Synthesis and Characterization of ABA Triblock and Novel Multiblock Copolymers from Ethylene Glycol, L-Lactide, and ϵ-Caprolactone

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ABSTRACT: Three types of copolymers were synthesized and characterized. First, triblock ABA copolymers [where A is a homopolymer of ϵ-caprolactone and B is poly(ethylene glycol)] were prepared by the ring-opening polymerization of poly(ethylene glycol) with ϵ-caprolactone in the presence of stannous octoate ($Sn(Oct)_2$). The spectral, thermal, and mechanical properties of one sample of these copolymers were studied, and it was discovered that these types of copolymers were more hydrophilic, possessed lower melting points, and had superior mechanical properties (greater toughness) than poly(ϵ-caprolactone). Second, triblock ABA copolymers [where A is a homopolymer of L-lactide and B is poly(ethylene glycol)] were prepared by the ring-opening polymerization of poly(ethylene glycol) with L-lactide in the presence of $Sn(Oct)_2$. The mechanical properties of these copolymers were studied, and it was found that they were tougher and softer than poly(L-lactide). Third, novel ABA triblock copolymers [where A is a copolymer of ϵ-caprolactone and L-lactide and B is poly(ethylene glycol)] were prepared, and ^{1}H-NMR and ^{13}C-NMR spectra of these copolymers indicated a microblock structure for the two end blocks. The stress–strain behavior revealed low yields and high toughness for these copolymers. © 2002 John Wiley & Sons, Inc. J Appl Polym Sci 83: 2072–2081, 2002

Key words: block copolymers; copolymerization; mechanical properties

INTRODUCTION

Synthetic bioresorbable polymers are of interest for a variety of biomedical, pharmaceutical, and industrial applications. Poly(L-lactide), polyglycolide, poly(ϵ-caprolactone), and their copolymers are widely used in various ways, ranging from surgical sutures to controlled drug-delivery systems.[1,2] These homopolymers are semicrystalline, high-strength materials,[3] whereas poly(DL-lactide), because of its stereoirregular polymer chain, is amorphous.[4] One of the simplest and most widely used approaches for modifying polymer properties to meet specific requirements is copolymerization. For copolymers, crystallinity depends on the monomer composition, configuration, and chain-sequence structure (random or

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Table I Mol % of Monomers in Reaction Mixtures and the Resultant Copolymers Together with Their Representative Endotherms in Their DSC Thermograms

Sample	Mol % in Reaction Mixture LA/CL/EO	Mol % in Copolymer LA/CL/EO	Endotherms in DSC (°C)	Water Absorption (%)
1	0/92/8	0/90/10[a]	52	10
2	0/60/40	0/58/42[a]	51.5	31
3	92/0/8	90/0/10[b]	160	7
4	83/0/17	75/0/25[b]	160	15
5	82/12/6	82/11/17[c]	—	—
6	67/22/11	70/21/9[c]	—	—
7	64/16/20	66/14/20[c]	61,120	—

[a] Peaks at δ 4.06 and δ 3.64 in ^{1}H-NMR spectra were used as references for the calculation of the mol % of CL and EO, respectively.

[b] Peaks at δ 5.17 and δ 3.56 in ^{1}H-NMR spectra were used as references for the calculation of the mol % of LA and EO, respectively.

[c] Peaks at δ 5.19, δ 4.13, and δ 3.64 in ^{1}H-NMR spectra were used as references for the calculation of the mol % of LA, CL, and EO, respectively.

LA, lactic acid; CL, ϵ-caprolactone; EO, ethylene oxide.

block copolymers). The aforementioned homopolymers and copolymers are hydrophobic, relatively rigid, and brittle, and as such, their compatibility toward soft tissues is low,[5] making them unsuitable as implants. For such applications, materials that are more ductile and more resilient are needed.

To overcome this biocompatibility problem, a few block copolymers of poly(ethylene glycol) (PEG) and L-lactide have been synthesized and characterized.[6–11] PEG is completely miscible with water, and its presence in a copolymer as a block increases the flexibility and hydrophilicity of the resultant material. However, the copolymerization of L-lactide with ϵ-caprolactone converts the rigid and brittle poly(L-lactide) into flexible or rubbery materials (depending on the monomer composition and sequence length of the monomers in the resultant copolymer, which are dependent on the copolymerization conditions).[12,13] To attain enhanced flexibility, Katz et al.[14] and Roby et al.[15] synthesized glycolide/trimethylene carbonate block copolymers to be suitable for use in monofilament surgical sutures. Also, block copolymers have been synthesized in which one block is PEG and the others are ran-

