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International Journal of Pharmaceutics 282 (2004) 19–34
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

The effects of molecular weight and porosity on the degradation and drug release from polyglycolide

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Received 24 March 2003; received in revised form 19 August 2003; accepted 20 August 2003
Available online 31 July 2004

Abstract

This paper explores the influence of initial molecular weight and porosity on the release of the drug, theophylline, from polyglycolide (PGA). PGA was made by a variety of processes to vary the molecular weight and was blended with NaCl with different crystal sizes and in different proportions to vary the pore size and volume. Overall, results showed that decreasing the molecular weight and increasing the pore size and volume increased the rate of drug release. The exact variation of these trends agreed well with the previously established four-stage degradation mechanism for PGA, but was more complex than a simple linear behaviour. Because both the molecular weight and the porosity of PGA have a substantial influence on the polymer degradation, and can be varied in a controlled manner, these parameters can play an important role in developing PGA as a controlled drug delivery material with tailored drug release.

Keywords: Polyglycolide; PGA; Porosity; Molecular weight; Controlled drug release; Theophylline

1. Introduction

Polyglycolide [poly(oxy-1-oxoethylene)] (PGA) is a semi-crystalline biodegradable aliphatic polyester. It is non-toxic and biodegradable in the body and consequently has found many uses in the field of medical technology, for example: as a wound closure material and surgical suture, and as a tissue engineering scaffold (Chu et al., 1997; Schwarz and Eppel, 1998). Previous research has also shown that it has potential as a controlled drug delivery material (Hurrell and Cameron, 2001a,b, 2002, 2003; Hurrell et al., 2003a,b; Milroy et al., 2003a; Milroy et al., 2003b; Milroy, 2001; Dickers, 2002). This paper considers issues im-

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doi:10.1016/j.ijpharm.2003.08.020

portant in the use of the polymer as a three dimensional, drug-releasing scaffold, by exploring the effects of porosity and molecular weight on the degradation and release.

PGA can be synthesized in several ways (Gilding and Reed, 1979). The most common method is via a ring opening polymerisation of the glycolide dimer, a cyclic diester, which produces a relatively high molecular weight material. An alternative synthesis route, discovered in 1894 by Bischoff and Walden (1894), produces a much lower molecular weight material. The synthesis process involves the one step solid-state polymerisation of halogenoacetates. The most common halogenoacetate used is sodium chloroacetate, which, when heated at around 140 °C, exothermically reacts to produce a mixture of low molecular weight PGA and NaCl crystals Eq. (1).

$$\mathrm{Cl–CH_2–COO^-Na^+} \rightarrow \frac{1}{n}\mathrm{–[CH_2–COO]}n\mathrm{–} + \mathrm{NaCl} \quad (1)$$

The NaCl crystals formed, which are present at a level of 40–50% (Schwarz and Eppel, 1998; Epple and Tröger, 1996; Epple and Herzberg, 1997, 1998), may be removed by washing with water, leaving a porous PGA structure. Such a porous degradable structure has potential as a tissue engineering scaffold in its own right, however, the crystals formed are only of size 0.2–5 μm. This is too small to allow cells to grow through the spaces they leave behind (Schwarz and Eppel, 1998), although porosity at this scale may be useful in providing surface topography favourable to cell attachment. The low molecular weight of the PGA formed is also a disadvantage since the polymer structure loses integrity over a few hours.

By mixing the polymers made from these two synthesis routes, it should be possible to create materials with controlled, bimodal molecular weight distributions. Furthermore, the concept of creating three dimensional structures within the polymer by washing out NaCl crystals, inherent in the solid state reaction method, maybe extended by the deliberate incorporation of NaCl crystals of known particle size distribution into PGA samples during processing. In this way, larger pores, more suitable for tissue engineering scaffolds, may be produced (Schwarz and Eppel, 1998; Epple and Herzberg, 1997, 1998). The ways in which these modifications affect the degradation and drug release are the subject of this paper.

The degradation of PGA is a complex process involving the scission of the polymer chains over several days and weeks to produce glycolic acid monomer. The delay in the completion of the reaction is due to the complex interplay between the diffusion rates (of water and reaction products through the polymer matrix) and the reaction rate (of the polymer with water). This interplay results in very little loss of the bulk polymer over the first few days, after which significant mass loss and water gain starts.

The degradation of PGA may be described by a four-stage reaction erosion front model (Hurrell and Cameron, 2001a,b). In stage I, which occurs over the first few hours after immersion, water diffuses into the polymer matrix and forms a homogeneous distribution. Scission of the chains begins as the polymer comes into contact with the water. During stage II, little water is further absorbed, and the polymer chains continue to undergo scission on reaction with the water. This causes the molecular weight to fall but, during this stage, the chains are still too large to diffuse from the bulk polymer and cause polymer erosion and drug release. At the beginning of stage III, the polymer reaches a critical molecular weight and some oligomers are small enough to dissolve into the degradation medium. This behaviour allows significant polymer erosion to begin, creating pores in the polymer matrix and allowing significant water ingress into the polymer promoting drug release. Reaction–erosion fronts of highly hydrated porous material start at the surface, the boundary moving inwards towards the polymer core. Drug is released quickly from behind the fronts and hence the rate of drug release follows the rate of front movement. At the start of stage IV, the reaction–erosion fronts meet in the sample centre and the drug release finishes. At this time the polymer is fully hydrated with a high level of porosity. Degradation continues until the polymer is fully eroded (Hurrell and Cameron, 2001a,b). Fig. 1 illustrates how the cumulative drug release profile is linked to the four stages of degradation.

It is clear that the distances over which the reaction–erosion fronts have to travel and over which the diffusion processes must occur will affect the release profile. Milroy et al. studied the effect of sample size on the duration of the stages (Hurrell et al., 2003a;

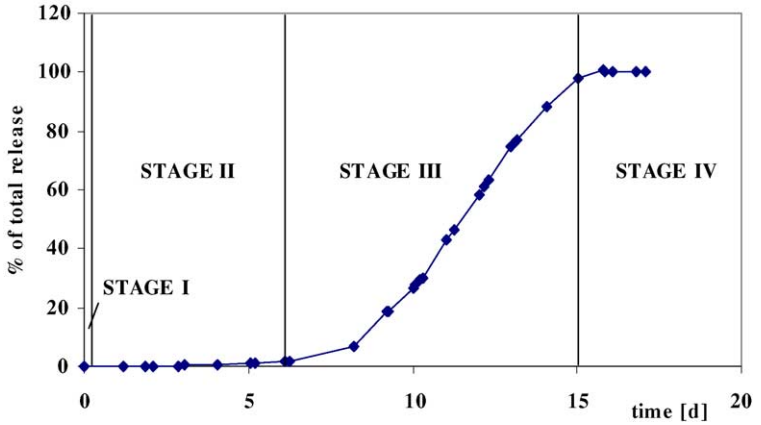

Fig. 1. The relationship between the drug release profile and the four-stage degradation process (Hurrell and Cameron, 2003; Hurrell et al., 2003a).

