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COMMUNICATIONS

Cmc of mixtures of chlorpromazine hydrochloride and polysorbate 80 determined by pH measurements

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The cmc of mixtures of chlorpromazine hydrochloride and polysorbate 80 was determined by pH titration. The values thus obtained coincided with those determined by the surface tension method. The mixtures studied could be divided into two groups according to the shape of their pH concentration curves. For mixtures containing less than 0·8 mole fraction chlorpromazine, the curves suggest that some interaction occurs in the premicellar concentration range. For mixtures containing more than 0·8 mole fraction chlorpromazine, the curves suggest that the micellar process occurs in more than one step.

The interaction between phenothiazines and non-ionic surfactants is accompanied by an important drop in pH. This is a micellar interaction and to account for the drop, it was suggested that the presence, in micelles, of non-ionic molecules along with phenothiazine molecules would encourage further dissociation of the phenothiazine head group by a competing hydrogen bonding interaction (Florence & Parfitt 1971).

The critical micelle concentration (cmc) of phenothiazines (like that of some other cationic and anionic surfactants, Lawrence & McDonald 1957) can be determined by pH measurements. This is because the micellar form of these compounds is more dissociated than the monomeric form. The nature of the interaction noted above between phenothiazines and non-ionic surfactants suggested that the cmc of mixtures of those compounds could also be determined by pH measurements. The present communication reports an attempt at determining the cmc of mixtures of chlorpromazine HCl (CPZ) and polysorbate 80 (P-80) with such a method. As a control, the cmc values were also determined with the more conventional surface tension method.

Method

CPZ (Poulenc) and P-80 (Atlas) were used as received. The water used was distilled and deionized. The concentration of surfactants in the various mixtures was expressed in terms of total molar concentration (CPZ plus P-80) and the relative proportion of the two compounds in terms of mole fraction of CPZ in the mixture. CPZ is a pure compound with a molecular weight 355·34. P-80 is a heterodisperse surfactant: the value chosen for the average molecular weight, in this case, was 1470*. All the measurements were made at 25 ± 0·5 °C.

The pH titrations were made with a Fisher, Accumet-320, pH-meter, using the expanded scale of the instrument. The titrations were performed by stepwise additions of water to measured volumes of the mixtures—always starting at concentrations higher than the expected cmc. The pH values (strictly speaking, these are 'pH numbers' (Feldman 1956)) were recorded at equilibrium. Nitrogen was bubbled throughout in order to eliminate carbon dioxide. The cmc of the mixtures was obtained at the break in the pH-concentration curves (Fig. 1).

Surface tension measurements were made with a DuNouy tensiometer. Wan & Lee (1974) have shown that the cmc of polysorbates could be accurately determined with the ring method, providing certain precautions were taken. Since polysorbates, like other non-ionic surfactants, diffuse slowly to the surface, the main precaution consisted in waiting at least 15 min before making the measurement after a new surface had been created. The data published by Wan & Lee could be easily reproduced and their method was adopted for all the mixtures studied.

Results and discussion

Fig. 1 shows the log cmc of the various mixtures of CPZ and P-80 plotted as a function of the mole fraction of CPZ in the mixture. It can be seen that, unless a

* This value was claimed to have an uncertainty of 'probably less than 10%'. Private communication from Paul Becher (Atlas), 1970.

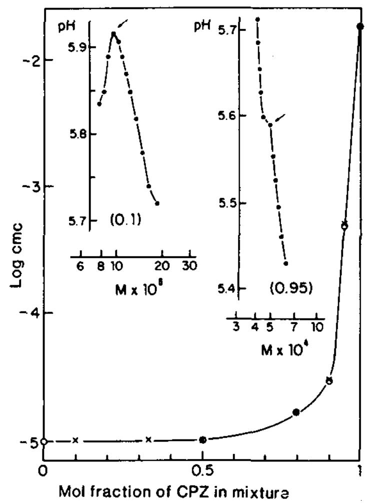

FIG. 1. Plot of the log cmc (concentrations expressed as total molar concentration of surfactant) of mixtures of P-80 and CPZ as a function of the mole fraction of CPZ in the mixture. Circles: values obtained with the surface tension method. Crosses: values obtained with the pH method. In insert: determination, with the pH method, of the cmc of two representative mixtures, containing 0·1 and 0·95 mol fraction of CPZ, respectively. In each case, the cmc is shown with an arrow.

relatively important proportion of CPZ was present in the mixture, the cmc of P-80, the non-ionic surfactant ('the stronger surfactant', Solov'eva et al 1973) was only slightly modified. At mole fraction of CPZ greater than 0·9, the cmc of the mixture increased sharply. This kind of behaviour was anticipated: the cmc of other mixtures of ionic and non-ionic surfactants has been determined and the same type of relationship has generally been reported (cf. Nishikido 1977).

The pH-concentration curves obtained with the titration method deserve some comment. At the onset of this project, it was thought that the mixtures of CPZ and P-80 would show the same type of titration behaviour as that observed with individual phenothiazines. In the case of CPZ, for example, although a sharp drop in pH is noted as the concentration is increased above the cmc, only minor changes are observed below the cmc (Florence & Parfitt 1971). In the present instance the only occasion where this type of behaviour was noted was that involving the mixture containing 0·8 mol fraction CPZ. At lower proportions of CPZ, the pH decreased upon dilution below the cmc (the extreme of this trend is shown in inset, Fig. 1, for the mixture containing 0·1 mol fraction CPZ) while, at higher proportions, the pH increased upon dilution below the cmc (the extreme of this trend is shown in inset, Fig. 1, for the mixture containing 0·95 mol fraction CPZ).

It was suggested earlier that, as the concentration of mixtures of CPZ and P-80 was increased above the cmc, the pH dropped partly as a consequence of the interaction between the two compounds. Since, for mixtures containing more than 0·8 mol fraction CPZ, the pH was also observed to drop when the concentration was increased towards the cmc, it had to be concluded that CPZ and P-80 probably also interacted with each other in that concentration region. This observation suggested, in turn, that, for these particular mixtures, the micellization process might occur in two or more steps. For mixtures containing less than 0·8 mol fraction CPZ, the trend was reversed: the pH dropped upon dilution. In an attempt to account for this unexpected behaviour, it was decided to monitor the pH of CPZ solutions upon dilution from 10 μmolar to 0·1 μmolar. As expected (CPZ HCl is the salt of a weak base), a small but constant increase in pH was noted upon dilution. Since, in the presence of P-80, the pH of these CPZ solutions (in the mixtures) dropped upon dilution, one had to conclude that there was some sort of interaction between the two compounds in the pre-micellar concentration range.

The interesting point of the study was the fact that the cmc values obtained with the pH titration method were in good agreement with those obtained with the surface tension method. The pH method evaluated was simple and relatively fast. It should be possible and advantageous to apply this method to other mixed micellar systems where a competing hydrogen bonding interaction between the ionic head groups of the ionic surfactant and the ethylene oxide chains of the non-ionic surfactant is expected. Many systems involving mixtures of cationic and non-ionic surfactants should qualify.

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