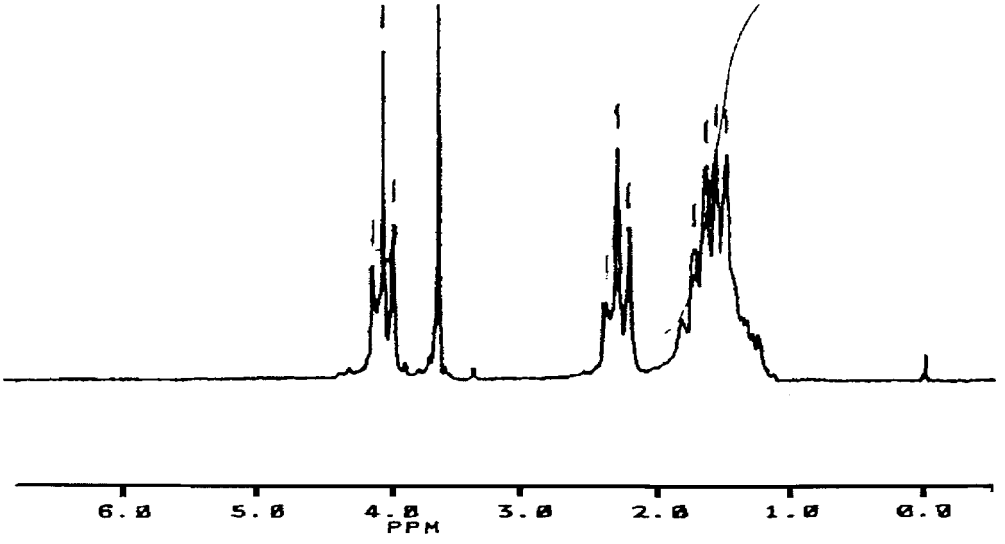


Figure 1 ^{1}H-NMR spectrum of sample 1 (Table I).

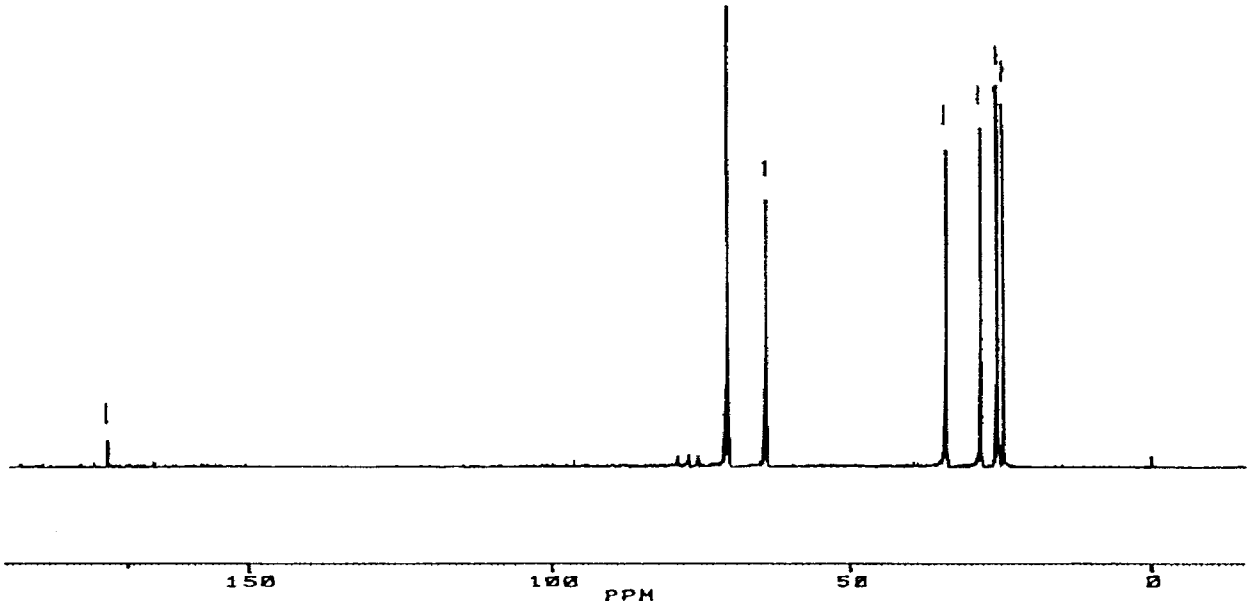


Figure 2 ^{13}C-NMR spectrum of sample 1 (Table I).

domized glycolide and trimethylene carbonate units.[16] Poly(ϵ-caprolactone) is a biodegradable polymer with a slow rate of biodegradation in human tissues.[17] From a mechanical point of view, it is classified as a brittle material with a high elastic modulus, but because of the presence of five methylene moieties in the polymer backbone, the modulus is lower than that of poly(L-lactide). However, ether bonds in the polymeric backbone enhance elasticity, as exemplified by poly(*p*-dioxanone) monofilament surgical sutures.[18] With these in mind, we synthesized and characterized triblock copolymers from PEG and ϵ-caprolactone. If the three monomer units mentioned (i.e., ethylene glycol, ϵ-caprolactone, and L-lactide) participate in the formation of a copolymer, an amorphous product with increased hydrophilicity and flexibility and improved biodegradability results. We also describe the syntheses and characterization of ABA triblock copolymers [where A is a copolymer of L-lactide and ϵ-caprolactone and B is PEG block] with the aim of obtaining some novel bioresorbable polymers with unique hydrophilic and mechanical properties.

