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Synthesis and Properties of Multiblock Copolymers Consisting of Oligo(L-lactic acid) and Poly(oxyethylene-*co*-oxypropylene) with Different Composition

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Abstract : Multiblock copolymer was synthesized by the copolycondensation of oligo(L-lactic acid) prepared by thermal dehydration of L-lactic acid, Pluronic^{TM}(PN) and dodecanedioic acid as carboxyl/hydroxyl adjusting agent. This polycondensation proceeded by catalysis of stannous oxide to give the multiblock copolymers with high molecular weight and wide range of compositions. Polymer film was prepared by casting the chloroform solution of the multiblock copolymers having different composition. The multiblock copolymers having relatively high contents of poly(L-lactide) were melt spun into filaments which were subsequently drawn at 60 °C. The copolymer films and the filaments showed an improved flexibility due to the incorporation of the soft segments.

Introduction

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, -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[2,12,13] and low hydrophilicity[14,15] 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 triblock and multiblock copolymerization.[16,17] Recent publications[18-20] demonstrated some syntheses of block copolymers from a poly(α-hydroxy acid) with polyethers such 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,[21] we have reported a new triblock and multiblock copolymerization of poly(L-lactide) with another telechelic polyether, poly(oxypropylene-*co*-oxyethylene)(PN; the common trade name: Pluronic^{TM}) which has primary hydroxyl groups on both terminals. PN having number-average molecular weight($\overline{M}_n$) of 8,400 has been approved by FDA[22] as a safe pharmaceutical surfactant and injective polymer,[23] and can be used as a safe component of biomedical material. The ring-opening polymerization of L-lactide initiated from the hydroxyl groups on both terminals of PN gives an A-B-A triblock type copoly(ester-ether)[24] which is also thought to be a safe biomaterial with improved flexibility and lower crystallinity compared with PLLA homopolymer. However, in this strategy using PN with $\overline{M}_n$=8,400, it is impossible to prepare high molecular weight copolymers incorporating PN in large amount because the molecular weight of the resulting copolymers is limited by PN/L-lactide composition. Consequently, it has been desired to increase molecular weight of the copolymers with large PN content.

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In the present study, polycondensation method was introduced to synthesize the same block copolymers. In this method oligo(L-lactide) prepared by thermal dehydration of L-lactic acid and PN were subjected to copolymerization in the presence of a dicarboxylic acid to obtain multiblock copolymers of PLLA and PN. The dicarboxylic acid was added to the system in order to adjust the concentrations relative of hydroxyl and carboxyl groups added in the system. By this direct polycondensation method, block copolymers with high molecular weight and wide range of compositions could be prepared. The resultant copolymers with various compositions were then characterized, and polymer films were also processed for evaluation of their mechanical properties.

Experimental

Materials. L-lactide was supplied from Purac Biochem(Netherland) and purified by recrystallization from ethyl acetate. Toluene was distilled under a nitrogen atmosphere. 4-Ethyl hexanoate, tin sulfate, L-lactic acid, diphenyl ether, and dodecanedioic acid(DDA) were purchased from Nacalai Tesque(Kyoto, Japan) and used as received. The PN comprising oxyethylene(EO) and oxypropylene(PO) blocks at a unit ratio of 2 : 8 (composition: wt%) was commercially available Pluronic^{TM} (F-68), which was supplied from Asahi Denka Co., LTD., Japan. PN was thoroughly dried at reduced pressure below 10^{-3} mmHg before use. Other reagents and solvents were used without further purification.

Measurements. ^{1}H-NMR spectra were measured on a Varian Gemini-200(at 200 MHz) spectrometer and a Brucker ARX 500 spectrometer(at 500 MHz) in $CDCl_3$ containing 1 vol% tetramethylsilane (TMS) as an internal reference. ^{13}C-NMR spectra were measured on a Brucker ARX 500 spectrometer(at 125 MHz) in $CDCl_3$. Number-average molecular weight($\overline{M}_n$) and molecular weight distribution($\overline{M}_w/\overline{M}_n$) were determined by gel permeation chromatography(GPC). GPC 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 mm i.d. × 300 mm, each) was used with tetrahydrofuran (THF) as an eluent at 35 °C. Molecular weight was calibrated according to polystyrene standards. Melting point(T_m) and glass transition point(T_g) of the polymeric products were determined by differential scanning calorimetry(DSC) on a Mac Science DSC-3100 thermal analyzer at a heating rate of 10 °C min^{-1}. α-Alumina was used as a reference sample. In the first scan, the analysis was made from room temperature to 200 °C, and the sample was quenched in a liquid nitrogen bath for 30 min. In the second scan, the sample was heated up from -30 to 200 °C.

