Structure–property relationships in the case of the degradation of massive poly(α-hydroxy acids) in aqueous media

Part 2 *Degradation of lactide–glycolide copolymers: PLA37.5GA25 and PLA75GA25*

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Degradation of two lactic–glycolic copolymers, namely PLA37.5GA25 (75% DL-lactide and 25% glycolide in the feed) and PLA75GA25 (75% L-lactide and 25% glycolide) was investigated *in vitro* using aqueous media to model physiological conditions. Various techniques were used to monitor the effects due to hydrolytic degradation including weighing, SEC (size-exclusion chromatography), potentiometry, cryometry, enzymatic assay, X-ray scattering, ^{1}H-nuclear magnetic resonance and differential scanning calorimetry. It was found that degradation proceeded faster in the centre than at the surface of standard parallelepipedic specimens. This feature had already been found for PLA50 (poly(DL-lactic acid)). The degradation rates of PLA37.5GA25 and PLA75GA25 were compared and it was found that intrinsically amorphous PLA75GA25 crystallized as degradation proceeded, in contrast to PLA37.5GA25. The crystallization of PLA75GA25 was related to the preferential degradation at glycolic units, which led to L-lactic-enriched fragments susceptible to crystallize. No major differences were observed between ageing in iso-osmolar saline and pH 7.4 phosphate buffer. In contrast, in the case of PLA37.5GA25, distilled water favoured surface–centre differentiation, probably because of osmotic exchange related to the absence of ionic strength.

1. Introduction

In a previous paper [1] we introduced the rationale of investigations undertaken in order to understand better the effects of macromolecular and solid-state morphologies on the degradation of poly(α-hydroxy acids) derived from lactic or glycolic acids, or both. These polymers are of increasing interest with respect to temporary therapeutic applications [2]. At the moment little is known about the factors that can affect the degradation of these polymers in aqueous media. In the case of racemic, intrinsically amorphous poly(DL-lactic acid) (PLA50) [1], co-ordinated investigations have confirmed that PLA50 undergoes bulk degradation in iso-osmolar aqueous media as reported in the literature [3–5]. However, we have demonstrated that the bulk degradation proceeds heterogeneously and goes faster in the inner part than at the surface, in contrast to what has so far been reported [4, 6]. This finding accounts well for the bimodal SEC chromatograms exhibited by partially degraded PLA50 devices. Indeed, bimodality could not be explained by the presence of crystalline microdomains, as PLA50 is intrinsically amorphous in contrast to the case of semicrystalline members of the poly(α-hydroxy acid) family [2, 7, 8].

In this paper we report data obtained for two lactic–glycolic (or LA–GA) copolymers, namely PLA37.5GA25 (75% DL-lactide and 25% glycolide in the feed) and PLA75GA25 (75% L-lactide and 25% glycolide), according to PLA*X*GA*Y* acronyms previously defined, where *X* is the percentage of L-lactic units and *Y* is the percentage of glycolic units in the feed [9]. Both copolymers were intrinsically amorphous in agreement with their intermediate contents in GA units [10]. For PLA50 investigations were carried out in two iso-osmolar aqueous media: saline and pH 7.4 phosphate buffer (PBS). Degradation was found to proceed similarly in both media. In order to limit the number of experiments, the degradation of PLA75GA25 was investigated in iso-osmolar phosphate buffer and saline as for PLA50, whereas the degradation of PLA37.5GA25 was investigated in PBS, for direct comparison with PLA75GA25, and in distilled water, in order to evaluate the effects of ionic strength.

2. Experimental

The experimental conditions selected for the present investigations were similar to those described in Part 1 [1]. The copolymers were processed by compression moulding of round plates (2 mm thick and 75 mm in diameter) further machined to yield parallelepipedic

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specimens (2 mm × 10 mm × 15 mm) as in the case of PLA50 [1].

Moulding was carried out with a hydraulic press equipped with heated plates. The mould temperature was set at 132° C. The powdered polymers were weighed (11.5 g), introduced into the mould and allowed to heat up for 5 min. Pressure was then applied (200 bar) and cooling allowed for 10 min, the round plates finally being recovered [11].

X-ray diffraction measurements were carried out using a diffractometer equipped with a Cu-K_α ($\lambda = 0.154$ nm) source and an INEL monochromator and a goniometric plate. ^{1}H-nuclear magnetic resonance (NMR) spectra were recorded at 60 MHz by a Varian T 60A spectrometer. Differential scanning calorimetry (DSC) thermograms were obtained by using a Dupont series 99 calorimeter equipped with a DSC 910 accessory.

