SURFACE-ERODIBLE BIOMATERIALS FOR DRUG DELIVERY

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I. Introduction

Bioerodible polymers offer a unique combination of properties that can be tailored to suit nearly any controlled drug delivery application. By far the most common bioerodible polymers employed for biomedical applications are polyesters and polyethers (e.g., poly(ethylene glycol), polylactide, polyglycolide and their copolymers). These polymers are biocompatible, have good mechanical properties, and have been used in

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many controlled release applications. However, their chemistries are limited, thereby restricting structural modifications resulting in tailored properties. Over the past two decades, researchers have begun investigating alternative biodegradable polymers, resulting in a vast body of literature on both the synthesis of, and mechanisms of drug release from, biodegradable polymers.

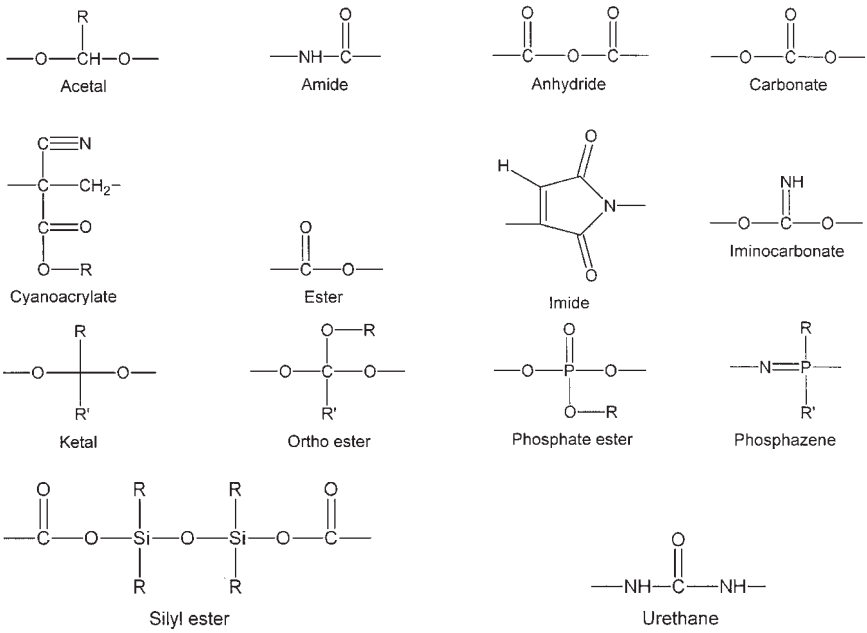
Drug release may be controlled by several mechanisms including diffusion of the drug through a matrix, dissolution of the polymer matrix, and degradation of the polymer. The chemistry of the polymer matrix may be tailored to facilitate drug stabilization, target delivery to specific tissues, or alter the release kinetics. Bioerodible polymers erode *in vivo*, thus obviating the need for surgical removal after the useful lifetime of the device has expired. The erosion may actually determine the drug release kinetics, or may occur on a time scale much slower than that of drug release.

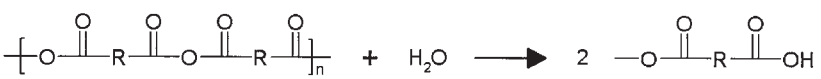
It is important to distinguish between erosion and degradation. Erosion is mass loss from a bioerodible polymer and may be a consequence of polymer dissolution or degradation of the polymer backbone, followed by dissolution of the degradation products. Degradation typically occurs by hydrolysis of the polymer backbone, the kinetics of which is a function of the polymer chemistry. Thus, erosion is the sum of several elementary processes, one of which may be polymer degradation.

Some biodegradable chemistries are listed in Table I (Pierre and Chiellini, 1986; Siepmann and Goepferich, 2001; Staubli *et al.*, 1990; Weinberg *et al.*, 1998). Pierre and Chiellini (1986) have summarized hydrolysis mechanisms for many biomedically relevant systems. Degradation half-lives range from millennia (for amides, carbonates, and urethanes) to minutes (for the fastest degrading anhydrides) (Pierre and Chiellini, 1986). Though all of these chemistries are hydrolyzable, hydrolysis rates vary depending not only on the functional group (Albertsson, 1995; Pierre and Chiellini, 1986), but also what lies between the functional groups. Polyanhydrides, for example, are one of the most labile classes, and their hydrolysis is shown in Scheme 1.

Erosion is typically characterized by either occurring on the surface or in the bulk. Surface erosion is controlled by the chemical reaction and/or dissolution kinetics, while bulk erosion is controlled by diffusion and transport processes such as polymer swelling, diffusion of water through the polymer matrix, and the diffusion of degradation products from the swollen polymer matrix. The processes of surface and bulk erosion are compared schematically in Fig. 1. These two processes are idealized descriptions. In real systems, the tendency towards surface versus bulk erosion behavior is a function of the particular chemistry and device geometry (Tamada and Langer, 1993). Surface erosion may permit the

TABLE I
FUNCTIONAL GROUPS FOUND IN BIOERODIBLE POLYMERS





SCHEME 1. Hydrolysis of polyanhydrides to carboxylic acids.

stabilization of macromolecular drugs and offers the potential to tailor release profiles by tailoring the composition and drug distribution.

Polyanhydrides are typically characterized as surface eroding because the anhydride bond itself is quite reactive with respect to hydrolysis, but the structure of the dicarboxylic acid monomer can render the polymer very hydrophobic, thereby limiting water ingress. These materials are interesting for controlled drug delivery due to the wide range over which the degradation kinetics can be varied. Thus, polyanhydrides have emerged as an extremely diverse and promising class of polymers for drug delivery and other biomedical applications. This review will discuss the novel chemistries and synthesis, characterization, and applications of polyanhydrides as surface erodible biomaterials for drug delivery.

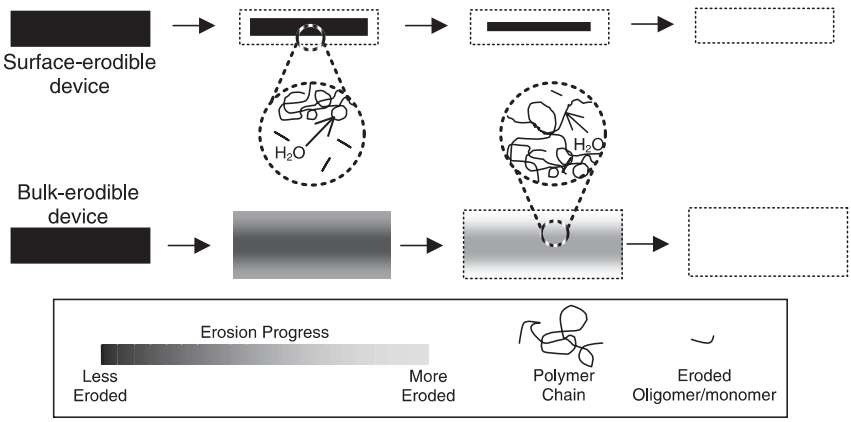


FIG. 1. Schematic comparing surface and bulk erosion. In surface erosion (top), water does not penetrate far into the bulk, but hydrolyzes functional groups on the surface. The resulting monomers dissolve and diffuse away from the device. In bulk erosion (bottom), water penetrates into the bulk, polymer may dissolve, and is ultimately hydrolyzed into monomer.

Several synthesis routes have been investigated to design polyanhydrides, and these are discussed in Section II. Section III reviews the microstructural characterization of homopolymers, blends, and copolymers of polyanhydrides. Section IV discusses the important features that affect erosion and drug release kinetics and reviews some of the modeling efforts that have been undertaken to predict erosion and drug release. Section V discusses the design of polyanhydride drug carriers with respect to delivery routes, mechanisms of release, and factors affecting release profiles. Finally, Section VI presents some of the future directions for polyanhydride research. Polyanhydrides have a variety of microstructural characteristics that affect the release profiles of encapsulated drugs. It is important to accurately describe the microstructure to predict and tailor drug release profiles. If the effects of these microstructural characteristics can be accurately understood, they can be exploited to control drug release profiles and effectively design controlled release formulations.

II. Chemistry and Synthesis

A. Early Synthesis of Polyanhydrides

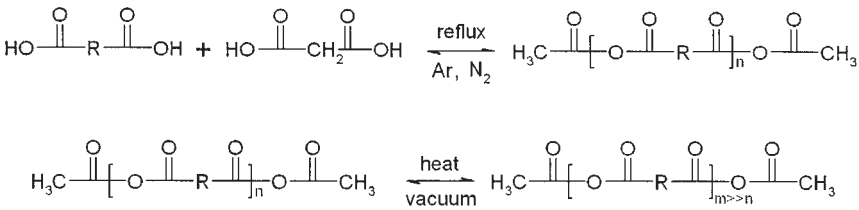
Synthesis of polyanhydrides from the aromatic dicarboxylic acids (isophthalic and terephthalic acids) by melt polycondensation was first

reported by Bucher and Slade in 1909. In the early 1930s, Hill and Carothers explored the synthesis of aliphatic polyanhydrides for use as fibers for the textile industry. Hill (1930) reported the polymerization of the aliphatic adipic acid, and later, Hill and Carothers (1932) reported the polymerization of sebacic acid, both by melt polycondensation and dehydrochlorination. The melting points of these polymers were too low and hydrolysis was too fast for them to be of use as fibers, and the study of anhydrides was abandoned.

In the late 1950s through the mid 1960s Conix (1957, 1958, 1966) reported the synthesis of the poly[α,ω-bis(*p*-carboxyphenoxy)alkanes], improving the fiber and film forming properties of polyanhydrides. From 1959 to 1962, Yoda (1959; Yoda and Akihisa, 1959), being encouraged by the work of Conix, synthesized random copolymers by melt polycondensation and alternating copolymers by dehydrochlorination, from a variety of aliphatic and aromatic monomers in attempts to improve the fiber and film properties of polyanhydrides. Windholz (1965) later patented a similar process for producing polyanhydrides as intermediates in the production of polyesters. Polyanhydride homopolymers and copolymers containing heterocyclic rings (Yoda, 1962a,b), and aliphatic and aromatic thioethers (Yoda, 1962c) were also synthesized by Yoda. Despite these efforts, polyanhydrides remained inferior to polyesters and other classes of polymers, never gaining prominence in the textile industry.

B. Synthesis of Polyanhydrides for Drug Delivery

Interest in polyanhydrides waned until the 1980s when Langer and coworkers (Rosen *et al*., 1983) suggested that their biodegradability would make them suitable for controlled drug delivery applications. Their initial study was conducted with poly[bis(*p*-carboxyphenoxy)methane] (PCPM) made by melt polycondensation and they showed near zero order release kinetics of a model drug (cholic acid) from compression-molded PCPM slabs (Rosen *et al*., 1983). These first results on drug release from polyanhydrides initiated what has now been two decades of extensive research. The same group studied additional chemistries (Leong *et al*., 1985) as well as alternate synthetic routes (Leong *et al*., 1987). The melt polycondensation and dehydrochlorination syntheses discussed in Section II.A were explored, along with a third route, dehydrative coupling (Chasin *et al*., 1988; Leong *et al*., 1987). An alternative solution technique for the polymerization of poly(terephthalic acid) (PTA) is offered by Subramanyam and Pinkus (1985). Domb *et al*. (1993) reviewed several polymerization methods including melt polycondensation, ring opening

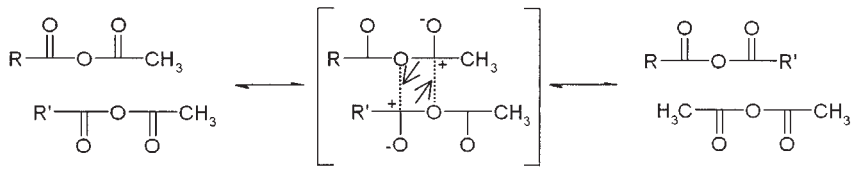


SCHEME 2. Polyanhydride synthesis via melt polycondensation involves first the formation of oligomeric acetylated prepolymers, followed by condensation under vacuum. Acetic acid is formed as a byproduct of the second reaction.

polymerization, solution polymerization (dehydrohalogenation and dehydrative coupling), and interfacial polymerization (dehydrohalogenation). A review of the important polyanhydride synthesis routes follows.

1. Melt Polycondensation

Melt polycondensation is performed by first acetylating the dicarboxylic acids by refluxing in excess acetic anhydride in a dry atmosphere, and then melting under vacuum to remove the condensation byproduct. This procedure is represented in Scheme 2. Domb and Langer (1987) improved upon the melt polycondensation technique (Scheme 2) to obtain higher molecular weight homopolymers and copolymers of aliphatic and aromatic dicarboxylic acids. They obtained weight average molecular weights of up to 137,300, for poly(sebacic acid) (PSA). In the same study (Domb and Langer, 1987), the synthesis of poly[1,3-bis(*p*-carboxyphenoxy)propane] (PCPP), poly[1,6-bis(*p*-carboxyphenoxy)hexane] (PCPH), poly(1,4-phenylenedipropionic acid) (PPDP), and poly(dodecanedioic acid) (PDDA), as well as the copolymers P(CPP–SA), P(CPP–DDA), and the copolymer of sebacic acid with isophthalic acid P(IPA–SA) was reported. A method for copolymer synthesis was patented by the same authors (Domb and Langer, 1988a). Methods employing a variety of coordination catalysts were also reported (Domb and Langer, 1987). The anhydride interchange reaction mechanism for the melt polycondensation (Scheme 3) has been proposed by Albertsson and Lundmark (1990a). This mechanism may also result in the formation of lower molecular weight cyclic macromers and contribute to the high polydispersity characteristic of the resulting polymers (Domb and Langer, 1987). Gupta (1989) patented a melt polycondensation procedure from a bis(trimethylsilyl)ester of a dicarboxylic acid and a diacid chloride that produces alternating copolymers. The majority of recent work with polyanhydrides has been conducted using the polycondensation



SCHEME 3. Anhydride interchange mechanism proposed for polymerization. The same mechanism may be responsible for cyclization.

synthesis originated by Conix (1966) and later improved upon by Domb and Langer (1987).

2. *Dehydrochlorination*

In the dehydrochlorination synthesis developed by Yoda (1959; Yoda and Akihisa, 1959) diacid chlorides are first formed by either reacting dicarboxylic acids with phosphorous pentachloride or refluxing dicarboxylic acids in thionyl chloride. Reaction is then carried out in the presence of pyridine. Dehydrochlorination (Schotten-Baumann condensation), offers two main advantages over melt polycondensation. First, it can be performed at much milder temperatures. Second, the copolymer sequence can be precisely controlled to form alternating copolymers. Leong *et al.* (1987) studied this route both as a solution technique, and at aqueous and non-aqueous interfaces. In general, somewhat lower molecular weights are obtained by this method than by the melt polycondensation (Leong *et al.*, 1987).

3. *Dehydrative Coupling*

The third synthesis mechanism studied by Leong *et al.* (1987) is an extension of a technique used by previous researchers (Cabré-Castellví *et al.*, 1981; Mestres, 1981) to form monomeric anhydrides, employing strong dehydration agents (e.g., organophosphorous compounds) such as those employed in peptide synthesis. A variety of dehydration agents were studied. Of the three synthesis methods studied by Leong *et al.* (1987), this one yielded the lowest molecular weight, and presented the most difficulties with respect to product purification.

