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Synthesis and characterization of poly(ethylene glycol)/poly(L-lactic acid) alternating multiblock copolymers

Kang Moo Huh, You Han Bae*

Department of Materials Science and Engineering. Kwangju Institute of Science and Technology, 572 Sangam-dong, Kwangsan-ku, Kwangju 506-712, South Korea

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Abstract

Thermoplastic hydrogels of alternating multiblock copolymers, consisting of poly(ethylene glycol) (PEG) and poly(L-lactic acid) (PLLA), were synthesized. Dicarboxylated oligomeric PLLAs were synthesized by the condensation reaction of L-lactic acid in the presence of succinic acid. Changing the feed ratio of L-lactic acid to succinic acid controlled PLLA molecular weights. Alternating multiblock copolymers with different block lengths of PEG and PLLA were obtained from the polycondensation reaction between PEG and dicarboxylated-PLLA in the presence of dicyclohexyl carbodiimide and *N*-dimethyl aminopyridine as catalysts. The chemical compositions of dicarboxylated PLLAs and multiblock copolymers were verified by ^{1}H-NMR and FT-IR, and the molecular weight and distribution were measured by gel permeation chromatography. DSC thermograms showed that there existed a high degree of phase mixing, as well as microphase separation in the multiblock copolymer, demonstrated by a large T_g peak from the amorphous phase-mixing domain and a small T_m peak from crystalline microdomains of the PLLA component. The block copolymers with low molecular weights were water-soluble and clouded at a temperature which is associated with a lower critical solution temperature (LCST) phenomonon. However, the high molecular weight polymers could swell in water and their optical transparency was influenced by temperature. This observation can be attributed to an enhanced hydrophobic interaction between hydrophobic moieties in the polymer chains, caused by an increase in temperature. The weight swelling ratio (absorbed water/polymer) of the polymers was controlled by polymer composition and molecular weight. These block copolymers may offer potential for applications in drug delivery and various other biomedical projects. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Poly(ethylene glycol) poly(L-lactic acid); Alternating multiblock copolymers; Physically cross-linked hydrogel

1. Introduction

Biodegradable polymers have been extensively investigated as polymeric drug carriers [1–6] and for other biomedical applications [7–10]. They have the advantage of not requiring surgical removal after use. Poly(L-lactic acid) (PLLA) [11–13] and its copolymer [14–16] have been very attractive materials for such works due to their controlled biodegradability and the safety of their degraded products. One useful strategy for modifying the physical and biological properties of PLLA has been to incorporate other proper components. Much attention has thus been paid to the preparation of di- or triblock copolymers of PLLA with poly(ethylene glycol) (PEG). Rashkov et al. [17,18] have synthesized PLA/PEG/PLA triblock copolymers by polymerizing L-lactide in the presence of dihydroxy PEG as a macroinitiator using Zn metal or CaH_2 as catalysts. The incorporation of PEG improved the hydrophilicity and reduced the brittleness of PLLA.

In this paper, a new copolymerization method is presented, using a coupling reaction to incorporate PEG into PLLA. Our method differs from that presented by Chen et al. [19], who produced multiblock copolymers based on PEG and PLLA via the ring opening copolymerization of L-lactide/ethylene oxide using various catalysts including isobutylalumioxane. They successfully synthesized various multiblock copolymers with different block lengths and molecular weights, by changing reaction conditions such as temperature, time, solvent and catalyst. However, adequate control of structural variables in the polymer chains, such as block length and distribution, was not easy using that method, making it difficult to design tailor-made polymers with desired properties. The coupling approach, by contrast, using well-defined prepolymers in an alternating fashion

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* Corresponding author. Tel.: +82-62-970-2305; fax: +82-62-970-2304.
E-mail address: yhbae@matla.kjist.ac.kr (Y.H. Bae)

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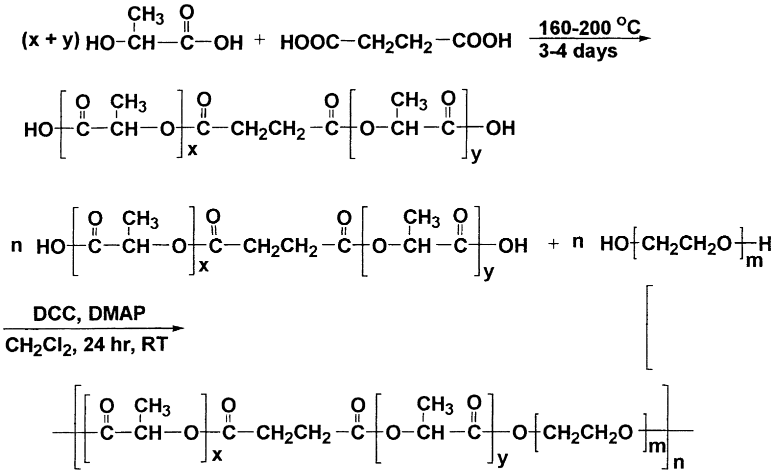

Scheme 1. Synthetic route for PEO/PLLA multiblock copolymer.

makes it easier to tailor polymer properties for a specific application.