Preparation of Polymerization Catalysts.

Stannous 4-ethylhexanoate: Stannous 4-ethylhexanoate was purified by distillation under high vacuum. Then, it was dissolved in a distilled toluene at a concentration of 0.1 g/mL.

Stannous oxide and Stannous lactate: In an appropriate flask 10 g of stannous sulfate was dissolved in 50 mL of distilled water, and the solution was adjusted to weak alkalinity by adding an aqueous sodium hydroxide(10 mol dm^{-3}) under nitrogen atmosphere. The solution was refluxed with stirring on a magnetic stirrer at 120 °C for 8 h. The resultant black precipitate, which was stannous oxide, was washed with distilled water, filtered, and washed with acetone.

A mixture of 6 g of stannous oxide, 30 mL of 90% aqueous L-lactic acid, and 30 mL of a distilled water was made and filtered. The filtrate was then evaporated to remove water and L-lactic acid at 120 °C under a reduced pressure of 10 mmHg. A white residue obtained was washed with water and dried *in vacuo*.

Copolymerization of Oligo(L-lactic acid) and PN. Prescribed amounts of oligo(L-lactic acid), and PN were charged into a flask equipped with a reflux condenser and an equimolar amount of DDA relative to the PN quantity, DDA that is equivalent to the molar quantity of PN, diphenyl ether as solvent, and a given amount of catalyst were added to it. The resulting mixture was refluxed with stirring on a magnetic stirrer at 180 °C under reduced pressure for a prescribed time. The coolant water passing the reflux condenser was adjusted at 60 °C to allow removal of water out of the reaction system and to feedback the distilled diphenyl ether into the reaction system. After 15 h, a brown precipitate deposited out. It was dissolved in 20 mL of chloroform and the solution was poured into an excess amount of methanol to isolate the polymeric product. The precipitated product was filtered and dried in *vacuo* to obtain white fibrous powders.

^{1}H-NMR ($CDCl_3$/TMS) ppm = 1.17(CH_3 for PO), 1.3(CH_2 for DDA), 1.57(CH_3 for LA), 2.4(CH_2CO for DDA), 3.3~3.5(CH_2CH for PO), 3.5~3.6 (CH_2CH for PO), 3.6~3.7(CH_2CH_2 for EO), 4.3 (CH_2CH_2 for EO bonded with LA), and 4.9~5.1 (CH for LA). ^{13}C-NMR($CDCl_3$/TMS) δ = 16.7(CH_3 for LA), 17.4(CH_3 for PO), 24.8[$CH_2(CH_2)_3CO$ for DDA], 29.3[$CH_2(CH_2)_3CO$ for DDA], 33.9 [$CH_2(CH_2)_3CO$ for DDA], 69.1(CH for LA), 70.6 (CH_2CH_2 for EO), 73.4(CH_2CH for PO), 75.5 (CH_2CH for PO), and 169.6 [$CHC(O)$ for LA].

By a similar method, a series of copolymers with different composition were prepared by changing the ratio of PN to oligo(L-lactic acid) in feed. The name of the products is abbreviated as "LN(m)-a", where L, N, (m), and a denote PLLA, PN(the constituent segments), multiblock type (copolymer type), and PN content, respectively.

Film Preparation. A concentrated solution (ca. 10 wt%) of multiblock PLLA/PN copolymers in chloroform was prepared. This solution was poured into a glass petri dish, solidified in air at 4 °C, and dried *in vacuo*. The resulting film was transparent and ca. 80 μm thick.

Melt-spinning and Drawing of Copolymer. Melt-spinning was carried out by using a laboratory-size screw extruder with a screw of 15 mmΦ in diameter and a mono hole nozzle of 1.0 mmΦ in diameter. Temperatures of the feeding, meltering, 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, and the extrudate was drawn and wound on a winder to give a filament of 100~300 μm in diameter. The filament was then drawn to various draw ratio at 60 °C by using a handy drawing apparatus (Koa Shokai, Kyoto).

Results and Discussion

Preparation of Multiblock Copolymers with Different Composition. PLLA/PN multiblock copolymers with different compositions were prepared by changing the feed ratio of PN relative to oligo(L-lactic acid) under the polycondensation conditions optimized above (temperature, 180 °C; time, 20 h; catalyst, stannous oxide; and solvent ratio, 50%). When the feed ratio of PN was higher than 30 wt%, the GPC curve of the polycondensate obtained after 20 h showed a bi-modal pattern as shown in Figure 1(b), which suggests that only a part of PN had been incorporated into the copolymer. An uni-modal peak was shown when the reaction continued for 30 h. Therefore, the reaction time was set at 30 h in these cases.