To address purification, Domb and Langer (1988b) developed two techniques involving phosgene or diphosgene as coupling agents, both of which are single step polymerizations yielding pure product, by selective dissolution of either the polymer or the byproducts. A variety of polymers were synthesized including PSA, PCPP, PTA, PAA, PDDA, though only with PSA was a weight-average molecular weight above 15,000 (16,300)

obtained. Most of the polymers had weight-average molecular weights less than 10,000. The advantages of this method are that relatively pure polymers are obtained without the exposure to extreme temperatures (Domb and Langer, 1988b).

4. *Ring Opening Polymerization*

Dicarboxylic acid monomers that form monomeric anhydride rings, such as adipic anhydride (oxepane-2,7-dione), can be polymerized by ring-opening polymerization (Albertsson and Lundmark, 1988). A catalyst such as tin 2-ethylhexanoate, tin octanoate, aluminum isopropoxide, or *n*-butyl lithium is added and the reaction proceeds via an insertion mechanism (Albertsson and Lundmark, 1990b; Edlund and Albertsson, 1999). Ring opening can be performed both in solution and in the melt (Albertsson and Lundmark, 1988, 1990b). Ropson *et al.* (1997) reported a mechanism for insertion in living polymerizations of adipic anhydride using aluminum alkoxides as initiators. Ring opening polymerizations are limited to chemistries capable of forming rings, but offer the capability of easily forming block copolymers via living polymerizations. Block copolymers of adipic anhydride with ε-caprolactone (Ropson *et al.*, 1997) and trimethylene carbonate (Edlund and Albertsson, 1999) have been formed by this synthetic route. Deng *et al.* (2003) have cleverly surmounted the chemistry limitation by using potassium poly(ethylene glycol)ate as a macro-initiator, thereby synthesizing a poly(adipic acid-*block*-ethylene glycol) copolymer. The same group has also recently studied the use of dibutylmagnesium as an alternative initiator (Li *et al.*, 2003).

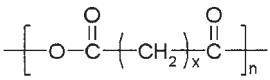
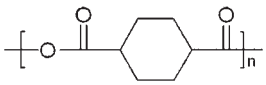
5. *Polymerization with Ketene*

In an attempt to avoid the polymerization/depolymerization equilibrium that occurs during melt polycondensation, Albertsson and Lundmark (1988) also studied the irreversible reaction of adipic anhydride with ketene. However, they reported very little difference in molecular weights when two ketene syntheses were compared to melt polycondensation and ring-opening polymerization using a zinc catalyst (Albertsson and Lundmark, 1988).

C. Chemistries of Polyanhydrides Used in Drug Delivery

We have already mentioned a few of the polyanhydride chemistries that have been studied in drug delivery applications. Tables II through VII present some of the polyanhydrides that have been explored for drug

TABLE II
ALIPHATIC POLYANHYDRIDES

Structure	Name	
	$x=4$ Poly(adipic acid)	PAA
	$x=5$ Poly(pimelic acid)	PPA
	$x=6$ Poly(suberic acid)	PSA
	$x=7$ Poly(azalaic acid)	PAZ
	$x=8$ Poly(sebacic acid)	PSA
	$x=10$ Poly(dodecanedioic acid)	PDDA
	$x=12$ Poly(dodecanedicarboxylic acid)	PDX
	Poly(1,4-cyclohexane dicarboxylic acid)	PCDA

delivery applications and we briefly discuss the literature on each one. Copolymers are discussed separately.

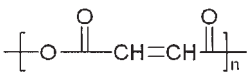
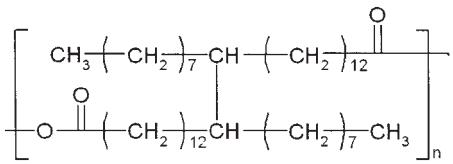
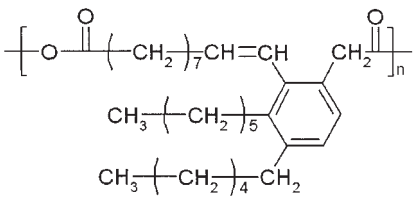
1. *Aliphatic Polyanhydrides*

Aliphatic polyanhydrides (Table II) together with the α,ω-bis(*p*-carboxyphenoxy)alkanes are the most commonly studied polyanhydrides for drug delivery applications. Poly(sebacic acid) (PSA) was first suggested as a polymer for drug delivery by Langer and coworkers in 1987 and was among the monomers on which they studied alternative synthesis methods (Domb and Langer, 1987; Leong *et al.*, 1987). Poly(dodecanedioic acid) (PDDA) is also synthesized by melt polycondensation and yields similar molecular weights (Domb and Langer, 1987). The synthesis of poly(adipic acid) (PAA) by multiple methods was discussed in Section II.B. Poly(1,4-cyclohexyldicarboxylic acid) (PCDA) was first synthesized via melt polycondensation by Zhang *et al.* (2000, 2001). Domb and Nudelman (1995) reported the synthesis of the series of aliphatic polyanhydrides from PAA to poly(dodecanedicarboxylic acid) (PDX).

2. *Polyanhydrides from Unsaturated and Fatty Acid-derived Monomers*

Polyanhydrides based on unsaturated and fatty acid-derived monomers are shown in Table III. Poly(fumaric acid) (PFA) was fist synthesized by Domb *et al.* (1991) by both melt polycondensation and solution polymerization. The copolymer of fumaric acid and sebacic acid (P(FA–SA)) has been synthesized and characterized (Domb *et al.*, 1991; Mathiowitz *et al.*, 1990b). The mucoadhesive properties of this polymer

TABLE III
POLYANHYDRIDES FROM UNSATURATED AND FATTY ACID DERIVED MONOMERS

Structure	Name	
	Poly(fumaric acid)	PFA
	Poly(Fatty acid dimer) (erucic acid)	PFAD
	Poly(Dimer acid)	PDA

have been shown to aid in increasing the bioavailability of encapsulated model drugs in oral delivery experiments (Chickering *et al.*, 1995, 1996).

Fatty acids have also been converted to difunctional monomers for polyanhydride synthesis by dimerizing the unsaturated erucic or oleic acid to form branched monomers. These monomers are collectively referred to as fatty acid dimers and the polymers are referred to as poly(fatty acid dimer) (PFAD). PFAD (erucic acid dimer) was synthesized by Domb and Maniar (1993) via melt polycondensation and was a liquid at room temperature. Desiring to increase the hydrophobicity of aliphatic polyanhydrides such as PSA without adding aromaticity to the monomers (and thereby increasing the melting point), Teomim and Domb (1999) and Krasko *et al.* (2002) have synthesized fatty acid terminated PSA. Octanoic, lauric, myristic, stearic, ricinoleic, oleic, linoleic, and lithocholic acid acetate anhydrides were added to the melt polycondensation reactions to obtain the desired terminations. As desired, a dramatic reduction in the erosion rate was obtained (Krasko *et al.*, 2002; Teomim and Domb, 1999).

Teomim and Domb (2001) report the termination of PSA with monoesters of ricinoleic acid (i.e., *cis*-12-hydroxyoctadeca-9-enoic acid) and fatty acids. The fatty acids used in this study range in length from C10 to C18. The combination of PSA with FAD is not limited to terminal

modification. P(FAD–SA) and P(fatty acid trimer–SA) (P(FAT–SA)) copolymers have been synthesized (Domb and Maniar, 1993) and their release properties have been studied (Shieh *et al*., 1994; Tabata and Langer, 1993; Tabata *et al*., 1993, 1994).

Xu *et al*. (2001) synthesized the copolymers of a dimer fatty acid (dimer of oleic and linoleic acids) and sebacic acid (P(DA–SA)) by melt polycondensation of acetylated prepolymers. Degradation and drug release kinetics showed that increasing dimer acid content decreased the release rate (Xu *et al*., 2001).

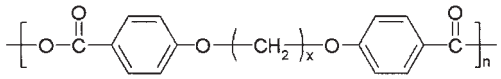
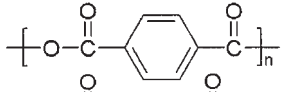
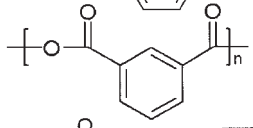
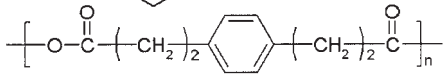
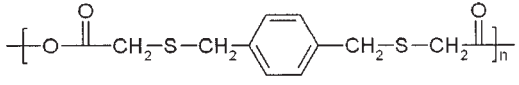
Another class of PSA–fatty acid-based copolymers has been synthesized from the ricinoleic acid and ricinoleic half-esters with maleic and succinic anhydride, poly(sebacic-*co*-ricinoleic acid maleate), poly(sebacic-*co*-ricinoleic acid succinate), and poly(sebacic-*co*-12-hydroxystearic acid succinate) (P(SA–RAM), P(SA–RAS), and P(SA–HSAS)) (Krasko *et al*., 2003; Teomim *et al*., 1999). These syntheses result in poly(anhydride-*co*-esters).

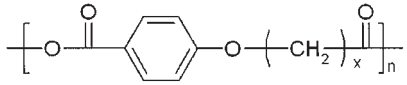
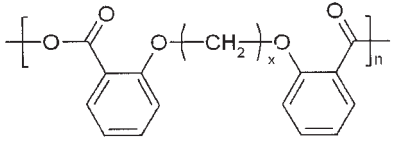
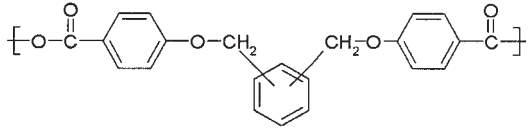
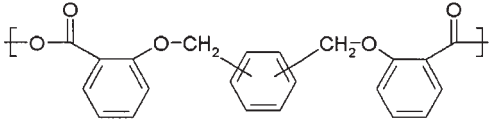
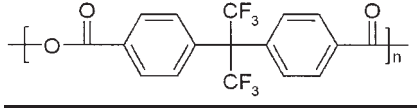
3. *Aromatic Polyanhydrides*

Aromatic polyanhydrides (Table IV) are typically characterized by slow degradation rates, high melting temperatures, brittle mechanical properties, and low solubility in organic solvents compared to the aliphatic polyanhydrides. PCPM was the first aromatic polyanhydride to be synthesized as a candidate for controlled drug delivery (Rosen *et al*., 1983). Other polymers in the family of poly[α,ω-(*p*-carboxyphenoxy)alkanes] that had originally been synthesized by Conix (1957, 1958, 1966) soon followed including PCPP, poly(terephthalic acid) (PTA) (Leong *et al*., 1985), and PCPH (Leong *et al*., 1987). Also included in the later study were poly(terephthalic-*alt*-sebacic acid) (P(SA-*alt*-TA)), poly(1,4-phenylene dipropionic acid) (PPDP) and poly[2,2′-(*p*-xylylenedithio)diacetic acid] (PXDA) (Leong *et al*., 1987). Domb *et al*. (1989) synthesized several polyanhydrides based on ω-carboxyphenoxyalkonoic acids including poly(carboxyphenoxy acetic acid) (PCPA), poly[5-(*p*-carboxyphenoxy)-valeric acid] (PCPV), and poly[8-(*p*-carboxyphenoxy)octanoic acid] (PCPO) by melt polycondensation and studied the release of model drugs from them. Domb (1992) also synthesized poly(isophthalic acid) (PIPA) and poly(terephthalic acid) (PTPA) by melt polycondensation.

Campo *et al*. (1999) synthesized the *ortho*-isomers of PCPP and PCPH, poly[1,3-bis(*o*-carboxyphenoxy)propane] (P*o*-CPP) and poly[1,6-bis(*o*-carboxyphenoxy)hexane] (P*o*-CPH), in an attempt to improve the solubility and processability of these two polymers. Solubility was improved

TABLE IV
AROMATIC POLYANHYDRIDES

Structure	Name	
	$x = 1$ Poly[bis(*p*-carboxyphenoxy)methane]	PCPM
	$x = 3$ Poly[1,3-bis(*p*-carboxyphenoxy)propane]	PCPP
	$x = 6$ Poly[1,6-bis(*p*-carboxyphenoxy)hexane]	PCPH
	Poly(Terephthalic acid)	PTA
	Poly(Isophthalic acid)	PIPA
	Poly(Phenylene dipropionic acid)	PPDP
	Poly[2,2′-(*p*-xylenedithio)diacetic acid]	PXDA

	$x = 1$ Poly[2-(*p*-carboxyphenoxy)acetic acid] $x = 4$ Poly[5-(*p*-carboxyphenoxy)valeric acid] $x = 7$ Poly[8-(*p*-carboxyphenoxy)octanoic]	PCPA PCPV PCPO
	$x = 3$ Poly[1,3-bis(*o*-carboxyphenoxy)propane] $x = 6$ Poly[1,6-bis(*o*-carboxyphenoxy)hexane]	P*o*-CPP P*o*-CPP
	Poly[*o*-bis(*p*-carboxyphenoxy)xylene] Poly[*m*-bis(*p*-carboxyphenoxy)xylene]	P*o*-*p*-CPX P*m*-*p*-CPX
	Poly[*o*-bis(*o*-carboxyphenoxy)xylene] Poly[*m*-bis(*o*-carboxyphenoxy)xylene] Poly[*p*-bis(*o*-carboxyphenoxy)xylene]	P*o*-*o*-CPX P*m*-*o*-CPX P*p*-*o*-CPX
	Poly[4,4′-(hexafluoroisopropylidine)bis-benzoic acid]	PHFB

and crystallinity reduced, but T_gs were also lowered to below physiological temperature, which may limit their applicability as biomaterials.

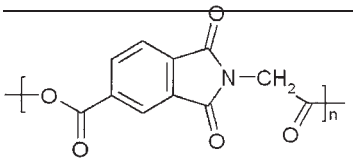
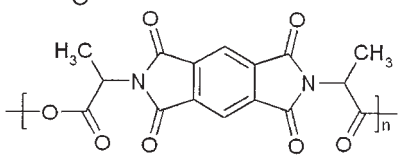
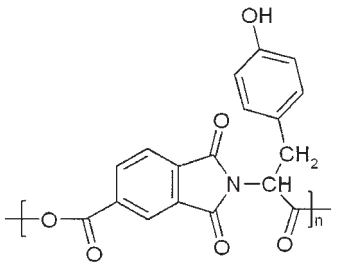
In an attempt to increase T_g of the poly[bis(*o*-carboxyphenoxy)alkanes], Anastasiou and Uhrich (2000a) replaced the alkane moiety by *ortho*-, *meta*-, and *para*-xylenes producing poly[*o*-/*m*-bis(*p*-carboxyphenoxy)xylene]s (P*o*-*p*-CPX, and P*m*-*p*-CPX) and poly[*o*-/*m*-/*p*-bis(*o*-carboxyphenoxy)xylene]s (P*o*-*o*-CPX, P*m*-*o*-CPX, and P*p*-*o*-CPX). They found P*o*-*p*-CPX to be relatively insoluble and were unable to synthesize poly[*p*-bis(*p*-carboxyphenoxy)xylene] because of the insolubility of the dicarboxylic acid (Anastasiou and Uhrich, 2000a). P*o*-*o*-CPX and P*m*-*o*-CPX demonstrated the most favorable solubility and neither exhibited a melting temperature. All of the polymers synthesized had T_gs between 71 and 101°C (Anastasiou and Uhrich, 2000a).

