



Preparation of biodegradable polylactide-co-poly(ethylene glycol) copolymer by lactide reacted poly(ethylene glycol)

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Abstract

Poly-DL-lactide-poly (ethylene glycol)-poly-D, L-lactide triblock copolymer (PELA) was synthesized with the initiator of potassium poly (ethylene glycol)ate. The effects of various factors, such as amount of solvent and initiator, reaction time and temperature, sort of solvent and molecular weight of poly (ethylene glycol) (PEG) on the polymerization reaction were investigated. The polymerization was conducted in the super-saturated solution of monomer and monomer was successively dissolved and polymerized. Therefore the reaction rate was controlled by the dissolving rate. An effort to solve polymerization of DL-lactide in THF initiated by potassium poly (ethylene glycol)ate with relatively low molecular weight of PEG was made. The copolymers were characterized by GPC, DSC, IR and $^1\text{H-NMR}$. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Poly-DL-lactide (PLA) was a very attractive biomaterials for pharmaceutical and medical application due to its non-toxicity, biocompatibility and biodegradability. Polyether, especially poly(ethylene glycol) has the superior properties of non-toxicity, flexibility, hydrophilicity and biocompatibility. A new family of block copolymers can be formed by copolymerization of lactide and poly(ethylene glycol). The biodegradation rate and hydrophilicity of this kind of biodegradable poly(ester-ether) may be controlled by adjusting the mole ratio of hydrophilic and hydrophobic segments and sequence distribution of segments.

In recent years many efforts have been made in synthesis of polylactide-poly(ethylene glycol) block

copolymer [1–5]. Deng et al. described the copolymerization of DL-lactide and PEG by $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ [6]. Kricheldorf et al. investigated the reaction mixture of L-lactide and PEG in bulk by metal oxides and stannous octoate [7]. However, little attention was paid to the preparation of polylactide homopolymer and polylactide-poly(ethylene glycol) copolymer (PELA) by anionic ring-opening polymerization of L-lactide in the presence of potassium methoxide (MeOK) [8,9] and sodium poly(ethylene glycol)ate [10]. Also, Kricheldorf et al. reported the synthesis of poly-L-lactide homopolymer initiated by potassium tert-butoxide ($\text{Bu}^{\text{t}}\text{OK}$) [11] and copolymers from L-lactide, poly(ethylene glycol) and potassium tert-butoxide in toluene at 80°C [12].

The present work aims at the synthesis of ABA type block copolymers comprising poly-DL-lactide (A) and poly (ethylene glycol) (B) segments via anionic polymerization of DL-lactide with potassium poly (ethylene glycol)ate macroinitiator.

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2. Experimental

2.1. Materials

DL-lactide (LA) with m.p. 125–127°C was synthesized according to the literature procedures [13]. Crude products were thrice recrystallized from ethyl acetate. Poly(ethylene glycol)-4000 was purified by precipitation from tetrahydrofuran (THF) solution into hexane and dried under vacuum at 30°C for a week [10]. Toluene was distilled under nitrogen after drying by refluxing over calcium hydride. THF was dried over sodium–potassium alloy and its blue solution was distilled in dry argon in a vessel.

2.2. Preparation of the macroinitiator

One gram of poly(ethylene glycol)-4000 and fresh potassium particle was placed in a previously flamed and nitrogen purged glass reactor equipped with magnetic stirring bar and reflux condenser. THF (25 ml) was added through rubber septa using a syringe. The reaction mixture was refluxed for 24 h and filtered. The concentration of the initiator solution was determined by titration with 0.04 M aqueous HCl. The result indicated that the whole hydroxy group of poly(ethylene glycol) was converted into alcoholate.

2.3. Polymerization of DL-lactide by anionic initiator

Polymerization was conducted in a previously flamed and nitrogen purged glass reactor equipped with magnetic stirring bar. DL-lactide was first added under a current of nitrogen, then solvent and initiator solution were sequentially introduced into the reactor with a syringe. The polymerization was kept at room temperature for 3 h. Then the reaction products were diluted with acetone and precipitated in large amount

of ethanol, filtered and washed by hot ethanol to remove unreacted poly(ethylene glycol) homopolymer. The final white solid products were dried under reduced pressure at 40°C to a constant weight.

