Structural Analysis and Degradation Behavior in Polyethylene Glycol/Poly(L-Lactide) Copolymers

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SYNOPSIS

The objective of this research is to investigate the molecular weight, degradation mechanism, and crystalline morphology of polyethylene glycol/poly(L-lactide) (PEG/PLLA) copolymers during hydrolytic degradation. PEG/PLLA copolymers were prepared from cyclic L-lactide and polyethylene glycol with molecular weights ranging from 1000 to 6000 Da. The structural analysis was carried out by GPC, DSC, FTIR, ^{13}C-NMR, and ^{1}H-NMR. Gel permeation chromatograms also indicate that the hydrolysis causes the change of mass distribution from a unimodal to a bimodal form. An exothermic recrystallization peak and its shoulder portion at the lower temperature range during melting appears immediately following the hydrolytic degradation. This indicates the heterogeneity of the crystals. The data of NMR and FTIR shows that during the initial period (0–200 h) of hydrolysis, there appears to be a formation of hydroxyl end groups connected to PEG blocks and carboxyl end groups connected to polylactide blocks. Due to the hydrophilic ethylene oxide segment in PEG/PLLA copolymers, the rate of hydrolysis is much faster during the first 200 h relative to longer hydrolysis time. It is therefore concluded that the chain scission during the initial period occurs at the ester linkage connecting PEG and PLLA blocks, in addition to ester groups within the PLLA blocks. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

Polyglycolide (PGA), polylactide (PLA), and their copolymers have been prepared through the ring-opening polymerization of glycolide and lactide since the 1970s. Their applications initially were in the area of resorbable synthetic sutures.[1-4] Since then researchers have devoted themselves to the utilization of biodegradable polymeric materials in orthopedics, dentistry, cosmetic surgery, and controlled release of drugs.[5-9]

Recently, the synthesis of biodegradable polymers, for example, polyamino acids, poly(ortho-esters),[10] and polyanhydrides[11] specifically suitable for drug delivery has been achieved. In addition, one of the major research interests receiving substantial attention is the incorporation of degradable or water-soluble moieties into hydrolyzable segments. More specifically, several approaches have been tried to copolymerize various lengths of segments of PGA and poly-ϵ-caprolactone to yield the block structures.[11,12] Another approach has been to attempt to copolymerize polyethylene oxide (PEO) and polyethylene terephthalate (PET).[13-15] Other examples include the copolymers of poly-ϵ-caprolactone with a series of polyamides,[16] the copolymers of a variety of contents of polyethylene glycol (PEG) with poly-ϵ-caprolactone,[17,18] as well as copolymers of PEG or polypropylene glycol (PPG) with lactide through the ring-opening polymerization to yield polyetheresters with different block lengths of polyethers and mole percentages.[19,20]

The initiators for lactide copolymerization consist of PbO, $SnCl_2 \cdot 2H_2O$, Sb_2O_3, H_3PO_4, and $Ti(OBu)_4$. Stannous octoate at a concentration of 0.05 wt % enables the reaction to reach the higher yield and a more uniform distribution of molar mass.[20,21]

An infrared study was done on the morphology of PEG/PLLA copolymers and tensile measurement on their stress–strain relationships. When the lactide content range is 20 to 84 mol% in PEG/PLA, the mechanical strength decreases significantly with

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the increase of PEG content and the equilibrium water content increases to 60%. The hydrophilicity of PEG/PLLA copolymers increase with the increase of PEG content. The contact angles with water on the polymer surface decreases from 76 to a value of 26° with the increase of PEG contents from 0 to 80 mol %.[22,23]

The increase of PEG content leads to the increase of the ratio of the total number of hydroxyl groups to that of the carboxy group in the PEG/PLLA copolymerization. This study utilized various lengths of PEG segments with molecular weights equal to 1000, 2000, 4000, and 6000, and the lower PEG weight percentages in feed ranging from 0 to 10 was used to achieve a uniform molecular weight distribution and the higher molar mass in PEG/PLLA copolymers. The objective of this work is to investigate the molecular structure, thermal behavior, and molecular weight for PEG/PLLA copolymers undergoing the hydrolysis, and to elucidate the reaction mechanism of hydrolysis through the analysis by NMR and FTIR spectroscopy.

EXPERIMENTAL

Synthesis

L-Lactic acid (Biochem. b.v., CCA Co.) was dehydrated at 140°C for 8–10 h in the presence of 2 wt % zinc oxide, under a pressure of 100 mmHg. The lactide was prepared by refluxing at about 250°C at a reduced pressure below 10^{-1} torr. The crude product was recrystallized several times from ethyl acetate.

PEG ($\bar{M}_w/\bar{M}_n$ = 1.1) with the number-average molecular weight $\bar{M}_n$ = 1000, 2000, 4000, and 6000 were supplied by Hanaka (Japan). The samples were thoroughly dried at 100°C at a pressure below 10 mmHg for 24 h and used without further purification. Stannous octoate was provided by Sigma. *N*-Hexane and ethyl acetate were commercially available and purified by distillation prior to use.

