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Polyglycolide: Degradation and drug release. Part II: Drug release

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This paper considers drug release from a polyglycolide (PGA) matrix and is divided into two sections. The first investigates the effects on the degradation of the polymer of incorporating a model drug, theophylline, into the polymer. Small and wide angle X-ray scattering, and mass loss and water uptake measurements indicate that the presence of this drug does not affect the time scale of the degradation process. However, the dissolved theophylline molecules affect the extent to which the polymer crystallizes during degradation. In the second section, theophylline release profiles, obtained using UV-spectrophotometry, show that the erosion of the polymer controls the release of the drug. The drug release results add further evidence to support the four stage degradation process which was described in Part I.

1. Introduction

During the last decade there has been increasing interest in poly(α-hydroxyacid)s as potential carriers for drugs, and consequently the release of a wide variety of drugs from these matrices has been investigated. Poly(lactide-co-glycolide) copolymers have received most of the attention, because they are relatively easy to process and the degradation and drug release rates can be altered by varying the proportion of glycolide and D-lactide and L-lactide in the polymer. Various types of devices such as monoliths, microparticles and nanoparticles have been developed, and a variety of drugs have been considered.

Unlike the lactide-co-glycolide copolymers, polyglycolide is only soluble in a limited range of solvents, none of which is acceptable for pharmaceutical processing, and melts at a high temperature. These limitations make drug incorporation difficult, and as a result PGA has rarely been considered as a matrix for controlled release.

A small number of studies have used solvent processing techniques to incorporate the drug. The (toxic) solvent hexafluoroisopropanol has been used to cast films of polymer and drug [1], and porous PGA microspheres have been produced by dissolving the polymer and additive in (the also toxic) hexafluoroacetone sesquihydrate, and dispersing the solution into a non-solvent, carbon tetrachloride [2]. The porous microspheres obtained by solvent extraction, solvent evaporation or freeze-drying showed release within a few days, a timescale considerably shorter than the timescale of degradation of the polymer.

Melt processing has also been considered. PGA of very low molecular weight (6000) melt pressed with. 20% theophylline, exhibits complete release within the short time of 8 h, with mass loss also being extremely fast (66% after 24 h) [3]. The release profiles fit Higuchi square root of time kinetics, indicating that drug release is diffusion and not reaction controlled. Ciprofloxacin in solution has been used to impregnate PGA in the form of Dexon fibers [4–6] which were subsequently melt-formed into cylinders. Only 55–60% of the predicted loading was recovered during release over a period of about 60 days; the rest of the drug was thought to be lost during processing. The sustained release suggests that melt processing the higher molecular weight polymer-drug combination can lead to release that occurs over a similar timescale to the degradation and may therefore be both reaction and diffusion controlled.

Notwithstanding the limitations imposed by processing, PGA has potential for use in drug delivery devices because it has a convenient timescale of degradation, semi-crystalline nature and biocompatibility. In this paper we use a melt processing route with relatively high molecular weight PGA and a heat stable drug to form resorbable delivery devices. We examine the link between the degradation properties of PGA explored in Part I [7], and the release profile of the drug.

Melt-processing is a solvent-free method of incorporating drugs into PGA, but the polymer melts at around 230 °C, and few drugs are stable at this temperature. For this reason theophylline was chosen as a model drug for this study [3], since it sublimes without degradation at 270–274 °C, has a reasonably high solubility in water and is only weakly basic [8, 9]. Theophylline is a bronchodilator and is used for the treatment of asthma and pulmonary disease [10].

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2. Materials and methods

Small pellets of PGA with intrinsic viscosity 1.2 dl/g were obtained from Medisorb Technologies International, Ohio. Powdered theophylline was obtained from Sigma-Aldrich. A mixture of theophylline and PGA was prepared by adding 5% by weight of powdered drug to PGA powder in a small specimen tube and mixing thoroughly and regularly. Although the particle sizes of drug and polymer were different, the drug coated the surface of the polymer particles, which resulted in a fairly even and stable mixture. Samples of mass 36 ± 1 mg were melted in DSC pans on a Linkam hotstage at 236 °C. Melting was accompanied by some sublimation of theophylline, visible as faint white fumes. The samples were quenched in iced water, and removed from the pans. Phosphate-buffered saline of pH 7.4 and concentration 0.01 M was prepared using tablets from Sigma-Aldrich.

