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Key aspects to yield low dispersity of PEO-*b*-PCL diblock copolymers and their mesoscale self-assembly

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ABSTRACT

Poly(ethylene oxide)-*block*-polycaprolactone (PEO-*b*-PCL) is one of the widely used biocompatible amphiphilic block copolymers which is able to self-assemble into a variety of 3D structures, including polymersomes. Controlled self-assembly into a 3D structure with a certain size and morphology might require uniform PEO-*b*-PCL ($Đ_M < 1.1$), which has not been possible to synthesize so far. In this work, we optimized the well-known synthesis of PEO-*b*-PCL, catalyzed by $SnOct_2$, leading to a low molecular-weight dispersity (< 1.1), and discussed the aging effects of $SnOct_2$ on the overall kinetics of the synthesis. To understand the effect of the dispersity of PEO-*b*-PCL on its self-assembly, we compared self-assembled structures formed by uniform PEO-*b*-PCL ($Đ_M < 1.1$) with the ones formed by non-uniform analogues ($Đ_M > 1.1$). Furthermore, we demonstrated the benefits of uniform PEO-*b*-PCL when a high degree of end-group activation is required through ω-tosylation.

1. Introduction

Micelles and vesicles are a few examples from the large variety of 3D structures which can be formed by molecular self-assembly. Among them, vesicles are of special interest due to the protected hydrophilic core where encapsulated drugs or enzymes are shielded from the external media [1–3]. For this purpose, vesicles are typically formed from natural lipids or amphiphilic synthetic block copolymers. Vesicles based on block copolymers, or polymersomes, exhibit higher mechanical stability and more advanced functionalization capability, and thus are increasingly more preferred to lipid-based vesicles [4–8]. The type of 3D structure strongly depends on the nature of the composing blocks and the hydrophilic weight fraction [9]. A prominent example of a biocompatible block copolymer forming polymersomes is poly(ethylene oxide)-*block*-polycaprolactone (PEO-*b*-PCL), where PEO is a hydrophilic, biocompatible, protein repellent polyether which prolongs blood circulation time of self-assembled structures [10], and PCL a hydrophobic, biodegradable polyester often used in drug delivery systems [11–14]. PEO-*b*-PCL self-assembles into a variety of meso- and nanoscale structures depending on the hydrophilic weight fraction, block lengths, and the method of preparation [15–19]. In general, an increase of a copolymer molecular-weight dispersity leads to the formation of a mixture of different self-assembled structures [20–23] and broadening of the size distribution of the corresponding aggregates [23,24]. Consequently, the self-assembly of distinct and uniform 3D structures might require PEO-*b*-PCL with a certain block length and rather narrow molecular-weight dispersity. For example, PEO (2K)-*b*-PCL(9.5K) with a dispersity of 1.14 forms predominantly mesoscale polymersomes [16], whereas the comparable copolymer PEO(2K)-*b*-PCL(9K) with a higher dispersity of 1.42 forms mostly mesoscale worms [17] by film rehydration.

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The synthesis of PEO-*b*-PCL diblock copolymers is usually performed using PEO as a macroinitiator for the polymerization of ε-caprolactone (ε-CL) with either tin(II) 2-ethylhexanoate ($SnOct_2$) as a catalyst [15–17,25–28] or triethylaluminium as a precursor [29,30]. ε-CL polymerization performed with triethylaluminium requires an excess of the precursor (~ 1.1 eq. with respect to PEO). For biomedical and food applications the residual aluminum has to be removed [31], which is usually done by quenching the polymerization with hydrochloric acid, which might lead to the degradation of the polyester backbone. To avoid intensive acidic purification, $SnOct_2$, an FDA approved catalyst [31] can be used, since PEO-*b*-PCL synthesis in this case requires only trace amount of the catalyst. Unfortunately, $Đ_M$ values scatter in a wide range (1.1–1.6) for PEO-*b*-PCL copolymers when the synthesis is catalyzed by $SnOct_2$. It is known that at short polymerization times during the homopolymerization of ε-CL the obtained polymers exhibit a rather narrow dispersity (< 1.1). After long polymerization times, however, side processes result in a broadening of the polymer molecular weight distribution [32]. In this work, we investigated the kinetics of a PEO-*b*-PCL synthesis catalyzed by $SnOct_2$ in order to clarify the rise of the PEO-*b*-PCL dispersity, and consequently optimized the synthesis towards uniform PEO-*b*-PCL block copolymers. We compared mesoscale self-assembled structures of synthesized uniform PEO-*b*-PCL ($Đ_M < 1.1$) with the ones assembled from its non-uniform analogues ($Đ_M > 1.1$), to gain insight into the effect of dispersity on the self-assembly process. Furthermore, we showed how to tosylate the PCL end of PEO-*b*-PCL for further modifications, and thus to expand the functionalization capability of PEO-*b*-PCL copolymers and their self-assembled structures.

