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Shape-memory and biocompatibility properties of segmented polyurethanes based on poly(*L*-lactide)

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Abstract A series of segmented poly(*L*-lactide)-polyurethanes (PLA-PU) were synthesized by a two-step method, with oligo-poly(*L*-lactide) (PLA) as the soft segments and the reaction product of 2,4-toluene diisocyanate (TDI) and ethylene glycol (EG) as the hard segments. The shape-memory properties and biocompatibility of PLA-PU were examined. The 50% compressed PLA-PU could recover almost 100% to their original shape within 10°C from the lowest recovery temperature (22°C–37°C). In the recovery process the PLA-PU showed a maximum contracting stress in the range of 1.5–4 MPa. Cell incubation experiments show that PLA-PU has biocompatibility comparable to that of pure PLA. Therefore, this kind of polyurethane can be used for implanted medical devices with shape memory requirements.

Keywords polyurethane, poly(*L*-lactide), shape memory, biocompatibility

1 Introduction

In the 1980s, shape-memory polyurethanes were first developed in Japan. During the last decade, new types of shape-memory materials were explored, and they found wide industrial applications [1–3]. Li et al. [4] introduced crystalline poly(ϵ -caprolactone) (PCL) into segmented polyurethanes. Yu et al. [5] developed shape-memory polyurethane with a recovery temperature (RT) near room temperature. Lendlein and Langer [6] indicated that biodegradable segmented polyester polyurethane materials

with shape memory properties had potential biomedical applications. Based on the investigation of *L*-lactide and its ring-opening polymerization [7,8], poly(*L*-lactide) (PLA)-based polyurethanes were synthesized, and their shape-memory behaviors were examined [9].

In this paper, a series of segmented poly(*L*-lactide)-polyurethanes were designed and synthesized, and their shape-memory behaviors were examined in detail, special attention was paid to the influence of processing temperature. The biocompatibility of this kind polyurethane was also investigated.

2 Experimental

2.1 Materials and measurements

L-Lactide (LA) was prepared in our own laboratory and recrystallized from ethyl acetate for three times before use. Ethylene glycol (EG), 1,4-butanediol (BDO) and 2,4-toluene diisocyanate (TDI) were distilled over freshly powdered calcium hydride under reduced pressure. Toluene and ethyl acetate were refluxed over CaCl₂ and distilled before use. Other reagents were commercially available from Beijing Chemical Co. and used as received.

The ¹H nuclear magnetic resonance (¹H NMR) spectra of samples were recorded on a Bruker AV 300M in CDCl₃ at 25°C. Chemical shifts were given in parts per million from tetramethylsilane. The gel permeation chromatography (GPC) measurements were conducted with a Waters 410 GPC with THF as eluent (flow rate: 1.0 mL/min). The molecular weights were calibrated with polystyrene standards. The dynamic mechanical analysis (DMA) was performed on a Netzsch DMA-242C. The tensile tests were carried out on an Instron 1121. The thermal mechanical analysis (TMA) was conducted on a Perkin-Elmer DSC-7.

2.2 Preparation of poly(*L*-lactide) polyurethane (PLA-PU)

A series of segmented poly(*L*-lactide)-polyurethanes (PLA-PU) with various HO-PLA-OH to TDI-EG ratios

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were synthesized in two steps. First, HO-PLA-OH was prepared by ring-opening polymerization of LA under the catalysis of SnOct₂ and in the presence of initiator BDO [10]. Then, PLA-PU were synthesized by end-capping the HO-PLA-OH with TDI, followed by chain extension with EG [9].

2.3 Shape-memory properties

The shape-memory properties of PLA-PU were examined by related mechanical measurements, such as TMA and tensile test according to Ref. [11].