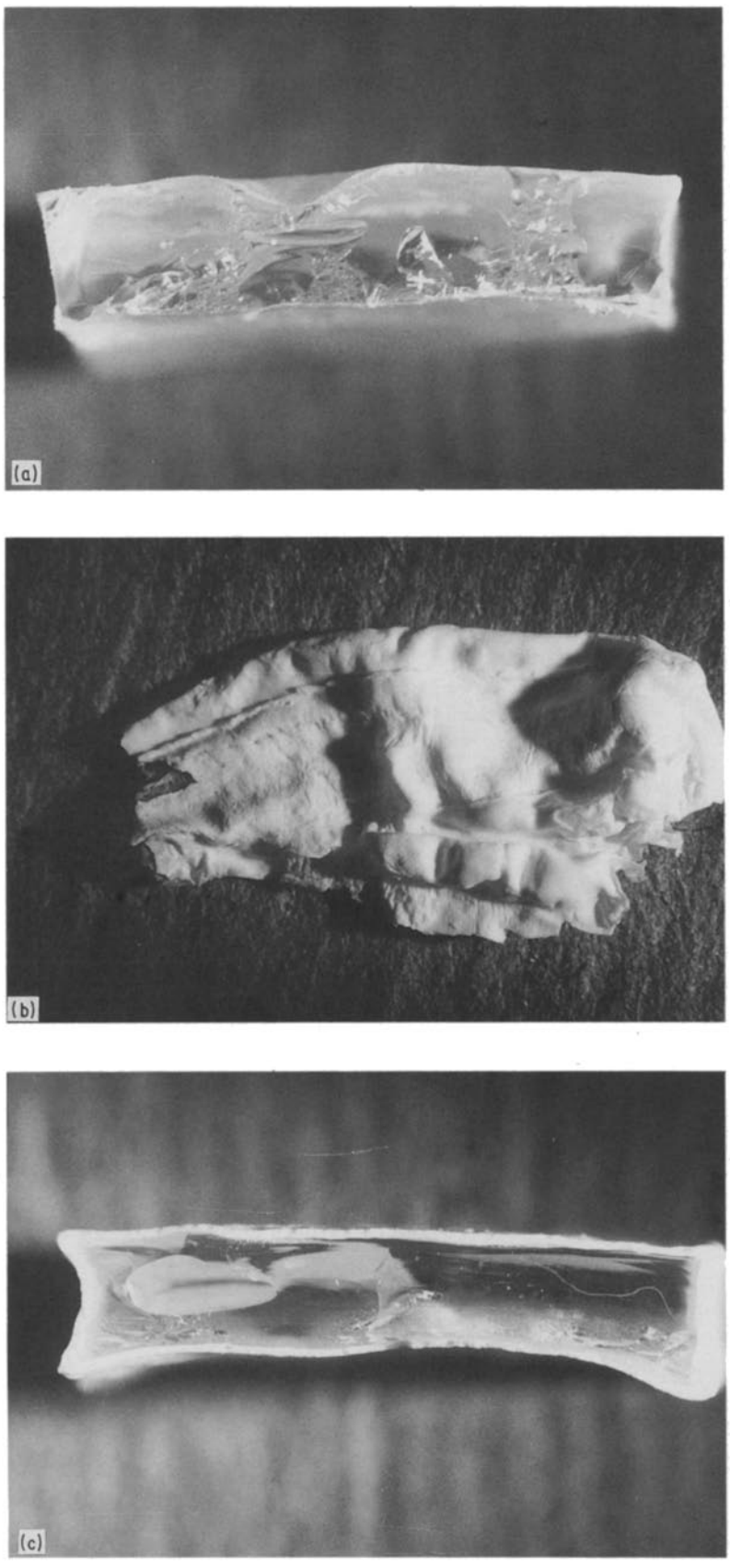

Figure 1 (a) Cross-section of a PLA37.5GA25 specimen after 10 days of degradation in the buffer. (b) Empty shell of a hollow PLA37.5GA25 specimen after 24 days of degradation in the buffer. (c) Cross-section of a PLA37.5GA25 specimen after 10 days of degradation in distilled water.

