

Effect of Composition and Synthetic Route on the Microstructure of Biodegradable Diblock Copolymer, Poly(ϵ -caprolactone-*co*-L-lactide)-*b*-Poly(ethylene glycol)

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Abstract: Biodegradable poly(ϵ -caprolactone-*co*-L-lactide)-*b*-poly(ethylene glycol) (PCLA-*b*-PEG) copolymers were synthesized via solution polymerization by varying the feed composition of ϵ -caprolactone (ϵ -CL) and L-lactide (LLA) (ϵ -CL: LLA=10:0, 7:3, 5:5, 3:7, 0:10). The feed ratio based on weight is in accordance with the copolymer composition except for the case of ϵ -CL: LLA=3:7 (C3L7), which was verified by $^1\text{H-NMR}$. Two different approaches were used for the exceptional case, which is an extension of the reaction time or the sequential introduction of the monomer. A copolymer composition of ϵ -CL: LLA=3:7 could be obtained in either case. The chemical microstructure of PCLA-*b*-PEG was determined using the $^{13}\text{C-NMR}$ spectra and the effect of the sequential structure on the thermal properties and crystallinity were examined. Despite the same composition ratio of the copolymer, the microstructure can differ according to the reaction conditions.

Keywords: biodegradable, copolymer, microstructure, PEG, sequence distribution.

Introduction

Poly(lactide) (PLA) and poly(ϵ -caprolactone) (PCL) is of special interest because of their unique biocompatibility and biodegradable property. These polymers are well established in the pharmaceutical and biomedical fields as a useful biomaterials.¹⁻⁴ Despite of their advantages, high crystallinity and low hydrophilicity of the homopolymer reduce its degradation rate and show poorer compatibility with soft tissues which needs improvement of material for tailor-made biomedical utilization.⁵ Copolymerization and blending⁶⁻⁸ of PLA and PCL is generally adopted method to reduce crystallinity of the polymer. Another approach is introducing hydrophilic component, especially poly(ethylene glycol) (PEG), to the homopolymers of PLA and PCL.⁹⁻¹³ Since attached PEG prevents protein and peptide adsorption onto the matrix surface,^{14,15} biocompatibility as well as degradation property can be enhanced by the incorporation of PEG. Thus copolymers based on PEG and PCL or PLA are

receiving increasing attention on the utilization of biomedical applications such as polymeric micelles, biodegradable nanoparticles and thermally reversible gels.¹⁶⁻²⁰

Recently, new biodegradable copolymer which is based on the both of aforementioned approach, that is random copolymerization of PLA and PCL and introduction of PEG onto aliphatic polyester, has been reported by us and other workers.²¹⁻²⁵ Because the crystallinity which affects the rate of degradation of this kind of biodegradable poly(ester-ether) can be controlled by adjusting the weight ratio of L-lactide and ϵ -caprolactone segments and sequence distribution of segment,^{26,27} not only composition of the copolymer but chemical microstructure is important for the tailor-made application of new polymer.

In this article, we present the synthesis and characterization of diblock copolymer based on the PEG (M_w of 5,000 was selected for the future application for nanoparticle drug delivery system and for the comparison of other previous block copolymers) and random copolymers of poly(L-lactide) (PLLA) and PCL varying feed ratio. Additionally, sequential analysis was determined and effect of chemical microstructure with same composition on the property was discussed.

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Experimental

Materials. L-lactide (LLA) and ε -caprolactone (99+% purity, ε -CL) were obtained from Aldrich (St. Louis, MO). Poly(ethylene glycol) monomethyl ether (MPEG, $M_w = 5,000$) was purchased from Polysciences, Inc and purified by azeotropic distillation. LLA was dissolved in ethyl acetate and recrystallized twice for purification before use. ε -CL was purified using CaH_2 by vacuum distillation prior to use. Stannous 2-ethyl hexanoate ($\text{Sn}(\text{Oct})_2$) which was used for the polymerization catalyst was obtained from Sigma and used as received. Pristine PLLA ($M_w = 40,000$ -70,000) and PCL ($M_w = 43,000$ -50,000), which are used as reference are from Polysciences, Inc. Solvents such as ethyl acetate, toluene, dichloromethane, methanol, and diethyl ether were purchased from Merck. Phosphate buffered saline (PBS) solution was prepared in our laboratory with 0.1 M NaOH, 0.1 M KH_2PO_4 , and 10 wt% NaN_3 . The other chemicals were of pharmaceutical or reagent grade and were used as received.

