Bioerodible polyanhydrides for controlled drug delivery

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Initial *in vitro* and *in vivo* (rat) studies using a poly(anhydride), poly[bis(*p*-carboxyphenoxy)methane], as a bioerodible matrix for controlled drug delivery are described. Drug delivery matrices fabricated from this material and containing cholic acid showed a period of nearly zero-order erosion kinetics during which this steroid was released at nearly the same constant rate.

Keywords: Drugs, drug delivery system, polymer, polyanhydride, bioerosion

Although controlled release of drugs can be accomplished by several mechanisms[1], biodegradation of an insoluble polymer carrier to soluble monomer units offers the advantage of eliminating the need for surgical removal of the device. Controlled release matrices composed of hydrophilic biodegradable polymers such as poly(lactic acid), poly(glycolic acid), and their copolymers generally erode in a homogenous manner[2,3]. This leads to a progressive loosening of the matrix which causes changes in both the permeability and mechanical strength of the devices during bioerosion[2,4]. It would be far more desirable if a matrix were to erode heterogeneously, from the surface first. Such erosion will lead to zero-order drug release provided that diffusional release is minimal and the overall shape of the device remains nearly constant; thus maintaining constant surface area[5]. To obtain a device that erodes heterogeneously, the polymer used should be hydrophobic yet contain water labile linkages. The only polymers designed for this purpose have been poly(orthoesters)[6]. However, because of the stability of the backbone bonds, these polymers erode slowly and require additives to promote biodegradation. The delivery systems containing additives, such as water soluble salts, swell considerably leading to diffusional release. It occurred to us that poly(anhydrides), which were originally synthesized as fibre forming polymers in the textile industry[7], but rejected because of their hydrolytic instability compared to polyesters of similar structure[7], might be sufficiently hydrolytically labile to produce heterogeneous erosion at rates suitable for controlled release applications. This paper reports the use of one of these polyanhydrides as a prototype for a new class of biodegradable drug delivery matrices.

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METHODS

Poly[bis(*p*-carboxyphenoxy) methane] (PCPM), was selected as a prototype poly(anhydride) because its erosion rate in NaOH[8] suggested to us sufficient hydrolytic lability for drug delivery application. PCPM was synthesized by the method of Conix[8] from the mixed anhydride of bis(*p*-carboxyphenoxy)methane and acetic acid. The polycondensation was performed *in vacuo* at 195–210°C[8,9]. The *Tg* and *Tm* of the melt pressed polymer were determined on a Perkin–Elmer DSC-2 differential scanning calorimeter.

To formulate drug-free matrices, PCPM was ground using a Fisher Scientific Micro Mill and the resulting particles sized using sieves. PCPM particles (150–300 μm diameter) were melt-pressed between sheets of aluminum foil at 121.1°C and 8000 lbs. (representing from 22–81 kpsi) on a Carver Laboratory Press using shims to regulate device thickness. The matrix dimensions examined ranged from having face areas of 0.2 to 0.8 cm^2 and having thicknesses of 0.05 to 0.10 cm. Specific formulations are given in the legends of *Figures 1 and 2.*

To incorporate a drug, unlabelled cholic acid from Sigma Chemical Co. (15 mg) was dissolved in 10 ml of ethanol. Tritiated cholic acid (2.4-^{3}H) from New England Nuclear, in 125 μl of ethanol (2.42×10^8 DPM, S.A. = 3.72×10^{10} DPM/mg) was added to the unlabelled solution and the solution was dried *in vacuo.* The drug powder (10.5 wt %) was mixed with the PCPM particles and melt-pressed as above. The drug containing device was then sandwiched between two very thin (<1 wt %) drug free layers of ground (150–300 μm diameter) PCPM to eliminate the presence of surface exposed drug particles and then repressed.

