

Synthesis and Thermal Behavior of Triblock Copolymers from L-Lactide and Ethylene Glycol with Long Center PEG Block

J. MOHAMMADI-ROVSHANDEH,¹ S. M. F. FARNIA,¹ M. N. SARBOLOUKI²

¹ Department of Chemistry, Faculty of Sciences, University of Tehran, Tehran, Iran

² Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran

Received 10 June 1997; accepted 3 November 1997

ABSTRACT: In this study, poly(L-lactide)–poly(ethylene glycol) (PLLA–PEG) ABA triblock copolymers with the PEG mole fraction ranging from 27 to 57% have been synthesized, and their thermal properties were investigated. Differential scanning calorimetric thermograms of copolymers obtained from specimens dissolved in CH₂Cl₂ solution and precipitated with hexane exhibit no crystallization exotherms, but those cast from CHCl₃ solution show some crystallinity. Water absorption depended on the PEG content of copolymers; thus, with a PEG mole fraction of 57, the water absorption was 82%. © 1998 John Wiley & Sons, Inc. *J Appl Polym Sci* 68: 1949–1954, 1998

Key words: poly(L-lactide); poly(ethylene glycol); ABA triblock copolymers; thermal behavior

INTRODUCTION

Poly(α -hydroxy acids), due to their hydrolytic degradation in aqueous media, are being used as suitable biodegradable polymers in various biomedical and pharmaceutical applications. The most widely utilized amongst the series, that is, polylactides, polyglycolides, and their copolymers, have applications in surgical sutures,¹ controlled drug delivery,² vascular grafts,³ implants,⁴ and sutures for fixation of fractures.⁵ Tacticity of the polylactides (that is, L or DL) and its copolymers with glycolide or other chiral entities is one of the prime determinant of the physical properties (morphology, hydrophilicity) and biodegradation characteristics. Due to the hydrophobicity of polylactides, their compatibility in soft tissues are low, and, as well, they are not suitable carriers for hydrophilic drugs, such as proteins. To overcome

such deficiencies, the synthesis of copolymers of lactide with ethylene glycol or other hydrophilic segments can be considered as a potential alternative. Polyethylene glycol (PEG) is nontoxic,⁶ soluble in water in all proportions, and is cleared by U.S. Food and Drug Administration for internal use in the human body. It is expected that these copolymers may produce water swellable polymers. Recently, a few block copolymers^{7–9} of lactide and ethylene glycol have been synthesized and characterized. The polymerization mechanisms and kinetic investigations have also been reported.¹⁰ In this article, we discuss synthetic details and thermal properties of copolymers of PEG and PLLA [poly(L-lactide)] with a long center PEG block.

EXPERIMENTAL

Materials

L-lactide was synthesized from 90% L-lactic acid solution (Merck Inc.) according to the published

Correspondence to: S. M. F. Farnia.

Table I Polymerization^a of L-lactide with PEG at 120°C

No.	PEG Mol % in Reaction Mixture	PEG Mol % ^b	Yield (%)	\bar{M}_n (calc) ^c in Copolymer	\bar{M}_n ^d	α (deg dm ⁻¹ g ⁻¹ cm ³)	$[\eta]$ Intr dL/g
1	62	57	88	71000	77000	—	—
2	51	54	85	84000	83000	-79	1.1
3	45	46	89	105000	102000	-99	1.2
4	35	33	88	145000	150000	-113	1.12
5	30	28	90	174000	186000	-132	1.6

^a Time, 48 h; catalyst, Sn(Oct)₂.^b Mole percent of PEG as determined by ¹H-NMR data on the isolated polymer.^c Calculated for 100% conversion.^d Estimated from ¹H-NMR data and rounded to the nearest number.