2.4. Characterization of PELA block copolymer

¹H-NMR spectrometer of the copolymers were recorded on a Varian FT-80A NMR spectrometer at room temperature using CDCl₃ as solvent, and with TMS as the internal standard. IR spectra were recorded on a Nicolet MX-1 IR spectrometer. The samples were prepared by casting films from acetone solution onto KBr plate. Average molecular weights and their distributions were determined by means of GPC using a Water Associates Model ALC/GPC 244 apparatus operating with THF and calibrated with polystyrene standards. The Intrinsic viscosity was measured on 0.2% (g/dl) solution of polymer in THF at 37°C with an Ubbelohde viscometer. Glass transition temperatures were obtained using a Perkin–Elmer DSC7 Thermal Analysis apparatus at a heating rate of 20°C/min.

3. Results and discussion

3.1. Synthesis of polylactide-poly(ethylene glycol)-polylactide triblock copolymer (PELA)

Because efforts to solution polymerization of DL-lactide in THF by potassium poly(ethylene glycol)-4000ate were not successful, the polymerization of DL-lactide was carried out by directly adding initiator solution into the monomer in the absence of solvent and as a result copolymers with high molecular weight were obtained. The results were listed in Table 1. Table 1 showed that the method of monomer being infiltrated by initiator solution was effective for the polymeriz-

Table 1

The results of polymerization of LA initiated by potassium poly(ethylene glycol-4000)ate^a

| No. | Monomer | Initiator solution (ml) ^b | Condition | M_n ($\times 10^4$) | M_w ($\times 10^4$) | M_w/M_n |
|-----|-------------------|--------------------------------------|------------------------|----------------------------|----------------------------|-----------|
| A1 | 1 g LA | 2 | 20°C, 2 h; 110°C, 2 h | 1.67 | 5.98 | 3.58 |
| A2 | 1 g LA | 1.2 | 20°C 10 min; 65°C, 4 h | 1.65 | 6.57 | 3.98 |
| A3 | 1 g LA | 1.2 | 20°C, 2 h; 65°C, 2 h | 1.60 | 6.20 | 3.87 |
| A4 | 1 g LA | 1.2 | 20°C, 21 h | 1.40 | 5.90 | 4.21 |
| A5 | 1 g LA | 1.2 | 20°C, 21 h | 1.09 | 4.57 | 4.18 |
| A6 | 2 g LA + 3 ml THF | 0.84 | 67°C, 4 h | 0.23 | 0.95 | 4.11 |
| A7 | 1 g LA | 0.42 | 20°C, 4 h | 0.27 | 1.13 | 4.13 |
| A8 | 1 g LA + 2 ml THF | 0.42 | 67°C, 5 min | 0.34 | 1.02 | 3.04 |

^a [Co]/[Mo] = 3.5‰.

^b Samples 1 and 2 in toluene solution, 2–8 in THF solution.