A prescribed amount of L-lactide and PEG were placed in a 100-mL round-bottomed flask equipped with a stirrer. The flask was evacuated by a vacuum pump for several hours in order to dry the reaction mixture thoroughly and was filled with nitrogen gas. The temperature was raised to 180°C with stirring under a nitrogen atmosphere and 0.05 wt % stannous octoate was added. The mixture was stirred at 180°C for 10 h. The products were extracted with a cold solvent mixture of ethyl acetate and *n*-hexane, and finally with distilled water. The copolymers were dried in a vacuum oven at 60°C for 24 h.

Physicochemical Characterization

^{1}H-NMR spectra were measured at 200 MHz with a Bruker AC200 spectrometer using tetramethylsilane (TMS) as the internal standard. The intensity of each peak due to chemical shift (δ) at 1.57 for $-CH_3$ in PLLA, 3.64 for $-CH_2-$ in PEG, 5.16 for $-CH$ in PLLA was used. In addition, the measured relative content of proton in PLLA and PEG blocks were used to calculate the mass percentage of PEG block. Then the block lengths of PLLA ($\bar{L}_{PLLA}$) and PEG ($\bar{L}_{PEG}$) are given by

$$\bar{L}_{PEG} = (M_w \text{ of PEG})/44 \quad (1)$$

$$\bar{L}_{PLLA} = \bar{L}_{PEG} \times \frac{(\text{content of H in PLLA})}{(\text{content of H in PEG})}. \quad (2)$$

Subsequently, the number-average molecular weight $\bar{M}_n$ is computed by assuming a PLLA–PEG–PLLA triblock structure,

$$\bar{M}_n = \bar{L}_{PEG} \times 44 + 2\bar{L}_{PLLA} \times 72. \quad (3)$$

DSC was performed under a nitrogen atmosphere on a DuPont 912-2000 thermal analyzer. The heating rate was set at 10°C/min with the sample amount of 10.0 mg. GPC was measured on a Shimadzu LC-6A fitted with an RID-6A detector and C-R4A data processor. Two Zorbax PSM Bimodal (6.2 mm ID × 25 cm) columns were used. The sample was injected at 40°C with chloroform as the eluent at a flow rate of 1.0 mL/min. The molecular weight was calibrated with monodisperse polystyrene ($\bar{M}_n$ = 2500, 20400, 47500, 122000, 200000). ^{13}C-NMR spectra were obtained with a Bruker AM300 equipment and $CDCL_3$ solvent. The FTIR spectra of samples in the film form were taken with a JASCO FTIR-3 spectrophotometer.

Hydrolytic Degradation

A 15 wt % PEG/PLLA solution in chloroform was used to cast the films with a thickness of 30–50 μm. Films were dried in a vacuum oven at 60°C for 12 h. The dried films were then immersed in the buffer solutions (pH = 4, 7, and 10) at a temperature of 37°C. The hydrolyzed samples were subsequently characterized at several time intervals to uncover the structural change of polymers.

RESULTS AND DISCUSSION

The solid product of PEG/PLLA copolymers appears transparent and pale yellow in color. The yield

Table I Structural Characteristics of Block Copolymers of L-Lactide With PEG

Sample No.	PEG Wt % in Feed	M of PEG	PEG Wt % in Copolymer (NMR)	Yield (%)	$\bar{L}_{PLLA}$[a]	Melting Point (°C)	T_g (°C)	Molecular Weight (M) (GPC)
1	2	2000	4.4	84	172	161.2	51.1	24100
2	3	2000	5.4	86	125	157.8	44.8	19812
3	4	1000	6.3	83	76	154.2	44.9	11231
4	5	2000	9.6	90	101	149.8	43.1	15783
5	10	6000	12.7	79	181	116.7	40.8	30760
6	10	1000	13.4	85	40	138.1	42.3	6070
7	10	4000	16.2	86	127	131.0	41.2	21035
8	10	2000	18.3	84	55	134.2	42.6	9801
9[b]	0	—	—	—	—	174.7	58.9	78964

[a] The average segment length of PLLA block.
[b] DuPont Medisorb®.

of the polymerization reaction is approximately 85%. This is partly offset by the sublimation of L-lactide during polymerization and by the attrition of mass while being recrystallized. Therefore, the PEG segment length remained the same[20] as the initial one; however, the average segment length of PLLA block ($\bar{L}_{PLLA}$) increases with the relative amount of L-lactide in the feed. Reaction times greater than 10 h did not significantly increase the yield. The length of PLLA, melting temperature, and glass-transition temperature, are shown in Table I. The PLLA homopolymer utilized was obtained from DuPont (Medisorb®).

Structural Analysis

The measured PEG content in Table I is based on the ^{1}H-NMR spectra ($CDCl_3$). Figure 1 shows the intensity of each peak due to chemical shift (δ) at 1.57 for $-CH_3$ in PLLA, 3.64 for $-CH_2-$ in PEG, and 5.16 for $-CH$ in PLLA. In addition, the measured relative proton content in PLLA and PEG

