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Modification of polylactide upon physical properties by solution-cast blends from polylactide and polylactide-grafted dextran

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Abstract

Polylactide (PLA)-grafted polysaccharides with various lengths and numbers of graft chains were synthesized using a trimethylsilyl protection method. The properties of the cast films prepared from graft-copolymers were investigated through thermal and dynamic mechanical analyses. The graft-copolymer films exhibited a lower glass transition temperature (T_g), melting temperature, and crystallinity, and higher viscosity properties compared to PLA films. Moreover, the usefulness of graft-copolymer as a plasticizer was investigated with 1:4 blend films prepared from the graft-copolymers and PLA. The blend films showed lower T_g and crystallinity, and higher viscosity properties compared to PLA films.

Keywords: Polylactide; Mechanical property; Biodegradable

1. Introduction

Biodegradable, biocompatible polymers are of interest for use in biomedical and pharmaceutical applications. Based on their biodegradability, biocompatibility, high mechanical strength, and good shaping and molding properties, poly-L-lactide (PLLA) is frequently utilized as implantable carriers for drug delivery systems as well as for surgical repair materials [1–6]. However, the high crystallinity of the polymer interferes with controlled degradation, reducing compatibility with soft tissues and presenting an obstacle to application as biodegradable soft plastics. Many approaches to overcome these problems in PLLA, for example, stereocopolymer according to enantiomeric composition, block copolymerization with other polyethers, branched PLLA or blend with other polymers were carried out to control the degradation rate by varying the crystallinity [7–17]. One promising approach to give the viscosity and hydrophilicity, controlled degradation to PLLA is the introduction of hydrophilic segments and branched structures. Polysaccharides are natural biodegradable hydrophilic polymers, which show enzymatic degradation behavior and possess relatively good biocompatibility properties, but are insoluble in common organic solvents.

Recently, block or graft-copolymers having hydrophobic and hydrophilic segments have been reported to form various types of microstructures and have been applied as biomaterials [18–21]. Saccharides and polysaccharides contain multiple hydroxyl groups, and have therefore found utility as hydrophilic and bioactive segments in some hybrid biomaterials. Syntheses of biodegradable polymers having both aliphatic groups and hydrophilic saccharide unit in their main chains have been reported [22–26].

Polylactide (PLA) is commonly synthesized by ring-opening polymerization of a lactic acid dimer (lactide, LA). This ring-opening polymerization reaction proceeds in the presence of an alkali metal alkoxide to give a PLA containing the alkoxide as its terminal group [27].

Our team has attempted to obtain graft-copolymers consisting of PLA and polysaccharides using the hydroxyl groups of the polysaccharides as initiators. Recently, we reported a new method to achieve graft-polymerization of LA on polysaccharides using trimethylsilyl (TMS)-protected polysaccharides [28,29]. By introducing TMS protecting groups with chlorotrimethylsilane/pyridine, low-molecular-weight polysaccharides become soluble in

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organic solvents, and the number of initiating groups (i.e. the number of graft chains) can be controlled. But high-molecular-weight polysaccharides do not completely dissolve in chlorotrimethylsilane/pyridine. We developed the TMS protection method to achieve the graft-polymerization of LA on high-molecular-weight polysaccharides. In this paper, high-molecular-weight polysaccharides in which most of the hydroxyl groups are protected by TMS were synthesized with hexamethyldisilazane/formamide [30]. Consequently, PLA-grafted dextran (Dex-*g*-PLA) could be obtained by homogeneous graft-polymerization of L-lactide (L-LA) on TMS-protected dextrans in THF and subsequent removal of the protecting groups. In the polymerization of L-LA, we used potassium alkoxide as catalyst to aim for biomedical and pharmaceutical applications.

The physical properties of Dex-*g*-PLA depend on molecular structure, length and number of graft chains, and proportion of hydrophilic and hydrophobic segments in the copolymers. Firstly, the thermal and mechanical properties of cast films prepared from Dex-*g*-PLA were investigated. Dex-*g*-PLA having both amphiphilic and branched structures works as a plasticizer of PLLA. Secondly, to evaluate the blend films for use as soft biomaterials, the thermal and mechanical properties of 1:4 blend films prepared from the graft-copolymers and PLLA were investigated. The blend films had lower glass transition temperature (T_g) and crystallinity, and higher viscosity properties compared to PLLA. The properties of the blend films could be controlled by changing the lengths and numbers of graft chains.

