

Degradation Characteristics of Poly(ϵ -caprolactone)-Based Copolymers and Blends

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ABSTRACT: The hydrolytic degradation of various bioresorbable copolymers and blends derived from ϵ -caprolactone, D,L-lactide and poly(ethylene glycol) (PEG) was investigated at 37°C in a pH 7.4 phosphate buffer. Poly(ϵ -caprolactone) (PCL) followed a slow degradation profile due to its hydrophobicity and crystallinity. The hydrophilicity and degradability of the materials can be improved by copolymerization with PEG and/or poly(D,L-lactide) (PLA). Homogenous degradation was shown in the cases of PCL, PCL/PEG copolymers and their blends, whereas PLA-containing copolymers followed a heterogenous degradation

due to internal autocatalysis. It was also shown that PCL-based materials gradually turned to PCL-enriched residues during degradation due to preferential hydrolysis of PLA segments and to diffusion of soluble species such as PLA oligomers and detached PEG blocks bearing short PLA segments. The results are discussed in comparison with literature data. © 2006 Wiley Periodicals, Inc. *J Appl Polym Sci* 102: 1681–1687, 2006

Key words: biodegradable; degradation; polyesters; block copolymers; blends

INTRODUCTION

Aliphatic polyesters, in particular FDA-approved bioresorbable poly(D,L-lactide) (PLA) and poly(ϵ -caprolactone) (PCL), constitute a class of biomaterials of growing interest in the fields of temporary therapeutic applications in surgery, sustained drug delivery, and tissue engineering.^{1–5} These materials have been proposed as sutures for wound healing,¹ as devices for bone fracture internal fixation,³ as carriers for delivery of bioactive molecules,^{1,2} or as scaffolds for cell culture to regenerate tissues or organs.^{4,5} Ideally, a bioresorbable scaffold has to degrade and be resorbed *in vivo* at a predefined rate so that the three-dimensional space occupied by the initial scaffold can be progressively replaced by the regenerated host tissue, minimizing the inflammatory response of the substrate.^{4,5}

PCL is very attractive in tissue engineering because of its good biocompatibility and processability.^{4,5} However, its high hydrophobicity and low degradability *in vivo* considerably restrain its potential applications.² On the other hand, PLA stereocopolymers with variable chain stereoregularity provide a worthwhile means to adjust the degradability, as well as the physical and mechanical

properties.^{1–3} We recently reported the synthesis and characterization of novel polyether–polyester block copolymers by ring-opening polymerization of sequentially added ϵ -caprolactone and D,L-lactide in the presence of ethylene glycol or water-soluble poly(ethylene glycol) (PEG), using nontoxic zinc metal as catalyst.^{6,7} This process offered the possibility of varying the ratio of hydrophobic/hydrophilic constituents to modulate the degradability and hydrophilicity while preserving the viscoelastic and thermal properties inherent to PCL.^{6,7} *In vitro* and *in vivo* cell culture studies were conducted on PCL/PEG block copolymer scaffolds manufactured via rapid prototyping robotic dispensing system by using primary human and rat bone marrow derived stromal cells (hMSC, rMSC). Increased cell density was observed not only at the outer surface, but also throughout the scaffold architecture.^{8,9} On the other hand, the copolymers showed better performance than the PCL homopolymer.

In previous articles, we also reported on the hydrolytic degradation of PCL-based copolymers containing PEG or PLA blocks.^{7,8} The hydrophilicity of the materials was enhanced as compared to a PCL homopolymer, but the degradability of PCL segments remained unchanged. On the other hand, copolymerization with PLA improved the degradability of the materials, but the hydrophilicity of PCL/PLA remained very low and comparable to homopolymers.