Milroy, 2001) and reported that the time of the onset of stage III, when the reaction–erosion fronts were formed, was not influenced by the sample size. Consequently, drug release from PGA disks of different thickness started at the same time and released at the same rate but finished at earlier time for thinner samples. These trends indicated that the start of front progression, which controls the start and rate of drug release, is independent of thickness. However, drug release finishes at earlier times in thinner samples because the fronts have further to penetrate into the sample form the surface before meeting in the centre. By introducing pores to the structure, the distances for diffusion and front movement are effectively changed and the degradation and drug release are expected to change accordingly.

The molecular weight will also affect the degradation and drug release. The reaction–erosion fronts are not formed until a critical molecular weight is reached whereupon some oligomers become soluble. This behaviour suggests that a higher initial molecular weight should delay the onset of stage III. On the other hand, if the molecular weight is very low at around 4000 g mol^{-1}, drug release occurs over a few hours rather than days, suggesting that the polymer is solubilised immediately (Moll and Ries, 1991). These results not only suggest that the effect of molecular weight is non-linear, but also that interesting effects could occur if a bimodal molecular weight distribution is introduced.

2. Methods and materials

Sodium chloroacetate (98%) and sodium chloride were obtained from Aldrich. Theophylline and phosphate buffered saline tablets were obtained from Sigma. DSC aluminium pans were purchased from TA Instruments.

PGA of four different molecular weights were used to make the samples studied in this research. Table 1 shows the molecular weight for each type. Molecular weights were determined by gel permeation chromatography in hexafluoroisopropanol (HFIP) kindly performed by Smith and Nephew Limited. To do this, a thermal characterisation for each type of PGA was performed using DSC. Samples were heated from 20 °C to 250 °C at 200 °C min^{-1}, then held at 250 °C for 2 min and rapidly cooled in liquid N_2 to make them amorphous and therefore soluble in HFIP, where they were left to dissolve overnight. Samples were filtered through 0.45 μm PTFE filters prior to analysis. The calibration was carried out versus PMMA calibrants, supplied by Polymerlabs. The results are therefore expressed as PMMA molecular weight equivalents.

The notation used in this paper refers to the samples with the code PGA (*x* k) where *x* is the molecular weight of the polymer in thousands, rounded to the nearest thousand (Table 1).

PGA (6 k) was made by heating sodium chloroacetate at 150 °C in an oven for approximately 20 h. The material was spread thinly over a Petri dish during re-

action to avoid excessive heat build up as a result of the reaction exotherm. The NaCl, formed during the reaction, was removed by stirring the PGA (6 k) powder in water for about 12 h and then rinsing with ethanol, a process that was then repeated twice. The powder was then filtered from the ethanol using a vacuum pump and dried in an oven over night at 60 °C.

PGA (36 k) was synthesised by ring-opening polymerisation, and supplied by Medisorb Technologies International, Ohio. It has a quoted intrinsic viscosity 1.25 dl/g, and glass transition temperature of 44.5 °C. PGA (25 k) was made by heating PGA (36 k) for 5 days at a temperature of 120 °C to lower its molecular weight through thermal degradation. PGA (13 k) was made by subjecting PGA (25 k) to several freeze–thaw cycles between freezer and room temperature. The use of the freezer as a storage place was not initially expected to lower the M_w of PGA (25 k) in this way.

Drug loaded samples, except where stated, contained theophylline at a nominal level of 5 wt.% of PGA. The theophylline was mixed with the PGA using a spatula and the powders ground together. 36 ± 1 mg of the resulting mixture was melted for 2 min in an aluminium DSC pan on a Linkam hot stage set at 248 °C to give a sample temperature of 236 °C (the melting temperature of PGA). Samples were then quenched in iced water to give a largely amorphous morphology. After removal from the aluminium pans, samples were degraded in bottles containing 100 ml of 0.01 M phosphate buffer saline (PBS) pH 7.4 and placed in a water bath at 37 °C until drug release has finished. All buffer solutions and bottles were autoclaved at 120 °C for 2 h before use.

Porosity was introduced into the samples by adding NaCl into the powder using the same method as for the incorpration of theophylline before melting on the hotstage. To control the size of the particles, NaCl was mortared and sieved with different mesh sizes. The different particle sizes of NaCl were determined using a Malvern Instruments Mastersizer 2000 particle analyzer with the NaCl particles suspended in ethanol. The NaCl was not washed out of the samples before characterisation.

The concentration of released theophylline was measured by UV spectroscopy using a Uvikon 931 double beam spectrophotometer from Kontron Instruments, with 1 cm quartz cuvettes. Small amounts of buffer were taken from the solutions at regular time intervals for analysis and subsequently returned to the bottles. The bottles were shaken before each measurement to remove any concentration gradients. A reference solution of 0.01 M PBS was used and the absorbance of the drug was measured at a wavelength of 271 nm. A standard solution of theophylline was used to calibrate the UV machine before the samples were tested. The concentration of drug was calculated using the Beer Lambert equation.

$$\text{concentration (mg/ml)} = [\text{UV absorbance}]\,\frac{[10]}{[E]} \quad (2)$$

where E = 563.4 ± 7% valid for UV absorbances between 0.15 and 2 (Harris and Bashford, 1987).

The actual total drug loading was determined for each formulation. Three samples of each type were tested to obtain a measure of the experiments error. The mass of the each sample was measured and placed in 100 ml of distilled water until the end of drug release. After centrifugation of this solution at 4500 rpm for 15 min, the UV absorbance of the eluent was measured and the total drug loading calculated. The drug loadings were generally within about 5% of the target loading and no significant difference was observed between the different grades of polymer. All drug release profiles were then normalised to the actual total loading, so that 100% release represented full release of the actual amount of drug present.

The mass loss profiles were determined for all samples. The mass of all pellets (36 ± 1 mg) were measured to an accuracy of ±0.0005 mg before they were placed into the PBS solution. After different time intervals, the samples were dried in a vacuum oven at 50 °C for 3 days to determine the dry mass (M_d). The percentage mass loss (M_l) is calculated from the measurements using this following equation:

$$M_l = \left[\frac{M_d - M_w}{M_w}\right] \times 100$$

where M_l is the mass loss, M_d the dry mass and M_w the wet mass.

The morphological features of the samples were imaged using a JEOL FEGSEM 6420L scanning electron microscope. Each pellet was sputtered with gold before it was examined at 3 kV and 5 kV.

Table 1
Molecular weights of the different PGAs used

	M_w	M_n	M_z	M_p	Pd
PGA (6 k)	5 615	2 995	8 540	5 190	1.88
PGA (13 k)	12 950	7 095	18 800	11 950	1.83
PGA (25 k)	24 700	13 100	36 733	21 533	1.88
PGA (36 k)	35 600	16 800	56 500	31 100	2.12

3. Results

3.1. Materials characterisation

3.1.1. Gel permeation chromatographs (GPC)

Tables 1 and 2 present GPC results for the different polyglycolides subjected to different treatments: in powder form prior to pellet formation, processed as pellets and after a degradation period followed by drying in the oven at 50 °C for 3 days. The range of values derived from repeat measurement of parameters from the same batches of samples measured on the same occasion is about 2%. The results show a marginal molecular weight decrease on pellet processing, presumably due to thermal degradation, and a significant decrease after degradation (measured after 2 days for PGA (6 k) and 16 days for PGA (25 k) and PGA (36 k)).

