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Journal of Chromatography A, 1037 (2004) 467–478
JOURNAL OF CHROMATOGRAPHY A
www.elsevier.com/locate/chroma

Review

Determination of critical micelle concentration of surfactants by capillary electrophoresis

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Abstract

Capillary electrophoresis (CE) has been proven to be a convenient and useful technique for the determination of the critical micelle concentration (CMC) of a surfactant in an electrophoretic system under operating conditions. In this review, methodological approaches to the determination of the CMC of surfactants by CE technique are described. The practical requirements for making such measurements and the CMC values of surfactants determined by CE methods are presented. In addition, difficulties and uncertainty, as well as misconceptions that may arise in the CMC determination are discussed.

Keywords: Reviews; Critical micellar concentration; Micellar electrokinetic chromatography; Capillary electrophoresis; Surfactants

Contents

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doi:10.1016/j.chroma.2003.11.059

1. Introduction

Capillary electrophoresis (CE) has been proven to be a powerful technique for the separation of a variety of analytes owing to the advantages of high efficiency, high resolution, rapid analysis, and very small volume of sample [1–3]. Capillary zone electropheresis (CZE) and micellar electrokinetic chromatography (MEKC) are the two most widely used separation modes of this technique. The operation of MEKC separation needs a background electrolyte (BGE) containing one or more surfactants above their critical micelle concentration (CMC) [4,5]. The separation principle of MEKC is based on the differential partitioning of analytes between the micellar and aqueous phases [6,7]. With the use of various ionic surfactants, the selectivity of both neutral and charged compounds is optimized [8,9]. On the other hand, surfactants are frequently added in the BGEs in CZE in order to affect the electroosmotic flow (EOF) and to improve the separation selectivity of analytes [10]. Hence, the optimization of the analytical conditions and the separation of analytes in CE have been the subjects of an important field of research [1–3]. In view of many advantageous applications of CE and the study of the micellization process being a key parameter in the optimization of analytical conditions in CE, particularly in MEKC, a good understanding of the micellization of a surfactant is of fundamental importance and the determination of the CMC of surfactants under the operating conditions of a system is certainly desirable.

A number of methods, including electrical conductivity [11–14], surface tension [15], light scattering [16,17], spectrophotometry [13,14,18], cyclic voltammetry [19], NMR [20], speed of sound [21], CE [5–7,22–33], etc., have been used to determine the CMC of a surfactant. As the CMC value of a surfactant is affected by the operating conditions of an electrophoretic system and the nature of the micellar buffer electrolyte, including the nature of the surfactant [8,9,34,35], the type and composition of the electrolyte solution [23,34,35], buffer pH [36,37], the ionic strength of the electrolyte solution [23,34,36,38], the type of counter-ion of the electrolyte solution [39], the type of counter-ion of the surfactant [39–41], the presence of various organic modifiers [23,34,42,43], the presence of various electrolyte additives [21,27,34,44–49], temperature [34,36,50], and the nature of solubilized solutes [7,26], CE is conveniently applied to the determination of the CMC of a surfactant in an electrophoretic system under any operating conditions in which some of the conventional methods such as conductivity and surface tension measurements are unsuitable. Moreover, the technique appears to be not only quick but also easy to be carried out.

Several approaches based on CE technique have been proposed to determine the CMC values of surfactants [5–7,22–33]. Among them, three major methods are emphasized in this article. The first method, proposed by Terabe et al. [4], is based on the linear relationship of the retention factor of a solute with micelle concentration using MEKC technique. The second method is based on the variation of the effective electrophoretic mobility of a marker compound as a function of surfactant concentration in the premicellar and micellar regions. By plotting the effective electrophoretic mobility of a marker compound against surfactant concentration, a sharp change in slope can be observed at the CMC [22–27]. The third method is based on the measurements of the electric current of micellar electrolyte solutions as a function of surfactant concentration using CE instrumentation at a given applied voltage [28].

In this review, methodological approaches to the determination of the CMC of surfactants by CE methods are described. The practical requirements for making CMC measurements and the CMC values of surfactants determined by CE methods are presented. In addition, difficulties, uncertainty, and misconceptions that may arise in the CMC determination are discussed.

2. Methodological approaches

2.1. Method based on the retention model—micellar electrokinetic chromatography method

It has been known that the effective electrophoretic mobility of a neutral solute (μ_{eff}) in MEKC is proportional to the mobility of the micellar phase (μ_{mc}) and is given by [6]:

$$\mu_{eff} = \frac{k}{1+k}\mu_{mc} \tag{1}$$

where k is the retention factor of the solute and the term $k/(1+k)$ represents the mole fraction of the solute in the micellar phase. Eq. (1) can be rearranged and expressed as:

$$k = \frac{\mu_{eff}}{\mu_{mc} - \mu_{eff}} \tag{2}$$

In CE, the electrophoretic mobility of a solute is related to the migration times by:

$$\mu_{eff} = \left(\frac{1}{t_r} - \frac{1}{t_{eo}}\right)\left(\frac{L_t L_d}{V}\right) \tag{3}$$

where t_r and t_{eo} are the migration time of the solute and that of the neutral marker, respectively, L_t and L_d the total length of the capillary and the distance from the upstream end to the detector, respectively, and V is the applied voltage. By substituting migration times for the mobilities in Eq. (2), the retention factor can be expressed in terms of migration times as [4–6]:

$$k = \frac{t_r - t_{eo}}{t_{eo}(1 - t_r/t_{mc})} \tag{4}$$

where t_{mc} is the migration time of a micelle marker. Accordingly, the retention factor of a neutral solute can be calculated from the migration times.

For an anionic solute, the effective electrophoretic mobility can be described as the weighted average of the mobility

of the solute in the micellar phase and its own mobility in the aqueous phase and is given by [6]:

$$\mu_{\text{eff}} = \left(\frac{k}{1+k}\right)\mu_{\text{mc}} + \left(\frac{1}{1+k}\right)\mu_0 \quad (5)$$

where μ_0 is the mobility in the absence of micelles in the aqueous phase. Similarly, Eq. (5) can be rearranged and expressed as [6]:

$$k = \frac{\mu_{\text{eff}} - \mu_0}{\mu_{\text{mc}} - \mu_{\text{eff}}} \quad (6)$$

and

$$k = \frac{t_{\text{r}} - t_0}{t_0(1 - t_{\text{r}}/t_{\text{mc}})} \quad (7)$$

where t_0 is the migration time of the anionic solute in the absence of micelles.