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TABLE I
Compositional and Molecular Characteristics of the Various PEG/PCL/PLA Polyether-Polyester Block Copolymers and Blends

Polymer	[EO]/[CL]/[LA] molar ratios ^a	PEG/PCL/PLA (wt %)	\bar{M}_n ^b	I_p ^b	θ_0 (°) ^c	X_c (%) ^d
PCL	—	—/100/—	50,000	1.7	88	49
PEG-PCL	0.25/1/—	9.0/91/—	33,000	1.6	51	50
PCL-PEG-PCL	0.27/1/—	9.4/90.6/—	30,000	1.8	42	51
PLA-PCL-PLA	—/1/1.4	—/53/47	61,000	1.5	84	27
PEG-PCL-PLA	0.14/1/1.9	2.4/44.6/53	20,000	3.3	84	27
PEG-PCL/PCL	0.08/1/—	3.1/96.9/—	36,000	1.6	83	60
PCL-PEG-PCL/PCL	0.10/1/—	3.8/96.2/—	40,000	1.5	83	61

^a [LA]/[CL]/[EO] molar ratio obtained by ¹H-NMR.

^b \bar{M}_n and I_p obtained by SEC.

^c θ_0 obtained by tensiometer.

^d X_c obtained by X-ray diffraction spectra.

In this study, we wish to compare the hydrolytic degradation characteristics of PCL-based block copolymers containing PEG or PLA with those of a PEG-PCL-PLA block terpolymer, with the aim of understanding the contribution of PEG and/or PLA segments to degradation. Comparison will also be made with blends of PCL and PEG-PCL diblock or PCL-PEG-PCL triblock copolymers. Degradation was carried out at 37°C in a 0.13M, pH 7.4 phosphate buffer to mimic *in vivo* conditions. Degradation-induced property changes were monitored by various analytical techniques, namely weighing, size-exclusion chromatography (SEC), proton nuclear magnetic resonance (¹H-NMR), capillary zone electrophoresis (CZE), and X-ray diffraction. The results are discussed herein in comparison with literature.

MATERIALS AND METHODS

Materials

PEG/PCL/PLA-based block copolymers were synthesized by ring-opening polymerization with successive addition of ϵ -caprolactone and D,L-lactide in the presence of ethylene glycol or PEG, using zinc metal as catalyst.^{6,7} PEG-containing copolymers were prepared from monohydroxyl PEG ($M_n = 5000$ g/mol) or dihydroxyl PEG ($M_n = 8000$), respectively. The obtained PEG-PCL diblock and PCL-PEG-PCL triblock copolymers were blended with PCL by the dissolution/precipitation method with a weight ratio of 1/1. The various materials were compression molded to yield 0.4-mm-thick films with a diameter of 75 mm. About $10 \times 10 \times 0.4$ mm³ square specimens were then cut from the films.

Measurements

¹H-NMR spectra were recorded with a Bruker spectrometer operating at 300 MHz, using deuterated chlo-

roform (CDCl₃) as solvent. Chemical shifts were expressed in ppm from the tetramethylsilane (TMS) resonance. SEC was performed by using a setting composed of a Waters 510 HPLC pump, a Waters 410 differential refractometer, and a PLgel 5 μ m mixed-C 60 cm column, the mobile phase being THF and the flow rate 1 mL/min. The number-average MW (\bar{M}_n) and weight-average MW (\bar{M}_w) data were expressed with respect to polystyrene standards from Polysciences. Contact angle (θ_0) of compression-molded films was measured in distilled water with a Krüss processor tensiometer K100. X-ray diffraction spectra were obtained with a Philips apparatus using a Cu K α source ($\lambda = 0.154$ nm). CZE data were collected using a P/ACE 5000 Beckman instrument equipped with UV detector at 254 nm and a fused-silica capillary (i.d. 75 μ m, length 57 cm) with reverse mode.

Hydrolytic degradation

Each specimen was introduced into a small vial filled with 5 mL of isoosmolar phosphate buffer (0.13M, pH 7.4) containing 0.02% of NaN₃ to prevent bacterial growth. The flasks were placed in a thermostated oven at 37°C. For each data point, three specimens were withdrawn, washed with distilled water, wiped, and weighed. They were then vacuum-dried up to a constant weight before being subjected to various analyses.

