Novel degradable amphiphilic 4-arm star PLA-*b*-POEOA and PLGA-*b*-POEOA block copolymers: synthesis, characterization and self-assembly

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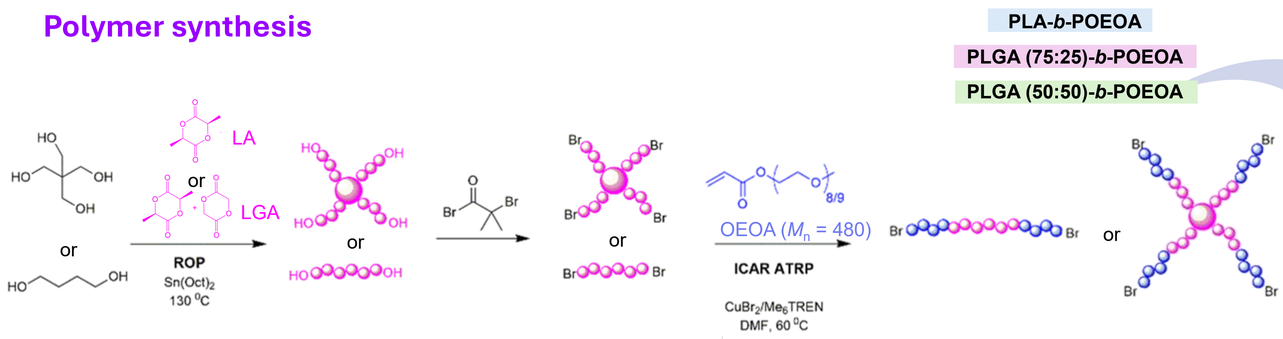
Introduction

The combination of ring-opening polymerization (ROP) and atom transfer radical polymerization (ATRP) represents an interesting strategy for the preparation of high-performance polymers that have well-defined molecular weight (MW), composition and architecture, while also exhibiting some level of biodegradability. These features are particularly important considering biomedical applications, such as drug delivery for the treatment of cancer and other relevant diseases. The preparation of amphiphilic block copolymers (BCPs), that possess hydrophobic polyester segments and hydrophilic blocks derived from vinyl monomers has been extensively reported, as these polymers can self-assemble in water, resulting in various nanostructures that can be loaded with different therapeutic agents. This poster summarizes the synthesis and characterization of PLA-*b*-POEOA and PLGA-*b*-POEOA BCPs, with different compositions, architectures and MWs, by combination of ROP and initiators for continuous activator regeneration (ICAR) ATRP, as potential carriers for drug delivery.

Experimental

Polymer synthesis



Scheme 1. Synthesis of 4-arm star and linear PLA-*b*-POEOA and PLGA-*b*-POEOA BCPs.

Table 1. Polymer code, MW and critical micelle concentration (CMC) of the different PLA-*b*-POEOA and PLGA-*b*-POEOA BCPs prepared by combination of ROP and ICAR ATRP.

Polymer code	M_n^{th} x 10^{-3}	M_n^{NMR} x 10^{-3}	M_n^{SEC} x 10^{-3}	M_w/M_n	CMC (mg/mL)
Star (PLA_5-*b*-$POEOA_{13}$)$_4$	28.2	27.9	16.0	1.33	7.12 x 10^{-3}
Star ($PLGA_6$-*b*-$POEOA_{12}$)$_4$ (PLGA 50:50)	26.5	26.2	14.9	1.40	1.03 x 10^{-3}
Star ($PLGA_6$-*b*-$POEOA_{11}$)$_4$ (PLGA 75:25)	28.1	26.1	18.8	1.31	8.72 x 10^{-3}
Star (PLA_6-*b*-$POEOA_{31}$)$_4$	76.5	65.1	22.6	1.62	1.32 x 10^{-2}
Star ($PLGA_7$-*b*-$POEOA_{32}$)$_4$ (PLGA 50:50)	74.8	65.7	33.4	1.20	1.49 x 10^{-3}
Star ($PLGA_6$-*b*-$POEOA_{25}$)$_4$ (PLGA 75:25)	76.1	52.6	26.9	1.30	4.54 x 10^{-3}
Linear PLA_{22}-*b*-$POEOA_{50}$	28.0	27.9	17.3	1.34	2.24 x 10^{-2}
Linear $PLGA_{27}$-*b*-$POEOA_{38}$ (PLGA 50:50)	28.8	22.2	13.7	1.32	1.48 x 10^{-2}
Linear $PLGA_{23}$-*b*-$POEOA_{39}$ (PLGA 75:25)	27.8	22.3	11.0	1.31	1.70 x 10^{-2}

M_n^{SEC} obtained by size exclusion chromatography (SEC) in tetrahydrofuran and using multidetectors calibration

Chemical structure

The chemical structure and the MW (M_n^{NMR} in Table 1) of the BCPs were evaluated by nuclear magnetic resonance (NMR) spectroscopy

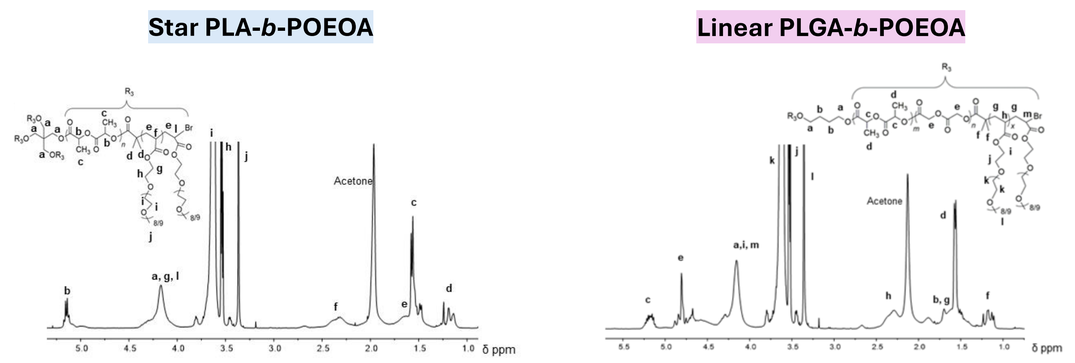


Figure 1. 400MHz ^{1}H NMR spectra of representative PLA-*b*-POEOA (left) and PLGA-*b*-POEOA (right) BCPs.

