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Poly(Ortho Esters): Recent Developments for Biomedical Applications

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Abstract: Poly(ortho esters) (POE) are hydrophobic and bioerodible polymers that have been under development since the early 1970s. Up to now, four generations of such polymers have been described. Of most interest are poly(ortho esters) III and poly(ortho esters) IV. POE III is a semi-solid material that has been shown to be highly biocompatible and is currently being investigated as a carrier for sustained drug delivery to treat diseases of the posterior segment of the eye. However, the polymerization is difficult to control and is not readily scaled up. POE IV can be easily prepared in a highly reproducible manner, is very stable provided moisture is rigorously excluded and has also been shown to be biocompatible. It is currently under development for a variety of applications, such as ocular delivery, protein release, and periodontal disease treatment.

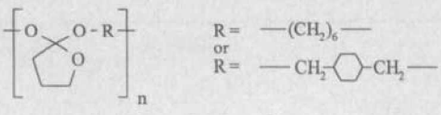
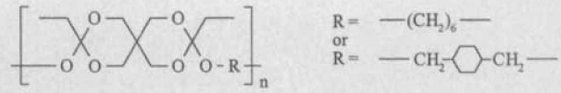
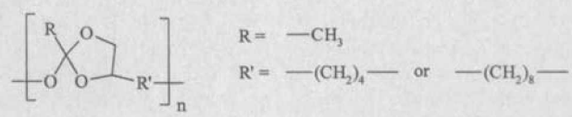
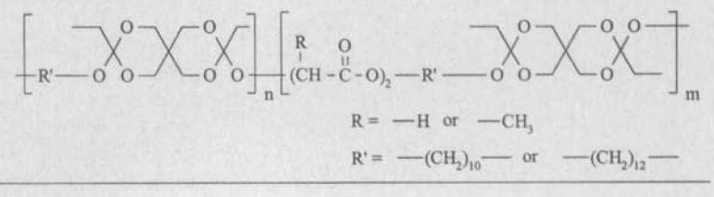
Keywords: Biodegradable polymers · Dentistry · Drug delivery · Ophthalmology · Poly(ortho esters)

1. Introduction

The interest in drug delivery systems, which control and prolong the action of therapeutic agents, has grown in importance over recent years with the development of bioerodible polymers. For example, poly(lactic acids), poly(glycolic acids) and their copolymers, polyanhydrides and poly(ortho esters) are particularly used for implantable pharmaceutical devices, since their use eliminates the step of removing the implant after the drug has been released. In some applications, this represents a significant advantage over other systems.

Poly(ortho esters) (POE) are hydrophobic polymers, which under certain conditions can undergo an erosion process confined to the polymer–water interface. Since the late 1970s, four families of POEs have been synthesized to provide bioerodible carriers for drug delivery [1][2]. These are shown in the Table. After a brief review of the four poly(ortho ester) families, emphasis will be placed on significant developments that have taken place within the last few years.

Table. Chemical structures of four families of poly(ortho esters)

Generation	Chemical structure
First	
Second	
Third	
Fourth	

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2. Poly(ortho ester) I

Poly(ortho ester) I was developed at the Alza Corporation and described in a series of patents [1]. All work with this polymer has now been discontinued. The main reason for this is the lack of control over polymer erosion. When placed in an aqueous environment, the polymer hydrolyzes as shown in Scheme 1. Because ortho ester linkages are acid sensitive and hydrolysis of this polymer produces γ-butyrolactone, which rapidly opens to γ-hydroxybutyric acid, the polymer must be stabilized with a base such as Na_2CO_3 to avoid an uncontrolled, autocatalytic hydrolysis reaction.

The polymer has been used in the treatment of burns [3], in the delivery of the narcotic antagonist naltrexone [4] and in the delivery of the contraceptive steroid levonorgestrel [5]. POE I has also been investigated by Sudmann in a number of orthopedic applications [6].

3. Poly(ortho ester) II

Poly(ortho ester) II was developed at the Stanford Research Institute [7]. Mechanical properties of POE II can be readily varied by choosing appropriate monomers during synthesis. Thus, materials can be prepared that are rigid, flexible, or low melting solids, or that at room temperature are semi-solids.

