Enhanced Crystallization of Poly(L-lactide-*co*-ε-caprolactone) During Storage at Room Temperature

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ABSTRACT: Copolymer of L-lactide and ε-caprolactone [P(LLA-CL)] (50/50) was synthesized using stannous octoate and was stored at room temperature. The change in physical properties occurring during this storage at room temperature was investigated by differential scanning calorimetry (DSC), X-ray diffractometry, polarizing optical microscopy, tensile and bending tests, and light absorbance measurements. It was concluded that the increase in mechanical properties and light absorbance during storage can be ascribed to gradual selective crystallization of the L-lactide sequence in P(LLA-CL) at room temperature. © 2000 John Wiley & Sons, Inc. J Appl Polym Sci 76: 947–953, 2000

Key words: poly(L-lactide-*co*-ε-caprolactone); crystallization; mechanical properties; storage effects; annealing effects

INTRODUCTION

Biodegradable copolymers of lactide and ε-caprolactone (CL) have been investigated as biomaterials to be used for surgery and drug delivery systems because of their high biodegradability and biocompatibility.[1–15] They are rubbery at room temperature, in contrast to their lactide and CL homopolymers, which are mostly stiff at this temperature.[7,9] The copolymers of L-lactide (LLA) or DL-lactide (DLLA) with CL can be synthesized using different catalysts and initiators.[16–30] Kricheldorf and Kreiser reported that copolymers of LLA and CL [P(LLA-CL)] synthesized using tin catalyst had block-type microstructure even when the two monomers were simultaneously copolymerized in the mixed state.[18] Recently, Choi et al. also showed that P(LLA-CL) synthesized using stannous octoate were semicrystalline and of block-type in the entire range of monomer mixing.[26] Seppälä et al. synthesized P(LLA-CL) of different LLA contents using stannous octoate and investigated the change of physical properties during aging in phosphate buffered solution,[11,12,29] and Grijpma and Pennings studied crystallization at room temperature for P(LLA-CL) (50/50) synthesized using tin catalyst.[7,19] These studies demonstrated that the P(LLA-CL) copolymers changed their physical properties during storage at room temperature. We also observed that a soft P(LLA-CL) (50/50) film became stiff upon subcutaneous implantation in rat.[15]

In an attempt to study the storage or aging effect of P(LLA-CL) on its crystallization and physical properties in more detail, a P(LLA-CL) copolymer was synthesized using stannous octoate and was processed to a thin film with the

solution casting method. The change in physical properties of thin copolymer film during storage in dried state at room temperature was investigated using differential scanning calorimetry (DSC), X-ray diffractometry, tensile and bending tests, polarizing optical microscopy, and light absorbance measurements.

EXPERIMENTAL

Materials

LLA and CL monomers were purified by repeated recrystallization using ethyl acetate and distillation under reduced pressure, respectively. Ring-opening copolymerization of LLA and CL (50 : 50 mol ratio in the feed) was performed at 190°C for 5 h using stannous octoate as a catalyst (0.03 wt %).[8] The resulting polymer was purified by repeated precipitation of chloroform solution to methanol and dried in vacuo for 1 week.

Copolymer films of 25–500 μm thickness used were prepared by the method described in previous papers.[31–33] Briefly, methylene chloride solution of the copolymer was prepared to have a polymer concentration of 1.0 g/dL and then cast onto a flat glass plate, followed by solvent evaporation at room temperature for approximately 24 h. To avoid formation of highly ordered structure, solvent evaporation was performed rapidly, as in our previous work, where cast films were utilized for the study of crystallization of poly(L-lactide) (PLLA) from the melt,[31–33] followed by drying in vacuo for 24 h. Film was stored at 25°C and 30% relative humidity after melting at 200°C for 3 min and quenching at 0°C.

A polymer foam of 600 μm thickness was prepared by casting 6 g/dL dioxane solution of the copolymer onto a flat glass plate. The solvent in the solution was allowed to completely crystallize at −30°C, followed by lyophilization. The obtained foam was dried in vacuo at 50°C for 12 h and then subjected to tensile tests. The pore size estimated by a scanning electron microscope (JEOL JSM-5800LV) was in the range from 5 to 100 μm.

