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Micellar properties of non-ionic surfactants in relation to their solubility parameters

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Summary

The solubility parameters of various polyoxyethylated non-ionic surfactants were calculated according to 3 different methods: by Fedors approach; from molar attraction constants; by including a hydrogen-bonding component to account for hydration. The computed solubility parameters for the surfactants were then correlated with their critical micelle concentrations (CMC). The relationships included 3 homologous surfactant series based on polyoxyethylated ethers, octyl- and nonyl-phenols, and fatty acid esters of sorbitan. The total solubility parameters, δ_0, corrected for hydrogen bonding increased linearly with increasing the CMC. The resulting linear relationships permit the prediction of the CMC of any surfactant within a homologous series from any of its calculated solubility parameters. Branching of decaoxyethylated octylphenol to give *t*-octylphenol decreased the CMC by a factor of 1.3, and increased δ_0 by 0.31 $(\text{cal/ml})^{1/2}$. The presence of double bond in TWEEN 80 decreased the CMC by a factor of 2, and increased δ_0 by only 0.03 $(\text{cal/ml})^{1/2}$. A greater double bond effect on solubility parameter of ~ 1.0 $(\text{cal/ml})^{1/2}$ was noticed in the case of long-chain polyoxyethylated ethers than in TWEENs. The double bond contribution to CMC and to the total solubility parameter is not additive for the different homologous series and varies with the surfactant structure. The solubility parameter concept was also applied to analyse some solubilization data.

Introduction

The non-ionic surfactants are classified as hydrophobic solutes in which self-association is mainly attributed to their flexible chains, although some of these compounds include unsaturated groups or aromatic moieties. These molecules are characterized by having non-polar and polar ends joined together (Mukerjee, 1974). Since this class fulfils the requirement that higher multimers are relatively more stable than the small oligomers, the existence of precise critical micelle concentration (CMC) values is expected (Mukerjee and Cardinal, 1976). Many methods are available for determining the CMC. However, there are systematic differences between the various techniques, depending upon how monomers and micelles are reflected in the measured property (Mukerjee, 1974). The meaning and significance of the micellar hypothesis with respect to the CMC were reported in detail by Mukerjee (1974). It has been reported that the ability of surfactants to

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decrease the contact angle of hydrophobic drugs is particularly marked in the range of the critical micelle concentration (Lippold and Ohm, 1986). The effect of CMC on the absorption of salicylic acid from solutions containing non-ionic surfactants was also considered (Whitworth and Carter, 1969).

Since the solubility parameter concept is indicative of the attractive forces between molecules and takes into consideration the nature of their hydrophilic as well as the hydrophobic moieties, it has been correlated successfully with the hydrophilic-lipophilic balance (HLB) of non-ionic surfactants (Little, 1978; Schott, 1984). It has been shown that the solubillity and aggregation characteristics of surfactants are related to their solubility parameters, and to the solubility parameters of the solvents in which they were dispersed (Little and Singleterry, 1964; Little 1975).

The ability of non-ionic surfactants to act as solubilizing agents for poorly soluble drugs has been extensively studied (Naggar et al., 1972; Barry and El Eini, 1976; Samaha and Gadalla, 1987). The complex nature of this class of surfactants makes the theoretical interpretation of solubilization data extremely difficult (Arnarson and Elworthy, 1980). From the CMC and solubilization studies, a model was proposed concerning the mixed micelles of polyoxyethylene type non-ionic and anionic surfactants (Nishikido, 1977). A relation between log P and log of the distribution coefficient of solubilizate between micelles and water was presented by Tomida et al. (1978). The purpose of this work is to correlate the solubility parameters of non-ionic surfactants with their critical micelle concentrations (CMC) and to investigate the application of the solubility parameter concept as an alternative method to examine the complex phase phenomena characteristic of surfactant-based systems.

Materials and Methods

Materials

The non-ionic surfactants used in this study were supplied by Atlas Chemical Industries Inc. (Wilmington, DE, USA).

Solubility parameters and molar volumes from Fedors method

The molar volumes (V_m) and solubility parameters (δ_F) for all nonionic surfactants and for pharmaceutical solids studied are calculated using the method of Fedors (1974). This method, which is based on group additive constants, was found to compare favourably with experimental solubility parameters (Samaha and Naggar, 1987; Bustamante and Sellés, 1986). The solubility parameter is given by:

$$\delta_F = \left(\frac{\Sigma \Delta E}{\Sigma \Delta V_m} \right)^{1/2} \tag{1}$$

where ΔE is the molar energy of vaporization, and ΔV_m is the molar volume at 25 ° C.

