Preparation, Characterization, and Properties of Polylactide (PLA)–Poly(ethylene Glycol) (PEG) Copolymers: A Potential Drug Carrier

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Synopsis

Polylactide (PLA)-poly(ethylene glycol) (PEG) copolymers were synthesized from polyethylene glycol and D,L-lactide using low toxic stannous octoate as catalyst at 180°C by bulk polymerization. The copolymers were characterized by GPC, IR, and ^{13}C-NMR. A full assignment NMR spectrum is presented. The physical, drug release, and biodegradable properties *in vitro* of PLA–PEG copolymers were investigated. The result indicates that the rates of drug release and biodegradation could be tailored by adjusting polymer composition. This amorphous material might be used as a drug carrier in medical applications.

INTRODUCTION

Biodegradable polymers used as drug carriers have received much attention.[1] The obvious advantage of such systems is the sustained release of drugs from the polymer matrix which has undergone biodegradation after a certain period *in vivo*. Furthermore, it is easier to prepare microcapsule drug formulae for injection administration, thereby eliminating surgery procedure, which has been necessary for the implant method. These kinds of polymers should be nontoxic, biocompatible, and biodegradable. Several polymers, for example, polylactide (PLA), lactide–glycolide copolymer, and lactide–ϵ-caprolacton copolymer, have been investigated for drug delivery systems.[2] Recently, we[3] have reported D,L-lactide (LA)–ethylene oxide (EO) copolymer synthesized by ring opening polymerization from D,L-lactide and ethylene oxide, in which hydrophilic and hydrophobic segments have been placed in the same molecule, and, by adjusting the polymer composition, the rates of drug release and polymer degradation can be controlled.

Poly(ethylene glycol) (PEG) is defined as those polyethylene oxides having hydroxyl end groups and a molecular weight of 20,000 or less. PEG is nontoxic and cleared by the U.S. Food and Drug Administration for internal use in the human body.[4] Furthermore, treatment of PEG is easier and safer than ethylene oxide. In this article we wish to report the preparation, characterization, and properties of PLA–PEG block copolymers for drug carrier use.

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EXPERIMENTAL

D,L-lactide was synthesized according to the literature procedures.[5] Crude products were thrice recrystalized from ethyl acetate, mp 125–126°C. Commercial poly(ethylene glycol) was purified by silica gel chromatography method.[6] PEG contained two end hydroxyl groups which was confirmed by hydroxyl group analysis and M_n of 1100 was determined by vapor phase osmometry, which was in good agreement with that calculated from the end group analysis. Stannous octoate (A.R.) was diluted to desired concentration with petroleum ether.

PEG, LA, and stannous octoate were mixed and kept in a polymerization tube, which was connected to a vacuum system. The mixture was gradually heated to 100°C. Then the vacuum was released, and the system was purged with nitrogen. The temperature was then raised to 180°C and maintained throughout the polymerization process. The products were extracted with a cold solvent mixture of ethyl acetate and *n*-haptane (2 : 1 v/v), and finally with distilled water. The copolymers were dried in a vacuum oven at 60°C for 3 days.

Infrared spectra of copolymers were recorded using a Nicolet DX spectrometer. Proton and carbon-13 NMR spectra were recorded on a JOEL 90Q NMR spectrometer (chloroform-d as solvent). Number average molecular weight was determined by VPO and the molecular weight distribution (MWD) by a Waters GPC Model 208. The transition temperatures of polymers were measured by Perkin-Elmer DSC-2C using a heating rate of 10°C/min. The stress–strain data were obtained using an Autograph DCS-500 instrument. The sample dimensions were 10 mm in gage length, 2 mm in width, and 0.2 mm in thickness. Wide angle X-ray diffraction (WAXD) experiments were performed on 1.0-mm-thick compression-molded samples using a Geigerfler D/max diffractometer. The rate of drug release and polymer degradation were determined by a method described in our previous paper.

RESULTS AND DISCUSSION

Polymerization

D,L-lactide can be polymerized in the presence of Sn^{2+} and Sn^{4+} salts, but the mechanism is not well understood.[7] In our experiments low toxicity stannous octoate was employed as the catalyst. The results of polymerization are summerized in Table I. This table shows that the polymer yield increased, but the molecular weight of polymers decreased with increasing PEG fraction in feed. It is in agreement with the effect of small molecules containing hydroxyl groups on LA polymerization behavior described by Барская (Balskaya) et al.[8]

The optimum polymerization temperature was in the range of 180–190°C. When the temperature was below 150°C, the reaction would not take place. If it was higher than 200°C, the products became dark brown, and the molecular weight of polymers decreased dramatically.