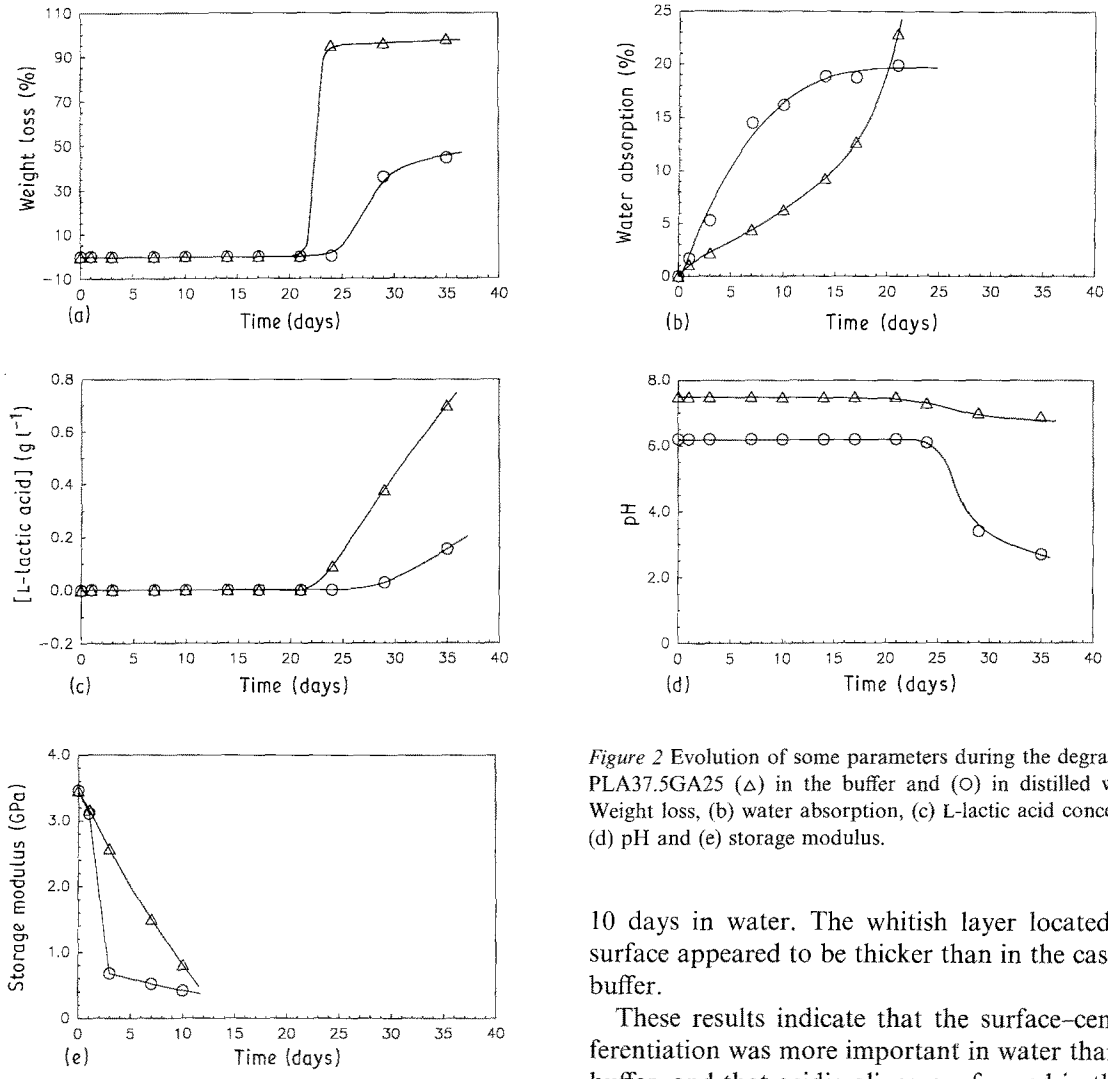

Figure 2 Evolution of some parameters during the degradation of PLA37.5GA25 (△) in the buffer and (○) in distilled water. (a) Weight loss, (b) water absorption, (c) L-lactic acid concentration, (d) pH and (e) storage modulus.

3. Results

For the sake of clarity and conciseness, the results are presented separately and the discussion is focused on the particular characteristics exhibited by the copolymers with respect to PLA50.

3.1. Ageing of PLA37.5GA25 in water and in iso-osmolar pH 7.4 PBS.

3.1.1. Visual examination

PLA37.5GA25 is a totally amorphous polymer, as is PLA50. In aqueous media PLA37.5GA25 specimens absorbed water and turned to a whitish colour within 10 days. Both media caused similar colour changes, but in water the colour changes occurred earlier than in the buffer. Furthermore, specimens appeared to be heterogeneous after breaking, the inner part being still transparent. At 21 days the inner part appeared as a very viscous liquid. After 24 days, in the buffer, hollow flattened specimens were recovered. In contrast, no hollow structures formed in water, the viscous liquid remaining in the centre, filling the volume defined by the deformed outer layer, even after 35 days.

Fig. 1a shows the cross-section of a specimen after 10 days in the buffer. A whitish layer was clearly detectable at the surface but was much thinner than in the case of PLA50. Fig. 1b shows the hollow structure of a specimen allowed to age for 24 days in the buffer. Fig. 1c shows the section of a specimen degraded for 10 days in water. The whitish layer located at the surface appeared to be thicker than in the case of the buffer.

These results indicate that the surface–centre differentiation was more important in water than in the buffer, and that acidic oligomers formed in the inner part of specimens dissolved more easily and to a larger extent in the buffer than in water, in agreement with the normal behaviour of carboxylic acid sodium salts with respect to carboxylic acid parents.

3.1.2. Weight loss (Fig. 2a)

The weight of specimens remained unchanged for the first 3 weeks of ageing. At 24 days we found a dramatic weight loss (about 95% of the initial weight) in the buffer, whereas in water only a small loss (0.3%) was detected. After 35 days the specimens had lost 98% of their initial material in the buffer and only 45% in water. This is readily understandable, since the carboxyl-terminated inner oligomers dissolved more easily in the buffer than in water, the carboxylic form $RCOO^-Na^+$ of organic acids being more hydrophilic than the carboxylic form RCOOH.

3.1.3. Water absorption (Fig. 2b)

There was a marked difference between the water absorption behaviour of PLA37.5GA25 specimens in the two media. During the first 2 weeks water absorption was much more important in water than in the buffered medium. Then the absorption levelled off in water, whereas it increased continuously at an increasing speed in the buffer. This difference probably resulted from osmotic phenomena, as water had no ionic strength to resist water absorption at the beginning, in contrast to iso-osmolar PBS. Consequently,

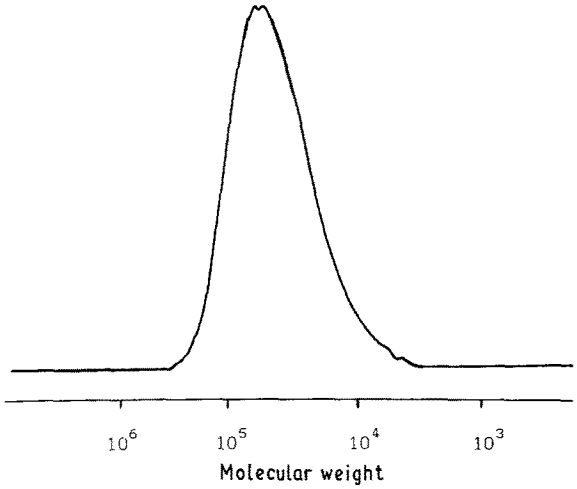

Figure 3 SEC chromatogram of PLA37.5GA25 at $t = 0$.

the surface–centre differentiation was much more significant in water than in the buffer during the first 2-week period.

3.1.4. Release of L-lactic acid (Fig. 2c)

In the buffer, L-lactic acid was detected for the first time at the 21st day and then its concentration increased rapidly, whereas in water no L-lactic acid was detected before day 29.

3.1.5. pH change (Fig. 2d)

In the buffered medium the pH remained relatively constant during the degradation time. At the end of the experiment (35 days) the pH was still 6.9. In water the pH remained constant until the 21st day. Then it decreased rapidly and reached 2.8 at the end of 35 days, a value sufficiently low to prevent ionization and thus solubilization of large amounts of acidic degradation products.

3.1.6. Storage modulus (Fig. 2e)

The loss of storage modulus E' was determined in order to monitor the loss of mechanical properties of the specimens. E' decreased more rapidly in water than in the buffer. This difference was certainly related to the plasticizing effect of the absorbed water. Indeed, the specimens absorbed more water and deformed more in water than in the buffer, at least in the first 2 weeks.