Table I summarizes the results of the copolycondensation at different feed ratios. Yield of the copolymer was in the range of 70~80% in every case. Lower yield was attributed to both the sublimation of lactide and the operational loss at the reprecipitation. The $\overline{M}_n$ value exceeded 50,000 in the most cases. Since the almost $\overline{M}_w/\overline{M}_n$ was almost 2, the $\overline{M}_w$ value reached 100,000 dalton, which is a threshold for establishing excellent mechanical properties for the PLLA derivatives.

Figure 2 shows typical GPC curves of these copolymer obtained after 30 h. Each shows unimodal peak. Being different from the triblock type copolymers obtained by the copolymerization of L-lactide and PN, the molecular weight was similar regardless with composition.

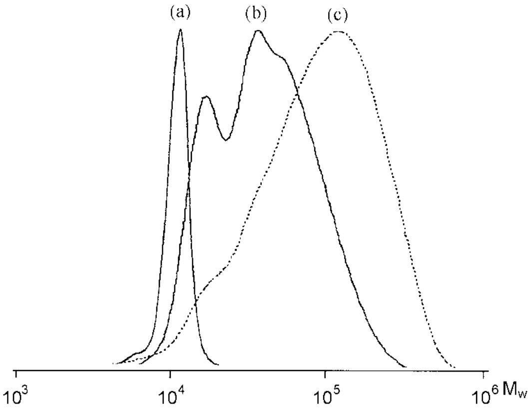

Figure 1. Typical GPC chromatograms of the copolymers obtained (a) 0, (b) 20, and (c) 30 h at a feed ratio of oligo(L-lactic acid) to PN of 30 : 70.

Table I. Typical Results of the Multiblock Copolymerization[a] of Oligo(L-lactic acid) and PN and DDA at the Optimum Conditions

Polymer	Feed Ratio		Polymeric Product						
	LA/PN (wt/wt)	LA/EO/PO (Composition)	Yield (%)	LA/PN (wt/wt)	LA/EO/PO[b] (Composition)	M_n[c]	M_w/M_n	T_m(°C)	T_g(°C)
LN(m)-11	90/10	85/12.0/3.0	78.7	89/11	84/12.8/3.2	47,400	1.79	156	25
LN(m)-23	80/20	72/22.4/5.6	68.1	77/23	69/24.8/6.2	69,200	1.93	132	3
LN(m)-36	70/30	54/36.8/9.2	79.5	64/36	54/36.8/9.2	53,400	2.17	N.D[d]	N.D
LN(m)-48	60/40	43/45.6/11.4	79.8	52/48	41/47.2/11.8	58,000	2.28	N.D	N.D
LN(m)-58	50/50	34/52.8/13.2	79.4	42/58	32/54.4/13.6	62,700	2.05	N.D	N.D
LN(m)-87	30/70	18/65.6/16.4	70.9	13/87	9/72.8/18.2	68,100	2.14	N.D	N.D

[a] At 180 °C for 30 h with 0.1 wt% of stannous oxide relative to all amount.

[b] Determined by ^{1}H-NMR spectra.

[c] Determined by GPC with tetrahydrofuran as the eluent.

[d] N.D : not detected.

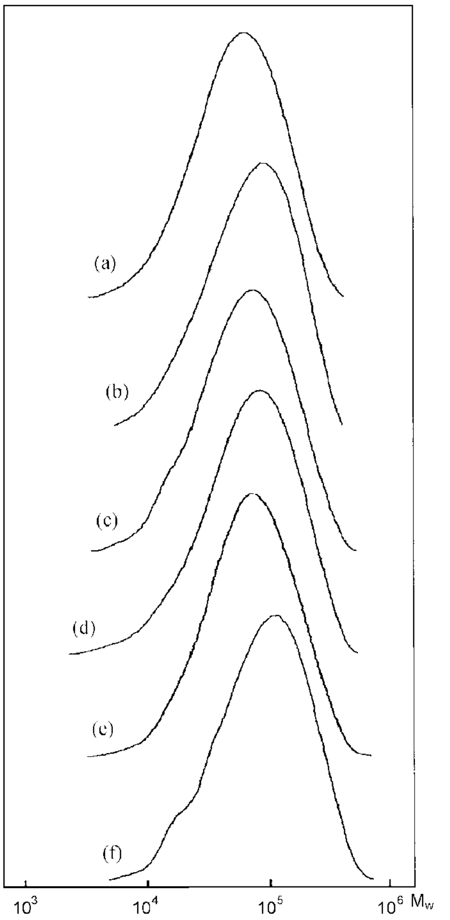

Figure 2. Typical GPC curves of (a) LN(m)-11, (b) LN(m)-23, (c) LN(m)-36, (d) LN(m)-48, (e) LN(m)-58, and (f) LN(m)-87 copolymers.

