Synthesis and Properties of A–B–A Block Copoly(ester–ethers) Comprising Poly(L-lactide) (A) and Poly(oxypropylene-*co*-oxyethylene) (B) with Different Molecular Weights

Chan Woo Lee and Yoshiharu Kimura*

Department of Polymer Science and Engineering, Kyoto Institute of Technology, Matsugasaki, Kyoto 606

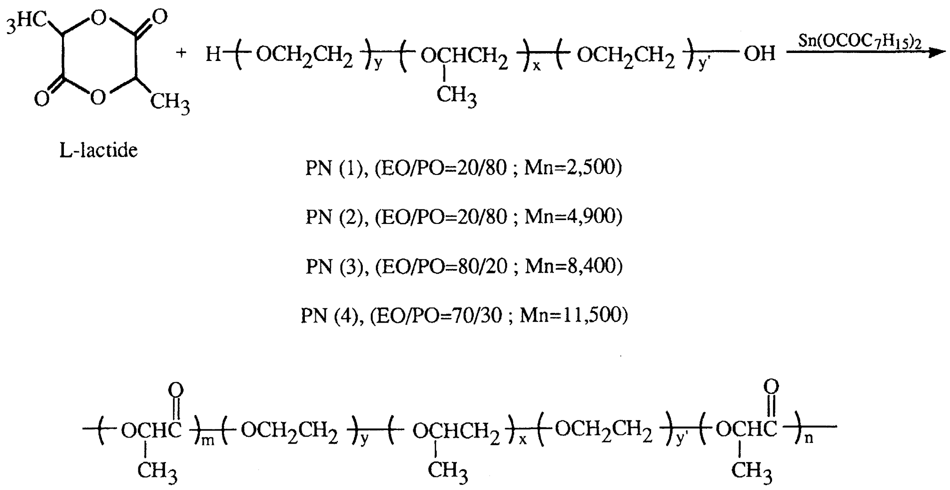
(Received November 27, 1995)

An A–B–A triblock copoly(ester-ether) comprising poly(L-lactide) (A) and poly(oxyethylene-*co*-oxypropylene) (B) was prepared by copolymerization of L-lactide and a commercially available telechelic copolyether, Pluronic® (PN), with different molecular weights by the catalysis of tin(II) octanoate. The low molecular weight PN gave the copolymers having a low or medium molecular weight and a unit composition slightly different from the feed ratio. With PN whose molecular weight was around 10000, high molecular weight copolymers were obtained in high yield. For the PN with molecular weight of 8400, the block copolymerization was examined at different feed ratios, in which the molecular weight and the unit composition were successfully controlled by changing the L-lactide/PN ratio in feed. The copolymer containing 10 wt% of this PN was melt-spun into a filament, which was drawn to various draw ratios at 40 and 60 °C. The tensile modulus and strength of the filament increased with the draw ratio increasing at 60 °C, while at 40 °C they reached a plateau above the draw ratio of 5.0. It was found that the copolymer filaments showed an improved flexibility due to the incorporation of the soft PN segments. The in vitro hydrolysis test of the drawn filaments showed that the block copolymer has much higher degradability than the homo poly-L-lactide.

Poly(α-hydroxy acid)s such as polyglycolide (PGA) and poly-L-lactide (PLLA) have been attracting great attention[1—4] as they are hydrolyzed in living tissues to their constituents, α-hydroxy acids, which can be excreted by the human metabolic cycles.[5,6] Their application, therefore, has been directed to various temporary bio-materials including drug carriers[7—9] and absorbable surgical sutures.[1,4,10,11] However, the high crystallinity[2,12—14] and low hydrophilicity[15,16] of these polymers have interfered with the controlled degradation and decreased the compatibility with soft tissues. One solution to these material problems is to introduce soft segments to the base polymers by block copolymerization.[17,18] Recent publications[19—21] demonstrated some syntheses of block copolymers of a poly(α-hydroxy acid) with such polyethers as poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG). Most of these copolymers, however, were of low molecular weight, owing to the insufficient control of polymerization, and had limited use except for uses as an absorbable coating material of drug pellets. Very recently,[22] we have reported a new block copolymerization of L-lactide with another telechelic polyether, poly(oxypropylene-*co*-oxyethylene) (PN; the common trade name: Pluronic®) which has primary hydroxyl groups on both terminals. The copolymerization proceeded quite easily by the catalysis of tin(II) octanoate to give the A–B–A block copoly(ester-ether) comprising PLLA and PN as the A and B segments, respectively. Since the molecular weight of the starting PN was as high as 11500, the molecular weight of the resultant block copolymer became higher than 100000. This block copolymer could be melt-spun into a flexible high-strength fiber which may be used as monofilament-type absorbable suture. However, the hydrolyzability of this block copolymer has not been evaluated so far. In addition, the preparation of the block copolymer comprising PN with molecular weight of 8400 has been thought to be the most important for the practical medical application, because this is the only derivative that has been approved by FDA as a safe pharmaceutical surfactant. In the present study, therefore, the block copolymerization was examined for PN with various average molecular weights lower than 10000 to clarify the scope of this block copolymerization (see Scheme 1), and the block copolymer comprising the PN with molecular weight of 8400 was prepared. It was found that the block length and molecular weight can be successfully controlled for each of PN, although the molecular weight cannot be so high when the molecular weight of the starting PN is low. It was also found that the block copolymer comprising the PN with molecular weight of 8400 can be of high molecular weight and can be melt-spun into fiber as thin as that comprising PN with molecular weight of 11500. Then, the monofilament fibers were made from the copolymers containing various compositions of this PN, and their properties and hydrolyzability were evaluated in order to clarify the potential application of these fibers to absorbable suture.

