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Review article

Poly(ortho esters) – their development and some recent applications

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Abstract

Poly(ortho esters) have been under development since the early 1970s and four families of such polymers have been described. Of most interest are poly(ortho ester) III and poly(ortho ester) IV. Poly(ortho ester) III is a semisolid material that has been shown to be highly biocompatible and is currently being investigated as an adjunct to glaucoma filtering surgery and other ocular applications. However, the polymerization is difficult to control and is not readily scaled up. Poly(ortho ester) 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 highly biocompatible. It is currently under development for a variety of applications, such as ocular delivery, protein release, post-operative pain treatment and post-operative cancer treatment.

Keywords: Poly(ortho esters); Developments; Applications; Polymerization

1. Introduction

Poly(ortho esters) have been under development since the early 1970s and have evolved through a number of structurally distinct families. These are shown in Scheme 1.

Development and applications of these polymers prior to 1992 has been comprehensively reviewed [1,2], and it is not the purpose of this chapter to comprehensively review all past work. Rather, after a brief review of the four poly(ortho ester) families shown in Scheme 1, emphasis will be placed on significant developments that have taken place within the last few years.

2. Poly(ortho ester) families

2.1. Poly(ortho ester) I

Poly(ortho ester) I, the first such polymer prepared, has been developed at the Alza Corporation and described in a series of patents by Choi and Heller [3–7]. This polymer was originally designated as Chronomer but the name was later changed to Alzamer®. The polymer is prepared as shown in Scheme 2. All work with this polymer has now been discontinued.

When placed in an aqueous environment, the polymer will hydrolyze as shown in Scheme 3.

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.

Little detailed published information is available and the structures have not been specifically disclosed. However, it is now known that the code name of C111 represents a polymer prepared using 1,6-hexanediol and C101ct is a polymer prepared using *cis*/*trans*-cyclohexanedimethanol. The polymer has been used in the treatment of burns [8], in the delivery of the narcotic antagonist naltrexone [9] and in the delivery of the contraceptive steroid levonorgestrel [10]. The polymer has also been investigated by Sudmann in a number of orthopedic applications [11–19].

2.2. Poly(ortho ester) II

Poly(ortho ester) II was developed at the Stanford Research Institute, now known as SRI International, under contract with the National Institute of Child Health and Human Development, and is prepared as shown in Scheme

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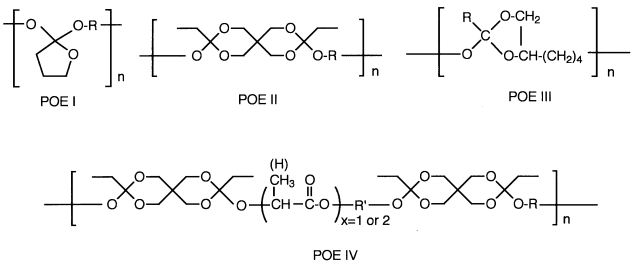


Scheme 1. Four families of poly(ortho esters).

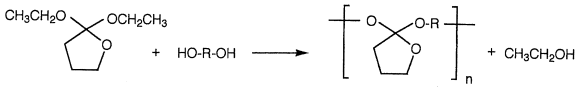
4. A history of the development of this polymer has been published [2].

As shown in Scheme 5, the polymer hydrolyzes to initially neutral products, so that it is not necessary to use bases to neutralize acidic hydrolysis products. Details of the hydrolysis mechanism have been published [20].

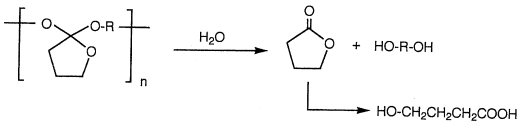
Even though ortho ester linkages are quite labile, polymers belonging to this family are extremely hydrophobic and uncatalyzed poly(ortho esters), as shown in Fig. 1, are very stable. Therefore, in order to achieve shortened erosion times, it is necessary to use small amounts of acidic excipients that are physically incorporated into the polymer [21,22]. Then, the rate of hydrolysis can be manipulated by varying the pK_a and/or concentration of the acidic excipient. While a number of different acidic excipients have been used with poly(ortho esters) [23], good results can be achieved by using suberic acid. When long delivery rates are desired, bases such as $Mg(OH)_2$ have been used to retard polymer erosion [24].

