



Thermoresponsive hydrogels from alginate-based graft copolymers



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ARTICLE INFO

Article history:

Received 28 July 2014

Received in revised form 11 September 2014

Accepted 12 September 2014

Available online 2 October 2014

Keywords:

Alginate

P(N-isopropylacrylamide)

N-tert-butylacrylamide comonomer

Graft copolymers

Thermosensitive

Hydrogels

ABSTRACT

Three samples of sodium alginate grafted by amino-terminated PNIPAM (low and high molecular weight poly(N-isopropylacrylamide)) and a random P(NIPAM-co-NtBAM) (NtBAM: N-tertiary butyl acrylamide) copolymer, were synthesized via the carbodiimide chemistry and their temperature-induced hydrogelation capability was evaluated by rheology. All the samples showed thermothickening behaviour depending on concentration, ionic strength and hydrophobic comonomer content, incorporated to the PNIPAM thermo-sensitive pendant chains. The main result of this study was that a slight hydrophobic enrichment (just 15 mol% NtBAM) of PNIPAM was sufficient to shift the gelation temperature well below the physiological temperature at 32 °C and at the lowest polymer concentration studied (i.e. 10 wt%). The consequence of that was that the ALG-g-P(NIPAM-co-NtBAM) graft copolymer hydrogel exhibited the best rheological thermo-responsive properties and might be used as injectable hydrogel for potential applications in biomedicine.

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1. Introduction

Thermo-responsive hydrogels based on a three dimensional, non-covalently formed, macromolecular structure, that undergo significant changes in their physical features and properties in response to temperature have attracted intensive interest because of their potential application in the field of biomedicine as injectable hydrogels [1]. The strategy usually adopted to design such kind of hydrogels is to prepare double hydrophilic block copolymers constituted of a permanent hydrophilic block bearing, either at both ends (telechelic) [2], or along the chain (grafted) [3], short hydrophilic blocks (potential stickers) that exhibit lower critical solution temperature (LCST) phase transition

in water. Thus, upon increasing temperature in aqueous environments, these blocks are transformed to hydrophobic above their LCST, driving the system to self-assemble forming a 3D network above a percolation threshold [4].

One of the most important features of these potential stickers is that their LCST should be close and below the physiological temperature such as the polymer/water system to behave as sol at room temperature and as gel inside the human body. One of the polymers that fulfil these requirements is poly(N-isopropylacrylamide) (PNIPAM) and for this reason it has been widely used as thermo-responsive building block to prepare block copolymers, exhibiting thermothickening behaviour in aqueous media [5]. The value of LCST for high molar mass PNIPAM is around 32 °C. However, this critical transition temperature depends on molar mass, polymer concentration, and ionic strength (salinity). More importantly, the critical temperature of interest is in fact the sol to gel transition which is also affected from the nature of the partner block (ionic

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versus non-ionic), the hydrophobic/hydrophilic balance and the macromolecular topology (telechelic versus graft) of the copolymer. All these factors have to be taken into account in order to regulate the thermo-sensitivity of the final hydrogel.

As far as LCST is concerned, it can be further tuned by the incorporation of comonomers using random copolymers instead of homopolymers [6]. In this way, the LCST can be tuned to a desired temperature range by copolymerization with a more hydrophobic comonomer which shifts the LCST to lower values, or a more hydrophilic one, resulting in the opposite effect [7–11].

Another significant factor is biocompatibility and biodegradability which is required in targeted bioapplications. To this end, polysaccharides grafted with a thermosensitive synthetic polymer have been designed; the polysaccharide backbone can supply biodegradability and non-toxicity to the matrix while, the synthetic polymer provides the thermal sensitivity [12]. In the seminal paper of Hourdet and coworkers it was shown that poly(ethylene oxide-co-propylene oxide) (PEPO) grafted onto three different polysaccharides exhibited strong thermothickening behaviour (sol to gel transition induced by heating) which depends on various parameters like grafting extend, polymer concentration and ionic strength, while each kind of systems has its own thermothickening signature [12].

