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Biodegradable shape-memory block co-polymers for fast self-expandable stents

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ABSTRACT

Block co-polymers PCTBVs (M_n of 36,300–65,300 g/mol, T_m of 39–40 and 142 °C) containing hyperbranched three-arm poly(ε-caprolactone) (PCL) as switching segment and microbial polyester PHBV as crystallizable hard segment were designed as biodegradable shape-memory polymer (SMP) for fast self-expandable stent and synthesized in 96% yield by the reaction of three-arm PCL-triol (M_n of 4200 g/mol, T_m of 47 °C) with methylene diphenyl 4,4′-diisocyanate isocynate (MDI) to form the hyperbrached MDI-linked PCL (PTCM; M_n of 25,400 g/mol and a T_m of 38 °C), followed by further polymerization with PHBV-diol (M_n of 2200 g/mol, T_m of 137 and 148 °C). The polymers were characterized by ^{1}H NMR, GPC, DSC, tensile test, and cyclic thermomechanical tensile test. PCTBVs showed desired thermal properties, mechanical properties, and ductile nature. PCTBV containing 25 wt% PHBV (PCTBV-25) demonstrated excellent shape-memory property at 40 °C, with R_f of 94%, R_r of 98%, and shape recovery within 25s. PCTBV-25 was also shown as a safe material with good biocompatibility by cytotoxicity tests and cell growth experiments. The stent made from PCTBV-25 film showed nearly complete self-expansion at 37 °C within only 25 s, which is much better and faster than the best known self-expandable stents.
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1. Introduction

Thermally-induced shape-memory polymers (SMPs) are materials able to change shapes when responsive to temperature change [1,2]. They have attracted much attention in biomedical application such as implantations [3,4]. The use of biodegradable SMPs as implants combines multi-functions, such as shape-memory effect at body temperature to actuate the shape change after insertion into the human body for minimally invasive surgery, and biodegradability to avoid a second surgery for implant removal [5]. Some SMPs have been made as sutures [6] and wound healing materials [7,8]. In principle, SMPs could also be useful for another highly desirable application, the biodegradable stent with self-expandability. However, no such example has been reported. Currently, the known biodegradable stents are the Igaki-Tamai (PLLA) [9], PLLA/PLGA [10], and chitosan stents [11,12]. Although the last two could achieve self-expansion at 37 °C which is higher than the T_g of the polymer, the fastest expansion time obtained so far is 2.5 min [9–14]. As a very important parameter, the self-expansion time of stents should be ideally less than a minute [10], since a fast self-expansion benefits the *in vivo* deployment and prevent migration after insertion. The slow expansion of PLLA/PLGA and chitosan stents is caused by T_g-based expansion which possesses a board change range. A T_m-based polymeric system could provide a fast and sharp temperature change. Therefore, we focus on the development of T_m-dependent biodegradable SMP as self-expandable stent to achieve a fast and complete self-expansion.

So far, the T_m-dependent SMPs [15] are often linear block co-polymers consisting of two segments: the switching one for the fixation of temporary shape and the hard one for the fixation of the permanent shape [16,17]. As for hard segment, *non*-crystallizable polyurethane (PU) is often used [18–22], but with difficulties in traditional thermal processing and in adjusting the mechanical property for desired applications. Crystallizable polymer block could be a better choice, with crystallizable poly(*p*-dioxanone) as a good hard segment in the preparation of a biodegradable SMP as suture [6]. Regarding to the application of SMP as stent, we are particularly interested in developing crystallizable microbial polyester poly[(*R*)-3-hydroxybutyrate-*co*-(*R*)-3-hydroxyvalerate] (PHBV) as the hard segment, due to its high Young's modules for easy adjusting the mechanical properties, a T_m about 140 °C [23] for better stabilization of permanent shape, good biodegradability, good biocompatibility, and its known application as scaffolds [24,25]. On the other hand, the switching segment for SMP as stent is required to control the switching temperature (T_s) at body temperature [16] and maintain the flexibility of SMP since inflexibility of stents may result in abrupt closure [26]. Under this

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consideration, biodegradable and non-cytotoxic poly(ε-caprolactone) (PCL) [27] is the most suitable switching segment, because it was shown to improve the chain flexibility in its copolymer [28] and three-arm PCL was recently developed by us as switching segment for a star SMP to achieve a T_s of 38 °C and high R_f of 92% [29]. Therefore, block co-polymers containing PHBV hard segment and PCL-based switching segment are designed as SMP for the application as fast self-expendable stent. The incorporation of two biodegradable segments PCL [30] and PHBV [25] should also give rise to good biodegradability of the resulting SMP.