Synthesis of PCLA-*b*-PEG. Synthesis of the PCLA-*b*-PEG copolymers were performed through ring-opening copolymerization reaction using MPEG and $\text{Sn}(\text{Oct})_2$ as an initiator and a catalyst respectively. The representative synthetic procedure was as follows; 3.0 g of MPEG was dissolved in 20 mL of dried toluene. 7.5 g of LLA and 7.5 g of ε -CL which were dissolved in 50 mL of toluene were added into PEG dissolved solution. 0.06 mL of $\text{Sn}(\text{Oct})_2$ was added and the reactant was under polymerization reaction at 140 °C for 6 h (3 h of solvent reflux followed by additional 3 h without reflux installation to remove solvent used). The products were cooled to room temperature, dissolved in dichloromethane, and then added to excess mixture of methanol and diethyl ether (1:1 volume ratio). Precipitates were washed with mixture of methanol and diethyl ether for three times and thoroughly dried in vacuum for 2 days. The series samples with different feed ratio (based on wt%) of LLA and ε -CL such as 10:0, 7:3, 3:7, and 0:10 (the weight of MPEG was constant.) were synthesized by same method. Total weight of reactant was fixed as aforementioned synthetic procedure for all the series. The schematic illustration of synthetic route is shown in Figure 1.

Characterization of PCLA-*b*-PEG. The structure of synthesized block copolymers with different composition and homopolymers were characterized by ^1H and ^{13}C -NMR spectra (CDCl_3 as solvent) using a Bruker 500 MHz spectrometer with tetramethylsilane as internal standard at room temperature.

DSC measurements were carried out under nitrogen atmosphere (30 mL/min) at a heating rate of 10 °C/min using Dupont TA 2100 DSC thermal analyzer in the temperature range of -150~200 °C.

The wide angle X-ray diffraction (WAXD) spectra were recorded using a Shimadzu GX3 diffractometer with a $\text{CuK}\alpha$ radiation at the scan speed of 3°/min.

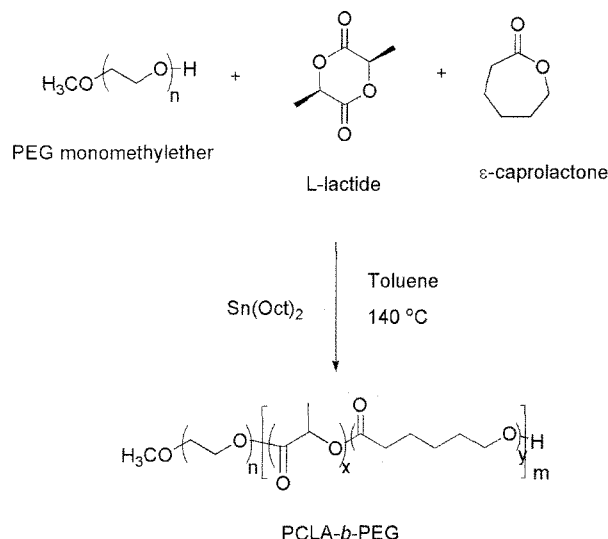


Figure 1. Synthetic scheme for the preparation of the PCLA-*b*-PEG copolymer.

Water Uptake Test and Contact Angle Measurement.

