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International Journal of Pharmaceutics 160 (1998) 83–89

international journal of pharmaceutics

Effect of geometry on the erosion characteristics of polyanhydride matrices

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Received 22 July 1997; accepted 10 September 1997

Abstract

The aim of this study was to investigate the effect of device geometry on the erosion characteristics of poly[1,3-bis(*p*-carboxyphenoxy) propane:sebacic acid], *p*(CPP:SA), matrices in phosphate buffer to obtain an insight into the mechanism of polyanhydride erosion. Matrices with different dimensions were prepared using a melt moulding technique and erosion was followed by determining changes in polymer molecular weight, water absorption, mass loss and release of monomers with time of immersion in phosphate buffer pH 7.4 at 37°C. In all matrices the erosion process was characterised by an initial lag phase during which there was a rapid decrease of polymer molecular weight but no significant water absorption, mass loss or release of monomers. The rates of absorption of water and loss of mass after the lag period showed characteristics of both surface and bulk eroding systems. © 1998 Elsevier Science B.V.

Keywords: Drug delivery systems; Biodegradable polymers; Erosion; Polyanhydrides; Device geometry

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1. Introduction

The polyanhydrides are one of a few types of biodegradable polymers that have received approval for use in humans. They have been tested clinically for use in the controlled delivery of a number of drugs (Chasin and Langer, 1990).

It is the hydrolytic instability of the anhydride linkage which renders polyanhydrides attractive as biodegradable drug-carrier matrices. The water-labile anhydride linkage provides the basis for using a variety of backbones and yet ensures biodegradability (Leong et al., 1985). The erosion period depends on the choice and ratio of comonomers, and can be altered by over 1000-fold by simple changes in the polymer backbone (Leong et al., 1990).

Polyanhydrides based on a variety of aromatic and aliphatic dicarboxylic acids have been devel-

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PII S0378-5173(97)00298-6

oped as bioerodible carrier matrices for controlled delivery applications. It has been proposed that polyanhydrides erode heterogeneously at rates suitable for controlled release, without requiring any additives (Ron et al., 1991). Devices fabricated with this group of biodegradable polymers have demonstrated zero-order drug release over several days, biocompatibility when implanted in the body, and have been shown to produce degradation products that are metabolised by the body and are non-toxic and nonimmunogenic (Leong et al., 1990; Laurencin et al., 1990).

Polyanhydrides can be designed with relatively low melting points, usually below 100°C, and are soluble in common organic solvents. Drug delivery devices fabricated using polyanhydrides are flexible enough before and during degradation so that they do not crumble or fragment during use. They are easy to manufacture at a reasonable cost and are hydrophobic enough to allow the drug to be released in a predictable and controlled manner (Domb and Maniar, 1993).

Polymer erosion can be classified into bulk (homogeneous) and surface (heterogeneous) erosion. In bulk erosion, material is lost from the entire volume of the device during the erosion process. The erosion rate depends on the total amount of material and generally decreases as material is depleted. In surface erosion, material is lost from the exterior surface of the polymer matrix. In the case of ideal surface erosion, the erosion rate is directly proportional to the external surface area of the device. Hence, for a surface eroding polymer, control of the erosion period can be achieved by adjusting the dimensions and shape of the polymer matrix. Studying the effect of device geometry can provide an insight as to whether the process is primarily one of surface or bulk erosion. Grizzi et al. (1995) examined the degradation rates of various devices derived from the same poly(DL-lactic acid) polymer and reported that the degradation rate was significantly dependent on the size of the device; the greater the thickness of the device, the greater the rate of degradation. A study of the effect of device thickness on the polyanhydride copolymer poly(fatty acid dimer-co-sebacic acid) showed that devices of different thickness have similar erosion rates, but thicker devices exhibited longer periods of erosion (Shieh et al., 1994). Similarly, in a study of poly(sebacic acid) erosion, thicker devices exhibited a longer period of erosion, but erosion occurred at the same rate as that of thin devices (Tamada and Langer, 1993).

It has been proposed that polymers based on poly[1,3-bis(*p*-carboxyphenoxy) propane:sebacic acid], p(CPP:SA), polyanhydride are surface eroding. The present study investigates the effect on the rate and period of erosion of changing surface area and thickness of p(CPP:SA) matrices prepared by a melt moulding technique. The erosion in phosphate buffer pH 7.4 was monitored by determination of molecular weight changes, water absorption, mass loss and release of monomer. The overall erosion profiles of three different sizes of p(CPP:SA) 40:60 copolymer devices were examined to determine to what extent geometry affected polymer erosion.

