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

Part 3 *Influence of the morphology of poly(L-lactic acid)*

SUMING LI, H. GARREAU, M. VERT
URA CNRS 500, Université de Rouen, Laboratoire des Substances Macromoléculaires, INSA, Rouen, BP 08, 76131 Mont Saint-Aignan, France

In order to assess the effects of morphology on the degradation characteristics of high-molecular weight poly(L-lactic acid) (PLA100), specimens of similar sizes were processed by compression moulding and made either amorphous by quenching (PLA100A) or semicrystalline by annealing (PLA100C). PLA100A specimens were allowed to age in iso-osmolar saline and pH 7.4 phosphate buffer at 37° C for periods up to 2 years, whereas PLA100C specimens were studied in the buffer only. Various techniques were used to monitor comparatively the effects of morphology on the mechanism of hydrolytic degradation for these two types of PLA100 specimens: weighing, enzymatic assay, potentiometry, viscoelasticimetry, size-exclusive chromatography, (SEC), X-ray scattering and differential scanning calorimetry. As in the case of non-crystallizable members of the poly(α-hydroxy acid) family, degradation was found to proceed more rapidly in the centre than at the surface for both PLA100A and PLA100C specimens. However, the observed multimodal SEC chromatograms have been assigned primarily to differences of degradation rates in amorphous and crystalline domains, regardless of the initial morphology. Indeed, it was found that initially amorphous PLA100A crystallized as degradation proceeded. Furthermore, PLA100A specimens retained mechanical properties for longer than semicrystalline PLA100C specimens, probably because of the sensitivity of the latter to stress and solvent microcracking. When the integrity of the polymer mass was lost, the residual crystalline matter, initially present or formed during degradation, appeared to be very resistant and was still present in a powdered form after 2 years. It is concluded that the morphology is a critical factor for the degradation of PLA100 and that the degradation of bioresorbable devices derived from this polymer should depend very strongly on both the thermal history and the initial crystallinity. The effects of the morphology do not depend significantly on the nature of the ageing medium, provided that the ionic strength is the same.

1. Introduction

In a previous paper [1] we introduced the rationale of investigations undertaken in order to understand better the effects of macromolecular structures and of solid-state morphologies on the *in vitro* degradation of poly(α-hydroxy acids) derived from lactic or glycolic acids, or both [2]. Indeed, these polymers are of increasing interest with respect to temporary therapeutic applications [3]. 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), concerted investigations have borne out that the polymer undergoes bulk degradation in aqueous media [1, 2], as previously reported in the literature [4, 5]. However, we have shown for the first time that bulk degradation proceeds heterogeneously and goes more rapidly in the central part of the specimens than at the surface. This finding brought new insights with respect to the data reported so far for hydrolysable aliphatic polyesters, recently reviewed by Holland *et al.* [6]. Furthermore, the existence of different degradation rates in the centre and at the surface accounted for the bimodal SEC chromatograms exhibited by partially degraded devices made of PLA50 [7]. Indeed, bimodality could not be explained by the presence of crystalline microdomains as in the case of semicrystalline PLA100 [8], since PLA50 is intrinsically amorphous. More recently, differentiations between surface and centre were also reported for two intrinsically amorphous LA–GA copolymers, namely PLA37.5GA25 and PLA75GA25 with the same LA–GA gross composition but derived from DL–LA and L–LA, respectively [9]. However, it was shown that PLA37.5GA25 remained amorphous up to total degradation whereas PLA75GA25 crystallized during degradation, probably because of the presence of longer stereoregular sequences due to the rather high initial content of L-LA units [2, 9].

All of the poly(α-hydroxy acids) that have been

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studied so far were intrinsically amorphous, i.e. unable to crystallize even through annealing because of irregular distributions of co-repeating units or of enantiomer repeating units, or both.

In this paper we report data obtained for an intrinsically semicrystalline member of the family: poly(L-lactic acid) (PLA100). Investigations were carried out on similar specimens in two different morphological states: amorphous (PLA100A), obtained by quenching from the melt, and semicrystalline (PLA100C), fabricated by annealing PLA100A, in order to evaluate the effects of initial morphology and especially morphological changes on the degradation mechanism. For PLA100A, ageing was performed in two iso-osmolar aqueous media: saline and pH 7.4 phosphate buffer (PBS). The degradation of PLA100C was investigated in PBS only, in order to limit the number of experiments.

2. Experimental

The experimental conditions selected for the investigations were similar to those described in Parts 1 and 2 [1, 9]. In particular, PLA100 prepared by the powdered zinc metal method [10] was processed by compression moulding of round plates (2 mm thick and 75 mm in diameter), further machined to yield parallelepipedic specimens (2 mm × 10 mm × 15 mm).

Moulding was carried out with a hydraulic press equipped with heated plates. The mould temperature was set at 178° C. The powdered polymer was weighed (11.5 g), introduced into the mould and allowed to melt for 6 min. Pressure (200 bar) was then applied to the molten polymer and cooling was set up for 10 min to allow the recovery of transparent amorphous round plates (PLA100A). Semicrystalline PLA100C was fabricated by annealing PLA100A in an oven at 130° C for 2 h. Its crystallinity was nearly 73% as deduced from X-ray diffractometry.

X-ray diffractometric measurements were carried out using a diffractometer equipped with a CuK_α (λ = 0.154 nm) source, an INEL monochromator and a goniometric plate. DSC thermograms were obtained by using a Dupont series 99 calorimeter equipped with a DSC 910 accessory. SEC chromatograms were obtained with a Waters apparatus equipped with μ-styragel columns. The mobile phase was dioxane, and data were expressed with respect to polystyrene standards.

3. Results and discussion

PLA100 is an intrinsically semicrystalline poly(α-hydroxy acid). Its ability to crystallize is related to the stereo-ordered isotactic chains composed of L-lactic acid repeating units. The morphology of PLA100 crystallites has been discussed in the literature [11, 12]. However, the correlation between molecular structures, crystalline morphologies and degradation behaviour is still poorly understood, although the fact that many factors can contribute has long been known, including the effects of the enantiomeric purity of PLA100 chains [13] and of the presence of residual monomer, as recalled recently in [14].

