3
Polyanhydrides

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3.1
Introduction

Polyanhydrides (PAs) were unearthed by Bucher and Slade in as early as 1909, but were not regarded as a "good polymer" until first utilized by Langer in early 1980s for controlled drug delivery [1]. Today, polyanhydride can be regarded as "designer polymers" because they can be synthesized in such a way to produce polymers with various degrees of crystallinity, degradation behavior, branching, crosslinking, etc., and have been used in various forms to deliver diverse active agents and other biomedical applications. For a surface-eroding device, the polymer must be hydrophobic but contain water labile linkages.

Some polyanhydrides are nontoxic and degrade finally into diacids which are either excreted as such in feces/urine or undergo extensive metabolism to form carbon dioxide and water in the body. The safety of polyanhydrides is evident from clinically used Glidel (wafers for BCNU delivery in glimoa) and Septacin (beads for delivery of gentamicin in osteomyelitis) products. Success in these products led to the development of an array of devices for various applications ranging from delivery of bioactive molecules to tissue engineering.

There has been a need to develop more rational approaches for creating improved biomaterials for drug delivery, especially biodegradable polymers. For such polymers, to maximize control over release, it is often desirable for a system to degrade only from its surface. These surface-eroding polymers are expected to release the drug at a constant release rate, thus the rate is directly proportional to the polymer erosion rate. For a surface-eroding device, the polymer must be hydrophobic but contain water labile linkages. Polyanhydrides are believed to predominantly undergo surface erosion due to (i) the high water lability of the anhydride bonds on the surface and (ii) hydrophobicity, which restricts water penetration into the bulk. A decrease in the device thickness throughout the erosion process, maintenance of the structural integrity, and the nearly zero-order degradation kinetics suggest the dominancy of heterogeneous surface erosion [2–4].

Handbook of Biodegradable Polymers: Synthesis, Characterization and Applications, First Edition. Edited by Andreas Lendlein, Adam Sisson.

High hydrolytic reactivity of the anhydride linkage provides an intrinsic advantage in versatility and control of degradation rates. By varying the type of monomer and their ratios, surface-eroding polymers with degradation times of 1 week to several years can be designed and synthesized. The hydrolytic degradation rates can be obtained varying several thousand folds by simple changes in the polymer backbone and by altering the hydrophobic and hydrophilic balance of the polymer [5–7]. Aliphatic polyanhydrides degrade in a few days, while some aromatic polyanhydrides degrade over a few years. Degradation rates of copolymers of aliphatic and aromatic polyanhydrides vary between these extremes, and this feature of polyanhydrides gives an opportunity for making a drug delivery system which can provide the release of drugs for a desired time length of treatment.

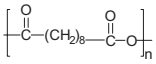
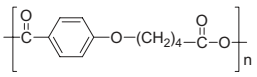
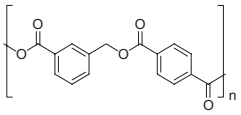
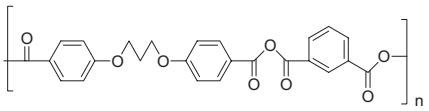
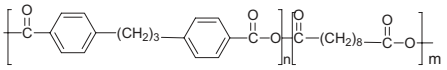
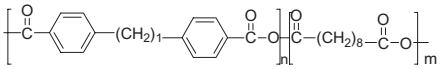
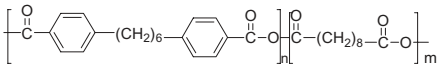
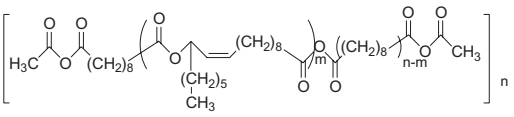
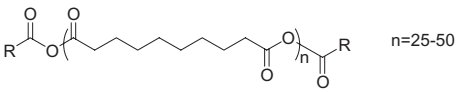
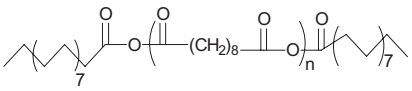
3.2 Types of Polyanhydride

Bucher and Slade synthesized aromatic polyanhydrides [8]; however, these were first explored by Conix after almost 50 years to form fibers for textile applications [9]. Hill and Carothers [10, 11] had worked in the 1930s on aliphatic PAs of adipic and sebacic acid (SA); because of hydrolytic instability, no further development was carried on these polymers until they were explored by Langer in the 1980s for drug delivery [1, 12]. Heterocyclic PAs were also developed in the meantime by Yoda *et al*. with good film and fiber-forming properties [13]. Once the degradable and biocompatible nature of PAs was uncovered, various types of copolymers were prepared thereon and utilized in drug delivery. One of the simplest classifications for PAs can be homo- and hetero-PAs; however, in the development of erodible materials, the use of copolymers (heteropolymers) is important for their different erosion rates, enabling the achievement of different target times for release, and this is possible by using different monomers and their ratio. In most PA copolymers, the aliphatic chain used is composed of polysebacic acid (PSA) and thus these are classified on the basis of the other part of the copolymer, which in turn governs the polymer properties. All the polyanhydrides with their representative chemical structure are shown in Table 3.1.

3.2.1 Aromatic Polyanhydrides

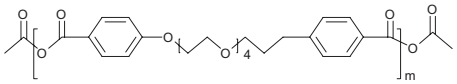
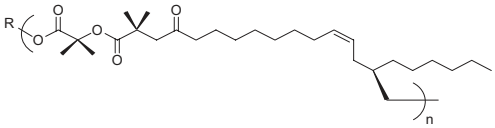
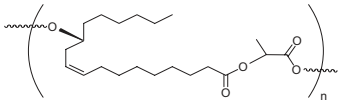
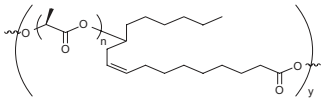
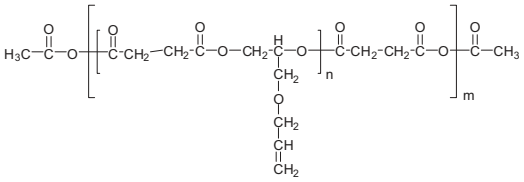
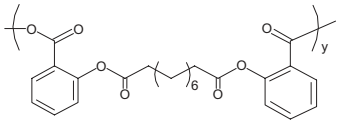
Aromatic homopolyanhydrides are insoluble in common organic solvents and melt at temperatures above 200 °C [6, 15]. These properties limit the use of purely aromatic polyanhydrides, since they cannot be fabricated into films or microspheres using solvent or melt techniques. Fully aromatic polymers that are soluble in chlorinated hydrocarbons and melted at temperatures below 100 °C were obtained by copolymerization of aromatic diacids such as isophthalic acid (IPA), terephthalic acid (TA), 1,3-bis(carboxyphenoxy)propane (CPP), or 1,3-bis (carboxyphenoxy)hexane (CPH).

Table 3.1 Types of the polyanhydrides and their representative chemical structures.

Polymer	Structure	Reference
Alipahtic polyanhydrides		
PSA		[7]
Aromatic polyanhydrides		
P(CPV)		[14]
P(TA-IPA)		[15]
P(CPP-IPA)		[15]
Aromatic polyanhydrides		
P(CPP-SA)		[14]
P(CPM-SA)		[14]
P(CPH-SA)		[14]
Fatty acid polyanhydrides		
P(RA-SA)		[16]
P(EAD-SA)		[17]
Stearic acid terminated with PSA		[18]

(*Continued*)

Table 3.1 (*Continued*)

Polymer	Structure	Reference
Pegylated polyanhydride		
P(CPOEG-5)		[19]
Recinoleic acid-based copolyesters	(a) Ring-opening polymerization using RA lactones (P[RA:LA])  (b) Transesterification (P[RA:LA])  (c) Melt condensation (P[RA:LA]) 	[20, 21]
Succinic acid functional polymers		[22, 23]
Amino acid-based crosslinked polyanhydrides (with anhydride linkages only)	Crosslinked polymer of *N*-trimellitylimido-amino acid and SA using 1,3,5-benzenetricarboxylic acid as crosslinker	[24]
Salicylate based		[25]

3.2.2
Aliphatic–Aromatic Polyanhydrides

Polyanhydrides of diacid monomers containing aliphatic and aromatic moieties, such as poly([*p*-carboxyphenoxy]alkanoic anhydride), were synthesized by either melt or solution polymerization, with molecular weights reaching up to 44,600 Da [6]. The polymers of carboxyphenoxy alkanoic acid having methylene groups ($n = 3$, 5, and 7) were soluble in chlorinated hydrocarbon solvents and melted at temperatures below 100 °C. These polymers displayed a zero-order hydrolytic degradation profile for 2–10 weeks. The length of the alkanoic chain positively correlates to the degradation time [6].

3.2.3
Poly(Ester-Anhydrides) and Poly(Ether-Anhydrides)

4,4-Alkane and oxa-alkanedioxydibenzoic acids were used for the synthesis of polyanhydrides. These polyanhydrides melted at a temperature range of 98–176 °C and had M_w up to 12,900 kDa. Di- and triblock copolymers of poly(caprolactone) (PCL), polylactic acid (PLA), and polyhydroxybutyrate (PHB) have been prepared from carboxylic acid-terminated low M_w prepolymers copolymerized with SA prepolymers by melt condensation. Similarly, di-, tri-, and brush copolymers of polyethylene glycol (PEG) with poly(sebacic anhydride) (PSA) have been prepared by melt copolymerization of carboxylic acid-terminated PEG [26, 27].

3.2.4
Fatty Acid-Based Polyanhydrides

These polyanhydrides were synthesized from dimer and trimer unsaturated fatty acids [17, 28–30]. The dimers of oleic acid and eurecic acid are liquid oils containing two carboxylic acids, which are available for polymerization; correspondingly, the homopolymers are viscous liquids. Copolymerization with increasing amounts of SA forms solid polymers with increased melting points. The polymers are soluble in tetrahydrofuran, 2-butanone, and acetone. Polyanhydrides synthesized from nonlinear hydrophobic fatty acid esters based on ricinoleic acid (RA), maleic acid, and SA possessed desired physicochemical properties such as low melting point and hydrophobicity and good flexibility [31] in addition to biocompatibility [32] and biodegradability [33].

3.2.5
RA-Based Polyanhydrides

Incorporation of the fatty acid in the biodegradable polymer backbone is advantageous but it is restricted by monofunctionality of most naturally occurring fatty acids. The unsaturated monofunctional fatty acids first need to be converted to dimers for further polymerization. The dimer contains a branched C–C linkage

which cannot be metabolized by the body and the dimer may remain in the body for 6 months [34]. RA (*cis*-12-hydroxyoctadeca-9-eonoic acid) was found to be the most appropriate alternative for the synthesis of the fatty acid-based polyanhydrides. It is one of the few commercially available fatty acids which have the additional 12-hydroxy group. The advantage of RA is that it is a bifunctional fatty acid containing a hydroxyl group along the acid group and, therefore, can be incorporated into the polyanhydride backbone by the formation of an ester bond.

RA-based polymers are the newest addition to the polyanhydride series which were first investigated in the late 1990s [16]. However, polymers produced were for solid implant that need surgical intervention for application to the body system. Recent work is more focused on converting this solid form to liquid injectable form which can form solid or semisolid implants after administration by injection [16]. For this, the first series of efforts were made with SA as the other monomer and this also included two subtypes; one is insertion of RA in preformed SA chains [35] and second is usual melt condensation carried out at lower temperature in one-pot synthesis, where dicarboxylic acid derivative of RA and SA are condensed together to from random copolymer rather than block copolymer [36]. Both of these efforts lead to the formation of polymers in the liquid injectable state. Although the common physicochemical properties such as low melting point, hydrophobicity, flexibility, biocompatibility, and biodegradability desired for a drug carrier possessed by all RA-based polyanhydrides, the liquid state was achieved only with the polymer having more than 70% of RA content.

Low molecular weight polymers synthesized by one pot-low temperature condensation method afforded the release of anticancer drug, methotrexate for around 10 days [36]. Although a change in the ratio of RA maleate (RAM) to SA was having a role, the faster release from the higher RAM containing polymer was elucidated on the basis of polymer crystallinity, which hinders the release by inhibiting water penetration in the device which decreases with increase in RAM content [16]. Similar kinds of results were found in polymers obtained by insertion of RA in SA chains [35, 37], where these polymers were loaded with cisplatin (5% w/w) and paclitaxel (5–20% w/w) and drug release was faster with the pasty polymers. *In vivo* evaluation of bupivacaine-loaded P(SA:RA)(2:8) injectable polymer was made in terms of efficacy and toxicity for producing motor and sensory block when injected near the sciatic nerve [38]. Single injection of 10% bupivacaine in the polymer caused motor and sensory block that lasted 30 h without causing any adverse effects.

Ricinoleic lactones were utilized for the synthesis of copolyester by ring-opening polymerization (ROP) [20]. RA lactones were synthesized by using dicyclohexylcarbodimide and (dimethylamino)pyridine as catalysts. Various macrolactones were obtained, mono- to haxalactone depending on the number of RA moieties which participate in the lactone ring formation. Polymerization of the RA lactones with catalysts commonly used for ring-opening polymerization of lactones, under specific reaction conditions, resulted in oligomers. Polymerization of chromatography-purified dilactone with $Sn(Oct)_2$ resulted in the formation of longer oligomers (weight average $M_w = 5700$). However, copolymerization with

lactide resulted in copolymers of low molecular weight. Polymers with molecular weights in the range 5000–16,000 were obtained with melting temperatures of 100–130 °C for copolymers containing 10–50% (w/w) RA residues. The polymers were off-white in color that became yellow with an increase of the RA content. The molecular weights of the polymers decreased with an increase in the content of the RA lactone. It was hypothesized that more reactive lactide activated first by catalyst polymerizes and only in the end some RA lactones react. The reaction was terminated because of the RA lactones' low reactivity. This low reactivity can be attributed to the low ring strain and to the steric hindrance of the ester bond by the fatty acid side chain. *In vitro* degradation of RA–LA copolymers showed that copolymerization with RA had some effect on the degradation rate and the polymer physical properties, which is related to the low incorporation of RA in the polymer. Addition of RA to PLA is expected to improve the hydrophobicity of the polymer and thus drug release profile.

In continuation of the above study, synthesis methods other than ROP like transesterification and melt condensation were also utilized [21]. The liquid state of the polymer, which makes it a potential candidate for directly injectable drug delivery carrier, was achieved when RA content increased more than 15% and 50% in case of melt condensation and transesterfication, respectively.

Polymers synthesized by all three methods were compared for the release of hydrophilic and hydrophobic drugs viz. 5-FU and triamcinolone, respectively. 5-FU release was faster in all cases with the total release lasting for 17 days from polymers prepared by transesterification and melt condensation. Slower 5-FU release was obtained from polymer prepared by ROP (40% in 17 days). The same pattern was observed for triamcinolone, where release was obtained only 5% in 17 days from ROP polymer in contrast to the 30% from polymer synthesized by transesterification. The difference was attributed to the diblock nature of ROP polymer, its high crystallinity, and melting point, all of which inhibit water penetration and thus degradation, which finally shows up in release profiles [21].

3.2.6
Amino Acid-Based Polyanhydrides

Amino acid-based PAs were first reported in 1990s by Domb [39]. However, recent progress in this class has been made in terms of producing crosslinked PAs which are suitable for *in vivo* use [24, 40]. Earlier, alanine-containing crosslinked PAs in which linkages were produced by irradiation of methacrylated end groups which when hydrolyzed gave rise to nonbiodegradable products having limited biocompatibility. To overcome these limitations, crosslinked amino acid PAs were produced having exclusively anhydride bonds which are hydrolabile in nature. Crosslinked amino acid-containing polyanhydrides based on *N*-trimellitylimido-β-alanine (TMA-ala) or *N*-trimellitylimido-glycine (TMA-gly) and SA were synthesized by copolycondensation using 1,3,5-benzenetricarboxylic acid prepolymer as a crosslinking agent. Crosslinking was confirmed by single melting peak of the polymer in differential scanning calorimeter (DSC) studies [40]. Monomeric SA

prepolymer was prepared to prevent phase separation and produce homogeneous polymeric matrix. *p*-Nitroaniline was incorporated in the polymer matrix by compression-molding in the form of a disk. They were then placed in buffer (0.1 M, 7.4 pH) and release of *p*-nitroaniline as well as TMA-gly was measured and found to be similar to its linear counterpart of the polymer (TMA-gly:SA 30:70) [41, 42], indicating that crosslinking has little effect on the degradation behavior of this particular polymer, possibly due to its high hydrophilicity and low degree of crosslinking. Thus, this system gives opportunity to further evaluate the degree of crosslinking and control over the same to produce material useful for varied applications.