In vitro erosion and drug release studies were performed by placing the PCPM devices weighing from 10–50 mg in glass scintillation vials containing 10 ml of

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0.2 M Na phosphate buffer (pH 7.4) at 37° or 60°C. The buffer was periodically changed by removing the device from the vial and placing it in a vial of fresh buffer. The absorbance of the collected buffer solutions was measured on a Gilford spectrophotometer at 243 nm to detect the diacid monomer, bis(*p*-carboxyphenoxy) methane. Concentrations were determined from a standard curve constructed by measuring the absorbance at 243 nm of the pure diacid monomer at concentrations from 0 to 0.02 mg/ml. The polymer devices containing tritiated cholic acid were eroded and the buffer solutions were analyzed on a LS-230 Beckman scintillation counter.

In vivo erosion was studied using three portions cut from a single melt-pressed PCPM slab each with the dimensions 0.26 cm^2 face area $\times$0.0695 cm thick and weighing 24 mg. The surfaces of these devices were disinfected under u.v. light for 30 mins. Each square was implanted subcutaneously in the abdominal region of a Sprague–Dawley rat. An animal was sacrificed at the end of 21, 44, and 153 days and the polymer removed, dried, and weighed.

RESULTS

Poly[bis(*p*-carboxyphenoxy)methane] (PCPM), was chosen as a prototype to examine the usefulness of poly(anhydrides) in controlled release devices. PCPM, synthesized by an adaption of the method of Conix[8], was a yellow translucent amorphous solid with a $Tg = 92°C$ (5°C higher than reported by Conix[8]) and no observable *Tm* (a sample with cholic acid incorporated did, however, show a $Tm = 192°C$ due to cholic acid melting). The molecular weight was reported to be 40 000[8]. The polymer had broad carbonyl stretching vibrations in the infrared of 1780 and 1720 cm^{-1} characteristic of a poly(anhydride) and no OH stretching vibrations (i.e. no stretching between 3300 to 2500 (cm^{-1}) characteristic of the diacid monomer.

Devices were pressed at temperatures and pressures ranging from 93°C to 163°C and 22 kpsi to 81 kpsi. At temperatures below 120°C the polymer did not flow well giving devices with poor mechanical properties. At temperatures above 145°C the devices formed were brittle. There were no discernable differences between devices pressed over the range of 22 to 81 kpsi. The conditions chosen to melt press PCPM were 121°C and 22 kpsi giving devices with suitable mechanical properties and minimizing the possible induction of morphological changes within the polymer during pressing. PCPM hydrolysed completely leaving no insoluble residue. The u.v. spectra of the erosion product was identical to that of the diacid monomer bis(*p*-carboxyphenoxy)methane.

The erosion curves for drug-free PCPM slabs at both 37°C and 60°C are shown in *Figure 1*. Both curves are characterized by an induction period followed by a linear region of mass loss at a nearly constant rate. Throughout the erosion, the devices decreased in size while maintaining their physical integrity suggesting surface erosion is occurring.

The erosion profile was unaltered by scraping the polymer matrix to remove the surface layer; the same induction period was observed. When the polymer matrices that were pre-eroded for 50 hours at 60°C (until the induction period ended), were removed, vacuum dried, and returned to fresh buffer solutions at either 37°C or 60°C, near zero-order erosion of the samples began almost immediately (*Figure 2*).

Drug release from PCPM was investigated *in vitro* using cholic acid which because of its low u.v. absorbance at 243 nm did not interfere with the matrix erosion measurement. The erosion and release profiles were nearly zero-order and had similar slopes (*Figure 3*). Both the drug and the polymer had completely disappeared at nearly identical times.

