Preparation of block copoly(ester–ether) comprising poly(L-lactide) and poly(oxypropylene) and degradation of its fibre *in vitro* and *in vivo*

Yoshiharu Kimura, Yuji Matsuzaki, Hideki Yamane and Toshio Kitao
Department of Polymer Science and Engineering, Kyoto Institute of Technology, Matsugasaki, Kyoto 606, Japan
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The **A–B–A** triblock copoly(ester–ether)s comprising poly(L-lactide) (**A**) and poly(oxypropylene) (**B**) were prepared by the copolymerization of L-lactide and polypropylene glycols (PPG) with mono-dispersed molecular weights of 2000 and 4000. A Me_3Al–H_2O catalyst system was utilized as the initiator. When the feed ratios of PPG 2000 and 4000 were over 5 and 10 wt% relative to L-lactide, respectively, the polymerization of L-lactide took place from the PPG hydroxy terminals to give the desired **A–B–A** block copolymers in high yields. Their molecular weights were found to be coincident with the values estimated from the monomer conversions and the feed ratios of PPG. At the lower feed ratios of PPG, the poly(L-lactic acid) (PLLA) homopolymer was formed together with the block copolymers. The copolymers were melt-spun by the conventional method and the fibres obtained were extended by drawing at 80–90°C. At the same draw ratio the modulus of the fibres was decreased with increasing PPG content in the copolymers. The fibres of the PLLA–PPG 4000 copolymers with different content of PPG were subjected to degradation both *in vitro* and *in vivo*. Upon immersion in a phosphate buffer (pH = 7.2) the fibres showed a time-dependent decrease in tensile strength with accompanying surface erosion. The rate of this degradation was much higher than that of the fibre of PLLA ($\bar{M}_n = 62\,000$). The same fibres, implanted under the dorsal skin of rats, caused a degradation similar to that observed *in vitro* without eliciting a significant rejection and inflammation. The block copolymers comprising PLLA and PPG, therefore, were shown to have high potentiality as the biodegradable polymers with improved flexibility and biodegradability.

(Keywords: block copolymerization; poly(L-lactide); polypropylene glycol; block copoly(ester–ether); bioabsorbable polymer)

INTRODUCTION

In the past decade there have been growing interests in bioresorbable polymers[1–3], because of their wide varieties of biomedical and pharmaceutical applications. Especially, poly(α-hydroxy acid)s such as poly(glycolic acid) (PGA) and poly(L-lactic acid) (PLLA) have been attracting the greatest attention[4–7] as they are hydrolysed in living tissues to their constituents, α-hydroxy acids, and excreted by the human metabolic cycles[8,9]. Their application, therefore, has been directed to various temporary bio-materials including drug carriers[10–12] and absorbable surgical sutures[4,7,13,14]. However, the high crystallinity[5,15–17] and low hydrophilicity[18,19] of these polymers interfere with the controlled degradation and cause the decrease in compatibility with soft tissues. One solution to these material problems is to introduce soft segments to the base polymers by block copolymerization[20,21]. Recent patent literatures[22–24] claimed the synthesis of block-copolymers of poly(α-hydroxy acid)s with such soft hydrophilic polyethers as polyethylene glycol (PEG) and polypropylene glycol (PPG). Cohn *et al.* have also reported the synthesis and properties of several derivatives of the similar poly(ester–ether)s[25]. These copolymers reported thus far, however, were of low molecular weight owing to the insufficient control of polymerization, and had limited use except for an absorbable coating material. Here, we report the block copolymerization of PPG and L-lactide to give the **A–B–A** block copoly(ester–ether)s comprising PLLA (**A**) and poly(oxypropylene) (**B**) segments and having high molecular weight and melt-spinnability. Since PPG is a telechelic polyether having secondary hydroxy groups on both terminals[26], it was thought to be copolymerized with lactones quite easily by ester interchange reaction[21] even in the absence of catalyst[25]. In the present copolymerizations the trimethylaluminium–water catalyst system was utilized as the initiator, and the block length and molecular weight of the copolymers could be successfully controlled. The copolymers obtained were then subjected to melt-spinning and drawing by the conventional methods, and the properties of the fibres were studied, including their degradabilities *in vitro* and *in vivo*.

EXPERIMENTAL

Materials

L-Lactide **1** (see *Scheme 1*) was prepared by the method reported previously[27] and purified by repeated recrystallization from ethyl acetate. Mono-dispersed PPGs ($\bar{M}_w/\bar{M}_n = 1.1$) of number average molecular weight $\bar{M}_n = 2000$ (**2a**) and 4000 (**2b**) were supplied by

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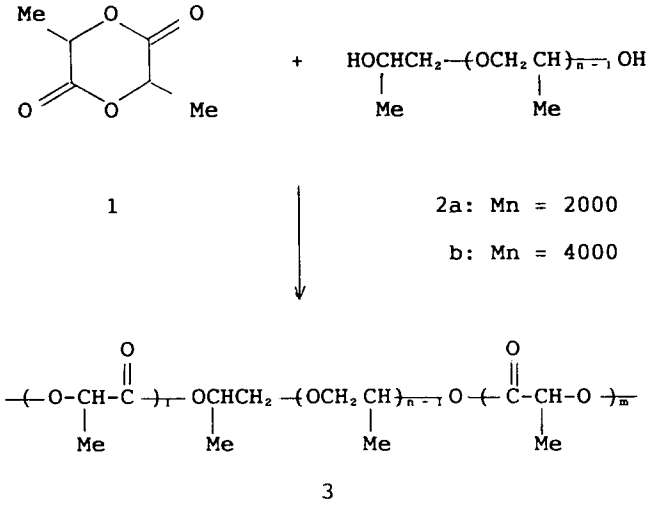


Scheme 1

Nacalai Tesque Ltd, Japan. Their average degrees of polymerization n were calculated to be 33 and 67, respectively. The samples were thoroughly dried under vacuum below 10^{-3} mmHg and used without further purification. Trimethylaluminium (TMA) was provided by Toyo-Stauffer Chemical Corp., Japan. Acetic anhydride, toluene (TOL), and 1,4-dioxane (DOX) were commercially available and purified by distillation before use.