Experimental

Materials. L-Lactide was prepared by the method reported previously and purified by repeated recrystallizations from ethyl ac-



Scheme 1.

etate. The PN comprising oxyethylene (EO) and oxypropylene (PO) units were the commercially available Pluronic® L-62 (PN(1)), L-122 (PN(2)), F-68 (PN(3)), and F-127 (PN(4)), which had different molecular weights and compositions, as shown in Scheme 1. They were supplied by Asahi Denka Co., Ltd., Japan, and thoroughly dried at a reduced pressure below 10^{-3} mmHg (1 mmHg = 133.322 Pa) before use. Tin(II) octanoate was a reagent grade commercial material. It was purified by distillation and dissolved in toluene to have a concentration of 1.0 mg ml^{-1}.

Measurements. ^{1}H NMR spectra were measured at 200 MHz on a Varian XL-200 spectrometer in $CDCl_3$ (internal reference: 1 vol% solution of TMS). The number-average molecular weight (M_n) and the molecular weight distribution (M_n/M_w) were determined by gel permeation chromatography (GPC). The analyzer was composed of a Shimadzu LC-10A pump, a Shodex RI SE-31 RI detector, a Shimadzu C-R7A Chromatopac data processor, a Shodex DEGAS KT-16 degassor, and a Sugai U-620 column oven. A combination of two polystyrene gel columns of Toso TSK gel G4000H and G2500H (7.5 mmi.d. × 300 mm, each) was used at 35 °C with chloroform as the eluent. The molecular weight was calibrated according to the polystyrene standards. DSC analysis was made on a Mac Science DSC-3100 thermal analyzer. The heating rate was 10 °C min^{-1}, and α-alumina was used as the reference sample. In the first scan, the sample was heated from room temperature to 200 °C and quenched in a liquid nitrogen bath. In the second scan, the analysis was made from -30 to 200 °C. Tensile measurement of each fiber was carried out on a tensile tester, TOM 200D (Shinko Tsushin, Tokyo, Japan).

Copolymerization of L-Lactide and PN. Four grams (27.8 mmol) of L-lactide and a prescribed amount of PN were placed in a flask equipped with a mechanical stirrer. The flask was evacuated by a vacuum pump for several hours in order to dry up the mixture thoroughly and then was filled with nitrogen gas. Then, 0.05 ml (0.045 mol%) of the above catalyst solution was added, and the flask was evacuated again for several hours to remove toluene, then it was filled with nitrogen gas. The resultant mixture was heated at 160 °C with stirring for 30 min. In this process the mixture turned from liquid to solid. After the reaction had finished, the product was dissolved in 20 ml of chloroform, and the solution was poured into an excess amount of methanol. The precipitated product was filtered, washed with diethyl ether, and dried in vacuo. The product finally obtained was a white fibrous solid. ^{1}H NMR ($CDCl_3$) δ = 1.17 (Me for PO), 1.57 (Me for LA), 3.3—3.7 (CH_2CH for PO), 3.6—3.7 (CH_2CH_2 for EO), and 4.9—5.1 (CH for LA), where LA denotes the L-lactate unit in PLLA. The expanded spectrum showed signals around $\delta = 4.3$ ppm for the ester methylene group of the bridging EO unit of PN with which the PLLA segment was bonded.[22)]

By a similar method, a series of copolymers with different PN and with different compositions were prepared by changing the PN and the PN to L-lactide ratio in feed.

Reaction of PLLA and PN as a Model Reaction of Transesterification. In a 50 ml flask equipped with a mechanical stirrer, 2.0 g of PLLA ($M_n = 107000$, $M_w/M_n = 1.99$), 0.21 g of PN(3), and 0.025 ml of the catalyst solution were charged and dissolved in 30 ml of chloroform. After evaporation of the chloroform, the mixture was dried up in high vacuum. Then, the mixture was heated at 160 °C with stirring for 30 min under nitrogen atmosphere. After the heating, the product was dissolved in 20 ml of chloroform, and the solution was poured into an excess amount of methanol. The precipitated product was filtered, washed with diethyl ether, and dried in vacuo. The yield of the product was 1.7 g. It was analyzed as described for the copolymerization products.

Melt-Spinning and Drawing. Melt-spinning was carried out by a laboratory-size screw extruder with a screw of 15 mmϕ in diameter and a mono-hole nozzle of 1.0 mm in diameter. The temperatures of the feeding, metering, and spinneret zones were adjusted at 150, 180, and 150 °C, respectively. The polymer melt was extruded at a rate of 0.15 g min^{-1}, and the extrudate was drawn and wound on a winder to give a filament of 70—180 mm in diameter. The filament was then drawn to various draw ratios at 40 and 60 °C by use of a handy drawing apparatus (Koa Shokai, Kyoto).

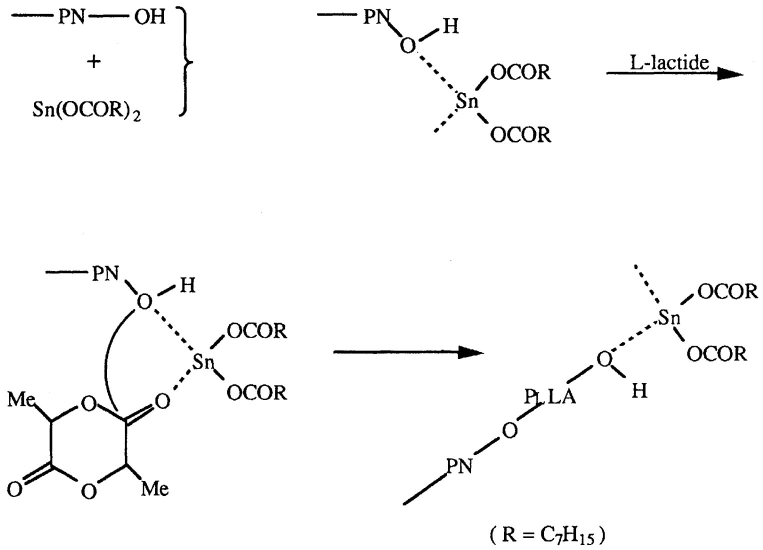
Hydrolysis of Filament. In each of ten glass ampoules, several pieces of the drawn filaments were immersed in 30 ml of a thermally sterilized phosphate buffer solution (pH = 7.4). Each ampoule was sealed and then held in a water bath thermostatted at 37 °C. After a prescribed time had passed, one of the ampoules was opened, and the filaments were taken out, washed in distilled water, dried, and subjected to the tensile test and the GPC analysis.

