

# Preparation of High-Molecular-Weight Poly(L-lactic acid)-Based Polymers Through Direct Condensation Polymerization in Bulk State

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**ABSTRACT:** Poly(L-lactic acid-co-succinic acid-co-1,4-butanediol) (PLASB) was synthesized by a direct condensation copolymerization of L-lactic acid, succinic acid (SA), and 1,4-butanediol (BD) in bulk state using titanium(IV) butoxide (TNBT) as a catalyst. Weight average molecular weight ( $M_w$ ) of PLASB increased from  $3.5 \times 10^4$  to  $2.1 \times 10^5$  as the content of SA and BD went up from 0.01 to 0.5 mol/100 mol of L-lactic acid (LA). PLASB having  $M_w$  in the range from  $1.8 \times 10^5$  to  $2.1 \times 10^5$  showed tensile properties comparable to those of commercially available poly(L-lactic acid) (PLLA). In sharp contrast, homopolymerization of LA in bulk state produced PLLA with  $M_w$  as low as  $4.1 \times 10^4$ , and it was too brittle to prepare specimens for the tensile tests.  $M_w$  of PLASB synthesized by using titanium(IV)-2-ethyl(hexox-

ide), indium acetate, indium hydroxide, antimony acetate, antimony trioxide, dibutyl tin oxide, and stannous-2-ethyl 1-hexanoate was compared with that of PLASB obtained by TNBT. Ethylene glycol oligomers with different chain length were added to LA/SA in place of BD to investigate effect of chain length of ethylene glycol oligomers on the  $M_w$  of the resulting copolymers. Biodegradability of PLASB was analyzed by using the modified Sturm test. Toxicity of PLASB was evaluated by counting viable cell number of mouse fibroblast cells that had been in contact with PLASB discs. © 2006 Wiley Periodicals, Inc. *J Appl Polym Sci* 100: 466–472, 2006

**Key words:** biodegradable polymers; poly(L-lactic acid); direct condensation polymerization

## INTRODUCTION

Poly(L-lactic acid) (PLLA) has received much interest in recent years because it is synthesized from renewable resources. It is degraded by hydrolytic cleavage of the ester bonds to produce lactic acid and its oligomers, which can be metabolized by many microorganisms.<sup>1</sup> PLLA is also resorbable in the human body and is nontoxic after biodegradation.<sup>2</sup>

Application of PLLA has been limited to biomedical purposes such as surgical sutures,<sup>3–5</sup> fractured bone fixation,<sup>6,7</sup> tissue engineering,<sup>8</sup> and drug delivery systems.<sup>9,10</sup> This is because PLLA has been much more expensive than the general purpose plastics.

Cargill Dow Co.<sup>11</sup> began to produce PLLA on a commercial scale under the trade name of Nature Works™. The price of PLLA has been reduced greatly owing to the technology developed by Cargill Dow Co. by combining agricultural processes with biological and chemical technologies.

As far as we know, Cargill Dow Co. produces PLLA through ring opening polymerization of L-lactide, which is formed by catalytic depolymerization of low-

molecular-weight PLLA prepolymer<sup>11</sup> synthesized by direct polycondensation polymerization of L-lactic acid (LA). Cargill Dow Co. employs this route mainly because direct condensation polymerization of LA in bulk state gives only low- to intermediate-molecular-weight polymers due to the low equilibrium constant of the condensation polymerization reaction.