procedures.¹¹ The crude product was first washed with ethyl ether and then recrystallized 3 times in ethylacetate (mp 98°C). Polyethylene glycol, $\bar{M}_n = 35000$ (Merck Inc.), was purified by dissolving in THF, reprecipitating in hexane, and drying in vacuum under anhydrous calcium chloride. Stannous octoate (tin-2-ethylhexanoate) (Sigma, St. Louis, USA) was purified by vacuum distillation. All other chemicals and solvents were reagent grade (Merck Inc.) and, if necessary, were purified by the established procedures.¹²

Polymerizations

The monomers, L-lactide and PEG, and the catalyst 0.5 ml (5% solution in toluene) were introduced into a polymerization tube. The mixture was kept under high vacuum at 80°C for 2 h. After all volatiles, including water, are removed, tubes were sealed under vacuum. Polymerizations were carried out at 120°C for a period of 48 h. Afterwards, the tubes were broken and the contents dissolved in dichloromethane, filtered, and precipitated in hexane. The pure polymer was dried in vacuum at 80°C overnight.

Measurements

¹H nuclear magnetic resonance (¹H-NMR) spectra were recorded on a Bruker AC-80. Chloroform-d₁ and TMS were used as solvent and as internal standard, respectively. The water absorption of copolymers were estimated by equilibrium swelling of the polymer film specimens (obtained by casting from a 25% solution of polymer in dichloromethane) in distilled water at 20°C for 1 week. Water content (in wt %) was calculated from the relative weight increase of the samples after their immersion in water. The intrinsic viscosities of the copolymers were measured in dilute chloroform solutions at 25°C using an Ubbelohde capillary viscometer. The specific optical rotations were measured in chloroform at room temperature using a Perkin-Elmer Polarimeter 241 MC at 589 nm. Differential Scanning calorimetry (DSC) thermograms were obtained with a Mettler Instrument DSC series PC11, and thermogravimetric analysis (TGA) was measured with a V5.1A Dupont 2000 thermoanalyzer. The PEG difunctionality was established by measuring hydroxyl number of the PEG homopolymer ($\bar{M}_n = 35000$).¹³

Table II Thermal Properties of Copolymers Type A^a

No.	PEG Mol % in Copolymer	T_m of PEG Block (°C)	PEG Exotherm (°C)	ΔH_m of PEG Block (J/g)	ΔH Exotherm of PEG Block (J/g)	T_m of Lactide Block (°C)	ΔH_m of Lactide (J/g)
1a	57	55.8	162.6	62.1	8.3	170.6	7.1
2a	54	53.5	184.5	56.3	16.6	173.7	37
3a	46	52.2	197.3	33.1	18.1	170.1	36
4a	33	47.7	185.5	5.5	17.3	173.4	36.6
5a	28	49.4	204.6	7.3	26.6	172.8	49.8

^a Temperature increment: 10°C/min.