Results and Discussion

In the present study, a telechelic oligomer PN having hydroxyl groups on both ends was selected as a soft segment for the following reasons. First, PN is frequently utilized not only as a pharmaceutical surfactant for making drug tablets for oral administration, but also as a surface-lubricant of various braided surgical sutures. This fact is an empirical proof that PN is biocompatible and less toxic in vivo. In particular, PN(3) (Pluronic® F-68) is the only pharmaceutical substance which has been approved by the FDA. Second, PN has been utilized as a soft segment for making various thermoplastic elastomers, and its elastic nature should be much higher than the other polyethers. Third, the two primary hydroxyl groups on the polymer ends should have higher reactivity than the secondary hydroxyl group of PLLA, and they are able to react with L-lactide in the initiation step to promote the block copolymerization. In the polymerization of L-lactide with tin(II) octanoate as the catalyst, alcohols and water can be the initiating species with which the monomers react successively to undergo polymerization. In the presence of PN, therefore, the polymerization of L-lactide can be initiated from its terminal hydroxyl groups to give the desired A–B–A-type block copolymers (Scheme 2).

Block Copolymerizations of L-Lactide with Various PN. We first optimized the reaction conditions of this block copolymerization by using PN(4), whose molecular weight was the highest of the four. At a constant catalyst/monomer ratio of 0.045 mol% and at a constant polymerization time of 1 h, the yield and the molecular weight of the copolymer increased with increasing the reaction temperature from 120 to 160 °C and reached a plateau above 160 °C. Above 170 °C the product became brownish in color, probably due to the thermal decomposition. The polymer yield after the reprecipitation changed slightly with reaction time at the reaction temperature of 160 °C. The highest yield was obtained when the time was 25—30 min. Based on these results, the polymerization temperature and time were determined to be 160 °C and 30 min, respectively. Then the amount of catalyst was changed from 0.02 to 0.10 mol% relative to L-lactide in feed, resulting in little change in the product yield and molecular weight. Hence, the amount of catalyst was kept at 0.045 mol%.

With these optimum polymerization conditions determined for PN(4), similar copolymerizations were examined for the four kinds of PN at a constant L-lactide to PN ratio (by wt.) of 90/10 in feed. The structures of the copolymers obtained after reprecipitation were identified as shown in Experimental, and their unit composition was determined by the integral ratio of the ^{1}H NMR signals of LA, EO, and PO units. Table 1 summarizes the typical results. PN(1), having



Scheme 2.

Table 1. Typical Results of the Block Copolymerization[a] of L-Lactide and PN with Different Molecular Weight

		Feed ratio		Polymeric product			Estimated values		
Run	PN (M_n)	L-Lactide/PN	LA/EO/PO	Yield[b]	LA/EO/PO[c]	$M_n \times 10^{-4}$ [d]	$M_n \times 10^{-4}$ [e]	T_g	T_m
No.		wt/wt	composition	%		dalton	dalton	°C	°C
1	PN(1) (2500)	90/10	95/1.0/4.0	64	98/0.4/1.6	0.4	2.5	13	87
2	PN(2) (4900)	90/10	95/1.0/4.0	85	96/0.8/3.2	1.2	4.9	22	166
3	PN(3) (8400)	90/10	95/4.0/1.0	93	95/4.0/1.0	8.1	8.4	31	171
4	PN(4) (11500)	90/10	95/3.5/1.5	93	95/3.5/1.5	10.9	11.5	32	173

a) At 160 °C for 30 min with 0.045 mol% of tin(II) octanoate relative to L-lactide. b) After reprecipitation. c) By ^{1}H NMR spectra. d) By GPC with chloroform as the eluent. e) Assuming that the polymerization of L-lactide took place preferentially from the terminal hydroxyl groups of PN.

low molecular weight, gave a waxy product in a low yield whose molecular weight was also very low. Since the low molecular weight oligomers were likely to be removed by reprecipitation, the composition of the precipitated copolymer was different from the feed ratio. In the cases of PN(3) and PN(4), the yield and the molecular weight of the copolymers were very high (Run Nos. 3 and 4), and the copolymer compositions were identical to the feed ratios, because most of the PN which reacted was involved in the product. PN(2) gave a product with medium molecular weight in a mean yield, in which the copolymer composition was slightly different from the feed ratio. Figure 1 shows the typical GPC curves of these copolymers. It was confirmed that the copolymers comprising PN(1)—(3) showed a single-modal curve, while the copolymer of PN(4) showed a shoulder peak at lower molecular weight region which may be ascribed to a small amount of PLLA homopolymer which has formed in the presence of moisture (vide infra). The peak maximum shifted to the higher molecular weight region as the molecular weight of PN increased. In the case of PN(3) or even PN(4), the molecular weight of the copolymer measured by GPC was almost comparable to the theoretical value calculated from the feed ratio assuming the exclusive formation of the PLLA–PN–PLLA triblock copolymer.

