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The Degradation of Polyglycolide in Water and Deuterium Oxide. Part I: The Effect of Reaction Rate

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Abstract

The relative importance of the rate of hydrolysis reaction and the rate of water diffusion in the degradation of polyglycolide (PGA) has been investigated. Samples were degraded in standard phosphate-buffered saline, and in fully and partially deuterated buffer solutions. Although the diffusion rate of deuterated water in PGA is similar to that of water, the acid-catalysed hydrolysis of the ester is significantly slower in D_2O because of the kinetic isotope effect. The degradation process was examined using small angle X-ray scattering, mass loss and water uptake measurements, pH measurements and drug release profiles. The results show that the hydrolysis rate has an important effect and that the system is not wholly diffusion controlled. The results are consistent with a four-stage reaction–erosion front model of degradation.
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Keywords: Polyglycolide; Poly(glycolic acid); Degradation

1. Introduction

Polyglycolide (PGA) is a semicrystalline polyester which has been approved for implantation in the human body, and proposed as a matrix for controlled drug release. Drug release profiles must be carefully predicted and regulated if this polymer is to be used successfully for drug delivery. PGA is hydrolysed in the presence of water to glycolic acid, which then autocatalyses the hydrolysis reaction. The hydrolysis reaction is complicated by the transport of various species though the bulk of the polymer, which is only partially accessible to the water. When a solid matrix is immersed in buffer solution, little change is observed for several days; then the mass loss, water uptake and drug release rates increase dramatically.

In other papers [1,2], we have hypothesised that PGA degrades by a four-stage mechanism. This is an extension of the theories developed by Vert and coworkers for other members of the polylactide/PGA family [3–6]. In stage I, water quickly diffuses throughout the polymer, reaching its maximum concentration in the undegraded polymer over the first few hours. In stage II, water diffuses in more slowly and the molecular weight throughout the sample falls steadily as hydrolysis proceeds. The lowered molecular weight and the plasticising effect of water cause the polymer chains in the amorphous phase to become more mobile, which results in insertion secondary crystallisation. This lowers the average repeat distance in the semicrystalline polymer, known as the long period, which is calculated from the peak in the small-angle X-ray scattering profiles (SAXS). At the beginning of stage III, a critical molecular weight is reached and oligomers start to diffuse from the surface into the buffer solution. Space is created into which water molecules diffuse, and this in turn facilitates the creation and removal of more oligomers. This co-operative effect creates sharp reaction–erosion fronts of hydrated material which progress through the sample. Faster water uptake and increased mass loss occur together with some swelling of the surface regions. The pH of a weakly buffered solution will fall as it reaches its buffer capacity, and if a drug is present most of it is released during this stage. The swelling causes the long period to increase, and shortly after the onset of stage III, a balance is reached between the opposing effects of insertion secondary crystallisation and swelling on the semicrystalline morphology. The long period therefore reaches a minimum value at this point. Finally, it is hypothesised that the fronts meet in the centre of the sample at the beginning of stage IV.

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The hypothesis behind the four-stage model is that both the diffusion of water and the hydrolysis rate of the polymer drive the degradation process. However, it could be argued that diffusion effects alone might explain a delayed release of drug. If water diffuses only slowly through the sample, swelling may be constrained until the diffusion fronts meet. At this point, the structure would open out and dramatic water uptake, mass loss and drug release would be seen. Such a model would explain the reported release results, although the reported diffusion co-efficient for water in PGA [7] and measurements of the glass transition temperature [1] cast doubt on this mechanism, as they suggest that water should be absorbed during the first few hours rather than over several days.

In this paper, we seek to test the hypothesis that the microstructural changes are affected by both diffusion and degradation, by immersing samples in buffers made with different degrees of D_2O and H_2O. Since the molecular mass of D_2O is only 11% greater than that of H_2O, the diffusion rates of these buffers in PGA are expected to be similar [8]. However, since H^+ is involved in the rate-limiting step of the acid-catalysed hydrolysis reaction, the hydrolysis rate in D_2O is likely to be much slower, due to the kinetic isotope effect [9]. If the diffusion of water controls the behaviour of the system, there should be little difference between samples degraded in buffers with different proportions of H_2O and D_2O. If, however, the reaction rate of the polymer is important, the degradation of the polymer will be appreciably slower in D_2O.

