Acta Biomaterialia 9 (2013) 6143–6149

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Structure formation and hydrogen bonding in all-aliphatic segmented copolymers with uniform hard segments ☆

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ARTICLE INFO

Article history:
Available online 4 October 2012

Keywords:
Thermoplastic elastomers
Segmented poly(ether ester amide)s
Bisester–bisoxalamide
Hydrogen bonding
X-ray scattering

ABSTRACT

Fully aliphatic segmented poly(ether ester amide) copolymers with uniform hard segments prepared by melt polycondensation of α,ω-hydroxyl end-functionalized polytetrahydrofuran and short glycine or β-alanine bisester–bisoxalamide units hold promise for biomedical applications. For polymers with the hard block contents varying from 10% to 27%, differential scanning calorimetry and atomic force microscopy reveal a highly phase-separated morphology, with ribbon-like nanocrystals dispersed in the soft segment matrix. To relate the polymer properties to the structure of the hard segment, the monomers were prepared and studied by optical and X-ray diffraction measurements. It was shown that the glycine and β-alanine carbonyl ester groups are tilted away from the oxalamide plane, which can affect the degradation rate via hydrolysis of the ester bond.

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1. Introduction

Thermoplastic elastomers based on aliphatic segmented block copolymers (SBCPs) target a broad range of biomedical applications [1–5]. These materials, with alternating soft and hard segments, combine the elastomeric behaviour of rubbers and the processability of plastics. In the melt, the hard segments (HSGs) are miscible with the soft segments (SSGs). Upon cooling, phase separation takes place, and the formed rigid HSG domains serve as reversible physical cross-links of the soft polymer matrix. In comparison to copolymers with non-uniform HSGs, the materials comprising uniform HSGs demonstrate an almost complete phase separation and therefore possess a much broader thermal service window along with improved ultimate mechanical properties [6,7]. Thus, even at an HSG concentration as low as 3 wt.%, the adipic acid tetraamide SBCP shows a distinct phase-separated morphology and hence good mechanical properties along with solvent resistance [8].

The mechanical properties and environmental response (degradation resistance, cytotoxicity, permeability, etc.) of SBCP are related to the chemical nature of each of the segments and the phase morphology of the material. As a hard segment, an oxalamide-based unit can be conveniently employed. Oxalamides are self-complementary hydrogen bonding molecules which assemble in robust multi-dimensional hydrogen-bonded structures. In this respect, oxalamide motif has been applied, for example, in supramolecular engineering [9,10] and also in organogelators [11]. Recently, we demonstrated that uniform oxalamide units in poly(ether amide)s are able to efficiently physically cross-link soft polymer matrices [12]. The poly(ester-amide)s have been intensively studied as materials with improved mechanical and degradation properties [3,13,14]. These SBCPs can be used as the hydrophobic HSG in physically cross-linked hydrogels [15,16]. For the amphiphilic biodegradable PEEAs, polyethylene oxide can be chosen as the hydrophilic matrix because of its non-toxicity and solubility in both water and organic solvents [17]. The potential of poly(ether ester amide) (PEEA) as a candidate for drug delivery systems was studied by Bezemer et al. [4]. It was shown that the degree of swelling, degradation rate and enzyme release were controlled by the soft block content. Barbato et al. [5] conveniently prepared microparticles of segmented PEEAs based on poly(ε-caprolactone) for the delivery of bioactive compounds. In this work the release of three drugs of different nature was studied in vitro: a positively charged drug was released within 2 h, while a longer sustained release (up to 30 days) was observed for a

☆ Presented at the E-MRS Biomaterials Symposium, organized by Prof. Kurosch Rezwan, Dr. Laura Treccani, Prof. Giovanni Marletta and Prof. Miguel Manso Silván.

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http://dx.doi.org/10.1016/j.actbio.2012.09.038

negatively charged drug incorporated. Deschamps et al. [2] investigated the use of PEEAs as biodegradable scaffolds. PEEAs implanted in rats degraded slowly, with a mass loss of 7–12% after 14 days implantation.

As far as the structure formation in PEEAs is concerned, the role of hydrogen bonds is clearly important. Thus, the inter-segmental hydrogen bond interactions favor the microphase segregation and retard the crystallization of the SSG in polyurethanes [18]. It is noteworthy that nature uses the secondary interactions to guide the complex self-organization phenomena in biological systems [19]. In this regard, one can compare the formation of hydrogen-bonded β-sheets by HSG units [12] with that for the structures of Karle et al. [20,21], which mimic the beta-hairpin structures of proteins or enzymes. In addition, the chemistry of the SBCPs allows the introduction of functional units into the HSG of the copolymer, while preserving decent mechanical properties. In the work of Wisse et al. [22], the functional units have been incorporated into urea HSG as a part of bisureidobutylene-functionalized azobenzene dye via hydrogen bonding. Using such an approach, biomaterials with specific functionalities can be readily prepared. Taking into account the fact that SBCPs may easily form a highly percolated morphology [23], it is envisaged that functional groups will build a percolated path in the polymer.