For an acidic solute, the situation becomes more complicated. The effective electrophoretic mobility is expressed as the weighted average of a solute with the mobility of the micellar phase and its own mobility in the aqueous phase as described in Eq. (5). However, depending on the pH of the buffer electrolyte, the electrophoretic mobility of an acidic solute in the absence of micelles is expressed as:

$$\mu_0 = \frac{K_{\text{a}}}{K_{\text{a}} + [H^+]}\mu_{\text{A}^-} \quad (8)$$

where μ_{A^-} is the mobility of the fully dissociated species and K_{a} is the acid dissociation constant. Therefore, the retention factor of an acidic solute can be expressed as the weighted average of the retention factor of its undissociated form (k_{HA}) and that of the fully dissociated form (k_{A^-}) as [6]:

$$k = \left(\frac{[\text{H}^+]}{[\text{H}^+] + K_{\text{a}}}\right)k_{\text{HA}} + \left(\frac{K_{\text{a}}}{[\text{H}^+] + K_{\text{a}}}\right)k_{\text{A}^-} \quad (9)$$

$$k = \frac{k_{\text{HA}} + (K_{\text{a}}/[\text{H}^+])k_{\text{A}^-}}{1 + K_{\text{a}}/[\text{H}^+]} \quad (10)$$

It should be noted that, in this case, the interactions of a selected acidic solute with surfactant monomers are usually assumed to be negligibly small.

For a basic solute with an anionic surfactant as a micelle forming agent, there involves an equilibrium due to ion-pairing interaction between a cationic solute and the anionic micelles, in addition to the equilibrium of base dissociation. Again, the effective electrophoretic mobility of a basic solute can be described as the weighted average of a solute with the mobility of the micellar phase and its characteristic mobility in the aqueous phase by the equation [7]:

$$\mu_{\text{eff}} = \frac{K_{\text{b}}/(1 + K_{\text{b}} + K_{\text{b}}K_1)}{1+k}\mu_{\text{c}} + \frac{k}{1+k}\mu_{\text{mc}} \quad (11)$$

where μ_{c} is the electrophoretic mobility of the nonion-paired species, K_{b} is defined as the base constant of the solute divided by the concentration of the hydroxide ion, and K_1 is the product of the CMC and the ion-pairing equilibrium constant. Thus, k can be expressed as [7]:

$$k = \frac{\mu_{\text{eff}} - [K_{\text{b}}/(1 + K_{\text{b}} + K_{\text{b}}K_1)]\mu_{\text{c}}}{\mu_{\text{mc}} - \mu_{\text{eff}}} \quad (12)$$

where $\mu_{\text{c}} = \mu_0(1 + K_{\text{b}})/K_{\text{b}}$.

On the other hand, k is related to the partition coefficient of a solute between the micellar and aqueous phases (P_{mw}) and the phase ratio ($V_{\text{mc}}/V_{\text{aq}}$) by the equation:

$$k = \frac{P_{\text{mw}}V_{\text{mc}}}{V_{\text{aq}}} \quad (13)$$

The phase ratio is governed by three parameters as shown in the following equation [5]:

$$\frac{V_{\text{mc}}}{V_{\text{aq}}} = \frac{\tilde{V}(C_{\text{T}} - \text{CMC})}{1 - \tilde{V}(C_{\text{T}} - \text{CMC})} \quad (14)$$

where $\tilde{V}$ and C_{T} are the molar volume and total surfactant concentration, respectively. At low micellar concentrations, the phase ratio is approximately equal to $\tilde{V}(C_{\text{T}} - \text{CMC})$. In this case, k is linearly related to C_{T} by the following equation [5]:

$$k = P_{\text{mw}}\tilde{V}(C_{\text{T}} - \text{CMC}) \quad (15)$$

By plotting k against C_{T}, the CMC of a surfactant can be easily determined from Eq. (15).

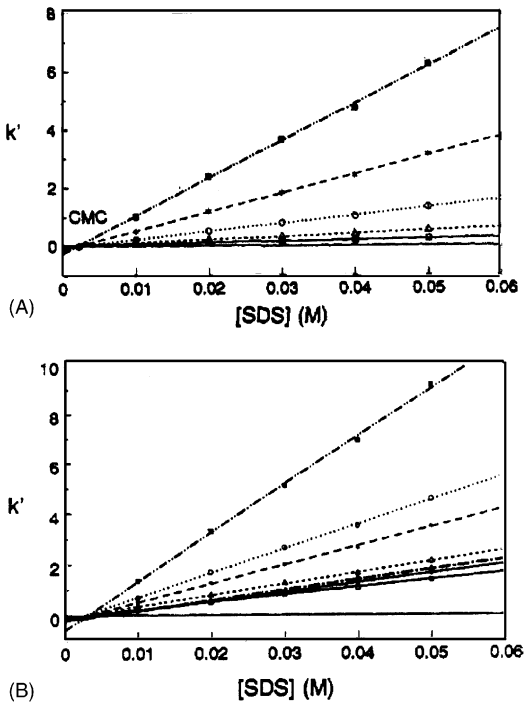

Fig. 1. Relationship between k and [SDS] for (A) some neutral solutes: 2-naphthol (■), toluene (∗), nitrobenzene (○), phenol (Δ), and resorcinol (□), and (B) some anionic solutes (chlorophenols, CPs): 2CP (□), 3CP (Δ), 23CP (○), 25CP (∗), 245CP (■), 246CP (▲), and pentaCP (●). Electropherograms measured in 50 mM phosphate buffer at pH 7.0 (40 °C). Reprinted from [6], with permission.

For illustration, Fig. 1 shows the plots of k versus sodium dodecylsulfate (SDS) concentration for some neutral solutes (benzene derivatives) using Eq. (4) to evaluate k values and some anionic solutes (chlorophenols) using Eq. (7) to evaluate k values. As shown, all lines almost pass through the same intercept, and the slope of the line (P_{mw}) increases with the hydrophobicity of the compound. The results indicate that a stronger interaction between the selected test solute and the surfactant may yield a smaller error in the determination of the CMC value.

2.2. Method based on the mobility model—capillary electrophoresis (mobility) method

In the evolution of the effective electrophoretic mobility of a marker compound as a function of surfactant concentration in the premicellar and micellar regions, a dramatic change in slope at a particular surfactant concentration is observed. This particular concentration is a good indication of the CMC of the surfactant.