When the hydrophobic polymer with a physically dispersed acidic excipient is placed into an aqueous environment, water will diffuse into the polymer, dissolve the acidic excipient in the surface layers and the lowered pH will accelerate hydrolysis of the acid sensitive ortho ester bonds. The ultimate behavior of a device is determined by the relative movement of two fronts, a hydration front and an erosion front. If hydration is faster than erosion the thickness of the reaction zone will gradually increase and at some time, the matrix will be completely permeated by water. At that point, all ortho ester linkages will hydrolyze at comparable rates and bulk hydrolysis will take place. If the movement of the two fronts is equal, then hydrolysis is confined to the surface layers and rate of polymer erosion will be completely determined by the rate at which water intrudes into the polymer.

Water sorption by poly(ortho esters) II has been found to be relatively small, about 0.30–0.75% with a diffusion coefficient ranging from a high of 4.07×10^{-8} cm^2 s^{-1} for a polymer based on 1,6-hexanediol (T_g 22°C) to a low of



Scheme 2. Synthesis of POEI.



Scheme 3. Hydrolysis of POEI.

2.11×10^{-8} cm^2 s^{-1} for a polymer based on *trans*-cyclohexanedimethanol ($T \sim 122$°C) [25]. However, even with such low water diffusion coefficients, the use of acidic excipients limits the design of surface eroding devices to lifetimes that do not exceed 2–4 weeks, depending on the actual device size.

However, because ortho ester linkages are stable in base, very long time surface erosion is possible, if the polymer is stabilized with a base such as $Mg(OH)_2$ which prevents hydrolysis even though the matrix is completely permeated by water. 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 [26].

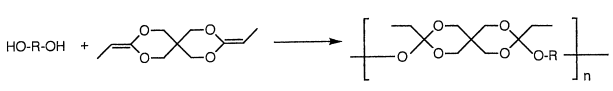
2.3. Poly(ortho ester) III

The third family of such polymers was originally developed at SRI International [27], and is currently under active development at the University of Geneva [28]. It is prepared as shown in Scheme 6. The intermediate does not have to be isolated and continuing reaction produces the final polymer.

When R is —$(CH_2)_4$—, the polymer is a semisolid at room temperature even though molecular weights can exceed 35 kDa. This semisolid consistency provides a number of unique advantages. Dominant among these is the ability to incorporate into the polymer therapeutic agents 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 7 for a polymer prepared from 1,2,6-hexanetriol [27]. As with poly(ortho ester) 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 the poly(ortho ester) II, no autocatalysis is observed. Details of the hydrolysis mechanism for polymers based on 1,2,6-hexanetriol and 1,1,4-cyclohexanetrimethanol have been published [29,30].

Unlike poly(ortho esters) II which are extremely hydrophobic [25], poly(ortho esters) III prepared from alkyl orthoacetates and 1,2,6-hexanetriol are quite hydrophilic



Scheme 4. Synthesis of POEII.

and water uptake at a relative humidity of 80% is shown in Fig. 2 [31]. For this reason, the uncatalyzed erosion of this polymer can proceeds at a relatively rapid rate.

2.4. Poly(ortho ester) IV

This polymer was developed at Advanced Polymer Systems [32,33] and to date, represents the most promising polymer. Poly(ortho ester) IV differs from poly(ortho ester 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 prepared as shown in Scheme 8 for a monolactide segment. A detailed characterization of the polymer has been published [34].

The hydrolysis is somewhat complex and is shown in Scheme 9. A detailed study of the hydrolysis process has been published [35].

The major advantage of this polymer is that polymer properties 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. The effect of latent acid concentration in the polymer on erosion rates is shown in Fig. 3.

The data show a good correlation between latent acid concentration and erosion rates, but also show that a substantial induction period is observed for very low latent acid concentrations. This induction period has been discussed previously [35] and is a consequence of the highly hydrophobic nature of the polymer since no hydrolysis can take place until sufficient water has penetrated the polymer matrix. The induction period can be decreased by increasing polymer hydrophilicity, the amount of latent acid diol and by using lower molecular weight materials. While in many applications an induction period is not desirable, it can be advantageously used to delay the release of an active agent.