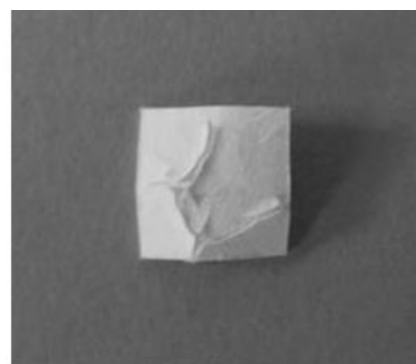
RESULTS

Table I shows the compositional and molecular characteristics of the various block copolymers and blends considered in this study. The [EO]/[CL]/[LA] molar ratios were determined from the integrations of the bands due to PEG blocks at 3.6 ppm, to PCL blocks at 4.0 ppm, and to PLA blocks at 5.2 ppm on the ¹H-NMR spectra as previously described.^{6–8} The [EO]/

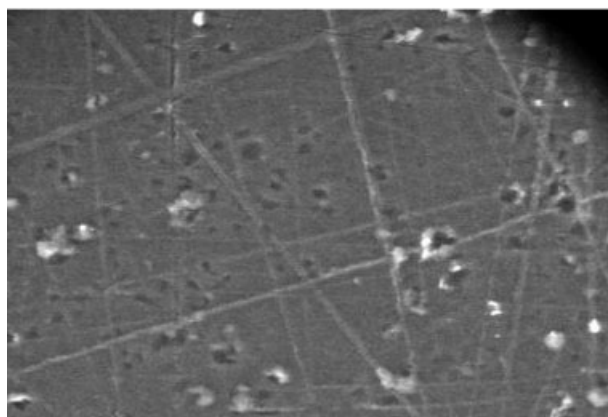
[CL] molar ratio of the copolymers was lower than that of the feed. This finding was assigned to the fact that PEG-rich species were eliminated during purification. Similarly, the [EO]/[CL] ratio of the blends was lower than what can be expected from the blending materials. The molecular weight distribution of the copolymers was monomodal with polydispersity index ($I_p = \overline{M}_w/\overline{M}_n$) in the range of 1.5–1.8, except for the PEG-PCL-PLA terpolymer which exhibited a larger I_p value ($\overline{M}_w/\overline{M}_n = 3.3$). Contact angle measurements indicated a large increase of the surface hydrophilicity of PCL/PEG copolymers in comparison with PCL. In contrast, PLA-PCL-PLA, PEG-PCL-PLA, and the blends showed little changes, which could be attributed to the much lower PEG contents. The X-ray diffraction patterns of the block copolymers were previously reported in comparison with those of PEG and PCL homopolymers.^{6–8} Typically, PEG exhibits two main peaks at $\theta = 9.4^\circ$ and 11.5° , whereas PCL shows an intense peak at $\theta = 10.6^\circ$ and a smaller one at 11.8° . All the copolymers and blends exhibited the crystalline structure of PCL type. No characteristic diffraction peaks of PEG were detected, indicating that PEG blocks were unable to crystallize due to low PEG contents. Crystallinity data derived from the X-ray diffraction spectra are shown in Table I. Both PEG-PCL and PCL-PEG-PCL showed a crystallinity value (X_c) close to that of PCL. On the other hand, the presence of amorphous PLA blocks in PEG-PCL-PLA or PLA-PCL-PLA strongly reduced the X_c value. In the cases of the blends, however, a slight increase in X_c was detected, which could be assigned to the incompatibility between PEG segments of the copolymer and the PCL phase during processing.

