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# Abnormal behaviors in the calibration curves of liquid chromatography–tandem mass spectrometry occurring in the quantitative analysis of surfactants near critical micelle concentrations

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## Abstract

Surfactants, including quaternary ammonium compounds, are widely used in daily life as part of consumer chemical products and, more recently, in the shale oil industry. Because of their unique amphiphilic properties, surfactants form micelles at concentrations above a certain threshold known as the critical micelle concentration (CMC). A previous electrospray ionization mass spectrometry studies conducted by Siuzdak et al. and others presented indirect evidence regarding micelle formation. Herein, we have used liquid chromatography–tandem mass spectrometry to explore how such micelle formations affect the quantitative analysis of surfactants. Results reveal abnormal behaviors in the calibration plots of a few selected anionic and cationic surfactants, such as sodium decyl sulfate (SDeS), sodium dodecyl sulfate (SDS), myristyltrimethylammonium bromide (MTAB), and benzyldimethyloctadecylammonium chloride (BAC-18). At concentrations close to the respective CMCs of these surfactants, the calibration plot for MTAB flattened, whereas the slopes of the calibration plots for SDeS, SDS, and BAC-18 suddenly changed. These abnormal behaviors can be related to micelle formation. From a practical perspective, the above observations suggest that in the quantitative analysis of surfactants, high micelle concentrations close to the CMC should be avoided to obtain accurate surfactant measurements.

**KEYWORDS**

LC-MS, mass spectrometry, micelle, micelle formation concentration (CMC), quaternary ammonium compound (QAC), surfactant

## 1 | INTRODUCTION

Surfactants are important compounds that enable the mixing of two immiscible liquids or phases by lowering the surface tension in their interfacial region.[1] Surfactants are amphiphilic compounds containing both polar and apolar components. The polar component can be an ionic (cationic or anionic), zwitterionic, or a neutral hydrophilic group. Surfactants are often categorized according to the nature of the polar group, that is, cationic, anionic, or neutral (nonionic).[2] Quaternary ammonium compounds (QACs), which are positively charged polyatomic ions with the structure of $NR_4^+$ (where R is an alkyl group), are a type of surfactant widely used in daily life[3]: disinfectants, fabric softeners, or antistatic agents in consumer chemical products (CCPs). However, QACs are toxic; thus, the content of certain QACs in

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designated CCPs, such as benzyl alkyl ammonium chloride (or benzalkonium, BAC; C12–C18) and dialkyldimethyl ammonium chloride (DDAC; C12–C18) in fabric softeners, must be mandatorily reported to the regulatory authorities. For instance, in the case of BAC, the Korean National Institute of Environmental Research has regulated the amount of QACs in fabric softener to be below 500 mg/kg.

In aqueous solutions, surfactants spontaneously form a micelle—an aggregate of surfactant molecules dispersed in a spherical form—at concentrations above a certain threshold. However, at concentrations below this particular threshold, surfactants tend to spread on the surface of water, thereby decreasing the liquid surface tension.[4] In a micelle, the polar head group faces toward the aqueous environment and the hydrophobic tails are inside the micelle, that is, away from the water. The hydrophobic effect is the main driving force for micelle formation in an aqueous environment.[2] The threshold concentration, above which the micelle forms, is called the critical micelle concentration (CMC), and this value is deemed one of the most important physicochemical properties of surfactants.

The concentration of QACs, and surfactants in general, can be reliably measured using liquid chromatography–tandem mass spectrometry (LC-MS/MS), for example, BAC, alkyltrimethylammonium chloride, DDAC, and Triton X-100 in various environmental and food samples.[5–11] For instance, Brownawell et al. and Jiang et al. identified and quantified BAC and diallyldimethylammonium chloride in the concentration range of micrograms per gram, from sediments and sewage sludges, using reversed-phase liquid chromatography–mass spectrometry (LC-MS).[5,6] Residual QACs in food samples such as vegetables, meat, and dairy products were also determined via LC-MS by different groups.[7–9] In these methods, the QAC concentrations were measured in the range of 5–500 μg/kg, in which the upper range of the concentrations is above the CMCs of long-chain QACs, for example, C16 and C18. For the Triton X-100 surfactant, which is a nonionic surfactant that has a polyethylene oxide chain, the Horváth group recently developed an analytical method based on hydrophilic interaction LC and estimated its elution time profile by applying a quadratic retention model.[10] The processed water used in the production of oil sand in the petroleum industry contains multiple surfactants, including BAC, sodium dodecyl sulfate (SDS), and nonylphenol. Kasperski et al. recently developed a high-performance liquid chromatography–mass spectrometry (HPLC-MS/MS) method for the separation of surfactants and the selective quantitation of each surfactant in processed water.[11] In these methods, the concentration ranges of both BAC and SDS were lower than their CMCs. However, in many experimental studies mentioned above, the effects of micelle formation on quantitative analysis using LC-MS(/MS) were not discussed, as the concentration of the surfactants and QACs of interest in the samples was lower than their respective CMCs.

