Macromol. Symp. ***193***, *143–158 (2003)*

Triblock Copolymers of Lactide with Poly(ethylene glycol) and Influence of Stereochemical Composition

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SUMMARY: Polymerization of L-lactide (LLA) and poly (ethylene glycol) (PEG) at 120°C using stannous 2-ethyl hexanoate results in ABA triblock copolymers in good yields. The glass transition temperature of the copolymers shows strong dependence on the composition. One- and two-phase triblock copolymers can be prepared by controlling the molecular weight of the PEG soft block, as well as the initial LLA/PEG charge ratio. Incorporation of racemic lactide during polymerization drastically affects the crystallinity of the block copolymers obtained. ^{1}H and ^{13}C (solid state) NMR are powerful tools for characterization of the polymer materials.

Introduction

Poly-hydroxy acids are one of the most important classes of biodegradable polymers for biomedical applications. There has been much interest in the use of poly (lactic acid) (PLA) in biodegradable sutures, drug delivery devices and surgical implants, since its biodegradation products are excreted in human metabolic processes [1-8]. The ease of preparation of PLA and its copolymers and their broad range of properties, as well as expected biodegradability, have resulted in a further increase in interest in these polymers. Recently a new resorbable monofilament suture derived from a copolymer of L-lactide and caprolactone has been reported [6]. The effects of the primary structure on the degradation of poly (caprolactone)/poly (L-lactide) block copolymers have been studied [9]. The synthesis and characterization of block copolymers of L-lactide (LLA) and poly (ethylene glycol) (PEG) have also received considerable attention [3-5, 10-13]. A wide variety of synthetic methods have been developed by which to prepare block copolymers

CCC 1022-1360/00/$ 17,50+.50/0

from LLA and PEG: Sn (11) 2-ethylhexanoate at 150°C [5], potassium tert-butoxide [10], sodium hydride [11] and calcium hydride/Zn [14] have been used. Block copolymers have also been prepared, also in the absence of added catalysts [12, 13]. Products with a wide range of percent yields and thermal properties have been reported. In principle, the introduction of hydrophilic segments of PEG into the more hydrophobic PLLA should enhance biocompatibility with soft tissues. In the present study we report on the preparation of block copolymers of PLLA and PEG using stannous 2-ethyl hexanoate, resulting in good % yields and predictable thermal properties. Since one- or two-phase block copolymers may be obtained, the effect of varying the molecular weight of the PEG soft block and incorporation of racemic lactide on polymer morphology will also be investigated.

Experimental

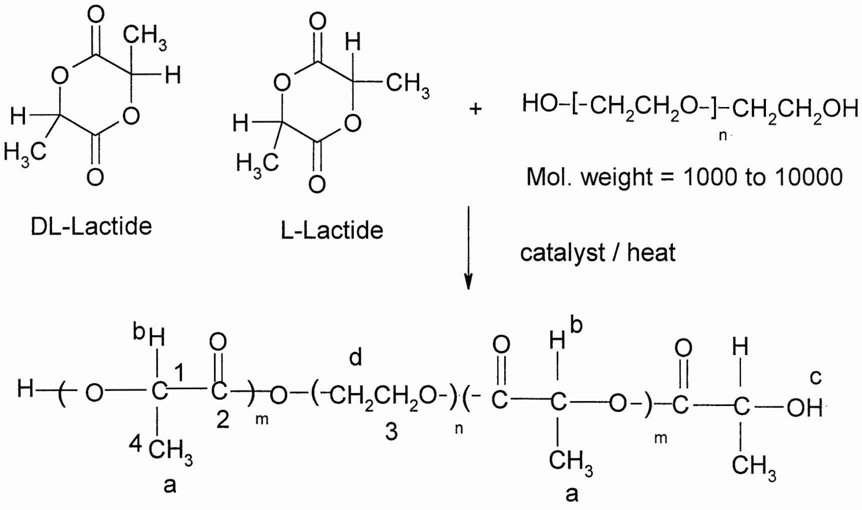
Materials: L-lactide (LLA) (Aldrich, > 98 %) was purified by recrystallization from toluene and dried in vacuum oven over P_2O_5 for 24 h. The purity was determined to be 99.97 % by differential scanning calorimetry, m.p. 98°C. Poly (ethylene glycol) (PEG-1000, 2000, 4000 and 8000) was obtained from Fluka AG. PEG (molecular weight 10000) and stannous 2-ethyl hexanoate were purchased from Sigma. All other solvents and chemicals were used as received, without further purification.