In another study by Zhang *et al.* [43], the effect of type of amide bonds present in the PA backbone and its blending with polyesters like PLA on degradation has also been studied. Polymers of *N*,*N*′-bis(L-alanine)-sebacoylamide (BSAM) and P(1,6-bis[*p*-carboxyphenoxy] hexane [CPH]-BSAM) were synthesized and blended with PLA. Hydrolytic degradation of polyanhydrides and their blends with PLA were evaluated in 0.1 M phosphate buffer pH 7.4 at 37 °C. The results indicate that the existence of amide bonds in the main chain of polymers slow down the degradation rate, and this tendency increases with the increasing amount of these. The copolymers and their blends with PLA possess excellent physical and mechanical properties, thus making them more widely used in drug delivery and nerve regeneration.

3.2.7
Photopolymerizable Polyanhydrides

Photocrosslinking is preferred over chemical crosslinking which utilizes chemicals that can cause adverse effects. Fiber-optic cables are used to provide photons immediately after introduction of the polymer system to the desired site via injection. The other main advantages of photoinitiated polymerizations over other crosslinking techniques are spatial and temporal control of the polymerization which allows the precise control of polymer formation by directing and shuttering the light source. The reactions are rapid enough to overcome oxygen inhibition and moisture effects and can be controlled to occur over a time frame of seconds to minutes. Ease of fashioning and flexibility during implantation in terms of physical and mechanical properties of materials without major modifications to the backbone chemistry, which can alter biocompatibility, is added advantage. However, the principal limitation to more extensive use of photopolymerizations in biotechnology and medicine is the lack of biocompatible monomers and/or oligomers that photopolymerize to form degradable polymer networks [44, 45].

Anhydride monomers with reactive methacrylate functionalities have been developed and used for the preparation of PAs which shows *in-situ* crosslinking on exposure to light. These systems were demonstrated to be biocompatible and were used for bone augmentation applications [46].

Shastri *et al.* have prepared a new family of photochemically cured PAs which can produce semi-interpenetrating degradable networks and evaluate them for

biocompatibility in subcutaneous tissue in rats. These systems appear to undergo degradation primarily by surface erosion. They observed that the inflammatory response to these implants was minimal at both short (3 and 6 weeks) and long (28 weeks) time points. Further, the fibrotic response was largely absent throughout the duration of this study. For reference, linear PA controls were tested and showed a foreign body response culminating in the formation of relatively non-vascular fibrous capsule several cell layers thick, which became thicker over time, a response similar to what is typically observed in Food and Drug Administration (FDA)-approved implantable polymeric device systems [47].

In another study, Poshusta *et al.* examined cell–polymer interactions in subcutaneous and bony tissue after implantation of *in situ* forming and surface-eroding photopolymerized disks of several polyanhydride compositions in rats. Varied histological responses were observed depending on the degrading polymer composition. It was shown that 50/50 poly(MSA)/poly(CPP:CPH) showed a cellular response that was similar to PLA controls. A model defect created in the proximal tibia was used to assess the effects of the photopolymerization reaction on local bony tissue. At 7 days, new bone spicules in the fibrous callous were found to be present which indicated healing of the polymer-treated defect with no adverse effects from the photopolymerization reaction [45].

Weiner *et al.* have recently evaluated the potential of photocrosslinked PAs networks as an injectable delivery system for sustained release of bioactive molecules. Crosslinked networks composed of sebacic acid dimethacrylate (MSA), 1,6-bis-carboxyphenoxyhexane dimethacrylate, and PEG diacrylate, supplemented with calcium carbonate were examined for *in vitro* release of two model proteins (horseradish peroxidase and bovine serum albumin labeled with fluorescein isothiocyanate). Release of protein ranging from 1 week to 4 months was achieved. In general, a more hydrophobic network resulted in slower rates of protein release. These results suggest that this system may be useful as an injectable delivery system for long-term delivery of macromolecules [48].

3.2.8
Salicylate-Based Polyanhydrides

Erdmann *et al.* [49] have reported salicylic acid-based polymers in year 2000 and these have then been investigated extensively in the last few years. These salicylate-based polyanhydride-esters were collectively referred to as PolyAspirin because they hydrolytically degrade into salicylic acid, a nonsteroidal anti-inflammatory drug. Salicylic acid-based polymers are unique example of polymer therapeutics wherein the drug (salicylate derivative) is an integrated part of the polymer backbone. Aminosalicylic acid is a useful bioactive agent for inflammatory bowl disease and the drug needs to be specifically delivered at the site of action, that is, colon. Synthesis of this category of the polymers can be carried out by usual preparation of prepolymers and then melt condensation to produce high molecular weight polymer [25]. Salicylic acid-based poly(ester-anhydride)s have also been tested for healing of long bone defects in rats with 5-mm mid-diaphyseal defects in femurs.

Microspheres of the polymer were packed into the defect and compared with collagen sponge for reduction in bone loss. Though initially there was no significant reduction in bone loss, after 8 weeks significant reduction in the bone, weight loss was observed in the polymer group [50]. In another study, polymers prepared from salicylic acid derivative were evaluated for cytotoxicity using L929 fibroblast cells in serum-containing medium on parameters like cell viability, proliferation, and morphology and these were found normal for most of the polymers evaluated [51].

All salicylate-based polymers degrade to produce salicylic acid and all of these were found to follow primarily surface erosion patterns [52]. Furthermore, effect of media on degradation rate was studied and found to increase marginally better (14%) in media containing actively growing bacterial culture than sterile media. A significant reduction in formation of *Pseudomonas aeruginosa* biofilm in a long-term (3 day) study with the salicylic acid containing polymers was demonstrated and a pathway was postulated using *P. aeruginosa* pMHLAS, containing a fluorescent reporter gene which involved inhibition of the las quorum sensing system [53]. In another study, a clear difference was seen between bacterial strains that form biofilms at the air–liquid interface (top-forming) and those that form at the surface–liquid interface (bottom-forming). The results lead to the conclusion that the polymers may not interfere with attachment; rather, the polymers likely affect another mechanisms essential for biofilm formation in Salmonella [54].

3.2.9
Succinic Acid-Based Polyanhydrides

Succinic acid is one of the naturally occurring substances of living tissues, and polymers prepared using this acid can be inherently biodegradable and biocompatible. Inclusion of succinic acid in the polymer chain has been made for various functions. Initially, it has been used to convert monocarboxylic monomers to dicarboxylic, as in case of RA, to help polymerization reaction [55–57]. In earlier work, succinic acid was directly used as one of the monomer units, for example, Ben-Sabat *et al*. having synthesized copolyanhydrides from trimers of fumaric acid, succinic acid, and propylene glycol [22]. These polymers were found to degrade and release the entrapped drug substance in a week's time, and *in vivo* testing in rat proved the polymer safe for further investigations as drug delivery carrier. Succinic acid derivatives were utilized more widely to synthesize unsaturated and functional polymers. Copolymers of 2-hexadecylsuccinic acid and SA were prepared using usual melt-condensation method and demonstrated to be potential drug carriers for localized drug delivery [58]. In another study, hydroxyl-group functional polylactones were prepared and converted to acid-terminated polyesters in a reaction with a series of alkenylsuccinic anhydrides containing 8, 12, or 18 carbons in their alkenyl chains [55]. These polyester units were then condensed in high molecular weight polymer. Polymer hydrolysis was found to decrease by the presence of alkenyl chain in case of low molecular weight precursors but converse was the case with polymers with high molecular weight prepolymers. There was no pronounced effect of differences in length of the alkenyl group

in degradation rate. Recently, succinic acid-based functional polymers have been synthesized with allyl pendent group which can be utilized for further copolymerization or attachment of other moieties to perform specialized function [23].

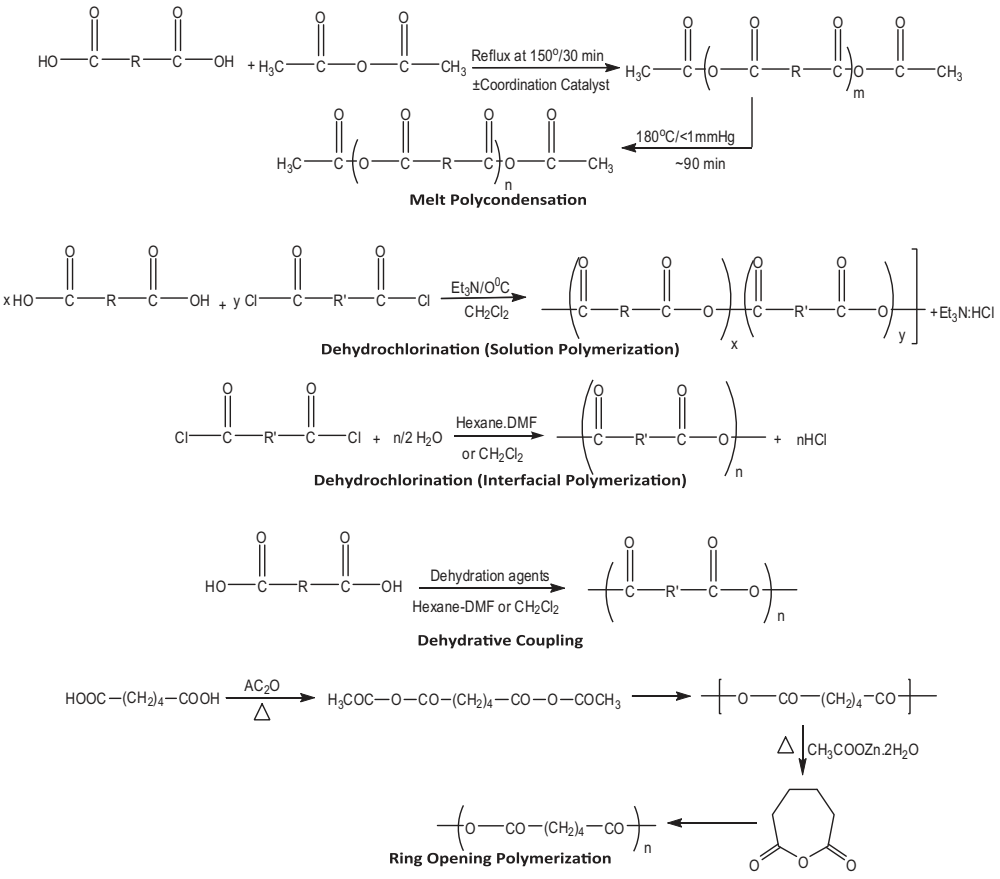
Synthesis of these functional polymers was carried out in three steps; initially carboxyl-terminated functional oligoesters with molecular weight 300–1000 Da were obtained by melt condensation of allyl glycidyl ether with an excess of succinic acid then the macromer with carboxyl end obtained were converted to mixed anhydride groups by refluxing in acetic anhydride, and finally, melt polycondesation of ester-anhydride prepolymers was carried out to form the polymer. Influence of molecular weight of initial oligoesters as well as of parameters of the process on selected properties of poly(ester-anhydride)s was examined. The hydrolytic degradation was monitored by the determination of mass loss and the ester-to-anhydride groups ratio. These poly(ester-anhydride)s display a two-phase degradation profile with a rapid initial degradation of anhydride bonds followed by relatively slower degradation of oligoester.

3.2.10 Blends

Blending, or mixing, appropriate polymers can alter the physical and mechanical properties of polyanhydrides. Blends of poly(trimethylene carbonate) with poly(adipic anhydride) were found biocompatible in both *in vitro* and *in vivo* experiments [59–61]. Blends were prepared by dissolving each polymer in methylene chloride followed by separately mixing in varying proportions using solvent-mixing technique [62]. The results indicate that the blend may be a promising candidate for controlled drug delivery [59–61] and varying the proportion of poly(trimethylene carbonate) and poly(adipic anhydride) can control the erosion rate of the polymer blend. Low molecular weight polyesters such as PLA, PHB, and PCL are miscible with polyanhydrides, whereas high molecular weight polyesters (M_w > 10,000 Da) are not compatible with polyanhydrides. Uniform blends of PCL with 10–90% by weight of poly(dodecanedioic anhydride) were prepared by melt mixing at 120 °C and exhibited good mechanical strength. Hydrolysis studies indicated that the anhydride component degraded and was released from the blend composition without affecting the PCL degradation [62]. Combinatorial methods have also been developed to study the phase behavior of biodegradable polyanhydrides for drug delivery applications [63].

3.3 Synthesis

Polyanhydrides have been synthesized by various techniques, viz. melt condensation, ROP, interfacial condensation, dehydrochlorination, and dehydrative coupling agents (Scheme 3.1) [64, 65]. Linear and crosslinked polyanhydrides have also been made using photoinitiated thiol-ene chemistry [66]. Solution



Scheme 3.1 General synthesis schemes for polyanhydrides.

polymerization in general yielded low molecular weight polymers. A variety of catalysts have been used in the synthesis of a range of polyanhydrides by melt condensation. Particularly, coordination catalysts facilitate anhydride interchange in the polymerization and enhance the nucleophilicity of the carbonyl carbon. Significantly higher molecular weights in shorter reaction time were achieved by utilizing cadmium acetate, earth metal oxides, and $ZnEt_2 \cdot H_2O$. Except for calcium carbonate, which is a safe natural material, the use of these catalysts for the production of medical grade polymers is limited due to their potential toxicity [7].

Since melt condensation occurs at high temperatures, it is not suitable for heat-sensitive monomers, which require milder reaction conditions. A variety of solution polymerizations at ambient temperature have been reported [65, 67]. Polyanhydride formation can be effected at room temperature by dehydrochlorination between a diacid chloride and a dicarboxylic acid. In an attempt to

prepare copolyanhydrides of regular structures, polycondensation was conducted in organic solvent pairs such as pyridine–benzene and pyridine–ether. The reaction between a diacid chloride and a diacid ethyl ester in the presence of zinc chloride was also studied. The formation of polyanhydrides in these reactions was confirmed only by IR spectroscopy. The polycondensation was achieved between acyl chloride and carboxylic acid in a single solvent in the presence of an acid acceptor such as triethylamine. Polymerization took place on contact of the monomers and was essentially complete within an hour as monitored by gel permeation chromatography. The degree of polymerization was in the range of 20–30 as determined by vapor phase osmometry. Comparable results in terms of molecular weights and yields were obtained for polymerization conducted in solvents such as dichloromethane, chloroform, benzene, and ethyl ether. The degree of polymerization was influenced by the mode of addition. Adding the diacid solution drop wise to the diacid chloride solution consistently produced higher molecular weights and yield as compared to the reverse order of addition. This could be understood as the terephthaloyl chloride complex which with triethylamine forms an ionic salt. Since a slight excess of acid acceptors was often used to solubilize the acid monomers, some of the terephthaloyl chloride would be lost due to complexation. The unbalanced stoichiometry therefore accounted for the inefficient polymerization. Adding the acyl chloride in a single portion yields satisfactory results, which suggests that the rate of dehydrochlorination is comparable to the rate of acid chloride–amine complexation. The inconvenience with this homogeneous Schotten–Baumann condensation in solution is the need to obtain the highly purified diacid chloride monomer. Stringent stoichiometric conditions must also be met.

ROP was used for the synthesis of poly(adipic anhydride) from cyclic adipic anhydride (oxepane-2,7-dione) using cationic (e.g., $AlCl_3$ and $BF_3 \cdot [C_2H_5]O$), anionic (e.g., $CH_3COO^- K^+$ and NaH), and coordination-type inhibitors such as stannous-2-ethylhexanoate and dibutyltinoxide [68]. ROP takes place in two steps in which the first step is the preparation of the cyclic monomer and the second step is the polymerization of the cyclic monomers as shown in Scheme 3.1. A one-step polymerization using diacyl chloride, phosgene, or diphosgene as coupling agents and various acid acceptors was reported [67]. Although phosgene and diphosgene are equally efficient, diphosgene as a liquid is preferred because of its ease of handling and lower vapor pressure. The polymers have similar molecular weights with regard to the type of amine bases used. The heterogeneous acid acceptor, poly(4-vinylpyridine) (PVP), produced satisfactory results, whereas the nonamine heterogeneous base K_2CO_3 yielded a lower molecular weight. When using soluble amines as acid acceptors, they form a soluble intermediate complex of acid–amine which improves the interaction with the coupling agent under homogeneous conditions. Although the PVP is insoluble in the reaction medium, it swells and forms a similar acid–PVP complex. K_2CO_3, however, forms a heterogeneous mixture with the acid and thus presumably reacts more slowly with the coupling agents to form the polymer.