Visual observation

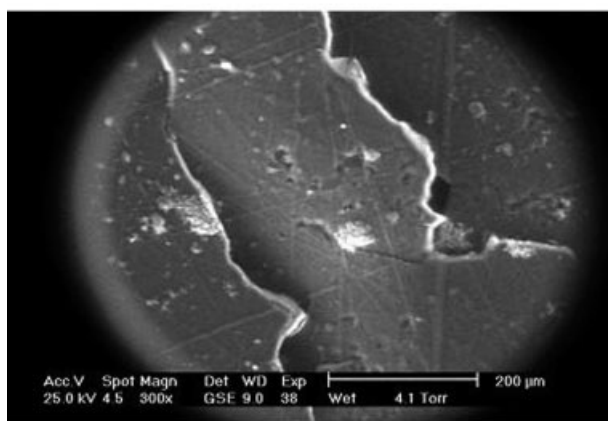
The various films initially appeared homogeneous and rigid. As degradation proceeded, the copolymers and blends became brittle after 18 weeks, whereas PCL became brittle after 60 weeks only. On the other hand, all films retained their initial shape during degradation. Some cracks were observed upon vacuum drying after 30 weeks' degradation in the case of PEG-PCL-PLA films [Fig. 1(a)]. PLA-PCL-PLA films were even cracked into two parts beyond 25 weeks as previously reported,⁷ indicating differentiation between the outer and inner parts. In the case of the PEG-PCL/PCL blend, a number of tiny pores were initially present at the surface [Fig. 1(b)], and delamination cracks were found after 45 weeks [Fig. 1(c)]. Insofar as the PCL-PEG-PCL/PCL blend is concerned, the surface was initially smooth and remained unchanged during degradation, revealing a better compatibility between PCL-PEG-PCL and PCL than between PEG-PCL and PCL components.



(a)



(b)



(c)

Figure 1 (a) Visual aspects of PEG-PCL-PLA film after 40 weeks' degradation, and ESEM photographs of PEG-PCL/PCL (b) before and (c) after 45 weeks' degradation.

Water absorption and weight loss

Figures 2 and 3 present the water absorption and weight loss profiles of the various block copolymers and blends during degradation, respectively.

PCL remained almost unchanged during the degradation period. Both water absorption and weight loss remained very low after 110 weeks (2%), in agreement with its hydrophobicity. In contrast, PEG-containing

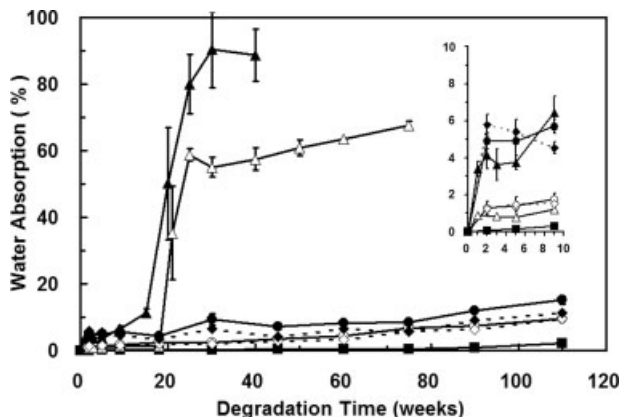


Figure 2 Water absorption profiles of (■), PCL; (○), PCL-PEG-PCL/PCL; (●), PCL-PEG-PCL; (△), PLA-PCL-PLA; (▲), PEG-PCL-PLA; (◇), PEG-PCL/PCL; and (◆), PEG-PCL during degradation.

copolymers (PEG-PCL, PCL-PEG-PCL, and PEG-PCL-PLA) absorbed about 5% of water within 2 weeks. Afterwards, water absorption increased slowly to reach 15% for PCL-PEG-PCL and 11% for PEG-PCL after 110 weeks. PEG-PCL-PLA showed a rapid water absorption increase up to 80% between 15 and 25 weeks, followed by a slow increase to reach 89% at week 40. Water absorption of both blends (i.e., PEG-PCL/PCL and PCL-PEG-PCL/PCL) reached about 2% within 30 weeks, and increased continuously to attain 9.5% after 110 weeks. In the case of PLA-PCL-PLA, only 1% of water absorption was obtained within 18 weeks, followed by a rapid increase, reaching 59% at week 25. Beyond that, water absorption increased slowly and reached 68% at week 75.

