Expert Opinion





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# Biochronomer™ technology

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Biochronomer™ (AP Pharma) is a fourth-generation poly(ortho ester) prepared by the condensation of diols and a diketene acetal. The polymer contains a copolymerised latent acid whose concentration controls erosion rate. The polymer has been shown to undergo a surface erosion process and a number of applications have been explored. Among these, the delivery of plasmid DNA for vaccines is currently of most interest. This application takes advantage of the acid-labile nature of the polymer, which leads to rapid polymer hydrolysis and hence rapid release of plasmid DNA once internalised in the acidic environment within the endosomes, and the non-acidic environment within the polymer that conserves plasmid DNA conformation. A low molecular semisolid polymer is now in Phase II clinical trials for the delivery of mepivacaine to control postoperative pain, and in Phase I clinical trials for the systemic delivery of granisetron to control nausea.

**Keywords:** bioerodible polymer, clinical trials, granisetron, mepivacaine, nausea, poly(ortho ester), postoperative pain, semisolid, surface erosion

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## 1. Overview of the market

Research aimed at prolonging the action of therapeutic agents goes back to the late 1940s with the introduction of the first commercial product Spansules®. Since then, research in controlled drug delivery has proceeded at an ever-increasing rate, and today it is being vigorously pursued by nearly every pharmaceutical company.

Systems that allow controlled drug delivery can be broadly classified according to the mechanism that provides rate control: diffusion-controlled, water-penetration controlled and erosion-controlled [1]. Although all three systems are important and enjoy significant commercial success, this article is only concerned with erosional systems, because such systems offer a number of unique advantages. Among these is their bioerodibility, which obviates the need to remove drug-depleted devices and the ability to deliver a wide range of therapeutic agents ranging from small molecules to very high molecular weight macromolecules.

Two synthetic polymer systems have achieved commercialisation: polyesters and polyanhydrides. Another polymer system, poly(ortho esters), known generically as Biochronomer™ (AP Pharma), is in advanced stages of commercialisation, as is a bioerodible block copolymer of poly(ethylene glycol) and a copolymer of lactic and glycolic acids known as Regel™ (Macromed, Inc.) [2]. Another polymer system is a poly(phospho ester) [3], which is no longer under development. This review will briefly cover polyesters and polyanhydrides, but will largely concentrate on poly(ortho esters).

To better understand the erosion of the three polymers listed, it is first necessary to discuss erosion mechanisms briefly.

### 1.1 Erosion mechanisms

Bioerodible polymers can erode by two extreme mechanisms: bulk erosion and surface erosion [4]. In fact, polymers will erode by a combination of both mechanisms and the erosion mechanism is best discussed as predominantly bulk erosion or predominantly surface erosion.


**Figure 1. Poly(lactic acid) and poly(glycolic acid) structures.**

#### *1.1.1 Bulk erosion*

In a bulk-eroding polymer the hydrolysis reaction occurs throughout the bulk of the material and drugs physically incorporated into the matrix are initially predominantly released by diffusion. As the matrix continues to hydrolyse, drug release is then controlled by both diffusion and matrix erosion. The relative contribution of diffusion and erosion depends on the nature of the incorporated drug, the particular copolymer composition and its molecular weight. It is, thus, very difficult to rationally design a polymer having constant and predictable drug release kinetics.

#### *1.1.2 Surface erosion*

In a surface-eroding polymer, the hydrolysis is confined to the surface layers of a solid device. Then, as the surface layers solubilise by the hydrolysis reaction, the incorporated drug is released. If diffusional release is minimal and the geometry of the device remains relatively constant throughout most of its lifetime, rate of drug delivery will be solely determined by the rate of erosion. Thus, unlike in a bulk-eroding system, rate of drug delivery can be accurately controlled provided that rate of erosion can be accurately controlled.

Clearly, surface erosion is a much-preferred mechanism. However, in order to achieve surface erosion a number of design criteria have to be met. The two most important criteria are: i) the polymer has to be highly hydrophobic in order to minimise water penetration into the bulk polymer; and ii) the linkages that connect segments of the polymer backbone have to undergo a rapid hydrolysis. An excellent analysis of degradation and water penetration rates has been published [5].

#### *1.1.3 Non-hydrolytic surface erosion*

A most interesting and unique erosion mechanism for poly(ethylene carbonate) has been described [6]. The polymer is prepared by copolymerising ethylene oxide and carbon dioxide using a catalyst prepared from a 1:1 mixture of diethyl zinc and water [7].

The polymer is completely stable between pH 1 and 12, but undergoes rapid degradation in a KOH solution at pH 13.5 [8]. However, the polymer is degraded *in vivo* and it has been shown that the degradation is catalysed by $O^{-}_{2}$· produced by the membrane-associated NADPH-oxidase of cells during close surface contact with the polymer implant [8].

The mechanism of erosion has been shown to be an unzipping reaction that starts at the polymer end and proceeds along the entire chain [6]. It is thus pure surface erosion, and determination of molecular weight of un-eroded polymer shows no change whatsoever. This retention of molecular weight is not observed with surface-eroding polymers that erode by a hydrolysis reaction.

Unfortunately, this unique erosion mechanism is specific to this polymer only and attempts to change polymer structure destroy the unzipping mechanism. Clearly, if other polymers that undergo an unzipping erosion mechanism could be devised, they also should undergo pure surface erosion.

### 1.2 Polyesters

Polyesters were the first polymer system investigated as a matrix for drug delivery, and their use dates back to the work of Yolles in 1970 [9]. That work utilised poly(lactic acid), and to this day polymers based on lactic acid and copolymers of lactic and glycolic acids occupy a pre-eminent place among bioerodible polymers. These polymers were originally developed as sutures and are degraded to lactic and glycolic acid. Because they had FDA approval as sutures, they were naturally an attractive system as a bioerodible matrix for drug delivery. The polymers are prepared by a cationic polymerisation of the lactide or mixture of lactide and glycolide [10]. They are polyesters and erode by a nonenzymatic hydrolysis reaction. The structure of poly(lactic acid) and poly(glycolic acid) is shown in **Figure 1**. Because lactic acid has a chiral atom, poly(lactic acid) can exist in four stereoisomeric forms, poly(L-lactic acid), poly(D-lactic acid), meso poly(D,L-lactic acid), and the racemic mixture of poly(L-lactic acid) and poly(D-lactic acid). The natural metabolite is L-lactic acid.

These polymers were developed as suture materials and not as drug delivery matrices, and because they erode predominantly by a bulk erosion process, they do have significant shortcomings; nevertheless, a number of systems have reached commercialisation.

Devices that have realised the highest commercial success release a luteinizing hormone releasing hormone (LHRH) analogue for the treatment of prostate cancer. This therapy is based on early work [11] that recognised the androgen dependency of prostatic adenocarcinomas, and one treatment modality is to suppress androgen levels by the systemic delivery of LHRH analogues. LHRH analogues are chemical modifications of the natural hormone, which are many hundreds of times more potent and downregulate its receptors with suppression of the production of testosterone, progesterone and oestrogen. Thus, repeated administration at 1- or 3-month intervals is now a common palliative treatment for prostate cancer of patients that are a poor surgical risk.

