

Synthesis and Characterization of Block Copolymers from D,L-Lactide and Poly(tetramethylene ether glycol)

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SYNOPSIS

The copolymer from D,L-lactide and poly(tetramethylene ether glycol) (PTMG) was prepared in bulk with an isotributyl aluminum–water–phosphoric acid complex catalyst as the initiator and characterized by ¹H-NMR, GPC, and DSC. The effects of the temperature and the amount of PTMG on the polymerization rate and the molecular weight of copolymers were studied. The behavior of the degradation and delivery rate of Levonorgestrel microspheres *in vitro* was observed. The results show that the degradation and the delivery rate can be controlled by adjusting the molar ratio of hydrophilic and hydrophobic segments of the copolymer © 1995 John Wiley & Sons, Inc.

INTRODUCTION

For decades, polylactide (PLA) has been known to be a biodegradable, biocompatible, nontoxic polymer.^{1,2} Because of these properties, PLA is widely used for drug delivery and surgical sutures.^{3–5} To adapt the good properties of PLA, many efforts have been made to improve this family of the polymer. Frequently, the method of copolymerization with other proper monomers has been utilized.^{6,7} In a recent article, we successfully synthesized the block copolymer from D,L-lactide and poly(ethylene glycol).⁸ It was shown that the degradation rate of the polymer matrix and the delivery rate of the drug microspheres can be monitored by adjusting the molar ratio of hydrophilic and hydrophobic segments of the copolymer. The purpose of this article was to investigate the copolymerization of D,L-lactide with poly(tetramethylene ether glycol) (PTMG) in the presence of the Al(i-Bu)₃–H₂O–H₃PO₄ complex catalyst and to measure the behavior of *in vitro* degradation and release.

EXPERIMENTAL

Materials

D,L-Lactide with an mp of 127°C was prepared according to the literature⁹ and recrystallized thrice from ethyl acetate. PTMG with a number-molecular weight of 2196 was synthesized in our laboratory and thoroughly dried under vacuum. Isotributylaluminum and other reagents were used without further purification. The polymerization catalyst Al(i-Bu)₃–H₂O–H₃PO₄ was prepared according to the literature.¹⁰

Copolymerization of D,L-Lactide and PTMG

Two grams of D,L-lactide and a prescribed amount of PTMG were placed in a dried polymerization tube. The tube was evacuated by a vacuum pump at 100°C for several hours in order to dry up the mixture thoroughly and then filled with nitrogen gas. The appropriate amount of the catalyst solution was added with a syringe. The tube was then placed in an oil bath under reduced pressure. After an appropriate time, the tube was sealed under vacuum, and then the polymerization was carried out at the range of temperature from 110 to 180°C. When the co-

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polymerization was completed, the reaction product was dissolved in acetone, the polymer solution filtered was poured into large amount of water, and then the fibrous polymer precipitated was removed from the water. The resulting product was dried in a vacuum oven at 60°C for 10 h.

Measurements

¹H—NMR spectra were recorded on a Varian FT-80A NMR spectrometer at room temperature in CDCl₃, with TMS as the internal standard. Glass transition temperatures were obtained using a Perkin-Elmer DSC7 thermal analysis apparatus. Molecular weights and weight distribution were evaluated by means of GPC using a Water Associates Model Alc/gpc 244 apparatus. The molecular weight was calibrated relative to monodispersed polystyrene.

In vitro degradation of the polymer films was evaluated in 0.9% chloride solution of water at 37°C. A piece of each sample was taken off from the solution mentioned above at the desired time for measuring intrinsic viscosity determined in ethyl acetate at 30°C.

The microspheres containing the same amount of the drug were immersed in a given amount of 5% ethanol-saline at 37°C and the amount of the drug release was measured by UV spectrometer at regular intervals of time.