POE II hydrolyzes to initially neutral products, so that it is not necessary to use bases to neutralize acidic hydrolysis products. Even though ortho ester linkages are quite labile, polymers belonging to this family are extremely hydrophobic and uncatalyzed POE II are very stable. Therefore, in order to achieve shortened erosion times, a lifetime of 2–4 weeks *e.g.* it is necessary to use small amounts of acidic excipients, such as suberic acid, that are physically incorporated into the polymer [8]. If longer delivery rates are desired, bases such as $Mg(OH)_2$ can be used to retard polymer erosion [9]. Because $Mg(OH)_2$ stabilizes the interior of the device, erosion can only occur in the surface layers where the base has been eluted or neutralized. Using this approach, surface erosion lasting up to 1 year has been achieved [10].

Poly(ortho esters) of the second generation have been tested in numerous applications, such as 5-fluorouracil delivery for the treatment of cancer [11], prostaglandin delivery for bone growth promotion [12], as well as insulin delivery [13].

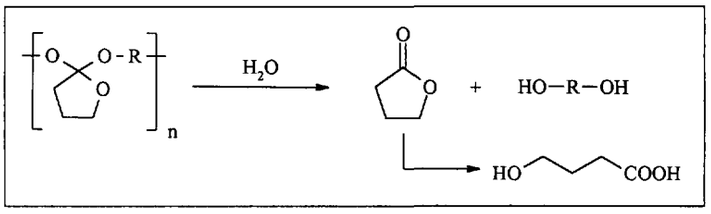
4. Poly(ortho esters) III

The third family of such polymers was originally developed at SRI International [14], and is currently under active development at the University of Geneva [15][16]. It is prepared as shown in Scheme 2. A precipitation procedure allows the removal of monomers and oligomers. Residual solvents can be removed by drying at 40 °C and 5 mbar for 24 h [15].

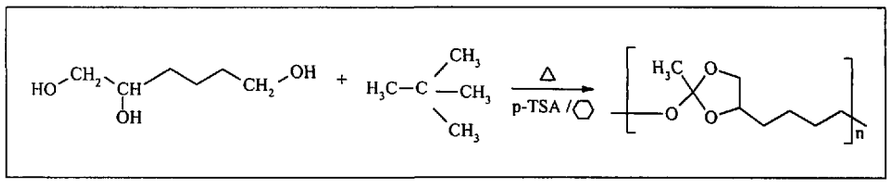
This polymer is a semisolid at room temperature even though molecular weights can exceed 35 kDa. The viscous consistency provides a number of unique advantages. Dominant among them is the ability to incorporate therapeutic agents into the polymer by a simple mixing procedure without the need to use solvents or elevated temperatures. The semisolid consistency also allows some unique means of administration of the polymer.

Polymer hydrolysis occurs as shown in Scheme 3 [14]. As with POE II, initial hydrolysis occurs at the labile ortho ester bonds to generate one or more isomeric monoesters of the triol. This initial hydrolysis is followed by a much slower hydrolysis of the monoesters to produce a carboxylic acid and a triol. Thus, as with POE II, no autocatalysis is observed. Unlike poly(ortho esters) II which are extremely hydrophobic, POE III prepared from alkyl orthoacetates and 1,2,6-hexanetriol are quite hydrophilic and take up a certain amount of water [17]. For this reason, POE III erosion can proceed at a relatively rapid rate.

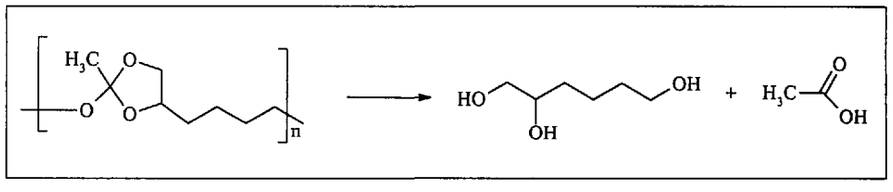
Due to the chemical lability of POE, the strategies for obtaining a sterile product are limited to aseptic processing and terminal sterilization using high energy radiation [18]. However, γ-radiation sterilization can lead to a change in polymer molecular weight [19]. Depending on the dose, two different mechanisms have been observed [20]. For doses lower than 2.0 Mrad the dominant degradation mechanism is scission of the polymer chain. Such cleavage leads to a decrease in polymer molecular weight and a consequent decrease of dynamic viscosity. At doses higher than 2.0 Mrad, chemical changes similar to polymer hydrolysis begin to take place. Radical formation and radical-induced polymer degradation after irradiation treatment were investigated with electron paramagnetic resonance (EPR) spectroscopy [21]. Several radical species could be distinguished. Two commonly applied methods for irradiation sterilization (*i.e.* γ- and β-rays) were also compared to the aseptic pro-



