Crystallization Behavior of Biodegradable Amphiphilic Poly(ethylene glycol)-Poly(L-lactide) Block Copolymers

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ABSTRACT: Poly(ethylene glycol)-poly(L-lactide) diblock and triblock copolymers were prepared by ring-opening polymerization of L-lactide with poly(ethylene glycol) methyl ether or with poly(ethylene glycol) in the presence of stannous octoate. Molecular weight, thermal properties, and crystalline structure of block copolymers were analyzed by ^{1}H-NMR, FTIR, GPC, DSC, and wide-angle X-ray diffraction (WAXD). The composition of the block copolymer was found to be comparable to those of the reactants. Each block of the PEG–PLLA copolymer was phase separated at room temperature, as determined by DSC and WAXD. For the asymmetric block copolymers, the crystallization of one block influenced much the crystalline structure of the other block that was chemically connected to it. Time-resolved WAXD analyses also showed the crystallization of the PLLA block became retarded due to the presence of the PEG block. According to the biodegradability test using the activated sludge, PEG–PLLA block copolymer degraded much faster than PLLA homopolymers of the same molecular weight. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 72: 341–348, 1999

Key words: poly(ethylene glycol)-poly(L-lactide) block copolymer; crystallization; biodegradability; time-resolved WAXD; modified Sturm test

INTRODUCTION

With the growing concern for the protection of the environment, there have been a great number of research on the biodegradable aliphatic polyesters.[1–3] Poly(L-lactide) (PLLA),[4–7] in particular, is not only biodegradable but also transparent with superior mechanical properties.[2,4] In general PLLA can be prepared by the direct polycondensation of lactic acid or by the catalytic ring-opening polymerization of lactide. Polymers with molecular weight of more than 100,000 are conventionally obtained by the ring-opening polymerization of lactide. However, recently researchers synthesized high molecular-weight PLLA by the direct polycondensation.[8]

Thanks to its excellent biocompatibility PLLA can be used for many biomedical applications such as controlled release of various drugs,[9] sutures,[10] and bone fixation materials.[11] To control the physical properties and biodegradability of PLLA, it has been blended with various other polymers[12–16] or chemically modified.[17–21] Molecular structure of the amphiphilic copolymers of poly(ethylene glycol) (PEG) and PLLA may be designed by adjusting the block lengths so as to introduce wide spectra of physical and chemical properties and biodegradability.

So far, most studies on the PEG–PLLA block copolymers have focussed on the elucidation of the kinetics and mechanisms of the syntheses based on the characterization by NMR, DSC, WAXD, etc.[18–21] Hydrolytic degradation of the PEG–PLLA block copolymers was also investigated, because the primary application of those PEG–PLLA block copolymers was intended for the controlled drug delivery systems. Therefore, they used relatively low molecular-weight PEG, whose molecular weight was less than 2000, as the macroinitiator for the synthesis of the block copolymer.[18–21]

In this study we were interested in the preparing PEG–PLLA diblock and triblock copolymers to be used as the compatibilizer for the biodegradable blend of poly(ethylene oxide) (PEO) and PLLA. Therefore, PEGs having the molecular weight higher than 2000 were used for the preparation of the triblock copolymers, and poly(ethylene glycol) methyl ether(PEGME) of the molecular weight 5000 was used in the synthesis of the diblock copolymers. Crystallization behavior and biodegradability of the PEG–PLLA block copolymers were investigated to ascertain the potential of these block copolymers as the compatibilizers for the biodegradable PEO/PLLA blends.

EXPERIMENTAL

Materials

L-Lactide (Aldrich Chemical Co.) was recrystallized from toluene. PEGs with the number-average molecular weight ranging from 2000 to 20,000 and PEGME were purchased from Aldrich Chemical Co. and Polysciences, Inc. respectively. Before use they were purified by dissolving in chloroform and by precipitating in *n*-hexane. Tin(II)bis(2-ethyl hexanoate) (stannous octoate, Sigma Chemical Co.) was used as received for the polymerization catalyst.