In this paper, we report the synthesis and characterization of a series of novel SMPs containing three-arm PCL-based switching segment and PHBV hard segment. The first example of using SMP as self-expandable stent is also demonstrated. In addition, the SMP containing three-arm PCL-based switching segment is compared with the SMP containing linear PCL-based switching segment, regarding to the shape-memory properties and the applications as stent.

2. Materials and methods

2.1. Materials

All solvents and reagents were purchased from Aldrich, and Novozym 435 (immobilized *Candida Antarctica* lipase B, 10000PLU/g) (CALB) was brought from Novozymes. Poly[(*R*)-3-hydroxybutyrate-*co*-(*R*)-3-hydroxyvalerate] (PHBV) with 19% PHV was produced by microorganism. ε-Caprolactone (99%), *N*,*N*-dimethylformamide (DMF, 99%), 1,4-dioxane (99.8%) and ethylene glycol (99.5%) were dried with CaH_2 or anhydrous sodium sulfate for 24 h and freshly distillated before use. Glycerol (>99%) was dried by azeotropic distillation in toluene before use. Methylene diphenyl 4,4′-diisocyanate isocynate (MDI) and Novozym 435 were dried in vacuum oven for 12 h at 40 °C.

2.2. Preparation of PHBV-diol

In a modified version of a known procedure [31,32], a mixture of dry PHBV (10 g), distillated ethylene glycol (15 mL), dry diglyme (40 mL), and dibutyltin dilaurate (0.3 g) were stirred at 130 °C for 4 h under N_2. After the reaction, the mixture was poured into water, and the precipitate was collected by filtration. The crude product was dissolved in chloroform (10 mL) and precipitated by adding methanol (50 mL). The product was collected by filtration and dried in vacuum oven at 40 °C for 24 h. 7.8 g of PHBV-diol was prepared. The product was characterized by ^{1}H MNR and DSC, with a M_n of 2200 g/mol (NMR) and a T_m of 137/148 °C (DSC).

2.3. Preparation of three-arm PCL-Triols

PCL-triol was synthesized according to the known procedure [29] by enzyme-catalyzed ring-opening polymerization of ε-caprolactone with glycerol. The product was characterized by ^{1}H MNR and DSC, with a M_n of 4200 g/mol (NMR) and a Tm of 47 °C and a X_c of 67% (DSC).

2.4. Synthesis of three-arm PCL-based hyperbranched poly(esterurethane)(PCTM) as switching segment of SMP

A mixture of PCL-triol (2.00 g) and MDI (0.27 g) in dry DMF (10 mL) was stirred at 75 °C for 8 h under N_2. After cooling to room temperature, methanol was added. The product was filtrated, dried, and characterized by ^{1}H NMR and DSC. The product PCTM has a M_n of 25,400 g/mol (NMR), a T_m of 38 °C (DSC), and a X_c of 29% (DSC).

2.5. Synthesis of poly(esterurethane)s containing hyperbranched three-arm PCL block and PHBV block (PCTBV)s

In step 1, a mixture of PCL-triol (2.00 g) and MDI (0.27 g) in dry DMF (10 mL) was stirred at 75 °C for 8 h under N_2. In step 2, a solution of PHBV-diol (0.73 g) in dry DMF (5 mL) were added to the reaction mixture of step 1 followed by stirring at 90 °C for 44 h. Afterwards, the reaction solution was poured into methanol (45 mL), and the mixtures were stirred for 1 h at room temperature. The product was then precipitated, collected by filtration, washed three times with dioxane/methanol, and dried under vacuum for 24 h to give 2.87 g PCTBV with 96% yield. The polymer showed a M_n of 47,200 g/mol analyzed by GPC with DMF as solvent and polystyrene as standards and T_m of 40 °C and 142 °C for switching and hard segment, respectively, analyzed by DSC.

