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Synthesis and characterization of thermosensitive graft copolymer of *N*-isopropylacrylamide with biodegradable carboxymethylchitosan

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ABSTRACT

A novel thermosensitive and hydrogel was designed and synthesized by graft copolymerization of *N*-isopropylacrylamide (NIPAAm) with biodegradable carboxymethylchitosan (CMCS). The influence of the content of CMCS grafted on the properties of the resulted hydrogels was examined. The morphology of the hydrogels was observed by scanning electron microscopy (SEM), their thermal property was characterized by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and deswelling/swelling kinetics upon external temperature changes. In comparison with the conventional PNIPAAm hydrogels, the resulted hydrogels have improved thermosensitive properties, including enlarged water content at room temperature and faster deswelling/swelling rate upon heating. The strategy described here presents a potential alternative to the traditional synthesis techniques for thermosensitive hydrogels.

1. Introduction

In recent years, "intelligent" or "smart" hydrogels constitute a fast-growing area of polymer science because of their rapid response to environmental sitimuli, high water content and biocompatibility (Huang & Lowe, 2005; Langer & Peppas, 2003; Zhang, Wu, Sun, & Chu, 2003). Those hydrogels can control drug delivery (Ankareddi & Brazel, 2007) through responding to thermal stimulation by swelling and deswelling. Various thermosensitive and biodegrable hydrogels have been developed for drug delivery based on thermoresponsive polymer poly(*N*-isopropylacryamide) (PNIPAAm) due to its unique phase transition at a lower critical solution temperature (LCST) in water around 32 °C which is near the human body temperature (Guilherme, Silva, Girotto, Rubira, & Muniz, 2003; Guo & Gao, 2007; Han & Bae, 1998; Kumashiro, Huh, Ooya, & Yui, 2001; Lowe, Virtanen, & Tenhu, 1999; Yoo, Sung, Lee, & Cho, 2000; Yoshida, Aoyagi, Kokufuta, & Okano, 2003). Below LCST, the polymer expands and swells in water. In contrast, the polymer shrinks and collapses above the LCST. PNIPAAm-based polymers may allow aqueous loading of protein drugs, protecting the drug from a hostile environment (Ramkissoon-Ganorkar, Liu, Baudys, & Kim, 1999) and modulating drug release in response to temperature change (Zhang, Huang, Cheng, & Zhuo, 2004). However, many current thermoresponsive PNIPAAm hydrogels have problems in nonbiodegradability and nonsustained drug release under physiological conditions (Qiu & Park, 2001; Zhang et al., 2004).

Degradation of the hydrogel matrix can not only circumvent removal of empty device but also be used to modulate drug release for a long period of time (Van Dijk Wolthuis, Hoogeboom, vanSteenbergen, Tsang, & Hennink, 1997). Hydrogel composed of carboxymethylchitosan (CMCS) has been extensively studied in medical materials (Don, Hsu, & Chiu, 2001; Jenkins & Hudson, 2001; Joshi & Sinha, 2006; Kojima, Yoshikuni, & Suzuki, 1994; Pourjavadi & Mahdavinia, 2003; Shanthi & Panduranga, 2001). Carboxymethylchitosan, a natural amphoteric polyelectrolyte derived from chitosan, has attracted considerable interest in a wide range of biomedical applications especially in its biocompatibility such as wound dressings, artificial bone and skin, bacteriostatic agents and blood anticoagulants etc (Chen, Wu, & Mi, 2004; Huang, Nayak, & Lowe, 2004; Kim, Gil, & Lowe, 2006; Meyer, Shin, Kong, Dewhirst, & Chilkoti, 2001; Thanou, Nihot, & Jansen, 2001; Turk, Dincer, Yulug, & Piskin, 2004). In CMCS molecule, the degree of substitution (DS) of $-NH_2$ groups is 0.1–0.2, (Chen, Du, Wu, & Xiao, 2002; Chen & Park, 2003), so it has abundant $-NH_2$ groups to take part in other reactions.

In this paper, the graft copolymerization of *N*-isopropylacrylamide (NIPAAm) with carboxymethylchitosan (CMCS) was carried out (Scheme 1) and the hydrogels obtained were characterized. In comparison with poly(*N*-isopropylacrylamide) (PNIPAAm) gel, the graft copolymer hydrogels would provide many more advantages, such as increased water content, mechanical properties and improved thermosensitive properties. The porous structure within