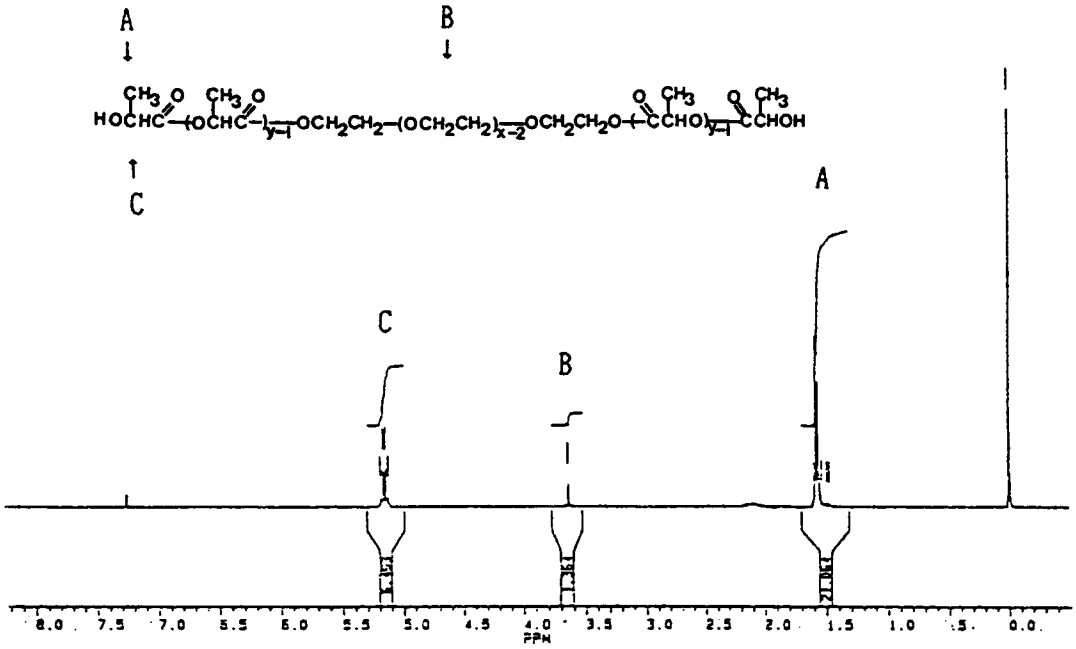

Figure 1 200 MHz ^{1}H-NMR spectrum of PEG/PLLA copolymer, content of PEG in copolymer = 6 wt % ($\bar{M}_n$ of PEG segment = 1000).

blocks were used to calculate the mass percentage of PEG block (Table I).

The calculated $\bar{M}_n$ data, compared with the molecular weight by GPC, was 2–10% higher than the experimental. The typical GPC chromatograms shown in Figure 2 exhibit the tailing of the lower molecular-weight fraction. It is therefore conceivable that the nonuniform length distribution for PLLA block causes the discrepancy between the calculated using the NMR data of composition analysis and M_w data directly obtained from GPC. This claim is also understandable in terms of the polydispersity indices of copolymers, which lie between 1.5 and 2.5.

Thermal Characterization

DSC samples were pretreated by heating to 180°C, then held at that temperature for 10 min, and cooled to room temperature at 5°C/min. Measurements were then taken at a heating rate of 10°C/min. The results are shown in Figure 3. The melting and glass-transition temperatures for copolymers with a PEG content of less than 20 wt % are up to 30°C lower than that of the PLLA homopolymer as indicated in Table I and Figure 3. The melting points of copolymers are dependent upon the PEG content with a decrease in the transition temperature and the increase in the content of soft segment. However, the melting temperatures are not significantly influenced by the length of PEG segments.

The exothermic recrystallization phenomena at temperatures below the melting points (i.e., approximately from 80 to 90°C) shown in Figures 3 and 4, occurs when the weight percentage of the PEG segments approaches 20 wt % or higher.

According to the work by Kimura et al.,[19] PPO/PLA exhibits similar results with the recrystallization occurring at approximately 100°C. Specifically, the exothermic recrystallization in PEG/PLLA gives a sharper peak than that in PPO/PLA. As reported in the literature, there is no recrystallization behavior for either quenched or annealed PLLA homopolymer.[19] It is therefore understandable that the melting and crystallization behavior of PLLA block is influenced by the PEG segment to a significant extent. In addition, the crystalline content and the crystallization rate, which are both influenced by the block length and the weight percentage of PEG, affects the recrystallization temperature to some extent. The DSC data shown that the microphase separation between blocks is controlled by PEG content in the copolymers.

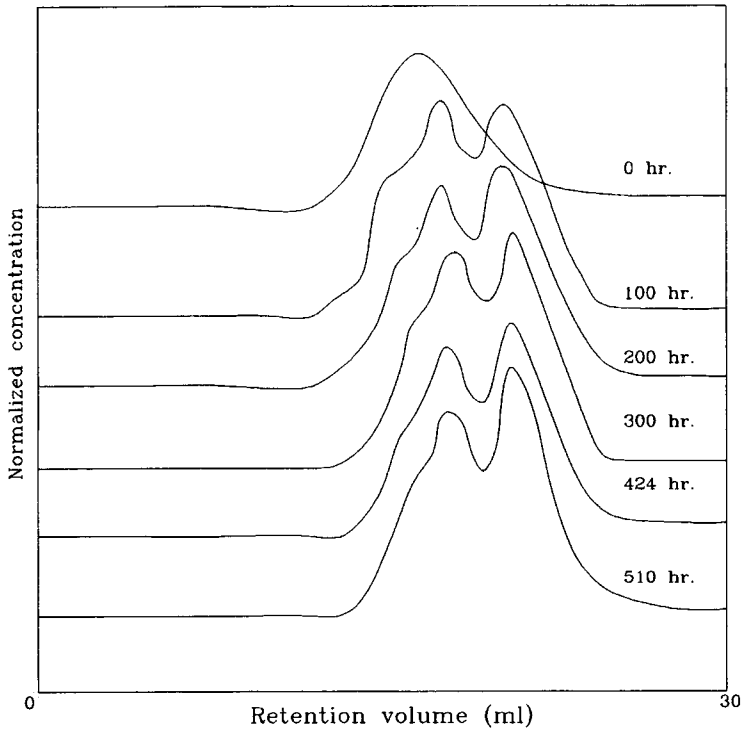

Figure 2 GPC chromatogram of copolymer in degradation at various times. Content of PEG in copolymer is 18.3 wt % ($\bar{M}_n$ of PEG segment = 2000).