Interestingly, previous electrospray ionization mass spectrometry (ESI-MS) studies on surfactants, independently performed by the Siuzdak et al. and Robinson et al., suggest that micelles could be formed under ESI solution conditions.[12,13] Some indirect evidence for the formation of micelles has been reported in their studies. Thus, the effect of micelle formation must be investigated in LC-MS/MS studies on surfactants, particularly when the surfactant concentration approaches its CMC. Herein, the behaviors of the calibration curves for the selected surfactants near their respective CMCs are investigated.

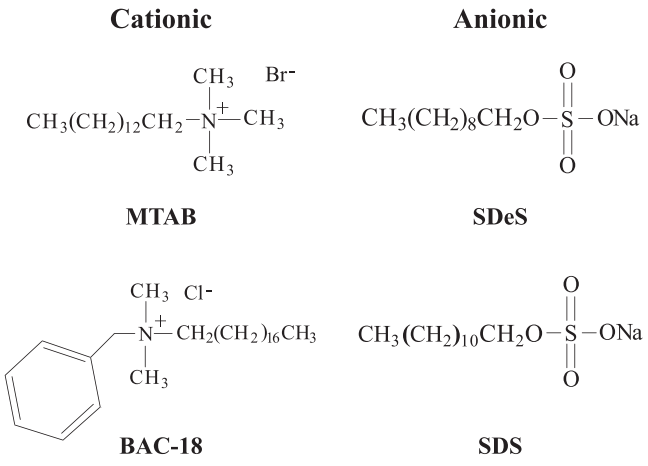
## 2 | EXPERIMENTAL

### 2.1 | Materials

Myristyltrimethylammonium bromide (MTAB or TTAB) (refer to Scheme 1), chloroform, ammonium acetate, ammonium formate, phosphoric acid, and formic acid were purchased from Sigma Aldrich (St. Louis, MO, USA). BAC-18, SDS, and SDeS, whose structures are also shown in Scheme 1, were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). The purities of the chemicals used were at least >97%. Organic solvents (methanol, acetonitrile, and 2-propanol) and water were all HPLC-grade and purchased from Daejung Chemicals & Metals (Siheung, Korea).

### 2.2 | Liquid chromatography

Chromatographic separation was performed using an Ultimate 3000 RS ultrahigh-performance liquid chromatograph (UPLC) equipped with an autosampler and a column oven (Thermo Fisher Scientific, San Jose, CA, USA). Acclaim™ Surfactant Plus column (3 μm, 120 Å, 2.1 × 150 mm) was used for analyzing SDeS and SDS. For the LC-MS/MS analysis of MTAB and BAC-18, reversed-phase separation was performed using an Acquity UPLC® BEH C8 column (1.7 μm, 130 Å, 2.1 × 100 mm) manufactured by Waters (Milford, MA, USA). For the quantitation of SDeS and SDS using LC-MS/MS, the following mobile phases were used: acetonitrile as mobile phase A and 100-mM ammonium acetate (pH 5.8) as mobile phase B. Mobile phases for the




**SCHEME 1** Chemical structures of the surfactant molecules used in this study

cationic surfactant reversed-phase separation comprised mobile phase A (0.1% formic acid in Water/ACN [*v*/v, 9:1]) and mobile phase B (0.1% formic acid and 8-μM phosphoric acid in 2-propanol). The temperature settings for the autosampler and the column oven were set as 25°C. The gradient elutions for both methods are provided in the Supplementary Information (ESI, Tables S1 and S2).