2. Experimental

2.1. Materials

Polyanhydride copolymers of 1,3-bis(*p*-carboxyphenoxy) propane (CPP) and sebacic acid (SA) with a molar ratio of 40:60 were synthesised and characterised as previously described (Domb and Langer, 1987).

Potassium dihydrogen orthophosphate (KH_2PO_4) and di-sodium hydrogen orthophosphate 2-hydrate (Na_2HPO_4 $2H_2O$) were supplied by BDH-Merck (Poole, UK). Distilled water was freshly obtained from a Milli-Q Plus water purification system (Millipore, Watford, UK).

Phosphorus pentoxide (P_2O_5), calcium chloride fused granular, and anhydrous silica gel, all GPR grade, were supplied by BDH-Merck (Poole, UK). Chloroform (HPLC grade) and acetonitrile (HPLC grade) were supplied by BDH-Merck. Anhydrous dichloromethane was supplied by Aldrich (Poole, UK).

2.2. Fabrication of matrices

Matrices were prepared using a melt moulding technique (D'Emanuele et al., 1992a,b). Polymer was ground using a mill (Polymix Kinematica, Switzerland) and sieved (Endecotts, UK) to a particle size of less than 250 μm. A weighed amount of polymer was placed into a polytetrafluoroethylene (PTFE) mould and compressed firmly by hand at room temperature. The mould was placed in a preheated oven at 10°C above the polymer melting point. After 15 min the mould was taken out of the oven and allowed to cool in a desiccator over phosphorous pentoxide at room temperature for 15 min after which time the mould was dismantled and the matrix removed. The matrices were stored under dry nitrogen at -80°C prior to use. Matrices were prepared with diameters, thicknesses and weights, respectively, of 5 mm; 0.5 mm and 20 mg; 9 mm, 0.8 mm and 100 mg; 12.5 mm, 1.4 mm and 200 mg. The approximate surface areas of these devices were 50, 150 and 300 mm^2, respectively.

2.3. Erosion studies

Erosion studies were performed on 20, 100 and 200 mg matrices immersed in 10, 50 and 100 ml phosphate buffer solution pH 7.4 respectively, and agitated at 60 rpm in an incubator-shaker (Model S150, Stuart Scientific, Merk, Lutterworth, UK) at 37 ± 0.1°C. Buffer solutions were changed at appropriate intervals of time to maintain sink conditions throughout. At predetermined intervals, matrices were removed from the media and rinsed with water to remove buffer salts. They were weighed and vacuum-dried over phosphorous pentoxide prior to being analysed.

2.4. Characterisation of polymer erosion

To investigate molecular weight changes during degradation of polyanhydride devices, the surface layer of eroded matrices was carefully scraped off and the resultant core pulverised. Samples of the powdered core were dissolved in chloroform and their molecular weight determined relative to polystyrene standards (Polymer Laboratories). A gel permeation chromatography (GPC) system consisting of a pump (Waters 510), Rheodyne syringe injector valve with a 100 μl loop, and a differential refractometer (Waters 410) was used. The samples were eluted with chloroform through a 0.3×30 cm PL gel Mixed-D column with a particle size of 5 μm (Polymer Laboratories), at a flow rate of 1 ml/min. Toluene was used as an internal marker. Data were analysed using commercial software (Millennium 2010, Waters-Millipore).

Mass loss and water absorption of matrices were evaluated by gravimetric analysis. The percentage mass loss (ML%) was deduced from equation 1:

$$\mathrm{ML\%} = 100(W_0 - W_r)/W_0 \qquad (1)$$

where W_0 and W_r are the initial weight and the residual weight of the same dried and partially eroded matrices.

The amount of absorbed water (WA%) was deduced from equation 2:

$$\mathrm{WA\%} = 100(W_h - W_r)/W_r \qquad (2)$$

where W_h is the weight of the hydrated matrix before drying.

Release of CPP monomers was followed by an isocratic HPLC system comprising a M510 pump, a Rheodyne syringe loaded valve (model 7010), a programmable multiwavelength detector (LDC/ Milton Roy Spectromonitor), and an integrator (LDC Analytical C14100). The mobile phase consisted of 1200 ml acetonitrile, 1500 ml distilled water, and 100 ml 1 M HCl solution. A RPR-1 Hamilton column of dimensions 4.1×150 mm, with 5 μm particles, was used as stationary phase. The main column was protected by a RPR-1 cartridge guard column. CPP was detected at 246 nm. The run time was 15 min at a flow rate of 1 ml/min. Six standard solutions were prepared from stock solutions. The standards contained CPP in the concentration range of 3–25 μg/ml and SA in the concentration range of 20–300 μg/ml. The solutions were prepared in pH 7.4 phosphate buffer. Each standard was injected six times, and a calibration curve was constructed.