2.4 Cell experiment

ECB-304 cells were chosen for investigating the biocompatibility of PLA-PU. ECB-304 cells were first cultured according to the literature [12]. PLA3000-PU132 was purified by dissolving in CHCl₃ and precipitating in ethanol and then dialysis against CHCl₃. The purified polymer was dissolved in CHCl₃, and the solution was cast onto glass slides. The solvent was removed under vacuum for 48 h. The glass slides were placed in the culture wells (ECB304 cells seeded at a cell density of 1×10^5 cells/well) with Dulbecco's modified Eagle's medium (the MEM culture medium supplemented with 10% heat-inactivated fetal bovine serum, 100 U/mL penicillin, and 100 mg/L streptomycin). After 1, 2, 4, 6, 12 and 24 h of incubation, cells on the glass slides were washed with a phosphate buffered solution, stained with Giemsa and observed by an inverted fluorescence microscope (TE2000-U, Nikon).

3 Results and discussion

With the ring-opening polymerization of LA, five poly(L-lactide) diols (HO-PLA-OH) in the molecular weight range of 1,500 to 9,500 (determined by ¹H NMR) were synthesized by changing the molar ratio of LA to BDO. A series of PLA-PU samples with ratios of $n(\text{PLA}) : n(\text{TDI}) : n(\text{EG})$ from

1 : 2 : 1 to 1 : 7 : 6 were obtained by controlling the molar ratio of PLA to TDI and EG. The molar number of NCO was equal to that of HO in the reaction system to ensure as high molecular weight of PLA-PU as possible. The molecular weight of PLA-PU determined by GPC was in the range of 6×10^4 – 10×10^4 g/mol and the molecular weight distribution was about 1.7 for all polymers. The basic data are summarized in Table 1.

3.1 Deformation-recovery procedure and mechanism for the shape recovery

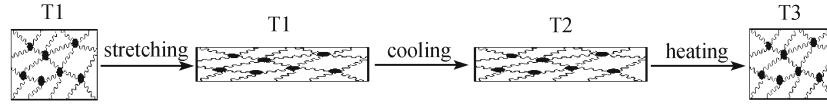
The shape-memory properties of segmented polyurethanes are determined by both their special microphase structure and the processing procedure. It is well known that there co-exist always a hard phase and a soft phase in segmented polyurethanes. The hard phase determines the permanent shape and thus is also termed as fixing phase. The soft phase is responsible for the reversible solidification and softening of the material at appropriate temperatures, and therefore, it is also termed as reversible phase. In the case of PLA-PU, the soft phase is made of PLA segments and the hard phase is composed of TDI-EG segments. In the literature, the shape memory is usually demonstrated by heating a specimen to a higher temperature, deforming the specimen at this temperature and then fixing the deformation at a lower temperature, and finally heating the deformed specimen to a higher temperature to recover its original shape.

The glass transition temperature (T_g) of PLA-PU is the critical temperature for its temporary deformation and shape recovery. The deformation-recovery procedure of PLA-PU based on its T_g is shown in Scheme 1, taking tensile deformation as an example. First, the specimen was heated to T_1 ($T_1 \geq T_g$) and then stretched at a specified ratio; with its length fixed, the specimen was cooled quickly to T_2 ($T_2 < T_g$). Because the movement of the PLA segments was frozen, the temporary shape of the specimen was fixed. When the deformed specimen was heated to T_3 ($T_3 \geq T_g$), its original shape was recovered.

Table 1 PLA-PU samples and their shape memory properties

Samples ^{a)}	M_n of PLA diol	Molar ratio PLA/TDI/EG	Mass fraction of hard segment (%)	T_g ^{b)} (°C)	Tensile Strength at 100% strain (MPa)	Maximum Contracting Force (MCF) (MPa)	Lowest Recovery Temperature (LRT) (°C)
PLA ^{c)}	–	–	0	60.0	0.56	–	–
PLA1500-PU132	1,530	1 : 3 : 2	29.7	51.7	3.17	2.30	36.8
PLA3000-PU121	3,180	1 : 2 : 1	11.4	53.5	2.95	1.50	31.6
PLA3000-PU132	3,180	1 : 3 : 2	16.9	41.7	3.54	2.62	29.5
PLA3000-PU154	3,180	1 : 5 : 4	26.0	38.9	4.32	3.34	28.0
PLA4500-PU154	4,760	1 : 5 : 4	19.0	33.0	3.82	2.81	22.0
PLA6500-PU132	6,500	1 : 3 : 2	9.0	33.8	2.34	3.60	24.1
PLA6500-PU154	6,500	1 : 5 : 4	14.7	32.5	–	–	24.8
PLA6500-PU176	6,500	1 : 7 : 6	19.7	37.0	3.71	3.45	25.5
PLA9500-PU132	9,600	1 : 3 : 2	6.3	31.5	2.23	3.26	23.8
PLA9500-PU154	9,600	1 : 5 : 4	10.4	32.8	–	–	23.4
PLA9500-PU176	9,600	1 : 7 : 6	14.2	33.5	3.19	3.64	22.1

