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Composition of mixed micellar systems of cetrimide and chlorhexidine digluconate

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Summary

The variation of the critical micelle concentration (CMC) with the molal ratio of components in mixed micellar systems of cetrimide and chlorhexidine digluconate has been determined by an automated conductivity technique. The equilibrium distribution of components between micelle and monomer phases was evaluated by analysis of the CMC data using a theoretical treatment based on excess thermodynamic quantities and by an empirical treatment of the conductivity data. The addition of isopropyl alcohol in concentrations up to 2 mol · dm^{-3} had little significant influence on the composition of the mixed micelles of these systems.

Introduction

Combinations of cetrimide and chlorhexidine digluconate (CG) are used in commercial antiseptic solutions. Cetrimide is a mixture of mainly 3 cationic surfactants, dodecyl-, tetradecyl-, and hexadecyl-trimethylammonium bromides (DTAB, TTAB and CTAB, respectively), of which TTAB is the major ingredient constituting approximately 70% of the mixture by weight. The solution properties of several samples of cetrimide have been reported (Barry et al., 1970; Barry and Russell, 1972). We have recently shown (Attwood and Patel, 1986, 1989) that chlorhexidine digluconate, which is a symmetrical dicationic molecule forms small aggregates of about 4 monomers in aqueous solution. Consequently mixtures of CG and alkyltrimethylammonium bromides (ATABs) are mixed micellar systems. This realisation has important consequences with regard to the distribution of components, particularly of CG, between micelle and monomer phase. The activity and stability of these mixed systems is largely determined by the free monomer concentration of the constituents and it is of practical interest to determine how this concentration changes with the overall composition of the system. Commercial antiseptic solutions may contain an added alcohol as a preservative and it is important to determine any influence which such an additive has on the equilibrium distribution of components in the mixed systems.

The properties of mixed systems in which the surfactants are of similar structure may be described by ideal mixing theories (Shinoda, 1954; Lange and Beck, 1973; Clint, 1975) or treatments

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based on regular solution theory (Rubingh, 1980). Recently a theoretical treatment has been proposed (Motomura et al., 1984) which is particularly well suited to the analysis of mixed systems such as those investigated here, in which the species in solution are of widely different structure and have different counterions. Ueno et al. (1987) have reported that this theory gives a better representation of the composition of the mixed micelles in binary mixtures of sodium cholate and octaoxyethylene glycol *n*-decyl ether than the regular solution theory. In a previous paper (Attwood and Patel, 1989) we have shown, by comparison with a direct determination of distribution using gel filtration chromatography, that this theoretical treatment is a convenient and reliable method for the determination of the composition of mixed systems of pure ATABs and of mixtures of TTAB and CG.

We now report the determination of the variation of the composition of micellar and monomer phases with overall composition of the system for mixtures of cetrimide and CG and the influence on the composition of the addition of isopropyl alcohol (IPA) in concentrations up to 2 mol · dm^{-3}.

Materials and Methods

Materials

Cetrimide BP and chlorhexidine digluconate (1,1′-hexamethylenebis[5-(4-chlorophenyl) biguanide] digluconate) were kindly donated by ICI Pharmaceuticals. The chlorhexidine digluconate was supplied as an aqueous solution of concentration 19.60 g · dl^{-1} as determined by high-performance liquid chromatography (HPLC). Isopropyl alcohol (Fisons) was SLR grade. Water was twice distilled from alkaline permanganate in an all-glass still.

Methods

Conductance measurements were carried out at 25 ± 0.02° C using a Wayne Kerr Autobalance Universal Bridge (Type B642) and a calibrated conductivity cell with blackened platinum electrodes. Concentrated solutions of the single or binary surfactant systems of known molal composition were progressively diluted with stirring, at a constant flow rate of approximately 3 ml · min^{-1}, with distilled water or solutions of isopropyl alcohol using a calibrated high precision peristaltic pump (Pharmacia). The output of the conductance bridge was continuously accessed by microcomputer during the course of the dilution. The flow rate of the peristaltic pump was determined both before and after each experiment and an independent check on the quantity of solvent added during the course of the experiment was performed by weighing the receiving vessel at the start and completion of each dilution process. The variation in flow rate did not exceed ±1%.

Results and Discussion

Effect of isopropyl alcohol on the CMCs of cetrimide / CG mixtures

Fig. 1 shows a representative plot of molal conductivity against (molality)$^{1/2}$ for cetrimide/CG mixtures of varying mole fractions in water. Similar plots were obtained in the presence of 0.5 and 2.0 mol · dm^{-3} IPA. CMC values determined from inflections in these plots are plotted as a function of the mole fractions of CG in Fig. 2.