Multiblock copolymers are designed to be degraded into non-toxic products. Short PEG chains can be readily excreted through the kidney and monomeric acids broken down from PLLA by hydrolysis can be eliminated through normal excretory routes. In addition to these properties, the microphase-separated structure which consists of hydrophilic soft and hydrophobic hard domains imparts thermoplastic hydrogel properties in an aqueous medium. Thermoplastic hydrogels, which can be processed in melt or solution, have advantages over thermoset hydrogels, which have often been used for biomedical purposes.

This study involves the synthesis and characterization of both oligomeric PLLAs with carboxylated end-groups by direct condensation polymerization and multiblock copolymers by a polycondensation reaction between PEG and PLLA in the presence of dicyclohexyl carbodiimide and *N*-dimethylaminopyridine. The PEG/PLLA alternating multiblock copolymer should be useful as a biomaterial because of its processability, biodegradability and biocompatibility. The block copolymers can be applied to drug delivery carriers and implantable membranes where fast degradation is required. The detailed degradation study is under progress.

2. Experimental

2.1. Materials

Poly(ethylene glycol)s (PEGs) with number average molecular weights (g mol^{-1}) of 3400, 2000, 1500 and 1000 (Aldrich) were used after drying under vacuum at 80–90°C for over 12 h. Methylene chloride was dried over CaH_2 and distilled. L-lactic acid (85% aqueous solution, Aldrich), succinic acid (Sigma), *N*-dimethyl aminopyridine (DMAP, Aldrich) and dicyclohexyl carbodiimide (DCC, Aldrich) were used as received, without further purification.

The synthetic routes for dicarboxylated PLLAs and the coupling reaction for the PEG/PLLA alternating multiblock copolymers are illustrated in Scheme 1.

2.2. Preparation of dicarboxylated PLLA

To obtain the desired molecular weights of PLLA, 100 g of L-lactic acid aqueous solution was placed into a two-neck flask with a predetermined amount of succinic acid. A stream of nitrogen was directed through the reaction flask and the temperature was gradually raised to 190°C–200°C in a thermostat oil bath. After 24 h of dehydration under these conditions, nitrogen flushing was discontinued, and a high vacuum was applied for 3–5 days. The resulting product was dissolved in acetone and then precipitated in distilled water, followed by drying in a vacuum oven for 2–3 days.

2.3. Polycondensation reaction

PEG (5 mmol) and equimolar dicarboxylated PLLA were dissolved in 70ml of anhydrous methylene chloride. DMAP was added to the solution as a catalyst (1.3 mmol) and DCC (13 mmol) was added as a coupling agent. The reaction flask was kept in a dry nitrogen environment at room temperature while stirring. After 10 min, a white dicyclohexylurea (DCU) precipitate formed as a reaction by-product. Reaction conditions were maintained for 12 h. The precipitated DCU was filtered off. The filtrate was concentrated under reduced pressure and then poured into a large excess amount of cold diethyl ether with vigorous stirring. The precipitate was again dissolved in methylene chloride and precipitated in the mixture (9:1 in volume fraction) of diethyl ether and methanol for purification. The purified product was dried in vacuum oven for 24 h. The various multiblock copolymers with different compositions were prepared using the same procedure.

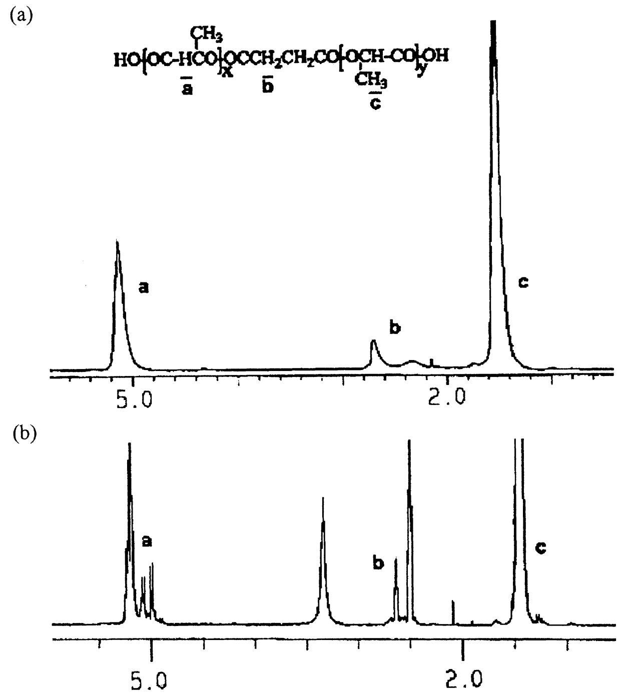

Fig. 1. ^{1}H-NMR spectra of dicarboxylated PLLA: (a) in $CDCl_3$; and (b) in DMSO-d_6.