Weight loss of PCL/PEG copolymers and blends was detected after 9 weeks. Beyond that, weight loss increased slowly to reach 8% for PEG-PCL, 11% for PCL-PEG-PCL, 6% for PEG-PCL/PCL, and 7% for PCL-PEG-PCL/PCL at week 110. In the case of PLA-PCL-PLA, less than 2% was lost during the first 18 weeks, followed by a burst reaching 43% between 18 and 25 weeks. Beyond that, weight loss slowly increased to reach 49% at week 75. PEG-PCL-PLA reflected the behaviors typical of both PEG and PLA blocks. A 7% weight loss was detected within 15 weeks, followed by a burst up to 49% between 15 and 25 weeks. Afterwards, weight loss increased slowly to attain 53% at week 40. It should be noted that the final weight loss ratios of PLA-containing copolymers were very close to their initial PLA contents.

MW changes

SEC was used to monitor the MW and MW distribution changes during degradation. PCL exhibited initially $\overline{M}_n = 50,000$ and a rather narrow MW distribu-

tion ($I_p = 1.7$). As the degradation proceeded, \overline{M}_n decreased continuously to reach its half value after 45 weeks. The same trend was found for the PCL/PEG copolymers and blends. In all cases, the MW distribution remained monomodal. In contrast, PLA-PCL-PLA exhibited a faster \overline{M}_n decrease, from 61,000 initially to 15,000 after 18 weeks. Afterwards, the degradation rate slowed down, \overline{M}_n being 14,000 and 11,000 after 30 and 50 weeks, respectively. The initially monomodal SEC curve broadened during degradation, I_p increasing from 1.7 to 2.8 after 18 weeks due to the formation of PLA oligomers. Beyond that, I_p decreased due to the dissolution of the soluble fraction of PLA oligomers. A rapid and heterogeneous degradation was also observed in the case of PEG-PCL-PLA (Fig. 4), \overline{M}_n decreasing to its half value and I_p reaching 3.6 after 15 weeks.

Compositional changes

Compositional changes of the copolymers and blends were monitored by $^1\text{H-NMR}$. The composition of PCL/PEG copolymers and blends remained unchanged during the first 9 weeks. From 9 to 18 weeks, the [EO]/[CL] ratio decreased from 0.25 to 0.23 for PEG-PCL and from 0.27 to 0.22 for PCL-PEG-PCL. Beyond that, it continued to decrease and reached 0.13 for PEG-PCL and 0.10 for PCL-PEG-PCL after 60 weeks. In the cases of the blends, the [EO]/[CL] ratio decreased from 0.08 to 0.04 for PEG-PCL/PCL and from 0.10 to 0.04 for PCL-PEG-PCL/PCL over 60 weeks. Therefore, one can conclude that the released soluble oligomers contained large amounts of PEG. In other words, the remaining materials were enriched in PCL component. On the other hand, PCL-rich residues were also formed progressively in the cases of PLA-PCL-PLA and PEG-PCL-PLA during degradation. For

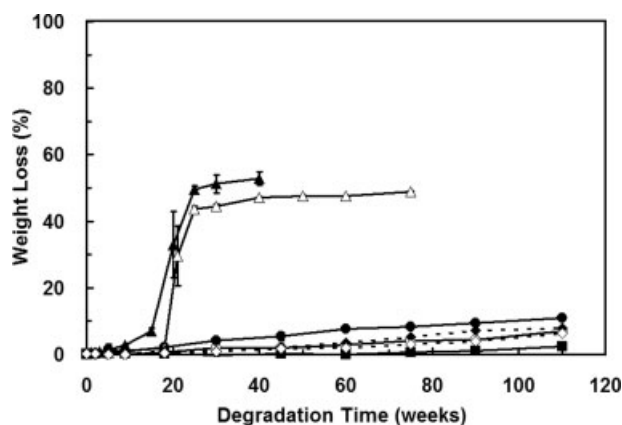
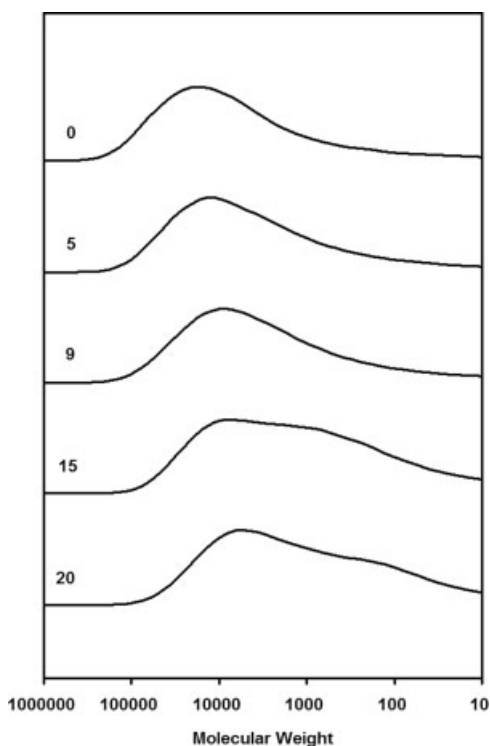