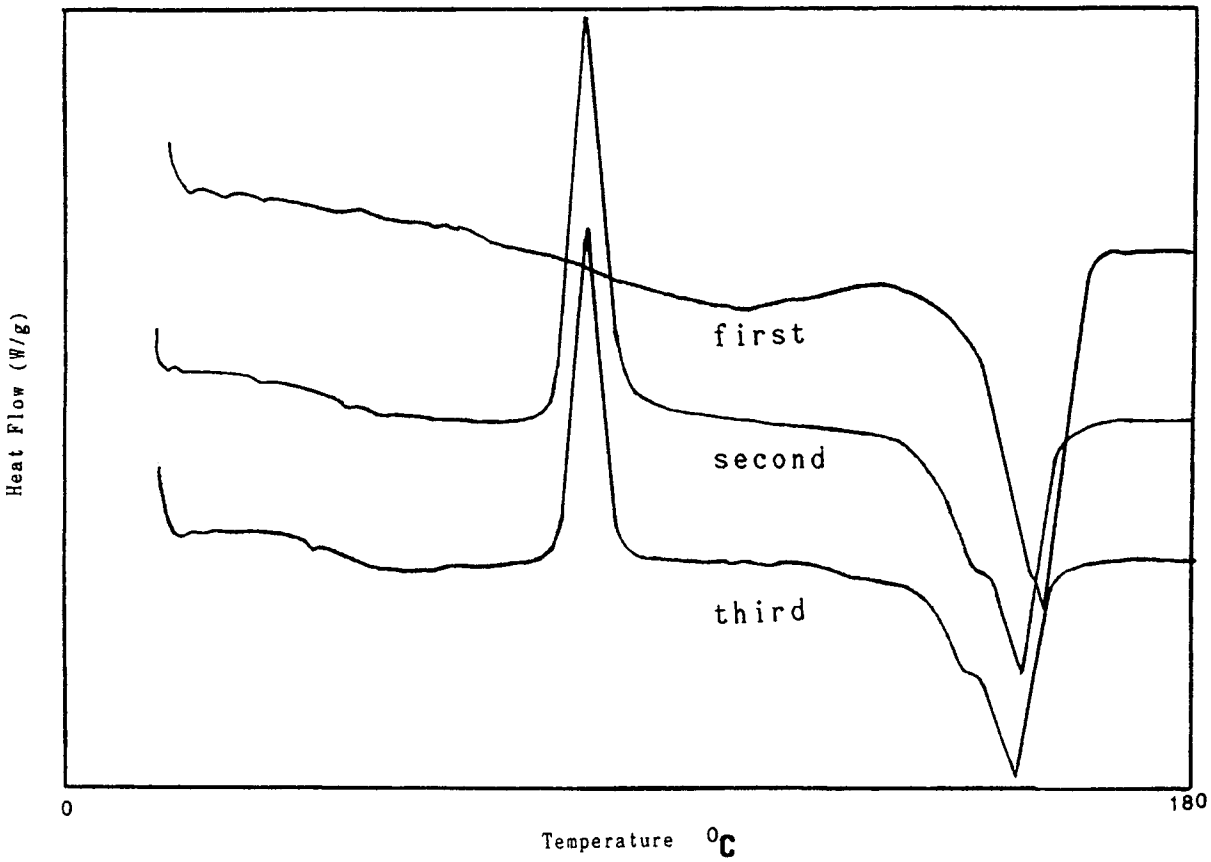

Figure 3 DSC thermograms of PEG/PLLA copolymer sample 8. First scanning was from room temperature to 180°C under N_2 at 10°C/min. The sample was cooled in the DSC cell from 180°C to room temperature at 5°C/min, and then the second and the third run was carried out under the same conditions.

Effect of Degradation on Structure

The GPC data in Figure 2 shows that the molecular weight distribution is unimodal prior to hydrolysis. After 200 h of hydrolysis, the molecular weight distribution is changed to bimodal. The polydispersity ($\bar{M}_w/\bar{M}_n$) becomes greater with a value of up to 5. During the hydrolysis period, the GPC peak area for the higher molecular-weight portion decreases, and the peak area of lower molecular-weight portion correspondingly increases. This effect is the same as that which occurs in the hydrolysis of PPO/PLLA. For PPO/PLLA the intrinic viscosity dropped from 0.25 to 0.15 dL/g after 14 days of hydrolysis at pH 7.[19]

The FTIR results for PEG/PLLA are shown in Figure 5. The characteristic peaks occur at 2996, 2945, and 2884 cm^{-1} for C—H stretch. As the PEG content increases, 2945 and 2884 cm^{-1} absorption peaks become more intense. This is attributed to the asymmetric and symmetric stretch of methylene groups in the PEG blocks.

