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SOLUBILIZATION OF CARBAMAZEPIN BY DIFFERENT CLASSES OF NONIONIC SURFACTANTS AND A BILE SALT

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ABSTRACT

Solubilization of carbamazepin, a slightly soluble antiepileptic drug is investigated in representative classes of eight nonionic surfactants, viz., Tweens 20,40,60 & 80; Myrjs 51 & 52; and Brijs 35 & 98. The solubility of carbamazepin in aqueous solutions of these detergents was determined over the concentration range of 0-0.09 mole/liter at 37^{0}. A marked increase in solubility is noticed with all the surfactants used. Dihydroxy bile salts such as sodium deoxycholate have many detergent-like properties derived from their unusual amphiphilic structure.

The solubility of carbamazepin in sodium deoxycholate was determined over the concentration range of 0-0.2 mole/liter at 37^{0}. Increasing the concentration of the bile salt, increased the solubilized amount of carbamazepin. Comparison with solubilization in typical micelle-forming systems indicates that the self-association of the bile salt is very complex and exhibit a very different pattern. Further examination of the solubilization data in terms of the mutual association of carbamazepin with aggregate species shows that the self-association of sodium deoxycholate is consistent with a model that includes the formation of dimers, pentamers, and large aggregates.

INTRODUCTION

The influence of crystal shape modifications for carbamazepin on the physical process of tabletting was the subject of a previous study (1) . Where an evaluation of the densification behavior for two different physical forms and a dihydrate was presented. Carbamazepin is widely used as an antiepileptic drug, and is available as a 2% aqueous suspension or as tablets. Comparative studies on the bioavailabilities of these dosage forms reported faster absorption from suspension than that from tablets (2-6). The difference in absorption was related to the smaller particle size of carbamazepin in suspension than in tablets, and also to the different crystal modification (5). Although the anhydrous form is used in

tablets whereas the carbamazepin dihydrate exists in aqueous suspension, transition between the two cited forms occurs and is a function of temperature and relative humidity (7). The rapid transition from the anhydrous form to the dihydrate one in water was recently explained by the whisker mechanism (8).

The pharmacokinetic parameters obtained from concentrations versus time curves for carbamazepin (9-I3) showed a maximum existing in connection with eating. This common observation was related to the solubilization of the drug by bile secreted following a meal or extensive enterohepatic cycles (I4). In an attempt to increase the solubility of carbamazepin in water, various N-Mannich bases of the drug with piperidine, diethylamine or dipropylamine as the amine components were prepared and evaluated as water soluble pro-drugs (I5). However, diminished carbamazepin plasma levels were observed from the pro-drug.

The ability of surfactants, especially the nonionic variety to act as solubilizing agents for poorly soluble drugs has been well documented (I6-20). Compared to simple nonionic surfactants, the self-association of the bile salts is very complex, since the micelles formation is preceded by the development of various small aggregates (2I-23). Thus the hydrophobic self-association in aqueous solution exhibit very different patterns according to the hydrophobic solutes structures (24).

The purposes of this study were to solubilize carbamazepin in aqueous solutions of different classes of nonionic surfactants

and to investigate how well the micellar models comply with the self-association of a bile salt, viz., sodium deoxycholate in its solubilizing action at a comparative level.

EXPERIMENTAL

MATERIALS

The drug, carbamazepin was obtained from (Pfannenschmidt, Hamburg, W.-Germany). All surfactants were supplied by (Atlas Chemical Industries Inc., Wilmington, Del., USA). Sodium deoxycholate was obtained from (Schwarz/Mann, W.-Germany).

METHODS

Solubilization Experiments:

For the solubilization studies by nonionic surfactants, 20 ml of aqueous solutions containing different concentrations of the nonionic surfactants used (concentration range from 0-0.09 mole/liter), or of sodium deoxycholate (concentration range from 0-0.2 mole/liter) were placed in 50 ml bottles to which carbamazepin was added in amount more than sufficient to produce saturation. Bottles were well stoppered, placed in a thermostatically controlled water bath, and rotated at $37^{0} \pm 0.I$ for 24 h in case of nonionic surfactants, and for 72 h in case of sodium deoxycholate at a speed of 60 ± 5 rpm, and then set aside at the same temperature for 24 h to attain equilibrium.