Solubility parameters from molar attraction constants

The solubility parameters of the surfactants are also estimated from the molar attraction constants F of their functional groups according to the following equation:

$$\delta_D = \frac{\Sigma F}{V_m} \tag{2}$$

The F, in $\mathrm{cal}^{1/2}\ \mathrm{cm}^{-3/2}/\mathrm{mol}$, values were selected from published data (Schott, 1984; Koenhen and Smolders, 1975). Since the dispersion forces constitute the major components of the F values, the subscript D is given to the dispersion solubility parameters calculated from molar attraction constants.

Solubility parameters corrected for hydrogen bonding

The solubility parameters obtained from either Fedors' or the molar attraction constants method are computed for anhydrous systems. These two approaches do not take into consideration the intermolecular hydrogen bonding between water and the ether oxygens and/or hydroxyl groups of non-ionic surfactants. Consequently, an underestimated solubility parameter would be expected. Intermolecular forces affecting the cohesive energy density of surfactants in the presence of water include the dispersion forces (D), dipole forces (P), and the hydrogen-bonding or in general the donor-acceptor interactions (H). The total solubility parameter δ_0 is then given by:

$$\delta_0^2 = \delta_D^2 + \delta_P^2 + \delta_H^2 \tag{3}$$

The polar force contribution, δ_P is small in comparison with the hydrogen bonding and can be ignored. A justification for cancelling the polar contribution was reported (Schott, 1984). Eqn. 3 becomes:

$$\delta_0^2 = \delta_D^2 + \delta_H^2 \tag{4}$$

The hydrogen-bonding component, δ_H is then calculated based on the assumption that each hydrogen bond contributes 5000 cal/mol to the energy of vaporization, and that each of the n-ether or OH groups interacts with water forming one hydrogen bond. The δ_H is then computed as:

$$\delta_H^2 = \frac{5000A}{V_m} \tag{5}$$

where A is the number of ether and hydroxyl groups in the molecule. For instance, for polyoxyethylated ethers and octyl- and nonylphenols containing n-oxyethylene units and one hydroxyl group, A is $(n+1)$, whereas the coefficient A is $(n+4)$ for TWEENS 20, 40, 60, and 80, to account for the ether linkage in the ring and the 3 hydroxyl groups present in the molecule. Justification for the use of a single δ_H parameter and the assumption of a constant of 5000 cal/mol to the molar energies of vaporization for all hydrogen bonds were reported by Schott (1984). The total two-components solubility parameter, δ_0 was calculated using Eqn. 4, from δ_D obtained according to Eqn. 2 and δ_H computed from Eqn. 5. The δ_0 values for the different classes of non-ionic surfactants are listed in the last columns of Tables 1–3. They are used in the correlation study with the CMC of surfactants since they include the effect of hydration on the polarity of these non-ionic surfactants.

CMC measurements

When more than one CMC value is reported in the literature for a specific surfactant, the CMC was determined for this surfactant in aqueous solutions at 25 °C. For instance, different CMC values were reported for polyoxyethylene 20 cetyl ether (Hugo and Newton, 1960). The CMC determined in this study (as described below) for this surfactant was found to be 3.6×10^{-6}M with a molar volume of 1005 ml/mol (Table 1). CMC values were obtained by observing changes in surface tension with concentration as measured by the plate pull method using an automatic tensiometer (Prolabo, Paris, France). The plate (no. 3294), made of depolished platinum, and all glassware were thoroughly cleaned. Adsorption effects on the walls of the flasks were avoided by making up the solutions, setting them aside for 2 h and draining them. Fresh solutions were then made up in the same flasks. The dish which held the solution for measurement was treated similarly. The surface tension of each solution was determined repeatedly until a constant result was obtained.

Results and Discussion

For a homologous series of compounds, the larger the hydrophobic moiety the stronger is the tendency towards association and the lower is the CMC value. Considering the first 3 surfactants listed in Table 1, they all have hexaoxyethylene unit with hydrocarbon chain lengths of 8, 10, and 12. Their CMC values decreased with increasing the hydrocarbon moiety as expected. A 10 × decrease in CMC resulted from the addition of 2 CH_2 molecules to the preceding surfactant, whereas δ_0 calculated for these compounds decreased by a constant value of nearly 0.3 $(cal/ml)^{1/2}$ for the 2 CH_2 units added. This pronounced decrease in CMC with increasing hydrocarbon length was previously noted for non-ionic surfactants, where the addition of one methylene group caused the CMC to decrease to approximately one-third of its original value (Attwood and Florence, 1983).