Block copolymerization: The macroinitiator was prepared by weighing PEG and two molar equivalent of catalyst into a reaction vessel equipped with N_2 gas inlet and a magnetic stirrer bar. The corresponding amount of LLA was added to obtain a LLA/PEG weight ratio of 7 to 59. Polymerization was carried out by stirring at 80°C for 1 h and then at 120°C for 23 h. After polymerization, the product was dissolved in chloroform, precipitated in an excess of cold methanol and dried under vacuum at 60°C for 24 h. Triblock copolymers of different stereochemical compositions were prepared by incorporating different amounts of L-/DL-lactide during the polymerization. All the block copolymers prepared using this procedure were obtained in good yields. Phase separation was investigated by using 30 to 50 weight percent PEG block of molecular weight 4000 to obtain corresponding PLA-PEG triblock copolymers.

Characterization: ^{1}H and ^{13}C NMR spectra were obtained on a 270 MHZ Bruker instrument (model AC-270) by dissolution of the polymer in $CDCl_3$. High-resolution solid state 75.4 MHZ NMR was also used to characterize the block copolymers. Solid-state infrared spectra were recorded using a FT-IR Nicolet instrument (100 scans, DTGS KBr detector). Differential scanning calorimetry (DSC) measurements were conducted with a Perkin Elmer DSC 7 instrument, at a heating rate of 20°C/min. The wide-angle x-ray scattering (WAXS) powder patterns were recorded using a Norelco diffractometer and Cu K_α radiation. The diffraction patterns were recorded at a power setting of 30 KV and 15 mA, using 500-5000 counts/sec. Gel permeation chromatography (GPC) was used to determine the molecular weights of the copolymers in THF using polystyrene standards. Thermogravimetric analysis (TGA) of the copolymers was performed using a TGA 7 Perkin Elmer instrument at a heating rate of 20°C, from 30 to 600°C, under nitrogen purge.

Results and Discussion

The reaction for the formation of PLA-PEG triblock copolymers is shown in Scheme below. A typical ^{1}H NMR spectrum obtained for the block copolymers is illustrated in Figure 1. The characteristic signals can be assigned as follows: $-CH_3$ (δ 1.6, doublet, 3 H), $-OCH_2CH_2O-$(δ 3.7, 4 H) and –CH (δ 5.2, quartet, 1 H) corresponding to proton types a, d and b respectively. The composition of the block copolymers was evaluated from the methine and methylene peak areas. The results indicate close agreement between the theoretical and experimental values as demonstrated by the results in Table 1.



Scheme 1. PLLA-block-PEG-block-PLLA preparation.

Block copolymers containing LLA and PEG have been synthesized using stannous octoate at 150°C with % yields varying from 54 to 95 % [5]. Generally, increasing the polymerization temperature results in a decrease of the molecular weight of PLLA.

