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Micellization of Sodium Octylsulfate with Sodium Salt of Ibuprofen in Aqueous Sodium Chloride

OINAM GOBIN SINGH

Department of Chemistry, Oriental College, Takyel Khuraijam Leikai, Imphal-795001, India

Corresponding author: E-mail: oinamgobinsingh@yahoo.com

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Conductance measurement was performed for mixtures of sodium octylsulfate (SOS) with sodium salt of ibuprofen (IBF) at 25 ºC both in absence and presence of sodium chloride. The experimental critical micelle concentration (CMC) values indicate non-ideal behaviour with synergism. Mutual interaction parameter (β_M) and composition (x_{SOS}) in the mixed micelle were calculated using Rubingh's model. The attractive interaction between the components in the mixed micelle decreases with increase in the NaCl concentration. The calculated micellar mole fraction values indicate predominance of the mixed micelle with SOS. The slope ratio method was used to calculate the counterion binding constant for both the pure and mixed systems. The Corrin–Harkins equation was found to be inapplicable to the systems studied. The Gibbs free energy of micellization (ΔG^o_{mic}) was also calculated and the values indicate the formation of stable micelles. The addition of NaCl was observed to thermodynamically enhance the micellization process.

Keywords: Sodium octylsulfate, Ibuprofen, Critical micelle concentration, Interaction parameter, Counterion binding constant.

INTRODUCTION

Most therapeutic drug molecules are hydrophobic, leading to poor solubility in aqueous media and low bioavailability, which has driven the search for better solubilization strategies [1-3]. Surfactants, due to their amphiphilic nature, form micelles that enhance the solubilization and stability of hydrophobic drugs, improve their bioavailability and reduce interactions with inactivating agents. Their ability to self-assemble into micelles makes them valuable components in drug-delivery systems [4,5].

Self-assembled structures formed by amphiphilic molecules have been extensively explored as potential drug delivery systems. For example, Akter *et al*. [6] investigated the effects of short-chain alcohols and urea on the aggregation behaviour of tetradecyltrimethylammonium bromide (TTAB) with the antidiabetic drug metformin hydrochloride, while Hasan *et al*. [7] examined the phase separation and thermodynamics in metformin–Triton X-100 mixtures in ammonium salt media. Joy *et al*. [8] reported the influence of short-chain alcohols and urea on dodecyltrimethylammonium bromide–cefixime trihydrate systems, whereas Aktar *et al*. [9] studied the temperature and salt/alcohol effects on TTAB/Triton X-100 interactions with moxifloxacin hydrochloride. Khan *et al*. [10] analyzed sodium salt effects on the clouding behaviour and thermodynamic nature of Tween-80 in the presence of neomycin sulfate.

Mixed micellar systems are nanoscale assemblies formed by combining two or more surfactants, often with lipids, which enhance the solubility of poorly water-soluble drugs. They improve drug delivery by increasing stability, bioavailability, and controlled release, making them widely used in pharmaceutical formulations. Cunningham *et al*. [11] demonstrated that incorporating lipids as co-surfactants in cholic acid-based block copolymer micelles enhanced siRNA loading and delivery efficiency. Zhang *et al*. [12] prepared soy phospholipid–sodium glycocholate mixed micelles and observed improved solubility, encapsulation efficiency, stability and anticancer activity of lenvatinib. Uchiyama *et al*. [13] reported enhanced solubilization of rebamipide in mixed micelles of transglycosylated stevia with trimethylammonium chlorides of varying chain lengths. Srivastava *et al*. [14] showed that mixed micelles of anionic sodium deoxycholate/sodium cholate with nonionic transglycosylated stevia improved the binding and solubilization of ethenzamide and ibuprofen.