2. Experimental

2.1. Materials

L-LA was supplied by Wako Pure Chemical (Tokyo). Dextran-1 ($M_n = 1.7 \times 10^4$, $M_w/M_n = 1.8$), Dextran-2 ($M_n = 1.1 \times 10^4$, $M_w/M_n = 2.6$) and Dextran-3 ($M_n = 5.6 \times 10^3$, $M_w/M_n = 1.6$) were purchased from Sigma Chemical Co. (St Louis, MO). The molecular weight was estimated by SEC [column: Shodex KB-805, eluent: water, detector: refractive index (RI), standard: pullulan] using a Tosoh chromatocorer21. Hexamethyldisilazane, formamide, and anhydrous tetrahydrofuran (THF) were purchased from Wako Pure Chemical (Tokyo). *t*-BuOK was purchased from Kanto Chemical (Tokyo). PLLA ($M_n = 4.0 \times 10^4$, $M_w/M_n = 2.2$) and Poly-D, L-lactide (PDLLA) ($M_n = 3.6 \times 10^4$, $M_w/M_n = 1.7$) were purchased from Sigma Chemical Co. The molecular weight was estimated by SEC [column: TSK-GEL Multipore HXL-M × 2, eluent: THF, detector: RI, standard: polystyrene]. Dextran was dried at 60 °C under vacuum before use. PLLA and PDLLA were precipitated from chloroform/methanol before use. L-LA, hexamethyldisilazane, formamide, anhydrous THF, and other organic solvents were used without further purification.

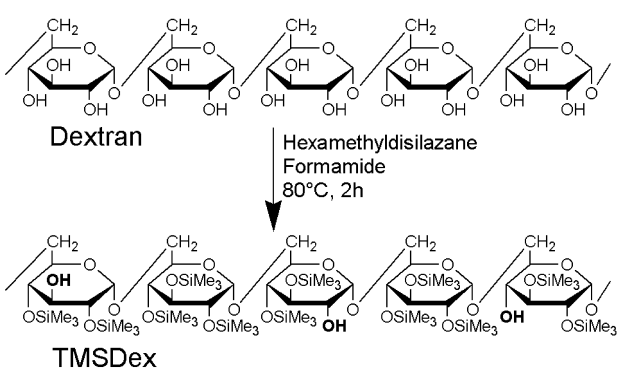
2.2. Preparation of trimethylsilyl polysaccharides

TMS-protected polysaccharides are commonly synthesized with chlorotrimethylsilane/pyridine. However, high-molecular-weight polysaccharides do not completely dissolve in pyridine. We synthesized high-molecular-weight polysaccharides with most of the hydroxyl groups protected by TMS using hexamethyldisilazane/formamide.

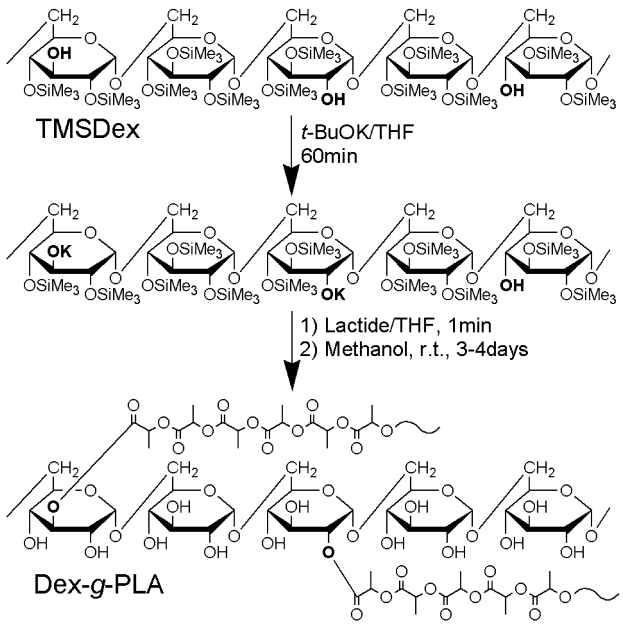
The TMS-protected dextrans were prepared according to Scheme 1. Dextran-1 (3.00 g, 18.5 mmol of glucopyranose unit) was dissolved in formamide (60 ml). Hexamethyldisilazane (60 ml, 288 mmol) was added dropwise to the reaction solution with vigorous stirring at 80 °C. After 2 h, the reaction mixture was separated into two phases. The upper layer was concentrated by evaporation. After precipitation with chloroform/methanol, the resulting solid was dried in vacuo to give mostly trimethylsilylated dextran (TMSDex-1). The introduction of TMS groups was confirmed by the methyl proton signal at $\delta = 0.1$ ppm and the broad methyne and methylene proton signals of dextran at $\delta = 3.5–5.5$ ppm in the ^{1}H NMR spectra (JEOL GSX-400) in $CDCl_3$. The molecular weight was estimated by SEC [column: TSK-GEL Multipore HXL-M × 2, eluent: THF, detector: RI, standard: polystyrene] using a Tosoh GPC-8020 series system to be $M_n = 3.9 \times 10^4$, $M_w/M_n = 1.5$. The degree of trimethylsilylation (DTMS) was estimated to be 81 mol%/hydroxyl group by ^{1}H NMR. Yield = 3.50 g (79%).

