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A viscous bioerodible poly(ortho ester) as a new biomaterial for intraocular application

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Abstract: The biocompatibility of a viscous, hydrophobic, bioerodible poly(ortho ester) (POE) intended for intraocular application was investigated. POE was evaluated as a blank carrier and as containing modulators of degradation. Each formulation was injected intracamerally and intravitreally in rabbit eyes, and clinical and histological examinations were performed postoperatively for 2 weeks. In the case of intracameral injections, polymer biocompatibility appeared to depend on the amount injected in the anterior chamber. When 50 μL was administered, the polymer degraded within 2 weeks, and clinical observations showed good biocompatibility of POE with no toxicity to the ocular tissues or increase in intraocular pressure. The injection of a larger volume, 100 μL, of POE, appeared inappropriate because of direct contact of polymeric material with the corneal endothelium, and triggered reversible edema and inflammation in the anterior chamber of the eye that regressed after a few days. After intravitreal administration, POE was well tolerated and no inflammatory reaction developed during the observation period. The polymer degraded slowly, appearing as a round whitish bubble in the vitreous cavity. The presence of modulators of degradation both improved POE biocompatibility and prolonged polymer lifetime in the eye. POE appears to be a promising biomaterial for clinical intraocular application. © 2000 John Wiley & Sons, Inc. J Biomed Mater Res, 50, 566–573, 2000.

Key words: biomaterial; poly(ortho esters); biodegradable polymers; intraocular; biocompatibility

INTRODUCTION

A viscous bioerodible poly(ortho ester) (POE) carrier has been developed as a biomaterial for sustained drug delivery and as a potential adjunctive treatment in pathological ocular conditions such as glaucoma filtering surgery failure or proliferative vitreoretinopathy (PVR) surgery.[1,2] Glaucoma filtration surgery is realized by creating a fistula between the anterior chamber of the eye and the subconjunctival space, allowing the drainage of aqueous humor to reduce the intraocular pressure and preserve vision in patients suffering from severe glaucoma.[3] Inhibition of subconjunctival fibrosis is desired, and the surgical procedure fails when the scarred conjunctiva adheres to the episcleral tissue and the bulbar sclera. The fibrosis flattens the filtration bleb and prevents further drainage of aqueous humor from the anterior chamber of the eye. Pharmacological modulation of wound healing, as achieved with the administration of anti-inflammatory or antifibroblastic agents, improves the efficacy of the filtration.[4] Among them, postoperative 5-fluorouracil injections have considerably increased the success of glaucoma filtration surgery in eyes that are at high risk of failure.[5] However, to maintain therapeutic drug levels, multiple subconjunctival injections are needed, leading to complications such as leakage through the conjunctiva and ulcers of the cornea.[6,7] A sustained drug delivery system would allow the frequency of injections to be reduced as well as the high, and possibly toxic, drug concentration following bolus subconjunctival administration.

Proliferative vitreoretinopathy is a pathologic condition occurring in part as a complication of retinal detachment, in which cells originating from the retina and transdifferentiating into fibroblasts proliferate, inducing the formation of retractile membranes on both

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surfaces of the detached retina.[8] The aim of the pharmacological treatment of PVR, in addition to surgery, is to intervene at different stages of the disease progression[9]: that is, first inflammation, then cellular proliferation. In the initial stage, i.e., the inflammatory phase, long-effect steroids such as dexamethasone are more suitable. In the proliferative phase, antifibroblastic drugs can be used. Because inflammatory factors may still continue to act in this stage, better control may be achieved if the antiproliferative drugs are administered concomitant with steroids.[10] PVR is a recurrent disease; even if surgical removal of the contractile membranes enables flattening of the detached retina, the proliferation process can reappear.[11] The controlled release of anti-inflammatory and antiproliferative drugs could both prevent the development of PVR in eyes at high risk of failure and hinder PVR recurrence while minimizing toxic side effects and improving patient comfort. Biodegradable biomaterials have an advantage over other controlled release systems in obviating the need for surgical removal of the drug-depleted device.[12,13]

Poly(ortho esters) are hydrophobic, bioerodible polymers that undergo a hydrolytic degradation confined to their surface, a so-called surface erosion, in contrast to bulk hydrolysis of hydrophilic polyesters such as poly(α-hydroxyacids) that hydrolyze directly to yield large amounts of acidic compounds, both soluble and insoluble when end-stage degradation is reached.[14–16] The chemical reaction of POE degradation occurs in two steps: the first is a rapid hydrolysis of the labile ortho ester bonds, and the second is a slower hydrolysis which produces acetic acid and hexanetriol.[17] Kinetics of drug release from POE, as well as polymer degradation rate, can be controlled by many factors such as polymer molecular weight and physicochemical properties of the excipients and drugs incorporated,[1] notably their water solubility, hydrophilic/hydrophobic balance, and acidobasicity.[18,19] The use of acids leads to a fast polymer degradation and drug release because ortho ester bonds are sensitive to acid catalysis. POE containing basic excipients such as magnesium hydroxide and sodium acetate or drugs such as dexamethasone sodium phosphate is stabilized and the release rate is sustained.[18]