3.1.2. Particle size analysis

Fig. 2 presents the particle size distribution data for the different crystal sizes of the sodium chloride incorporated into the PGA pellets to create pores.

3.2. The effects of changing molecular weight

Fig. 3 presents the release data for quenched PGA samples with different molecular weights. PGA (6 k) is studied with the reaction product NaCl still within the sample, and also with the reaction product NaCl removed prior to processing. The drug release starts immediately in both cases, and occurs slightly faster in the samples containing NaCl. Significant release begins after about 1 day for PGA (13 k), about 3 days for PGA (25 k) and after about 7 days for PGA (36 k).

In Fig. 4, the release profiles from pellets made from blends of different fractions of PGA (6 k) and PGA (36 k) are shown. The reaction product NaCl was washed out of the PGA (6 k) with water before mixing and melting with PGA (36 k), to avoid porosity from NaCl present in these samples. It is clear that incorporation of just 10% PGA (6 k) into PGA (36 k) has a significant effect on the release. The curves for the various blend fractions lie between the curves for the pure components.

Fig. 5 shows the drug release profiles from samples made from blends of PGA (13 k) and PGA (36 k). Fig. 6 shows the release profiles of different fractions of PGA (25 k) and PGA (36 k). Again, the curves for the various blend fractions lie between the curves for the pure components.

3.3. The effects of introducing porosity

3.3.1. Varying the pore fraction

Fig. 7 shows the drug release profiles for PGA (36 k) mixed with different weight fractions of NaCl with an average crystal size of 57 μm. The nominal drug loading in each sample was 5% by weight of the total sample rather than of PGA. Overall, the data shows an increase in degradation and drug release rate with increasing NaCl concentration. In particular, as was seen when adding PGA (6 k) to PGA (36 k), the addition of only 10 wt.% NaCl has a marked effect on the release. Introducing porosity seems to shorten or remove the incubation time and release is less linear once it begins.

Table 2
GPC analysis for samples before and after heat treatment (melting at 236 °C) and after degradation

	PGA (6 k)		PGA (25 k)		PGA (36 k)	
	M_w	%	M_w	%	M_w	%
Powder, produced and stored in fridge	5615	100	24700	100	35600	100
Processed (hostage 236 °C, 2 min)[a]	5497	98	24233	98	34500	97
Degraded[b]	3583	64	3543	27	5610	16

[a] Pellets made from fridge stored powder.
[b] PGA (6 k) degraded for 2 days, PGA (25 k) and PGA (36 k) degraded for 16 days.

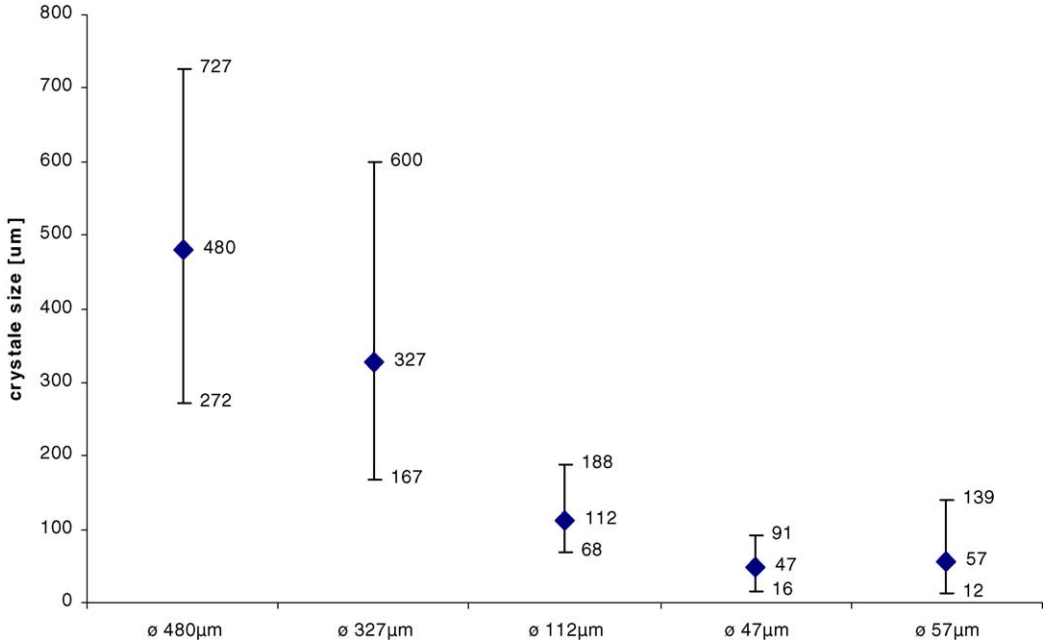

Fig. 2. Average NaCl crystal sizes as measured by particle size analyser. The error bar represents the particle size range between 10 and 90% by order of the cumulative size.

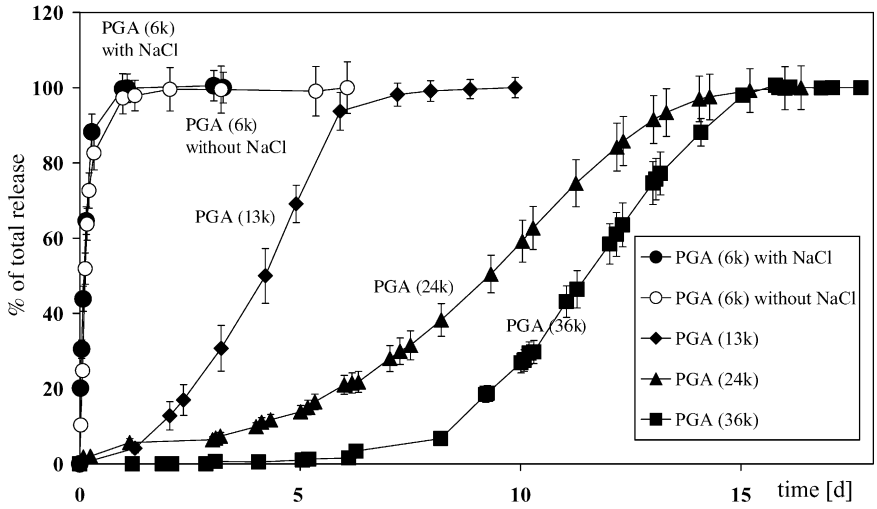

Fig. 3. Drug release profiles of PGA with different molecular weights: PGA (6 k) with NaCl remaining and NaCl washed out, PGA (13 k), PGA (25 k) and PGA (36 k). Drug loading is nominally 5% by weight of PGA.

