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A study on the rate of degradation of the bioabsorbable polymer polyglycolic acid (PGA)

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Abstract As part of a study to characterise bioabsorbable scaffolds for tissue engineering an investigation has been conducted into the rate of degradation of polyglycolic acid (PGA). This is one of the most commonly used bioabsorbable materials and has been used in sutures since the 60s and more recently in cell scaffolds, drug delivery devices and bone fixation pins. This study looks at the influence that surface-to-volume ratio i.e. thickness of material, has on degradation. By degrading various thicknesses of PGA in a buffer saline solution over 24 days and testing their properties at regular intervals, a knowledge of how surface-to-volume ratio affects degradation was developed. Properties such as weight loss, crystallinity, molecular weight and structural integrity were measured. Results showed that rate of mass loss was dependent on sample thickness but crystallinity, melting point and molecular weight were independent of thickness.

Introduction

Tissue engineering is the growing of living tissue from cells for applications such as organ replacement, artery wall repair and skin grafts. Bioabsorbable polymers are increasingly being used as scaffolds in tissue engineering [1]. The scaffold needs to be produced in the shape of the final tissue engineered construct and needs to have an open porosity to allow cell seeding and infiltration of growing tissues. It also needs to bioabsorb as it is gradually replaced by growing tissue.

The interest in materials selection and scaffold manufacture has to date been targeted towards promoting biocompatibility and cell adhesion and growth. The bias towards the chemical and biological needs of tissue engineering has tended to ignore the mechanical engineering issues. This report represents the first stage in an ongoing study aimed at developing knowledge of mechanical properties during hydrolytic degradation.

Degradation of aliphatic polyesters has been investigated by many authors e.g. the bulk heterogeneous degradation of PLA [2–4], however, this report examines the bioabsorbable polymer polyglycolic acid (PGA). It was first manufactured as a synthetic absorbable suture material [5] and its success has led to development for other medical applications such as controlled drug release systems [6–8], orthopaedic fixation [9–11] and scaffolds [1, 12–14]. Some studies have reported the changes in properties during degradation [7, 15–20] but none have looked at how the surface-to-volume ratio affects these changes.

Materials and methods

Materials and sample preparation

The raw material for these experiments was supplied in the form of small granules of Purasorb PG (PGA supplier Purac, www.purac.com). For the purpose of these studies the raw material was compression-moulded into sheets

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using a Rondol Bench Top Hydraulic Press with upper and lower thermostated heated plates. The material was placed between two non-stick sheets of Chemlan 6, (supplied from RS Clarke Ltd, Saintfield) to prevent the molten polymer from sticking to the heated plates. Once the plates stabilised to the set temperature 230 °C, the sample was placed on the lower plate and then raised manually using the hydraulic arm towards the top plate. The sheets were then removed and cooled at room temperature. To define the thickness of the sheet, shims of varying thickness were placed in between the plates. The resultant thicknesses of samples were 0.6 mm, 0.9 mm, 0.13 mm and 0.3 mm.

In vitro degradation

For the in vitro degradation study a buffer solution was prepared according to ISO 15814. The samples were immersed in the buffer solution in a glass specimen tube (75 mm × 25 mm) and placed into an air-circulating oven (Heraeus, Model 6200 air-circulating oven, Fisher Scientific, UK) maintaining the temperature at a constant 37 °C. In each case the ratio of the buffer solution in millimetres to the polymer in grams was greater then 30:1 as specified in ISO 15814. The buffer solution was not changed throughout the duration of the in vitro degradation. The properties of the polymer samples were determined at different aging time intervals of 0, 3, 6, 9, ..., 24 days.

Weight loss

This was evaluated using an analytical balance with an accuracy of 0.001 mg. Two weights were measured:

- Initial weight—This was when the sample was dry.
- Final weight—After degradation the sample was vacuum dried in a vacuum oven (Towson + Mercer, Altrincham, England) at approximately 30 °C for 48 h at a vacuum of 0.68 bar (517 mmHg) and was weighed until weight stabilised and all water was evaporated.