Another application involves the use of a cryogenic method [12] to encapsulate recombinant human growth hormone (rhGH) using an 8 kDa, 1:1 copolymer of lactic and glycolic acid. A single injection of microspheres using a 23-gauge needle, suspended in 3 wt/vol low-viscosity

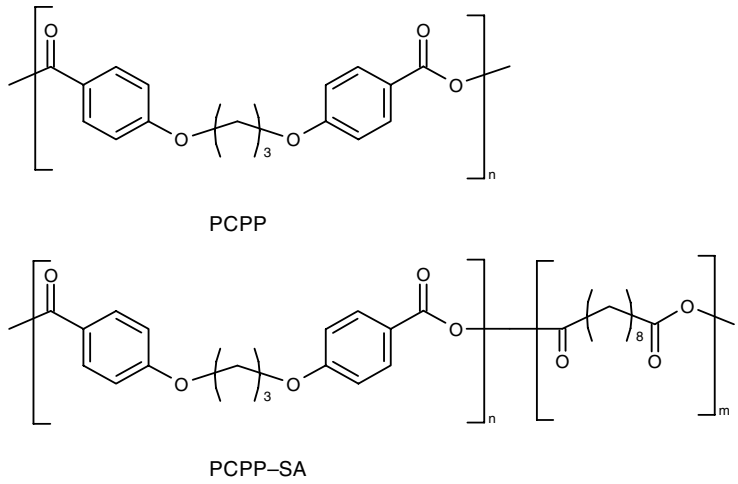


**Figure 2. The structure of a polymer based on *bis*(*p*-carboxyphenoxy) propane and sebacic acid.**
PCPP: Poly[*bis*(*p*-carboxyphenoxy) propane].

carboxymethylcellulose, 1% polysorbate 20 and 0.9% NaCl in monkeys (*Macaca mulatta*), resulted in elevated blood plasma levels for > 1 month. The protein is stabilised during the encapsulation process and during *in vivo* release by complexing with zinc [13]. This product is commercially available as Nutropin® (Genentech, Inc.).

Another important polyester is poly(ε-caprolactone), which is prepared by the ring-opening polymerisation of caprolactone. Although this polymer was initially developed as an environmentally degradable plastic, it has found application as a biodegradable material in drug delivery. However, its degradation is very slow and is measured in years [14-16].

### 1.3 Polyanhydrides

These materials were first prepared in 1909 [17] and were subsequently investigated as potential textile fibres, but were found unsuitable due to their hydrolytic instability. Although, polyanhydrides based on poly [*bis*(p-carboxyphenoxy)alkane-anhydrides] have significantly improved hydrolytic stability, they retain sufficient hydrolytic instability to prevent commercialisation despite their good fibre-forming properties. However, it is this hydrolytic instability that makes these materials excellent candidates for the construction of bioerodible drug delivery systems. At this time, two families of polyanhydrides have been described.

#### *1.3.1 Family I*

The first family of polyanhydrides is based on *bis*(*p*-carboxyphenoxy) propane and sebacic acid, and its use as a bioerodible matrix for the controlled release of therapeutic agents was first reported in 1983 [18]. Because aliphatic polyanhydrides hydrolyse very rapidly, whereas aromatic polyanhydrides hydrolyse very slowly, good control over hydrolysis rate can be achieved by using copolymers of aliphatic and aromatic polyanhydrides. In this way, erosion rates from days to many months have been demonstrated [19,20]. The structure of a polymer based on *bis*(*p*-carboxyphenoxy) propane and sebacic acid is shown in **Figure 2**.

This family of polymers has been extensively investigated for the treatment of brain cancer, and particularly glioblastoma multiforme, in pivotal studies [21]. A striking feature of malignant brain tumours is that they do not metastasise, but rather recur within 2 cm of the original tumour. Thus, if a drug delivery device containing a suitable antineoplastic agent such as 1,3-*bis*[2-chloroethyl]-1-nitrosourea (BCNU) is placed at the site of tumour resection, survival times should be improved because localised drug delivery would destroy malignant cells not removed by the tumour resection procedure.

A device known as Gliadel® (Guilford Pharmaceuticals) has been approved by the FDA as a therapy for patients that have failed surgical treatment of glioblastoma multiforme. Gliadel is a wafer ~ 1.45 cm in diameter and 1 mm thick. Each wafer contains 192.3 mg of a 80:20 poly[*bis*(*p*-carboxyphenoxy)propane [PCPP] and sebacic acid, and 7.7 mg BCNU. A maximum of eight wafers per procedure are used. The wafers are brittle and unstable, and must be stored at - 20°C.

#### *1.3.2 Family II*

The second family of polyanhydrides is based on nonlinear dimers and trimers of erucic acid and sebacic acid [22]. These polyanhydrides have significantly improved mechanical properties relative to Family I, and by varying the ratio of erucic acid dimer to sebacic acid, materials having a wide range of mechanical properties could be prepared. However, hydrolysis of the polymer produces sebacic acid and the dimer of erucic acid, which being a 36-carbon material is highly water insoluble. The structure of the polymer based on erucic acid dimer is shown in **Figure 3**.

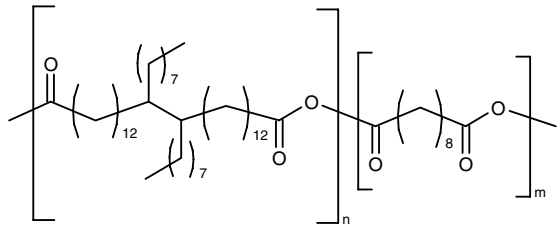

**Figure 3. The structure of a polyanhydride based on a nonlinear dimer of erucic acid.**

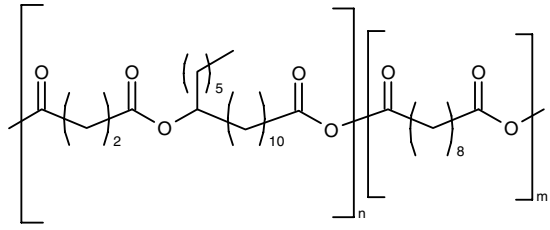

**Figure 4. The structure of a polyanhydride based on ricinoleic acid.**

A Phase II clinical trial of the erucic dimer/sebacic acid polyanhydride containing gentamycin for the treatment of osteomyelitis has been described [23]. The clinical trial has now been discontinued.

A copolymer based on ricinoleic acid and sebacic acid has also been described [24]. The polymer has been shown to be biocompatible, but no tissue clearance data have been published. The structure of the polymer based on ricinoleic acid is shown in **Figure** 4.

### 1.4 Poly(ortho esters)

Unlike polyesters and polyanhydrides, which were first developed for applications other than drug delivery, poly(ortho esters), a new polymer system, were specifically developed for drug delivery applications and were constructed to maximise surface erosion. The rationale for selecting an ortho ester linkage has been published, along with the design criteria [25]. Since 1970, four families of such polymers have been described and comprehensive reviews have been published [26,27]. The structure of the four families is shown in **Figure** 5.

## 2. Biochronomer™ technology

Although four families of poly(ortho ester) have been developed, and each has certain useful attributes, only Biochronomer (POE IV) has all the required attributes that allow successful commercialisation. These are: i) ease of synthesis and reproducibility; ii) stability; iii) ability to vary mechanical and thermal properties; and iv) ability to control erosion rates. These will now be discussed separately.