### 2.3 | Mass spectrometry

A triple quadrupole mass spectrometer (TSQ Quantum Ultra, Thermo Fisher Scientific, San Jose, CA, USA) equipped with a HESI II source was used for the direct-infusion ESI-MS analysis and the quantification of the selected surfactants using a selected reaction monitoring (SRM) approach. Surfactant solutions were directly infused into the mass spectrometer at a flow rate of 15 μL $min^{-1}$, and ESI-MS spectra for the directly infused samples were obtained by averaging 20 scans. Cationic and nonionic surfactants as well as anionic surfactants were analyzed in positive- and negative-ion modes, respectively. The ESI parameters in the positive-ion mode were as follows: spray voltage, +4.0 kV; heated capillary temperature, 300°C; vaporizer temperature, 0–300°C; sheath gas ($N_2$), 20 (arbitrary unit); and tube lens, +96 V. Those in negative-ion mode were as follows: spray voltage, −5.0 kV; heated capillary temperature, 300°C; vaporizer temperature, 0–300°C; sheath gas ($N_2$), 20 (arbitrary unit); and tube lens, −100 V. Skimmer offset (or source fragmentation) was used in the range of 0–100 V. The parameter settings for SRM for both positive- and negative-ion modes were the same: scan width, *m/z* 1.25; scan time, 0.100 s; Q1 peak width (full width at half maximum [FWHM]), and 0.8; Q3 peak width (FWHM), 0.7. Table 1 lists the precursor ions, product ions, and collision energies for the targeted quantification of surfactant samples. The SRM spectra were analyzed using Xcalibur 3.0 software (Thermo Fisher Scientific, San Jose, CA, USA).

### 2.4 | Sample preparation

Surfactants analyzed via direct-infusion ESI-MS were prepared at different concentrations. For anionic surfactants, SDeS was prepared at 1, 5, and 30 mM, and SDS was prepared at 0.1, 1, and 10 mM by dissolving adequate amounts of the surfactant in a solution of 50-mM ammonium acetate in water:ACN (*v*/v, 1:1) to ensure that pH of the solvent becomes approximately 5.5. The cationic surfactants, MTAB and BAC-18, were prepared at two different concentrations in a solution of IPA:water:ACN (*v*/v, 90:9:1): 0.05 and 3 mM for MTAB and 0.001 and 0.1 mM for BAC-18.

## 3 | RESULTS

### 3.1 | Direct-infusion ESI-MS

To understand the mass spectral behavior and characteristics, direct-infusion ESI-MS spectra were obtained for some of the aforementioned anionic and cationic surfactants.

#### 3.1.1 | Anionic surfactants (SDeS and SDS)

Two anionic surfactants, SDeS and SDS, were chosen to investigate the behavior of the calibration curves near their respective CMCs. Figure 1 shows the direct-infusion ESI-MS spectra of SDeS and SDS at concentrations lower and higher than their CMCs, which are reported to be 24–32 mM and 1.86–8.2 mM, respectively.[14–20] To this end, a solution of 50-mM ammonium acetate in water:ACN (*v*/v, 1:1) was used as an ESI solvent, which also corresponded to the solvent in the elution of the anionic surfactants in the chromatographic gradient run of the LC-MS/MS experiments; a change in the slopes of calibration curves occurred approximately in this solvent composition (see below). The use of 50-mM ammonium acetate buffer ensured that the pH of the solvent became approximately 5.5, which improved the separation of the anionic surfactants. For SDeS, a monomeric form of $[DeS–H]^-$, a deprotonated decyl sulfate ion formed by the loss of its counterion from SDeS, appeared as the dominant ion in the spectra (see Figure 1A,B) at concentrations lower than the CMC, that is, 1 and 5 mM. Here, it should be noted that the reported CMCs given above may be different from the effective CMCs in our experimental conditions. In general, the CMC is dependent upon the solvent composition, and the solvent composition used in this study was different from those in literature.[14–20] As the concentration approached or exceeded the reported CMC value, that is, 30 mM, multimeric forms were observed, including dimeric, trimeric, and tetrameric forms (Figure 1C); the larger cluster ion, such as pentameric peak, however, was not observed.