The overall percentage mass change is calculated using:

$$\% \text{ Mass change} = \frac{\text{Inital weight} - \text{Final weight}}{\text{Final weight}} \times 100\%$$

Morphology

Scanning Electron Microscopy (SEM) was utilised to look at the surface of the samples. The surface was sputter coated in gold–palladium alloy. A Joel Winsen—JSM 6400 SEM was used.

Differential Scanning Calorimetry (DSC)

The thermal properties of these samples were analysed using a Pyris Diamond DSC. Samples weighing between 5 and 10 mg were placed in small aluminium pans and heated from 50 °C to 250 °C at a rate of 200 °C/min. The melting temperature (T_m) was taken as the maximum temperature of the endothermal peak. The melting enthalpy (ΔH in J/g) was derived with reference to the corresponding energies (the peak areas above the base line) during the melting range. The crystallinity was calculated by ratioing the melting enthalpy of the samples to 139 J/g [21] the melting enthalpy of 100% crystalline PGA:

$$\% \text{ Crystallinity} = \left(\frac{\Delta H}{139}\right) \times 100\%$$

Gel Permeation Chromatography (GPC)

The molecular weight profiles were obtained using GPC with hexafluoroisopropanol (HFIP) as the mobile phase. Samples were placed in HFIP and left overnight. Samples were filtered through 0.45-μm PTFE filters prior to analysis according to SOP/AD/311. Calibration was carried out versus PMMA calibrants supplied by Polymerlabs; results are therefore expressed as PMMA molecular weight equivalents. The solution was injected (50 nm^3) into PL HFIP-gel 300 mm × 7.8 mm column with a flow rate of 1×10^{-6} m^3/min. The columns and differential refractometer (RI detector) were operated at 40 °C.

Results and discussion

Morphology

Figure 1 shows a macro view of the samples after 12 days degradation. It can be readily observed that the thinner the sample the greater the break-up. The 0.3-mm samples are almost intact or with some isolated cracks.

Figure 2 shows the micrographs of the samples at different stages of degradation. All pictures are taken with a magnification of 4,000× with an accelerating voltage of 5 kV.

Figure 2a, b and c show changes in 0.13 mm samples at 6, 12 and 24 days. Small cracks appear at 6 days, which are slightly larger after 12 days. These cracks may be due to the drying of the sample.

Figure 2c, d and e show 24-day degraded samples. The cracks have all disappeared leaving a highly degraded surface with some surface porosity developing.

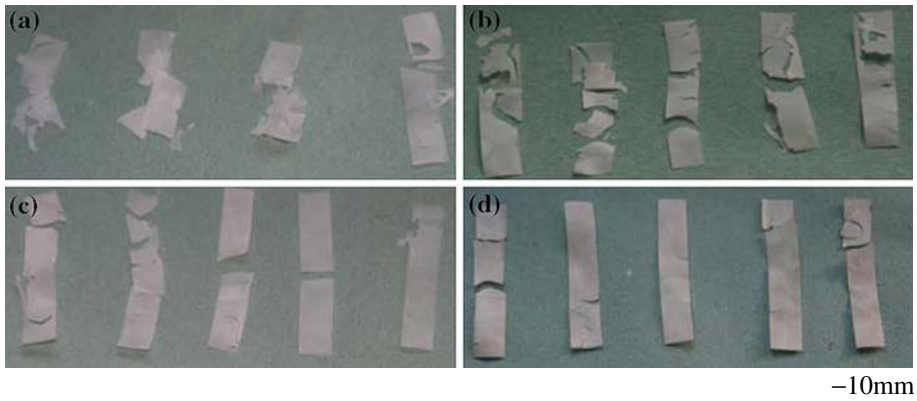

Fig. 1 Pictures of samples after 12 days hydrolytic degradation: (**a**) 0.06 mm, (**b**) 0.09 mm, (**c**) 0.13 mm, and (**d**) 0.3 mm