Figure 1 shows the effect of polymerization time on yield and molecular weight of polymers. After a short inductive period the yield of the polymers increased rapidly and then leveled off. The inductive period was dependent on catalyst concentration. The lower the concentration of the catalyst, the longer

TABLE I
Polymerization of PLA–PEG Copolymers[a]

Sample no.	Feed (PEG wt %)	Time (h)	Catalyst (wt %)	Yield (%)	$M_n \times 10^{-3}$	M_w/M_n
B-22	10.0	1	0.050	33	3.16	2.4
B-23	16.7	1	0.050	53	2.94	2.3
B-24	25.0	1	0.050	65	1.87	2.1
B-25	41.7	1	0.050	71	1.41	2.6
B-26	10.0	10	0.050	85	8.91	2.7
B-27	16.7	10	0.050	96	6.01	2.5
B-28	10.0	10	0.020	86	8.21	2.0
B-29	16.7	10	0.020	91	5.87	2.2
B-37	10.0	4	0.006	85	5.28	2.3
B-38	10.0	4	0.012	88	5.88	2.5
B-39	10.0	4	0.024	84	5.94	2.7
B-40	10.0	4	0.048	86	4.98	2.4
B-41	10.0	4	0.096	87	5.60	2.4

[a] Catalyst, stannous octoate; 180°C, in bulk.

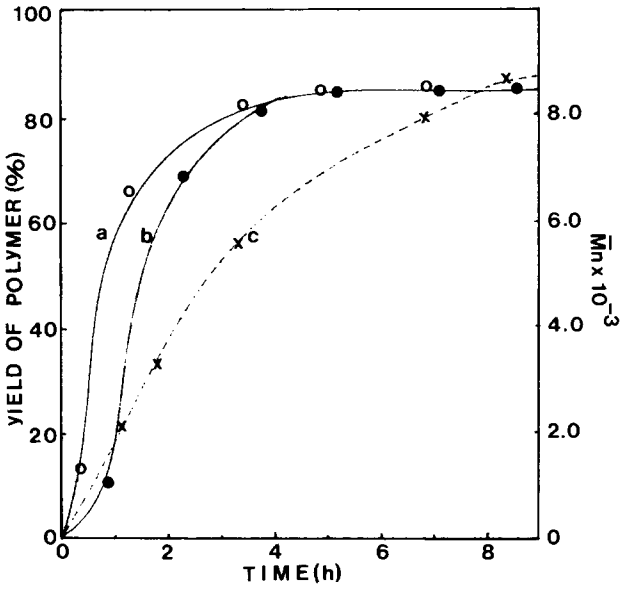


Fig. 1. Relationship between yield, M_n, and polymerization time (PEG, 10 wt %; catalyst, stannous octoate; at 180°C). (a) yield time, cat. 0.05 wt %; (b) yield time, cat. 0.02 wt %; (c) M_n time, cat. 0.05 wt %.

was the inductive period. The molecular weight of polymers gradually increased with polymerization, and the ratios of M_w to M_n were in the range of 2.0–3.0. This behavior indicates a typical step polymerization character.

Characterization and Carbon-13 NMR Study

After purifying the copolymers, we obtained a single symmetric peak on GPC spectrum (toluene as solvent, concentration 0.2 wt %, μ-styragel 10^3, 10^4

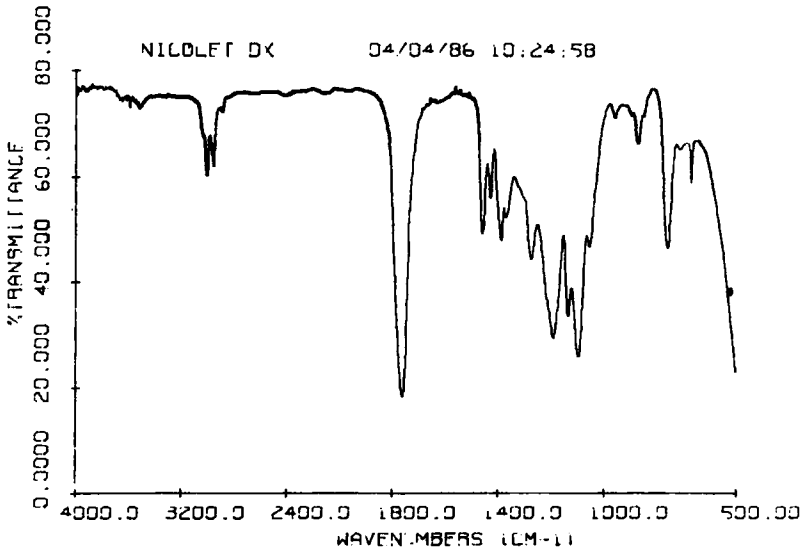


Fig. 2. IR spectrum of PLA–PEG copolymer (B-25) (film, chloroform).