### 2.1 Ease of synthesis

POE IV is synthesised, as shown in **Figure 6**, by the reaction of diols with a diketene acetal, in this case 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane (DETOSU). The rationale for selecting DETOSU has been described [25].

Biochronomer is prepared by the addition of diols to a diketene acetal. The reaction is exothermic, proceeds virtually instantaneously and has been scaled up to kilogram quantities. It can be carried out neat or in solvents such as tetrahydrofuran. In either case, a trace of an acidic catalyst (e.g., salicylic acid or *p*-toluene sulfonic acid) is used.

### 2.2 Stability

Poly(ortho esters) are completely stable at room temperature, provided that moisture is rigorously excluded. Therefore, unlike polyanhydrides that have to be stored at -20°C even in the rigorous absence of moisture, no special storage conditions other than exclusion of moisture are required.

### 2.3 Ability to vary mechanical and thermal properties

By varying the nature of the R-group in the diol(s), polymers that range from gel-like materials to soft flexible materials to hard materials can be prepared. Of particular importance are the gel-like materials because drugs can be incorporated by a simple mixing procedure at room temperature and without use of solvents. Such materials can be

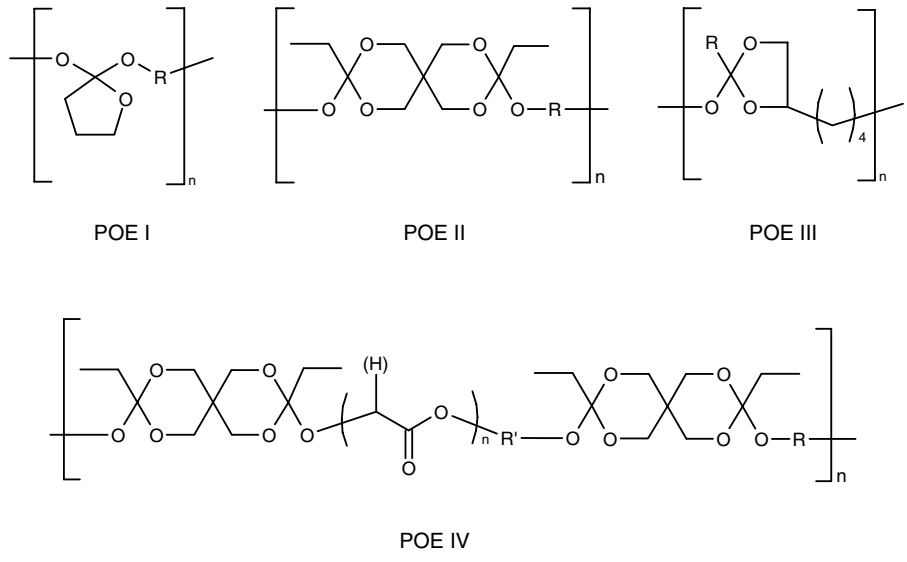


**Figure 5. Poly(ortho ester) family structures.**

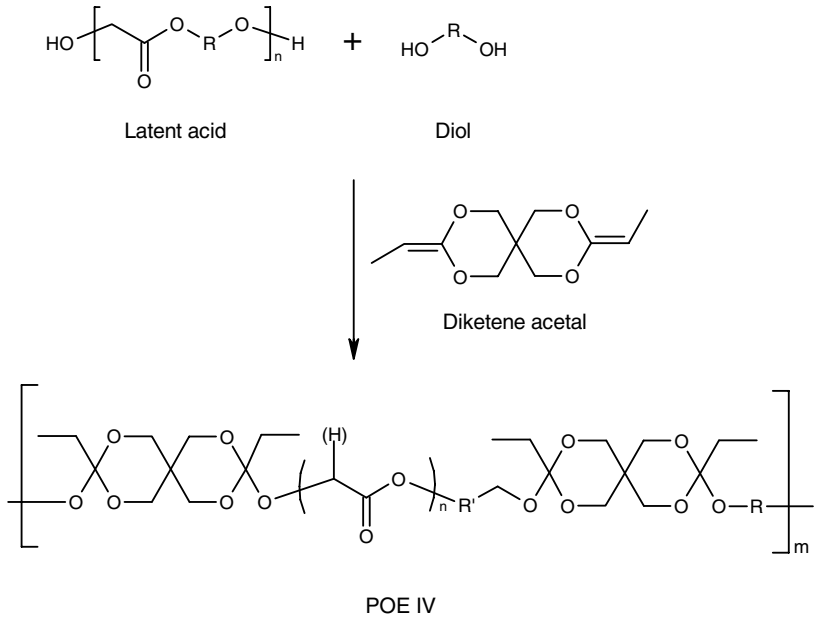


**Figure 6. Synthesis of Biochronomer™.**

formulated to allow direct injection, and will be further discussed later.

### 2.4 Ability to control erosion rate

Because poly(ortho esters) are acid labile, the ability to control the pH at the polymer–water interface translates into an ability to control erosion rates. As shown in **Figure 6**, one of the diols used incorporates a short segment of glycolic acid, or in some cases lactic acid. This diol is denoted as 'latent acid'. The use of a latent acid is a key feature that allows accurate control of erosion rates. It also distinguishes this polymer from POE II, which lacks that segment.

## 3. Physical forms

By selecting appropriate diols, materials that are solid or that have a gel-like consistency can be prepared. Such materials are best discussed separately.