2.3. Preparation of graft-copolymer

Graft-polymerization of L-LA on trimethylsilylated dextrans was carried out according to Scheme 2. The procedure was conducted in a dry glove box under argon atmosphere. TMSDex-1 (0.50 mg) was dissolved in anhydrous THF. *t*-BuOK (35 mg, 0.31 mmol) was added to the solution. After stirring for 1 h, LA (4.49 g, 31 mmol) in THF (15 ml) was added. After 1 min, the polymerization was terminated by the addition of acetic acid. The product



Scheme 1. Synthetic route for trimethylsilylated dextrans (TMSDex).



Scheme 2. Synthetic route for PLA-grafted dextrans (Dex-*g*-PLA).

was precipitated with chloroform/methanol to give PLA-grafted TMSDex. Characterization of the TMS-protected graft-copolymer was performed by ^{1}H NMR.

^{1}H NMR ($CDCl_3$): $\delta = 0.10$ [s; $-Si(CH_3)_3$], 1.55 [d; $-CH(CH_3)-$], 3.5–5.5 (broad and very weak; dextran), 4.10 [q; $-CH(CH_3)OH$], 5.15 [q; $-CH(CH_3)O-CO-$].

The deprotection of TMS groups was performed by stirring into chloroform/methanol for 3–4 days to give Dex-*g*-PLA. Deprotection of the hydroxyl groups was confirmed by the disappearance of the methyl proton signal at $\delta = 0.10$ ppm in the ^{1}H NMR spectrum. The broad and weak methyne and methylene proton signals of dextran occurred at $\delta = 3.5$–5.5 ppm. The molecular weight of the copolymers, and the amount and molecular weight of the homo-PLA produced in the polymerization of LA, were estimated by SEC [column: TSK-GEL α-5000 × 2, eluent: DMF, detector: RI, standard: pullulan] using a Tosoh GPC-8020 series system.

^{1}H NMR ($CDCl_3$): $\delta = 1.55$ [d; $-CH(CH_3)-$], 3.5–5.5 (broad and very weak; dextran), 4.10 [q; $-CH(CH_3)OH$], 5.15 [q; $-CH(CH_3)O-CO-$].

2.4. Thermal analysis

Dex-*g*-PLA, PLLA and PDLLA were cast from chloroform solution (4 wt%) and dried overnight to give their films 0.15 mm thick, respectively. The blend films 0.15 mm thick were prepared from a 4:1 mixture of PLLA ($M_n = 4.0 \times 10^4$) and the graft-copolymers by the following procedure. PLLA and PDLLA ($M_n = 3.6 \times 10^4$) were used as reference polymers. T_g, melting temperatures (T_m), and enthalpy of fusion (ΔH) of the polymer films were measured by differential scanning calorimetry (DSC) (Rigaku TAS-200). The polymer films (4–6 mg) were heated at 10 °C/min. The temperature ranged between −50 and +200 °C. The polymer films were quenched with liquid nitrogen at −50 °C.