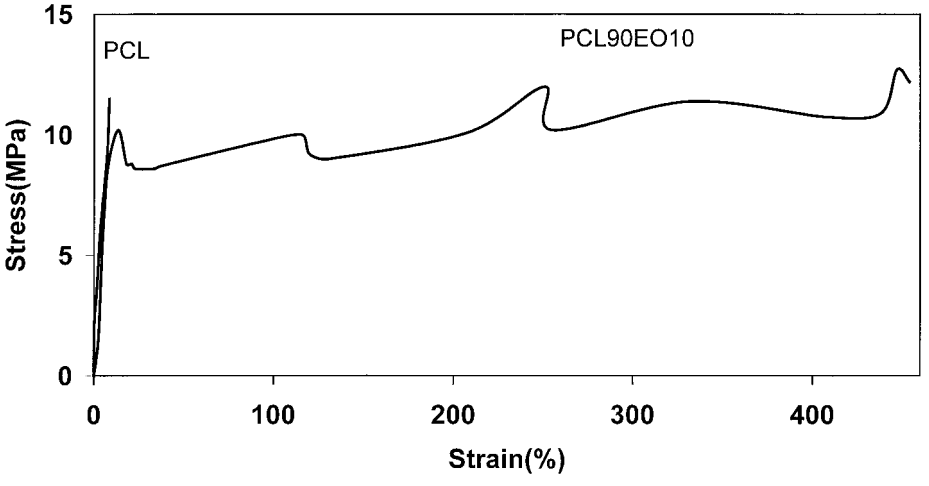


Figure 3 Stress–strain diagram of sample 1 (Table I) and poly(ϵ-caprolactone).

EXPERIMENTAL

Materials

ϵ-Caprolactone (Merck, Inc., Darmstadt, Germany) was used after purification by vacuum distillation. PEG, with a number-average molecular weight of 35,000 (Merck) was purified by dissolution in tetrahydrofuran and precipitation in hexane. L-Lactide was prepared from a 90% L-lactic acid solution (Merck) according to Gilding and Reed[19] and then was purified by multiple recrystallization from ethyl acetate. The catalyst, tin-2-ethyl hexanoate (Sigma, St. Louis, MO) was purified by vacuum distillation. All other chemicals or solvents were reagent-grade (Merck) and, if necessary, were purified according to established procedures.[20]

Polymerizations

ABA Triblock Copolymers (L-Lactide and PEG or ϵ-Caprolactone and PEG)

Appropriate amounts of lactone and PEG macroinitiator were charged into a polymerization tube and kept *in vacuo* at 70°C for 2 h. Thereafter, a 0.5-mL catalyst solution [3% stannous octoate ($Sn(Oct)_2$) in toluene] was added and kept *in vacuo* until all volatiles were removed. The tubes were then sealed *in vacuo*, and polymerizations were carried out at 110°C (L-lactide and PEG) and 100°C (ϵ-caprolactone and PEG) for a period of 1 week. Tubes were subsequently broken, and the contents were dissolved in chloroform, filtered, and finally precipitated with methanol.

Homopolymers, Poly(L-lactide), and Poly (ϵ-caprolactone)

Monomer was charged into a polymerization tube with a catalyst [$Sn(Oct)_2$ in toluene]. After removal of volatiles by vacuum, the tube was heat-sealed *in vacuo*. The temperature and time of polymerization for L-lactide and ϵ-caprolactone were 110 and 100°C and 6 and 7 days, respectively. The homopolymers were purified by dissolution in dichloromethane and precipitation in methanol.

Multiblock Copolymers from L-Lactide, ϵ-Caprolactone, and PEG

Appropriate amounts of L-lactide, ϵ-caprolactone, and PEG macroinitiator were charged into a polymerization tube and kept *in vacuo* at 70°C for 2 h. Thereafter, a 0.1-mL catalyst solution [3% $Sn(Oct)_2$ in toluene] was added and kept *in vacuo* until all volatiles were removed. The tubes were then sealed *in vacuo*, and the polymerizations were carried out at 100°C (at this temperature, L-lactide dissolves in ϵ-caprolactone) for a period of 1 week. Tubes were subsequently broken, and the contents were dissolved in chloroform, filtered, and finally precipitated with methanol.

Blend Films

Blends were prepared by the poly(L-lactide) homopolymer and copolymer 6 (Table I) being mixed in various proportions. The mixture was dissolved in chloroform, and films were prepared by solution casting. After the films were dried, their stress–strain behavior was measured.