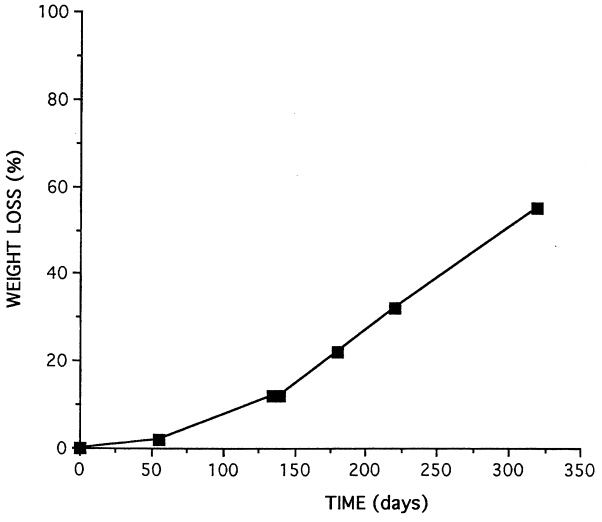
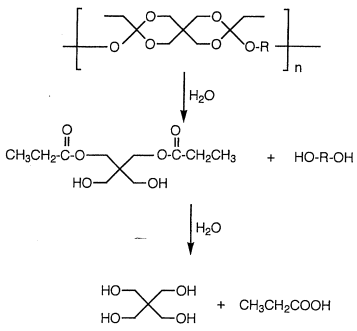


Fig. 1. Weight loss as a function of time for a polymer prepared from 3,9-dimethylene-2,4,8,10-tetraoxaspiro[5.5]undecane and 1,6-hexanediol. 0.05 M phosphate buffer, pH 7.4, 37°C. Reprinted with permission from [48].



Scheme 5. Hydroslysis of POEII.

3. Recent applications

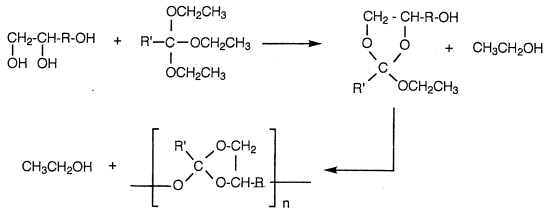
In this section, a number of recent applications using poly(ortho ester) III and poly(ortho ester) IV will be briefly illustrated.

3.1. Poly(ortho ester) III

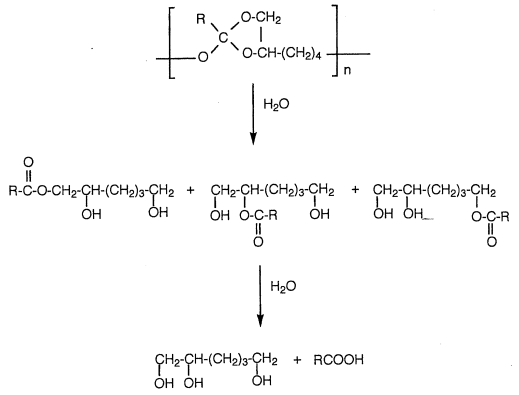
3.1.1. Ocular applications

The numerous advantages of using biodegradable polymers for sustained ophthalmic drug delivery has led to an intensive investigation of poly(ortho ester) biocompatibility in various parts of the eye. The polymer has been shown to be well tolerated in the subconjunctival site, as well as in the anterior chamber and in the vitreous cavity [36]. No significant inflammatory reaction was triggered, and the polymer degraded within 1–2 weeks, depending on the drug substance incorporated within the polymer matrix [37]. Subretinal injections are currently under investigation, to administer drugs to the retina or the choroid in diseases such as age-related macular degeneration (AMD).

A novel drug delivery concept based on poly(ortho esters) 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, the conditions can be corrected by a surgical intervention where a fistula is made in the anterior chamber so that excess fluid can drain [38]. However, unless an agent such as 5-fluorouracil (5-FU) is administered post-surgically by a daily injection



Scheme 6. Synthesis of POEIII.



Scheme 7. Hydrolysis of POEIII.

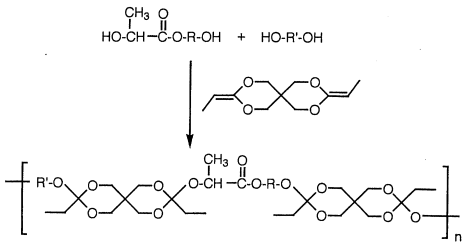
over 2 weeks, fibroblast proliferation will eventually close the fistula. With a poly(ortho ester) delivery system, the need for daily subconjunctival injections is eliminated if a bioerodible device containing 5-FU is placed subconjunctivally at the time of surgery. POE containing 5-FU was shown to effectively reduce intraocular pressure in rabbits undergoing experimental glaucoma filtering surgery (Einmahl et al., to be published).