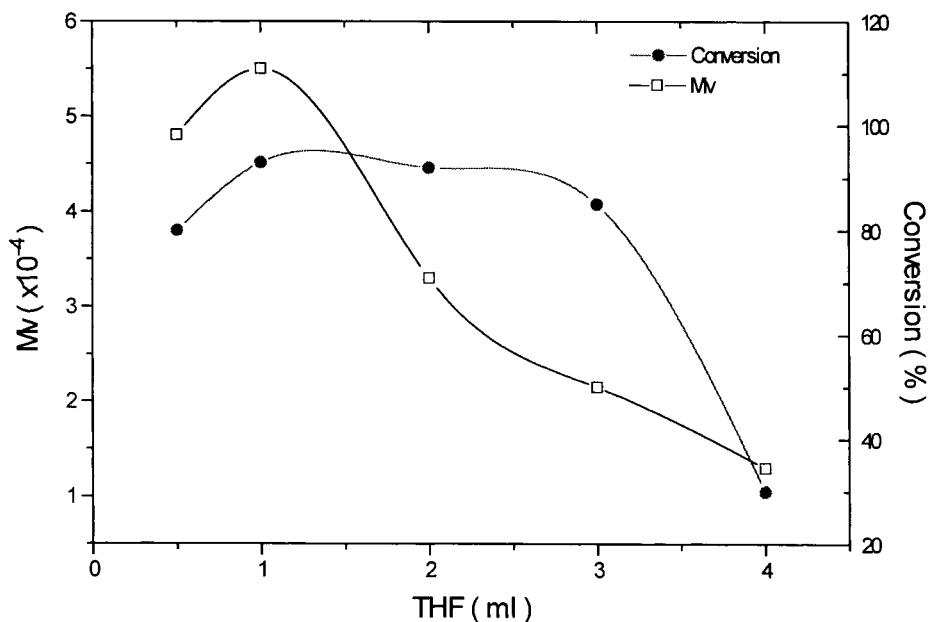


Fig. 1. Polymerization of D,L-LA with different amounts of THF (1 g D,L-LA with 0.55 ml PEG-4000 potassium salt in THF solution, Co/Mo = 3‰, at 16°C).

ation of DL-LA and L-LA. However the reaction extent was dependent on the wetting extent of the monomer by initiator solution, and stirring cannot be performed during polymerization, therefore it was difficult for homogeneous polymerization. From samples A6 and

A8 we can see that the solvent addition and reaction temperature greatly influenced the polymerization. In the following experiments a little solvent was added to make the polymerization, which was conducted under stirring.

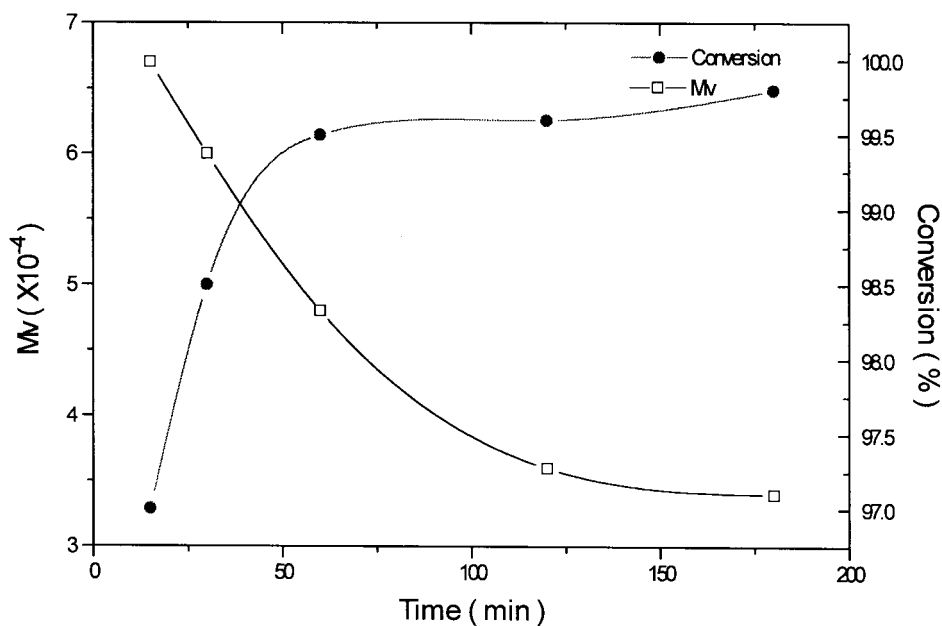


Fig. 2. Effect of reaction time on the polymerization (1 g D,L-LA in 2 ml THF, Co/Mo = 3‰, at 16°C).