^{a)} Numbers after PLA stand for the molecular weights of PLA diols, those after PU stand for the molar ratio $n(\text{PLA}) : n(\text{TDI}) : n(\text{EG})$, e.g. $n(\text{PLA}) : n(\text{TDI}) : n(\text{EG}) = 1 : 3 : 2$; ^{b)} T_g was measured by DMA; ^{c)} Mw is ca. 1×10^5 g/mol, synthesized in our lab.



Scheme 1 Schematic representation of the programming and recovering process for PLA-PU

3.2 Shape-memory properties

3.2.1 Deformation recovery force

During a deformation-recovery procedure, the inner stress frozen in the stretched specimen during pre-deformation and fixation began to release as a contracting force when the specimen temperature is raised to a certain temperature. It is the driving force for shape recovery and determines the shape-memory properties of the material. Figure 1 shows the typical contracting force-temperature curves for PLA-PU and PLA, which are measured at fixed specimen length. Under this condition the contracting force increases with temperature, passes through a maximum and finally decreases. The increase in contracting force indicates the tendency of shape recovery (contraction); its decrease is because of the stress relaxation; and the peak is formed due to the balance between the inner-stress release and the stress relaxation. The maximum contracting force (MCF) determined by this way may be considered as a measure of the shape-recovery ability in the deformed specimen. As shown in Fig. 1, both PLA and PLA-PU display an MCF over 3 MPa, much higher than that of PCL-PU [11] which is determined under comparable conditions, indicating a better shape-memory behavior under a small deformation and more rapid response to the thermal stimuli. Compared with the contracting force versus temperature curve of PLA, that of PLA-PU showed three features: (1) it began to rise at a lower temperature, implying a lower recovery temperature; (2) its rising speed was comparable to that of PLA, indicative of a rapid shape-recovery of the both; (3) beyond the maximum, it decreased much slower and this was helpful to complete shape-recovery. These differences are attributed to the physical crosslinking in PLA-PU (Fig. 1). As shown in Table 1, the MCF is dependent mainly on the M_n of PLA segments. When the M_n of PLA is lower than 6,500, the MCF is between 1.5–3.4 MPa, approximately in the same order as the tensile strengths at 100% strain. When it is higher than 6,500, the MCF is about 3.5 MPa and does not have any relationship with the tensile strengths at 100% strain. It is noticed that the measured MCFs were always fewer than the corresponding tensile strengths at 100% strain. Taking the pre-stretching of 200% into consideration, it can be concluded that a high fraction of the frozen inner stress had been relaxed by the MCF peak was reached.

3.2.2 Shape-recovery ratio and recovery temperature range

The shape-memory behavior was studied via TMA, where the specimen thickness was measured as a function of

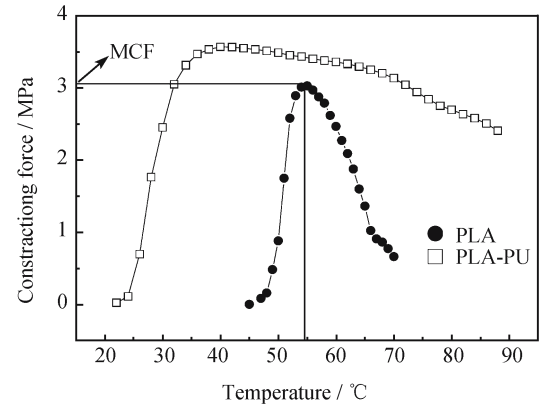


Fig. 1 Contracting force curves of PLA and PLA6500-PU132

temperature for a pre-compressed specimen. As shown in Fig. 2, it could give the lowest recovery temperature (LRT) and complete recovery temperature (CRT). As shown in Table 1, the PLA-PU with different molecular weights of PLA and TDI-EG chain lengths have a LRT in the range of 22°C–36°C. This is determined by the T_g but lower than the T_g of the samples. All the samples could recover almost 100% to their original shape within 10°C from LRT. Therefore, it is possible to realize shape-recovery at the body temperature for medical devices made of PLA-PU.