All erosion experiments were performed in triplicate.

3. Results and discussion

3.1. Molecular weight changes

Fig. 1 shows the changes in the weight-average molecular weight of p(CPP:SA) 40:60 in matrices with different geometry. The profile was similar for all matrices, with rapid initial reduction in molecular weight. The initial rate of decrease of molecular weight was related to device geometry; matrices of lesser thickness and diameter showing faster rates of decrease. This behaviour is a consequence of the gradual penetration of water from the surface into the matrix centre, the thinner the matrix the shorter the time required for water to reach the centre and hence the more rapid the reduction in molecular weight.

Fig. 2 shows typical GPC chromatograms which depict the overall changes in the molecular weight distributions of p(CPP:SA) 40:60 matrices of 12.5 mm diameter with time of exposure to the aqueous buffer solution. The relatively broad molecular weight distribution (polydispersity index > 3) of samples prior to degradation is characteristic of the polyanhydrides (Domb and Langer, 1987). An interesting feature of the chromatograms is the development of a bimodal distribution after 18 h of aqueous immersion which became more noticeable as erosion proceeded. Chromatograms for matrices with diameters of 5 and 9 mm (not shown) exhibited the onset of a bimodal distribution after 12 and 15 h, respectively.

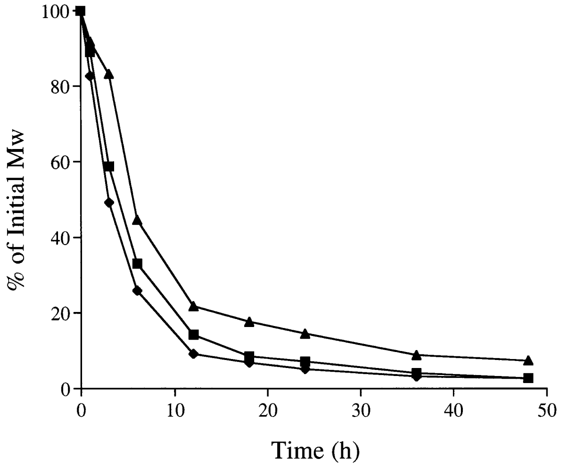

Fig. 1. Molecular weight changes of p(CPP:SA) 40:60 polymer in matrices with diameters of (◆) 5 mm; (■) 9 mm; and (▲) 12.5 mm.

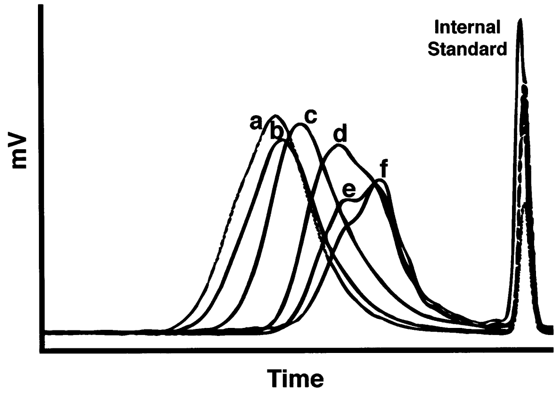

Fig. 2. Typical GPC chromatograms for p(CPP:SA) 40:60 matrices with diameters of 12.5 mm eroded for; (a) 0 h; (b) 3 h; (c) 6 h; (d) 12 h; (e) 18 and (f) 24 h.

A bimodal distribution would normally be expected in samples undergoing pure surface erosion due to the presence of polymer both from the surface erosion layer (sometimes referred to as the reaction zone), and from the intact core. However, in the devices under examination here, the molecular weight changes observed are primarily associated with the device core; although a minor contribution arising from incomplete removal of the outer reaction zone cannot be completely excluded. Accordingly, the bimodality of the molecular weight distribution, where it exists in these samples, is likely to arise due to differences in the degradation rate of crystalline and amorphous polymer regions within the device core as previously observed in poly(lactic acid), PLA, devices (Gogolewski et al., 1993; Nakamura et al., 1989). In a study of the effect of the morphology on the degradation of PLA, comparison between the GPC chromatograms and the X-ray spectra showed a correlation between the appearance of low molecular weight material and increase of crystallinity of devices, which occurred almost simultaneously in the degradation process (Li et al., 1990). As degradation proceeded, the specimens became increasingly crystalline, and the reduction of molecular weight became significant leading eventually to a narrow GPC peak. Therefore, it is believed that the appearance of the narrow peak was related to degradation products resulting from crystallites formed during degradation or ageing in water, or both, giving shorter chains that were more mobile than longer ones, and probably more susceptible to crystallisation. The crystalline domains formed during PLA degradation appeared to be very resistant to further degradation. The accumulation of crystalline material within the device and the greater resistance of this phase to erosion compared with amorphous regions explains the narrow GPC peaks observed for the later time points in PLA/GA (Vert et al., 1991). In the case of p(CPP:SA) polyanhydrides, DSC and X-ray analysis of eroded devices confirmed that devices initially become more crystalline during the first 24 h of erosion (Gopferich and Langer, 1993) and this was attributed to an increase in the ratio of CPP to SA during erosion. The samples examined in the present study initially contain similar amounts of both monomers (40:60 ratio) but preferentially lose SA during erosion and hence would be expected to increase their crystallinity as a consequence of the resulting high CPP content. This leads to a merging of the two peaks to form a narrower peak as seen in Fig. 2f. Irrespective of the mechanism, bimodality takes a longer time to develop in thicker matrices indicating a slower degradation rate in these devices.