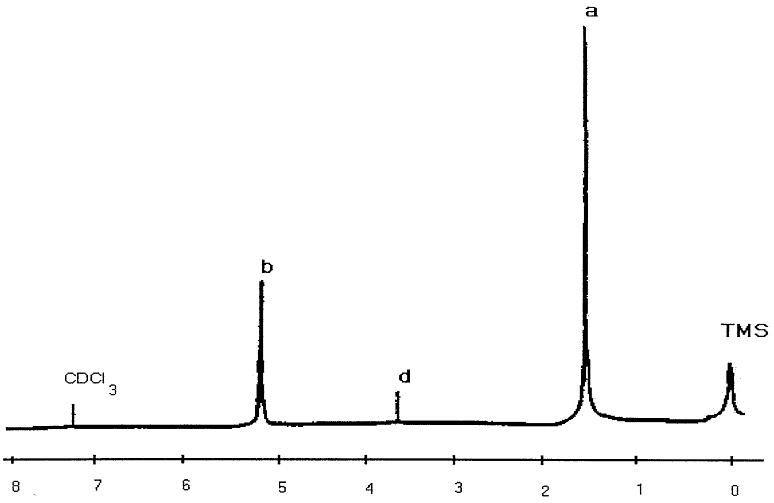


Figure 1. ^1H NMR spectrum of PLLA-block-PEG-block-PLLA

Table 1. Conditions of preparation and results of LLA and PEG block copolymers

Sample code	Mn of PEG	LLA/PEG	LLA/PEG♦	Yield (%)*
LPEG 50X	1000	51	67	87
LPEG100X	1000	104	121	92
LPEG 200X	1000	200	177	96
LPEG 400X	1000	406	492	84
LPEG 50Z	2000	100	131	95
LPEG 100Z	2000	201	227	97
LPEG 200Z	2000	398	485	94
LPEG 400Z	2000	785	677	98
LPEG 50Y	4000	203	222	96
LPEG 100Y	4000	400	471	98
LPEG 200Y	4000	782	844	98
LPEG 400Y	4000	1602	1756	97

initial LLA/PEG mol charge ratio * % yield after $CHCl_3/CH_3OH$ purification

♦ LLA/PEG ratio determined by ^1H NMR (peak b/peak d)

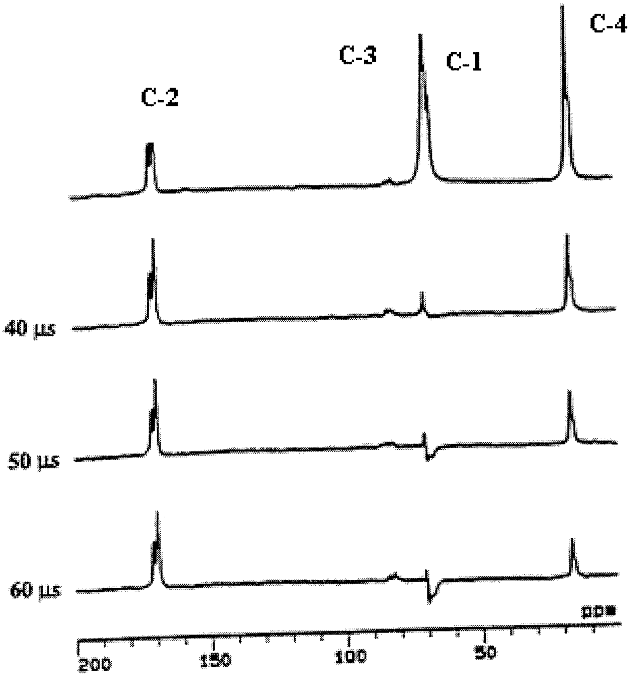


Figure 2. 75.4 MHZ ^{13}C solid state NMR spectra of LPEG 50Y copolymer.

^{13}C NMR analysis of the block copolymers revealed the characteristic PLLA signals at 16.6 and 69.0 ppm, corresponding to carbon types 4 and 1 respectively, in addition to the carbonyl signal (C-2) at 169.6 ppm, as illustrated in Figure 2. Another striking feature observed was the $-CH_2$ (C-3) at 70.5 ppm, attributable to the PEG segments. The PEG (C-3) and PLLA (C-1) signals were, however, not well resolved due to the broadening of the peaks in the solid state spectra, in contrast to the sharp, distinct lines observed in the solution ^{13}C NMR spectra. In the liquid state, all of the anisotropic interactions (line broadening interactions) were averaged to their isotropic values, due to rapid tumbling of the molecules. A ^{13}C solid state spectrum obtained for PEG homopolymer revealed that the C-3 signals occur at 71 ppm compared to the PLLA C-1 type observed at approx. 68 ppm. Confirmation of this assignment is illustrated in Figure 2. This was done by performing CP with polarization inversion (spectral editing) experiments with delay times of 40, 50 and 60 μs, which causes inversion of the C-1 type. ^{13}C NMR has been used for the sequence analysis of polyesters. ^{13}C solution nmr results yielded the characteristic signals of the isotactic tetrads sequence distributions at δ 169.6 and 69.01 ppm, as also reported by other workers [11]. The triblock copolymers formed exhibited a high degree of isotacticity. The solid state IR spectra obtained for the block copolymers showed characteristic absorption bands in the region 3000 to 2850 cm^{-1} due to C-H stretch and C=O ester absorption band at 1765 $cm.^{-1}$.

