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Thermoresponsive behavior of sodium alginate grafted with poly(*N*-isopropylacrylamide) in aqueous media

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ABSTRACT

Thermoresponsive graft copolymers were synthesized. Thermally induced properties were introduced by grafting poly (*N*-isopropylacrylamide) (PNIPAM) side chains onto a sodium alginate backbone. The resulting graft copolymers cover a broad range in PNIPAM composition and molecular weight. Remarkable thermothickening behavior in water and 0.1 M NaCl is observed by viscometry when the temperature, concentration, weight ratio of PNIPAM side chains to backbone, and PNIPAM molecular weight are higher than certain critical values. This behavior is reversible and could have applications in oil rigs and drug delivery systems.

1. Introduction

Thermothickening aqueous formulations, i.e., systems whose viscosity increases with increasing temperature, have been thoroughly studied during the last two decades. They are mostly based on graft copolymers, prepared by grafting side chains that precipitate upon heating on a hydrophilic backbone. (De Vos, Möller, Visscher, & Mijnlieff 1994; Durand & Hourdet 1999; Hourdet, L'Alloret, & Audebert, 1994; Hourdet, L'Alloret, & Audebert 1997; L'Alloret, Hourdet, & Audebert, 1995).

Polymers in solution usually precipitate upon cooling, but some water-soluble polymers precipitate upon heating, showing lower critical solution temperature (LCST) behavior. (Heskins & Guillet 1968; Saeki, Kuwahara, Nakata, & Kaneko, 1976). Such LCST polymers, exhibiting inverse solubility behavior, have been used for the synthesis of the above-mentioned thermothickening graft copolymers, and include poly (ethylene oxide), (Hourdet et al., 1994; L'Alloret et al., 1995) ethylene oxide-propylene oxide random copolymers, (De Vos et al., 1994) and poly(*N*-isopropylacrylamide) (PNIPAM), the most well-studied LCST polymer, phase separating in water by increasing temperature at approximately 32 °C. (Heskins & Guillet, 1968; Schild, 1992).

The hydrophilic backbone of the thermothickening graft copolymer consists of a water-soluble polymer of relatively high molecular weight, such as poly(acrylic acid), (Durand & Hourdet 1999; Hourdet et al., 1994; Hourdet et al., 1998) partly hydrolyzed polyacrylamide, (De Vos et al., 1994) or 2-acrylamido-2-methyl-propane sulfonic acid. (Hourdet et al., 1997; L'Alloret et al., 1995) In many cases, polysaccharide backbones such as carboxymethylcellulose, (Bokias, Mylonas, Staikos, Bumbu, & Vasile, 2001; Hourdet et al., 1997; Karakasyan, Lack, Brunel, Maingault, & Hourdet, 2008) chitosan, (Bhattarai, Ramay, Gunn, Matsen, & Zhang, 2005) hyaluronan, (Kitazono, Kaneko, Miyoshi, & Miyamoto, 2004) dextran, and sodium alginate (NaAlg) (Karakasyan et al., 2008) have been successfully used.

The thermoresponsive behavior of all these graft copolymers, obeys to the following general scheme. As the temperature increases, the side chains tend to precipitate and form aggregates, which function as thermo-responsive stickers interconnecting the hydrophilic backbones of the graft copolymers, finally leading to the formation of a physical reversible network. This thermoresponsive behavior could be exploited when improved rheological properties above a given temperature are required, and its study is of great interest for bioengineering (Rzaev, Dinçer, & Piskin, 2007) and biomedical (Klouda & Mikos, 2008) applications, with drug release (Bhattarai et al., 2005) and tissue engineering (Drury & Mooney, 2003) being the most studied.

Alginic acid is a biopolymer broadly used in food and beverage, pharmaceutical, and medical industries, (Tønnesen & Karlsen, 2002) and it has attracted a broad interest due to its biocompatibility and biodegradability. Moreover, due to the carboxylic acid unit contained in its repeating unit, it can be functionalized with chemical modifications that could endow it with new properties and uses in novel applications. In a previous study, it was shown that graft copolymers of NaAlg with PNIPAM (Cheaburu, Ciocoiu, Staikos, & Vasile, 2013) present a strong thermothickening effect, which was studied by steady shear, oscillatory shear, and step-strain measurements. After fluorescence measurements, this behavior was attributed to the formation of hydrophobic microdomains consisting of micro-phase separated

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PNIPAM side chains as the temperature increased beyond the LCST of PNIPAM. Other studies regarding the synthesis reaction between NaAlg and amino-functionalized PNIPAM have also been published (Kim, Lee, Kim, & Lee, 2002; Lencina, Iatridi, Villar, & Tsitsilianis, 2014; Ju, Kim, & Lee, 2001; Vasile & Nita, 2011).

Nevertheless, despite the broad interest on the copolymers of NaAlg grafted with PNIPAM, there is not in literature, as it is in our knowledge, a systematic study indicating the conditions for obtaining a strong thermothickening behavior in aqueous media, which could be exploited in various biomedical applications.

In this work, we report such a systematic study of the viscosity behavior of graft copolymers of NaAlg with PNIPAM in solution in water and in 0.1 M NaCl, seeking to elucidate the influence of different factors on the appearance of thermothickening behavior. Parameters studied include the solution concentration, the degree of grafting, and the molecular weight of the PNIPAM side chains.