Figure 3 Weight loss profiles of (■), PCL; (○), PCL-PEG-PCL/PCL; (●), PCL-PEG-PCL; (△), PLA-PCL-PLA; (▲), PEG-PCL-PLA; (◇), PEG-PCL/PCL; and (◆), PEG-PCL during degradation.



Time (weeks)	\bar{M}_p	\bar{M}_n	I_p
0	65,000	20,000	3.3
5	55,000	17,000	3.3
9	44,000	15,000	3.2
15	40,000	9,000	3.6
20	32,000	9,000	3.4

Figure 4 MW changes of PEG-PCL-PLA after 0, 5, 9, 15, and 20 weeks' degradation (\bar{M}_p : peak molecular weight).

PLA-PCL-PLA, the [LA]/[CL] ratio remained almost unchanged within the first 18 weeks, and rapidly decreased from 1.4 to 0.1 between 18 and 30 weeks. Insofar as PEG-PCL-PLA is concerned, the [EO]/[CL] ratio remained almost unchanged within the first 20 weeks and decreased from 0.14 to 0.10 beyond 25 weeks. On the other hand, its [LA]/[CL] ratio remained almost unchanged within the first 9 weeks, followed by a rapid decrease from 1.9 to 0.4 between 9 and 20 weeks. PLA component was no longer detected beyond 40 weeks for both PLA-PCL-PLA and PEG-PCL-PLA copolymers.

Water-soluble oligomers in the aqueous phase

CZE was used to evaluate the release of water-soluble species in the degradation medium. 6-Hydroxyhexanoate (6-HH) was detected at week 2 for PEG-PCL

and PCL-PEG-PCL and at week 5 in the cases of PCL and the blends. However, the amounts of 6-HH remained at very low levels as compared to the initial weights of the films (below 1.0 wt %) over 110 weeks. There was no dimer, trimer, or higher oligomers detected. These findings suggested that the initial release of 6-HH was due to the presence of residual caprolactone within the matrix. The situation was very different in PLA-containing copolymers, i.e., PLA-PCL-PLA and PEG-PCL-PLA.⁷ Figure 5 presents the CZE diagrams of the PEG-PCL-PLA containing buffer solution after 1, 9, 15, 20, and 25 weeks' degradation. The peak intensity of lactate strongly increased in the period where important weight loss and compositional changes occurred, i.e., between 15 and 25 weeks. LA dimer and 6-HH were also detected in this period, showing that large amounts of LA species were released into the solution. Therefore, PLA segments present in the terpolymer preserved its degradability.

The formation of micelles by the amphiphilic water-soluble species in the degradation medium were examined by using a water-insoluble dye, namely yellow OB, which is known to dissolve in the hydrophobic core of polymeric micelles or aggregates.⁸ After sonication and centrifugation in the presence of yellow OB, the degradation medium remained uncolored, which indicated that the concentration of amphiphilic degradation products was below the critical micelle concentration during the whole degradation period.