For SDS, only a monomeric form of $[DS–H]^-$ appeared at concentrations lower than the CMC, that is, 0.1 and 1.0 mM (Figure 1D,E),

**TABLE 1** List of precursor ions, product ions, and the collisional energies of the surfactants used in the quantitation studies using UPLC-ESI-SRM/MS

| Type | Sample | Polarity | Precursor ion (*m/z*) | Product ion (*m/z*) | Collisional energy (V) |
|---|---|---|---|---|---|
| Cationic | Myristyltrimethylammonium bromide | Pos | 256.5 | 59.8 | 22 |
| | Benzyldimethyloctadecylammonium chloride | | 388.5 | 90.8 | 36 |
| Anionic | Sodium decyl sulfate | Neg | 237.5 | 96.8 | 26 |
| | Sodium dodecyl sulfate | | 265.5 | 96.8 | 28 |

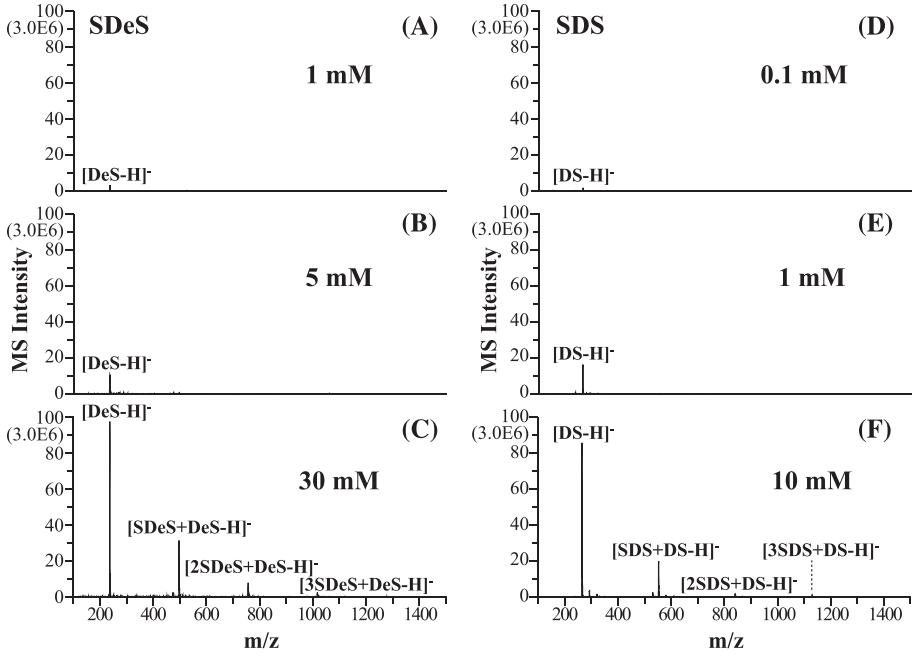



**FIGURE 1** Direct-infusion electrospray ionization mass spectra of sodium decyl sulfate (SDeS) at the concentrations of (A) 1, (B) 5, and (C) 30 mM. Those of sodium dodecyl sulfate (SDS) are also shown at concentrations of (D) 0.1, (E) 1, and (F) 10 mM

wherein $[DS–H]^-$ is a deprotonated dodecyl sulfate ion formed by the loss of the counterion from SDS. At a concentration higher than the CMC, that is, 10 mM, multimeric forms are observed, including dimeric, trimeric, and tetrameric ions; the larger cluster ion (higher than tetramer), however, was not observed at high concentrations. Tandem mass spectrometry indicated that the multimetric ions mainly comprised $[DeS–H]^-$/$[DeS + SDeS–H]^-$ and $[DS–H]^-$/$[DS + SDS–]^-$ ions, clearly indicating that these ions are noncovalent multimeric forms of SDeS and SDS, respectively (see Figures S1 and S2). In the previous study conducted by Siuzdak et al., the observation of multimeric ions was given as an indirect evidence to support the formation of micelles from surfactant molecules.[12]

To effectively quantify SDeS and SDS, reducing the abundance of dimeric peaks was necessary. To minimize the abundance of the multimeric forms, the skimmer offset potential (leading to in-source fragmentation) and the ESI source temperature were optimized. The skimmer offset potential was adjusted between 0 and 20 V. The relative abundance of the monomeric form increased with the skimmer offset potential. At a skimmer offset potential higher than +20 V, the spectrum quality of the ESI deteriorated. In addition, the optimal source temperature of ESI for maximizing the abundance of $[DS–H]^-$ was 100°C.