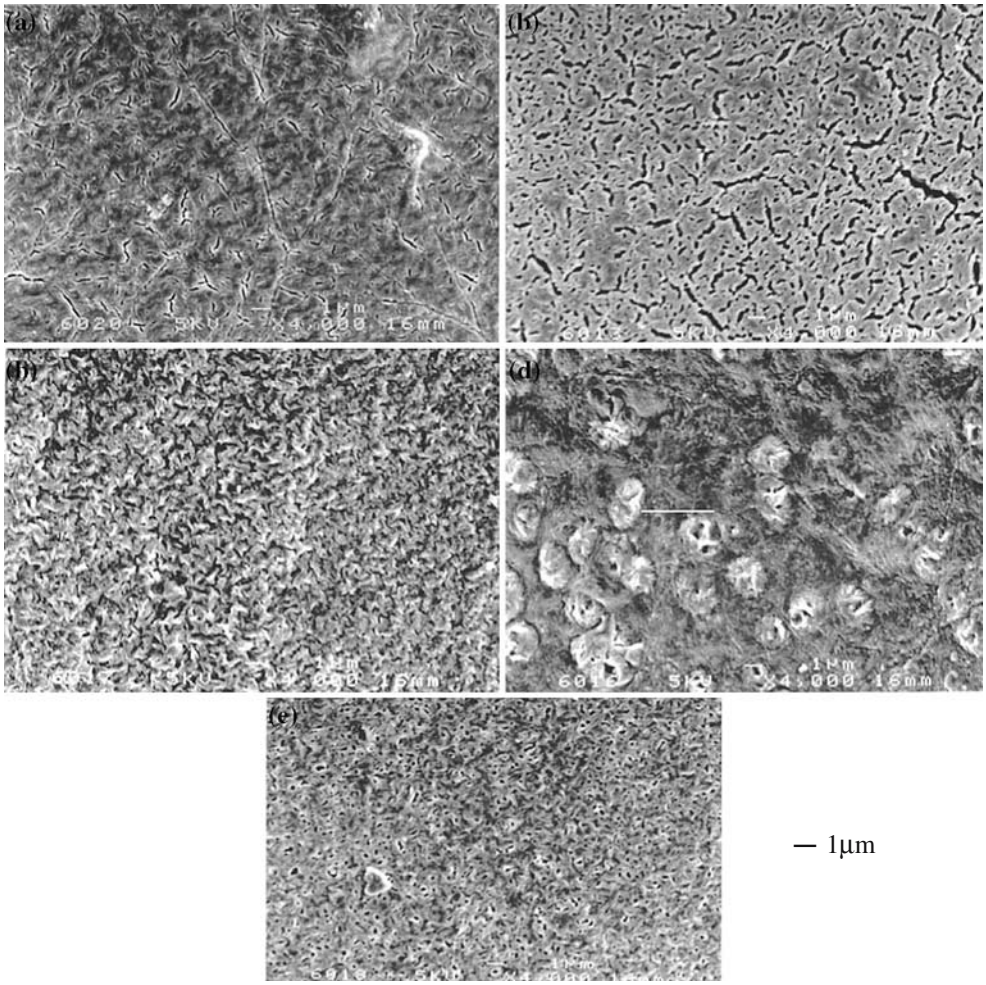

Fig. 2 SEM micrographs—0.13 mm at (**a**) 6 days, (**b**) 12 days, (**c**) 24 days, (**d**) 0.3 at 24 days, and (**e**) 0.1 at 24 days

Weight loss

During degradation the thinnest sample fragmented at the fastest rate. This fragility caused the samples to break even due to movement in the fluid in the test tube when moving them and also rinsing before drying. This caused a slight error in the mass measurement as some fragments may have remained in the fluid. The 0.3-mm sample did not suffer the same amount of break-up as the 0.06 thickness, which broke into many pieces and once dried the 0.06-mm sample was almost a powder. This is reflected in the % mass loss curve (Fig. 3). The 0.3-mm curve is very smooth compared with the wavy 0.06-mm curve where error was induced due to handling and weighing of the fragile samples.

Figure 3 shows the average percentage mass loss of varying thicknesses during degradation.

