Macromolecules **1994,** *27,* 3107-3110

Communications to the Editor

Morphological Changes Resulting from the Hydrolytic Degradation of Stereocopolymers Derived from L- and DL-Lactides

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Received December 28, 1993
Revised Manuscript Received March 24, 1994

Introduction. Aliphatic polyesters, especially those of the PLAGA family which derive from lactic acid enantiomers (L-LA and D-LA) and glycolic acid (GA), are being investigated worldwide for applications in the field of surgery (suture material, devices for internal bone fracture fixation, etc., ...) and pharmaceutics (sustained drug delivery systems).[1-3] For the sake of simplicity, the acronym PLA_xGA_y is currently used to designate these polymers, where x represents the percentage of L-LA units in the monomer feed and y that of GA units, the remaining $(100 - x - y)$ giving the percentage of D-LA units whenever they are present. Their biocompatibility and bioresorbability are well established,[4-6] and a number of products are now on the market. Despite these extensive investigations, controversial data are still found in literature insofar as the degradation mechanism (hydrolytic *vs* enzymatic cleavages) and degradation location (erosion from the surface or degradation in the bulk) are concerned.[5,6] Recently, essential advances have been accomplished by our group in the understanding of the degradation characteristics. It has been shown that, for large-size devices, degradation is faster in the internal part than at the surface and that nonrandom intrachain cleavage occurs, leading to composition and morphology changes.[7-10] Degradation-induced morphology changes are now considered as a major phenomenon in the degradation process because an initially amorphous polymeric material can lead to crystalline residues which can remain at last much longer in the body as a result of the well-known slower degradation of crystalline domains. For example, initially quenched PLA_{100} and PLA_{96} and intrinsically amorphous $PLA_{75}GA_{25}$ and $PLA_{85}GA_{15}$ were shown to become partially crystalline during *in vitro* degradation at 37 °C in aqueous media.[8-10] Under similar aging conditions, PLA_{50} yielded small amounts of crystalline degradation residues too, these residues being identified as composed of an oligomeric stereocomplex formed by L-LA, D-LA, and/or L-LA-rich and D-LA-rich crystallizable oligomeric fragments. The formation of such a stereocomplex was correlated to the fact that DL-lactide ring-opening polymerization leads to polymer chains containing rather long poly(L-LA) and poly(D-LA) sequences which become crystallizable once they are set free by degradation.[11]

In order to study the influence of chain composition on the formation and nature of degradation-induced crystalline residues, three intrinsically amorphous PLA_x stereocopolymers, namely, $PLA_{87.5}$, PLA_{75}, and $PLA_{62.5}$, were investigated comparatively under similar *in vitro* conditions. They were all noncrystallizable because of the presence of more than 12.5% of D-LA repeating units, as already mentioned in the literature.[12] In this paper, we briefly report and discuss the degradation characteristics of these polymers, with attention being preferentially paid to typical morphology changes. Other characteristics of the hydrolytic degradation of PLAGA polymers have been extensively described and reviewed in recent literature.[5,6]

Experimental Section. $PLA_{87.5}$, PLA_{75}, and $PLA_{62.5}$ stereocopolymers were synthesized by bulk polymerization using zinc powder as initiator, according to the standard procedure used for many years in our group.[13] The resulting crude polymers were purified by the dissolution/precipitation method using acetone as solvent and ethanol as nonsolvent. The elimination of residual monomers and oligomeric compounds was checked by size-exclusion chromatography (SEC). Round plates (75 mm diameter, 2 mm thick) were then processed by compression molding at 132 °C, with a pressure of 150 bar. From these plates, parallelepiped specimens (10 × 10 × 2 mm) having the same thermal history were machined, as previously reported.[7] For each stereocopolymer, the various specimens were placed into small flasks filled with 30 mL of 0.13 M isoosmolar phosphate buffer (pH 7.4) containing 0.02% NaN_3 to prevent bacterium development. The flasks were allowed to stand in a thermostated oven at 37 °C for predetermined periods of time. At each degradation time, two specimens were withdrawn, washed with distilled water, and vacuum dried at 35 °C for 1 week before analysis. When necessary, surface and interior parts were separated physically after cutting.

SEC was performed by using a Waters apparatus equipped with two μ-Styragel columns and refractive index detection, the mobile phase being dioxane. Data were expressed with respect to Polysciences polystyrene standards. X-ray diffraction spectra were registered with a diffractometer composed of a Cu Kα (λ = 1.54 Å) source, a quartz monochromator, and a goniometric plate.