Further studies have highlighted the potential of drug–surfactant mixed micelles are self-assembled nanostructures composed of amphiphilic molecules that encapsulate hydrophobic drugs within their core. These micellar systems enhance aqueous solubility, protect labile drugs from degradation and can modulate pharmacokinetics, thereby offering a versatile platform for improved drug delivery and therapeutic efficacy. Srivastava *et al*. [15] prepared nanosized mixed micelles of diphenhydramine hydrochloride with sodium deoxycholate and transglycosylated stevia, observing enhanced solubility and release of ethenzamide. Weng *et al*. [16] found that mixed micelles of sodium dodecyl sarcosine with Tween 20 or Tween 60 significantly improved the solubility of bisdemethoxycurcumin, with the SDS–Tween 60 system showing superior performance. Kumar *et al*. [17] demonstrated that mixed micelles of chlorpheniramine maleate with SDS or sodium dioctylsulfosuccinate enhanced encapsulation of poorly soluble ibuprofen. Lalthlengliani *et al*. [18] reported solubilization of phenothiazine drugs in Triton X-100 micelles modified with various cationic and anionic surfactants. Srivastava *et al*. [19] further showed that diphenhydramine hydrochloride and cetirizine hydrochloride improved the micellization of sodium dodecyl-benzenesulfonate and enhanced the solubility of itraconazole. Kumar *et al*. [20] used tartrazine–cetyltrimethylammonium bromide mixed micelles to improve the binding and encapsulation of cetirizine hydrochloride and chlorpheniramine maleate. Jannu *et al*. [21] developed lithocholic-acid–tryptophan conjugate-based mixed micelles for niclosamide delivery and demonstrated enhanced anticancer efficacy against prostate cancer.

Collectively, these studies underscore the extensive interest in the surfactant–drug micellization systems. However, despite this progress, investigations into the influence of added electrolytes on the drug–surfactant interactions remain limited. In this context, the present work examines the effect of NaCl concentration on the micellization behaviour of sodium octyl sulfate (SOS) in the presence of sodium ibuprofen (IBF), a widely used non-steroidal anti-inflammatory drug, using conductometric analysis.

EXPERIMENTAL

The anionic surfactant, sodium octylsulfate (SOS, purity > 99%) and drug, ibuprofen (IBF, purity > 98%) were purchased from Sigma-Aldrich, India and used without further purification. Sodium chloride (NaCl, purity ≥ 99.9%) was purchased from Sisco Research Laboratories, India. Double distilled water with specific conductance less than 3 μS cm^{-1} was used for making all the solutions. A binary mixed solution of SOS and IBF of a particular composition was prepared by mixing required volumes of SOS and IBF solutions in water/aqueous NaCl solution depending on the requirement. Small volumes of these concentrated solutions were progressively added to a known volume of aqueous NaCl solution taken in a glass vessel. The conductance of the resultant solution after thorough mixing was measured using a digital conductivity meter (Model 306, Systronics, India) and a dip type conductivity cell with cell constant of 1.0 cm^{-1}. The temperature of the solution in glass vessel was maintained at 25 ºC by using a thermostated water bath. The CMC was determined from the break point in the specific conductance *versus* concentration plot.

RESULTS AND DISCUSSION

The plots of specific conductance (κ) values *versus* total concentration (C) at different NaCl concentrations for SOS + IBF binary mixed systems are shown in Fig. 1. CMC values were determined from the break points of these plots and are given in Table-1. The CMC values for the pure SOS and IBF in water was found to be 130.10 and 178.45 mM, respectively and are comparable to those previously reported works [22,23]. The CMC of both pure and binary mixed systems decreases with increase of NaCl concentration. The CMC of an ideal binary mixed surfactant system (C_{mix}) is related to the bulk composition (α) and CMC of the individual components (C_1) and (C_2) by the Clint's equation [24]:

TABLE-1
VALUES OF CMC, x_{SOS}, f_{SOS}, f_{IBF}, β_C AND ΔG^o_{mic} FOR SOS + IBF MIXED SYSTEMS

α_{SOS}	[NaCl] (mM)	CMC (mM)	x_{SOS}	f_{SOS}/f_{IBF}	β_C (β_{Avg})	ΔG^o_{mic} (kJ/mol)
0	0	178.45			0.31 (0.28)	-18.21
	10	157.27			0.29	-18.61
	20	137.20			0.29	-19.05
	40	115.97			0.24	-19.58
0.25	0	137.20	0.362	0.73/0.90	0.33 (0.31)	-19.49
	10	125.50	0.352	0.76/0.92	0.32	-19.78
	20	112.70	0.349	0.83/0.95	0.30	-20.13
	40	100.81	0.331	0.90/0.98	0.28	-20.49
0.50	0	127.95	0.559	0.88/0.81	0.33 (0.31)	-19.72
	10	119.60	0.560	0.92/0.87	0.31	-19.94
	20	104.89	0.572	0.94/0.89	0.32	-20.36
	40	94.81	0.574	0.98/0.96	0.30	-20.69
0.75	0	120.59	0.736	0.94/0.64	0.35 (0.33)	-20.21
	10	114.26	0.757	0.97/0.75	0.35	-20.39
	20	100.58	0.783	0.99/0.84	0.30	-20.81
	40	87.71	0.787	0.99/0.89	0.31	-21.26
1.00	0	130.10			0.37 (0.35)	-20.26
	10	116.62			0.36	-20.63
	20	97.62			0.35	-21.22
	40	84.35			0.32	-21.71