2. Experimental section

2.1. Materials

All glassware was dried overnight at 120 °C prior to use. All chemicals were obtained from Sigma-Aldrich and used as received unless otherwise mentioned. Milli-Q water with a resistivity of 15 MΩ cm was used from a Purelab Option-R 7/15 system (ELGA). Poly(ethylene oxide) monomethyl ether (PEO) with a molar mass of 2000 g mol^{-1} was dissolved in water and then lyophilized to obtain the polymer in a form of a dry powder. ε-Caprolactone (ε-CL) was dried under reduced pressure over CaH_2 for at least 12 h. ε-CL was purified by vacuum distillation and stored under argon atmosphere (not longer than 2 days). Toluene was dried over CaH_2 and distilled under argon atmosphere prior to use. Just before use tin(II) 2-ethylhexanoate ($SnOct_2$) was purified by vacuum distillation. Bodipy 630/650 NHS ester was purchased from Thermo Fisher Scientific Inc.

2.2. Nuclear magnetic resonance spectroscopy

^1H NMR spectra were recorded at 295 K in $CDCl_3$ on a Bruker Avance III NMR spectrometer operating at 400.13 MHz proton frequency. The instrument was equipped with a direct observe 5-mm BBFO smart probe. Chemical shifts are reported in ppm relative to tetramethylsilane. ^{119}Sn NMR, diffusion-ordered NMR spectroscopy (DOSY), and ^{119}Sn-HMBC (heteronuclear multiple bond correlation) experiments were performed in CD_2Cl_2 on a Bruker Avance III NMR spectrometer operating at 600.13 MHz proton frequency. The instrument was equipped with a direct observe 5-mm BBFO smart probe. The experiments were performed at 298 K and the temperature was calibrated using a methanol standard showing accuracy within ±0.2 K. The external reference for ^{119}Sn was tetramethyl tin at 0 ppm. NMR spectra were processed with MestReNova software, DOSY NMR experiments were processed with TopSpin software.

2.3. Gel permeation chromatography

GPC traces were analyzed and recorded in WinGPC (v 8.20 build 4815, PSS systems). The chloroform GPC system was equipped with 2 PSS SDV columns (1000 Å and 100,000 Å, each 30 cm long, 5 μm particles, 0.8 cm diameter) and a refractive index (RI), UV–vis, and viscosity detectors ran at 35 °C and 1 ml min^{-1}. The system was calibrated against narrow distributed polystyrene standards.

2.4. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS)

Molecular weight and end groups of PEO starting material were determined by MALDI-TOF. The data was acquired on a Bruker microflex LT instrument equipped with a 337 nm pulsed nitrogen laser in linear mode. The samples were prepared using multiple-layer spotting approach [33]. First, the matrix (0.5 μl of saturated dithranol in $CHCl_3$) was spotted on the MALDI target. Then 0.5 μl of NaI saturated in acetone was applied followed by 0.5 μl of 25 mg ml^{-1} of a polymer. The data analysis and predictions were performed using the Bruker DataAnalysis software.

2.5. Laser scanning microscopy

LSM images were recorded on an inverted Zeiss LSM510 META/ConfoCor 2 FCS microscope using a Zeiss Plan-Apochromat 100x/1.4 Oil DIC objective. Bodipy 630/650 and calcein disodium salt were excited by the 633 nm He—Ne laser line (10 %