3.2. Poly(ortho ester) IV

3.2.1. Management of post-operative pain

Poly(lactic acid) microspheres have been evaluated as a sustained delivery system for local anesthetics such as butamben, tetracaine and dibucaine [39,40]. The use of poly(lactic-*co*-glycolic) acid copolymers was also investigated as a delivery system for the release of bupivacaine and dexamethasone using a rat sciatic nerve blockage model [41,42]. However, in many applications, such as treatment of post-operative pain, an analgesic activity of only a few days would be desirable. Because erosion times of poly(-lactic acid) is measured in months, and even years and the erosion time of poly(lactide-*co*-glycolide) copolymers is measured in weeks, these erosion times are clearly not optimal for short term therapy. Because the erosion time of poly(ortho ester) can be varied from days, to many months and the polymer can be easily fabricated into any desired shape, these polymers are of interest in the development of short- and long-acting delivery systems of analgesic agents, such as bupivacaine.

To develop such delivery systems, 60 wt% of micronized



Scheme 8. Synthesis of POEIV.

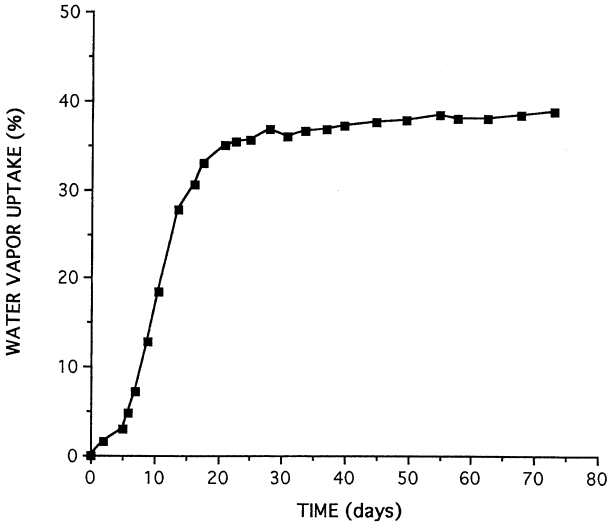
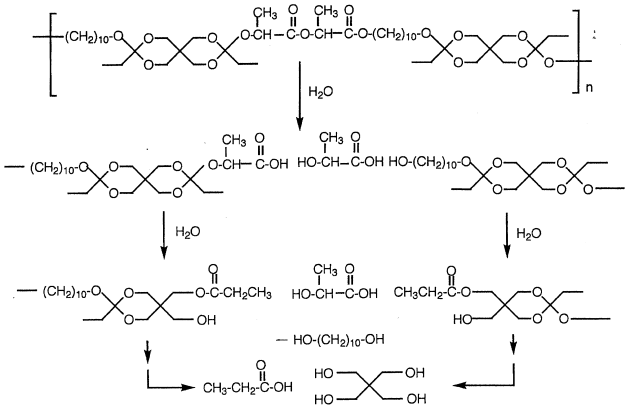


Fig. 2. Water vapor uptake of a 21.5 kDa polymer prepared from a trimethylorthoacetate and 1,2,6-hexanetriol at 80% relative humidity. Reprinted with permission from [31].

bupivacaine was physically mixed with a finely powdered poly(ortho ester) followed by extrusion and cryogenic grinding of the rods into microparticulates which after sieving had a mean size of less that 106 μm. The microparticulates were then placed in close proximity to the sciatic nerve of rats followed by electrical stimulation of the hind limb. Lack of limb withdrawal was interpreted as complete nerve block. A total of five animals were used. Results of that study, shown as bupivacaine blood levels and percent nerve block, are shown in Fig. 4. Clearly, the microspheres are highly effective in inducing nerve blockage and there is a good correlation between bupivacaine blood levels and nerve block. Work is currently ongoing to extend the duration of nerve blockage and on the development of longer acting systems capable of use in chronic pain control.