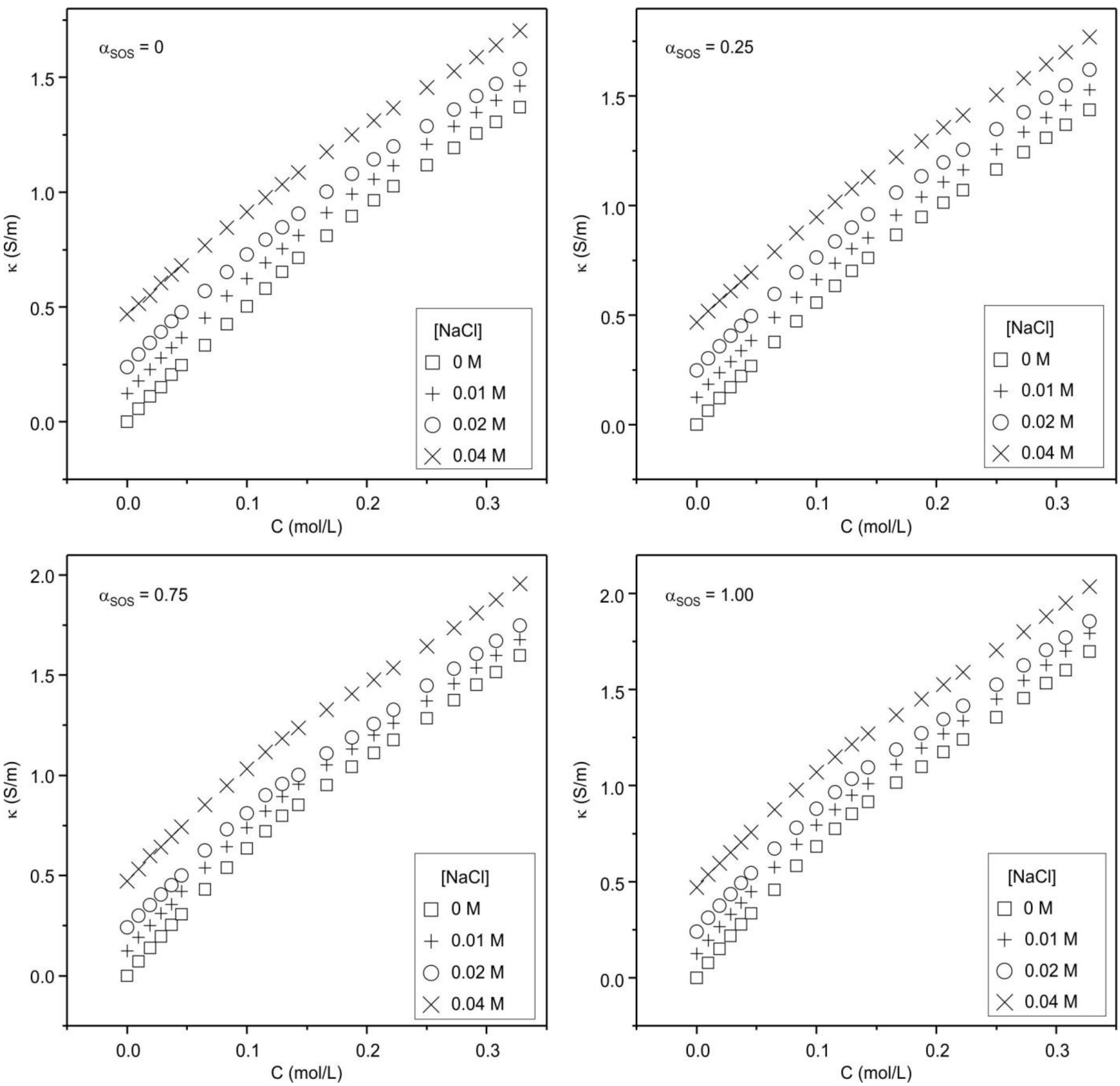

Fig. 1. Plots of specific conductance (κ) values against concentration (C) at different NaCl concentrations for SOS + IBF mixed systems