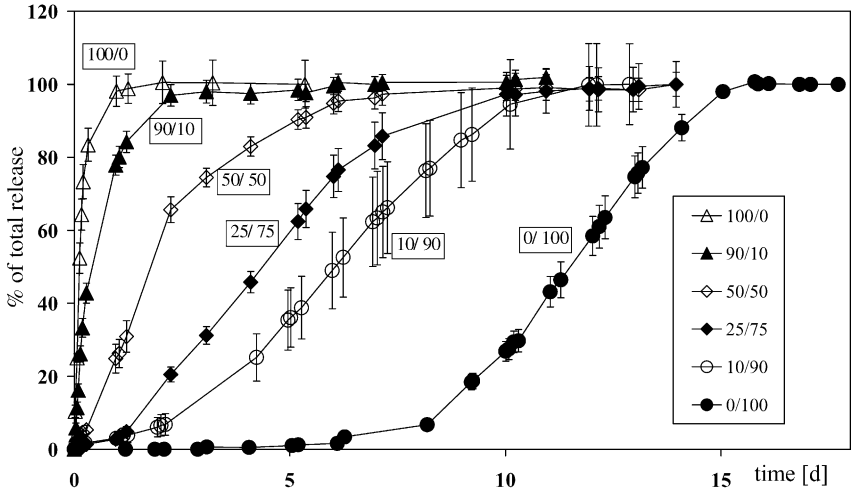

Fig. 4. Drug release profiles of blends of PGA (6 k) and PGA (36 k). The weight ratios of PGA (6 k)/PGA (36 k) are 100/0, 90/10, 50/50, 25/75, 10/90 and 0/100. Each sample is loaded with a nominal 5 wt.% theophylline with respect to the total weight of PGA.

Fig. 8 shows the change in mass for pellets of PGA (36 k) with 50 wt.% NaCl due to the dissolution of NaCl of average size 57 μm into PBS after submerging the sample. The profile shows that the NaCl in the pellet has fully dissolved into the buffer after approximately 4 h, a timescale much shorter than the release of the drug.

Fig. 9 shows the percentage mass loss determined gravimetrically for pure PGA (36 k) and mixed PGA (36 k) samples with 50 wt.% NaCl of average size 57 μm. The profiles are in keeping with dissolution of the NaCl crystals seen on the first day. After about 7 days, significant mass loss begins. Fig. 10 shows the percentage mass loss of a PGA (36 k) sample and a

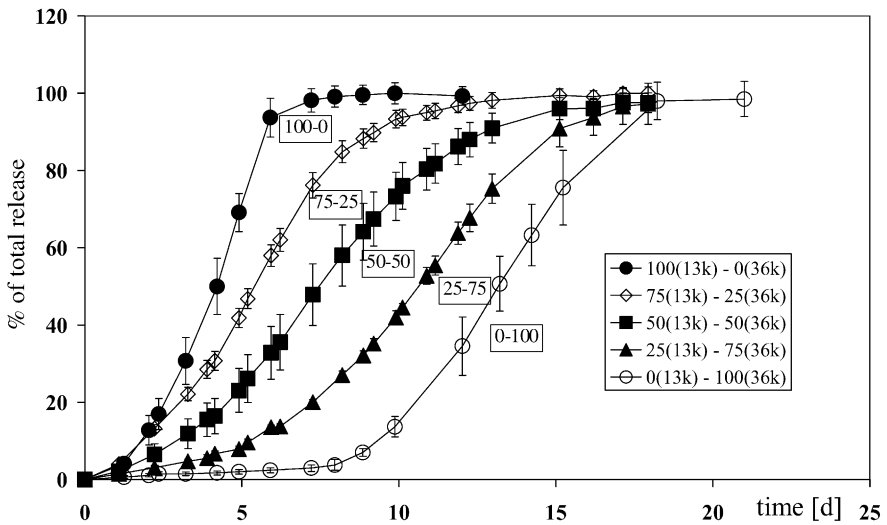

Fig. 5. Drug release profiles of blends of PGA (13 k) and PGA (36 k). The weight ratios of PGA (13 k)/PGA (36 k) are 100/0, 90/10, 75/25, 50/50 and 0/100. Each sample is loaded with a nominal 5 wt.% theophylline with respect to the total weight of PGA.

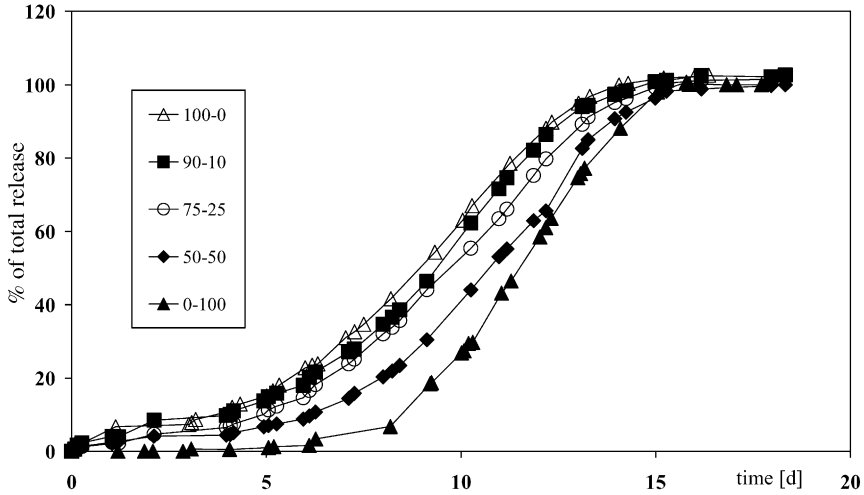

Fig. 6. Drug release profiles of blends of PGA (25 k) and PGA (36 k). The weight ratios of PGA (25 k)/PGA (36 k) are 100/0, 90/10, 75/25, 50/50 and 0/100. Each sample is loaded with a nominal 5 wt.% theophylline with respect to the total weight of PGA.

sample of PGA (36 k) with 50 wt.% NaCl, scaled to exclude the effect of NaCl.

3.3.2. *Varying the pore size*

Figs. 11–18 show SEM micrographs of PGA (36 k) samples with a 50 wt.% concentration of NaCl and a range of crystal sizes, corresponding to those shown in Fig. 2. The samples were washed in water overnight to remove the NaCl. The images show a homogeneous distribution of square-shaped pores and the expected increase in average pore sizes with increasing NaCl crystal size.

Fig. 19 presents the drug release for these samples. In these samples the drug loading was 5% by weight of PGA. The data shows that the initial drug release rate increases with decreasing NaCl crystal size. However, it would appear that the release finishes at about the same time irrespective of sample size.