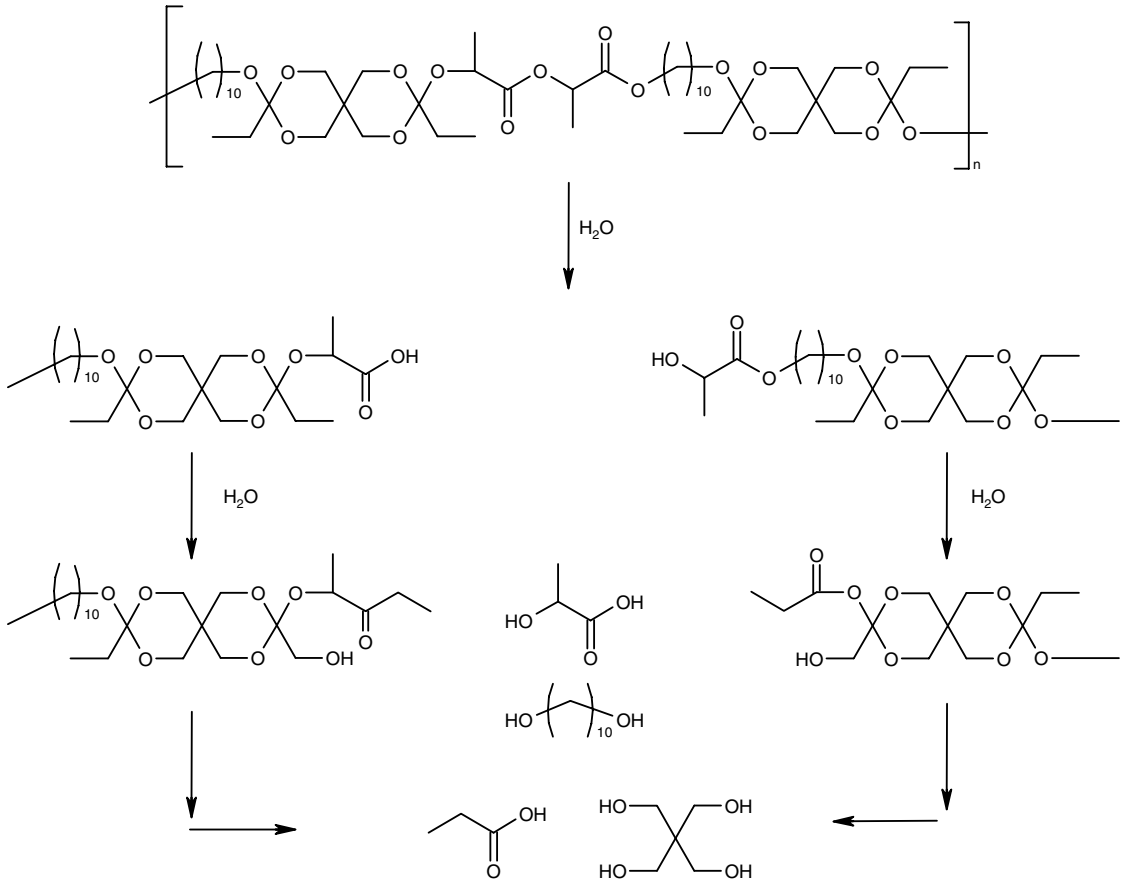


**Figure 7. Polymer hydrolysis.**

## 3.1 Solid materials

### *3.1.1 Fabrication*

Biochronomer is an excellent thermoplastic material that can be easily compression molded, extruded or injection molded. It has reasonable thermal stability, provided that fabrication temperatures do not exceed about 100°C for extended periods of time. It is also soluble in a range of organic solvents so that film casting, coating of devices such as cardiovascular stents, or preparation of microspheres can be readily achieved.

### *3.1.2 Erosion control*

Even though ortho ester linkages are fairly labile when exposed to water, the polymer is highly hydrophobic so that the amount of water that can penetrate the polymer is severely restricted. In fact, the amount of absorbed water is only in the order of about 1 wt% [28]. Polymer hydrolysis is shown in **Figure** 7. When the polymer is exposed to an aqueous environment cleavage of the ester bond creates two polymer fragments, one of which contains an acid functionality that will induce a pH decrease. Another cleavage liberates lactic acid that acts to catalyze cleavage of ortho ester bonds in the polymer backbone.

In **Figure** 7, the latent acid was shown as a dimer of poly(lactic acid) because at that time it was believed that this was the correct structure. It is now known that the reaction between a diol and lactide or glycolide produces a mixture of species ranging from dimer to heptamer [27]. However, the erosion mechanism as shown in **Figure** 7 and conclusions derived from this study remain unchanged. Furthermore, Biochronomer utilises a latent acid that is based on glycolic acid.

Clearly, the amount of glycolic acid liberated during polymer hydrolysis will establish the rate at which the polymer erodes, and that amount is easily controlled by varying the ratio of diol to diol containing the glycolic acid segment in the reaction mixture, as shown in **Figure 6**.

The functionality of this approach is evident by examining **Figure 8**, which shows erosion rates as a function of latent acid concentration.

### *3.1.3 Erosion mechanism*

Biochronomer was specifically designed to undergo an erosion process confined predominantly to the surface layers of a solid device. To establish that the erosion proceeds as anticipated, a number of devices containing a lactic acid latent acid were

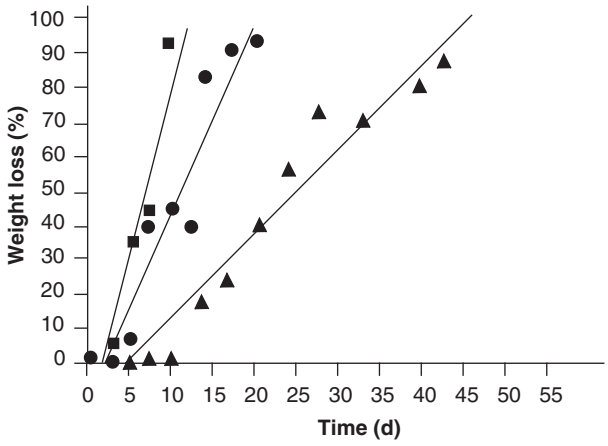


**Figure 8. Effect of latent acid content on erosion rates for a polymer prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, cyclohexanedimethanol, decanediol, triethylene glycol and triethylene glycol glycolide.** (squares) 40/45/10/5; (circles) 40/49/10/1; (triangles) 40/49.9/10/0.1. Reprinted with permission from HELLER J, BARR J: Poly(ortho esters) - from concept to reality. *Biomacromolecules* (2004)**5**:1625-1632. Copyright (2004) American Chemical Society [25].

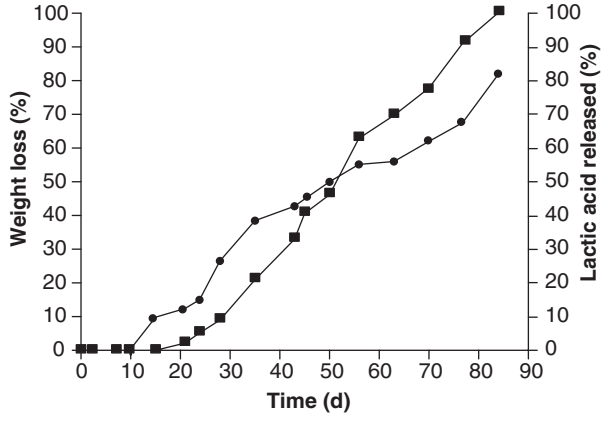


**Figure 9. The relationship between lactic acid release (circles) and weight loss (squares) for a poly(ortho ester) prepared from 3,9 diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, and a 100/70/30 mixture of 1,10-decanediol and 1,10-decanediol lactide. 0.13M, pH 7.4 sodium phosphate buffer at 37°C.** Reprinted with permission from SCHWACH-ABDELLAOUI K, HELLER J, GURNY R: Hydrolysis and erosion studies of autocatalyzed poly(ortho ester) containing lactoyl-lactyl acid dimers. *Macromolecules* (1999) **32**:301-307. Copyright (1999) American Chemical Society [29].

placed in a pH 7.4 phosphate buffer maintained at 37°C. At predetermined intervals both the amount of liberated lactic acid and the weight loss of the device was determined [29]. A