The differences between data concerning the various poly(L-lactic acids) mentioned in the literature are mostly due to the lack of careful identification and characterization of the materials investigated [13]. We decided, several years ago, to perform our investigations on compounds synthesized and purified according to standard procedures. Therefore, the amorphous and semicrystalline PLA100 materials used for the present work were made from the same PLA100 sample processed to specimens under suitable conditions to achieve the two different solid-state morphologies.

Moulding of PLA100 is known to be more difficult than moulding of amorphous LA–GA copolymers or LA stereocopolymers because of chemical instability at rather high temperatures. SEC analysis showed that the selected moulding conditions were molecular weight-respecting. Another problem was to avoid crystallization of the material during mould cooling. Rapid cooling was necessary for that. In the case of PLA100A specimens the amorphousness was deduced from the absence of sharp peaks that are normally present in the X-ray diffractometric spectra of semicrystalline PLA100.

For the sake of easier comparison, the degradation behaviour of PLA100A and PLA100C in pH 7.4 PBS are presented together in the following.

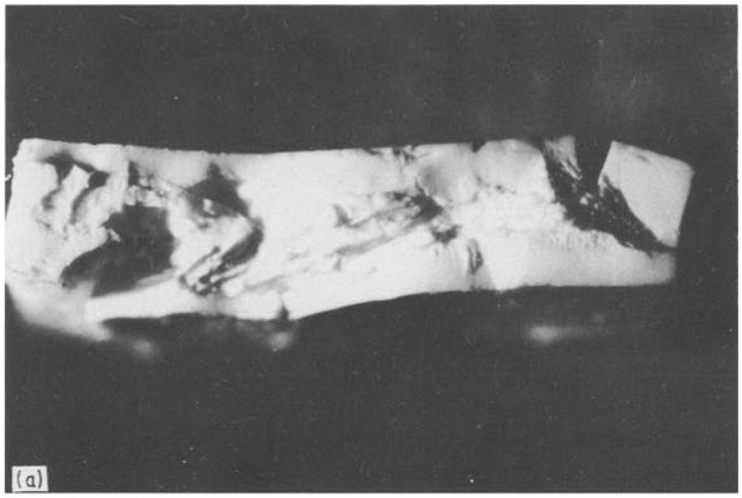
3.1. Visual examination

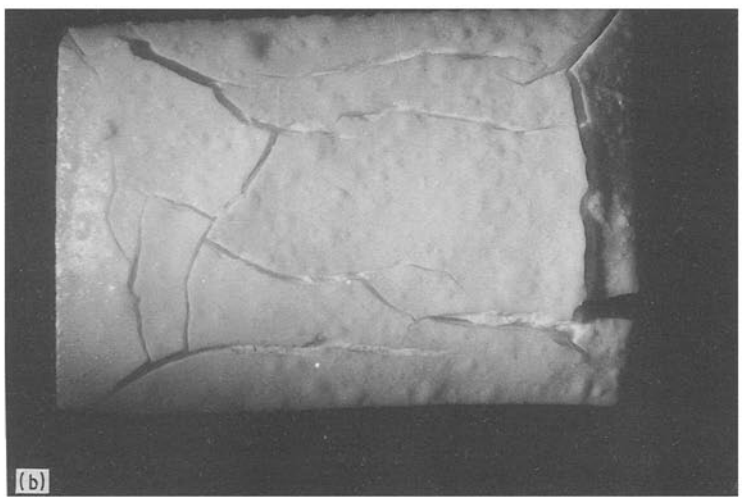
PLA100 is very resistant to hydrolysis compared with other members of the poly(α-hydroxy acid) family [13]. In pH 7.4 PBS the initially amorphous PLA100A specimens remained transparent for 18 weeks and then turned whitish. At week 40 cross-sections appeared white from the surface to the centre instead of exhibiting the yellowish and transparent centre observed in the case of intrinsically amorphous PLA50. Furthermore, PLA100A specimens recovered at week 40 showed that degradation had proceeded heterogeneously with a surface–centre differentiation (Fig. 1a). The surface was still dense, whereas the centre was porous. Large cracks became visible at the surface beyond week 50 (Fig. 1b). From week 70 to the end of the experiment (week 110) the recovered specimens appeared brittle with size contraction. Recently, broken PLA100 plates have been reported to exhibit an unexpected inner surface after *in vivo* ageing in rabbits [14]. This feature might reflect the occurrence of a surface–centre differentiation as described in this paper for *in vitro* ageing, or as observed in the case of PLA96 specimens [2].

The initially semicrystalline and thus opaque PLA100C specimens also became gradually whitish when in contact with the buffer, but cross-sections were found to be only slightly heterogeneous as shown for week 18 (Fig. 1c). At week 40 the specimens were totally white and brittle and small cracks were observed at the surface (Fig. 1d). In contrast to PLA100A, the size and shape of PLA100C specimens did not change during ageing.