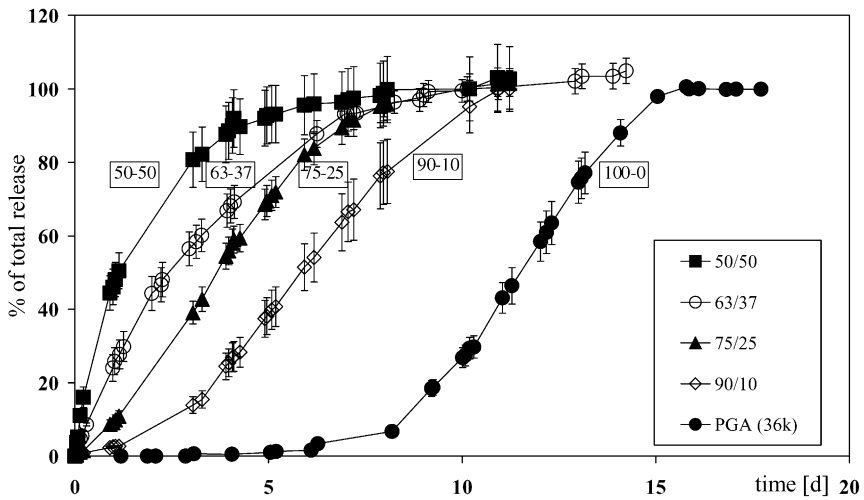

Fig. 7. Drug release profiles of blends of PGA (36 k) with NaCl of average size 57 μm. The weight ratios of PGA (36 k)/NaCl are 50/50, 63/37, 75/25 and 90/10. The nominal drug loading is 5% by total weight of the sample.

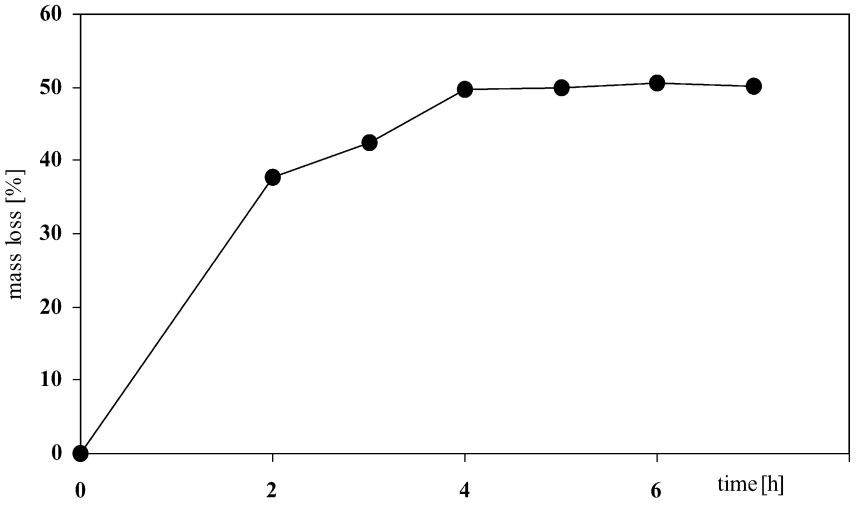

Fig. 8. The change in dry mass of pellets of PGA (36 k) blended with 50 wt.% of NaCl by weight of the polymer on immersion in PBS at 37 °C.

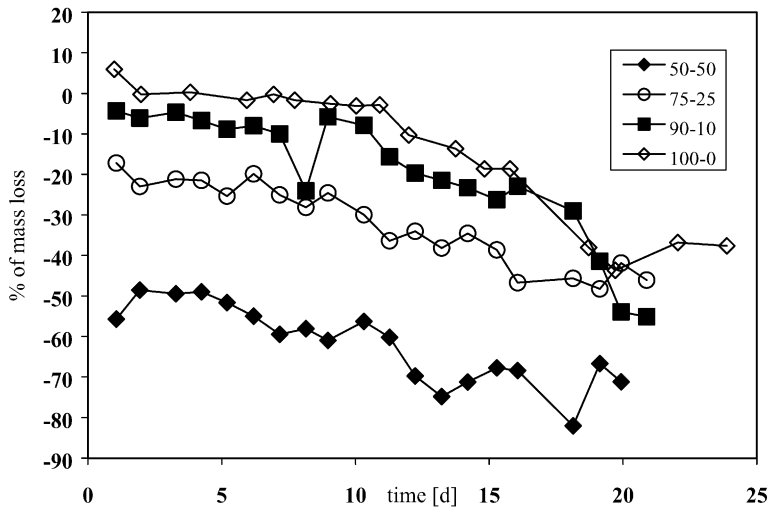

Fig. 9. The mass loss from blends of PGA (36 k) with NaCl of average particle size 57 μm. The weight ratios of PGA (36 k)/NaCl are 50/50, 75/25 and 90/10. The error on each point is approximately ±5%.

Fig. 20 shows the percentage mass change due to polymer mass loss determined gravimetrically for samples of PGA (36k) with 50 wt.% NaCl with different NaCl pore sizes. The data in Fig. 20 show that for all crystal sizes a 50 wt.% mass loss is seen with the first day of degradation indicating complete NaCl dissolution, and consistent with the findings in Fig. 8. A further slow increase in mass loss is seen after about 7 days.

4. Discussion

4.1. Molecular weight changes on processing

It is clear that polymer molecular weight has a significant effect on the release of drug from PGA. It is therefore instructive to consider the effects that sample processing has on the molecular weight distribution of the polymer. Three factors may be identified.

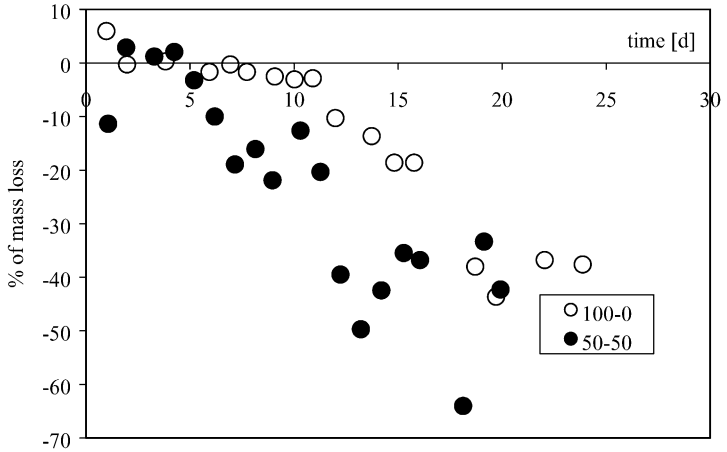

Fig. 10. Mass loss from PGA (36 k) and a blend of PGA (36 k) 50 wt.% NaCl of average particle size 57 μm, scaled to exclude the mass loss of NaCl, and hence showing the % mass loss of the polymer phase only. The error on each point is approximately ±5%.

Firstly, from the dramatic fall in molecular weight on treating PGA (36 k) for 5 days at 120 °C, it is clear that thermal degradation is significant. It is therefore reassuring to note that the processing of the PGA powders into pellets at 236 °C produced only a marginal 2% drop in molecular weight (Table 2). Presumably the short times of processing do not allow the degradation to proceed to any great extent.

Secondly, as expected, immersion in a buffer solution produced a dramatic fall in molecular weight (Table 2).

