



Association states of multisensitive smart polysaccharide–*block*–polyetheramine copolymers

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ABSTRACT

The water soluble properties of different copolymers based on pullulan–*block*–polyetheramine have been deeply studied. The polyetheramine group (PEA) corresponding to a propylene oxide/ethylene oxide ratio (PO/EO) of 29/6, is condensed, via amine link, to pullulans with various chain lengths. Different polysaccharide/PEA (PS/PEA) ratio copolymers have been investigated through macroscopic (cloud point, enthalpy) and mesoscopic scale approaches (critical aggregation concentration (CAC), mean number average hydrodynamic diameter (D_h) or aggregation number (N_{ag})). These systems are both pH and/or thermo-sensitive. Finally, it seems that three states can describe such systems (i) isolated copolymers (unimers) below the CAC, (ii) water soluble aggregates above the CAC and whatever the PS/PEA ratio is due to hydrophobic interactions and (iii) non-soluble aggregates (above the critical temperature) due to dehydration of polyetheramine groups but only if PS/PEA ratio is low enough.

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1. Introduction

Amphiphilic polymer systems (Strauss & Jackson, 1951) and their self-assembly in aqueous media have attracted a lot of scientific interests thanks to their variety of applications such as surfactants (polysoaps) (Martínez, González, Porras, & Gutiérrez, 2005) as enhanced rheological agents (associative polymers) (Charpentier-Valenza, Merle, Mocanu, Picton, & Muller, 2005) or drug vector (Endres, Beck-Broichsitter, Samsonova, Renette, & Kissel, 2011). Therefore, such systems are also largely used in several fields (pharmaceuticals, paints and coatings, cosmetics, etc.) (Henni-Silhadi et al., 2007). Among the amphiphilic system used, copolymers based on biopolymers seem to be very promising. More precisely, polysaccharides are particularly interesting due to their expected biocompatibility and low toxicity (Qiu, Feng, Wu, Zhang, & Zhuo, 2009) and as well as their recoverable origin. Several polysaccharides (such as dextran, alginate, chitosan, pullulan or glucuronoxylan) have already been hydrophobically modified by grafting hydrophobic groups (alkyl, polycaprolactone and so on)

(Colinet, Dulong, Hamaide, Le Cerf, & Picton, 2009; Dulong, Mocanu, Picton, & Le Cerf, 2012; Ebringerova, Sroková, Talaba, Kacurakova, & Hromadkova, 1998; Esquetet & Bulher, 2001; Rouzes, Durand, Leonard, & Dellacherie, 2002). These modifications result in very attractive physicochemical properties in aqueous media, which are mainly due to intra- and/or intermolecular associations leading to more or less aggregated structures susceptible to be used as hydrophobic clusters for drug delivery (Henni et al., 2005). Such systems also permit rheological or interfacial control (Charpentier-Valenza et al., 2005; Colinet et al., 2009; Henni et al., 2005; Simon, Le Cerf, Picton, & Muller, 2002).

In order to obtain a better control of the associative properties, more interests have been focused last years on the development of smart polymers which are also called sensitive polymers. Further, they exhibit strong modification of their physicochemical properties when a suitable stimulus is varied on a very narrow domain (Liu, Cellesi, Tirelli, & Saunders, 2009; Weiss & Laschewsky, 2012). Stimuli as ionic strength, pH (Ichikawa & Fukumori, 2000), applied to associative polymers in aqueous media, appear of great interest opening a large way in new applications in cosmetics or biomedical domains (Schatz & Lecommandoux, 2010). Thermosensitivity of water-soluble polymer is generally obtained by chemically modification with specific low critical solubility temperature (LCST) groups (Durand & Hourdet, 2000; Karakasyan, Lack, Brunel, Maingault, & Hourdet, 2008; Mocanu, Mihai, Dulong, Picton,

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& Le Cerf, 2012; Tizzotti et al., 2010). At low temperature in aqueous media, such LCST polymers lead to an homogenous solution but heating promotes phase separation appearing up to a critical temperature called cloud point (CP). The minimum value of CP in the phase diagram, is more precisely called LCST (Durand & Hourdet, 2000).