Water uptake for synthesized diblock copolymers was carried out as followed. The samples having each weight ratio of ε -CL : LLA as 7:3, 5:5, 3:7 were dissolved in THF solution. The solution was cast onto Teflon mold and solvent was slowly evaporated for 10 h. Residual solvent was removed by vacuum drying for 1 day. Other samples which were not suitable for film formation by solvent evaporation were prepared by temperature modulated hot press (Sin-II Science Machinery) and quenched at room temperature. Dried films were cut into 1 cm \times 1 cm test sections and weighed (the starting weight W_0). Micrometer (Mitsutoyo micrometer) was used to determine film thickness. Film samples were immersed in PBS solution water and incubated at 37 °C with stirring. Duplicate film samples were incubated and recovered at intervals of 1, 3, 6, 12, 24, 30, 42 h for water uptake measurement. The samples were measured after the removal of water droplets on the surface by absorbent paper. Water uptake measurement was continued until the weight of films remained constant. Polymer solutions (3 wt/vol%, THF) were spin coated (1,770 rpm, home-made) for 3 min onto silicon wafer and water contact angle measurements were performed with contact angle microscope (Model G23, Krüss) using ultra pure water.

Results and Discussion

Characterization of PCLA-*b*-PEG. A series of PCLA-*b*-PEG were synthesized by ring opening polymerization of LLA and ε -CL initiated with hydroxyl group of MPEG using stannous octoate as a catalyst. Chemical structures of PCLA-*b*-PEG copolymers are confirmed by ^1H -NMR analysis. Figure 2 shows the representative ^1H -NMR spectrum

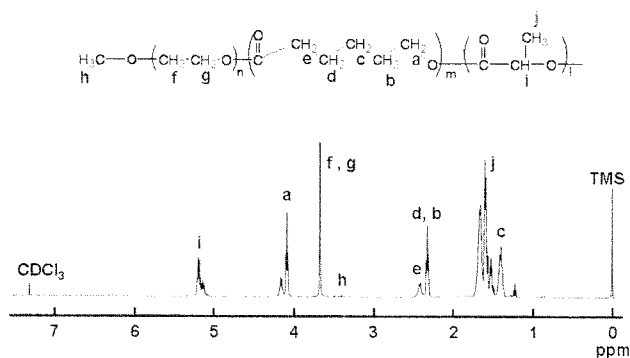


Figure 2. $^1\text{H-NMR}$ spectrum of C5L5 copolymer.

of diblock copolymer with peak assignments. “C5L5” notes PCLA-*b*-PEG copolymer having equal feed weight ratios of ϵ -CL and LLA as 5:5 in the figure. In a same way, “C0L10”, “C3L7”, “C7L3”, and “C10L0” indicate diblock copolymers with the feed weight ratios of reactants are 0:10, 3:7, 7:3, and 10:0 respectively. Copolymerization was confirmed by the peak at 3.65 ppm, corresponding to the methoxy groups of the MPEG. The multiplets at 5.2 ppm and 4.06 ppm correspond to the proton peaks of methyne in lactic unit and the methylene adjacent to oxygen in caprolactone, respectively.^{28,29} High complexities of the peaks result from different L-lactic acid and caprolactone sequences in the polymer backbone. The number-average molecular weights (M_n) of the copolymers could be calculated from the relative intensities of protons at $^1\text{H-NMR}$ spectra. Equation used for calculation is as follows;

$$M_n = 5,000 + \{(I_d/2)/(I_h/3)\} \times 114 + \{(I_f/2)/(I_g/3)\} \times 144$$

Where, I represents the peak area of subscript character.

Characterization results of copolymers are summarized in Table I. From the table, it clearly shows that feed ratio is almost consistent with copolymer composition for C7L3 and C5L5. However, there was difference in the values between feed ratio and copolymer composition for the