Assay Procedure:

After equilibrium has been reached, aliquots of the supernatant liquids were withdrawn with a pipet whose tip was connected to an adaptor containing non absorbed cotton wool, to filter excess crystals remaining in the solution. The samples were then suitably diluted with 0.I N Hydrochloric acid, and assayed spectrophotometrically at 285 nm for their carbamazepin content. The presence of the surfactants or the bile salt in the diluted solutions showed no interference with the assay either by absorption at the wave length used, or by shifting the absorption peak. All experiments were run in duplicate. In case of bile salt, the solubilization expe-riment was performed as described above. However, this di-hydroxy bile salt was observed to form gel or to precipitate from solution after dilution with 0.I N Hydrochloric acid. In tis case, the solubility of carbamazepin was determined after filtration through 0.2 um Sartorious membranes, and then assayed spectrophotometrically at 285 nm.
In order to study the effect of ionic strength, on the solubilization data obtained for sodium deoxycholate, the experiment was repeated by appropriate dilution with distilled water instead of 0.I N Hydrochloric acid. A maximum wave length of 283 nm was used for the assay of carbamazepin in water.

RESULTS AND DISCUSSION

On the basis of their sructures, hydrophobic solutes were classified into four broad classes(24). As a class, the nonionic surfactants are characterized by having nonpolar and polar ends joined together. The association of these molecules is mainly attributed to their flexible chains. The chain can coil around each other and fill up space by themselves forming spheroidal aggregates, viz., micelles. Many physical properties of these surfactants can be explained in terms of micelles formation (24).

The solubilization curves for carbamazepin by different classes of nonionic surfactants are illustrated in Figures I-3. The effect of various concentrations of polysorbates (Tweens), well beyond their reported CMC (25), on the apparent solubilities of carbamazepin was shown in Figure I. A marked increase in the drug solubility resulted with the addition of different polysorbates. For instance, with Tween 20, an increase in concentration from 0.0 to 0.078 mole/liter, increased the solubility of carbamazepin I0 times, viz., from I.86 x $I0^{-3}$ to I.86 x $I0^{-2}$ mole/liter. Whereas, in case of Tween 40, an increase in concentration from 0.0 to 0.078 mole/liter leads to a higher increase in carbamazepin solubility than with Tween 20, viz., II.3 folds. A I0 times increase in the solubility was obtained with 0.067 mole/liter of Tween 40 (Figure I). Similar results were found with Tween 60 and 80, to those obtained with Tween 40 (Figure I).