2.4. Measurements

The chemical compositions of dicarboxylated PLLAs and multiblock copolymers and the block ratios of PEG and PLLA blocks in multiblock copolymers were characterized by ^{1}H-NMR and FT-IR (Perkin-Elmer 200 series). ^{1}H-NMR spectra were recorded using the JEOL JNM-LA 300 WB FT-NMR system operating at 300 MHz. The polymers were dissolved in $CDCl_3$ with tetramethylsilane as an internal reference. The molecular weights and distributions of the polymers were measured by gel permeation chromatography which was conducted using a Waters LC system coupled with a Waters 410 Differential Refractometer. Polymer samples were dissolved in tetrahydrofuran (HPLC grade) at a concentration of 0.3 wt.%. THF as an eluent was degassed under reduced pressure and eluted at 1.0 ml min^{-1} through three Waters Styragel columns (HR1, HR2 and HR4). The number and weight average molecular weights of the polymers were determined by universal calibration obtained from polystyrene reference samples having narrow molecular weight distributions. The internal and column temperatures were kept constant at 36°C. A differential scanning calorimeter (DSC) (TA Instruments 2100) was used to measure thermal properties of the polymers. The thermograms covered the −80°C–150°C temperature range in a nitrogen atmosphere at a 10° min^{-1} heating rate. The first scan measured the melting endotherm, and the second measured T_g values. The clouding points for the aqueous polymer solutions were measured by a Varian CARY 1E UV-VIS spectrophotometer equipped with Varian CARY temperature controller. The % transmittance was measured from visible sources at 500 nm, with a temperature increase of 0.5°C min^{-1}. Solvent casting in acetone was used to prepare the polymer films for transmittance measurement. Each 10 wt.% polymer in acetone was poured into a glass casting mold coated with Teflon and dried in ambient conditions for 1 day and then under vacuum for 2 days. The dried film was cut to the desired dimensions and attached onto the lateral inside surface of a UV cell, followed by the addition of a pH 7 buffer solution. When the swelling reached the equilibrium state, the transmittance of the hydrogel was measured at a visible wavelength of 500 nm with a temperature increase at the rate of 0.5° min^{-1}. To measure the weight swelling ratio (absorbed water weight per unit weight of polymer) of the polymers, the polymer films were cut into squares of about 1 cm × 1 cm (0.4 mm in thickness) and then dried at room temperature in vacuo for 24 h. After immersion in a pH 7 buffer solution at the desired temperatures for fixed time periods, the weights of the swollen polymers were measured after removal of excess surface water by patting the samples with filter paper.

3. Results and discussion

3.1. Synthesis and characterization

To obtain linear multiblock copolymers, the starting oligomers must have reactive end groups for consecutive coupling reactions. Various dicarboxylated PLLAs of different molecular weights were obtained from the polycondensation of L-lactic acid in the presence of succinic acid. The L-lactic acid/succinic acid mole ratio in the feed ranged from 6/1 to 50/1.

Fig. 1 shows the typical ^{1}H-NMR spectra of dicarboxylated PLLA measured in $CDCl_3$ [Fig. 1(a)] and DMSO-d_6 [Fig. 1(b)]. ^{1}H-NMR spectra of dicarboxylated PLLAs in $CDCl_3$ were used to determine the molecular weight of the polymer from the integration ratio of resonances at 5.14 ppm originated from CH of the PLLA block and CH_2CH_2 of the succinic acid residue at 2.70 ppm. The MW of the polymer was deduced from the integration ratio (= $DP_{PLLA}/4$) by using the following relationship:

$$M_{nPLLA} = DP_{PLLA} \times 72 + 100_{\text{succinic acid}}$$

The molecular weight of dicarboxylated PLLA was controlled by changing the feed ratio of L-lactic acid and succinic acid. For the use of dicarboxylated PLLA as a macromonomer in polycondensation reactions, end-group characterization is of great importance. The funtionality of the end-groups of the polymer may be a significant factor affecting the molecular weight of multiblock copolymers. As shown in Fig. 1(b), it was found that, in contrast to the spectrum from $CDCl_3$, the characteristic peaks from the end-groups of a dicarboxylated PLLA were well defined. Both the carboxyl and hydroxyl end units were of interest

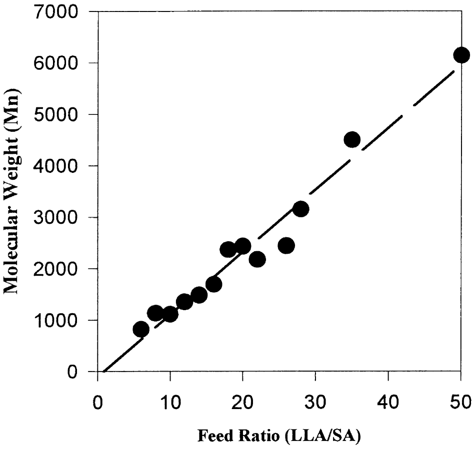

Fig. 2. Molecular weight dependence of dicarboxylated PLLA on the feed ratio of L-lactic acid to succinic acid.

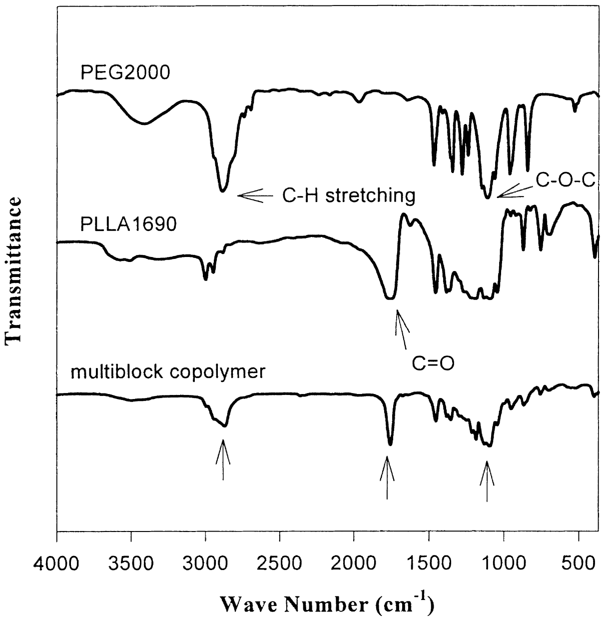

Fig. 3. Infrared spectra of PEG ($M_n = 2000$), dicarboxylated PLLA ($M_n = 1690$) and their multiblock copolymer ($M_n = 42\ 300$).