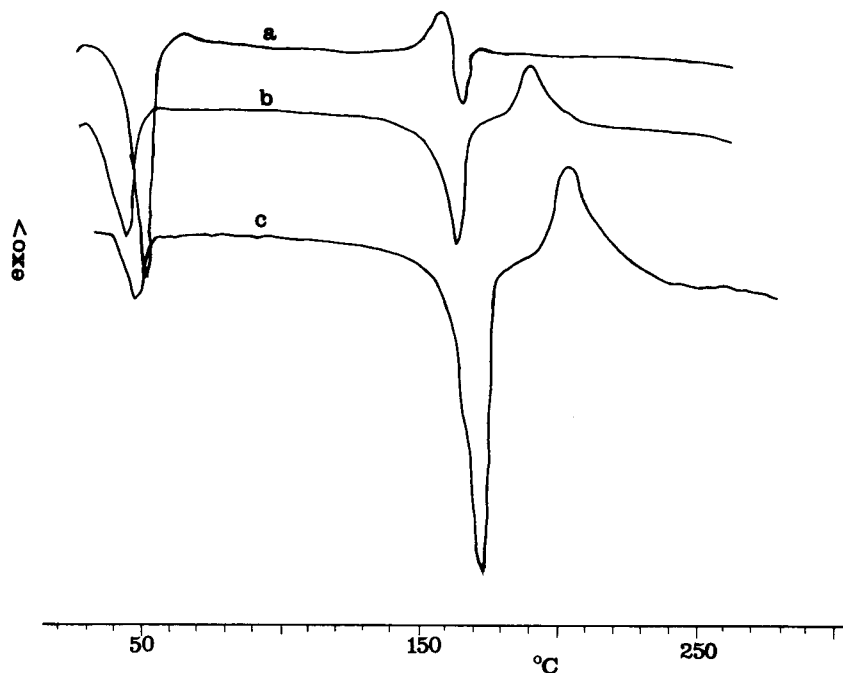


Figure 1 DSC thermograms (heating run) of type A copolymers with compositions. PEG: LLA (a) 57 : 43; (b) 46 : 54; (c) 28 : 72.

The hydroxyl number was measured in the range of 3–4 mg KOH/g in agreement with a dihydroxylated PEG. \bar{M}_n was estimated from $^1\text{H-NMR}$ data by considering relative intensities of the CH_2 oxyethylene (795.5 repeating units) and CH moiety of lactyl fragments, designated as I_p and I_l , respectively, according to the following equations:

$$\bar{M}_n(\text{total}) = \bar{M}_n(\text{PEG}) + \bar{M}_n(\text{PLLA});$$

$$\bar{M}_n(\text{PLLA}) = 4 \cdot \frac{I_l \cdot M_w(\text{lactyl}) \cdot 795.5}{I_p}$$

(For example, in sample No. 3, I_l and I_p were 15.6 and 53.9 from the NMR data, and the $M_w(\text{lactyl})$

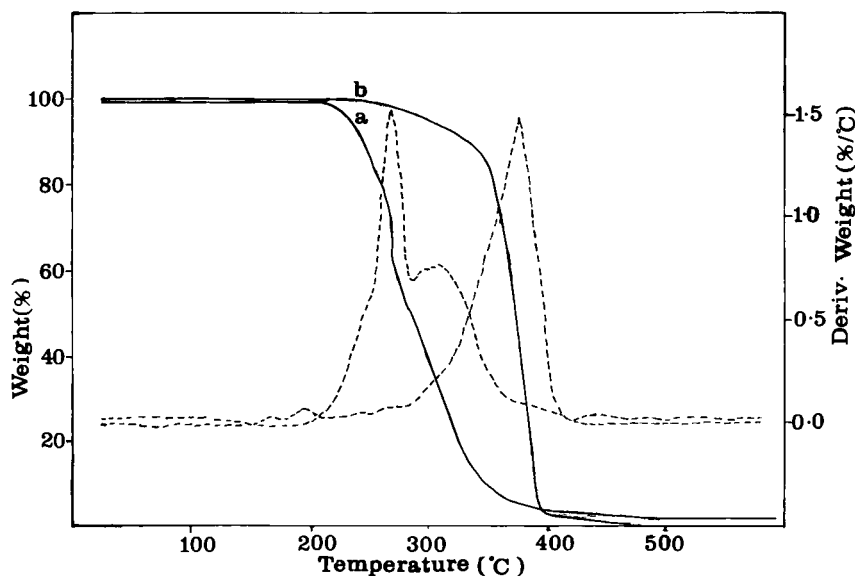


Figure 2 TGA thermograms of (a) PEG 35000 and (b) copolymer 5a; temperature increments, 20°C/min.