3.4 Properties

Thermal. Because crystallinity is an important factor in controlling polymer erosion, the effect of polymer composition on crystallinity was studied [69, 70]. Almost all polyanhydrides show some degree of crystallinity as manifested by their crystalline melting points. Polymers based on SA, CPP, CPH, and FA were particularly investigated. Some of the important physicochemical properties of P(CPP:SA) and P(FAD:SA) are given in Table 3.2. Homopolyanhydrides of aromatic and aliphatic diacids, for example, poly(CPP) and poly(FA), were crystalline (>50% crystallinity), whereas the copolymers possess a less degree of crystallinity, which increases by enhancing the mole ratio of either aliphatic or aromatic diacid monomers [15]. The heat of fusion (ΔH) values for poly(CPP-SA) demonstrated a sharp decrease from 36.6 to 2.0 cal/g as CPP is gradually added up to 40%, while an increase in ΔH value was observed up to 26.5 cal/g on further addition of CPP [71]. The trend of decreasing crystallinity, as one monomer is added, was noted using X-ray diffraction or DSC methods. The decrease in crystallinity is a direct result of the random presence of other units in the polymer chain. A detailed analysis of the copolymers of SA with the aromatic and unsaturated monomers, CPP, CPH, FA, and trimellitic-amino acid derivative, showed that copolymers with high ratios of SA and CPP, TMA-gly, or CPH were crystalline while copolymers with equal ratios of SA and CPP or CPH were amorphous [69]. In contrasts, the poly(FA-SA) series displayed high crystallinity regardless of comonomer ratio [72]. Aliphatic polyanhydrides generally melt at lower temperatures than do aromatic polyanhydrides. The melting point of aromatic–aliphatic copolymers is proportional to the aromatic content in the copolymer. Introduction of fatty acids in copolymers also lowers the melting point of the bulk polymer. Thermal properties along with the molecular weight of representative fatty acid-based polyanhydrides are given in Table 3.3.

Inclusion of an aromatic amide linkage in the backbone is found to increase the transition temperatures. The formation of intermolecular hydrogen bonds is believed to cause this high crystallinity. Polyanhydrides-*co*-amide also have high thermal stability [39].

Mechanical. Polyanhydrides show poor mechanical properties in comparison to other polymers such as polyesters. Mechanical properties of various polyanhydrides and their copolyanhydrides were tested as transparent and flexible films made by melt compression and solvent casting. It was observed that increasing the CPP content in copolymer composition increases the tensile strength as well as elongation of various polyanhydrides tested [7]. Despite the low molecular weight (M_n = 6400) of poly(CPP-SA) (60:40), it has a higher tensile strength of 981 MPa (100 kgf/cm^2) than it has in the 20:80 composition (M_n = 18,900), 441 MPa (45 kgf/cm^2). Decreasing the M_n of films of the same CPP content (60%) from 12,100 to 6400 results in lower tensile strength. The elongation at break of these films ranges from 17% to 23%. Table 3.2 shows the mechanical

Table 3.2 Physicochemical properties of P(CPP:SA) and P(EAD:SA).

Analysis	Units	Conditions	Typical data/information								Reference
			Poly(EAD-SA)				Poly(CPP-SA)				
Thermal properties	Mol%	DSC−10°C/min	*0:100*	*8:92*	*22:78*	*100:0*	*0:100*	*22:78*	*46:54*	*100:0*	[15, 73]
	K	T_m	358.0	348.0	337.0	293.0	359.0	339.0	458.0	513.0	
	K	T_g	333.1	283.0	283.0	273.0	333.1	320.0	274.8	369.0	
	kJ/kg	ΔH	150.7	250.2	13.0	4.0	150.7	64.0	13.0	110.9	
Crystallinity	%	W_c	*0:100*	*8:92*	*22:78*	*100:0*	*0:10*	*22:7*	*46:5*	*100:*	
			66	54	35	<5	66.0	35.0	14.2	61.4	
Mechanical			*22:78*				*40:60*				[17, 74]
Tensile strength	MPa	Film by melt	42				14.9				
Tensile modulus	MPa	22:78, M_w = 155 kDa	4.5								
Elongation yield	%		85								
Elongation at break	%		14								
Solubility	% w/v	Equilibrium	*50:50*				*20:80*				
			Dichloromethane > 30				>30				
			Chloroform > 30				>30				
			Tetrahydrofuran > 10				2.1				
			2-Butanone 5.0				0.1				
			4-Methyl-2-pentanone 3.1				0.02				
			Acetone 3.0				0.00				
			Ethyl acetate 2.4				0.02				

(*Continued*)

Table 3.2 (*Continued*)

Analysis	Units	Conditions	Typical data/information		Reference
			Poly(EAD-SA)	Poly(CPP-SA)	
Spectral					[17, 75, 76]
^{1}H NMR	ppm	1% (w/v) in $CDCl_3$, 22 °C	2.33 (t, 4H), 1.32 (m, 8H), 1.23 (s, 60H), 0.8–0.9 (T, 8H)		
FTIR	cm^{-1}	Film on NaCl plate	1740; 1810	1740; 1770; 1810	
Raman	cm^{-1}			1723; 1765; 1804	
UV-wavelength	nm		253	265	
Molecular weight	10^4 g/mol	Gel permeation chromatography-polystyrene standard	M_w = 3–30; M_n = 1–3	M_w = 3–20, M_n = 0.5–3	[73, 77]
Viscosity	dL/g	25 °C, in CH_2Cl_2	η_{sp} = 0.2–1.4	η_{sp} = 0.2–0.9	
Mark–Houwink constants	mL/g	23 °C, in CH_2Cl_2	k = 3.46; a = 0.634	k = 3.88; a = 0.658	
Surface and bulk					[78, 79]
XPS		Film by spin casting	Quantitative elemental and functional group information, molecular specificity, and surface morphology of polymer	Quantitative elemental and functional group information, molecular specificity, and surface morphology of polymer	
TOF-SIMS		on aluminum sheet,			
AFM		0.1% (w/v) in $CHCl_3$			

Table 3.3 Properties of some representative fatty acid-based polyanhydrides.

Polymer	M_w	M_n	T_m (°C)	ΔH (J/g)c	Crystallinity	Reference
Fatty acid-terminated polymers						[18, 28, 80]
P(OCTA:SA) 30:70	7800	5600	70.2	72.5	–	
P(LAUA:SA) 30:70	5300	3900	71.3	78.5	–	
P(MYR:SA) 30:70	4800	3600	78.3	82.7	–	
P(OA:SA) 30:70	6300	4500	73.1	59.9	–	
P(StA:SA) 30:70	7400	5400	77.8	103.7	–	
P(OA:SA) 30:70	6350	3206	71.3	59.9	–	
P(LA:SA) 30:70	5807	3367	69.5	57.4	–	
P(LitA:SA) 30:70	6575	3804	68.35	95.2	–	
P(RA:SA) 30:70	7961	4952	71.29	60.1	–	
P(RAStA:SA) 30:70	7300	5000	79.0	64.6	–	
Dimer acid (DA)-based polymer						[81, 82]
P(DA-DDDA) 50:50	24,220	21,625	70.1	–	16	
P(DA-TA) 50:50	38,561	35,904	80.2	–	48	
P(DA-SA) 50:50	26,000	11,000	67.1	–	–	
C_{12}-,C_{13}-, C_{14}-, C_{15}-based polymer				–	–	[83]
P(DDDA-TA) 50:50	29,600	24,200	75.1	–	28	
P(BA-PA) 50:50	25,700	22,800	72.4	–	29	
RA-based polymer						[16, 36, 84]
P(RAM:SA) 50:50	31,200	12,800	59.3	–	–	
P(RAS:SA) 50:50	48,700	21,700	61.1	–	–	
P(HSAS:SA) 50:50	41,000	19,700	70.4	–	–	
P(RAM:SA) 50:50 (one pot low M_w)	3768	1983	41.06	–	–	
P(RA-PSA) 5:5 (RA insertion in SA chain)	19,000	8000	55.7	–	–	
Ricinoleic acid (RA)-based copolyesters						[85]
P(L-LA-RA) 50:50 (ROP)	9800	7300	105	–	–	
P(L-LA-RA) 50:50 (melt condensation)	4500	3500	Liquid at RT	–	–	
P(L-LA-RA) 50:50 (transesterification)	8200	5600	Liquid at RT	–	–	

properties of fatty acid-based polyanhydrides. Films of fatty acid polyanhydrides were transparent and flexible with a tensile strength of 4–19 MPa and elongation at break in the range of 77–115%. The terpolymer of (fatty acid trimer [FAT]-CPP-SA] in a 1:1:1 weight ratio formed the strongest film. The polymer had a tensile strength of 2.5–3.2 MPa and yield stress at break of around 20% in comparison to poly(EAD-SA) (1:1) and PSA, which had tensile strengths of 5.7 and 7.2 MPa and yield stress at break of 10% and 1.5%, respectively. Thus, introduction of nonlinear fatty acid structures in polyanhydrides provides hydrophobicity and flexibility to the polymers.

Stability. The stability of polyanhydrides in solid state and dry chloroform solution was studied [86]. Aromatic polymers such as poly(CPP) and poly(1,1-bis[*p*-carboxyphenoxy] methane) maintained their original molecular weight for at least 1 year in the solid state. In contrast, aliphatic polyanhydrides, such as PSA, showed decreased molecular weight over time. The decrease in molecular weight shows a first-order kinetics, with activation energies of 7.5 kcal/(mol K). The decrease in molecular weight was explained by an internal anhydride interchange mechanism, as revealed from elemental and spectral analyses. This mechanism was supported by the fact that the decrease in molecular weight was reversible and heating the depolymerized polymer at 180 °C for 20 min yielded the original high molecular weight polymers. However, under similar conditions, the hydrolyzed polymer did not increase in molecular weight [86]. In many cases, it was observed that the stability of polymers in the solid state or in organic solution did not correlate with its hydrolytic stability [86]. A similar decrease in molecular weight as function of time was also observed among the aliphatic–aromatic copolyanhydrides and imide-containing polyanhydrides [6, 87]. Gamma-irradiation technique is typically used to sterilize polyanhydrides [88]. Aliphatic and aromatic homo- and copolymers were irradiated at 2.5 Mrad dose and the change in properties was monitored before and after irradiation. Properties such as molecular weight, melting temperature, and heat of fusion remained the same, and ^{1}HNMRand FTIR spectra of the polymer were also similar before and after irradiation [34, 89]. Using the same concept, these studies were extended for saturated and unsaturated polyanhydrides [90]. RA-based copolymers with SA and poly(CPP:SA) were irradiated under dry ice and at room temperature, while poly(FA:SA) was irradiated only at room temperature. Saturated polyanhydrides are stable enough during irradiation; however, the presence of double bonds conjugated to an anhydride bond creates an unstable structure and leads to the formation of free radicals [90]. These free radical polyanhydrides degrade into less conjugated polyanhydrides. The outcome of this process is self-depolymerization via inter- and/or intramolecular anhydride interchange to form polymers with lowered molecular weight. In general, polymers with high melting points and crystallinity give the highest yield of room temperature observable radicals. These endogenous free radicals were used to study processes of water penetration and polymer degradation *in vivo* [88]. The detection of gamma-sterilization-induced free radicals *in vivo* using EPR could

be of significance because changes in the mobility of the radicals can be used to study drug release kinetics in a noninvasive and continuous fashion, without introducing paramagnetic species [34].

3.5 *In Vitro* Degradation and Erosion of Polyanhydrides

Polyanhydrides are made of sparingly water-soluble diacid monomers connected to each other by anhydride bonds, which are hydrolytically very labile and split readily into two carboxylic acids in the presence of water molecules. Hydrolysis of the anhydride bond is base catalyzed, and thus, pH of the surrounding media can significantly affect the rate of degradation of the polymer. The diffusion of oligomers and monomers formed by polymer degradation depends on pH of the surrounding medium and solubilities of these compounds in the medium. Since polyanhydrides degrade into carboxylic acids, solubilities of these degradation products are more at higher pH and hence erosion is higher at higher pH [91]. At low pH, these degradation products are in their unionized form, difficult to solubilize in surrounding biological media at implantation site and thus polyanhydrides in general degrade more rapidly in basic media than in acidic media [92]. Degradation of the polymer designates the process of polymer chain cleavage [93], while erosion is the sum of all processes that lead to the loss of mass from a polyanhydride matrix [92]. Erosion of the polymer matrices depends on processes such as rate of degradation, swelling, porosity, and ease of diffusion of oligomers and monomers from the matrices. Such erosions maintain constant surface area and hence lead to zero-order drug release [93]. Although polyanhydride degrades by surface erosion, there are many factors that influence the mechanism and rate of degradation, for example, type of monomers and their composition is one of the most important attributes. Aliphatic homopolymer like PSA are usually highly crystalline (about 66%) with unfavorable mechanical properties [94]. The *in situ* AFM images have provided the evidence that amorphous polymer areas erode faster than crystalline ones [77]. All aliphatic polyanhydrides are rigid, crystalline materials, and their melting point increases with their monomer chain length. They usually erode fast and therefore are not much used alone for pharmaceutical applications except some aliphatic polyanhydride such as P(FA:SA) having bioadhesive properties. Aromatic polyanhydrides are high melting polymers and degrade slowly. P(CPP) has a melting point of approximately 240 °C and its degradation rate is extremely slow [14, 15]. Combined properties of aliphatic and aromatic polyanhydride have been used to get the copolymer with improved mechanical characteristics and adjustable erosion times. The most successful polyanhydride is a copolymer of P(CPP:SA) and has been reported to erode at a constant rate [2, 95]. Erosion velocity of P(CPP:SA) decreases with increasing CPP content. Erosion zones in P(CPP:SA) are highly porous and separated from noneroded polymer by erosion fronts which move at constant velocity from the surface of a matrix into its center [92, 96]. P(FAD:SA) has also showed erosion zone but due to low

solubility of FAD, the erosion zone mainly consisted of a semisolid mixture of FAD and FAD salts, instead of porous erosion zone. The semisolid layer forms a permeation barrier and SA acid was found to precipitate inside the erosion zone; this ultimately leads to slow release of SA as well as drug. Later polyanhydrides based on RA were reported to undergo sharp decreases in molecular weight during first 24 h of erosion *in vitro* and lost 40% of their anhydride bonds in 48 h [16]. Polyanhydride chains terminated with linear fatty acid like lauric, oleic, or stearic acid also show exponential loss of molecular weight and erosion behavior similar to RA-based polymer [18]. The increase in amount of fatty acid and the chain length induced the bulk erosion properties of polyanhydrides [92]. The photocrosslinked polyanhydride obtained from MSA, MCPP, and 1,6-bis-carboxyphenoxyhexane dimethacrylate showed linear erosion profiles, when eroded *in vitro* [33, 97, 98]. Increase in the hydrophilicity of polyanhydride by increasing PEG content in the polymer enhances the degradation rate even though it maintains the surface-eroding property of polyanhydride [27]. Another important factor which affects the polyanhydride degradation and erosion is geometry of the matrix. It is very interesting to understand the macroscopic and microscopic degradation properties of the polyanhydrides at the molecular level. It is reported that erosion of matrices is strongly related to their geometry and rate of degradation for bigger matrices was lower than smaller ones due to smaller surface area [27, 99–101]. For example, during *in vitro* erosion of microspheres made of p(FAD-SA) 8:92, p(FAD-SA) 25:75, and p(FAD-SA) 44:56 with average diameters below 100 μm, SA was released completely in 100 h, while the release time was in weeks from matrix form of the polymer [102]. Some theoretical models have been proposed which allowed description and prediction of the erosion behavior of polyanhydride matrices [103]. Empirical models are based on the assumption of linear moving erosion front [104–106]. Monte Carlo based models offered the advantages of degradation modeling of the polymer as a random event that obeyed first-order kinetics rather than describing the degradation of individual bonds [100, 107–109].

3.6 *In Vivo* Degradation and Elimination of Polyanhydrides

Polyanhydrides were initially developed in matrix form as implantable drug carrier systems. Thus, it is critical to understand the processes involved in degradation and erosion in an *in vivo* environment and the differences between *in vitro* and *in vivo* degradation of polyanhydrides. Surface erosion of polyanhydrides depends on the penetration of water into the matrix system to hydrolyze the anhydride bonds. After hydrolysis, matrices degrade into degradation products of polyanhydrides and solubilize in the biological environment of the implantation site and are eliminated. Polyanhydrides are composed of sparingly water-soluble diacid monomers and thus elimination *via* solubilization in biological environment is a slow process [110]. Aliphatic monomers such as SA will most likely participate in the β-oxidation pathway yielding acetyl-coA which could be used in a typical bio-

synthetic pathway, while aromatic monomers are eliminated without further metabolic transformation [111]. Dang *et al.* studied surface erosion of Gliadel wafers during *in vivo* degradation in rat brain as well as during *in vitro* degradation in phosphate-buffered saline [2]. Morphological changes of the wafer during erosion were studied and SEM was used to present a visual proof of the erosion process. The wafer cross section before and after implantation in the brains of rats for various time periods has been studied. Before implantation, the surface of a BCNU-loaded polyanhydride wafer appeared very uniform with spray-dried microspheres densely packed together on the outer surface. Two hours after the wafer implantation, the porous structure extended approximately 20–30 μm from the surface into the interior of the wafer with outer thin layer of the wafer being eroded in the beginning and rest remained intact. Cross section of the degrading wafer followed dynamic process of water penetration from the surface to interior. One day following implantation, the wafer surface became highly porous and porosity decreased toward the region closer to the interior of the wafer. Higher magnification of the erosion zone revealed that the eroded microspheres had a dense structure at the external surface, while the materials from the inner core had already eroded and disappeared. As the advancing waterfront erodes deeper layers of the wafer, the porosity of the wafer increases resulting in increased numbers of channels and pores for water to access the interior of the wafer. Five days after wafer implantation, the entire cross section of the wafer displayed a uniformly high porosity without any individual microspheres being present. It indicates that water had penetrated through the whole wafer and degraded the interior as well as the exterior of the wafer. These results indicated that SEM analysis and weight loss studies were in a good correlation of *in vitro–in vivo* degradation behavior. Domb *et al.* studied the metabolic disposition and elimination process of (P[CPP-SA] 20:80) by implantation in adult Sprague-Dawley rat brain using radiolabeled polymers [112]. The results clearly showed that P(CPP-SA) 20:80 copolymer is extensively hydrolyzed 7 days postimplantation and revealed that the anhydride bonds in the copolymer are gradually degraded to give water-soluble SA monomer which are extensively metabolized in the body and excreted mostly as carbon dioxide. The elimination of the CPP component was slow due to its minimal solubility. The main route of elimination of insoluble CPP is by macrophages and inflammatory cells after its disintegration into small fragments.