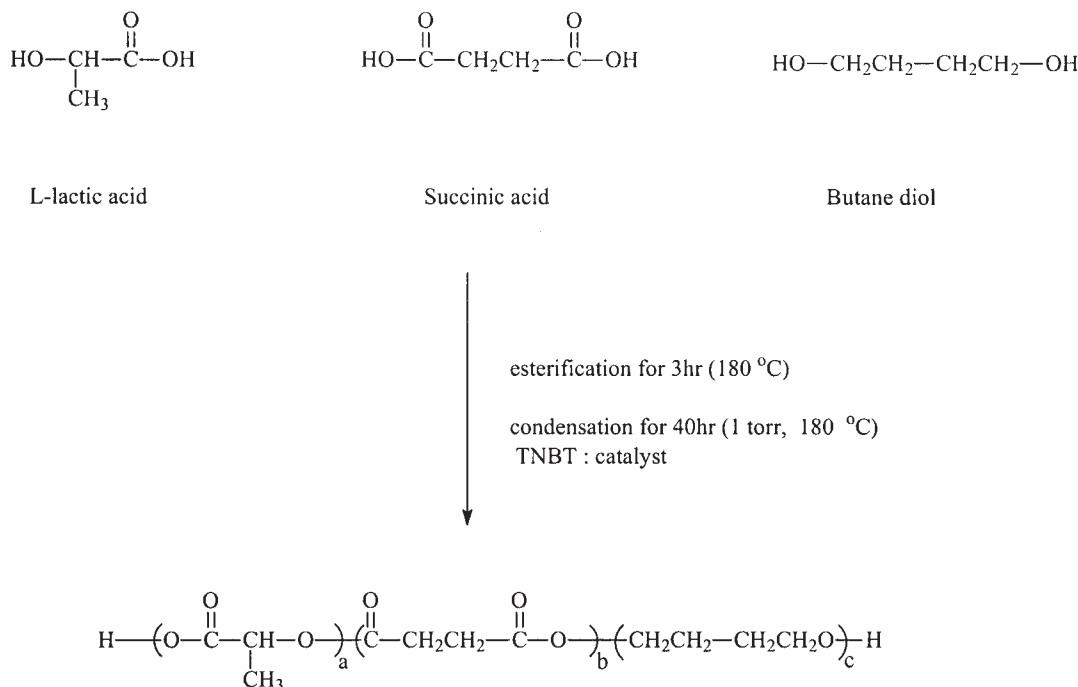
A solvent with high boiling point, such as dicyclohexylcarbodiimide or diphenyl ether, which is compatible with PLLA, is used for the removal of dissociated water by means of the so-called azeotropic distillation technique<sup>12</sup> to shift the equilibrium state to the polymer side. PLLA with high molecular weight can be produced through this solution polymerization route.

This route requires large reactor volume and facilities for evaporation and recovery of the solvent, which increases the production cost of PLLA.<sup>11</sup>

Recently, Mitsui Chemicals opened a new process based on direct polycondensation of low-molecular-weight PLLA in solid state without the use of an organic solvent<sup>11</sup> to produce high-molecular-weight PLLA.

High-molecular-weight PLLA-based copolymers were successfully produced in our laboratory for the first time through direct condensation polymerization of LA with succinic acid (SA) and 1,4-butanediol (BD).

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**Scheme 1** Synthesis of the copolymers with L-lactic acid, SA, and BD.

The copolymerizations were carried out in an attempt to shift the equilibrium state of the polymerization of LA. Effects of type and content of the comonomers and the catalysts on the molecular weight of the produced copolymers were explored. Biodegradability and toxicity of the copolymers were compared with those of PLLA homopolymer.

## EXPERIMENTAL

### Materials

L-Lactic acid (85% aqueous solution, Tedia), 1,4-butanediol (BD) (Aldrich), succinic acid (SA) (Aldrich), diethylene glycol (DEG) (Aldrich), triethylene glycol (TEG) (Aldrich), hexaethylene glycol (HEG) (Aldrich), poly(ethylene glycol) 200 (PEG 200) (Aldrich), PEG 400 (Aldrich), PEG 600 (Aldrich), and PEG 1000 (Aldrich) were used as received, without further purification. Titanium(IV) butoxide (TNBT) (Aldrich), Titanium(IV)-2-ethyl(hexoxide) (Aldrich), indium acetate (Aldrich), indium hydroxide (Aldrich), antimony acetate (Aldrich), antimony trioxide (Aldrich), dibutyl tin oxide (Aldrich), stannous-2-ethyl-1-hexanoate (Aldrich) were used as received<sup>13</sup> to catalyze the condensation polymerization reactions.