Measurements and Observation

The L-lactate (half of L-lactide) unit content [x_L (mol %) and w_L (wt %)] of the copolymer was determined from the 270-MHz ^{1}H NMR spectrum obtained in deuteriated chloroform with a JEOL
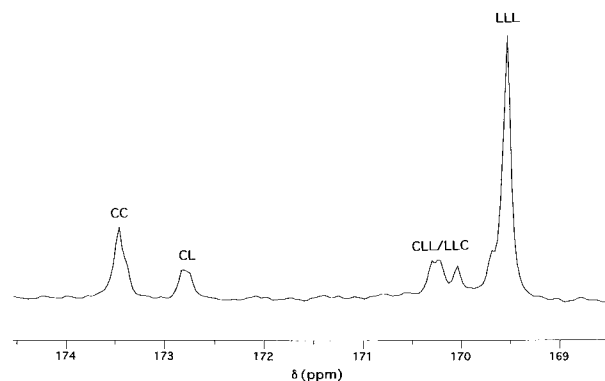

Figure 1 ^{13}C NMR spectrum of carbonyl carbon of P(LLA-CL).

JNM-GX270 using tetramethylsilane as an internal standard. The ratio of the integrated intensity at 5.2 ppm (the methyne group of LLA unit) to that at 4.1 ppm (the γ-methylene group of CL neighbouring oxygen of ester bond)[16,26] was used to determine the chemical composition of the copolymer. w_L was calculated from eq. (1):

$$w_L \text{ (wt \%)} = 100 \cdot x_L \cdot 72.1/[(100 - x_L) \\ \cdot 114.1 + x_L \cdot 72.1] \quad (1)$$

The average monomer sequence length of L-lactate (l_L) and CL (l_C) was determined from the 67.8 MHz ^{13}C NMR spectrum measured in deuteriated chloroform using tetramethylsilane as an internal standard. The spectrum was obtained under the conditions of 24,000 scans, 0.5 s acquisition time, and 3.4 μs pulse width. Figure 1 shows the ^{13}C NMR spectrum of carbonyl carbon of the copolymer. The assignment of the sequences was performed according to the literature.[16,17,21,24,26] l_L and l_C were estimated on the basis of relationship between the average comonomer sequence length and the intensity of triad sequence (I) as follows:[16,17,21,24,26]

$$l_L = (I_{LLL} + I_{LLC} + I_{CLL} + I_{CLC})/ \\ [I_{CLC} + (I_{LLC} + I_{CLL})/2)] \quad (2)$$

$$l_C = (I_{CC} + I_{CL})/I_{CL} \quad (3)$$

The subscripts "L" and "C" in eqs. (2) and (3) denote L-lactate and CL units, respectively. The average molecular weight of the copolymer was determined by gel permeation chromatography (GPC) obtained with a Shimadzu LC-6A system and SHIM pack columns (GPC806, GPC804, and

Table I   Molecular Characteristics of Copolymer

x_L (mol %)	w_L (wt %)	M_w (g/mol)	M_w/M_n	l_L	l_C
69.8	59.4	2.2×10^5	2.5	7.2	3.3

GPC802) and then calibrated using standard polystyrenes. Molecular characteristics of the copolymer are listed in Table I.

The melting temperature ($T_{m,PLLA}$) and enthalpy of fusion ($\Delta H_{m,PLLA}$) of LLA unit sequences were determined with a Shimadzu DT-50 differential scanning calorimeter at a heating rate of 10°C/min under nitrogen gas flow. Both $T_{m,PLLA}$ and $\Delta H_{m,PLLA}$ were calibrated using indium as a standard. The crystallinity of LLA unit sequence ($x_{c,PLLA}$) in copolymer was calculated from eq. (4).[31–33]

$$x_{c,PLLA}(\%) = 10^4 \cdot (\Delta H_{m,PLLA})/(93 \cdot w_L) \qquad (4)$$

where 93 (J/g of PLLA) is the enthalpy of fusion of PLLA crystals having the infinite crystal thickness.[34]

X-ray diffractometry was performed at 25°C using a Rigaku RINT-2500 equipped with a CuKα source. The light absorbance of the copolymer film with thickness of 420 μm was measured at 500 nm and 25°C using a Beckman DU650 spectrometer.