Figure 3 and 4 show typical ^{1}H-NMR spectra of the copolymers with different compositions. The signal assignment is involved in Figure 3 and 4. Figure 5 shows a typical 500MHz ^{1}H-NMR spectrum of the copolymer [LN(m)-23] obtained by oligo(L-lactic acid)/PN = 80/20. The signal assignment is also involved. The methyl and methyne signals of PLLA units can be clearly detected at 1.57 and 5.18 ppm, respectively. The methyl, methyne, and methylene signals of PO units are detected around 1.17, 3.4, and 3.5~3.6 ppm, respectively, while methylene signal of EO units also appears at 3.6~3.7 ppm. The unit composition of the copolymer determined by the integral ratio of these signals. Small signals b, d, and h were detected at 1.3, 2.4, and 4.3 ppm in the expanded spectra. These signals are assigned to the methylene groups at β-δ positions of DDA, the methylene groups at α positions of DDA, and the oxymethylene groups in the terminals of PN, respectively. Their integral indicates that molar content of DDA introduced to the copolymer was equivalent to the PN ratio. These results indicates that the multiblock copolymer was formed as we expected.

Figure 6 shows typical DSC curves of the copolymers with different compositions as compared with that of PN. For the copolymers having a relatively higher PN content, the endothermic peak due to the crystal fusion of PN segment appeared. This peak became smaller with decreasing PN composition and disappeared in the copolymer

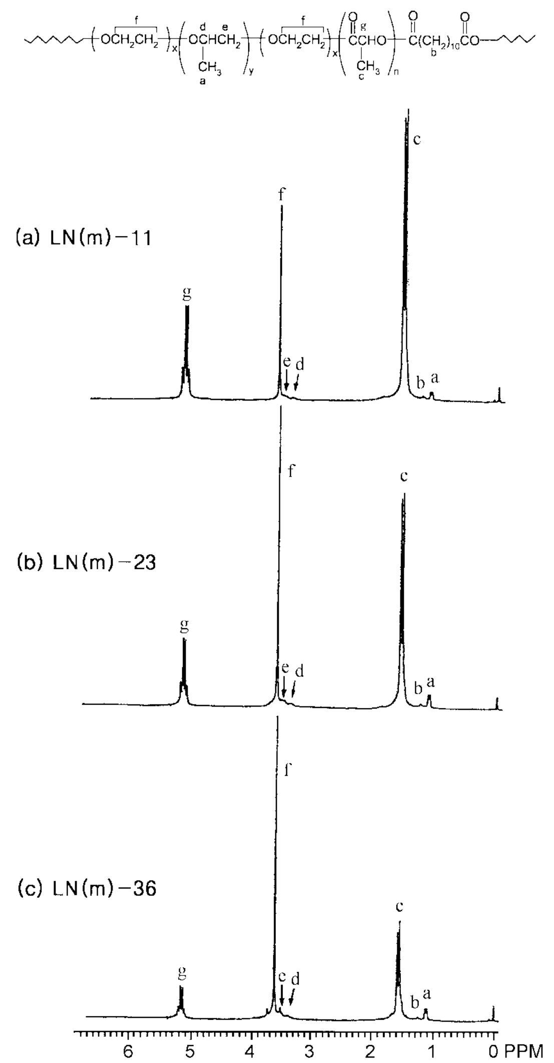

Figure 3. Typical ^{1}H-NMR spectra of (a) LN(m)-11, (b) LN(m)-23, and (c) LN(m)-36.