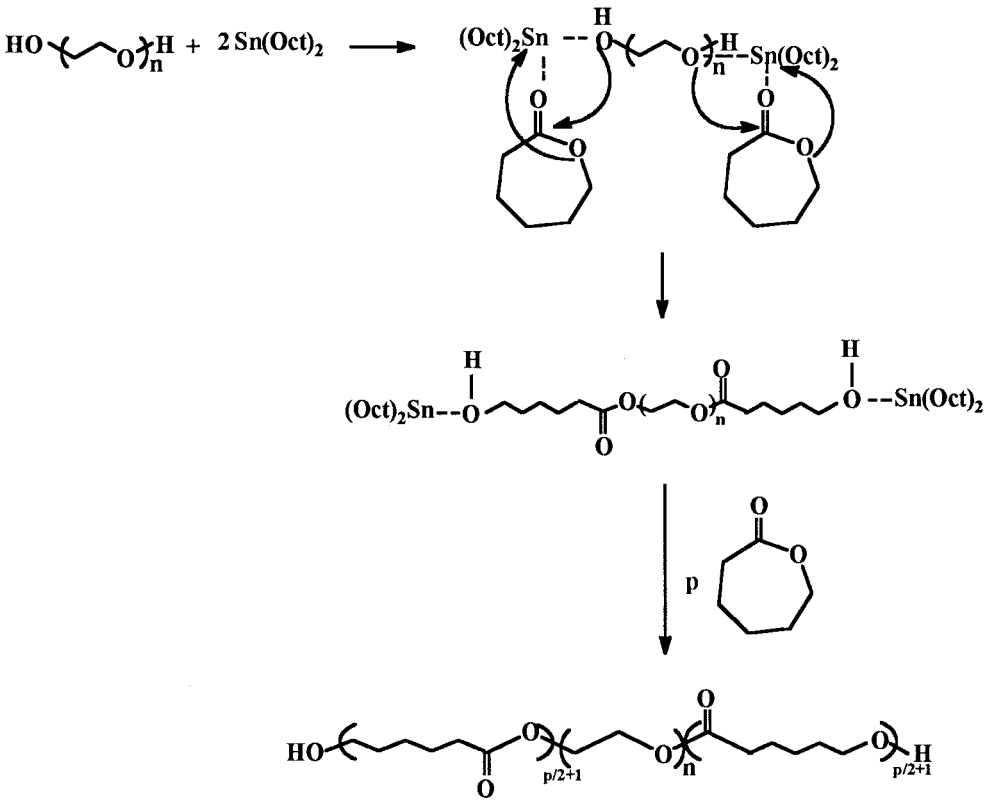
Measurements

^{1}H-NMR and ^{13}C-NMR spectra of the copolymers were recorded on a Brucker-AC-80 spectrometer (Rheinstetten-Forchheim, Germany) at 80 and 20 MHz, respectively. Chloroform-d_1 and tetramethylsilane were used as the solvent and internal standard, respectively. The stress–strain behavior of the copolymer films was studied with an Instron model 4204 universal testing machine (Massachusetts) with a 100 mm/min crosshead speed. Film specimens (70 mm × 20 mm × 0.1 mm) were prepared by solution casting from a 20% chloroform solution. Differential scanning calorimetry (DSC) thermograms were obtained with a Mettler series PC11 DSC instrument (Greifensee, Switzerland). The water absorptions of copolymers were estimated by equilibrium swelling of the polymer film specimens in distilled water at 20°C for 1 week. The water content (wt %) was calculated from the relative weight increase of the samples after their immersion in water.

RESULTS AND DISCUSSIONS

Triblock Copolymers from PEG and ϵ-Caprolactone

In the copolymerization of PEG with ϵ-caprolactone, PEG acts as a macroinitiator, and its two end-terminal hydroxyl groups participate in forming the center block of the copolymer. The two end blocks are formed from homopolymers of poly(ϵ-caprolactone). Based on a mechanism suggested by Kricheldorf and coworkers[21,22] and Duda et al.[23] for the polymerization of lactones in the presence of $Sn(Oct)_2$ as a catalyst and alcoholic coinitiators, the following steps are proposed for the formation of triblock copolymers:



According to Duda et al.'s recent work, polymerization proceeds via an active chain-end mechanism, that is, on the Sn–alkoxide bonds present at the chain ends.

Table I shows the molar percentages of monomers in the reaction mixture and resultant copolymers together with the endotherms in the DSC thermograms. Samples 1 and 2 represent copoly-