3.7
Toxicological Aspects of Polyanhydrides

The toxicological aspect of polyanhydrides deals with the host response in terms of cytotoxicity, allergic responses, irritation, inflammation, and systemic and chronic toxicity. Cytotoxicity tests are the first in a sequential program of tests for assessing the biocompatibility of a polymer for which, tissue culture methods are used [111]. In a study, bovine aortic endothelial cells and bovine smooth muscle cells were used to evaluate the *in vitro* biocompatibility of three polyanhydrides

P(CPP-SA) 45:55, P(TA-SA) 50:50, and P(TA). These cultured mammalian cells are sensitive to the changes in growth medium and substrate [113]. The study showed the absence of acute toxicity of these polymers or their degradation products to sensitive mammalian cells. Chemical carcinogenesis usually proceeds by a mutagenic route; therefore, mutagenicity testing has been used as a rapid screening test for neoplastic transformation. The *in vitro* results for mutagenicity and the corresponding cytotoxicity of the degradation products of polyanhydrides particularly P(CPP-SA) showed that they are noncytotoxic, nonmutagenic, and have a very low teratogenic potential [113].

Polyanhydrides for intramuscular or dermal applications are tested for local tissue irritation and inflammation by muscle and skin tests. Leong *et al.* studied the local tissue response of polyanhydrides (P[CPP] and PTA-SA 50:50) by implantation of polymer samples into the cornea of rabbits [113]. No observable inflammatory characteristics were reported for the entire 6 weeks implantation period of polymers in rabbit corneas. The clarity of the corneas was maintained throughout, and proliferation of new blood vessels was absent. Histological examination confirmed the absence of inflammatory cells throughout the corneas. Laurencin *et al.* administered high doses of P(CPP-SA) 20:80 subcutaneously in rats to study the acute systemic toxicity of the polyanhydrides [32]. Polymer implants in the form of disks were administered subcutaneously for a period of 8 weeks at two different doses in two groups. One group was implanted with one matrix each and the other group implanted with three matrices each, whereas the control group received no polymer matrices. The systemic toxicological effects and effects on individual organs were evaluated based on blood clinical chemistry, hematological parameters, and histological evaluation of the organ sites and implant sites. Pre-necropsy examination of all rats in the study showed no changes in physical appearance or activity due to implantation of polyanhydride matrices. Gross examination of the body cavities and tissues at the time of necropsy did not show any evidence of changes due to polymer implantation, and histological examination of all organ tissues revealed no histomorphological evidence of induced systemic toxicity of the polyanhydride copolymer implantation.

There are no reports available regarding the long-term carcinogenicity studies on polyanhydrides or their degradation products. However, Leong *et al.* showed from histological examination that subcutaneous implantation of P(CPP) in rats over a 6-month period showed no evidence of tumor formation [113]. The brain biocompatibility of P(CPP-SA) 20:80 was established in rat brain by Tamorgo *et al.* [114]. They experimentally proved that none of the animals showed any behavioral changes or neurological deficits suggestive of either systemic or localized toxicity from biodegradable polyanhydrides P(CPP-SA) 20:80 after implantation in rat brain. Brem *et al.* have also evaluated the brain biocompatibility of polyanhydride P(CPP-SA) 50:50 by implantation in rabbit brain [115]. The animals were evaluated daily after the surgery for behavioral changes such as decreased alertness, passivity, impaired grooming, restlessness, irritability, fearfulness, and focal motor neurological deficits. None of the animals showed any behavioral changes or neurological deficits (suggestive of toxicity) and all the animals survived

till they were sacrificed. It was concluded that P(CPP:SA) 50:50, a polyanhydride matrix that can be used for the interstitial delivery of drugs in the brain is biocompatible in the rat brain. Thus, the various types of *in vitro* and *in vivo* toxicity studies on polyanhydrides show that these polymers are well tolerated by the body and can be considered biocompatible.

Various fatty acid-based polyanhydrides have also been found biodegradable, biocompatible, and nontoxic in various *in vivo* studies. *In vivo* biodegradation and biocompatibility studies in rats of the 30% stearic acid terminated P(SA) revealed that these polymers are biocompatible and gradually degrade and eliminate within 10 weeks [18]. Fatty acid dimer-based polymers have been thoroughly investigated for their biocompatibility. Brem *et al*. also studied the *in vivo* biocompatibility of P(FAD-SA) 50:50 in rat brain [30]. All animals survived to the scheduled date of sacrifice with no evidence of behavioral changes or neurological deficits suggestive of toxicity. The biocompatibility of P(DA-SA) (50:50) was preliminary evaluated in rabbits brain and it was found that all the experimental rabbits survived healthily and actively to the date of their sacrifice, and histopathological examination indicated that the copolymer is well tolerated by the brain tissue of rabbit [116].

Toxicity of ricinolic acid-based polyanhydride was studied in rats by implanting the polymer strips in subcutaneous, muscle, and brain tissues. It has been found that all animals were healthy throughout the experiment, and the implantation site or any other organ tested did not show any abnormal gross histopathological changes. Blood chemistry and blood count levels were similar for the treated, untreated, and control rats [16, 117–119]. Injectable P(SA:RA) 2:8 loaded with bupivacaine was evaluated for the efficacy and toxicity in producing motor and sensory block when injected near the sciatic nerve[38]. Histological evaluation of the sciatic nerves surrounding tissues (fat and muscle) and the major organs at day 3 and 7 did not showed evidence of active inflammatory reaction or tissue irritation. All the examined organs (lung, liver, heart, brain, and spleen) were normal throughout the period. In all these polymers, fatty acid components undergo extensive metabolism in the body and are mainly excreted in the form of carbon dioxide and minimally through urine and feces. The *in vitro* [120] and *in vivo* toxicity data point to the fact that these polymers are well tolerated by the tissues and can be generally considered to be a biocompatible class of polymers.

3.8
Fabrication of Delivery Systems

Two basic techniques can be utilized for incorporating drug into the polymer matrix, viz. melt mixing and using common organic solvent. Polyanhydrides have low melting point and good solubility in common organic solvents, for example, methylene chloride and chloroform allow for the easy dispersion of a drug into their matrix [121]. Polymer slabs loaded with drug can also be prepared by compression molding a powder containing the drug [122]. Similarly, one can injection mold the drug–polymer formulation into beads or rods [123]. Polymer films can

be prepared by solvent casting the polymer solution containing the drug onto Teflon-coated dish [124]. Microsphere-based delivery systems can be formulated by the common techniques including solvent removal, hot-melt encapsulation, and spray drying [125–132]. Some recent studies report nanoparticles formulation with polyanhydride and thus increasing the spectrum of application for polyanhydrides [133–137]. However, it is essential that all processes be performed under anhydrous conditions to minimize hydrolysis of the polymer.

3.9 Production and World Market

Polyanhydrides are not commercially available. One polyanhydride composition, poly(CPP-SA) (20:80), is manufactured at Guilford Pharmaceuticals in Baltimore on a kilogram scale, as part of the Gliadel implant for the treatment of brain tumors. Poly(dimer eurecic acid-*co*-sebacic acid) was developed for large-scale production by Abbott Lab (Chicago) for the fabrication of the Septacin implant for prevention of bone infections. The Septacin product was manufactured by injection molding of the polymer–drug composition. The development of this product was stopped for marketing reasons. Samples of polyanhydrides may be obtained by a request from the corresponding author.

3.10 Biomedical Applications

Polyanhydrides themselves and there hetero-copolymers with -amide, -ester, etc., have been used for diverse biomedical applications. Polyanhydrides find major application in controlled drug delivery. Delivery of chemotherapeutic drugs in cancer is the major area of research for localized delivery using polyanhydrides. There are about 60% of cancer patients with localized disease and it has been estimated that around 32% of localized cancer patients face recurrence, following initial treatment. Most of the anticancer drugs which are in clinical use do not have specific effects on invasiveness or the tendency to metastasize but they are only antiproliferative [138], and therefore, these drugs affect all the rapidly dividing cells including normal tissues and show dose-limiting toxic effects.

First-order targeting is increased delivery of drug to the body compartment, while second-order targeting is increased drug delivery to tumor cells; and intracellular delivery is third-order targeting [138]. First- and second-order targeting is achieved by local delivery using polyanhydrides through systems like implant, surgical paste, microspheres, etc. Drug delivery in brain tumor (Glioblastoma multiforme) is important aspect as many of the anticancer drugs are large, ionically charged or hydrophilic, and not able to cross the BBB; intolerably high systemic drug levels are required to achieve the therapeutic doses within CNS [139, 140]. Localized delivery resolves the problem associated with permeability of chem-

otherapeutic agents through BBB [141]. Various polyanhydrides and drug combinations have been used to obtain the optimum release profile and treat the brain tumor or glioma. Gliadel wafer is one of the most successful delivery systems using polyanhydride and is commercially available. Gliadel has been approved in 1996 by the US-FDA for the use as an adjunct to surgery to prolong survival in patients with recurrent Glioblastoma multiforme for whom surgical resection is indicated [142]. An additional approval from US-FDA in February 2003 has been granted for the use of Gliadel in patients with newly diagnosed high-grade malignant gliomas, as an adjunct to surgery and radiation. A study has been performed by Frazier *et al*. [143] to find the efficacy of local delivery of minocycline and systemic BCNU on intracranial glioma. Minocycline, an antiangiogenic agent, was incorporated in P(CPP:SA) at a ratio of 50:50 by weight and found that the combination of intracranial minocycline and systemic BCNU extended median survival by 82% compared to BCNU alone ($p < 0.0001$) and 200% compared to no treatment ($p < 0.004$). Polyanhydride matrix has been used to deliver heparin and cortisone acetate as antineoplastic agent. They have reported the inhibition of growth of 9L glioma and found out that in the presence of heparin and cortisone, and of cortisone alone, there was a 4.5- and 2.3-fold reduction, respectively, in the growth of 9L glioma [144]. A potential paclitaxel (taxol) formulation in polymeric disk of P(CPP:SA, 20:80) with 20–40% of taxol loading, and maintained concentration of 75–125 ng taxol/mg brain tissue, within 1–3 mm radius of the disk [145]. Another polyanhydride system for delivery of taxol has been formulated using P(FAD:SA, 50:50) but, due to the hydrophobic nature of the FAD, the release rate was very slow and therapeutic concentration could not be achieved [146]. 4-HC, a hydrophilic derivative of cyclophosphamide, with and without *t*-buthionine sulphoxine (inhibiting glutathione synthesis, which catalyzes inactivators of alkylating agents), was incorporated in P(FAD:SA) and found to be effective in rat intracranial 9L gliosarcoma and F98 glioma model [147–149]. Fluorodeoxyuridine, an antimetabolite, has also been optimally released from P(FAD-SA) polymer *in vitro* and *in vivo* [150]. Adriamycin incorporated in P(CPP:SA) has shown improved median survival in rat intracranial 9L glioma model [151]. Fifty percent 5-iodo-2′-deoxyuridine containing P(CPP:SA, 20:80) have been used successfully for radiosensitization of experimental human malignant gliomas [152] Methotrexate–dextran conjugate (to improve stability and inhibit degradation of MTX) when incorporated in P(FAD:SA) offered significant improvement over controls in rat intracranial 9L glioma [151]. Recently, antineoplastic RANse encapsulated in P(RA-SA) implants showed promising efficacy against 9L glioma, while evading neurotoxicity in the cerebellum. The controlled release of Amphibinases forms the potential for a new therapy against brain tumors [153]. Carboplatin and camptothesin are the other anticancer molecules which have shown promising results when incorporated in the P(CPP:SA) [154, 155]. Further, various chemotherapeutic drugs such as ciplatin, methotreaxte, etc., have been delivered using fatty acid-based polyanhydride in squamous cell carcinoma of head and neck. [16, 35, 156, 157].

Osteomyelitis is another disease condition where polyanhydride implant (Septacin) has been found successful in efficacious delivery of gentamicin clinically

[158–160]. Lately, another polyanhydride, poly(OAD/LOAD:SA) indicated its usefulness in delivering gentamicin and to treat chronic osteomyelitis [161]. Blends of PSA with PLA have also found potential as carriers for delivery of ofloxacin in osteomyelitis [162]. Because of controlled release behavior of polyanhydride implants, they find good application in regional anesthesia for clinical areas involving acute or chronic pain including postsurgical pain. Implants of P(CPP:SA) and P(FAD-SA) have been used for delivery of local anesthetics like bupivacaine [92], dibucaine, etc. [122].

Flexibility to control degradation rate and period with polyanhydrides gives opportunity to utilize them in various disease conditions. One such case is restenosis where drug release is required at local site for around 6 months. P(FAD:SA) have been used perivascularly to release heparin to microvascular anastomoses [124, 163]. It was found that the vessel potency rates were significantly greater in vessels treated with polyanhydride–heparin compared to controls, after surgery [163, 164]. PLA have been used to coat the P(FAD:SA) sheets to improve the release profile and strength of the films. [164]. Glaucoma is another disease where delivery of antifibrotic agent can prolong filtration surgery. Disks of P(CPP:SA) containing different drugs such as 5-fluorocil, 5-fluorouridine, taxol, and etoposide have been evaluated and some of the devices were very successful in maintaining intraocular pressure to the postsurgery level [165–168]. Polyanhydride microspheres have also been tried to deliver the drug in controlled manner in vitreoretinal disorders, to avoid the repeated intravite injection to achieve intraocular drug levels within the therapeutic range [169].

Besides the conditions described above, polyanhydrides have been used for many other applications. Delivery of macromolecules especially DNA, proteins, and peptides *via* polymer is an important issue. Delivery of DNA molecules for gene therapy is a challenge and nonviral carriers are always under search. Photocrosslinked polyanhydrides could allow repeated transfection, with an appropriate amount of DNA for the rate of local cell division and the cells capacity for DNA uptake [170, 171]. Bioadhesive nanoparticles of polyanhydrides were also found to have potential for oral delivery of DNA [172]. Polyanhydride matrices can be used for controlled delivery of proteins or polymer–drug conjugates. [173]. Polyanhydride-*co*-imides have been used for controlled release of bovine serum albumin as a model compound which suggest that polyanhydrides may be appropriate for delivery of many therapeutic proteins, including vaccine antigens [174–177]. Moreover, stability and activity of proteins and peptides can also be maintained by using polyanhydride as a carrier [128, 135, 178, 179]. Lucas *et al*. have done early trials on localized protein delivery, where they have incorporated water-soluble protein-possessing chondrogenic stimulating activity in polyanhydride polymeric vehicle. The delivery system was capable of inducing cartilage and bone up to 50% of the time. It was concluded that polyanhydride could be used as a controlled release delivery vehicle for soluble bioactive factors that interacts with local cell population [180]. PSA-*b*-PEG and (P[TMA-Glycine-*co*-SA]-b-PEG) were used as isolating layers for their good processing properties at room temperature. These polymers were advantageous for pulsatile protein delivery due to their pH sensitivity and appro-

priate erosion duration [181]. Kubek *et al*. incorporated an endogenous neuropeptide thyrotropin-releasing hormone (protirelin), and were first to provide evidence in support of *in situ* pharmacotherapy for potential delivery in intractable epilepsy and possibly other neurological disorders. [182] Cai *et al*. have synthesized a novel polyanhydride, P([CBF]-ASA), with 5-aminosalicylic acid (5-ASA) incorporated in the backbone. They hypothesized the potential of colon-specific delivery of 5-ASA moieties considering high drug loading (50.2% of 5-ASA moieties in the backbone) and degradation characteristics [183]. Localized intracerebral delivery of neurotransmitters using SA copolymer has also been tried and was concluded by authors that intracerebral polymeric drug delivery successfully reversed lesion-induced memory deficit and has potential as a neurological treatment for Alzheimer's disease and other neurological disorders [184].