The work presented in this paper is followed by a separate study in Part II, which used imaging techniques to explore the distribution of water in samples degrading in deuterated and partially deuterated buffers directly. The results from the imaging techniques build on the findings in this paper to give a thorough investigation of the effect of deuterated conditions on PGA degradation.

2. Experimental

Small pellets of PGA with intrinsic viscosity 1.2 dl/g were obtained from Alkermes Medisorb Polymer, Ohio, USA, and were ground to a powder. Theophylline, D_2O and phosphate-buffered-saline tablets (for saline of pH 7.4) were obtained from Sigma-Aldrich. Samples of powdered PGA or a 5 wt% theophylline–polymer powder mixture of mass 36 ± 1 mg were melted in DSC pans on a Linkam hotstage at 236 °C and then quenched in iced water. The samples were removed from the DSC pans and placed, without agitation, at 37 °C in 0.01 M phosphate-buffered saline made from H_2O, D_2O or a 50:50 mixture of D_2O and H_2O. The solutions, bottles and equipment were autoclaved at 120 °C and 1 bar for 30 min before use.

Small-angle X-ray data were collected on stations 2.1 and 8.2 at the Daresbury Laboratory synchrotron radiation source from wet degraded samples in 30 s time frames. The data were normalised to correct for fluctuations in the beam intensity and the thickness of the samples by dividing by the signal from an ionisation chamber placed after the sample. The intensity was divided by the response of the detector to uniform illumination from a ^{55}Fe source, and background scattering subtracted. The scattering angles were calibrated using wet rat-tail collagen. The Lorentz correction was applied in order to convert the scattering to that predicted from a single lamellar stack. The long period was calculated from the peak position using the Bragg equation.

The initial mass of the samples was found to an accuracy of 0.001 mg. After degradation, the samples were removed from the buffer, dabbed dry with a tissue and weighed immediately to an accuracy of 0.01 mg. The samples were then placed in a vacuum oven for 3 days (to reach constant weight) and reweighed, again to an accuracy of 0.001 mg. The mass loss and water content of the samples were calculated as a percentage of the original mass.

After a known degradation time, the concentration of theophylline in the buffer was measured in 1 cm cuvettes at 271 nm using a UVIKON 860 double beam spectrophotometer. The pH of the solutions was found using indicator strips from Sigma-Aldrich, which ranged from pH 4.5 to 10.0 and 7.0 to 14.0 with an accuracy of 0.5. The bottles were shaken before a reading was taken. (The term pH is used throughout this paper, although, of course, both $D+$ and $H+$ ions are being measured in the D_2O/H_2O mixtures.)

3. Results

Fig. 1 shows the long periods of samples degraded in H_2O, D_2O and 50% D_2O/H_2O buffer solutions. The same fall and subsequent rise in long period is observed in all buffers, but everything occurs more slowly in the deuterated buffers.

Fig. 2 shows that dramatic mass loss and water uptake begins later in the more deuterated buffers and the subsequent rates of mass loss and water uptake are lower.

Fig. 3 shows how the pH of the buffer drops later in

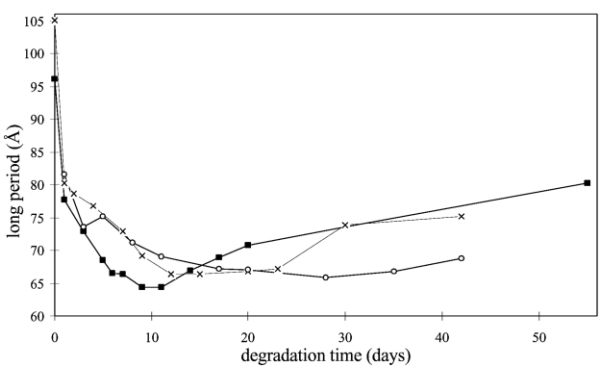

Fig. 1. Changes in the long periods of samples degraded in H_2O (square), D_2O/H_2O 50:50 (cross) and D_2O (open circle).