for estimating the content of the carboxyl end group. Espartero et al. [20] have given a detailed report on NMR analysis of low molecular weight PLLAs. They showed the well-resolved CH contributions of both hydroxyl and carboxyl end units, appearing at 4.20 and 4.99 ppm, respectively, in oligomeric PLLAs. Our results were in good agreement with their results except for the fact that we observed no contributions of the hydroxyl end units. However, there exists a very small peak from the CH contribution of the hydroxyl end units. As a result, the content of the carboxyl end units of the PLLAs, which was calculated by the integration of the peaks from the CH contributions of both the carboxyl and hydroxyl end units, were evaluated to be higher than 95%.

The molecular weights of the dicarboxylated PLLAs were controlled by changing the feed ratio of L-lactic acid and succinic acid. As shown in Fig. 2, the molecular weights were found to be inversely proportional to the amount of succinic acid added in the range of feed ratio applied. The adjustable block length of the PLLA macromonomer may lead to the easy control of physicochemical properties in the multiblock copolymers. The polydispersity of dicarboxylated PLLA obtained from GPC ranged from 1.27 to 1.67.

The multiblock copolymers were synthesized through the polycondensation of two bifunctional macromonomers, dihydroxy PEG and dicarboxylated PLLA, in the presence of catalysts. The results of the multiblock copolymer synthesis are summarized in Table 1. The block ratio of relatively high molecular weight polymers approached 1. The polymer yields, however, ranged from 80% to 90% which includes polymer loss during the recovery process. Thus the actual yield is believed to be around 85% ~ 95% for the high molecular weight block copolymers. Fig. 3 shows the IR spectra of PEG, dicarboxylated PLLA and their multiblock copolymer. For PLLA, an ester carbonyl band appears at around 1760 cm^{-1} and for PEG a C–H stretching band

Table 1
Molecular weight, molecular weight distribution and block ratio of PEG/PLLA multiblock copolymers. nd: not determined

Block length (PEG/PLLA)	Yield (%)	M_n[a]	M_w[a]	M_wD[a]	Block ratio[b] (PEG/PLLA)
1000/1690	82	19 400	26 100	1.35	1.02
1500/1690	nd	14 000	23 100	1.65	1.05
2000/820[c]	77	8800	15 300	1.74	1.25
2000/1130[c]	80	14 800	21 900	1.48	0.95
2000/1130	nd	31 100	40 100	1.29	1.07
2000/1430[c]	nd	9300	13 200	1.42	1.60
2000/1480	nd	31 400	41 400	1.32	1.13
2000/1690	86	33 100	41 300	1.25	1.10
2000/1990	84	25 000	33 400	1.34	0.97
2000/2170	87	15 700	23 800	1.52	0.94
2000/3150	90	12 300	21 000	1.71	1.18

[a] Determined by GPC.

[b] Calculated from ^{1}H-NMR spectra.

[c] Water-soluble block copolymers.

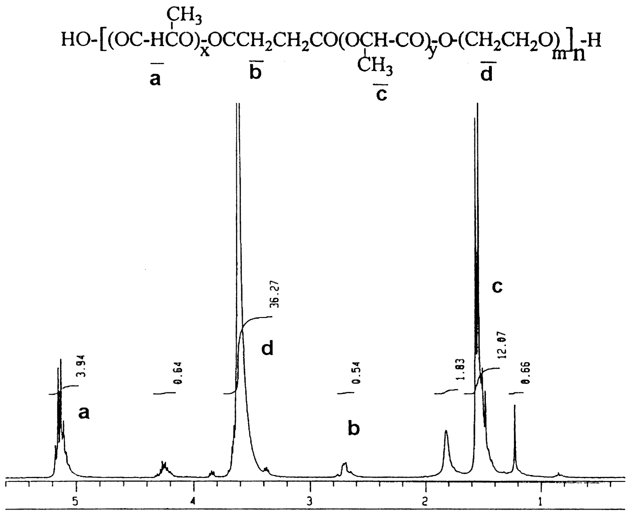

Fig. 4. ^{1}H-NMR spectrum of PEG/PLLA multiblock copolymer in $CDCl_3$.

appears at 2885 cm^{-1}. It is clearly found that the multiblock copolymer exhibits these two characteristic peaks corresponding to each prepolymer.

The ^{1}H-NMR spectrum shown in Fig. 4 ascertains the chemical composition of the PEG/PLLA multiblock copolymer. The peaks at 5.1 ppm (CH) and 1.5 ppm (CH_3) belong to PLLA blocks and the peak at 3.6 ppm is characteristic of main chain methylene units in the PEG blocks. The α-methylene protons of PLLA-connecting ethylene glycol units (PLLA-COO-CH_2-) appear at 4.25 ppm, together with CH protons from the hydroxylated lactyl end units. Methyl protons in these end units appear at 1.25 ppm and are distinguishable from other methyl groups. These results correspond well to those reported in the literature for PEO/PLLA block copolymers of different block types [17, 18, 21]. The integration values of the CH_2 peaks from PEG and CH from PLLA were used for calculation of the PEG/PLLA block ratio, using the following equation:

$$\text{Block ratio} = (\text{the number of PEG blocks / the number of PLLA blocks}) = [X / (4 \times DP_{PEG}) / (Y/DP_{PLLA})]$$

where X is the integration value for the PEG ethylene units peak and Y is that of PLLA's CH peak.