The polymerization catalyst TMA–H_2O was prepared[28] as follows. Into a stirred solution of 20 mmol of TMA in 5.79 ml of TOL was slowly added 10 mmol of water (0.5 equivalent relative to TMA) dissolved in 3.42 ml of DOX at −30°C. After the addition was over, the solution was kept stirred at room temperature for 10 h. This solution was found to contain poly(methylaloxane) in *circa* 2.2 M concentration relative to aluminium atom, and was directly used for the polymerization. This catalyst solution could be kept in a refrigerator for a month without loss of catalyst activity.

Measurements

^{1}H n.m.r. spectrum was measured at 200 MHz on a Varian XL-200 spectrometer with tetramethylsilane (TMS) as the internal standard. I.r. spectrum was measured by JASCO IRA-1 spectrometer. D.t.a. was recorded under a nitrogen atmosphere on a Shimazu DT-30 thermal analyser. The rate of heating was set at 10°C min^{-1} for a 5.0 mg sample. G.p.c. was measured on a Toyo Soda HLC-802A analyser fitted with an r.i. detector and a TSK-CP8000 data processor. The column was a polystyrene gel column (7.5 mm i.d. × 60 cm) of TSK Gel G4000 H8 which was of 16 000 TP with limited exclusion molecular weight of 4×10^5. The sample was injected at 38°C with tetrahydrofuran (THF) as the eluent. The molecular weight was calibrated relative to mono-dispersed PPG standard. Scanning electron micrographs (SEM) were taken on a JASCO TSM-25S II microscope. Tensile measurement of fibre was carried out on a tensile tester (the type TOM 200D, Shinko Tsushin (Tokyo, Japan)) at a cross-head speed of 5 mm min^{-1} for the sample of 10 mm in length.

Copolymerization of L*-lactide and PPG*

Two grams (13.9 mmol) of L-lactide and a prescribed amount of PPG were placed in a 20 ml round-bottomed 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 was filled with nitrogen gas. The mixture was then heated up to 150°C with stirring under a nitrogen atmosphere, and 0.1 ml of the above catalyst solution was added. After the system was maintained under these conditions for a period of 5 min, the pressure of the system was gradually reduced to 100 mmHg by a vacuum pump. With this pressure maintained, the mixture was stirred for 6 h at 150°C. At the end of the reaction a few drops of acetic anhydride were added and reacted with the product for 3 h for deactivation of the propagating species. The product finally obtained was cooled and dissolved in 10 ml chloroform, which was poured into an excess amount of methanol. The product precipitated was filtered, washed with a diethyl ether, and dried *in vacuo*, to give white fibrous materials in high yield. The precipitant combined with the diethyl ether was evaporated to dryness, and the residue was subjected to the g.p.c. analysis. By the similar method a series of copolymers with different compositions were prepared by changing the feed ratio of PPG relative to L-lactide from 3 to 15 wt%. The homopolymerization of PLLA was also carried out in a similar manner for comparison.

Melt-spinning and drawing

Melt-spinning was carried out by a ram extruder having an orifice of 0.5 mm in diameter. The pulverized sample was packed in the cylinder and heated to 150°C. Once the polymer melted, the piston was pressed shortly for degassing from the melt. The extruder was fitted with a micropressing machine (Furue Science J-2209) and the piston was pressed at a constant speed (6.9 mm min^{-1}). The polymer melt extruded was drawn and wound on a winder to give a filament of *circa* 50–80 μm in diameter. The filament was then extended to various draw ratios at 80–90°C, and was heat-treated at the same temperature for 10 min.

Hydrolysis of fibre in vitro

In each of ten glass ampules, several pieces of the drawn fibre (*ca.* 10 mg) were immersed in 10 ml of a thermally sterilized phosphate buffer solution (pH = 7.2). Each ampule was sealed and then held in a thermostatted water bath at 37°C. After a prescribed time passing, one of the ampules was opened and the fibre was taken out and dried. It was then subjected to both the tensile test and the g.p.c. analysis.

Testing of fibre degradation in vivo

The drawn fibre (*circa* 15 cm in length) was coiled to a small loop and fixed with an unabsorbable suture of silk. It was then sterilized with ethylene oxide gas and implanted under the dorsal skin of male wister rats (260–278 g in weight). For one test three rats were used and three kinds of fibres were put into the three dorsal sites of a rat. After a prescribed time, the three rats were dissected to take out the fibres from the tissues, which were subjected to the tensile test and to the SEM observation. The three data for the respective fibre were averaged and plotted as a function of implantation time.

RESULTS AND DISCUSSION

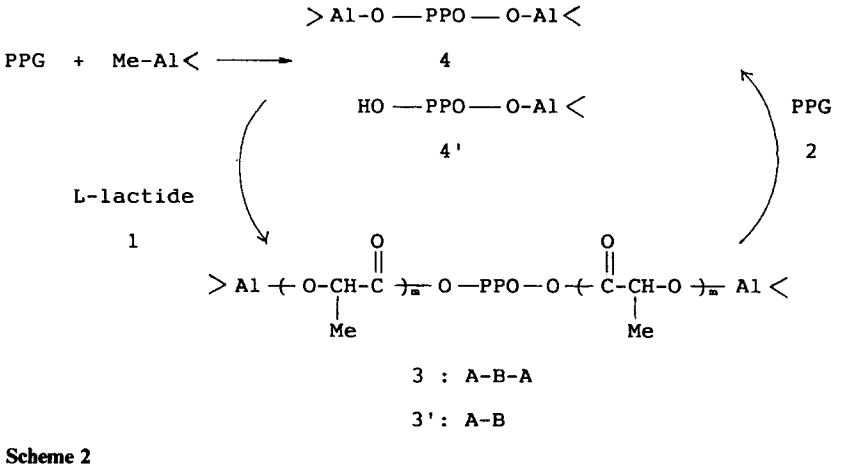
Block copolymerization of L-*lactide with PPG*