2.5. Dynamic mechanical thermal analysis

The dynamic mechanical properties of the films were determined with a non-resonance forced vibration viscoelastometer (UBM Rheogel-E4000) in air. Test bars were cut from the tensile bar specimens (dimensions $W \times H \times L = 5 \times 0.15 \times 25$, in mm). The frequency and amplitude of the vibration were adjusted to 10 Hz and ±5 μm. The polymer films were heated at 2 °C/min. The temperature ranged between −150 and +200 °C.

2.6. Tensile testing

Tensile testing was carried out on an Instron tensile testing machine (Shimadzu AGS-100A) with a crosshead speed of 30 mm/min. The initial length of the specimen was kept at 18 mm.

3. Results and discussion

3.1. Preparation of trimethylsilylated dextran

The majority of the hydroxyl groups of dextran were protected by TMS groups in order to achieve solubility in organic solvents and to control the number of reaction sites with the alkali metal initiator. Preparation of TMSDex was carried out by the procedure shown in Scheme 1.

Table 1 summarizes the results of TMS protections using hexamethyldisilazane/formamide. DTMS of the TMS-dextrans was determined by ^{1}H NMR. TMS protection of the dextrans could be carried out homogeneously despite their high molecular weights. DTMS of TMSDexs were 80–93 mol% per hydroxyl group (i.e. one free hydroxyl group exists per 1.7–4.8 glucopyranose residues). All of the TMSDexs were soluble in THF and chloroform, but not soluble in dimethylformamide, dimethylsulfoxide and water.

Table 1
Results of TMS protection of dextran

Polymer	Yield (%)	M_n[a] × 10^{-4} (M_w/M_n)[a]	DTMS[b] (%)
TMSDex-1[c]	79	3.1 (1.7)	81
TMSDex-2[d]	67	3.9 (1.4)	80
TMSDex-3[e]	51	1.1 (1.4)	93

[a] Determined by GPC.
[b] Degree of trimethylsilylation calculated from ^{1}H NMR.
[c] Prepared from dextran-1 with $M_n = 1.7 \times 10^4$ and $M_w/M_n = 1.8$.
[d] Prepared from dextran-2 with $M_n = 1.1 \times 10^4$ and $M_w/M_n = 2.6$.
[e] Prepared from dextran-3 with $M_n = 5.6 \times 10^3$ and $M_w/M_n = 1.6$.

Table 2
Characterization of Dex-*g*-PLA obtained through the graft-polymerization of lactide onto TMSDex-1 and deprotection of TMS groups

Polymer	Molar ratio of lactide to *t*-BuOK in feed	Dex-*g*-PLA				Homo-PLA	
		M_n[a] $\times 10^{-4}$ (M_w/M_n)[a]	Degree of Polymerization of lactide[b]	Number of graft chains[c]	Content of sugar unit (wt%)	M_n[a] $\times 10^{-4}$	Content of homo-PLA[a] (wt%)
G-55-12-(11)	100	11.0 (1.5)	55	12	16	1.7	11
G-27-30-(32)	50	13.3 (1.4)	27	30	13	1.4	32
G-60-22-(8)	100	20.5 (1.3)	60	22	8	1.4	8
G-91-2-(35)	150	34.7 (1.2)	91	25	5	2.5	35

Polymerization was carried out with *t*-BuOK in THF at room temperature. Initial concentration of lactide = 1.0 mol/l.
[a] Determined by SEC.
[b] Number average; calculated from ^{1}H NMR.
[c] Per molecule.

3.2. Preparation of PLA-grafted dextran

The preparation of Dex-*g*-PLA was carried out according to the procedure shown in Scheme 2. All of the graft-copolymers obtained were soluble in THF, chloroform, dimethylformamide, dimethylsulfoxide and other organic solvents, but not soluble in water.