C3L7 case. This is due to the large difference in reactivity of LLA and ϵ -CL.³⁰ Since LLA polymerizes more rapidly than ϵ -CL, portion of LLA in copolymer exceeds the ratio of initial feed for the case of higher LLA ratio in the feed. For the systematic evaluation of the properties of the copolymer with the copolymer composition variation, attempts to coincide the feed ratio and final composition of C3L7 are conducted. We tried two different synthetic routes for C3L7 to overcome the reactivity difference of the LLA and ϵ -CL, which are named as “long time-scale synthesis” and “sequential synthesis”. For the first method, MPEG, LLA and ϵ -CL were simultaneously synthesized using the same method we have already described in experimental section but for longer reaction time scales (48 h). “C3L7 SI” indicate C3L7 sample synthesized for 48 h. For the sequential synthesis, ϵ -CL having relatively low reactivity was reacted with MPEG in advance and followed by adding LLA monomer into the reaction medium after 30 min. “C3L7 SE” represents that C3L7 samples synthesized by sequential introduction of three reactants for 6 h. Both of synthetic methods were satisfactory for the preparation of C3L7 copolymer with similar composition as feed ratio and this is shown in Table II.

Comonomer Sequence Distribution. In order to characterize the microstructure of copolymers, sequential analysis of the copolymer using $^{13}\text{C-NMR}$ spectra were performed. Figure 3 shows $^{13}\text{C-NMR}$ spectra of C5L5 and $^{13}\text{C-NMR}$ spectra of carbonyl regions of various PCLA-*b*-PEG copolymers. “LL” and “C” stand for LLA and ϵ -CL units in the copolymer sequence structure, respectively. From the figure, new sequences such as CLC and CLLLC which is due to the scission of one lactidyl (LL) unit into two lactyl (L) units are observed. Transesterification causes the redistribution of copolymer microstructure and generates new sequences. The relative signal intensity of each triad sequence reflects the monomer unit sequence distribution of the copolymer in the figure. $^{13}\text{C-NMR}$ spectra positions and assignments of C7L3, C5L5, C3L7, and C3L7 SI samples showed good agreement with previous work based on poly[(L-lactide)-

Table I. Composition and Characterization Results of PCLA-*b*-PEG^a

Samples ^a	f_L/f_C^b	F_M/F_L^d	$10^{-3} M_n$	T_g (°C)	T_m (°C)	ΔH_m (J/g)
PCL	-	-	-	-63.9	57.7	81.4
C10L0	0 / 100	0 / 100	50	-64.4	56.3	100.1
C7L3	30 / 70	28 / 72	72.8	-44.6	42.7	8.6
C5L5	50 / 50	49 / 51	52	-29.7	28.3	3.9
C3L7	70 / 30	86 / 14	32	-30.7, 13.2	55.6, 140.6	0.3, 26.7
C0L10	100 / 0	100 / 0	45.3	7.9	59.6, 169.2	0.4, 52.9
PLA	-	-	-	61.5	175.2	50.4

^aMolecular weight of MPEG used was set to 5,000. ^bPCLA-*g*-PEG was abbreviated as CxLy and x, y represents the weight ratio of ϵ -caprolactone and L-lactide, respectively. ^c% weight ratio of the feed composition for diblock copolymer synthesis. Where L is L-lactide and C is ϵ -caprolactone, respectively. ^d% weight ratio of L-lactide and ϵ -caprolactone in the diblock copolymer calculated from the $^1\text{H-NMR}$ spectrum.

Table II. Characterization of C3L7 with Different Synthetic Conditions^a

Polymer	F_M/F_I^b	$10^{-3} M_n$	T_g (°C)	T_m (°C)	ΔH_m (J/g)
C3L7	85.6 / 14.4	32	-30.7, 13.2	55.6, 140.6	0.3, 26.8
C3L7 SE	76.2 / 23.8	37	-34.7, 8.9	49.7, 134.5	0.4, 21.4
C3L7 SI	70.7 / 29.3	52.1	10.3	52.0, 117.9	0.6, 0.5

^aFeed composition was fixed as ϵ -caprolactone : L-lactide = 3:7 by weight ratio.

^b% weight ratio of L-lactide and ϵ -caprolactone in the diblock copolymer calculated from the ¹H-NMR spectrum.