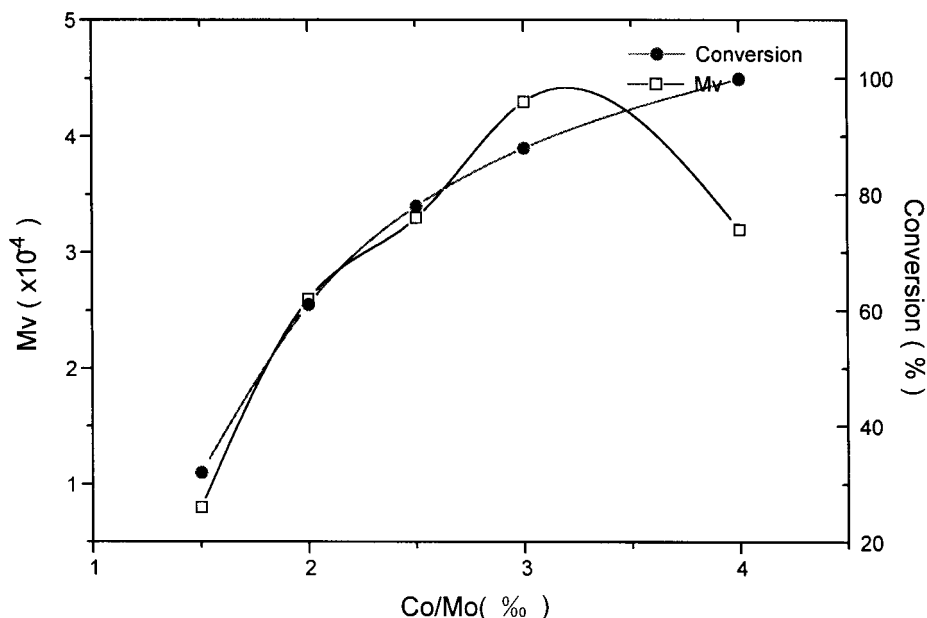


Fig. 3. Influence of the amount of initiator on the molecular weight of polymer and conversion of the monomer (1 g D,L-LA in 1 ml THF, at 16°C for 3 h).

Fig. 1 shows that the polymerization was greatly influenced by added solvent. Conversion of the monomer and molecular weight of the copolymer gradually decreased with increase of the amount of solvent. The optimum content of THF was 1 ml for 1 g DL-lactide.

It is obvious that 1 ml THF cannot dissolve 1 g DL-LA at room temperature, but after a period of time, viscous solution appeared accompanied by disappearance of the monomer particle. This can be explained by the fact that the dissolved monomer was rapidly polymer-

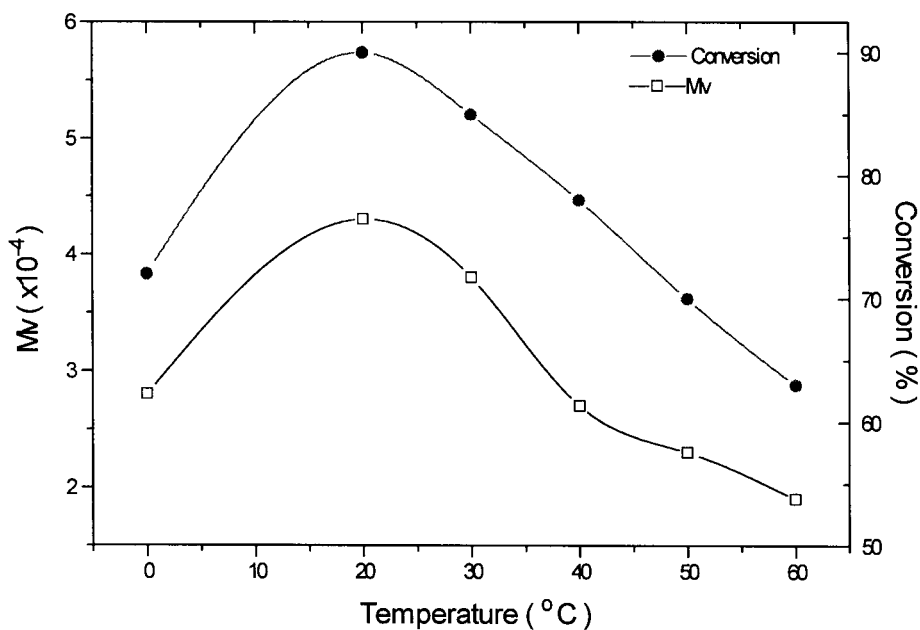


Fig. 4. Dependence of molecular weight of polymer and conversion of the monomer on the reaction temperature (1 g D,L-LA in 1 ml THF, Co/Mo = 3‰ for 3 h).