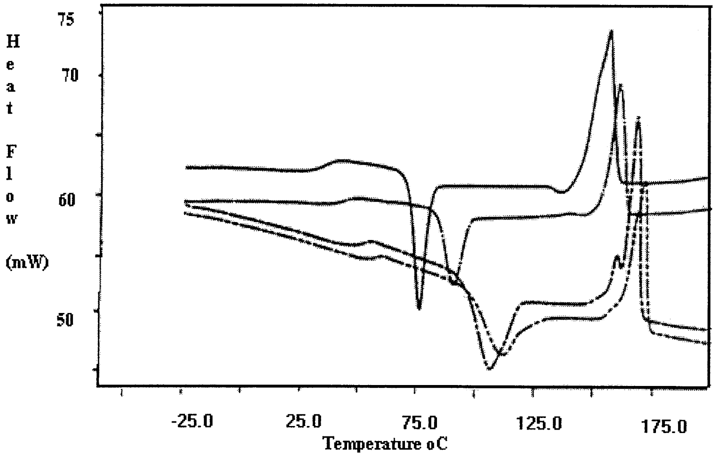


Figure 3. DSC glass transition temperature profiles for LPEG 50X-400X copolymers.

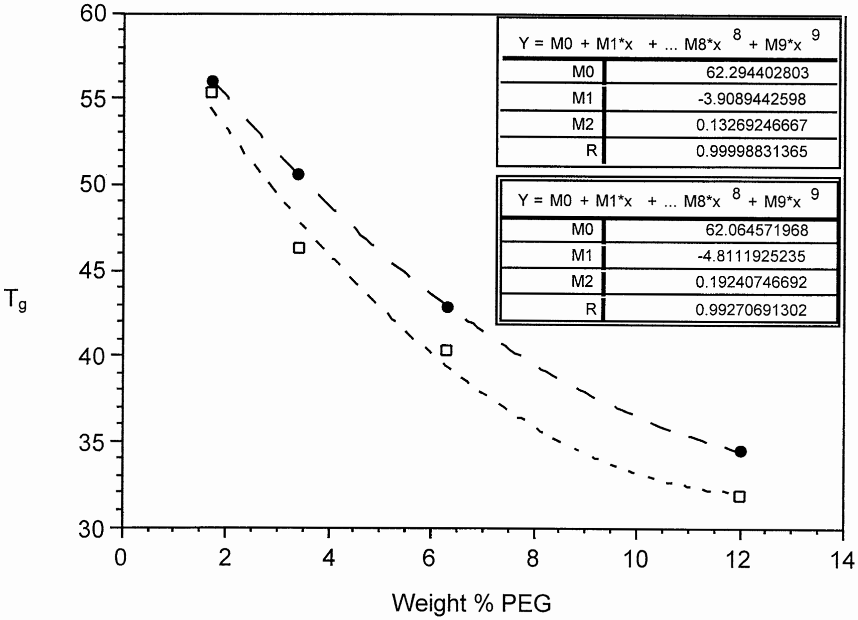
Figure 3 and Table 2 summarize the results of the DSC measurements of the block copolymers. The morphology of the copolymers was studied by heating from -60 to 200°C at 20°C /min (1st scan), quenched from the melt and then recording the second heating cycle. The glass transition (T_g), melting (T_m) and crystallization (T_c) temperatures presented in Table 2 show strong dependency on the compositions of the block copolymers. Figure 3 illustrates the trend of increasing T_g with decreasing content of the PEG block.

Table 2. Transition temperatures and heats of fusion of PLLA-block-PEG-block-PLLA copolymers (second heating cycle after quenching from the melt).