### 3.1.2 | Cationic surfactants (MTAB and BAC-18)

For the investigation conducted herein, two cationic surfactants, alkyltrimethylammonium bromide (ATMAB) and BAC, were selected as they are widely used CCPs, for example, they are used in detergents and fabric softeners. Both surfactants have a long hydrophobic hydrocarbon chain with a chain carbon number ranging from 8 to 18. In this study, only one specific member of the ATMAB and BAC families each, that is, MTAB with C14 and BAC-18 with C18 (see Scheme 1), was chosen for investigation. The results and methods shown in this study are expected to be applicable to the other members of the families.

First, direct-infusion ESI-MS spectra were obtained for MTAB and BAC-18 at concentrations lower and higher than their reported CMC values, which is 3.4–3.9 mM and 0.093 mM for MTAB and BAC-18, respectively (see Figure 2).[1,17,21,22] In obtaining the direct-infusion ESI-MS spectra of both surfactants, a solution of IPA:water:ACN (*v*/*v*, 90:9:1) was used as an ESI solution as it corresponded to the solution in the elution of the cationic surfactants in the chromatographic gradient run of the LC-MS/MS experiments (see below). For MTAB, only $[MTA]^+$ was observed at *m/z* 256.3 at a concentration lower than its CMC, that is, 0.05 mM, wherein $[MTA]^+$ is the cation of MTAB that lost its bromide counterion (Figure 2A). However, at 5 mM, which is higher than its reported CMC, a dimeric form $[MTAB + MTA]^+$ appeared at *m/z* 593.6 (Figure 2B); the identity of which was confirmed in the MS/MS spectrum (see Figure S3b). High multimeric forms of MTAB were, however, not observed in the ESI-MS spectrum, even at high concentrations above the CMC.

Identical results were also observed for BAC-18. At high concentrations above its reported CMC, a dimeric peak of $[BAC + BA]^+$ was observed (BA refers to the cation that lost its chloride counterion from BAC). As observed in the case of MTAB, high multimeric forms were not observed in the direct-infusion ESI-MS spectrum. The absence of the multimeric forms for the cationic surfactants may be due to the weaker binding affinity among the cationic surfactants in comparison with the anionic surfactants. Strong interactions in SDeS and SDS can occur through the three oxygen atoms; however, these are absent in the two cationic surfactants.

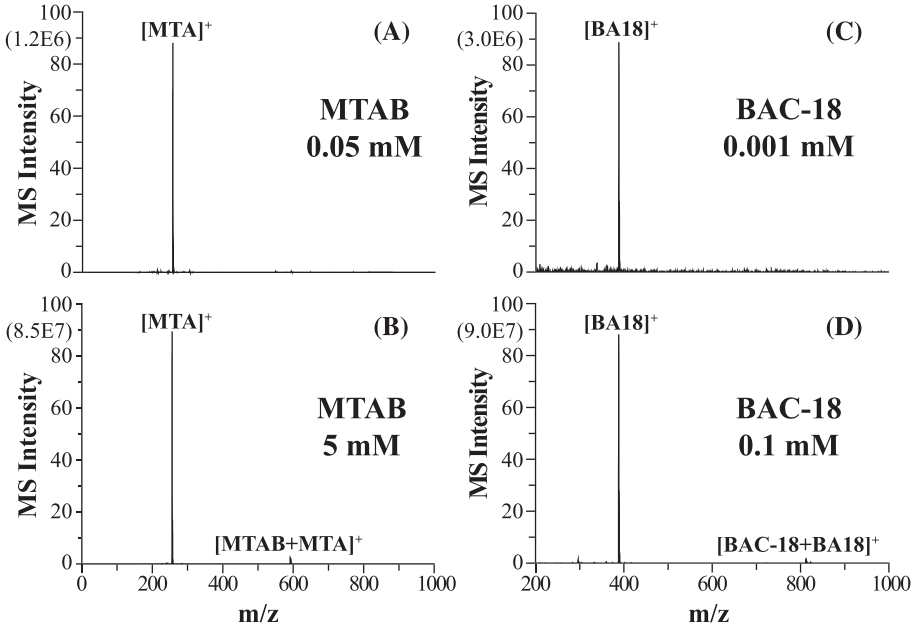



**FIGURE 2** Direct-infusion electrospray ionization mass spectra of myristyltrimethylammonium bromide (MTAB) at (A) 0.05 and (B) 3 mM. Those of benzyldimethyloctadecylammonium chloride (BAC-18) at (C) 0.001 and (D) 0.1 mM

In addition, similar to the case of the anionic surfactants, the two experimental parameters, that is, skimmer offset potential and ESI source temperature, were carefully optimized to effectively quantify MTAB and BAC-18.