4. *Copolymers of Aliphatic and Aromatic Polyanhydrides*

Researchers interested in polyanhydrides as candidates for drug delivery realized the value of co-polymerizing aliphatic and aromatic residues. In this way, a large number of polymers could be made from only a handful of chemistries and chemical and physical properties could be tailored by combination. Initially, the goal was to obtain a variety of release times by making simple changes to the copolymer composition. The first such copolymer was P(CPP–SA) synthesized via melt polycondensation by Leong *et al.* (1985). The alternating copolymers of adipic acid, sebacic acid, and dodecanedioic acid with terephthaloyl chloride (P(AA-*alt*-TA), P(SA-*alt*-TA), and P(DDA-*alt*-TA)) and sebacic acid with isophthaloyl chloride and P(IPA-*alt*-SA)) were produced by dehydrochlorination and the random copolymers P(CPM–SA) and P(CPH–SA) were produced by melt polycondensation for the first time in the extensive study by Leong *et al.* (1987). The copolymers P(IPA–SA) and P(CPP–DDA) via melt polycondensation were added to the repertoire of copolymers by Domb and Langer (1987). Domb (1992) later synthesized the copolymers P(CPP–IPA), P(IPA–TA), P(IPA–FA), P(CPP–FA), P(FA–TA), P(SA–TA), and P(IPA–SA).

Sanders *et al.* (1999) attempted to lower the melting points of aromatic polyanhydrides by substituting branched alkyl groups in place of the linear alkyls of P(CPP–SA). They synthesized poly[1,2-bis(*p*-carboxyphenoxy)-propane-*co*-sebacic acid] (P(1,2-CPP-SA)), poly[1,3-bis(*p*-carboxyphenoxy)-2-methyl propane-*co*-sebacic anhydride] (P(CPMP-SA)), and poly[1,3-bis(*p*-carboxyphenoxy)-2,2-dimethyl propane-*co*-sebacic anhydride] (P(CPDP–SA)), all of which had melting points below 165°C.

TABLE V
POLY(ANHYDRIDE-*co*-IMIDE)S

Structure	Name	
	Poly(trimellitylimido glycine)	PTMAgly
	Poly(pyromellitylimido alanine)	PMAala
	Poly(trimellitylimido tyrosine)	PTMAtyr

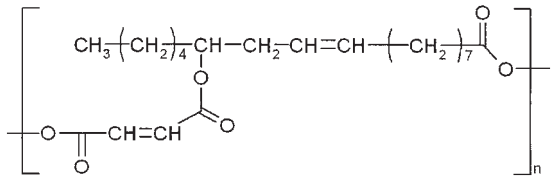
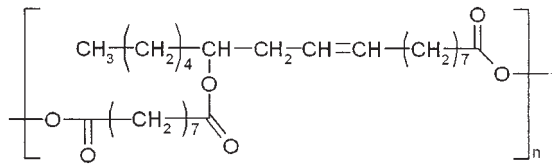
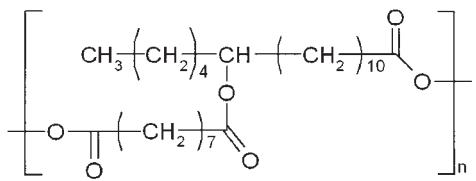
5. *Poly(anhydride-co-imide)s*

Another important class of polyanhydrides is the poly(anhydride-*co*-imide)s (Table V). This class of polymers was first synthesized by Fontán and co-workers (De Abajo *et al*., 1971; González *et al*., 1976) as potential candidates for fiber forming polymers. Staubli *et al*. (1990) developed a technique for incorporating amino acids into polyanhydrides by first reacting them with N-trimellitic acid. Uhrich *et al*. (1995) synthesized copolymers of trimellitylimido glycine, pyromellitylimido alanine and the monomers of PSA and PCPH by melt polycondensation and proposed the use of (P(TMAgly–SA), P(TMAgly–CPH), P(PMAala–SA), and P(PMAala–CPH)) as potential candidates to improve the mechanical properties of polyanhydrides. Hanes *et al*. (1996) later synthesized the copolymer of trimellitylimido L-tyrosine with PSA and PCPP (P(TMAtyr–CPP–SA)) as a candidate polymer for vaccine delivery.

6. *Poly(anhydride-co-ester)s and Poly(anhydride-co-ether)s*

Poly(anhydride-*co*-ester)s (Table VI) were suggested as potential polymers for drug delivery and synthesized by Pinther and Hartmann (1990),

TABLE VI
POLY(ANHYDRIDE-*co*-ESTER)S

Structure	Name	
	Poly(Riconleic acid maleate)	RAM
	Poly(Ricinoleic acid succinate)	RAS
	Poly(12-hydroxystearic acid succinate)	HSAS

	Poly[bis(*o*-carboxyphenoxy) sebacate	PCPS
	$x = 2$ poly(*p*-carboxyphenoxy succinic monoester anhydride)	PCPSM
	$x = 4$ poly(*p*-carboxyphenoxy adipic monoester anhydride)	CPAM

and Kricheldorf and Jürgens (1994). Other poly(anhydride-*co*-ester)s already mentioned in Section II.B.4 include poly(adipic acid-*block*-ε-caprolactone) (P(AA-*block*-ε-CL)), poly(adipic acid-*block*-trimethylene carbonate) (P(AA-*block*-TMC)), and poly(adipic acid-*block*-ethylene glycol) (P(PAA-*block*-EG). Others have synthesized poly(anhydride-*block*-ethylene glycol) copolymers. Jiang and Zhu (1999) synthesized and characterized poly(sebacic acid-*block*-ethylene glycol) (P(SA-*block*-EG)) and poly[(sebacic acid-*co*-trimellitylimidoglycine)-*block*-ethylene glycol] (P[(SA-*co*-TMA)-*block*-EG]) by melt polycondensation. The ethylene glycol segments were added by first acetylating polyoxyethylene dicarboxylic acid and then adding it to the PSA polymerization (Jiang and Zhu, 1999). Qiu and Zhu (2001) proposed the use of this material in laminated devices for pulsed release. P(SA-*co*-TMA-*block*-EG) and PSA were also used by Qiu and Zhu (2000) to make blends of poly[bis(glycine ethyl ester)phosphazene] in order to regulate the degradation rate of the phosphazene as well as to decrease its cost. The *in vitro* and *in vivo* erosion kinetics of the P[(SA-*co*-TMA)-*block*-EG] containing blend was later studied in detail by Qiu (2002).

Wu *et al*. (2000) showed the formation of self-assembled nanoparticles of P(SA-*block*-EG) in an aqueous environment and studied their degradation as a function of pH and temperature. Fu *et al*. (2002) repeated the synthesis of P(SA-*block*-EG) and studied the morphology and erosion kinetics of microspheres which they propose as vehicles for mucosal drug delivery.

Poly(lactic acid) (PLA) has also been added to poly(SA) via melt polycondensation to produce the triblock copolymers poly(lactic acid-*block*-sebacic acid-*block*-lactic acid) (P(LA-*block*-SA-*block*-LA)) by Slivniak and Domb (2002). The PLA (D-, L-, and DL-) was incorporated by acetylation and addition to the PSA synthesis. They showed the formation of stable stereocomplexed particles with increased melting points and reduced solubility, and studied the degradation and drug release characteristics of the same (Slivniak and Domb, 2002). The stereocomplexes self-assemble as a consequence of the chirality in the PLA portions of the chains (Slivniak and Domb, 2002).

Erdmann and Uhrich (2000; Erdmann *et al*., 2000) recently synthesized novel poly(anhydride-*co*-ester)s containing salicylic acid in the backbone, by melt polycondensation of the disalicylic acid ester of sebacic acid, poly[bis(*o*-carboxyphenoxy)sebacate] (PCPS) and the copolymer P(CPH–CPS). The release of salicylic acid (the active form of aspirin) from the former was studied *in vitro* and from the latter was studied *in vivo* (Erdmann and Uhrich, 2000; Erdmann *et al*., 2000). Similar polymers that release 5-amino salicylic acid, and *p*-nitro salicylic acid have been prepared

by the same group for the treatment of Crohn's disease and tuberculosis, respectively (Anastasiou and Uhrich, 2000b; Krogh-Jespersen *et al.*, 2000).

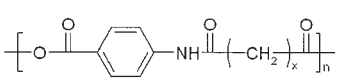
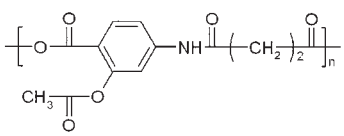
Jiang and Zhu (2001) reported on the synthesis of poly(*p*-carboxyphenoxy succinic monoester anhydride) and poly(*p*-carboxyphenoxy adipic monoester anhydride) (PCPSM and PCPAM), and the copolymer P(CPAM–CPSM) as polymeric antimicrobial prodrugs for diseases such as malaria and hepatitis B. They also reported that PCPSM exhibits strong fluorescence, the intensity of which increases linearly with its molecular weight (Jiang *et al.*, 2001a,b). They showed that when co-polymerized the fluorescence is maintained, though diminished approximately in proportion to the copolymer composition.

7. *Poly(anhydride-co-amide)s*

The synthesis of poly(anhydride-*co*-amide)s (Table VII) of various chemistries was pursued by Hartmann and Schulz (1989) as a means of improving biocompatibility and extending the degradation times of polyanhydrides. This work also contains calorimetry data on the thermal transitions and spectroscopic characterization.

Jiang and Zhu (2001) became interested in synthesizing additional polyanhydrides with fluorescence after their discovery of the fluorescent properties of PCPS. They synthesized the series of poly(anhydride-*co*-amide)s poly{*p*-[carboxyphenoxy(ethyl/propyl/butyl)formamido]benzoic anhydride} (PCEFB, PCPFB, and PCBFB) (Jiang *et al.*, 2001c). Only the ethyl polymer emitted strong fluorescence, which was consistent with their previous study of the poly(anhydride-*co*-ester)s of similar chemistry

TABLE VII
POLY(ANHYDRIDE-*co*-AMIDE)S

Structure	Name	
	$x=2$ poly{*p*-[carboxyphenoxy (ethyl)formamido]benzoic acid}	PCEFB
	$x=3$ poly{*p*-[carboxyphenoxy (propyl)formamido]benzoic acid}	PCPFB
	$x=4$ poly{*p*-[carboxyphenoxy (butyl)formamido]benzoic acid}	PCBFB
	Poly[*o*-acetyl-*p*(carboxyethylformamido) benzoic acid]	PACEFB

(Jiang and Zhu, 2001). PCEFB can be modified with an acetyl *ortho* to the anhydride bond to form poly[*o*-acetyl-*p*(carboxyethylformamido)benzoic acid] (PACEFB), which also fluoresces and may have potential as a polymeric prodrug for the treatment of tuberculosis (Jiang *et al*., 2001b). The copolymers of P(CEFB–SA) and P(CACEFB–SA) were also synthesized and shown to exhibit decreased fluorescence in proportion to the decrease in mole fraction of the fluorescent monomer (Jiang *et al*., 2001b). These polymers may prove to be very valuable for combining *in vivo* controlled release and drug targeting studies with non-invasive imaging techniques. The dependence of fluorescence on molecular weight may offer a powerful mechanism to conduct *in situ* analysis of *in vivo* degradation profiles (Jiang and Zhu, 2002).

8. *Other Novel Anhydride Chemistries*

The chemistry of polyanhydrides is by no means limited to the categories discussed in the preceding sections. A brief review of some of the additional chemistries that have recently been synthesized follows with a mention of their potential for application in drug delivery.

a. Branched polyanhydrides. Branched PSA was synthesized by Maniar *et al.* (1990) by reacting sebacic acid in the presence of 1,3,5-benzene-tricarboxylic acid and polyacrylic acid to improve the processability and mechanical properties of PSA. Weight average molecular weights above 200,000 were obtained in four of the eight compositions tested and all of the branched polymers had weight average molecular weights above 140,000, though very little difference in the polymer properties from the properties of PSA other than molecular weight were observed (Maniar *et al*., 1990). Degradation profiles of the branched polymers were also similar to that for PSA (Maniar *et al*., 1990). Drug release profiles for these polymers are discussed in Section IV.A.

b. Poly(anhydride-co-alkylene carbonate)s. Xiao and Zhu (2000) suggested accelerating the degradation of polycarbonates by incorporating anhydrides into the polymer backbone. This was accomplished by melt polycondensation of acetylated bis-α,ω-(hydrodxy)alkalene carbonate oligomers. The polymers synthesized were poly(tetramethylene carbonate succinic half-ester anhydride) (PTMCSA) and poly(hexamethylene carbonate succinic half-ester anhydride) (PHMCSA). They observed an initially fast loss of molecular weight followed by much slower degradation in *in vitro* degradation studies and attributed this to initial hydrolysis of

the more labile anhydride bond, followed by slower hydrolysis of the carbonate bonds.

c. Fluorinated polyanhydrides. Kaur *et al.* (2002) synthesized poly[4,4′-(hexafluoroisopropylidine)bis benzoic acid] (PHFB) as an alternative to aromatic polyanhydrides with relatively low solubilities. Acetylated prepolymer did not polymerize readily by melt polycondensation, so trifluoroacetylated prepolymer was used instead and weight average molecular weight of up to 14,000 was obtained with some unreacted monomer (Kaur *et al.*, 2002). The authors suspected cyclization in the case of the acetylated prepolymer. The stability and degradation kinetics of PHFB were reported in the same study (Kaur *et al.*, 2002).

d. Poly(lithocholic acid). Gouin *et al.* (2000) reported the synthesis of poly(lithocholic acid) (PLCA) and its copolymer with sebacic acid (P(LCA-*co*-SA)) via both melt polycondensation and dehydrative coupling. The material was characterized thermally, and drug release kinetics and biocompatibility studies were also reported. Modulation of the release kinetics was shown via changes in the copolymer composition (Gouin *et al.*, 2000).

e. Poly(anhydride-co-urethane)s. In their investigation of polyanhydrides with novel chemistries, Hartmann *et al.* (1993) synthesized several poly(anhydride-*co*-urethane)s and compared their degradation kinetics to the poly(anhydride-*co*-ester)s and poly(anhydride-*co*-amide)s with similar structures. Poly(anhydride-*co*-amide)s, and poly(anhydride-*co*-urethane)s degraded by hydrolysis of the anhydride bond only, but poly(anhydride-*co*-ester)s degraded at both the ester and the anhydride bond.

