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Thermoresponsive hydrogels with low toxicity from mixtures of ethyl(hydroxyethyl) cellulose and arginine-based surfactants

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ABSTRACT

Ethyl(hydroxyethyl) cellulose (EHEC) is known to form hydrogels in water at elevated temperatures in the presence of an ionic surfactant. In this paper, the potential use of arginine-based surfactants is explored considering the production of a low toxicity thermoresponsive hydrogel for pharmaceutical and biomedical applications. The interactions between EHEC and the monomeric surfactant N^{α}-lauroyl-L-arginine methyl ester (LAM) and two gemini surfactants N^{α},N^{ω}-bis(N^{α}-acylarginine) α,ω-dialkyl amides were evaluated by Rheo-Small Angle Light Scattering measurements. The complex viscosity of the systems was dependent on surfactant concentration and temperature. Under specific conditions, soft gels of homogeneous structure were produced. The cloud point (CP) of the EHEC–LAM system varied significantly with surfactant concentration, while only moderate CP changes were found in the presence of the gemini surfactants. Finally, the effect of the surfactants on the viability of a human cell line was evaluated. Despite the lower toxicity of LAM, the superior gel forming efficiency of the gemini surfactants at lower concentrations revealed their advantageous suitability as components of a biocompatible thermoresponsive gel system.

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1. Introduction

The interactions between polymers and surfactants in aqueous solution have been a subject of great interest over the past decades. These systems can show notable and complex properties, significantly caused by structure variations. This makes them interesting in a number of industrial applications, for instance in products for personal care (surface conditioning) and pharmaceutical products, detergents and foams (Kwak, 1998). One remarkable example is the combination of amphiphilic polymers with ionic surfactants, in which striking viscosification effects can be observed (Kwak, 1998; Malmsten, 2002).

Ethyl(hydroxyethyl) cellulose (EHEC) is a non-ionic amphiphilic polysaccharide that has been widely studied in combination with ionic surfactants such as the anionic sodium dodecyl sulfate (SDS) (Hoff et al., 2001; Kjøniksen et al., 1998, 2005; Lund et al., 2001; Nyström and Lindman, 1995; Nyström et al., 1995) and sodium dodecanoate (SDoD) (Bo et al., 2005; Dal-Bó et al., 2011), and the cationic cetyltrimethylammonium bromide (CTAB) (Lund et al., 2001; Nyström and Lindman, 1995; Nyström et al., 1995). EHEC exhibits a lower critical solution temperature (LCST), above which it phase-separates. Specifically, as the temperature is increased, the polymer becomes more hydrophobic and less water-soluble, inducing the formation of large aggregates that separate from the water phase (Hoff et al., 2001; Kwak, 1998). However, in the presence of ionic surfactants this scenario can be significantly changed. It has been suggested that the surfactant molecules interact with the hydrophobic microdomains of the polymer, forming mixed micellar-like structures that can involve substituents from more than one polymer chain (Kjøniksen et al., 1998, 2005). The formation of these micelle-like clusters can both create new connection points and strengthen already existing connections between polymer chains. In addition, the presence of charges in the surfactant molecules endows a polyelectrolyte character onto the otherwise

Abbreviations: LAM, N^{α}-lauroyl-L-arginine methyl ester; $C_6(LA)_2$ and $C_9(LA)_2$, N^{α},N^{ω}-bis(N^{α}-acylarginine) α,ω-dialkyl amides with C_6 and C_9 spacers, respectively; *cac*, critical aggregation concentration; *cmc*, critical micelle concentration; CP, cloud point; CTAB, cetyltrimethylammonium bromide; EC_{50}, half maximal effective concentration; EHEC, ethyl(hydroxyethyl)cellulose; GP, gel point; LCST, lower critical solution temperature; Rheo-SALS, Rheo-Small-Angle Light Scattering; SDS, sodium dodecyl sulfate.

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uncharged polymer, causing the matrix to swell due to charge repulsion. As the temperature is increased, a combination of events involving an enhanced connectivity, together with the swelling of the network can lead to an increase in viscosity and, at specific conditions, to a sol–gel transition (Hoff et al., 2001; Kjøniksen et al., 1998, 2005; Lund et al., 2001).

Accordingly, the EHEC–ionic surfactant system can be particularly interesting for industrial applications requiring temperature-induced viscosification of a solution or a mixture. Nonetheless, it cannot be disregarded that the use of surfactants poses a number of concerns related with their inherent environmental toxicity, low chemical and biological biodegradability and poor biocompatibility (Morán et al., 2004). In the pharmaceutical, cosmetic and medical fields, the use of surfactants is considerably restrained, due to the low toxicity required for all preparation components (Ruel-Gariepy and Leroux, 2004). The production of more biocompatible and environment-friendly surfactants is therefore of great interest (Morán et al., 2004).

In recent years, the synthesis of surfactants with structures based on natural compounds has attracted much attention (Clapés and Rosa Infante, 2002; Holmberg, 2001; Infante et al., 1997; Morán et al., 2004; Takehara, 1989). Surfactants based on amino acids have been shown to be environment friendly. They exhibit low toxicity and high biodegradability, while still retaining good surface activity and aggregation features (Brito et al., 2009; Infante et al., 1997; Martinez et al., 2006; Sánchez et al., 2007). This is the case for the cationic N$^{\alpha}$-lauroyl-L-arginine methyl ester (LAM), a surfactant synthesized from arginine by the group of Infante et al. (1984). The properties of this surfactant have been extensively investigated over the last decades (Castillo et al., 2004; Martinez et al., 2006; Pinazo et al., 1999; Sánchez et al., 2007). Apart from the good surface activity, this surfactant is also an active antibacterial agent against both Gram-positive and Gram-negative bacteria. This is due to its capacity to adsorb and interact with the negatively-charged bacterial membranes and thereby cause their disruption (Castillo et al., 2004; Infante et al., 1984). The surfactant is significantly less hemolytic in isotonic medium than the commercial cationic counterpart hexadecyltrimethylammonium bromide (HTAB), while an important protective antihemolytic effect was additionally observed at low concentrations (Sánchez et al., 2007).