Thirdly, a somewhat unexpected result was seen in the effect of thawing and re-freezing on the molecular weight of PGA (25 k). The thawing and refreezing cycles lowered the molecular weight by a factor of two compared with PGA (25 k) stored in the refrigerator with silica gel. It seems likely that the fall in molecular weight is related to hydration of the polymer chains as a result of water condensation during the thawing process. It is also possible that the prior thermal degradation of PGA (25 k) had rendered it more susceptible to further degradation in this way. It is interesting to note that the PGA (36 k) supplied by Medisorb had also been stored in the freezer and removed several times before being stored in the fridge. This had not received

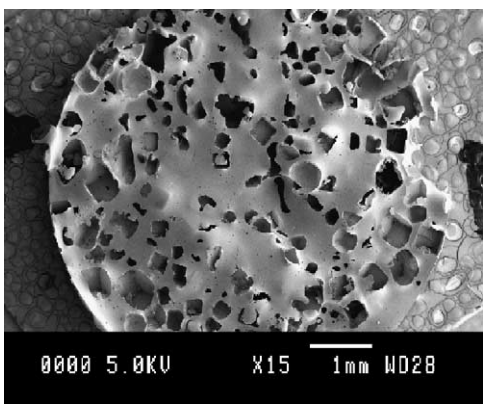

Fig. 11. SEM image of PGA (36 k) containing 50 wt.% NaCl of average particle size 480 μm.

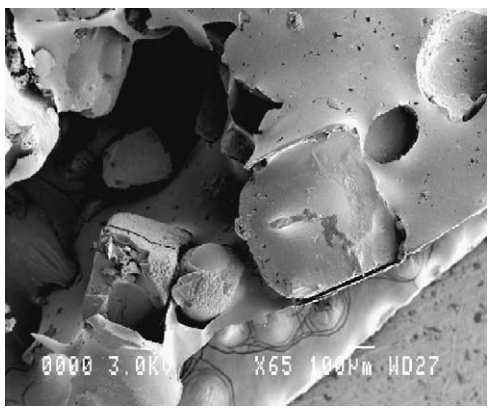

Fig. 12. SEM image of PGA (36 k) containing 50 wt.% NaCl of average particle size 480 μm. The NaCl was washed out overnight and the sample dried in air for 1 day.

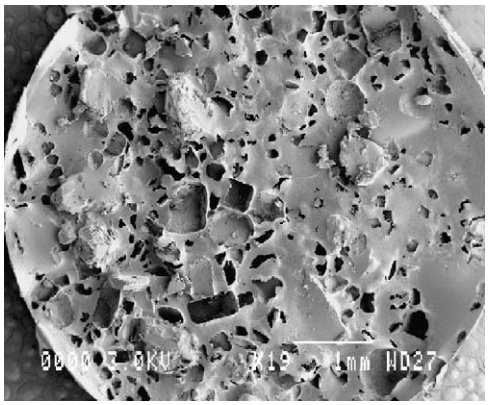

Fig. 13. SEM image of PGA (36 k) containing 50 wt.% NaCl of average particle size 327 μm.

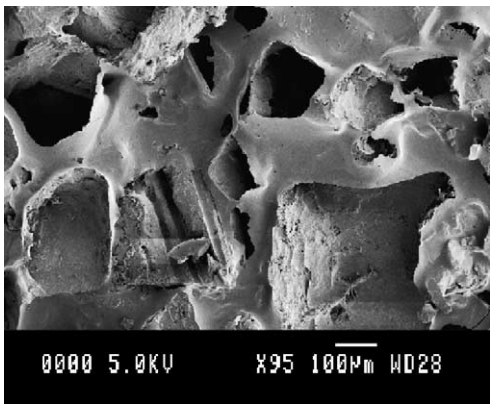

Fig. 14. SEM image of PGA (36 k) containing 50 wt.% NaCl of average particle size 327 μm. The NaCl was washed out overnight and the sample dried in air for 1 day.

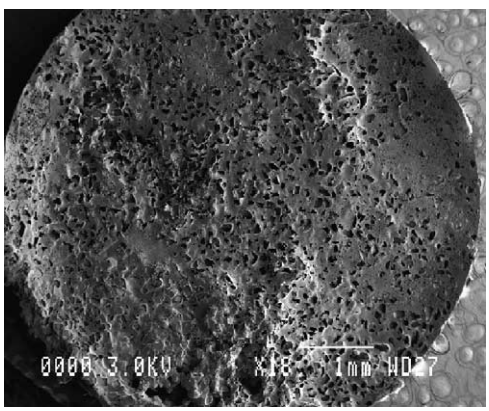

Fig. 15. SEM image of PGA (36 k) containing 50 wt.% NaCl of average particle size 112 μm.

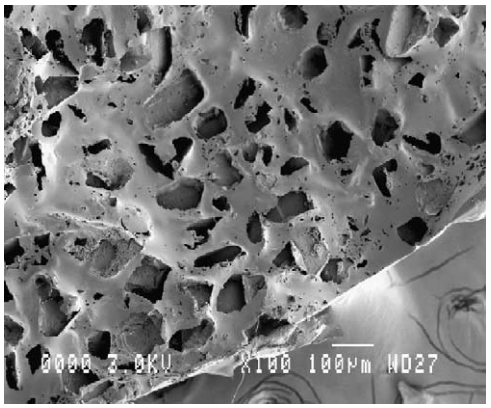

Fig. 16. SEM image of PGA (36 k) containing 50 wt.% NaCl of average particle size 112 μm. The NaCl was washed out overnight and the sample dried in air for 1 day.

any prior heat treatment and did not show any major changes in the drug release properties.

4.2. The effect of varying the molecular weight

Fig. 3 shows the effects of molecular weight on the drug release from PGA. The onset of drug release occurs at earlier times for samples with decreasing initial molecular weight. Release begins immediately for PGA (6 k), after 1 day for PGA (13 k), after 3 days for PGA (25 k) and after 6 days for PGA (36 k). These results are consistent with the four-stage degradation

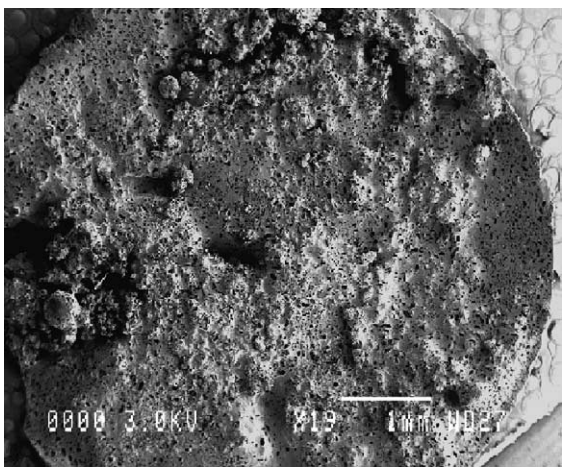

Fig. 17. SEM image of PGA (36 k) containing 50 wt.% NaCl of average particle size 46 μm.