3.2.2. Release of peptides and proteins

The importance of delivery systems that can release peptides and proteins with full retention of activity by



Scheme 9. Hydrolysis of POEIV.

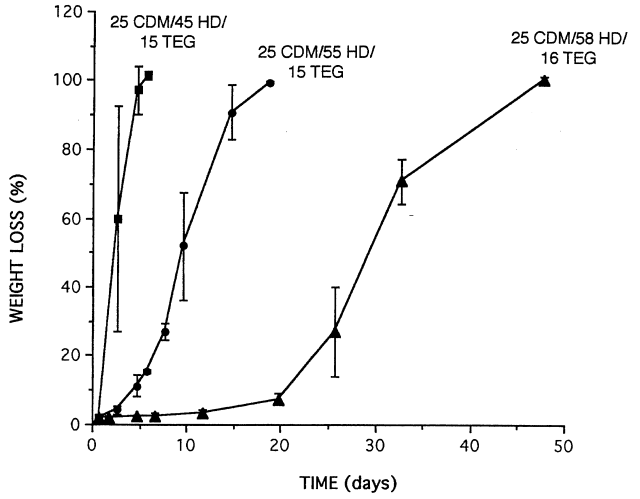


Fig. 3. Effect of triethylene glycol monoglycolide (TEG mono-GL) concentration on erosion rates for poly(ortho esters) prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane and mixtures of diols as shown: (■) 15 mol% TEG mono-GL, (●) 5 mol% TEG mono-GL, (▲) 1 mol% TEG mono-GL. 0.05 M phosphate buffer, pH 7.4, 37°C. CDM, *trans*-cyclohexanedimethanol; HD, 1,6-hexanediol; TEG, triethylene glycol, Reprinted with permission from [47].

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 [43] so that conventional microencapsulation methods can not be used unless specialized methods are developed [44]. Thus, development of solventless methods to create such delivery systems is clearly of significant interest.

When suitable diol pairs are used, poly(ortho esters) that can be extruded at temperature ranges between 50 and 70°C can be readily prepared and these temperatures are low enough so that it is anticipated that many dry proteins will

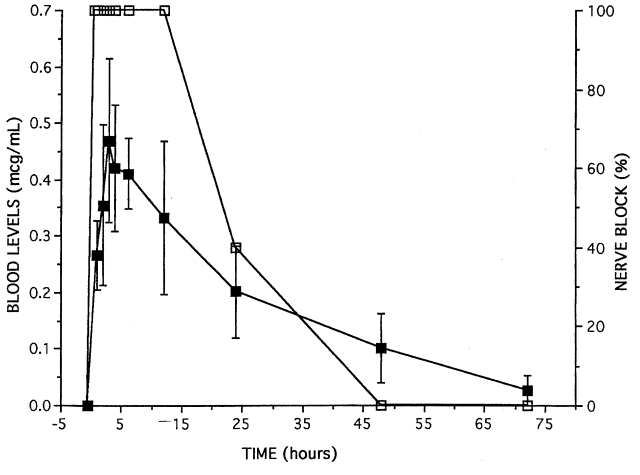


Fig. 4. Blood levels (■) and nerve blockage (□) in a rat sciatic nerve model using a poly(ortho ester) prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane and *trans*-cyclohexanedimethanol/triethylene glycol/triethylene glycol diglycolide (35/25/40). Microspheres, average size $<$ 100 μm, bupivacaine loading 60 wt%, $n = 5$.

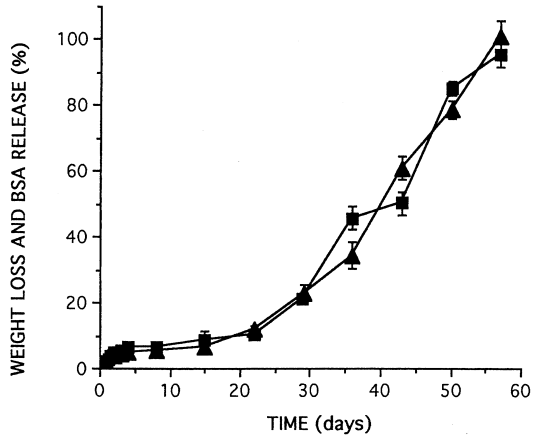


Fig. 5. Release of FITC-bovine serum albumin from poly(ortho ester) rods prepared by extruding a mixture of protein and polymer at 70°C. Polymer prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane and 1,4-pentanediol/1,6-hexanediol monoglycolide (95/5). Rods, 1 × 10 mm, HTC-BSA loading 15 wt%. (▲) weight loss. (■) FITC-BSA release. 0.05 M phosphate buffer, pH 7.4, 37°C.

survive the extrusion process with full retention of their activity.