3.2. Water absorption

As seen from Fig. 3, device geometry has a significant effect on the water absorption profile. The initial lag phase seen in all three plots correlates with the molecular weight reduction (Fig. 1) and can be attributed to the time required for the polymer molecular weight to decrease to a critical value (D'Emanuele et al., 1992a). A significant difference in the rate of water uptake after this initial phase was observed depending on matrix geometry. Rates of water uptake of approximately 0.9, 0.5 and 0.1 mg/h can be calculated from the water uptake plots assuming linearity immediately after the initial lag phase, for diameters of 12.5, 9 and 5 mm, respectively. Normalisation of these rates to unit surface area gives values of 3×10^{-3}, 3×10^{-3} and 2×10^{-3} mg/h/mm^2, respectively. The similarity of these values suggests that water absorption is primarily a function of the surface area of the matrix. However, it should be noted that the relatively large amounts of water found in the matrix are not characteristic of pure surface erosion. A large amount of water was reported to be taken up by poly(lactide-co-glycolide) devices at 37°C and pH 7.4 (Fildes et al., 1990) which are known to undergo bulk erosion.

3.3. Mass loss study

The effect of geometry of the matrices on mass loss profiles is shown in Fig. 4. An indication of the processes occurring as water penetrates the devices can be obtained by comparing rates of mass loss during the period immediately after the lag phase, covering the time interval 12–48 h, and those calculated from data at time ≥ 48 h. The approximate values calculated assuming linearity of the plots over the initial time period are 0.26, 0.77 and 1.05 mg/h for the 5, 9 and 12.5 mm diameter matrices respectively. Normalisation of these rates to unit surface area gives values of 5.6×10^{-3}, 5.1×10^{-3} and 3.5×10^{-3} mg/h/mm^2

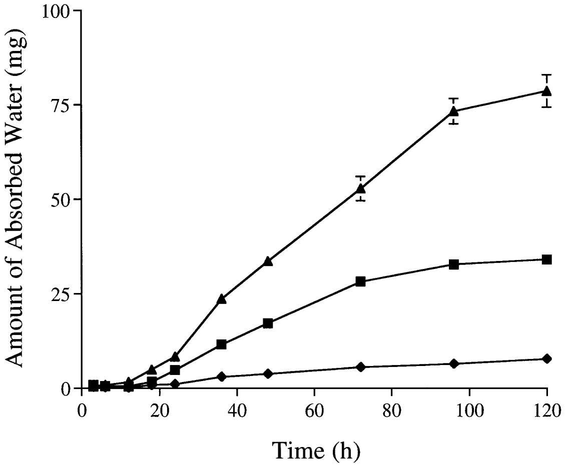

Fig. 3. Water absorption by p(CPP:SA) 40:60 matrices with diameters of (◆) 5 mm; (■) 9 mm; and (▲) 12.5 mm.