Poly(ortho ester) biocompatibility has been extensively investigated after subcutaneous[20] as well as subconjunctival administration.[21,22] Significant improvement of biotolerance has been obtained by using aseptically synthesized polymers instead of γ-sterilized batches[2] and by controlling the microenvironmental pH around the device during polymer degradation.[23] So far, the overall intraocular biocompatibility has yet to be assessed. Because the system investigated here is intended to be placed intraoperatively in cases of trabeculectomies in eyes where a fistula has been created between the anterior chamber and the subconjunctival space, its biocompatibility has to be evaluated in every part of the eye where the polymer and its degradation by-products are likely to be present. Polymer safety also has to be assessed in case of errors in manipulation. That is why systematic biocompatibility investigations have been performed both in the anterior and posterior parts of the rabbit eye.

Poly(ortho ester) is an attractive biomaterial carrier for administering drugs to the eye with a sustained release and good biocompatibility. This viscous ointment-like material allows the incorporation of drugs into the polymer by simple mixing at room temperature, without the use of a solvent. This characteristic is of considerable interest with respect to peptide and protein delivery, as well as for other thermolabile or fragile drugs. POE can be injected using a syringe with an appropriate hypodermic needle, which is a significant advantage compared with solid devices that must be placed either with a trocar or through a more complex surgical procedure. Intraocular administration of a sustained-release polymeric carrier represents a considerable advantage for the treatment of various ophthalmic pathologic conditions, compared with conventional dosage forms. The present study evaluates POE as a potential biocompatible biomaterial for intracameral and intravitreal use. The polymer was investigated blank or containing modulators of degradation—that is, magnesium hydroxide and dexamethasone phosphate.

MATERIALS AND METHODS

Polymer synthesis

As previously described,[17] POE was synthesized by a transesterification reaction between 1,2,6-hexanetriol and trimethyl orthoacetate (Aldrich® Chemie, Steinheim, Germany) under anhydrous conditions. POE was further purified by a precipitation procedure to remove impurities such as residual monomers and oligomers. POE was produced aseptically by drying the polymer under vacuum at 40°C on a rotoevaporator to eliminate all residual solvents, and eventually by breaking the vacuum with nitrogen which prevents contact with air. The structure of the polymer was confirmed by ^{1}H and ^{13}C nuclear magnetic resonance, as well as by infrared spectroscopy.[17]

The average molecular weight of the batches used in this study was approximately 4 (low molecular weight, POE_{LMW}) and 14 kD (high molecular weight, POE_{HMW}), as determined by size exclusion chromatography (SEC) using a Waters® 150 CV instrument with four Ultrastyragel® columns of 500, 10^3, 10^4, and 10^5 Å pore size in series (Waters, Volketswil, Switzerland) and stabilized tetrahydrofuran as eluent. Monodisperse polystyrene standards were used for calibration.[2] All chemicals used were reagent grade.