Sample	M_n of	LLA/PEG		T_g	T_m	ΔH_m	T_c	ΔH_c
code	PEG	mol	wt	°C	°C	J/g	°C	J/g
	X 10^3	ratio	%					
LPEG 50X	1	51	88/12	34.5	156	47.1	76.2	-25.9
LPEG 100X	1	104	94/6	42.9	161	44.5	91.0	-32.6
LPEG 200X	1	200	97/3	50.6	167	48.4	107	-42.0
LPEG 400X	1	406	98/2	56.0	171	54.7	112	-50.7
LPEG 50Z	2	100	88/12	32.0	159	43.1	82.5	-25.8
LPEG 100Z	2	201	94/6	41.1	165	45.8	89.8	-33.0
LPEG 200Z	2	398	97/3	50.9	169	46.8	123	-51.5
LPEG 400Z	2	785	98/2	50.5	169	44.0	104	-45.9
LPEG 50Y	4	203	88/12	31.9	163	47.6	78.0	-26.1
LPEG 100Y	4	400	94/6	40.3	166	46.8	85.2	-29.5
LPEG 200Y	4	782	97/3	46.3	168	44.7	99.3	-41.8
LPEG 400Y	4	1602	98/2	55.3	171	43.4	123	-40.0
LPEG 50P	10	504	88/12	nd	165	45.6	81.7	-27.3
LPEG 100P	10	997	94/6	39.9	166	42.9	90.7	-33.4
LPEG 200P	10	2008	97/3	43.7	166	48.0	100.7	-35.6
LPEG 400P	10	4047	98/2	47.1	166	56.0	97.5	-38.7
PLA 500				56.2	173	55.0	108	-46.1
PEG 1	1				40.8	160		
PEG 2	2				57.6	168		
PEG 4	4				66.6	178		
PEG 10	10			-38.7	68.9	188		

Poly (L-lactide) homopolymer prepared using stannous octoate (LLA/cat=500).
nd: not determined using DSC.

The results in Table 2 demonstrate the broad range of thermal properties obtained by incorporating different PEG block lengths and copolymer compositions. Evidently, as the PEG content is systematically decreased in a given series, a corresponding increase in the crystallization temperature is observed. The first heating DSC cycle of the block copolymers only reveals the melting endotherms corresponding to the PLLA crystalline phase.



Y = M0 + M1*x + ... M8*x ^{8} + M9*x ^{9}	
M0	62.294402803
M1	-3.9089442598
M2	0.13269246667
R	0.99998831365

Y = M0 + M1*x + ... M8*x ^{8} + M9*x ^{9}	
M0	62.064571968
M1	-4.8111925235
M2	0.19240746692
R	0.99270691302

Figure 4. Effect of varying the PEG block length on T_g of PLLA-PEG-PLLA copolymers. PEG-1000 (●), PEG-4000 (□)