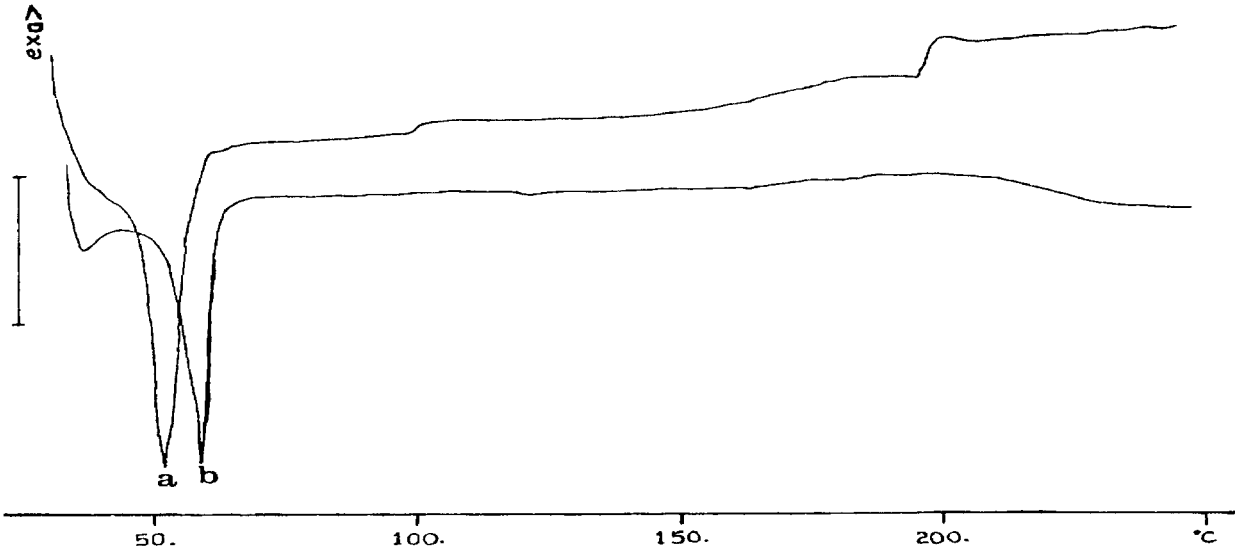


Figure 4 DSC thermograms of (a) the original copolymer film and (b) sample 1 (Table I) after elongation.

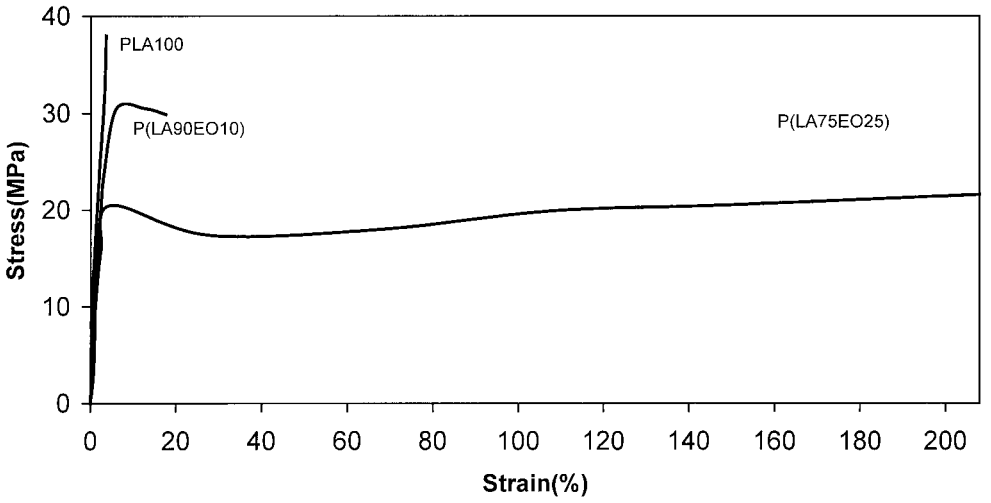


Figure 5 Stress–strain diagrams of polylactide and its copolymers with 10 and 25% polyethylene oxide.

merization products of PEG and ϵ-caprolactone with melting points around 52°C. The compositions of the copolymers were determined through analysis of the ^{1}H-NMR spectra. In these triblock copolymers, a characteristic ^{1}H-NMR methylenic moiety in PEG appears at δ = 3.64, caprolactyl methylenic protons appear at δ = 4.06 (CH_2—O—) and δ = 2.3 (—CH_2—CO—), and inner methylenic protons appear at δ = 1.2–1.95 (m). For the calculation of the caprolactone molar percentage in the copolymers, the peak area at 4.06 ppm was taken as a reference (Fig. 1). In the ^{13}C-NMR spectrum, all methylenic carbons of the ϵ-caprolactone moiety give separate signals and are carefully resolved (Fig. 2).

Figure 3 shows the stress–strain diagram for a film specimen of sample 1 (Table I) along with that of the ϵ-caprolactone homopolymer. An extremely high elongation is achievable in comparison with the ϵ-caprolactone homopolymer. On elongation, the crystallinity is increased, leading to an increase in the crystalline melting point. This is confirmed by a comparison of DSC thermograms (Fig. 4) of stretched and unstretched copolymer film specimens (there is a 4°C difference). These observations may be explained as follows: during film preparation accompanied by solution casting, the end blocks, that is, poly(ϵ-caprolactone), coil up their chains, and during elongation, these coils deform, elongate, and become oriented, leading to increasing stiffness.

Poly(ϵ-caprolactone) itself is a hydrophobic polymer, but the introduction of the PEG block causes the copolymer to absorb more than 30% water, depending on the PEG molar percentage. It is thought that this phenomenon strongly affects the degradation characteristics of the copolymer.