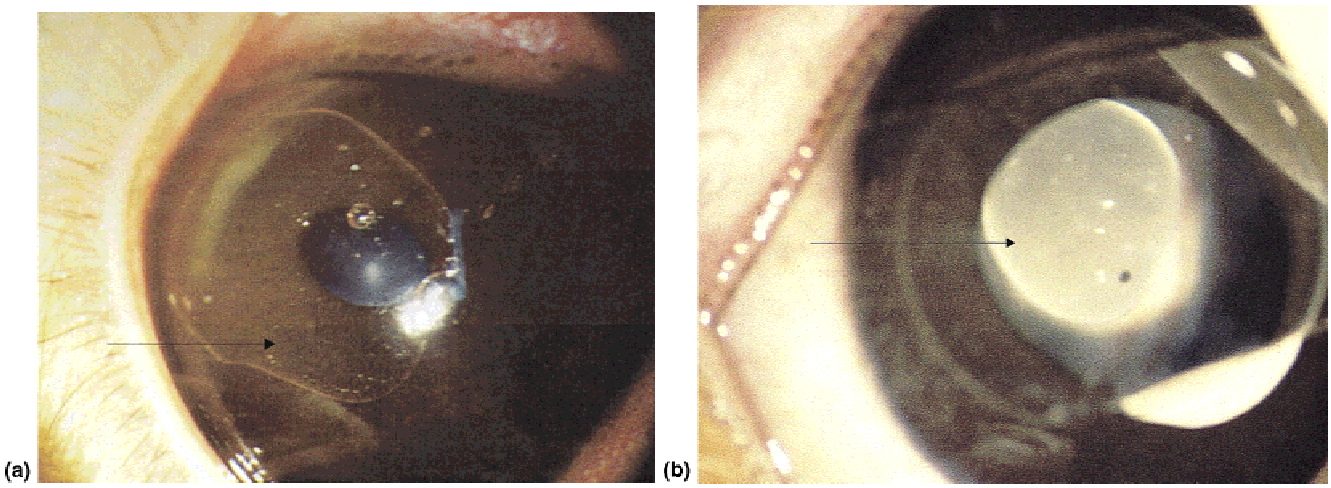

Figure 1. (a) Rabbit eye: External photograph immediately after intracameral injection of 100 μL POE_{HMW}. Arrow shows POE bubble in the anterior chamber. (b) Rabbit eye: External picture taken under the operating microscope with a glass slide on the cornea immediately after intravitreal injection of 100 μL POE + $Mg(OH)_2$. Arrow shows POE bubble in the vitreous cavity.

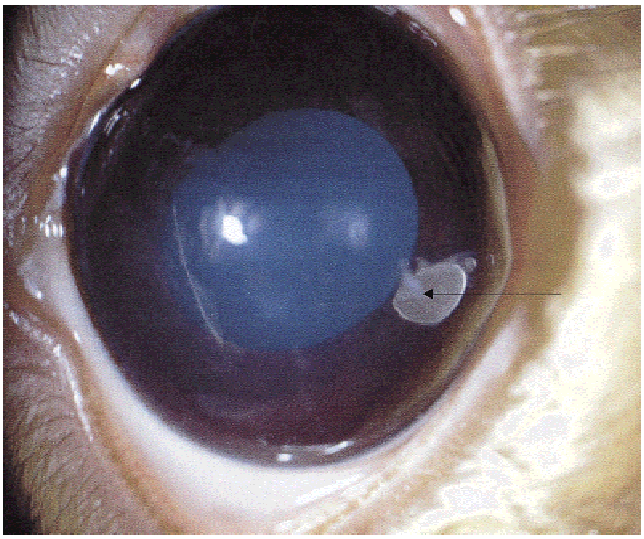

Figure 2. Rabbit eye: External photograph 5 days after intracameral injection of 50 μL POE_{HMW}. Arrow shows POE in the anterior chamber.

Sample preparation

The samples were prepared under a laminar air-flow hood. The added substances, magnesium hydroxide [$Mg(OH)_2$] or dexamethasone sodium phosphate (DEX) (Sigma Chemie AG, Buchs, Switzerland), were previously γ-sterilized at 2.0 MRad and mixed with the aseptically prepared polymer under sterile conditions at room temperature.[2] The final concentration of incorporated substance was 1% w/w. The mixture was then poured into a 1.0-mL hypodermic syringe, each injection amounting to 50 or 100 μL. Different formulations were tested: POE_{LMW}, POE_{HMW}, POE_{HMW} with $Mg(OH)_2$, and POE_{HMW} with DEX.

Animals

Pigmented Fauve de Bourgogne female rabbits weighing from 2.3 to 3 kg, 10–12 weeks of age, were used for this study (J.P. Ravaut, Institut de la Recherche Agronomique, Nouzilly, France), and experiments were conducted in accor-