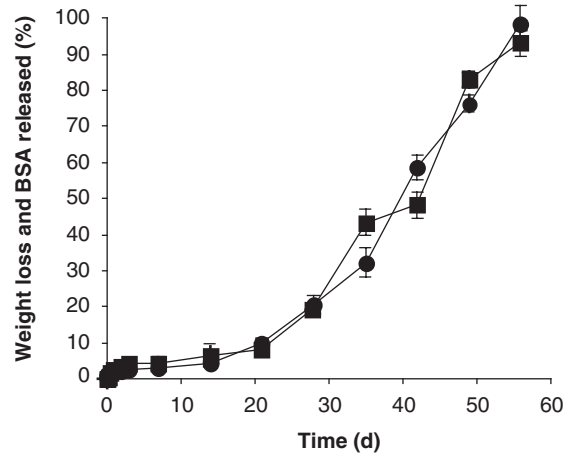


**Figure 10. Release of FITC-BSA (circles) and weight loss (squares) from a poly(ortho ester) prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, 1,4-pentanediol and 1,6-hexanediol glycolide (100/95/5). Strands, 1x10 mm, extruded at 70°C. 0.01 M phosphate buffered saline, pH 7.4, 37°C. FITC-BSA loading 15 wt%.** Reprinted from *J. Controlled Rel.* Vol. **71**, ROTHEN-WEINHOLD A, SCHWACH-ABDELLAOUI K, BARR J, NG SY, SHEN H-R, GURNY R, HELLER J: Release of BSA from poly(ortho ester) extruded thin strands, 31-37, Copyright (2001), with permission from Elsevier [30].

plot of weight loss and cumulative amount of lactic acid released is shown in **Figure 9**.

The concomitant weight loss and release of lactic acid argues convincingly for an erosion process confined predominantly to the surface layers of the polymer matrix. However, the process is not pure surface erosion because there is a significant drop in molecular weight of the remaining polymer, indicating that some bulk erosion has taken place. As no polymer is so hydrophobic that no water can penetrate the bulk, there will always be some bulk erosion. However, because water concentration in the bulk is very low, rate of hydrolysis is also low. Because water concentration in the outer eroding layers is high, rate of hydrolysis is also high. This difference in water concentration between bulk and outer layers will result in an erosion process confined predominantly to the surface layers.

### *3.1.4 Drug release*

If drug release is controlled predominantly by polymer erosion, then its release should closely parallel polymer erosion. As shown in **Figure 10**, this is the case for the release of bovine serum albumin (BSA); the excellent correlation between BSA release and polymer erosion verifies that BSA is indeed released by an erosion-controlled mechanism [30]. In this particular instance there is a significant delay before drug release and polymer erosion takes place. The delay is a manifestation of polymer hydrophobicity that retards water-penetration into the polymer and consequent hydrolysis of the labile linkages

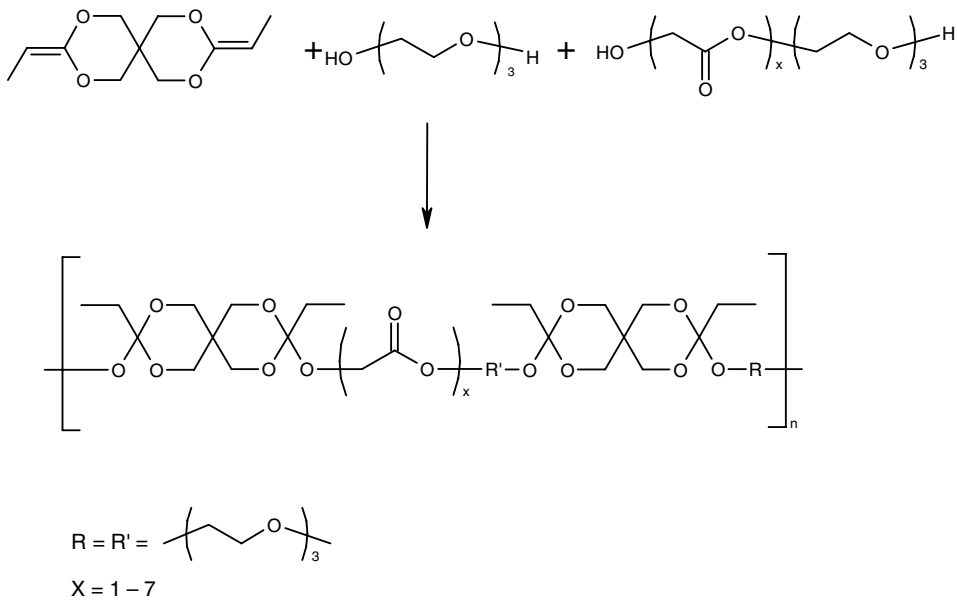


**Figure 11. Structure of Biochronomer™ used in clinical trials.**

in the polymer backbone. The lag can be shortened by increasing polymer hydrophilicity [30].

### 3.2 Gel-like materials

The use of highly flexible diols allows the construction of materials that have a gel-like consistency at room temperature, and suitably formulated materials allow administration using a hypodermic syringe. However, such materials, even when formulated, are viscous so that a 16-gauge needle, or a specially designed needle, is required. It is important to point out that unlike thermogelling materials [31] or polymer precipitation [32], there is no physical change in the material during administration.

#### *3.2.1 Fabrication*

The gel-like consistency of these materials allows the incorporation of therapeutic agents by simple mixing at room temperature and without the use of solvents. Clearly, this is a significant advantage when highly sensitive therapeutic agents are used. A preferred final product is a prefilled, sterile syringe that allows direct administration without the need of further manipulations.

#### *3.2.2 Injectability*

Such materials are injectable, but only if the viscosity is reduced by limiting the molecular weight to about 6 kDa and additionally, an excipient is used to further reduce viscosity. The excipient most frequently used is methoxy poly(ethylene glycol), having a molecular weight of 550 (MPEG 550). The molecular weight can be easily controlled either by using an excess of the diols relative to the diketene acetal or by using a monofunctional alcohol that acts as a chain-stopper [33].

#### *3.2.3 Erosion control*

Erosion rate of such low molecular weight materials is highly dependent on both amount of latent acid and polymer hydrophilicity. It has been found that a material constructed from DETOSU and the hydrophobic diol 1,10-decanediol has an *in vivo* lifetime of about 1 month, whereas a similar material constructed from the hydrophilic diol triethylene glycol has an *in vivo* lifetime of only a few days. Both materials contained the same amount of latent acid.

#### *3.2.4 Drug release*

Clearly, with such low molecular weight materials, the drug is poorly immobilised in the matrix so that release occurs predominantly by diffusion. The relative contribution of diffusion and erosion to release kinetics depends on the nature of the drug and matrix hydrophilicity. At this time good quantitative data are lacking.

## 4. Gel-like materials: preclinical, Phase I and Phase II studies

Currently, two such formulations are in clinical trials. One is intended to treat postoperative pain, and the other is intended to treat chemotherapy-induced nausea.

### 4.1 Treatment of postoperative pain

Following surgery, currently used local anaesthetics are only effective for a few hours following a simple injection. Clearly, an important advance would be the development of a system that would result in the sustained delivery of a local anaesthetic for a few days, thus reducing the need for opiate use with their well-known side effects. Furthermore, if the deliv-

ery system is placed within the surgical incision, it should be possible to maintain a high local concentration without a concomitant high systemic concentration. This is important in view of the toxicity that mepivacaine, the local anaesthetic used, shares with other amide local anaesthetics [34].

#### 4.1.1 Formulation used

The structure of the gel-like material used is shown in **Figure 11**. In order to improve injectability and ease of handling, the molecular weight of the polymer was limited to about 6 kDa, and methoxy poly(ethylene glycol), having a molecular weight of 550 Da, was used as an excipient.

