

Synthesis and Characterization of Poly(L-lactide)-Poly(ethylene glycol) Multiblock Copolymers

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ABSTRACT: Poly(L-lactide)-poly(ethylene glycol) multiblock copolymers with predetermined block lengths were synthesized by polycondensation of PLA diols and PEG diacids. The reaction was carried out under mild conditions, using dicyclohexylcarbodiimide as the coupling agent and dimethylaminopyridine as the catalyst. The resulting copolymers were characterized by various analytical techniques, such as GPC, viscometry, ¹H-NMR, FTIR, DSC, X-ray diffractometry, and contact angle measurement. The results indicated that these copolymers presented outstanding properties pertinent to biomedical use, including better miscibility between the two components, low crystallinity, and hydrophilicity. Moreover, the properties of the copolymers can be modulated by adjusting the block length of the two components or the reaction conditions. © 2002 Wiley Periodicals, Inc. *J Appl Polym Sci* 84: 1729–1736, 2002; DOI 10.1002/app.10580

Key words: poly(L-lactide); poly(ethylene glycol); multiblock copolymer; crystallinity; hydrophilicity

INTRODUCTION

Recently, growing attention has been paid to a new class of biomaterials, the polyether–polyester block copolymers. The multicomponent nature of these systems affords the required versatility in terms of mechanical properties and biodegradability, as well as biocompatibility. Poly(ethylene glycol) (PEG) is the most widely used polyether component in such copolymers because of its outstanding properties, including hydrophilicity, water solubility, biocompatibility, and nontoxicity, which are very valuable for biomedical applications such as a controlled release substrate for hydrophilic drugs, implanting devices, materials for tissue engineering, and cell scaffold. In the

family of polyesters, polylactide (PLA) appears most interesting due to its biocompatibility and biodegradability. Both PEG and PLA are accepted by U.S. Food and Drug Administration for internal uses in the human body. Copolymerization offers the possibility to combine the hydrophilicity of PEG and the biodegradability of PLA and to lower the crystallinity of the copolymers. A wide range of polymeric materials can be thus obtained that should be promising for temporary therapeutic applications.

Various PLA–PEG block copolymers have been reported in the literature. Cohn and Young synthesized these polymers from the polyesterification reaction of lactide, in the presence of PEG chains (covering 600–6000 molar mass range). The obtained materials showed high hydrophilicity.¹ Deng et al. investigated the copolymerization of D,L-lactide with PEG in the presence of ring opening catalysts.² Zhu et al. synthesized PLA–PEG–PLA triblock copolymers from PEG and D,L-lactide, using stannous 2-ethylhexanoate as

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catalyst at 180°C through bulk polymerization. The authors indicated that the drug release and biodegradation could be tailored by adjusting copolymer composition.³ Cerrai et al. obtained PLA-PEG-PLA triblock copolymers by bulk ring opening polymerization of L-lactide with PEG at 120–140°C in the absence of a catalyst.⁴

All the above-mentioned copolymers are of the triblock type. It is of interest to consider other multiblock copolymers. Chen et al. reported the ring-open copolymerization of L-Lactide and ethylene oxide (EO) by using various catalysts: analysis of products by ¹H-NMR showed that methanol-insoluble copolymers fractions had multiblock structures.⁵ But the multiblock segment length and its distribution, which can have great influence on properties of the copolymer, cannot be well controlled this way. Lee et al. have prepared PLLA-PEG multiblock copolymers, and investigated the crystallization behavior of the copolymers.⁶ However, a much wider investigation should be done on the molecular structure, characterization, and property of the PLLA-PEG multiblock copolymers. This is also one aim of our work in this article. Lee's multiblock copolymers were composed with rather long blocks of PEG (\bar{M}_n : 2000–10,000) and PLLA (\bar{M}_n : 2000–4500) to serve as compatibilizers in PLLA/PEG blends of the homopolymer. We synthesized PLLA-PEG multiblock copolymers with much shorter PEG ($\bar{M}_n = 600, 2000$) and PLA ($\bar{M}_n = 1000, 2000, 3000$), which are meant to be used as hydrophilic biodegradable polymeric materials themselves in bulk. Different from triblock structures with equal molecular mass, or a multiblock one with rather long blocks, the multiblock copolymers in this article have much more and shorter PEG and PLA segments, alternated evenly in the molecular chains. Consequently, they should present different properties such as better miscibility between the two components⁷ and lower crystallinity. In this article, the synthesis and characterization of PLA-PEG multiblock copolymers are reported.