The CMC of cetrimide in water (3.08 mmol · kg^{-1}) is lower than the previously determined (Attwood and Patel, 1989) value for TTAB (3.55 mmol · kg^{-1}) which constitutes about 70% of this commercial mixture. Although cetrimide contains more DTAB than CTAB, the latter has a very much lower CMC than the other components (the CMC of ATABs decrease logarithmically with the number of carbon atoms in the alkyl chain) and consequently has a more pronounced influence on the CMC of the mixture, bringing it below the values for the other components. A similar conclusion was noted by Barry et al. (1970), although these workers reported a lower cetrimide CMC (2.6 mmol · dm^{-3}) than that determined here, possibly due to differences in the cetrimide composition.

Inspection of the lower curves of Fig. 2 shows that the CMCs of cetrimide and mixtures with a cetrimide mole fraction exceeding 0.5 were decreased by the addition of 0.5 mol · dm^{-3} IPA but

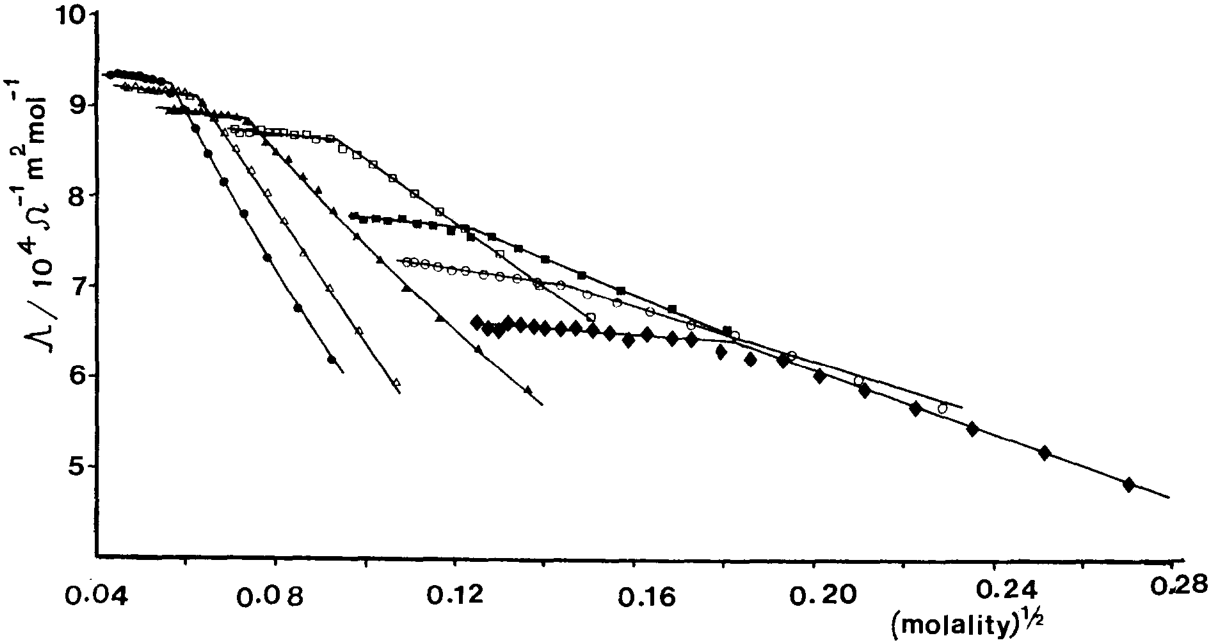

Fig. 1. Molal conductivity, Λ, against (molality)$^{1/2}$ for cetrimide/CG/H_2O systems with CG molal ratios of: ●, 0; △, 0.22; ▲, 0.46; □, 0.71; ■, 0.88; ○, 0.94; ◆, 1.00.

increased above the value obtained with water when 2 mol · dm^{-3} IPA was added. The CMC of cetrimide, for example, decreased to 2.50 mmol · kg^{-1} in 0.5 mol · dm^{-3} IPA and subsequently rose to 3.25 mmol · kg^{-1} in 2 mol · dm^{-3} IPA. Previous results have shown that TTAB itself and TTAB/CG mixtures showed a decreased CMC following the addition of concentrations of IPA up to 0.5 mol · dm^{-3} (Attwood and Patel, 1987). Bahadur et al. (1987) have recently examined the influence of isopropanol on the CMCs of several ATABs including DTAB, TTAB and CTAB. All compounds studied exhibited a decrease and subsequent rise of CMC with increasing concentration of alcohol, the position of the minimum CMC moving to lower alcohol concentration with increase in the alkyl chain length. The minimum CMC observed for cetrimide is thus expected in the light of these studies. In contrast, cetrimide/CG mixtures rich in CG showed a continued decrease of CMC with IPA addition (Fig. 2). The lack of any increase of CMC at high IPA concentration indicates the influence of the CG on the properties of the mixtures since CG itself showed a marked decrease of CMC in solutions of IPA.