III. Polyanhydride Characterization

A. Chemical Characterization of Polyanhydrides

1. Chemistry of Polyanhydrides Assessed by FTIR and ^{1}H NMR

Fourier transform infrared spectroscopy (FTIR) and proton nuclear magnetic resonance spectroscopy (^{1}H NMR) have become standards for verifying the chemistry of polyanhydrides. The reader is referred to the synthesis literature in the previous section for spectra of specific polymers. The FTIR spectrum for PSA is shown in Fig. 2. In FTIR the absorption

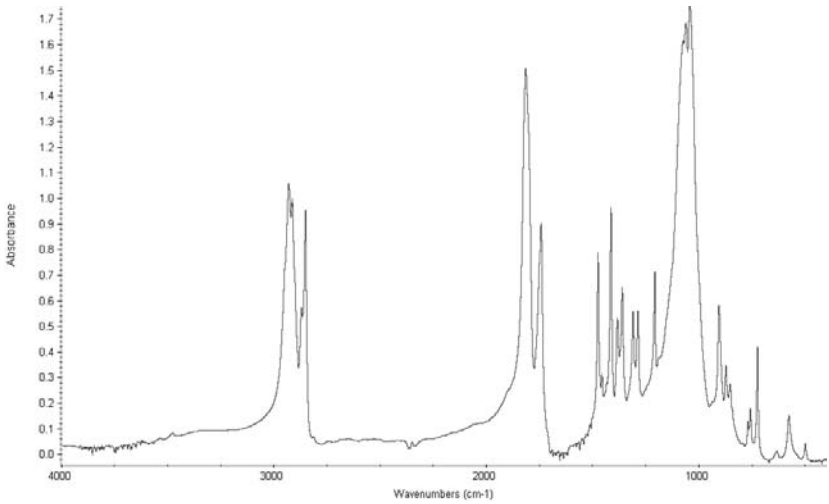


FIG. 2. FTIR spectra for PSA showing characteristic anhydride peaks between 1750 and 1900 cm^{-1}.

characteristic of the anhydride doublets are typically found around 1740 and 1810 cm^{-1} for the aliphatic residues and 1720 and 1780 cm^{-1} for the aromatic residues (Domb *et al.*, 1993). Excitation of the anhydride bond also absorbs at 1050 cm^{-1} (Leong *et al.*, 1985). The acidic O–H bond absorbs between 3300 and 2500 cm^{-1} (Rosen *et al.*, 1983). The combination of these absorbances can be used to assess hydrolytic degradation, and the relative intensities of the anhydride bonds can be used to verify copolymer composition.

The analysis of ^{1}H NMR spectra of aliphatic and aromatic polyanhydrides has been reported by Ron *et al.* (1991), and McCann *et al.* (1999) and Shen *et al.* (2002), and ^{13}C NMR has been reported by Heatley *et al.* (1998). In ^{1}H NMR, the aliphatic protons have chemical shifts between 1 and 2 ppm, unless they are adjacent to electron withdrawing groups. Aliphatic protons appear at about 2.45 ppm when α to an anhydride bond and can be shifted even further when adjacent to ether oxygens. Aromatic protons typically appear with chemical shifts between 6.5 and 8.5 ppm and are also shifted up by association with anhydride bonds. The sequence distribution of copolymers can be assessed, for example in P(CPH–SA), by discerning the difference between protons adjacent to CPH–CPH bonds, CPH–SA bonds, and SA–SA bonds (Shen *et al.*, 2002). FTIR and ^{1}H NMR spectra for many of the polymers mentioned in Section II can be found in their respective references.

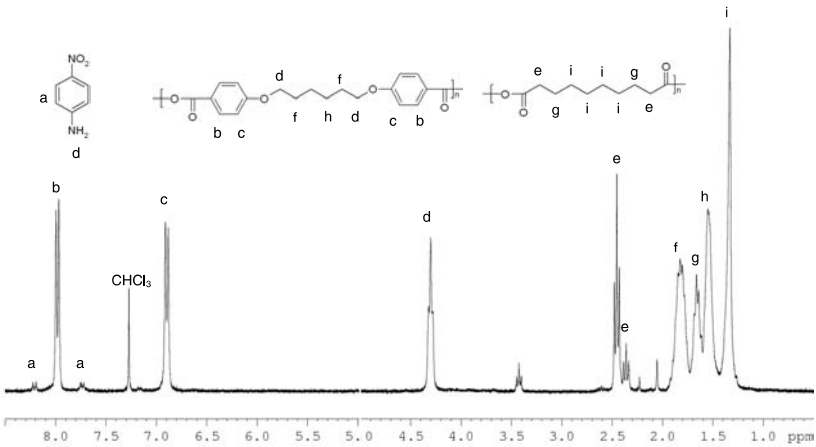


FIG. 3. ^{1}H NMR of P(CPH-SA) 50:50 loaded with *p*-nitroaniline.

Spectroscopy can also be used to assess drug-loading in these systems. Figure 3 is a ^{1}H NMR spectrum for *p*-nitroaniline-loaded P(CPH–SA) (50:50). The combination of these two techniques provides a standard for verifying the chemistry of polyanhydrides. UV spectroscopy has also been reported for determining the chemistry of copolymers (Leong *et al.*, 1985).

2. *Solubility of Polyanhydrides*

When Bucher and Slade first synthesized PTA and PIPA, they reported insolubility in low pH, aqueous media, and solubility of PTA in alkaline solutions. Most polyanhydrides synthesized in the century that has passed since then show similar behavior. Many polyanhydrides also exhibit extremely limited solubility in organic solvents. This can cause problems in both characterization and processing as many characterization techniques are conducted in solution, and co-dissolution is a common method of fabricating both polymer/polymer blends and polymer/drug systems. A careful survey of the literature reveals that chlorinated solvents (chloroform and dichloromethane (DCM)) are almost universal solvents (and in some cases the only solvents) for polyanhydrides. Leong *et al.* (1985) reported that PCPP and PCPH were soluble in tetrahydrofuran (THF) and *N*,*N*′-dimethylformamide (DMF) only immediately following polymerization, making characterization by GPC on these polymers rather inconvenient. Domb and Langer (1987, 1988b; Domb *et al.*, 1989) report the use of chloroform as a solvent for P(CPP–SA), PSA, PCPH, PPDP, PDDA, PCPV, and PCPO, but that PCPP, and PCPA are both insoluble in

chloroform (Domb and Langer, 1988b; Domb *et al.*, 1989). PDDA, PAA, and are also reported to be soluble in chloroform (Albertsson and Lundmark, 1990b). Domb (1992) also studied the solubilities of PTA, PCPP, PIPA, and PFA in DCM, chloroform, and carbon tetrachloride and reported that all of them had less than 0.1% solubility (w/v). However, altering copolymer composition proved to be an effective method of improving the solubility of aliphatic polyanhydrides. Domb (1992) indicated slightly increased solublities of the 70:30 copolymers P(TA–SA), P(CPP–SA), P(IPA–SA), and P(FA–SA), and increasing solubility as the PSA fraction was increased. More surprisingly, the copolymers made exclusively of the aromatic moieties (the homopolymers of which were insoluble) showed solubilities of greater than 1% (w/v) for some compositions (Domb, 1992).

Several of the synthetic efforts outlined in Section II were motivated partially by the necessity of increasing the processability of polyanhydrides. Solubilities of the 20:80 copolymers of P(CPP–SA) and P(FAD–SA) are compared by Domb and Maniar (1993). They reported improved solubility of the later over former in several organic solvents including (in order of decreasing solubility) THF, 2-butanone, 4-methyl-2-pentanone, acetone, and ethyl acetate.

Altering the linearity of aromatic polyanhydrides has proven to be a successful strategy for increasing solubility. Campo *et al.* (1999) reported the solubility of P*o*-CPP and P*o*-CPH in THF to be 124 mg/ml and 130 mg/ml, respectively. Anastasiou and Uhrich (2000a) reported that the *ortho*-isomers P*o*-*o*-CPX, P*m*-*o*-CPX, P*p*-*o*-CPX, and P*o*-*p*-CPX also had improved solubilities in DMF, and all but the P*p*-*o*-CPX had improved solubility in THF, whereas the P*p*-*p*-CPX could not be synthesized because its corresponding methyl ester monomer was not even soluble due to the rigidity of the three *para*-aromatic moieties in sequence. Other chemistries also demonstrated improved solubilities. The poly(anhydride-*co*-ester)s and poly(anhydride-*co*-imide)s synthesized by Jiang and Zhu (2001; Jiang *et al.*, 2001c) demonstrated solubility in THF and the esters were also soluble in DMSO in addition to DCM.

B. Characterization of Thermal Properties, Crystallinity, and Phase Behavior of Polyanhydrides

1. Thermal Transitions

It is important to characterize the thermal properties of polyanhydrides that are proposed for drug delivery applications, as changes in crystallinity

can affect degradation profiles and drug release kinetics. The anticipated dependences of chain structure on glass transition temperature (T_g) are evident in most of the polyanhydrides studied. The most rigid polymer, PTA, has a glass transition temperature of 245°C and a melting point reported alternatively at 372°C (Leong *et al.*, 1985) and 400°C (Yoda, 1963). As methylene groups are added to the *p*-aromatic polyanhydrides, the T_g and T_m generally exhibit systematic reductions. PCPM has a T_g reported at 86 and 92°C and a T_m reported at 196°C. PCPP has a T_g that has been reported to be between 92 and 96°C and T_m of between 230 and 266°C, while PCPH has a T_g that is difficult to detect, but found at 47–48°C and T_m between 123 and 147°C (Campo *et al.*, 1999; Domb and Langer, 1988b; Domb, 1992; Leong *et al.*, 1985, 1987; Mathiowitz *et al.*, 1990b; Rosen *et al.*, 1983).

The branched aromatic polyanhydrides synthesized by Sanders *et al.* (1999; Mathiowitz *et al.*, 1990b) demonstrated lower T_gs than the corresponding P(PCPP–SA) copolymers. The *para*-xylyl polymers synthesized by Anastasiou and Uhrich (2000a) (P*p*-*o*-CPX and P*p*-*m*-CPX) had systematically higher T_gs than the *ortho*-isomers (P*o*-*o*-CPX, P*m*-*o*-CPX, P*p*-*o*-CPX).

For the aliphatic polyanhydrides, Albertsson and Lundmark (1990a) report that the melting point increases as the number of methylenes between the anhydride bonds increases. For the series PAA, PSA, and PDDA, the melting points are 73, 80, and 107°C, respectively (Albertsson and Lundmark, 1990a). Also, altering PSA by addition of fatty acid terminals lowers the melting point by as much as 12°C from 82°C to as low as 70°C, depending on the specific fatty acid used (Teomim and Domb, 1999, 2001). And PFAD is completely amorphous (Tabata and Langer, 1993).

Staubli *et al.* (1991) offer an in depth analysis of the effects of sequence distribution on the T_g of poly(anhydride-*co*-imide)s and discuss the experimental results with respect to several applicable theoretical models of T_g.

The change in melting point and glass transition of the copolymers as a function of copolymer composition are also of particular interest because this reveals information about the copolymer microstructure. This is discussed along with the crystallinity characterization in the following section.

2. *Crystalline Morphology of Polyanhydrides*

Most of the commonly used polyanhydrides, including the copolymers, are semicrystalline. Crystallinity is characterized by a variety of techniques

including differential scanning calorimetry (DSC) small-angle X-ray scattering (SAXS) and X-ray diffraction (XRD). Optical microscopy of films can also be used to investigate the crystallinity of polyanhydrides. Because most polyanhydrides have T_ms near or above room temperature, the crystallinity is a strong function of the thermal history. Therefore, the weight percents of crystallinity (W_c%) reported here are primarily for neat polymer purified and precipitated from the synthesis reaction and dried under vacuum.

Most of the polyanhydride homopolymers discussed here have W_c% in the range of 50–60. For the aromatic polyanhydrides PTA and PCPP W_c% is around 60 (Domb, 1992; Mathiowitz *et al*., 1990b). As chain flexibility is increased, a corresponding decrease in the crystallinity is observed. PIPA and PCPH have W_c% of 50 and 20, respectively (Domb, 1992; Mathiowitz *et al*., 1990b). PFA, PSA, and PDDA all have a W_c% between 55 and 66 (Domb, 1992; Mathiowitz *et al*., 1988, 1990b). Mathiowitz *et al*. (1990b) provide an excellent summary of the crystallinity of homopolymers and copolymers of PSA, PCPP, PCPH, PFA, P(SA–FA), P(SA–CPP) and P(SA–CPH) (Fig. 4). Of the copolymers studied, only the copolymers P(FA–SA) in the composition range from 20:80 to 70:30 exhibited two melting temperatures, indicating two separate types of crystals (Mathiowitz *et al*., 1990b). Data on thermal transitions, W_c%, and heats of fusion (ΔH_f) are presented for an extensive range of copolymer ratios. Plots of the copolymer crystallinities as a function of the composition are reproduced in Fig. 4. Crystallinity and heat of fusion data are summarized

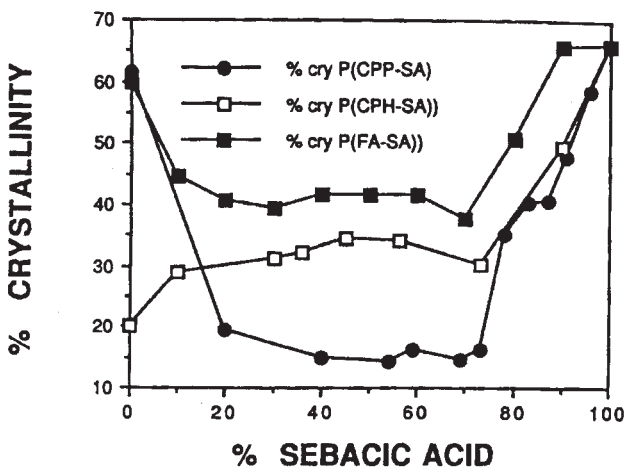


FIG. 4. Crystallinity of several polyanhydride copolymers as a function of composition. From Mathiowitz *et al*. (1990b). Reprinted with permission.

in Table VIII. X-ray diffraction spectra can be found in the work by Subramanyam and Pinkus (1985), Leong *et al.* (1985), Mathiowitz *et al.* (1990b), and Jiang *et al.* (2001c).

When drugs are incorporated into semicrystalline polymers, the crystallinity may be altered, depending on the interactions between the polymer and the drug (Shen *et al.*, 2001b). The effects of drug loading on polymer crystallinity may offer some insights into release kinetics as will be discussed in Section IV.A. Mathiowitz *et al.* (1990a) reported the changes in melting point and degree of crystallinity for PSA and P(CPP–SA) 50:50 loaded with various model drugs at different loading levels. The effects on polymer crystallinity and melting point for different drugs provides information on the solubility of the drugs in the polymer matrix, which may be used to predict how drug loading will modify the polymer erosion kinetics and thus the drug release kinetics. Shen *et al.* (2001a) used wide-angle X-ray diffraction (WAXD) and DSC to characterize the changes in crystallinity of PSA as a function of the loading of a compatible drug, *p*-nitroaniline (PNA), and an incompatible drug, brilliant blue (BB) (Shen *et al.*, 2001a). The compatible drug reduces the crystallinity, while the incompatible drug has no effect on the polymer crystallinity (Fig. 5).