Our objective in this work was to consider the hydrogen bond-driven organization and self-assembly of PEEA from the viewpoint of the observed or expected material properties. The PEEA copolymers comprising uniform bisester–bisoxalamide segments and polytetrahydrofuran (PTHF) soft segments were characterized with the help of Atomic force microscopy (AFM), differential scanning calorimetry (DSC), wide-angle X-ray diffraction (WAXD) and small-angle X-ray scattering (SAXS). In order to correlate the polymer properties to the HSGs structure, a series of bisoxalamide monomers substituted with glycine and β-alanine moieties were analyzed.

An important property for biomedical applications is the polymer biodegradability. It is most likely that the degradation of the PEEAs takes place via hydrolysis of the ester bonds [15,24,25]. The hydrolysis resistance is determined by how accessible the ester bond is to the solvent. In the case of the hydrophilic SSGs, the access of the solvent to the ester bonds will be facilitated if the latter are not part of the HSG crystals. Therefore, it is important to know if the ester bonds are incorporated in the bisoxalamide crystals or are located in the interphase between amorphous and crystalline phases of PEEAs.

2. Experimental

2.1. Materials

The synthesis and characterization of the bisester–bisoxalamide monomers and corresponding segmented PEEAs have been described elsewhere [26].

2.2. TGA

Thermogravimetric analysis (TGA) was carried out under a nitrogen atmosphere in the 50–700 °C range at a heating rate of 10 °C min^{-1}, using a Perkin-Elmer TGA 7 thermogravimetric analyzer. The sample mass was typically of 5–10 mg.

2.3. Differential scanning calorimetry

DSC experiments were conducted using a Mettler Toledo DSC-1 instrument. The temperature and power calibrations were done using pure indium. The measurements were performed under a nitrogen atmosphere; the sample weight ranged between 40 and 50 mg. The non-isothermal crystallization behavior was studied by heating the samples to 30–40 °C above the melting temperature of the HSG, dwelling at this temperature for 3 min, then crystallizing the sample during cooling at different cooling rates between 1 and 20 °C min^{-1}.

2.4. Polarized optical microscopy

Polarized optical microscopy (POM) images in transmission were obtained using an Olympus BX51 microscope equipped with a Olympus DP70 digital color camera. The bisoxalamide monomers were first melted between glass coverslips and then slowly cooled down to room temperature. Single crystals were prepared by precipitation in toluene, then floating on 1% hydrofluoric acid aqueous solution.

2.5. Atomic force microscopy

AFM images were obtained using a MultiMode instrument (Veeco Metrology Group, Santa Barbara, CA) with a Nano-Scope IV controller running software version 5.12. The TESP probes used were 125 μm long, and had a tip radius of 8 nm and a force constant of 40 N m^{-1}. A moderate ratio of the imaging amplitude and free oscillation amplitude in the tapping mode of about 0.5 was applied in all measurements. The samples were prepared by drop casting a 1.0 mg ml^{-1} chloroform solution onto silicon wafers.

2.6. Wide-angle X-ray diffraction and small-angle X-ray scattering

WAXD and SAXS+ experiments were conducted on the BM26B beamline of the European Synchrotron Radiation Facility in Grenoble, France, using X-ray photons of 12 keV. Two-dimensional (2-D) X-ray patterns were collected in transmission geometry using a Frelon® CCD with a 2 × 2 binning, ending up with a pixel resolution of 100 μm in both lateral directions. For the measurements of the monomers, the uniaxially oriented samples were prepared by extruding the material above the melting temperature through a die of 300 μm diameter, followed by fast cooling to room temperature to prevent the reorientation of crystals. The polymer films for the stretching experiments were cut from the compression-molded bars (3 × 10 × 1 mm^3). The uniaxial drawing of the films was conducted with a Linkam tensile stage.

The modulus of the scattering vector $s = 2\sin(\theta)/\lambda$, where θ is the Bragg angle and λ is the wavelength, was calibrated using several diffraction orders of silver behenate and corundum for SAXS and WAXD, respectively. The data reduction and analysis, including geometrical and background correction, visualization and resampling into polar coordinates, were performed using home-built routines written in the Igor Pro® software package from WaveMetrics™.

3. Results and discussion

3.1. Synthesis

The synthesis of symmetrical bisoxalamides with neighboring glycine ethyl ester or β-alanine ethyl ester groups is shown in Scheme 1. First, bisoxalamide precursors were prepared by reacting α,ω-diamines with an excess of diethyl oxalate. The monomers were obtained in good yields after purification as described previously [26].

In the second step, the bisester–bisoxalamides **1a–c** and **2** (see Table 1) were obtained from the bisoxalamide precursors upon reaction with glycine or β-alanine ethyl esters. Finally, the

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