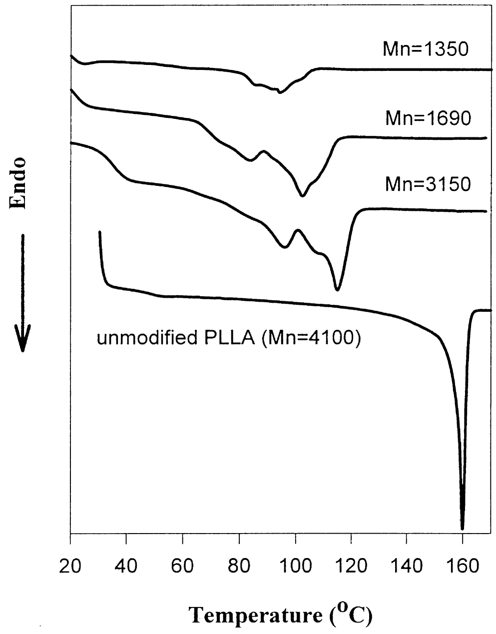

Fig. 5. DSC thermograms of dicarboxylated PLLAs and unmodified PLLA.

3.2. Thermal properties

The thermal properties of dicarboxylated PLLAs were traced. Results from DSC measurement are represented in Fig. 5. Depending on the molecular weight of the polymer, glass transition appeared in the range of 15°C–35°C and broad melting endothermic peaks ranged from 60°C to 120°C. It is of interest to note that considering the typical T_m (120°C–160°C) of normal PLLAs with equivalent molecular weights, the melting temperatures of dicarboxylated PLLAs were shifted to a lower temperature region. In addition, the melting peaks from the crystalline part of the polymers are quite considerably smaller and broader than that from unmodified PLLA. The change in the PLLA melting endotherm caused by structural modification has been reported by Bachari et al. [22]. They prepared dihydroxy PLLA by polymerizing L-lactide in the presence of ethylene glycol and tin bis(2-ethyl hexanoate) and observed that the melting temperature of dihdroxy PLLA decreased. This was attributed to the central ethylene glycol moiety. The same trend, the downshift and decrease of T_m, was observed in this study due to the presence of the succinic acid moiety. The incorporation of succinic acid into the chain backbone of the polymer hinders the chain ordering of the polymer, resulting in a decrease in crystallinity and crystal defects in the polymer. As the molecular weight of the polymer increased, the T_m increased, although these values are still lower than that of unmodified PLLA.

DSC thermograms for PEG and the multiblock copolymer are shown in Fig. 6. PEG showed a sharp and strong melting peak around 50°C–60°C. In the multiblock copolymer, the PEG melting peak was shifted to the low temperature of 40°C. This is because the PLLA block partially disturbs the crystallization of PEG, resulting in a decreased melting point. In the second run for the multiblock copolymer, the T_m peak from PEG segments disappeared while the T_m peak from PLLA segments remained. The results showed that PLLA blocks, but not PEG block, were readily recrystallized. This did not result from the greater crystallization tendencies of PLLA but from its higher melting temperature. When the copolymer cools down after melting, PLLA blocks are solidified and crystallize at higher temperatures.

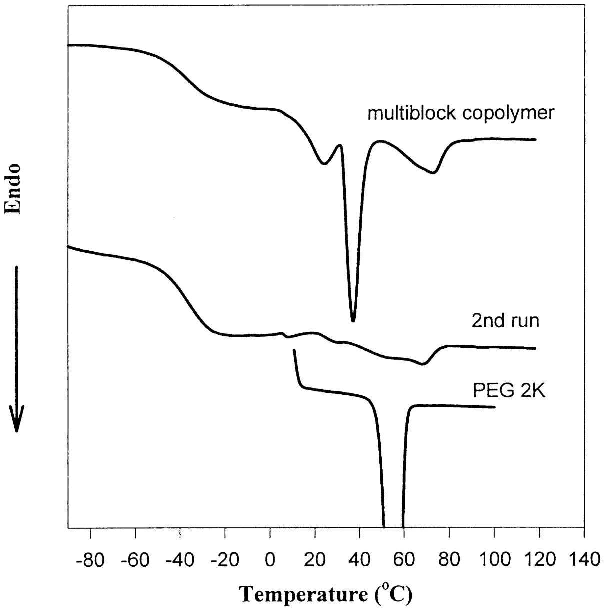

Fig. 6. DSC thermograms of PEG2000/PLLA1990 multiblock copolymer ($M_n = 26\ 100$).

This limits the mobility of the soft PEG segments. Consequently, the crystallization of the PEG is severely hindered by the already solidified PLLA chains.