For the SAXS, WAXS and mass measurements, the samples were placed in bottles containing 20 ml of buffer solution, and into a waterbath without agitation at 37 °C at regular time intervals. Samples for the drug release experiments were put into bottles containing 100 ml of 0.01 M phosphate-buffered saline and placed in a waterbath at 37 °C. One hundred ml was chosen because the UV absorbance of this volume of solution is around unity when the total theoretical release point is reached. The bottles were removed daily and shaken to produce an even concentration of drug.

The mass loss and water content were found by weighing samples three times. The initial mass was found to an accuracy of ± 0.001 mg. The degraded samples were dabbed dry and weighed immediately giving the wet mass accurate to ± 0.01 mg. The samples were then placed in a vacuum oven at 50 °C for 3 and weighed again giving the dry mass accurate to ± 0.001 mg. Both mass loss and water uptake are expressed as a percentage of the original mass.

Small and wide-angle X-ray scattering (SAXS and WAXS) experiments were performed on station 8.2 at the Daresbury SRS. All data were normalized to even out the effects of fluctuations in the beam intensity and the thickness of the samples, and divided by the response of the detector to an even ^{55}Fe irradiation. Background scattering was subtracted. Calibration of scattering angles was carried out using high-density polyethylene and wet rat-tail collagen for the WAXS and SAXS data respectively. The Lorentz correction was applied to the SAXS data to convert the scattering to that predicted from a single lamellar stack, and the long period, or average lamellar repeat distance of the semicrystalline polymer was then calculated from the SAXS peak positions. The percentage crystallinity was calculated from the WAXS profiles by dividing the area under the crystalline peaks by the total area under the profile.

A UVIKON 860 double-beam spectrophotometer was used to measure the drug release profiles. Samples were taken from the 100 ml solutions at regular intervals for analysis and subsequently returned to the bottles. Solutions with known concentrations of the theophylline in buffer were used to construct a calibration curve. The solutions were examined in 1 cm cuvettes, with buffer solution used as a reference. There was a peak in the absorbance at 271 nm for theophylline, which agreed with the literature [8, 9]. Peak heights were measured and converted to concentrations using the calibration curve, which was linear between absorbances of 0 and 1.2. Subsequent measurements were therefore calibrated with only one stock solution, the absorbance of which was measured daily.

3. Results

Theophylline caused the polymer to melt more quickly during processing than pure polymer, and to form transparent samples, in contrast to pure PGA samples which were more opaque. The samples appeared to be homogeneous, and there was no evidence of undissolved drug crystals inside the samples or on their surfaces.

The SAXS profiles of theophylline-loaded samples were very similar to the profiles of unloaded or ''blank'' samples. The experiment was run on several occasions at Daresbury and Fig. 1 shows a typical set of long periods calculated from the peak in the SAXS curves. The long periods of the theophylline and blank samples display a very similar fall and rise, although the nature and extent of these features are not identical. The long period of the theophylline samples falls to a minimum at around 10 days, but although this minimum occurs at the same time as that of the blank samples, it is not so deep, falling to approximately 67 rather than 63 .

Fig. 2 shows the WAXS profiles of powdered theophylline and undegraded PGA samples containing 5% theophylline. There is no evidence of crystalline drug in the scattering patterns of the polymers, which suggests that either the drug had dissolved fully in the polymer matrix, or that any residual drug crystals were too few in number to detect. Only very small PGA crystal peaks were observed in the undegraded theophylline samples, indicating that the polymer was almost completely amorphous. The crystallinity of the blank samples was generally higher than the loaded samples at each stage of degradation, but the increase occurred over the same timescale (Fig. 3).

Mass loss and water content as a function of degradation time for both theophylline-loaded and blank samples are presented in Fig. 4. The profiles are very similar: a slight increase in dry mass is observed over the first few days, and extensive mass loss begins after 10 days; the water content of the samples increases slowly over the first 10 days and more quickly thereafter.

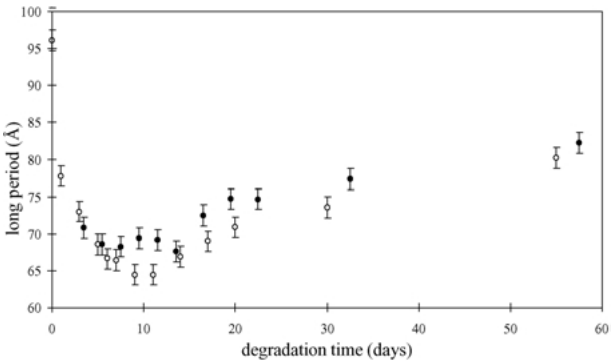

Figure 1 The effect of degradation on the long period of quenched samples containing theophylline (full symbols) and blank samples.