Prior to the hydrolysis, both the FTIR of PLLA and PEG/PLLA exhibit the peak for hydroxyl group at 3610 cm^{-1}. The hydrolysis renders very little change in the FTIR spectra of PLLA. However, a more significant increase in the intensity and width of the absorption bands happen to PEG/PLA at 3610 to 3334 cm^{-1}. This is due to more hydrogen bonding of terminal OH groups in copolymers with other hydroxyl and carboxyl groups. Figure 5 also indicates a sharp peak for C=O absorption at 1760 cm^{-1} for undegraded PLA and PEG/PLLA. Moreover, the involvement of C=O in hydrogen bonding at chain ends of L-lactide becomes more pronounced for degraded PEG/PLLA, leading to a broader band over the wavenumber from 1730 to 1780 cm^{-1}.

The chemical shifts for unhydrolyzed PEG/PLLA (Fig. 1) and hydrolyzed PEG/PLLA (Fig. 6) were examined to see the change of chain ends. The PEG wt % in PEG/PLLA copolymer was determined by the ^{1}H-NMR intensity for $-CH_2$ (δ = 3.64) in PEG, $-CH_3$ (δ = 1.57), and $-CH$ (δ

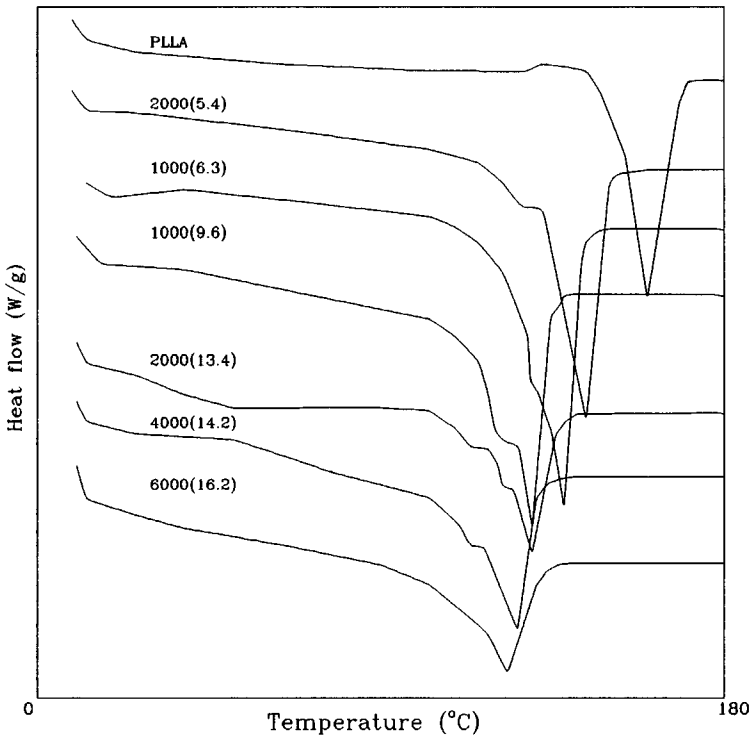

Figure 4 DSC thermograms of PEG/PLLA copolymers with various molecular weights of PEG and percentages of PEG.

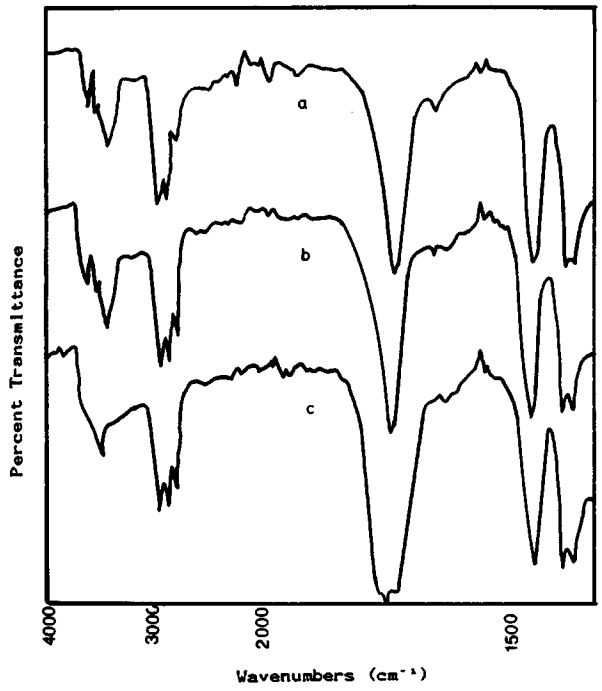

Figure 5 FTIR spectra of (a) PLLA homopolymer; (b) PEG/PLLA copolymer, content of PEG in copolymer = 2 wt % (PEG $\bar{M}_n$ = 2000); (c) after 100 h hydrolysis of (b).