3.1.7. Molecular weight changes

Fig. 3 shows the monomodal SEC chromatogram of the processed PLA37.5GA25 specimens at time 0. The SEC-relative weight average molecular weight ($\bar{M}_w$) was 51 000 and the polydispersity ($\bar{M}_w/\bar{M}_n$ was 1.6. Figs 4a and b present SEC chromatograms of the surface and the centre of specimens allowed to age for 17 days in the two model media. The surface exhibited higher molecular weights than the centre for both media, but the molecular weight difference was larger in water than in the buffer. After 35 days in the buffer only the empty shell was still present and it was composed of rather high-molecular weight macromolecules ($\bar{M}_w \approx 12\,000$; (Figs 5a). In contrast, the specimens ageing in water were still full, although the inner part was composed of oligomers with very low molecular weights ($\bar{M}_w \approx 1500$). The surface showed a bimodal SEC distribution (Fig. 5b).

The results indicate that the presence of 25% GA units made the copolymer PLA37.5GA25 degrade much more rapidly than PLA50 [1], but through a similar autocatalytic phenomenon in the central part of the specimens.

3.1.8. Chemical composition

The ^{1}H-NMR investigations showed that very little changes in composition occurred during the degradation of PLA37.5GA25. The initial composition of this LA–GA copolymer which was actually 73–27 (slightly different from that of monomers blend 75–25) varied to 74–26 in the buffer and in water at the end of 24 days. These results showed that degradation occurred almost similarly at glycolic and lactic units of PLA37.5GA25 macromolecular chains.

3.2. Ageing of PLA75GA25 in saline and in iso-osmolar pH 7.4 PBS.

For this copolymer derived from L-LA and GA, no major difference was found between degradation in the buffer and in saline, in agreement with what had

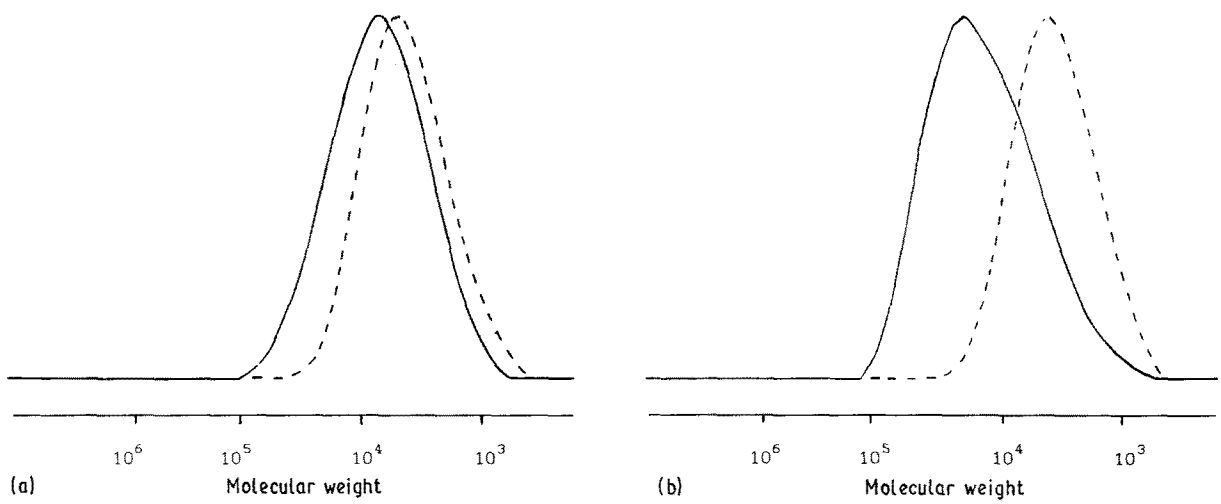

Figure 4 (a) SEC chromatograms of the (——) surface and (– – –) centre of PLA37.5GA25 after 17 days of degradation in the buffer. (b) SEC chromatograms of the (——) surface and (– – –) centre of PLA37.5GA25 after 17 days of degradation in distilled water.

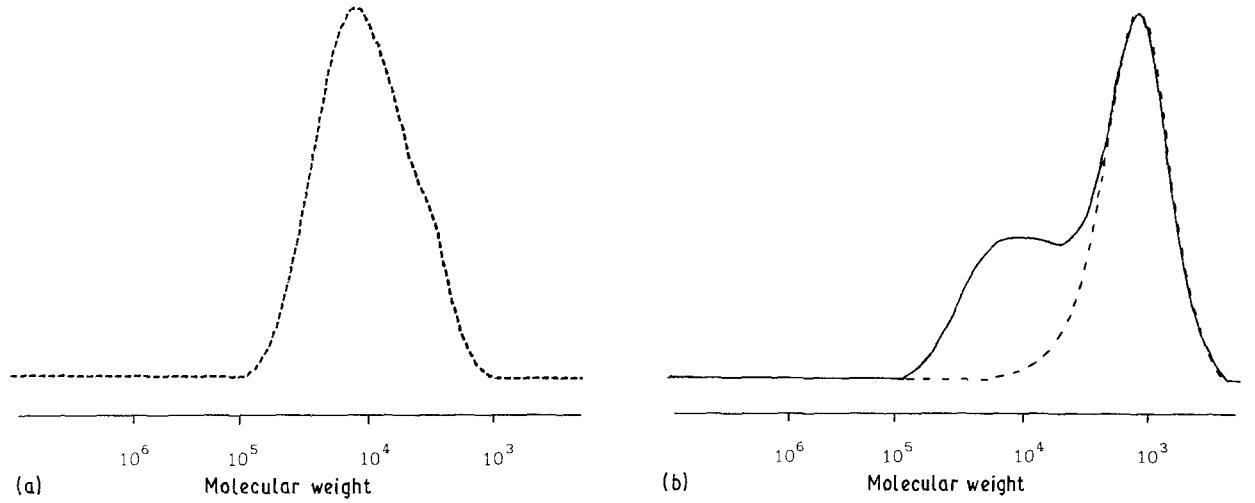

Figure 5 (a) SEC chromatogram of the empty shell of a PLA37.5GA25 specimen after 35 days of degradation in the buffer. (b) SEC chromatograms of the (——) surface and (– – –) centre of PLA37.5GA25 after 35 days of degradation in distilled water.

already been observed for PLA50. Accordingly, only the results of the degradation in the buffer are presented in detail.

