

Synthesis and Characterization of temperature-sensitive oligo(ethylene glycol) grafted poly(L-glutamate) copolymers

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Statement of Purpose: Stimuli-responsive polymers have received extensive attention for their potential applications in biomedical field [1,2]. Among the intelligent polymers, temperature-sensitive polymers have attracted considerable interest due to their unique advantages in practical applications. However, most of currently used temperature-sensitive polymers are nonbiodegradable and exhibit limited biocompatibility, resulting in limitations for their biomedical applications. In this work, a series of novel temperature-sensitive copolymers based on biodegradable and biocompatible polypeptides were synthesized by the combination of ring opening polymerization (ROP) and Click chemistry, and the temperature-dependent solution behaviors of the copolymers were investigated.

Methods: Clickable poly(γ -propargyl-L-glutamate) (PPLG) was synthesized by the ROP of γ -Propargyl-L-glutamate N-carboxyanhydride (PLG-NCA) using n-hexylamine as an initiator [3]. The oligo(ethylene glycol) grafted PPLG copolymers (PPLG-g-OEG) were synthesized via a click reaction between PPLG and azide functionalized OEG. The compositions of PPLG-g-OEG were evaluated by ^1H NMR, and the molecular weights and polydispersities were measured by gel permeation chromatography (GPC). The thermal induced phase transitions and aggregation behaviors of the copolymers were investigated by turbidimetric measurements and dynamic light scattering (DLS). The secondary structure of the copolymer was tested by circular dichroism (CD) spectra. Critical micelle concentrations (CMCs) of the copolymers in aqueous solutions were measured by fluorescence spectroscopy using pyrene as a probe.

Results: The PPLG-g-OEG copolymers were synthesized via the click reaction between clickable PPLG and azide functionalized OEG. The ^1H NMR and GPC results confirmed the successful synthesis of the PPLG-g-OEG copolymers. The degree of polymerization of the PPLG backbone was adjusted from 25 to 112 by varying the feed ratio of PLG-NCA/n-hexylamine. The number of repeat units of the OEG side chain was 2 or 3 dependent on the OEG azides used for the click reaction. CD spectra indicated that all the PPLG-g-OEG copolymers existed as an α -helical structure in aqueous solutions. The phase-transitions of the copolymers in aqueous solutions were characterized by monitoring the turbidity of the polymer solution. As shown in Figure 1, all the PPLG-g-OEG copolymers exhibited sharp thermal-induced phase transitions, and the lower critical solution temperature (LCST) of the copolymer was markedly affected by the lengths of both the copolymer backbone and the OEG side chains. The LCST of the copolymer could be adjusted from 25 to 73 °C. For the copolymers with same OEG side chains, the LCST of the copolymer decreased gradually as the PPLG backbone length increased, indicating the solubility of the copolymer reduced with

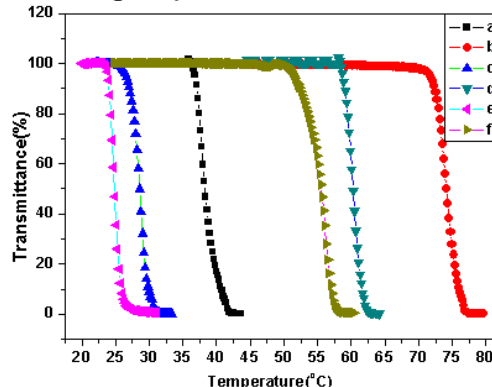


Figure 1. The thermal-induced phase transition curves of the 10 mg/ml PPLG-g-OEG aqueous solutions with different lengths of the PPLG backbone and OEG side chains. a: PPLG₂₅-EG₂; b: PPLG₂₅-EG₃; c: PPLG₈₄-EG₂; d: PPLG₈₄-EG₃; e: PPLG₁₁₂-EG₂; f: PPLG₁₁₂-EG₃.

the increase of the rigid PPLG backbone length. In contrast, the LCST increased markedly with increasing the length of the OEG side chains. This may be attributed to the fact that the solubility of the copolymer increased with the increase in the length of hydrophilic OEG side chains. The lengths of PPLG backbone and OEG side chains exhibited similar effects on the CMC of the copolymer. A higher PPLG backbone length or a lower OEG side chain length led to a lower CMC. DLS results suggested that the particle size of the PPLG-g-OEG micelles reduced as the temperature increased above its LCST. This may be due to the contraction of the hydrophobic PPLG core caused by the increase of the hydrophobic interactions between the PPLG backbones at temperatures above the LCST. In addition, further studies by turbidimetric measurements suggested that the LCSTs of the copolymers decreased gradually with the increase in either the copolymer concentration or the concentration of sodium chloride in the solution.

Conclusions: A series of novel temperature-sensitive oligo(ethylene glycol) grafted poly(L-glutamate) were synthesized and characterized. The copolymers exhibited sharp phase transitions with the increase in temperature. The LCST of the copolymer could be adjusted from 25 °C to 73 °C by varying the PPLG backbone length and the OEG side chain length. Since they exhibited LCSTs around the physiological temperature, the novel biodegradable and biocompatible polypeptide-based copolymers may have potential in biomedical applications.

References:

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