As the number of oxyethylene units increases, the CMC values increase only very slightly for the

TABLE 1

Values of CMC, molar volumes (V_m), and solubility parameters (in $(cal/ml)^{1/2}$) for polyoxyethylated ethers at 25 °C

Surfactant	CMC (M)	V_m (ml/mol)	δ_F	δ_D	δ_H	δ_0
C_8OE_6	9.3×10^{-3}	372.2	9.76	8.68	9.70	13.01
$C_{10}OE_6$	9.0×10^{-4}	404.4	9.67	8.65	9.30	12.70
$C_{12}OE_6$	8.7×10^{-5}	436.6	9.59	8.62	8.95	12.43
$C_{12}OE_8$	1.3×10^{-4}	508.6	9.56	8.71	9.41	12.82
$C_{12}OE_{12}$	1.4×10^{-4}	652.6	9.52	8.85	9.98	13.34
$C_{12}OE_{29}$	2.2×10^{-4}	1264.6	9.45	9.08	10.89	14.18
$C_{12}OE_{49}$	4.4×10^{-4}	1984.6	8.83	9.17	11.22	14.49
$C_{16}OE_7$	1.7×10^{-6}	537.0	9.46	8.62	8.63	12.20
$C_{16}OE_9$	2.1×10^{-6}	609.0	9.45	8.71	9.06	12.57
$C_{16}OE_{12}$	2.3×10^{-6}	717.0	9.44	8.80	9.52	12.97
$C_{16}OE_{15}$	3.1×10^{-6}	825.0	9.43	8.87	9.85	13.25
$C_{16}OE_{17}$	3.4×10^{-6}	897.0	9.42	8.91	10.02	13.41
$C_{16}OE_{20}$	3.6×10^{-6}	1005.0	9.42	8.95	10.22	13.59
$C_{16}OE_{21}$	3.9×10^{-6}	1041.0	9.42	8.97	10.28	13.64
$C_{16}OE_{32}$	1.1×10^{-5}	1437.0	9.40	9.07	10.72	14.04
$C_{16}OE_{44}$	1.8×10^{-5}	1869.0	9.40	9.13	10.97	14.27
$C_{16}OE_{63}$	2.0×10^{-5}	2553.0	9.39	9.18	11.20	14.48
$C_{22}OE_{21}$	6.9×10^{-7}	1209.0	9.41	8.38	9.54	12.70
$C_{22}OE_{24}$	8.7×10^{-6}	1240.4	9.36	9.48	10.04	13.81
$C_{32}OE_{41}$	9.1×10^{-6}	2018.5	9.30	9.01	10.20	13.61
$C_{35}OE_{40}$	1.0×10^{-5}	2031.5	9.25	8.96	10.05	13.46

CMC values were either determined experimentally or taken from Elworthy and Patel (1982), Schott (1985), Nishikido (1977), Elworthy and Macfarlane (1962), El Eini et al. (1973), Arnarson and Elworthy (1980), or Arnarson and Elworthy (1981). δ_F was calculated from Fedors' method according to Eqn. 1; δ_D was calculated from molar attraction constants using Eqn. 2; δ_H was computed by Eqn. 5, and δ_0 was calculated by Eqn. 4.

dodecanol derivatives (Table 1). The δ_F values obtained from Fedors' method are slightly higher than the δ_D calculated from molar attraction constants for all surfactants investigated in this study (Tables 1–3). The δ_F and δ_D did not change markedly with increasing the oxyethylene units, while an increase in δ_H and δ_0 was noticed. For hexadecyloxyethylene ethers $C_{16}OE_n$, it can be seen that lengthening the polyoxyethylene chain increases the CMC. This is attributed to the increase of the hydrophilic properties of the hydrated surfactant as reflected by the increase in its total solubility parameter, δ_0 (Table 1). A plot of solubility parameters versus CMC was drawn for $C_{16}OE_n$ (Fig. 1). The δ_F did not change with increasing the polyoxyethylene units, whereas δ_D and δ_0 were increased with increasing CMC up till n equalled 21 at a CMC value of 3.9×10^{-6}, where a break point was noticed with a change in slope for the surfactants containing higher oxyethylene units. This may be attributed to the intrusion of part of the polyoxyethylene chain into the hydrocarbon core of the micelles.