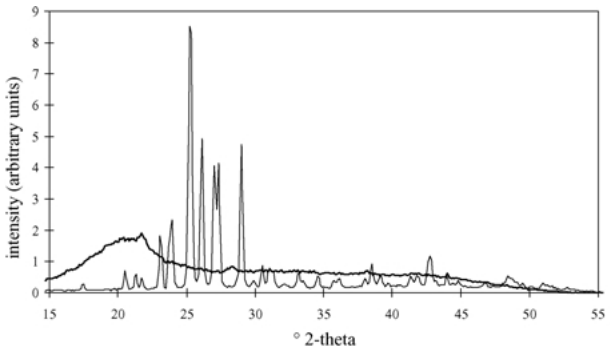

Figure 2 WAXS profile of theophylline drug (thin lines) and quenched PGA-theophylline mixture (thicker lines).

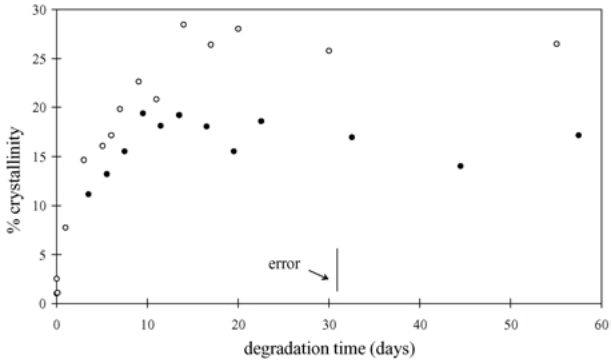

Figure 3 Changes in crystallinity during degradation for theophylline (full symbols) and blank (open symbols) samples.

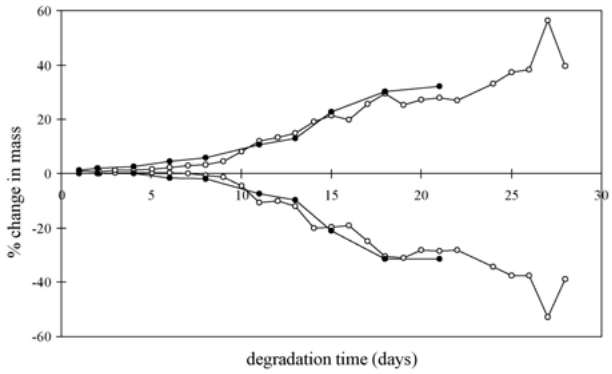

Figure 4 The mass loss and water content profiles of theophylline (full symbols) and blank (open symbols) samples. Lines are drawn through the points for clarity. Errors are greater for more highly-degraded samples, and are around 20% of the value given. Within the error, these curves superimpose.

Drug release results from three samples are presented in Fig. 5 as a percentage of total release. Over the first 6 days, the release rate was very low and the majority of the drug was released between 8 and 15 days. After 15 days, the concentration of drug in solution did not change appreciably. In order to ensure that total release had occurred after 20 days, three samples were made, weighed, heated to 90 °C in water and stirred vigorously for 5 days. During this time the samples fragmented, releasing the drug into solution. The mass of theophylline in each sample was calculated and converted to a percentage of the mass of the sample. The average fraction of drug measured in the three samples was $3.57 \pm 0.4\%$, which confirmed that some theophylline had sublimed from the surface of the sample during the sample preparation. This value corresponded with the concentration of drug in solution after 20 days; confirming that very little theophylline remained in the sample.

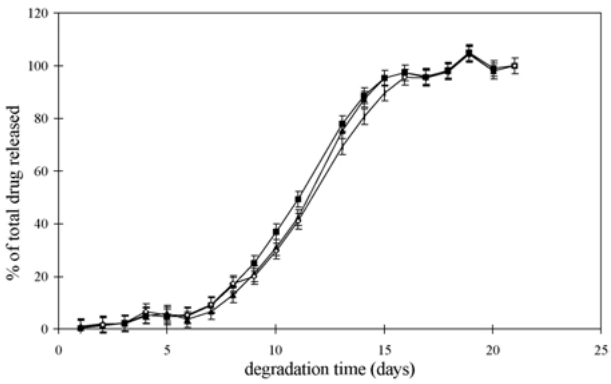

Figure 5 The percentage of the total theophylline released on each day. Three independent sets of data are presented.