$$\frac{1}{C_{mix}} = \frac{\alpha_1}{C_1} + \frac{\alpha_2}{C_2} \quad (1)$$

For a non-ideal binary mixed surfactant system, the relationship can be expressed as follows:

$$\frac{1}{C_{mix}} = \frac{\alpha_1}{f_1 C_1} + \frac{\alpha_2}{f_2 C_2} \quad (2)$$

$$f_i = \frac{\alpha_i C_{mix}}{x_i C_i} \quad (3)$$

where x_i, f_i and C_i in eqn. 3 refer to the micellar mole fraction, activity coefficient in the mixed micelle and CMC of the i^{th} component, respectively. When the activity coefficients are equal to unity ($f_1 = f_2 = 1$), eqn. 2 reduces to the Clint's equation.

Plots of experimental CMC values along with the ideal CMC values calculated using eqn. 1 for SOS + IBF binary mixed systems are shown in Fig. 2. The experimental CMC values of the studied binary mixtures are found to be less than the ideal CMC values indicating synergism. However, on increasing NaCl concentration the experimental CMC values become closer and closer to the ideal CMC values indicating decrease in the degree of synergism.

Mixed micelle composition from Rubingh's method: The non-ideality in the mixed micelle due to the mutual interaction of surfactant components has been described theoreticcally by Rubingh [25,26]. The relation between the mutual