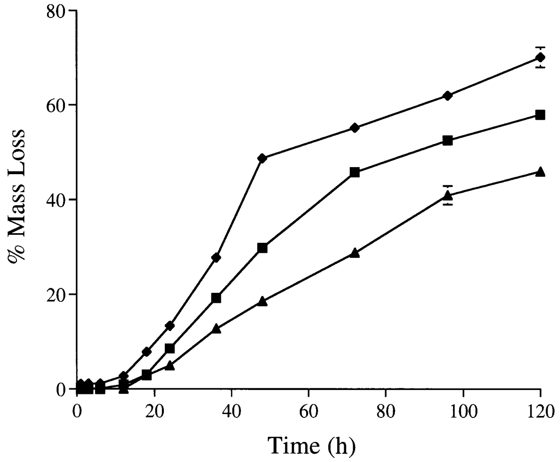

Fig. 4. Mass loss of p(CPP:SA) 40:60 matrices with diameters of (◆) 5 mm; (■) 9 mm; and (▲) 12.5 mm.

for the 5, 9 and 12.5 mm diameter matrices respectively whilst normalisation to unit volume gives values of 0.027, 0.015 and 0.006 mg/h/mm^3 indicating that during this initial period the rate of erosion is affected primarily by the surface area of the matrix. The approximate rates of mass loss calculated from the data for times 248 h assuming linearity are 0.06, 0.38 and 0.78 mg/h for the 5, 9 and 12.5 mm diameter matrices respectively. Normalisation of these rates to unit surface area gives values of 1.3×10^{-3}, 2.5×10^{-3} and 2.6×10^{-3} mg/h/mm^2 for the 5, 9 and 12.5 mm diameter matrices, respectively, whilst normalisation to unit volume gives values of 6.1×10^{-3}, 7.5×10^{-3} and 4.5×10^{-3} mg/h/mm^3. The normalised rate constants calculated in this region do not indicate clearly predominance of either surface end bulk effects.

3.4. Monomer release

The cumulative release of CPP monomer was monitored over an extended time period as a means of determining the life time of each device. The monomer release profiles (Fig. 5) show an initial lag period of about 10–15 h where the rate of release was at a low value for all matrices. After the lag period the rates of CPP release increased rapidly. Matrices with a diameter of 12.5 mm lost 30% of their total CPP after 1 week, compared with losses of 45 and 60% for those of diameter 9 and 5 mm, respectively over the same time period. Results obtained from environmental scanning electron microscopy (not shown) indicate that erosion of p(CPP:SA) matrices takes place from the exterior of the matrix inwards and consequently thicker matrices will still have an intact interior zone and display a high erosion rate at the time when the thinner ones are effectively exhausted.

The matrix size dependency of erosion kinetics of the polyanhydrides is in contrast to the erosion kinetics of polyesters. The results of a study of the effect of the size on the hydrolytic degradation of poly(DL-lactic acid) devices showed that large discs degrade heterogeneously and much faster than submillimetric films (Grizzi et al., 1995). In polyesters, material is released uniformly from the entire volume and a device with twice the thickness and volume produces monomers at twice the rate as the thinner device, but takes the same time to erode (Tamada and Langer, 1993).

4. Conclusion

The present work demonstrates that the rates of degradation and erosion of matrices prepared

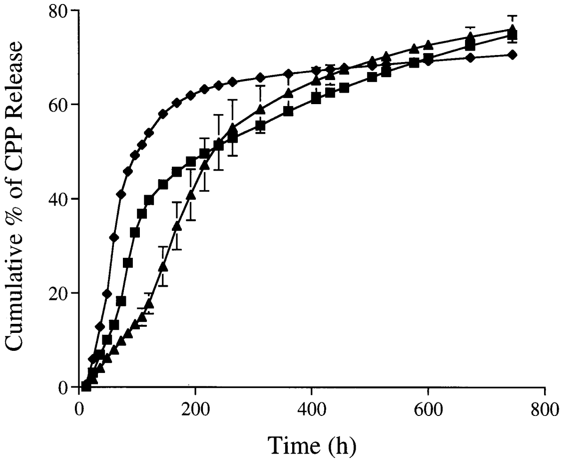

Fig. 5. Cumulative release of CPP monomers from p(CPP:SA) 40:60 matrices with diameters of (◆) 5 mm; (■) 9 mm; and (▲) 12.5 mm.

from a p(CPP:SA) 40:60 polymer depend on device geometry.

In all of the matrices examined, the erosion process was characterised by an initial lag phase during which there was no significant water absorption, mass loss or release of monomers. This lag phase or induction period was correlated with the time required for polymer molecular weight to decrease to a critical value. Study of molecular weight changes indicated that during this lag phase p(CPP: SA) matrices undergo bulk degradation without any mass loss or release of monomer. Hence, most of the hydrolysis of anhydride bonds in the matrix occurs during the first hours of aqueous incubation.

Although the degradation process for polyanhydrides is indicative of bulk, rather than pure surface erosion, the results of erosion studies showed some surface erosion characteristics including a pattern of material loss from outside to inside, rate dependence on the surface area of the polymer device and longer lifetimes for thicker devices.

Acknowledgements

This work was supported by a grant award from the Ministry of Health and Medical Education of the Islamic Republic of Iran.

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