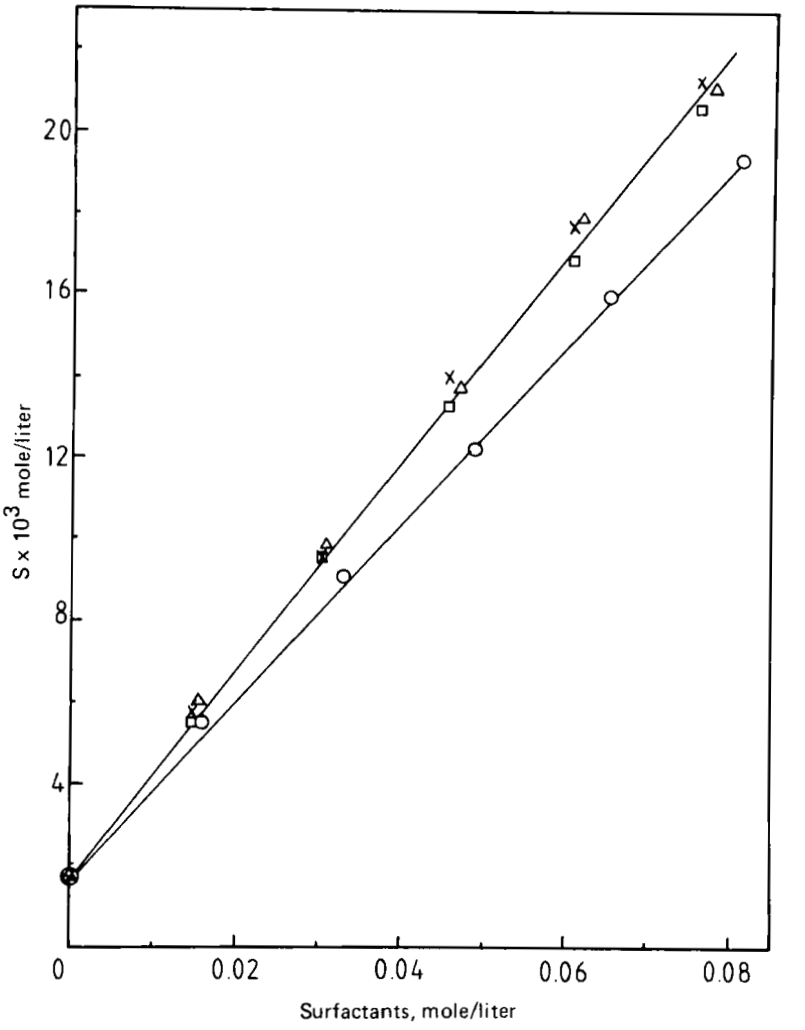

Figure I- Solubility of carbamazepin, S, in aqueous solutions of: O , Tween 20; Δ , Tween 40; X , Tween 60; and □ , Tween 80.

The increase in carbamazepin solubility can be attributed to micellar solubilization. Many investigators reported (16,25) the solubilization of slightly soluble, hydrophobic solutes by aggregating micelle-forming surfactants (24).

Increasing polysorbates concentrations resulted in an increase

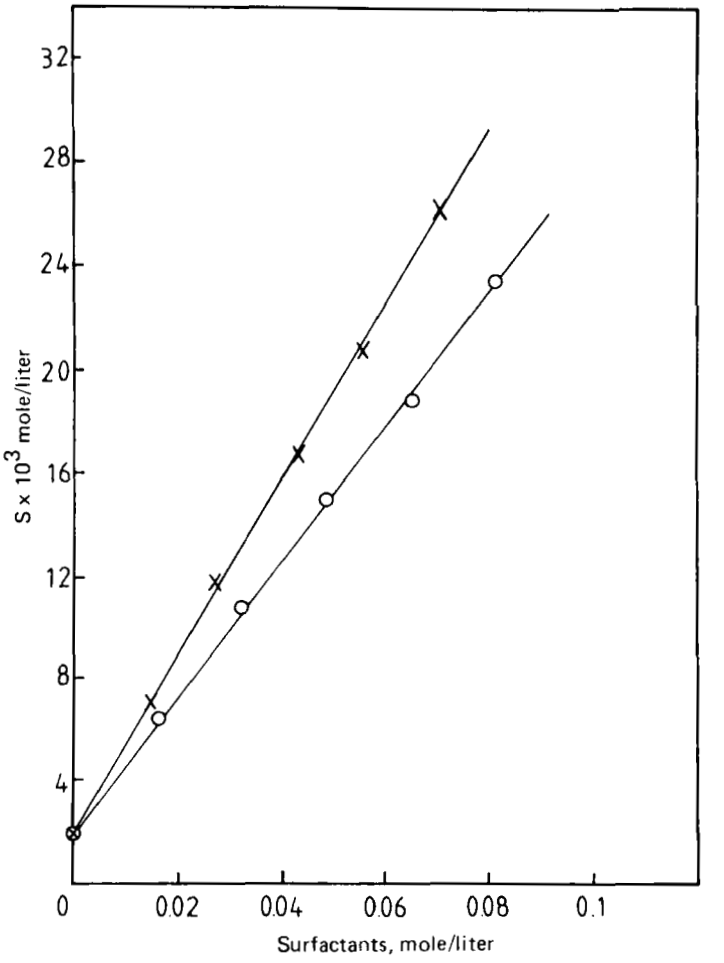

Figure 2- Solubility of carbamazepin, S, in aqueous solutions of: X, Brij 35; and O, Brij 98.

in drug solubility (Figure I). In turn, this is due to the increase in micelle number in solutions.