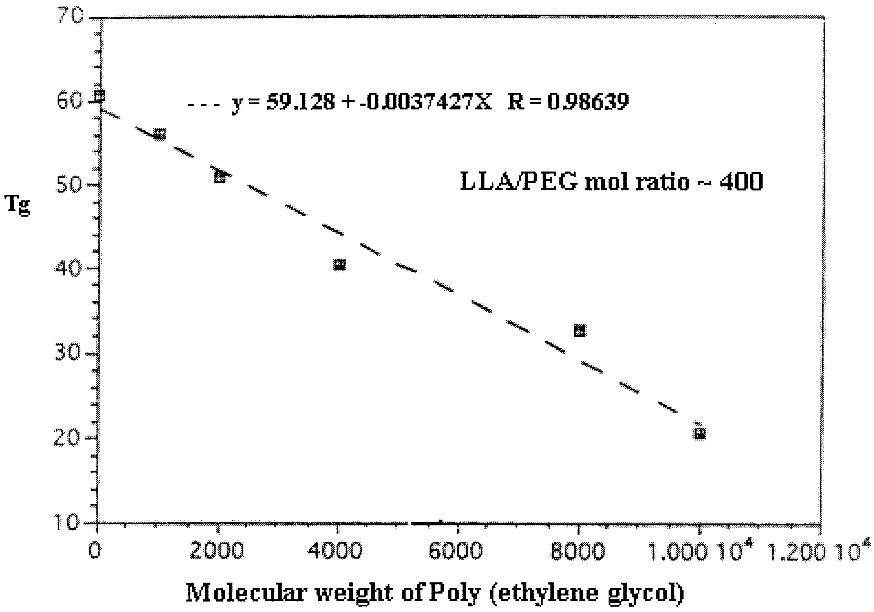


Figure 5. Effect of molecular weight of PEG block on T_g of triblock copolymers

In addition, no melting endotherms corresponding to the PEG segments were detected in both the first and second heating cycles. The results suggest that the morphology of the block copolymers containing up to 12 wt % PEG content essentially consist of a one-phase matrix (both amorphous and crystalline regions). No evidence of phase separation was observed for the PEG blocks 1000, 2000 and 4000 investigated. Both the T_g and T_m values increased with increasing length of the PLLA blocks. Since no melting endotherms of PEG blocks were observed, it appears that the crystallization of the predominant PLLA blocks suppresses the crystallization of the PEG blocks. Figure 4 gives the T_g profiles of two types of block copolymers representing different PEG blocks of molecular weight 1000 and 4000. It is shown that block copolymers of lower glass transition temperatures may be obtained by increasing the PEG soft-block length. Also of interest is the observation that for a given LLA/PEG molar ratio (example 400) T_g values of 56.0, 50.9, 40.3, 32.6 and 20.6° C were obtained for the block copolymers corresponding to the incorporation of PEG-1000, 2000, 4000, 8000 and 10000 blocks respectively.

This decrease reflects the increasing flexibility in the polymer chain as a result of the increasing length of the PEG soft blocks. Figure 5 shows the relationship between T_g values of the ABA triblock copolymers of LLA/PEG molar ratio of approximately 400. The glass transition temperatures obtained for PLLA and PEG-10000 homopolymers are 60.8 [15] and -38.7°C respectively. These results indicate that the triblock copolymers formed are compatible in the amorphous region, with predictable T_g values typical of single-phase systems. The modification of the glass transition temperature of the block copolymers is easily achieved by incorporation of appropriate PEG block and copolymer composition. The DSC curves obtained for block copolymers containing 30 to 50 weight % PEG (MW 4000) are presented in Fig. 6. As can be seen, two endothermic events are observed, corresponding to the melting temperatures of PEG and PLLA. Table 3 summarizes the T_m values and enthalpy of fusion data for the triblock copolymers.

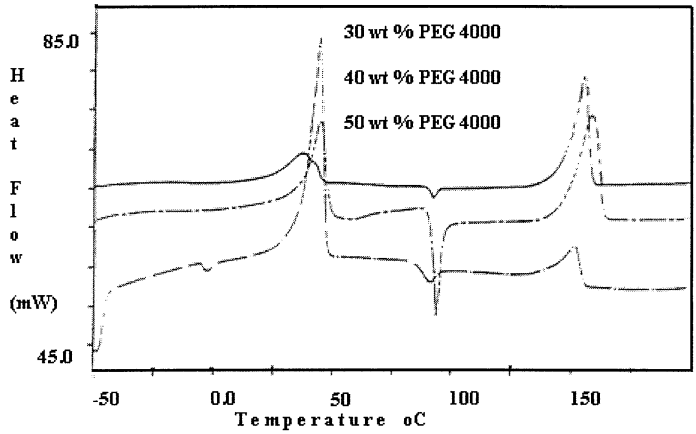


Figure 6. DSC thermograms illustrating the effect of varying the PEG content.

Evidently, phase separation occurs in the crystalline phase for these types of triblock copolymers. Basically, two main trends can be seen. As the PEG content is increased, a depression of the crystallinity of the PLLA phase is observed, while the crystallinity of the PEG block increases accordingly.