3. *Amorphous Phase Behavior and Microstructure of Polyanhydrides*

Blending of polymers is a strategy commonly used to design materials with desirable properties for many applications. Few studies have investigated the amorphous phase behavior of polyanhydrides. Domb (1993) developed two techniques for qualitatively assessing polymer miscibility and reported the results for a variety of binary polyanhydride blends as well as blends of polyanhydrides with other biodegradable polymers. Shakesheff *et al.* (1995) studied the phase behavior of PSA blends with poly(DL-lactic acid) (PLA) and the effects of the phase behavior on erosion kinetics by novel techniques allowing *in situ* atomic force microscopy (AFM) and surface plasmon resonance (SPR). Surface enrichment in PSA/PLA blends has also been assessed by AFM (Chen *et al.*, 1998). Chan and Chu (2002) used calorimetry and IR to characterize the phase behavior of PSA/poly(ethylene glycol) blends. Rigorous analysis of the phase behavior of polyanhydrides based on theoretical predictions is not found in the published literature.

When describing erosion of and drug release from surface erodible polymers, it is often implicitly assumed that the matrix erodes uniformly, thus resulting in a uniform release profile for a homogenously dispersed drug. While this may be a valid assumption for some homopolymer systems, neglecting the effects of crystallinity, some multicomponent

TABLE VIII
CRYSTALLINITY AND THERMAL PROPERTIES FOR A VARIETY OF POLYANHYDRIDES

Polymer	T_g (°C)	T_m (°C)	ΔH_f (J/g)	W_c%	References
Aliphatic polyanhydrides					
PAA		70–79	37–78		Albertsson and Lundmark, 1988, 1990b; Domb and Nudelman, 1995
PPA		71.5			Domb and Nudelman, 1995
PSU		77.9			Domb and Nudelman, 1995
PAZ		71.8			Domb and Nudelman, 1995
PSA	60	80–89	126–153	57–66	Albertsson and Lundmark, 1990b; Domb and Langer, 1987; Domb and Nudelman, 1995; Mathiowitz *et al.*, 1990b, 1988
PDDA		88–95	107–123	56	Albertsson and Lundmark, 1990b; Domb and Langer, 1987; Domb and Nudelman, 1995; Mathiowitz *et al.*, 1988
PDX		94.4			Domb and Nudelman, 1995
Aromatic polyanhydrides					
PTA	245	372–400		60	Leong *et al.*, 1985; Yoda, 1963
PIA		259		50	Domb, 1992
PDP	[a]	100–113			Domb and Langer, 1987; Leong *et al.*, 1987
PCPM	86–92	196			Leong *et al.*, 1987; Rosen *et al.*, 1983
PCPP	92–96	230–266	96.3–111	53–61.4	Campo *et al.*, 1999; Domb and Langer, 1988b; Domb, 1992; Leong *et al.*, 1985; Mathiowitz *et al.*, 1990b, 1988

PCPH	47–48[b]	123–143	7.1	20	Campo *et al.*, 1999; Domb and Langer, 1987; Leong *et al.*, 1985, 1987; Mathiowitz *et al.*, 1990b
PCPA		185–205			Domb *et al.*, 1989
PCPV	12	50–74[c]			Domb *et al.*, 1989; Mathiowitz *et al.*, 1992
CPO		48–54			Domb *et al.*, 1989
P*o*-CPP	50				Campo *et al.*, 1999
P*o*-CPH	34				Campo *et al.*, 1999
P*o*-*o*-CPX	82	[d]			Anastasiou and Uhrich, 2000a
P*m*-*o*-CPX	71	[d]			Anastasiou and Uhrich, 2000a
P*p*-*o*-CPX	84	114			Anastasiou and Uhrich, 2000a
P*o*-*p*-CPX	101	[d]			Anastasiou and Uhrich, 2000a
P*m*-*p*-CPX	89				Anastasiou and Uhrich, 2000a
Other polyanhydrides					
PFA	41	246	67	60	Domb, 1992; Mathiowitz *et al.*, 1990b
PFAD		25–30		0	Domb and Maniar, 1993
PCPAM	35.8				Jiang and Zhu, 2001
PCPSM	36.4				Jiang and Zhu, 2001
CEFB	81				Jiang *et al.*, 2001c
CPFB	73				Jiang *et al.*, 2001c
CBFB	60				Jiang *et al.*, 2001c

[a] Leong *et al.* (1987) reported that no T_g was observed above room temperature.
[b] Leong *et al.* (1987) reported that no T_g was observed above $-20^{\circ}C$.
[c] Mathiowitz *et al.* (1992) reported to be amorphous.
[d] No melting point observed (Anastasiou and Uhrich, 2000a).

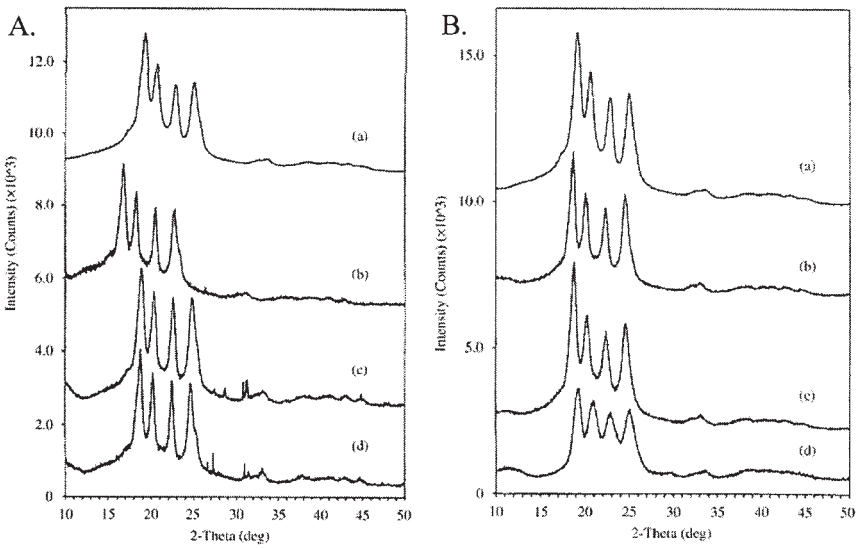


FIG. 5. WAXD spectra for: (A) BB-loaded PSA, and (B) PNA-loaded PSA. (A) BB loading is (a) 0, (b) 15, (c) 30, and (d) 45. Note that as loading increases, the spectrum shows no change for the PSA crystallinity, but crystals of BB appear, indicating that the solute and polymer are immiscible. (B) PNA loading is (a) 0, (b) 5, (c) 10, and (d) 15. Note that there are no peaks corresponding to PNA as the loading increases, however, the polymer crystallinity decreases with increased loading, indicating polymer/solute compatibility. From Shen *et al.* (2001a). Reprinted with permission.

polymer matrices may exhibit microphase separation, even when the copolymers are random (Shen *et al.*, 2001b). In such phase-separated systems, a drug will thermodynamically partition.

The erosion of copolymers requires the hydrolytic cleavage of three bond types: the A–A bond, the A–B bond, and the B–B bond. If the degradation rates of these three bonds are unequal, as is likely the case, then the erosion will be inhomogeneous. And, if drugs are inhomogeneously distributed in the polymer matrix, the drug release profile will not follow overall device erosion (Shen *et al.*, 2002). Therefore, it is necessary to accurately describe the microstructure of microphase-separated systems.

The length scale on which this microphase separation occurs can be obtained by considering the sequence distribution of monomers in the copolymers. For instance, number-average sequence lengths can be determined from ^{1}H NMR (Mathiowitz *et al.*, 1990b; Ron *et al.*, 1991; Shen *et al.*, 2002; Tamada and Langer, 1992). One may estimate that the length scale of the phase-separated domains is likely to be less than < 10 nm. The characterization proves to be challenging as there are few

microscopy or spectroscopy techniques that can resolve such small length scales. However, the effects on drug release kinetics are apparent (see Section IV.A).

C. Biocompatibility of Polyanhydrides

Biocompatibility is an essential property of new biomaterials for drug delivery. Biocompatibility is always assessed with respect to specific applications and may be assessed with respect to cytotoxicity, allergic responses, irritation, inflammation, mutagenicity, teratogenicity, and carcinogenicity (Katti *et al.*, 2002). The reviews by Katti *et al.* (2002) and Domb *et al.* (1997) provide good discussions on the biocompatibility studies that have been conducted with polyanhydrides over the past two decades.

Leong *et al.* (1986) conducted experiments with the degradation products of P(CPP–SA) to determine mutagenicity and teratogenicity. In the same study, PCPP and PTA were implanted in rat corneas and PCPP was implanted subcutaneously in rat abdomens for histology. Endothelial and smooth muscle cell cultures on P(CPP–SA), P(SA–TA), and PTA were also conducted to assess cytotoxicity. Mutagenicity and teratogenicity tests were both negative, and the *in vivo* experiments revealed no inflammation. Cell cultures exhibited normal proliferation and no abnormal morphologies (Leong *et al.*, 1986).

The biocompatibility of P(CPP–SA) implants in the brain was assessed by Brem *et al.* (1989) and Tamargo *et al.* (1989). In the former study the 50:50 copolymer was implanted in rabbit brains and compared to a gelatin based implant used in neurological surgery (Gelfoam) and induced similar mild reactions (Brem *et al.*, 1989). In the latter study the 20:80 copolymer was implanted in rat brains and was compared to Gelfoam® and a cellulose-derived product (Surgicel®). Inflammatory response was similar to that induced by the Surgicel®, but more severe than the Gelfoam®. No local or systemic toxicity was observed (Tamargo *et al.*, 1989). The brain biocompatibility of P(FAD–SA) was investigated by Brem *et al.* (1992) and found to be comparable to that of P(CPP-SA).

Laurencin *et al.* (1990) conducted extensive local and systemic toxicity studies with P(CPP–SA), which also showed excellent biocompatibility and toxicology. Domb (1992) studied the biocompatibility of P(CPP–IPA), P(CPP–IPA–SA), and P(CPP–SA) by subcutaneous and intramuscular implants in rabbits. Inflammation occurred at week one and was more pronounced for the intramuscular implants, but subsided in all cases by week 4 (Domb, 1992). Domb and Nudelman (1995) conducted

subcutaneous biocompatibility studies in rats with poly(pimelic acid) (PPA), poly(azelaic acid) (PAZ), PSA, and PDDA resulting in mild inflammation but no encapsulation or other pathologies. The systemic and local biocompatibility of the ricinoleic acid-based polymers was investigated and confirmed by Teomim *et al.* (1999) by subcutaneous implantation in rats. Jiang *et al.* (2001a) assessed the biocompatibility of the poly(anhydride-*co*-ester)s PCPA, PCPS, and P(CPA-*co*-CPS) by subcutaneous implants in rats. Mutagenicity and toxicity were not observed, though mild inflammatory responses were observed.

IV. Degradation, Erosion, and Drug Release Kinetics

A. Experiments

1. Polymer Stability

The degradation kinetics of several polyanhydrides have been assessed under different storage conditions, to determine the useful shelf life. Rate constants and activation energies for degradation of a variety of polyanhydrides in solution have been reported (Domb and Langer, 1989). In solution, degradation rate is an increasing function of temperature. Aromatic polymers such as PCPM, PCPP, and PCPH, and PDP all maintain their molecular weights both in the solid state and in organic solution for up to a year, but aliphatic polymers show a first order decrease in molecular weight with time (Chasin *et al.*, 1990; Domb and Langer, 1989). Domb *et al.* (1989) reported that the PCPV and PCPO were stable for six months when stored *in vacuo* at room temperature. However, when stored in concentrated chloroform solution, the molecular weights of both polymers were reduced by 50% in only about 3 h. The degradation products could be repolymerized, proving that the degradation occurred primarily via the anhydride interchange and could be reversed (Domb *et al.*, 1989). Chan and Chu (2003) showed that in humid environments, depolymerization results primarily in the formation of diacid products, and therefore occurs by hydrolysis. Domb (1992) also demonstrated the stability of aromatic copolymers stored both under dry argon and in DCM solution, and under exposure to γ-irradiation. The *ortho*-substituted aromatic polyanhydrides, salicylic acid-based poly(anhydride-*co*-ester)s, and ricinoleic acid based poly(anhydride-*co*-ester)s also demonstrate stability to γ-irradiation (Bedell *et al.*, 2001; Erdmann *et al.*, 2000; Krasko *et al.*, 2003). From a study of these results and the studies of other

polyanhydrides, storage in a dry atmosphere below −20°C is recommended if polymers are not going to be used within a few days of synthesis (Tamada and Langer, 1992).

2. *In vitro Degradation, Erosion, and Drug Release Kinetics*

In vitro kinetics experiments are usually conducted on compression molded monolithic polymer tablets, slabs, or cylinders with well-defined surface areas. Compression molding is done above the glass transition and near the melting point. Drugs are incorporated by co-dissolution with the polymer or mechanical mixing in the melt. If erosion profiles are desired, the polymer samples can be removed from the dissolution media at the specified times, dried, and massed. Degradation and drug release requires an assay for the monomer or drug content of the dissolution media. UV Spectrophotometry or HPLC are common techniques. Monitoring the appearance of a single component in the dissolution media is not a reliable method for characterizing the overall erosion rate of a multicomponent system, even when that system is surface-erodible. Such generalizations should be carefully avoided, particularly when the system contains hydrophilic and hydrophobic moieties. For example, Shieh *et al.* (1994) demonstrate that different drugs release from the same matrix with different kinetics. In this study, the model hydrophilic drug acid orange (AO) released faster than the PSA monomer from P(FAD–SA) (50:50) systems, diffusing out of the polymer matrix, while rhodamine b base (RhoB) released more slowly than the PSA monomer from the same system (Shieh *et al.*, 1994). For other compositions, the AO release profile more closely matched the PSA degradation profile (Shieh *et al.*, 1994).