In evaluating the solubilizing capacity of the different homologs, the nature of such homologs must be considered. Polysorbates 20,40,60 and 80 have the same hydrophilic portion in their molecules, but differ in the length of the carbon atom

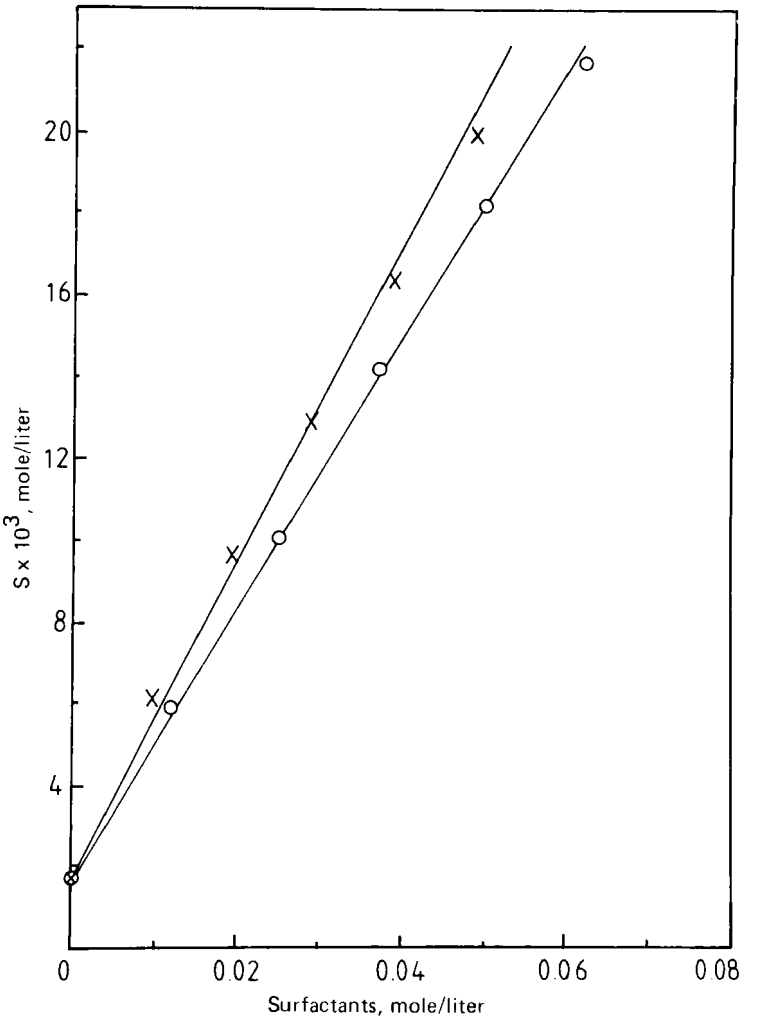

Figure 3- Solubility of carbamazepin, S, in aqueous solutions of: O, Myrj 51; and X, Myrj 52.

chain of their lipophilic portion. In addition, the degree of solubilization by a surfactant depends on the chemical structure of the solubilizate. Nonpolar compounds are generally solubilized in the hydrocarbon interior of the micelle as was demonstrated by an increase in long X-ray spacings (26). Accordingly, the

increase in carbamazepin solubility is due to an increase in the volume of the hydrocarbon in the micelle interior. Lengthening of the alkyl chain increases the size of the surfactant micelle and hence augments its solubilizing capacity (16).