EXPERIMENTAL

Materials

PEG diols of molar masses 600 and 2000 were purchased from Tianjin Tiantai Refined Chemical Co. Ltd., and used after being dried to constant weight under vacuum. L-lactic acid (80%, Shang-

hai Yierbao) was used as purchased. Ethylene glycol was distilled under reduced pressure and pyridine under atmospheric pressure. Succinic anhydride, dicyclohexylcarbodiimide (DCC), and dimethylaminopyridine (DMAP, Merck) are all A.R. grade reagents, and used without further purification. All the solvents, including chloroform, dichloromethane, ethyl ether, and acetone were dried and distilled before use.

Synthesis Methods

PEG diacid macromonomers were prepared by reacting corresponding PEG diols with succinic anhydride.⁸ The degree of substitution was determined by titration: 97.0% for PEG600 diacid (yield 78.2%), 98.0% for PEG2000 diacid (yield 90.1%).

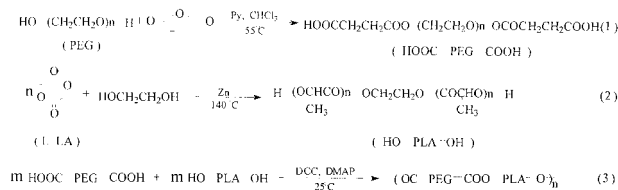
L-Lactide was prepared from commercial L-lactic acid.⁹ Then the PLA diol macromonomer was synthesized by polymerizing L-lactide in the presence of a predetermined amount of ethylene glycol and Zn powder.¹⁰ In the following, "diol" and "diacid" will be omitted for the sake of simplicity: PEG600 and PEG2000 are diacids with \bar{M}_n of 600 and 2000 respectively; PLA1000, PLA2000, and PLA3000 are diols with \bar{M}_n of 1000, 2000, and 3000, respectively.

PLA-PEG multiblock copolymers were prepared by polymerization of equimolar PEG and PLA bifunctional macromonomers in the presence of a coupling agent, DCC, and a catalyst, DMAP.¹¹ The reaction was carried out at room temperature for 10 h in CH₂Cl₂ solution. Then the resulting copolymer was recovered and purified according to the literature method described by Petrova et al.¹²

Measurements

¹H-NMR spectra were obtained at room temperature with a Bruker DMX300(WB) spectrometer operating at 300 MHz, eight scans, with the resolution if <0.3 Hz (BBI PROBHD, 0.1% EB), by using 5% (w/v) solutions in CDCl₃. The software used was a Winnmr2.2 workstation. Chemical shifts were given in ppm using tetramethylsilane (TMS) as the internal reference. Infrared spectra were recorded on a Perkin-Elmer 2000 FTIR spectrometer. The sample films were prepared by casting chloroform solutions onto KBr plates.

Gel permeation chromatography (GPC) analysis was performed at room temperature with a Waters apparatus equipped with a differential



Scheme 1 Synthetic procedure of PLA-PEG multiblock copolymers.

refractometer detector and a 60-cm PLgel 5 μm MIXED-C column. Tetrahydrofuran (THF) was used as the mobile phase at a flowing rate of 1 mL/min. Sample concentration was 0.5% (wt/v): 20 μL of solution were injected for each analysis. Calibration was based on Polystyrene standards, manufactured for Waters Corporation by PSS Polymer Standards Service.

Differential scanning calorimetry (DSC) thermograms were recorded in the range of -100 to 200°C on a DuPont Universal V2.5 TA instrument at a heating rate of $10^\circ\text{C}/\text{min}$. X-ray diffraction analyses were carried out with a Rigaku Dmax-3B X-ray diffractometer equipped with a Cu $\text{K}\alpha$ ($\lambda = 0.154 \text{ nm}$) source and a graphite monochromator.