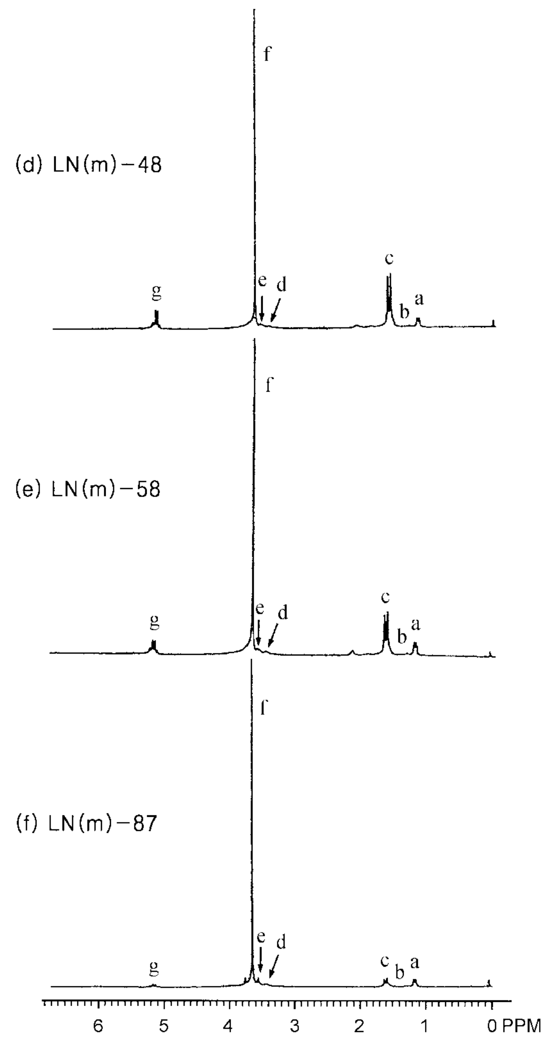

Figure 4. Typical ^{1}H-NMR spectra of (d) LN(m)-48, (e) LN(m)-58, and (f) LN(m)-87.

LN(m)-23. The copolymers having a high PLLA content [LN(m)-11] showed a single endothermic peak at 160 °C due to the crystal fusion of PLLA segment. The other copolymers having lower PLLA contents showed two endotherms at 120~140 °C and 80~100 °C, which may be also attributed to the crystal fusions of the PLLA segments with different segment ordering in the crystals. Chen *et al.* reported a multiblock copolymer of L-lactide and ethylene oxide prepared by using various metallic catalysts.[25] This copolymer also exhibited two melting endotherms, which were attributed to the difference in block length of the PLLA and poly(oxyethylene) segments. In this study the block lengths of PLLA and PN were not determined, but the observation of the two endotherms for crystal fusion of PLLA may depend on the distribution of the segment length of PLLA.

Properties of Multiblock Type Copolymer Films. Polymer film 80 μm thick was prepared by casting a chloroform solution of the multiblock copolymers having different composition. Most of the films obtained were transparent, except for the film of LN(m)-87 which had turned opaque by

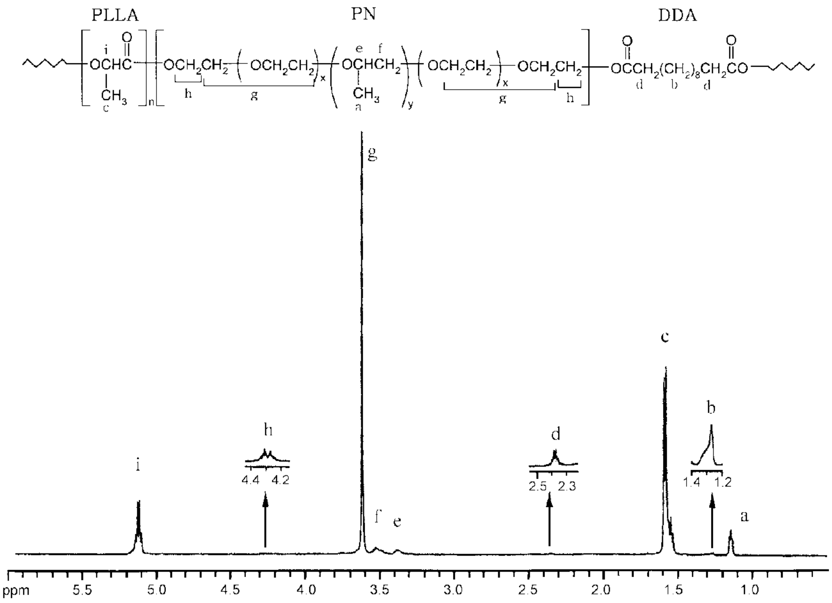

Figure 5. 500MHz ^{1}H-NMR spectrum of LN(m)-23.