The *in vitro* degradation and drug release of polyanhydride formulations is not necessarily equivalent to the *in vivo* kinetics. For information on the *in vivo* kinetics, the interested reader is referred to the recent review by Katti *et al.* (2002) and the review by Domb *et al.* (1997).

a. Modulating erosion rates and drug release rates. The erosion rate constants reported in the literature or estimated from degradation or erosion data for many of the polyanhydrides discussed in this review are summarized in Table IX. Many of the homopolymers exhibit zero-order degradation over the majority of the release time. As polymer hydrophobicity is increased, the erosion rates generally decrease, presumably due to the decrease in reactivity of the anhydride bond. However, increase in polymer hydrophobicity corresponds to increase in monomer hydrophobicity as well. The corresponding decrease in erosion may therefore be

TABLE IX
EROSION RATE CONSTANTS FOR MANY COMMON POLYANHYDRIDES

Polymer	Erosion rate constant (mol cm^{-2} day^{-1})	Weight-average molecular weight	Reference
PSA	2.7×10^{-5}	23,900	Leong *et al.*, 1987
PDDA	5.4×10^{-5} [a]	32,700	Albertsson and Lundmark, 1990a
PCDA	9.3×10^{-5}		Zhang *et al.*, 2001
PCPA	3.1×10^{-5}		Domb *et al.*, 1989
PCPV	1.3×10^{-5}	44,600	Domb *et al.*, 1989
PCPO	2.5×10^{-6}	33,300	Domb *et al.*, 1989
PTA	3.2×10^{-5}		Leong *et al.*, 1985
PCPM	3.4×10^{-5} [b]	11,800	Rosen *et al.*, 1983
PCPP	1.1×10^{-7}	15,000	Leong *et al.*, 1985
P*o*-CPP	6.3×10^{-7}		Bedell *et al.*, 2001
PCPH	1.4×10^{-8}	9530	Leong *et al.*, 1985
P*o*-CPH	1.2×10^{-5}		Bedell *et al.*, 2001
PCPS	1.2×10^{-5}		Jiang *et al.*, 2001a
PCPA	5.3×10^{-5}	21,000	Jiang *et al.*, 2001a
PXDA	3.1×10^{-5}	7920	Leong *et al.*, 1987
PFAD			Tabata and Langer, 1993
PHFB	1.6×10^{-6}	15,700	Kaur *et al.*, 2002

CopolymerP (CPP–SA)	Erosion rate constant (μg cm^{-2} day^{-1})	Weight-average molecular weight	Reference
100:0	1.4	15,000	Leong *et al.*, 1985
85:15	6.0	9,840	Leong *et al.*, 1985
45:55	80.0	6,140	Leong *et al.*, 1985
21:79	160.0	12,030	Leong *et al.*, 1985
0:100	210	23,900	Leong *et al.*, 1987
Polyanhydrides with other functional groups	**Erosion rate constant (μg cm^{-2} day^{-1})**	**Number-average molecular weight**	**Reference**
P(A-*co*-U)	8400	5900	
	3600	9100	Hartmann *et al.*, 1993
	2160	13,700	
P(A-*co*-A)	9120	6800	
	5280	10,800	Hartmann *et al.*, 1993
P(A-*co*-E)	2880	6,390	
	480	10,900	Hartmann *et al.*, 1993

[a] Erosion experiment conducted at pH 7.2.
[b] Estimated from linear portion of sigmoidal profile.

due to both degradation kinetics and/or monomer dissolution kinetics (Hanes *et al*., 1998). Evidence has also been presented (see, for example, Shakesheff *et al*., 1994) that crystalline domains erode much more slowly than amorphous domains. Thus, careful control of crystallinity may be necessary to accurately modulate erosion and drug release kinetics.

Erosion rates of copolymers can also be modulated by changing the copolymer composition. As an example, erosion rates for three compositions of P(CPP–SA) are reported in Table IX. Similar results were reported by Domb and Maniar (1993) for the copolymers of P(FAD–SA). This study also showed that the copolymers degrade in a heterogeneous fashion, that is, at later times, the composition is richer in the more slowly degrading monomer. Note that erosion rates are varied over two orders of magnitude (Table IX). The same phenomenon was demonstrated by Shakesheff *et al*. (1995) for PSA/PLA blends by a novel technique allowing *in situ* AFM and SPR measurements. Further characterization of these blends revealed surface segregation of the PLA phase, which slowed erosion for high PLA content blends (Davies *et al*., 1996).

Whether in copolymers or blends, inhomogeneous erosion has a nontrivial effect on drug release kinetics as will be shown later. Leong *et al*. (1985) demonstrated that the pH of the degradation media also has a dramatic effect on the erosion rate, which increases with increasing pH. The acceleration of degradation of polyanhydrides with increase in pH is widely reported and has been used to speed up experiments (Shakesheff *et al*., 1994).

Molecular weight may also affect the erosion rate. Table IX shows the degradation rate of a representative poly(anhydride-*co*-urethane), a poly(anhydride-*co*-amide), and a poly(anhydride-*co*-ester) of different molecular weights (Hartmann *et al*., 1993). For all of these polymers reported, the erosion rate decreases as the molecular weight increases.

In their study of branched PSA, Maniar *et al*. (1990) found that the molecular architecture of branched polymers affects the release kinetics in a variety of ways. They found that the branched polymers degraded faster than linear PSA of comparable molecular weight (Maniar *et al*., 1990). They also noted that drug (morphine) release profiles were more characteristic of bulk erosion than surface erosion: An initial lag time during which very little drug was released was associated with the time required for water to swell the polymer. This was followed by a period of relatively fast release, which tapered off as the device disintegrated. The polymer matrix lost its mechanical integrity before the release experiment was complete (Maniar *et al*., 1990). Despite the increase

in degradation rate, release rates from the polymer randomly branched with 1,3,5-benzene tricarboxylic acid were much lower than release rates from PSA (Maniar *et al*., 1990). The release from the graft type polymer branched with poly(acrylic acid) approached that of PSA (Maniar *et al*., 1990).

Evidence that drug loading modifies the erosion rate can be found in many drug release studies. Particularly at higher loadings, hydrophilic drugs tend to increase the overall erosion rate of the polymer (Park *et al*., 1996; Shen *et al*., 2002). This phenomenon is attributed to the contribution that the drug makes to the overall chemistry of the system, as well as porosity and voids that may form as hydrophilic drug crystals rapidly dissolve from the exposed surface (Sandor *et al*., 2002). One study of drug release from bioerodible polyanhydrides found a change in the drug release kinetics from zero-order to first order by simply changing the pH of the media or by changing the hydrophobicity of the drug (Park *et al*., 1997).

Finally, drug release profiles can be altered by altering the distribution of the drug in the polymer matrix. For purely surface eroding systems, it is theoretically possible to obtain any desired drug release profile by fabricating a device with the corresponding drug distribution profile. Design and fabrication of devices with non-uniform drug distribution is discussed in Section V.

b. Surface changes during erosion. Albertsson and Lundmark (1990a) reported that during the degradation of PDDA, the surface showed a lower C/O ratio (from electron spectroscopy for chemical analysis (ESCA) studies) than in the neat polymer, indicating partial oxidation. Mathiowitz *et al*. (1993) discussed the effects of crystallinity and liquid crystallinity on the degradation kinetics in P(CPH–SA) and P(CPP–SA) copolymers. Evidence that crystalline domains degrade more slowly than amorphous domains is also reported in several studies (Shakesheff *et al*., 1994).

The monomer solubility has a crucial effect on the surface characteristics of eroding polymer systems. Undissolved monomer deposited on the surface complicates erosion and release kinetics by presenting a diffusional barrier for drug release as well as water ingress. The compounding effect slows not only the release of monomer and drug, but also the prerequisite hydrolysis of the polymer backbone that results in release (Goepferich *et al*., 1996). The solubilities of the class of aliphatic polyanhydride monomers from adipic acid (six carbons) to dodecandicarboxylic acid (14 carbons) vary from 50 mg/ml to <0.01 mg/ml,

generally decreasing as the length of the methylene chain increases (Domb and Nudelman, 1995).

c. Chemical changes during erosion. Because the degradation products of polyanhydrides are acidic (see p*K*a's reported in Goepferich and Langer, 1993a), and the degradation is a strong function of pH, it has been hypothesized that during erosion the pH of the microenvironment very near the surface of a device may not be the same as that of the dissolution media. Dissolved drugs may also affect the local pH. This local pH is difficult to measure or estimate (Goepferich and Langer, 1993a), but may have profound effects on the erosion and drug release profiles. Mäder *et al.* (1997) employed spectral spatial paramagnetic resonance imaging and measured pH values inside eroding samples of P(CPP–SA) as low as 4.5, though the dissolution media was buffered at 7.4.

The composition of copolymers usually changes during erosion due to the disparity between the degradation kinetics of the two corresponding homopolymers. Actually, in binary copolymers there are three types of bonds that may all have different degradation kinetics: the A–A bond, the A–B bond, and the B–B bond. Spectroscopic techniques such as IR and NMR can be used to follow the kinetics of specific bond cleavage in copolymers (Heatley *et al.*, 1998; McCann *et al.*, 1999; Uhrich *et al.*, 1998). Changes in molecular weight during degradation are frequently reported. The formation of relatively stable oligomers in copolymer erosion studies has been shown (Santos *et al.*, 1999). The changes in molecular weight may also result in drastic shifts in thermal transitions during erosion (Bedell *et al.*, 2001).

Figure 6 summarizes some of the important effects contributing to drug release kinetics discussed in this section. Drug release from a simple, homogeneous surface eroding system is shown schematically in Fig. 6a and graphically in Fig. 6c. Zero order release is obtained when the drug (represented by the circles) is uniformly distributed and the system erodes uniformly from the surface. Drug release from a phase-separated surface eroding system is shown schematically in Fig. 6b. In this system, two polymer phases are present, one which erodes quickly (light gray), and one which erodes slowly (dark gray). Drug release accelerates initially because the inhomogeneous erosion and bursting of drug from the slow eroding phase lead to increase in surface area. At later times, the fast eroding phase is completely gone, and the degradation products from the slow eroding phase (triangles) form an insoluble barrier to transport, retarding the release. The result is a sigmoidal release profile shown in Fig. 6d. Additional effects, such as partitioning of the drug are not represented.

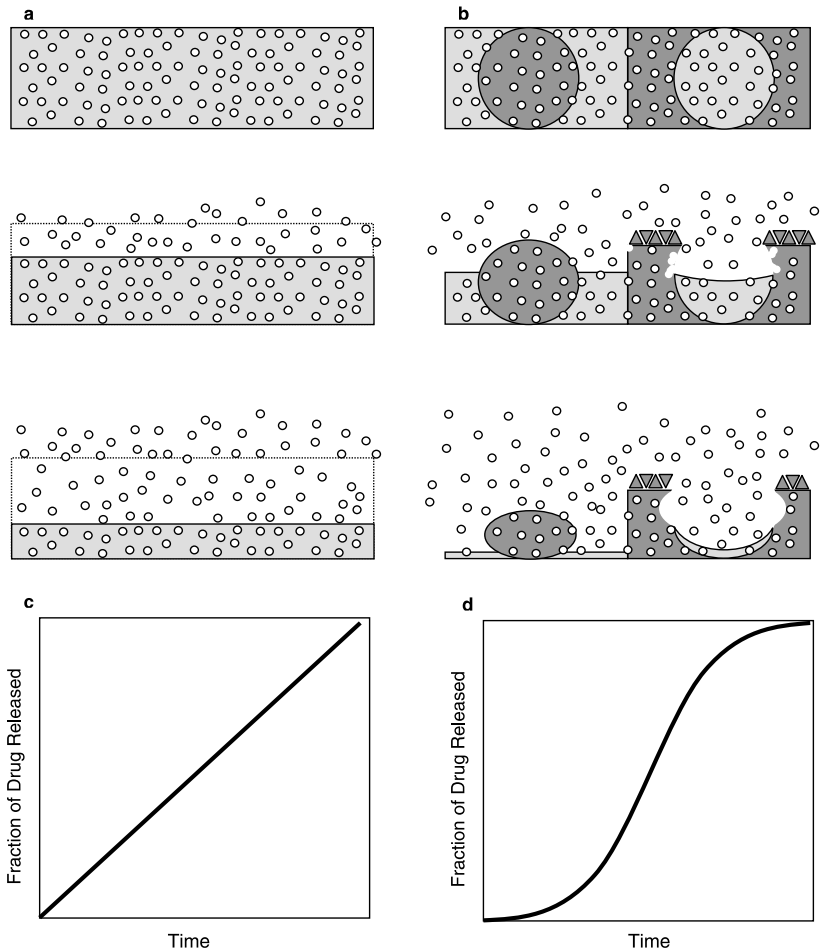


FIG. 6. Mechanism of drug release from (a) homogenous, surface-eroding system, and (b) phase-separated surface-eroding system demonstrating some of the key factors affecting release as discussed in Section IV.A. The corresponding drug release profiles are represented in (c) and (d). Length scale of phase separation is enlarged for emphasis.

B. Modeling Degradation, Erosion, and Drug Release Kinetics

Modeling the behavior of bioerodible polyanhydrides is complicated by the many phenomena contributing to release profiles described in the previous section. The degradation kinetics may be coupled to other processes, such as diffusion and dissolution, and the overall erosion kinetics represent the sum of all of these multiple processes (Goepferich, 1996a).

The phenomena that contribute to erosion kinetics may be difficult or impossible to study independently (Goepferich, 1996b). Therefore, great care must be taken when formulating or applying a model to ensure that the phenomena described by the model are the dominant phenomena controlling the kinetics. A variety of models have been developed that account for different aspects of polymer microstructure, degradation kinetics, and drug loading. The recent review by Goepferich and Tessmar (2002) discusses degradation and erosion of polyanhydrides with an eye to developing more accurate models. And the review by Siepmann and Goepferich (2001) discusses many of the recent models and could be used to aid in selection of the appropriate model for a given system.

Burkersroda *et al*. (2002) provide a model that can be used to estimate whether a polymer is more accurately characterized as surface eroding or bulk eroding. In this model, the ratio of a characteristic time scale for diffusion to a characteristic time scale for degradation (comparable to a Deborah number) determines the "erosion number," ε (Burkersroda *et al*., 2002). For $\varepsilon \gg 1$, a device is surface eroding, whereas for $\varepsilon \ll 1$, a device is bulk eroding (Burkersroda *et al*., 2002). A key component of this model is the device dimensions. Theoretically, even very hydrophobic polymers can be bulk eroding, provided the device is sufficiently small. If the polymer matrix itself is hydrophobic, the polymer degradation rate can be decreased by several orders of magnitude.

The simplest model for pure erosion control with kinetics dominated by a single rate constant and uniformly distributed drugs was described by Hopfenberg (1976). This model says nothing about the various physical phenomena that contribute to erosion, and therefore fails to describe drug release profiles from many polyanhydride systems. Below we classify some of the models that can be found in the literature.

1. Phenomenological Models

The broadest class of models, phenomenological models, account explicitly for individual phenomena such as swelling, diffusion, and degradation by incorporation of the requisite transport, continuity, and reaction equations. This class of models is useful only if it can be accurately parameterized. As phenomena are added to the model, the number of parameters increases, hopefully improving the model's accuracy, but also requiring additional experiments to determine the additional parameters. These models are also typically characterized by implicit mean-field approximations in most cases, and model equations are usually formulated such that explicit solutions may be obtained. Examples from the literature are briefly outlined below.

The transport and continuity equations for surface eroding polymers with two moving boundaries (defining a diffusion zone for drugs inside the polymer matrix) were solved by Thombre and Himmelstein (1984). No account was made for inhomogeneities either in polymer matrix or the drug distribution, but the model was extended to account for the presence of a membraneous diffusive barrier at the surface. A later extension of the model accounted for an external mass transfer coefficient and changes in degradation rate and drug diffusivity with pH and the progress of degradation (Thombre and Himmelstein, 1985). This model was solved numerically.

Batycky *et al*. (1997) developed a model applicable for bulk eroding systems. An interesting component of this model is the explicit accounting of the changes in the molecular weight distribution with time via both end chain scission and random chain scission. Larobina *et al*. (2002) developed a model for release from copolymers that accounts for microphase separation in copolymers and partitioning of drugs into the phase separated microdomains. Two moving erosion fronts are assumed, leading to three regimes of release. Analytical solutions are obtained.