column, flow speed 1.5 mL/min). IR and proton NMR spectra for a typical PLA–PEG copolymer are shown in Figures 2 and 3, respectively. The spectra bear similarity to those of LA–EO copolymers.[3]

Additional information about the structure of PLA–PEG copolymers has been obtained by carbon-13 NMR studies. Figure 4 shows the typical carbon-13 NMR spectrum of PLA–PEG copolymer. In comparison with the spectra of polyethylene glycol and polylactide, it is clear that peaks at 16.63, 68.99, and 169.48 ppm correspond to CH_3, CH, and C=O in PLA segments, respectively, and the peak at 70.45 ppm corresponds to CH_2 in PEG segments of the copolymer. The technique of insensitive nuclei enhanced by polarization

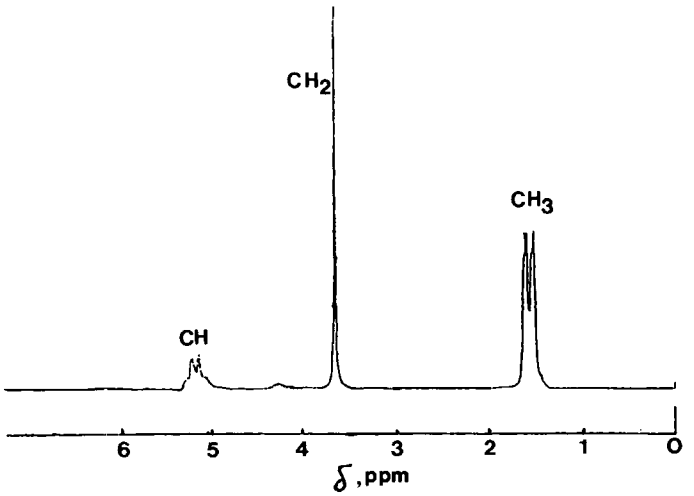


Fig. 3. ^{1}H-NMR spectrum of PLA–PEG copolymer (B-25), measured in $CDCL_3$ at 30°C.

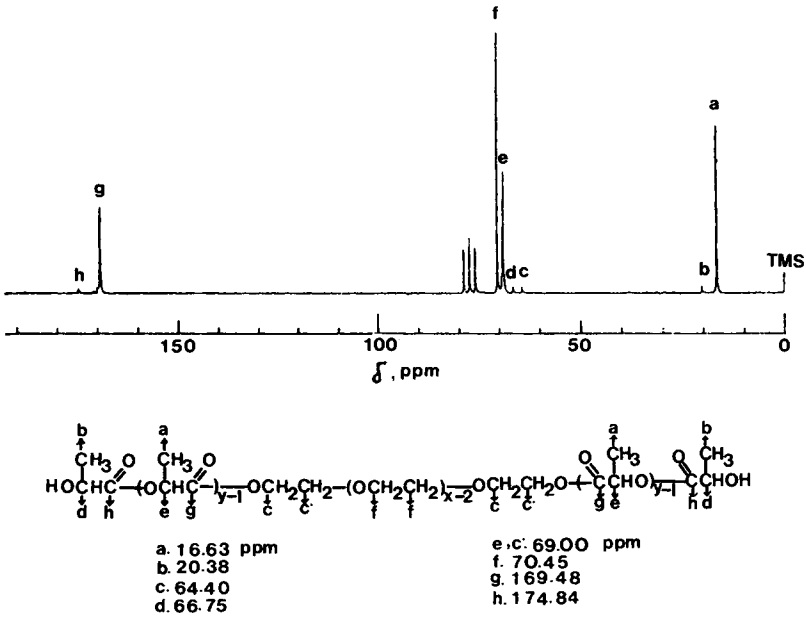


Fig. 4. 22.49 – ^{13}C-NMR spectrum and assignment of PLA–PEG copolymer (B-25), measured in $CDCL_3$ at 30°C.