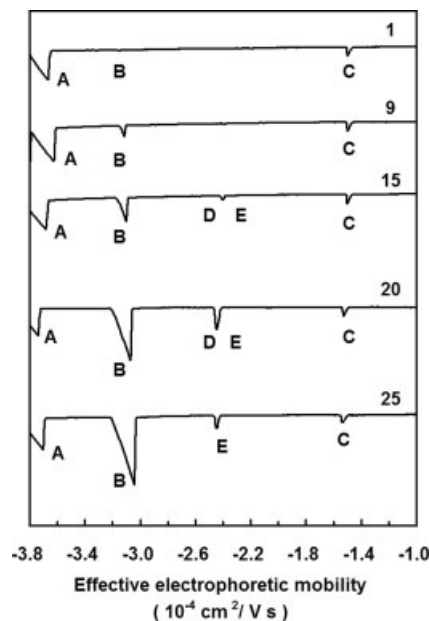


Figure 5 CZE diagrams of the PEG-PCL-PLA containing buffer solution after 1, 9, 15, 20, and 25 weeks' degradation (peaks A, B, C, D, and E, correspond to phosphate, lactate, cholate, LA dimer, and 6-HH monomer).

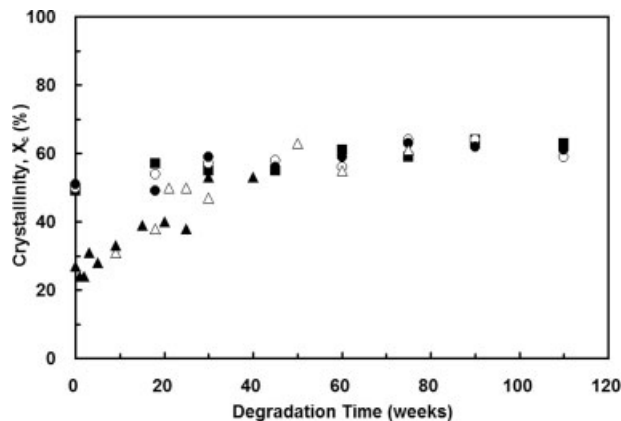


Figure 6 Crystallinity changes of (■), PCL; (○), PEG-PCL; (●), PCL-PEG-PCL; (△), PLA-PCL-PLA; and (▲), PEG-PCL-PLA during degradation.

Crystallinity changes

Figure 6 shows crystallinity changes of the various polymers during degradation. PCL exhibited a rapid increase of crystallinity, from an initial value of 49% to 57% at week 18, which was attributed to degradation-induced crystallization within the amorphous domains.¹⁰ In fact, PCL is able to crystallize at 37°C, a temperature well above its glass-transition temperature (T_g).⁷ Thereafter, X_c slowly increased to reach 63% after 110 weeks. The same trend was found for the PCL/PEG copolymers. For PLA-PCL-PLA and PEG-PCL-PLA, X_c was initially lower than the other polymers due to the presence of PLA. However, a steady X_c increase was observed during the early stages of degradation where the PLA component was degraded. Crystallinity increase of these polymers was confirmed by DSC measurements.^{7,8}

DISCUSSION

Degradation of aliphatic polyesters involves many diffusion-reaction phenomena, including water absorption, ester hydrolysis, diffusion, and solubilization of soluble species.^{1,2} In the case of large-size devices, ester cleavage is autocatalyzed by carboxylic acid end groups initially present or generated by hydrolytic degradation. Pitt et al. showed that the mechanism of *in vivo* degradation of PCL, PLA, and their random copolymers was qualitatively the same. The degradation rates of random copolymers was much higher than those of the homopolymers under the same conditions.¹¹ On the other hand, the degradation rate of PCL/PLA block copolymers was found between those of the two homopolymers and increased with increasing PLA content in the 0–40% range.^{12,13} But when the PLA content was over 40%, the degradation rate of copolymers was found to be somewhat faster than the PLA homopolymer. In this study, the degradation rate

of PLA-PCL-PLA with 53% PLA content was much higher than that of PCL homopolymer, which is in agreement with literature data.