The method based on this concept was first introduced by Jacquier and Desbene [22] using naphthalene as a marker compound for determining the CMC of SDS. A sharp change in slope was observed at around 5 mM when mobility curves were plotted as a function of SDS concentration in the premicellar and micellar regions. The mobility equations for describing the migration behavior of naphthalene in the premicellar and micellar concentration regions are given by [22]:

$$\mu_{\text{eff}} = \frac{K_{\text{solv}}[C_{\text{T}}]}{1 + K_{\text{solv}}[C_{\text{T}}]}\mu_{\text{solv}} \quad (C_{\text{T}} < \text{CMC}) \tag{16}$$

and

$$\mu_{\text{eff}} = \frac{K_{\text{solv}}[\text{CMC}]}{1 + K_{\text{solv}}[\text{CMC}]}\mu_{\text{solv}} + \frac{K_{\text{mc}}[M]}{1 + K_{\text{mc}}[M]}\mu_{\text{mc}} \quad (C_{\text{T}} > \text{CMC}) \tag{17}$$

where K_{solv} and μ_{solv} are the binding constant and the limiting mobility of solvophobic complexes formed between the test solute and surfactant monomers through solvophobic interactions, K_{mc} is the binding constant of the solute to the micelles, and $[M]$ is the micelle concentration which is equal to $(C_{\text{T}} - \text{CMC})/n$, where n is the aggregation number.

This method has been further developed by Lin et al. [24–27]. When the interaction between the selected neutral solute and surfactant monomers becomes significantly strong, the mobility equation for describing the migration behavior of solutes in the micellar concentration region needs to be modified as follows [24]:

$$\mu_{\text{eff}} = \frac{K_{\text{AS}}(\text{CMC})\mu_{\text{AS}} + K_{\text{AM}}[M]\mu_{\text{mc}}}{1 + K_{\text{AS}}(\text{CMC}) + K_{\text{AM}}[M]} \quad (C_{\text{T}} > \text{CMC}) \tag{18}$$

where K_{AS} and μ_{AS} (corresponding to K_{solv} and μ_{solv}, respectively, in Eq. (17)) are the binding constant and the limiting mobility of the complexes formed between the neutral solute (A) and surfactant monomers(s). For demonstration, Fig. 2 shows the variation of the electrophoretic mobility of propazine as a function of dodecyltrimethylammonium bromide (DTAB) concentration in the range 4–25 mM using a phosphate buffer (70 mM) at pH 6.0. By curve-fitting the simulated mobility curves to the experimental points obtained in the premicellar and micellar concentration regions, the CMC value can be precisely determined from the intersection point of the two curves.

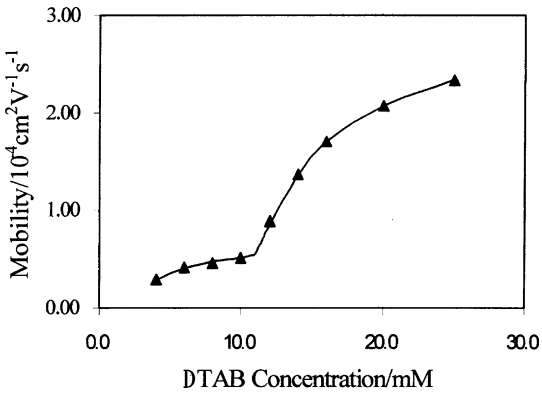

Fig. 2. The agreement between the predicated (represented by solid line) and observed (shown by data points) mobility curves of propazines as a function of DTAB concentration in 70 mM phosphate buffer at pH 6.0. Reprinted from [24], with permission.

Different mobility equations should be derived for describing the migration behavior of various types of test solutes in different electrophoretic systems [24–27]. For example, the effective electrophoretic mobility of a negatively charged solute (A^-) in the premicellar and micellar concentration regions, respectively, can be described by the following equations [25,26]:

$$\mu_{\text{eff}} = \frac{\mu_{\text{A}^-} + K_{\text{A}^-\text{S}}[S]\mu_{\text{A}^-\text{S}}}{1 + K_{\text{A}^-\text{S}}[S]} \quad (\text{below the CMC}) \tag{19}$$

and

$$\mu_{\text{eff}} = \frac{\mu_{\text{A}^-} + K_{\text{A}^-\text{S}}(\text{CMC})\mu_{\text{A}^-\text{S}} + K_{\text{A}^-\text{M}}[M]\mu_{\text{mc}}}{1 + K_{\text{A}^-\text{S}}(\text{CMC}) + K_{\text{A}^-\text{M}}[M]} \quad (\text{above the CMC}) \tag{20}$$

where μ_{A^-} is the electrophoretic mobility of the negatively charged solute, $K_{\text{A}^-\text{S}}$ and $\mu_{\text{A}^-\text{S}}$ are the binding constant and electrophoretic mobility, respectively, of the negatively charged solute associated with the anionic surfactant monomers, and $K_{\text{A}^-\text{M}}$ is the binding constant of the charged solutes to the micelles. In the case of a cyclodextrin (CD), the mobility equations derived become very complicated because SDS monomers interact strongly with CD and many chemical equilibria are involved among analytes, CD, SDS monomers, and SDS micelles [27].

The CMC values of cationic surfactants such as tetradecyltrimethylammonium bromide (TTAB) and dodecyltrimethylammonium bromide (DTAB) with propazine and cephalosporins chosen as marker compounds were de-

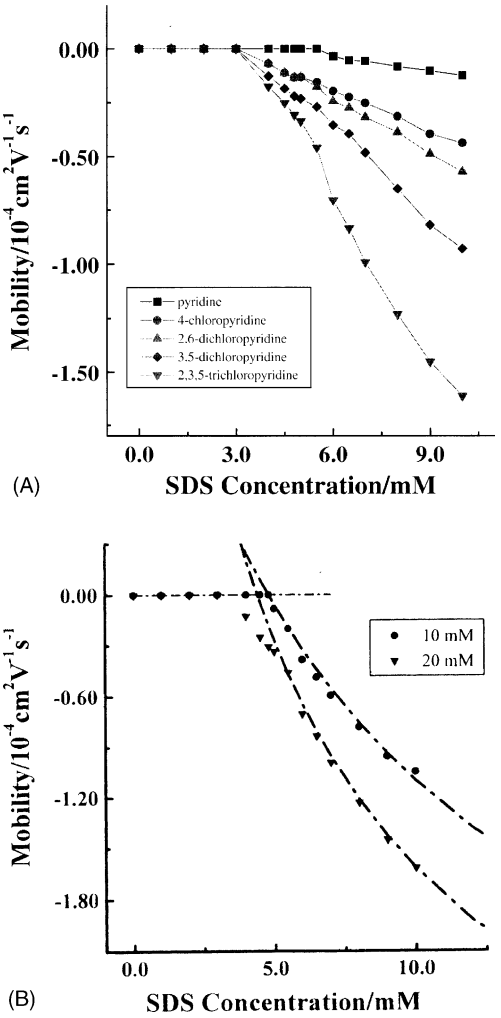

Fig. 3. Variations of the effective electrophoretic mobility of some chloropyridines as a function of SDS concentration in a phosphate buffer at pH 7.0. (A) effect of solubilized solutes, and (B) effect of buffer concentration with 2,3,5-trichloropyridine as a marker compound. The CMC values are listed in Table 2. Reprinted from [26], with permission.