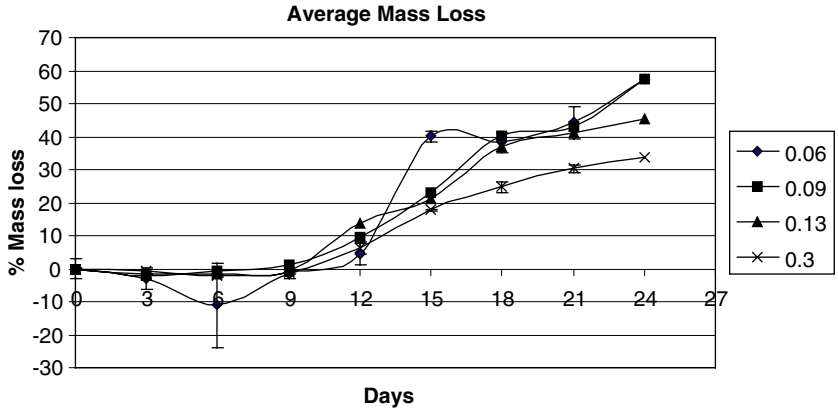

Fig. 3 Average % mass loss of samples during hydrolytic degradation

It can be seen that there is a slight increase in mass up to day 9. After day 9 mass loss begins. Standard deviation bars are only shown for the thickest and thinnest samples curves showing that there was more error in the 0.06-mm results than with the 0.3-mm results.

Figure 4 shows curves from day 9 to show a linear relationship between mass loss and time.

The R^2 values show how well the curve fits the straight line, one being a perfect fit. It can be seen that the three thickest samples have high R^2 values, from 0.96 to 0.98, compared to 0.06-mm, which has the lowest value of 0.88. The rate of mass loss appears to be dependent on the thickness of the sample. The gradient of the thinnest sample is greater than that of the thickest. After 24 days the 0.3-mm sample has lost 32% compared to the 0.06-mm sample, which has lost 59%, almost double. Although the difference in mass loss would have been slightly affected by the thinner samples fragmenting more than the thicker ones, thus becoming difficult to collect all of the degraded material.

DSC results

DSC was conducted on samples of all thicknesses. Traces for the 0.06-mm samples at different degradation times are shown in Fig. 5. From these curves the melting point and crystallinity were calculated.

Figure 6 shows the change in melting point over time.

The results showed a decrease in melting temperatures during degradation. Best-fit straight lines were placed on the graph to show the decrease more easily. It can be seen that the thicker samples melt at a slightly higher temperature than the thinnest, but the difference is only 4 °C. It is likely that the thicker samples cooled more slowly than the thin samples. This would result in a higher crystallinity and thus higher melting temperature for the thicker samples. The R^2 values again show that the curve for the thickest sample (0.9546) has a better fit to the linear line than the thinnest (0.7122). It can be seen that there is little difference in the gradient of the trend lines. This would suggest that thickness does not