= 5.16) in PLLA, and calculated by a procedure similar to eqs. (1), (2), and (3). The ^{1}H-NMR spectrum for hydrolyzed PEG/PLLA (Fig. 6) at the δ = 2.17 peak is attributed to methylene groups connected to the hydroxyl groups in the PEG blocks. The δ = 4.69 peak is due to the methylene group in the ester linkage joining PEG and L-lactide, and the δ = 8.10 peak is attributed to hydroxyl groups at the chain ends. The proton NMR data for the change of PEG wt % with the hydrolysis are given in Table II. It may be notable that, in the initial period of hydrolysis up to 300 h, the PEG wt % tends to increase and the rate of change gradually slows down at the time of degradation longer than 300 h. Notably, the degradation in the initial stage was caused by the PLLA segments leaving away from A–B–A triblock copolymers as well as the cleavage of lactic acid from PLLA segments.

The ^{13}C-NMR spectra for carbon chemical shifts in undegraded and degraded PEG/PLLA copolymers are shown in Figures 7 and 8, respectively. It is noted that δ = 16.63 is for $-CH_3$ in PLLA, δ = 169.59 for $-C=O$ in PLLA, δ = 69.02 for $-CH$ in PLLA, and δ = 70.54 for $-CH_2-$ in PEG chain ends. They indicate the increase of intensity versus hydrolysis time due to the increase of PEG content.

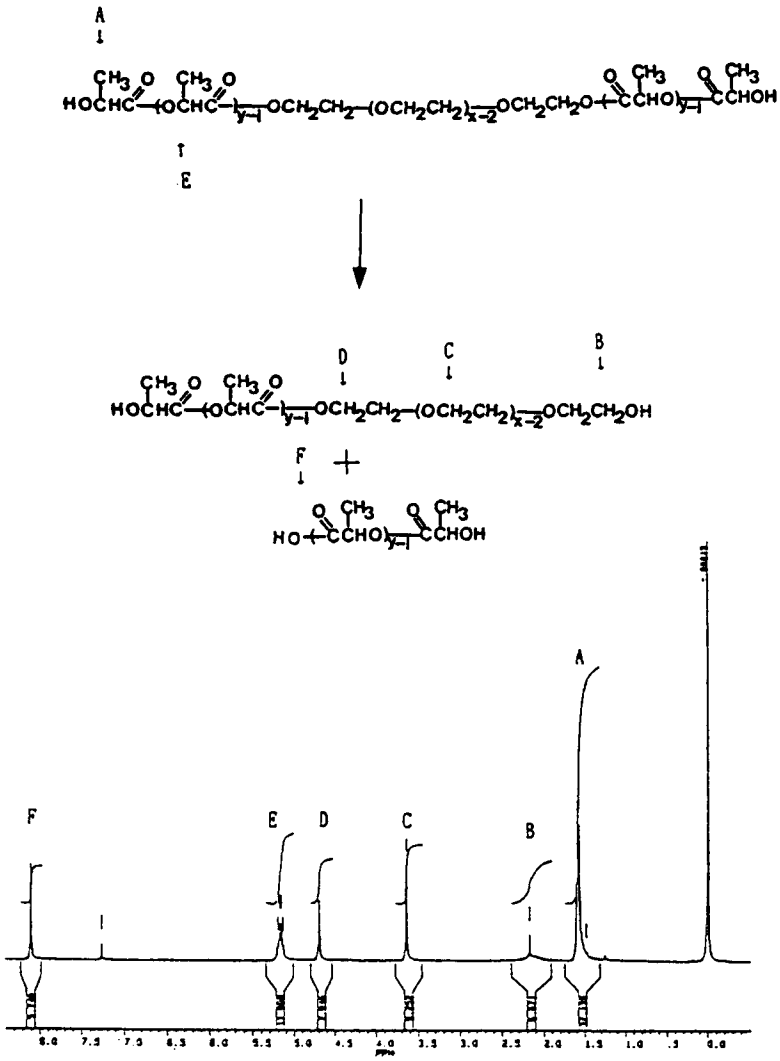

Figure 6 200 MHz ^{1}H-NMR spectrum of PEG/PLLA copolymer, content of PEG in copolymer = 12 wt % ($\bar{M}_n$ of PEG segment = 6000), at 100 h of hydrolysis.

Table II PEG Wt % of PEG/PLLA Copolymers in Various Time of Hydrolysis

Hydrolysis Time (h)	Feed Wt % of PEG Monomer			
	2	3	5	10
0	4.40	5.41	9.63	18.3
40	—	—	9.22	20.38
100	4.54	6.89	12.49	20.27
200	4.89	8.55	12.78	22.15
300	—	8.51	—	—
424	4.71	8.17	12.58	21.25
510	4.65	—	—	—
600	—	8.04	11.58	—

Figure 8 shows carbon chemical shifts at δ = 62.75 and 165.29. It was reported in the literature[20] that δ = 62.75 is due to the secondary carbon atoms on ethylene glycol segment which is near the methylene

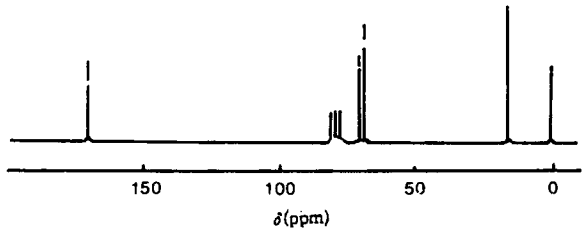

Figure 7 300 MHz ^{13}C-NMR spectrum of PEG/PLLA copolymer, content of PEG in copolymer = 6 wt % ($\bar{M}_n$ of PEG segment = 1000).