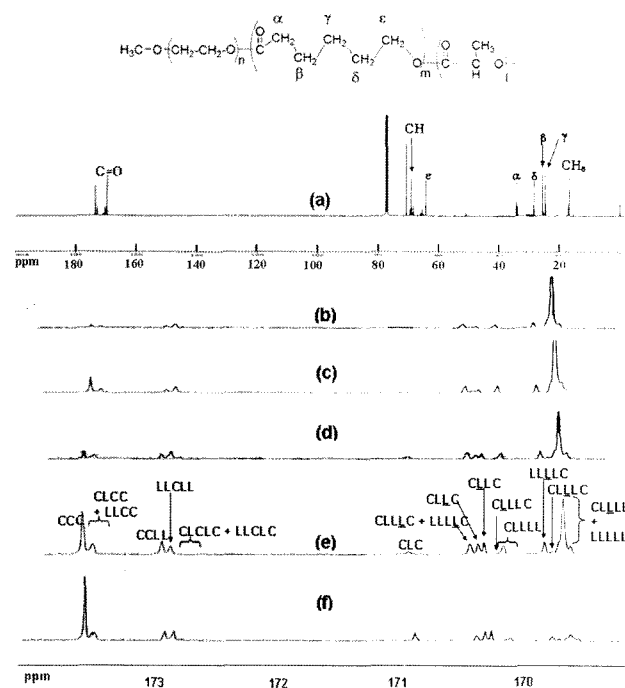


Figure 3. (a) ¹³C-NMR spectra of C5L5 and carbonyl regions in ¹³C-NMR spectra for (b) C3L7; (c) C3L7 SE; (d) C3L7 SI; (e) C5L5; (f) C7L3 samples.

co-(ϵ -caprolactone)] polymerized using $Al(C_2H_5)_3 + Zn(C_2H_5)_2 + H_2O$ initiator.³¹ However, for the case of C3L7 SE sample, transesterification occurred on the basis of lactidyl (LL) and caproyl (C) units (first mode of transesterification) contrary to others which underwent transesterification on the basis of lactyl (L) and caproyl (C) units as structural units (second mode of transesterification). Table III summarizes the frac-

tional sequence distribution of the series samples of PCLA-*b*-PEG copolymers on the lactyl (L) unit. The average comonomer sequence length, l_{LL} and $l_{\epsilon CL}$ were calculated from the comonomer sequence distribution data by integrating ¹³C-NMR peak areas. We selected triad sequences including the lactyl unit "L" instead of "LL" to consider the transesterification effect on the calculation of l_{LL} and $l_{\epsilon CL}$ values. Average comonomer sequence lengths of LLA and ϵ -CL related with the intensities of triad sequences are calculated by the following equations:^{31,32}

$$l_{LL} = \frac{(X_{LLL} + X_{LLC} + X_{CLL} + X_{CLC}) \times 0.5}{X_{CLC} + (X_{LLC} + X_{CLL}) \times 0.5}$$

$$l_{\epsilon CL} = \frac{(X_{LCL} + X_{CCL} + X_{LCC} + X_{CCC}) \times 0.5}{X_{LCL} + (X_{CCL} + X_{LCC}) \times 0.5}$$

The calculated l_{LL} and $l_{\epsilon CL}$ values are listed in Table IV. These results show the tendency that the increment degree of l_{LL} is larger than that of $l_{\epsilon CL}$ as the feed amount of each unit increases and the similar result was reported from other workers.³³ This tendency can be explained using the definition and formula of the reactivity. Since the reactivity of LLA ($r_L = 34.7$ at 130 °C) is much higher than that of ϵ -CL ($r_C = 0.72$ at 130 °C),³⁰ LLA monomer units can react with other LLA blocks more easily than with ϵ -CL blocks after chain scissions during transesterification. So it seems that average comonomer sequence length of LLA monomer units can be longer relatively and our result is also agree with that point, but l_{LL} of C3L7 SI is much smaller than that of C3L7 SE or C3L7 in spite of same feed weight ratio of LLA monomer. This difference comes from dissimilar reaction condition and reaction time variation. That is, as reac-