There exists a large T_g peak for the multiblock copolymer in the −45°C to −28°C temperature range. This peak is attributed to the phase mixing of two different blocks. It is well known that both overall composition and sequential length play a fundamental role in determining the morphology of the matrix. In the case of a block copolymer containing the long segments, if both components are able to crystallize, there exists phase separation in the matrix. Microphase segregation is demonstrated by the existence of two distinct, separate melting endotherms, corresponding to the two components of the copolymer. However, although phase separation is a dominant phenomenon taking place in the matrix of these copolymers, considerable phase mixing occurs. In the case of block copolymers containing relatively short segments, the reverse is true. That is, phase mixing becomes dominant. The PEG and PLLA-based multiblock copolymer is expected to show a high degree of phase mixing resulting from relatively short block length and connectivity of the two components. As shown in Fig. 6, the T_g shift of PEG and the fact that there exists no significant T_g peak from amorphous PLLA describe the high phase mixing between the PEG and the PLLA blocks. The decrease in the crystalline melting point of PEG is considered to be additional evidence for phase mixing.

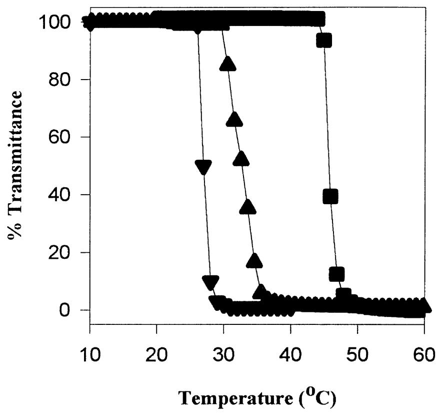

Fig. 7. Temperature-dependent light transmittance of the aqueous polymer solution (1 wt.%) of water-soluble PEG/PLLA multiblock copolymers in pH 7 buffer. ▼: PEG/PLLA 2000/1430, $M_n = 9300$; ▲: PEG/PLLA 2000/1130, $M_n = 14800$; ■: PEG/PLLA 2000/820, $M_n = 8800$.

Consequently, from DSC analysis, it was assured that a high degree of phase mixing plus microphase separation occurs in the block copolymer.

3.3. Temperature effect on PEG/PLLA multiblock copolymer phase

There are many polymers that exhibit clouding at elevated temperatures or lower critical solution temperatures (LCST) in an aqueous solution. This phase transition is due to temperature-dependent hydrogen bonding and hydrophobic interaction of water-soluble homo- and copolymers which balance hydrophilicity and hydrophobicity in repeating units or along the polymer chains [23,24]. This balance effect in the alternating multiblock copolymers may influence the phase transition, since block copolymers with a high PEG content and low molecular weight become soluble in water. Soluble multiblock copolymers with relatively low molecular weights were synthesized by slightly adjusting the feed ratios of PEG and PLLA. Indeed, the polymers were put through a phase transition from the soluble to insoluble states by raising their temperatures. The result of clouding point measurement by transmittance of visible light is presented in Fig. 7. Each polymer with a different composition exhibits different clouding points, depending on the hydrophobic block length. With a fixed PEG block length at 2000, shorter PLLA blocks shifted the clouding point, defined as the inflection point in light transmittance, to higher temperatures from 27°C for PLLA 1430 to 33°C for PLLA 1130 and to 45°C for PLLA 820. Such changes can be explained by the positive effect of the PLLA block length on hydrophobic interaction. It has been well known that increases in hydrophobicity in radical polymers induce decreases in LCST. The results from this study expand this observation to alternating multiblock copolymers.

When the block copolymers have high molecular weights and a high PLLA content for physical crosslinking, they become water-insoluble but can swell in water. The ability of the polymer to absorb and hold the water results from the physical crosslinking formed at PLLA domains in the polymers. A segmented block copolymer, consisting of a hydrophilic soft segment and a hydrophobic hard segment, is able to form physical crosslinking in an aqueous environment. Such physical crosslinking can be accomplished by several

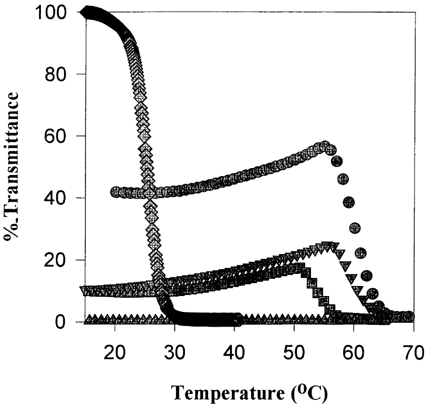

Fig. 8. Light transmittance change of PEG/PLLA multiblock copolymer hydrogels as a function of temperature in pH 7 buffer solution. ◆: PEG/PLLA 2000/1130, $M_n = 31\ 100$; ●: PEG/PLLA 2000/1690, $M_n = 33\ 100$; ▼: PEG/PLLA 2000/1990, $M_n = 25\ 000$; ■: PEG/PLLA 1500/1690, $M_n = 14\ 000$; ▲: PEG/PLLA 1000/1690, $M_n = 19\ 400$.

complex factors such as hydrophobic interaction among the polymer chains, crystalline microdomains and chain entanglement. The physical association of hydrophobic domains holds swollen soft domains together and makes the polymer stable in water. The hydrogels showed a transition in light transmittance which may be associated with the clouding phenomenon observed in water-soluble polymers. Fig. 8 shows the phase transition in light transmittance of the PEG/PLLA multiblock copolymers with different block lengths for PEG ($M_n = 2000$, 1500 and 1000) and PLLA ($M_n = 1690$ and 1990). The polymer films prepared by solvent casting were transparent in the dried state, but their transparency changed when transferred to an aqueous medium.