The results obtained for polyoxyethylene octyl- and nonyl-phenols indicate that, as the ethylene oxide chain increases in length at constant hydrophobic group, the CMC increases and the total solubility parameter δ_0 increases (Table 2). Plots of CMC, for polyoxyethylated octyl- and nonyl-phenols, vs different solubility parameters, viz., δ_F, δ_D, and δ_0 are illustrated in Figs. 2 and 3. The same pattern was followed by the two series of surfactants. The solubility parameter δ_F slightly decreased and δ_D increased with increasing CMC. The total solubility parameter δ_0 of hydrated

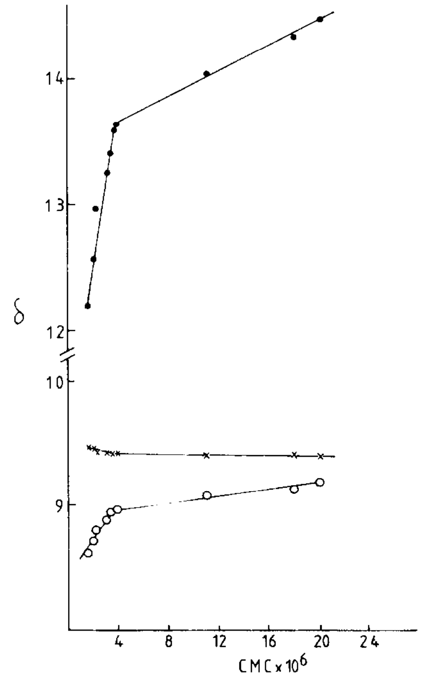
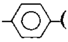
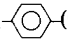


Fig. 1. Solubility parameters of hexadecyloxyethylated ethers ($C_{16}OE_n$, with n = 7–63) obtained by 3 methods vs CMC. (○), δ_D calculated by Eqn. 2: (×), δ_F calculated by Eqn. 1; (●), δ_0 corrected for hydration according to Eqn. 4.

TABLE 2

Values of CMC, molar volumes (V_m)*, and solubility parameters (in* $(cal/ml)^{1/2}$*) for polyoxyethylated octyl- and nonyl-phenols at 25 °C*

Surfactant	CMC (M)	V_m (ml/mol)	δ_F	δ_D	δ_H	δ_0
$CH_3\text{-}(CH_2)_7\text{-}$$\text{-}(OCH_2\text{-}CH_2)_n\text{-}OH$						
$(OCH_2CH_2)_3$	1.03×10^{-4}	335.6	10.00	8.59	7.82	11.62
$(OCH_2CH_2)_4$	1.29×10^{-4}	371.6	9.95	8.64	8.20	11.91
$(OCH_2CH_2)_5$	1.72×10^{-4}	407.6	9.90	8.70	8.58	12.22
$(OCH_2CH_2)_6$	2.15×10^{-4}	443.6	9.86	8.75	8.88	12.47
$(OCH_2CH_2)_7$	2.68×10^{-4}	479.6	9.82	8.80	9.13	12.68
$(OCH_2CH_2)_8$	2.83×10^{-4}	515.6	9.79	8.83	9.34	12.86
$(OCH_2CH_2)_9$	3.04×10^{-4}	551.6	9.76	8.87	9.52	13.01
$(OCH_2CH_2)_{10}$	3.40×10^{-4}	576.8	9.75	8.89	9.63	13.11
1-*t*-octyl-4-$(OCH_2CH_2)_{10}$	2.70×10^{-4}	568.1	9.82	9.13	9.84	13.42

Surfactant	CMC (M)	V_m (ml/mol)	δ_F	δ_D	δ_H	δ_0
$CH_3\text{-}(CH_2)_8\text{-}$$\text{-}(OCH_2\text{-}CH_2)_n\text{-}OH$						
$(OCH_2CH_2)_{5.8}$	0.30×10^{-4}	452.5	9.82	8.73	8.67	12.30
$(OCH_2CH_2)_{6.6}$	0.40×10^{-4}	481.3	9.79	8.76	8.89	12.48
$(OCH_2CH_2)_{8.5}$	0.56×10^{-4}	549.7	9.74	8.83	9.30	12.82
$(OCH_2CH_2)_{9.8}$	0.64×10^{-4}	596.5	9.71	8.87	9.52	13.01
$(OCH_2CH_2)_{10.0}$	0.75×10^{-4}	603.7	9.71	8.88	9.54	13.04
$(OCH_2CH_2)_{11.7}$	0.80×10^{-4}	664.9	9.68	8.92	9.77	13.23