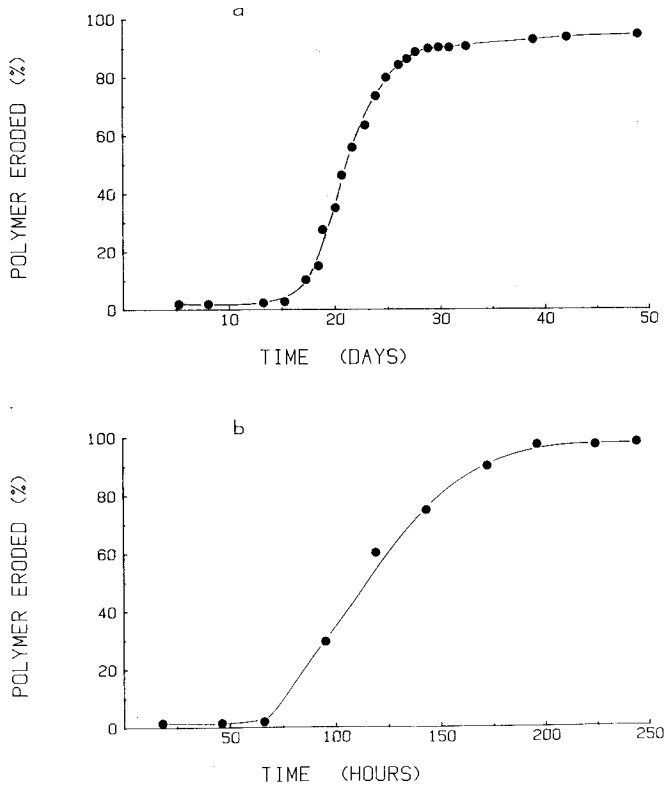

Figure 1 Erosion curves for drug-free PCPM matrices in phosphate buffer at 37°C (a) and 60°C (b). Percent polymer eroded is 100x the cumulative mass eroded at each sample point divided by the total mass of the matrices eroded at 37° and 60°C which were 23 and 18 mg, respectively. The PCPM matrices eroded at 37°C and 60°C were pressed in the same rectangular mould and had the dimensions 0.24 cm^2 face area X 0.08 cm thick and 0.33 cm^2 face area X 0.05 cm thick, respectively

The *in vivo* erosion of drug-free PCPM slabs showed a half-life of about 47 days or approximately five days shorter than *in vitro* erosion at 37°C in pH 7.4 buffer. After 153 days <1% of the polymer remained. The devices were only slightly encapsulated by tissue.

DISCUSSION

These initial studies using PCPM as a prototype poly(anhydride) suggest the suitability of this polymer class for use in bioerodible drug delivery systems. PCPM completely degrades to its monomer, under physiological conditions at rates useful for drug delivery applications. The erosion profile (*Figure 1*) is characterized by an induction period followed by a period of nearly linear zero-under erosion. An investigation of this undesirable induction period was conducted by scraping the surface layers from the polymer matrix. The fact that such treatment did not eliminate or shorten the induction period indicates that morphological surface changes, occurring during the melt pressing, are not the cause of this induction period. The induction period was, however, eliminated by pre-eroding followed by vacuum drying the device. The effectiveness of this pretreatment step suggests that two rate constants might control the rate of device erosion. The first is the rate of hydrolysis of the anhydride linkage and the second the rate of polymer dissolution. In order to begin