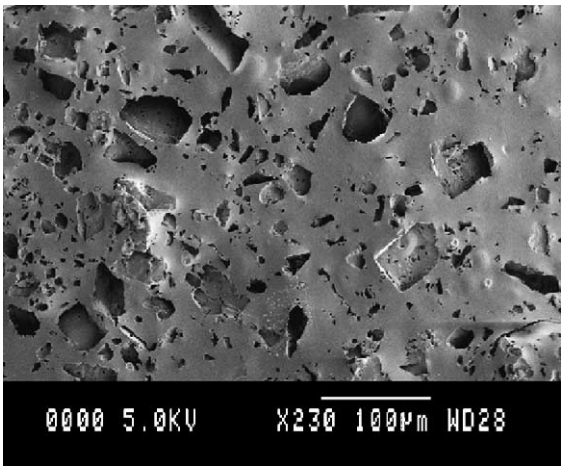

Fig. 18. SEM image of PGA (36 k) containing 50 wt.% NaCl of average particle size 46 μm. The NaCl was washed out overnight and the sample dried in air for 1 day.

model in which drug release begins when the polymer reaches a critical molecular weight. As predicted by the model, the critical molecular weight is achieved more quickly the lower the initial molecular weight. The molecular weight of PGA (6 k) is already lower than the critical molecular weight, since release is immediate. On the basis of these results, it would appear that the critical molecular weight is a little less than 12 950 g mol^{-1}, since the incubation time in the PGA (13 k) is very short, indicating that the initial molecular weight is very close to the critical value.

The rate of drug release after onset is also affected by the molecular weight. Drug is released from PGA (6 k) immediately and rapidly. Presumably, since the polymer is of sufficiently low molecular weight to be quite soluble in the buffer, release is not controlled by the reaction–erosion mechanism, but by simple dissolution. The rate of release appears to be slightly higher if the NaCl formed during synthesis is not removed, although this effect is small and within the error of measurement. It is possible that the presence of NaCl crystals facilitates hydration and dissolution. In the higher molecular weight material, release occurs more slowly, since the slower movement of reaction–erosion fronts controls the rate. There does not seem to be a simple relationship between the rate of release during stage III and the initial molecular weight. The rate is similar in PGA (13 k) and PGA (36 k), but slower in PGA (25 k). It is possible that the exact distribution of molecular weight plays a role in controlling the rate of front movement.

Forming binary blends of the polymers of different molecular weights creates drug release profiles that lie between those of the pure components. Blending PGA (36 k) with PGA with an initial molecular weight lower than the critical value, as in the blends with PGA

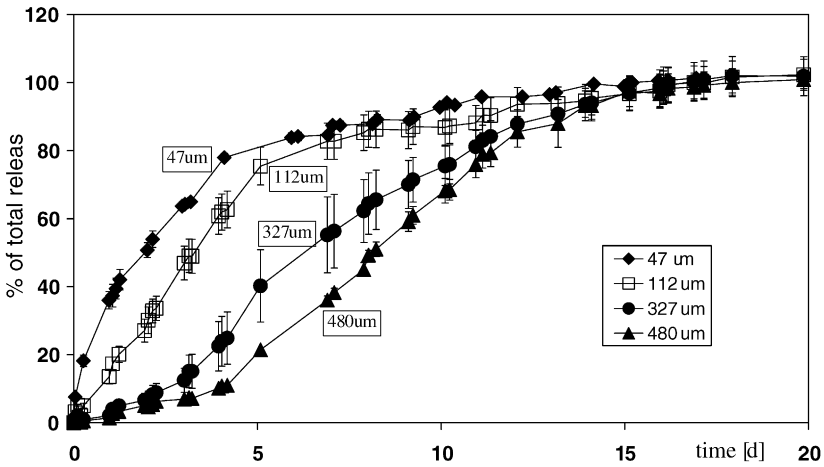

Fig. 19. Drug release profiles of blends of PGA (36 k) with 50 wt.% NaCl of average particle size 46 μm, 112 μm, 327 μm and 480 μm. The nominal drug loading is 5% by total weight of the PGA.

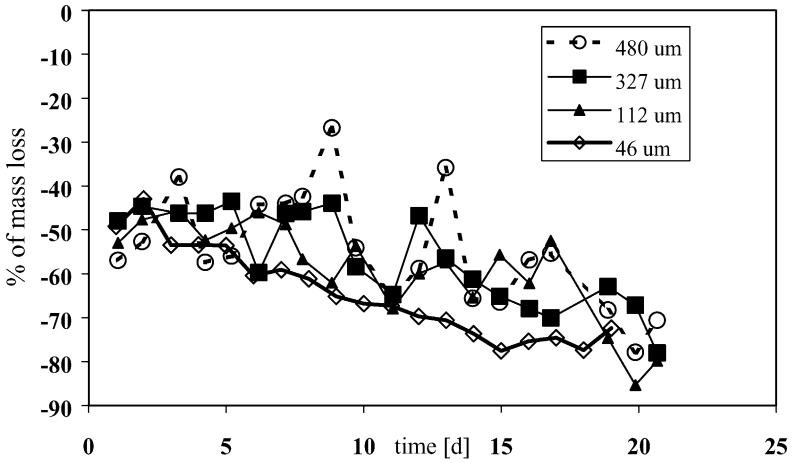

Fig. 20. The mass loss from blends of PGA (36 k) with 50 wt.% NaCl of average particle size 46 μm, 112 μm, 327 μm and 480 μm. The uncertainty in the measurement increased with particle size. For particles of size 46 μm and 112 μm the error was ±1.5%, for particles of average size 327 μm, the error was ±4.5%, and for particles of average size 480 μm, the error was ±7%.

(6 k), gives an almost immediate start to release (Fig. 4). The subsequent rate of release is then dependent on the fraction of lower molecular weight material. Since the creation of reaction–erosion fronts is related to the dissolution of soluble oligomers, it would seem likely that introducing a small soluble fraction of PGA into the higher molecular weight material allows reaction erosion fronts to be immediately set up, and stage III immediately entered. This explains why the addition of only a small fraction of soluble material has such a marked effect on the release. In blends with a higher fraction of soluble material, the release is increasingly dominated by the dissolution of the polymer. Presumably, at a certain percentage of low molecular weight PGA, reaction–erosion fronts are not set up at all, as too great a fraction of the pellet is soluble. This would explain the deviation from linear release seen in the samples with a fraction of PGA (6 k) of 50% and above. The release in these samples is no longer controlled by the linear movement of reaction–erosion fronts, but by the processes of diffusion and dissolution, in which the rate decays with time.

When the polymers in the blend are both above the critical molecular weight, such as the blends of PGA (13 k) and PGA (36 k) (Fig. 5) and PGA (25 k) and PGA (36 k) (Fig. 6), the release does not start immediately. The kinetics of release in these samples is consistent with reaction–erosion fronts continuing to influence release, the time of onset and the rate of release of the blends lying between those of the pure components.

4.3. The effect of introducing porosity

It is clear from Figs. 7 and 18 that porosity produces a wide range of drug release rates and that the effects of porosity can be substantially manipulated by varying pore size and volume fraction.

4.3.1. Pore volume fraction

Introducing a 50 wt.% fraction of NaCl with crystals of average size 57 μm has a dramatic effect on the release profile of PGA (36 k) (Fig. 7). Release begins immediately in all the porous samples, and the rate of release increases with increasing pore fraction.