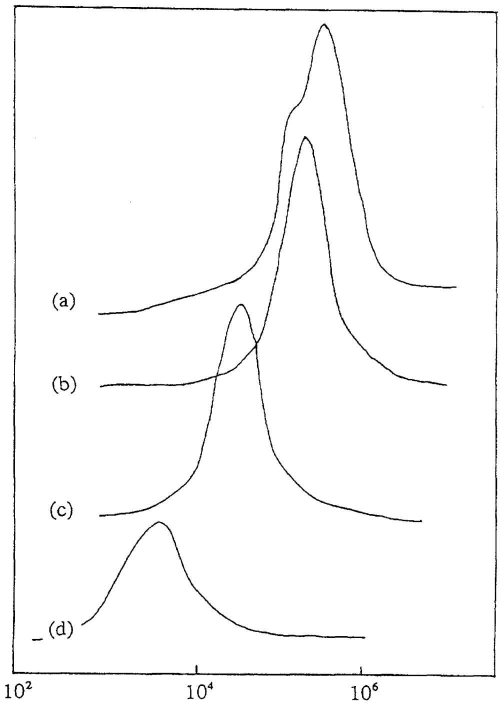


Fig. 1. Typical GPC curves of PLLA–PN–PLLA prepared at L-lactide/PN ratios of 90/10 for (a) PN(4), (b) PN(3), (c) PN(2), and (d) PN(1).

For all of these copolymers, the endothermic peak ascribed to the crystal fusion of PLLA segments was observed at temperatures lower than the melting point (T_m) of PLLA. Although the lowering of T_m for the copolymer comprising PN(1) was exceptionally large because of its waxy nature, there was found to be a tendency that the T_m and glass transition temperature (T_g) of the copolymer became higher with increase in the molecular weight of PN or the copolymer. These data suggested that the molecular weight of the copolymer increases with the molecular weight of PN increasing and that PN(3) may give a copolymer having a molecular weight that is high enough to spin a fiber.

Preparation of Block Copolymers with Different Composition of PN(3). With PN(3) the block copolymerization was further studied at various L-lactide to PN(3) feed ratios. Table 2 shows some of the results. The yield of the precipitated polymer exceeded 90% in every case, in spite of some operational loss at the reprecipitation. In these cases only a small amount of L-lactide was detected in the soluble part, which had been recovered from a mixture of the precipitant (methanol) and the washing solvent (diethyl ether). The absence of PN in this part supports the incorporation of the fed PN in the copolymer. Therefore, the unit composition of the copolymer determined by ^{1}H NMR spectrum was almost identical to the L-lactide/PN composition in the feed.

Figure 2 shows the typical GPC curves of these copolymers. It is shown that the peak maximum shifted to the lower molecular weight region as the feed ratio of PN increased. The copolymers containing 10—50 wt% of PN (Run Nos. 3—5) showed a single-modal curve centered at a higher Mn region than that of PN, while the copolymer containing 5 wt% of PN (Run No. 2) showed a bi-modal peak as the copolymer containing 10 wt% of PN(3). The small shoulder peak may also be ascribed to the aforementioned PLLA homopolymer,

Table 2. Typical Results of the Block Copolymerization[a] of L-Lactide and PN(3) (EO/PO = 80/20; M_n = 8400)

Run No.	Feed ratio L-Lactide/PN wt/wt	 LA/EO/PO composition	Polymeric product Yield %	 LA/EO/PO[b]	 $M_n \times 10^{-4}$ [c] dalton	Estimated values $M_n \times 10^{-4}$ [d] dalton	M_w/M_n
1	100/0	100/0/0	95	100/0/0	16.7		1.21
2	95/5	98/1.6/0.4	96	98/1.6/0.4	14.2	16.8	1.60
3	90/10	95/4.0/1.0	93	95/4.0/1.0	8.1	8.4	1.62
4	80/20	89/8.8/2.2	93	89/8.8/2.2	3.9	4.2	1.30
5	50/50	58/33.6/8.4	90	61/31.9/7.1	1.7	1.7	1.22

a) At 160 °C for 30 min with 0.045 mol% of tin(II) octanoate relative to L-lactide. b) By ^{1}H NMR spectra. c) By GPC with chloroform as the eluent. d) Assuming that the polymerization of L-lactide took place preferentially from the terminal hydroxyl groups of PN.

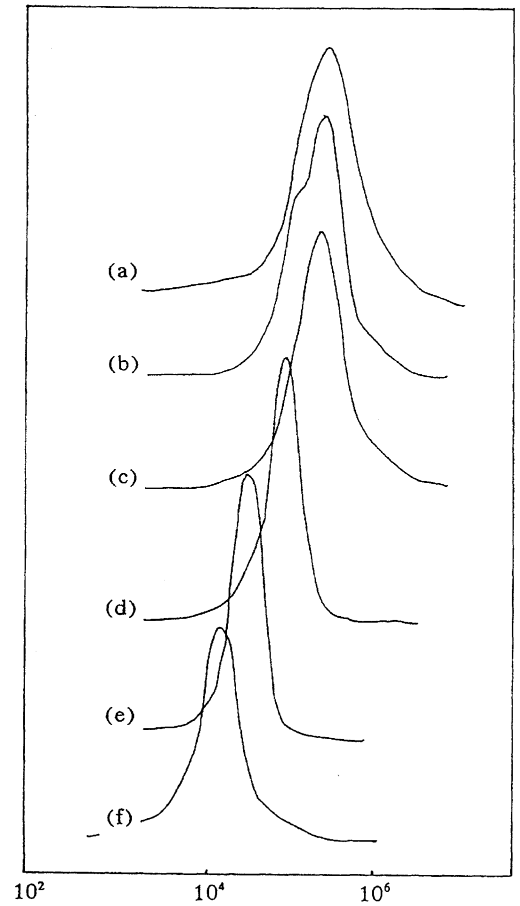
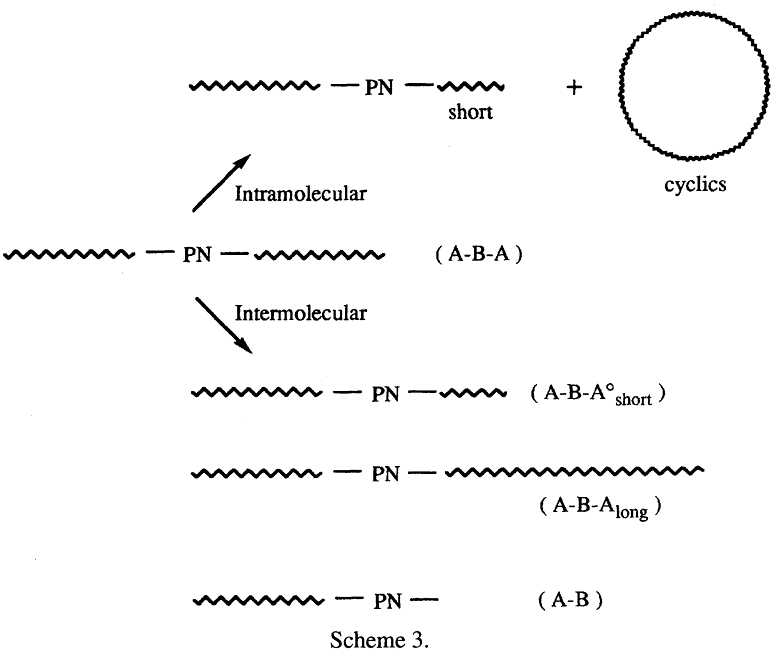