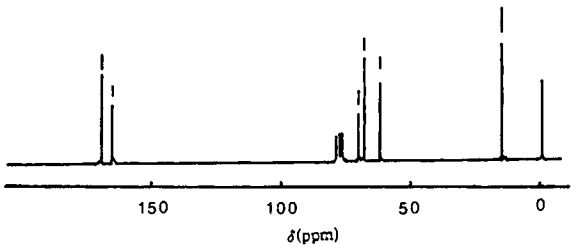

Figure 8 300 MHz ^{13}C-NMR spectrum of PEG/PLLA copolymer, content of PEG in copolymer = 12 wt % ($\bar{M}_n$ of PEG segment = 6000), at 100 h of hydrolysis.

groups connected to ester groups. The δ = 165.29 is believed to be contributed by C=O in the PLLA segment as well.[20]

DSC thermograms of hydrolyzed samples were found to exhibit a distinct shoulder portion in the low temperature range during the melting transition as indicated in Figures 9 and 10. The endothermic peak during the melting transition becomes broader and there is a slight decrease of melting temperature (T_m). The copolymer containing 2% of PEG by weight, does not exhibit the recrystallization. Nevertheless, in Figure 10, the recrystallization appears for degraded PEG/PLLA copolymers undergoing 100 h of hydrolysis. This recrystallization phenomenon occurs in unreacted copolymers with the higher content of PEG. This is a manifestation of the incompatibility of gradually increasing hydrophilic PEG segments with the ester portion. It is inferred that the hydrolysis makes the content of the hydrophilic segments increase. This tends to lead to the poorer miscibility of hard and soft segments. There

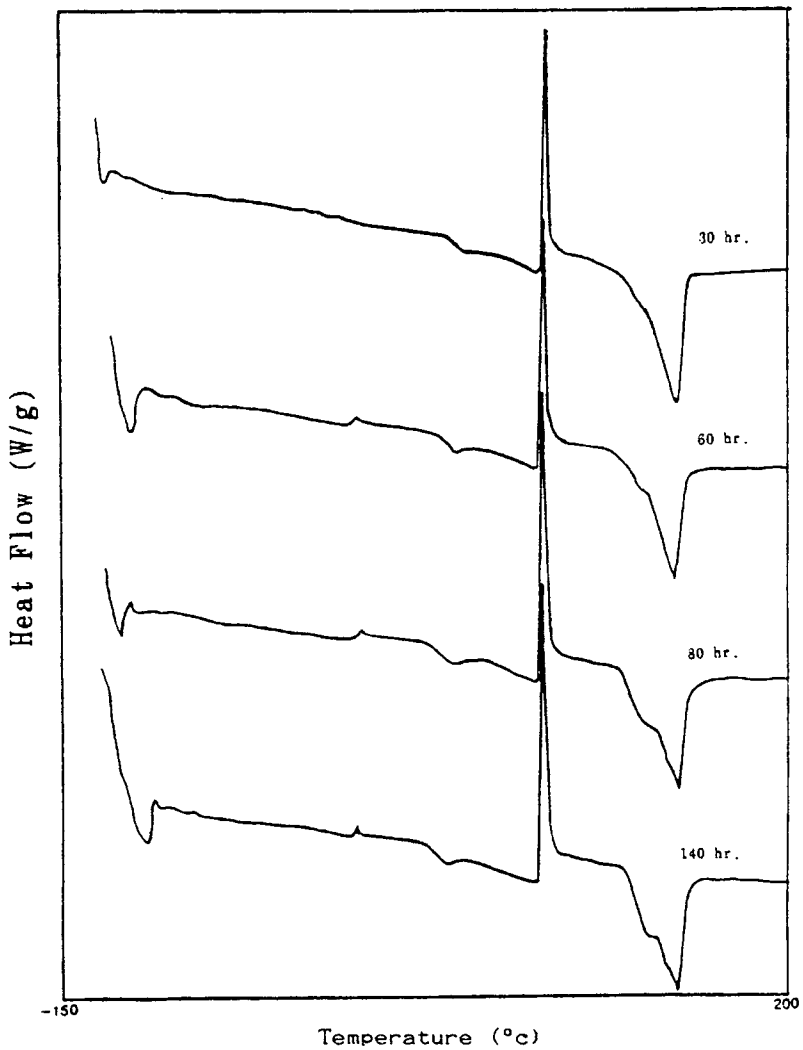

Figure 9 DSC thermograms of PEG/PLLA copolymers with various time of hydrolysis (PEG wt % = 18.3, $\bar{M}_n$ = 2000).