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4
Poly(Ortho Esters)

Jorge Heller[1)]

4.1
Introduction

Poly(ortho esters) (POE), developed following the use of poly(glycolic acid) and poly(glycolic acid-*co*-lactic acid) copolymers, were first described in 1970 and have been under development since then. They were the first new biodegradable polymers synthesized specifically for drug delivery applications. Four different families have been developed as shown in Scheme 4.1.

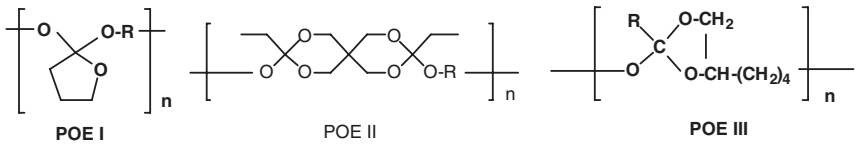
POE I was developed at the ALZA Corporation in the 1970s [1–4] and its synthesis is shown in Scheme 4.2. POE I undergoes a hydrolysis as shown in Scheme 4.3. Since a primary hydrolysis product is butyrolactone that rapidly hydrolyzes to butyric acid, and since poly(ortho esters) are acid-labile, the polymer undergoes an uncontrolled autocatalyzed hydrolysis resulting in rapid disintegration. To prevent that, a base such as sodium carbonate must be added. The need to use a base to stabilize the polymer, a difficult synthesis and unsatisfactory mechanical properties, has prevented the commercialization and this polymer is no longer under development.

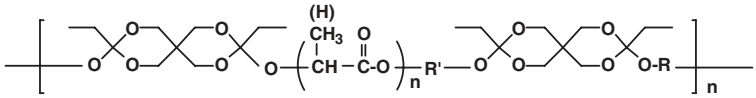
POE III is synthesized as also shown in Scheme 4.2 [5]. It has been extensively investigated in ocular applications [6]. Although the polymer has been found to be highly biocompatible and excellent drug release has been achieved, difficulties in achieving a reproducible synthesis and an inability to scale up the reaction have prevented its commercialization and this polymer system is also no longer under development.

However, POE II and POE IV are highly successful polymers that are currently undergoing commercialization and as of this writing, POE IV has completed a

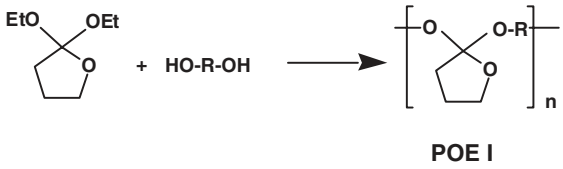
1) Deceased.

Handbook of Biodegradable Polymers: Synthesis, Characterization and Applications, First Edition. Edited by Andreas Lendlein, Adam Sisson.

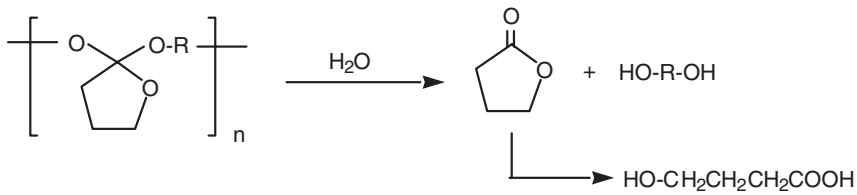




Scheme 4.1 The four families of poly(ortho esters).



Scheme 4.2 Synthesis of POE I and POE III.



Scheme 4.3 Hydrolysis of POE I.

Phase III clinical trial for the prevention of chemotherapy-induced immediate and delayed nausea and vomiting using the delivery of granisetron. It has also completed a Phase II clinical trial to treat postoperative pain using the delivery of mepivacaine. The developments of various proprietary products using POE II are also ongoing.

4.2
POE II

Even though ortho ester linkages are very hydrolytically labile, and indeed a water-soluble poly(ortho ester) will completely hydrolyze in a matter of hours, a hydrophobic polymer has a very long lifetime in water, as shown in Figure 4.1 [7].

Erosion rates of POE II can be adjusted by incorporating into the polymer acidic excipients such a suberic acid, but this method was never very successful. However, because the polymer is so labile in an aqueous environment, erosion rates can also be manipulated by controlling the hydrophilicity of the polymer by using hydrophilic diols such as triethylene glycol (TEG).

4.2.1
Polymer Synthesis

POE II is prepared by the reaction between the diketene acetal 3,9 diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane (DETOSU) as shown in Scheme 4.4 [8, 9].

DETOSU is not commercially available and is prepared by the rearrangement of diallyl pentaerytritol as shown in Scheme 4.5 by using either *n*-BuLi in ethylene

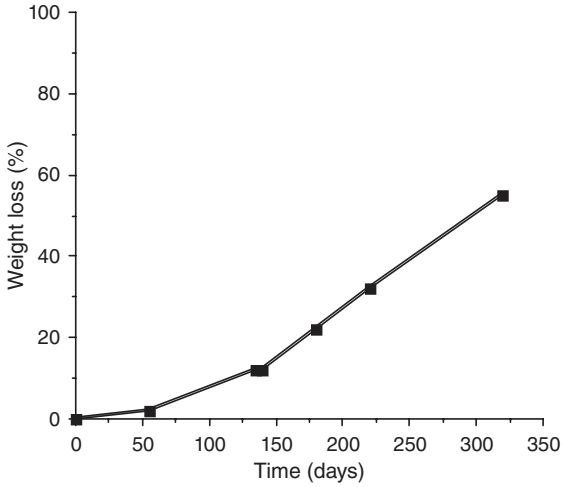
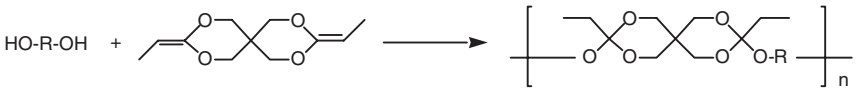
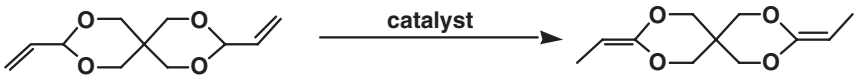


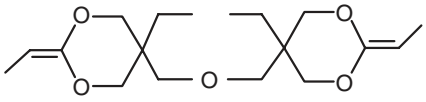
Figure 4.1 Weight loss as a function of time for a polymer prepared from 3,9-dimethylene-2,4,8,10-tetraoxaspiro [5.5] undecane and HD; 0.05 M phosphate buffer, pH 7.4, 37 °C.



Scheme 4.4 Synthesis of POE II.



Scheme 4.5 Synthesis of 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane (DETOSU).



Scheme 4.6 Structure of di(5-methyl-2-ethylidene[1.3]dioxan-5yl)methyl ether.

diamine [9], KOtBu in ethylene diamine [10], a photochemical rearrangement [11], or an $Ru(PPh_3)_3Cl_2$ catalyzed rearrangement [12].

4.2.1.1 Rearrangement Procedure Using an $Ru(PPh_3)_3Cl_2$ Na_2CO_3 Catalyst

A round-bottom flask was charged with 224 g of 3,9-divinyl-2,4,8,10-tetraoxaspiro[5.5] undecane, 0.8 g dichlorotris(triphenylphosphine)ruthenium ($Ru(PPh_3)_3Cl_2$) and 0.8 mg Na_2CO_3. The mixture was heated at 120 °C under nitrogen for a minimum of 16 h. The progress of the reaction was followed by ^1H NMR in D_2O. After cooling to room temperature, the product was distilled under reduced pressure and purified by recrystallization from *n*-pentane containing a few drops of triethylamine. To obtain a polymerization-grade product, two more recrystallizations were required.

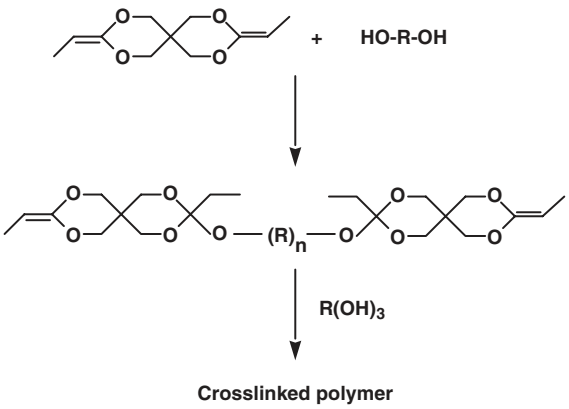
4.2.1.2 Alternate Diketene Acetals

Even though the great majority of the work was carried out using DETOSU, another diketene acetal, di(5-methyl-2-ethylidene[1.3]dioxan-5yl)methyl ether, was briefly investigated. The structure of this diketene acetal is shown in Scheme 4.6.

Polymers prepared using this diketene acetal will be discussed under Section 7.1.

4.2.1.3 Typical Polymer Synthesis Procedure

In a dry-box, 2.163 g (15 mmol) of *trans*-cyclohexanedimethanol (CDM), 4.727 g (40 mmol) of 1,6-hexanediol (HD), and 6.760 g (45 mmol) of TEG were dissolved in 40 g of tetrahydrofuran (THF). Then, 21.437 g (101 mmol) of 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane were weighed into a round-bottom flask and added to the diols solution with the aid of 20 g THF, in several portions. The flask was removed from the dry-box, rapidly connected to a condenser and nitrogen inlet, and a few drops of *p*-toluenesulfonic acid solution (10 mg/mL) added. After the exotherm subsided, the solution was slowly poured into 3 L of methanol, containing about 1000 ppm of triethylamine. After isolation by filtration and drying in a vacuum oven at 40 °C for 24 h, the yield was 32.1 g (89.7%).



Scheme 4.7 Synthesis of crosslinked POE II.

4.2.2 Drug Delivery

4.2.2.1 Development of Ivermectin Containing Strands to Prevent Heartworm Infestation in Dogs

The most extensive investigation of POE II for drug delivery was carried out at the former Interx Laboratories of Merck (Kansas City, MO). In this application, a crosslinked polymer was used.

A crosslinked POE II can be prepared as shown in Scheme 4.7 [13]. Briefly, a prepolymer of DETOSU and a diol is prepared so that the prepolymer has ketene acetal end-groups. This prepolymer is then reacted with a triol, or polyols having a functionality greater than 2 to form a crosslinked network.

In this particular instance, the objective was to develop an ivermectin device capable of preventing heartworm infestation in dogs for at least 6 months [14]. Since ivermectin is not stable at 140–155 °C, extrusion of strands was not a viable method so that a device based on a crosslinked POE II was developed. Ivermectin has three hydroxyl groups and can thus compete with the crosslinker, 1,2,6-hexanetriol, for the ketene acetal end-groups. Consequently, in the final device, ivermectin is chemically bound to the matrix.

4.2.2.2 Experimental Procedure

The poly(ortho ester) matrix was prepared by a two-step procedure involving the preparation of a low molecular weight prepolymer followed by a crosslinking reaction. HD (3.72 g, 31.5 mmol) was dissolved in 20 mL of freshly distilled (from sodium) THF. DETOSU (10.03 g, 47.3 mmol) in a 50 mol% excess over HD was added via an oven-dried syringe. The mixture was refluxed 1 h under nitrogen to form a ketene acetal end-capped prepolymer. The THF was removed at room temperature under reduced pressure (ca. 4 mmHg). An aliquot (3.122 g) of the prepolymer was triturated with 0.151 g of magnesium hydroxide (hydrolytic

stabilizer) and 0.329 g of ivermectin. The crosslinking agent, *n*-hexane-1,2,6-trio1 (0.289 g), was mixed with the composite and quickly extruded into l/32″ ID FEP tubing (Cole-Parmer) and cured at 70 °C for 16 h. The tubing was cut and removed to yield highly flexible elastomeric matrices which were cut to length. Drug-free matrices were prepared in similar fashion.

4.2.2.3 Results

The behavior of the strands was investigated in dogs and the rate of ivermectin release was estimated from an implant retrieval study since plasma levels were below assay detection limits. The *in vivo* release rate was approximately 38 μg/month/cm of device. A correlation of the amount of drug remaining in the device with the amount of residual polymer suggested that erosion was a major determinant in the release of ivermectin, as would be expected for a system where ivermectin is chemically bound to the polymer.

On the basis of the data obtained, it was concluded that the crosslinked strands are capable of providing canine heartworm profilaxis for more than 6 months [14]. Unfortunately, it was not possible to develop devices that would erode in a predictable and reproducible fashion so that this system was never commercialized.

4.3 POE IV

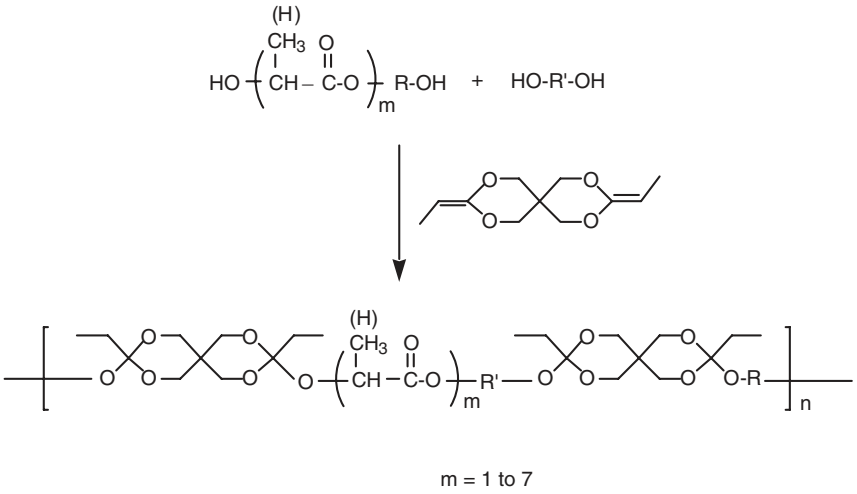
POE IV was developed to overcome difficulties in controlling the rate of erosion of POE II and to make it more generally useful.

4.3.1 Polymer Synthesis

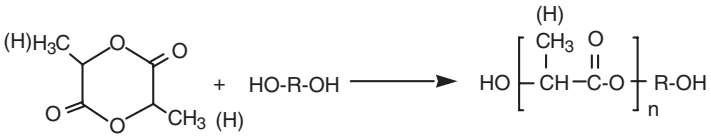
POE IV is prepared by the reaction between the diketene acetal DETOSU, a diol, or mixture of diols and a latent acid diol, as shown in Scheme 4.8 [15]. An alternate diketene acetal described under Section 4.2.1 and a diol can also be used.

4.3.1.1 Typical Polymer Synthesis Procedure

In a dry-box, 2.163 g (15 mmol) of *trans*-CDM, 4.727 g (40 mmol) of HD, 6.007 g (40 mmol) of TEG, and 1.041 g (5 mmol) of the triethylene glycol glycolide (TEG-GL) were dissolved in 40 g of THF. Then, 21.437 g (101 mmol) of 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane were weighed into a round-bottom flask and added to the diols solution with the aid of 20 g THF, in several portions. The flask was removed from the dry-box, rapidly connected to a condenser and nitrogen inlet, and a few drops of *p*-toluenesulfonic acid solution (10 mg/mL) added. After the exotherm subsided, the solution was slowly poured into 3 L of methanol, containing about 1000 ppm of triethylamine. After isolation by filtration and drying in a vacuum oven at 40 °C for 24 h, the yield was 32.1 g (89.7%).



Scheme 4.8 Synthesis of POE IV.



Scheme 4.9 Synthesis of latent acid based on lactide and a diol.

4.3.1.2 **Latent Acid**

The latent acid is prepared by an uncatalyzed high-temperature reaction between a diol and ether lactide, or glycolide as shown in Scheme 4.9 [16]. Mainly due to transesterification reactions, a mixture of products is obtained, as shown in Figure 4.2 [17]. The exact structure of the latent acid is not important and it is the total concentration of the α-hydroxy acid segments in the polymer that controls erosion rate.

4.3.1.3 **Experimental Procedure**

Into a round-bottom flask sealed with a rubber septum, 7.25 g (50 mmol) of DL-lactide and 8.713 g (50 mmol) of 1,10-decanediol were introduced under an argon atmosphere. The mixture was vigorously stirred for 3 days at 160 °C. The viscous diol–lactide was used without further purification.

4.3.2 **Mechanical Properties**

The ability to use diols having different structures allows the preparation of polymers having an extraordinarily broad range of physical properties, and materials

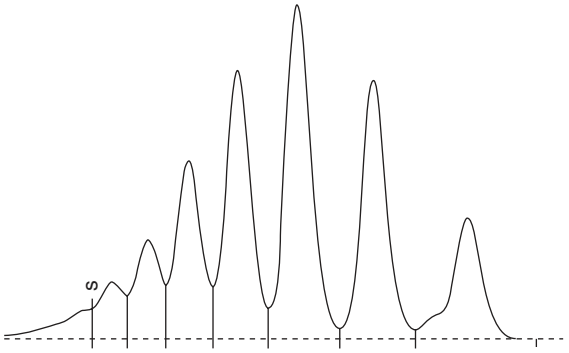


Figure 4.2 Gel permeation chromatograph of reaction products between lactide and TEG. Reprinted from [17], p. 1022, with permission from Elsevier.

