



# Polysulfobetaine-surfactant solutions and their use in stabilizing hydrophobic compounds in saline solution



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## ABSTRACT

A star shaped poly(sulfobetaine methacrylate) (PSBMA) and its linear analogs, display upper-critical-solution-temperature (UCST) type behavior in 0.1 M NaCl. The presence of sodium dodecyl sulfate (SDS) or cetyl trimethyl ammonium bromide (CTAB) has a significant effect on the thermal transition of the polymer. The association of the polymer with the surfactants is confirmed by isothermal titration calorimetry (ITC) and infrared (IR) spectroscopy. SDS forms hydrophobic domains along the polymer chains, preventing the polymers from undergoing a thermal phase transition. These domains can be used to capture 1-anilino-8-naphthalenesulfonate (1,8-ANS), pyrene and curcumin, and increase their fluorescence intensity. Curcumin, which is unstable in aqueous solutions, is stabilized against degradation upon solubilization by the PSBMA-SDS complexes.

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## 1. Introduction

The excellent antifouling properties and biocompatibility of zwitterionic polymers have sparked general interest in these polymers [1–3]. The zwitterionic poly(sulfobetaine methacrylate) (PSBMA) exhibits an upper critical solution temperature (UCST) type behavior in aqueous solutions. The thermoresponsive properties of PSBMA are influenced by several factors, such as concentration, molecular weight, presence of salts, and branching of the polymer [4–9].

Zwitterionic star polymers, consisting of poly(-dimethylaminoethyl methacrylate)-*block*-poly(sulfobetaine methacrylate) [10,11], poly(carboxybetaine) [12], poly( $\epsilon$ -caprolactone)-*b*-poly(N,N-diethylaminoethylmethacrylate)-*r*-poly(N-(3-sulfopropyl)-N-methacryloxyethyl-N,N-diethylammoniumbetaine) [13], and poly(phosphorylcholine) [14–16] were recently reported as drug delivery vehicles and are readily taken up by cells. A dendritic core of poly(amidoamine) has also been utilized in producing star-shaped poly(sulfobetaine methacrylate) (PSBMA). However, the authors did not discuss the thermal response of their polymers

[17].

The solution properties of star polymers are different from their linear counter parts. They may even be considered as unimolecular micelles. The phase separation temperature (the cloud point) of thermoresponsive polymers has been shown to be greatly affected by the polymer architecture [18]. The cloud point of star-shaped polymers occurs at lower temperatures, compared to linear analogs. The cloud point can be further decreased by increasing the number of star arms. The difference in the cloud points observed between stars and linear polymers, is due to the spatial arrangement and restricted mobility of the star arms, and thus an increase in the local polymer concentration. In addition, the core of the star can also influence the solubility of the polymer [19,20].

Not much is known about the association and thermoresponsive behavior of zwitterionic polymers with surfactants. Ivanov et al. have shown that sodium dodecyl sulfate (SDS) can bind to the zwitterionic moieties. At low concentrations, SDS increases the solubility of PSBMA by affecting the bonds between the ionic groups in the polymer. As SDS is bound to PSBMA, the local surfactant concentration increases and micelles are formed along the polymer chains. Thus, with increasing SDS concentration additional crosslinking nodes are formed by the hydrophobic tails of the bound SDS molecules [21,22]. Similar observations have been made with phosphorylcholine-based polybetaines [23,24], acrylamide-

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based polysulfobetaines [25], zwitterionic thiophene polymer [26], and hydrophobically modified zwitterionic polymers [27,28]. Isothermal titration calorimetry (ITC) has been utilized in investigating the association of surfactants with hydrophobically modified zwitterionic polymers [28] and phosphorylcholine-based polybetaines [23,24].

In this study, we take a closer look at the thermoresponsive behavior of high molecular weight PSBMA, including a star polymer (230 kg/mol) and two linear polymers (54 and 330 kg/mol), in 0.1 M NaCl. We chose to work with a simple star polymer with three arms, as it has been reported that branching of the polymer can cause the cloud point to disappear. In branched PSBMA polymers, the presence of short PSBMA chains can prevent the collapse of the polymers [5].

It is known that in saline solutions PSBMA has a negative net charge, due to bound counterions. We want to examine if PSBMA can harvest negatively charged surfactant molecules (SDS) in saline solutions, be bound by positively charged micelles (cetyltrimethylammonium bromide, CTAB), or break down these positively charged micelles. We also investigate the effect of SDS and CTAB on the thermoresponsive behavior of PSBMA. Isothermal titration calorimetry and IR spectroscopy are used in investigating the binding of SDS and CTAB to PSBMA. The PSBMA-surfactant complexes are probed with fluorescence spectroscopy, to get information regarding the hydrophobicity of the complexes. In addition, the complexes were used to stabilize curcumin, a notoriously unstable substance in aqueous solutions. The obtained results are encouraging in using PSBMA-surfactant complexes as collectors or as nano reactors for hydrophobic compounds in aqueous solutions.

## 2. Experimental

### 2.1. Materials

Unless otherwise stated, all reagents and chemicals were purchased from Sigma-Aldrich (MO, USA) and used as received. Azobisisobutyronitrile (AIBN) and [2-(methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide were recrystallized from methanol prior to use. Dimethylaminoethyl methacrylate (DMAEMA) was distilled over potassium hydroxide, under reduced pressure prior to use.