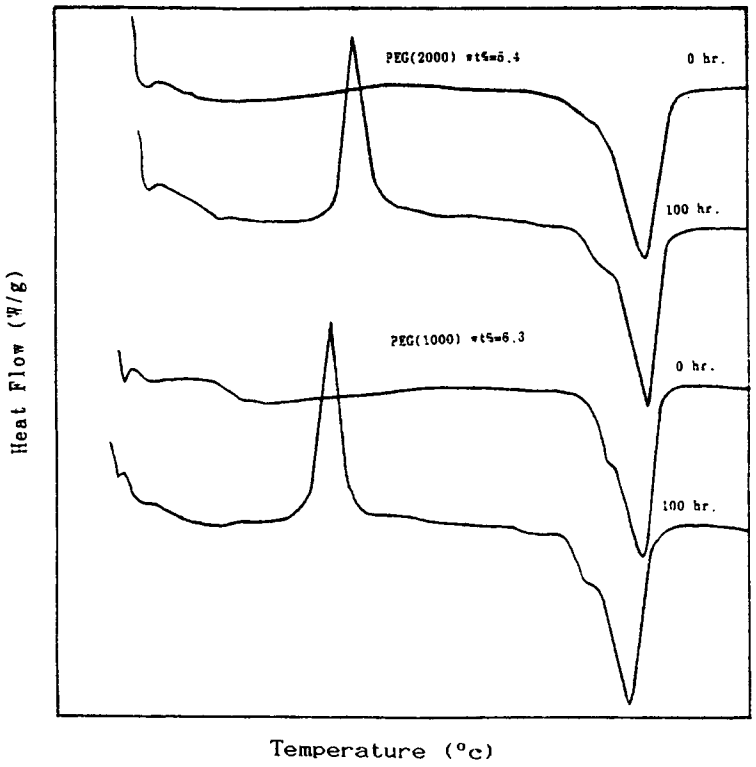

Figure 10 DSC thermograms of two PEG/PLLA copolymers before and after hydrolysis.

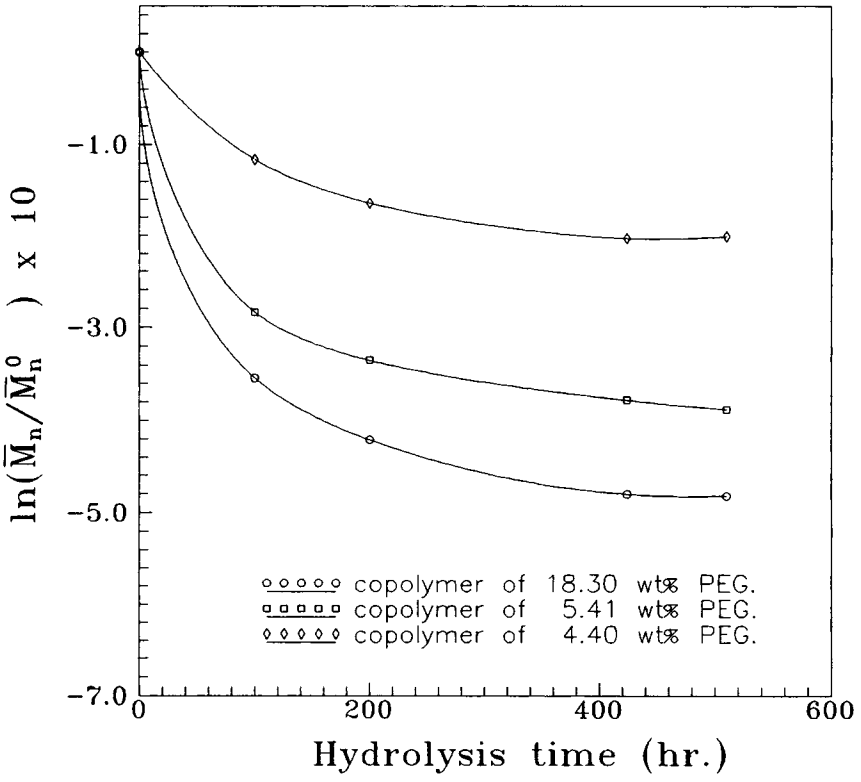

Figure 11 Ln versus hydrolysis time for PEG/PLLA copolymers (chain length of PEG = 2000) with different PEG contents at pH = 7 and 37°C.

is a demixing or recrystallization phenomenon after the content of PEG exceeds a threshold, which is, say, 20 wt % in the PEG/PLLA copolymer with a PEG length of 2000 Da. The hydrolysis rate constants using the first order kinetics are given in Figure 11. At a certain instant of time of the plots of the logarithm of the ratio of the number-average $\bar{M}_n$ to that of the undegraded polymer versus time represents the rate constants. The hydrolysis rate constants are much greater in the first 200 h than those in the latter stage. The higher content of PEG causes the apparent rate to be much greater than that of the PLLA homopolymer.

CONCLUSIONS

The T_m of PEG/PLLA block copolymers are reduced with increasing amounts of PEG. The molecular weights of soft segments has minimal, if any, influence on the T_m. As the content of PEG is reduced below 20% by weight, the melting temperatures are correspondingly reduced by as much as 30°C lower than that for PLLA. In addition, the function of PEG is to increase the hydrophilicity and decomposition rate in copolymers.

The results show that the molecular weight distribution of degraded copolymers appears to be bimodal from the initial unimodal one for the undegraded. The shoulder portion of the endothermic melting peak at the lower temperature side becomes more pronounced. The hydrolysis causes more end groups, such as hydroxyl connected to PEG blocks and carboxyl connected to PLLA blocks, to appear during the initial period of hydrolysis. It is therefore concluded that in addition to the cleavage of lactic acid in the PLLA block during the initial 200 h of hydrolysis, there is a substantial amount of ester linkage between PEG blocks and PLLA blocks to cleave, accelerating the degradation rate in the initial period.

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