### Copolymerization

A typical procedure was as follows: After LA, SA, and BD were added into a flask (SA and BD in the range of 0.01–2.0 mol/100 mol of LA), the flask was heated in

an oil bath at 120°C with stirring under dried nitrogen at about 300 Torr. After 2 h, it was heated in an oil bath to 180°C under nitrogen atmosphere for 3 h so that the esterification reaction took place. After the esterification reaction, the reactor pressure was reduced to 1 Torr step-by-step for 2 h, and then the reaction was continued at 1 Torr and 180°C for another 40 h. The resulting copolymer was dissolved in chloroform, and then was precipitated twice in excess methanol. The product was dried in a vacuum oven at 60°C until constant weight was attained (Scheme 1).<sup>14</sup>

### Measurements

<sup>1</sup>H NMR analysis was performed on a Bruker DPX250 FT-NMR (Bruker Instruments, Billerica, MA).

Molecular weight was measured by using a gel permeation chromatography (GPC; Waters 410; RI detector, column (porosity: 10 μm, Styragel HR 1, HR 2, HR 4, linear)) with tetrahydrofuran as eluent (flow rate of 1 mL/min). Calibration was performed by using polystyrene standard.<sup>15</sup>

Thermal properties of the copolymers were determined by a differential scanning calorimetry (DSC) (Perkin-Elmer DSC 7, Norwalk, CT). Thermal history of the products was removed by scanning from 30 to 150°C at the heating rate of 20°C/min. After cooling down the sample at -2°C/min from 150 to 30°C, it was reheated at 20°C/min to 150°C and the 2nd scan DSC thermograms were obtained.

Mechanical properties of the samples were determined with a universal test machine (Instron Model

No. 4200, Canton, MA) at a cross head speed of 10 mm/min, according to ASTM D 638 at  $(15 \pm 1)^\circ\text{C}$  and relative humidity of 65%.

### Modified Sturm test

Biodegradability was evaluated through the modified Sturm test. Samples were suspended in a sheet form with 0.1 mm thickness. Amount of  $\text{CO}_2$  was monitored at  $27^\circ\text{C}$  by the experimental setup assembled according to ASTM D 5209–91.

### Toxicity

L929 mouse fibroblast cells (KCLB-10001) were supplied by the Korea Cell Line Bank (KCLB). The cells were cultured in 50-mL cell culture flasks containing Dulbeccos modified Eagles medium (DMEM; Gibco). The cell culture was maintained in a gas-jacket incubator equilibrated with 5%  $\text{CO}_2$  at  $37^\circ\text{C}$ . When the cells had grown to confluence, the cells were digested by 1 mL 0.05% trypsin for 1–2 min, then 3 mL of culture medium was added to stop digestion, and the culture medium was aspirated to cause cell dispersion after counting the cells.

Synthesized polymers were cut into small disks (10 mm in diameter, 0.2 mm in thickness) with the aid of a cork borer and located into a 24 well cell culture plate. All the disks were sterilized by Ultraviolet light for 2 h. One milliliter of cell suspension was evenly placed on the samples. The cell-seeded disks were maintained at  $37^\circ\text{C}$  under 5%  $\text{CO}_2$  condition. Subsequently, the culture medium was removed and then the samples were rinsed with 0.01M phosphate buffered saline (PBS; pH 7.2) to remove any of the residual culture medium and unattached cells. After the attached cells on the disks were digested by trypsin, the cell attachment efficiency was determined by counting the number of cells remaining in the well.<sup>16</sup>

## RESULTS AND DISCUSSION

### Copolymerization

Figure 1 shows the  $^1\text{H}$  NMR spectrum of poly(L-lactic acid-co-succinic acid-co-1,4-butanediol) (PLASB) synthesized in this study. The peaks at 5.14 ppm and those at 1.5 ppm correspond to the methine and methyl protons of LA units, respectively. The methylene protons of SA units exhibit their peaks at 2.70 ppm,<sup>13</sup> and those of BD units appear at 1.5 and 4.15 ppm.<sup>17,18</sup> The composition of PLASB was determined from the intensity of the peaks at 5.14, 4.15, and 2.70 ppm corresponding to LA, BD, and SA units respectively.