Scheme 1. Hydrolysis of POE I



Scheme 2. Synthesis of POE III



Scheme 3. Hydrolysis of POE III

cess. The weight and number average molecular weight of POE decreased drastically after irradiation treatment; higher molecular weight polymers were more affected, and γ-irradiation lead to more degraded products than β-treatment. Irradiation treatment has been concluded not to be a suitable process and therefore aseptic preparation is preferred [21]. Preferred storage conditions are in sealed glass bottles under an argon atmosphere. Under these conditions, POE molecular weight remained virtually unchanged for 180 days [17].

Drug release from POE is almost constant, following zero-order kinetics, without any burst effect. It can be controlled by factors such as polymer molecular weight [22] and physicochemical properties of the incorporated substances [23][24]. Indeed, ortho ester linkages are sensitive to acid catalysis. Notably, the incorporation of basic additives, such as sodium acetate or magnesium hydroxide, allows the polymeric backbone to be stabilized and hence prolongs the lifetime of the polymer. Also drugs with basic characteristics, such as dexamethasone sodium phosphate, possess this stabilizing property [24].

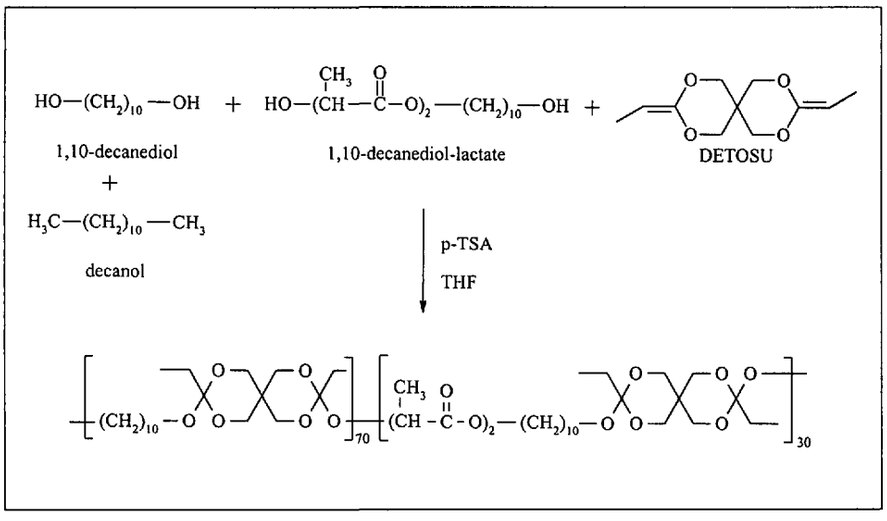
5. Poly(ortho ester) IV

Poly(ortho ester) IV was developed at Advanced Polymer Systems in collaboration with our laboratory [25] and to date, represents the most promising generation. POE IV differs from POE II in that a mono, or dilactide or a mono, or diglycolide segment has been incorporated into the polymer backbone. These segments act as latent acid catalysts because on their hydrolysis, lactic or glycolic acid is generated which then catalyzes hydrolysis of ortho ester linkages in the polymer backbone. It is synthesized as shown in Scheme 4.

By varying the relative amounts of the two diols, polymers containing varying amounts of mono or dilactic acid, or mono and diglycolic acid segments can be prepared [26][27]. In addition, since drug release from POE depends on polymer molecular weight and molecular distribution [22][28], it is extremely important to reproducibly control molecular weight and molecular weight distribution. For this purpose, a monofunctional monomer that is able to condense and then act as a 'chain stopper' can be added, such as decanol [29].

Hydrolysis of POE IV proceeds in consecutive steps [30]. In the first step, the lactic acid dimer segment hydrolyzes to generate a polymer fragment containing a carboxylic acid end group, which will catalyze ortho ester hydrolysis. A second cleavage produces free lactic acid, which also catalyzes hydrolysis of the ortho ester links. The hydrolysis of ortho esters then proceeds in two steps, to first generate the diol or mixture of diols used in the synthesis, and pentaerythritol dipropionate, followed by ester hydrolysis to produce pentaerythritol and propionic acid [30]. In an extensive study on POE IV hydrolysis [31], it has been found that a linear polymer weight loss occurs concomitantly with release of lactic and propionic acid, which argues convincingly for a process of hydrolysis predominantly to the surface layers of the polymer matrix. However, the process is clearly not a pure surface erosion because there is a significant drop in molecular weight of the uneroded polymer, indicating that some hydrolysis is taking place in the bulk material.