Results and Discussion. 1. $PLA_{87.5}$. Initially, $PLA_{87.5}$ exhibited a monomodal SEC trace with $\bar{M}_w$ = 190 000 and $\bar{M}_w/\bar{M}_n$ = 1.9. The molecular weight (MW) decreased rapidly with aging time, as a result of the hydrolytic cleavage of ester bonds. A surface/interior differentiation was detected in agreement with the characteristics of the faster internal degradation mechanism previously observed as a general behavior of PLAGA large-size devices.[7] For instance, after 85 weeks, i.e., when weight loss was as large as 54.8%, the shape of the specimens was almost unchanged although the outer part was slightly deformed, whitish, and brittle. In contrast, the interior was cracked and turned to granules. SEC chromatograms of the materials from the surface and the interior are shown in Figure 1. The surface contained partially degraded macromolecules with a rather large polydispersity ($\bar{M}_w$ = 24 500, $\bar{M}_w/\bar{M}_n$ = 2.3), whereas the interior was composed of oligomers with a narrow MW distribution ($\bar{M}_w$ = 5800, $\bar{M}_w/\bar{M}_n$ = 1.4).

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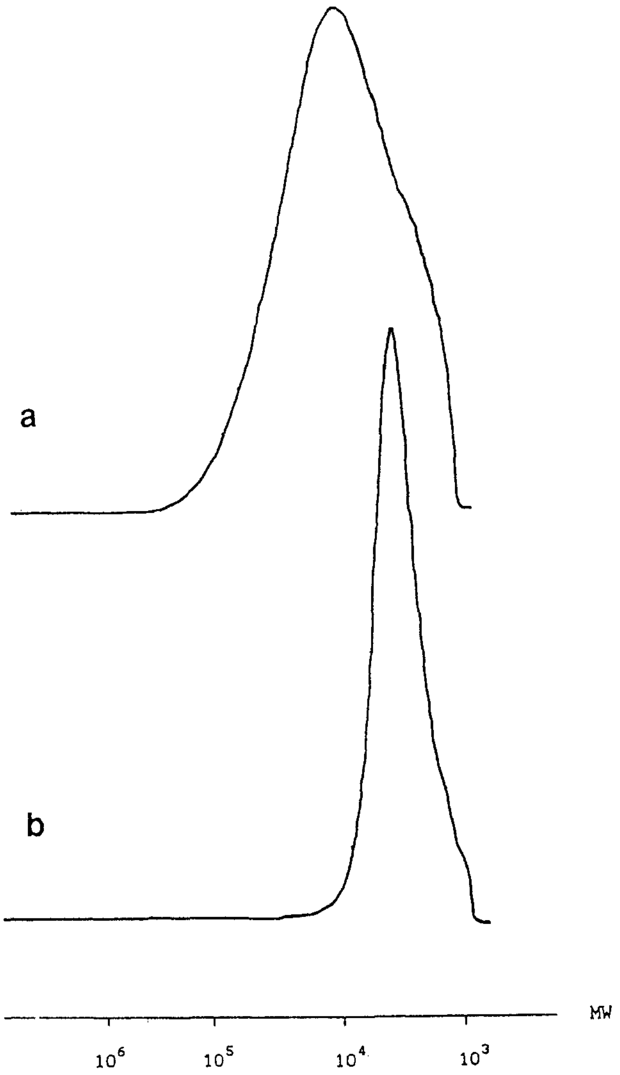

Figure 1. SEC chromatograms of a $PLA_{87.5}$ specimen after 85 weeks of degradation in pH 7.4 isoosmolar phosphate buffer at 37 °C: (a) surface; (b) interior.