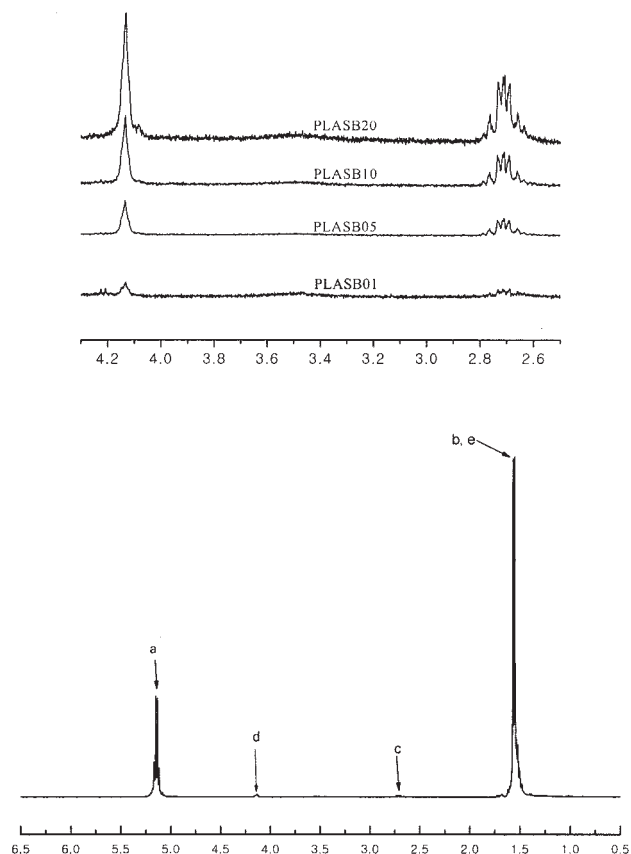
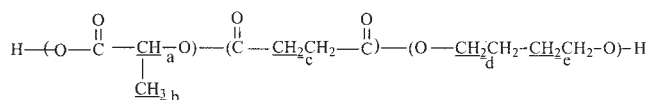


Figure 1  $^1\text{H}$  NMR spectra of PLASB.

Table I summarizes the copolymer composition and number average ( $M_n$ ) and weight average ( $M_w$ ) molecular weight measured from the GPC.

A direct condensation polymerization of LA gave PLLA with  $M_w$  as low as  $4.1 \times 10^4$ . In sharp contrast,  $M_w$  of PLASB increased to  $2.1 \times 10^5$  as the content of SA and BD in the copolymerization medium rose to 0.5 mol/100 mol of LA. However, further increase of the content of SA and BD to 1.0 mol and 2.0 mol/100 mol of LA lowered  $M_w$  of PLASB down to  $1.8 \times 10^5$  and  $5.5 \times 10^4$ , respectively.

At present, we do not have a clear explanation for the reason why  $M_w$  of PLLA increases and then decreases after showing a maximum as the content of SA and BD in the copolymerization medium increases. However, we propose the following inferential explanation:

Condensation polymerization of SA/BD with an alkoxide catalyst gives much higher molecular weight polymer than that of LA does, indicating that the equilibrium state of the former reaction is much more favorable for the polymer formation when compared

TABLE I  
Characterization of Poly(*l*-lactic acid-*co*-succinic acid-*co*-1,4-butane diol)