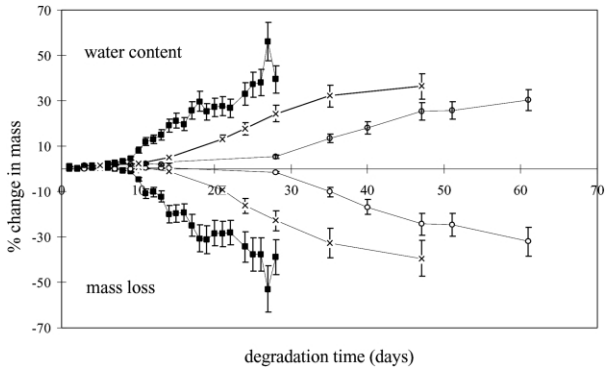

Fig. 2. Mass loss and water uptake. Samples degraded in H_2O buffer solution (square), D_2O/H_2O 50:50 (cross) and D_2O (open circle). Samples were prepared by melting the polymer on a Linkam hotstage as described in the text.

solutions containing more D_2O and the rate at which the pH decreases is lower.

Fig. 4 shows the drug release profiles of theophylline from PGA samples degraded in H_2O, D_2O/H_2O 50:50 and D_2O 0.01 M PBS. The onset of major drug release occurs later in more deuterated solutions. Although the drug release results are necessarily from samples containing theophylline, rather than from the unloaded samples used for the other techniques, we have shown in a previous paper that the presence of theophylline does not affect the time-scale of the degradation [2].

Table 1 lists the times at which 10% of the drug has been released in each case. In addition, the theophylline release rate is lower in D_2O-containing buffers after the onset of major drug release. The most important results are summarised in Table 1.

4. Discussion

It is clear from these results that the microstructural changes occur more slowly in more deuterated buffers. Therefore, models which are based on the diffusion of water alone are not adequate to describe the experimental results,

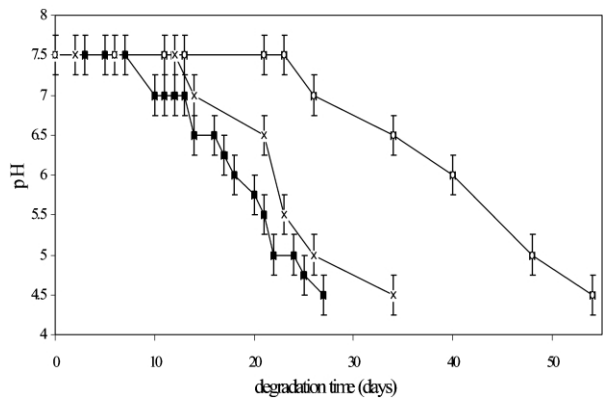

Fig. 3. pH of the buffer solution during degradation: samples degraded in H_2O (square), D_2O/H_2O 50:50 (cross) and D_2O (open circle).

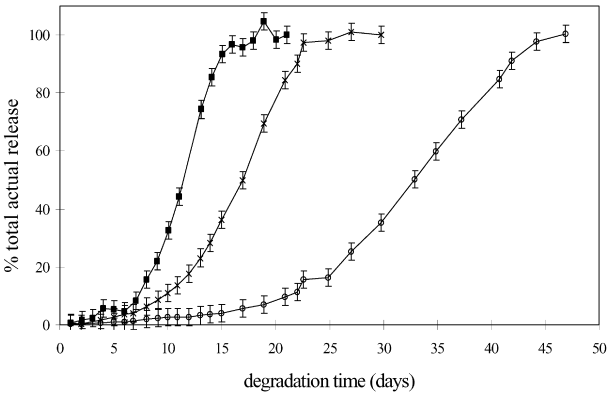

Fig. 4. Theophylline release from PGA samples degraded in H_2O (square), D_2O/H_2O 50:50 (cross) and D_2O (open circle).

since the diffusion rates of D_2O and H_2O in PGA are expected to be very similar. The sudden swelling and sudden release of drug from PGA samples must therefore be dependent on the hydrolysis rate of the polymer. This conclusion is consistent both with the published diffusion coefficient of water in PGA and with the four-stage reaction–erosion front mechanism outlined below.