transfer (INEPT) was employed to assign the remaining peaks, with the delay τ set at 5.1 ms, which is $3/(4J_{CH})$ for the direct CH couplings in the copolymer. Figure 5 shows the partial INEPT spectrum of PLA–PEG copolymer, in which CH and CH_3 appears in positive, but CH_2 in negative signals. Assigned peak B (20.38 ppm), D (66.75 ppm), and H (174.84 ppm) correspond to CH_3, CH, and C=O in lactic acid residues of the end units in PLA–PEG copolymer, respectively; peak C corresponds to CH_2, which is directly linked with the ester group in the unit between PEG and PLA blocks

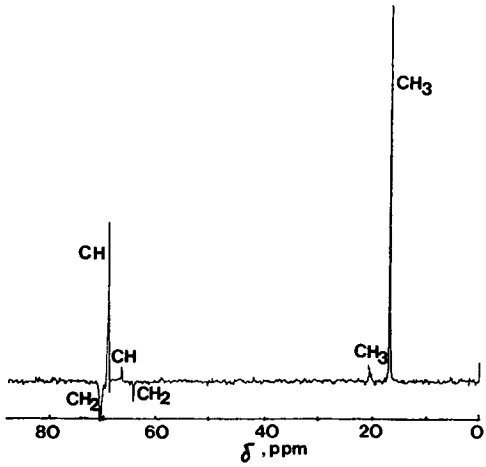
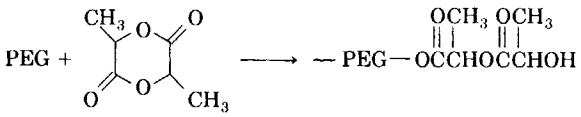


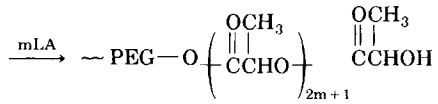
Fig. 5. Partial ^{13}C-NMR spectrum of PLA–PEG copolymer obtained by the insensitive nuclei enhanced by polarization transfer (INEPT) method.

(—$COOCH_2CH_2O$—). In comparison with CH_2 of the middle units of PEG block (69.00 ppm), peak C has shifted to higher field (64.40 ppm). This is in good agreement with model compound $H_3CCOOCH_2CH_2OCH_3$, in which the chemical shifts of methylene carbons are 63.5 and 70.5 ppm, respectively.[9] The PLA–PEG copolymer structure and the assignment of spectrum are summarized in Figure 4.

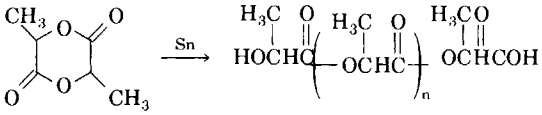
According to polymerization behavior and polymer structure, the polymerization mechanism might be described as following:



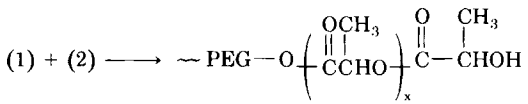
(LA)

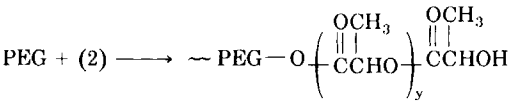


(1)



(2)





Evaluation for Drug Matrix Properties

Partial data of PLA–PEG and LA–EO copolymer properties are shown in Table II. PLA–PEG shows only one T_g, but LA–EO copolymer shows two T_g and a T_m (Fig. 6). The absence of PEG T_g and T_m is due to low molecular weight. Although it is a block copolymer in chemical structure, PEG segment apparently is miscible with PLA. X-ray diffraction patterns support this result (Fig. 7). In the case of D,L-lactide and ethylene oxide polymerization, the reactivity of ethylene oxide is higher than that of lactide, so that long PEO segments formed easier and, as a result, form a crystal structure. From the view of application as a drug carrier matrix, the amorphous material of PLA–PEG copolymer might be preferred.

The mechanical properties of both PLA–PEG and LA–EO copolymer depends on the composition of polymers. The modulus and tensile strength

TABLE II
Partial Data of Physical Properties for PLA–PEG and LA–EO Copolymers

Sample no.	LA in polymer (mol %)	M_n ($\times 10^{-4}$)	M_w/M_n	T_{g1} (°C)	T_{g2} (°C)	T_m (°C)	Modulus (kg/cm^2)	Elongation (%)	Tensile strength (kg/cm^2)
B-26	72	0.89	2.7		8		166	500	21
B-27	57	0.61	2.5		5		119	516	17
B-31	42	0.77	2.6		1		100	586	15
PLE112	73	2.1	1.5	−62	14	59	530	26	31
PLE111	64	2.0	1.4	−62	12	60	400	32	25
PLE81	50	2.0	1.5	−63	11	62	330	45	11
PLA102	100	3.6	1.6		57		6600	6.4	390

