

PEO–PPO–PEO-based poly(ether ester urethane)s as degradable reverse thermo-responsive multiblock copolymers

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Abstract

Aiming at developing biodegradable thermo-responsive polymers that display enhanced rheological properties, a family of PEO–PPO–PEO based poly(ether ester urethane)s, was developed. The materials were produced following a two-step synthetic pathway. The PEO–PPO–PEO triblocks were first end-capped with LA or CL oligo(ester)s whereby pentablocks were produced. Then, the different precursors were chain extended using hexamethylene diisocyanate to create the respective polymers. The length and type of the ester block influenced the behavior of the molecules in water, especially their viscosity versus temperature response. The gelation temperature increased from 23 °C for a 20 wt% F127 solution to 26 and 31 °C for pentablocks with 4.4 and 7.5 lactoyl units, respectively. Materials containing longer LA units failed to show any reverse thermo-responsiveness. The presence of the oligo(ester) blocks also reduced the viscosity of the gel at 37 °C. While F127 displayed a viscosity of around 28,000 Pa s, pentablocks containing 4.4 and 7.5 LA units showed values of 15,400 and 12,600 Pa s. Also, the viscosity at 37 °C as well as the gelation temperature decreased as the molecular weight of the oligo(ester)s increased.

Finally, the degradation process of the gels was studied by monitoring their viscosity at body temperature and determining the molecular weight of the polymers, over time. Polymers were tailored so to combine high initial viscosity values with diverse degradation rates, as a function of the length and type of the oligo(ester) present along the polymeric backbone.

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1. Introduction

Aqueous solutions of poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide) (PEO–PPO–PEO) triblocks (e.g., Pluronic™ F127) display a lower critical solution temperature (LCST), resulting in a transition from a low viscosity solution to a solid gel when they are heated up [1,2]. Undoubtedly, materials that display this sol–gel transition at a biologically relevant temperature interval, have drawn much interest in the biomedical field. Different mechanisms were proposed as the driving force for this

behavior, typically denoted as reverse thermal gelation (RTG) [3–7].

Owing to their distinct reverse thermo-responsive behavior, PEO–PPO–PEO triblocks have been explored as injectable materials for diverse biomedical applications, such as the controlled release of drugs [8] and as the matrix for tissue repair [9]. Having said that, the viscosity increase attained by these triblocks has proven to be insufficient, typically resulting in systems displaying poor mechanical properties, high permeability and very limited stability. These drawbacks rendered these biomaterials unsuitable for most of the uses [10–12].

In previous studies, we reported the synthesis of new RTG-displaying polymers, generated by covalently binding repeating units along a multiblock copolymeric backbone. One of the synthetic strategies we pursued focused on the polymerization of PEO–PPO–PEO triblocks using hexamethylene diisocyanate (HDI) as a chain extender [13,14],

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where the amphiphilic triblock performed as the basic “monomeric” repeating unit along the chain. The poly(ether urethane)s (PFs) produced achieved viscosities 20-fold higher than the basic triblock, at 37 °C. Dynamic light scattering (DLS) measurements revealed the formation of markedly larger nano-structures (20–400 nm) than those generated by PEO–PPO–PEO triblocks (~20 nm). Also, when a model drug was released *in vitro* from a PF polymer, as opposed to the triblock, the delivery period increased from seven to over 40 days [13,14].

Notwithstanding their superior rheological properties and much enhanced stability, the relatively high molecular weight of these polymers may pose a problem since it may hamper their removal from the body. Efforts were, therefore, devoted to render these polymers degradable by incorporating short aliphatic oligo(ester)s along the backbone, *prior* to the chain extension stage. The cleavage of the polymeric backbone will result in an easier removal process of the low molecular weight fragments formed.

The work presented herein describes the design of degradable poly(ether ester urethane)s, produced following a two-step synthetic pathway. Firstly, the PEO–PPO–PEO triblock was end-capped with short poly(ester) blocks by the ring opening polymerization reaction between the end hydroxyl groups of Pluronic F127 and various lactones (e.g., lactide and ϵ -caprolactone) [15–17]. The different pentablock precursors formed were then chain extended using HDI. The pentablocks and the respective high molecular polymers were characterized and their temperature-dependent rheological behavior was investigated as a function of both the length and type of the oligo(ester) blocks present.

2. Experimental part

2.1. The syntheses

The synthesis was carried out under bulk conditions and the resulting polymers were denominated $P[(LA)_n\text{-F127-(LA)}_n\text{-HDI}]_p$ or $P[(CL)_n\text{-F127-(CL)}_n\text{-HDI}]_p$, where n is the number of lactoyl or caprolactone repeating units *per* poly(ester) block, while p is the degree of polymerization.