4. Discussion

In Part I [7] we proposed that the degradation of PGA samples immersed in a buffer solution progresses via a four-stage mechanism. In stage I, water is absorbed quickly into the sample. In stage II, the molecular weight falls throughout the sample and insertion crystallization causes the long period to fall. At the beginning of stage III, a critical molecular weight is reached and oligomers begin to diffuse from the surface. A co-operation between oligomers diffusing out of this surface region and water molecules diffusing into it causes the formation of sharp reaction-erosion fronts, which separate the porous surface from the dense autocatalyzing inner region. The degradation rate in the surface region falls, owing to a reduction in the concentration of autocatalyzing acidic end-groups. These ideas are based on those of Vert *et al*. which were proposed to describe the degradation of the lactide-based members of the polyglycolide/lactide family [11–14]. It is hypothesized that the fronts move through the sample and meet at the beginning of stage IV, after which the degradation proceeds homogeneously. Behind the reaction–erosion fronts the material is more swollen and porous. This results in increasing mass loss and water uptake and causes the average long period to rise as the effects of swelling outweigh those of insertion crystallization. The results presented here are considered in the context of this mechanism.

4.1. The effect of drug on the degradation of the polymer

The results show that the presence of theophylline in the PGA matrix has an effect on both the original structure and the changes to that structure which occur as the polymer degrades. SAXS results show that the semi-crystalline structure of the theophylline loaded samples changes in a similar but not identical fashion to the blank samples.

The presence of dissolved theophylline appears to

inhibit crystallization in PGA samples. This was apparent from the transparency of the freshly prepared samples, the very low initial crystallinity, and the lower crystallinity after 10 days compared with blank samples. There are, however, two factors affecting the measured values of crystallinity: the actual crystallinity of the polymer and the presence of water molecules, whose scattering is inseparable from the true amorphous halo. The actual crystallinity of the polymer may be lower because theophylline molecules are inhibiting crystallization, both during sample preparation and during degradation. But also, when large quantities of water are present, usually after 10 days, the measured crystallinity is lower than the actual crystallinity. Since theophylline is a hydrophilic drug, it may increase the affinity of PGA for water, which will decrease the apparent crystallinity. A combination of these two effects may be responsible for the lower measured crystallinities of theophylline-containing samples

As the theophylline loaded samples degraded, the long period fell over the first 10 days in the same manner as the blank samples, but the minimum was not so low. Insertion crystallization is thought to be predominantly responsible for the fall in the long period. It appears that theophylline molecules also inhibit this crystallization, as they do during the initial quenching step. These results are also consistent with the heterogeneous bulk erosion mechanism, which attributes the subsequent increase in long period to the formation of reaction–erosion fronts at the surface of the sample. Since the mass loss and water uptake profiles of theophylline samples are very similar to the blank samples, it appears that theophylline does not alter the hydrolysis reaction rate, and neither does it dramatically affect the absorption of water into the polymer.

4.2. Drug release

Theophylline release profiles also show a discontinuity at around 10 days at the same time as the onset of stage III described in [7]. It is likely that the factors which cause mass loss and swelling at the start of stage III also affect the drug release profile. The profiles show a low initial drug release rate, with almost all of the drug being released between 8 and 15 days. The small amount of drug released during stage II is presumably due to a combination of the release of drug molecules on, or near to the surface of the sample, and slow diffusion through a matrix with gradually decreasing molecular weight. According to the heterogeneous bulk erosion mechanism, sample swelling begins when the erosion fronts begin to form on the surfaces of the sample after 10 days. As the erosion fronts move through the sample, progressive regions of the polymer become porous and the trapped drug molecules are freed. This process continues until the erosion fronts meet in the centre of the sample.

5. Conclusions

The incorporation of theophylline into a PGA matrix does not affect the time scale of degradation but does inhibit the crystallization of the polymer to a small extent. Theophylline is released mainly during stage III, when reaction–erosion fronts move from the surface to the centre of the sample. Drug diffuses easily from the porous, water swollen regions behind the front, but more slowly from the central unswollen regions. Release is therefore controlled by both reaction and diffusion.

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