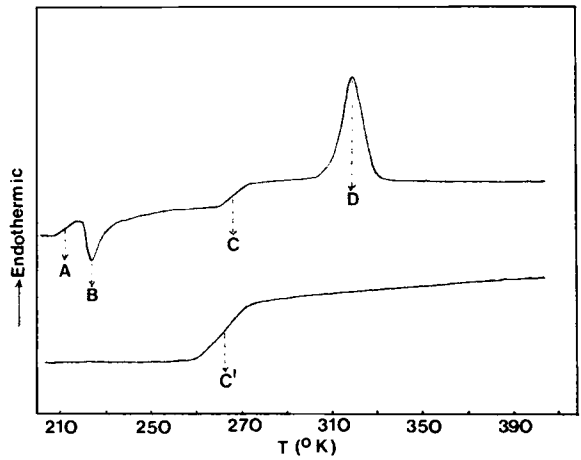


Fig. 6. DSC thermogram for PLA–PEG copolymer (B-26) and LA–EO copolymer (PLE-112) (heating rate 10°C/min., in N_2). (A) T_{g1} for PEO in copolymer; (B) crystallization for PEO in copolymer; (C) T_{g2} for PLA in LA–EO copolymer; (C') T_g for PLA–PEG copolymer; (D) melting point for PEO in LA–EO copolymer.

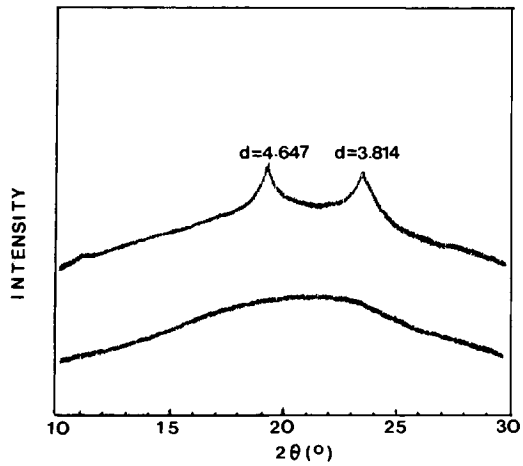


Fig. 7. x-Diffraction for PLA-PEG copolymer and LA–EO copolymer.

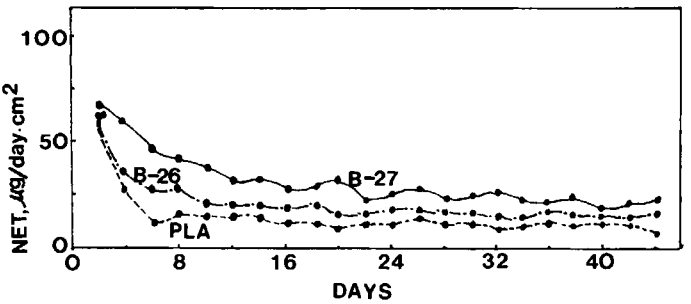


Fig. 8. Norethisterone (NET) release rate from PLA–PEG polymer matrix at 37°C in water (drug load, 30 wt %).

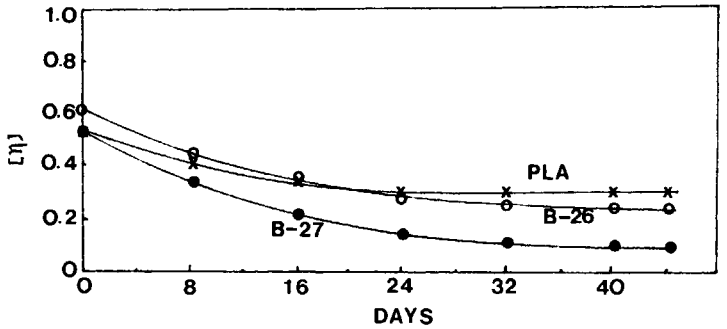


Fig. 9. Degradable tests of PLA–PEG copolymers *in vitro* at 37°C in water.

increased, but the elongation decreased with the increase of LA content in the copolymers.

Figures 8 and 9 show the drug release patterns and degradable behavior of PLA–PEG copolymers *in vitro*. After an initial period the drug release keeps relatively constant. The rates of drug release and polymer degradation depend on the polymer composition. It could be explained that, with the hydrophilic PEG segments increasing, the diffusion of water and drug are facilitated. As a consequence, both the drug release and the hydrolytic erosion of copolymer are enhanced. The above results indicate that the properties of PLA–PEG copolymer could be tailored by adjusting polymer composition.

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