3.2.1. Visual examination

During the ageing in the buffer, PLA75GA25 specimens absorbed water and then deformed. Their surface became gradually whitish, the cross-sections showing a thin surface layer which appeared embossed (Fig. 6). In contrast to PLA50 and PLA37.5GA25, the inner part of PLA75GA25 specimens did not turn to a viscous liquid. Only a white powder was found beyond 9 weeks. This white powder appeared to be very resistant to degradation and remained until 50 weeks.

3.2.2. Weight loss (Fig. 7a)

The weight of the specimens remained unchanged until week 7, when a small weight loss (0.4%) was detected. At week 9 an important weight loss (24.4%) was observed. Within the next 2 weeks the specimens lost nearly 70% of their initial material. After that the rate of weight loss slowed down.

3.2.3. Water absorption (Fig. 7b)

During the first 5 weeks water absorption of the PLA75GA25 specimens increased slowly and continuously. Between 7 and 9 weeks there was an important acceleration of water absorption, corresponding to the beginning of weight loss. Beyond 9 weeks it was no longer possible to weigh the well-degraded specimens.

3.2.4. Release of L-lactic acid (Fig. 7c)

A small quantity of L-lactic acid was detected at the 7th week. Then the L-lactic acid concentration increased rapidly. The release of L-lactic acid was apparently in good agreement with the weight loss.

3.2.5. pH change (Fig. 7d)

The pH of the buffer remained constant during the first 7 weeks. After that a slight decrease of pH was observed and a pH of 6.4 was attained after 20 weeks, which was also in agreement with the weight loss.

3.2.6. Osmolarity variation (Fig. 7e)

The osmolarity of the medium was unchanged for the first 7 weeks, and then it increased rapidly. Beyond 12 weeks the changes slowed down. Obviously, the pH changes, the release of L-lactic acid and the osmolarity variations agreed well with the fact that, from week 7, large amounts of acidic compounds such as L-lactic acid, glycolic acid and oligomers dissolved in the buffer.

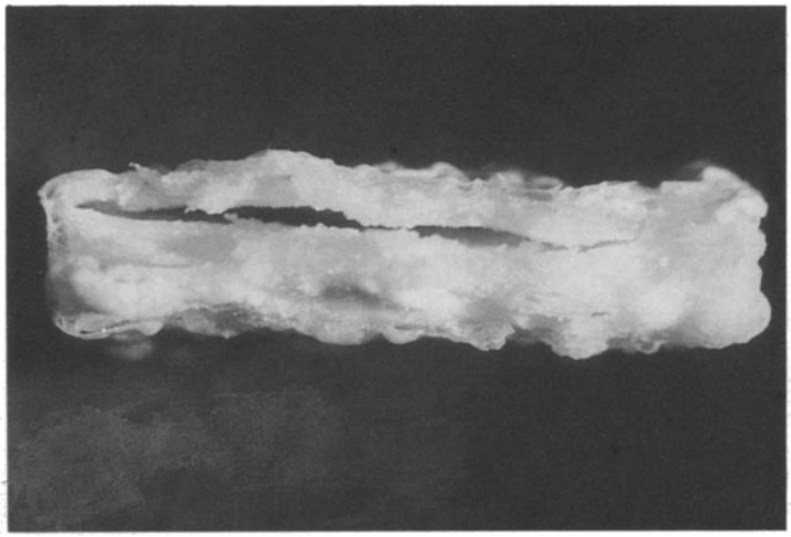

Figure 6 Cross-section of a PLA75GA25 specimen after 9 weeks of degradation in the buffer.