Syntheses

Predetermined amounts of PEG or PEGME, L-lactide, and stannous octoate (PEG or PEGME to catalyst molar ratio was about 1000) were introduced into a 100-mL round-bottomed flask with stirring. The flask was connected to a vacuum system and heated to 50°C for 12 h in an oil bath to eliminate residual water. Then the vacuum was released, and the system was purged with nitrogen. The temperature was then raised to 140°C and maintained for 24 h. Reaction product was dissolved in chloroform, and precipitated by *n*-hexane. The precipitate was filtered and dried in a vacuum oven at 40°C for a week.

Characterization

IR spectra of the block copolymers were obtained by FTS-40 (Digilab) FTIR spectrometer using the chloroform solution of the block copolymer. Chemical structure of the block copolymer in *d*-chloroform(TMS 0.03%) was identified by ^{1}H-NMR spectrometer (AM-300, Bruker). Molecular weight was measured by both GPC (Waters, solvent = THF, flow rate = 1 mL/min) and ^{1}H-NMR spectrometer. Calibration for the GPC measurement was carried out with polystyrene standards (Shodex Standard SM-105, Showa Denko) in the weight-average molecular weight range of 1300–3,131,000. Columns (Waters) were consisted of one Styragel HR1 (100 Å), one Styragel HR2 (500 Å), and two Ultrastyragel Linears (mixed bed). DSC (PL-DSC, Polymer Laboratories) was employed to evaluate thermal properties. The DSC specimens were heated to 180°C at a rate of 10°C/min, cooled slowly to room temperature, and then reheated to 180°C at a rate of 10°C/min to record the second scan data.

The crystalline structure of the solvent cast block copolymer film was analyzed by wide-angle X-ray diffraction(WAXD) (X′PERT-MPD, PY-616, Philips) by scanning at 0.04°/s. The crystallization behavior was also observed by time-resolved WAXD experiment at Pohang Light Source (beamline 3C2) in Pohang, Korea, using monochromatic X-ray with a wavelength of 1.608 Å. Details of the experimental procedure was described elsewhere.[22] Samples were hot pressed into 1-mm sheets, and the scattering pattern was obtained isothermally and as a function of the temperature as well. The heating rate in the temperature scan was 5°C/min. For the isothermal measurement the sample was melted completely for 5 min by using the jumping hot stage equipped with two temperature controllers, and then it was transferred immediately to the sample stage of 40°C to record the time dependent growth of the crystalline peak intensity. The sample stage was purged with nitrogen to prevent thermal degradation and was scanned for 10 s to obtain each data point. A modified Sturm test was used to measure biodegradability of the block copolymer according to the ASTM D5209-91. Block copoly-

Figure 1 ^{1}H-NMR spectra of PEG–PLLA block copolymers: (a) 2kTRI2k, (b) 5kDI20k, (c) 10kTRI10k, (d) 20kTRI5k.

mer specimen in the standard aqueous solution of inorganic salts at 25 ± 2°C was assumed to be the sole carbon source for the microorganism metabolism. The percentage biodegradability was calculated by dividing the CO_2 generation as a result of the metabolism by the activated sludge by the theoretical CO_2 generation.

RESULTS AND DISCUSSION

Various PEG–PLLA block copolymers were synthesized by polymerizing L-lactide with PEG or PEGME macroinitiator. PLLA block length in the block copolymer was controlled by changing the amount of L-lactide. Molecular weights of PLLA blocks at both ends of the ABA type triblock copolymer were assumed to be equal, because the functionality of the two end groups of PEG was same. 4kTRI16k is a triblock copolymer in which the PEG mid block (mol wt = 4000) is connected to two PLLA blocks at both ends, each PLLA block with molecular weight of 8000. Likewise, 5kDI10k is a diblock copolymer of PEGME block (mol wt = 5000) and PLLA block (mol wt = 10,000). Block copolymers obtained appeared pale yellow in color, and the yield was 80–90%.