The feasibility of such a method is now under investigation and preliminary data obtained with rh-GH seem to support the validity of this approach. Fig. 5 shows release of the model protein FITC-BSA from a polymer extruded at 70°C, as well as weight loss of the extruded rods. While attempts to decrease the lag time are currently underway, work is also in progress that takes advantage of the delay in applications where a delay having the desired length is followed by controlled release.

Although the release and weight loss show a significant

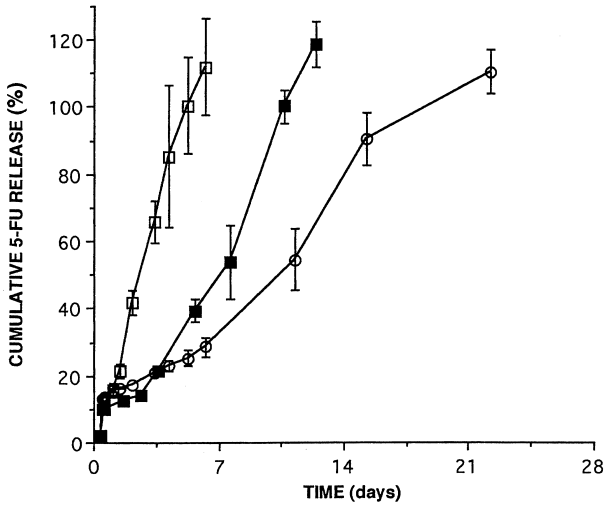


Fig. 6. 5-FU release from a polymer prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane, *trans*-cyclohexanedimethanol glycolide (CDM-Gly) and *trans*-cyclohexanedimethanol (CDM) as a function of diol ratios. (●) 75/25 CDM-CDM-Gly, (■) 80/20 CDM-CDM-Gly, (▲) 90/10 CDM-CDMGly. 0.05 M phosphate buffer, pH 7.4, 37°C. Drug loading 10 wt%. Reprinted with permission from [46].

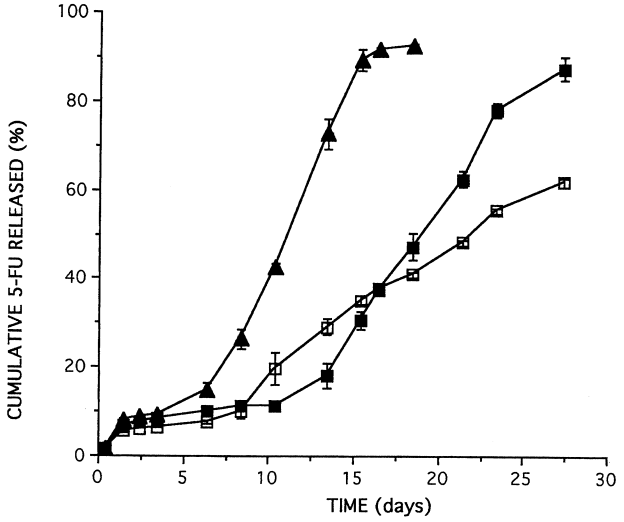


Fig. 7. Effect of hydrophilicity on rate of release of 5-FU from a poly(ortho ester) prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane, *trans*-cyclohexanedimethanol (CDM), 1,6-hexanediol (HD) and triethylene glycol (TEG) containing 28 wt% 5-FU. All polymers contain 5 mole% triethylene glycol monoglycolide. (▲) 35 CDM/30 HD/30 TEG, (■) 35 CDM/30 HD/30 TEG, (□) 35 CDM/45 HD/15 TEG. 0.05 M phosphate buffer, pH 7.4, 37°C. Reprinted with permission from [47].

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 periods has been discussed previously and is the result of the highly hydrophobic nature of the polymer which makes water penetration difficult. Current work indicates that the induction period can be significantly shortened when polymers having molecular weight in the 15 kDa range are used, instead of 60 kDa that was used in the study shown in Fig. 5.