termined [24,25]. The influence of solubilized solutes on the CMC using three different structural types of test solutes has been investigated [26]. It is worthy to emphasize that the CMC value of a surfactant may vary quite significantly when the interactions between test solutes and the micelles are different. Fig. 3 shows the variations of the electrophoretic mobility of pyridine and some chloropyridines as a function of SDS concentration in the range 0–10 mM in 20 mM phosphate buffer at pH 7.0 to demonstrate such effect. The influence of β-CD on the CMC of SDS using pentachlorophenol and 2,3,4,6-tetrachlorophenol as marker compounds has also been studied both experimentally and theoretically [27].

Concurrently, the determination of the CMC values of seven anionic surfactants by CE using 2-naphthalenemethanol as a test solute was reported by Nakamura et al. [29]. In this study, the variation of the migration time, instead of mobility, of the test solute was plotted against surfactant concentration. No theoretical treatment was considered.

Bare fused-silica capillaries are usually used for the determination of the CMC of surfactants employing various CE techniques. However, Nagamine and Nakamura [30] reported that, due to the adsorption of cationic surfactants onto the capillary wall through electrostatic interaction with silanol groups which could lead to irreproducible EOF, the measurement of precise CMC values of cationic surfactants was impossible. They proposed to treat the inner wall of capillary with (3-aminopropyl)trimethoxy silane (3-APTS). With the use of this type of capillary, the CMC values of cationic surfactants were determined by plotting the relative mobility of acetophenone against surfactant concentration, where the relative mobility was defined as $(t_r - t_{eo})/t_{eo}$.

2.3. Method based on the measurements of electric current using capillary electophoresis instrumentation—capillary electophoresis (current) method

Cifuentes et al. [28] reported a method of measuring electric current by a CE instrument, based on the concept that the conductivity of ionic surfactants in an electrolyte solution depends on the aggregation state of the surfactant [51]. This approach essentially consists of a CE version of the traditional method of measuring the CMC value by conductivity.

Assuming that the micelle is composed of n ionic surfactant monomers or amphiphiles (S^-) and m co-ions (e.g., Na^+), the main contribution to the overall conductivity of the electrolyte solution comes from the specific conductivities of co-ions and amphiphiles when surfactant concentration is less than the CMC, while the main contribution comes from the specific conductivity of micelles, with some number of co-ions, when surfactant concentration is greater than the CMC. Consequently, a decrease in the conductivity of the micellar solution is expected at surfactant concentrations above the CMC. By plotting the electric current against surfactant concentration at a given voltage, two lines with different slopes corresponding to the monomeric and micellar aggregation states of the surfactant are obtained and the CMC value can then be determined from the intersection point of the two straight lines. However, the drawback of the third method is that the slopes of the straight lines corresponding to the premicellar and micellar states of a surfactant in the two concentration ranges may not differ significantly so that the CMC value can be unambiguously determined. Moreover, as the current variation detected by a CE instrument is usually very small, the precision of this method is not very good.

2.4. Other methods reported in the literature

The following two methods were reported in the literature for the CMC determination. However, these two methods are questioned for their appropriateness.

2.4.1. Method based on the measurements of electroosmotic mobility

In a study of the effect of cetyltrimethylammonium bromide (CTAB) on the electroosmotic mobility of a phosphate buffer at pH 3.5, Underhill and Lucy [52] reported that the CMC of CTAB was consistent with the concentration at which the reversal EOF become constant. However, different results were obtained by Kaneta et al. [53] and Tavares et al. [54] in their studies of the effect of cationic surfactants on the electroosmotic flow. The concentration at which the reversed EOF became constant is much less than the CMC of a cationic surfactant. Moreover, in the plots of the electroosmotic mobility curve as a function of the concentration of cationic surfactants, no characteristic change in the mobility curve could be observed at concentrations near the CMC [24]. Furthermore, it has been known that the property of a surfactant solution is adapted to determine the CMC of the surfactant, if the variation of the property can be expressed as a function of the surfactant concentration [55]. In the case of anionic surfactants, as the electroosmotic mobility remains virtually constant with increasing surfactant concentration in the regions above or below the CMC [56,57], apparently, the electroosmotic mobility does not match with this requirement. Thus, we may conclude that the electroosmotic mobility is not an appropriate parameter for the CMC determination.

2.4.2. Method based on ligand-exchange micellar electrokinetic chromatography

Recently, a method for the determination of the CMC of anionic surfactants based by ligand-exchange MEKC (LE-MEKC) was reported by Chen et al. [32,33]. In their studies of the separation of amino acid enantiomers by LE-MEKC using Cu(II)-L-hydroxyproline complex as a chiral selector, the resolution of the enantiomeric pair of an amino acid decreased upon addition of an anionic surfactant at concentrations in the premicellar region, while the resolution of the enantiomeric pair increased with increasing surfactant concentration in the micellar region. They proposed that the surfactant concentration at which the reversal of the migration order of the enantiomers of an amino acid occurred corresponded to the CMC of the surfactant [32,33]. However, no confirmation on the CMC values of those anionic surfactants by other experimental methods under the same electrolyte conditions was actually made. Since the reversal of the enantiomer migration order can occur by varying the concentration of a chiral selector when the two enantiomer, having different binding constants to chiral selector and/or different limiting mobility, interact with the chiral selector to a different extent [58–63]. Therefore, it is suspected that the two diastereomeric complexes interact differently with the anionic surfactants, thus leading to the reversal of the enantiomer migration order by varying the concentration of an anionic surfactant and that the migration reversal has nothing to do with the CMC in their LE-MEKC studies [32,33]. Moreover, there are reproducibility problems linked to Cu^{2+} adsorption on the capillary wall at pH 4. Based on these arguments, we may conclude that the correlation of the reversal of the enantiomer migration order with the CMC of a surfactant is conceptually questionable or even erroneous.