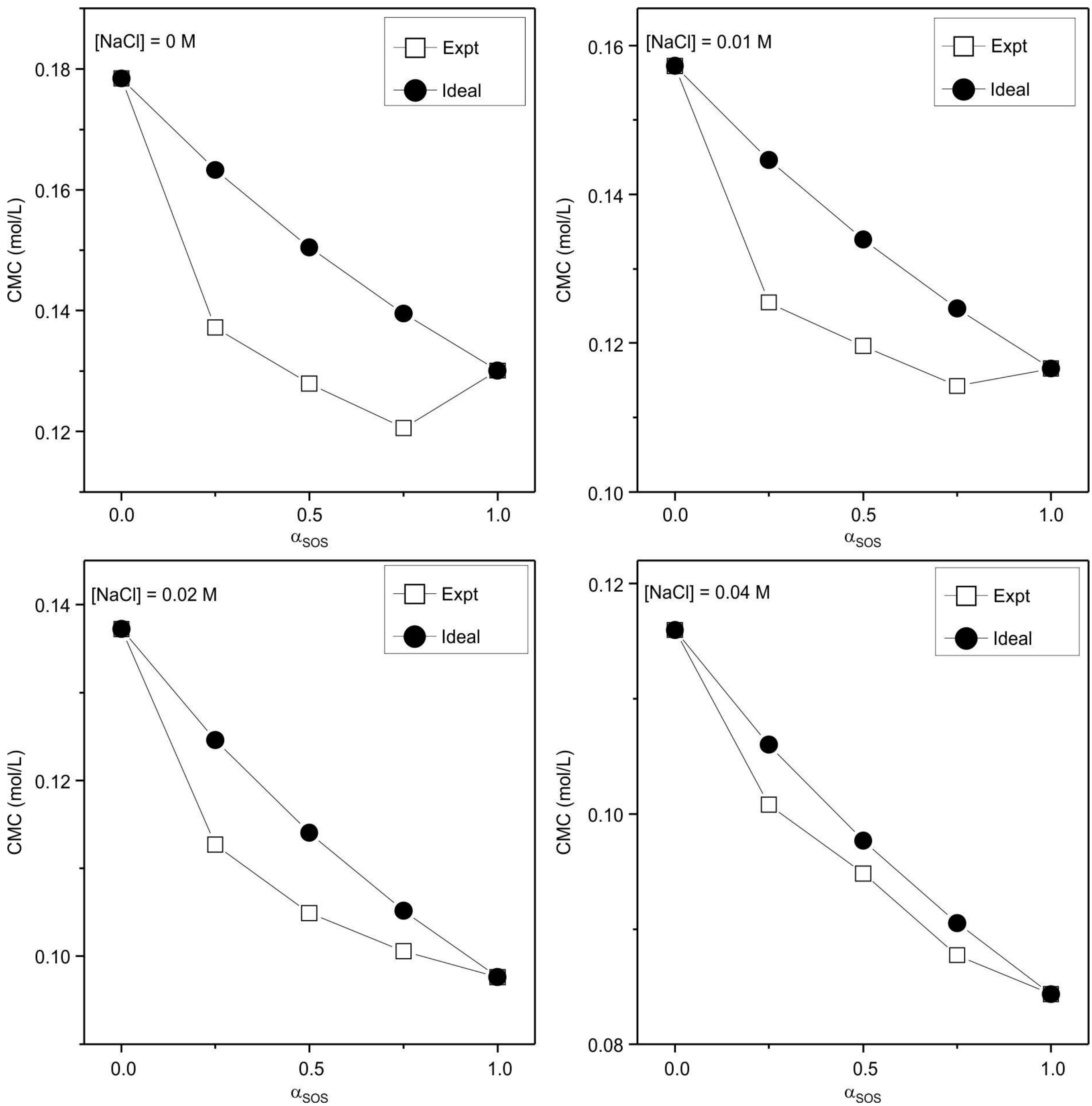

Fig. 2. Plots of experimental and ideal CMC values against the mole fraction of SOS in the bulk solution for SOS + IBF mixed systems

interaction parameter (β_M) in the mixed micelle responsible for non-ideality and the activity coefficient is given by:

$$\beta_M = \frac{\ln f_1}{(1-x_i)^2} = \frac{\ln f_2}{x_1^2} \quad (4)$$

Substituting for the activity coefficients in eqn. 4, we get the expression:

$$x_1^2 \ln \frac{\alpha_1 C_{mix}}{x_1 C_1} = (1-x_1)^2 \ln \frac{(1-\alpha_1) C_{mix}}{(1-x_1) C_2} \quad (5)$$

For a particular bulk composition of the mixture, α_1, value of mixed micelle composition x_1 was computed from eqn. 5 by using an iterative method. The ideal mixed micelle composition has been calculated using eqn. 6:

$$x_1^{id} = \frac{\alpha_1 C_2}{\alpha_1 C_2 + \alpha_2 C_1} \quad (6)$$

The x_1 and x_1^{id} values so obtained at different NaCl concentrations are shown as x_{SOS} and x^{id}_{SOS} in Fig. 3. It is observed that the mixed micelle is enriched with SOS, the component with lower CMC value and this enrichment with SOS increases with increase in NaCl concentration for the mixtures with bulk composition α_{SOS} = 0.5 and 0.75. Thus added NaCl pushes more and more SOS surfactant compo-

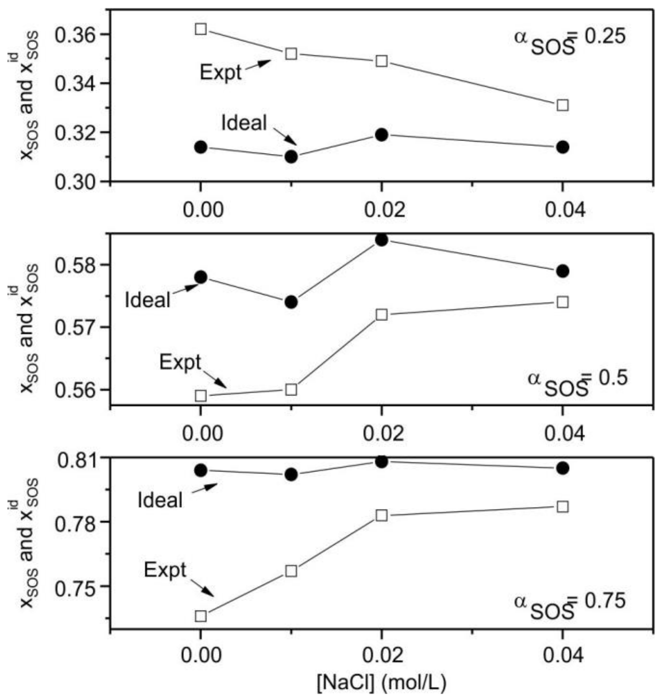

Fig. 3. Values of experimental and ideal mixed micelle composition (x_{SOS} and x^{id}_{SOS}) as a function of NaCl concentration for SOS + IBF mixed systems