In the present study PPG was selected as the soft block component for the following reasons. First, PPG is biocompatible and less toxic in tissues although it is still unknown whether it would be biodegradable and absorbable or not[29,30]. At present, PPG is utilized as surface-lubricant of various absorbable braided surgical sutures and implanted in tissues[25]. This fact may be an empirical proof that the existence of a small amount of PPG produces no hazardous effect *in vivo*. Second, PPG has been utilized as the soft segment of various block copolymers because of its high elastomeric properties[30]. In addition, it has a considerable affinity to water so that its copolymer might have an increased hydrophilicity[30,31]. At least, its introduction would not make the copolymer hydrophobic. Third, the secondary hydroxy groups on the PPG terminals are considered to have a reactivity similar to that of the hydroxy end of PLLA, and they are able to react with L-lactide by scrambling reaction to allow the intended block copolymerization.

Thus, the copolymerization was carried out by adding PPG to the bulk polymerization system of L-lactide with the TMA–H_2O catalyst. The mixture kept homogeneous state throughout the polymerizaton. A conceivable reaction mechanism for the block copolymerization is accomplished as shown in *Scheme 2*. In the initiation, the catalyst reacts with PPG to form **4** and/or **4'** which are responsible for the polymerization of L-lactide. The metal alkoxides of these types have been known as the effective catalysts for the polymerization of L-lactide[32,33]. In the propagation **4** and **4'** react with L-lactides successively and **A–B–A 3** and **A–B** type copolymers **3'** are produced. The propagation is interrupted by the chain-transfer reaction of **3** and **3'** with PPG to regenerate **4** and **4'**, and the above polymerization steps are recycled.

We first optimized the polymerization conditions with regard to the polymerization temperature, time and pressure by using a L-lactide/**2b** system with the feed ratio of **2b** set at 10 wt% relative to L-lactide. At first, the optimum polymerization temperature was sought. The molecular weight and the yield of the product were found to increase with the rise of the reaction temperature from 100°C. They both, however, reached a limit above 150°C and the colour change in the product was noted above 160°C, which was ascribed to the initiation of decomposition. Hence, it was decided that the polymerization temperature should be 150°C. The molecular weight of the product was found to depend on the inner pressure of the polymerization system. It increased by reducing the pressure from atmospheric to 100 mmHg, while it sharply declined below 100 mmHg where the sublimation of L-lactide became too rapid. So, it was decided to set the pressure at 100 mmHg. The molecular weight and the yield were also affected by both the catalyst quantity and the reaction time. When the amount of the catalyst was below 0.1 ml in volume (1.6 mol% relative to L-lactide) the polymerization did not occur. At the higher amount than 0.5 ml, on the other hand, the molecular weight distribution became broader with a slight decrease in average molecular weight. The copolymer yield increased with increasing reaction time at the constant temperature of 150°C, and it reached the highest at 4–6 h passing, when the amount of the catalyst was within the range of 0.1–0.5 ml. A longer reaction time than 6 h brought a slight decrease in the copolymer yield and molecular weight. This phenomenon was ascribed to the depolymerization of PLLA chain by the back-biting of the active species[34] and the following sublimation of the L-lactide recurred. From these studies the optimum conditions for the copolymerization were determined as follows: polymerization temperature = 150°C, pressure = 100 mmHg, time = 6 h and catalyst amount = 0.1 ml. After the polymerization, acetic anhydride was reacted with the product in order to deactivate the catalyst[35].

Table 1 shows some results of the copolymerizations which were carried out at the above conditions with various feed ratios of **2a** and **2b** relative to L-lactide. The soluble part recovered from the precipitant (methanol) and the washing solvent (diethyl ether) comprised mainly L-lactide, but contained no PPG, as analysed by g.p.c. Since free PPG is soluble in both solvents, this indicated that all the fed PPG was incorporated in the polymeric product precipitated. The total recovery of both the precipitated and soluble parts exceeded 85% in every case. The loss was ascribed not only to the monomer sublimation during the polymerization, but also to the operational loss at the reprecipitation. The incorporation of the PLLA and PPG blocks in the copolymer was supported by the following spectroscopic data: ^{1}H n.m.r. ($CDCl_3$) δ 1.17 (*d*, Me for PPG), 1.57 (*d*, Me for PLLA), 3.3–3.7 (*m*, CH_2CH for PPG), 4.9–5.1 (*q*, CH for PLLA); i.r. (KBr) 1750 ($\nu_{C=O}$), 1100 cm^{-1} (ν_{C-O}), etc. The segment



Scheme 2

Table 1 Block copolymerizations of L-lactide with PPG[a]

Run no.	PPG in feed			Recovered from precipitant (%)	Polymeric product			Estimated values[f]		
	$\bar{M}_n$	Parts[b]	LA/OP[c]		Yield (%)	LA/OP[c,d]	$\bar{M}_n \times 10^{-4}$ [e]	Conv.[g] (%)	LA/OP[c]	$\bar{M}_n \times 10^{-4}$
1	–	0			90	100/0	6.2			
2	2000	3	97/3	9	83	97/3	4.8	82	96/4	5.7
3		5	94/6	6	87	92/8	3.5	86	93/7	3.6
4		10	89/11	5	89	88/12	1.7	88	88/12	1.9
5	4000	3	97/3	8	90	96/4	5.0	89	96/4	12.5
6		5	94/6	13	73	90/10	4.6	72	92/8	6.1
7		10	89/11	10	80	86/14	3.4	78	86/14	3.5
8		15	84/16	8	80	79/21	2.2	77	80/20	2.4

[a] L-lactide: 2 g, catalyst: TMA–H_2O (0.1 ml), conditions: 150°C, 100 mmHg, 6 h
[b] Relative to L-lactide
[c] The monomeric unit ratio of oxyethylidenecarbonyl (LA) to oxypropylene (OP)
[d] By ^1H n.m.r. spectrum
[e] Molecular weight by g.p.c. relative to PPG standard
[f] From the yield and the feed ratio on the assumption that all PPG was incorporated in the polymeric product
[g] Conversion of L-lactide

composition was determined by the integral ratio of both methyl signals. The results are included in *Table 1*. Because the conversion of L-lactide was not quantitative, as mentioned earlier, the PPG content in the copolymers became higher than the feed ratio (see below).