Tensile properties of copolymer film (thickness of 200 μm) and foam (thickness of 600 μm) were measured at 20°C and 50% relative humidity using an Instron Model 4302 Universal Testing Machine at a crosshead speed of 200%/min. The initial length of the specimen was always fixed at 50 mm. Bending modulus of copolymer film (thickness of 300 μm) was measured at 20°C and 60% relative humidity using a Kato Tech KES-FB2 at a head speed of 5 mm/sec, fixing the initial length of the specimen at 10 mm. Morphology of the copolymer film with thickness of 25 μm was observed with a Zeiss polarizing microscope.

RESULTS

Absorbance

The appearance of the copolymer film became whitish with storage time. This appearance change was easily recognizable when the film was stored for longer than 3 days. To quantitate this appearance change of film with storage, the light absorbance was measured for a 420 μm-thick P(LLA-CL) film at 500 nm. The result is plotted in Figure 2 as a function of the storage time. It is clearly seen that the absorbance increased with the storage time, at least up to 100 days, in agreement with the appearance change.

X-ray Diffractometry

X-ray diffractometry was performed for the P(LLA-CL) film stored for 35 days. The result is shown in Figure 3, along with that of the initial copolymer film (0 day), as-cast PLLA, and PCL films. The initial copolymer film before storage has a broad diffraction profile specific to amorphous polymeric materials. However, at 35 days of storage, the copolymer film gave a diffraction profile very similar to that of as-cast PLLA film but distinctly different from that of as-cast PCL film. This is in agreement with the result reported by Grijpma and Pennings.[7,19]
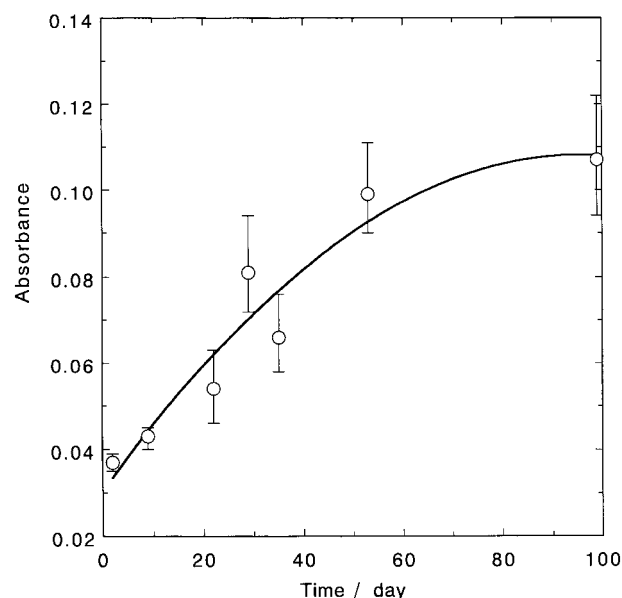

Figure 2   Absorbance of P(LLA-CL) film at 500 nm as a function of storage time.
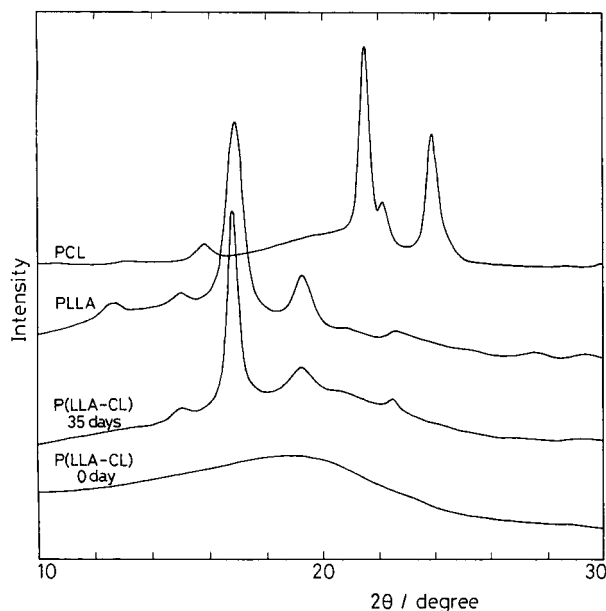
Figure 3 X-ray diffraction profiles of P(LLA-CL) film, as-cast PLLA, and PCL films.