3.2. Weight loss (Fig. 2a)

During the first 18 weeks the weight of PLA100A specimens remained unchanged. The weight loss was





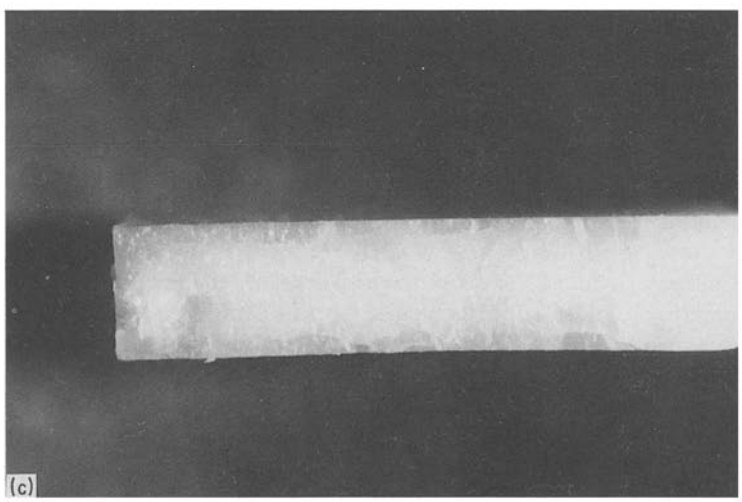


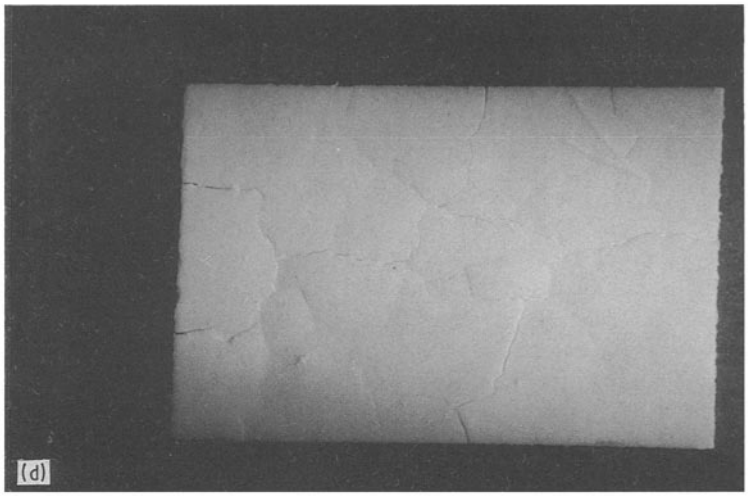
Figure 1 (a) Cross-section of a PLA100A specimen after 40 weeks in pH 7.4 PBS. (b) Surface of a PLA100A specimen after 50 weeks in PBS. (c) Cross-section of a PLA100C specimen after 18 weeks in PBS. (d) Surface of a PLA 100C specimen after 70 weeks in PBS.

in the range of 4.0% at week 31 and increased continuously to reach 48.6% at week 110. For PLA100C no weight loss was detected until week 7. After that, specimens started losing degradation products and the weight loss increased almost linearly. From week 7 until week 31 the weight loss of PLA100C was larger than that of PLA100A. However, the opposite was observed from week 40. At week 110 PLA100C had lost only 24.6% of its initial mass.

3.3. Water absorption (Fig. 2b)

During the first 18 weeks both types of specimens absorbed water very slowly. Beyond week 18 the two sets of specimens behaved differently, the absorption rate increasing significantly for PLA100A up to week 31, whereas it decreased for PLA100C during the same period. Beyond week 31 water absorption continued to increase slowly for both sets, attaining 105% at week 110 for PLA100A. For PLA100C, which retained a compact structure, water absorption was smaller than for PLA100A. At week 70 it reached only 28%. For longer ageing times it became impossible to weigh PLA100C specimens because of brittleness.

Figure 1 Continued



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

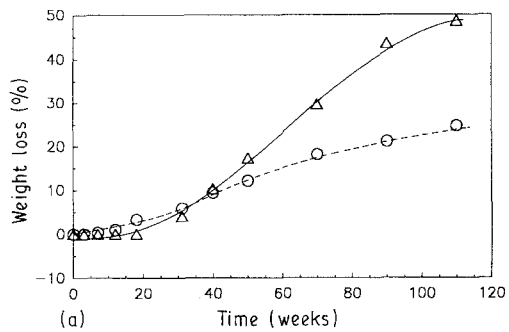
For PLA100A, L-lactic acid was not detected until week 31, i.e. at the time corresponding to the beginning of weight loss. Then the concentration of L-lactic acid in the ageing medium increased continuously. In the case of PLA100C, L-lactic acid was detected at week 12. The increase with time was similar to that found for PLA100A, but the absolute values of the two curves were not directly comparable because of the difference in the initial total weights of PLA100A and PLA100C specimens (9.2 and 13.2 g, respectively).

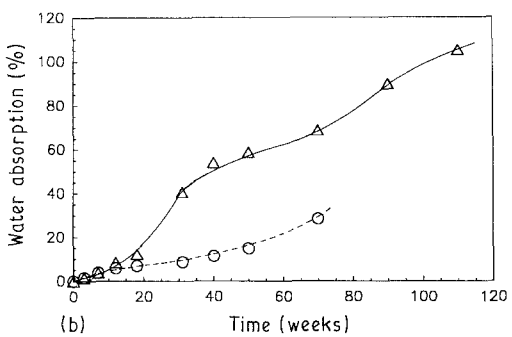
3.5. pH changes (Fig. 2d)

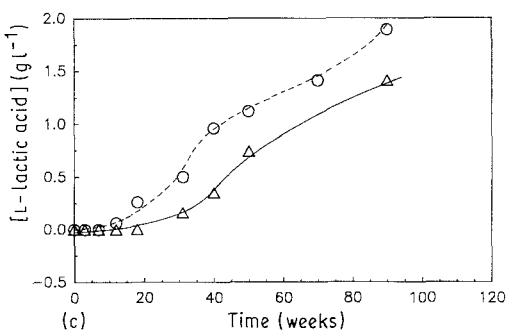
For both PLA100A and PLA100C, the pH of the buffered ageing media remained almost constant. After 110 weeks it was still 7.0, starting from 7.4.