Fig. 2. Typical GPC curves of PLLA–PN–PLLA with the L-lactide/PN(3) compositions of (b) 95/5, (c) 90/10, (d) 80/20, and (e) 50/50 as compared with those of (a) PLLA and (f) PN(3).

whose formation became apparent at low concentration of the initiating hydroxyl groups relative to the water impurity present in the polymerization system. The effect of this water impurity would be neglected at the higher feed ratio of PN. The M_n and M_w/M_n measured for these copolymers are summarized in Table 2. It should be confirmed that the M_n values determined by GPC were comparable with the values estimated from the feed ratios, assuming the formation of the PLLA–PN–PLLA triblock copolymer.

In the last stage of the block polymerization, there might be a possibility of inter- or intra-molecular transesterification involving the terminal hydroxyl groups and the ester backbones. By such a process, the PLLA block segments might scramble among the initially formed block copolymers to form a cyclic oligomer or a PLLA–PN di-block copolymer in an extreme case (Scheme 3). Therefore, we studied the polymer reaction between a PLLA homopolymer ($M_n = 108000$, $M_w/M_n = 1.90$) and PN(3) at the same reaction conditions as the block copolymerization in order to see if the latter's hydroxyl groups would react with the former's main-chain ester groups. The reaction product isolated by the reprecipitation contained no PN, as analyzed by the ^{1}H NMR spectrum, and its molecular weight and molecular weight distribution ($M_n = 107000$, $M_w/M_n = 1.99$) were almost identical with those of the original PLLA. These data suggested that the transesterification should be negligible at the present polymerization conditions. We found that such a transesterification proceeded if this polymer reaction was carried out above Tm of PLLA (e.g., > 180 °C). In this case the M_w/M_n value became larger than 2.5 and reached 4.5 with the M_n value decreasing. If we judge from the narrow molecular weight distribution of the copolymerization products, shown by the small M_w/M_n values in Table 2, the transesterification would not be important in the present block copolymerization. It was therefore concluded that the copolymerization products



Scheme 3.

have the structure of PLLA–PN–PLLA triblock copolymer, as they were designed to have.

Figure 3 shows the typical DSC curves of the copolymers with different unit compositions as compared with those of PLLA (a) and PN(3) (e). The copolymers exhibited an exothermic peak at around 80—90 °C and an endothermic peak at a temperatures lower than the T_m of PLLA. They are ascribed to the crystallization and crystal fusion of the PLLA segments, respectively. There is a tendency that T_m became lower with increasing PN(3) composition. While PN(3) showed an endothermic peak at 56 °C due to the crystal fusion of poly(oxyethylene) segments, the copolymers showed no peak around the temperature range. Only the copolymer containing 20 wt% of PN(3) showed a complex curvature around this temperature, probably because of the active motion of the polyether segment. The inflection due to the glass transition of the amorphous phase of PLLA shifted to a lower temperature region with increasing PN(3) composition. These results suggested that the PN segments and PLLA are well compatible and mixed in the amorphous phase of PLLA without forming a microphase separation in solid state. The compatibility of both polymers, however, would not be so high as to prevent crystallization of PLLA.

Properties of Melt-Spun Filament. The block copolymer containing 10 wt% of PN(3) was melt-spun into a filament by the conventional melt-spinning method. The as-spun filament obtained (diameter : 280 mm) was drawn 2.5—15 times in length at 40 and 60 °C. The maximum draw ratios at 40 and 60 °C were 12.5 and 15, respectively, and the diameters of the drawn filaments became about 70—180 mm depending on the draw ratio. Both the spinnability and drawability were excellent. Figure 4 shows the changes in

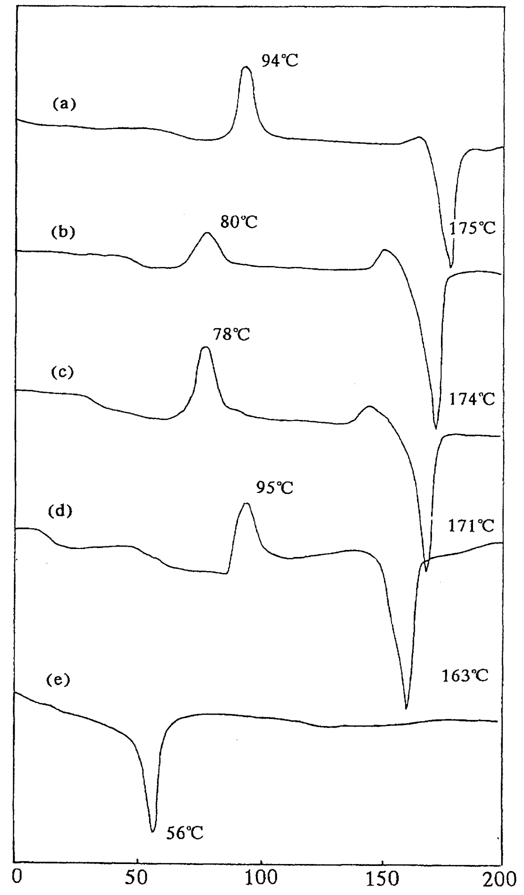


Fig. 3. Typical DSC curves of PLLA–PN–PLLA with the L-lactide/PN(3) compositions of (b) 95/5, (c) 90/10, and (d) 80/20 as compared with those of (a) PLLA and (e) PN.