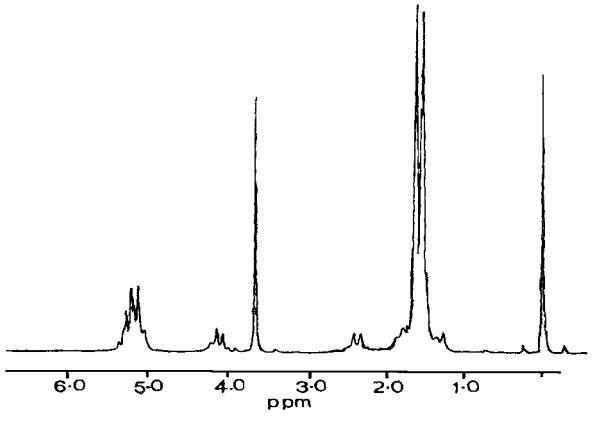
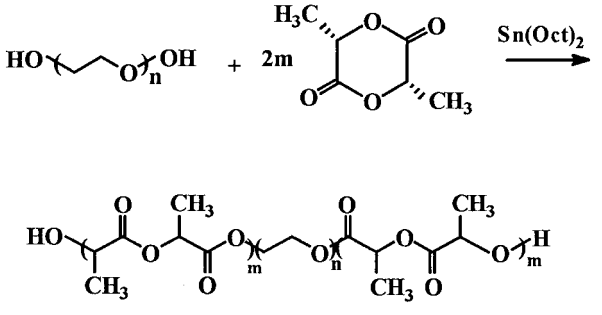


Figure 6 ^{1}H-NMR spectrum of sample 6 (Table I).

Triblock Copolymers from PEG and L-Lactide

These copolymers were prepared from PEG and L-lactide in the presence of $Sn(Oct)_2$ according to the following equation:



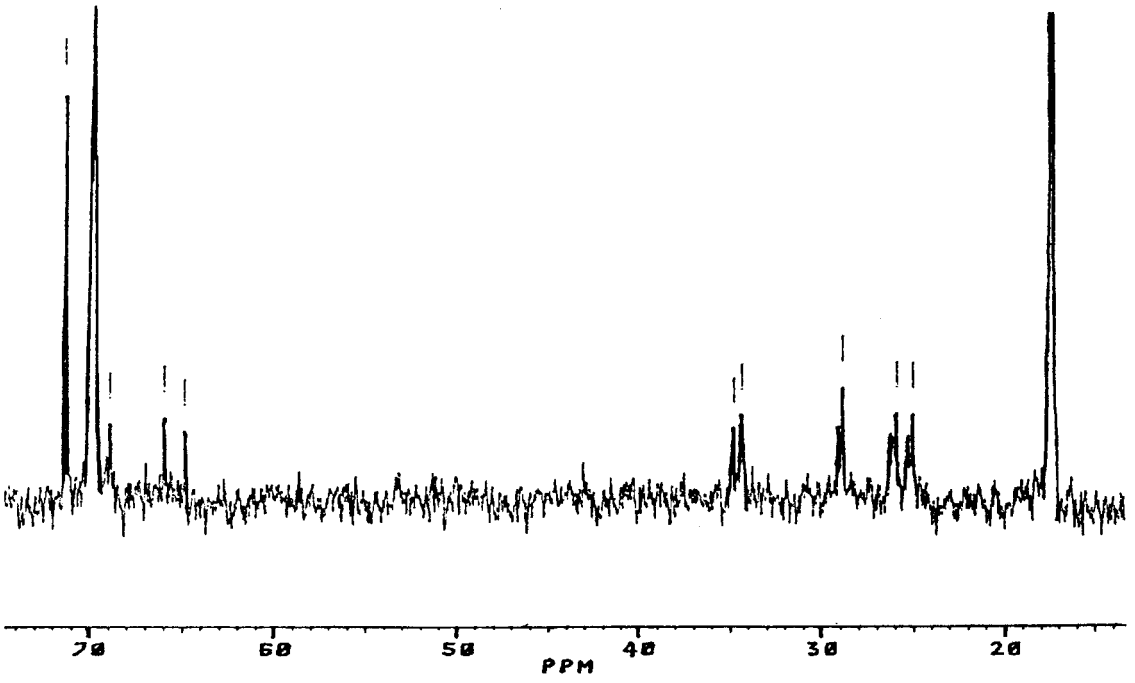


Figure 7 Part of the ^{13}C-NMR spectrum of sample 6 (Table I).

Entries 3 and 4 in Table I show properties of two representative samples of these copolymers. As can be seen, the melting points of the copolymers are lower than that of poly(L-lactide) [the melting point of the poly(L-lactide) homopolymer is dependent on the molecular weight and tacticity and varies from 170 to 190°C]. With the incorporation of PEG as the center block in the poly(L-lactide) homopolymer, the elasticity and toughness of the resultant copolymer increase with respect to those of poly(L-lactide) (Fig. 5). The thermal and spectral properties of these copolymers have been characterized, and the results have been published.[9]

