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Synthesis of surfactant-free hydroxypropylcellulose nanogel and its dual-responsive properties☆

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ABSTRACT

Surfactant-free hydroxypropylcellulose (HPC) nanogels were synthesized by using thermo-sensitive HPC as a template to form HPC/PMAA nanoscale complex. The formation mechanism was owing to the interpolymer hydrogen bonding between HPC and PMAA induced phase transition of HPC in aqueous media. The average size of the resulting HPC nanogels ranges from about 98 to 241 nm. It was found that the average size of HPC nanogels changed little with increasing polymerization temperature below 26 °C, whereas it greatly increased above 26 °C. When the concentration of HPC was increased from 0.1 to 0.9 wt.%, the diameter of nanogels decreased firstly and then increased. Besides, an increasing crosslinker BIS concentration led to a reduced size of HPC nanogels, and the nanogels had the narrowest size distribution when its concentration was 0.1 wt.%. In addition to intrinsic thermo-sensitivity, HPC nanogels also display pH-induced phase transition due to pH-responsive PMAA contained in HPC nanogels. Surfactant-free, dual-responsive HPC nanogels would have promising applications in biotechnology and nanomedicine.

1. Introduction

Hydroxypropylcellulose (HPC) is a kind of hydroxy-substituted cellulose derivatives and has been used in pharmceutical, adhesives, food, cosmetic and controlled drug release (Ledwon, Andrade, Lapkowski, & Pawlicka, 2015; Luchs, Nelinson, Macy, & Grp, 2010; McDonald, D'Aversa, Perry, Wittpenn, & Nelinson, 2010; Mori et al., 2015; Nechifor, Barzic, Stoica, Closca, & Dorohoi, 2015; Qi et al., 2015). Nowadays, its thermo-sensitive property has caused scientists' interest. This thermo-induced phase transition may be due to a number of equilibrium bond configurations for the propylene oxide groups (Ahlnaes, Karlstroem, & Lindman, 1987; Karlstroem, 1985; Karlstroem, Carlsson, & Lindman, 1990). One propylene oxide group in HPC consists of two C—O bonds and two C—C bonds. At a low temperature in water below the lower critical solution temperature (LCST), oxygen atoms tend to maintain a gauche orientation about C—C bonds and a trans configuration about C—O bonds. The dipole moment of such special bond conformation is relatively large. As temperature is increased to the LCST, bond conformations with a less dipolar moment may become more favorable. The dipole moment of the propylene oxide moieties may be decreased in water and the hydrophobic interaction of HPC is so strong that the phase separation of HPC aqueous solution occurs. Liao et al. discovered that interpolymer hydrogen bonding between HPC and PAA led to a dramatic decrease of phase transition (Liao, Shao, Wang, Qiu, & Lu, 2012; Lu, Hu, & Schwartz, 2002). More interestingly, with the help of hydrogen bonding interaction between AA, PAA and HPC (Lu et al., 2002), HPC chains dehydrated to form nanocolloids around room temperature and then PAA chains attached on the surface of HPC nanocolloids collapsed to form PAA nanogels, in which HPC acted as a template for the formation of nanogels.

Herein, using HPC as a template in the absence of surfactant, we synthesized HPC/PMAA nanogels which were dual-responsive to pH and temperature owing to the interpolymer hydrogen bonding between HPC and PMAA, and the influence of polymerization temperature, crosslinker concentration, and HPC concentration to effect size and size distribution of dual-responsive nanogels were systematically studied.

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2. Experimental

2.1. Materials

Hydroxypropylcellulose (HPC) powders (average $M_w = 1.0 \times 10^5$), methacrylic acid monomers (MAA, 99%), *N*,*N*′-methylenebisacrylamide (BIS, crosslinker, 99%), ammonium persulfate (APS, 99%, initiator), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) were all purchased from Sigma–Aldrich Chemical Co. and used as received. Sodium hydroxide (NaOH) was supplied by Sinopharm Chemical Reagent Co., Ltd.

2.2. Aqueous synthesis of nanogels

The aqueous solution of 1 wt.% HPC was prepared by dissolving HPC powder in deionized water under gentle stirring for one week at room temperature. HPC nanogels were prepared as follows: 20 g of 1.0 wt.% HPC, 0.3 g MAA, and 0.1 g crosslinking agent BIS, and 0.1 g APS dissolved in 79.4 g DI water under stirring for 60 min to make a homogenous solution. The HPC/MAA solution was purged with nitrogen for 40 min and heated up to 30 °C. After stabilizing for 20 min at 30 °C, 0.05 g TEMED was added in the solution to initiate polymerization and crosslinking, which was then allowed to proceed for 60 min. The resulting nanogels were dialyzed for 3 days to remove the unreacted MAA, BIS, and TEMED (Beierle et al., 2014; Lee et al., 2012; Liao, Shao, Wang, et al., 2012). The resulting nanogels were deprotoned to pH = 6.5 ± 0.1 by NaOH. The same procedure were applied to the preparation of nanogels at different temperature, HPC concentration and Bis concentration which was shown in Table 1.