The presence of crystalline oligomeric compounds with rather low polydispersity within largely degraded PLAGA devices has already been observed many times for PLA_{100}[9,14] as well as for PLA_{96}[10] and PLAGA copolymers.[8,10] The very narrow distribution of the inner crystalline material well agreed with the presence of crystalline microdomains composed of oligomers with similar low MW. Actually, Fischer et al. had detected by SEC a very narrow MW distribution corresponding to lamellae traverse length after cleavage at the foldings in the case of $PLA_{92.5}$ monocrystals after alcaline degradation in methanol/water media.[15] The formation of crystalline material in partially degraded $PLA_{87.5}$ was borne out by the presence of narrow peaks emerging from the X-ray diffraction patterns typical of amorphous domains. The spectra obtained for samples taken at the surface (Figure 2a) and in the interior (Figure 2b) exhibited two peaks located at 8.3° and 9.4°, which correspond exactly to those typical of PLA_{100} (Figure 2c). These spectra suggested that the crystalline structures of the oligomeric compounds and of PLA_{100} were comparable. However, the presence of small amounts of D-LA units could not be excluded because PLA_x with high x values are known to give similar crystalline structures.[10]

2. PLA_{75}. This polymer behaved differently insofar as the fate of the interior part was concerned. The faster internal degradation resulted in the formation of a very viscous liquid which remained entrapped within the outer membrane until diffusion through this membrane became

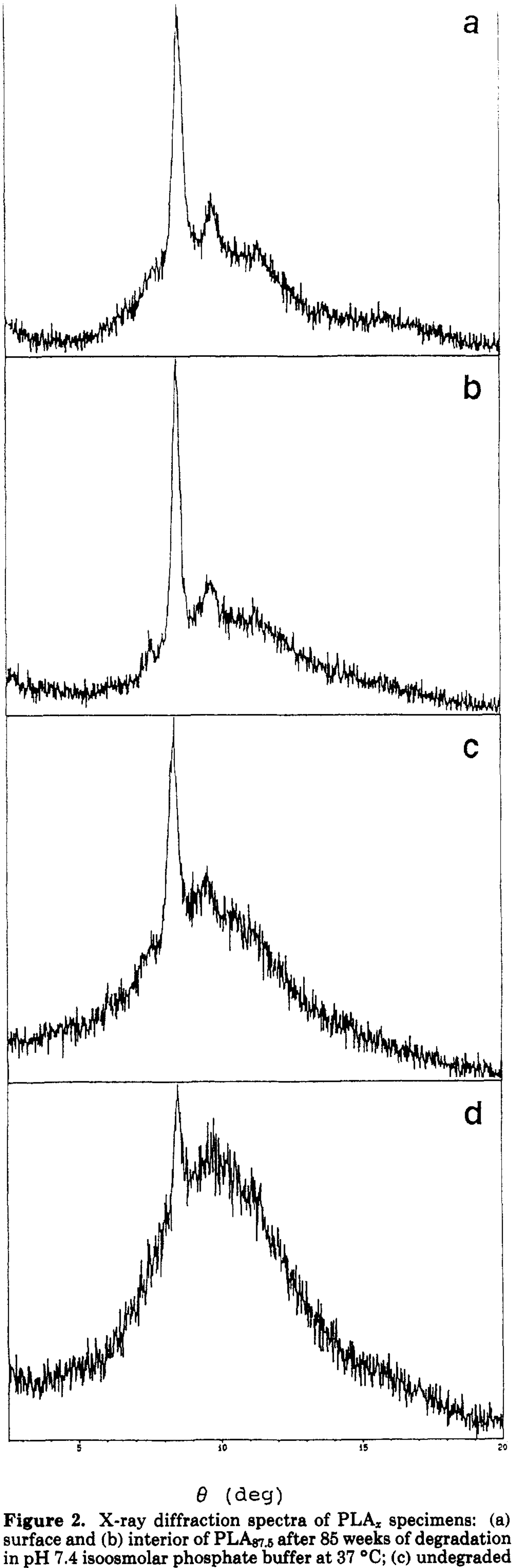

Figure 2. X-ray diffraction spectra of PLA_x specimens: (a) surface and (b) interior of $PLA_{87.5}$ after 85 weeks of degradation in pH 7.4 isoosmolar phosphate buffer at 37 °C; (c) undegraded PLA_{100}; (d) PLA_{75} after 90 days of degradation *in vivo* (surface).