DSC

DSC thermograms of the copolymer film stored for different times are shown in Figure 4. Apparently, the initial film of 0 day has no melting peak in the scanning temperature range between 30 and 200°C. This suggests that the copolymer film
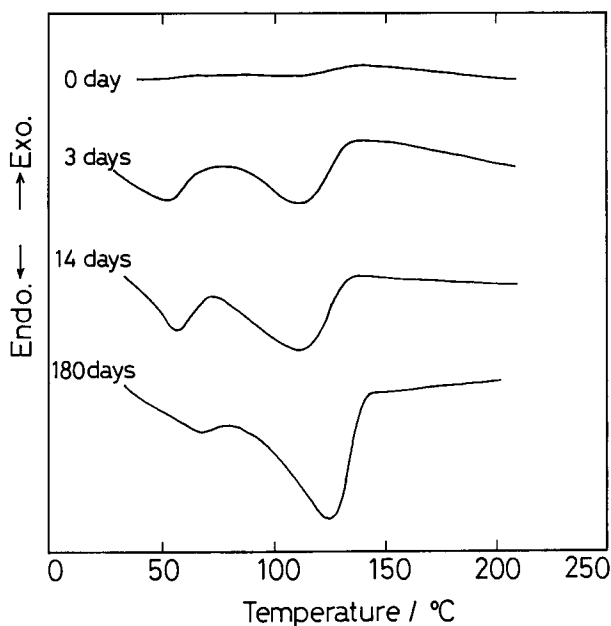

Figure 4 DSC thermograms of P(LLA-CL) film stored for different times.
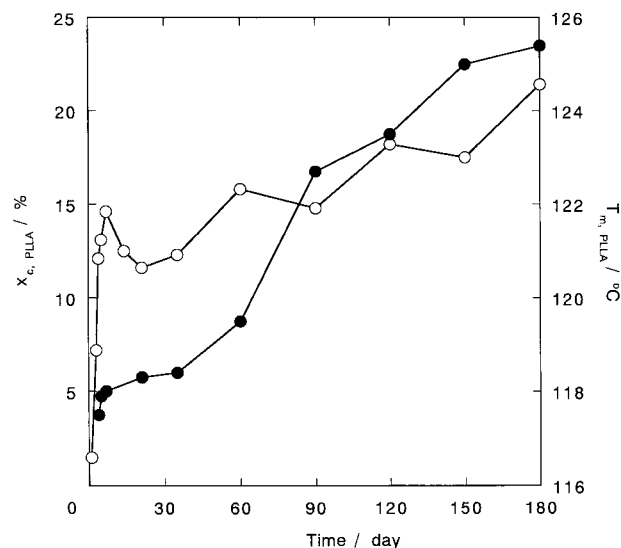

Figure 5 $x_{c,PLLA}$ (○) and $T_{m,PLLA}$ (●) of P(LLA-CL) film as a function of storage time.

has no crystalline region before storage, in good agreement with the result observed by X-ray diffractometry. A melting peak appeared around 120°C when film was stored for 3 days, and its area increased with the storage time up to 180 days. The peak around 120°C can be ascribed to melting of the crystallites of LLA-unit sequences in the copolymer but not that of CL-unit sequences, because the melting temperatures of PLLA and PCL homopolymers are around 180 and 60°C, respectively. The peak around 60°C may be ascribed to T_g of LLA-unit sequences in amorphous region of the copolymer as revealed by Grijpma and Pennings.[19]

The $x_{c,PLLA}$ and $T_{m,PLLA}$ values of the copolymer film estimated from the DSC thermograms are plotted in Figure 5 as a function of the storage time. The increase in $x_{c,PLLA}$ and $T_{m,PLLA}$ started without any induction period. It is interesting to note that their increase continued as long as 180 days. The $x_{c,PLLA}$ increase occurred significantly in the first 7 days, but became slower when film was stored for more than 7 days.

Morphology

The polarizing optical micrographs of the copolymer film stored for 3 and 7 days are shown in Figure 6. It is seen that the area covered by spherulites increased with storage and became 100% at 7 days.