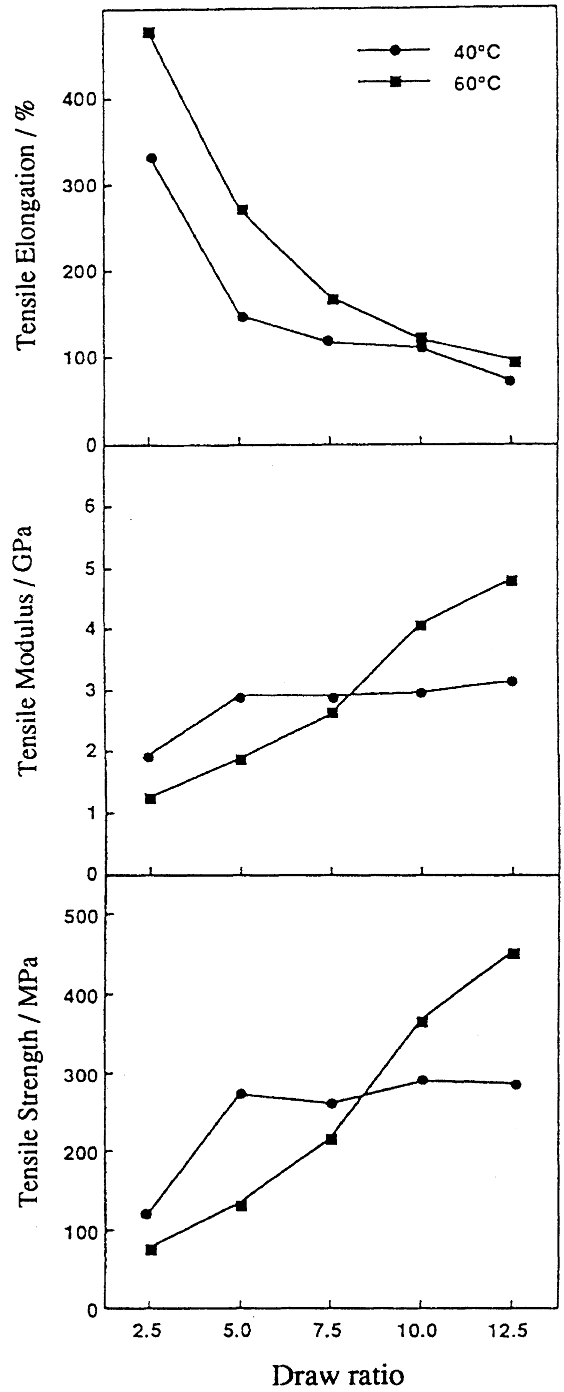


Fig. 4. Changes in tensile properties with draw ratio at two different drawing temperatures for the PLLA–PN–PLLA filament with the L-lactide/PN(3) composition of 90/10.

tensile properties of the filament as a function of draw ratio. At a draw temperature of 60 °C, the tensile strength and modulus increased with the draw ratio increasing, while at 40 °C they reached a plateau at draw ratios higher than 5. Since the modulus of the copolymer filament is 1/2—1/5 times that of PLLA filament, the introduction of PN segment should be quite effective to improve the flexibility of the PLLA fiber.