CMC values were either determined experimentally or taken from Becher (1967), Schott (1985), Otsuka et al. (1973), or Schick et al. (1962). δ_F was calculated from Fedors' method according to Eqn. 1, δ_D calculated by Eqn. 2, δ_H computed by Eqn. 5, and δ_0 calculated by Eqn. 4.

surfactants increased markedly with increasing CMC. From the resulting linear relationships, the CMC of any surfactant within the homologous series can be predicted from any of the calculated solubility parameters, viz., δ_F, δ_D, or δ_0.

If we compare the results obtained for the straight-chain decaoxyethylated octylphenol with the corresponding *t*-octylphenol (Table 2), we can see that the CMC of the latter decreases by a factor of 1.3, and its δ_0 increases by 0.31 $(cal/ml)^{1/2}$, i.e., from 13.11 for the linear octylphenol to 13.42 for the branched surfactant. This result is in accordance with a previously found conclusion that branching of analogous linear structures increases hydrophilicity (Rehn et al., 1984).

As a class, the TWEEN series of polyoxyethylene sorbitan esters is considered as hetero-

TABLE 3

Values of CMC, molar volumes (V_m)*, and solubility parameters (in* $(cal/ml)^{1/2}$*) for TWEENS at 25 °C*

Surfactant POE(20)	CMC (M)	V_m (ml/mol)	δ_F	δ_D	δ_H	δ_0
Sorbitan monolaurate (TWEEN 20)	4.8×10^{-5}	1010.5	10.36	9.44	10.90	14.42
Sorbitan monopalmitate (TWEEN 40)	2.4×10^{-5}	1074.9	10.26	9.37	10.57	14.12
Sorbitan monostearate (TWEEN 60)	2.1×10^{-5}	1107.1	10.22	9.34	10.41	13.98
Sorbitan mono-oleate (TWEEN 80)	1.1×10^{-5}	1101.9	10.23	9.35	10.44	14.01
Sorbitan tristearate (TWEEN 65)	2.7×10^{-5}	1705.3	9.38	8.83	8.03	11.94
Sorbitan trioleate (TWEEN 85)	1.2×10^{-5}	1689.7	9.39	8.85	8.07	11.97

CMC values from Wan and Lee (1974). δ_F calculated from Fedors method according to Eqn. 1, δ_D calculated from molar attraction constants using Eqn. 2, δ_H computed by Eqn. 5, and δ_0 calculated by Eqn. 4.

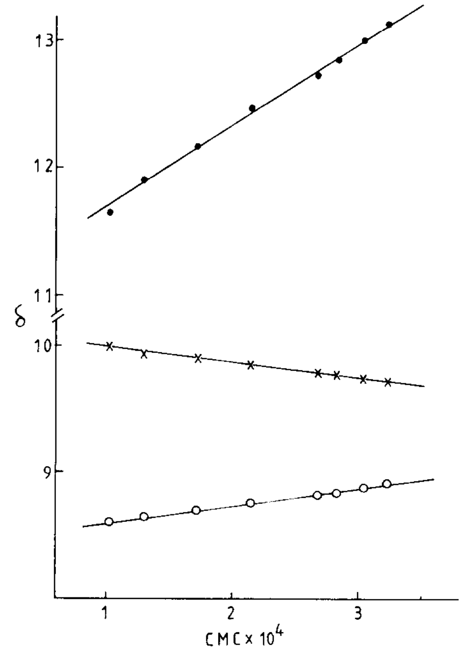


Fig. 2. Solubility parameters of polyoxyethylated octylphenols vs CMC. (○), δ_D calculated by Eqn. 2; (×), δ_F calculated by Eqn. 1; (●), δ_0 corrected for hydration according to Eqn. 4.