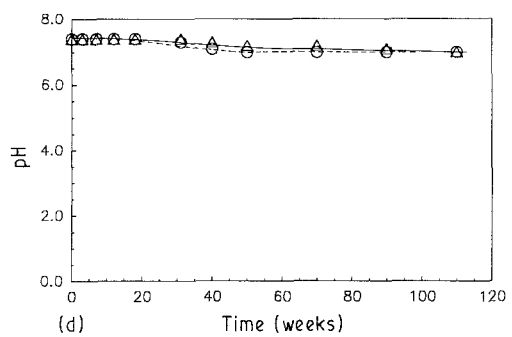
3.6. Storage modulus variations (Fig. 2e)

The initial value of the storage modulus, E', of PLA100C specimens was slightly higher than that of PLA100A specimens. However, the decrease of this parameter occurred earlier for PLA100C than for PLA100A. Indeed, E' started decreasing after 3 weeks for PLA100C specimens, whereas the PLA100A specimens retained their initial value for 12 weeks. It was no longer possible to measure E' beyond week 31 for PLA100A, due to the swelling of the specimens, and beyond week 50 for PLA100C, because of brittleness. After 8 months the two sets of specimens still exhibited some mechanical strength and E'-values were approximately 20 and 40% of the initial values, respectively.









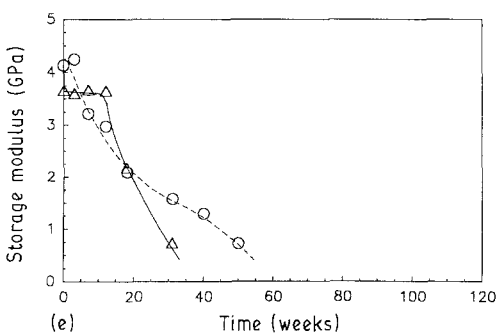


Figure 2 Evolution of some parameters during the degradation of (△) PLA100A and (○) PLA100C specimens in PBS. (a) Weight loss, (b) water absorption, (c) L-lactic acid concentration, (d) pH and (e) storage modulus.

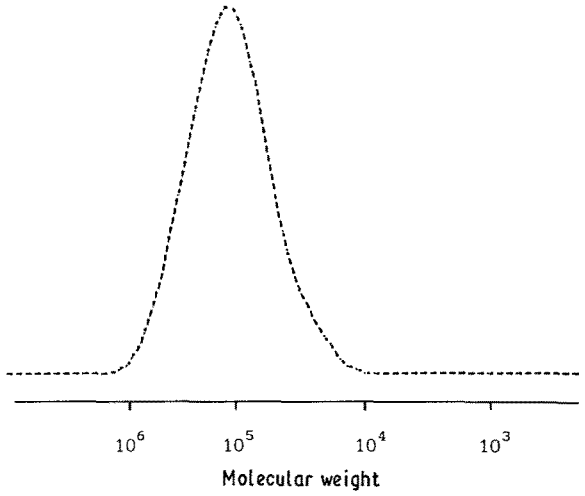


Figure 3 SEC chromatogram of PLA100 at $t = 0$.

These results agree well with those reported recently in the literature [14].

3.7. Molecular weight changes

Fig. 3 shows the monomodal SEC chromatogram common to both PLA100A and PLA100C specimens before degradation ($\bar{M}_w = 130\,000$ and $\bar{M}_w/\bar{M}_n = 1.8$). As already mentioned in [15], degradation of PLA100 macromolecules started immediately as shown in Figs 4a and b. However, it is of interest to recall that, in the case of highly crystalline long-lasting PLA100C devices with rather large dimensions, a delayed molecular weight decrease has been reported [16]. After 12 weeks little difference in molecular weight appeared between the surface and the centre for both PLA100A and PLA100C. The molecular weight decreases slowed down after nearly 31 weeks. SEC chromatograms of PLA100A showed a shoulder in the zone of low molecular weight at week 18, and then this shoulder became increasingly important to give a bimodal molecular weight distribution at week 50. In contrast, multimodal molecular weight distributions were observed for PLA100C after 18 weeks. Typical multimodal SEC chromatograms of partially degraded PLA100 are shown in Fig. 5 (week 50), Fig. 6 (week 70) and Fig. 7 (week 90).

For PLA100A, the SEC chromatograms at week 50 exhibited a rather narrow peak corresponding to low-molecular weight materials with a slight difference between the surface and the centre (Fig. 5a). The elution volume corresponding to the narrow peak was still higher than the total volume of the SEC columns. At week 70 both the relative magnitude of the narrow peak and the difference between the surface and the centre had enlarged (Fig. 6a). At week 90 only a broad shoulder was appearing on the high-molecular weight edge of the intense narrow peak (Fig. 7a).

The SEC chromatogram of PLA100C before degradation was the same as that of PLA100A (Fig. 3). At week 50 two narrow peaks were observed (Fig. 5b), the peak corresponding to high molecular weight being more important for the surface than for the centre. At week 70 the peak corresponding to high-molecular weight macromolecules appeared very much decreased, so did the surface–centre differentiation (Fig. 6b). At week 90 the SEC chromatogram was almost monomodal and composed of a narrow low-molecular weight peak. No difference between the surface and the centre was detectable (Fig. 7b). Between weeks 50 and 90 the relative magnitude of the two narrow peaks varied, but their positions on the elution volume scale did not change.

It is noteworthy that the first narrow peak visible in Figs 5b and 6b corresponded to an average molecular weight about twice as large as that of the second narrow peak. Fischer *et al.* [17] have reported that the degradation of PLA92.5 monocrystals is characterized by preferential degradation in amorphous zones, which results in multimodal molecular weight distributions with peaks representing respective molecular weight of one, two and three traverse lengths of crystalline lamellae. Although these findings were obtained in alcoholic alkaline medium (0.02 to 0.04 M NaOH in 1 : 2 water–methanol mixture), the given interpretation fits well with the features found in the present investigation. Accordingly, the two narrow peaks observed by SEC during the degradation of PLA100C have been assigned to well-defined oligomers formed by cleavage at the foldings of polymer chains in the regular array of crystalline lamellae, reflecting one and two traverse lengths, respectively. As degradation advanced, the SEC peak corresponding to one traverse length became increasingly important at the expense of the other. Finally, when the amorphous domains were completely degraded, only the peak corresponding to one traverse length remained, as shown for week 90.