Table 2 summarizes the reaction conditions and results of graft-polymerizations using TMSDex-1. The molar ratio of LA: *t*-BuOK in the feed was 50:1, 100:1 or 150:1. The degree of polymerization (DP) of LA for Dex-*g*-PLA was calculated using ^{1}H NMR spectroscopy based on the area ratio of the terminal methyne proton signal at $\delta = 4.10$ ppm to the internal methyne proton signal at $\delta = 5.15$ ppm. DP of LA could be controlled by the feeding ratio of LA to *t*-BuOK. DP of LA tended to increase with increasing LA to *t*-BuOK molar ratio. The amount of sugar unit (wt%) in the graft-copolymers was calculated by the following equation:

Content of sugar unit (wt%)

= (glucopyranose unit in g/PLA-grafted dextran in g)

× 100

= (M_n of dextran/M_n of PLA-grafted dextran) × 100

The content of sugar unit tended to decrease with increasing LA to dextran weight ratio. The number of graft chains in the graft-copolymer was calculated by the following equation:

Number of graft chains

= (M_n of PLA-grafted dextran − M_n of dextran)/

(molecular weight of LA (MW = 144)

× DP of LA)

As shown in Table 2, we could obtain Dex-*g*-PLA with various lengths and numbers of graft chains which contained some amounts of homo-PLA. We named graft-copolymers: G-(DP of LA)-(number of graft chains)-(content of homo-PLA).

3.3. Thermal properties of the copolymer films

Table 3 summarizes the results of the thermal analysis of the Dex-*g*-PLA, PLLA and PDLLA films cast from chloroform solution (4 wt%). The Dex-*g*-PLA films had lower T_g, T_m and crystallinity values compared to those of PLLA. T_m of Dex-*g*-PLA films tended to decrease with increasing sugar unit content in the graft-copolymer. These results suggested that the polysaccharide segments roughed the condition of non-crystalline region, and promoted the movement of copolymers. In graft-copolymers (G-27-30-(32), G-60-22-(8), G-91-25-(35)) having a similar number of graft chains, crystallinity tended to decrease with increasing DP of LA. In graft-copolymers (G-55-12-(11), G-60-22-(8)) having a similar DP of LA, the graft-copolymer (G-55-12-(11)) with the lowest number of the graft chain possessed the highest crystallinity. These results suggested that low crystallinity occurred at a high DP and/or a large number of the graft chains are entangled. The crystallinity of Dex-*g*-PLA could be controlled by adjusting the length or number of PLA chains.

3.4. Dynamic mechanical properties of the copolymer films

The storage modulus (E') and loss modulus (E'') of

Table 3
Thermal properties of Dex-*g*-PLA, PLLA and PDLLA films

Polymer	T_g[a] (°C)	T_m[a] (°C)	X_c[b] (%)
G-55-12-(11)	16	103	18.5
G-27-30-(32)	18	106	22.1
G-60-22-(8)	19	113	9.4
G-91-25-(35)	19	140	7.2
PLLA	55	176	44.3
PLLA	33	–	–

[a] Determined by DSC.
[b] Crystallinity estimated from ΔH values.

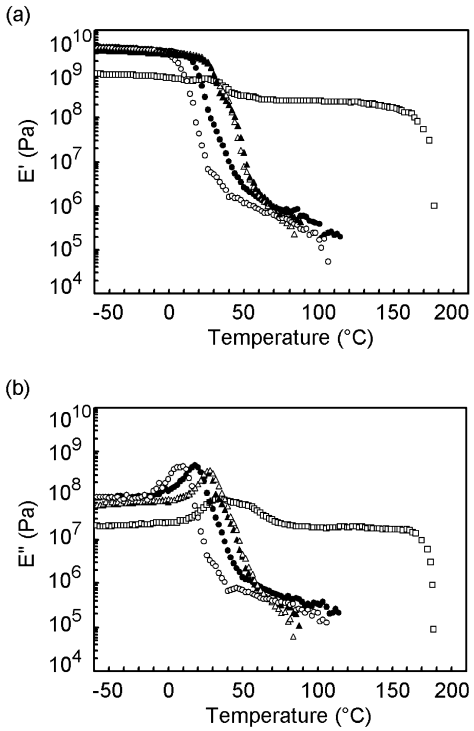


Fig. 1. (a) Storage modulus (E') for Dex-*g*-PLA films and PLLA film. (b) Loss modulus (E'') for Dex-*g*-PLA films and PLLA film. (○) G-55-12-(11); (●) G-27-30-(32); (△) G-60-22-(8); (▲) G-91-25-(35); (□) PLLA.