Cytotoxicity

The NIH3T3 fibroblast cell line was used as an *in vitro* model to evaluate the effects of concentration, composition, hydrophilic segment length, and architecture of the developed BCPs.

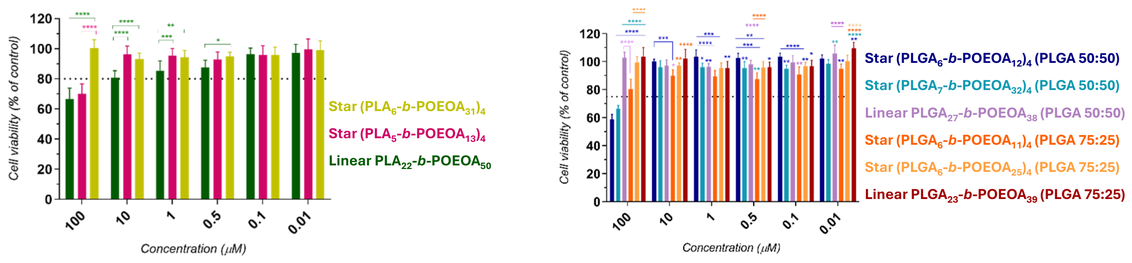


Figure 2. Cell metabolic activities as a marker of cell viability of NIH3T3 fibroblast cell following incubation with PLA-*b*-POEOA (left) and PLGA-*b*-POEOA (right) BCPs.

- Linear PLGA-based BCPs showed higher cytocompatibility than star-shaped analogs
- Architecture did not influence the cytocompatibility of PLA-based BCPs
- PLGA (50:50) induced more toxicity than PLA and PLGA (75:25)
- Polyester/POEOA ratio must be balanced to decrease BCP toxicity, according to the type of polyester

Self-assembly

Representative BCPs were self-assembled into micellar nanostructures in aqueous medium, by film-hydration method using ethanol.

Table 2. Size and size distribution of the micelles formed by linear and 4-arm star PLA-*b*-POEOA or PLGA-*b*-POEOA BCPs.

Polymer code	Hydrophobic/hydrophilic block (% wt)	Size (nm)	PDI
Star (PLA_5-*b*-$POEOA_{13}$)$_4$	13/87	130	0.231
Linear PLA_{22}-*b*-$POEOA_{50}$	13/87	153	0.436
Star ($PLGA_6$-*b*-$POEOA_{12}$)$_4$ (PLGA 50:50)	15/85	108	0.284
Linear $PLGA_{27}$-*b*-$POEOA_{38}$ (PLGA 50:50)	15/85	131	0.198

- Star-shaped BCPs produced micelles with smaller size than linear analogs
- PLGA (75:25)-based BCPs and BCPs with DP_{OEOA} ≥ 100 produced aggregates with PDI > 0.5

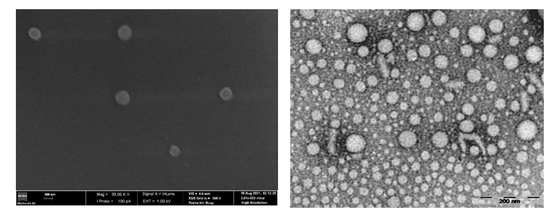


Figure 3. Scanning electron microscopy (left) and transmission electron microscopy (right) images of micelles formed by the star (PLA_5-*b*-$POEOA_{13}$)$_4$ BCP.

Degradability

The *in vitro* hydrolytic degradation of the BCPs was evaluated in physiological mimicking conditions, PBS (pH = 7.4) at 37 °C, following the decrease of MW.

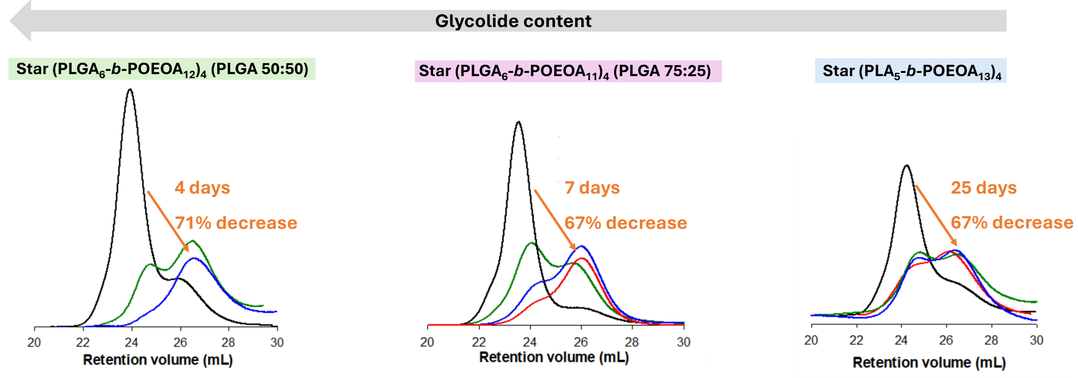


Figure 4. SEC traces (RI signal) of representative BCP at different degradation times.

- Increasing content of glycolide monomer led to faster degradation of the BCPs

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