The major advantage of POE IV is that polymer properties, as well as release and erosion rates, can be independently varied by controlling the nature of the R-group in the diol and the latent acid diol, and by varying the relative proportion of these two diols. For example, in a case study concerning 5-fluorouracil [32], it has been shown that the rate of drug release depends on the alkyl chain length of the diol in the polymer structure, a C8-diol polymer releasing 5-fluorouracil much faster than a C12-diol polymer. The drug was released predominantly by an erosion process from a polymer containing 10 or 20% of diol-lactate. Concerning the proportion of the acid diol, it has been shown [33] that a higher percentage of lactate diol leads to a faster release rate and a decrease of the lag time initially present in the release profile.



Scheme 4. Synthesis of POE IV

6. Biomedical Applications

As mentioned before, POEs present several advantages that make them ideal candidates for biomaterials. Some POEs are injectable, their administration is a simple procedure compared to solid devices which have to be implanted using more complex interventions. Moreover, the viscous consistency allows drugs to be incorporated by simple mixing, without the use of heat or solvents, which allows the formulation of fragile and thermolabile drugs such as peptides, proteins or oligonucleotides. Being biodegradable, there is no need to remove the polymer once all the drug has been released. For the time being particular interest has been focused on ocular drug delivery [34] and treatment of periodontal diseases [35].

6.1. *Ophthalmic Application*

6.1.1. *Ocular Biocompatibility*

The numerous advantages of using biodegradable polymers for sustained ophthalmic drug delivery has led to an intensive investigation of POE III biocompatibility in various parts of the eye. The polymer has been shown to be well tolerated in the subconjunctival site [36–39], as well as in the anterior chamber and in the vitreous cavity [40]. No significant inflammatory reaction was triggered, and the polymer degraded within 1–2 weeks,

depending on the drug substance incorporated within the polymer matrix [24].

Suprachoroidal and subretinal injections are currently under investigation, to administer drugs to the retina or the choroid in diseases such as age-related macular degeneration (AMD) [41].

6.1.2. *Glaucoma Filtering Surgery*

A novel drug delivery concept based on POE III has been developed as an adjunct treatment to glaucoma filtering surgery. Glaucoma is a disease mainly characterized by an increase in intraocular pressure. In some cases where the use of topical drugs is not effective to decrease the intraocular pressure, the condition can be corrected by a surgical intervention where a fistula is made in the anterior chamber so that excess fluid can drain [42]. However, unless an agent such as 5-fluorouracil (5-FU) is administered postsurgically by a daily injection over two weeks, fibroblast proliferation will eventually close the fistula. With a POE delivery system placed subconjunctivally at the time of surgery and releasing 5-FU over two weeks, the need for daily subconjunctival injections is eliminated. The POE + 5-FU formulation was shown to effectively reduce intraocular pressure in rabbits undergoing experimental glaucoma filtering surgery (Fig. 1) while significantly reducing 5-FU toxicity when compared to conventional 5-FU administration, *i.e.* intraoperative 5-FU tamponade [43][44].

6.2. *Dental Application*

Periodontitis is a group of dentoalveolar infections that are one of the major causes of tooth loss. These infections are caused by a pathogenic flora established within the gingival sulcus which later deepens to form a periodontal pocket. Treatments are based on strategies that shift the microflora within the periodontal pocket to that observed around healthy teeth and gingival tissues; a widely used treatment is to mechanically remove plaque and calculus, followed by local treatment with antimicrobial agents. Clearly, controlled release devices that would maintain a therapeutically effective concentration of an antimicrobial agent within the pocket for the desired length of time may significantly improve treatment [35].

Semisolid POE IV based on 1,10-decanediol and 1,10-decanediol dilactide are currently under investigation as a tetracycline delivery system for the treatment of periodontal disease [33]. In this application, the semisolid POE with incorporated tetracycline is injected in the periodontal pocket using a blunt needle. Excellent *in vitro* release with concomitant polymer erosion has been achieved. A recent human clinical trial showed that therapeutic tetracycline concentrations exceeding the minimum inhibitory concentration could be maintained in the gingival crevicular fluid for a period of at least seven days [33].