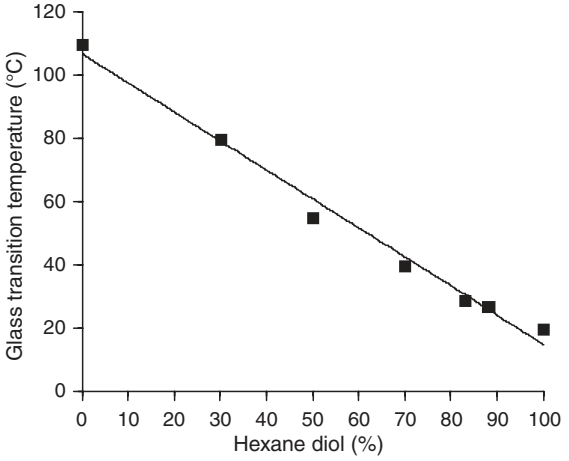


Figure 4.3 Glass transition temperature of 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, *trans*-CDM, HD polymer as a function of mol% HD.

ranging from hard, solid materials to viscous ointment-like materials can be prepared.

One of the more useful methods of achieving control over mechanical properties is to use a mixture of a rigid diol, for example, *trans*-CDM, and a flexible diol, for example, HD. When the glass transition temperature is determined for mixtures ranging from pure rigid diol to pure flexible diol, the plot shown in Figure 4.3 is obtained [18]. When linear, aliphatic diols having varying number of methylene groups are used, the plot shown in Figure 4.4 is obtained [19].

Figures 4.3 and 4.4 have been generated with POE II that has no latent acid in the polymer backbone. When POE IV is used, the latent acid in the polymer backbone does have a significant effect on the glass transition temperature, as shown

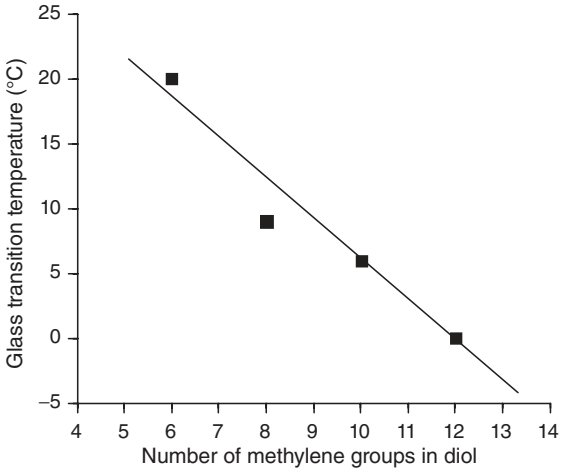


Figure 4.4 Effect of diol chain length on the glass transition temperature of polymers prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane and α,ω-diols.Reprinted from [19], p. 47, with permission from Harwood Academic Publishers.

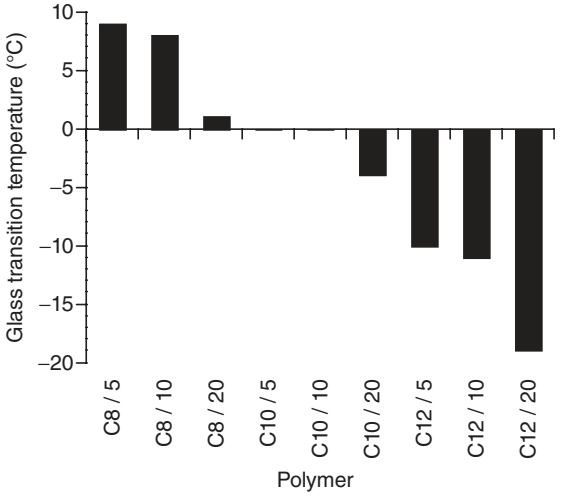


Figure 4.5 Glass transition temperatures for poly(ortho ester) prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane and *n*-octanediol, *n*-decanediol, and *n*-dodecanediol, each with 5, 10, and 20 mol% of the corresponding lactide. Reprinted from [17], p. 1025, with permission from Elsevier.

in Figure 4.5 [17]. Thus, both the diol structures, the latent acid diol structure and their ratios must be considered when designing polymers having desired thermal and mechanical characteristics.

The ability to vary mechanical properties by proper choice of diols allows the synthesis of a wide range of materials, but the two most useful ones are solid polymers and gel-like materials.

4.4
Solid Polymers

4.4.1
Fabrication

A successful POE drug delivery system requires the development of suitable fabrication methods that can produce devices able to achieve the desired drug release profiles. Desired release profiles that are free from drug burst and are reasonably linear can best be achieved with devices that are fabricated to minimize internal porosity, and where the drug is uniformly dispersed in the matrix with minimal particle-to-particle contact.

There are many different types of solid devices used in controlled drug delivery. The two most often used are microspheres and strands prepared by an extrusion process. Of these, strands prepared by extrusion have a number of significant advantages. Dominant among these is the ability to fabricate devices without the use of solvents, and the ability to prepare dense devices with drugs that are uniformly dispersed along the length of the strand.

Extrusion requires the use of moderately elevated temperatures and a typical small-scale extrusion requires about 20–30 min. For this reason, it was of interest to investigate potential changes in molecular weight as a function of time by sectioning the entire extruded strand into 10 mm pieces and determining the molecular weight of selected pieces. Results of one such study are shown in Figure 4.6 [20].

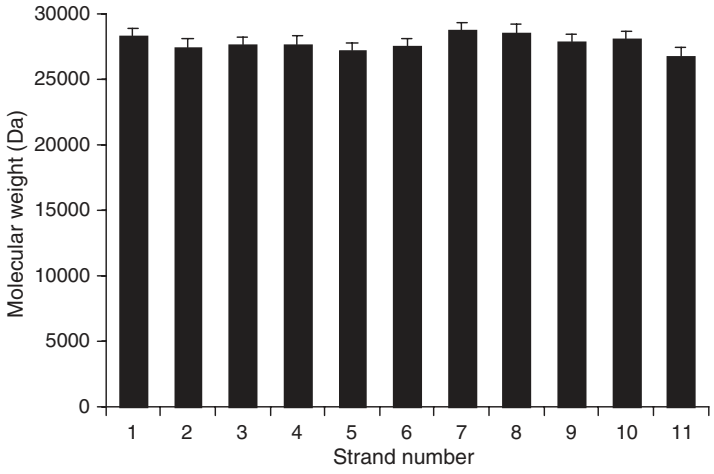


Figure 4.6 Molecular weight of each segment of an entire extruded strand cut into 10×1 cm sections along the entire length of the strand. Polymer prepared from 3,9 diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, *cis/trans*-CDM, TEG, 1,10-decanediol, and TEG-GL (100/40/10/49.9/0.1). Reprinted from [20], p. 98, with permission from CRC Press.

In this particular case, there was no significant change in molecular weight along the length of the extruded strand despite a long exposure to 95 °C, the extrusion temperature. Based on these studies, POE IV is found to be suitable for the preparation of extruded strands, provided that the temperature does not exceed about 100 °C.

Because POE II and IV are readily soluble in solvents such as methylene chloride, ethyl acetate, or THF, microspheres can be easily prepared using conventional procedures.

4.4.2 Polymer Storage Stability

As shown in Figure 4.7, poly(ortho esters) have excellent stability and are stable at room temperature, when stored under anhydrous conditions [17]. The particular polymer used in this stability study was a hydrophilic polymer containing 40 mol% latent acid that had been ground to produce microparticles thus greatly increasing surface area. This is a very rapidly eroding polymer that will completely erode in a matter of a few days if placed in an aqueous buffer. Despite this high reactivity, when stored under anhydrous conditions, it is stable for a number of months.

4.4.3 Polymer Sterilization

The polymer is also relatively stable when sterilized by irradiation [17]. As shown in Figure 4.8, there is a decrease in molecular weight after irradiation, but the

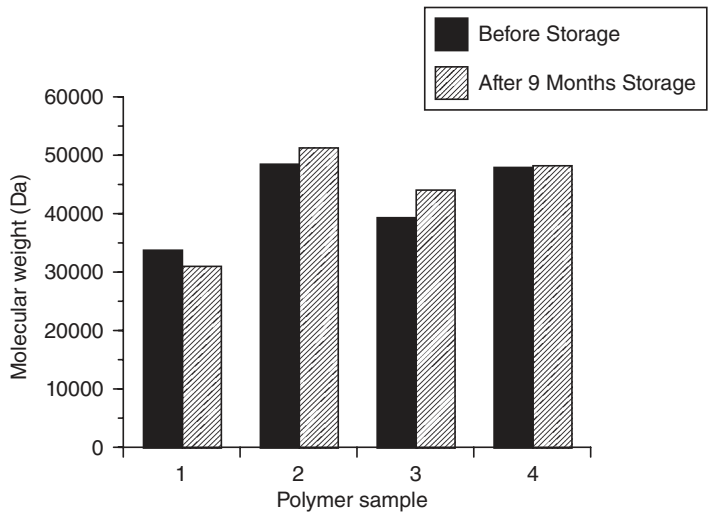


Figure 4.7 Stability of a polymer prepared from 3,9 diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, *cis/trans*-CDM, TEG, and TEG-GL (100/35/25/40) stored at room temperature and under anhydrous conditions. Reprinted from [17], p. 1026, with permission from Elsevier.

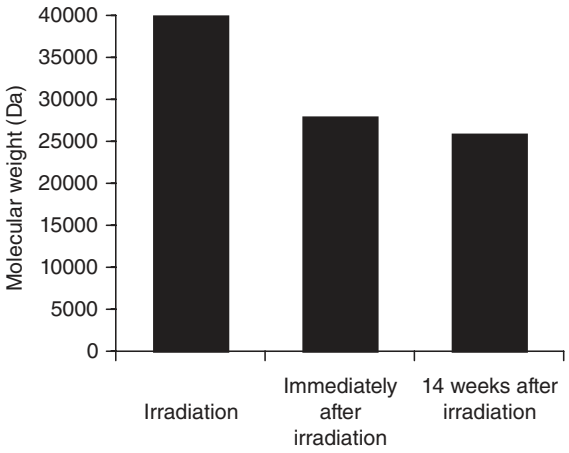


Figure 4.8 Effect of β-irradiation at 24 kGy on a poly(ortho ester) prepared from 3,9 diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, *trans*-CDM, HD, TEG, and TEG-GL (15/40/40/5). Polymer stored postirradiation at 5 °C in a dessicator. Reprinted from [17], p. 1026, with permission from Elsevier.

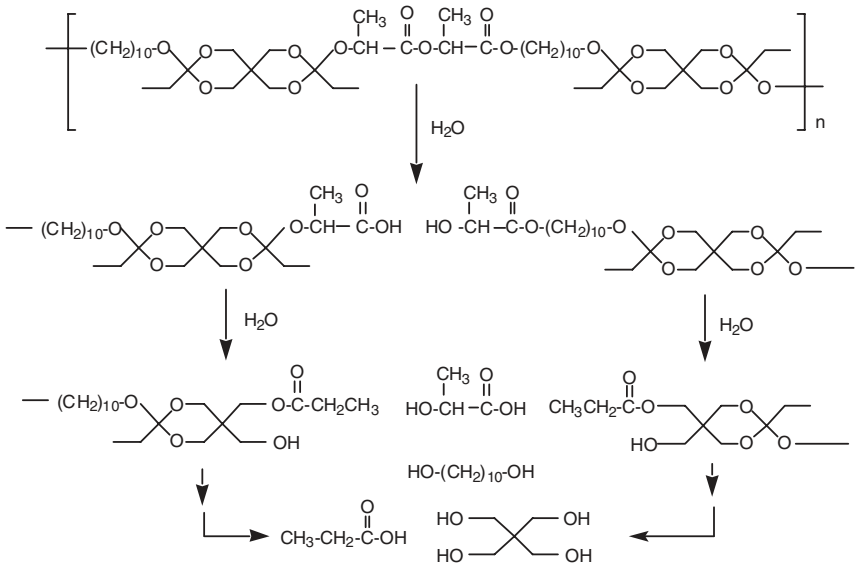
decrease is of the same order of magnitude as that observed with other bioerodible polymers. Because irradiation generates free radicals that in a solid matrix can be long-lived, stability studies were extended to 3 months to determine if postirradiation chain cleavage takes place. Thus, the polymer is stable after the initial drop in molecular weight and electron paramagnetic resonance (EPR) studies have shown that free radicals dissipate in less than 24 h.

4.4.4 Polymer Hydrolysis

The hydrolysis proceeds in three consecutive steps [21]. In the first step, the low short latent acid segment, either glycolic acid or lactic acid, in the polymer backbone hydrolyzes to generate a polymer fragment containing a carboxylic acid endgroup that will catalyze ortho ester hydrolysis. A second cleavage produces free glycolic, or lactic acid that also catalyzes hydrolysis of the ortho ester links. Further hydrolysis of the polymer then proceeds 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.

Scheme 4.10 shows details of polymer hydrolysis [21]. In this particular case, and for simplicity sake, we have depicted the latent acid as a dimer of lactic acid.

The most significant finding of the hydrolysis study is the linearity of weight loss and the concomitant release of lactic and propionic acid as shown in Figure 4.9. While linear rate of weight loss alone does not necessarily indicate surface erosion [22], the concomitant linear weight loss and release of lactic acid argues



Scheme 4.10 Details of polymer hydrolysis. For simplicity, the latent acid has been depicted as a dimer of lactic acid.

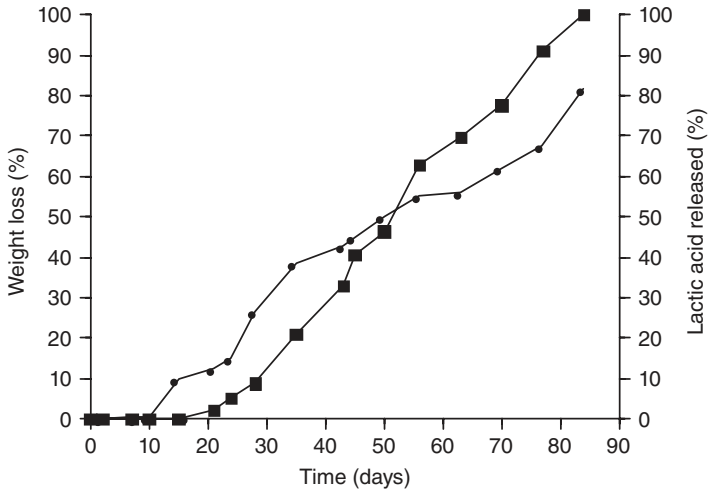


Figure 4.9 The relationship between lactic acid release (J) and weight loss (B) for a poly(ortho ester) prepared from 3,9 diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, and a 100/70/30 mixture of 1,10-decanediol and 1,10-decanediol lactide; 0.13 M, pH 7.4 sodium phosphate buffer at 37 °C. Reprinted from [21], p. 304, with permission from American Chemical Society.

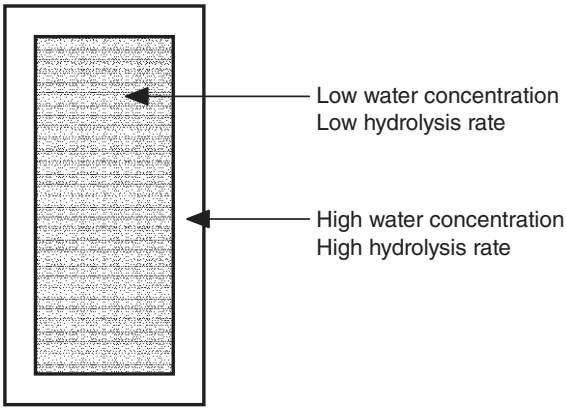


Figure 4.10 Schematic of proposed erosion mechanism.

convincingly for a process confined predominantly to the surface layers of the polymer matrix.

The erosion process is shown schematically in Figure 4.10 [20]. Surface erosion demands a much higher rate of hydrolysis in the surface layers of a solid device as compared to the interior of the device, and pure surface erosion can only take place if no hydrolysis occurs in the interior of the device. This can only take place if no water penetrates the polymer and since no polymer is so hydrophobic that no water can penetrate the matrix, some hydrolysis will always take place in the interior of the matrix. However, there is a significant difference in hydrolysis rates between surface and interior due to differences in water concentration. In the surface layers, the concentration of water is fairly high, and the rate of hydrolysis is also high. But there is a progressively lower concentration of water with deeper layers, so the rate of hydrolysis will also progressively decrease with end-result being that erosion is confined predominantly to the surface layers.

Implicit in the use of latent acid is an expectation that an increased amount of latent acid in the polymer backbone would translate into increased rate of polymer erosion. That this is actually the case can be seen in Figure 4.11 where the latent acid content was varied from 5 to 0.1 mol% [23]. Clearly, there is a correlation between latent acid content and polymer erosion rate.