Figure 1 shows the typical g.p.c. curves of the copolymers of the L-lactide/**2b** system (Runs 5–8 in *Table 1*), which are compared with those of the PLLA homopolymer (Run 1), PPG **2b**, and the copolymer of L-lactide/**2a** with the PPG feed ratio of 10 wt% (Run 3). The peak maximum corresponding to the $\bar{M}_n$ of *Table 1* shifted to the lower molecular weight region as the PPG ratio increased. If it is assumed that all the fed PPG was incorporated in the isolated product and that all PLLA segments linked with the both end-groups of PPG by forming only **A–B–A** type copolymers as postulated in *Scheme 2*, the net conversion of L-lactide, the theoretical $\bar{M}_n$ of the copolymer, and the unit composition can be estimated from the copolymer yield and the feed ratio. The values obtained are given in the last three columns of *Table 1*. It is shown here that the estimated unit ratios of oxyethylidenecarbonyl (LA) to oxypropylene (OP) are coincident within an experimental error with those determined by the ^1H n.m.r. spectra of the products. With regard to the molecular weight, the estimated $\bar{M}_n$ is slightly different from the observed values, as the latter was determined by g.p.c. relative to PPG standard. However, the products of Runs 3, 4, 7 and 8 in which the PPG content was relatively large were found to have almost comparable $\bar{M}_n$ to the estimated one. So, these products are reasonably supposed to consist of **A–B–A** triblocks of PLLA and PPG as the **A** and **B** segments, respectively. In the products having a smaller content of PPG (Runs 2, 5 and 6), on the other hand, the observed $\bar{M}_n$ was much lower than the calculated values, probably due to the presence of homopolymer of PLLA. The above postulate was qualitatively supported by the curvatures of g.p.c. in *Figure 1*. The products of Runs 3, 4, 7 and 8 showed a single-modal curve centred at a higher $\bar{M}_n$ region than that of PPG, while those of Runs 2, 5 and 6 involved bi-modal peaks corresponding to the two species with different molecular weight and molecular weight distribution; the broader one of the higher molecular weight is for the homopolymer and the sharper one for the **A–B–A** block copolymer. The former was possibly

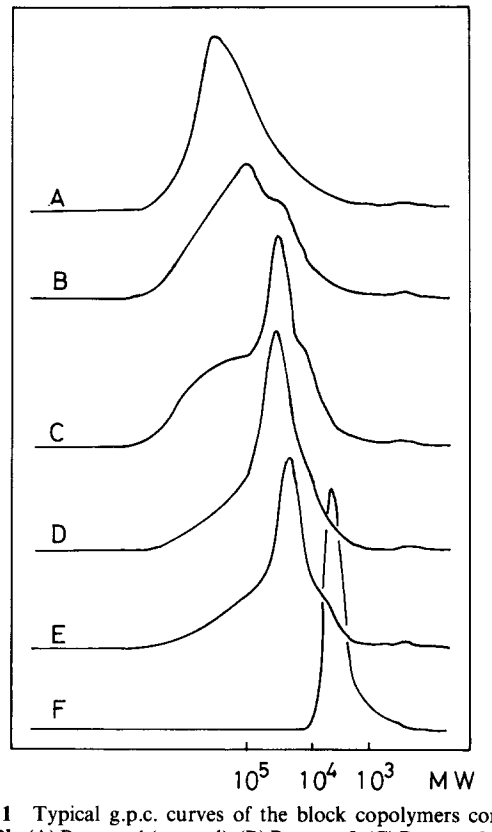


Figure 1 Typical g.p.c. curves of the block copolymers comprising PLLA/**2b**; (A) Run no. 1 (control), (B) Run no. 5, (C) Run no. 6, (D) Run no. 7, (E) Run no. 8, (F) **2b**

generated by the direct initiation of L-lactide by the TMA–H_2O catalyst system which had remained unreacted with PPG terminals because of the smaller PPG content in feed. No data was obtained with regard to the presence of **A–B** di-block copolymer **3'**, but its possibility seems to be very small, judging from the aforementioned relations between yield, molecular weight and copolymer composition. The formation of both the homopolymer and the **A–B–A** copolymer with one short **A** block might possibly be considered if the transesterification might be induced from the active sites to the PLLA chain as in the usual polymerizations of L-lactide[5,34]. In the present polymerization, however, the

presence of such copolymer with one short **A** block should be negligibly small, because the TMA–H_2O catalyst system[32,36] used has been known to induce no such transesterification.

As described above, the $\bar{M}_n$ of the copolymers decreased with decreasing molecular weight of PPG at the same feed ratio in weight. It was natural considering that the molar content of PPG was larger in the case of the lower molecular weight and that the average segment length of PLLA would be lowered. The theoretical $\bar{M}_n$ of the copolymers of the L-lactide/**2a** system ought to be nearly one half of that of the L-lactide/**2b** copolymers. This relation was found between the cases of Runs 4 and 7 in which the **A–B–A** block copolymer was exclusively formed. But in the other cases where the presence of homopolymer was apparent, the molecular weights of the **2a** system were 0.75–0.9 times those of the **2b** system. The preparation of the copolymers of L-lactide and PPG with $\bar{M}_n = 1000$ was also examined, but their molecular weight became considerably lower, as expected theoretically. For example, the product prepared from L-lactide–PPG 1000 with the feed ratio of 100/5 (by weight) was found to have a molecular weight less than 10000.