RESULTS AND DISCUSSION

Copolymerization

According to the literature,^{8,11,12} ring-opening polymerization of D,L-lactide can be initiated by antimony, zinc, lead, or, preferably, tin catalysts. It would generally take hours to complete a reaction at the normal polymerization temperature (160–220°C), below which no reaction occurred. Here,

the improved triisobutyl aluminum–water–phosphoric acid complex catalyst was utilized to initiate copolymerization reaction of D,L-lactide and PTMG. The catalyst seemed to be of high activity for the polymerization system. The copolymerization could take place even at a temperature as low as 110°C, which is lower than the T_m of D,L-lactide. This process is somewhat like the property of solid-phase polymerization. The dependence of the polymerization time on the polymerization temperature is summarized in Table I. It takes a shorter time to complete copolymerizations at higher temperatures. The yields of the resulting copolymers increased with the increase of temperature in the range of 110–160°C. The product gradually changed yellowish to red in the range of temperature from 160 to 180°C, with a slight decrease in average molecular weight. This is ascribed to the initiation of decomposition.

Table II shows the effect of the amount of PTMG on the molecular weight of PLA–PTMG copolymers. It is significant that the M_n of the copolymers decrease with the rise of the amount of PTMG added, which is due to the hydroxyl-containing compound presented in the polymerization system. Here, we can say that the most important factors that have a great influence on the M_n of the product are the feed ratio of PTMG and the quantity of the catalyst itself. The relationship between the feed ratio of the monomers and the component of the copolymers are shown in Figure 1 from trace A. It can be seen that the feed ratio of the monomers is almost in correspondence with the component of the copolymer when the amount of PTMG is below 10 wt %. This indicates that the rate of block copolymerization is high in the range of the composition. The amount of PTMG in the copolymer is more than that in the mixture of monomers when the amount of it is in excess of 10%. At the same time, the unreacted D,L-lactide increased. Trace B reveals the fact that the conversion of D,L-lactide decreases with increase in the amount of PTMG in the copolymers. This is assigned to the hydroxyl-containing com-

Table I Block Copolymerization of D,L—Lactide with PTMG^a

Samples	1	2	3	4	5	6
T (°C) ^b	110	130	150	160	170	180
t (min) ^c	180	140	40	30	20	16
Yield (%)	49.3	79.5	83.6	90.2	89.0	86.4

^a D,L—Lactide: 0.8 g; PTMG: 0.2 g, 0.7 mmHg; Al: 1.5%.

^b Polymerization temperature.

^c Polymerization time.

Table II Block Copolymerization of D,L—Lactide with PTMG^a

Samples	PTMG in Feed (Wt %)	Conv ^b (Wt %)	M_n^c ($\times 10^{-4}$)	M_w/M_n	M_n^d ($\times 10^{-4}$)
1	3	95.4	3.93	2.58	6.76
2	6	94.0	2.80	2.70	3.22
3	9	91.0	2.08	2.73	1.98
4	12	87.5	1.99	3.00	1.37

^a Copolymerization conditions: 160°C, 0.7 mmHg, 20 min.

^b Conversion of D,L—lactide.

^c By GPC relative to polystyrene standard.

^d From the conversion and the feed ratio on the assumption that all PTMG was incorporated into the polymer product.

pound (PTMG), which has great influence both on the polymerization of D,L-lactide and on the activity of the catalyst.

Characterization

The GPC trace of each copolymer has a single peak. This is the evidence used to identify the block copolymer produced.

PTMG 2196 can dissolve in acetone but cannot reprecipitate in water. This makes it possible to remove it from the copolymer. The ¹H-NMR spectrum of the copolymer shows that the peaks at 5.10 and 1.5 ppm are assigned to methine protons and methyl protons of PLA homopolymer units and the peak at 3.30 is due to methylene protons on the carbon atoms neighboring oxygen atoms, whereas the peak at 1.5 ppm is due to methylene protons on the other two carbon atoms of the PTMG unit.