Among others, alginate is a natural polysaccharide that has been used as the backbone polymer chain for the preparation of biodegradable thickeners [13–15]. Alginates are the salts of alginic acid, a lineal polysaccharide obtained from brown algae constituted of two uronic acids as repetitive units, mannuronic acid (M) and guluronic acid (G), in the form of homopolymeric (MM- or GG-blocks) and heteropolymeric sequences (MG- or GM-blocks) [16]. The mannuronic acid forms β (1–4) linkages, so that the M-block segments show linear and flexible conformations while the guluronic acid, its C5-epimer, gives rise to α (1–4) linkages, introducing in this way a steric hindrance around the carboxyl groups. For this reason the G-block segments provide folded and rigid structural conformations, responsible of a pronounced stiffness of the molecular chains [17,18].

Alginates importance mainly lies in its hydrocolloid properties, e.g., the ability to hydrate in hot or cold water to form viscous solutions, dispersions, or gels. Alginate has been regarded as an excellent polysaccharide for gel systems because of its unique features such as biocompatibility, biodegradability, immunogenicity, and non-toxicity [19]. Alginates are, in this way, unique in terms of their properties such as emulsifiers, thickeners, stabilizers, gelling and film forming, resulting in several applications for the food and pharmaceutical industries [14,20].

In this work, biodegradable thermo-responsive hydrogels formed by self-assembly of alginate-based graft copolymers has been investigated. The main motivation of the present work was to explore the influence of hydrophobic enrichment of PNIPAM grafts on the sol to gel transition and the viscoelastic properties of the resulted hydrogels in salt free and under ionic strength. For this purpose, an amino-terminated statistical copolymer comprising NIPAM and the hydrophobic monomer

N-tert-butylacrylamide (NtBAM) was synthesized and grafted onto the alginate backbone. For the sake of comparison, alginates grafted with pure PNIPAM were also synthesized and explored. As it will be shown, a small amount of hydrophobic NtBAM comonomer (e.g. 15%mol) generates significant effects to the alginate hydrogel properties.

2. Experimental

2.1. Materials

The monomers N-isopropylacrylamide (NIPAM) and N-tert-butylacrylamide (NtBAM) were used as provided by Aldrich and Alfa Aesar, respectively. Ammonium persulfate (APS), provided by Aldrich, was used as initiator and 2-aminoethanethiol hydrochloride (AET, HCl), obtained from Alfa Aesar, was used as chain transfer agent. 1-ethyl-3-(3'-(dimethylamino) propyl) carbodiimide hydrochloride (EDC) was obtained from Alfa Aesar and used as received as coupling agent. A low viscosity sodium alginate was provided by Alfa Aesar. The mannuronic/guluronic ratio (M/G) was estimated in 2.2 by ^1H NMR according to the literature [16,21]. Deuterium oxide (D_2O) was obtained from Aldrich. Ultra-pure water was obtained by means of a SG apparatus water purification unit.

2.2. Synthesis of amino-terminated polymers and graft copolymers

2.2.1. Synthesis of PNIPAM-NH₂

The polymerization reaction was accomplished following the method proposed by Durand and Hourdet with some slight modifications [22]. An aqueous solution containing 10 g (0.088 mol) of NIPAM were degassed with Argon. Appropriate amounts of APS and AET, HCl were separately dissolved in water and added to the NIPAM solution. The concentration of NIPAM in the final volume was 1 M in all reactions. The solutions were left under stirring and under Argon at room temperature for 24 h. The final homopolymers were recovered by dialysis against pure water (membrane cutoff: 12 kDa) and lyophilization. Two PNIPAM-NH₂ homopolymers with different molar mass were synthesized (Table 1).

2.2.2. Synthesis of poly(NIPAM-co-NtBAM)-NH₂

The same procedure as described for PNIPAM-NH₂ was used for the synthesis of the P(NIPAM-co-NtBAM)-NH₂ random copolymer. In this case, an aqueous solution containing both monomers NIPAM and NtBAM was prepared. The final concentration of monomers was 10 wt% and the feed composition used was 85%mol NIPAM, 15%mol NtBAM (Table 1).

2.2.3. Synthesis of graft copolymers

A condensation reaction was used to synthesize the alginate-g-PNIPAM or alginate-g-P(NIPAM-co-NtBAM) copolymers. The graft copolymers were obtained by coupling reaction between the carboxyl groups of sodium alginate and the terminal amine groups of PNIPAM or

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