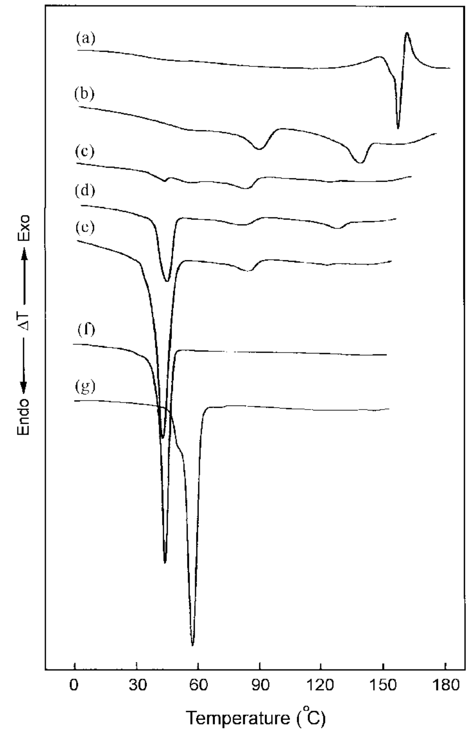

Figure 6. Typical DSC curves (a) LN(m)-11, (b) LN(m)-23, (c) LN(m)- 36, (d) LN(m)-48, (e) LN(m)-58, (f) LN(m) -87, and (g) PN.

crystallization of the PN segments. Table II summarizes the tensile properties of the films. It is known that their tensile strength and modulus decreased with increasing PN composition. There was a great difference in the mechanical properties between the film of LN(m)-11 and LN(m)-23, which may be because of the difference in crystallinity of the PLLA segments detected by DSC. These results indicate that the introduction of the PN segment in the multiblock sequence is more effective for improving the flexibility into the PLLA as compared with its introduction in triblock sequence.

Properties of Melt-spun Filament. The multiblock copolymers, LN(m)-11 and LN(m)-23, were melt-spun into a mono-filament with the diameter of 200~260 μm by the conventional melt-spinning method. The as-spun fibers obtained were then drawn 5~15 times in length at 60°C. The diameter of the drawn filament became about 50~130 μm depending on the draw ratio as shown in Table III. Both the spinnability and drawability were excellent. The tensile strength and modulus of the fibers were found to be proportional to the draw ratio. The tensile strength and modulus were lower in the fiber having

Table II. Tensile Properties of the Films of the PLLA/PN Multiblock Copolymers

Polymer	Feed Ratio		Tensile Strength (MPa)	Tensile Modulus (MPa)	Tensile Elongation (%)
	LA/PN (wt/wt)	LA/EO/PO[a] (Composition)			
LN(m)-11	89/11	84/12.8/3.2	40	906	240
LN(m)-23	77/23	69/24.8/6.2	35	388	390
LN(m)-36	64/36	54/36.8/9.2	24	33	1050
LN(m)-48	52/48	41/47.2/11.8	21	31	1160
LN(m)-58	42/58	32/54.4/13.6	16	26	1460
LN(m)-87	13/87	9/72.8/18.2	8	60	800

[a] Determined by ^{1}H-NMR spectra.

Table III. Tensile[a] Properties of the Mono-filament Fibers Comprising of PLLA/PN Multiblock Copolymers

Polymer	Polymer Composition		Melt Draw Ratio (times)	Draw Ratio (times)	Tensile Strength (MPa)	Tensile Modulus (GPa)	Tensile Elongation (%)	Diameter (μm)
	LA/PN (wt/wt)	LA/EO/PO[b] (Composition)						
LN(m)-11	89/11	8/12.8/3.2	3	5	330	1.5	120	123
			3	10	430	2.0	60	78
			3	15	480	2.2	60	77
LN(m)-23	77/23	69/24.8/6.2	28	5	160	0.7	300	95
			28	9	300	1.6	150	56

[a] Spinning condition : temparature, 160 °C.

[b] By ^{1}H-NMR spectra.

higher PN content. This tendency was identical with that shown for the films. The tensile strength of the fiber of LN(m)-11 was slightly lower than that of commercially available sutures, reaching the minimum strength required for suture material.

Conclusions

The molecular weight of the copolymers reached 50,000~60,000 at any feed ratio in spite of rather low yield of 70~80%. Polymer films of the multiblock type copolymers were prepared by a solution casting method, and fibers were melt-spun with the LN(m)- 11 and the LN(m)-23 and drawn at 60 °C. The copolymer films and fibers showed their improved flexibility due to the incorporation of the soft PN segments, and their potential as biomaterials were convinced to be high.

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