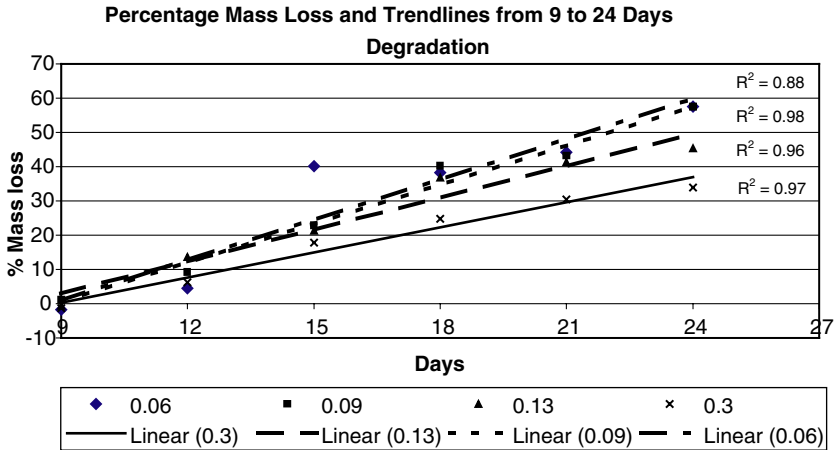

Fig. 4 Best-fit straight lines from day 9 to day 24

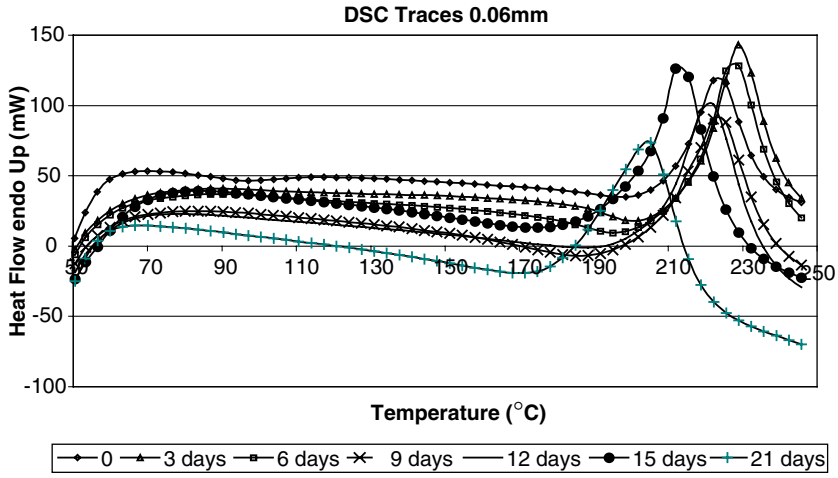

Fig. 5 DSC traces for 0.06-mm samples at different degradation times

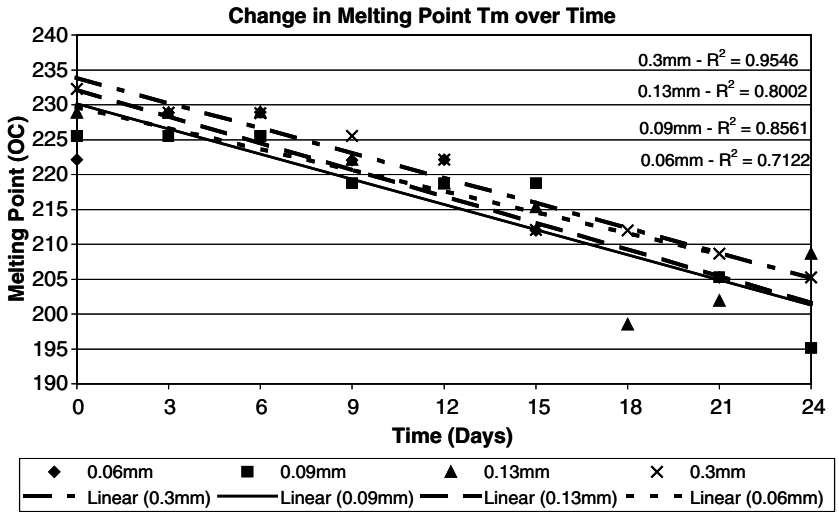

Fig. 6 Best-fit straight lines of changes in melting point against time

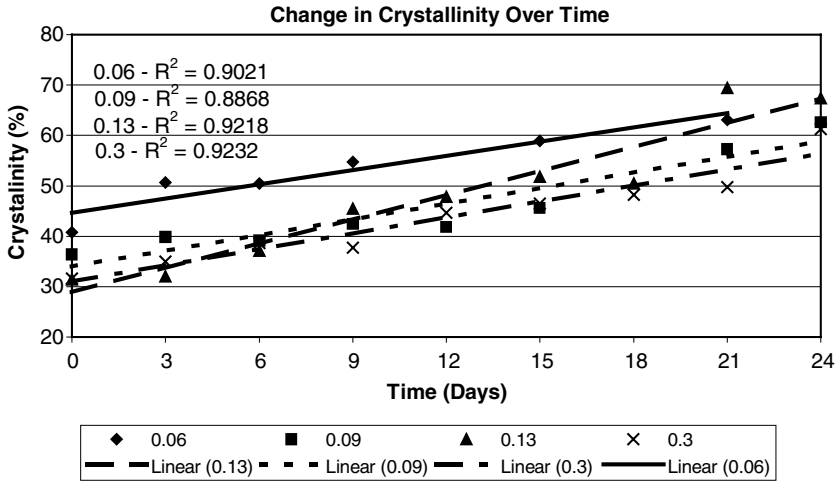

Fig. 7 Best-fit straight lines of changes in crystallinity against time

affect the rate of change in melting point during degradation.