Table 3. Effect of varying the PEG content on thermal properties of triblock copolymers

Sample code	wt % PEG 4000	T_{m1}	ΔH_1	T_{m2}	ΔH_2
LPEG 30	30	38.3^a	16.1	159	37.5
		37.5^b	16.5	156	33.4
		36.3^c	15.1	155	32.2
LPEG 40	40	44.8^b	24.5	159	26.4
LPEG 50	50	44.6^b	43.9	152	10.1

Temperature in °C and enthalpy in J/g
^{a}, ^{b} and ^{c} I, II and III scans respectively

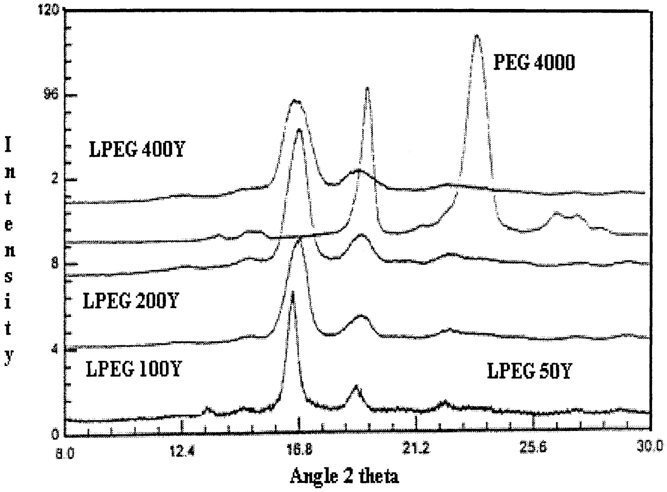


Figure 7. Typical WAXS powder patterns of PLLA-block-PEG-block-PLLA and PEG.

Further investigation of the one-phase behavior observed for the block copolymers (2 to 12 weight % PEG) was performed using wide angle x-ray analysis (WAXS). The characteristic WAXS powder patterns are illustrated in Figure 7. For the PEG homopolymer the interplanar d-spacings were found to be 4.53 and 3.78 Å, corresponding to angle 2θ values of 19.4 and 23.5° respectively. It is also interesting to note that the

WAXS powder patterns observed for the ABA triblock copolymers (Fig.7) were essentially identical to that of the PLA 500 homopolymer. The absence of d-spacing values corresponding to PEG provides further evidence that the triblock copolymers are truly a one-phase system as demonstrated by DSC measurements. Dividing the intensities of the peaks at 5.33 and 4.69 Å for the poly (L-lactide) compared to values of 2.5 to 3.0 for the triblock copolymers a ratio of 2.9 is obtained. These results suggest therefore that the PEG blocks do not crystallize in the triblock copolymers investigated in this study.
The molecular weights presented in Table 4 demonstrate the close agreement observed between the GPC results and values obtained using ^{1}H NMR analysis.

Table 4. Typical molecular weight data for triblock copolymers

Parameter	LPEG 50X	LPEG 100X	LPEG 200X
LLA/PEG mol ratio	51	104	200
$M_n{}^a$	10657	18440	26511
$M_n{}^b$	12293	15636	23318
M_w	20590	27296	40344
MWD	1.67	1.75	1.73

^{a} determined using ^{1}H NMR spectroscopy

b determined using GPC

The above results show that the block copolymers were of predictable molecular weight. The molecular weight distribution parameter of the triblock copolymers varied from 1.67 to 1.75.

Polymer stereochemistry influences not only the crystalline properties but also the degradation properties of polymers. In Figure 8 it is shown that incorporation of approximately 10 weight % dl-lactide during the polymerization process is sufficient to disrupt the PLLA crystalline phase of the triblock copolymers. The addition of small amounts of racemic lactide (less than 10 wt %) during formation of the block copolymers therefor provides one possibility of controlling the high crystallinity of the PLLA phase and associated processing problems. Generally, the lower physical strength properties of amorphous polymers render semi-crystalline polymers more attractive. Our results show that by careful control of the stereochemical composition of the lactide monomer it is possible to prepare PLLA-PEG-PLLA triblock copolymers of desired crystallinity specifications. The processing advantages of this approach include: reduction in the melting temperature, crystallinity and modification of degradation properties of PLLA copolymers. The degradation of both PLLA [16, 17] and PEG [18, 19] is well documented in the literature. Consequently, block copolymers of lactide and poly(ethylene glycol) can also be expected to be degradable.