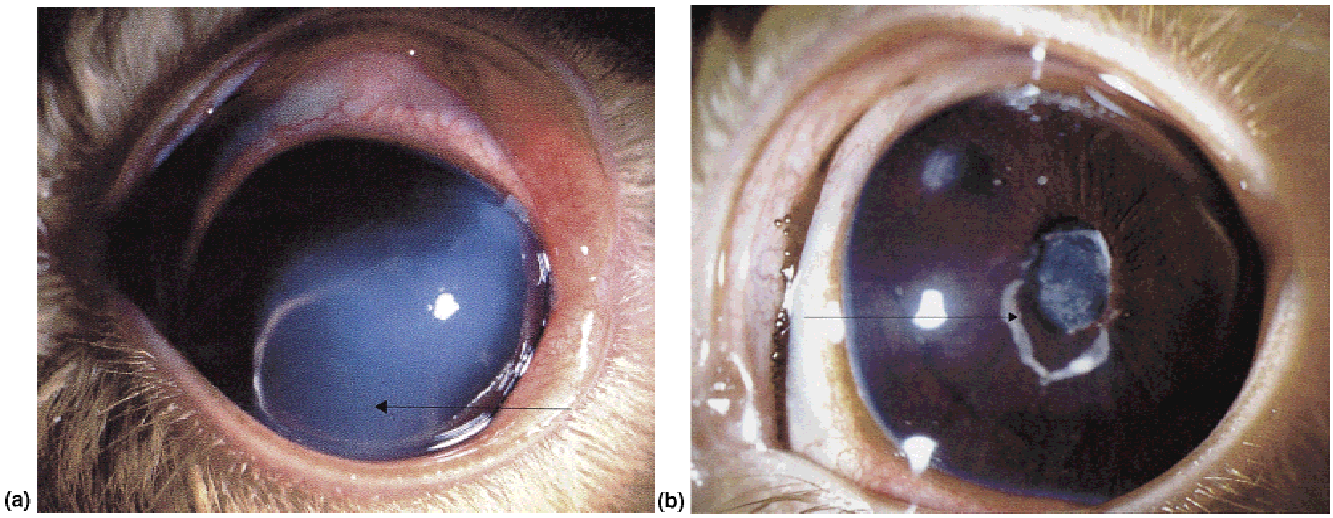

Figure 3. (a) Rabbit eye: External photograph 24 h after intracameral injection of 100 μL POE + DEX. Arrow shows POE in the anterior chamber. (b) Rabbit eye: External photograph 1 week after intracameral injection of 100 μL POE + DEX. Arrow shows POE in the anterior chamber.

dance with the ARVO *Statements on the Use of Animals in Ophthalmic and Vision Research*.

Intracameral injections

Intracameral tolerance was evaluated in rabbit eyes ($n = 6$) receiving a determined amount (50 or 100 μL) of each formulation. Under local anesthesia with oxybuprocain 0.4% (Novesin®; Ciba Vision, Switzerland), a lid speculum was positioned under a surgical microscope. A transfixing tunnelized corneal incision (2 mm) was realized in the temporo-superior part of the peripheral cornea with a 45° surgical knife to make the insertion of the needle easier. Then, a 0.9-mm needle (25 gauge) was inserted in the anterior chamber in the eye and each formulation was slowly injected [Fig. 1(a)]. No suture of the corneal incision was made.

Intravitreal injections

Intravitreal tolerance was evaluated in rabbit eyes ($n = 6$) receiving 100 μL of each formulation. The rabbits were sedated with 2 mg/kg nidazolam intramuscularly (IM) and then anesthetized with 60 mg/kg ketamine IM. Pupils were dilated with topical 10% neosynephrine and tropicamide instillated every 10 min starting 1 h before surgery. Under local anesthesia with oxybuprocain 0.4%, a lid speculum was placed and a transconjunctival incision of the sclera was realized in the temporo-superior quadrant of the eye at 3 mm of the limbus, using a 45° surgical knife, under a surgical microscope. Then, a 0.9-mm needle was inserted in the vitreous cavity with a glass slide over the cornea to allow visual control of the needle, and polymer formulation was slowly injected [Fig. 1(b)]. Precautions were taken to avoid contact with the lens. No suture was needed.

Clinical observations

Slit-lamp observations and photographs of the conjunctiva and the anterior chamber of the eye were performed regularly for 2 weeks after the injections. Observations of the posterior segment with a Volk Superfield lens were also realized periodically until the end of the experiment. The corneal epithelium was examined under blue light after instillation of 0.5% fluorescein solution to detect epithelial damage. Intraocular pressure was determined using a Goldmann tonometer and compared with the intraocular pressure of uninjected contralateral eyes.

Histological analysis

Rabbits were sacrificed by injection of a lethal dose of pentobarbital, and their eyes were enucleated and fixed to be studied histologically by conventional optical microscopy. For classical histology, enucleated eyes were fixed in Bouin's solution and embedded in paraffin. Anteroposterior sections at the optic nerve level were stained with hematoxylin–eosin. All samples were treated simultaneously to reduce variations among fixation procedures.

For semithin sections, corneas, irises, and retinas were dissected and fixed for 2 h in 2.5% glutaraldehyde in cacodylate buffer after careful orientation of the samples with respect to the polarity (center to periphery). Samples were then further processed in 0.1*M* cacodylate buffer (pH 7.3) after fixing in osmium epoxide and embedding in LX 112 resin (Epon®; Ladd Research, Burlington, VT). Subsequent semithin sections were obtained using an ultramicrotome (OMU2®; Reichert, Vienna, Austria) and counterstained with Toluidine blue. Semithin sections were analyzed using photonic microscopy and polarization (Nikon, Melville, NY).