Composition of mixed cetrimide/CG systems in water and isopropyl alcohol

The distribution of the components of the mixed systems between the micellar and monomer phases was evaluated from a theoretical treatment of the CMC data using a method proposed by Motomura et al. (1984) and by an analysis of the conductivity results using an empirical method described by Mysels and Otter (1961).

In the theoretical treatment of Motomura the CMC of the mixed system, $\widehat{\mathrm{CMC}}$ and the mole fraction of components in the system, $\hat{X}_i$, are defined in terms of the following variables:

$$\widehat{\mathrm{CMC}} = (v_1 X_1 + v_2 X_2)\mathrm{CMC} \qquad (1)$$

$$\hat{X}_i = v_i X_i / (v_1 X_1 + v_2 X_2) \quad \text{for i} = 1, 2 \qquad (2)$$

Eqns. 1 and 2 relate to a binary surfactant mixture where X_1 and X_2 are the mole fractions of surfactants 1 and 2 and $v_1 = v_{1,a} + v_{1,c}$ and $v_2 =$

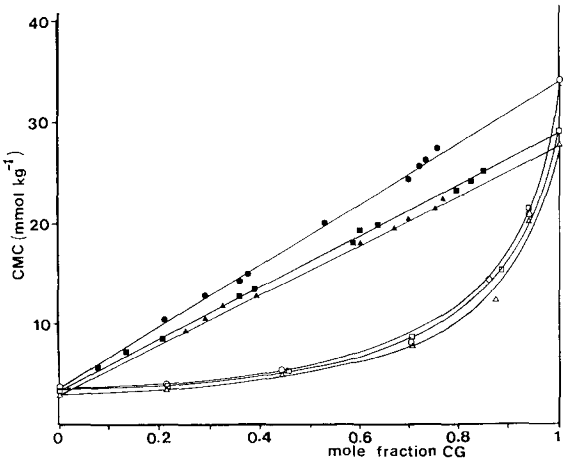

Fig. 2. Variation of CMC with composition of cetrimide/CG system in: ○, H_2O; □, 0.5 mol·dm^{-3} IPA; △, 2.0 mol·dm^{-3} IPA (lower curves). The upper curves represent the total concentration of free monomeric surfactant against mole fraction of CG in mixed micelle as calculated from the theory of Motomura et al. (1984) (continuous lines) and by the method of Mysels and Otter (1961) (closed symbols).

$v_{2,b} + v_{2d}$. $v_{1,a}$ and $v_{1,c}$ are the number of cations and anions on dissociation of surfactant 1 and $v_{2,b}$ and $v_{2,d}$ are the number produced on dissociation of surfactant 2. Although cetrimide is itself a multicomponent mixture of ATABs, its composition remains fixed and it is treated as a single surfactant in the preparation of the binary mixtures of this study. Thus this treatment allows only the determination of the mean distribution between micellar and monomer phases of the monomers composing the cetrimide mixture, rather than that of each individual constituent of cetrimide. More importantly, however, it permits the evaluation of the equilibrium distribution of chlorhexidine in these systems.

Since the chlorhexidine ion is divalent, Eqns. 1 and 2 become:

$$\overline{\mathrm{CMC}} = (2X_1 + 3X_2)\mathrm{CMC} \tag{3}$$

$$\hat{X}_2 = 3X_2/(2X_1 + 3X_2) \tag{4}$$

where component 2 refers to chlorhexidine.

The mole fraction of CG in the mixed micelle, $\hat{X}_2^{\mathrm{M}}$, was determined from plots of $\overline{\mathrm{CMC}}$ against $\hat{X}_2$ using the relation:

$$\hat{X}_2^{\mathrm{M}} = \hat{X}_2 - \left(\hat{X}_1\hat{X}_2/\overline{\mathrm{CMC}}\right)\left(\partial\overline{\mathrm{CMC}}/\partial\hat{X}_2\right) \\ /\left[1 - \delta_{\mathrm{d}}^{\mathrm{c}} v_{1,\mathrm{c}} v_{2,\mathrm{d}}/\left(v_{1,\mathrm{c}} v_2 \hat{X}_1 + v_{2,\mathrm{d}} v_1 \hat{X}_2\right)\right] \tag{5}$$

where $\delta_{\mathrm{d}}^{\mathrm{c}}$ is the Kronecker delta defined by $\delta_{\mathrm{d}}^{\mathrm{c}} = 0$, $\mathrm{d} \neq \mathrm{c}$ and $\delta_{\mathrm{d}}^{\mathrm{c}} = 1$, $\mathrm{d} = \mathrm{c}$. Since the counterions differ, $\delta_{\mathrm{d}}^{\mathrm{c}} = 0$ and Eqn. 5 reduces to:

$$\hat{X}_2^{\mathrm{M}} = \hat{X}_2 - \left(\hat{X}_1\hat{X}_2/\overline{\mathrm{CMC}}\right)\left(\partial\overline{\mathrm{CMC}}/\partial\hat{X}_2\right) \tag{6}$$