Polyetheramine (PEA) as methoxypoly(oxyethylene/oxypropylene)-2-propylamine (Jeffamine[®], commercialized by Hunstman) is one of these LCST system families. In our group, we have already worked on a specific mono-functional polyetheramine named Jeffamine[®]-M2005 composed by propylene oxide (PO) and ethylene oxide (EO) unit with a PO/EO ratio of about 29/6. Such interesting system exhibits a cloud point temperature of about 25 °C in pure water at 10 g L⁻¹ (Mocanu, Mihai, Dulong, Picton, & Le Cerf, 2011). Interestingly thermosensitive polysaccharides can be synthesized by grafting such LCST groups onto anionic polysaccharide as carboxymethylpullulan (CMP) and the resulting physicochemical properties are studied in aqueous solution (Esquenet & Bulher, 2001). Most of the studied thermosensitive systems reported in the literature concern grafted polymers. That is why we have proposed recently a new approach based on an original synthesis leading to block copolymers (Belbekhouche, Ali, Dulong, Picton, & Le Cerf, 2011). In this work, we have reported the coupling of a polysaccharide (i.e. pullulan) with various lengths with the Jeffamine[®]-M2005 resulting in an homologous series of copolymers with a secondary amine link leading to a pH dependant cationic character (pK_a ~9.5). Preliminary results evidence that the physicochemical properties of such copolymers are directly linked to the HLB (hydrophilic/lipophilic balance), given by the polysaccharide/polyetheramine (PS/PEA) ratio. However, in this study it has also been highlighted the importance of the environmental medium (pH and temperature). Significantly, the thermosensitive properties present peculiar interest since the macroscopic thermal transition occurs near the ambient temperature. Indeed, previously size exclusion chromatography/multi angle laser light scattering/differential refractive index (SEC/MALS/DRI) and absorbance measurements clearly displayed the copolymers association depending on both temperature and pH parameters for all studied systems. Controlling physicochemical property of copolymer by temperature and pH parameters have triggered interest mainly due to the fact that these parameters can be varied in biological and chemical systems. By introducing an ionizable backbone in a neutral system, the resulting copolymer become reacting to either an increase or decrease in the pH. The copolymer ability to be monitored by both temperature and pH leads to an additional control over the copolymer properties (Dimitrov, Trzebicka, Müller, Dworak, & Tsvetanov, 2007). In the present work, the physicochemical properties of the above-cited multisensitive macromolecular amphiphilic systems have been studied deeply with a focused attention on the influence of pH, temperature, PS/PEA ratio (HLB) and copolymer concentration.

2. Materials and methods

2.1. Materials

2.1.1. Copolymer controlled synthesis

The controlled synthesis of an homologous copolymer series, pullulan-*block*-polyetheramine, was reported in the previous manuscript (Belbekhouche et al., 2011), together with their chemical characterization and some preliminary results on their associative behavior depending on both pH and temperature. Briefly, the synthesis strategy is based on a coupling reaction between the reducing sugar of the polysaccharide and the amino-terminated polyetheramine. The last glucose unit of pullulan chain

is in thermodynamic equilibrium between closed and opened form. Consequently, each polysaccharide chain reacts with only one amino terminated polyetheramine chain, resulting in only linear copolymer (Fig. 1). Conventional reductive amination of carbonyl compounds needs the presence of reducing agent such as hydride (Brown, 1961). In the present synthesis, sodium cyanoborohydride (NaCNBH₃, a highly selective reducing agent, for reductive amination of aldehydes and ketones) has been chosen to couple the two blocks (Borch, Bernstein, & Dupont Durst, 1971). One of the encountered problem is that unreacted pullulan remains after reaction. The quantity of unreacted pullulan has been quantified around 30% in the optimum synthesis condition. However, to study the physicochemical property of these systems in the optimal condition, unreacted pullulan was successfully removed by cation exchange resin (SO₃⁻), which permits to retain the copolymer in its cationic form. This purification method has already been used to purify polysaccharide (Yalin, Yuanjiang, & Cuirong, 2005).

Hereafter, the abbreviations of the homologous copolymers series will be “P (Mn)-*block*-PO₂₉-EO₆”, where P is used for pullulan, Mn is the pullulan number molar mass. In these serie the polysaccharide/polyetheramine (PS/PEA) ratio is characteristic of the hydrophilic/lipophilic balance HLB. Their characteristics are given in Table 1.

Our previous results (Belbekhouche et al., 2011) have clearly demonstrated the aggregation tendency in dilute regime at pH 9 and at 15 °C. Logically, the aggregation number (*N*_{ag}) increased when HLB decreased. But in acidic media, the aggregation was strongly diminished (polyetheramine pK_a is near 9.2 ± 0.1 and copolymer pK_a is near 9.5 ± 0.1) due to the effect of electrostatic repulsions which inhibit association.

2.1.2. Other reagents

Dimethyl sulfoxide (DMSO), sodium hydroxide (NaOH), hydrochloric acid (HCl) were purchased from Acros. Dialysis tubing (SpectraPore) was purchased from Fisher Scientific. Pyrene and cetylpyridinium chloride were purchased from Sigma–Aldrich. All reagents were used without further purification. Water was purified with the Milli-Q reagent system (Millipore).

2.2. Methods

2.2.1. Surface tension measurements

The equilibrium surface tension of the aqueous solutions was measured according to the Wilhelmy plate method (Krüss K12 tensiometer, Germany). The platinum plate was cleaned before each measurement by immersion in deionised water followed by heating in a flame. The surface tension, γ (mN m⁻¹), was measured under controlled temperatures as a function of concentration to determine the critical aggregation concentration (CAC). The measure time was 15 min, which was sufficient to reach the equilibrium state (uncertainty ±1 mN m⁻¹).

2.2.2. Absorbance measurement

The cloud point temperature (CP) of aqueous copolymer solution (prepared in Milli-Q at a controlled pH) was detected by absorbance measurements at 400 nm, using a PerkinElmer Lambda 7UV/vis spectrophotometer (USA) at the inflection point of the curve. The temperature of the solution was raised at a constant rate of 0.5 °C min⁻¹. All temperature transition values were repeatable and reproducible (±0.1 °C).

2.2.3. Differential scanning microcalorimetry (μ DSC)

Measurements were performed with a μ DSC3 Evo from Setaram (France) from 5 to 50 °C (scanning rate 0.5 °C min⁻¹) on copolymer solution. The volume of the sample cells was around 0.5 mL; equilibrated with a reference filled with the same weight of solvent.

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