The effect of two different polyoxyethylene ethers (Brijs) on the solubility of carbamazepin was shown in Figure 2. Brij 35 exhibited a better solubilizing action than Brij 98. For example, at 0.06 M surfactants concentrations, a solubility of 18 x 10^{-3} mole/liter was obtained for Brij 98, while a value of 22.5 x 10^{-3} mole/liter was recorded for Brij 35. In comparing the solubilizing power of this class of surfactants, it could be concluded that the change in the solubilization capacity is due to the difference between their hydrocarbon chain length. The effect of the chemical structure of the solubilizate upon the degree of solubilization, by a surfactant, must also be kept in mind.

Figure 3 demonstrates the effect of different concentrations of polyoxyethylene stearate surfactants (Myrjs), on the solubility of carbamazepin. Drug solubility was markedly increased in the presence of these solubilizers. Increasing the concentration of the polyoxyethylene stearate detergents, augmented their solubilizing capacity. The effect of Myrj 52 on the carbamazepin solubility was slightly greater than Myrj 51. At 0.04 M surfactants concentrations, the solubility of carbamazepin in presence of Myrj 52 showed a value of

15×10^{-3} mole/liter. Meanwhile, a value of 17×10^{-3} mole/liter was obtained with the addition of the same concentration of Myrj 51. The linear relationships obtained with each of the two Myrj compounds are typical of the solubilization curves, and correspond to results obtained by other researchers using nonionic surfactants to solubilize nonpolar molecules (26). Where the differences in the degree of solubilization by different Myrjs, for the various solubilizate were compared on the basis of their molar ratios (26).

Compared to simple detergents, the self-association of the bile salts is very complex since the formation of typical micelles is very gradual and preceeded by the formation of various small aggregates. The reported studies on the mechanism by which bile salts solubilize various solutes were contradictory in their conclusions. Some investigators (27,28) adopted the model for detergent micelles, assuming that a reversible equilibrium exists between monomeric species and micelles. Whereas, other studies (21,22) reported that the self-association of the bile salts occur in a stepwise fashion with various defined concentration limits for the association process. Recently, Mukerjee and Cardinal (29) concluded that the solubilization data were inconsistent with the concentration limit model, and agree with a model including the formation of dimers and some higher oligomers. Based on the analysis of light-scattering data (30,31), similar conclusions were attained.

In Figure 4, the solubility in mole/liter of carbamazepin in sodium deoxycholate solutions up to 0.2 M was illustrated. The data below 0.01 M sodium deoxycholate were plotted separately on a magnified scale (Figure 5) to determine the CMC of the bile salt. Following the procedure of linear extrapolation of data below and above the CMC (29), a CMC value of 5×10^{-3} M was obtained. The estimated CMC was in good agreement with the previously reported ones for this dihydroxy bile salt (32). The model presented by Mukerjee and Cardinal (29), is applied to the data obtained in this study, to gain further insight into the self-association of sodium deoxycholate. In this model, the solubilization of the slightly soluble carbamazepin was used as a measure for the extent of association. The association scheme can be represented by:

$$n\left[M_I\right] \overset{k_n}{\rightleftharpoons} \left[M_n\right]$$

Scheme I

and:

$$k_n = \frac{\left[M_n\right]}{\left[M_I\right]^n} \qquad \text{Eq. I}$$

Where $\left[M_I\right]$ is the monomer concentration, $\left[M_n\right]$ is the aggregate concentration, and k_n is the equilibrium constant for association. The amount of carbamazepin solubilized, defined as $\Delta X = S - S_o$, where S is the solubility in the presence of