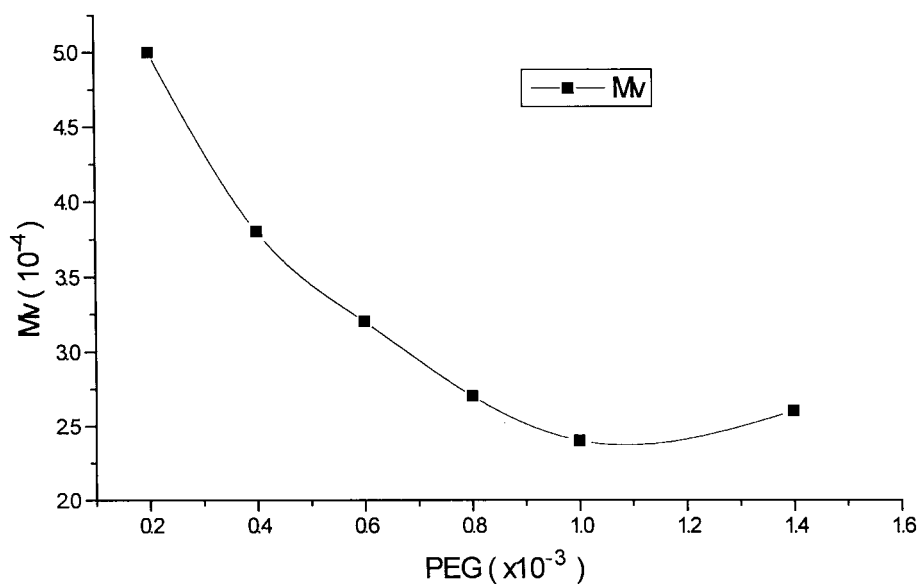


Fig. 5. Relationship between molecular weight of copolymer and the molecular weight of PEG (1 g D,L-LA in 1 ml THF, Co/Mo = 4‰, at 15°C for 4 h).

ized and the monomer was successively dissolved and polymerized again until all the monomer was dissolved and polymerized. Therefore we can draw a conclusion that reaction rate was controlled by the dissolving rate which is determined by solvent, temperature and size of monomer particle.

The effect of the reaction time on the polymerization is shown in Fig. 2. The molecular weight of the copolymer gradually decreased with increase of reaction time, while the conversion of the monomer was reached above 95%. It should be attributed to the transesterification.