In Figure 1 ^{1}H-NMR spectra of various PEG–PLLA block copolymers are shown. Common to all the block copolymers, there were peak around 1.4–1.5 ppm due to methyl protons in the lactide main chain, strong peak around 3.4–3.6 ppm due to methylene protons in the PEG main chain, and weak peak around 5.0–5.2 ppm due to methine proton in the lactide main chain. Taking into account those absorptions due to methine and methylene protons, the molecular weight of the PLLA block of the block copolymer was calculated as follows.[21]

M.W. of PLLA block =

$$\left(\frac{\begin{array}{c}\text{Intensity of methine proton} \\ \times \text{ No. of protons in PEG or PEGME}\end{array}}{\text{Intensity of methylene proton}} \right) \times 72$$

Table I lists the molecular weights of the block copolymers, determined by GPC and ^{1}H-NMR,

Table I   Molecular Weights of PEG–PLLA Block Copolymers

Copolymers	L-Lactide Content in the Feed (wt %)	Mol wt. of PLLA Block		Polydispersity[a]
		NMR	GPC	
5kDI2.5k	33	1,700	—	—
5kDI5k	50	3,900	4,300	1.2
5kDI10k	67	9,600	9,000	1.2
5kDI20k	80	20,400	22,900	1.3
2kTRI2k	50	1,500	—	—
4kTRI2k	33	2,700	2,000	1.1
4kTRI4k	50	6,500	4,000	1.2
4kTRI16k	80	13,400	14,000	1.4
10kTRI2k	17	1,300	2,700	1.1
10kTRI10k	50	9,100	10,100	1.4
20kTRI5k	20	5,200	6,300	1.1

[a] Determined by GPC.

Figure 2 GPC curves of block copolymers: (a) 4kTRI2k, (b) 4kTRI4k, (c) 4kTRI16k, (d) 5kDI10k, (e) 5kDI20k.

Figure 3 FTIR spectra of diblock copolymers: (a) 5kDI2.5k, (b) 5kDI5k, (c) 5kDI10k, (d) 5kDI20k.

respectively. It clearly shows that the two methods yield very similar results. The size of the PLLA block in the block copolymer was nearly identical to those predicted by the compositions of L-lactide and PEG in the reactant mixture, which suggests almost all the monomers were engaged in the copolymerization.

In Figure 2 GPC curve of the block copolymer shows a unimodal, single peak with a relatively narrow molecular weight distribution. Peaks due to unreacted PEG or PEGME homopolymer were not detected. Based on the GPC and NMR results, it is believed that there is virtually no PLLA homopolymer in the PEG–PLLA block copolymers. To make sure homopolymerization of L-lactide does not occur simultaneously with copolymerization of L-lactide with PEG, homopolymerization of L-lactide was carried out under the same reaction condition as the copolymerization using the same catalyst. The number-average molecular weight was ca. 43,000, which is far greater than that of the PLLA block in the copolymer. Thus, we could assume there was no PLLA homopolymer in our system. Pennings et al.[5] studied the polymerization of L-lactide by varying the catalyst concentration and they reported similar results to the ones we obtained.

Figure 3 shows FTIR spectra of block copolymers. Independent of the block copolymer composition the strong absorption around 1750 cm^{-1} was observed due to carbonyl group in the ester linkage.[20,21] As the length of the PLLA block in the copolymer increased, the intensity of the car-

bonyl absorption around 1750 cm^{-1} also increased with respect to the intensity of the methylene absorption in PEG around 2900 cm^{-1}. On the other hand, the absorption intensity of the crystalline phase of PEG around 950 and 850 cm^{-1} gradually decreased.

DSC curves of block copolymers are compared in Figure 4 with those of homopolymers of PEO and PLLA, respectively, and of the PEO/PLLA blend. It should be noted that the DSC curves in Figure 4 are second scan data. PEO, with molec-

Figure 4 DSC thermograms of (a) PEGME, (b) 20k PEO, (c) 37k PLLA, (d) 20k PEO/37k PLLA 40/60 blend, (e) 4kTRI4k, (f) 5kDI10k.

Figure 5 WAXD patterns of block copolymers: (a) 4kTRI4k, (b) 5kDI5k, (c) 10kTRI10k, (d) 20kTRI20k.