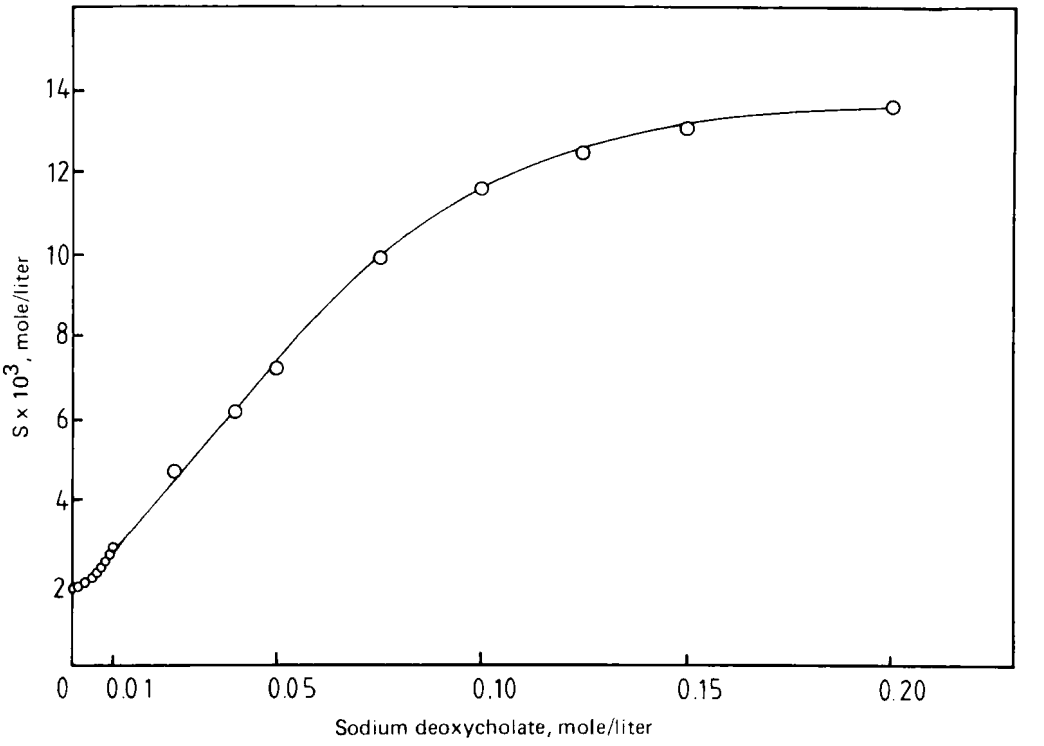

Figure 4- Solubility of carbamazepin, in mole/liter, in aqueous solutions of sodium deoxycholate at 37°.

sodium deoxycholate and S_o is the solubility in water, can then be represented by:

$$\Delta X = K\, n\, [M_n] \qquad \text{Eq. 2}$$

Where $n\,[M_n]$ is the monomer-equivalent concentration of the aggregates, and K is a proportionality constant. The validity of this equation (Eq.2) was discussed before (29).