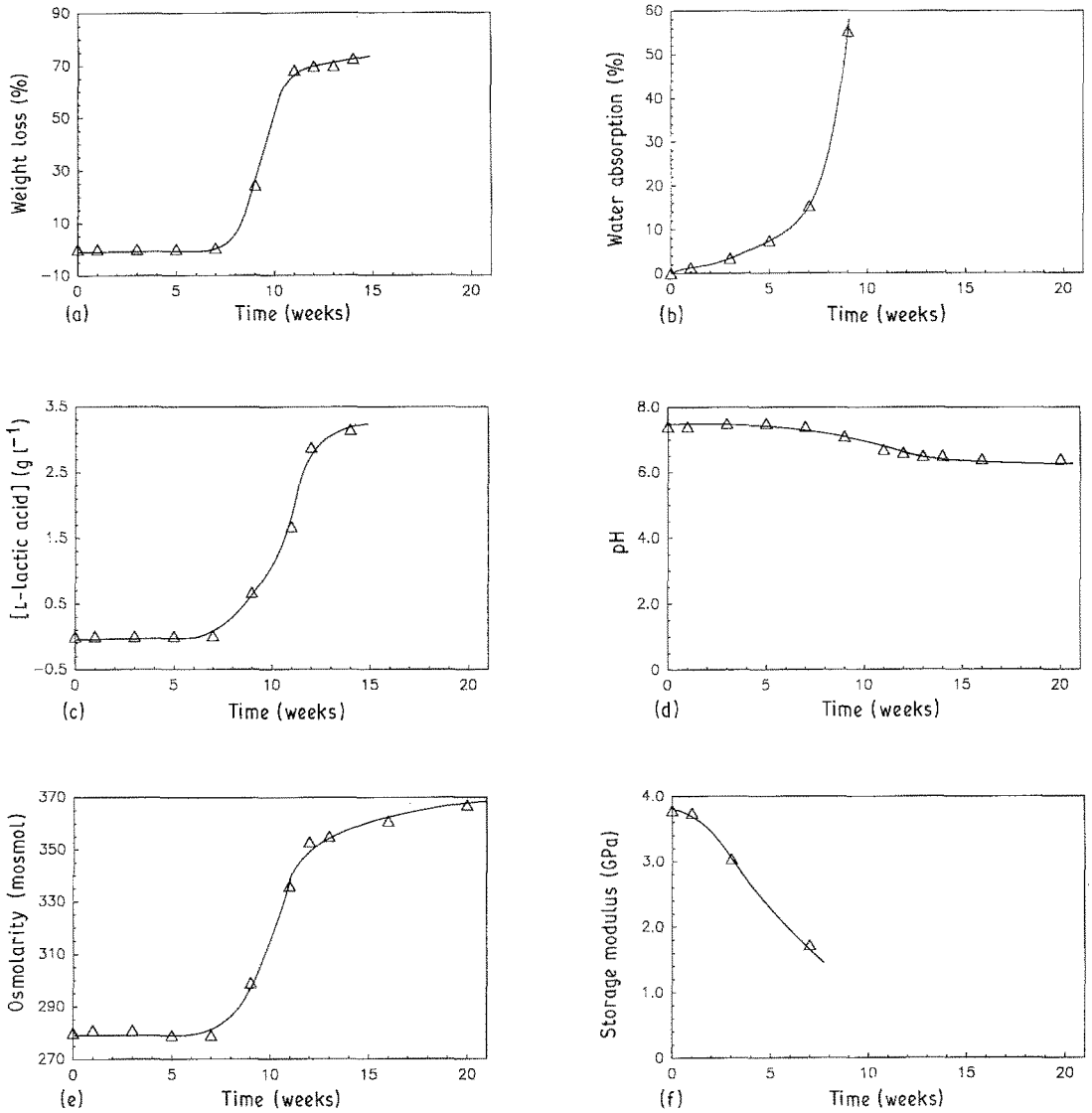

Figure 7 Evolution of some parameters during the degradation of PLA75GA25 in the buffer. (a) Weight loss, (b) water absorption, (c) L-lactic acid concentration, (d) pH, (e) osmolarity and (f) storage modulus.

3.2.7. Storage modulus (Fig. 7f)

The PLA75GA25 specimens conserved their storage modulus, E', for only 1 week. Then E' decreased almost linearly until the 7th week. After that it was no longer possible to carry out E' measurements because of the deformation of the specimens.

3.2.8. Molecular weight changes

Fig. 8 presents the SEC chromatogram of the initial copolymer (SEC-relative $\bar{M}_w$ = 111 000 and $\bar{M}_w/\bar{M}_n$ = 1.8). Figs 9a and b present the chromatograms of surface and inner part of PLA75GA25 specimens degraded for 5 and 12 weeks. At the 5th week a surface–centre differentiation was observed. At the 12th week the surface presented a bimodal distribution, whereas the centre had a very narrow and monomodal distribution ($\bar{M}_w/\bar{M}_n$ = 1.1). Fig. 10 presents the SEC chromatogram of the powder still present at week 50. A very narrow and monomodal distribution was observed ($\bar{M}_w/\bar{M}_n \leqslant 1.1$, $\bar{M}_w \approx 1900$). These features are typical of the degradation of crystallized poly(α-hydroxy acids), as will be shown in subsequent papers dealing with semicrystalline members of the family.

3.2.9. Crystallinity

Fig. 11 presents several X-ray spectra of PLA75GA25 at different degradation times. The copolymer was initially amorphous, as stated above. At week 7 two small peaks appeared, the intensities of which increased rapidly with time. Beyond week 11 no further changes were observed.

Table I presents the crystallinity changes of the PLA75GA25 specimens with degradation time as deduced from X-ray spectra.

3.2.10. Chemical composition

The initial copolymer was intrinsically amorphous and annealing failed to generate any crystallization. Therefore, it is concluded that crystallization was related to the degradation and, especially, to a change in chemical composition. ^{1}H-NMR spectra of PLA75GA25 specimens were recorded at various degradation times. The relative magnitude of the doublet corresponding to GA units with respect to

TABLE I Crystallinity evolution of PLA75GA25

Degradation time (weeks)	0	7	9	11	12	13	16	20
Crystallinity (%)	0	6	23	26	27	24	25	28

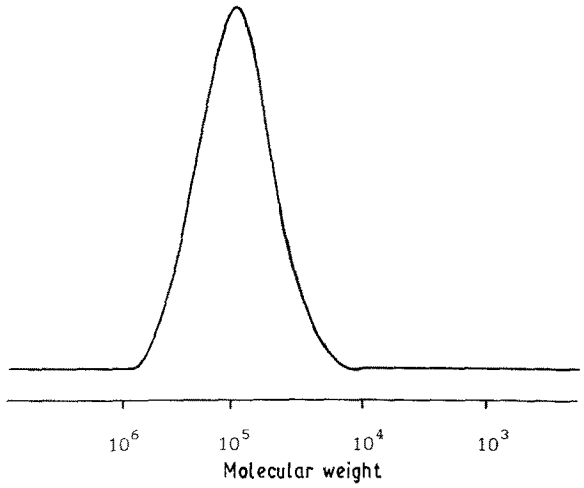

Figure 8 SEC chromatogram of PLA75GA25 at $t = 0$.

GA + LA signals decreased as degradation proceeded, thus showing a decrease of the percentage of GA units in the residual material.

Table II presents the changes in chemical composition for PLA75GA25 specimens with respect to the degradation time.