Poly(D,L-lactide) is an amorphous polymer with

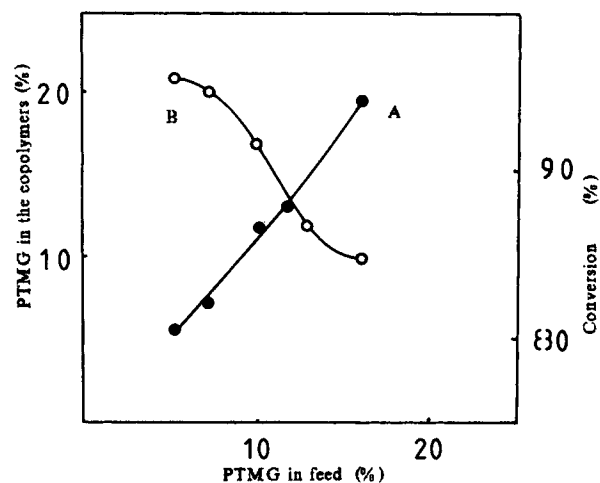


Figure 1 Relationship among PTMG in feed, PTMG in the copolymers, and conversion of D,L-lactide.

a glass transition temperature at about 60°C.⁹ PTMG is a crystalline material with a melting point at about 30°C. The DSC traces of PLA-PTMG block copolymers are given in Figure 2. The change of the amount of PTMG in copolymers from 5 to 20% led to the change of the T_g of the copolymers from 51 to -24°C. Only one transition was observed on DSC traces of the copolymers when the amount of PTMG in the copolymers was below 14%. However, there are three transitions on a DSC trace of a copolymer in which the amount of PTMG is up to 20%. Transitions at -75, -21, and 30°C may be

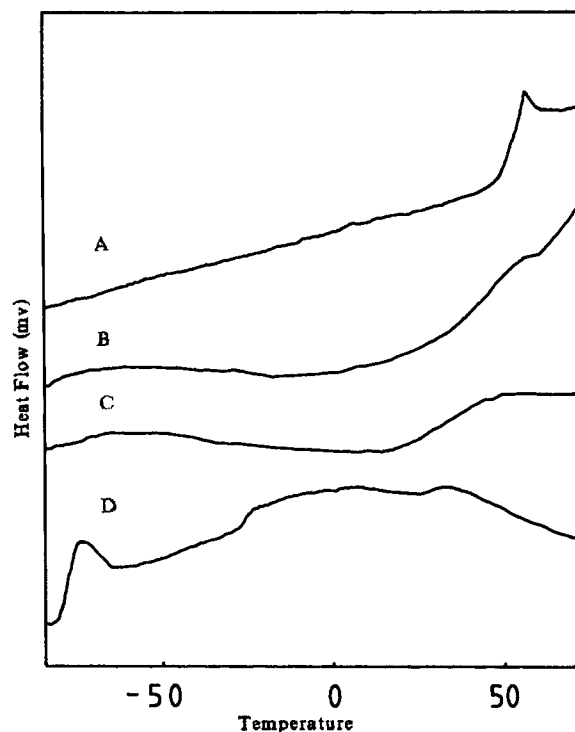


Figure 2 DSC trace of the block copolymers comprising PTMG: (A) 5.8%; (B) 7.1%; (C) 13.3%; (D) 19.7%.