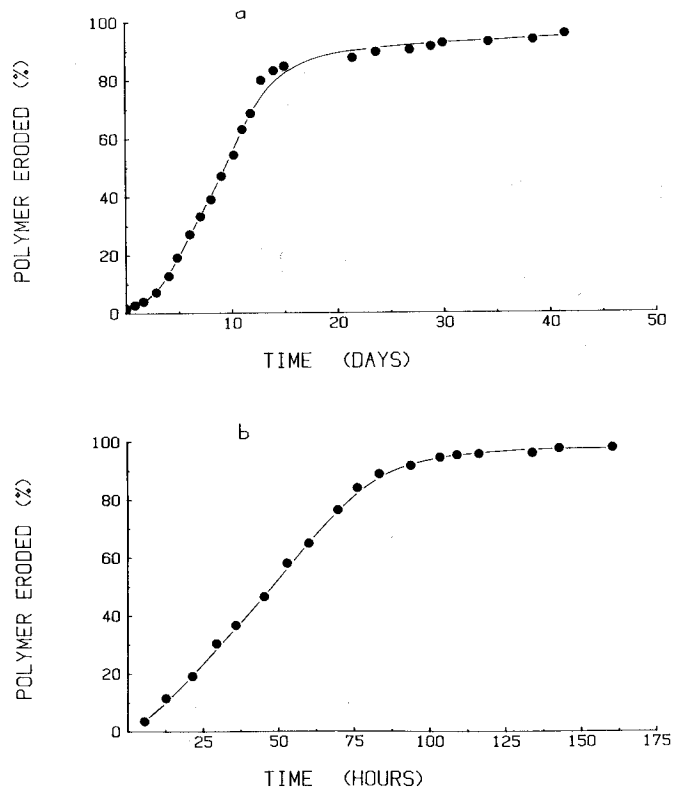

Figure 2 Erosion curves for the drug-free PCPM matrices which have been pre-eroded at 60°C for 50 h. Erosion took place in phosphate buffer at 37°C (a) and 60°C (b). Percent polymer erosion is 100x the cumulative mass eroded at each sample point divided by the total mass of the matrices eroded at 37° and 60°C which were 74 and 25 mg, respectively. The PCPM matrices eroded at 37°C and 60°C had the dimensions 0.57 cm^2 face area ×0.06 cm thick and 1.13 cm^2 face area X 0.05 cm thick, respectively

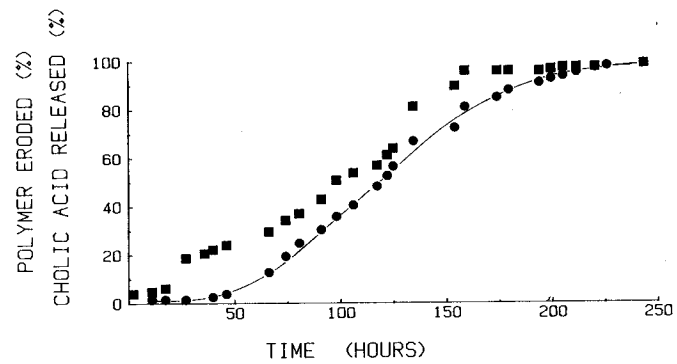

Figure 3 Erosion and release curves for a PCPM matrix containing cholic acid at 10.5 wt.% eroded in phosphate buffer at 60°C. PCPM erosion (●) is plotted as percent polymer erosion which equals 100X the cumulative mass eroded at each sample point divided by total mass of the matrix, 25 mg. Cholic acid release (■) is plotted as the percent cholic acid released which equals 100x the cumulative counts per minute at each sample point divided by the total number of counts per minute within the polymer matrix. The matrix has the dimensions 0.5 cm^2 face area ×0.06 cm thick

to measure monomer units in the buffer it seems likely that many anhydride linkages on the polymer's surface must be cleaved. This non-productive hydrolysis corresponds to the observed induction time. Pre-erosion of the device presumably decreases the surface polymer's chain length and in the subsequent erosion the anhydride hydrolysis rate and device dissolution rate become equivalent. Alternatively the observed induction period and its elimination by pre-erosion may be the result of an initially hydrophobic surface becoming increasingly hydrophilic as hydrolysis occurs. The rate of erosion would increase up to the point where it becomes limited by both the rate of hydrolysis and the rate of water penetration into the polymer.

The decrease in the device thickness throughout the erosion and the maintenance of the matrice's structural integrity as well as the nearly zero-order erosion kinetics suggests that heterogeneous surface erosion predominates. PCPM eroded *in vivo* slightly faster than its *in vitro* erosion in phosphate buffer at pH 7.4 at the same temperature. The thin, partially eroded, polymer slabs were difficult to completely remove from the rats and hence may be the cause for the slightly accelerated *in vivo* erosion rate measurement. Although no tissue irritation was apparent and only slight device encapsulation occurred within the test animals, the toxicity of the polymer matrix and monomer erosion products remains to be investigated. Currently, work is underway in this laboratory[9] to extend the types of drugs released from this matrix and to examine the synthesis of other novel poly(anhydrides) from naturally occurring diacid monomers which might reduce the potential toxicological problems associated with a bio-erodible drug delivery matrix.

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