ular weight of 20,000, showed higher and broader melting endotherm than PEGME with molecular weight of 5,000 The blend of PEO (mol wt = 20,000) and PLLA (mol wt = 37,000) showed two separate melting endotherms [Fig. 4(d)], each at a lower temperature than the melting temperature of the individual homopolymer with the same molecular weight. As Younes and Cohn[12] pointed out in their experimental results, the PEO/PLLA blends, whose molecular weights are relatively small, can show limited miscibility. However, it does not imply the complete miscibility on the molecular level. PEG–PLLA block copolymers also showed two independent melting peaks. However, the melting temperatures of PEO and PLLA were lower than those of the PEO/PLLA blend. It may be because the block lengths of PEO and PLLA in the block copolymer were relatively short and the two blocks were connected through chemical bonding. By the same token as the PEO/PLLA blend, the PEG–PLLA block copolymer was phase separated because it showed two independent melting temperatures. It was even more evident by the WAXD results in Figure 5. Melting temperature of each block in 4kTRI4k triblock copolymer was lower than that in 5kDI10k diblock copolymer, because the molecular weight of PEG in the triblock copolymer was lower than that of PEGME in the diblock copolymer and, moreover, the molecular weight of PLLA of the triblock copolymer (4000) was smaller than that of the diblock copolymer (10,000).

The effect of the block length on the melting behavior of the block copolymer is shown in Figure 6. For 20kTRI5k, where the PLLA block is much shorter than the PEG block, the melting peak of PLLA was not detected and only the melting endotherm of the PEG block was observed. When the PEG block length and the PLLA block length are similar, two melting peaks due to individual block appeared [Fig. 6(c)]. However, if the PLLA block is much longer than the PEG block (e.g., 5kDI20k), the second scan DSC curve showed only the melting endotherm of the PLLA block [Fig. 6(b)]. It is interesting to note that the first scan of 5kDI20k showed the melting peak of PEG around 70°C in addition to the melting peak of PLLA; however, in the second scan the melting peak of PEG totally disappeared. The crystallization of PLLA cannot proceed easily before the first DSC scan due to the relatively high T_g of PLLA (~60°C) and the crystallization of the PLLA block occurs during the first DSC scan. And the crystalline phase of PLLA thus formed might have suppressed the crystallization of the PEG block. Therefore, in contrast to the polymer blends, the crystallization of one block in the block copolymer had far greater influence on the crystalline structure of the other block that was chemically connected to it.

WAXD patterns of the block copolymers are shown in Figure 5. Characteristic crystalline peaks of PEG should be observed at $2\theta = 19$ and 23°, and those of PLLA should be observed at $2\theta =$

Figure 6 DSC thermograms of block copolymers: (a) 5kDI20k without annealing (1st scan), (b) 5kDI20k, (c) 10kTRI10k, (d) 20kTRI5k.

Figure 7   Time-resolved WAXD patterns of 37k PLLA as a function of temperature (heating rate = 5°C/min).

16.5 and 19°. Regardless of the structure and the molecular weight of the block, all the block copolymers showed crystalline peaks at 16.5, 19, and 23°, characteristic of PEG and PLLA, which means that the PEG block and the PLLA block are phase separated in the crystalline state. Scattering peak intensity, however, was changed by the block lengths of PEG and PLLA. It may be because both PEG and PLLA are crystalline polymers and the crystallization rate of PEG is so fast that the crystallization of PEG introduces the phase separated morphology. In Figures 7 and 8

Figure 8   Time-resolved WAXD patterns of 4kTRI4k as a function of temperature (heating rate = 5°C/min).

Figure 9   Relative WAXD intensity at 17.3° as a function of temperature.

time-resolved WAXD patterns of 37k PLLA and 4kTRI4k triblock copolymer are plotted. The crystalline scattering peaks were diminished as the temperature was raised. At 44°C 37k PLLA showed crystalline peaks near $2\theta = 17$ and 20°, the same characteristic peaks as those observed in Figure 5. Peaks in Figures 7 and 8 were observed at slightly larger scattering angles than those in Figure 5, because the wavelength of the synchrotron X-ray (1.61 Å) for the time-resolved analysis was longer than the wavelength from the conventional source (~1.54 Å) that was used to obtain data in Figure 5. Because the melting temperature of PLLA was 170°C, when the temperature reached 160°C, the scattering intensity of the crystalline peaks dropped rapidly and the peaks disappeared completely at 180°C. Upon heating the block copolymers up to 60°C, the intensity of the crystalline peak at 20° was reduced much faster than that at 17°. And near 150°C the peak at 20° totally disappeared. Therefore, the peak at 20° is not only attributable to PLLA but also to PEG.