nent into the mixed micelle. However, for the mixture with α_{SOS} = 0.25 the enrichment with SOS decreases with increase in NaCl concentration. The values of the activity coefficient f_i at different NaCl concentrations were calculated using eqn. 3 after substituting x_1 values which were computed employing eqn. 5. The f_i values so obtained are listed in Table-1 as f_{SOS} and f_{IBF}. Activity coefficient is a measure of the effect and contribution of an individual surfactant component in the mixed micelle. In the mixed systems studied, the activity coefficient of the components increases with increase of the NaCl concentration.

The values of the mutual interaction parameter β_M were calculated using eqn. 4 and are presented in Fig. 4. A positive β_M value indicates repulsive interaction between the components, while a negative β_M indicates attraction. In water, the β_M values are negative indicating attractive interaction between the components. On increasing NaCl concentration, it is observed that the β_M value increases indicating that the attractive interaction between the components decreases which is an opposite trend to that observed for sodium dodecylsulfate (SDS) + sodium dioctylsulfosuccinate (AOT) mixed systems [27].

Counterion binding constant: Counterion binding constant values of both pure and mixed surfactant systems can be determined using the slope ratio method and Corrin-Harkins (CH) equation [28]. In the slope ratio method, the counterion binding constant, β_C, is calculated using the relation:

$$\beta_C = 1 - \frac{S_2}{S_1} \quad (7)$$

where S_1 and S_2 are the slopes in the pre and post micellar regions in the plots of the specific conductance (κ) *vs.* total

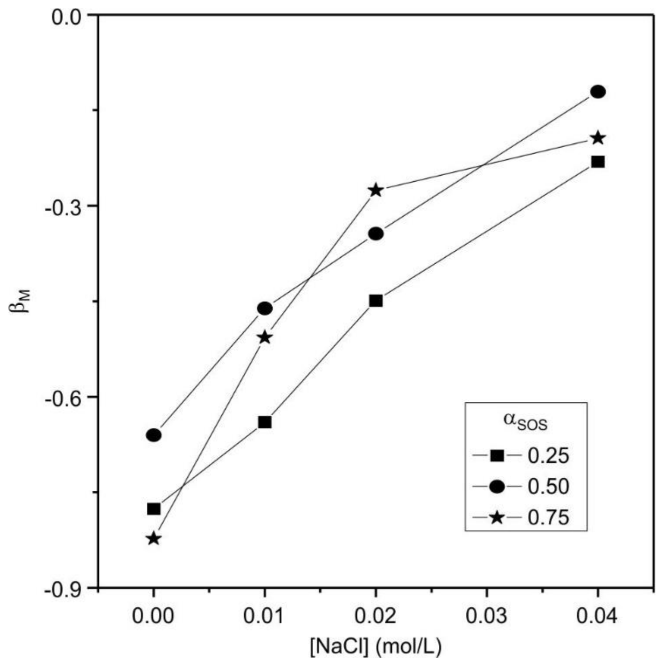

Fig. 4. Values of the interaction parameter (β_M) in the mixed micelle as a function of the NaCl concentration for SOS + IBF mixed systems

surfactant concentration (C). The β_C values (Table-1) for the mixed micelles are comparable to those of the pure micelles indicating that the surface charge density in the mixed micelles is comparable to that of the pure micelles. In general, the β_C values decrease with increase in NaCl concentration.

The Corrin–Harkins (CH) equation can be written as:

$$\ln CMC = A_1 - \beta_{CH} \ln(CMC + C_e) \quad (8)$$

where C_e is the added NaCl concentration; β_{CH} is the counterion binding constant; A_1 is a constant related to the standard free energy of micellization.