Sample code	Molar composition		Thermal properties					
	Feed LA/ SA/BD	Polymer LA/ SA/BD	$M_w$ ( $\times 10^4$ )	PDI	$T_m$ (°C)	$\Delta H$ (J/g)	$T_g$ (°C) 1st scan	$T_g$ (°C) 2nd scan
PLLA <sup>a</sup>	—	—	10.0	1.63	170.9	47.2	69.6	64.2
PLASB	100/0/0	100/0/0	4.1	1.78	152.4	34.1	62.9	53.7
PLASB001	100/0.01/0.01	—	3.5	1.59	140.6	29.2	57.4	50.7
PLASB005	100/0.05/0.05	—	7.6	2.79	132.7	30.0	50.2	52.3
PLASB01	100/0.1/0.1	100/0.26/0.26	8.8	2.38	138.1	25.7	59.8	53.9
PLASB05	100/0.5/0.5	100/0.82/0.69	21.0	3.26	124.6	19.1	65.7	60.1
PLASB10	100/1.0/1.0	100/1.68/1.35	17.7	4.25	120.2	17.0	53.6	55.4
PLASB20	100/2.0/2.0	100/2.13/1.90	5.5 <sup>b</sup>	—	110.9	2.1	49.7	49.3

<sup>a</sup> PLLA purchased from Shimadzu Co.

<sup>b</sup> The base line of the GPC curve was not clear-cut enough to determine  $M_n$  and  $M_w$  accurately.

with the latter reaction. Thus,  $M_w$  of PLASB increases as the content of SA and BD rises because of the shift of the equilibrium state.

When the content of SA and BD becomes high, reactions between SA and BD take place preferentially, compared with those between LA and SA or between LA and BD, because the former reaction proceeds faster than the latter one. Thereby, oligomers composed of SA and BD units are formed first, and then condensation reaction between LA and the oligomers follows subsequently. When the content of SA and BD goes over 0.5 mol/100 mol of LA, the chain length of the oligomers formed *in situ* becomes long to decrease the reactivity between the oligomers and LA, and in turn  $M_w$  of PLASB produced becomes lower.

Table III demonstrates  $M_w$  of the copolymers synthesized by copolymerization of LA with SA and with different kinds of diols at 100/0.5/0.5M ratio. DEG, TEG, HEG, PEG 200, PEG 400, PEG 600, and PEG 1000 were used as diols in which the number after the abbreviation, "PEG," corresponds to approximate  $M_n$  of the PEG. In case of DEG and TEG,  $M_w$  of the copolymer exceeded  $1.0 \times 10^5$ . However,  $M_w$  of the copolymer decreased sharply as the chain length of the ethylene glycol oligomer increased. These results

are contrary to the expectations because the reactivity of the functional groups in condensation polymerization has been known to be nearly independent of the chain length of the reactants.<sup>19</sup>

The decrease of  $M_w$  with increase in the chain length of the diols confirms the previously cited conclusion that the reactivity between SA/BD oligomers and LA decreases as the chain length of the SA/BD oligomers becomes longer.

It is to be noted that, according to Table I, the molar content of BD units in PLASB is higher than that of SA units, even though the initial molar content of BD in the polymerization medium is the same as that of SA. This is because the primary hydroxy group of BD is more reactive toward the carboxylic group than the secondary hydroxy group of LA, implying that PLASB produced is mostly terminated by hydroxyl groups. Therefore, number of moles of BD reacted should be larger than that of SA when based on unit mole of LA.

Table II shows  $M_w$  of PLASB synthesized by copolymerization of LA/SA/BD at 100/0.5/0.5M ratio with different catalysts. Performance of a catalyst depends on the thermal stability as well as deactivation of the catalyst because of H<sub>2</sub>O produced *in situ* during