3.8. Crystallinity changes

Fig. 8 shows the X-ray spectra of PLA100A at different degradation times. The spectrum of the initial polymer was typical of an amorphous polymeric

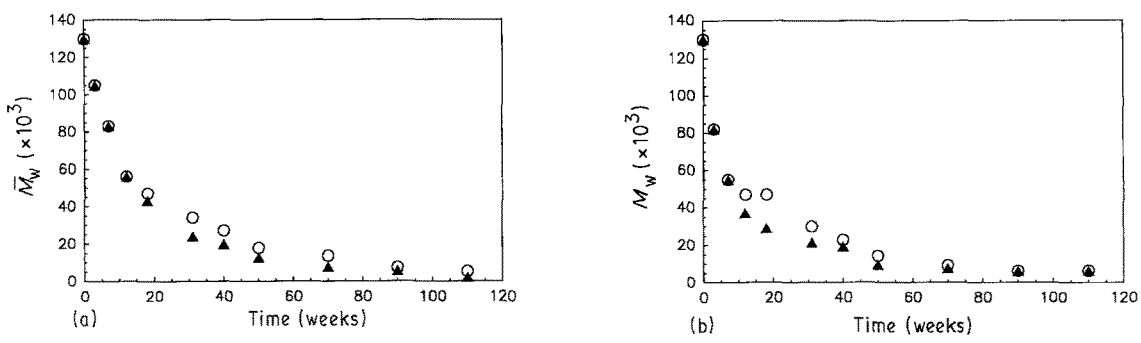


Figure 4 Relative $\bar{M}_w$ evolution of (a) PLA100A and (b) PLA100C with time in PBS: (○) surface and (▲) centre.

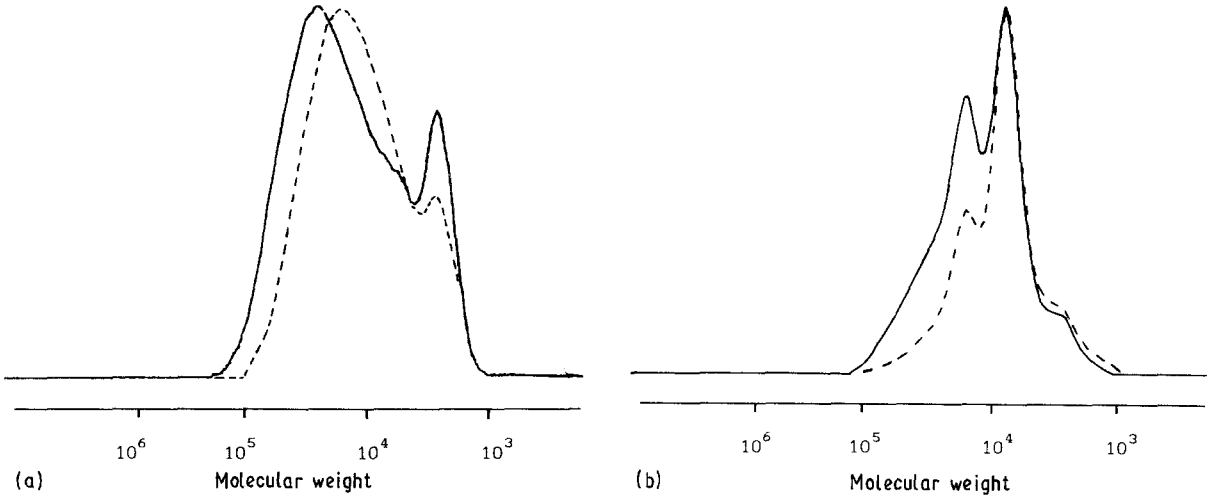


Figure 5 SEC chromatograms of the (——) surface and (– – –) centre of (a) PLA100A and (b) PLA100C specimens after 50 weeks in PBS.

material. After 12 weeks of degradation a small, narrow peak appeared, revealing morphological changes. Beyond week 12 this peak enlarged and a second narrow peak appeared at the expense of the scattered energy due to amorphous domains. The presence of these two peaks being typical of PLA crystallinity, relative integration of peak surface with respect to total scattered energy was used to quantify the crystallization process. Data are presented in Table I.

Comparison between the SEC chromatograms and the X-ray spectra of PLA100A showed that low-molecular weight material and crystallinity appeared at almost the same time, i.e. after 12 weeks. As degradation advanced, the specimens became increasingly crystalline, whereas low-molecular weight material became increasingly important and led to a narrow SEC peak. Therefore, it is believed that the appearance of the narrow peak is related to degradation products resulting from crystallites formed during degradation or ageing in water, or both, degradation giving shorter chains that are more mobile than long ones, and probably more susceptible to crystallization at 37° C (the temperature of the PBS). The crystalline microdomains formed during degradation appeared to be very resistant to further degradation, as in the case of PLA100C.

Fig. 9 shows the X-ray spectra of semicrystalline PLA100C at time 0 and during degradation. These spectra were very similar to those of partially degraded and crystallized PLA100A. However, no significant change in crystallinity was detected for PLA100C, which was very crystalline from the very beginning. From X-ray patterns, it can be concluded that crystallites initially present in PLA100C and those formed during the degradation of PLA100A correspond to similar chain arrays, but probably of different sizes and thicknesses. Indeed, these arrays lead to oligomers of different molecular weight, PLA100A yielding smaller oligomers than PLA100C (Figs 7a and b). This feature can be explained by the difference in crystallization conditions: PLA100C was annealed at 130° C, whereas the crystallites of PLA100A resulted from slow crystallization in pH 7.4 PBS, i.e. at very low temperature (37° C) with respect to chain mobility and thus to the ability to crystallize.