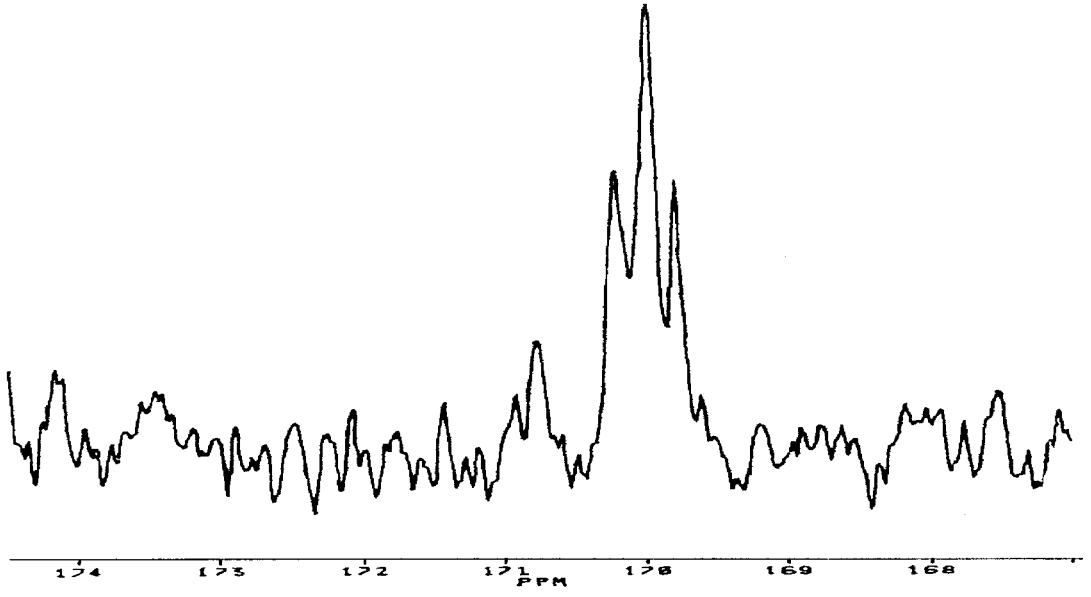


Figure 8 Extended carbonyl region of the ^{13}C-NMR spectrum of sample 6 (Table I).

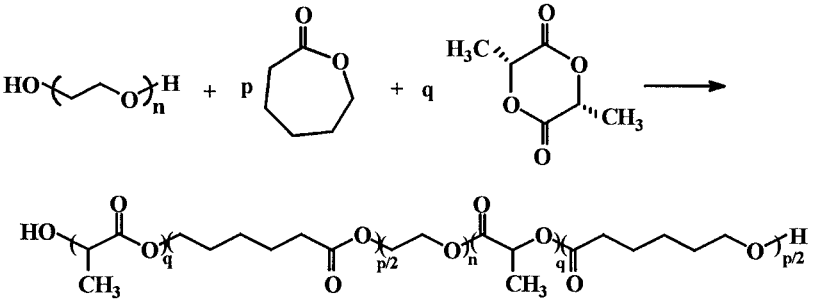
Table II Mechanical Properties of the Copolymers

Sample	Mol % of Copolymer LA/CL/EO	Stress at Break (MPa)	Stress at Yield (MPa)	Strain at Break (%)	Strain at Yield (%)
1	0/90/10	12.5	10.34	454	7.0
3	75/0/25	21.6	20.5	208	4.8
4	90/0/10	29.9	30.5	17.6	6.0
5	82/11/7	12.25	19.9	36	8
6	70/21/9	11.45	—	480	—
7	66/14/20	16.1	—	414	—

LA, lactic acid; CL, ϵ-caprolactone; EO, ethylene oxide.

Multiblock Copolymers from PEG, ϵ-Caprolactone, and L-Lactide

Novel ABA multiblock copolymers were also synthesized from PEG, L-lactide, and ϵ-caprolactone. In these copolymers, the end blocks consisted of copolymers of L-lactide and ϵ-caprolactone with the center block, as before, being PEG:



Samples of copolymers 5–7 show ^{1}H-NMR spectral characteristic of the lactyl CH protons at $\delta = 5.19$. Methylenic protons for caprolactyl units that appear at $\delta = 4.13$ and methylenic PEG that appears at $\delta = 3.64$ were used as references for the determination of the copolymer composition (Fig. 6).

A comparison of the ^{13}C-NMR spectra of sample 6 (Fig. 7) and sample 1 (Table I, Fig. 2) shows that each methylenic carbon of a caprolactyl unit splits into doublets (a decoupled spectrum). These splittings are related to the sequences of the monomers in the two end blocks. The extended carbonyl region of the ^{13}C-NMR spectrum of the lactyl unit is shown in Figure 8. The carbonyl moiety of the caprolactyl unit has a very low intensity due to the low molar percentage of caprolactyl unit in the copolymer. Kasperczyk et al.[24] characterized the carbonyl resonance of block and random copolymers of L-lactide and ϵ-caprolactone, and the end blocks of these copolymers are structurally categorized as microblock copolymers accordingly. The reactivity ratio of L-lactide is higher than that of ϵ-caprolactone,[12,13] and this difference in reactivities leads to block copolymers. However, with increasing reaction time, these blocks may become randomized by transesterification reactions. Table II shows a comparison of the mechanical properties of all the copolymers. These copolymers exhibit very interesting mechanical properties with respect to those of the homopolymers (Fig. 9).