Figure 2 (B–E) shows the typical d.t.a. curves of the copolymers with different unit content of PPG for the L-lactide/**2b** system as compared with the curve of PLLA (**A**). The copolymers with a relatively higher PPG content exhibited an exothermic peak around 100°C. This peak disappeared if the samples had been molten and cooled slowly prior to the measurement. It was therefore suggested that the exothermic peak is related with the crystallization of the PLLA segments that might have been interfered with by the presence of PPG segments. The endotherm ascribed to the crystal fusion of PLLA segments was observed at temperatures lower than the melting point of PLLA. There was found to be a tendency that the melting range of the copolymer became lower with increasing PPG content. *Figure 2* (F) shows the d.t.a. curve of the block copolymer comprising PLLA/**2a** with a unit content of 88/12. Its melting point was found to be considerably lower than that of the corresponding PLLA/**2b** copolymer, while its crystallization temperature changed little. These results indicated that both the segments of the PLLA/PPG block copolymers take a so-called microphase separation[21] in the solid state.

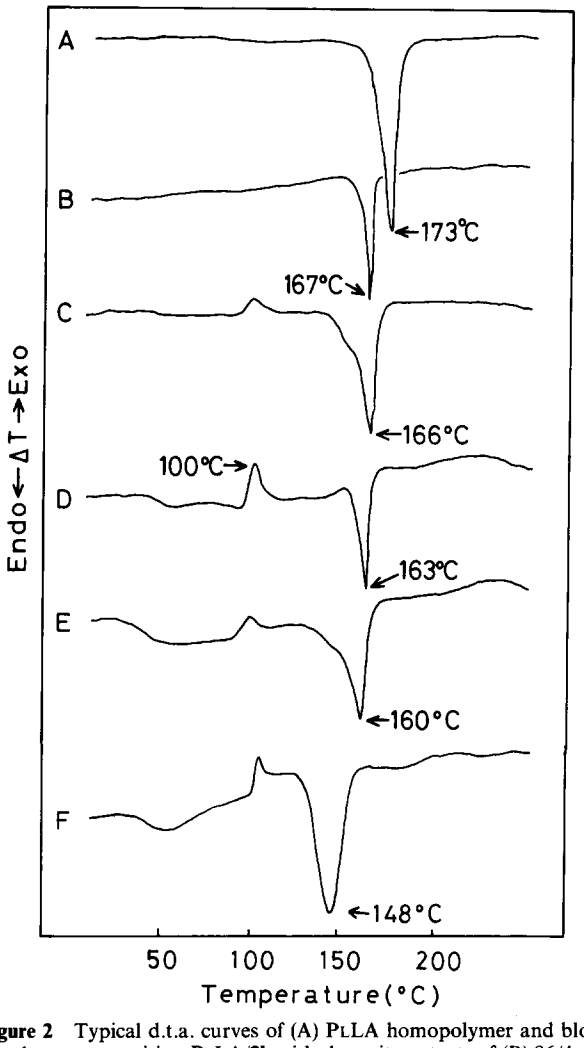


Figure 2 Typical d.t.a. curves of (A) PLLA homopolymer and block copolymers comprising PLLA/**2b** with the unit contents of (B) 96/4, (C) 90/10, (D) 86/14, (E) 79/21, (F) PLLA/**2a** in the unit ratio of 88/12

Properties of the melt-spun fibres

The PLLA–PPG block copolymers were melt-spun into thin fibres by the conventional method[36] and the as-spun fibres were then extended 7–10 times in length at 80–90°C. The diameter of the drawn fibres became about 30–60 μm. Both the spinnability and drawability were excellent for all the copolymers except that of Run number 4, whose molecular weight was less than 20000. The tensile strength of these fibres was found to be proportional to the draw ratio as usual. In *Table 2* the tensile properties of the fibres are compared under the same draw ratio of 7. With increasing PPG content of the copolymers, the tensile strength and modulus were decreased. This tendency implied that the incorporation of PPG segments in PLLA is significantly effective for increasing flexibility of the fibre. In the present study, the tensile elongation did not directly correlate with the PPG content, because it was dependent on the fibre quality, as well. However, among the fibres of Runs 1, 5, 6 and 7 whose spinnability and quality were excellent, a linear relationship between the elongation and PPG content was noted. For the fibres of Runs 5 and 6, the highest strength and modulus were obtained at the draw ratio of 13, which were *circa* 600 MPa and 15 GPa, respectively. These values are relatively lower than those of the commercially available sutures, but reach the minimum strength required for the suture material.

Table 2 Tensile properties of the fibres comprising PLLA/PPG block copolymers at the same draw ratio of 7

Run no.	Polymer composition		Tensile strength (MPa)	Tensile modulus (GPa)	Tensile elongation (%)
	$\bar{M}_n$ of PPG	LA/OP[a]			
1	–	100/0	250	7.8	40
2	2000	97/3	260	7.3	56
3		92/8	250	6.7	54
4		88/12	140	5.9	8
5	4000	96/4	240	6.1	55
6		90/10	220	5.6	70
7		86/14	180	5.0	90
8		79/21	130	4.6	53

[a] The monomeric unit ratio of LA to OP measured by ^{1}H n.m.r. spectrum. See footnotes to *Table 1*

Degradation of fibres in vitro

The fibres comprising PLLA/**2b**, whose qualities were relatively better, were immersed in a phosphate buffer in order to investigate their degradability by hydrolysis[37]. *Figure 3* shows the changes in residual strength as a function of immersion time for the three sample fibres with different content of **2b**. The decrease in strength of the PLLA fibre, a control reference, was very slow, although the rate of degradation seemed to be considerably faster compared with the ordinary fibre[15] that was prepared from a higher molecular weight PLLA (e.g. 300000) than ours (62000). The fibre comprising PLLA/**2b** with the unit content of 86/14, however, showed a rapid drop of strength, while the other fibres with smaller contents of PPG exhibited a slower decrease in strength and maintained more than 50% of the original strength even after four weeks. It is clear that the degradation of these fibres was much accelerated by incorporation of PPG segments. Since no significant change in molecular weight was found after hydrolysis by their g.p.c. analyses, the hydrolysed fragments seemed to be removed from the fibre surface by diffusion or extraction. *Figure 4* shows the s.e.m. photographs of the fibres comprising the PLLA/**2b** copolymer with the unit content of 86/14 before and after the immersion. The original fibre exhibited a microtexture on the surface. It is reasonable to consider that the texture consists of at least three domains, i.e. the crystalline and amorphous PLLA domains, and the elastomeric PPG-rich domains. This structure, therefore, should have been produced by the