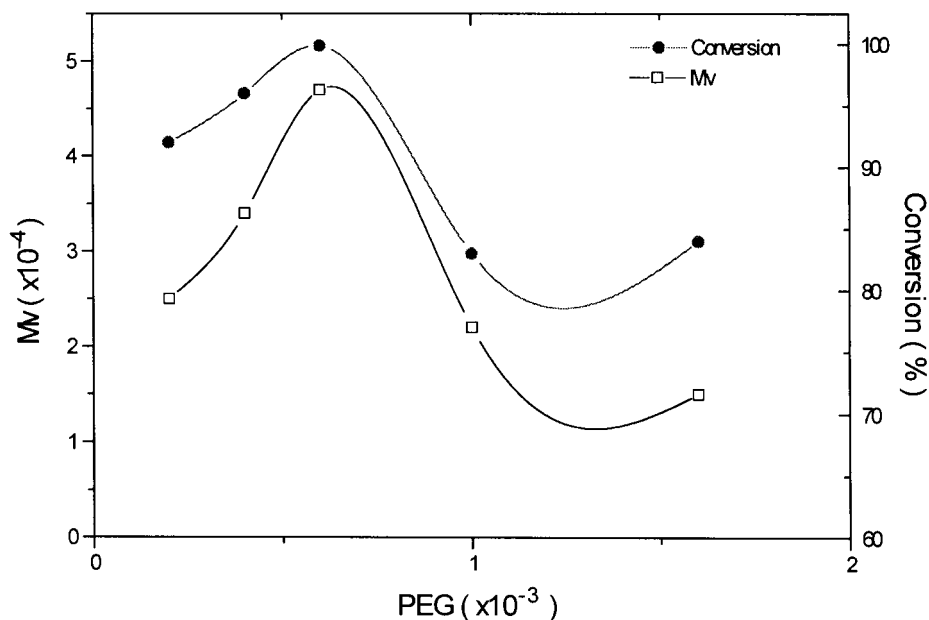


Fig. 6. Solution copolymerization of D,L-LA with different molecular weight of PEG (Mo = 1.4 M, Co/Mo = 4‰, at 15°C for 4 h).

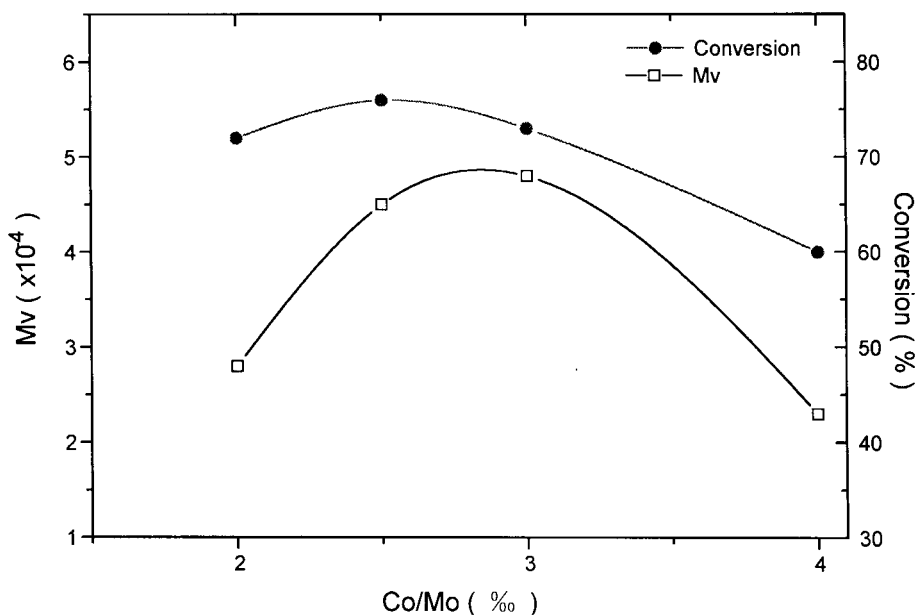


Fig. 7. Copolymerization of D,L-LA with PEG-4000 in toluene (1 g D,L-LA in 1 ml toluene, at 16°C for 3 h).

The polymerization reaction was also influenced by the amount of initiator (Fig. 3). The conversion of the monomer and molecular weight of the copolymer increased with the increase of amount of initiator until the mole ratio of initiator to monomer (I/M) reached 3‰ with the highest molecular weight of the copolymer. Then it decreased with increase of I/M.

Anionic polymerization of DL-lactide was sensitive to the temperature (Fig. 4). Conversion of the monomer and molecular weight of the copolymer gradually increased with increase of temperature from 0° to 15°C. Above 15°C, both gradually decreased, which

may be explained by the fact that the degree of transesterification increased with the increase of reaction temperature. However, the conversion of the monomer and molecular weight of the polymer being relatively low at 0°C may be due to the dissociation of initiator low temperature.

To prepare copolymers with different composition, potassium poly(ethylene glycol)ates with different molecular weights of PEG were used as initiators in the ring-opening polymerization of DL-lactide. Fig. 5 shows that the molecular weight of copolymer decreased with the increase of the molecular weight of

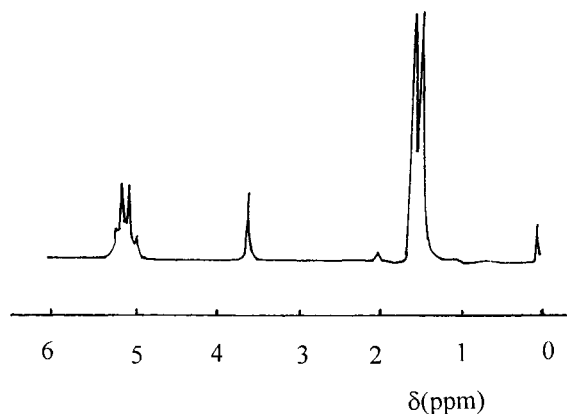


Fig. 8. ¹H-NMR spectrum of PELA copolymer (1 g D,L-LA in 1 ml THF, Co/Mo = 3.5‰, at 12°C for 5 min).