It was previously reported that introduction of PEG sequences did not enhance the degradability of PCL or PLA blocks in the cases of PCL/PEG multiblock and PLA-PEG-PLA triblock copolymers because of the phase separation between PCL or PLA and PEG segments.^{14,15} However, this is in contrast to the conclusions of Sbarbati del Guerra et al.¹⁶ and Bei et al.¹⁷ derived from degradation of devices in the form of powder or cast films. On the other hand, the autocatalytic effect not only accelerates the internal degradation, but also enhances the surface/interior differentiation, as it is the case for large-size PLAGA polymers.^{18–22} In the present study, the results of visual examination and MW distribution revealed a heterogeneous degradation in the cases of PLA-containing copolymers.

The blends conserved the bulk hydrophilicity and degradability of the copolymers, while the surface hydrophilicity showed only a slight increase as compared to PCL. Bei et al.²³ compared the incorporation of PEG into PCL by copolymerization and blending. The authors indicated that the hydrophilicity of the materials increases with PEG content, water absorption ratio being the same for both the copolymers and blends. However, the contact angle of the PCL/PEG copolymers is smaller than that of PCL/PEG blends with the same PEG content, i.e., surface hydrophilicity of the copolymers is stronger than the blends. The authors attributed the increase of surface wettability to the incorporation of PEG into PCL by copolymerization. In literature, PCL/PEG block copolymers were rarely used as blending agents. Tjong et al.²⁴ incorporated PCL-PEG-PCL triblock copolymer into polypropylene to increase its decomposition rate. Water absorption and contact angle measurements indicated that the hydrophilicity of the material was slightly improved, due to the incompatibility between PEG segments of the copolymer and polypropylene phases. However, the two separated phases could be compatibilized with a tertiary agent, maleic anhydride. The compatibilized blend was more hydrophilic than the uncompatibilized one. Shuai et al.²⁵ reported that the PEG segments in PEG-PCL or PCL-PEG-PCL were miscible with another aliphatic polyester, poly(3-hydroxybutyrate) (PHB), while the PCL segments of the copolymers are immiscible with PHB. On the basis of these results, PCL/PEG block copolymers were added as a compatibilizer to PCL/PHB blends. The improvement in the mechanical properties such as tensile strength and elongation-at-break of the blends demonstrated that PCL/PEG copolymers have a potential for compatibilizing immiscible PCL/PHB blends. The increase of mechanical properties of the blends compatibilized with PCL-PEG-PCL was more

significant than that of the blends compatibilized with PEG-PCL. In the present study, visual examination during degradation also revealed that PCL-PEG-PCL/PCL blend exhibited a more homogeneous structure than PEG-PCL/PCL.

CONCLUSIONS

PCL homopolymer degrades extremely slowly by hydrolysis. After 110 weeks in an aqueous medium modeling body fluids, water absorption, weight loss and monomer formation remained at very low levels. PEG-PCL and PCL-PEG-PCL exhibited a higher hydrophilicity because of the presence of PEG blocks. The SEC chromatograms were monomodal and shifted to lower MW during degradation, in agreement with a homogeneous hydrolysis. Weight loss and compositional changes revealed the release of PEG-rich species out of the bulk, but no micelle formation was observed. The blends conserved the bulk hydrophilicity and degradability of the copolymers, while the surface hydrophilicity showed only a slight increase. In the cases of PLA-containing copolymers, the results of visual examination and MW distribution revealed heterogeneous degradation. $^1\text{H-NMR}$ and CZE data showed that large amounts of PLA species were released into the solution between 15 and 25 weeks, indicating that PLA in the copolymers preserved its degradability. In conclusion, PCL-based copolymers tend progressively to PCL-rich residues during degradation due to the hydrolysis of PLA and the diffusion of PLA and PEG oligomers into the solution. This feature has to be confronted to the requirements for temporary therapeutic applications, especially for tissue engineering.

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