Lower critical solution temperature of copolymers of *N*-vinyl-2-caprolactam and its derivative: effects of pH and polymer compositions

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Statement of Purpose

Stimuli responsive polymers continue attracting great interests for various biomedical applications, such as drug delivery from biomedical implant surfaces. In our pervious study, a series of copolymers based on *N*-vinyl-2-caprolactam (VCL) and its derivative 3-(*tert*-butoxycarbonyl)-*N*-vinyl-2-caprolactam (TBVCL) were prepared and exhibited responsiveness to both pH and temperature[1]. However, cloud point (T_c) of those copolymers spanned a wide range, from 29 to 64 °C when pH varied from 2 to 7.4. Driven by the goal of tuning the T_c to be more physiologically relevant, we proposed to increase the hydrophobicity of the VCL derivative. Specifically, an aliphatic spacing group was introduced between the lactam ring and carboxylic acid group. The newly synthesized monomer was 3-(*tert*-butoxycarbonylmethyl)-*N*-vinyl-2-caprolactam (TBMVCL) and it was copolymerized with VCL to examine the effect of hydrophobicity of the substitution group on the responsiveness of VCL-based polymers.

Materials and Methods

The new functional monomer TBMVCL was designed and synthesized via the formation of enolate ions followed by nucleophilic substitution reaction using VCL and *tert*-butyl bromoacetate. The newly prepared monomer was thoroughly characterized by mass spectroscopy (MS), nuclear magnetic resonance (NMR) spectroscopy, and infrared (IR) spectroscopy. Functionalized pH-dependent temperature sensitive polymers were prepared by copolymerizing VCL with TBMVCL via free radical solution polymerization followed by acid deprotection. Chemical compositions of the copolymers were determined by ^{1}H NMR and thermogravimetric analysis (TGA). Thermo-responsive behavior of the copolymers was characterized by following the turbidity of the polymer solution at 540 nm as a function of temperature under various pH conditions. T_c was defined as the temperature corresponding to the transmittance 50% of that at room temperature. Cytotoxicity of functionalized PVCL copolymers was also studied on NIH/3T3 fibroblast cells using a WST assay.

Results and Discussion

The chemical structure of TBMVCL was shown in Fig. 1a and confirmed based on the ^{1}H NMR data (Fig. 1b). Furthermore, molar mass of the monomer was proved with MS and functional groups verified with IR.

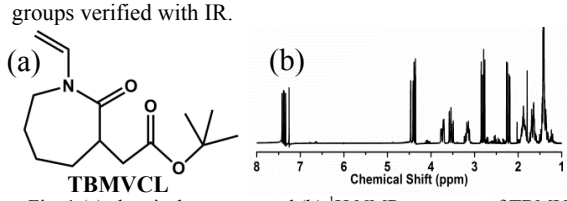

Fig. 1 (a) chemical structure and (b) ^{1}H NMR spectrum of TBMVCL

A series of copolymers (Fig. 2) were obtained by varying the molar feeding ratios of TBMVCL to VCL from 1% to 15%. The carboxylic acid groups were easily recovered by hydrolysis. Due to structural similarity, the two monomers copolymerized well and the final composition was relatively comparable to the initial feeding.

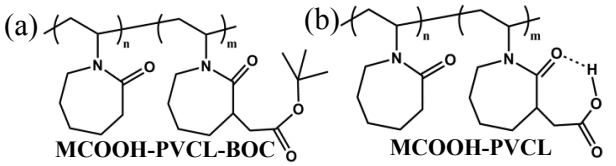

Fig. 2 Chemical structures of (a) protected and (b) deprotected copolymers

The obtained copolymers were thermo-responsive, and the phase transition temperature can be modulated by pH and the copolymer composition (Fig. 3). The MCOOH-PVCL9 copolymer (i.e., 9 mol% carboxyl groups) showed a narrower range of T_c than that of MCOOH-PVCL19 when pH varied from 2 to 5. The pH responsiveness is due to the protonation-deprotonation of the carboxyl group. Furthermore, when comparing to the copolymer with the same degree of carboxylation obtained by TBVCL, a lower T_c for MCOOH-PVCL9 was observed at pH 2, because of the hydrophobicity of extra methylene group.

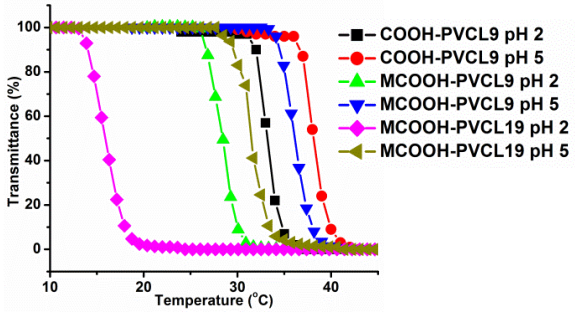

Fig. 3 Phase transition profiles of polymer solutions at different pH values

Cytotoxicity studies of the copolymer on NIH/3T3 fibroblasts showed good biocompatibility up to a polymer concentration of 2.5 mg/mL (Fig. 4).

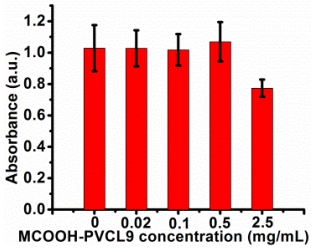

Fig. 4 Cell viability treated with various dosage of MCOOH-PVCL9

Conclusion

We have synthesized a new VCL derivative that can impart pH sensitivity to PVCL-based copolymers. It was found that the additional methylene moiety in the substitution functional group changed hydrophobicity of the copolymer and subsequently affected the thermal behavior. Applications of this biocompatible copolymer for localized drug release from neural implants are being explored.

References:

1. Yu Cao, Wei He. *Macromol. Chem. Phys.* **2011**, *212*, 2503−2510

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