Table III Thermal Properties of Type B Copolymer Films in First Heating^a

No.	Oxyethylene Mol % in Copolymer	T_m of PEG (°C)	T_m of PLLA (°C)	Exotherm of PLLA (°C)	Exotherm of PEG (°C)	Crystallinity of PLLA (%)
1b	57	52	—	—	153	—
2b	54	52.5	166	—	—	—
3b	46	50	—	—	155	—
4b	33	—	170	101	160	38
5b	28	—	170	69	150	28

^a Temperature increment: 20°C/min.

repeating unit is equal to 72. By replacing these numbers into the above equations, \bar{M}_n (lactyl) and \bar{M}_n (total) were calculated as 66,568 and 101,568, respectively.)

RESULTS AND DISCUSSION

Addition of L-lactide to PEG in various molar ratios in the presence of catalytic amounts of tin octoate produces ABA triblock copolymers according to the following equation:

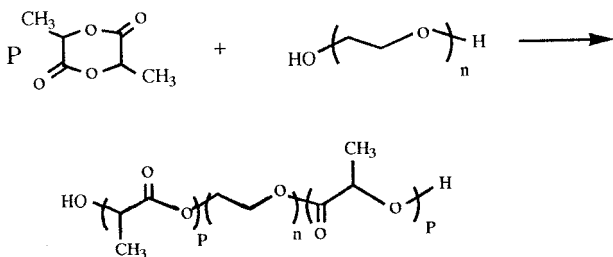


Table I shows mole fractions of PEG used in the reaction mixture and those found in the copolymer from their analyses of ¹H-NMR data together with their estimated molecular weights. Characteristics of the proton spectra are a quartet at δ 5.17 for lactyl methinic protons, a singlet at δ 3.56 for oxyethylenic methylenic protons, and a doublet at δ 1.6 for lactyl methyl protons. As shown, the estimated molecular weights from ¹H-NMR data correspond well to their calculated analogs. The DSC thermograms show a thermal dependency to the final physical treatment of the copolymers. Copolymers designated type A were first dissolved in CH₂Cl₂ and then precipitated in hexane; whereas for type B copolymers, films were prepared by casting from CHCl₃ solution and used as such for DSC studies. Table II reflects thermal properties of type A copolymers. Evidently, the exotherms are higher than 150°C, indicating a

noncrystalline state under these conditions. Homopolymers of PEG exhibit an exotherm at 158°C attributable to a decomposition or a self-generated reaction.

The DSC of copolymer 1a with high molar content of PEG [Table II and Fig. 1(a)] show endotherms at 55.8 and 170.6°C related to the melting points of PEG and PLLA blocks, respectively. It also shows an exotherm at 162.6°C, which is very similar to the exotherm of PEG homopolymer. Interestingly, when the PLLA block molar ratio increases in the series (Fig. 1(a)–(c), the endo-

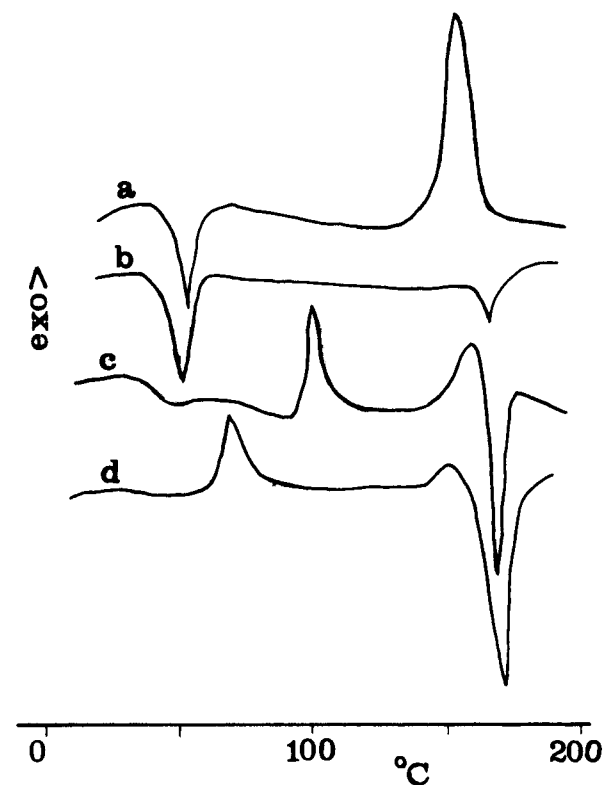


Figure 3 DSC thermograms (first heating) of type B copolymers with compositions. PEG: LLA (a) 57 : 43; (b) 54 : 46; (c) 33 : 67; (d) 28 : 72.