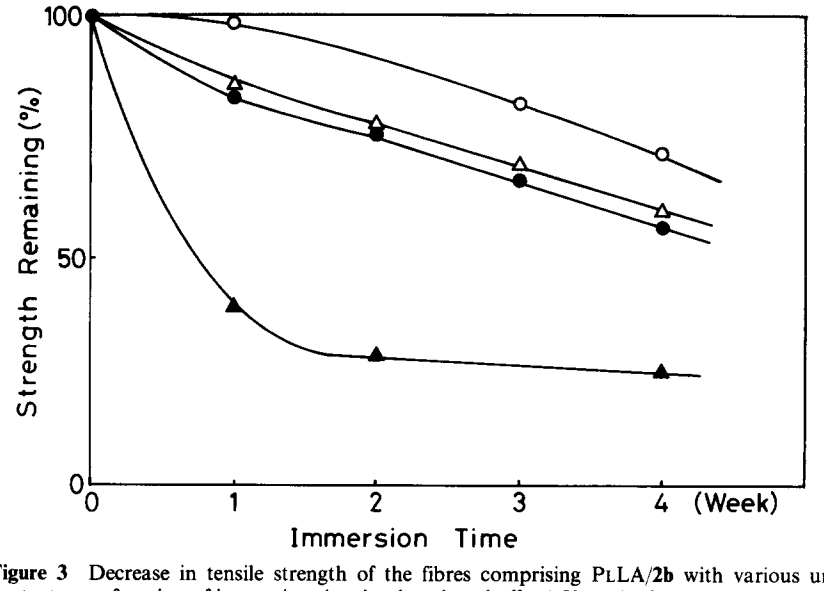


Figure 3 Decrease in tensile strength of the fibres comprising PLLA/**2b** with various unit contents as a function of immersion time in phosphate buffer (pH = 7.2); for the fibres of PLLA (○), and PLLA/**2b** with the unit contents of 96/4 (△), 90/10 (●) and 86/14 (▲)

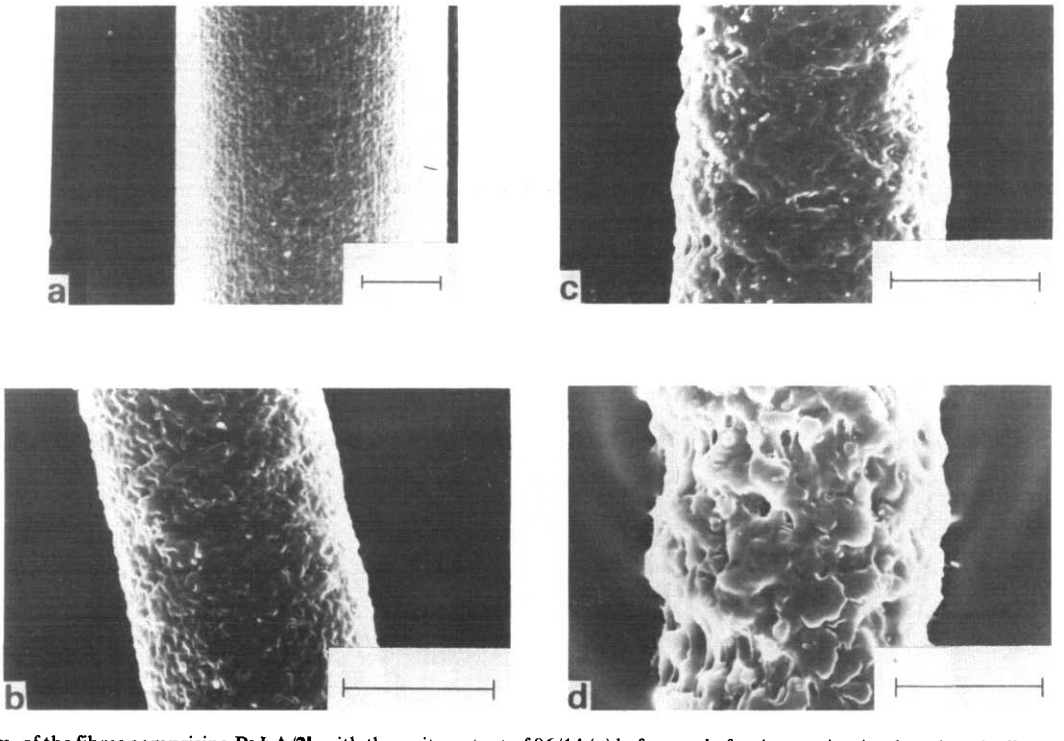


Figure 4 S.e.m. of the fibres comprising PLLA/**2b** with the unit content of 86/14 (a) before and after immersion in phosphate buffer (pH = 7.2) for (b) 4 weeks, (c) 5 weeks and (d) 6 weeks. Scale bar = 20 μm

drawing accompanying both the crystallization of PLLA and the aforementioned microphase separation between PPG and PLLA segments[21], although the details have not yet been clarified. For the immersed fibres, the surface was shown to be eroded by hydrolysis, with growth of microcracks and pores probably in the amorphous and PPG-rich domains of the original fibre. These results supported the fact that the tensile strength of the fibres deteriorated without significant decrease in molecular weight.