Further steps of association can be represented as a series

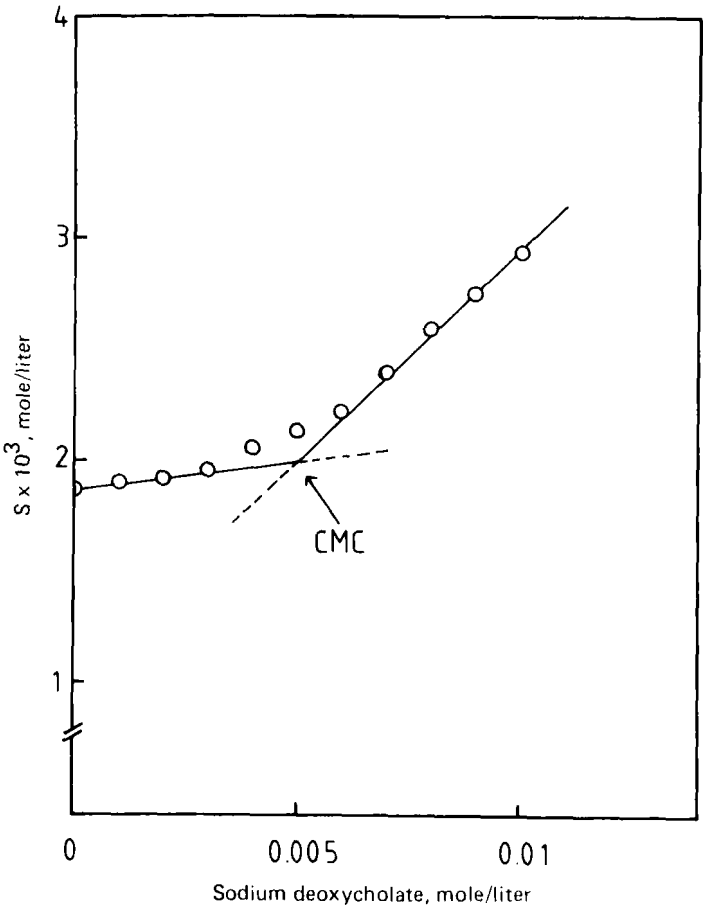

Figure 5- Solubility of carbamazepin, in mole/liter, in aqueous solutions of sodium deoxycholate at 37°. CMC, is the critical micelle concentration.

of mutual association equilibria between M_n and carbamazepin, X, such as:

$$M_n + X \underset{}{\overset{k_1}{\rightleftharpoons}} M_n X, \quad M_n + 2X \overset{k_2}{\rightleftharpoons} M_n X_2,$$

$$M_n + 3X \overset{k_3}{\rightleftharpoons} M_n X_3, \ldots\ldots$$

Scheme 2

Then the total amount of carbamazepin solubilized is given by:

$$\Delta X = \sum_{i=I}^{\infty} i \left[M_n X_i\right] = \sum_{i=I}^{\infty} i K_i \left[M_n\right] \left[X\right]^i \qquad \text{Eq. 3}$$

In dilute solutions, the contribution from the $\left[M_n X_i\right]$ species to the total concentration, C , is negligible (29), accordingly:

$$C = \left[M_I\right] + n \left[M_n\right] \qquad \text{Eq. 4}$$

By application of Schemes I and 2 and Eqs. I-4, which assume ideality and ignore charge effects and counterion binding (33), so that:

$$C = \left[M_I\right] + n k_n \left[M_I\right]^n \qquad \text{Eq. 5}$$

and

$$\Delta X = K n k_n \left[M_I\right]^n \qquad \text{Eq. 6}$$

Thus:

$$P = \frac{d \ln \Delta X}{d \ln C} = \frac{\left(Kn^2 k_n \left[M_I\right]^{n-I} \right) \left(\left[M_I\right] + n k_n \left[M_I\right]^n \right)}{\left(I + n^2 k_n \left[M_I\right]^{n-I} \right) \left(Kn\, k_n \left[M_I\right]^n \right)} \qquad \text{Eq. 7}$$

In order to discuss some specific models of association for sodium deoxycholate, $\log \Delta X$ was plotted versus log C and compared with the plots obtained for the nonionic surfactants (Figure 6). The slopes of these plots, P, were then computed. For the nonionic surfactants, the slopes were