The actual composition of the clinical formulation designated as APF 112 is 77.6 wt% polymer, 19.4 wt% methoxy poly(ethylene glycol) and 3 wt% mepivacaine.

#### 4.1.2 Preclinical toxicology

Two types of studies were carried out: in one study the polymer was hydrolysed and the hydrolysate tested, and the other study utilised the actual formulation.

##### 4.1.2.1 Polymer hydrolysate

Hydrolysing the polymer into its hydrolysis products simulates the instantaneous erosion of an implant and thus repesents a worse case scenario.

The hydrolysate was prepared by hydrolysing the polymer in phosphate buffered saline at 80°C for 24 h, adjusting the pH to 7.4 with NaOH, adding the methoxy poly(ethylene glycol), mixing thoroughly, adding de-ionised water to adjust osmolarity and finally filtering through a 0.45 µm filter. The solution was then injected subcutaneously into male and female Sprague–Dawley rats and into male and female beagle dogs. In the rat study, the doses used were 0, 1, 3 and 10 ml/kg, and in beagle dogs, the dose was 0, 0.05, 0.1 and 0.2 ml/kg. Both animal species were observed for 14 days and no adverse effects by clinical observation and gross necropsies were found. In addition, no histological evidence of systemic toxicity was observed in all organs evaluated.

##### 4.1.2.2 APF-112 formulation

The following incisional wound instillation study was carried out in rats. A 1 cm full thickness incision was made, a subcutaneous pocket thus created by blunt dissection, the APF-112 formulation administered into the subcutaneous pocket, and the skin closed with 4-0 nylon sutures, which were removed after 7 days.

The study was carried out using Sprague–Dawley male and female rats using 500 and 1000 µl in a single dose, and the rats sacrificed at day 8. Both doses were well tolerated, but the 1000 µl dose resulted in some leakage and wound distension.

#### 4.1.3 Phase II clinical trials

A clinical trial with APF-112 is currently ongoing. The objectives of this trial are to evaluate the safety and tolerability of APF-112 when administered into the surgical incision at the end of a herniorrhaphy. The study is divided into two parts. The first part was an open-label, safety evaluation of 12 subjects followed for 30 days after dosing with 10 g of APF-112 containing 300 mg mepivacaine. The second part, currently ongoing, is an observer-blind, active-controlled, three-arm study in 90 subjects. The study compares the safety and efficacy of 5 or 10 g APF-112 containing 150 and 300 mg of mepivacaine, respectively, and bupivacaine/HCl at a dose of 75 mg. So far, 60 subjects have been enrolled and 40 subjects have completed the 30-day evaluation.

##### 4.1.3.1 Safety

The safety profile in these subjects has been favourable, with no serious or severe adverse events; all reported events have been typical of uncomplicated postoperative recovery. Wound healing has been satisfactory in all subjects so far.

##### 4.1.3.2 Pharmacokinetics and metabolism

The results of pharmacokinetic analysis of the first cohort of 12 subjects indicate that the $C_{max}$ of mepivacaine is ~ 6 h with measurable levels detectable at 24, 48 and 72 h. No drug levels were detected at 7 days (168 h) postdose.

### 4.2 Treatment of chemotherapy induced nausea

Nausea and vomiting are serious adverse effects of chemotherapy and because of the severity of these episodes, some patients have refused subsequent chemotherapy cycles. In addition, serious complications such as dehydration, electrolyte imbalance and metabolic alkalosis have been reported [35,36].

Granisetron (Kytril®; Roche) is an approved and widely used antiemetic, but its half-life following intravenous administration is only about 8 h so that more than one administration is required following the chemotherapy cycle. The recommended dose is 10 µg/kg by intravenous injection. Clearly, a formulation that would maintain a therapeutically effective granisetron blood concentration for a few days would represent a significant advance.

#### 4.2.1 Formulation used

The polymer used in this application is identical to that used for mepivacaine. The actual composition designated as APF-530 is 78.4 wt% polymer, 19.6 wt% methoxy poly(ethylene glycol) 550, and 2 wt% granisetron. The formulation is administered as a subcutaneous injection using a 16-gauge needle or a specially designed needle.

#### 4.2.2 Preclinical toxicology

Because the polymer is identical to that used to control postoperative pain, no polymer hydrolysate studies were required.

##### 4.2.2.1 APF-530 formulation

In a study of rats, male and female Sprague–Dawley rats (n = 20/sex/group) were administered APF-530 as a single total

subcutaneous dose of 0.25 or 1.0 ml/animal. The 1 ml dose was administered at four sites at 0.25 ml/site. It has been found that for rats, a 0.25 ml dose/site is the maximum feasible dose for the polymer formulation based on leakage from the injection site. The total mass of granisetron administered in the APF-530 formulation was ~ 5 and 20 mg/animal. The 5 mg dose was ~ 14 – 19 and 21 – 28 mg/kg of granisetron in males and females, respectively, and the 20 mg dose was approximately 57 – 77 and 85 – 113 mg/kg of granisetron in male and females, respectively.

Additional animals (n = 20/sex/group) were administered 1 ml/animal of saline control divided equally into four sites, or aqueous granisetron at an intravenous dose of 9 ml/kg, or a subcutaneous dose of 1 m/animal (0.25 ml/site). Saline control and test formulations were administered through a 16-gauge needle. Five rats/sex/group were sacrificed on days 4, 8, 15 and 29.

Administration of APF-530 was well tolerated both locally and systemically. Histopathological evaluation of the APF-530 injection sites revealed several reversible changes consistent with injection of a biodegradable polymer. By day 29, the response to the polymer had resolved without any residual or untoward effects.

A study in beagle dogs was also conducted to further characterise the systemic and local toxicity profile of APF-530. Male and female beagle dogs (n = 6/sex/group) were administered APF-530 at a single total subcutaneous dose volume of 1 or 4 ml/animal. For beagle dogs, it has been found that 1 ml/site is the maximum feasible dose for the polymer formulation based on leakage from the injection site. For the 1 ml dose, two sites received 0.25 ml and one site received 0.5 ml. For the 4 ml dose volume, 1 ml was administered at four separate sites. The total mass dose of granisetron administered in the APF-530 formulation was ~ 20 and 80 mg/animal, or ~ 1.5 – 2.5 and 6 – 10 mg/kg of granisetron, respectively. Additional animals (n = 6/sex/group) were administered aqueous granisetron at an intravenous dose of 3 ml/kg or a subcutaneous dose of 4 mg/animal (1 ml/site), or 2.75 ml/animal of saline control divided into four sites (0.25 and 0.5 ml in one site; 1 ml in two sites). The total mass dose of aqueous granisetron administered subcutaneously translated to ~ 0.3 – 0.5 mg/kg. Saline control and test formulations were administered through a 16-gauge needle.

Administration of APF-530 was well tolerated both locally and systemically. Histopathological evaluation of the APF-530 injection sites revealed several reversible changes consistent with injection of a biodegradable polymer. All effects appeared to be resolving by day 15.