The CH plots using eqn. 8 for SOS + IBF binary mixed systems are shown in Fig. 5. The CH plot is a linear plot with negative slope and the slope corresponds to the counterion binding constant. However, in the present SOS + IBF binary mixed systems linearity with negative slope is not observed in the CH plots. Therefore, CH equation is not applicable in the present binary mixed system and counterion binding constant value could not be determined. The non-applicability of CH equation is due to very high value of CMC compared to that of C_e. Similar observations were made in micellizaton of sodium dioctylsulfosuccinate (AOT) as well as sodium dodecylsulfate (SDS) in water + ethylene glycol mixtures [29,30].

Gibbs free energy of micellization: The standard Gibbs free energy of micellization per mole of surfactant, ΔG^o_{mic}, for ionic surfactant systems is given by the relation [31]:

$$\Delta G^o_{mic} = (1+\beta) RT \ln X_{CMC} \quad (9)$$

where, R is the gas constant (8.314 J K^{-1} mol^{-1}), T is absolute temperature, X_{CMC} is the CMC in the mole fraction unit and β is the counterion binding constant. Using the experimental CMC and average value of counterion binding constant (β_{Avg}), the ΔG^o_{mic} values for the studied pure and binary mixed systems were calculated using eqn. 9. The calculated ΔG^o_{mic} values

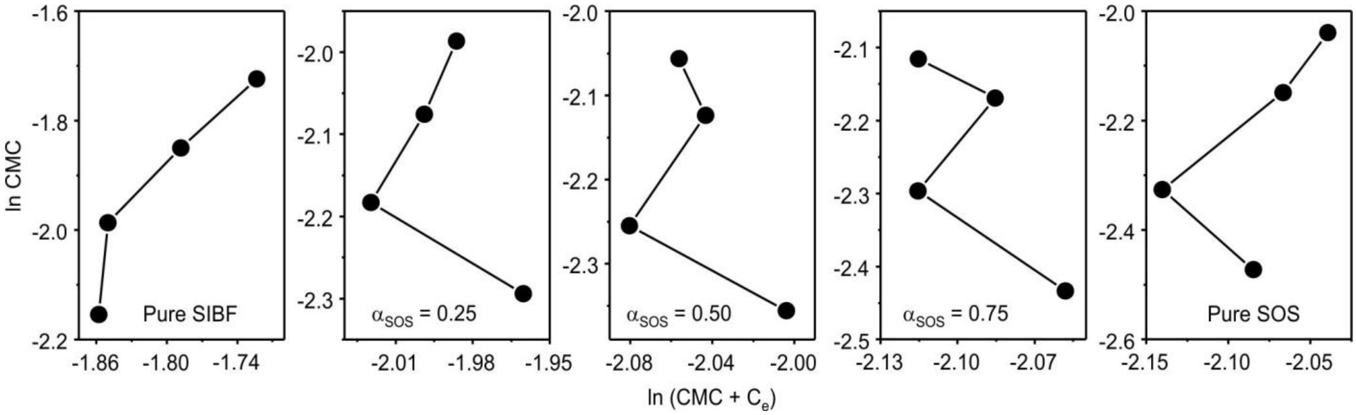

Fig. 5. Corrin-Harkins (CH) plots for SOS + IBF mixed systems

are presented in Table-1 and it is observed that in all cases, ΔG^o_{mic} becomes more negative with increase in NaCl concentration thereby enhancing thermodynamically the process of micellization.

Conclusion

Critical micelle concentration (CMC) of sodium octylsulfate (SOS) + ibuprofen (IBF) binary mixed systems in absence and presence of aqueous NaCl has been determined using conductance measurement method at 25 ºC. In water, the mixtures exhibited synergism. However, increasing NaCl concentration is found to reduce synergism. The mutual interaction parameter (β_M) values calculated using Rubingh's model indicate that the attractive interaction between the components in the mixed micelle decreases with increase in the NaCl concentration which is an opposite trend to that observed for SDS + AOT mixed systems. The mixed micelle was found to be enriched with SOS and the enrichment with SOS increased with NaCl concentration except for the mixture with bulk composition, α_{SOS} = 0.25. The Corrin–Harkins (CH) equation is not applicable in the present binary mixed system and counterion binding constant value could not be determined using CH equation. The ΔG^o_{mic} becomes more negative with increase in NaCl concentration thereby enhancing thermodynamically the process of micellization.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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