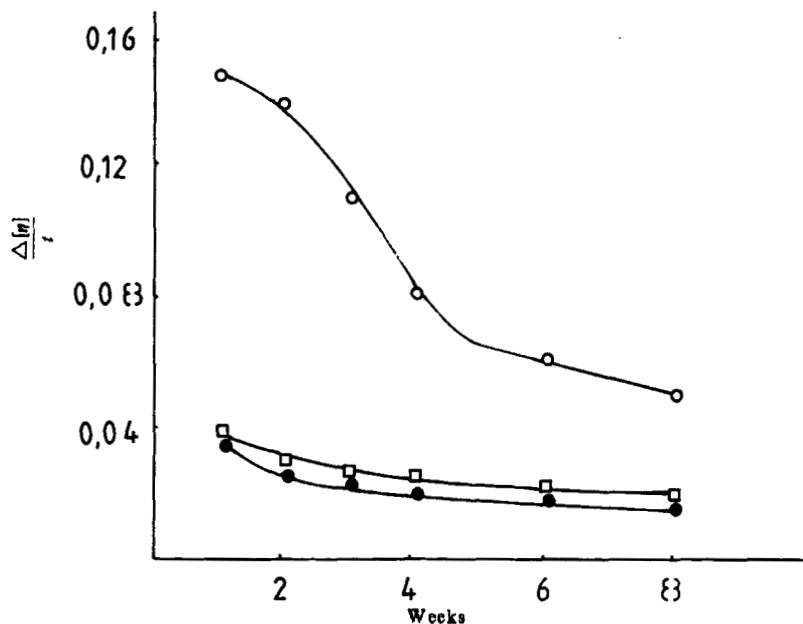


Figure 3 Degradation of (○) PLA, and two block copolymers comprising PTMG: (□) 10%; (●) 15%.

due to the glass transition of PTMG, the PLA-PTMG copolymer, and the melting point of the PTMG segment, respectively.

Evaluation of Degradation and Drug Release *In Vitro*

The copolymers comprising 10 and 15% PTMG related to D,L-lactide were immersed in distilled water

at 37°C to investigate their degradation behavior by hydrolysis. Figure 3 shows the changes in relative rate [defined as $(\Delta[\eta])/t$] of degradation as a function of immersion time for the two copolymers and the PLA homopolymer. It has been demonstrated that the rate of degradation of PLA is faster than that of copolymers at the entire degradation period and the decrease in the rate of degradation of PLA is notable during the process, whereas the rate of

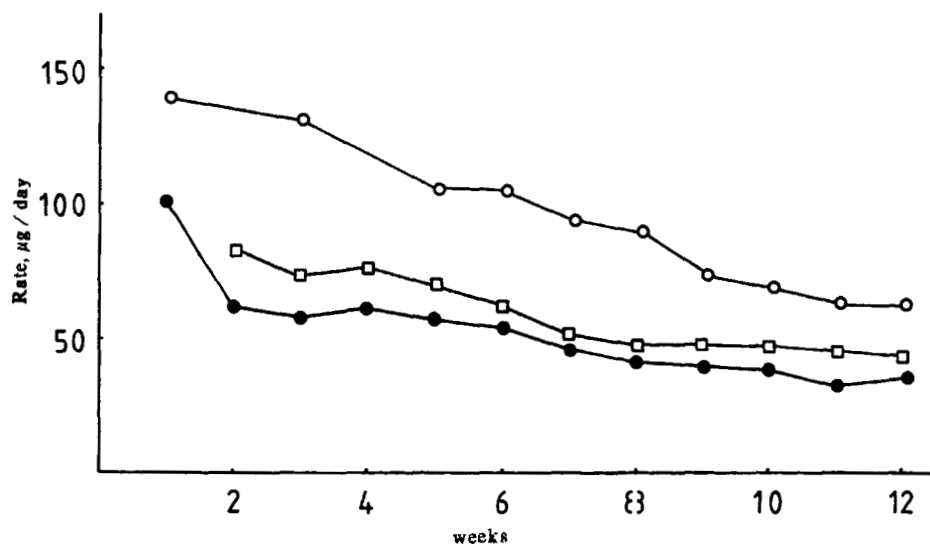


Figure 4 Comparison of delivery rate of Levonorgestrel from MCLM prepared from the coating materials with different PTMG content, *in vitro*, at 37°C: (○—○) 0%; (□—□) 10%; (●—●) 15%.

degradation of the copolymer is relatively steady except for the initial period.

Levonorgestrel was coated with the copolymers by the solvent-evaporation process and microspheres containing Levonorgestrel MCLN with diameters less than 50 μ were obtained in our laboratory. The release data *in vitro* are shown in Figure 4. From this figure it can be seen that there is an initial high release of activity, following which the release pattern become almost level, while the drug release rate of MCLN-PTMLA is slower than that of MCLN-LA. It may be concluded that the degradation rate in PTMLA and the drug-release rate in MCLN-PTMLA can be controlled by adjusting the molar ratio of hydrophilic and hydrophobic segments of the copolymer.

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