An erosion process that is confined predominantly to the surface layers has a number of important benefits. First, if the drug is well immobilized in the matrix, its release is controlled by polymer erosion so that an ability to control polymer erosion translates into an ability to control rate of drug release. Second, because drug release is controlled by polymer erosion, drug release and polymer erosion take place concomitantly and when drug release has been completed, no polymer remains. Third, because most of the hydrolysis occurs in the outer layers of the device, acidic hydrolysis products can diffuse away from the device and do not accumulate in the bulk material. Thus, the interior of the matrix does not become

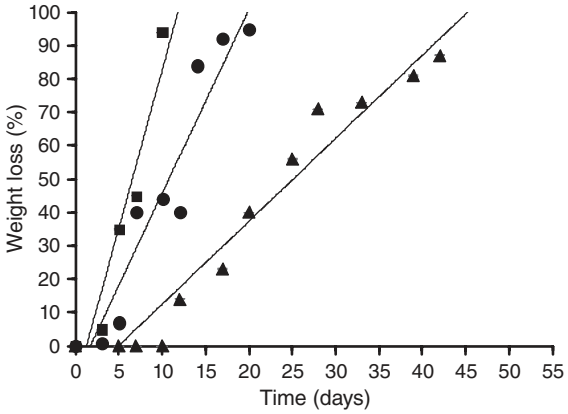


Figure 4.11 Effect of latent acid content on erosion rates for a polymer prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, CDM, decanediol, TEG, and TEG-GL. (B) 40/45/10/5; (J) 40/49/10/1; (H) 40/49.9/10/0.1.Reprinted from [23], p. 1629, with permission from American Chemical Society.

highly acidic, as is the case of poly(lactide-*co*-glycolide) copolymers, or poly(lactic acid) [24], and acid-sensitive drugs can be released without loss of activity.

4.4.5 Drug Delivery

A great many studies have been carried out and only the more important ones will be described here.

4.4.5.1 Release of Bovine Serum Albumin from Extruded Strands

As discussed in Section 4.1., POEs can be readily extruded and since the glass transition temperature can be adjusted to any desired value, extrusion temperatures can be tailored for the protein of interest. Of particular interest is a procedure by which finely ground polymer and a micronized protein are intimately mixed and then extruded into thin strands at temperatures low enough so that protein activity is not compromised.

Figure 4.12 shows release of FITC-BSA from extruded strands and the weight loss of the strands as a function of time [25]. Three features are notable. First, there is only a minimal burst despite the fact that 15 wt% of a water-soluble material has been incorporated. Second, there is a significant lag before release of FITC-BSA begins. And third, release is linear and concomitant with weight loss.

While a long induction period may be desirable in some applications, for example, in vaccine delivery, for general protein delivery it is not desirable and an investigation to eliminate the induction period was carried out. One means of accomplishing this is to use an AB block copolymer of poly(ortho ester) and polyethylene glycol. When such a block was used, BSA release kinetics shown in Figure 4.13 was obtained [25].

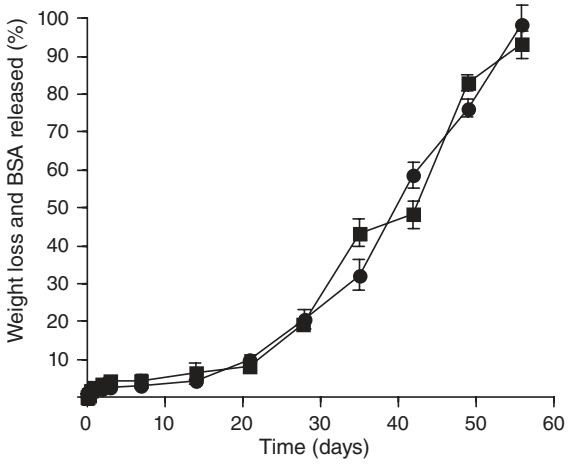


Figure 4.12 Release of FITC-BSA (H) and weight loss (B) from a poly(ortho ester) prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, 1,4-pentanediol, and HD glycolide (100/95/5). Strands, 1 × 10 mm, extruded at 70 °C. 0.01 M PBS, pH 7.4, 37 °C. FITC-BSA loading 15 wt%. Reprinted from [25], p. 34, with permission from Elsevier.

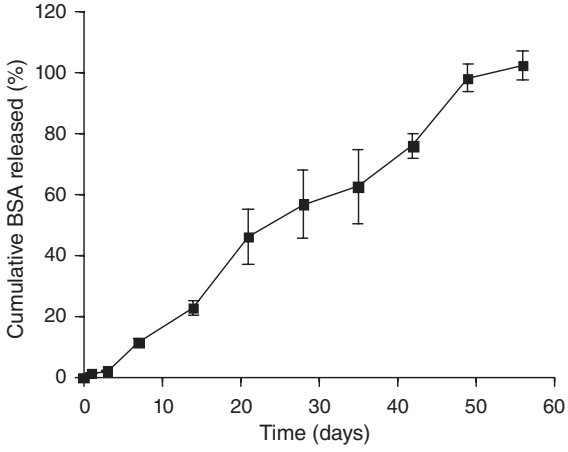
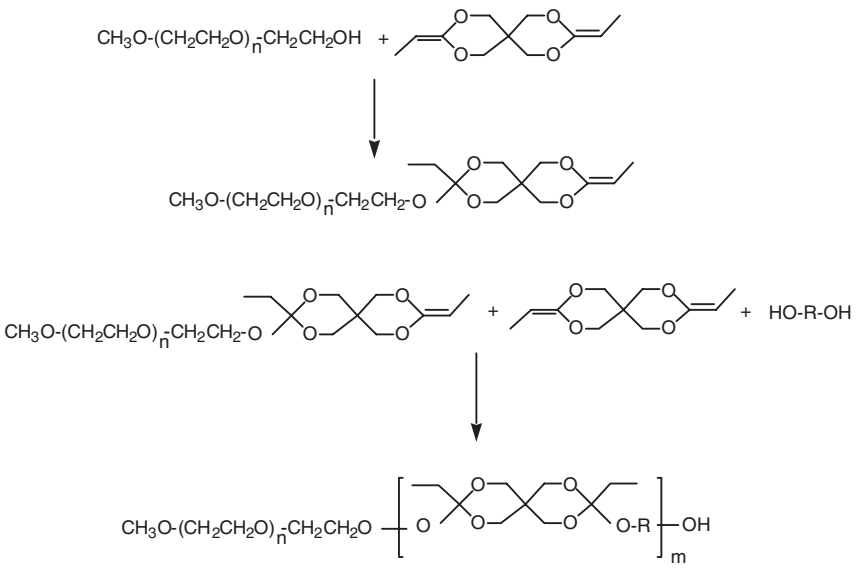


Figure 4.13 Release of FITC-BSA from an AB block copolymer containing 6 wt% 2 kDa polyethylene glycol. Poly(ortho ester) prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, 1,3-propanediol, and TEG-GL (100/85/15). Strands, 1 × 10 mm, extruded at 70 °C. 0.01 M PBS, pH 7.4, 37 °C. FITC-BSA loading 15 wt%. Reprinted from [25], p. 36, with permission from Elsevier.

Clearly, this represents a significant improvement and demonstrates the potential of AB, or ABA block copolymers of POE and polyethylene glycol as matrices for the controlled release of proteins. However, this potential has not yet been fully exploited. The AB block copolymer was prepared as shown in Scheme 4.11 [25].



Scheme 4.11 Synthesis of AB block copolymer.

4.4.5.2 **Experimental Procedure**

Under anhydrous condition, a mixture of 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane (21.225 g, 100 mmol) and the monomethyl ether of a 2-kDa polyethylene glycol (2 g, 1 mmol) was dissolved in 50 mL of THF. To the solution was added 0.05 mL of a *p*-toluenesulfonic acid solution (20 mg/mL) in THF. The solution was stirred using a magnetic stirrer and warmed to about 50 °C. After 15 min, another 0.05 mL of a *p*-toluenesulfonic acid solution was added, and the reaction was allowed to proceed at 50 °C for an additional 30 min. Next, 1,3-propanediol (6.436 g, 84.5875 mmol) and 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane (3.108 g, 11.684 mmol) were added to the solution with the aid of 20 mL THF. After the addition of another portion of 0.05 mL *p*-toluenesulfonic acid solution, the reaction was stirred for an additional 1 h. The reaction mixture was then added to 600 mL hexane and the precipitated polymer was collected and dried overnight in a vacuum oven at about 40 °C.

4.4.6
Delivery of DNA Plasmid

The delivery of DNA from poly(ortho esters) is of particular interest because an erosion-controlled release as well as an essentially neutral pH in the interior of the matrix have been demonstrated. Thus, the incorporation of DNA into the polymer and its subsequent release should not adversely affect DNA integrity.

Microspheres of 5 μm were prepared by a double emulsion method [26]. When the microspheres were placed in a pH 7.2 buffer and release of DNA

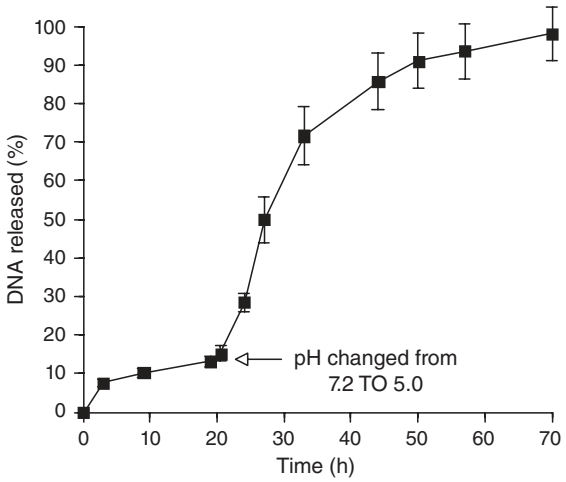


Figure 4.14 Release of DNA from a poly(ortho ester) prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, TEG, 1,2-propane diol, and TEG-GL (100/35/15/45/5). Microspheres, 5 μm, phosphate buffer (pH 7.4) or sodium acetate buffer (pH 5.0) at 37 °C.

followed using the pico green method, release was slow, corresponding to slow polymer erosion, as shown in Figure 4.14 [27]. However, when the pH of the buffer was changed to 5.0, the pH of endosomes, an immediate and significant acceleration of DNA release was noted. Since a lowered pH results in an increased erosion rate, this plot provides unequivocal evidence of an erosion-controlled DNA release.

4.4.6.1 **DNA Plasmid Stability**

As analyzed by gel electophoresis, DNA plasmid retained its active conformation (supercoiled and relaxed) when released from the POE microspheres placed into a pH 7.4 buffer and also that remained in the microspheres. However, when the microspheres were placed into a pH 5.0 buffer, significant damage to the DNA plasmid was noted. This is consistent with the known acid sensitivity of DNA. The DNA plasmid remaining in the microspheres dispersed in the pH 5.0 buffer retained its active conformation.

This is a significant finding indicating that the internal pH within the poly(ortho ester) matrix must be above pH 5.0 and that the microspheres are able to protect the DNA plasmid from a low pH external environment.

4.4.6.2 **Microencapsulation Procedure**

Microspheres were prepared by a modified water-in-oil-water double emulsion, solvent evaporation procedure. The two phases consisting of 250 μL of DNA solution (250 mg of DNA) and 7 mL of methylene chloride containing 200 μg POE were

emulsified by sonication for 10 s at room temperature. The primary emulsion temperature was then lowered below the freezing point of the aqueous inner phase by liquid nitrogen immersion, and 50 mL of a 5% PVA solution (4–7 °C) was added and homogenized at 5000–9000 rpm for 14 s. After homogenizing, the resulting emulsion was diluted in 100 mL of 1% PVA and the system stirred magnetically for 3 h to allow for evaporation of the organic solvent. Microspheres were finally collected by centrifugation and washed three times with water to remove excess PVA. All PVA solutions were adjusted to the osmotic pressure of the inner aqueous phase using agents such as saccharides. The microspheres were resuspended in approximately 1 mL of water, frozen in liquid nitrogen and lyophilized at room temperature for 24 h.

4.4.7
Delivery of 5-Fluorouracil

Unlike BSA or DNA that are high molecular weight, water-soluble molecules, 5-fluorouracil (5FU) is a small water-soluble molecule. Therefore, there is the potential for significant diffusion from the polymer. However, as shown in Figure 4.15, when 5FU release from thin wafers and weight loss of the wafers was determined, within experimental error, both processes occurred concomitantly suggesting that the dominant drug release mechanism was polymer erosion [28].

This is an encouraging result and indicates that a wide range of therapeutic agents can be delivered from poly(ortho esters), as has been validated in numerous studies.

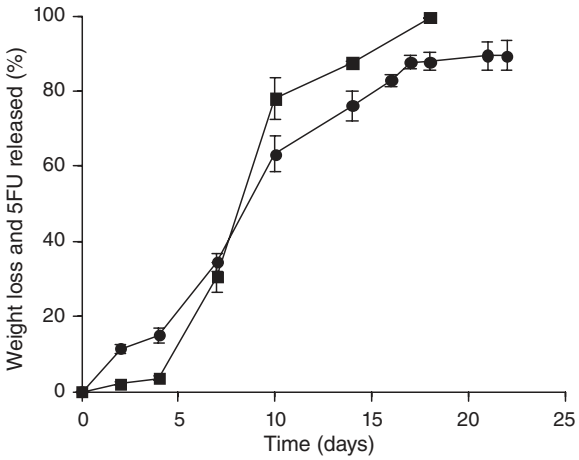


Figure 4.15 Polymer weight loss (H) and 5-fluorouracil (5-FU) release (B) from a polymer prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, 1,3-propanediol, and TEG-GL (90/10). Drug loading 20 wt%. 0.05 M phosphate buffer, pH 7.4, 37 °C. Reprinted from [28], p. 126, with permission from Elsevier.

4.5
Gel-Like Materials

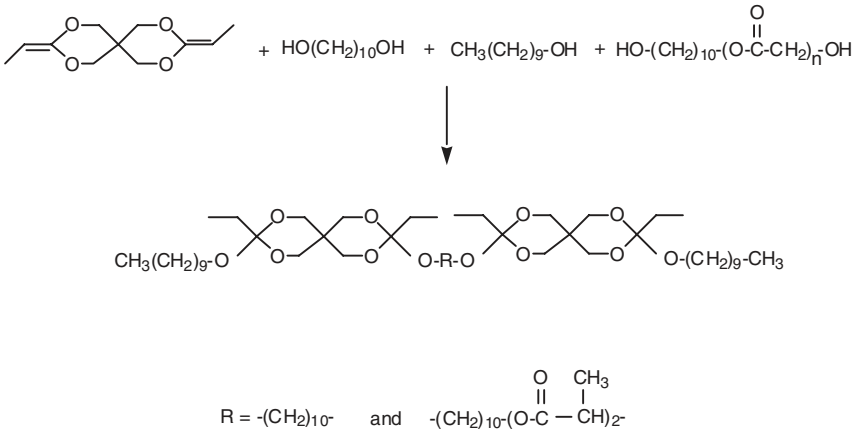
To prepare gel-like materials, it is necessary to use highly flexible diols and their viscosity must be limited by having molecular weights no higher than about 6 kDa. To limit toxicology studies required for regulatory approval, only two diols, TEG and 1,10-decanediol, were used. Polymers based on TEG produce hydrophilic materials, while polymers based on 1,10-decanediol produce hydrophobic materials [29].

The most significant advantage of gel-like materials is the ability to incorporate therapeutic agents at ambient temperature and without the use of solvents by a simple mixing procedure. Mixing can be accomplished on a small scale by using a mortar and pestle, but on a somewhat larger scale it is better carried out using a three roll mill [19].

4.5.1
Polymer Molecular Weight Control

Polymer molecular weight control can be achieved by using an excess of diol relative to the diketene acetal, or by using a chain-stopper. When a chain-stopper is used, a calculated amount of a monofunctional alcohol is used [30]. As shown in Scheme 4.12, when *n*-decanol is used as a chain-stopper in combination with 1,10-decanediol, both polymer ends have *n*-decanol residues so that a chain-stopped material is somewhat more hydrophobic relative to a stoichiometry-controlled material that has terminal hydroxyl groups.

The use of chain-stoppers allows excellent and reproducible molecular weight control by varying the ratios of 1,10-decanediol to *n*-decanol as shown in Figure 4.16 [30]. The existence of terminal methyl groups has been established by ^{1}H NMR studies [30].



Scheme 4.12 Use of a monofunctional alcohol as chain stopper to control molecular weight.