Bending Modulus

Bending modulus of the copolymer film is plotted against the storage time in Figure 7. Clearly, the
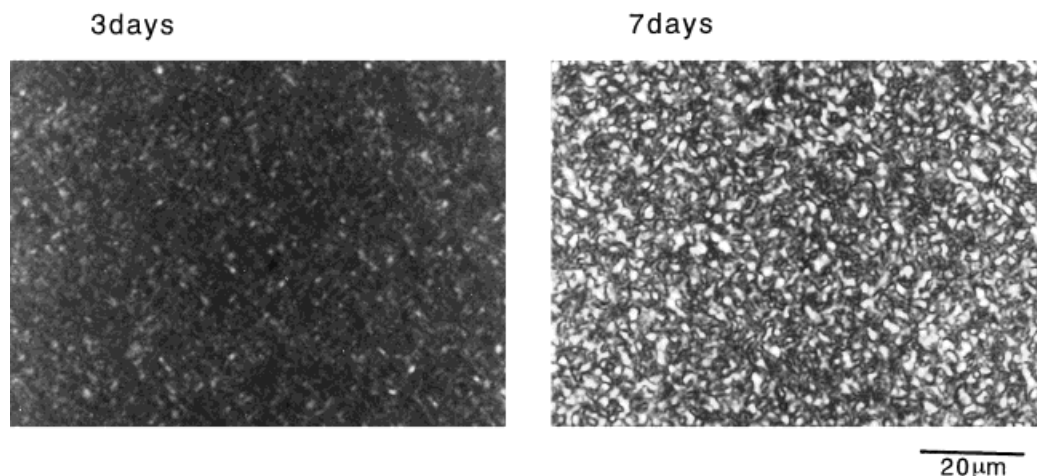
3days   ### 7days

Figure 6   Polarizing optical photomicrographs of P(LLA-CL) film stored for 3 and 7 days.

bending modulus of film increased rapidly in the first 60 days and leveled off at 180 days of storage.

Tensile Properties

Table II shows the change of tensile properties for the copolymer film and foam upon storage at 25°C. As is obvious, the tensile strength, yield stress, and Young's modulus of P(LLA-CL) film dramatically increased after storage for 60 days.
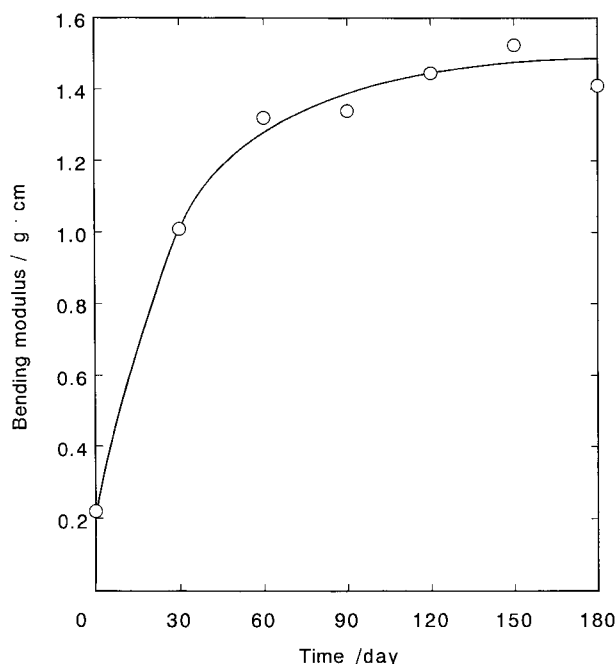

Figure 7   Bending modulus of P(LLA-CL) films as a function of storage time.

The insignificant change in tensile strength and modulus for the foam suggests that the porous structure more strongly dictates the mechanical properties of the polymer foam than the bulk properties of the substrate polymer.