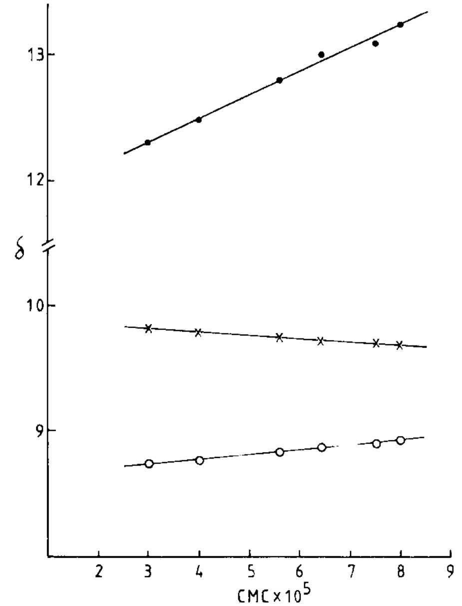


Fig. 3. Solubility parameters of polyoxyethylated nonylphenols vs CMC. (○), δ_D calculated by Eqn. 2; (×), δ_F calculated by Eqn. 1; (●), δ_0 corrected for hydration according to Eqn. 4.

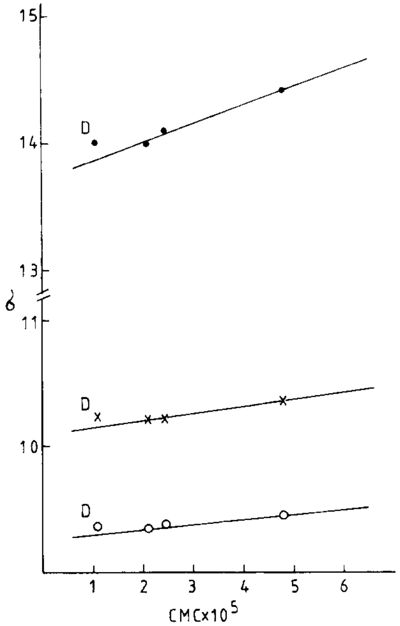


Fig. 4. Solubility parameters of TWEENS 20, 40, 60, and 80 vs CMC. (○), δ_D calculated by Eqn. 2; (×), δ_F calculated by Eqn. 1; (●), δ_0 calculated by Eqn. 4; D, double bond.

disperse, i.e., the distribution of its components is a multivariant one. The CMCs of these surfactants are presented in Table 3, in molar units for comparative reason, although it is more useful due to their heterodisperse character to give them in w/v concentration units. The order of magnitude of the CMC are the same as those obtained for other non-ionic surfactants (Tables 1 and 2). The effect of a double bond is investigated for this class of compounds. The addition of one double bond to TWEEN 60 to give TWEEN 80, decreased the CMC by a factor of two, i.e., from 2.1×10^{-5} to 1.1×10^{-5}. The total solubility parameter δ_0 corrected for hydration increased by 0.03 $(\text{cal/ml})^{1/2}$ per double bond (Fig. 4). In going from TWEEN 65 to TWEEN 85, 3 double bonds were introduced into sorbitan tristearate to give the trioleate (Table 3). However, the contributions of the 3 double bonds to the CMC and to δ_0 are equal to the effects of the single double bond added to TWEEN 60 to give TWEEN 80. The CMC decreased by a factor of 2.25 and δ_0 increased by 0.03 $(\text{cal/ml})^{1/2}$ per 3 double bonds, which led to

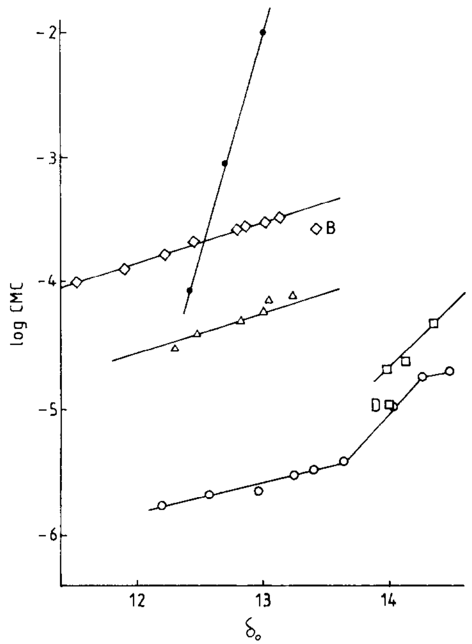


Fig. 5. Total solubility parameter δ_0 versus log CMC. (●), C_nOE_6 with $n = 8$, 10, and 12; (○), $C_{16}OE_n$, with $n = 7$–63; (◇), octylphenols; (△), nonylphenols; (□), TWEENS 20, 40, 60, and 80; B, branching; D, double bond.

the conclusion that the double bond contribution is not additive.

