Polymer Preprints 24, 47-48 (1983)

BIOERODABLE POLYANHYDRIDES FOR CONTROLLED DRUG DELIVERY

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BACKGROUND

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 hydrophillic 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 fiber 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.

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 $Tg=92^{o}C$ ($5^{o}C$ higher than reported by Conix (8)) and no observable Tm (a sample with cholic acid incorporated did, however, show a $Tm=192^{o}C$ 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 vibrators (i.e. no stretching between 3300 to 2500 (cm^{-1}) characteristic of the diacid monomer.

Devices were pressed at temperatures and pressures ranging from $93^{o}C$ to $163^{o}C$ and 22 kpsi to 81 kpsi. At temperatures below 120^{o} C the polymer did not flow well giving devices with poor mechanical properties. At temperatures above $145^{o}C$ 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^{o} C and 22 kpsi giving devices with suitable mechanical properties and minimizing the possible induction of morphological changes within the polymer during pressing. PCPM hydrolyzed completely leaving no insoluble residue. The UV 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 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 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, 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 UV absorbance at 243 nm did not interfere with matrix erosion measurement. The erosion and release profiles were nearly zero-order and had similar slopes (Figure 3).

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 encapusulated 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 is characterized by an induction period followed by a period of nearly linear zero-order erosion. An investigation of this undesirable induction period was conducted by scraping the surface layers form 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 to measure monomer units in the buffer

it seems likely that many anyhdride linkages on the polymer's suface must be cleaved. This non-productive hydrolysis corresponds to the observed induction time. Pre-erosion of the device presumably decreases the surface polymers 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 initally hydrophobic surface becoming increasingly hydrophillic 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 thicknesss throughout the erosion and the maintenace of the matrices 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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