Viscosities of the polymers were measured in 1.0-g/dL chloroform solutions using a Ubbelohde viscosimeter at 30°C . The intrinsic viscosity $[\eta]$ were calculated by the "One-Point Method" and expressed in dL/g:

$$[\eta] = [2(\eta_{\text{sp}} - 1n\eta_r)]^{1/2}/c$$

where $\eta_r = \eta/\eta_0$ and $\eta_{\text{sp}} = \eta_r - 1$, η and η_0 being the viscosity of the polymer solution and that of the solvent, respectively.

Contact angles of the polymer films were measured on a FACE CA-D contact angle-meter (Kyowa Kaimenkagaku Co.) at room temperature. Contact angle vs. time curves were obtained by measurements at different time intervals. The sample films were prepared by casting dichloromethane solutions of the copolymers at a concentration of 5 wt % onto a smooth glass slide. After solvent evaporation, under room condition for 3 days, the films were detached from glass and dried at 30°C under vacuum for 10 days.

RESULTS AND DISCUSSION

The synthetic procedure of the PLA-PEG multiblock copolymer can be outlined as Scheme 1.

A series of multiblock copolymers with PEG and PLA segments of different length were synthesized by this procedure. The various copolymers were named as $\text{PLA}_x\text{-PEG}_y$, where x and y are the molar masses of the PLA and PEG macromonomers, respectively. Table I presents the molecular characteristics of the copolymers and corresponding macromonomers.

PEG600 was a liquid, and PEG2000 a white powder. The three PLA diols were all in the form of waxy solids. The multiblock copolymers were all white solids, except PLA1000-PEG600, which was a waxy solid.

From Table I, it can be seen that both PEG 600 and PEG2000 had very small polydispersity indices ($I = \bar{M}_w/\bar{M}_n$) equal to 1.1, because the original PEG diols were narrow distribution reagents. The polydispersity index of the three PLA macromonomers was higher for the bulk polymeriza-

Table I Molar Mass and $[\eta]$ Data of PLA-PEG Multiblock Copolymers and Their Macromonomers

Copolymer	$\bar{M}_w^a/10^3$	$\bar{M}_n^a/10^3$	\bar{m}_w/\bar{M}_n^a	PLLA/PEG ^b	$[\eta]/\text{dL} \cdot \text{g}^{-1}$
PEG600	1.1	1.0	1.1	—	0.06
PEG2000	2.4	2.2	1.1	—	0.11
PLA1000	2.0	1.4	1.4	—	0.06
PLA2000	5.5	2.8	2.0	—	0.10
PLA3000	6.6	3.9	1.7	—	0.13
PLA1000-PEG600	14.3	11.0	1.3	1.04	0.28
PLA2000-PEG600	27.4	18.1	1.5	0.95	0.48
PLA3000-PEG600	30.7	20.3	1.5	1.00	0.50
PLA1000-PEG2000	13.2	8.6	1.5	0.86	0.33
PLA2000-PEG2000	16.7	11.3	1.7	0.95	0.45
PLA3000-PEG2000	14.9	10.3	1.5	1.08	0.38

^a Determined by GPC measurement.

^b Molar ratio of the two component segments in the copolymers, calculated from $^1\text{H-NMR}$ spectra.

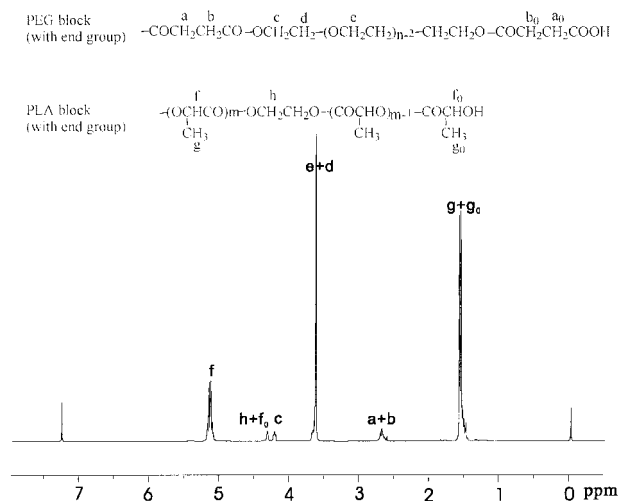


Figure 1 $^1\text{H-NMR}$ spectrum of the PLA2000-PEG600 multiblock copolymer.

tion condition. The copolymers presented molar mass distributions with polydispersity indices below 1.7. The number-average molar masses of the copolymers were in the range of 8.6×10^3 to 20.3×10^3 . It appears that the molar mass and $[\eta]$ values of the copolymers were much higher than those of the starting macromonomers. However, the fact that M_n values were rather low could be assigned to the fact that bifunctional substitution ratio of the diols and/or diacids were not very high. In other words, there was a small portion of macromonomers with only one functional group.