2.1.1. Synthesis of poly(lactic acid)-F127-poly(lactic acid) pentablock $((LA)_n\text{-F127-(LA)}_n)$

In total, 110 g (8.7 mmol) F127 ($M_w = 12.6$ kDa, %PEO = 70%, Sigma, St. Louis, MO) were dried at 120 °C under vacuum for 3 h with magnetic stirring. Then, L-Lactide (Boehringer Ingelheim, Germany) and the catalyst (stannous 2-ethyl-hexanoate, SnOct, 1/50 molar ratio to L-lactide, Sigma) were added and the reaction mixture was heated at 150 °C for 2.5 h with magnetic stirring in a dry nitrogen atmosphere. The amount of L-lactide was in accordance with the desired number of repeating units in each block. For example, 9.0 g L-lactide were reacted to obtain an average of four lactoyl units *per* block. Finally, the reaction mixture was cooled to room temperature, dissolved in 250 ml chloroform (Frutarom, Israel), precipitated in 1.2 L of a 1:1 mixture of petroleum ether 40–60 (Frutarom) and diethyl ether (Frutarom), filtered and dried under vacuum at room temperature.

The procedure above was repeated for the $(CL)_n\text{-F127-(CL)}_n$ pentablocks, with ϵ -caprolactone (Sigma) replacing L-Lactide. In this case, the catalyst/caprolactone molar ratio was 1/40 being used in this case.

2.1.2. The synthesis of the poly(ether ester urethane)s

The synthesis is exemplified hereby for a polymer having four lactoyl units *per* block ($n = 4$) and $p = 4.1$. 30.1 g (2.3 mmol) $(LA)_4\text{-F127-(LA)}_4$ were poured into a three-necked flask and heated to 80 °C. Then, 0.4 g (2.3 mmol, molar ratio 1:1 to pentablock) (HDI, Sigma) and 0.2 g SnOct were added to the reaction mixture and reacted at 80 °C for 30–60 min, depending on the system, under mechanical stirring and in a dry nitrogen atmosphere. The polymer produced was dissolved in chloroform (100 ml) and precipitated in a petroleum ether 40–60:ethyl ether (1:1) mixture (600 ml). Finally, the polymer was washed repeatedly with portions of petroleum ether (3 \times 100 ml) and dried under vacuum at room temperature. In order to obtain different degrees of polymerization several HDI/pentablock molar ratios were used. For example, molar ratios of 1.0, 1.1 and 2.2, resulted in degrees of polymerization of approximately 2, 3 and 4, respectively.

2.2. The gels

The water solutions (wt%) were prepared by mixing the polymer with deionized water at 4 °C and periodically stirring until complete dissolution. The gels were then generated by raising the temperature to 37 °C.

2.3. Characterization

2.3.1. Gel permeation chromatography (GPC)

The average-molecular weights and polydispersity were determined by gel permeation chromatography (Differential Separations Module Waters 2690 with Refractometer Detector Waters 410 and Millennium Chromatography Manager), using polystyrene standards between 472 and 360,000 Da.

2.3.2. Nuclear magnetic resonance spectroscopy (NMR)

The number of lactoyl and caprolactone repeating units was determined by $^1\text{H-NMR}$ spectroscopy (Bruker 400 MHz AMX 400). All spectra were obtained at room temperature from CDCl_3 solutions (Sigma).

2.3.3. Infrared spectroscopy (FTIR)

The samples were prepared by solvent casting from chloroform solutions on NaCl crystals (Sigma) and analyzed using a Nicolet 510 FTIR spectrometer.

2.3.4. Viscosity measurements

The viscosity versus temperature profile of the different water solutions was studied using a Brookfield Viscometer DV-II, with Bath/Circulator TC-500 and Wingather Software, using a T-F spindle at 0.05 cycles/min. The temperature was stabilized for at least 7 min before each measurement.

2.3.5. Thermal analysis

The samples (9–11 mg) were sealed in 40 μl Al-crucible pans and studied using a Mettler TA-400 differential scanning calorimeter (DSC). The materials were subjected to three consecutive DSC runs: first, they were heated up to 160 °C, then cooled down to –100 °C and finally they were heated up to 160 °C. All runs were conducted using 10 °C/min heating or cooling rates. The crystallinity is directly proportional to the heat of fusion, ΔH_f . By integrating the normalized area of PEO's melting endotherm, determining its heat of fusion and rationing it to that of PEG6000 homopolymer, the relative degree of crystallinity (C_r) of the PEO segments was assessed. The ΔH_f for PEG6000 is 196.6 J/g.

2.3.6. Dynamic light scattering (DLS)

The average hydrodynamic radius of the aggregates present in the aqueous solution was measured by DLS (Zetasizer 3000HAS, Malvern Instruments, UK) using an external laser (Ar-laser, 488 nm, power 70 mW; detector angle 90, 25 °C, dispersant viscosity 0.89 cP) in

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