3. Difficulties and uncertainty encountered in the critical micelle concentration determination

In MEKC, the migration behavior of neutral or charged compounds can be described with a retention model or a mobility model [6,7,64]. As the interactions involving between micelles and charged solutes are more complicated than those between micelles and neutral solutes, the derivation of different mobility equations is necessary for describing the migration behavior of different types of compounds involving interactions other than micellar solubilization [6,7,64]. The migration behavior of monovalent weak acids in a SDS micellar system has been discussed with both models by Muijselaar et al. [64]. They have shown that the calculation of retention factors is troublesome for hydrophobic compounds, due to interaction with surfactant molecules in the aqueous phase. This difficulty has also been addressed by others [65,66]. Moreover, difficulties in the prediction of the interaction between charge solutes and micelles in the aqueous phase [7,64], and the uncertainty in the measurement of t_{mc}, as well as t_0 in Eq. (7), may be encountered [67,68]. Hence, the CMC values determined by the method based on the retention model may not be accurate and reliable [5,7]. Therefore, the method based on the mobility model is preferable for the CMC determination.

It was reported that the CMC values of SDS determined by MEKC method with ephedrine, norephedrine, epinephrine (adrenaline) and norepinephrine (noradrenalin) as marker compounds were 1.3, 3.1, 5.1, and 9.2 mM, respectively, in a phosphate buffer at pH 7.0 and at 40 °C [7]. Although the CMC values may considerably be affected by different structural types of solubilized solutes, the difference in the CMC values between epinedrine and norepinephrine is unexpectedly large. Due to insufficient experimental data near the CMC, the accuracy of the CMC values of SDS determined by MEKC method in this work is questioned. Further study is needed. Nevertheless, it should be emphasized that the effect of solubilized solutes on the micellation and consequently the CMC value of SDS is remarkable.

As aforementioned, the CMC value of a surfactant may be considerably affected by solubilized solutes. In fact, the CMC value of SDS determined with 2,4,5-trichlorophenol should be much less than that with *o*-nitrophenol at pH 7.0; likewise, the CMC value determined with butylparaben is considerably less than that with methylparaben at pH 9.0 [69]. Therefore, without taking account of the effect of solubilized solutes, the CMC value of a surfactant determined may derivate considerably from the actual value.

4. Practical requirements for making critical micelle concentration measurements

4.1. Micellar electrokinetic chromatography method and capillary electrophoresis (mobility) method

For making precise CMC measurements using CE technique, it is important to note that, to be a good marker compound, a test solute requires the following characteristic properties. First, the test solutes should have a high UV molar absorptivity for easy detection when using CE instruments with UV detection [22]. Second, depending on the nature of surfactants, the test solute should be able to incorporate into the micelles to a certain extent. For example, according to linear solvation energy relationship (LSER) studies [70–72], SDS micelles possess a hydrophobic interior structure with strongly hydrogen bond donating character. Thus, solutes with a greater hydrophobicity and/or with strongly hydrogen bond accepting character intend to incorporate into SDS micelles to a greater extent. This is because the greater the difference in the binding constants of the selected solute with surfactant monomers and with the micelle is, the more dramatic the change in the slope of the curves of the electrophoretic mobility as a function of the total surfactant concentration at the CMC is. Consequently, the more precise will be the CMC value determined. Third, a test solute should have a proper solubility in a micellar electrolyte solution, because lack of solubility may result in a low separation efficiency of the electrophoretic system and uncertainty in the measurement of migration times, thus leading to systematic errors in the determination of the CMC value [22].

In order to solve solubility problems and/or to improve separation, selectivity and/or resolution in CE, an organic modifier is frequently added to the electrolyte solution. However, addition of organic modifiers to the micellar electrolyte solutions may induce the modification of the micelle structure and/or micelle properties. With addition of a large amount of organic modifiers, the disruption of micelles even occurs [23,73–76]. The influence of different organic solvents on the CMC of SDS has been investigated by CE [23]. Recent developments in theoretical as well as application studies concerning the use of organic solvents in the sample matrix and/or separation buffer for affecting sample pretreatment and improving separation performances in CE, and the role of organic solvents in the separation of nonionic compounds by CE as well, have been presented in recent review articles [42,43].

It is also important to note that in order to obtain consistent and reproducible results, the temperature in the capillary should be well controlled and regulated and the electric field should be kept constant for an experiment set. It is also important to emphasize that sufficient data points should be taken in the low micellar concentration range in order to reduce the experimental errors.

4.2. Capillary electrophoresis (current) method

As the electric current of an electrolyte system measured by a CE instrument is usually very small, care should be taken to manipulate the sensitivity of this method by choosing the adequate capillary size. For instance, for the determination of the CMC of CTAB, a capillary of a larger inner diameter (100 μm) and a shorter length (27 cm) than the one used for determining the CMC of SDS should be used [28] because CTAB solutions of very low concentration (<1.6 mM) are measured. Their low conductivity results in a very low electric current, thus inducing a very small current variation. Moreover, high applied voltage is selected in order to improve the sensitivity of method. However, systematic errors may arise from the increase in temperature due to the effect of Joule heating if heat is not properly dissipated. Therefore, it is advised that the power generated in the capillary should be kept below 2 W/m [28].

5. The critical micelle concentrations of surfactants determined by capillary electrophoresis methods

5.1. Anionic surfactants

SDS is the most frequently used anionic surfactant in MEKC separations. The CMC value of SDS in the pure water at 25 °C reported in the literature is 8.1 mM [5]. However, the CMC value of SDS differs from this value in electrolyte solutions because the CMC is affected by many factors that modify the structure and/or the properties of micelles. The CMC values of SDS determined by three major CE methods in some selected electrolyte solutions are summarized in Tables 1–3. In general, the CMC decreases with addition of electrolytes because the interactions of the charged hydrophilic headgroups are weakened, thus favoring the formation of micelles [5,7,37,77,78]. The influence of organic solvents on the CMC values of surfactant depends on the nature of organic solvents [23]. Generally, the aprotic solvents such as acetonitrile and acetone, stabilize the micelles (decreasing the CMC) with addition of organic modifiers at low content (<10%), but destabilize the micelles (increasing the CMC) at higher concentrations (15% for acetonitrile and 20% for acetone) [23]. The amphiprotic solvents differ in their effect. The CMC value of methanol increases with increasing methanol content up to 35%, whereas ethanol stabilize the micelles over a broad range of volume percentage, with a minimum in CMC at 15% [23].