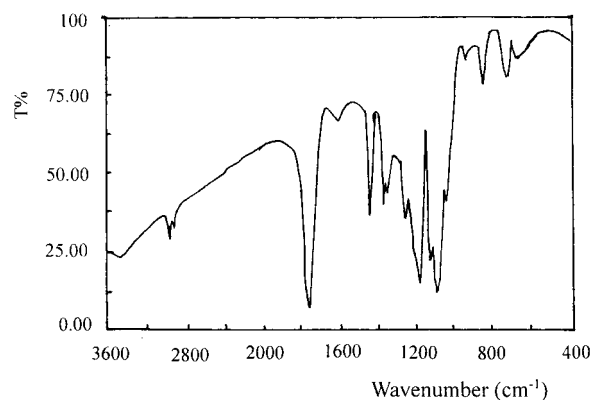


Fig. 9. IR spectrum of PELA copolymer (1 g D,L-LA in 2 ml THF, Co/Mo = 3‰, at 16°C for 2 h).

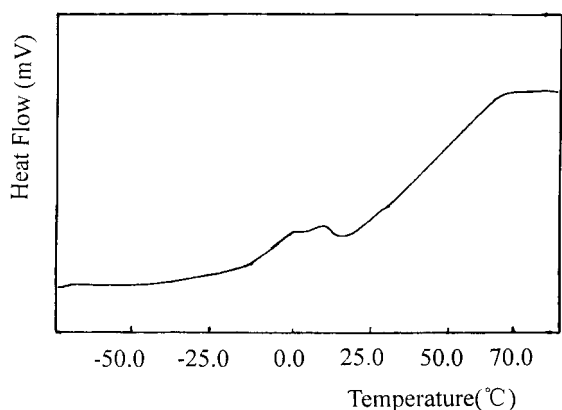


Fig. 10. DSC curve of PELA copolymer.

PEG. It may be proposed that initiators with high molecular weight have less activity than those with low molecular weight.

Efforts to solution polymerization of DL-lactide in THF by potassium poly(ethylene glycol-4000)ates were not successful. However solution polymerization of DL-lactide can be initiated by potassium salt of PEG with relatively low molecular weight (Fig. 6). Conversion of the monomer and molecular weight of the copolymer both gradually increased with increase of the molecular weight of PEG from 200 to 600. On the contrary both

gradually decreased when the molecular weight of PEG is higher than 600.

Anionic polymerization is greatly influenced by the polarity of solvent. It is found by comparing Fig. 7 with Fig. 3 that polymerization of DL-LA in THF proceeded more easily than that on toluene. Conversion of the monomer and molecular weight of the copolymer were lower, and higher concentration of initiator was required by using toluene as solvent. This may be explained that the anionic initiator can be easily associated in toluene. The existence of more compact ion-pairs decreased the concentration of active centers of initiators in toluene so that it showed the relatively low reactivity, but THF can dissociate part compact ion-pairs of potassium poly(ethylene glycol)ate into loose ion-pairs and free ions by solvation of cationic potassium. The monomer can be easily initiated by loose ion-pairs and free ions so the reactivity of initiator was enhanced.

3.2. Characterization of PELA copolymers

The $^1\text{H-NMR}$ spectrum of PELA copolymer (Fig. 8) showed that the peaks at 5.10 and 1.5 ppm were assigned to methine protons and methyl protons of the PLA unit. The formation of the triblock copolymer can be confirmed by the appearance of a sharp singlet at 3.57 ppm due to methylene protons of homosequences of PEG oxyethylene units.