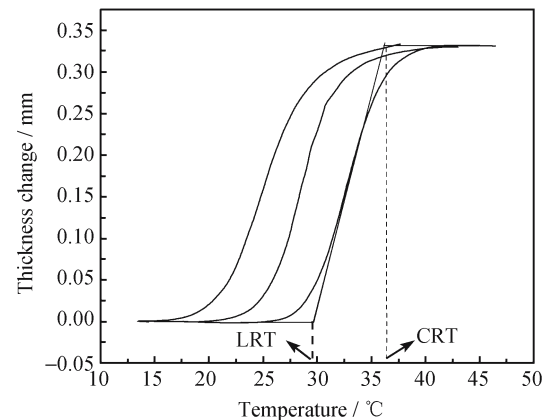


Fig. 2 Shape recovery curves
(a) PLA9500-PU176; (b) PLA4500-PU154; and (c) PLA3000-PU132

3.2.3 Influence of processing condition on the shape-recovery properties of PLA-PU

It was found that the deforming temperature (DT) and fixing temperature (FT) had an influence on the contracting force

and recovery temperature. Taking PLA4500-PU154 as an example (Table 2), the MCF varied between 1.9–4.2 MPa with different DT and FT. It seemed that DT had a more significant effect on MCF than FT. When DT decreased from 40°C to 30°C, and FT maintained at 20°C, the MCF increased from 1.92 to 3.94 MPa. Lower DT leads to higher MCF. This is because lower DT may result in increased deforming force, and the contracting force increases correspondingly. On the other hand, lowering FT may result in effectively freezing the movement of PLA segments to obtain higher MCF. It is believed that the lower DT and FT are both favorable to higher MCF and better shape-recovery behavior.

Table 2 MCF and LRT of PLA4500-PU154 ($T_g = 33^\circ\text{C}$) programmed with different deforming and fixing temperatures

Program codes ^{a)}	Deforming temperature ($^\circ\text{C}$)	Fixing temperature ($^\circ\text{C}$)	MCF ^{b)} (MPa)	LRT ^{b)} ($^\circ\text{C}$)	CRT ^{b)} ($^\circ\text{C}$)
S ₄₀ -C ₂₀	40	20	1.92	25	35
S ₃₅ -C ₂₀	35	20	2.81	25	32
S ₃₀ -C ₂₀	30	20	3.94	25	30
S ₃₅ -C ₁₅	35	15	3.33	22	32
S ₃₅ -C ₁₀	35	10	3.84	22	32
S ₃₅ -C ₅	35	5	4.20	22	32

Note: ^{a)} S40-C20 stands for “deformed at 40°C and fixed at 20°C”, others have the similar meanings; ^{b)} MCF, LRT and CRT are “maximum contracting force”, “lowest recovery temperature” and “complete recovery temperature”, respectively.

The DT and FT also have a significant influence on LRT and CRT (Fig. 3 and Table 2). As shown in Fig. 3(a), when DT decreased from 40°C to 30°C, and FT maintained at 20°C, the LRT is almost the same; but the CRT decreased from 35°C to 30°C. The recovery temperature range decreased from 10°C to 5°C. It can be seen from Fig. 3(b) that when the DT is fixed at 35°C and the FT decreases from 20°C to 5°C, the CRTs of the four samples are 32°C, and the LRTs of all

samples are 22°C with an exception of the one cooled at 20°C. Therefore, when the FT is low enough, it does not have an obvious influence on LRT.

Based on these results, it can be said that the DT determines the CRT, and the FT determines the LRT of the materials. This is mainly because the T_g , which determines the temporary shape fixing and the lowest shape recovery, is over a broad temperature range. Within this temperature range, the processing temperature has more influences on the LRT and CRT, but it has no obvious influence beyond this temperature range.