## 3.2 | LC-ESI-SRM/MS analysis of the surfactant samples

### 3.2.1 | Anionic surfactants

For monomeric SDeS and SDS, UPLC-ESI-SRM/MS chromatograms were obtained over a wide concentration range that included the reported CMC values of SDeS and SDS. The chromatographic peak areas of the monomeric SDeS and SDS with respect to their concentrations are plotted (Figure 3). For each calibration curve in Figure 3A, B, the reported CMC of each surfactant is denoted using the gray shade. Interestingly, in both cases, the slopes of the calibration curve are markedly different at low and high concentrations. Specifically, as clearly shown in Figure 3A, the linear slope of the SDeS calibration plot changed from 0.9927 to 0.9870 just below the reported CMC at 24–32 mM.[14–17] For SDS, the same phenomenon is observed near the reported CMC at 1.86–8.2 mM.[14,17–20]

The decrease in the slopes at high concentrations above the reported CMC can be related to the observation of noncovalent multimers at concentrations higher than the reported CMCs as observed in the direct-infusion ESI-MS (see above). Thus, it can be attributed to micelle formation (further discussion will be provided below).

### 3.2.2 | Cationic surfactant

UPLC-ESI-SRM/MS chromatograms were also obtained over a wide concentration range for monomeric MTAB and BAC-18. The chromatographic peak areas of the two surfactants with respect to their concentrations are plotted, as shown in Figure 4. In these plots, two notable characteristics are observed. First, below the reported CMCs, which is denoted by a shaded area or by a dotted line, the chromatographic peak areas increase more or less linearly as the concentration increases. However, at the concentrations higher than the reported CMCs, the plot of the MTAB flattens and the slope of the BAC-18 plot changes. In particular, it could be speculated that the flattening of

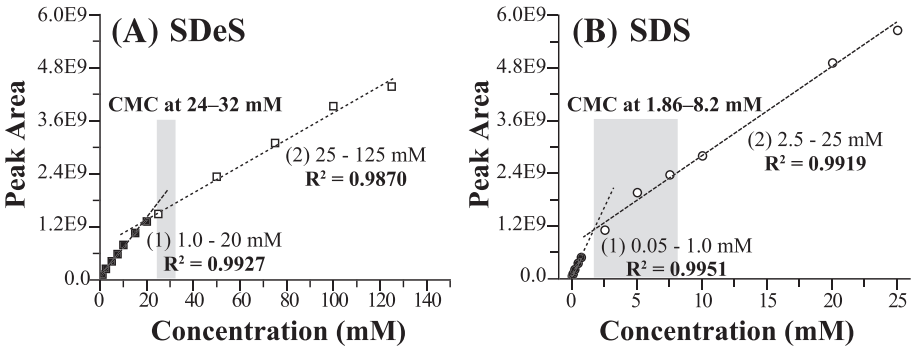



**FIGURE 3** Calibration plots for (A) sodium decyl sulfate (SDeS) and (B) sodium dodecyl sulfate (SDS). The critical micelle concentrations are denoted in a shaded box

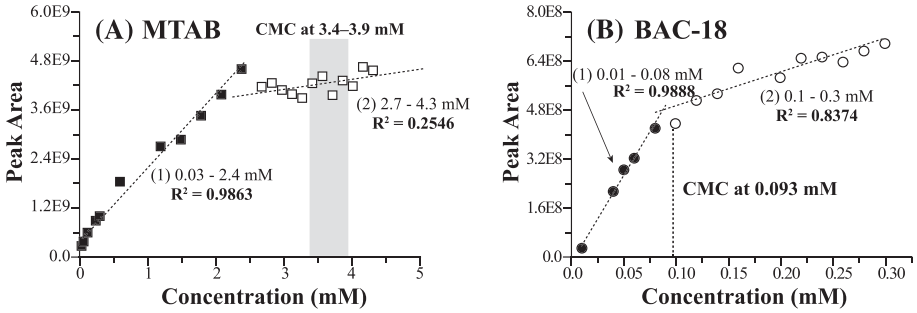



**FIGURE 4** Calibration plots for (A) myristyltrimethylammonium bromide (MTAB) and (B) benzyldimethyloctadecylammonium chloride (BAC-18). The critical micelle concentrations are denoted either in a shaded box (A) or with a dotted line (B)

the MTAB might be attributed to the saturation of the mass analyzer at high concentrations; however, it was confirmed that this was not the case in this experiment.