The influence of β-CD on the CMC has been investigated by CE [27]. The elevation of the CMC value of SDS, resulted from a strong inclusion complexation between β-CD and SDS monomers, depends not only on the concentration of β-CD in the buffer electrolyte but also on the methanol content in the sample solution. The CMC value of SDS increased with increasing β-CD when marker compound was dissolved in a methanol solution [27].

Table 1
The CMC values of SDS determined by MEKC method in some selected electrolyte solutions

CMC (mM)	Electrolyte solution/remark	Analyte	Ref.
10.4	10 mM borate–50 mM phosphate, pH 7.0, 35 °C, (the CMC value is higher than expected)	2-Naphthol, toluene, etc.	[5]
4.0	50 mM phosphate, pH 7.0, 40 °C	2-Naphthol, toluene, etc	[6]
4.3	50 mM phosphate, pH 7.0, 25 °C (*k* values evaluated from Eq. (2))	Catechol	[7]
4.0	50 mM phosphate, pH 7.0, 25 °C (k values evaluated from Eq. (2))	Methylcatechol	[7]
4.2	50 mM phosphate, pH 7.0, 25 °C (k values evaluated from Eq. (6))	*p*-Hydroxyphenylalanine	[7]
3.8	50 mM phosphate, pH 7.0, 25 °C (k values evaluated from Eq. (6))	Methyldopamine	[7]
3.7	50 mM phosphate, pH 7.0, 25 °C (k values evaluated from Eq. (2))	Dopamine	[7]
3.7	50 mM phosphate, pH 7.0, 25 °C (k values evaluated from Eq. (2))	*p*-Hydroxybenzamine	[7]
3.1	50 mM phosphate, pH 7.0, 25 °C (*k* values evaluated from Eq. (2))	Norephedrine	[7]
1.3	50 mM phosphate, pH 7.0, 25 °C (*k* values evaluated from Eq. (2))	Ephedrine	[7]
9.2	50 mM phosphate, pH 7.0, 25 °C (*k* values evaluated from Eq. (2))	Noradrenaline	[7]
5.1	50 mM phosphate, pH 7.0, 25 °C (k values evaluated from Eq. (2))	Adrenaline	[7]
2.0	100 mM sodium tetraborate–100 mM phosphate, pH 6.0, 25 °C	Dichlorophenols	[37]
2.4	100 mM sodium tetraborate–100 mM phosphate, pH 6.5, 25 °C	Dichlorophenols	[37]
3.1	100 mM sodium tetraborate–100 mM phosphate, pH 7.0, 25 °C	Dichlorophenols	[37]
4.0	100 mM sodium tetraborate–100 mM phosphate, pH 7.7, 25 °C	Dichlorophenols	[37]
2.9	50 mM sodium tetraborate–100 mM phosphate, pH 7.0, 35 °C	2-Naphthol, toluene	[77]
5.5–9.6	20 mM sodium tetraborate, 20% methanol, pH 8.0, 30 °C (effect of solubilized solutes on the CMC of SDS is indicative)	Hydroxylated flavonoids	[78]
3.9	50 mM AMPSO, pH 9.0, 25 °C	Corticosteroids	[79]

The CMC value measured by conductometric titration is 3.6 mM. AMPSO: [(1,1-dimethyl-2-hydroxyethyl)-amino]-2-hydropropanesulfonic acid.

Table 2
The CMC values of SDS determined by CE (mobility) method in some selected electrolyte solutions

CMC (mM)	Electrolyte solution/remark	Analyte	Ref.
5.3	5 mM borax buffer, pH 9.2, 25 °C	Naphthalene	[22]
5.3–8.0	5 mM borax buffer + methanol (0–35%, v/v), pH 9.2, 25 °C (the CMC increases with increasing methanol content)	Naphthalene	[23]
5.3–3.7–7.8	5 mM borax buffer + acetonitrile (0–5 to 15%, v/v), pH 9.2, 25 °C (the CMC increases with increasing the volume content of organic modifiers, but decreasing first with a minimum in CMC at 5%)	Naphthalene	[23]
5.3–4.7–7.8	5 mM borax buffer + acetone (0–5 to 20%, v/v), pH 9.2, 25 °C (the CMC increases with increasing the volume content of organic modifiers, but decreasing first with a minimum in CMC at 5%)	Naphthalene	[23]
5.3–3.6–4.0	5 mM borax buffer + ethanol (0–15 to 20%, v/v), pH 9.2, 25 °C (the CMC increases with increasing the volume content of organic modifiers, but decreasing first with a minimum in CMC at 15%)	Naphthalene	[23]
6.1	10 mM phosphate, pH 7.0, 25 °C	Pyridine	[26]
4.8	20 mM phosphate, pH 7.0, 25 °C	Pyridine	[26]
4.7	10 mM phosphate, pH 7.0, 25 °C	4-Chloropyridine	[26]
3.6	20 mM phosphate, pH 7.0, 25 °C	4-Chloropyridine	[26]
4.8	10 mM phosphate, pH 7.0, 25 °C	2,6-Dichloropyridine	[26]
3.7	20 mM phosphate, pH 7.0, 25 °C	2,6-Dichloropyridine	[26]
4.8	10 mM phosphate, pH 7.0, 25 °C	2,3,5-Trichloropyridine	[26]
4.4	20 mM phosphate, pH 7.0, 25 °C	2,3,5-Trichloropyridine	[26]
4.0	10 mM phosphate, pH 7.0, 25 °C	Cephradine	[26]
3.3	20 mM phosphate, pH 7.0, 25 °C	Cephradine	[26]
4.5	10 mM phosphate, pH 7.0, 25 °C	Cefazolin	[26]
7.7	70 mM phosphate buffer, pH 7.0, 25 °C, β-CD (2.0 mM)	2,3,4,6-Tetrachlorophenol	[27]
8.9	70 mM phosphate buffer, pH 7.0, 25 °C, β-CD (3.0 mM)	2,3,4,6-Tetrachlorophenol	[27]
9.9	70 mM phosphate buffer, pH 7.0, 25 °C, β-CD (4.0 mM)	2,3,4,6-Tetrachlorophenol	[27]
10.9	70 mM phosphate buffer, pH 7.0, 25 °C, β-CD (5.0 mM)	2,3,4,6-Tetrachlorophenol	[27]
11.9	70 mM phosphate buffer, pH 7.0, 25 °C, β-CD (6.0 mM)	2,3,4,6-Tetrachlorophenol	[27]
12.9	70 mM phosphate buffer, pH 7.0, 25 °C, β-CD 7.0 mM (sample was dissolved in 20% methanol solution for the six CMC measurements above)	2,3,4,6-Tetrachlorophenol	[27]
3.92	20 mM sodium phosphate, pH 7.0, 40 °C	2-Naphthalenementhanol	[29]
~6.2	20 mM Tris–*ortho*-phosphoric acid, pH 7.0, 25 °C	*o*-Nitrophenol	[63]
~6.8	20 mM Tris–boric acid, pH 9.0, 25 °C	Methylparaben	[63]
4.0	20 mM phosphate–borate buffer, pH 7.5, 10% acetonitrile	Bile salts	[80]