3.3 Biocompatibility of PLA-PU

The biocompatibility of PLA-PU was evaluated by culturing ECB 304 cells. The cover slides coated with PLA and PLA-PU films were placed in each well of the tissue culture plates with ECB304 cells to observe cell adhesion and spreading after different incubating time. As shown in Fig. 4, after incubation for 1 h the cells began to adhere onto the cover slides coated with PLA. Two hours later, the number of adhered cells increased and a few cells began to change their shape from spherical to oval. The shape of cells continued to change after 6 h. Pseudopodia from the cells could be observed clearly after 12 h of incubation. The cell adhesion and growth on the PLA-PU films were similar to those on the PLA films (Fig. 5). Therefore, PLA-PUs have biocompatibility comparable to that of the pure PLA.

4 Conclusions

A series of segmented polyurethanes with PLA as the soft segments and TDI-EG as the hard segments were prepared. The Mn of PLA segment was 1,500–9,500, and PLA-PU samples with molar ratios of $n(\text{PLA}) : n(\text{TDI}) : n(\text{EG})$ from

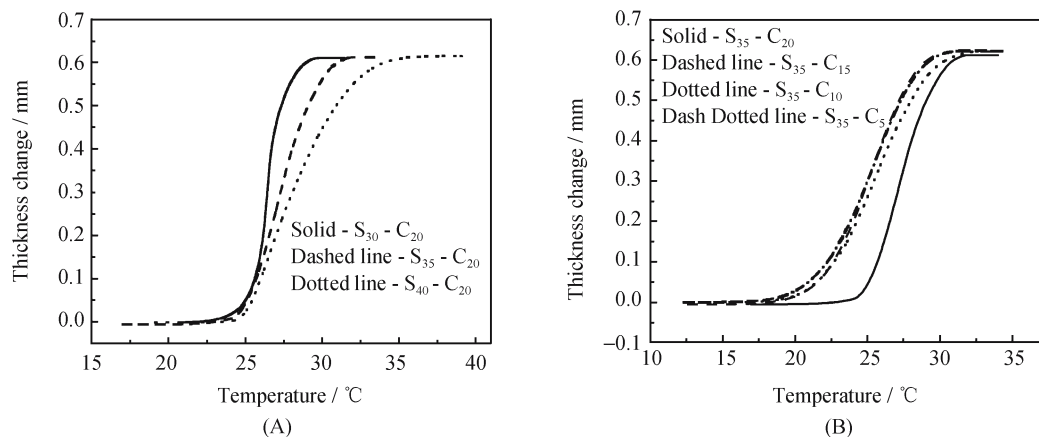


Fig. 3 Shape recovery curves of PLA4500-PU154

(A) Deforming at different temperatures and fixing at 20°C, 1—S₃₀-C₂₀, 2—S₃₅-C₂₀, 3—S₄₀-C₂₀; (B) deforming at 35°C and fixing at different temperatures, 1—S₃₅-C₂₀, 2—S₃₅-C₁₅, 3—S₃₅-C₁₀, 4—S₃₅-C₅