#### *4.2.3 Phase I clinical trials*

The first part of the initial clinical study was conducted in a single centre as a double-blind, sham-controlled, ascending single subcutaneous dose. Six subjects received a single 125 mg APF-530 (2.5 mg granisetron) injection in one side of the abdomen, as well as a 0.125 ml subcutaneous injection of sterile saline (placebo) in the opposite side of the abdomen.

##### *4.2.3.1 Safety*

Single subcutaneous doses of APF-530 were safe and well tolerated at a dose level of 125 mg APF-530 in healthy male volunteers. There were no clinically significant laboratory abnormalities. The findings at this dose level support progression to the next dose level of formulation. The second part of the Phase I study is currently ongoing.

##### *4.2.3.2 Pharmacokinetics and metabolism*

Following a single subcutaneous injection of APF-530 containing 2.5 mg of granisetron, there was a slow sustained release of granisetron, with maximum plasma concentration occurring at a median $T_{max}$ of 8 h (range 8 – 72 h). In some subjects, secondary peaks in the plasma profile occurred between 24 and 96 h postdose, indicating prolonged absorption from the subcutaneous depot. The study is currently in progress, but where calculable, the terminal elimination half-lifes were 26.2 and 33.9 h.

## 5. Solid materials: potential applications

Although virtually any therapeutic agent other than acidic compounds can be successfully delivered from Biochronomer, of particular interest are proteins, DNA and oligonucleotides. The suitability of Biochronomer to serve as a delivery platform for such compounds arises from two factors: i) the ability to release such agents by an erosion-controlled process, which essentially eliminates an initial burst and allows good control over rate of delivery; and ii) the activity of even sensitive compounds is preserved because the interior of the matrix, unlike that of poly(lactide-*co*-glycolide) (PLGA) copolymers, is not acidic. Perhaps of most interest is developing means of delivering DNA.

### 5.1 DNA vaccines

Vaccination with plasmid DNA offers many advantages over conventional vaccines using attenuated or inactivated pathogens, proteins or protein subunits. However, naked DNA is readily degraded by enzymes and its efficacy as an immunogen is limited, so there is considerable interest in developing delivery technologies that will protect DNA from degradation and enhance its immune responses for clinical use [37,38].

The use of Biochronomer microspheres having an average diameter of about 5 µm, have been investigated as a means of delivering plasmid DNA via uptake by antigen-presenting cells, such as dendritic cells, but not by other cells [39].

In developing a delivery system for plasmid DNA, a Biochronomer that contains tertiary amines in the polymer backbone has been used. The synthesis of this polymer is shown in **Figure 12**. This polymer will be referred to as POE-2, and a polymer without the tertiary amines will be referred to as POE-1. The rationale for using POE-2 is to allow a complex-

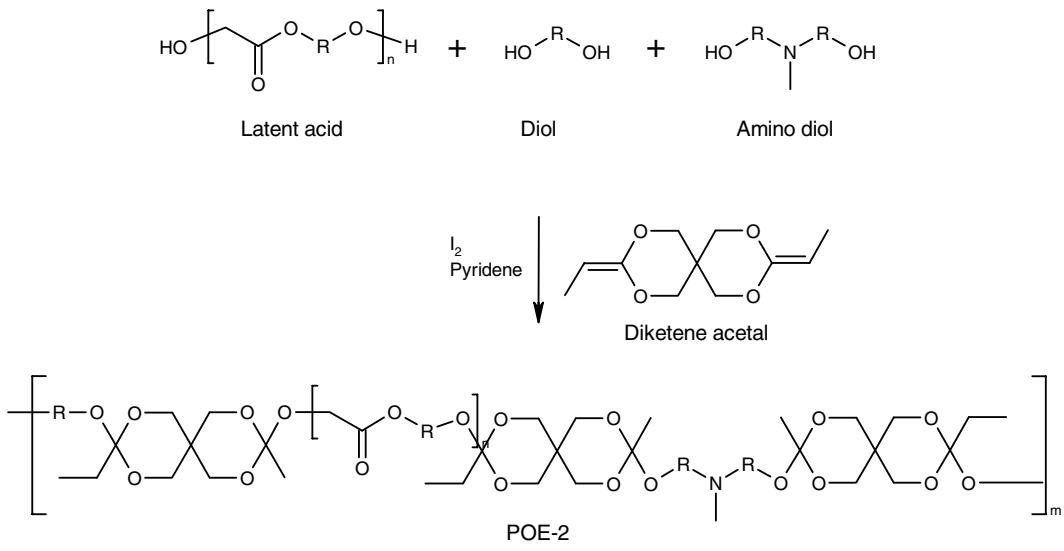


**Figure 12. Synthesis of POE-2.**

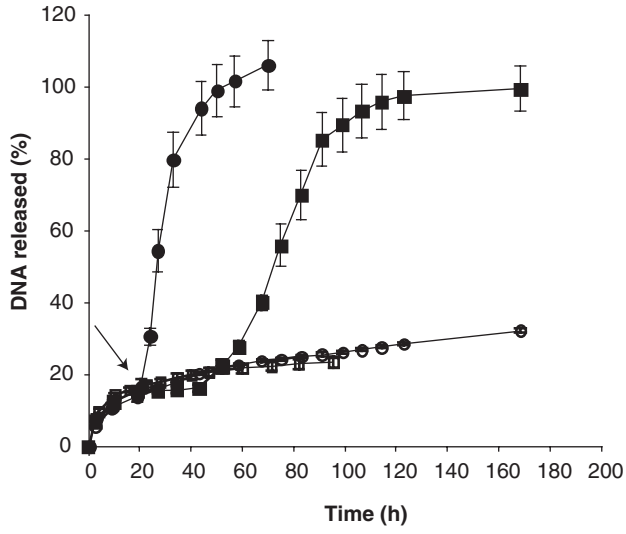


**Figure 13. Release kinetics of DNA from poly(ortho ester) microspheres. (open circles) POE-1, pH 7.4, (closed circles) POE-1, pH 5.0, (open squares) POE-2, pH 7.4, (closed squares) POE 2, pH 5.0.** pH changed from 7.4 to 5.0 at the time indicated by the arrow. Error bars for pH 7.4 are within the symbols. Reprinted from [39].

ation of the negative charges on the plasmid DNA with the positive charges on the polymer arising from protonation of the tertiary amine groups at the phagosomal pH.

Plasmid DNA was encapsulated in the polymers by a double-emulsion technique resulting in microspheres ~ 5 µm in diameter with a very narrow size distribution. **Figure 13** shows the release of plasmid DNA at pH 7.4, the cytoplasmic pH and change in release rate when the pH was abruptly lowered to pH 5.5, the pH within phagosomes to simulate microsphere uptake for both amino, and non-amino polymers. Clearly, there is a significant difference between the two polymers in that the amino-containing polymer shows a 24-h delay before DNA is released. This delay is very likely due to a complex formation between the negatively charged DNA and the positively charged polymer, which prevents DNA release until the polymer has undergone significant hydrolysis. This delay has been found to be important when 5 µm microspheres are taken up by antigen-presenting cells, and it has been shown that in a cancer model, the amino-polymer is significantly superior to the non-amino polymer [39]. Work to further refine this delivery system, largely by improving the ability of the microspheres to escape phagosomes, is currently underway.