Table 3
The CMC values of SDS determined by CE (current) method in some selected electrolyte solutions

CMC (mM)	Electrolyte solution/remark	Ref.
8.3	Water, pH 7.0, 25 °C/20 kV	[28]
3.6	30 mM NaCl, pH 7.0/20 kV	[28]
3.1	20 mM borax, pH 9.2/15 kV	[28]
7.3	5 mM borax, 15% acetonitrile/20 kV (the change in slopes is very small in this electrolyte solution)	[28]
14.8	10 mM β-cyclodextrin/20 kV	[28]
3.5	10 mM phosphate, pH 7, 25 °C/30 kV	[50]
3.18	10 mM phosphate, pH 7, 30 °C/30 kV	[50]
3	10 mM phosphate, pH 7, 35 °C/30 kV	[50]
3.62[a]	10 mM phosphate, pH 7, 40 °C/30 kV (the CMC value at 40 °C is not very consistent with the other data at lower temperatures)	[50]

[a] The CMC value at 40 °C is not very consistent with the other data at lower temperatures.

The influence of solubilized solutes on the CMC of SDS has also been studied by Lin et al. [26]. Interesting, the micellization of SDS may occur over a range of SDS concentration, with the aggregate size increasing over the range. Depending on the nature of solubilized solute and the extent of the interactions between solubilized solutes and SDS micelles, the CMC values of SDS may vary from one solute to the others when the extent of the solubilization is different [26,57].

The CMC of anionic alkyl chain surfactants increases rather dramatically with decreasing alkyl chain-length. The CMC of sodium tetradecyl sulfate (STS) determined in 5 mM phosphate at pH 7.0 and 40 °C was 0.87 mM [29], whereas that of sodium decyl sulfate in 20 mM phosphate was 30.3 mM. Surfactants with high CMC values, in practice, are not very useful in MEKC separation because high surfactant concentration induces high current which results in problems with Joule heating. Anionic alkyl chain surfactants with a sulfonate headgroup, such as sodium *N*-lauroyl-*N*-methyltaurate (LMT), has been used in MEKC separation [5]. Bile salts, which are anionic surfactants, have been widely used alone or with combination of ionic surfactants as mixed micelles for separation of both neutral and ionic analytes in MEKC [9]. The two most frequently used bile salts in MEKC are sodium cholate (SC) and sodium taurocholate (STC). Table 4 lists the CMC values of some anionic surfactants (excluding SDS) determined by CE methods in some electrolyte solutions.

5.2. Cationic surfactants

Most cationic surfactants have an alkyltrimethylammonium group and have bromide or chloride as counter-ions. CTAB and TTAB are the two most frequently used cationic surfactants in CE. Cationic surfactants can cause a reversal of the EOF in MEKC due to electrostatic interactions between the negatively charged fused-silica wall and the positively charged surfactant monomers. The reversal of EOF occurs at surfactant concentration even below the CMC [24,25]. The CMC values of cationic surfactants determined by CE methods are summarized in Table 5.

5.3. Neutral and zwitterionic surfactants

Neutral surfactants are used for the separation of charged compound and are also advantageously used as mixed micelles with ionic surfactants in MEKC separation. The CMC values of neutral surfactants are generally much lower than those of ionic surfactants as long as they have the same alkyl chain length. Neural surfactants such as Brij 35 (polyoxyethylene (23) lauryl ether) and Tween 20 (polyoxyethylene sobitan monolaurate) are frequently used as mixed micelles with SDS. As a matter of fact, so far, no CMC value of a neutral surfactant determined by CE methods has been reported.

Zwitterionic surfactants, used even less than neutral surfactants in MEKC are used as a modifier of the micelle or used as mixed micelles with ionic surfactants [83,84]. The CMC of *N*-dodecyl-*N*,*N*-dimethylammonium-3-propane-1-sulfonic acid (SB-12) is 3 mM [83], and that of 3-(*N*,*N*-dimethylhexadecylammonium)propane-sulfonate (PAPS) in 200 mM phosphate buffer at pH 2.5 is only 25 μM [84]. The

Table 4
The CMC values of some anionic surfactants (excluding SDS) determined by CE methods in some selected electrolyte solutions

Surfactant	CMC (mM)	Electrolyte solution/remark	Analyte	Ref.
STS	2.2	10 mM borate–50 mM phosphate, pH 7.0, 35 °C	2-Naphthol, toluene	[5]
STS	0.87	5 mM phosphate, pH 7.0, 40 °C	2-Naphalenemethanol	[29]
LMT	8.7	20 mM phosphate, pH 7.0, 40 °C	2-Naphthol, toluene	[5]
Sodium decylsulfate	30.3	20 mM phosphate, pH 7.0,40 °C	2-Naphalenemethanol	[29]
Sodium dodecylsulfonate	12.1	10 mM borate-50 mM phosphate, pH 7.0, 35 °C	2-Naphthol, toluene	[29]
Sodium decanesulfonate	34.5	20 mM phosphate, pH 7.0, 40 °C	2-Naphalenemethanol	[29]
Sodium laurate	7.15	20 mM phosphate, pH 7.0, 40 °C	2-Naphalenemethanol	[29]
Sodium cholate	12.8	20 mM phosphate, pH 7.0, 40 °C	2-Naphalenemethanol	[29]
Sodium deoxycholate	4.16	20 mM phosphate, pH 7.0, 40 °C	2-Naphalenemethanol	[29]
FC-129	0.5[a]	12.5 mM sodium tetraborate, pH 9.9, 25 °C		[56]

STS: sodium tetradecyl sulfate; LMT: sodium *N*-tauroyl-*N*-methyltaurate; FC-129: *N*-ethyl-*N*-[(heptadecafluorooctyl)sulfonyl]glycine potassium salt.
[a] The CMC value of FC-129 determined by conductivity.