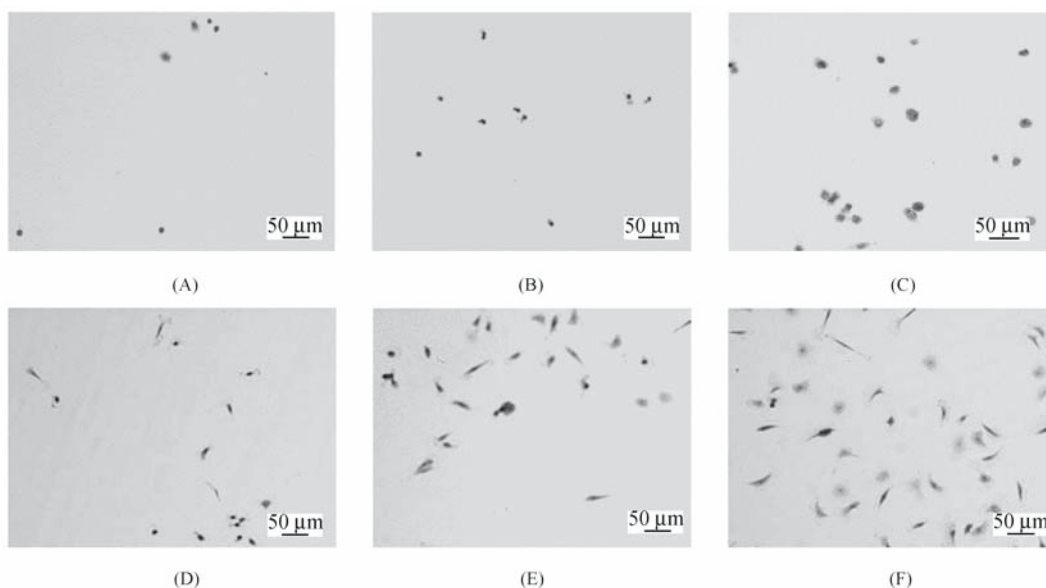


Fig. 4 Photographs of the dyed vein endothelium cells (ECB304) incubated for (A) 1 h; (B) 2 h; (C) 4 h; (D) 6 h; (E) 12 h and (F) 24 h on the PLA film cast on a glass substrate

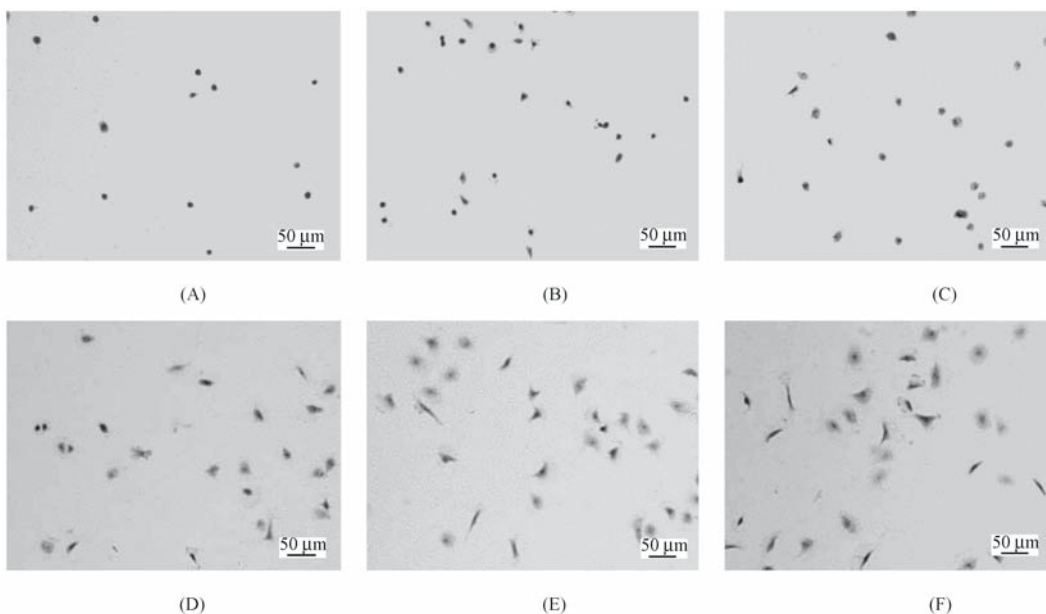


Fig. 5 Photographs of the dyed vein endothelium cells (ECB304) incubated for (A) 1 h; (B) 2 h; (C) 4 h; (D) 6 h; (E) 12 h and (F) 24 h on the PLA-PU film cast on a glass substrate

1 : 2 : 1 to 1 : 7 : 6 were obtained by controlling the molar ratio of PLA to TDI and EG. The deformation-recovery procedure and mechanism for the shape recovery were discussed. The shape memory properties such as shape-recovery ratio and recovery temperature range and the influence of processing conditions on the shape-recovery properties of PLA-PU were investigated. Cell incubation experiments showed that PLA-PU has biocompatibility comparable to that of pure PLA, fulfilling the essential requirements of medical applications.

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