For the improvement of the elasticity of poly(L-lactide), blended films with various compositions of poly(L-lactide) and copolymer 6 (Table I) were prepared by solution casting. Also, the mechanical properties of these blends were compared with those of poly(L-lactide) (Fig. 10). The elasticity of the blends increases as the weight percentage of the copolymer increases in comparison with poly(L-lactide). Thus, these polymer blends have suitable mechanical properties. One of the main applications of these thermoplastic elastomers seems to be sustained, degradable drug-release systems.

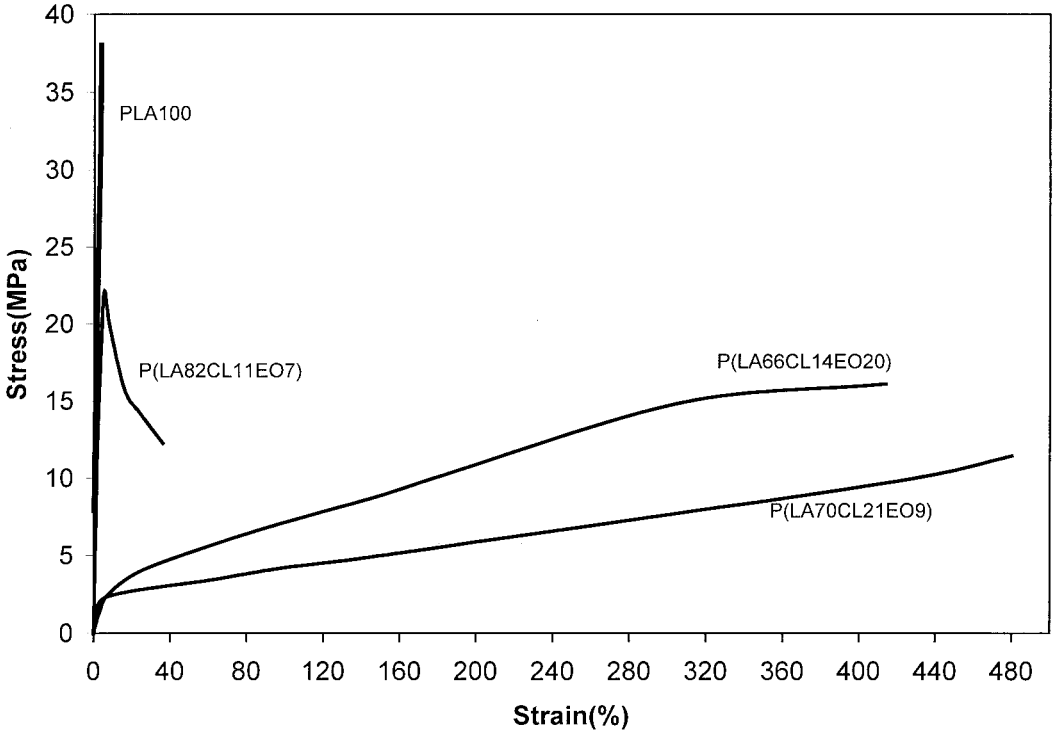


Figure 9 Stress–strain diagrams of copolymers 5–7 (Table I) and poly(L-lactide).

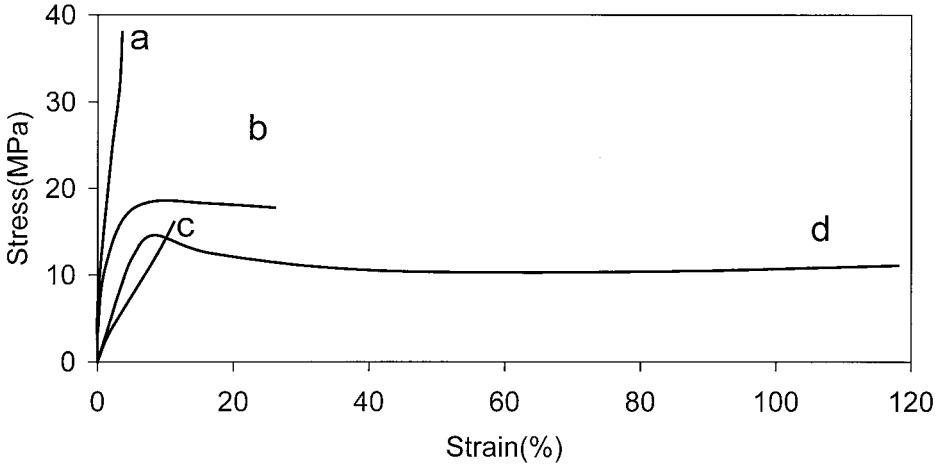


Figure 10 Stress–strain diagrams of blends prepared from poly(L-lactide) and copolymer 6 (Table I). The weight percentages of copolymer 6 in the blends were (a) 0, (b) 21, (c) 51, and (d) 79.

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