In the GPC chromatogram, the copolymer exhibited a narrow and monomodal molar mass distribution, indicating that the copolymer did not contain unreacted PEG diacid or PLA diol.

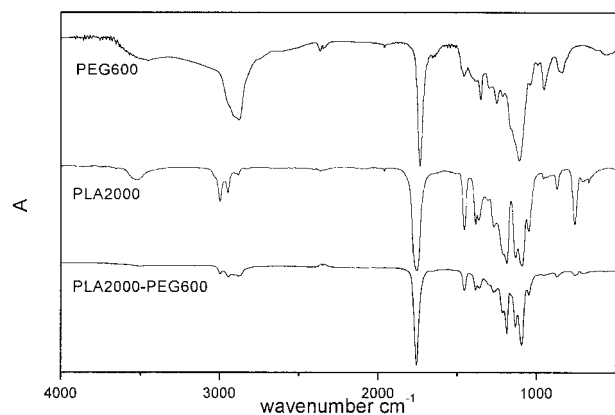


Figure 2 FTIR spectra of PEG600, PLA2000, and PLA2000-PEG600.

The $^1\text{H-NMR}$ spectrum of PLA2000-PEG600 is shown in Figure 1. Signals typical of both PEG and PLA blocks are observed. Assignment of the signals is shown on the spectrum. The bands a and b belonging to methylene protons of the succinic anhydride half ester end units shifted downfield after copolymerization. Similarly, the band corresponding to $-\text{CH}-$ in PLA end units shifted downfield from 4.33 to 5.13 ppm. These shifts confirmed that copolymerization did occur between the two macromonomers.

The molar component ratio of PLA/PEG in the multiblock copolymers can be obtained from the integration values of (e+d) and f, as shown in the

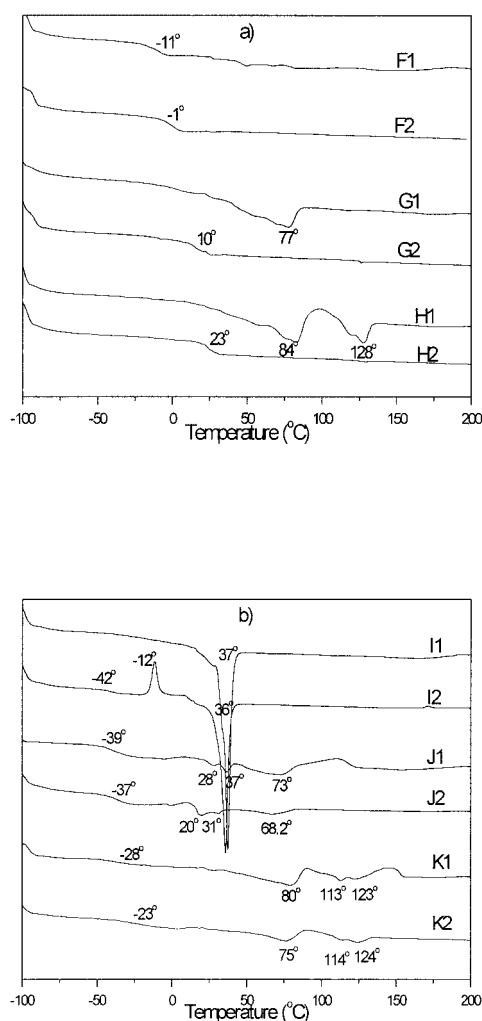


Figure 3 DSC thermograms of the multiblock copolymers: (a) PLA $_x$ -PEG600 multiblock copolymers: PLA1000-PEG600 (F), PLA2000-PEG600 (G), PLA3000-PEG600 (H); (b) PLA $_x$ -PEG2000 multiblock copolymers: PLA1000-PEG2000 (I), PLA2000-PEG2000 (J), PLA3000-PEG2000 (K). (1: first run, 2: second run).