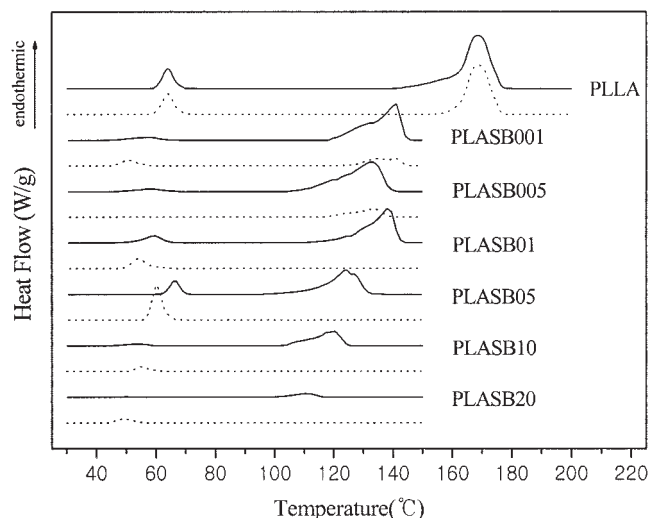
TABLE II  
Molecular Weight of the Copolymers Synthesized in Bulk State by Direct Condensation Polymerization of Lactic Acid/Succinic Acid/Ethylene Glycol Oligomers at 100/0.5/0.5M ratio

Ethylene glycol oligomers	$M_n$ ( $\times 10^4$ )	$M_w$ ( $\times 10^4$ )	$M_w/M_n$
DEG	2.4	13.2	5.45
TEG	3.5	11.6	3.26
HEG	3.0	8.6	2.96
PEG 200	1.3	2.3	1.72
PEG 400	2.5	5.6	2.18
PEG 600	2.4	4.4	1.83
PEG 1000	1.7	2.8	1.67

TABLE III  
Molecular Weight of PLBSA050 Produced by Different Catalysts

Catalysts	GPC results		
	$M_n$ ( $\times 10^4$ )	$M_w$ ( $\times 10^4$ )	$M_w/M_n$
Titanium(IV) butoxide	6.7	21.0	2.26
Titanium(IV)2-ethyl(hexoxide)	1.6	3.5	2.24
Indium acetate	1.6	2.4	1.47
Indium hydroxide	1.6	2.9	1.83
Antimony acetate	1.7	4.0	2.29
Antimony trioxide	1.9	3.8	2.00
Dibutyl tin oxide	1.7	4.8	2.75
Stannous-2-ethyl-1-hexanoate	0.9	1.6	1.73





**Figure 2** DSC thermograms of PLLA and PLASB: 1st scan, ..... 2nd scan.

the condensation polymerization. Moreover, the activation energy of the catalysts is different from each other. Hence, evaluation of the catalyst performance should be based on experimental data carried out at different conditions.

However, among TNBT, titanium(IV)-2-ethyl(hexoxide), indium acetate, indium hydroxide, antimony acetate, antimony trioxide, dibutyl tin oxide, and stannous-2-ethyl-1-hexanoate, TNBT gave PLASB with the highest  $M_w$ , when the condensation copolymerization was performed at 180°C.

### Thermal and mechanical properties

Thermal properties of PLASB were measured by using a differential scanning calorimetry (DSC) and the results are reported in Table I. The DSC thermograms are depicted in Figure 2 for PLLA and PLASB.

PLLA homopolymer exhibits melting peak ( $T_m$ ) as well as glass transition peak ( $T_g$ ) on both the 1st and the 2nd DSC thermograms.  $T_g$  peak of PLLA on the 1st DSC thermogram appears at a higher temperature than that on the 2nd one, because the melting peak of the 1st scan is more intense than that of the 2nd scan. This indicates that PLLA in the 1st scan was more crystalline than PLLA in the 2nd scan and thus movement of PLLA molecules in the amorphous region was more restricted by the more crystalline phase during the 1st scan.

The as-polymerized PLASB showed  $T_m$  peak during the 1st DSC scan, while  $T_m$  was not detected on the 2nd DSC thermogram as soon as a trace amount of SA and BD was added for the synthesis of PLASB. This implies that LA units in sequence of PLASB became short because of the random incorporation of SA and BD units in PLASB, so that the crystallization of the

segments composed of the sequential LA units was greatly suppressed.

The significant decrease of the crystallization rate of PLASB confirms that PLLA homopolymer or PLASB containing negligible amount of SA and BD units was not produced during the copolymerization even though the content of SA and BD in the copolymerization medium was as low as 0.1 mol/100 mol of LA.