Figure 5 shows the WAXS of the filaments drawn up to

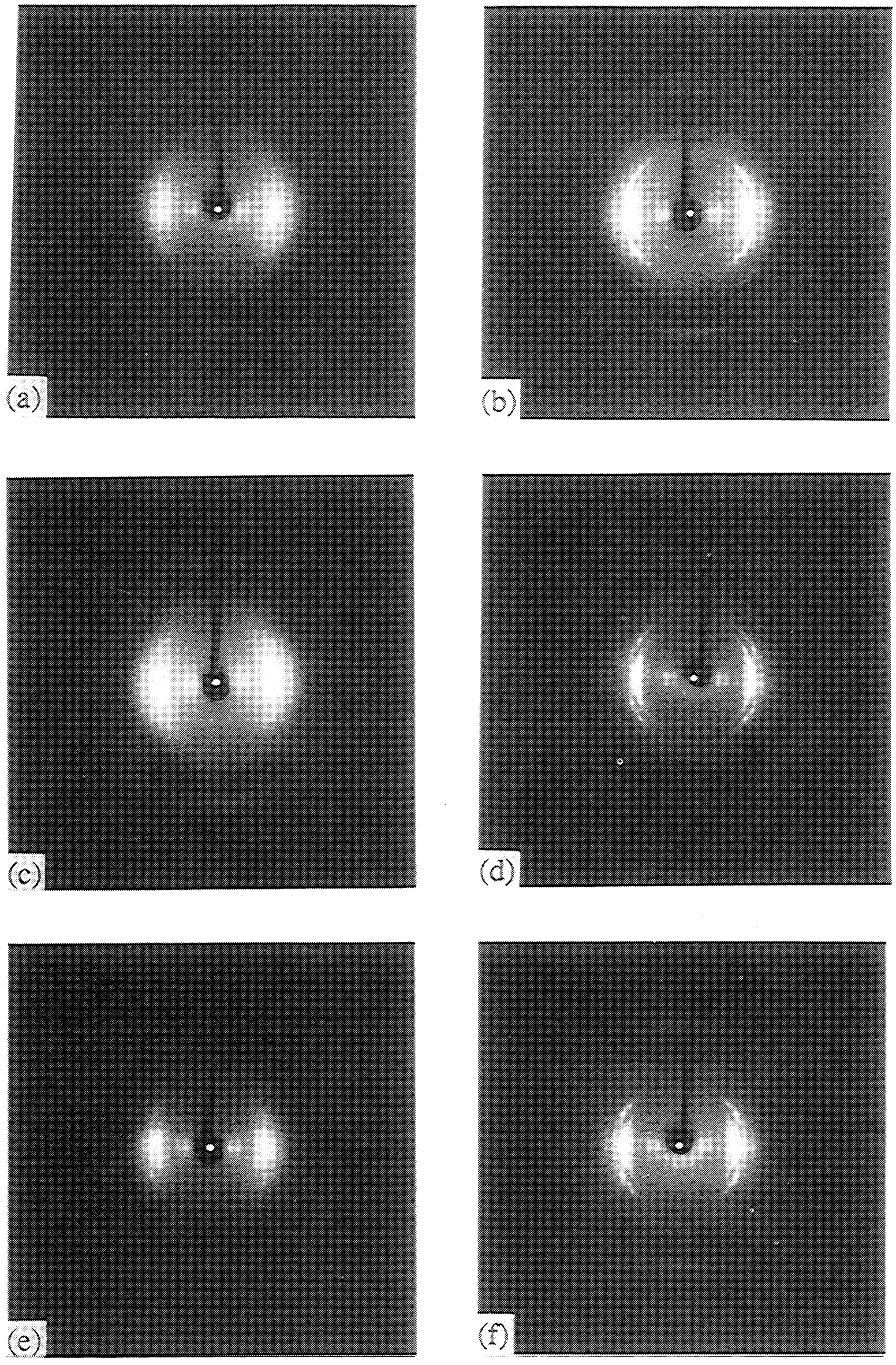


Fig. 5. WAXS of the PLLA–PN–PLLA filaments drawn to different ratios (λ) at different temperatures (T_d). The L-lactide/PN(3) ratio of the copolymer was 90/10. (a) $\lambda = 5$, $T_d = 40$ °C; (b) $\lambda = 5$, $T_d = 60$ °C; (c) $\lambda = 10$, $T_d = 40$ °C; (d) $\lambda = 10$, $T_d = 60$ °C; (e) $\lambda = 12.5$, $T_d = 40$ °C; and (f) $\lambda = 12.5$, $T_d = 60$ °C.

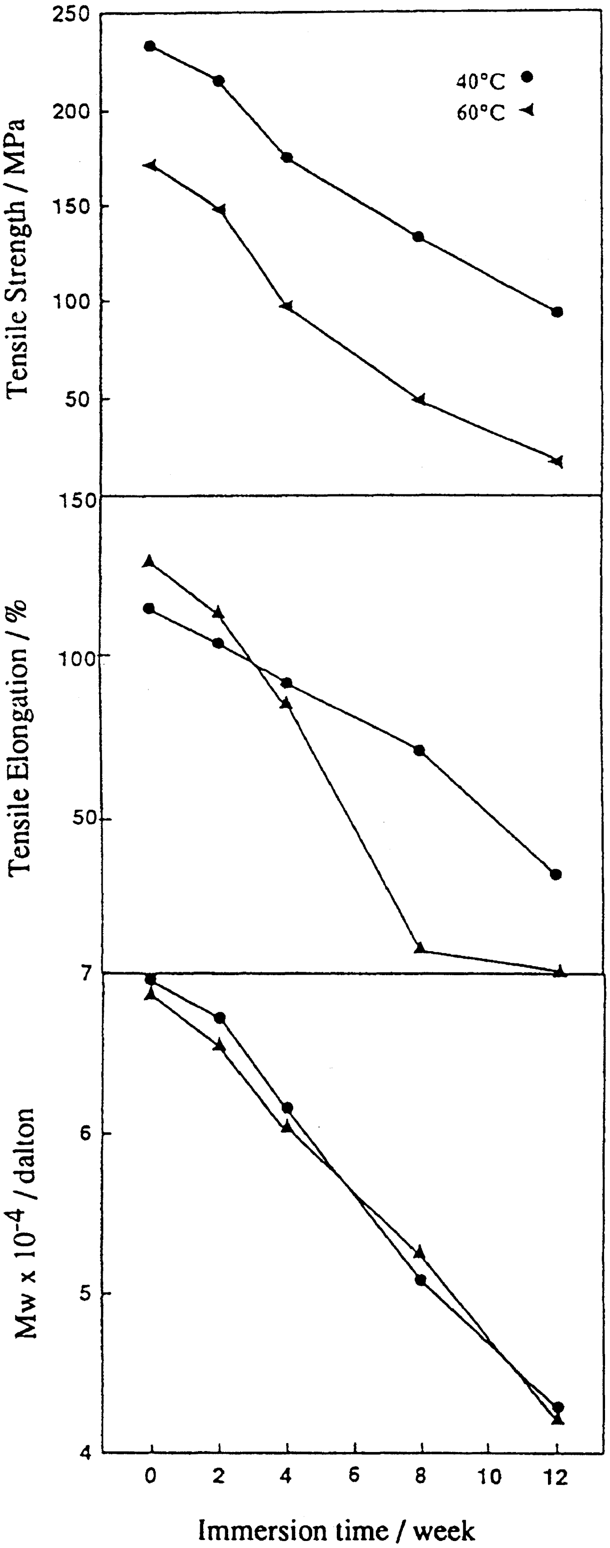


Fig. 6. Changes in tensile properties and molecular weight of the PLLA–PN–PLLA filaments drawn to 5 times at 40 and 60 °C with immersion time in phosphate buffer (pH = 7.4). The L-lactide/PN(3) ratio of the filaments was 90/10.