Table II Thermal Data and Crystallinity of the Macromonomers

Macromonomer	Heating Run	T_g (°C) ^a	T_c (°C) ^a	T_m (°C) ^a	Crystallinity (%) ^b
PEG600	1st	-45	10	24	0
	2nd	-46	8	26	
PEG2000	1st	—	—	50	42.6
	2nd	—	—	49	
PLA1000	1st	5	—	62,85	9.1
	2nd	15	—	—	
PLA2000	1st	30	—	122	43.5
	2nd	35	—	—	
PLA3000	1st	27	—	123,140	52.2
	2nd	44	—	132	

^a Determined from DSC graphs of two heating runs.

^b Determined from X-ray diffraction spectra.

following formula. The values thus determined were very close to the ratios in feed (1 : 1), as show in Table I.

$$\text{PLA/PEG} = \frac{f}{2m} / \frac{e+d}{4(n-1)}$$

FTIR spectra are shown in Figure 2. In the spectrum of PEG600, the wide band at 3400 cm^{-1} was assigned to —COOH end groups, while the bands at 2877, 1739, and 1109 cm^{-1} corresponding to —CH₂—, C=O, and —C—O—C—, respectively. The band at 1644 cm^{-1} referred to the presence of traces of water in PEG600. For PLA2000, the band at 3526 cm^{-1} corresponded to —OH end groups, the bands at 2996 and 2945 cm^{-1} to —CH₃ and —CH—, the band at 1753 cm^{-1} to C=O, and the two big bands at 1150 and 1091 cm^{-1} to —C—O—C—. In the spectrum of the copolymer PLA2000–PEG600, all of these typical absorbing bands of PEG and PLA were detected, thus proving the presence of the two component blocks in the copolymer. Moreover, the bands of —OH and —COOH end groups were much smaller than those of the two macromonomers, in agreement with the much higher molar mass for the copolymer.

The thermal properties of the copolymers and their macromonomers were investigated by DSC, as shown in Figure 3 and Table II, respectively. At the end of the first heating run, the samples were quenched by immersion in liquid nitrogen to make the material amorphous; thus, glass transition and crystallization phenomena

could be observable during the second heating run.¹³ In the first run, PEG600 showed a glass transition temperature (T_g) at -45°C , a crystallization temperature (T_c) around 10°C , and a melting temperature (T_m) at 24°C . During the second heating, it behaved similarly, with little changes in the temperatures. This is because PEG600 was a liquid at room temperature, and no difference could be expected between the two runs. PEG2000 was so highly crystallizable that it showed a strong melting endotherm peak in both runs at 50 and 49°C . No T_g was detected during the second heating because it crystallized so fast that even rapid cooling could not make it amorphous.

In comparison with PEG, PLA macromonomers showed different DSC profiles. PLA1000 was slightly crystalline with a glass transition at 5°C and a double melting peak at 62 and 85°C . At the second heating, only a T_g was detected at 15°C . Similarly, PLA2000 showed a T_g at 30°C and a T_m at 122°C in the first run, and only a T_g at 35°C in the second one. In the case of PLA3000, it exhibited a T_g at 27°C and a double melting peak at 123 and 140°C at the first run, while a T_g was detected at 44°C and a very small melting peak at 132°C at the second run. Therefore, both T_g and T_m of PLA macromonomers increased with molar mass. The fact that no crystallization was observed during the second heating can be assigned to the low crystallizability of low molar mass PLA.

In the DSC graphs of PLA1000–PEG600, no T_m was detected, which means both components

could hardly crystallize. A T_g was detected at -1°C in the second run. PLA2000-PEG600 showed a T_m at 77°C , and the second run showed a T_g at 10°C . PLA3000-PEG600 showed a double melting peak at 84 and 128°C , while a T_g was detected at 23°C at the second run. The melting peaks observed for both PLA2000-PEG600 and PLA3000-PEG600 were attributed to PLA blocks. As in the cases of PLA macromonomers, PLA x -PEG600 copolymers exhibited increasing T_g and T_m values with increasing molar mass of PLA blocks. On the other hand, the T_g and T_m values of PLA x -PEG600 copolymers were lower than corresponding PLA macromonomers due to the interference between the two components.