6.3. *Protein Delivery*

The importance of delivery systems that can release peptides and proteins with full retention of activity by well-defined kinetics without an initial burst is now well recognized. It is also known that many proteins lose activity when exposed to an organic solvent-water interface so that conventional microencapsulation methods cannot be used unless specialized methods are developed [45]. Thus, development of solventless methods to create such delivery systems is clearly of significant interest. When suitable diol pairs are used, POE IV can be extruded at temperature ranges between 50 and 70 °C, temperatures that are low enough to maintain full retention of the protein activity. Fig. 2 shows release of the model protein FITC-BSA from a polymer extruded at 70 °C, as well as weight loss of the extruded rods.

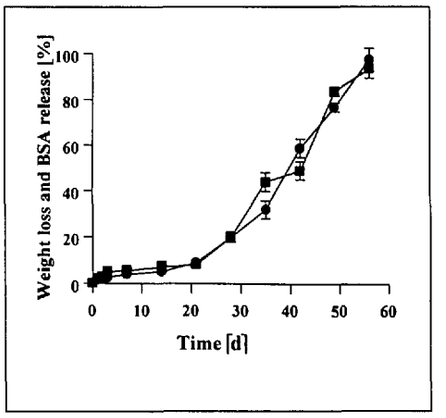


Fig. 2. Release of FITC-BSA (●) and weight loss (■) from a poly(ortho ester) IV prepared from DETOSU, 1,4-pentanediol and 1,6-hexanediol glycolide (100/95/5). Strands, extruded at 70 °C. 0.01 M phosphate buffered saline, pH 7.4, 37 °C. FITC-BSA loading 15 wt%.

Although the release and weight loss show a significant lag time, these results are highly encouraging in that excellent linear kinetics with concomitant weight loss have been achieved with only a negligible initial burst. The induction period is the result of the highly hydrophobic nature of the polymer which makes water penetration difficult. Attempts to decrease the lag time are currently underway, notably by incorporating poly(ethylene glycol) (PEG) in the POE matrix or by using POE-PEG-POE block copolymers [46].

When the extrusion was carried out with rh-GH at 70 °C and the protein ex-

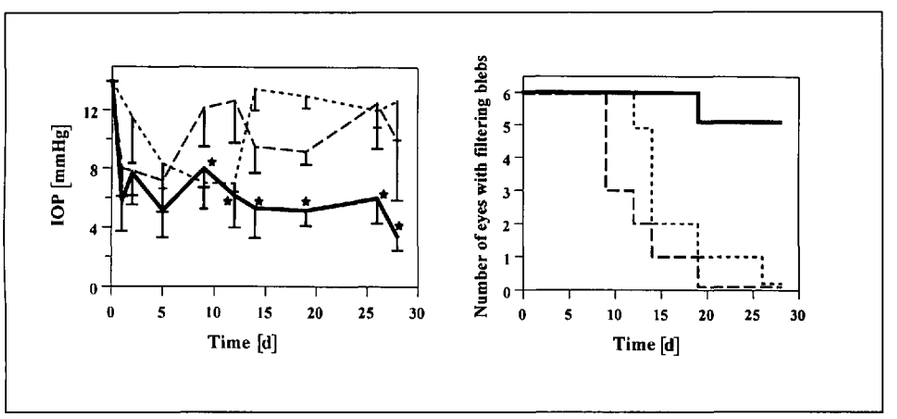


Fig. 1. Postoperative IOP (*left*) and filtering bleb persistence (*right*) in rabbits. Eyes undergoing surgery alone (– – –), eyes receiving POE alone (---) and eyes receiving POE containing 5-FU(—). (n=6, mean ± sd). Asterisks indicate significant difference from control ($p<0.05$).

tracted from the rods, it was found to contain 90.5% native protein which compares very favorably to 95.2% native protein in the rh-GH prior to extrusion. A pharmacokinetic study with rh-GH in rats is currently underway using rods that were extruded at a lower temperature [2].

7. Conclusions

Poly(ortho esters) have evolved through a number of families to the latest family, poly(ortho ester) IV which has a number of important advantages over previous families. Dominant among these is excellent control over polymer properties and erosion rate, concomitant erosion and drug release, ease of synthesis, excellent biocompatibility and very good room temperature stability. Poly(ortho esters) look promising for several biomedical applications, notably in ophthalmology and dentistry.

Acknowledgments

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