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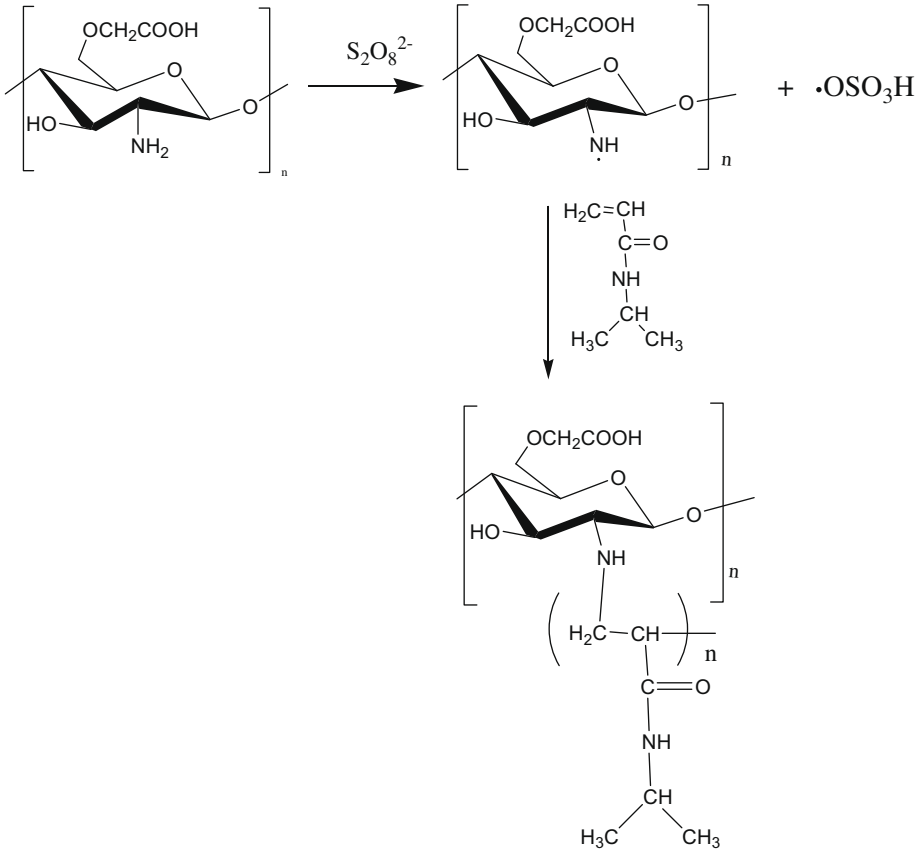

Scheme 1. Schematic illustration for the grafting of NPIAAm onto carboxymethylchitosan (CMCS).

the hydrogels observed by scanning electron microscopy (SEM) was formed and resulted in rapid deswelling in the presence of hydrophilic CMCS component during the graft copolymerization process, which is advantageous to the migration of water molecules out of the gel network.

2. Experimental

2.1. Materials

N-isopropylacrylamide (NIPAAm) (Acros, Belgium) was recrystallized from a 65:35(v/v) mixture of hexane and benzene and dried in vacuum. Carboxymethylchitosan (CMCS) was obtained from Nantong Xincheng Biological Industrial Co., Ltd. (Nantong, China). *N*,*N*′-Methylenebisacrylamide (BIS) (Acros, Belgium), ammonium persulfate (APS) and sodium pyrosulfite (SPS) are analytical reagents from Aldrich. All other reagents and solvents were of analytical grade and used without further purification.

2.2. Methods

2.2.1. Synthesis of poly(NIPAM-g-CMCS)

The synthesis of copolymers of poly(NIPAAm-g-CMCS) is illustrated below. A total of 1 g of NPIAAm and 0.12 g of carboxymethylchitosan (CMCS) were dissolved in 10 mL of deionized water under a nitrogen atmosphere for 30 min, then 0.015 g of ammonium persulfate (APS) as a initiator was added to the solution and the solution was stirred at 70.0 °C for 3 h (Wang, Yang, & Qiu, 1994). After the reaction was completed, the solution was dried in vacuum at 30.0 °C for 24 h. To remove the homopolymer (PNIPAAm), the rude dried hydrogel was immersed in excess acetone for 24 h and filtered to separate products. The homopolymer (PNIPAAm) was dissolved in acetone, but the poly(NIPAAm-g-CMCS) wasn't.

2.2.2. Grafting ratio and efficiency

The percentage and efficiency of grafting (%) were calculated by the difference of weights before and after grafting reaction according to the following formula:

$$\text{Grafting percentage (G\%)} = (W_g - W_c)/W_c \times 100\%;$$
$$\text{Grafting efficiency (GE\%)} = (W_g - W_c)/W_m \times 100\%;$$

where W_g, W_c and W_m denote weights of pure graft copolymer, carboxymethylchitosan and NIPAAm monomer, respectively.

2.2.3. Fourier-transformed infrared spectroscopy (FT-IR)

FT-IR spectra were recorded with AVATAR-360 FI-IR spectrometer (Nicolet, USA) and scanned from 4000 to 400 cm^{-1} with a resolution of 2 cm^{-1}, using KBr pellets at room temperature.

2.2.4. X-ray diffraction (XRD)

X-ray powder diffraction diagrams (XRD) by Ni-filtered Cu Ka radiation were generated at 30 kV and 30 mA as the X-ray source. Dried hydroxygel were whetted into small pieces when adhered to the matrix and scanned from 5 to 60° at a rate of 1°/min.

2.2.5. Thermogravimetric analysis (TGA)

The thermal properties of poly(NIPAAm-g-CMCS) and chitosan were measured by thermogravimetric ananlysis (TGA). Decomposition profiles of TGA were recorded with a heating rate of 10 °C/min in nitrogen between 0.0 °C and 800.0 °C.