$\hat{X}_2^{\mathrm{M}}$ was evaluated as a function of $\overline{\mathrm{CMC}}$ by computer analysis of the CMC data. The results of the analysis, converted back to the form of CMC against micelle mole fraction have been plotted on Fig. 2. The continuous lines drawn through the experimental points of these plots have been recalculated from the derived $\hat{X}_2^{\mathrm{M}} - \overline{\mathrm{CMC}}$ lines and show good representation of CMC data.

In the empirical method proposed by Mysels and Otter (1961) the equilibrium concentration of monomers in the mixed system is determined by analysis of plots of conductivity as a function of solution molality for each molal ratio of the two components. Curvature of such plots for mixed systems in the post-CMC region arises because of changes in the composition of the micellar and monomer phases with change in the overall concentration. Conductivity–concentration plots for 'single' component solution of cetrimide and of CG were linear in the post-CMC region. The procedure used for the analysis of the conductivity plots involved the extrapolation of the curves for the mixed systems along lines with slopes intermediate between those of CG and cetrimide and determined by the mole fraction of these components in the mixture. The treatment gives groups of points for each molal ratio of components which when combined provide a representation of the composition of the mixed system over the entire range.

Fig. 2 shows good agreement between predictions from both methods of data treatment, the computed points lying on diagonals joining the

CMCs of the pure components. Similar results were obtained previously for TTAB/CG, DTAB/CG and CTAB/CG systems (Attwood and Patel, 1989). The plots of Fig. 2 may be regarded as analogous to phase diagrams since they express the relationship between the composition of the surfactant in the micelle and that in the solution at equilibrium. The upper line gives the equilibrium total monomeric concentration for a given solution composition, whilst the lower curve gives the mole fraction of each component in monomeric form. For example, a cetrimide/CG/H_2O system in which the mole fraction of CG in the micelle is 0.38 will have a total monomer concentration of 0.015 $mol \cdot kg^{-1}$ and the mole fraction of CG in the monomer phase in equilibrium with the micelle will be 0.87. Tie lines may be constructed in this manner linking the upper and lower curves of each system. It has been shown (Mysels and Otter, 1961) that at high solution concentration (approximately 10 CMC) the composition of the mixed micelle becomes identical to that of the system as a whole. Hence it is seen that these plots provide a way of estimating the composition of the monomer phase in the system. The relationship between the composition of the system and that of the monomer phase, as derived from these plots is shown in Fig. 3. Inspection of this figure shows that for any given cetrimide/CG ratio, the solution in equilibrium with the micelles will always contain a greater proportion of CG than that of the system itself. This may have important consequences with regard to the stability of these systems. Fig. 3 shows that the addition of isopropyl alcohol had little significant effect on the distribution of components between the two phases, the predicted lines for all systems being virtually superimposable

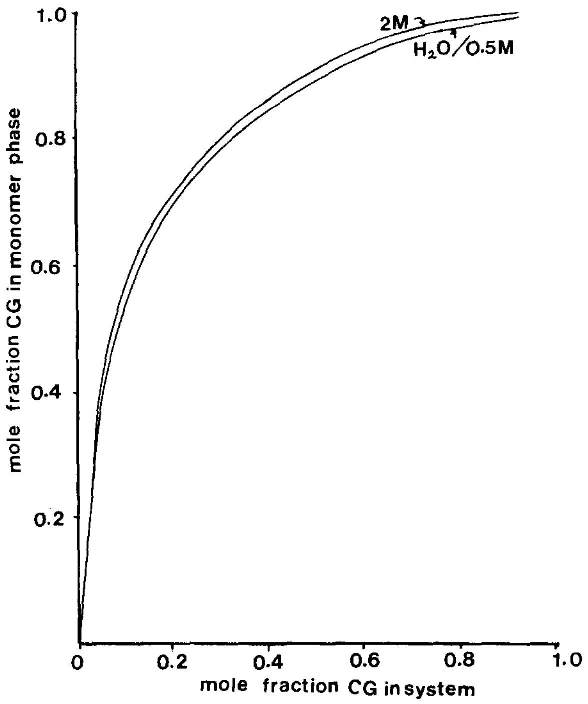

Fig. 3. Relationship between mole fraction of CG in monomer phase and the mole fraction of CG in the cetrimide/CG system in H_2O, 0.5 $mol \cdot dm^{-3}$ IPA and 2 $mol \cdot dm^{-3}$ IPA.

Acknowledgements

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