Dex-*g*-PLA films as a function of the temperature are shown in Fig. 1. Below T_g, both E' and E'' of Dex-*g*-PLA were higher than those of PLLA. The high E' was derived from the physical cross-linking among crystalline domains consisting of PLA segments by the branched Dex-*g*-PLA molecules, and also from the entanglement of graft chains in the non-crystalline regions. The high E'' is due to polysaccharide segments in non-crystalline domains acting as a plasticizer. Above T_g, both E' and E'' of Dex-*g*-PLA were lower than those of PLLA. This result was derived from the low crystallinity of Dex-*g*-PLA, and the introduction of polysaccharide segments and branched structures that act as plasticizers. E' results suggested that T_g of Dex-*g*-PLAs films tended to decrease with increasing sugar unit content of the graft-copolymer. The mechanical properties of Dex-*g*-PLA films at 37 °C could be adjusted by varying the molecular structure.

3.5. Thermal properties of the blend films

Table 4 summarizes the results of the thermal analysis of the blend films prepared from a 4:1 mixture (PLLA/Dex-*g*-PLA) of PLLA and Dex-*g*-PLA. The PLLA/Dex-*g*-PLA blend films showed lower T_g and crystallinity compared to PLLA. These results also suggested that the polysaccharide segments roughed the condition of non-crystalline region. On the other hand, because the blend films contained a high PLLA content, the drop in T_m did not occur. In the blend films of PLLA and Dex-*g*-PLA (G-27-30-(32), G-60-22-(8), G-91-25-(35)) having a similar number of graft chains, the crystallinity tended to decrease with increasing DP of LA. On the other hand, in the blend films of PLLA and Dex-*g*-PLA (G-55-12-(11), G-60-22-(8)) having a similar DP of LA, the influence of graft chain number on crystallinity was not evident because of the crystallinity formed by much blended PLLA. As described above, the Dex-*g*-PLA films did not give such thermal properties because of their low contents of homo-PLA (Table 3).

Table 4
Thermal properties of PLLA/Dex-*g*-PLA blend, PLLA and PDLLA films

Polymer	T_g [a] (°C)	T_m [a] (°C)	X_c [b] (%)
PLLA/G-55-12-(11)	17	175	28.8
PLLA/G-27-30-(32)	18	175	33.5
PLLA/G-60-22-(8)	18	176	29.0
PLLA/G-91-25-(35)	19	176	28.4
PLLA	55	176	44.3
PLLA	33	–	–

[a] Determined by DSC.
[b] Crystallinity estimated from ΔH values.

3.6. Dynamic mechanical properties of the blend films

E' and E'' of the blend films as a function of temperature are shown in Fig. 2. Below T_g, both E' and E'' of the blend films were higher than E' and E'' of PLLA. Such trends

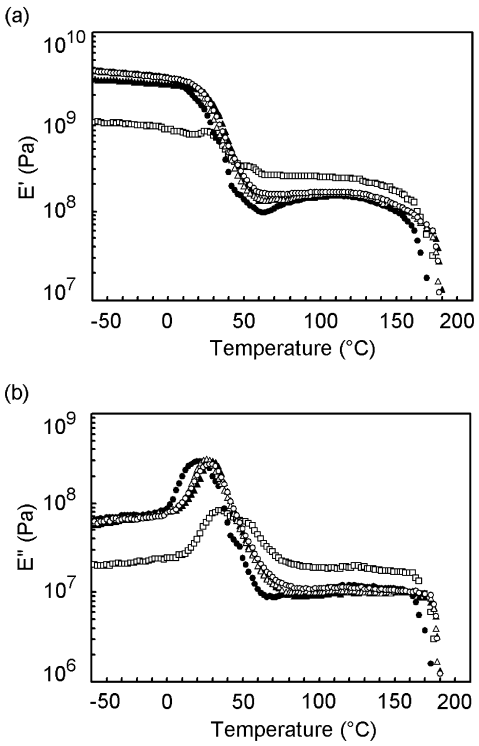


Fig. 2. (a) Storage modulus (E') for PLLA/Dex-*g*-PLA blend films and PLLA film. (b) Loss modulus (E'') for PLLA/Dex-*g*-PLA blend films and PLLA film. (○) PLLA/G-55-12-(11); (●) PLLA/G-27-30-(32); (△) PLLA/G-60-22-(8); (▲) PLLA/G-91-25-(35); (□) PLLA.

resulted from the increase of the entanglement of PLA graft chains in the non-crystalline region by branched structure of Dex-*g*-PLA. Above T_g, both E' and E'' of the blend films were lower than those of PLLA. Such trends resulted from the roughness by the polysaccharide segments in non-crystalline region. The mechanical properties of PLLA could be modified by adding Dex-*g*-PLA. However, the influence of molecular structure of Dex-*g*-PLA on the mechanical properties of the blend film could not be demonstrated by non-resonance forced vibration viscoelastometry.