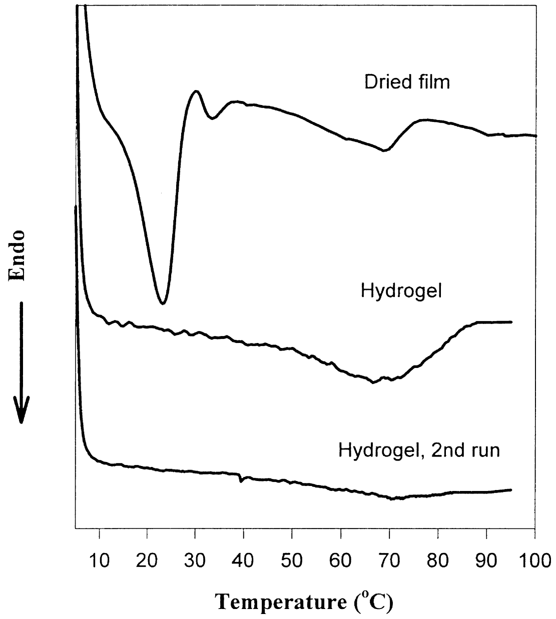

Fig. 9. DSC thermograms of PEG/PLLA 2000/1990 ($M_n = 25\ 000$) copolymer.

The initial transparency of the hydrogels was primarily dependent on the chemical composition of the polymer and was reduced by introducing shorter PEG blocks and longer PLLA blocks. In addition, it was also found that the phase transition point for the hydrogels decreased with increases of the hydrophobic PLLA component. For hydrogels with a PEG block of $M_n = 1000$, the initial % transmittance approached zero and did not show any change over the experimental temperature range, whereas the hydrogel of PEG/PLLA 2000/1130 showed high transparency in water below 15°C and became opaque at 30°C. It is interesting to note that the transmittance of hydrogels of PEG/PLLA 2000/1690, 2000/1990, and 1500/1690 increased gradually to different degrees by temperature before undergoing sudden decreases (transition). This change in transmittance is associated with the thermal behavior of the polymer hydrogel observed by DSC. Fig. 9 presents DSC thermograms for a dried film and a hydrogel from the PEG2000/PLLA1990 multiblock copolymer. As in previous studies on the thermal properties of multiblock copolymers, the dried polymer showed two endothermic peaks resulting from crystalline melting. One peak is from the PEG segment and the other small, broad peak is from the PLLA segment. It is noteworthy that the hydrogel as well as the polymer film showed a melting peak from the crystalline domain of PLLA segment. This indicates that the polymer preserves its crystalline domain even in the swollen state in an aqueous medium. However, as can be found in the hydrogel thermograms, there existed no melting peak of PEG in the first scan and the PLLA melting peak disappeared in second scan of the hydrogel. This crystalline melting of hydrogels may be responsible for their increase in transmittance. The temperature range where the transmittance increases is in accordance with the broad melting peak from the crystalline domain. In addition, polymers having no melting endotherm in the first scan showed high initial transparency.

The common feature of such hydrogels is represented as short block lengths of PLLA, which are not long enough to form crystalline domains in the multiblock copolymer structure. The initial changes in transmittance of the polymer hydrogels were thus attributed to block lengths, which strongly influenced crystalline domain formation. After PLLA melting in the hydrogels, hydrophobic interaction between PLLA segments is responsible for the sudden decrease in optical transmittance. Fig. 10 shows the reversibility in optical transparency of the hydrogels with repeated thermal cycles. The hydrogel of PEG/PLLA 2000/1690 showed strong cycle dependency in the first three cycles. In the first cycle, as described previously the transmittance increased with temperature before becoming opaque in the 55°C–65°C temperature range. However, in the second cycle, the transparency at low temperatures was greatly improved and the transition occurred from 40°C to 48°C. From the third cycle, the transparency at low temperatures returned back to the level of the first cycle, but it decreased very gradually along the experimental