$T_g$  of poly(butylene succinate) (PBS) appears at  $-42.3^\circ\text{C}$ , which is much lower than that of PLLA, saying that segmental motion of SA and BD units is easier than that of LA units.

$T_g$  of PLASB05 appeared at a higher temperature than that of PLASB01, even though the former copolymer had higher content of SA and BD than the latter one. This is attributed to lower  $M_w$  of PLASB01 when compared with that of PLASB05. Both the lower  $M_w$  and the easier segmental motion of SA and BD units when compared with that of LA units should be responsible for the lower  $T_g$  of PLASB10 and PLASB20 when compared with that of PLASB05.

Tensile properties of PLASB were measured by using UTM according to ASTM D 638 and the results are summarized in Table IV.

Not only PLLA homopolymer synthesized from the direct condensation polymerization of LA but also PLASB001 and PLASB005 were too brittle to prepare specimens for the tensile tests. In marked contrast, PLASB05 and PLASB10 produced from the reaction medium of LA/SA/BD at 100/0.5/0.5 and at 100/1.0/1.0M ratio, respectively, showed tensile properties similar to those of PLLA produced commercially by Shimadzu Co. by way of the solution process.

### Biodegradability

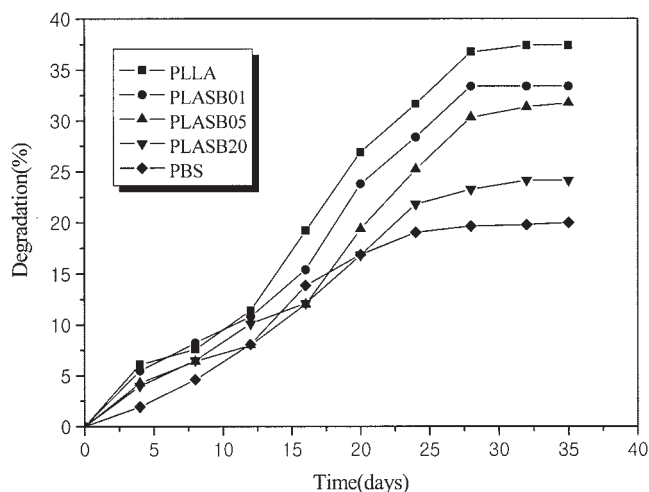
Biodegradation of both PLLA and PBS proceeds very slowly,<sup>20,21</sup> because few microorganisms are able to degrade PLLA.<sup>22,23</sup> Hence, PLLA should be first hydrolyzed abiotically into low-molecular-weight products, which afterwards permeate into microbial cells to be metabolized into  $\text{CO}_2$ .

Figure 3 demonstrates that PLASB also degrades very slowly in the modified Sturm test, and that bio-

**TABLE IV**  
Tensile Properties of Poly(*l*-lactic acid-*co*-succinic acid-*co*-1,4-butane diol)

	Elongation at break (%)	Stress at max. load (MPa)	E. modulus (MPa)
PLLA <sup>a</sup>	7.83 ± 1.05	47.51 ± 3.03	1151 ± 83
PLASB01	3.76 ± 1.48	43.64 ± 2.41	1177 ± 121
PLASB05	7.40 ± 1.73	39.38 ± 3.00	994 ± 126
PLASB10	7.83 ± 2.29	35.06 ± 4.80	1103 ± 204
PLASB20	1.32 ± 1.85	7.50 ± 2.13	1380 ± 325

<sup>a</sup> PLLA purchased from Shimadzu Co.



**Figure 3** The modified Sturm test results for PLLA and PLASB.

degradation rate of PLASB is in between that of PLLA and PBS, in spite of the fact that PLASB is less crystalline than PLLA and PBS.

When biodegradation takes place very slowly in the modified Sturm test, sufficient time is allowed for water molecules to permeate not only into the amorphous region but also into the crystalline phase of the samples. Therefore, the degree of crystallinity of the samples does not influence crucially on the biodegradation rate, because the rate determining step for the mineralization into  $\text{CO}_2$  in the modified Sturm test is not the diffusion of water molecules into the samples.