possible, i.e., until oligomers became small enough to be soluble in the aqueous degradation medium and to leave hollow specimens as has already been reported for PLA$_{50}$ and PLA$_{37.5}$GA$_{25}$.[7,8] Initially PLA$_{75}$ had a monomodal MW distribution ($\bar{M}_w$ = 48 600, $\bar{M}_w/\bar{M}_n$ = 1.6). After 34 weeks, when weight loss attained 95.5%, the weight-average molecular weight of the remaining outer part was rather small with a narrow MW distribution ($\bar{M}_w$ = 3400, $\bar{M}_w/\bar{M}_n$ = 1.4). Unfortunately, no sufficient material remained at this stage of degradation for X-ray diffraction analysis. In order to nevertheless collect some information on the degradation residues, we proceeded undirectly by considering a PLA$_{75}$ specimen which had been degraded *in vivo* independently. Indeed, we have already shown, in the case of PLA$_{50}$, PLA$_{37.5}$GA$_{25}$, and PLA$_{75}$GA$_{25}$, that *in vivo* and *in vitro* degradations proceeded similarly when *in vitro* experiments are carried out under the selected conditions which mimic physiological temperature, ionic strength, and pH without stirring, as is the case of this work.[16] This finding was considered to be sufficient to make the conclusions collected from the PLA$_{75}$ specimen degraded *in vivo* for 90 days. As in the case of PLA$_{87.5}$, the X-ray spectrum of the remaining shell showed two very weak peaks located at 8.3° and 9.4° (Figure 2d) and comparable to those observed for PLA$_{100}$ (Figure 2c). These peaks reflected the formation of a very small amount of crystalline domains during the slow degradation of the outer part of PLA$_{75}$ specimens. Because PLA$_{75}$ polymer chains contained only a very small proportion of short stereoordered segments, the formation of crystalline residues could not occur in the fast-degrading interior part of the specimens.

3. **PLA$_{62.5}$.** As in the case of PLA$_{75}$, largely degraded PLA$_{62.5}$ formed hollow structures composed of oligomeric residues with low MW and narrow MW distribution. However, a remarkable difference was detected. After 30 weeks of degradation, i.e., when weight loss was 94.8%, the X-ray diffraction spectrum of the remaining residues showed three weak peaks located at 5.9°, 10.3°, and 12.0° (Figure 3a) and thus noncomparable to those of Figure 2. These three peaks were actually located at the angles which are typical of a PLA$_{100}$–PLA$_0$ stereocomplex (Figure 3b) or of the oligomeric stereocomplex derived from the L-LA(-rich) and D-LA(-rich) oligomers present at the ultimate stage of PLA$_{50}$ degradation.[11] Therefore, it was concluded that the partially crystalline degradation residues of PLA$_{62.5}$ resulted from the stereocomplexation of L-LA(-rich) and D-LA(-rich) oligomers too.

These results complement the previously reported main characteristics of the heterogeneous degradation of large-size devices of PLAGA polymers, copolymers, and stereocopolymers. Degradation-induced partial crystallization appears as a general phenomenon which can be observed whenever crystallizable residual oligomeric material is formed during degradation. The main finding is that the structure of the resulting crystalline microdomains depends dramatically on the initial enantiomeric composition of the stereocopolymers which also determines the lengths of poly(L-LA) and poly(D-LA) sequences. Listed in Table 1 are probability data for triads, pentads, heptads, and nonads within PLA$_{87.5}$, PLA$_{75}$, and PLA$_{62.5}$ polymer chains, as deduced from the pair-addition polymerization mechanism of L- and DL-lactides.[11] Contributions due to transesterification side reactions were discarded since they are rather limited under the selected polymerization conditions.[12]