## 6. Alternative technologies

Some of the most important alternative technologies currently under development and their advantages as well as their disadvantages can be summarised as follows:

### 6.1 Poly(lactide-*co*-glycolide) copolymers

As already described, these materials were originally developed as sutures and because they hydrolyse to natural metabolites and have FDA approval as sutures they were clearly excellent candidates as drug delivery platforms. However, such materials erode by a bulk erosion process with drug release controlled both by diffusion and polymer erosion. In general, release kinetics, especially for peptides and proteins, are characterised by an initial burst, followed by a lag-time and finally complete release. Because only lactic and glycolic acid are used, control over erosion rate is achieved by varying lactic acid

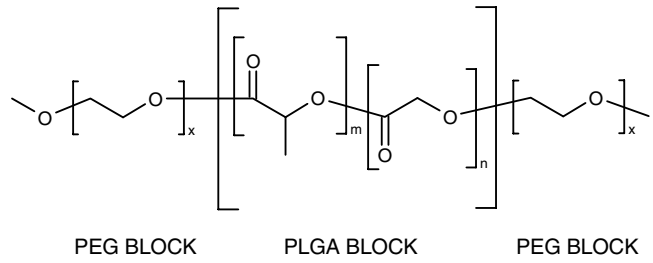


**Figure 14. The structure of PEG and PLGA copolymers.**
PEG: Poly(ethylene glycol); PLGA: Poly(lactide-co-glycolide).

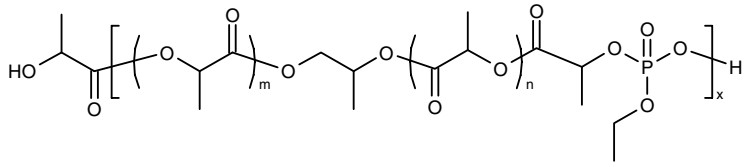


**Figure 15. The structure of poly(phospho esters).**

stereochemistry, ratio of the two monomers and polymer molecular weight.

To overcome some of these disadvantages, various modifications such as block copolymers [40] or grafting onto hydrophilic backbones [41] were investigated. These appear to be promising approaches, but are still very much in the research stage.

### 6.2 Polyanhydrides

A polyanhydride is the first non-PLGA polymer that has reached commercialisation as Gliadel: a wafer containing BCNU to treat glioblastoma multiforme. It is also the first polymer commercialised that undergoes surface erosion.

However, polyanhydrides are unstable due to an internal anhydride interchange reaction [42], so that even in the rigorous absence of moisture they must be stored at -20°C. In addition, the synthesis of polyanhydrides is relatively difficult, and the reactivity of anhydride linkages toward amine and hydroxyl groups can be a problem unless fabrication conditions are carefully controlled. Thus, polyanhydrides are not commercially attractive and currently no additional products are under development.

### 6.3 Block copolymers of poly(ethylene glycol) and poly(lactide-*co*-glycolide) copolymers

These block copolymers have the structure shown in **Figure 14**. If the molecular weight of the blocks and their composition is chosen correctly, the block copolymer is water soluble at room temperature and forms a firm gel at the body temperature of 37°C. It can thus be injected using a small gauge needle. The polymer has been investigated as a delivery system for the local delivery of paclitaxel in the treatment of breast cancer. A Phase I clinical trial has been carried out in Germany [43] with excellent results. This delivery system has been trademarked as OncoGel™ (Macromed, Inc.).

### 6.4 Poly(phospho esters)

Poly(phospho esters) have the structure shown in **Figure 15**. This particular polymer is a combination of poly(lactic acid) and ethyl phosphate, and has been designated as polylactophate [44]. The polymer undergoes a two-stage bulk erosion process, with a relatively rapid mass loss due to hydrolysis of phosphate bonds, followed by a much slower hydrolysis of the lactide ester bonds. Despite benign hydrolysis products, polylactophate has no obvious advantages over poly(lactic-*co*-glycolic acid) copolymers, and commercial development of this system has been discontinued.

## 7. Conclusion

Research into bioerodible polymers has made significant progress since the initial work by Yolles, Eldridge and Woodland in 1970 [9], and there is little doubt that the systemic delivery of drugs from bioerodible implants represents an important method of drug delivery. However, a bioerodible drug delivery system must satisfy a number of stringent requirements before it can be successfully commercialised. Aside from the obvious requirement that it must degrade to well-defined and toxicologically innocuous products, it must also be able to release incorporated drugs by a well-controlled process. In order to do that, drug release should be controlled by erosion and not by a combination of erosion and diffusion, and accurate drug-release control by erosion can only take place with surface-eroding polymers. Additional requirements are ease of synthesis and the ability to scale up the synthesis,

stability that does not require storage at low temperatures, ease of fabrication and the ability to control mechanical and thermal properties. Because the delivery of acid-labile therapeutic products is becoming increasingly important, the interior of the matrix should remain close to neutrality, so that the bioactivity of the incorporated therapeutic agent is not compromised. At this time, poly(ortho esters) and specifically Biochronomer best meet these requirements.

## 8. Expert opinion

One important component for the successful development of a bioerodible drug delivery system is the proper choice of a drug and a polymer that is tailor-made to achieve the desired release kinetics. This latter need has been the driving force in the development of bioerodible polymers.

However, it is becoming increasingly obvious that it is not only the polymer that is important, but also the method of administration. Aside from uses such as Gliadel, in which the device is implanted while the patient is under anaesthesia; or intratumoural injections, in which pain is secondary to a successful treatment of cancer, means must be developed to administer a device with minimal discomfort in therapies that do not address a life-threatening condition.

At this time, the most popular method of administering a bioerodible polymer formulation is the use of microspheres that are injected while suspended in a suitable medium. The other means of administering a device are thin strands that are implanted subcutaneously, intramuscularly or intraocularly; all of which are accompanied by significant discomfort, and in some cases, significant pain.

For this reason, means of delivering a formulation that uses a thin needle, preferably 26 gauge, will be the driving force in the further development of this field. At this time, there are two approaches that meet this need. One is an injection of a polymer solution in a biocompatible solvent, and the other is the use of a thermogelling material.

Although it is difficult to argue against the use of a solvent in view of the commercial success of Atrigel® (QLT, Inc.) for the treatment of prostate cancer, there are certain toxicological drawbacks in using a solvent, and the fact that a porous implant is created when the polymer precipitates in the tissues that makes precise control over drug delivery rate difficult, if not impossible.

A better approach is one that uses amphiphilic block copolymers to create thermogelling materials. This approach has been pioneered by MacroMed and is exemplified by Regel. Another approach, not being commercialised, is the use of amphiphilic graft copolymers [45]. However, Regel and the graft copolymer are based on copolymers in which the bioerodible segment is a poly(lactic-*co*-glycolic acid) copolymer, with attendant difficulties in achieving erosion control.

It is our opinion that the future direction of this field resides in the development of thermogelling materials that combine thermogelling properties with good control over bioerodibility and good control over release kinetics of incorporated therapeutic agents. Clearly, this is not an easy endeavour as we are now combining the structural constraints inherent in the construction of a thermogelling material with a need to control the rate of release of incorporated drugs.

However, we believe that the potential rewards of such systems will amply justify the considerable effort that will be required to create such polymers.

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