PLA1000-PEG2000 presented a strong melting peak at 37°C during the first run, while the second run showed T_g , T_c , and T_m at -42 , -12 , and 36°C , respectively. The two melting peaks meant that the PEG2000 segments could crystallize in the PLA1000-PEG2000 copolymer, but less easily than PEG2000 macromonomer. PLA2000-PEG2000 showed three small melting peaks in both runs. The two peaks between 20 and 40°C could be attributed to PEG2000 segments, and the peak around 70°C to PLA2000 segments. In the case of PLA3000-PEG2000, multiple melting peaks were detected between 75 and 124°C in both runs and assigned to PLA3000 segments.

It is of interest to note that all the copolymers showed only one glass transition. This finding means improved miscibility between the two components in the multiblock copolymers, at least in the amorphous domains, in contrast to polymer blends of PEG and PLA¹⁴ or PEG-PLA-PEG triblock copolymers.³

Another noticeable phenomenon is the multiple melting peaks observed in the cases of PLA1000 and PLA3000 macromonomers as well as PLA3000-PEG600, PLA2000-PEG2000 and PLA3000-PEG2000 copolymers. They were tentatively assigned to imperfect crystallization due to the rather large distribution of polymer chains. In the case of the copolymers, the location of the segments could also influence the melting temperature. For example, PLA3000 segments located inside polymer chains could have different T_m s in comparison with those located at chain ends because of the difference in mobility. In all cases, PEG and PLA segments showed decreased crystallinity after copolymerization due to the hindrance between them; the longer the segment length of one component, the higher its crystal-

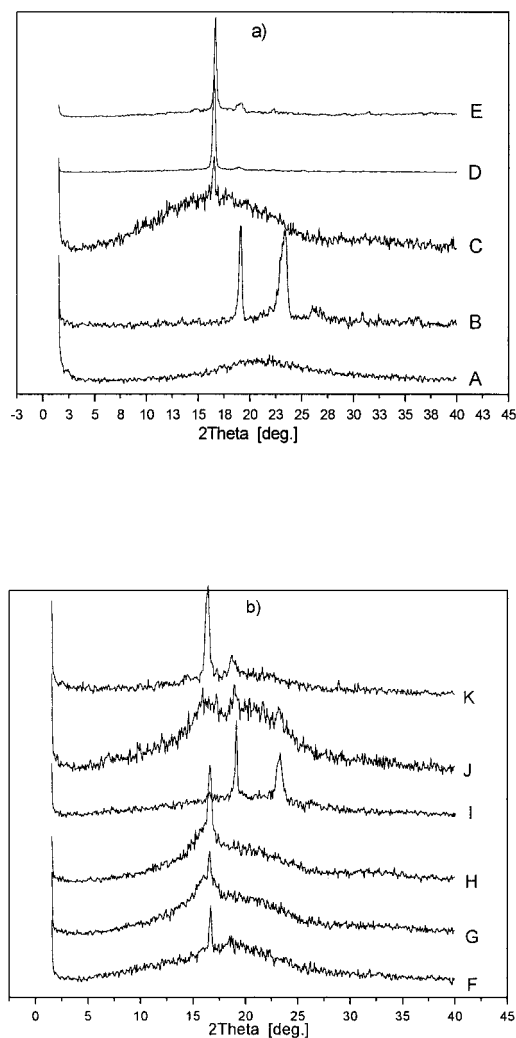


Figure 4 X-ray diffractograms of (a) macromonomers: PEG600 (A), PEG2000 (B), PLA1000 (C), PLA2000 (D), PLA3000 (E); (b) copolymers: PLA1000-PEG600 (F), PLA2000-PEG600 (G), PLA3000-PEG600 (H), PLA1000-PEG2000 (I), PLA2000-PEG2000 (J), PLA3000-PEG2000 (K).

linity, and the lower the crystallinity of the other component.