DISCUSSION

The results observed by X-ray diffractometry, DSC, and polarizing microscopy strongly suggest that the light absorbance increase during storage seen in Figure 2 can be ascribed to nucleation and growth of crystallites in P(LLA-CL) film during storage. Figures 3 and 4 indicate that the crystallization and crystalline region of the copolymer film seem to be attributable to LLA-unit sequences, not CL-unit sequences. In other words, the average length of LLA-unit sequences (l_L = 7.3) in the copolymer is large enough to form crystallites during storage at 25°C; whereas, the length of CL-unit sequences (l_C = 3.3) seems to be insufficient for crystallization. However, this length of L-lactate unit sequences is smaller than the minimum L-lactate unit (15) for crystallization of LLA-unit sequences in L-lactide rich copolymers synthesized from D- and L-lactide.[35] This is probably because the mobility of LLA-unit sequences in the P(LLA-CL) copolymer was enhanced by copolymerization of LLA with soft CL-unit sequences. The l_L value decreases with an increase in polymerization temperature and LLA in the feed. For example, Grijpma and Pennings reported that l_L was 11.0, 8.5, 5.5, and 3.9 when

Table II   Tensile Properties of Copolymer Film and Foam Before and After Storage at 25°C for 60 Days

	Storage Time (day)	Tensile Strength (MPa)	Young's Modulus (MPa)
Film	0	7.6 ± 0.7	0.10 ± 0.01
	60	11.7 ± 3.9	0.94 ± 0.10
Foam	0	0.5 ± 0.1	0.01 ± 0.01
	60	0.5 ± 0.1	0.02 ± 0

copolymerization of LLA/CL (50/50) was carried out with stannous octoate at 80, 110, 120, and 160°C, respectively.[19] Choi et al. found that l_L was 20.8, 7.5, 3.7, and 3.4, when LLA/CL monomer feed ratios of 95/5, 80/20, 65/35, and 50/50 were used for copolymerization at 140°C with stannous octoate, respectively.[26] Melting peaks were observed at 149 and 44°C for LLA- and CL-units sequences in P(LLA-CL) polymerized at temperature as low as 80°C ($l_L = 11.0$, $l_C = 5.5$), respectively. In contrast, only the melting peak of LLA-unit sequences was recognized at 102°C when a mixture of LLA/CL (50/50) was allowed to polymerize at 110°C ($l_L = 8.5$, $l_C = 3.7$).[19] Our DSC result for the P(LLA-CL) with $l_L = 7.2$ and $l_C = 3.3$ was very similar to that observed by Grijpma and Pennings for P(LLA-CL) synthesized at 110°C ($l_L = 8.5$, $l_C = 3.7$).[19]

Figure 5 implies that both the content of crystalline region and the crystalline thickness increase with the storage time. Comparison of the result obtained by DSC with that of polarizing optical microscopy reveals that the initial dramatic increase in $x_{c,PLLA}$ during storage less than 7 days can be ascribed to spherulites growth. The subsequent slower increase of $x_{c,PLLA}$ may be mainly attributable to thickening of the crystallites of LLA sequences in the formed spherulites. The increase in content of crystalline region and crystalline thickness during storage continued at least for 180 days.

The increase in Young's modulus is more dramatic than that in tensile strength. The increase in Young's modulus of the copolymer film must be attributable to the increase in crystallinity during storage. The stronger dependence of tensile strength and Young's modulus on the crystallinity of P(LLA-CL) than that reported for PLLA homopolymer film[31] may be ascribed to the difference in T_g between P(LLA-CL) for CL-unit-rich segments (below room temperature)[19] and PLLA

(above room temperature, T_g = ca. 60°C). In other words, the difference in Young's modulus between the crystalline and the amorphous region should be larger for P(LLA-CL) than PLLA. It is very likely that this soft amorphous region of the P(LLA-CL) copolymer film allowed the LLA-unit sequences to crystallize even at room temperature during storage, in marked contrast with PLLA.

Such a tensile property increase as observed in the present study was reported for a compression molded P(LLA-CL) copolymer (x_L = 62%) in phosphate buffered solution at 23 and 37°C up to 10 and 20 days, respectively, and at room temperature for 2 weeks.[12] A solution-cast PCL homopolymer also showed a tensile property increase at 37°C up to 8 months in phosphate buffered solution.[36] It seems probable that the phosphate buffered solution utilized as storage medium must have accelerated the chain crystallization, operating as a plasticizer and increasing the mobility of chains by their hydrolytic scission.

CONCLUSION

The LLA sequences in P(LLA-CL) were crystallized and formed spherulites at room temperature. The growth of crystallites continued as long as 6 months. The increase in mechanical properties and visible light absorbance of P(LLA-CL) film was concluded to be attributable to crystallization of the LLA sequences in the copolymer that contained softer amorphous regions than PLLA.

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