RESULTS

Intracameral injections

Clinical observations clearly showed a relationship between the intracameral biocompatibility and the quantity of polymer injected. In the rabbit eyes which received a small quantity of polymer, i.e., 50 μL, the injected polymer appeared as a translucent bubble adherent to the iris. In the first 24 h, a slight fibrin exudate developed in the anterior chamber, forming a thin pupillary membrane, but rapidly resolved within 24–48 h. The polymer degraded within approximately 1 week (Fig 2), causing neither corneal edema nor iris depigmentation. There was no conjunctival hyperemia. The intraocular pressure was normal throughout the period of observation compared with the contralateral, noninjected eye. Histological analysis of eyes enucleated at 14 days after injection confirmed the integrity of the cornea, conjunctiva, and iris, except a slight depigmentation of the iridal stroma compared with uninjected eyes. No cell infiltration or sign of necrosis was observed on any of the tissues studied.

In the first hours after injection of 100 μL POE, the polymer was located in the inferior part of the eye up to the pupillar area and appeared as a dense material with an opaque surface. Considerable fibrin exudate was present in the anterior chamber in most of the eyes, but disappeared after 2 days. The cornea was diffusely edematous, more markedly at the sites where POE was in contact with the corneal endothelium [Fig. 3(a)]. In rare cases, a corneal desepithelialization zone was evidenced by a fluorescent area under blue light observation. The injection site was generally edematous and showed discrete synechia between the cornea and iris. The conjunctiva and episclera were hyperemic up to 1 week. After 8 days, the

polymer was considerably degraded. The corneal edema regressed and the anterior chamber cleared up following the resorption of POE and the fibrin exudate. The iris showed some small depigmented areas. The lens remained clear in all eyes all over the period of observation [Fig. 3(b)]. At 14 days, eyes recovered but the iris remained focally depigmented. The intraocular pressure was normal in all eyes throughout the experiment time.

Rabbits receiving approximately 100 μL of POE_{LMW} showed more of a severe corneal edema 24 h after intracameral injection. The polymer alone also degraded faster than POE_{HMW}. POE containing 1% of DEX triggered less inflammation, and the polymeric bubble remained longer in the anterior chamber. Figure 4 summarizes the evolution of ocular inflammation in the eyes of each group as a function of time. Clinical signs of inflammation were scored as follows: Grade 0 = clear anterior chamber and cornea; Grade 1 = minimal fibrin exudate and localized corneal edema; Grade 2 = significant fibrin exudate and diffuse corneal edema; Grade 3 = opaque cornea hindering the examination of the anterior chamber (Fig. 4).

On histological sections 14 days after injection, the cornea appeared to be normal with rare inflammatory cell infiltration in the stroma (Fig. 5): no sign of necrosis was observed on any of the tissues studied. The iris was discretely depigmented in the anterior layers of the stroma with melanophages distributed irregularly, which had phagocytosed an optically inert material consistent with POE (Fig. 6). A granulous exudate with an inflammatory cellular infiltrate was present in the anterior chamber. The rest of the globe was normal, notably the posterior segment. Figure 7 summarizes the frequency of anomalies observed in the eyes after 100 μL injection of various formulations of POE. The use of a high-molecular-weight polymer or the presence of the anti-inflammatory DEX significantly improved the tolerance of POE.

Intravitreal injections

In the first hours after intravitreal injection, the polymer appeared as a round bulk lying on the retina but moving in the vitreous cavity concomitant to eye movement. The intraocular pressure was normal in every eye and no clinical inflammatory reaction was observed in any group tested. The anterior chamber, as well as the vitreous cavity, was clear and the retina seemed unaffected by the presence of the polymer. POE containing 1% of magnesium hydroxide appeared noticeably as a round, whitish, opaque bleb in the vitreous cavity (Fig. 8).

At day 5, POE alone was markedly degraded and almost disappeared from the vitreous cavity, whereas the presence of the basic substances $Mg(OH)_2$ or DEX significantly prolonged polymer lifetime in the vitreous cavity up to 2 weeks. There was still no inflammatory reaction. At sacrifice, i.e., after 2 weeks, the polymer completely disappeared from all eyes which appeared clinically normal.

Semithin histological sections showed normal anatomy of the retina. In some cases, inflammatory cells were found in the vitreous gel and at the optic nerve head (Fig. 9). Other tissues of the eye, i.e., cornea, iris, ciliary body, choroid, sclera, and optic nerve, were without anomalies. Table I summarizes the lifetime of the polymer bubble within the vitreous cavity, as well as the frequency of the presence of inflammatory cells in the vitreous cavity upon histological analysis. Stabilizing $Mg(OH)_2$ or anti-inflammatory DEX completely inhibited the inflammatory reaction; moreover, they prolonged polymer persistence in the eye.

