



Macromolecular Nanotechnology

Phase behavior, microstructure and cytotoxicity in mixtures of a charged triblock copolymer and an ionic surfactant



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ABSTRACT

In the present study, aqueous solutions of a thermo-responsive negatively charged triblock copolymer methoxy-poly(ethylene glycol)-*block*-poly(*N*-isopropylacrylamide)-*block*-poly(2-succinic acid-propyloxyl methacrylate) (MPEG₄₅-*b*-PNIPAAM₄₈-*b*-PSAPMA₁₀), have been characterized in the presence of sodium dodecyl sulfate (SDS) or dodecyltrimethylammonium bromide (DTAB) surfactant, at a constant concentration of polymer and various levels of surfactant addition. For this purpose, dynamic light scattering (DLS) was used to probe the effect of the ionic surfactants on the size of the block copolymer species, and small-angle neutron scattering (SANS) was applied as a complementary technique to probe the structure on a mesoscopic length scale. The results obtained revealed that the addition of a surfactant to the copolymer solution leads to a decrease of the particle size, due to electrostatic repulsions and solubilization of the hydrophobic microdomains. By zeta potential analysis it was shown that the charge density of the surfactant-coated polymer moieties increases with increasing surfactant concentration. The turbidities of the polymer-surfactant mixtures were measured using a cloud point analyzer. Our data revealed that the behavior not only depends on the surfactant concentration, but it is also affected in some cases by temperature. In addition, cytotoxicity studies were carried out on mouse fibroblasts cells NIH-3T3 to evaluate the potential of the systems as drug delivery carriers. Results showed that the cytotoxicity of the polymer changes with surfactant addition, rising as the concentration of SDS increases but falling off with increasing DTAB concentration.

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1. Introduction

Block copolymers have been widely studied in recent years due to their ability to self-assemble into nanostructures in aqueous solution, and for their potential in applications such as enhanced oil recovery, targeted drug delivery and sensor design [1–4]. Given the functional versatility of block polymers, the main focus in the present work has been to develop

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systems based on this type of polymers with potential for drug delivery applications. For this purpose, it is necessary to find block copolymers capable of forming tunable and responsive aggregates that also possess high levels of biocompatibility.

Poly(*N*-isopropylacrylamide) (PNIPAAm) is one of the most intensively studied temperature-responsive polymers [5]. In aqueous solution, it exhibits a low critical solution temperature (LCST), around 32 °C [6–8]. When the solution temperature is increased above the transition temperature, a coil to globule transition occurs, which is then followed by the creation of aggregates, and if the solution is not too dilute, macroscopic phase separation takes place [7]. To create nano-structures and load them with drugs, one usually takes advantage of their ability to form polymer micelles at elevated temperatures. By designing copolymers consisting of PNIPAAm and other blocks of different hydrophobicity, it is possible to tune the physical properties of the copolymer and the self-assembling features.

There are several publications [9–13] dealing with the self-assembly of responsive amphiphilic copolymers and the formation of core–shell structures. However, there is a lack of studies that address the interplay between charged amphiphilic copolymers and ionic surfactants, especially a comparison of polymer–surfactant effects induced by anionic and cationic surfactants, and the subtle balance between electrostatic and hydrophobic interactions. The formed polymer–surfactant complexes are of great interest as potential drug and gene delivery vehicles [14,15]. They may be used as carriers of nucleic acids and other biological components into living cells for therapeutic purposes [16–20].

In this work, the interactions between methoxy-poly(ethylene glycol)-*block*-poly(*N*-isopropylacrylamide)-*block*-poly(2-succinic acid-propyloxyl methacrylate) (MPEG₄₅-*b*-PNIPAAm₄₈-*b*-PSAPMA₁₀), a temperature- and pH-responsive negatively charged triblock copolymer, and the ionic surfactants sodium dodecyl sulfate (SDS) and dodecyltrimethylammonium bromide (DTAB) were analyzed in aqueous solution by various experimental methods. Methoxy-poly(ethylene glycol) (MPEG) is a hydrophilic block and in combination with more hydrophobic blocks in the copolymer, the species may form core–shell structures, and in aqueous solutions this block frequently constitutes the corona that stabilizes the supramolecular structure [21–23]. Poly(2-succinic acid-propyloxyl methacrylate) (PSAPMA) is a hydrophobic block, completely insoluble in water, that deprotonates in aqueous solutions hence becoming negatively charged; this block provides the pH-sensitivity of the copolymer. The combination of the three blocks in this amphiphilic triblock copolymer (MPEG₄₅-*b*-PNIPAAm₄₈-*b*-PSAPMA₁₀) gives rise then to a dual responsive negatively charged polymer, which exhibits special interactions in the presence of an anionic surfactant (SDS) as well as with the cationic surfactant (DTAB). In this investigation, the polymer–surfactant interactions were probed by different experimental techniques at a constant concentration of polymer and various levels of surfactant addition.

The principal objective of this work has been to study the interactions between ionic surfactants and a dual-responsive triblock copolymer to gain insight into how polymer, surfactant concentration, and temperature affect the size and structure of these complexes. Investigation of the properties of the copolymer–surfactant systems that can be modulated is of utmost importance as this type of systems can be used in drug delivery applications.

2. Experimental

2.1. Materials

All the chemicals used for the synthesis of the triblock copolymer were purchased from Sigma–Aldrich and Fluka, and they were employed as received, unless mentioned otherwise. Sodium dodecyl sulfate (SDS) and dodecyltrimethylammonium bromide (DTAB) were purchased from Sigma–Aldrich and used as received. *N*-isopropylacrylamide (NIPAAm, Acros) was recrystallized from a toluene/*n*-hexane mixture and dried under vacuum before use. 2-hydroxypropyl methacrylate (HPMA) from Fluka comprises an isomeric mixture of 75% HPMA and 25% 2-hydroxyisopropyl methacrylate, but for clarity only the chemical structure of the major HPMA isomer is considered in this study. HPMA was purified to remove the trace inhibitor present in the sample by allowing the component to pass through a short basic Al₂O₃ column, prior to use. Triethylamine (TEA, Aldrich) was dried over anhydrous magnesium sulfate (Aldrich), filtered, distilled under N₂ atmosphere and stored over 4 Å molecular sieves. Copper (I) chloride from Aldrich was washed with glacial acetic acid (Aldrich), followed by washing with methanol, diethyl ether, and then dried under vacuum and kept under N₂ atmosphere. N,N,N',N'',N''',N'''' - (hexamethyl triethylene tetramine) (Me₆TREN) was synthesized according to a previous description [24]. The synthesis of the MPEG macroinitiator was performed in accordance with a reported procedure by the reaction of monomethoxy-capped poly(ethylene glycol) (MPEG₄₅-OH with an average number molecular weight of $M_n = 2000$ was provided by the manufacturer) with 2-bromoisobutyryl bromide in the presence of trimethylamine [25,26]. All water used in this study was purified with a Millipore Mill-Q system with the resistivity of 18 MΩ cm.

2.2. Synthesis and characterization of polymer

The responsive copolymer used in this study was synthesized via a 'one-pot' two-step aqueous atom transfer radical polymerization procedure, followed by esterification with succinic anhydride of the hydroxylated precursor copolymer (Scheme 1) according to a modified reported procedure [27,28]. The chemical structure of this polymer and the approximate length of the three blocks were ascertained by the ¹H NMR spectra (Fig. 1). The ¹H chemical shifts in CD₃OD are referred to

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