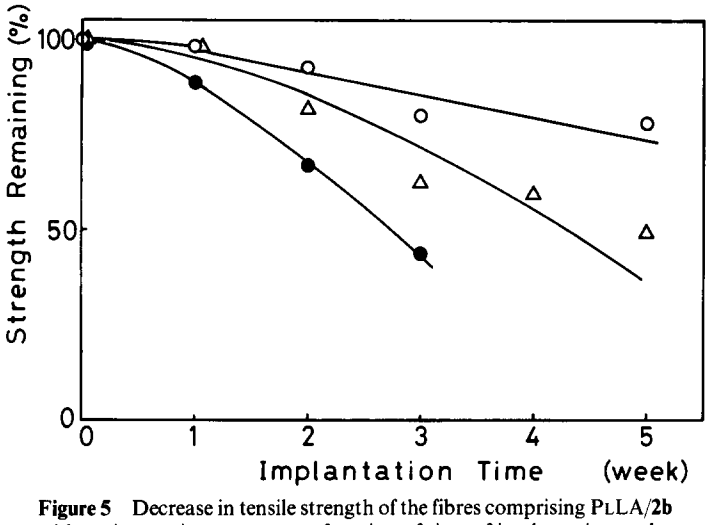


Figure 5 Decrease in tensile strength of the fibres comprising PLLA/**2b** with various unit contents as a function of time of implantation under the dorsal skin of rats; for the fibres of PLLA (○) and PLLA/**2b** with the unit contents of 96/4 (△) and 86/14 (●)

Degradation of fibres in vivo

The drawn fibres comprising PLLA/**2b** were implanted under the dorsal skin of the rats in order to investigate their degradation *in vivo*[9,15]. At intervals of one week after implantation, three rats were dissected, and the fibres were taken out and subjected to the tensile tests. At the dissection the fibres were found to be enfolded by the tissues without adhesion to the cells occurring. Judging from the appearance of the tissues, there were no apparent signs of rejection, inflammation or death of cells. The relationships between the residual strength of the fibres and implantation time are shown in *Figure 5*. The decrease in tensile strength was faster for the fibre comprising higher content of **2b**. This tendency was parallel to the results of the *in vitro* degradations. It is therefore assumed that the mechanism of degradation of the fibre is similar in both cases. *Figure 6* shows the s.e.m. photographs of the fibre comprising PLLA/**2b** in 86/14 before and after the implantation. The surface of the fibre was eroded rather heterogeneously because the hydrolysis was limited to the surface in contact with the tissues. The longer the implantation time, the larger the pores and voids on the surface, causing greater deterioration of the fibre. The erosion seemed to be induced from the amorphous and PPG-rich domains again. It is thus concluded that the biodegradability of PLLA can be much improved by introduction of such a small amount of PPG segments and that the degradation rate can possibly be regulated by the PPG content. The hydrolysis rate of the present block copolymers comprising PLLA/**2b** is comparable to that of PGA and even higher than that of PLLA. These block copolymers, therefore, are potentially useful as bioabsorbable

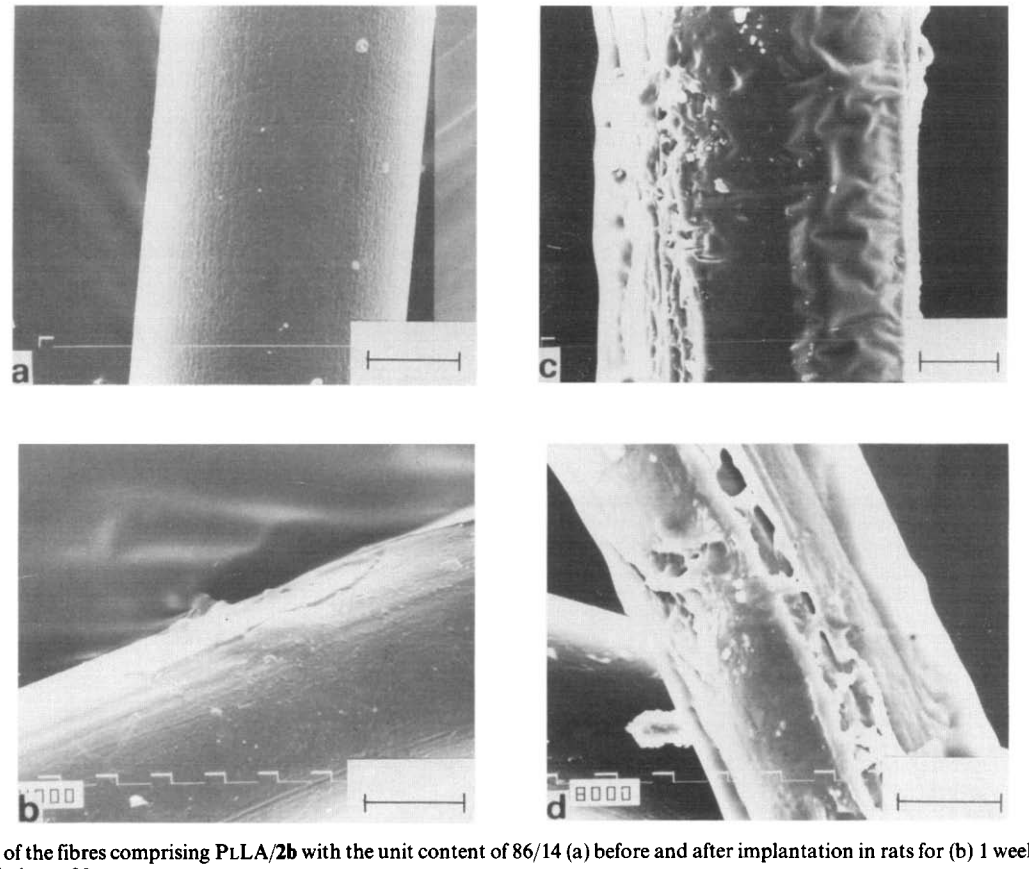


Figure 6 S.e.m. of the fibres comprising PLLA/**2b** with the unit content of 86/14 (a) before and after implantation in rats for (b) 1 week, (c) 2 weeks and (d) 3 weeks. Scale bar = 20 μm

materials, including the surgical suture with an improved flexibility and the polymeric drug carrier with a controlled release rate.