3.7. Tensile properties of the blend films

Fig. 3 shows stress–strain curves for PLLA and the blend films. The blend films showed smaller stress and the greater strain than the PLLA film, due to the roughness in non-crystalline region by the action of polysaccharide segments as a plasticizer, and physical cross-linking among crystalline domains (consisting of PLLA and PLA segments) by branched Dex-*g*-PLA molecules. In the blend films of PLLA and Dex-*g*-PLA (G-27-30-(32), G-60-22-(8), G-91-25-(35)) having a similar number of graft chains, the maximum strain tended to decrease with increasing DP of LA. In the blend films of the PLLA and Dex-*g*-PLA (G-55-12-(11), G-60-22-(8)) having a similar DP of LA, those of PLLA and Dex-*g*-PLA (G-55-12-(11)) with the smallest number of graft chains showed the lowest maximum stress, due to the low-efficiency of physical cross-linking among the crystalline domains of Dex-*g*-PLA. Thus, the mechanical properties of PLLA could be modified by varying the Dex-*g*-PLA structure as a plasticizer.

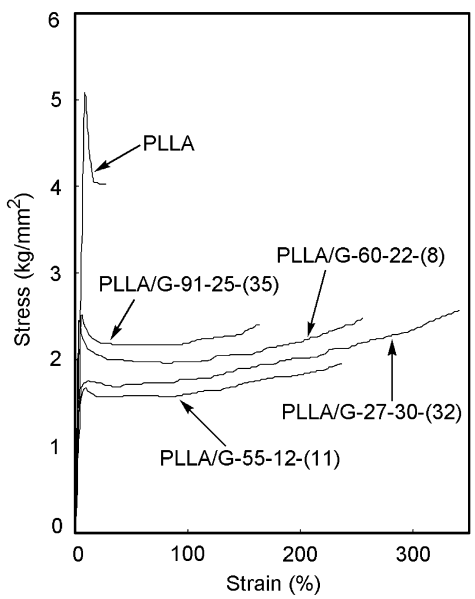


Fig. 3. Stress–strain curves for PLLA/Dex-*g*-PLA blend films and PLLA film.

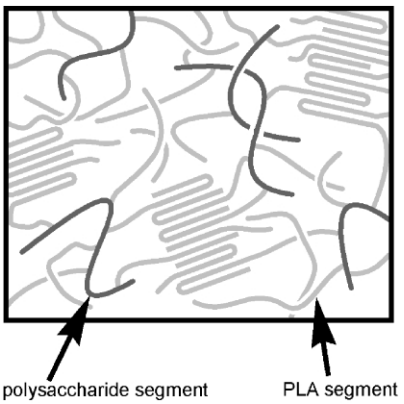


Fig. 4. Schematic representation of estimated molecular morphology of PLLA/PLA-grafted polysaccharide blend film.

4. Conclusions

We synthesized graft-copolymers having an amphiphilic structure composed of dextran backbone polymer and PLA graft chains through a new TMS protection technique. The resulting PLA-grafted polysaccharide films showed lower T_g, T_m, and crystallinity, and higher viscosity properties compared with PLLA, due to the introduction of polysaccharide segment and branched structures. We were able to control the thermal and mechanical properties by controlling the molecular architecture. Moreover, PLA-grafted polysaccharide could modify PLLA by the addition of small amounts of PLA-grafted polysaccharide. Fig. 4 is a schematic representation of the molecular morphology of the blend film prepared from PLLA and PLA-grafted polysaccharide. PLA-grafted polysaccharide makes physical cross-linking among crystalline domains by branched structure. The polysaccharide segment of PLA-grafted polysaccharide roughs the condition of non-crystalline region. Therefore, PLA-grafted polysaccharide was concluded to act as an effective modifier for high crystalline PLLA. So, the blend film of PLLA and PLA-grafted polysaccharide is expected to be utilized as a novel biomedical material possessing pliant structure.

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