therm of PEG block decreases while its exotherm increases. For sample 5a [Table II and Fig. 1(c)], the exotherm appears at 204.6°C and endotherms appear at 49.4 and 172.8°C, respectively. This phenomenon is attributed to the stabilizing effect of the PEG block when reacted with higher proportions of PLLA, as evidenced by the ΔH , exotherm which is changing from 8.3 to 26.6 for samples 1–5a, respectively. To assess further the thermal stability of PEG copolymerized with LLA, TGA analyses were performed. Figure 2 shows gradual decomposition of PEG begins at 200°C, and its maximum appears at 269°C; whereas those of the copolymer occur at 380°C, clearly indicating the stabilizing effect upon copolymerization.

Thermal properties of type B copolymers for the first heating at 0–200°C are shown in Table III. The resultant thermal properties are very dif-

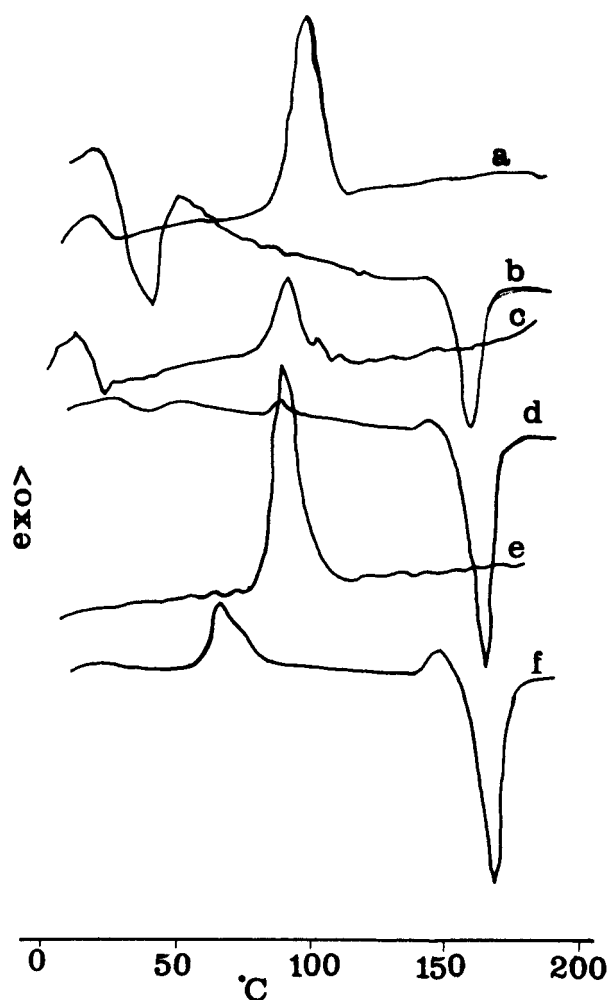


Figure 4 DSC thermograms (cooling then heating) of type B copolymers. Composition PEG: LLA (a) and (b) 57 : 43; (c) and (d) 33 : 67; (e) and (f) 28 : 72.