2. *Discretized Models*

Zygourakis (1990; Zygourakis and Markenscoff, 1996) developed a discretized model in which cells are assigned a degradation time, upon exposure to solvent, based on their identity as either drug, polymer, solvent, or void. The initial distribution of cells can be modeled after the microstructure of the polymer matrix and multiple phases are explicitly accounted for. The solution is found numerically.

Goepferich and Langer (1993b) developed a similar model, except that finite probabilities are assigned for the erosion of each cell type rather than predetermined erosion times. No account of drug release was made in this model, but the model was applied to materials with two types of polymer cells, designed to signify crystalline and amorphous phases. In a second publication, Goepferich and Langer (1995) also accounted for monomer diffusion through the eroding zone. The solution to this model is also obtained numerically.

V. Design of Polyanhydride Carriers for Controlled Release

Many model formulations of polyanhydrides have been tested both *in vitro* and *in vivo*. The delivery schemes that polyanhydrides have been

used for can be broadly grouped into three classifications—implantable systems for localized drug release, injectable systems, and aerosols for mucosal delivery. Each of these delivery routes presents a unique set of challenges and these are discussed below.

A. Implantable Systems

1. BCNU-Loaded Polyanhydride Discs for Treatment of Glioblastoma Multiforma

The encapsulation and release of 1,3-bis(2-chloroethyl)nitrosourea (BCNU) in P(CPP-SA) 20:80 wafers was the first implantable controlled release device based on polyanhydrides that was FDA-approved and marketed (Gliadel®) (Chasin *et al*., 1988). BCNU was encapsulated by two techniques, trituration and co-dissolution, resulting in different release profiles (Chasin *et al*., 1990, 1991). The triturated samples released faster than those prepared by co-dissolution, presumably due to more homogeneous loading in the samples prepared by co-dissolution.

2. Laminated Devices for Pulsatile Release

Jiang and Zhu (2000) and Qiu and Zhu (2001) have reported the fabrication of multilayered devices composed of stacks of compression-molded disks of alternating compositions. One type of disk is either P(SA–EG) or P[SA-*co*-TMAgly)-*b*-EG] and the other is a pH-sensitive, protein-loaded blend of, for example, poly(methacrylic acid) and polyethoxazoline. The release of model proteins, myoglobin, bovine serum albumin, and FITC-dextran, and compounds such as brilliant blue have been studied and pulsatile release profiles have been demonstrated (Jiang and Zhu, 2000; Qiu and Zhu, 2001).

3. Other Devices

Erdmann *et al*. (2000) report the fabrication of devices for the localized delivery of salicylic acid from the poly(anhydride-*co*-ester)s mentioned in Section II.C. A unique feature of this drug delivery system is that the drug compound is part of the polymer backbone. Devices were implanted intraorally and histopathology was reported (Erdmann *et al*., 2000). Chasin *et al*. (1990) review fabrication and testing of implantable formulations for other drugs including angiogenesis inhibitors for treatment of carcinomas and bethanechol for the treatment of Alzheimer's disease.

B. Injectable Systems

Injectable polyanhydride systems for drug delivery usually consist of polymer microspheres suspended in an injection media. Langer and co-workers reported on three techniques for the fabrication of drug loaded polyanhydride microspheres: hot-melt, solvent removal, and spray drying (Bindschaedler *et al*., 1988; Mathiowitz and Langer, 1987; Mathiowitz *et al*., 1988, 1990a, 1992). The hot-melt technique used by Mathiowitz and Langer (1987) is performed by heating the polymer and drug in a nonsolvent to a temperature above the melting point of the polymer and stirring to disperse the molten droplets. Subsequent cooling freezes polymer microspheres loaded with dissolved drug. This technique is only useful for polymers with melting points sufficiently low that the activity of the drugs is not affected by the heating. In the spray drying technique, polymer and drug are dissolved in a suitable solvent and a spray dryer is used to disperse small droplets into air where precipitation occurs (Mathiowitz *et al*., 1992). The third and most common technique found in the literature is solvent removal. In this technique, a polymer solution (containing drug) is dispersed in a non-solvent (Mathiowitz *et al*., 1988). An emulsion is formed. The solvent is extracted out of the droplets by the non-solvent, precipitating the microspheres. Variations on the solvent removal technique have been optimized for several polymer/drug systems. Double emulsion or phase inversion techniques are used when the drug and polymer are not soluble in the same solvent (Chiba *et al*., 1997; Chickering *et al*., 1997; Thomas *et al*., 1997). Double walled microspheres have been produced by precipitating a second polymer solution onto previously fabricated microspheres (Goepferich *et al*., 1994), and by allowing thermodynamic partitioning of two polymer solutions during the solvent removal process (Leach *et al*., 1999; Pekarek *et al*., 1994). *In vitro* and *in vivo* degradation studies showed that the inner layer of P(CPP–SA) degraded before an outer layer of PLA in double walled systems (Leach and Mathiowitz, 1998; Leach *et al*., 1998).

Microspheres with precisely controlled sizes have been produced by a novel apparatus that uses acoustic excitation and a non-solvent carrier stream to form each droplet in the emulsion separately (Berkland *et al*., 2003). The morphology and hence the drug release kinetics of the microspheres are affected by the fabrication technique. The size of the microspheres can be modulated by changing the stirring rate in the hot melt and solvent removal techniques, however both of these techniques produce highly polydisperse size distributions (Mathiowitz and Langer, 1987; Mathiowitz *et al*., 1988). The surface and internal morphology of microspheres produced by various techniques have also been characterized, as these will affect the drug release kinetics. The hot-melt technique produces non-porous microspheres with

crenellated surfaces (Mathiowitz and Langer, 1987). Solvent removal techniques can produce smooth microspheres, though porosity is difficult to control and crystalline polymers tend to have greater surface roughness (Mathiowitz *et al.*, 1988, 1990a). Spray dried microspheres also have polydisperse size distributions and can have very porous structures. Mathiowitz *et al.* (1992) had difficulty preventing the microspheres made from some polymers from fusing into aggregates with this technique. Drug loading efficiencies and uniformity can vary depending on the compatibility of the drug with the polymer matrix and other characteristics of the fabrication technique. These morphological variations will also have a significant impact on the drug release kinetics, which are discussed in the next subsection.

An advantage of this type of delivery system is that microspheres displaying different release profiles (e.g., being composed of different polymers or different sizes) can be combined in cocktails to obtain release profiles that are the sum of the various release profiles from the individual formulations (Kipper *et al.*, 2002). Multiple drugs could also be delivered this way in a single injection.

Berkland *et al.* (2003) showed that for systems made by solvent removal, the precipitation kinetics play a crucial role in determining drug distribution within the microspheres, and thus the release profiles. For drugs that are incompatible with the polymer matrix, slow precipitation may result in surface segregation of the drug (Berkland *et al.*, 2003). One way of controlling the precipitation kinetics is to carefully control the microsphere size. *Smaller* microspheres precipitate more quickly and therefore exhibit the most *extended* release profiles when the polymer/drug compatibility is low (Berkland *et al.*, 2003). In a study comparing release profiles from tablets and injectable granules (Tabata *et al.*, 1994), it was shown that inhomogeneously distributed drug has little or no detectable effect on release profiles from tablets, while the release profiles from granules exhibit drug bursts at the beginning of the experiment.

Proteins may be stabilized by encapsulation in polyanhydride microspheres. Stability of proteins with respect to water-induced aggregation has been demonstrated to be a function of polymer hydrophobicity for insulin and bovine somatotropin as model proteins (Ron *et al.*, 1993). Encapsulation and enzymatic activity of a variety of other proteins encapsulated in P(SA–FAD) was studied by Tabata *et al.* (1993).

C. Aerosols and Systems Designed for Mucosal Delivery

Many therapeutic proteins must be delivered by injection as alternative delivery routes (e.g., oral) result in low bioavailability. This can be difficult,

inconvenient, and painful, particularly for long-term treatments, for example, in the case of insulin administration for diabetes patients. Mucosal delivery offers an attractive alternative to injection, but poses some unique challenges. The formulation must stabilize the drug, target delivery to the mucosa, remain at the delivery site for extended periods, and facilitate trans-mucosal transport of the drug (Harris and Robinson, 1990). The characteristics of the various mucosa (buccal, nasal, gastrointestinal, and ocular) that can be quantified for design of controlled release devices are summarized by Harris and Robinson (1990). Theories of bioadhesion are briefly outlined by Chickering *et al.* (1995).

Chickering and Mathiowitz (1995) developed a technique for investigating the bioadhesive properties of polymers and showed that p(FA–SA) demonstrated good bioadhesion. Two mechanisms of bioadhesion were proposed: surface free energy effects and hydrogen bonds between carboxylic acid residues in degradation products and mucin or epithelia (Chickering and Mathiowitz, 1995). The same authors showed that encapsulation of a model drug (ducimerol) in P(FA–SA) improved bioavailability in oral delivery experiments (Chickering *et al.*, 1996).

Fu *et al.* (2002) report the optimization of a fabrication procedure for microspheres based on the poly(anhydride-*co*-ether) P(SA–EG). The microspheres are fabricated by solvent removal process that produces a porous structure with densities in the range of 0.344 and 0.077 g cm^{-3} and sizes that are optimized for delivery to the deep lung by inhalation (Fu *et al.*, 2002). An appropriate *in vitro* cell culture model for characterization of the particle–epithelia system was also developed (Fiegel *et al.*, 2003).

VI. Conclusions and Future Opportunities

The past two decades have produced a revival of interest in the synthesis of polyanhydrides for biomedical applications. These materials offer a unique combination of properties that includes hydrolytically labile backbone, hydrophobic bulk, and very flexible chemistry that can be combined with other functional groups to develop polymers with novel physical and chemical properties. This combination of properties leads to erosion kinetics that is primarily surface eroding and offers the potential to stabilize macromolecular drugs and extend release profiles from days to years. The microstructural characteristics and inhomogeneities of multi-component systems offer an additional dimension of drug release kinetics that can be exploited to tailor drug release profiles.

The development of new polyanhydrides has sparked researchers to developed new device fabrication and characterization techniques, instrumentation, and experimental and mathematical models that can be extended to the study of other systems. The growing interest in developing new chemistries and drug release systems based on polyanhydrides promises a rich harvest of new applications and drug release technologies, as well as new characterization techniques that can be extended to other materials. Future endeavors will likely focus on multicomponent polyanhydride systems, combining new chemical functionalities to tailor polyanhydrides for specific applications.

The release characteristics of polyanhydride systems could be used not only to develop clinical treatments, but also to induce chronic disease states as models for studying immune function. Many current models of chronic diseases are based on induction of acute effects, which do not exhibit the same long-term behavior as the disease being modeled.

REFERENCES

Albertsson, A. C., and Lundmark, S. *J. Macromol. Sci. Pure. Appl. Chem.* **A25,** 247 (1988).
Albertsson, A.-C., and Lundmark, S. *Brit. Polym. J.* **23,** 205 (1990a).
Albertsson, A.-C., and Lundmark, S. *J. Macromol. Sci. Chem.* **A27,** 397 (1990b).
Albertsson, A.-C. *J. Appl. Polym. Sci.* **57,** 87 (1995).
Anastasiou, T. J., and Uhrich, K. E. *Macromolecules* **33,** 6217 (2000a).
Anastasiou, T. J., and Uhrich, K. E. *Polym. Prepr.* **42,** 1366 (2000b).
Batycky, R. P., Hanes, J., Langer, R., and Edwards, D. *J. Pharm. Sci.* **86,** 1464 (1997).
Bedell, C., Deng, M., Anastasiou, T. J., and Uhrich, K. E. *J. Appl. Polym. Sci.* **80,** 32 (2001).
Berkland, C., Kipper, M. J., Kim, K. K., Narasimhan, B., and Pack, D. W., *J. Controlled Rel.* **94,** 129 (2004).
Bindschaedler, C., Leong, K., Mathiowitz, E., and Langer, R. *J. Pharm. Sci.* **77,** 696 (1988).
Brem, H., Domb, A., Lenartz, D., Dureza, C., Olivi, A., and Epstein, J. I. *J. Control. Rel.* **19,** 325 (1992).
Brem, H., Kader, A., Epstein, J. I., Tamargo, R. J., Domb, A., Langer, R., and Leong, K. W. *Sel. Canc. Ther.* **5,** 55 (1989).
Bucher, J. E., and Slade, W. C. *J. Am. Chem. Soc.* **31,** 1319 (1909).
Burkersroda, F. V., Schedl, L., and Goepferich, A. *Biomaterials* **23,** 4221 (2002).
Cabré-Castellví, J., Palomo-Coll, A., and Palomo-Coll, A. L., Synthesis 616 (1981).
Campo, C. J., Anastasiou, T., and Uhrich, K. E. *Polym. Bull.* **42,** 61 (1999).
Chan, C.-K., and Chu, I.-M. *Biomaterials* **23,** 2353 (2002).
Chan, C.-K., and Chu, I.-M. *J. Appl. Polym. Sci.* **89,** 1423 (2003).
Chasin, M., Domb, A., Ron, E., Mathiowitz, E., Langer, R., Leong, K., Laurencin, C., Brem, H., and Grossman, S. *Drugs Pharm. Sci.* **45,** 43 (1990).
Chasin, M., Hollenbeck, G., Brem, H., Grossman, S., Colvin, M., and Langer, R. *Drug Dev. Ind. Pharm.* **16,** 2579 (1991).
Chasin, M., Lewis, D., and Langer, R. *Biopharm. Manuf.* **1,** 33 (1988).