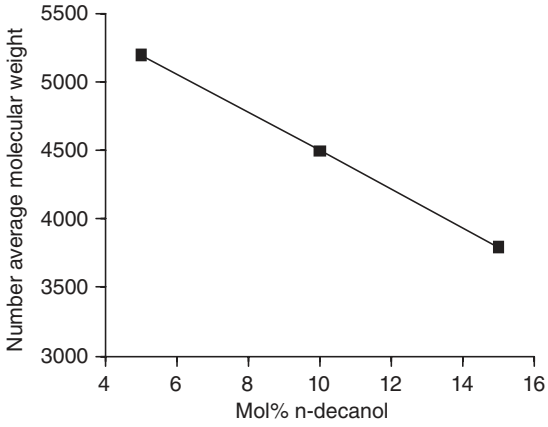


Figure 4.16 Effect of *n*-decanol on the molecular weight of a poly(ortho ester) prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro [5.5] undecane, 1,10-decanediol and 1,10-decanediol lactide (100/70/30).

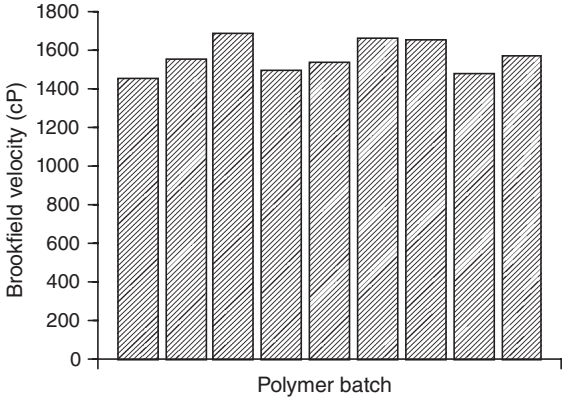


Figure 4.17 Variation in Brookfield viscosity for nine typical preparations at 25 °C. Injectable formulation prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5] undecane, TEG, and TEG-GL (60/50/50). Formulation contains 20 wt% monomethoxy polyethylene glycol, molecular weight 550. Reprinted from [31], p. 4399, with permission from Elsevier.

Because the principal means of administration of gel-like materials is by injection, preparation of materials having reproducible viscosities is important. Synthesis reproducibility as measured by Brookfield viscosity for a number of different preparations is shown in Figure 4.17 [31]. Clearly, the synthesis is sufficiently reproducible to assure that the same viscosity materials can be repeatedly prepared.

4.5.2 Polymer Stability

Figure 4.18 shows changes in molecular weight of a gel-like polymer after storage at room temperature under anhydrous conditions for 9 months [31]. As with the solid polymers, within experimental error, there is no change.

Figure 4.19 shows the effect of irradiating the polymer at a dose of 22.9 to 25.6 kGy [31]. Within experimental error, no changes in molecular weight could be detected. This is consistent with previous finding for POE III and indicates that low molecular weight polymers, unlike their high molecular weight analogs, do not significantly change molecular weight on irradiation.

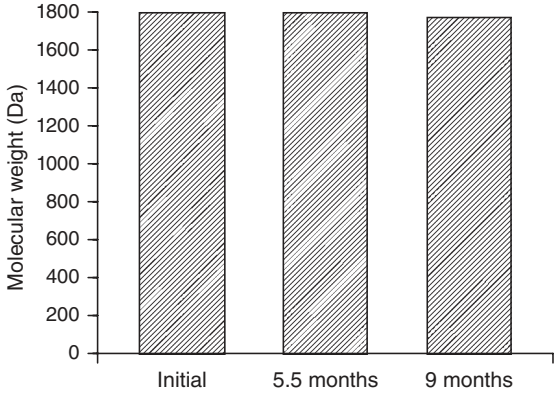


Figure 4.18 Room temperature stability for a polymer prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane, TEG, and TEG-GL (60/50/50). Material stored under anhydrous conditions. Reprinted from [31], p. 4399, with permission from Elsevier.

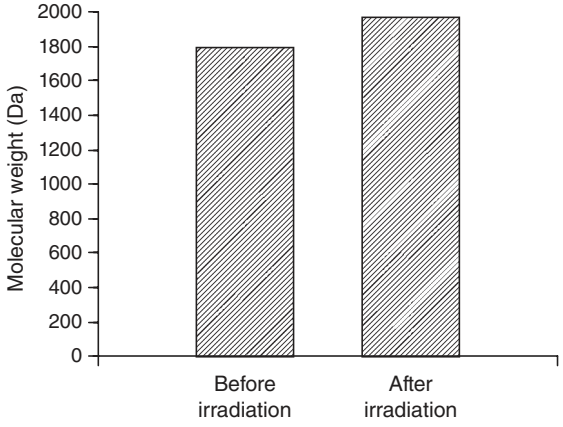


Figure 4.19 Stability of a polymer prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5] undecane, TEG, and TEG-GL (60/50/50) irradiated at 24 kGy. Reprinted from [31], p. 4400, with permission from Elsevier.

4.5.3 Drug Delivery

Gel-like materials based on POE IV constitute AP Pharma's "Biochronomer" delivery technology, and a Phase III clinical trial for the delivery of granisetron, an established 5-HT_3 receptor antagonist, to prevent chemotherapy-induced nausea and vomiting (CINV) has just been completed. In addition, a Phase II clinical trial to treat postoperative pain using the analgesic agent mepivacaine has also been completed.

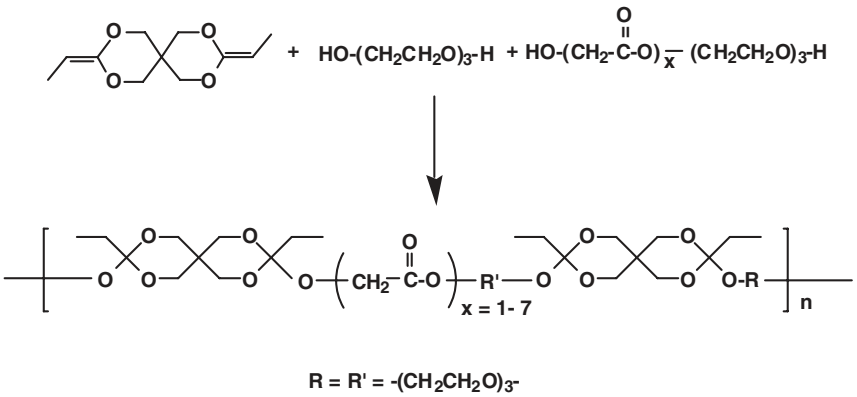
4.5.3.1 Development of APF 112 Mepivacaine Delivery System

Following surgery, currently used local anesthetics using a simple injection are only effective for a few hours. An important advance would be the development of a system that would result in the sustained delivery of a local anesthetic for a few days thus reducing the need for opiate use with their well-know side-effects. Further, if the delivery 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 anesthetic used, shares with other amide local anesthetics [32].

4.5.3.2 Formulation Used

The structure of the gel-like material used is shown in Scheme 4.13. In order to improve injectability and ease of handling, the molecular weight of the polymer was limited to about 6 kDa and methoxy polyethylene glycol having a molecular weight of 550 Da was used as an excipient.

The actual composition of the clinical formulation designated as APF 112 was 77.6 wt% polymer, 19.4 wt% methoxy polyethylene glycol, and 3 wt% mepivacaine.



Scheme 4.13 Structure of AP 530 used in clinical trials.

4.5.4 Preclinical Toxicology

Two types of studies were carried out. In one study, the polymer was hydrolyzed and the hydrolysate tested and the other study utilized the actual formulation [33].

4.5.4.1 Polymer Hydrolysate

Hydrolyzing the polymer into its hydrolysis products simulates the instantaneous erosion of an implant and thus represents a worst case scenario.

The hydrolysate was prepared by hydrolyzing the polymer in phosphate-buffered saline (PBS) at 80 °C for 24 h, adjusting the pH to 7.4 with NaOH, adding the methoxy polyethylene glycol, mixing thoroughly, adding deionized 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.

4.5.4.2 Wound Instillation

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, 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.

4.5.5 Phase II Clinical Trial

The objectives of this trial was to evaluate the safety and tolerability of APF 112 when administered into the surgical incision during inguinal hernia repair, a moderately to severely painful procedure. Results indicated excellent safety and tolerability, and pharmacokinetics showed sustained release of mepivacaine over 72 h [34].

However, due to an unexpectedly low level of pain displayed by the control group in the study, it was not possible to demonstrate that APF 112 is effective in controlling postsurgical pain.

4.5.6 Development of APF 530 Granisetron Delivery System

4.5.6.1 Preclinical Toxicology

Since APF 530 uses the same polymer as that used in APF 112, no polymer hydrolysate studies were needed.

4.5.6.2 Rat Study

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. For rats, a 0.25-mL dose/site was 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 approximately 5 and 20 mg/animal. The 5-mg dose was approximately 14–19 and 21–28 mg/kg of granisetron in males and females, respectively. 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 an subcutaneous dose of 1 mL/animal (0.25 mL/site). Saline control and test formulations were administered through a 16-gage 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 the injection of a biodegradable polymer. By day 29, the response to the polymer had resolved without any residual or untoward effects.

4.5.6.3 Dog Study

A study in beagle dogs was also conducted to further characterize 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 1.0 or 4 mL/animal. For beagle dogs, a 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 approximately 20 and 80 mg/animal, or approximately 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 approximately 0.3–0.5 mg/kg. Saline control and test formulations were administered through a 16-gage 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 the injection of a biodegradable polymer. All effects appeared to be resolving by day 15.

4.5.6.4 Phase II and Phase III Clinical Trials

Phase II and Phase III clinical trials have been completed.

In a Phase II clinical trial, the safety, tolerability, and pharmacokinetics in cancer patients were evaluated. In addition, efficacy end-points were evaluated relating to emetic events and the use of additional medication.

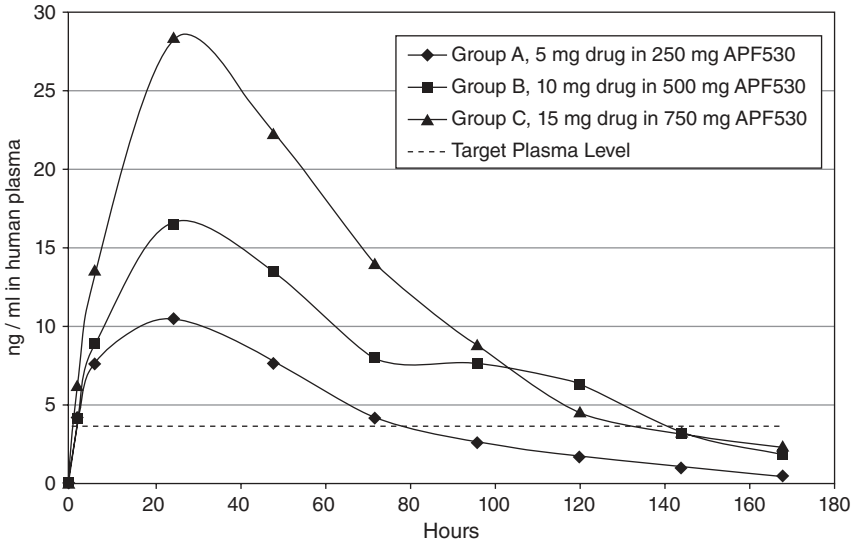


Figure 4.20 Granisetron plasma levels in patients from Phase II clinical trial of APF 530. From AP Pharma 2006 Annual Report.

A pharmacokinetic evaluation of three dose groups, 250, 500, and 750 mg injection doses corresponding to 5, 10, and 15 mg of granisetron, respectively, has demonstrated plasma levels of granisetron shown in Figure 4.20. On the basis of this study, a 10-mg dose was selected for a Phase III clinical trial [34].

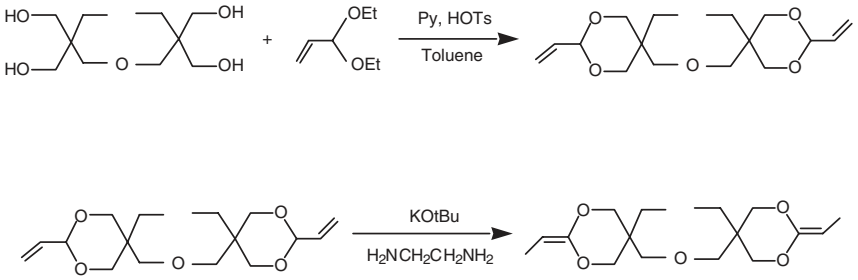
A Phase III clinical trial compared APF 530 to Aloxi which contains the 5-HT_3 antagonist palonesetron, and is administered either as an intravenous single dose 30 min prior to chemotherapy, or as an oral dose 1 h prior to chemotherapy. The Phase IIII clinical trial involved 1395 patients in 103 centers. The trial assessed acute and delayed onset of CINV for highly, or moderately emetogenic chemotherapy. As of this writing, APF 530 demonstrated equivalence, but not superiority to Aloxi.

4.6
Polymers Based on an Alternate Diketene Acetal

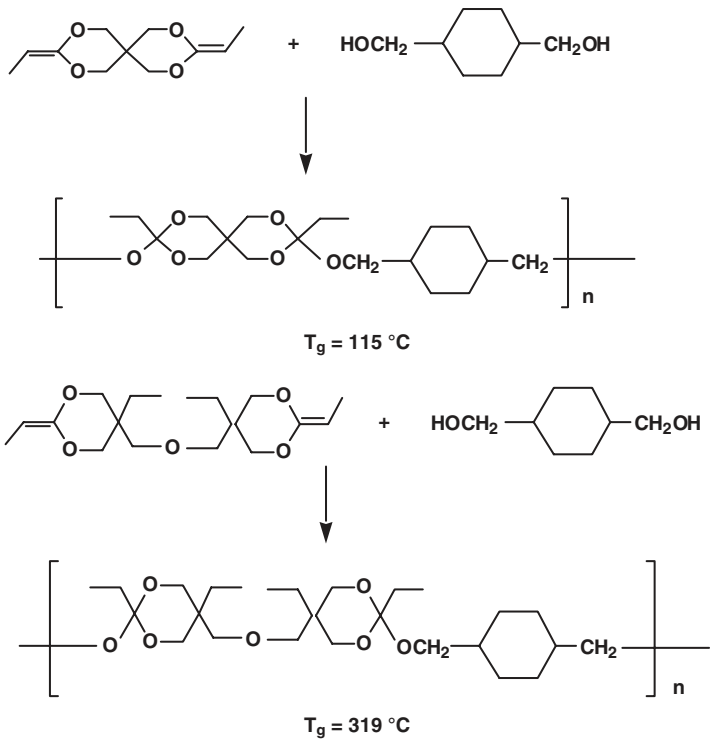
Preparation of gel-like materials requires very flexible polymers. Because DETOSU is a very rigid molecule, an attempt was made to replace DETOSU with another, less rigid, diketene acetal. The structure of this diketene acetal was shown under Section 4.2.1.

Only very preliminary data are available. Preparation of this diketene acetal is shown in Scheme 4.14.

Scheme 4.15 shows glass transition temperatures for polymers prepared using the rigid diol, *trans*-CDM with both DETOSU and the more flexible alternate



Scheme 4.14 Synthesis of di(5-methyl-2-ethylidene[1.3]dioxan-5yl)methyl ether.



Scheme 4.15 Glass transition temperatures for polymers prepared from DETOSU and di(5-methyl-2-ethylidene[1.3]dioxan-5yl)methyl ether, each with *trans*-CDM.

diketene acetal. Since glass transition temperatures are a direct indication of chain flexibility, it is clear that polymers prepared using the alternate diketene acetal are significantly more flexible and that use of the alternate diketene acetal should produce useful materials at higher molecular weight than those based on DETOSU.

4.7 Conclusions

Poly(ortho ester) have been under development since 1970, and while it is a very well-understood system, its commercialization has been slow in coming. This was primarily due to the fact that much of the early poly(ortho ester) work was carried in an academic setting at the former Stanford Research Institute, now SRI International.

Beginning in 1985, serious attempts by the former Interx Laboratories of Merck to develop a 6-month ivermectin delivery implant based on POE II to prevent heart-worm infestation in dogs was initiated. However, even though desired ivermectin blood levels have been achieved for many months and in a clinical trial the formulation was 100% effective in preventing heart-worm infestations in dogs, it was not possible to prepare devices that had reproducible erosion times. This irreproducibility problem eventually doomed commercialization.

Beginning in 1994, the fourth family of poly(ortho ester), POE IV, was developed at Advanced Polymer Systems, now AP Pharma. This polymer system is currently under active development at AP Pharma for a number of applications, and a Phase II clinical trial using mepivacaine for postoperative pain control was completed. This trial demonstrated for the first time that a specific family of poly(ortho ester) has a benign toxicology and that it is a suitable system for use in humans.

Based on the benign toxicology of this particular family of poly(ortho esters), the development of a granisetron delivery system to control chemotherapy-induced nausea and vomiting was initiated. This system has recently completed a Phase III clinical trial and work preparatory to an NDA filing is underway.

In addition, a number of proprietary systems based on POE II are also under development.

Thus, after a very long induction period, a number of delivery systems based on poly(ortho esters) are on their way of becoming a commercial reality.

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