3.9. Thermal analyses

DSC investigations were achieved in two steps. The vacuum-dried specimens were subjected to a first heating run, which reflected thermal effects related to the morphology resulting from processing and ageing in pH 7.4 PBS. A second run was carried out immediately after rapid cooling of the polymeric sample

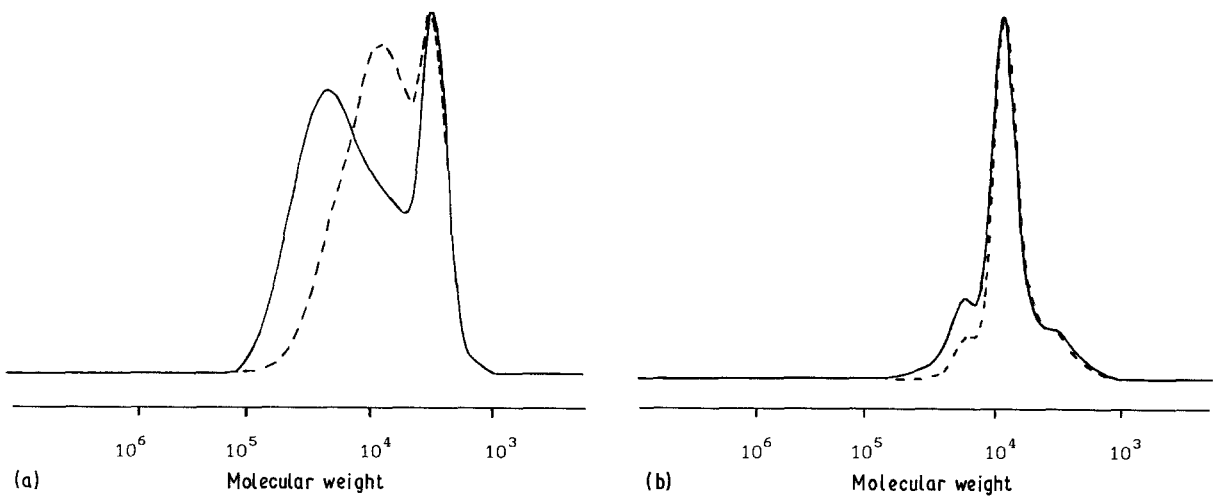


Figure 6 SEC chromatograms of the (——) surface and (– – –) centre of (a) PLA100A and (b) PLA100C specimens after 70 weeks in PBS.

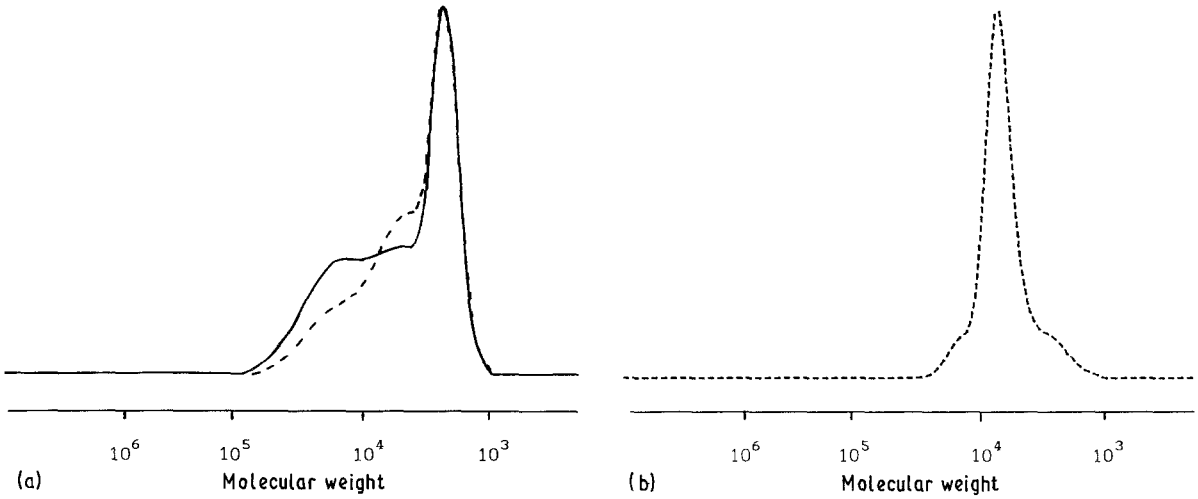


Figure 7 SEC chromatograms of the (——) surface and (– – –) centre of (a) PLA100A and (b) PLA100C specimens after 90 weeks in PBS.

melted at the end of the first run. Under these conditions comparisons between the thermograms of the two runs allowed us to notice some memory effects connected with physical changes caused by ageing.

Fig. 10 shows some of the DSC thermograms of PLA100A and PLA100C obtained at different degradation times. We consider here the thermograms of the inner part only, in order to limit the size of the figure. DSC thermograms corresponding to surfaces were similar but with a time lag, in agreement with the slower degradation described above.

At $t = 0$ PLA100A specimens were amorphous and the thermogram showed an exothermic crystallization peak at 98° C (T_c) and an endothermic melting peak at 171° C (T_m). On the second run, T_c and T_m appeared at 120 and 168° C, respectively. The increase of T_c can be assigned to the fact that melting suppressed historical morphology characteristics and slow chain-relaxation effects. Consequently, randomized polymer chains required more energy to crystallize on heating. As far as semicrystalline PLA100C specimens are concerned, the thermogram showed only a melting peak at 169° C on the first run. After rapid cooling the material became amorphous, and a crystallization peak at 120° C and a melting peak at