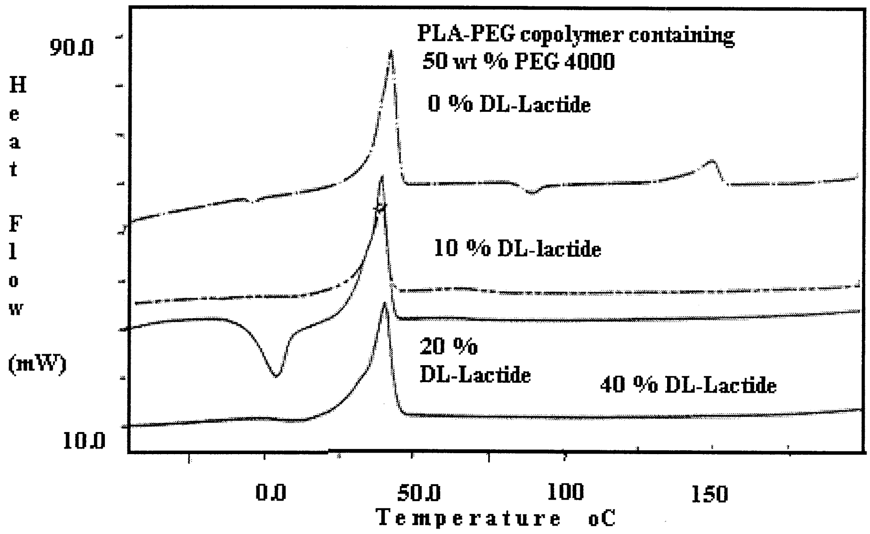


Figure 8. DSC thermograms showing the influence of stereochemical composition

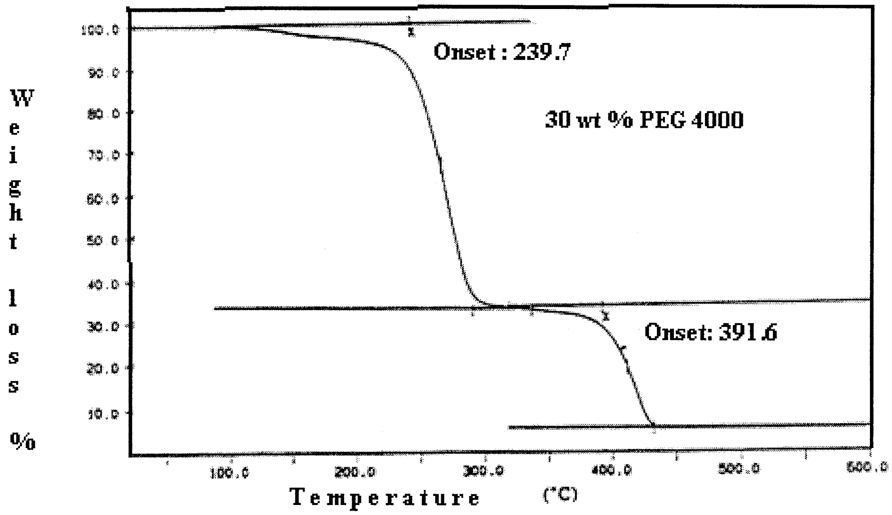


Figure 9. TGA profile of PLLA-PEG-PLLA copolymer containing 30 wt % PEG 4000.

Conclusions

We have shown that triblock copolymers of L-lactide and poly (ethylene glycol) can be prepared in good yields using stannous 2-ethyl hexanoate catalyst. The catalyst has been shown to be very efficient and prevents racemization. Whereas a wide variety of other catalysts such metal oxides, salts, CaH_2 or zinc metal have been used, stannous (II) 2-ethylhexanoate is preferred, particularly for the production of polymers for biomedical applications. The glass transition temperatures of the copolymers show a strong dependency on the composition. Single-phase and two-phase triblock copolymers can be prepared by careful control of the molecular weight of the PEG soft block and the L-lactide/PEG charge ratios. PLA/PEG triblock copolymers of desired stereo-chemical composition and predictable properties could also be prepared. Varying the stereochemical composition of lactide monomer can modify the usual high crystallinity of poly (l-lactide) and associated processing problems. The broad range of hydrophobic-hydrophilic properties, low glass-transition temperatures, crystallinities and expected biodegradabilities should enhance the compatibility of the triblock copolymers with soft tissue.

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