2.6. Gel permeation chromatography (GPC)

The molecular weight (M_n and polydispersity index M_w/M_n) of polymers was analyzed by GPC using a Waters instrument consisting of Waters 510 pump, Waters 410 refractive index detector, and Waters HR4E, HR5E and HR6 columns placed in series. THF was used as the eluent at a flow rate of 1.0 mL/min at 30 °C for analyzing PCL-triol and PHBV-diol. DMF containing 0.05 M LiBr was used as the eluent at a flow rate of 1.0 mL/min at 55 °C for the analysis of other polymers. Sample concentration was about 0.1% (w/v) and the injection volume was 100 μL. Polystyrene standards with M_n of 370, 2970, 13,900, 30,200, 197,000 and 696,000 g/mol were used to generate a calibration curve.

2.7. Nuclear magnetic resonance (NMR)

^{1}H NMR (500 MHz) spectrum was recorded with a Bruker AMX500 NMR instrument in DMSO-d_6 at 333 K. Chemical shifts were referred to TMS at 0 ppm.

2.8. Differential scanning calorimetry (DSC)

The thermal properties of polymers were measured on a Mettler Toledo DSC 822 system. Nitrogen was used as purge gas with a flow rate of 20 mL/min. Samples were heated from −20 °C to 180 °C with a heating rate of 20 °C/min, cooled down to −100 °C with a cooling rate of −20 °C/min, and then heated again to 180 °C at the same heating rate. T_m was determined from the second heating curves, and X_c (PCL part) were calculated by comparing the heat of fusion to the standard value of PCL.

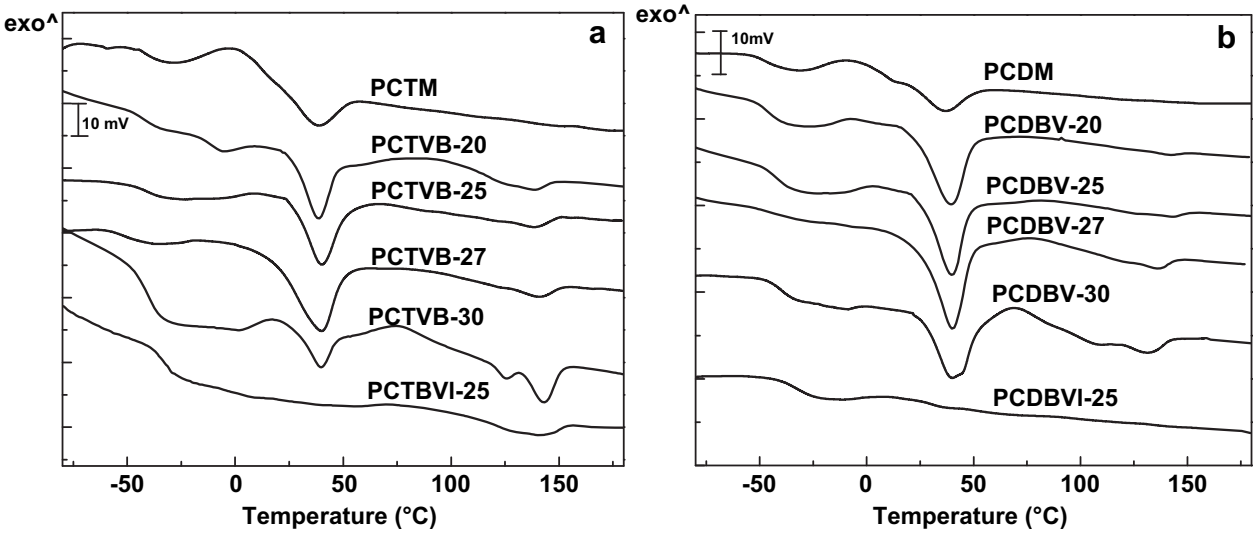

Fig. 1. DSC curves of (a) PCTBVs and (b) PCDBVs.

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