To the best of our knowledge, this is the first report that shows the flattening or a slope change in the calibration curves close to the CMCs of the examined surfactants. In most literature, the concentration range for measurements was much lower than the CMC because majority of research focuses on residual surfactants in environmental samples, such as river water, sludges, and soils.[5,6,23,24] Notably, the concentration at which the leveling-off or the slope change occurred does not explicitly match the CMC of the surfactants. It appears at concentrations slightly lower than the actual CMC values.

## 4 | DISCUSSION

We observed a change in the slopes of the calibration plot for certain surfactants, such as SDeS, SDS, and BAC-18, as their concentrations approached the reported CMC of the individual surfactant. On the other hand, the MTAB calibration plot plateaued as its concentrations approached the reported CMC. How can this abnormal chromatographic behavior be explained?

The hint to this question can be found in the previous study conducted by Siuzdak et al.[12] They explained that as the concentration of the selected surfactants approached their CMCs, micelles formed. When the formed micelles were electrosprayed to form a fine mist in the gas phase, some of the droplets containing micelles were directed toward the inlet of the mass spectrometer. On traveling toward the mass spectrometer inlet, a droplet would experience fast evaporation, and positive or negative charges accumulated in the droplet. The ionic repulsion between the like-charges within the diminishing droplet destabilized both the micelles and the droplet. Surfactant molecules could be repelled out of the micelle, causing micelle disruption. Then a single surfactant molecule or multimeric formed from the supercharged droplets would eject out of the droplet, finally entering the inlet of the mass spectrometer. The micelle formation within a droplet could be affected by many processes involved in the electrospraying, such as evaporation and transport into the mass spectrometer, thus inducing a significant change in the total amount of surfactants that enter a mass spectrometer. The change in the slopes of the calibration plot or the flattening of the calibration plot could occur in this manner.

Several other factors should be considered in explaining the abnormal chromatographic behavior. For example, the chromatographic gradient profile and the solution composition (including the buffer solution), which surrounds the surfactant molecules, may affect micelle formation. In hydrophobic solvent conditions, reverse micelles may form, wherein the hydrophobic tails would face the hydrophobic solvent and the polar head group would be inside the reverse micelles, away from the hydrophobic solvent. Potentially, even reverse micelles in a droplet could similarly affect the total amount of surfactants that could be introduced into a mass spectrometer.

As shown in Figures 3 and 4, the abnormality of the calibration curves began appearing at concentrations lower than their reported CMCs. Siuzdak et al. pointed out that the ESI droplet evaporation significantly increased the surfactant concentration within a droplet and reached CMCs at concentrations much lower than the original CMCs.[12] Even in UPLC-ESI-MS, the same evaporation process is expected to make the droplet reaches the CMCs at much lowered nominal surfactant concentrations.

## 5 | CONCLUSIONS

Abnormal behaviors in the calibration curves, that is, flattening of the curve or changes in the linearity, were observed for selected cationic and anionic surfactants near their respective CMCs in UPLC-ESI-SRM/MS quantitative analysis. In direct-infusion ESI-MS analysis of the selected surfactants, multimeric ions, which presumably originated from micelles formed at concentrations near or higher than the CMC, were observed for the two anionic surfactants examined here. In an electrosprayed droplet that undergoes fast evaporation, the micelles formed within the droplet may experience highly accumulated charges, thereby disrupting into monomeric surfactants and multimeric surfactants. Similarly, micelles formed during UPLC-ESI-SRM/MS could increase the number of multimeric surfactants, which could induce the underestimation of the monomeric ions. In addition, micelles formed within a droplet could be affected by many processes themselves, such as electrospraying, evaporation, and transport into a mass spectrometer, thus lowering the total amount of surfactants that could enter a mass spectrometer.

In the future, we will examine nonionic surfactants to investigate whether noncharged surfactants exhibit the same behavior as that observed herein. Our results also suggest that the abnormal behavior

in the calibration curve of the charged surfactants may provide an opportunity to roughly estimate their CMCs, at least for the surfactants explored in this study. Finally, from a practical perspective, our results suggest that in the quantitative studies on surfactants, surfactants of interest should be analyzed at concentrations well below their CMCs to accurately determine their concentrations.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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