Chen, X., McGurk, S. L., Davies, M. C., Roberts, C. J., Shakesheff, K. M., Tendler, S. J. B., Williams, J. R., Davies, J., Dawkes, A. C., and Domb, A. *Macromolecules* **31,** 2278 (1998).
Chiba, M., Hanes, J., and Langer, R. *Biomaterials* **18,** 893 (1997).
Chickering, D. E., and Mathiowitz, E. *J. Control. Rel.* **34,** 251 (1995).
Chickering, D. E. I., Jacob, J. S., Desai, T. A., Harrison, M., Harris, W. P., Morrell, C. N., Chaturvedi, P., and Mathiowitz, E. *J. Control. Rel.* **48,** 35 (1997).
Chickering, D. E. I., Jacob, J. S., and Mathiowitz, E. *React. Polym.* **25,** 189 (1995).
Chickering, D., Jacob, J., and Mathiowitz, E. *Biotechnol. Bioeng.* **52,** 96 (1996).
Conix, A. *Makromol. Chem.* **24,** 76 (1957).
Conix, A. *J. Polym. Sci.* **29,** 343 (1958).
Conix, A. *Macromol. Synthesis* **2,** 95 (1966).
Davies, M. C., Shakesheff, K. M., Shard, A. G., Domb, A., Roberts, C. J., Tendler, S. J. B., and Williams, J. R. *Macromolecules* **29,** 2205 (1996).
De Abajo, J., Babé, S. G., and Fontán, J. *Angew. Makromol. Chem.* **19,** 121 (1971).
Deng, X., Li, Z., Yuan, M., and Hao, J. *J. Appl. Polym. Sci.* **88,** 2194 (2003).
Domb, A. *J. Polym. Sci. A.* **31,** 1993 (1973).
Domb, A. J. *Macromolecules* **25,** 12 (1992).
Domb, A., and Langer, R. *J. Polym. Sci. A.* **25,** 3373 (1987).
Domb, A. J., and Langer, R. S. US Patent 4,789,724 (1988a).
Domb, A. J., and Langer, R. *Macromolecules* **21,** 1925 (1988b).
Domb, A. J., and Langer, R. *Macromolecules* **22,** 2117 (1989).
Domb, A. J., and Maniar, M. *J. Polym. Sci. A.* **31,** 1275 (1993).
Domb, A. J., and Nudelman, R. *Biomaterials* **16,** 319 (1995).
Domb, A., Amselem, S., Shah, J., and Manoj, M. *Adv. Polym. Sci.* **107,** 93 (1993).
Domb, A. J., Elmalak, O., Shastri, V. R., Ta-shma, Z., Masters, D. M., Ringel, I., Teomim, D., and Langer, R. *Drug Target. Deliv.* **7,** 135 (1997).
Domb, A., Gallardo, C., and Langer, R. *Macromolecules* **22,** 3200 (1989).
Domb, A. J., Mathiowitz, E., Ron, E., Giannos, S., and Langer, R. *J. Polym. Sci. A* **29,** 571 (1991).
Edlund, U., and Albertsson, A.-C. *J. Appl. Polym. Sci.* **72,** 227 (1999).
Erdmann, L., and Uhrich, K. E. *Biomaterials* **21,** 1941 (2000).
Erdmann, L., Macedo, B., and Uhrich, K. E. *Biomaterials* **21,** 2507 (2000).
Fiegel, J., Ehrhardt, C., Schaefer, U. F., Lehr, C.-M., and Hanes, J. *Pharm. Res.* **20,** 788 (2003).
Fu, J., Fiegel, J., Krauland, E., and Hanes, J. *Biomaterials* **23,** 4425 (2002).
Goepferich, A. *Biomaterials* **17,** 103 (1996a).
Goepferich, A. *Eur. J. Pharm. Biopharm.* **42,** 1 (1996b).
Goepferich, A., and Langer, R. *J. Polym. Sci. A* **31,** 2445 (1993a).
Goepferich, A., and Langer, R. *Macromolecules* **26,** 4105 (1993b).
Goepferich, A., and Langer, R. *J. Control. Rel.* **33,** 55 (1995).
Goepferich, A., and Tessmar, J. *Adv. Drug Deliv. Rev.* **54,** 911 (2002).
Goepferich, A., Alonso, M. J., and Langer, R. *Pharm. Res.* **11,** 1568 (1994).
Goepferich, A., Schedl, L., and Langer, R. *Polymer* **37,** 3861 (1996).
González, J. I., De Abajo, J., González-Bebé, S., and Fontán, J. *Angew. Makromol. Chem.* **55,** 85 (1976).
Gouin, S., Shu, X. X., and Lehnert, S. *Macromolecules* **33,** 5379 (2000).
Gupta, B., US Patent 4,868,265 (1989).
Hanes, J., Chiba, M., and Langer, R. *Macromolecules* **29,** 5279 (1996).
Hanes, J., Chiba, M., and Langer, R. *Biomaterials* **19,** 163 (1998).
Harris, D., and Robinson, J. R. *Biomaterials* **11,** 652 (1990).

Hartmann, M., and Schulz, V. *Makromol. Chem.* **190,** 2141 (1989).
Hartmann, M., Geyer, A., Wermann, K., Schulz, V., Knips, C., and Pinther, P. *J. Macromol. Sci. Pure Appl. Chem.* **A30,** 91 (1993).
Heatley, F., Humadi, M., Law, R. V., and D'Emanuele, A. *Macromolecules* **31,** 3832 (1998).
Hill, J. W., and Carothers, W. H. *J. Am. Chem. Soc.* **54,** 1569 (1932).
Hill, J. W. *J. Am. Chem. Soc.* **52,** 4110 (1930).
Hopfenberg, H. B., *in* "Controlled Release Polymeric Formulations, ACS Symposium Series No. 33" (D. R. Paul and F. W. Harris, Eds.), p. 26. American Chemical Society, Washington DC (1976).
Jiang, H. L., and Zhu, K. J. *Polym. Int.* **48,** 47 (1999).
Jiang, H. L., and Zhu, K. J. *Int. J. Pharm.* **194,** 51 (2000).
Jiang, H. L., and Zhu, K. J. *Biomaterials* **22,** 211 (2001).
Jiang, H. L., and Zhu, K. J. *Biomaterials* **23,** 2345 (2002).
Jiang, H. L., Tang, G. P., Weng, L. H., and Zhu, K. J. *J. Biomater. Polym. Ed.* **12,** 1281 (2001a).
Jiang, H. L., Zhu, K. J., and Dai, L. J. *Macromol. Rapid. Commun.* **22,** 414 (2001b).
Jiang, H. L., Zhu, K. J., and Dai, L. J. *Polym. Int.* **50,** 722 (2001c).
Katti, D. S., Lakshmi, S., Langer, R., and Laurencin, C. T. *Adv. Drug Deliv. Rev.* **54,** 933 (2002).
Kaur, S., Doerr, A., Thompson, A., and Dalby, C. *J. Polym. Sci. A* **40,** 3027 (2002).
Kipper, M. J., Shen, E., Determan, A., and Narasimhan, B. *Biomaterials* **23,** 4405 (2002).
Krasko, M. Y., Shikanov, A., Kumar, N., and Domb, A. J. *Polym. Adv. Technol.* **13,** 960 (2002).
Krasko, M. Y., Shikanov, A., Ezra, A., and Domb, A. J. *J. Polym. Sci. A* **41,** 1059 (2003).
Kricheldorf, H. R., and Jürgens, C. *Eur. Polym. J.* **30,** 281 (1994).
Krogh-Jespersen, E., Anastasiou, T. J., and Uhrich, K. E. *Polym. Prepr.* **41,** 1048 (2000).
Larobina, D., Kipper, M. J., Mensitieri, G., and Narasimhan, B. *AIChE J.* **48,** 2960 (2002).
Laurencin, C., Domb, A., Morris, C., Brown, V., Chasin, M., McConnell, R., Lange, N., and Langer, R. *J. Biomed. Mater. Res.* **24,** 1463 (1990).
Leach, K. J. P., and Mathiowitz, E. *Biomaterials* **19,** 1973 (1998).
Leach, K. J. P., Takahashi, S., and Mathiowitz, E. *Biomaterials* **19,** 1981 (1998).
Leach, K., Noh, K., and Mathiowitz, E. *J. Microencap.* **16,** 153 (1999).
Leong, K. W., Brott, B. C., and Langer, R. *J. Biomed. Mat. Res.* **19,** 941 (1985).
Leong, K. W., D'Amore, P., Marletta, M., and Langer, R. *J. Biomed. Mater. Res.* **20,** 51 (1986).
Leong, K., Simonte, V., and Langer, R. *Macromolecules* **20,** 705 (1987).
Li, Z., Hao, J., Yuan, M., and Deng, M. *Eur. J. Phys.* **39,** 313 (2003).
Mäder, K., Nitschke, S., Stosser, R., Borchert, H.-H., and Domb, A. *Polymer* **38,** 4785 (1997).
Maniar, M., Xie, X., and Domb, A. J. *Biomaterials* **11,** 690 (1990).
Mathiowitz, E., and Langer, R. *J. Control. Rel.* **5,** 13 (1987).
Mathiowitz, E., Saltzman, W. M., Domb, A., Dor, P., and Langer, R. *J. Appl. Polym. Sci.* **35,** 755 (1988).
Mathiowitz, E., Amato, C., Dor, P., and Langer, R. *Polymer* **31,** 547 (1990a).
Mathiowitz, E., Ron, E., Mathiowitz, G., Amato, C., and Langer, R. *Macromolecules* **23,** 3212 (1990b).
Mathiowitz, E., Bernstein, H., Giannos, S., Dor, P., Turek, T., and Langer, R. *J. Appl. Polym. Sci.* **45,** 125 (1992).
Mathiowitz, E., Jacob, J., Pekarek, K., and Chickering, D. I. *Macromolecules* **26,** 6756 (1993).
McCann, D. L., Heatley, F., and D'Emanuele, A. *Polymer* **40,** 2151 (1999).
Mestres, R. *Synthesis* 218 (1981).
Park, E.-S., Maniar, M., and Shah, J. *J. Controlled Rel.* **40,** 111 (1996).
Park, E.-S., Maniar, M., and Shah, J. C. *J. Controlled Rel.* **48,** 67 (1997).

Pekarek, K., Jacob, J. S., and Mathiowitz, E. *Nature* **367,** 258 (1994).
Pierre, T. S., and Chiellini, *J. Bioactive Compatible Polym.* **1**, 467 (1986).
Pinther, P., and Hartmann, M. *Makromol. Chem. Rapid Commun.* **11,** 403 (1990).
Qiu, L. Y. *Polym. Int.* **51,** 481 (2002).
Qiu, L. Y., and Zhu, K. J. *Polym. Int.* **49,** 1283 (2000).
Qiu, L. Y., and Zhu, K. J. *Int. J. Pharm.* **219,** 151 (2001).
Ron, E., Mathiowitz, E., Mathiowitz, G., Domb, A., and Langer, R. *Macromolecules* **24,** 2278 (1991).
Ron, E., Turek, T., Mathiowitz, E., Chasin, M., Hageman, M., and Langer, R. *Proc. Nat. Acad. Sci. USA.* **90,** 4176 (1993).
Ropson, N., Dubois, P., Jérôme, R., and Teyssié, P. *J. Polym. Sci. A* **35,** 183 (1997).
Rosen, H. B., Chang, J., Wnek, G. E., Linhardt, R. J., and Langer, R. *Biomaterials* **4,** 131 (1983).
Sanders, A. J., Li, B., Bieniarz, C., and Harris, F. W. *Polym. Prepr.* **40,** 888 (1999).
Sandor, M., Bailey, N. A., and Mathiowitz, E. *Polymer* **43,** 278 (2002).
Santos, C. A., Freedman, B. D., Leach, K. J., Press, D. L., Scarpulla, M., and Mathiowitz, E. *J. Control. Rel.* **60,** 11 (1999).
Shakesheff, K. M., Chen, X., Davies, M. C., Domb, A., Roberts, C. J., Tendler, S. J. B., and Williams, P. M. *Langmuir* **11,** 3921 (1995).
Shakesheff, K. M., Davies, M. C., Roberts, C. J., Tendler, S. J. B., Shard, A. G., and Domb, A. *Langmuir* **10,** 4417 (1994).
Shen, E. E., Chen, H.-L. and Narasimhan, B. *Proc. Mat. Res. Soc.* 662 (2001a).
Shen, E., Pizsczek, R., Dziadul, B., and Narasimhan, B. *Biomaterials* **22,** 201 (2001b).
Shen, E., Kipper, M. J., Dziadul, B., Lim, M.-K., and Narasimhan, B. *J. Control. Rel.* **82,** 115 (2002).
Shieh, L., Tamada, J., Tabata, Y., Domb, A., and Langer, R. *J. Control. Rel.* **29,** 73 (1994).
Siepmann, J., and Goepferich, A. *Adv. Drug Deliv. Rev.* **48,** 229 (2001).
Slivniak, R., and Domb, A. *Biomacromolecules* **3,** 754 (2002).
Staubli, A., Mathiowitz, E., and Langer, R. *Macromolecules* **24,** 2224 (1991).
Staubli, A., Ron, E., and Langer, R. *J. Am. Chem. Soc.* **112,** 4419 (1990).
Subramanyam, R., and Pinkus, A. V. *J. Macromol. Sci. Chem.* **A22,** 23 (1985).
Tabata, Y., and Langer, R. *Pharm. Res.* **10,** 391 (1993).
Tabata, Y., Domb, A., and Langer, R. *J. Pharm. Sci.* **83,** 5 (1994).
Tabata, Y., Gutta, S., and Langer, R. *Pharm. Res.* **10,** 487 (1993).
Tamada, J., and Langer, R. *Biomater. Sci. Polym. Ed.* **3,** 315 (1992).
Tamada, J. A., and Langer, R. *Proc. Nat. Acad. Sci. USA* **90,** 552 (1993).
Tamargo, R. J., Epstein, J. I., Reinhard, C. S., Chasin, M., and Brem, H. *J. Biomed. Mater. Res.* **23,** 253 (1989).
Teomim, D., and Domb, A. J. *J. Polym. Sci. A.* **37,** 3337 (1999).
Teomim, D., and Domb, A. J. *Biomacromolecules* **2,** 37 (2001).
Teomim, D., Nyska, A., and Domb, A. J. *J. Biomed. Mater. Res.* **45,** 258 (1999).
Thomas, P. A., Padmaja, T., and Kulkarni, M. G. *J. Control. Rel.* **43,** 273 (1997).
Thombre, A. G., and Himmelstein, K. J. *Biomaterials* **5,** 249 (1984).
Thombre, A. G., and Himmelstein, K. J. *AIChE J.* **31,** 759 (1985).
Uhrich, K. E., Gupta, A., Thomas, T. T., Laurencin, C. T., and Langer, R. *Macromolecules* **28,** 2184 (1995).
Uhrich, K. E., Ibim, S. E. M., Larrier, D. R., Langer, R., and Laurencin, C. T. *Biomaterials* **19,** 2045 (1998).
Weinberg, J. M., Gitto, S. P., and Wooley, K. L. *Macromolecules* **31,** 15 (1998).
Windholz, T. B., US Patent 3,082,191 (1965).

Wu, C., Fu, J., and Zhao, Y. *Macromolecules* **33,** 9040 (2000).
Xiao, C., and Zhu, K. J. *Macromol. Rapid Commun.* **21,** 1113 (2000).
Xu, H.-B., Zhou, Z.-B., Huang, K.-X., Lei, T., Zhang, T., and Liu, Z.-L. *Polym. Bull.* **46,** 435 (2001).
Yoda, N. *Makromol. Chem.* **32,** 1 (1959).
Yoda, N. *Makromol. Chem.* **55,** 179 (1962a).
Yoda, N. *Makromol. Chem.* **56,** 10 (1962b).
Yoda, N. *Makromol. Chem.* **56,** 36 (1962c).
Yoda, N. *J. Polym. Sci. Pt. A.* **1,** 1323 (1963).
Yoda, N., and Akihisa, M. *Bull. Chem. Jpn.* **32,** 1120 (1959).
Zhang, T., Gu, M., and Yu, X. *Polym. Bull.* **45,** 223 (2000).
Zhang, T., Gu, M., and Yu, X. *J. Biomater. Polym. Ed.* **12,** 491 (2001).
Zygourakis, K. *Chem. Eng. Sci.* **45,** 3259 (1990).
Zygourakis, K., and Markenscoff, P. A. *Biomaterials* **17,** 125 (1996).