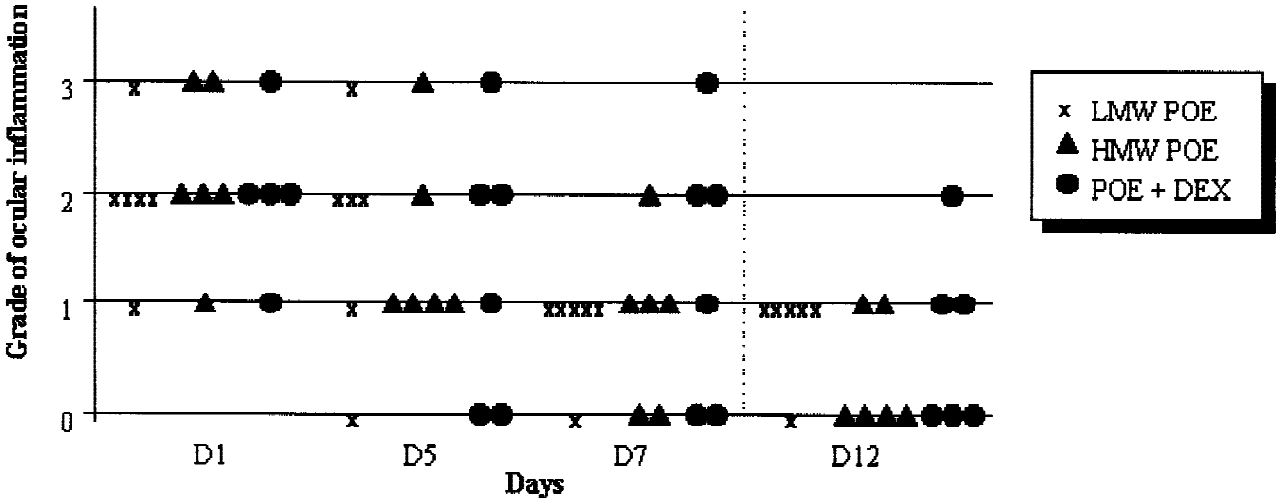

Figure 4. Evolution of ocular inflammation in each group as a function of time after intracameral injection of 100 μL of various POE formulations.

Figure 5. Histologic section through the cornea after intracameral injection of 100 μL POE_{LMW}. Inflammatory cell infiltration in the stroma (arrows) Toluidine blue, gross. Original magnification ×125.

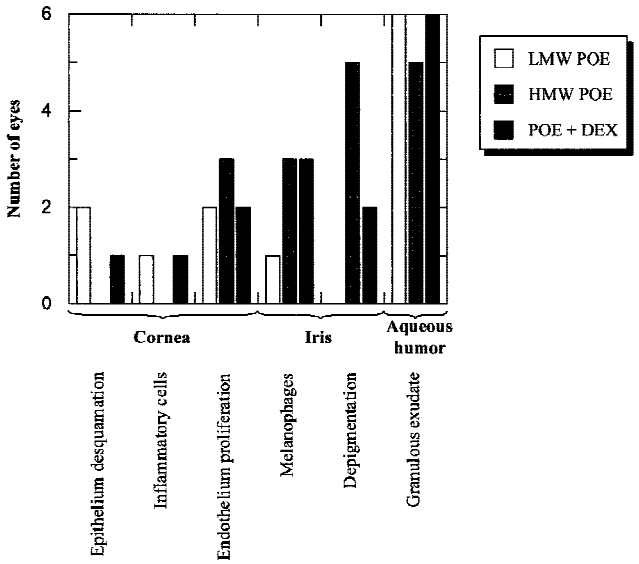

Figure 7. Intracameral injection of 100 μL POE_{LMW} and POE_{HMW} loaded or not with DEX. Number of eyes showing anomalies after histological analysis, at the end of the experiment (day 14).