Another essential strategy to minimize the toxic effect of surfactants is to decrease the amount of surfactant used. This can be achieved by using surfactants with improved efficiency and enhanced performance, as is the case for gemini or dimeric surfactants (Infante et al., 2010). These surfactants are composed of two hydrophobic chains and two hydrophilic head groups, linked through a covalently bound spacer. This unique structure usually causes them to have much lower critical micelle concentrations (*cmc*) than the conventional monomeric surfactants. They are also more effective in adsorbing at the water/air interface and in reducing the surface tension of water (Xia and Zana, 2004). The production of gemini surfactants based on natural compounds such as amino acids would thus provide an enhanced solution toward a 'Green Chemistry' with improved properties and efficacy. Based on this concept, a new class of gemini cationic surfactants has been synthesized from arginine. They have a structure that consists of two symmetrical long chain N^{α}-lauroyl-L-arginine residues linked by amide covalent bonds to an α,ω-alkylidenediamine spacer chain of various lengths (Perez et al., 1996). These N^{α},N^{ω}-bis(N^{α}-acylarginine) α,ω-dialkyl amides or bis(Args) are effective low toxicity antibacterial agents and upon chemical degradation only non-toxic and ecologically friendly products are generated (Perez et al., 1996).

In this work, we investigate the potential use of LAM, the monomeric surfactant, and two bis(Arg) surfactants with distinct spacer length in their ability to interact with EHEC and produce a thermoresponsive gelling system with enhanced environmental and biocompatibility properties. The rheological properties of the system, as well as the potential toxicity of the surfactants on a human cell line are investigated. The results are discussed having in mind their prospective use in human pharmaceutical or medical applications.

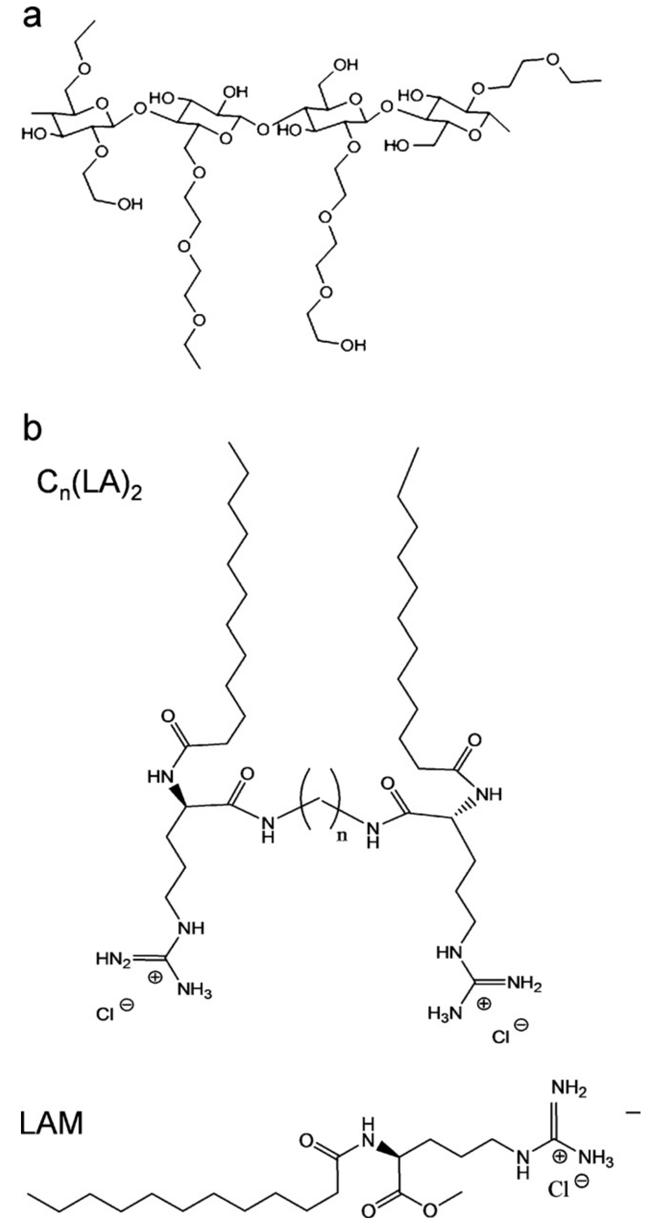

Fig. 1. (a) Structure segment of EHEC. (b) Schematic drawings of the surfactants used. $C_n(LA)_2$ – N$^{\alpha}$ N$^{\omega}$-bis-(N$^{\alpha}$-lauroyl arginine) α-ω-alquildiamine, $n = 6$ [$C_6(LA)_2$], $n = 9$ [$C_9(LA)_2$]; LAM – N$^{\alpha}$ lauroyl arginine methyl ester hydrochloride.

2. Materials and methods

2.1. Materials and solution preparation

EHEC (structure segment shown in Fig. 1a), product DVT 89017, was obtained from Akzo Nobel Surface Chemistry AB, Stenungsund, Sweden. The polymer had a number average molecular weight (M_n) of 80,000, a degree of substitution of ethyl groups $DS_{ethyl} = 1.9$/anhydroglucose unit, and the molar substitution of ethylene oxide groups $MS_{EO} = 1.3$/anhydroglucose unit. The sample

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