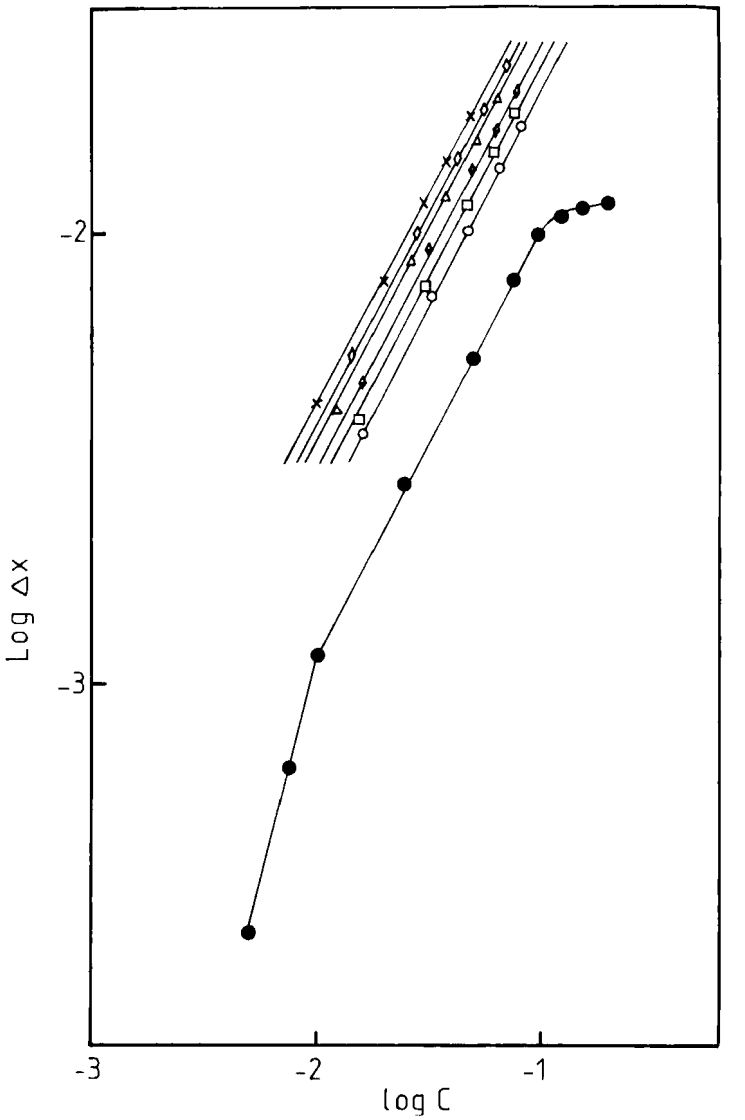

Figure 6- Logarithm of the increase in concentration of the solubilizate, $\Delta X = S - S_o$, where S_o is the solubility of carbamazepin in aqueous solution, plotted versus logarithm of the solubilizing agent concentration. Key: o, Tween 20; □, Tween 80; ◇, Brij 35; ◆, Brij 98; Δ, Myrj 51; X, Myrj 52; and ●, Sodium deoxycholate.

constants with a value of I.0, indicating a constant and uniform aggregation number formation. This, in turn implies that the systems are monodispersed.

Concerning the sodium deoxycholate, the value of P, according to Eq. 7 is maximum in dilute solutions: $P \rightarrow n$ as $C \rightarrow 0$, and decreases continuouly from n as C increases until it approaches unity at high concentrations.

The curve obtained for sodium deoxycholate has a slope of 2 in dilute solutions, which is indicative for the formation of dimers. At log C equals to -2, viz., at 0.0I M sodium deoxycholate, an inflection point is detected (Figure 6).

A value of n of nearly 5 is derived for the inflection point assuming ideality, then a slope of unity is obtained at higher concentrations, where the plot becomes parallel to the ones obtained with the nonionic detergents. This was followed by a decreased slope at much higher concentrations , viz., 0.I5 M of the dihydroxy bile salt. The data implies a polydispersity in this particular system, and are inconsistent with the formation of any single oligomer or multimer with a constant aggregation number (29). From the complex pattern of association for sodium deoxycholate, deduced from Figure 6, and from the above discussion, a model of association that includes dimers, pentamers, and large micelles would be appropriate for the solubilization of carbamazepin in this dihydroxy bile salt.

Further examination of the solubilization data was concerned with the observed gelation of bile salt, when acidified with 0.I N Hydrochloric acid at room temperature, to assay for the carbamazepin solubilized. X-ray diffraction and electron microscopy on these acidified bile salt gels, revealed the presence of long helical fibres with a cross-sectional radius of 20 Å (34). The gelation phenomena in acidified deoxycholate solutions was attributed (35) to the extensive growth of the rodlike micelles with some degree of intertwining or cross-linking between them. In order to investigate the effect of ionic strength on the solubilization data obtained, the solubility of carbamazepin in sodium deoxycholate was repeated by diluting with water instead of 0.I N Hydrochloric acid (at a wave length of 283 nm) for the assay. Based on the results obtained in distilled water instead of 0.I N Hydrochloric acid, the pattern of association of sodium deoxycholate was unaffected by the change in the ionic strength of the medium. This result was in agreement with a reported study (3I) on the effects of ionic strength on the self-association of sodium cholate.

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