Iran Polym J (2017) 26:957–969
DOI 10.1007/s13726-017-0571-8

ORIGINAL PAPER

Morphology and drug release behavior of *N*-isopropylacrylamide/acrylic acid copolymer as stimuli-responsive nanogels

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Received: 2 February 2017 / Accepted: 10 October 2017 / Published online: 11 November 2017

Abstract Thermo- and pH-responsive *N*-isopropylacrylamide (NIPAM) nanogels can be obtained by copolymerization of acrylic acid (AA) comonomer through differential microemulsion polymerization. The effects of comonomer, cross-linker, surfactant contents, and water/oil ratio were preliminarily investigated by a 2^4 full factorial design in order to eliminate the insignificant parameters from the polymerization analysis. The smallest poly(NIPAM-*co*-AA) nanogel particles were 40 ± 1 nm in diameter with 6 wt% of solid content and 98% conversion without coagulation. The comonomer amounts controlled the morphologies and LCST of the poly(NIPAM-*co*-AA) nanogels. The hairy microgels of poly(NIPAM-*co*-AA) with a 10:90 mol ratio of AA/ NIPAM had a lower critical solution temperature (LCST) of 6 °C. With an increase in the AA amount to a 17 mol ratio, the LCST increased to 27 °C, resulting in core-shell morphology. The morphology of resultant nanogels was characterized by transmission electron microscopy (TEM), Fourier transform infrared spectroscopy, and differential scanning calorimetry. Nuclear magnetic resonance spectroscopy was used to calculate the mole ratio of NIPAM and AA in resultant nanogels after dialysis. Both nanogel mole ratio and morphology effectively retained the cationic anti-cancer drug of methylene blue for several hours, an important basic requirement for a drug delivery system. Compared to core-shell microgels, a higher methylene blue release was obtained from the hairy microgels in simulated intestinal fluid.

Keywords *N*-isopropylacrylamide · Acrylic acid · Nanogels · Differential microemulsion polymerization · Hairy morphology · Core-shell morphology

Introduction

Since Pelton and Chibanate synthesized poly(*N*-isopropylacrylamide) (PNIPAM) microgels by free radical polymerization in 1986 [1], the PNIPAM microgels have attracted a considerable amount of attention because of their excellent thermo-responsive properties [2], good conformational transition in aqueous solution at temperature around 32 °C, and lower critical solution temperature (LCST) [3, 4]. Importantly, at LCST a polymer can be modified by copolymerization with a hydrophilic or hydrophobic monomer. Besides, it has a more pronounced pH-sensitivity for the system [5], the advantage of the copolymerization with a hydrophilic monomer is to increase LCST from 32 to 37 °C, the temperature which is close to human body temperature suitable for controlled drug delivery systems [6–8].

Emulsion polymerization and surfactant-free emulsion polymerization (SFEP) have been widely used to synthesize macro- and nano-sized PNIPAM copolymers with a

Electronic supplementary material The online version of this article (doi:10.1007/s13726-017-0571-8) contains supplementary material, which is available to authorized users.

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