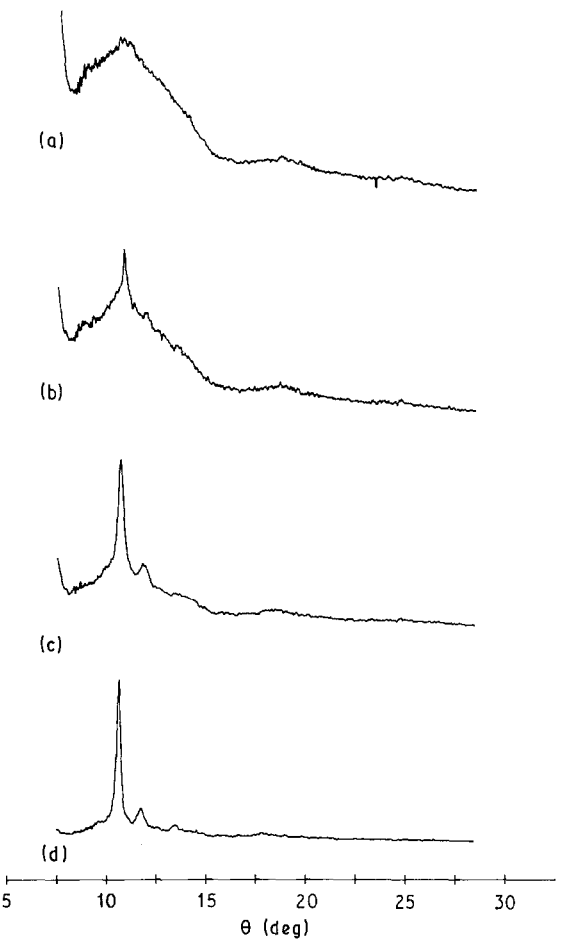


Figure 8 X-ray spectra of PLA100A at different degradation times in PBS: (a) $t = 0$, (b) $t = 18$ weeks, (c) $t = 50$ weeks and (d) $t = 90$ weeks.

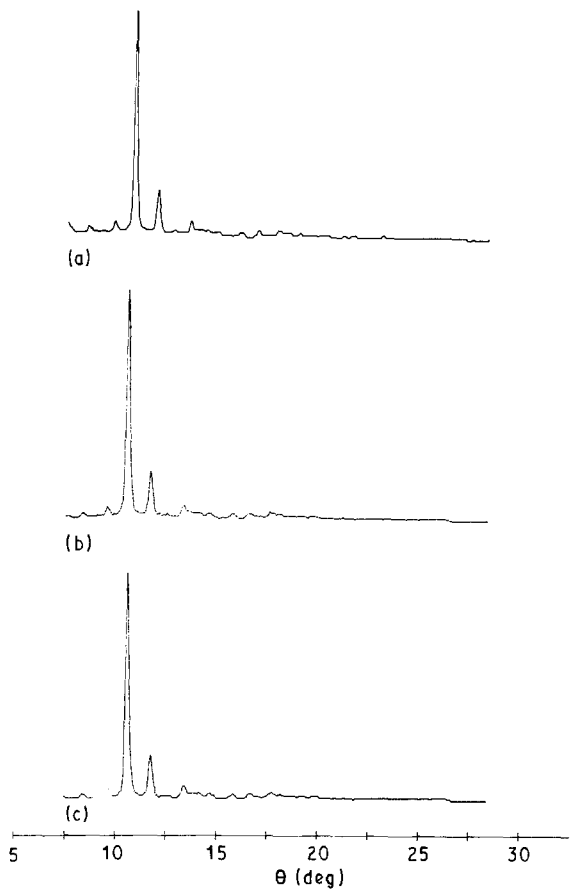


Figure 9 X-ray spectra of PLA100C at different degradation times in PBS: (a) $t = 0$, (b) $t = 50$ weeks and (c) $t = 90$ weeks.