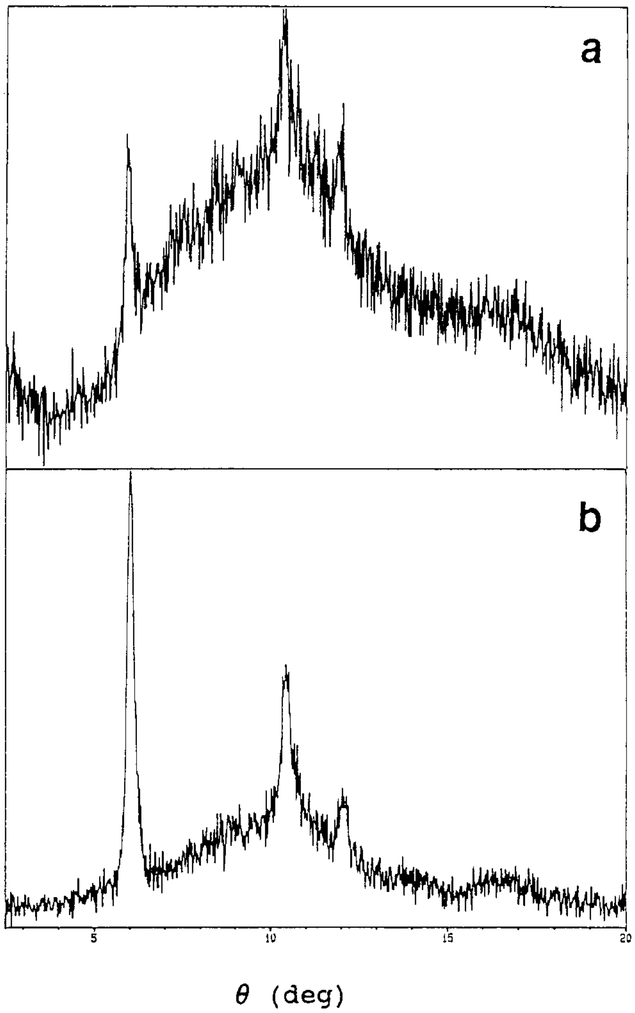

Figure 3. X-ray diffraction spectra: (a) residual surface part of PLA$_{62.5}$ after 30 weeks of degradation in pH 7.4 isoosmolar phosphate buffer at 37 °C; (b) undegraded PLA$_{100}$–PLA$_0$ stereocomplex.

Table 1. Probability Data of Isotactic Sequences in the Three PLA$_x$ Stereocopolymer Matrices

designation	sequence	formula	probability PLA$_{87.5}$ (p = 0.875)	PLA$_{87.5}$ (p = 0.75)	PLA$_{62.5}$ (p = 0.625)
triad	LLL(L)	p^2 [a]	0.766	0.563	0.391
	DDD(D)	q^2 [b]	0.016	0.063	0.141
pentad	LLLLL(L)	p^3	0.670	0.422	0.242
	DDDDD(D)	q^3	0.002	0.016	0.053
heptad	LLLLLLL(L)	p^4	0.586	0.316	0.153
	DDDDDDD(D)	q^4	2×10^{-4}	0.004	0.020
nonad	LLLLLLLLL(L)	p^5	0.513	0.237	0.095
	DDDDDDDDD(D)	q^5	3×10^{-5}	0.001	0.007

[a] p = [L-LA]/([L-LA] + [D-LA]). [b] $q = (1 - p)$.

The calculated relative weights of poly(L-LA) and poly(D-LA) sequences well account for the crystallization phenomena observed at the ultimate stage of the degradation process. In the case of PLA$_{87.5}$, the probability of L-LA nonads exceeds 50%, whereas that of D-LA triads is only 1.6%. Therefore, ester bond cleavage generates predominantly poly(L-LA) sequences which are then susceptible to form crystalline microdomains of the poly(L-LA) type. For the same reason, poly(L-LA) sequence crystallization was also predominant in the case of PLA$_{75}$. However, one must keep in mind that crystallization involved only a very small amount of the original material in this case. In contrast, PLA$_{62.5}$ contains relatively more poly(D-LA) blocks of a given size than PLA$_{87.5}$ and PLA$_{75}$. Basically, poly(L-LA) and poly(D-LA) blocks are able to crystallize separately. However, experimental data showed that stereocomplexation was preferred in the case of PLA$_{62.5}$ as in the case of PLA$_{50}$,[11] the excess of poly(L-LA) blocks being unable to crystallize separately under the selected degradation conditions. It is worthy to note that crystallites of the stereocomplex are known to be much more stable than crystallites of the homopolymers.[17]

In conclusion, hydrolytic degradation of large-size devices made of PLA stereocopolymers can lead to morphology changes with partial crystallization of degradation byproducts or residues, provided rather long poly(L-LA) (or poly(D-LA) or both) sequences are initially present in polymer chains. In poly(L-LA) or poly(D-LA)-rich polymers, crystallization of stereoregular sequences prevails either for the whole mass ($PLA_{87.5}$) or only for the surface part of the hollow structures (PLA_{75}). In contrast, if the difference between the frequencies of poly(L-LA) and poly(D-LA) blocks is not larger than 1 order of magnitude as in the case of $PLA_{62.5}$, or of PLA_{50} as previously reported, stereocomplexation occurs preferentially. It is of great importance to note that degradation-induced crystallization concerns a rather small amount of the initial amorphous material, generally the outer part, except for highly stereoregular PLA_x with x values larger than ca. 80, or smaller than 20 because of symmetry.

Acknowledgment. The authors thank Mr. Richard Medeiros for his advice in editing the manuscript.

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