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

3.2.3. Post-operative treatment of cancer

Bioerodible drug delivery systems containing antineoplastic agents have been placed at sites where tumor resection has been performed in the expectation that release of a drug will destroy whatever tumor cells were not removed during surgery. The success of Gliadel® [45] is now well documented.

Development of poly(ortho ester) devices containing 5-FU has been in progress for some time now and the release of 5-FU from such devices can be used to illustrate various parameters that control the release of 5-FU from this polymer. Fig. 6 shows release of 5-FU from polymer disks as a function of latent acid in the polymer [46]. As seen, 5-FU release is proportional to the amount of latent acid and release is linear with only a minimal burst. Furthermore,

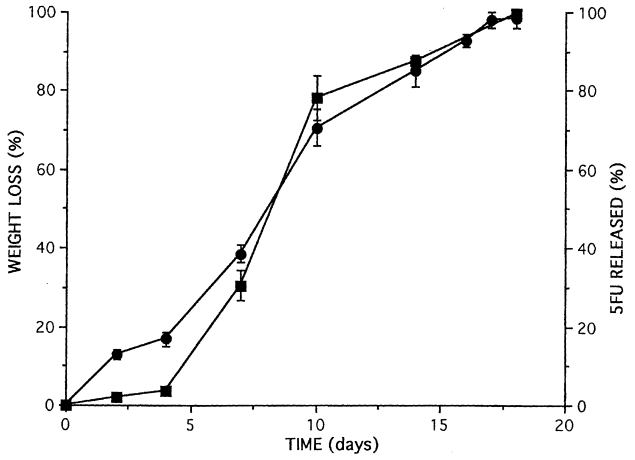


Fig. 8. Polymer weight loss (▲) and 5-FU release (■) from a polymer prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane and 1,3-propanediol/triethylene glycol diglycolide (90/10). Drug loading 20 wt%. 0.05 M phosphate buffer, pH 7.4, 37°C.

drug depletion coincides with complete polymer erosion, an important feature common to many poly(ortho ester) IV delivery system.

Fig. 7 shows the effect of hydrophilicity on rate of 5-FU release, using materials having the same concentration of latent acid [47]. Hydrophilicity can be controlled by using varying amounts of the hydrophilic diol, triethylene glycol. As the data show, for a constant amount of latent acid, an increase in the amount of triethylene glycol corresponds to an increase in polymer erosion time and hence an increase in the delivery rate of 5-FU.

Fig. 8 shows that release of 5-FU from poly(ortho ester) IV is a predominantly surface erosion controlled process

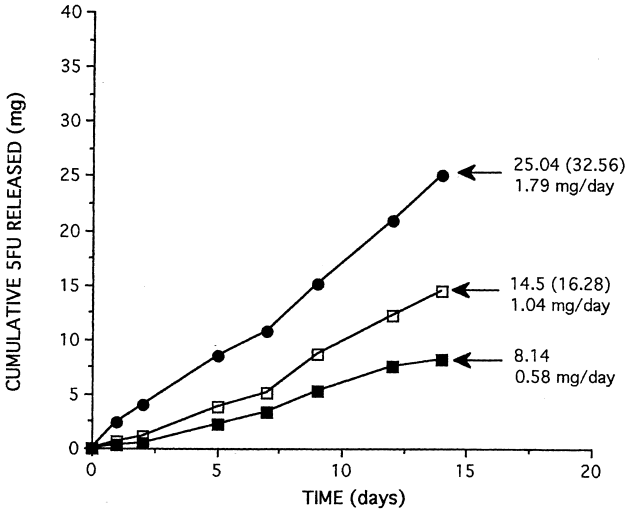


Fig. 9. Effect of loading on rate of 5-FU released from a poly(ortho ester) prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane, *trans*-cyclohexanedimethanol, 1,6-hexanediol, triethylene glycol and triethylene glycol monoglycolide (15/40/40/5), (■) 5.5 wt% 5-FU (14 mg), (□) 11.6 wt% 5-FU (28 mg), (●) 23.6 wt% 5-FU (56 mg). 0.05 M phosphate buffer, pH 7.4, 37°C. Reprinted with permission from [47].

because drug release and 5-FU occur concomitantly And because it is a surface eroding system, rate of 5-FU release should be proportional to drug loading. That this is indeed so, is shown in Fig. 9 [47].

4. Conclusion

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.

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