Table III. Fractional Sequence Distribution of PCLA-*b*-PEG Copolymers Based on the Lactyl (L) Unit

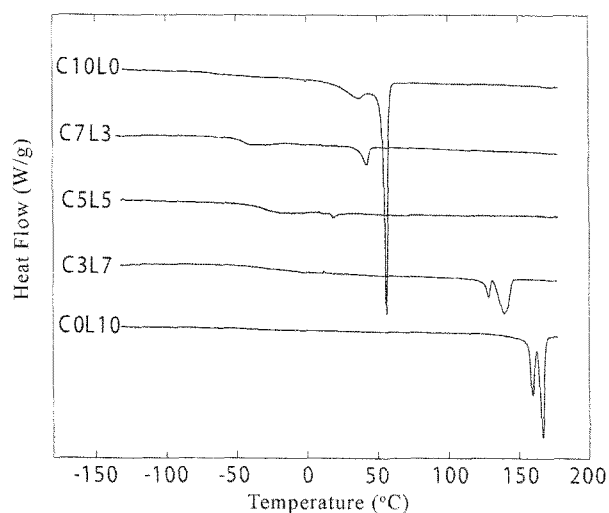
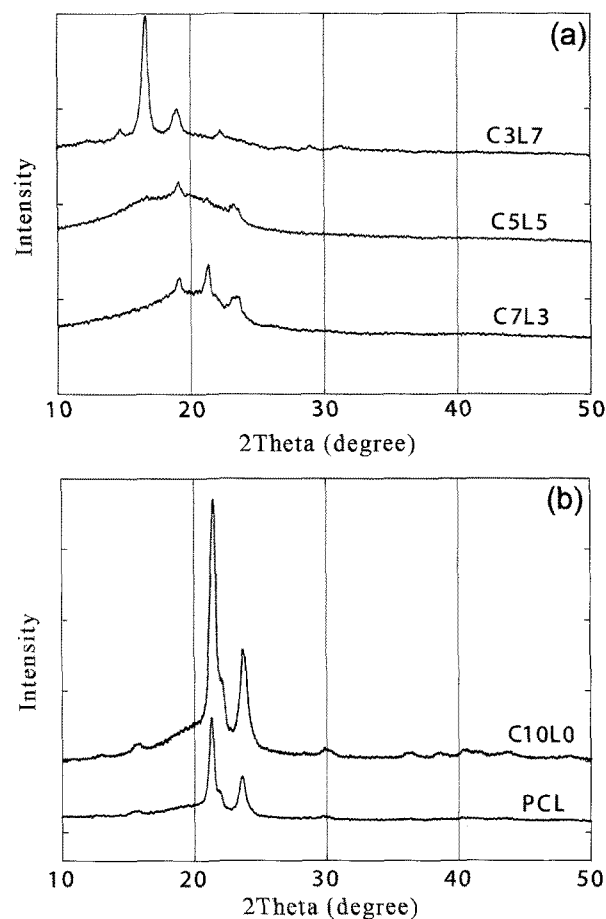
Sample	<i>L</i> -LA Unit				ϵ -CL Unit			
	X_{LLL}	X_{LLC}	X_{CLL}	X_{CLC}	X_{CCC}	X_{CCL}	X_{LCC}	X_{LCL}
C3L7	0.854	0.073	0.073	0.000	0.188	0.197	0.222	0.393
C3L7 SE	0.880	0.060	0.060	0.000	0.398	0.131	0.175	0.297
C3L7 SI	0.703	0.138	0.135	0.025	0.210	0.226	0.179	0.386
C5L5	0.641	0.168	0.167	0.025	0.500	0.175	0.187	0.139
C7L3	0.387	0.241	0.240	0.133	0.539	0.176	0.172	0.109

Table IV. Average Comonomer Sequence Lengths of LLA and ϵ -CL Units in the Sequential Structure of PCLA-*b*-PEG Diblock Copolymers

Sample Name	l_{LL}	$l_{\epsilon CL}$
C3L7	6.84	1.66
C3L7 SE	8.33	2.22
C3L7 SI	3.10	1.70
C5L5	2.60	3.09
C7L3	1.34	3.52

tion time is increased, copolymer is more randomized and less crystallized by the second mode of transesterification. So when three components are synthesized sequentially for short time, their copolymers tend to be more blocky microstructures. So we confirmed that we could adjust the average comonomer sequence length and transform the microstructure of copolymer by changing not only feed weight ratios but also reaction condition.

