout this review, the surgical complications of device implantation have been considered, namely, vitreous hemorrhage, retinal detachment, and endophthalmitis. These complications have occurred rather often, especially when surgical penetration of the vitreous cavity is required for device implantation.

Future research should thus focus on the development of devices that are geometrically smaller and do not require full-thickness penetration of the vitreous cavity but rather relies on drug diffusion across the sclera. It is envisaged that the use of nanotechnology would provided this much needed alternative. Device applicability should also be established in the early stages of design. Investigators should identify what a 'sufficient dose for a reasonable duration' is for the targeted disease, where 'sufficient dose' is the steady-state concentration of drug needed to produce the desired effect in the animal model and, ultimately in humans, and "reasonable duration" is the duration needed to either cure the disease or to ameliorate and maintain suppression of disease symptoms. Only brief exposure (effective steady-state concentration for a few hours, days, or weeks) is required in cases where the target disease is acute. Contrarily, for chronic conditions, a more prolonged exposure (months or years) to an effective steady-state concentration of the drug is necessitated. Historically it has been acknowledged that biodegradable devices (with relative ease of implantation and lower side-effects profile) are more applicable for short-term (hours, days) or intermediate-term (weeks, months) drug delivery and is all that is required to treat acute disease and where chronic therapy is required (>1 year) nonbiodegradable devices may provide superior control of drug release, improved retrievability in the case of serious side-effects, and fewer invasive procedures than a biodegradable device. However, with the advent of several innovative technologies in polymeric and biomaterials science, researchers are continuing to identify biocompatible polymeric materials that are capable of providing prolonged drug delivery with the novelty of biodegradability. In addition, the commercialization of intravitreal devices is another significant obstacle, which rests largely on psychological factors inherent to clinicians and patients, who generally feel more at ease with traditional eye-drop therapy.

Several achievements and failures in the marketplace has brought further clarity to the field in recognizing that the development of implantable intravitreal drug delivery devices is not simply a matter of *in vitro* engineering of the device in order to achieve a controlled rate and duration of drug release. Both patient and physician factors are just as critical, if not more significant, in the successful application of the technology. These factors continue to confound scientists in their quest to develop successful intraocular devices that can deliver drug for significantly prolonged periods of time for the treatment of posterior segment eye diseases that require chronic suppressive maintenance therapy. Furthermore, various biomaterials have been employed for designing intraocular drug delivery devices. The use of biomaterials in intraocular drug delivery will inevitably increase in the future as the frontiers of biomaterials science are surpassed. However their biocompatibility and patient comfort will need to be improved in tandem.

CONCLUSIONS

The therapeutic advantages offered by the use of implantable intraocular devices are numerous and significant. In spite of this, the devices that are available have not yet gained widespread acceptance even though a few new products have been commercialized as a result of the research into intraocular drug delivery devices. This situation may change as improved devices such as those described in this review are in various stages of development and are mandated by the emergence of important new drugs that have very short biological half-lives. Intravitreal drug delivery technologies that provide continuous controlled drug release may in time find significant application in the treatment of ophthalmic diseases that, because of epidemiological circumstances, are otherwise difficult to treat effectively. In summary, a reasonable strategy to circumvent the drawbacks of the challenges associated with intravitreal drug delivery technologies is to combine technologies with the necessary balance in order to achieve sustained or controlled intravitreal drug release with patient comfort and ease of manufacturing and use. At this stage, it is apparent that no single intravitreal drug delivery device can fulfill all the clinician's expectations and needs. Thus, intravitreal implantable drug delivery devices are to be specifically designed and adapted to the targeted tissue, the physicochemical

properties of the drug to be used, physicomechanical properties of the polymer-based device and to the desired kinetics of intraocular drug release.

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