In these samples, the drug loading was 5% of the total mass of sample rather than the mass of polymer. Therefore, as the NaCl fraction increases, the concentration of drug in the polymer also increases since it is partitioned to the polymer phase. Hence, in the 50 wt.% sample the concentration of drug in polymer is actually 9.5% rather than 5%. Release studies not presented in this paper performed on PGA (36 k) pellets with theophylline loadings of 5 and 10 wt.% showed a marginal increase in the onset and rate of release with increasing loading. This trend may partially explain the difference in the drug release behaviour for the PGA (36 k) sam-

ples with and without 50 wt.% NaCl, but is not thought to account entirely for the changes seen.

The mass loss profiles for these samples are shown in Figs. 9 and 10. These curves show a drop in mass over the first day at proportions consistent with the loss of salt after the first day of immersion. The drop in mass for the 50 wt.% NaCl sample is 50%, suggesting complete loss of the salt over the first day. This agrees with the NaCl release rates implied in Fig. 8 for the same sample. The fast release of the salt suggests an interconnection between the pores at this loading level. The drop in mass for the samples with lower fractions of NaCl is perhaps slightly less than would be expected, and it is possible that some salt remains within the sample and does not have a clear diffusion path for removal.

Although the mass loss curves are noisy, an increase in rate of mass loss is visible after about 7 days in the sample without porosity. This increase in mass loss is the signature of the onset of stage III, when soluble oligomers begin to diffuse into the buffer medium (Hurrell and Cameron, 2001a,b). There is some indication that this behaviour may occur earlier in samples with higher levels of NaCl. This is shown more clearly when the effect of NaCl dissolution is removed from the curves as in Fig. 9, where only the percentage mass loss of the non-salt fraction is shown. It would seem that the high hydration levels encouraged by porosity facilitate the eventual dissolution of the polymer fraction.

In samples with low volume fractions of NaCl, the drug release profiles are not typical of diffusion-controlled release since release is delayed and is relatively linear once it has begun. However, the mass loss curves suggest that any hastening of the onset of stage III is not sufficient to entirely account for the release, since stage III is still reached too late. It seems probable that release is controlled partly by the increased surface area encouraging diffusion and partly by degradation. As the pore fraction increases, the curves become more typical of release controlled by diffusion alone, with the rate decreasing with time. It would seem therefore that, in porous samples with a high volume fraction of pores, the drug release is largely controlled by water ingress and diffusion rather than polymer erosion. With increasing pore volume fraction, the rate of release increases because of the greater surface area from which diffusion can occur.

4.3.2. Pore size

Fig. 19 shows the drug release profiles of samples where the NaCl fraction is kept constant at 50 wt.%, and the size of the crystals is varied. In these samples, the drug loading is 5% of the weight of PGA. Release starts and finishes at the same time for the same pore volume independent of the pore size.

Fig. 20 shows the mass loss during degradation. Within the uncertainty of measurement, which is substantial, the size of the crystals has not affected the mass loss, although as before, it seems that a porosity of 50% may have hastened the increase in mass loss that marks the onset of stage III, when compared with a non-porous sample.

The larger pore sizes show release that is delayed and relatively linear and is clearly modified by the degradation. As the pore size decreases, the release becomes more typical of release from diffusion. The smaller the pores, the larger the surface area and the more that diffusion-controlled drug release dominates. There seems to be some degree of equivalence between a higher pore fraction and a finer pore structure. In both cases, the surface to volume ratio of the construct is increased which encourages release by diffusion rather than degradation.

Fig. 21 shows the drug release profile from two 50 wt.% PGA (36 k) mixtures. The first is PGA (36 k) blend with PGA (6 k) with 5 wt.% of drug and the second PGA (36 k) blend with NaCl of average size 57 μm with 9.5 wt.% of drug. Both mixtures show very similar release profiles, with the drug release starting immediately and finishing after about 9 days.

It would perhaps be over simplistic to suggest that the processes affecting release are identical in the two cases. With NaCl incorporation, the NaCl is quickly released from the polymer and creates pores within the structure of the same size as the original NaCl crystals. It seems unlikely that this behaviour is happening on the same scale in the PGA (6 k) blends, not least because it is likely that the polymers of different molecular weights are mixed to some degree at a molecular level. However, it is clear that both processes facilitate a diffusional release of drug rather than one controlled by degradation, and it is interesting to note that almost identical release profiles can be obtained by the careful choice of parameters.

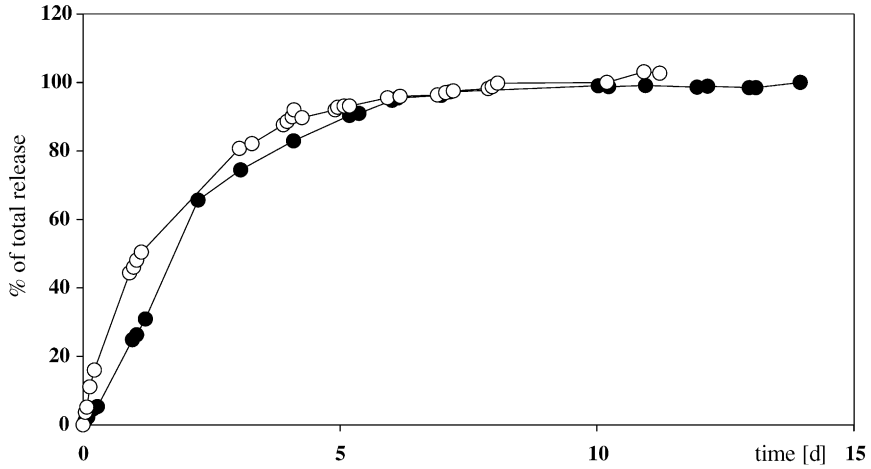

Fig. 21. Drug release profiles from two 50 wt.% binary PGA (36 k) mixtures. The first (closed circles) is PGA (36 k) blend with PGA (6 k) with 5 wt.% of drug and the second (open circles) is PGA (36 k) blend with NaCl of average size 57 μm with 9.5 wt.% of drug.

5. Conclusions

The results in this paper show that the degradation and drug release behaviour can be tailored by varying PGA molecular weight and porosity. It is clear that small changes to these parameters can have a substantial impact on the degradation and that the effects can be explained in the context of the four-stage reaction–erosion front model.

In high molecular weight PGA, the release begins when a critical molecular weight is reached on degradation. As the initial molecular weight decreases, the degradation time required to achieve this is reduced and drug release begins earlier. When high molecular weight PGA is blended with PGA substantially below the critical molecular weight, the low molecular weight polymer fraction is soluble and drug release begins immediately. Samples with a high fraction of PGA well below the critical molecular weight release by diffusion and dissolution rather than degradation.

Porous structures with a high surface to volume ratio release through diffusion and are relatively unaffected by degradation. As the surface to volume ratio reduces, either by increasing the pore size at constant pore fraction, or by decreasing the pore fraction at constant pore size, degradation also plays a role in controlling the release.

The effects of molecular weight and porosity on PGA degradation show that both parameters can play a significant role in the tailoring of drug release from controlled release devices made from PGA. The principles outlined in this paper provide key tools in the design of drug releasing tissue engineering scaffolds from PGA.

Acknowledgments

JB is grateful to Swiss Federal Institute of Technology of Zurich (ETHZ) for financial support. The GPC analyses were carried out at Smith and Nephew.

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