DISCUSSION

Subconjunctival injection of antifibroblastic drugs remains the most appropriate site for the treatment of selected cases at high risk of failure of glaucoma filtering surgery. Because the system investigated here is intended for eyes with a past history of multiple surgery, and considering that eyes undergoing a trabeculectomy present a fistula between the subconjunctival space and the anterior chamber, the polymer and its degradation by-products are susceptible to moving into the anterior and farther to the posterior segment of the eye, specifically in aphakic patients. From this position under the conjunctiva, the polymer and its degradation by-products can follow several pathways: directly into the anterior chamber through the fistula,

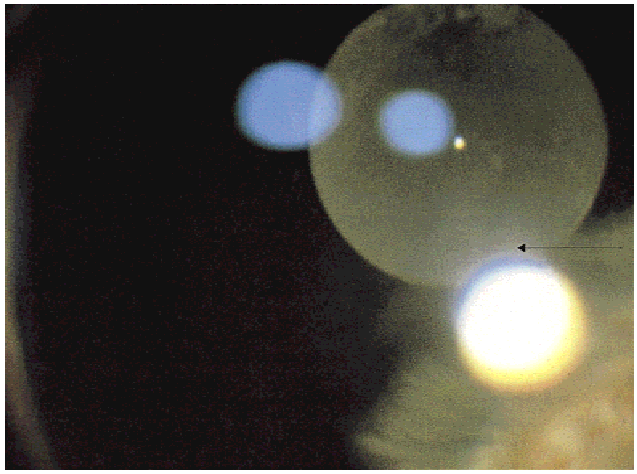

Figure 8. Rabbit eye: Indirect ophthalmoscopic picture of POE + $Mg(OH)_2$ in the vitreous cavity 5 days after intravitreal injection. Arrow shows POE in the vitreous cavity.

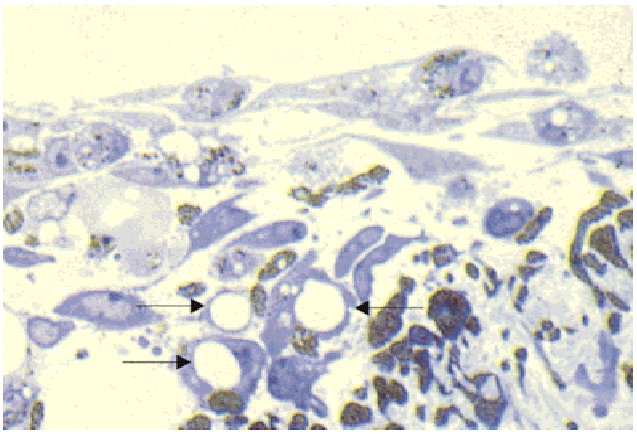

Figure 6. Semithin section of the iris after intracameral injection of 100 μL POE_{LMW}. Arrows show melanosomes having phagocytosed optically inert material. Toluidine blue, gross. Original magnification ×62.

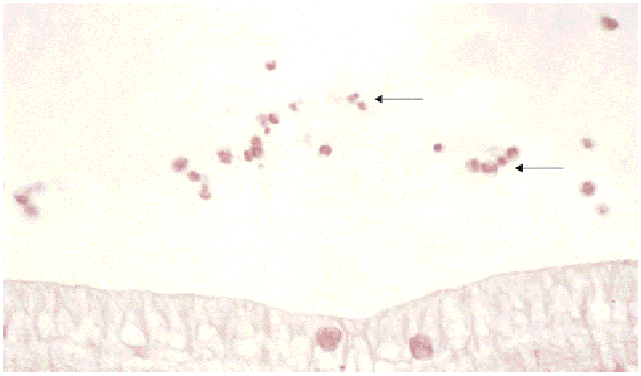

Figure 9. Histologic section through the retina and vitreous cavity after intravitreal injection of 100 μL POE_{HMW}. Note the discrete inflammatory cell infiltration in the vitreous gel (arrows). H&E, gross. Original magnification ×125.

to the ciliary body, into the vitreous body, and into the retina.[24] Once in the vitreous gel, POE and its degradation by-products are subject to the transport and diffusional systems that eliminate them from the vitreous cavity, across the retina.[24] Therefore, it is important to assess POE biocompatibility in these various parts of the eye. Furthermore, considering POE as an intravitreal drug delivery system, posterior segment biocompatibility is imperative. Blank polymer as well as polymer loaded with excipient and drugs have been evaluated, because the incorporation of such substances modulates the degradation rate of the polymer and thus indirectly influences tissue response.

Following intracameral injection, biocompatibility depends mainly on the quantity of biomaterial injected. As long as the polymer is not in contact with the cornea, it is well tolerated and degrades within approximately 1 week. If doses larger than 50 μL are introduced in the anterior chamber, close contact with the corneal endothelium becomes unavoidable and a reversible corneal edema develops, leading to corneal edema and opacification, accompanied by iritis. The cause of this transient corneal clouding relates to polymer degrading partly in acetic acid; it is likely that focal chemical burns result at the site of corneal contact. Interestingly, the intraocular pressure did not increase throughout the whole experiment time, contrary to what is generally observed with sodium hyaluronate when injected intracamerally.[25] These results appear similar to those described by Peyman et al.[26]: Intracameral injection containing more than 50 μL of crosslinked hyaluronic acid in rabbits produced severe inflammatory reaction such as hyperemia of the conjunctiva, episclera, and iris, and progressive corneal edema and opacification, while smaller amounts were well tolerated.