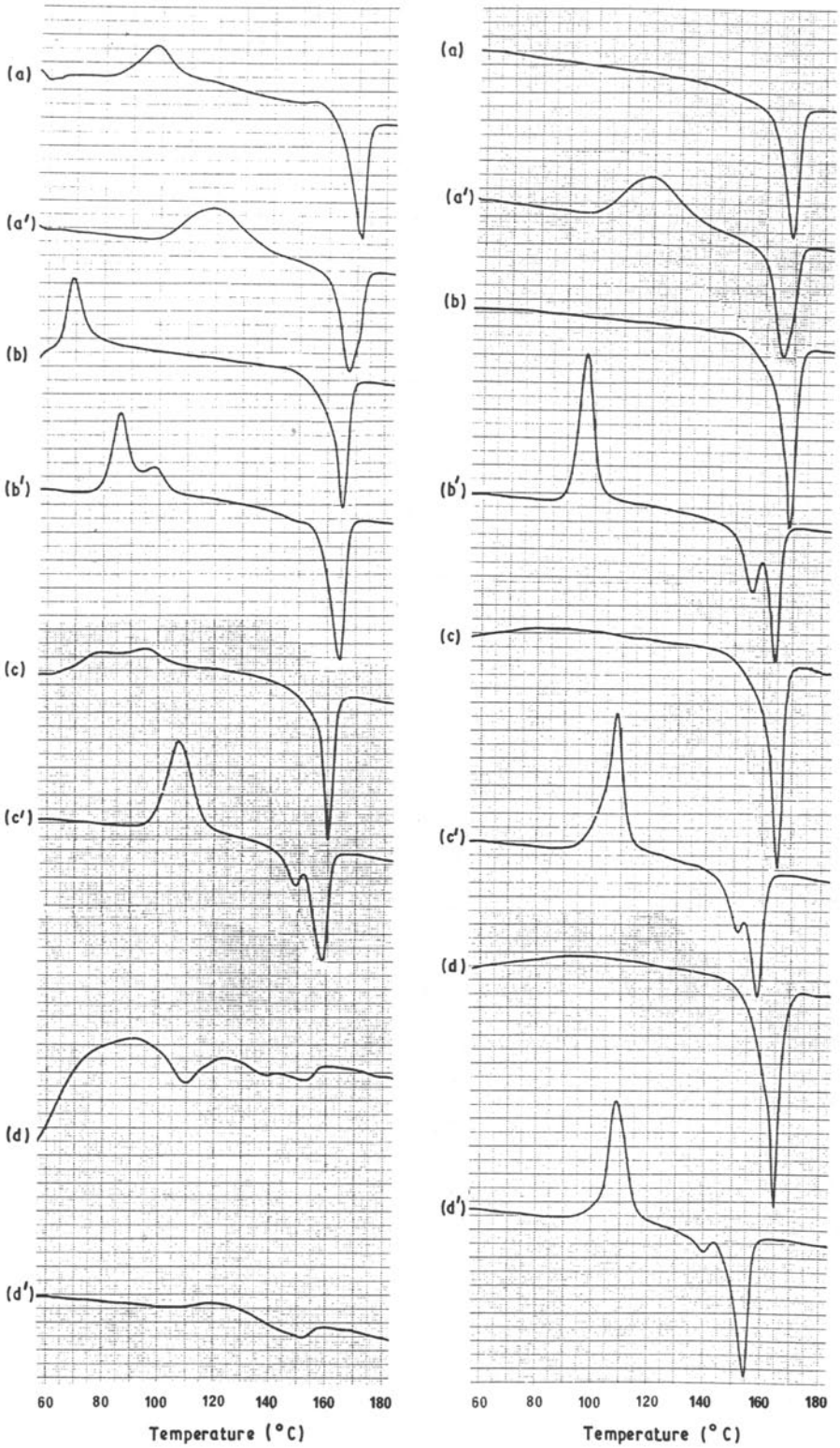


Figure 10 DSC thermograms of (left) PLA100A and (right) PLA100C at different degradation times in PBS. (a, a′) $t = 0$, (b, b′) $t = 18$ weeks, (c, c′) $t = 50$ weeks and (d, d′) $t = 90$ weeks (a′, b′, c′ and d′ represent the second run).

166° C were observed, which were similar to those found for melted PLA100A.

At week 18 the first run gave T_c and T_m at 70 and 165° C, respectively, in the case of PLA100A. The second run gave a double crystallization peak at 86 and 98° C, T_m appearing at 164° C. The origin of this double peak is not yet understood. The decrease of T_c compared with T_c at time 0 can be attributed to slow chain relaxations and molecular weight decrease related to degradation in the buffer, whereas the lowering of T_m can be assigned to a molecular weight decrease. For PLA100C the first run was unchanged with respect to time 0, whereas the second run showed a narrow crystallization peak at 97° C and a double melting peak at 156 and 164° C. This double melting peak might reflect the fact that macromolecular chains of different molecular weight, which are known to be

TABLE I Crystallinity changes of PLA100A

Degradation time (weeks)	0	12	18	31	40	50	70	90
Crystallinity (%)	0	2	4	17	19	21	37	49

present according to SEC, tended to form crystallites of different sizes.

After 50 weeks of degradation the crystallization peak of PLA100A appeared very diminished, in agreement with the fact that the specimens had partially crystallized, leaving less-crystallizable material. At this time T_m was lowered to 160° C. The second run showed a T_c of 107° C and a double fusion peak at 148 and 158° C. The increase of T_c with respect to week 18 shows that the well-degraded chains became more difficult to crystallize. In the case of PLA100C the first run gave a diminished T_m at 165° C, whereas the second run led to higher T_c (108° C) and a double melting peak at 152 and 158° C.

At week 90 PLA100A residues presented no typical crystallization peak, but several endothermal peaks at 110, 140 and 153° C. The peak at 110° C might be assigned to the fusion of low-molecular weight crystallites formed during the degradation, whereas the two others probably resulted from the fusion of crystallites formed on heating. After cooling, the second run presented T_c at 120° C and T_m at 152° C, corresponding peaks being large and weak, in agreement with the presence of short chains whose ability to crystallize was greatly decreased immediately after melting. In contrast, the second run for PLA100C showed a T_c at 108° C, a weak melting peak at 140° C and an important melting peak at 155° C, indicating that PLA100C degradation products formed from initially present crystallites remained capable of crystallizing immediately after melting.

During degradation T_m decreased gradually in the case of PLA100A, probably because the degraded material allowed to crystallize led to smaller crystallites. For PLA100C T_m for the first run did not change significantly until week 90 (from 169 to 165° C), in agreement with the fact that the crystallites initially present were very resistant to degradation and that degradation occurred in amorphous domains as well as at the surface of crystallites without affecting the crystallized chain arrays. In contrast, the second runs revealed the molecular weight-dependence of T_m (from 166 to 155° C), because the fusion destroyed the initial crystallites and recrystallization involved degraded chains.

Carried out under comparable conditions, DSC thermograms seem to contain much information on morphology changes. However, further investigations are necessary to take advantage of this technique which can be a source of misinformation. In any case, data reported here clearly show the differences in the behaviour of PLA100A and PLA100C, and thus suggest the complexity of initially semicrystalline PLA polymers.

The degradation of PLA100A in saline was found to be very similar to that of PLA100A in PBS and will not be discussed further here. The pH decrease caused by the release of acidic degradation products did not affect the degradation behaviour of PLA100A specimens significantly.

4. Conclusions

The degradation of PLA100 confirms the inner autocatalytic degradation mechanism shown for intrinsically amorphous homologues of the poly(α-hydroxy acid) family. However, for this intrinsically semicrystalline polyester, the initial morphology and morphological changes related to degradation phenomena are the factors that govern the evolutions occurring on ageing in aqueous media. In the case of initially amorphous PLA100A, the degradation of polymer chains, its effect on chain relaxation and perhaps water uptake allow chains to undergo cold crystallization at 37° C in aqueous media. The derived crystalline structures appear to be very resistant to degradation and result in multimodal molecular weight distributions. As far as PLA100C is concerned, degradation is typical of a semicrystalline structure and leads to multimodal SEC chromatograms due to the preferential degradation of amorphous domains, although the inner autocatalytic effect also contributes. For both morphologies the highly crystalline residues appear to be very resistant to degradation. This feature agrees well with the findings of polymer residues after 4 years of *in vivo* degradation reported in the literature for the case of long-lasting PLA100 bone-plate devices [16].

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