3.2.11. Thermal properties

Fig. 12 shows DSC thermograms at different degradation times. Before degradation DSC reflected only a glass transition (T_g) at about 56° C, in agreement with the amorphous morphology. After 5 weeks T_g decreased to 51° C due to the plasticizing effect of absorbed water. At the 7th week thermograms of the surface and the centre exhibited small melting peaks at 64 and 65° C, respectively. At the 9th week the melting temperatures increased to 70 and 74° C for the two parts. The glass transition zones were broadened. At week 11 the surface still presented a small melting peak located at 94° C, whereas the centre exhibited a relatively important melting peak at 96° C. At week 12 the surface was found to exhibit two melting peaks at 74 and 97° C, respectively, whereas the centre showed a very important and very narrow melting peak at 100° C. Beyond 13 weeks no further significant change was detected for the residual highly crystalline oligomers enriched in L-lactic acid repeating units.

TABLE II Chemical composition of PLA75GA25

	Degradation time (weeks)							
	0	7	9	11	12	14	20	50
Percentage lactic acid	73	79	83	83	86	86	88	89
Percentage glycolic acid	27	21	17	17	14	14	12	11

The crystallization of the residual oligomers was probably related to slow morphological changes in the plasticized degrading polymer mass. Indeed, it has never been possible to recrystallize the oligomers after melting [11].

4. Discussion

As in the case of PLA50 [1] and PLA37.5GA25, PLA75GA25 specimens undergo inner autocatalysed degradation. However, the whole process is strongly perturbed by morphological changes. The initially amorphous copolymer had a blocky structure that can be assigned to the L-lactic units-enriched composition and perhaps the faster polymerization of glygolide, although transesterification reactions probably minimize the effects of the latter [12]. According to ^{1}H-NMR, it can be concluded in this particular case that GA units constitute vulnerable points on the macromolecular chains, so degradation occurs preferentially on the GA bonds and gives fragments with higher contents of L-LA units which are thus susceptible to crystallization [10]. Another possibility is that crystallization started preferentially with fragments enriched in L-LA units and allowed the segments in amorphous domains which contain too many GA units, to crystallize, thus making it more acceptable to degradation.

The crystallization of the copolymer is strongly related to the preferential degradation at GA sites. On the one hand, the departure of GA units renders the chains more isotactic and so potentially crystallizable. On the other hand, the diminution of $\bar{M}_w$ gives freedom to chain segments and allows them to crystallize under the degradation conditions (37° C, aqueous medium). Indeed, the copolymer did not crystallize until the 7th week, when the percentage of GA decreased to 21% and L-LA-enriched segments appeared. Beyond 11 weeks the centre presented a

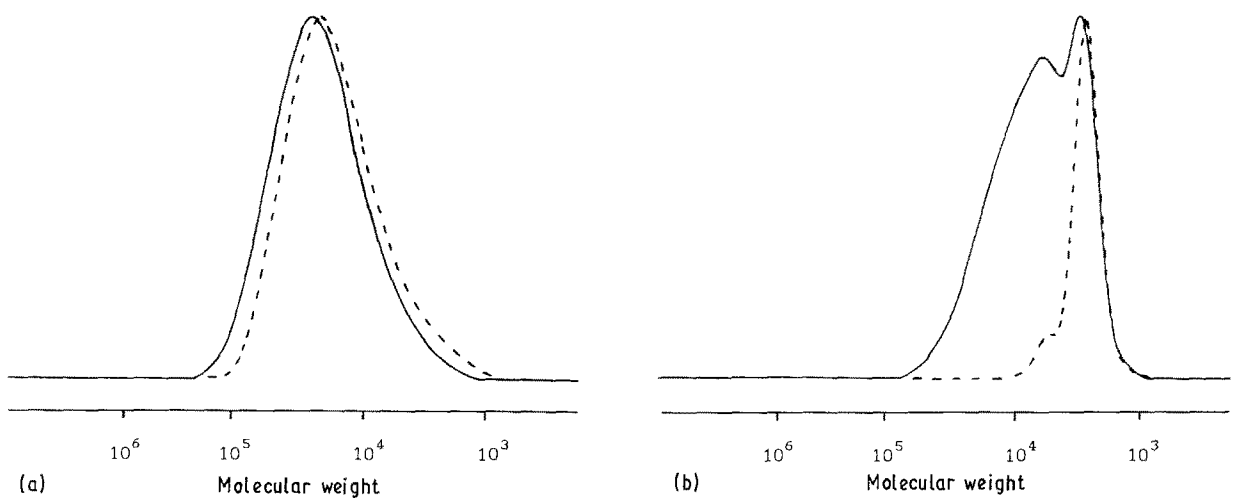

Figure 9 (a) SEC chromatograms of the (——) surface and (– – –) centre of PLA75GA25 after 5 weeks of degradation in the buffer. (b) SEC chromatograms of the (——) surface and (– – –) centre of PLA75GA25 after 12 weeks of degradation in the buffer.

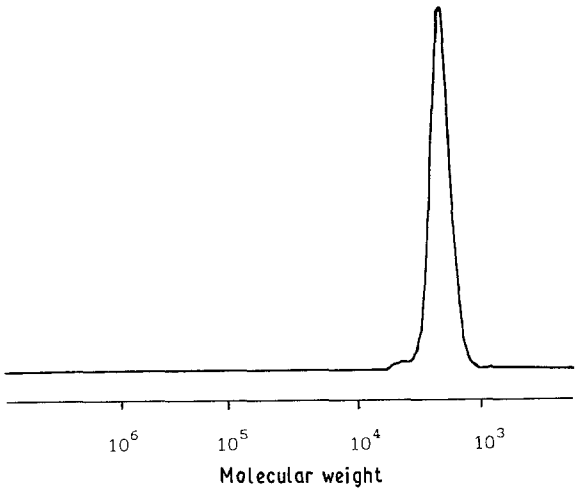

Figure 10 SEC chromatogram of residual material of PLA75GA25 after 50 weeks of degradation in the buffer.