The different POE formulations tested trigger different reactions. Rabbits receiving POE_{LMW} show more corneal edema because a POE_{LMW} is by nature more degraded than a POE_{HMW}. POE_{LMW} tends to hydrolyze faster and triggers more inflammation. POE_{HMW} shows a slower degradation rate, and consequently its presence within the eye is prolonged. The addition of 1% DEX improves POE biocompatibility by reducing the hyperemia of the conjunctiva and iritis to a minimal level, and by decreasing the extent and duration of the corneal edema. DEX also moderately prolongs the intracameral presence of the polymer, although this prolongation was not as marked as when injected subconjunctivally.[27] This is explained by the stabilization of POE by the basic nature of DEX, as described in an *in vitro* study.[19] The *in vivo* prolonged presence of polymer containing DEX could also result from a reduced inflammatory cell infiltration, notably a decreased accumulation of macrophages, due to the anti-inflammatory properties of DEX. In fact, the interfacial pH between macrophages and the biodegradable polymer surface may be as low as 3, and an acidic environment is known to increase POE degradation rate.[18] Similarly, macrophages are the principal producers of a series of lysosomal enzymes, such as hydrolases or esterases, which can also trigger massive polymer degradation, although no data support this hypothesis.

Intravitreal injection of POE is well tolerated. No inflammatory reaction could be observed clinically throughout the study. Ocular tissues, including special observation of the entire retina, are normal upon histopathological analysis. A discrete cellular infiltration in the vitreous adjacent to the inner limiting membrane and at the optic nerve head is observed in some eyes. The incorporation of $Mg(OH)_2$ or DEX in the polymeric matrix significantly reduces this inflammatory cell infiltration to a minimal grade.

Other biodegradable polymers have been implanted intravitreally as sustained delivery systems, notably poly(α-hydroxyacids) such as poly(lactic acid) (PLA) and poly(glycolic-*co*-lactic acid) (PLGA). Scleral plugs of PLGA induced a slight infiltration of inflammatory cells in the conjunctiva and the sclera around the plug, but the retina showed no abnormalities.[28] Giordano et al.[29] injected blank PLGA microspheres into the vitreous of rabbit and observed a foreign-body reaction around the microspheres and a glial proliferation around the particles that were in contact with the retina. A mild inflammatory reaction was still visible at 2 months after injection. This reaction seems unavoidable and compatible with the introduction of foreign material in animal tissues. Enyedi et al.[30] implanted nonbiodegradable devices, blank or containing cyclosporine and dexamethasone in the rabbit vitreous; focal posterior capsule opacifications were noted in each group. These complications are probably the result of contact between the device and the lens.

The results obtained in this study show that intravitreal POE is a promising potential drug delivery system: It is safe and nontoxic to the retina and other ocular tissues. POE biodegradability is a major advantage because there is no need to remove the device once it is depleted of drugs, and it is possible to incorporate fragile drugs such as thermolabile compounds or oligonucleotides.

TABLE I
Intravitreal Injection of POE Loaded or Not with $Mg(OH)_2$ and DEX: Duration of Persistence and Occurrence of Inflammatory Cell Infiltration

Formulation Injected	Duration of Persistence within Eye (d)	Presence of Inflammatory Cells in Vitreous Gel (Eyes)
POE	7	3/6
POE + $Mg(OH)_2$	14	0/6
POE + DEX	14	0/6

CONCLUSION

This study was primarily conducted to determine the overall intraocular biocompatibility of a viscous bioerodible POE. After injection in the anterior chamber of the rabbit eye, biocompatibility evaluation showed tolerance up to 100 μL of POE. Indeed, small amounts of POE were well tolerated and degraded within 1 week. When a larger volume was introduced in the anterior chamber, contact with the corneal endothelium became unavoidable and transient corneal edema developed owing to the release of acetic acid during the polymer degradation. When intravitreally injected, POE was well tolerated, as observed by indirect ophthalmoscopy, and the degradation rate could be modulated by the appropriate choice of drugs and/or excipients. The presence of magnesium hydroxide or dexamethasone sodium phosphate prolonged polymer lifetime up to 2 weeks, compared with POE alone, which degraded within 1 week. Moreover, polymer biocompatibility was affected by $Mg(OH)_2$ or DEX, both improving polymer tolerance within the eye. POEs are promising biomaterials as drug delivery systems for the adjunctive medical treatment of ocular pathologic conditions such as glaucoma filtration surgery failure and PVR surgery.

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