Thermal Analysis of PCLA-*b*-PEG. Glass transition temperature (T_g) and melting point (T_m) of copolymers are physical properties that are connected with the microstructures of synthesized copolymers. The melting behaviors of diblock copolymers with different ratios are investigated by DSC. PLLA and PCL homopolymers are also included for comparison. Figure 4 and Table I show the characteristic DSC curves and thermal behavior results of the PCLA-*b*-PEG. It is clearly shown that heat of fusion is dramatically decreased when one component is randomized. When the heat of fusion of diblock copolymer were compared with corresponding homopolymer, C0L10 and C10L0 which is composed of only pure LLA or ϵ -CL with MPEG are higher than those of homopolymers. Since, melting peak of pristine MPEG and PCL is observed around 60 °C, WAXD


Figure 4. DSC curves of PCLA-*b*-PEGs.

Figure 5. X-ray diffractograms of (a) PCLA-*b*-PEG with different composition and (b) PCL-*b*-PEG (C10L0) and PCL homopolymer.

experiments were performed to confirm higher crystallinity of C10L0 compared to that of PCL homopolymer. Figure 5 illustrates the crystalline structure of each copolymer. The MPEG ($M_n = 5,000$) diffraction pattern exhibits two high characteristic peaks located at $2\theta = 23.0^\circ$ and 19.0° ³³ while PCL showed two main peaks at 21.4° and 23.7° and a smaller one at 21.8° . It can be also seen that the WAXD intensities of C10L0 are much higher than those of PCL in Figure 5(b). It is thought that flexibility of PEG induced higher crystallization of C0L10 and C10L0 diblock copolymers compared that of homopolymers. C5L5 sample having equal wt. ratios of LLA and ϵ -CL is most randomized and so we can observe almost amorphous region except MPEG diffraction peaks. We could confirm that PCLA-*b*-PEG is more suitable in biomedical applications where amorphous or low crystallinity is needed compared to simple diblock copolymers consisting of hydrophilic MPEG and homopolymer of aliphatic ester.

Table II illustrates the thermal characteristics of C3L7 diblock copolymer with different synthetic conditions. C3L7 and C3L7 SE copolymers synthesized for relatively shorter reaction time (6 h) shows two T_g s, while those of C3L7 SI

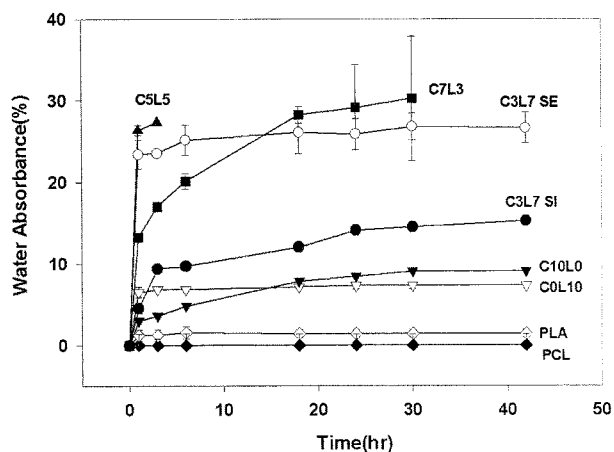


Figure 6. Water uptake profiles of PCLA-*b*-PEGs at 37°C.

which allowed to have longer reaction time reflect only single T_g . Block copolymer usually exhibits two glass transition temperatures which represent each domain in contrast to a random one having the unique T_g . Single T_g of C3L7 SI indicates that more random structure could be obtained for longer reaction time. This is in agreement with the sequence length calculated by microstructure analysis in Table IV.