Figure 7 shows the change in sample crystallinity over time.

The degree of crystallinity of the samples increases significantly during degradation e.g. the 0.3-mm sample increases from 31% to 56% over 24 days. The initial % crystallinity of the samples differs for each thickness but is

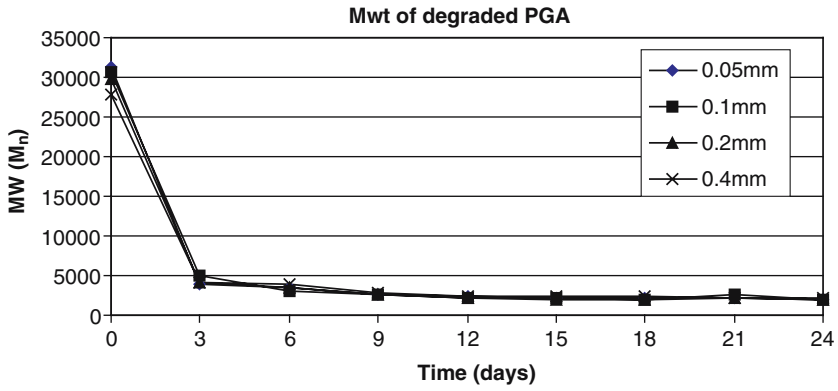

Fig. 8 Number average molecular weight M_n as a function of time

within a 10% range. The R^2 values show the lines are a good fit to the curves. From the curves it can be seen that the gradients are all similar which again would suggest that the thickness does not affect the rate of increase in crystallinity.

GPC results

The GPC data is shown in Fig. 8.

The general trend for each of the thicknesses of PGA show a large drop in molecular weight from the initial time point to 3 days followed by a slight drop from 3 to 12 days. From day 12 to day 24 results remain reasonably constant. The results for the different sample thicknesses are very similar, with the exception of the initial time point where the molecular weight for the 0.05-mm sample is higher than the 0.4-mm sample. The initial drop can be related to typical bulk hydrolysis where the amorphous regions are degraded first leading to a decrease in molecular weight. Given that the mass loss for each sample began at day 9, one can surmise that the minimum molecular weight to allow diffusion of molecules out of the sample is in the region of 2,500.

Conclusion

The hydrolytic degradation of PGA has been studied in vitro for 4 different thicknesses. The mass loss results showed that all samples begin to loose mass after day 9 and the rate of mass loss is greater for the thinner samples. Therefore mass loss is dependent on surface-to-volume ratio with the thicker samples showing mass loss at a lower rate due to the greater diffusion path length for samples. Crystallinity increased and melting point decreased during degradation but surface-to-volume ratio does not affect the rate of change of either of these properties. The molecular weight dropped until day 3 when it levelled off. The results also showed that the change in molecular weight was also independent of thickness.

As well as showing the affect of surface-to-volume on degradation the results further enhance the theory that the polymer degrades by bulk hydrolysis [7, 15, 17, 18, 20]. Molecular weight decreases continuously during degradation with little weight loss. Then when the molecular weight has been reduced to a critical value, in our case approximately 2,500, when it can be diffused into water, weight loss begins. Hurrell et al. [20] also witnessed a critical time when degrading PGA. They observed no change in pH and drug release until approximately day 10 when pH dropped and drug release started to increase. It can be assumed that these changes must relate to a critical molecular weight being reached when oligomers can diffuse out of the sample.

Also the fact that crystallinity increases [16, 19] supports the theory that water penetrates and degrades the amorphous zone first. This leaves a higher volume of crystalline material, thus increasing its crystallinity.

It is anticipated that the knowledge gained from this study on PGA will contribute to understanding and predicting the degradation behaviour of porous polymer scaffolds.

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