### 2.2. Atom-transfer radical-polymerizations (ATRP) of DMAEMA and SBMA

The poly(dimethylaminoethyl methacrylate) (PDMAEMA) precursor for PSBMA-54k was prepared as follows. CuCl (49.9 mg, 0.50 mmol), dimethylformamide (DMF, 4 mL), and 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA, 120 mg, 0.55 mmol) were charged in a sealed flask and purged with nitrogen. DMAEMA (18.7 g, 0.12 mol), dimethylformamide (DMF, 10 mL), and ethyl-2-bromoisobutyrate (0.13 g, 0.68 mmol) were charged in another flask and purged with nitrogen. The two solutions were combined under nitrogen flow, and the polymerization was conducted at 60 °C for 19 h. The polymerization mixture was passed through a silica column to remove the copper ions and dialyzed against water. After freeze drying, 7.2 g of polymer was obtained. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ ppm): 0.90, 1.04, and 1.25 (–CH<sub>3</sub>), 1.81 and 1.91 (–CH<sub>2</sub>–), 2.27 (N-CH<sub>3</sub>), 2.56 (N-CH<sub>2</sub>–), and 4.04 (O-CH<sub>2</sub>–).

The PDMAEMA precursor for PSBMA-330k was polymerized in a similar way using CuCl (172 mg, 1.73 mmol), 0.6 mL HMTETA (0.51 g, 2.21 mmol), DMAEMA (11.2 g, 0.08 mol), and dioxane (16 mL) as a solvent, yielding in 5.0 g polymer. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ ppm): 0.92, 1.06, and 1.26 (–CH<sub>3</sub>), 1.83 and 1.92 (–CH<sub>2</sub>–),

2.30 (N-CH<sub>3</sub>), 2.59 (N-CH<sub>2</sub>–), and 4.07 (O-CH<sub>2</sub>–).

The PSBMA-10k polymer was obtained by polymerizing 1.03 g [2-(methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide in methanol/water (1:1, 9 mL), with CuBr (64.7 mg, 0.45 mmol), a copper (Cu<sup>0</sup>) chip, and HMTETA (85 mg, 0.37 mmol), and ethyl-2-bromoisobutyrate (20 mg, 0.10 mmol) at room temperature for 72 h. After dialysis and freeze-drying, 0.6 g of polymer was obtained.

### 2.3. Preparation of the star polymer by Macromolecular Design via Reversible Addition–Fragmentation Chain Transfer Xanthates–polymerization (MADIX)

#### 2.3.1. Star polymer

Dipentaerythritol-core (204.7 mg, 0.15 mmol), AIBN (16.45 mg, 0.10 mmol), and DMAEMA (4.2 g, 26.6 mmol) were dissolved in dioxane (8 mL). The solution was purged with nitrogen for 1 h and heated to 70 °C. The polymerization was stopped after 3 h by freezing the solution. The polymer was purified by precipitating it twice in cold hexane from acetone. 2.14 g of poly(dimethylaminoethyl methacrylate) (PDMAEMA) was obtained. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ ppm): 0.92, 1.07, and 1.27 (–CH<sub>3</sub>), 1.83 and 1.93 (–CH<sub>2</sub>–), 2.30 (N-CH<sub>3</sub>), 2.58 (N-CH<sub>2</sub>–), and 4.08 (O-CH<sub>2</sub>–). The synthesis of the core is described in the supporting information.

#### 2.3.2. Hydrolysis of stars

In order to determine the molecular weight of the star arms, the arms need to be detached from the core (Fig. 1). However, selective hydrolysis of the ester bonds linking the arms to the core is not possible, while not hydrolyzing the side groups. Therefore, it was decided to perform a complete hydrolysis of the polymer. The hydrolysis of PDMAEMA into poly(methacrylic acid) and hydrolysis of the ester bonds attaching the arms to the core was conducted as described by Semen et Lando [29]. PDMAEMA star polymer (200 mg) was dissolved in H<sub>2</sub>SO<sub>4</sub> (30 mL, 98%) and heated to 40 °C for 3 days. The polymer was precipitated in diethylether, filtered, washed with diethylether, and dried *in vacuo*. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O + KOH, δ ppm): 0.87, 0.98, and 1.20 (–CH<sub>3</sub>); 1.58 and 1.93 (–CH<sub>2</sub>–).

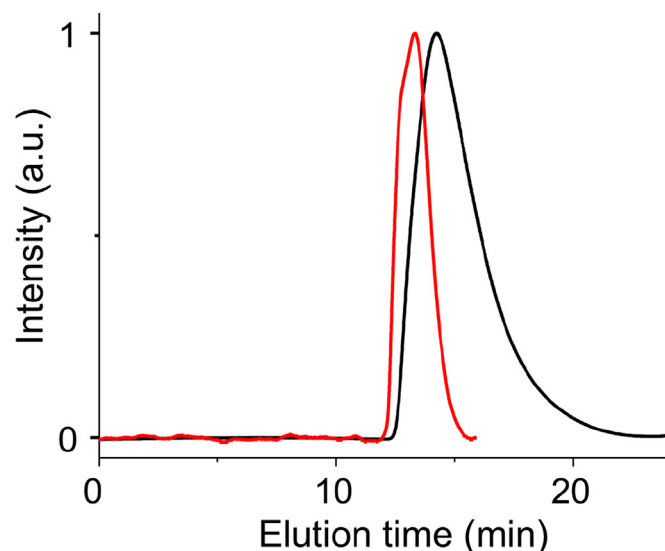


Fig. 1. Size exclusion chromatography traces of the star polymer, PDMAEMA star precursor (black, in DMF + LiBr) and hydrolyzed star arms (red, poly(methacrylic acid), in buffer solution, pH 9). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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