Figure 4 shows the X-ray diffraction spectra of the macromonomers and multiblock copolymers. PEG600 was liquid at room temperature, thus, it had no crystalline diffraction peak. PEG2000 showed two strong peaks at $2\theta = 19.1$ and 23.4° . PLA1000, PLA2000, and PLA3000 showed a main peak at $2\theta = 16.6^\circ$, the intensity increasing with the molar mass. For PLA1000-PEG600, PLA2000-PEG600, and PLA3000-PEG600, only the diffraction peak of PLA was detected. This means that PEG600 segments could not crystal-

lize in these copolymers. PLA1000-PEG2000 exhibited only the diffraction peak of PEG2000 segments, while PLA2000-PEG2000 showed the peaks of both components. Finally, only the peak of PLA3000 segments was detected in the spectrum of PLA3000-PEG2000. All these results were in good agreement with DSC data. Crystallinity data derived from the X-ray diffraction spectra are shown in Table II for the macromonomers and in Table III for the copolymers.

Figure 5 shows the contact angle vs. time curves of the copolymers and PLA macromonomers. PEG being highly hydrophilic, water drops spread out along its surface in a couple of seconds. Contact angle values obtained were close: 7.0° for PEG600 and 10.8° for PEG2000. PLA macromonomers had almost the same initial contact angle ($72\text{--}73^\circ$). Nevertheless, the contact angle decreased more quickly for PLA1000 than for PLA2000 and PLA3000. The initial contact angles of the copolymers were in the range of 44 to 67° , which were lower than those of PLA macromonomers. The contact angle curves fell into two distinct types due to different composition (PEG content) of the copolymers. Copolymers with low PEG content (<27 wt %), namely PLA2000-PEG600 and PLA3000-PEG600, showed similar trends as PLA, i.e., almost a linear decrease with time. In contrast, the other copolymers with relative high PEG content (38–70 wt %), namely PLA1000-PEG600, PLA1000-PEG2000, PLA2000-PEG2000, and PLA3000-PEG2000, presented a very rapid decrease of contact angle. That means that the hydrophilicity of these copolymers was greatly improved compared to PLA macromonomers, which is very advantageous for biomedical applications. Even PLA2000-PEG600 and PLA3000-PEG600 showed higher hydrophi-

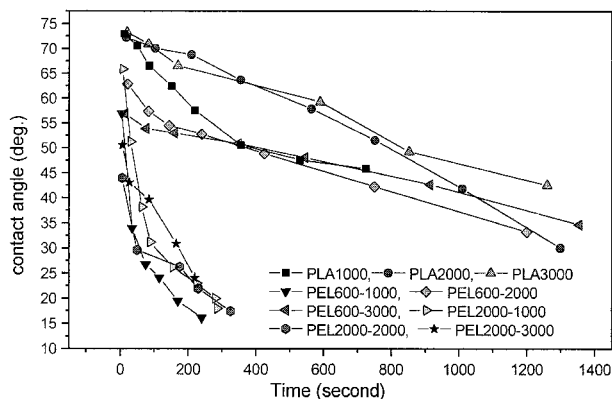


Figure 5 Contact angle vs. time curves of PLA macromonomers and the copolymers.

licity than the corresponding PLA macromonomers. The time in which the contact angle decreased to 35° , t_{35} , was employed to define the hydrophilicity.¹ Data are shown in Table III.

CONCLUSION

Multiblock PLA-PEG copolymers were successfully synthesized by polycondensation of PLA diols and PEG diacids. These novel copolymers showed improved miscibility between the two components. The crystallinity of the copolymers was largely decreased in comparison with PLA and PEG homopolymers, and could be modulated by adjusting the block lengths of both components. Contact angle measurement confirmed the strong improvement in hydrophilicity as referred to PLA homopolymers. These properties should be interesting for biomedical uses, in particular in substrates for controlled drug delivery.

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Table III Molecular Composition, Crystallinity, and Hydrophilicity Data of the Copolymers

Copolymer	PEG wt % ^a	Crystallinity (%) ^b	t_{35} (S)
PLA2000-PEG600	26.4	7.3	1171
PLA3000-PEG600	17.1	15.2	1409
PLA1000-PEG600	37.5	4.5	34
PLA1000-PEG2000	70.2	18.0	75
PLA2000-PEG2000	52.1	11.8	34
PLA3000-PEG2000	38.5	19.6	130

^a Mass content ratio of the two components in the copolymers, determined from $^1\text{H-NMR}$ spectra.

^b Determined from X-ray diffractometry.

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