Table 5
The CMC values of cationic surfactants determined by CE methods in some electrolyte solutions

Method	Surfactants	CMC (mM)	Electrolyte solution/remark	Analyte	Ref.
MEKC	TTAB	1.1	70 mM phosphate buffer, pH 7.0, 25 °C	β-Blockers	[81]
	OTAB	140	20 mM sodium acetate, pH 5.2, 25 °C	2-Naphthol, etc.	[82]
CE (mobility)	TTAB	1.5	70 mM phosphate buffer, pH 6.0, 25 °C	Propazine	[24]
	DTAB	11.0	70 mM phosphate buffer, pH 6.0, 25 °C	Propazine	[24]
	DTAB	12.0	20 mM phosphate buffer, pH 7.5, 25 °C (sample concentration: 50 μg/ml)	Cephalosperins	[25]
	DTAB	11.6	20 mM phosphate buffer, pH 7.5, 25 °C (sample concentration: 100 μg/ml)	Cephalosperins	[25]
	LTAC	18.8	20 mM Britton–Robinson buffer, pH 3.0, 40 °C	Acetophenone	[30]
	CTAC	0.75	20 mM Britton–Robinson buffer, pH 3.0, 40 °C	Acetophenone	[30]
	CPC	0.57	20 mM Britton–Robinson buffer, pH 3.0, 40 °C	Acetophenone	[30]
CE (current)	DTAB	12.1	20 mM phosphate buffer, pH 7.5, 25 °C		[25]
	CTAB	0.93	Water, pH 7.0, 25 °C/20 kV		[28]

OTAB: octyltrimethylammonium bromide; CTAC: cetyltrimethylammonium chloride; LTAC: lauryltrimethylammonium chloride; CPC: cetylpyridinum chloride.

CMC of zwitterionic surfactants determined by CE methods has not been reported.

5.4. Mixed surfactants

In MEKC separation, mixed surfactant systems provide various analytical advantages, because hydrophobic interactions between hydrophobic solutes and micelles can be reduced in strength or some additional interactions can be introduced in the separation system so that separation selectivity of analytes is optimized simply by varying the molar ratio of the components of mixed surfactants [69,80,82,85]. For example, a mixed micellar system composed of SDS and SC [79] and that composed of SDS and Tween 20 were used to effect the separation of corticosteroids and hydrophobic cations, respectively, in MEKC. Moreover, mixed micellar systems can also be used to modify the electroosmotic flow [79] or to increase the elution range in MEKC [82].

The CMC of mixed surfactants is, in some cases (but not always), intermediate in value between those of the individual component [34]. The CMC value of mixed surfactants composed of SDS and SC at the molar ratio of 3.06 in 50 mM AMPSO electrolyte solution at pH 8.7 was determined to be 5.0 mM [80]. Based on the NMR study of a mixed micellar system composed of SDS and SC [80], SC is incorporated into the SDS micelles as mixed micelles even when SC is at low concentration. Their CMC values depending strongly on the orientation of the OH groups of bile salts and the tautoconjugation as well, vary in a wide range [57].

6. Critical micelle concentration determination in non-aqueous electrolytes

It has been known that there is no sharp change in the aggregation number over a narrow concentration range and consequently no marked change in the surfactant or bulk properties of the solution in that region [34]. This is because the aggregation numbers of surfactants in non-polar non-aqueous media are generally very small (seldom exceeding 10). When the polarity of the solvent is large, solvent–surfactant interaction is not very different from that between surfactant molecules themselves. Thus, no micelles can be formed in highly polar non-aqueous media.

So far, only one article concerning the CMC determination of surfactants in non-aqueous media appeared in the literature. The CMC values of SDS and of di-(ethylhexyl)sodium sulfosuccinate (AOT) and taurodeoxycholic acid sodium salt (STDC) in formamide determined by CE technique were reported [31]. Hobo and his co-workers [31] thought that uncharged hydrophobic compounds could not be separated when no micelles were formed in non-aqueous electrolytes. Thus, they defined the CMC of a surfactant in non-aqueous medium as the concentration of a surfactant at which the electrophoretic mobility of a test solute in non-aqueous MEKC was equal to zero. On this basis, the CMC value of SDS determined in formamide with three *p*-alkylacetophenones was in the range 17.2–25.8 mM, whereas the CMC values determined for AOT and STDC were in the ranges 13.1–17.3 and 8.9–21.7 mM, respectively [31]. As no micelles were formed in *N*-methylformamide and *N*,*N*-dimethylformamide, the CMC values of these anionic surfactants could not be determined in these two non-aqueous media [31]. However, in view of the facts that partial separation of hydrophobic compounds such as corticosteroids was achieved in the presence of some premicellar aggregates of SDS [78], and that four chloro-*s*-triazines in CZE could effectively be separated even in the presence of cationic surfactant monomers [86], the CMC of surfactants in non-aqueous media defined by these authors seemed to be not very rigorous and consequently the CMC values so determined need to be verified.

7. Conclusion

Among the three major CE methods for the determination of the CMC of surfactants, CE (mobility) method is preferable because the CMC value can be precisely determined by curve-fitting procedures, provided that the mobility equations for describing the migration behavior of a selected solute in the premicellar and micellar concentration regions are appropriately derived. MEKC method which is based on the linear relationship between the retention factor of a test solute and the micelle concentration is not reliable in some occasions because difficulties in the prediction of the interaction between charged solutes and micelles in the aqueous phase, together with the uncertainty in the measurement of t_{mc}, may be encountered. The drawback of CE (current) method is that the current variation detected by a CE instrument is usually very small and that the slopes of the straight lines corresponding to the premicellar and micellar aggregation states of a surfactant may not differ significantly.

With the use of CE (mobility) method, the binding constants of test solutes to micelles, and to surfactant monomers as well, can advantageously be evaluated so that interactions between the test solutes and surfactants can be better understand.

Acknowledgements

Financial support from the National Science Council of Taiwan is gratefully acknowledged.

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