### Toxicity

PLLA and PLASB were pressed under a hot press at  $180^\circ\text{C}$ , 1 atm to prepare samples in round-disc shape having 0.2 mm of thickness and  $0.785\text{ cm}^2$  of surface area. Mouse fibroblast cells were cultivated for 3 days in contact with the disc samples. Viable cells were counted after the cultivation and the results are represented in Figure 4. In case of the control experiment where the cells were cultivated in the absence of the samples, the viable cells were counted to be  $5.45 \times 10^5$  cells/mL. However, the number of the viable cells went down to  $3.50 \times 10^5$  cells/mL when the cells were contacted with the PLLA discs.

Since lactic acid and its oligomers produced from the PLLA degradation can be metabolized in human body, PLLA has been considered to be a good biocompatible polymer. Thus, it was expected that PLASB should be more toxic than PLLA. However, contrary to the expectation, Figure 4 reveals that the toxicity decreases in the order of  $\text{PLLA} > \text{PLASB01} > \text{PLASB05} > \text{PLASB10}$ .

According to Figure 3, PLASB was metabolized more slowly into  $\text{CO}_2$  by microorganisms than PLLA.

The higher the content of SA and BD in PLASB, the slower the metabolization rate. Therefore, it can be said that rate of accumulation of low-molecular-weight products due to the hydrolysis of PLASB became slower, and thus the viable cells were larger in number as the content of SA and BD increased.

### CONCLUSIONS

PLASB was prepared by polymerizing LA in the presence of SA and BD in bulk state using TNBT as a catalyst.

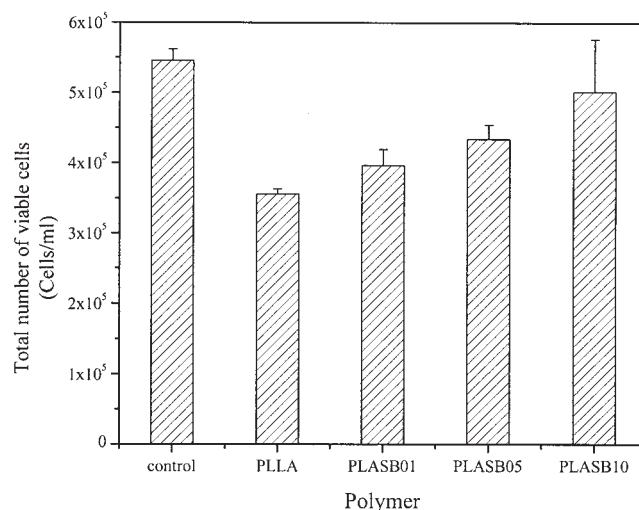
Weight-average-molecular-weight ( $M_w$ ) of PLASB increased from  $3.5 \times 10^4$  to  $2.1 \times 10^5$  as the content of SA and BD in the polymerization medium increased from 0.01 to 0.5 mol/100 mol of LA. Tensile properties of PLASB were comparable to those of high-molecular-weight PLLA produced commercially by Shimadzu Co. through the solution polymerization of LA.

TNBT produced PLASB with higher molecular weight than titanium(IV)-2-ethyl(hexoxide), indium acetate, indium hydroxide, antimony acetate, antimony trioxide, dibutyl tin oxide, and stannous-2-ethyl-1-hexanoate did.

When ethylene glycol oligomers were used instead of BD,  $M_w$  of the resulting copolymer decreased sharply as the chain length of the oligomers increased.

Biodegradation rate of PLASB in the modified Sturm test was slower than that of PLLA, in spite of the fact that PLASB was less crystalline than PLLA.

Mouse fibroblast cells surviving after 3 days of the cultivation in contact with PLASB were larger in number than those with PLLA, indicating that PLASB was less toxic than PLLA to the animal cells.



**Figure 4** The number of fibroblast grown on 10% FBS-DMEM after 3 days. All experiments were performed in triplicate and the error bars indicate the standard deviation.

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