Water Uptake of PCLA-*b*-PEG. Figure 6 shows the water uptake profiles with time which are calculated by the following equation.

$$\text{Water Uptake}(\%) = \frac{W_t - W_d}{W_d} \times 100$$

Where, W_t represents the weight at time is t and W_d the weight of dry film at initial state.

Diblock copolymers such as C10L0 and C0L10 reveal smaller content of water adsorption than that of random copolymers but larger content than that of homopolymers as expected. In the case of copolymers randomized by combining lactyl and caproyl units alternately during their synthesis the crystallinity is reduced and thus randomized diblock copolymers show high water uptake (%) results. Interestingly, for the cases of C7L3 and C5L5 copolymers, the films were torn apart after 5 and 30 h respectively and so we couldn't continue the experiment until their adsorption equilibriums in two cases. However, the maximum water uptake result appears in the case of C5L5 as shown in figure, because the melting point of C5L5 (28.3 °C) is below experiment temperature (37 °C) and it shows smallest heat of fusion together with randomized structure (smallest disparity between I_{LL} and $I_{\epsilon CL}$). These are seemed to be the reason for higher water absorption. Water contact angle was measured for the copolymer samples prepared by spin coating on slide glass and the result is provided in Figure 7. Lowest contact angle was observed for the C5L5 sample and this also shows hydrophilic character at the surface compared to other

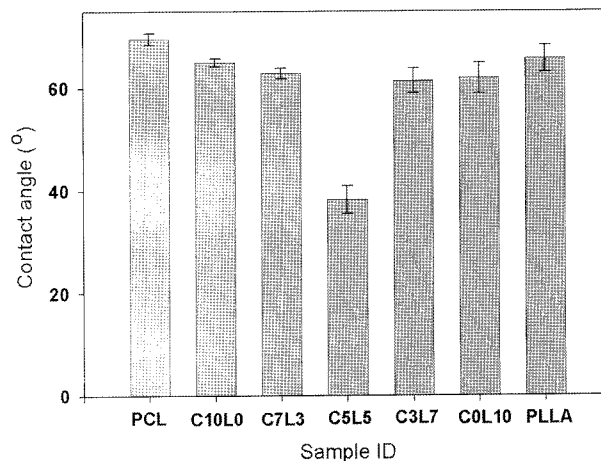


Figure 7. Water contact angle of the PCLA-*b*-PEG copolymer films.

samples. This is in agreement with the high water uptake obtained for C5L5. Block copolymers show low water contact angle because PEG chains concealed in the rich amount of LLA or ϵ -CL region extend outward as water drop is applied to the film surface.¹¹

Conclusions

A series of block copolymers based on polyester and polyether were successfully prepared by solution polymerization. From ¹H-NMR data, we found that product compositional weight ratios were affected by not only feed weight ratios but the differences in the reactivity of each reactant. We could also generate a variety of microstructures and adjust the degree of randomization in each copolymer during the transesterification reaction by changing the feed ratios of reactants or their reaction time and by adopting different ways to introduce the reactants into the reaction medium. We proved that average comonomer sequence lengths calculated from ¹³C-NMR spectra analysis could be very important clues in predicting the basic properties and microstructures of diblock copolymers newly synthesized through ring-opening polymerization.

It was also demonstrated by DSC results that thermal properties of C3L7 and C3L7 SE synthesized during relatively shorter reaction time are dissimilar to those of C3L7 SI which reacted during long time in spite of same feed composition. Water uptake results revealed that average comonomer sequence lengths, thermal properties such as crystallinity and hydrophilicity affected their water absorption abilities of copolymers. In conclusion, diblock copolymers synthesized using MPEG, LLA, and ϵ -CL monomers are very attractive in various biomedical applications because of the reduction of crystallinity and the enhancement of hydrophilicity as PLGA and PEG block copolymers. Information of the microstructure is important to obtain tailor-made biomaterials for the specific applications.

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