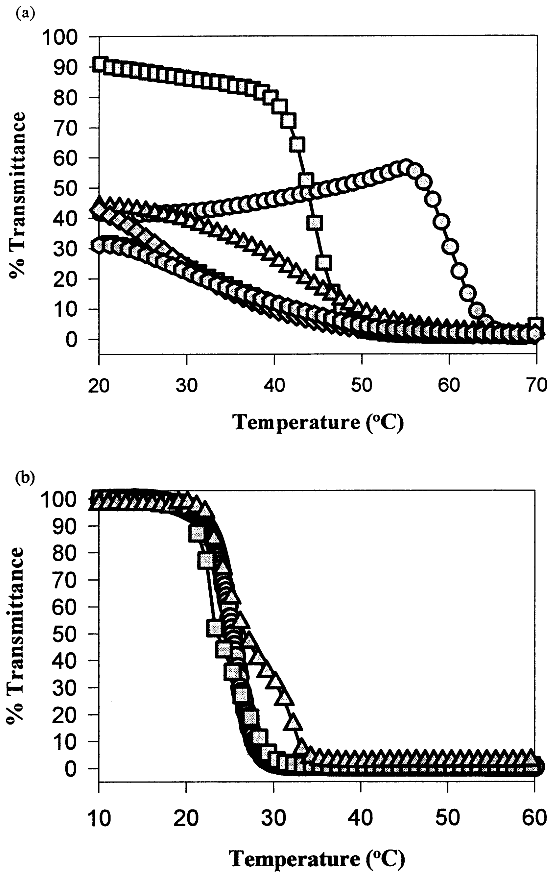

Fig. 10. Thermal cycle dependent light transmittance of multiblock copolymer hydrogels in pH 7 buffer solution. (a) PEG/PLLA 2000/1690, $M_n = 33\,100$; ●: 1st cycle, ■: 2nd cycle, ▲: 3rd cycle, ▼: 4th cycle, ◆: 5th cycle and ⬢: 6th cycle. (b) PEG/PLLA 2000/1130, $M_n = 31\,100$, ●:1st cycle, ■: 2nd cycle and ▲: 3rd cycle.

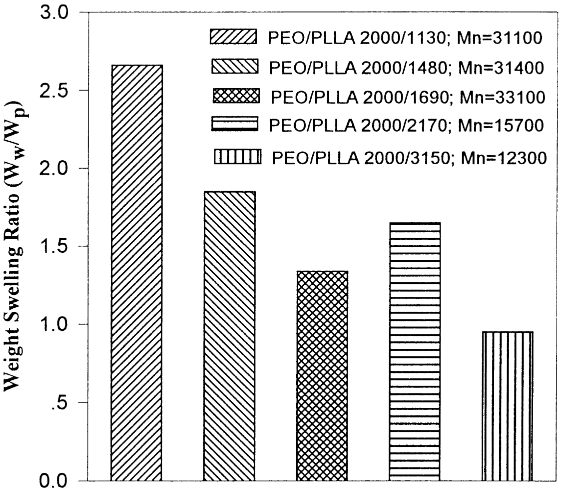

Fig. 11. The weight swelling ratio of the PEG/PLLA multiblock copolymers with different block lengths of PLLA and polymer molecular weights at 37°C in pH 7 buffer solution.

temperature range. This unusual observation is not clearly understood, but is probably associated with complex behavior of the cycle-dependent phase, mixing between two components, polymer relaxation from entanglement and hydrophobic interaction in the PLLA blocks. In contrast, the temperature-dependent transparency of PEG/PLLA 2000/1130, which is highly transparent at low temperatures from the first scan, is not significant. This may indicate that the short PLLA blocks do not form a separate phase and only reversible hydrophobic interaction is involved in this particular hydrogel.

3.4. Swelling of PEG/PLLA multiblock copolymers

The weight swelling ratio of the PEG/PLLA multiblock copolymers with various block lengths of PLLA was measured and the result is illustrated in Fig. 11. The weight swelling ratio for multiblock copolymers was calculated from the following equation:

$$\text{Weight swelling ratio} = (W_{\text{swollen}} - W_{\text{dried}}) \,/\, W_{\text{dried}}$$

where W_{swollen} and W_{dried} are the weights of the swollen and dried polymer, respectively. When the polymer molecular weights were close, the swelling ratio decreased with increasing block lengths of hydrophobic PLLA, as expected. The molecular weight of the polymers is another factor influencing swelling. The lower molecular weight polymer had a greater propensity for swelling, even though it was synthesized with longer PLLA blocks.

4. Conclusion

Dicarboxylated PLLAs with low molecular weight were synthesized through the incorporation of succinic acid into the polymer chain during a condensation reaction with L-lactic acid. Molecular weight was controlled by changing the feed ratio of L-lactic acid and succinic acid. The incorporation of succinic acid into the PLLA chain backbone decreased the crystallinity of the dicarboxylated PLLAs, and as the molecular weight increased, the polymer showed higher T_m and crystallinity.

The control ability of the hydrophobic PLLA block may open possibilities for custom-designing the chemical composition and physical properties of multiblock copolymers. From DSC analysis of PEG/PLLA multiblock copolymers, it is suggested that there coexists phase mixing and microphase separation in the polymers, expressed as a large T_g peak from amorphous phase mixing area and T_m peaks from the crystalline domains of the PEG and PLLA components.

The water-solubility of the block copolymers was influenced by the chemical composition and molecular weight of the multiblock copolymers. Polymers with low molecular weight or composed of shorter PLLA blocks became soluble in water, whereas high molecular weight polymers and polymers with longer PLLA blocks formed physically crosslinked hydrogels. The water soluble polymers underwent clouding at higher temperatures and this transition temperature varied according to polymer composition. The insoluble polymers (hydrogel) also reflected this transition in light transmittance through cast films. The transparency of the hydrogel films increased as the temperature was raised due to PLLA crystalline melting, and then became opaque suddenly when the temperature was elevated above a critical temperature; an analogue of the clouding phenomenon in water-soluble polymers. This unique behavior of the polymers in an aqueous medium are based on the fact that an increase in temperature promotes hydrophobic interaction between hydrophobic moieties in the polymer chains, resulting in a phase transition in the hydrogels.

The water content of the block copolymers at 37°C was controlled by the composition as well as the molecular weight of the polymers. Copolymers synthesized with longer PLLA blocks underwent less swelling.

These alternating multiblock copolymers may be useful for applications in controlled drug delivery and other biomedical situation where fast degradation is required. A detailed degradation study of these block copolymers is now underway.

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