2.3. Dynamic light scattering (DLS) characterization

The size and size distribution of HPC nanogels (1.2×10^{-5} g/ml) was characterized by dynamic light scattering with a BI-9000 AT digital time correlator (BI-200SM, Brookhaven CO., Ltd) at 25 °C and a scattering angle of 90°. The light source was a He–Ne laser (35 mW and 633 nm).

For dynamic laser light scattering (LLS) (Gao & Wu, 1997), the line-width distribution $G(\Gamma)$ can be converted to the translational diffusion coefficient distribution $G(D)$ and to the hydrodynamic diameter distribution $f(D_h)$ using the Stokes–Einstein equation:

$$D_h = \frac{k_B T}{3\pi\eta D}$$

here k_B, T, and η are the Boltzmann constant, the absolute temperature, and the solvent viscosity, respectively.

2.4. UV–Vis spectrophotometer characterization

The aqueous dispersions of 1.0 wt.% nanogels at pH = 3.0, 6.5, and 9.0 were measured at 0.2 °C/min by means of Lambda 35 UV–Vis spectroscopy (Perkin Elmer, USA), respectively.

Table 1
Formulation of synthetic HPC nanogels at different conditions.

Sample	T (°C)	HPC (wt.%)	Bis (wt.%)	Sample	T (°C)	HPC(wt.%)	Bis (wt.%)
1	18	0.2	0.1	8	32	0.2	0.1
2	20	0.2	0.1	9	24	0.1	0.1
3	22	0.2	0.1	10	24	0.6	0.1
4	24	0.2	0.1	11	24	0.9	0.1
5	26	0.2	0.1	12	24	0.2	0.05
6	28	0.2	0.1	13	24	0.2	0.2
7	30	0.2	0.1				

2.5. Fourier transform infrared (FTIR) spectroscopy

The freeze-dried samples (2 mg) of nanogels and HPC powders were each ground with KBr. The FTIR spectra were recorded by means of a Fourier transform spectrometer (NEXUS-670, Nicolet Co., Ltd.) running at a 4 cm^{-1} resolution.

2.6. Transmission electron microscopy (TEM)

The TEM micrographs of the air-dried samples were taken with a Hitachi CO. H-800 at an accelerating voltage of 200 kV.

2.7. Atomic force microscopy (AFM)

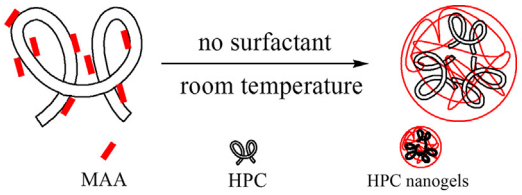
All AFM experiments were performed with a NanoScope IV SPE system (Veeco, USA) using a large multipurpose scanner (maximum scan range approximately 125 μm × 125 μm and vertical 2.5 μm).

3. Results and discussion

Aqueous synthesis of surfactant-free nanogels is of significant importance in practical applications, especially for drug delivery system. Our group has developed a facile "green" synthesis method to prepare nanogels in aqueous solution using HPC as a template (Liao, Shao, Wang, et al., 2012; Lu, Hu, & Gao, 2000). By this method, MAA can attach on the chains of natural polymers due to hydrogen bonding between HPC and MAA. As MAA polymerizes to PMAA polymer, stronger hydrogen bonding forms between HPC and PMAA, which triggers the phase transition to occur around room temperature. Then HPC collapses around room temperature and forms nanocolloids, thus it leads PMAA which attach on HPC to form nanogels without surfactant, which is shown in Scheme 1.

3.1. Effect of polymerization temperature

The effect of polymerization temperature on the size and size distribution of the resulting nanogels was ever reported by our group (Liao, Shao, Qiu, & Lu, 2012). It was found that the average size of nanogels slightly changed with increasing polymerization temperature from 18 to 26 °C, whereas the size greatly increased at 30 °C. And the resulting nanogels had a narrow size distribution with polydispersity index (PDI) of about 0.1. We further studied the effect of polymerization temperature on the size and size distribution of nanogels at another four different temperatures of 20, 24, 26, and 32 °C, respectively. The synthesis formulation consisted of 0.2 wt.% HPC, 0.3 wt.% MAA, and 0.1 wt.% crosslinker BIS. The resulting nanogels were measured by DLS measurement at 25 °C. The size and size distribution of nanogels are shown in Fig. 1. The results show that the average size of nanogels slightly decreased with increasing polymerization temperature from 20 to 24 °C, while a further increasing polymerization from 28 to 32 °C led to an increasing average size. Combined with the average size and polydispersity of nanogels synthesized at 18, 22, 26 and 30 °C (Liao, Shao, Qiu, et al., 2012), the effect of polymerization temperature on the average size and polydispersity is shown in Table 2. In a range of



Scheme 1. Schematic illustration of surfactant-free and dual-responsive synthesis of nanogels.