CONCLUSION

Block copolymerization of L-lactide and PPG was successfully carried out by catalysis of the partial hydrolysis product of TMA, and the **A–B–A** block copolymers of PLLA (**A**) and PPG (**B**) were obtained. The copolymers were then melt-spun into thin fibres. After drawing, the fibres were found to have an improved flexibility due to the incorporation of the soft PPG segments. The degradation of the fibres comprising PLLA/PPG 4000 was investigated both *in vitro* and *in vivo*. The results showed that the hydrolysis rate of the copolymer became higher with increasing PPG content. *In vivo*, the degradation of the fibres was found to be induced at the amorphous and PPG-rich surface domains in contact with the tissues, without producing any serious effect on tissues.

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REFERENCES

1 Kronenthal, R. L., Oser, Z. and Martin, E. 'Polymer Science and Technology, Vol. 8: Polymers in Medicine and Surgery', Plenum, New York, 1975
2 Williams, D. F., Chu, C. C. and Dwyer, J. *J. Appl. Polym. Sci.* 1984, **29**, 1865
3 Vert, M. *Makromol. Chem., Makromol. Symp.* 1986, **6**, 109
4 Frazza, E. J. and Schmitt, E. E. *Biomed. Mater. Res., Symp.* 1971, **1**, 43
5 Gilding, D. K. and Reed, A. M. *Polymer* 1979, **20**, 1459
6 Gogolewski, S. and Pennings, A. J. *Makromol. Chem. Rapid Commun.* 1983, **4**, 213
7 Fredericks, R. J., Melveger, A. J. and Dolegiewitz, J. *J. Polym. Sci., Polym. Phys. Edn.* 1984, **22**, 57
8 Alexander, H., Parsons, J. R., Strauchler, I. D., Corcoran, S. F., Gona, O., Mayott, C. and Weis, A. B. *Orthop. Rev.* 1981, **10**, 41
9 Echeverria, E. and Jimenez, J. *Surgery* 1970, **131**, 1
10 Sanders, H. J. *Chem. Eng. News* 1985, 31
11 Okada, H., Ogawa, Y. and Yashiki, K. (Takeda Chem. Ind.) Jpn. Kokai Tokkyo Koho JP 60,100,516, 1985; *Chem. Abstr.* 1985, **103**, 166162z
12 Iwa, T., Hirano, M., Yamashita, R. and Sakatoku, M. *Igaku No Ayumi* 1984, **128**, 655; *CA* 1984, **101**, 43491g
13 Dardik, H., Dardik, I. and Laufman, H. *Am. J. Surg.* 1971, **121**, 656
14 Eling, B., Gogolewski, S. and Pennings, A. J. *Polymer* 1982, **23**, 1587
15 Jamshidi, K., Hyon, S.-H., Nakamura, T., Ikada, Y., Shimizu, Y. and Teramatsu, T. in 'Biological and Biomechanical Performance of Biomaterials' (Eds P. Christel, A. Meunier and A. J. C. Lee), Elsevier, Amsterdam, 1986, p. 227
16 Eling, B., Gogolewski, S. and Pennings, A. J. *Polymer* 1982, **23**, 1587
17 Kalb, B. and Pennings, A. J. *Polymer* 1980, **21**, 607
18 Chu, C. C. in 'Biomaterials' (Eds. G. D. Winter, D. F. Gibbons and H. Plenk Jr.), John Wiley, New York, 1982, p. 781
19 Miller, R. A., Brady, J. M. Cutright, D. E. *J. Biomed. Mater. Res.* 1977, **11**, 711
20 Reed, A. M. and Gilding, D. K. *Polymer* 1981, **22**, 499
21 Gallot, B. R. M. 'Advances in Polymer Science, 29, Structure and Properties of Polymers', Springer Verlag, Heidelberg, FRG, 1978, 85
22 Casey, D. J. and Huffman, K. R. (Am. Cyanamid Co.) US 4 438 253, 1984
23 Vitalis, E. A. (Am. Cyanamid Co.) US 2 917 410, 1959; *Chem. Abstr.* 1960, **54**, 7173d
24 Kitao, T., Kimura, Y., Ohtani, N., Matsuzaki, Y. and Yabuuchi, K. Jpn. Kokai Tokkyo Koho, 1986, Applied
25 Cohn, D. and Younes, H. 'Transactions of the 3rd World Biomaterials Congress', Kyoto, Japan, 1988, p. 278
26 Simons, D. M. and Verbanc, J. J. **J. Polym. Sci.** 1960, **44**, 303
27 Carothers, W. H., Dorough, G. L. and Natta, F. J. V. *J. Am. Chem. Soc.* 1932, **54**, 761
28 Saegusa, T., Fujii, H. and Furukawa, J. *J. Macromol. Chem.* 1962, **55**, 232
29 Herold, D. A., Rodeheaver, G. T., Bellamy, W. T., Fitton, L. A., Bruns, D. E. and Edlich, R. F. *Toxicol. Appl. Pharmacol.* 1982, **65**, 329
30 Yamashita, I. *Hyomen* 1979, **17**, 776; *CA* 1980, **92**, 169072k
31 Nyilas, E. *Blood Vessels* 1976, 165
32 Kricheldorf, H. R., Jonte, J. M. and Berl, M. *Makromol. Chem. Suppl.* 1985, **12**, 25
33 Gross, R. A., Zhang, Y., Konrad, G. and Lenz, R. W. *Macromolecules* 1988, **21**, 2657
34 Frisch, K. C. and Reegen, S. L. 'Ring-Opening Polymerization', Marcel Dekker, New York, 1969, p. 8
35 Deibig, H., Geiger, J. and Sander, M. *Makromol. Chem.* 1971, **145**, 123
36 Williams, H. L. 'Polymer Engineering', Elsevier, New York, 1975
37 Kitao, T., Kimura, Y., Konishi, T., Araki, M., Sugiyama, Y. and Ohya, S. *Kobunshi Ronbunshu* 1984, **41**, 717; *Chem. Abstr.* 1985, **102**, 119588n