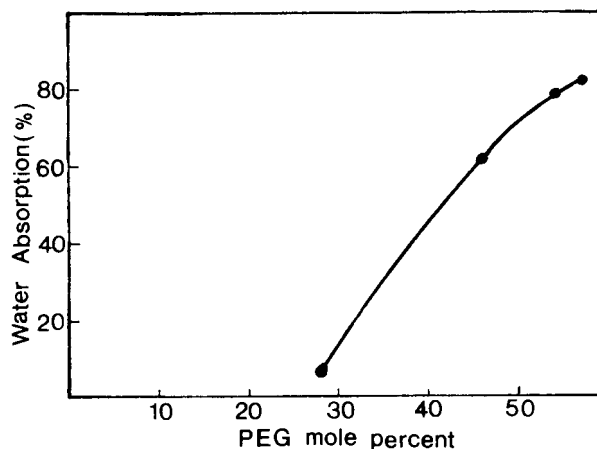


Figure 5 Water absorption versus PEG mole percent for block copolymers.

ferent from those of type A. The DSC thermogram of the copolymer 1b with PEG 57 mol % resembled pure PEG, whereas those of 5b with PEG 28 mol % were similar to PLLA. The results taken together with the lack of any exotherm below 150°C clearly indicate that at high PEG contents, very low crystallinity is attainable. Figure 3 shows thermal properties of type B copolymers for the first heating at 0–200°C, and, in Figure 4, the results of cooling and subsequent heating of these copolymers are shown. Obviously, when the temperature is reduced, two exotherms at 95 and 15°C are observed, indicating the crystallization transitions of PLLA and PEG blocks, respectively. Upon reheating, the endotherms of PEG and PLLA blocks appear at 41 and 161°C, respectively [Fig. 4(a) and (b)]. In addition to the two endotherms observed in second heating of sample 4b [Fig. 4(d)], an exotherm appears at 88°C.

At higher molar ratios of PLLA, a similar behavior is observed except that the PEG exotherm at cooling tends to disappear. Moreover, the exotherm in the second heating of PEG and endotherm of PLLA block were observed at 147 and 169°C, respectively.

Figure 5 shows water absorption of copolymers as a function of the mole percent of PEG. As expected, copolymers with PEG contents above 20% can impart absorption of large amounts of water, a desirable feature, as it would accelerate the degradation rate of vicinal polylactide block.

REFERENCES

1. J. Conn, R. Oyasu, M. Welsh, and J. M. Beal, *Am. J. Surg.*, **128**, 19 (1974).

2. A. K. Kwong, S. Chou, A. M. Sun, M. V. Sefton, and M. F. A. Goocca, *J. Controlled Release*, **4**, 47 (1986).
3. G. E. Visscher, R. L. Roison, and G. J. Argentieri, *J. Biomat. Appl.*, **2**, 118 (1987).
4. D. W. Grijpma, A. J. Nijenhuis, and A. J. Pennings, *Polymer*, **31**, 2201 (1990).
5. J. W. Leenslag, A. J. Pennings, R. M. Bos, F. R. Rozeman, and G. Boering, *Biomaterials*, **8**, 70 (1987).
6. J. M. Harris, *J.M.S.—Rev. Macromol. Chem. Phys.*, **C25**, 325 (1985).
7. K. J. Zhu, L. Xiangzhou, and Y. Shilin, *J. Polym. Sci., Part C: Polym. Lett.*, **24**, 331 (1986).
8. Z. Jedlinski, P. Kurcok, W. Walach, H. Janeczek, and I. Radecka, *Macromol. Chem.*, **194**, 1681 (1993).
9. K. J. Zhu, L. Xiangzhou, and X. Shilin, *J. Appl. Polym. Sci.*, **39**, 1 (1990).
10. X. J. Du, P. J. Lemstra, A. J. Nijenhuis, H. A. M. vanAert, and C. Bastiaansen, *Macromolecules*, **28**, 2124 (1995).
11. D. K. Gilding and A. M. Reed, *Polymer*, **20**, 1459 (1979).
12. R. Keese, R. K. Müller, and T. P. Toube, *Fundamentals of Preparative Organic Chemistry*, John Wiley & Sons, 1982.
13. A. Krause and A. Lange, *Introduction to the Chemical Analysis of Plastics*, Liffé Books Ltd. 1969.