SEC chromatogram that consisted of a very narrow peak only, whereas the surface contained macromolecular chains with both high and low molecular weights. Consequently, the inner part appeared to be more crystalline than the surface, as observed by DSC. Furthermore, the chains of high molecular weight located in the surface layer were susceptible to crystallization during rapid heating, thus explaining the second melting peak observed beyond week 11. Apparently, the crystalline zones had well-defined molecular weights, since the central polymeric material exhibited a very narrow polydispersity.

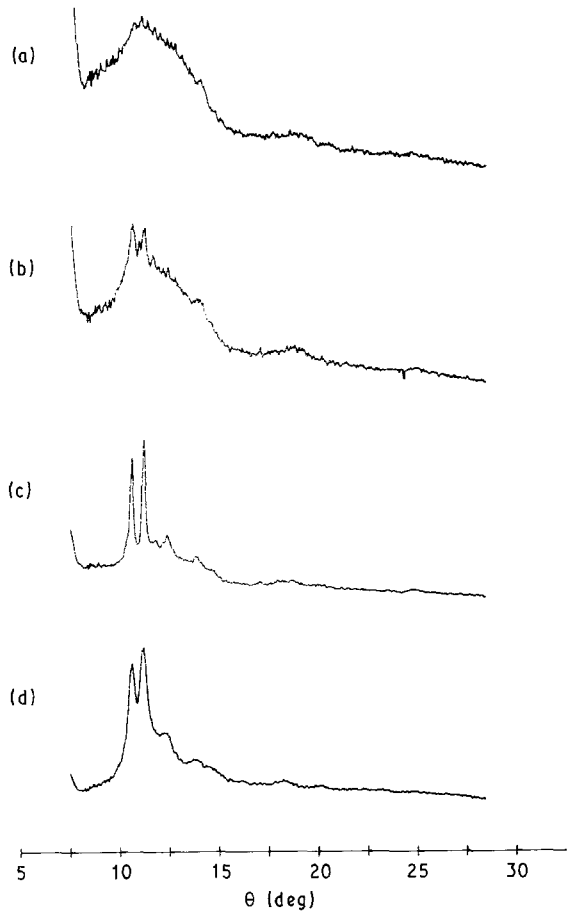

Figure 11 X-ray spectra of PLA75GA25 at different degradation times. (a) $t = 0$, (b) $t = 7$ weeks, (c) $t = 9$ weeks and (d) $t = 20$ weeks.

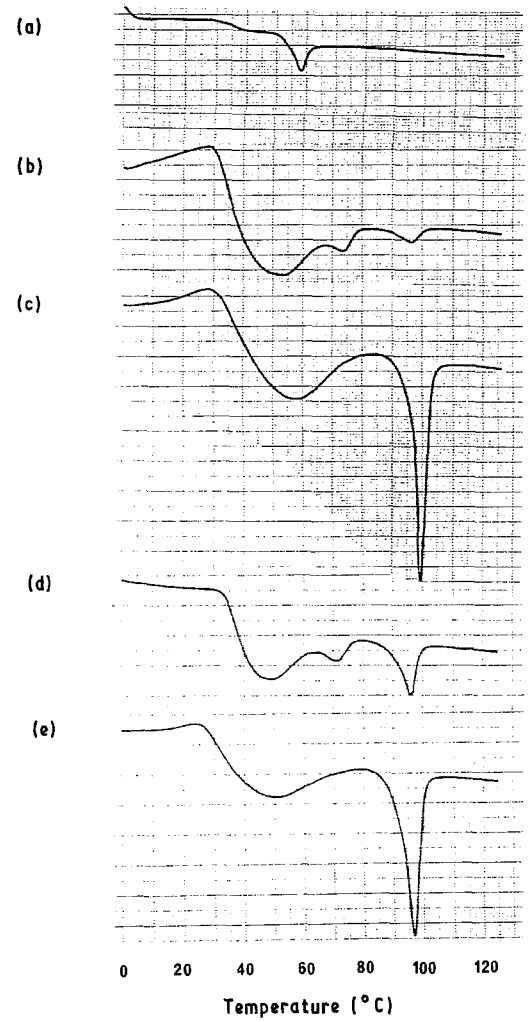

Figure 12 DSC thermograms of PLA75GA25 at different degradation times. (a) $t = 0$, (b) $t = 12$ weeks (surface), (c) $t = 12$ weeks (centre), (d) $t = 16$ weeks (surface) and (e) $t = 16$ weeks (centre).

It must be noted that the bimodal distribution observed at week 12 for the surface is not due to the difference in molecular weight between the surface and the centre, in contrast to the case of PLA50. For PLA75GA25, bimodality at the surface might be assigned to the crystallization, the second peak reflecting the well-defined molecular weights of the crystallized domains.

The crystallity of the copolymer remained relatively constant beyond week 12. Moreover, the preferential degradation of GA units was apparently limited since, between 20 and 50 weeks, the chemical composition changed little (88–12 to 89–11). It is well known that LA–GA copolymers with low contents of GA units can crystallize [10]. Therefore, it is likely that the crystallization of partially degraded macromolecules included the remaining GA units in crystalline zones, thus preventing them from further selective degradation.

5. Conclusion

In conclusion, inner autocatalysed degradation, detected for PLA50, also occurs in the case of LA–GA copolymers. For PLA37.5GA25, which is a copolymer of racemic lactide and glycolide, the hydrolytic behaviour appears to be similar to that of PLA50, except that the copolymer degrades much more rapidly. The comparison between degradation

characteristics in pure water and in iso-osmolar media showed that ionic strength is a major factor.

For PLA75GA25 made of L-lactide and glycolide, the degradation is characterized by a crystallization of degradation products. The crystallization is strongly related to a preferential degradation of GA units which gives fragments a more stereoregular structure. Accordingly, it can be presumed that the higher the L-LA content is, the greater the trend to crystallization, the whole process being governed by the composition of the intermediate partially degraded macromolecules.

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