5—12.5 times. For the filaments drawn at 40 °C, diffractions can be seen in broad hollows with incomplete crystallization during drawing. This may be related to the above least increases in tensile strength and modulus at draw ratios higher than 5. The molecular orientation, however, increased in the amorphous parts with the draw ratio increasing. The filaments drawn at 60 °C showed sharp diffraction arcs in the equatorial regions due to the crystal orientation, which is compatible with the constant increase in modulus. Because the crystallization temperature of this copolymer was 78 °C, as shown by the DSC (Fig. 3 (c)), the crystal orientation could be induced around 60 °C, but was not allowed at 40 °C even under the mechanical shearing applied.

Hydrolysis of Filament In Vitro. In order to study the hydrolyzability of the copolymer, the above filaments drawn 5 times were immersed in a phosphate buffer (pH = 7.4). The time-dependent changes both in mechanical properties and molecular weight of the filaments are shown in Fig. 6. With increasing immersion time, both the tensile strength and elongation decreased sharply. These decreases corresponded to the decrease in molecular weight of the copolymer. It is known that the degradation rate of the filament drawn at 40 °C was a little slower than that of the filament drawn at 60 °C in terms of the elongation. This may be because the latter had a polycrystalline structure and the degradation would more concentrated on the amorphous parts present in between the crystals.

Conclusion

The A–B–A block copolymers comprising PLLA (A) and PN (B) were prepared by the tin-catalyzed bulk polymerization of L-lactide in the presence of PN with various molecular weights. The low molecular weight derivatives, PN(1) and PN(2), gave the copolymers with low or medium molecular weight, and their unit composition was slightly different from the feed ratio. With PN(3) and PN(4) whose molecular weight was around 10000, high molecular weight copolymers were obtained in high yield, and their unit composition was identical to the feed ratio. The copolymer containing 10 wt% of PN(3) was melt-spun into filaments which were drawn at 40 and 60 °C. The drawn filaments showed an improved flexibility due to the incorporation of the soft PN segments. The in vitro hydrolysis test of the drawn filaments showed that the copolymer containing 10 wt% of PN(3) can be hydrolyzed in a much faster rate than PLLA homopolymer. Although the strength of this filament was slightly lower than that of the commercially available sutures, it reached the minimum strength required for the suture material. Therefore, this copolymer should have high potential as a biodegradable polymer with improved flexibility and biodegradability.

References

1) E. J. Frazza and E. E. Schmitt, *Biomed. Mater. Res.*, *Symp.*, **1**, 43 (1971).

2) D. K. Gilding and A. M. Reed, *Polymer*, **20**, 1459 (1979).

3) S. Gogolewski and A. J. Pennings, *Makromol. Chem. Rapid Commun.*, **4**, 213 (1983).

4) R. J. Fredericks, A. J. Melveger, and J. Dolegiewitz, *J. Polym. Sci.*, *Polym. Phys. Ed.*, **22**, 57 (1984).

5) H. Alexander, J. R. Parsons, I. D. Strauchler, S. F. Corcoran,

O. Gona, C. Mayott, and A. B. Weis, *Orthop. Rev.*, **10**, 41 (1981).

6) E. Echeverria and J. Jimenez, *Surgery*, **131**, 1 (1970).

7) H. J. Sander, *Chem. Eng. News*, **31**, 67 (1985).

8) H. Okada, Y. Ogawa, and K. Yashiki, (Takeda Chem. Ind.), Jpn. Kokai Tokyo Koho JP 60-100516, 1985; *Chem. Abstr.*, **103**, 166162z (1985).

9) T. Iwa, M. Hirano, R. Yamashita, and M. Sakatoku, *Igaku No Ayumi*, **128**, 655 (1984); *Chem. Abstr.*, **101**, 43491g (1984).

10) H. Dardik, I. Dardik, and H. Laufman, *Am. J. Surg.*, **121**, 656 (1971).

11) B. Eling, S. Gogolewski, and A. J. Pennings, *Polymer*, **23**, 1587 (1982).

12) K. Jamshidi, S.-H. Hyon, T. Nakamura, Y. Ikada, Y. Shimizu, and T. Teramatsu, in "Biological and Biomechanical Performance of Biomaterials," ed by P. Christel, A. Meunier, and A. J. C. Lee, Elsevier, Amsterdam (1986), p. 227.

13) B. Eling, S. Gogolewski, and A. J. Pennings, *Polymer*, **23**, 1587 (1982).

14) B. Kalb and A. J. Pennings, *Polymer*, **21**, 607 (1980).

15) C. C. Chu, in "Biomaterials," ed by G. D. Winter, D. F. Gibbons, and H. Plenk, Jr., John Wiley, New York (1982), p. 781.

16) R. A. Miller, J. M. Brady, and D. E. Cutright, *J. Biomed. Mater. Res.*, **11**, 711 (1977).

17) A. M. Reed and D. K. Gilding, *Polymer*, **22**, 499 (1981).

18) B. R. M. Gallot, "Advances in Polymer Science, 29, Structure and Properties of Polymers," Springer Verlag, Heidelberg, FRG (1978), p. 85.

19) D. J. Casey and K. R. Huffman, (Am. Cyanamid Co.), U. S. Patent 4438253 (1984).

20) E. A. Vitalis, (Am. Cyanamid Co.), U. S. Patent 2917410, 1959; *Chem. Abstr.*, **54**, 7173d (1960).

21) T. Kitao, Y. Kimura, N. Ohtani, Y. Matsuzaki, and K. Yabuuchi, Jpn. Kokai Tokyo Koho JP 211504 (1986).

22) C. W. Lee and Y. Kimura, *Kobunshi Ronbun Shu*, **52**, 692 (1995).