In stage I, a small quantity of water diffuses into the sample over the first few hours. This stage is probably not much affected by the presence of D_2O in place of H_2O. In stage II, the long period falls as a consequence of insertion secondary crystallisation. This is facilitated by the decreasing molecular weight and by the plasticising effects of the absorbed water, and since the water content at this stage is not dependent on the buffer system, the plasticisation effect should be similar in each case. However, since the reaction rate is slower in the deuterated systems, the reduction in molecular weight at a given time will be smaller. This is thought to be the reason for a slower decrease in the long period of samples degrading in deuterated solutions (Fig. 1).

Stage III begins when a critical molecular weight is reached and reaction–erosion fronts form at the surfaces of the sample. The onset of major mass loss, water uptake and drug release, and a fall in the pH of the buffer solution are all indicators of the onset of stage III, and are presented in Table 1. The values correspond well and indicate that stage III is reached later in more deuterated systems, which is certainly due to the slower hydrolysis reaction rate. The minimum in the long period arises when there is a balance between insertion secondary crystallisation and swelling, and therefore occurs slightly later than the onset of stage III measured by the other techniques used in this study.

The results also suggest that the relationship between D_2O concentration and reaction rate may not be linear, since the values from the 50% D_2O/H_2O buffer do not always lie midway between those for the H_2O and D_2O buffers. Mixed D_2O–H_2O systems are very complex and simple relationships are not usually found [9].

During stage III, the reaction–erosion fronts progress towards the centre of the sample. Again, this progression

Table 1
Results that indicate the onset of stage III

Nature of buffer	Time of long period minimum (days)	Time of onset of major mass loss and water uptake (days)	Time at which pH of buffer begins to fall (days)	Time at which 10% of drug has been released (days)
H_2O	10	8	8	8
50% H_2O/D_2O	14	12	13	11
D_2O	28	24	24	23

depends on the rate at which the molecular weight of the polymer decreases, and the movement of the fronts would therefore be slower in the deuterated systems. Figs. 1–4 show that the rate at which the long period increases, the rate of mass loss, the rate of water uptake, the rate at which the pH falls, and the drug release rate are all lower in the deuterated systems. These results indicate that the reaction–erosion fronts are indeed moving more slowly from the surface to the centre of the sample in deuterated buffer solutions.

The results are consistent with the conclusions of an earlier study on poly(D,L lactide-co-glycolide) which found that degradation occurred more slowly in deuterated water [10].

5. Conclusions

The microstructural changes that occur during the degradation of PGA in phosphate-buffered saline depends on the hydrolysis rate of the polymer and the mobility of the degradation products. These factors affect the microstructural changes by controlling the diffusion of water into the polymer during the later stages of degradation. Drug release profiles are found to be directly related to the microstructural changes, and the results are fully consistent with the four-stage reaction–erosion model proposed in earlier papers.

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References

[1] Hurrell S, Cameron RE. J Mater Sci (Mater Med) 2001;12:811.
[2] Hurrell S, Cameron RE. J Mater Sci (Mater Med) 2001;12:817.
[3] Li SM, Garreau H, Vert M. J Mater Sci (Mater Med) 1990;1:123.
[4] Li SM, Garreau H, Vert M. J Mater Sci (Mater Med) 1990;1:131.
[5] Li SM, Garreau H, Vert M. J Mater Sci (Mater Med) 1990;1:198.
[6] Grizzi I, Garreau H, Li SM, Vert M. Biomaterials 1995;16:305.
[7] Zaikov GE. J Mater Sci—Rev Macromol Chem Phys C 1985;25:551.
[8] Drew DW, Clough AS, Jenneson PM, Shearmur TE, van der Grinten MGD, Riggs P. Nucl Inst Meth Phys Res B 1996;119:429.
[9] Bell RP. The proton in chemistry. London: Chapman & Hall; 1973.
[10] Schmitt EA, Flanagan DR, Linhardt RJ. Macromolecules 1994;27:743.