2. Materials and methods

2.1. Materials

Sodium alginate (NaAlg) was an Aldrich product No. 180947. After being dissolved in 0.005 M NaOH at 7.0×10^{-2} g/cm^3, it was purified by dialysis against water through a membrane (cutoff ≈ 12 kDa, Sigma) and finally freeze-dried. Its viscosity average molecular weight, $\overline{M}_V$ was determined in 0.1 M NaCl at 25 °C by the equation:

$$[\eta] = 6.9 \times 10^{-4} \overline{M}_V^{1.13} \quad (1)$$

given by Martinsen et al. (Martinsen, Skjåk-Bræk, & Smidsrød, 1991) for sodium alginates originating from *L. hyperborea* and was found to be 1.4×10^5 Da, in the range $1{,}2 \times 10^5$–$1{,}9 \times 10^5$ Da, given by the provider. Its mannuronate/guluronate, M/G, ratio was determined from the ^{1}H NMR spectrum obtained in a 2.0% (w/v) solution in D_2O at 90 °C with a 30° pulse angle and a recycle time of 4 s, by using the relation M/G = $(I_B + I_C - I_A)/I_A$, where I_A is the intensity of the peak appeared at 5.1 ppm, assigned to the anomeric proton of G, I_B at 4.7 ppm is assigned to the anomeric proton of M and H-5 of G-units adjacent to M, while I_C at 4.5 ppm is assigned to the H-5 of G-units adjacent to G. (Grasdalen, Larsen, & Smirdsrød, 1979; Salomonsen, Jensen, Larsen, Steuernagel, & Engelsen, 2009) and found to be equal to 1.49, while after a partial hydrolysis in solution in water at 100 °C under reflux at pH = 5,0 for 10 min and then at pH = 3.0 again for 20 min, following Salomonsen et al. (Salomonsen et al., 2009), was found equal to 1.50, close to 1.56, value given by the provider.

N-Isopropylacrylamide (NIPAM, Aldrich), 2-aminoethanethiol hydrochloride (AET, Aldrich), potassium persulfate (KPS), 1-ethyl-3-(3-dimethylaminopropyl carbodiimide) hydrochloride (EDC, Aldrich), and N-hydroxybenzotriazole (HOBt, Alfa Aesar) were used as received. Water was purified through a Medica system from Elga. Acetone used for analysis was from Carlo ERBA.

2.2. Synthesis of amino-functionalized PNIPAM

The monomer, NIPAM, was dissolved in water (100 mmol in 80 mL of water), and the solution was deaerated by purging with nitrogen for 30 min. The initiator, 1.5 mmoles of KPS, and the accelerator, AET, were dissolved separately in 5 mL of water, deaerated in a supersonic water bath, and added successively to the monomer solution. The temperature was adjusted to 29 °C using a water bath. The reaction time was 3 h. The product was purified by dialysis against water and freeze-dried. By varying the AET quantity, we obtained three amine-terminated (PNIPAM-NH_2) samples of different molecular weights. Their number average molecular weight, $\overline{M}_n$, was determined by end group analysis through potentiometric titration with 0.1 M NaOH, using the 751 GDP Titrino system from Metrohm, while their viscosity average molecular weight, $\overline{M}_v$, was determined after intrinsic viscosity measurement in 0.5 M $LiNO_3$ at 25 °C using the equation:

$$[\eta] = 0.047 \times M_V^{0.61} \quad (2)$$

Table 1
Amine terminated poly(*N*-isopropylacrylamide) (PNIPAM-NH_2) samples prepared.

AET (mmoles)	$\overline{M}_n$ (kDa)	$\overline{M}_v$ (kDa)
2.0	6.0	10
1.0	9.2	19
0.67	15	35

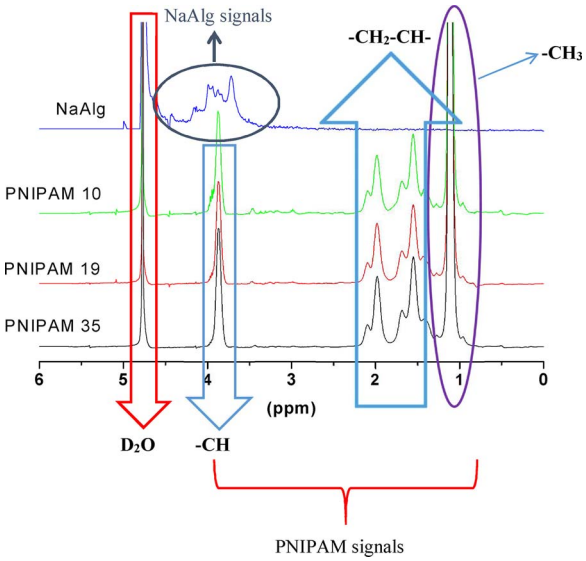

Fig. 1. ^{1}H NMR spectra of NaAlg and PNIPAM homopolymers.

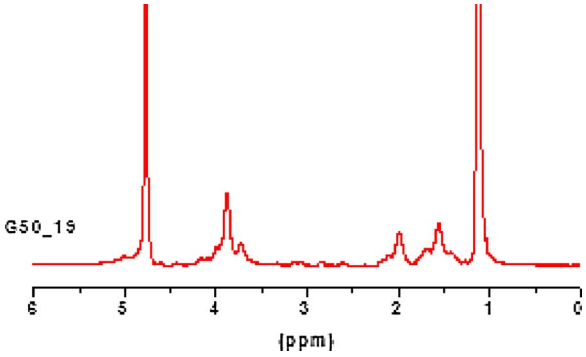

Fig. 2. ^{1}H NMR spectra of the graft copolymer G50_19.

Table 2
Designation and composition of the graft copolymers obtained.

Sample designation, GX_Y	Composition in PNIPAM, wt.%, X	$\overline{M}_v$ of the PNIPAM side chains, kDa, Y
G30_10	30	10
G30_19	30	19
G30_35	30	35
G40_10	40	10
G40_19	40	19
G40_35	40	35
G50_10	50	10
G50_19	50	19
G50_35	50	35
G65_10	65	10
G65_19	65	19
G65_35	65	35