Figure 9 shows the decay of the crystalline peak of each block copolymer as a function of the temperature. The longer the block length, the higher the temperature at which the crystalline peak begins to disappear. To monitor the crystallization of the block copolymer in greater detail, the isothermal crystallization was carried out. Because the crystallization temperature was 40°C, the crystalline peaks of PLLA, not of PEG, were obtained. Fully grown crystalline peaks of

Figure 10 Relative WAXD intensity at 17.3° as a function of time at 40°C.

Figure 12 Biodegradability of diblock copolymers: (a) 5kDI2.5k, (b) 5kDI5k, (c) 5kDI20k.

homopolymers were obtained in less than 5 min. However, the longer the PEG block of the block copolymer, the lower the growth rate of the PLLA crystalline peaks, as shown in Figure 10. This may be because the crystallization of the PLLA block became retarded due to the presence of the PEG block. And, it is in good agreement with the DSC results in Figure 6.

Figures 11–13 describe biodegradability of the PEG–PLLA block copolymers and PLLA homopolymer, measured by the modified Sturm test. Theoretical CO_2 generation was calculated

by assuming that both of PEG and PLLA blocks are the carbon source, and it was plotted by using the open symbols in the figure. Similar calculation was also made by assuming only the PLLA block of the block copolymer is degraded by the activated sludge. Thus, closed symbols in the figure represent the amount of the theoretical CO_2 generation based on the carbons in the PLLA block. In Figure 11, the molecular weight of the PEG block in the triblock copolymer was fixed at 4000, and the molecular weight of the PLLA block was varied from 2000 to 8000. On the other hand,

Figure 11 Biodegradability of triblock copolymers: (a) 4kTRI4k, (b) 4kTRI8k, (c) 4kTRI16k.

Figure 13 Effect of molecular weight on biodegradability of PLLA.

in Figure 12, the molecular weight of the PEG block in the diblock copolymer was fixed at 5000, and the molecular weight of the PLLA block was changed from 2500 to 20,000. For both diblock and triblock copolymers, the shorter the PLLA block, the faster the biodegradation of the block copolymer. As the molecular weight of PLLA was doubled from 5800 to 11,700, biodegradability was sharply reduced, and as it increased further, the effect of the molecular weight on biodegradability became negligible. The total extent of biodegradation (open symbol) of 5kDI5k and 5kDI20k after 48 days is 27% [Fig. 12(b)] and 12% [Fig. 12(c)], respectively, while that of PLLA 5.8k and PLLA 11.7k after 55 days is 26% [Fig.13(a)] and 9.8% [Fig.13(b)], respectively. Thus, the PEG––PLLA block copolymer biodegraded slightly faster than PLLA homopolymer. If only the PLLA block of the block copolymer is assumed to biodegrade (closed symbol), the extent of biodegradation of 5kDI5k and 5kDI20k after 48 days will be 61 and 15%, respectively, and thus the PLLA block in the block copolymer degrades much faster than the PLLA homopolymer. Hydrophilicity of the PEG block in the block copolymer may have facilitated degradation of the PLLA block.

CONCLUSION

With the potential usage as the biodegradable compatibilizers for the PEO/PLLA blends in mind, diblock and triblock copolymers of PEG and PLLA were synthesized by polymerization of L-lactide and poly(ethylene glycol) methyl ether or poly(ethylene glycol) in the presence of stannous octoate as the catalyst. The molecular weight of PEGME macroinitiator was 5000, and that of PEG macroinitiator was 2000–20,000. Using ^{1}H-NMR and FTIR spectra, the structure of the block copolymer was identified, and the copolymer composition was found to be comparable to that of the feed, as determined by GPC and NMR. DSC and WAXD analyses indicated that each block of the PEG–PLLA block copolymer was phase separated at room temperature. However, in contrast to the polymer blends the crystallization of one block in the block copolymer had far greater influence on the crystalline structure of the other block that was chemically connected to it. Time-resolved WAXD results showed the crystallization of the PLLA block became retarded due to the presence

of the PEG block. The biodegradability of the block copolymer was investigated by the modified Sturm test using the activated sludge, and the PEG–PLLA block copolymer was found to degrade faster than the PLLA homopolymer with the same molecular weight.

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