IR spectrum of PELA copolymer (Fig. 9) showed that the absorption band at 3520 cm^{-1} was assigned to terminal hydroxy groups. In comparison with spectra of PLA and PEG, the bands at 2994 and 2897 cm^{-1} were assigned to the C—H stretch of $-\text{CH}_3$ (ester segments). A strong band at 1758 cm^{-1} corresponded to the C=O stretch. The most characteristic absorption of C—O—C (ether) at 1186 cm^{-1} was overlapped with C—O stretch (ester).

A typical example of DSC analysis for PELA copolymers is shown in Fig. 10. There were three transitions at -57° , -9.4° and 24.2°C due to the glass transition of PEG, β -transition and glass transition of the copolymer, respectively. The appearance of two glass transitions indicated that micro-phase separation in the copolymer had occurred and the copolymer is a double phase copolymer. Because of the low mole ratio of PEG oxyethylene unit in the copolymer, the glass transition of PEG segment was weak and a fusion endotherm of PEG segment was not found.

GPC traces (Fig. 11) and M_w/M_n (Table 1) showed that the molecular weight distribution were relatively broad and became broader with the increase of the reaction time (Table 1). This may be caused by the intra- and intermolecular transesterification during polymerization.

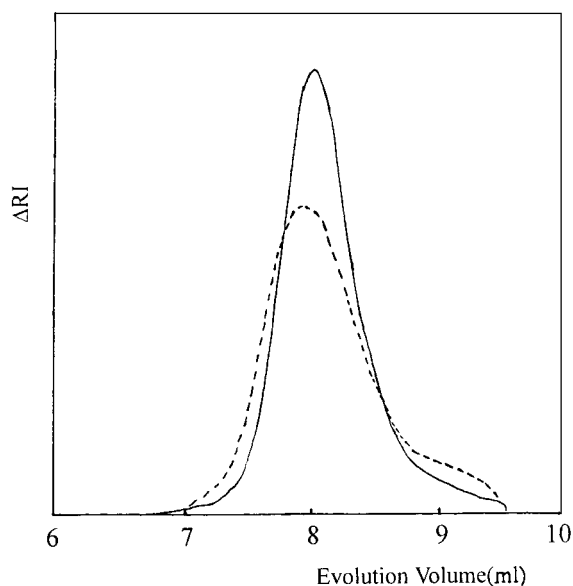
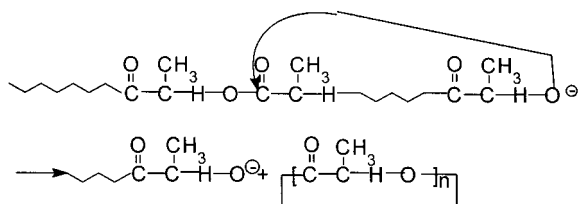
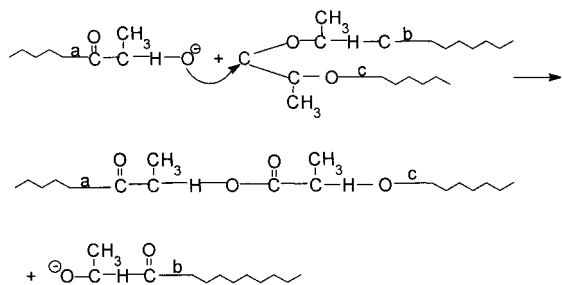


Fig. 11. GPC trace of PELA copolymer. (—) polymerization for 5 min; (.....) polymerization for 52 min.



4. Conclusion

Biodegradable triblock copolymers were produced through the polymerization of DL-lactide in the presence of potassium poly (ethylene glyco)ate. Initiators of PEG with lower molecular weight exhibited higher activity of initiation. The polymerization was con-

ducted in the super-saturated solution of monomer and monomer was successively dissolved and polymerized until all the monomer was dissolved and polymerized. Therefore the reaction rate was controlled by the dissolving rate, which is determined by solvent, temperature and size of monomer particle. There existed transesterification during polymerization and the degree of transesterification increased with increase of reaction time.

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