Plots of log CMC versus δ_0 for the different homologous series are illustrated in Fig. 5. The two straight lines obtained for octylphenol and nonylphenol derivatives are parallel with a constant slope. The effect of branching (B) on the solubility parameter δ_0 is noted, as well as the double bond effect (D). The latter is introduced into TWEEN 60 to give TWEEN 80. The slope is greater in the case when the hydrophobic moiety is increased with constant oxyethylene units, viz., in case of C_nOE_6.

Analysis of the results obtained by Barry and El Eini (1976) for the solubilization of steroids by long-chain polyoxyethylene surfactants was performed on a solubility parameter basis. Steroid molecules per micelle decreased with increasing polyoxyethylene units, i.e., increasing the solubility parameter of the surfactant (Table 4). Hydrocortisone with the highest solubility parameter of 12.38 $(cal/ml)^{1/2}$, computed using Fedors' approach, had the largest number of steroid molecules per micelle for a specific surfactant, whereas progesterone with the smallest δ_F value of 9.85 $(cal/ml)^{1/2}$ exhibited the smallest number of steroid molecules for that surfactant.

In order to gain more insight into the usefulness of solubility parameter concept in solubilization studies, more published solubilization data (Arnarson and Elworthy 1980) are presented in Table 5, together with the solubility parameters of the solubilizates calculated using Fedors' method, as well as the two-component solubility parameters of hydrated surfactants. The solubilizates were chosen to represent a fairly severe screen as they vary widely in structure, with molecular volumes ranging from 127 to 374 ml/mol (computed according to Fedors' method).

The non-ionic surfactant $C_{22}OE_{24}$ contains a *cis*-double bond (polyoxyethylene-1-docosyl-13-ene-ether) with a δ_0 value of 13.81 $(cal/ml)^{1/2}$, whereas a δ_0 of 12.70 was calculated for $C_{22}OE_{21}$

TABLE 4

Total solubility parameters δ_0 for some polyoxyethylated ethers, micellar solubilization data and Fedors' solubility parameters δ_F for steroids at 25°C

Surfactant	δ_0	Steroid molecules per micelle			
		Hydrocortisone ($\delta_F = 12.38$)	Dexamethasone ($\delta_F = 11.98$)	Testosterone ($\delta_F = 10.87$)	Progesterone ($\delta_F = 9.85$)
$C_{16}OE_{17}$	13.41	9.1	6.7	6.0	5.6
$C_{16}OE_{32}$	14.04	7.6	5.3	4.6	4.3
$C_{16}OE_{44}$	14.27	5.8	4.2	3.6	3.3
$C_{16}OE_{63}$	14.48	4.0	3.3	2.4	2.3

Total solubility parameters calculated according to Eqn. 4. Micelle solubilization data taken from Barry and El Eini (1976).

TABLE 5

Solubility parameters (in (cal/ml)$^{1/2}$) and molar volumes (V_m) for some materials, and solubilization results in 3 polyoxyethylated non-ionic surfactants

Solubilizate	δ_F	V_m ml/mol	Surfactants		
			$C_{16}OE_{20}$ ($\delta_0 = 13.59$)	$C_{22}OE_{21}$ ($\delta_0 = 12.70$)	$C_{22}OE_{24}$ ($\delta_0 = 13.81$)
Azobenzene	11.68	152.8	33.4	17.9	43.7
Cortisone acetate	11.66	291.6	1.8	2.6	1.6
Griseofulvin	10.41	374.0	3.0	2.2	3.3
Sulfadiazine	13.17	154.2	−0.2	1.1	1.0
Phenylbutazone	11.34	243.2	6.4	4.5	8.4
Betamethasone	11.98	282.2	4.0	5.5	4.3
Tolbutamide	10.77	211.2	9.5	6.2	12.2
Menaphthone	12.60	127.1	20.3	9.6	24.9

Solubilization data from Arnarson and Elworthy (1980). δ_F calculated according to Fedors method using Eqn. 1. Total solubility parameter δ_0 for hydrated surfactants, calculated according to Eqn. 4. Amount solubilized is 100 mol/mol.

(polyoxyethylene-1-docosane ether). Cetomacrogol ($C_{16}OE_{20}$) has a δ_0 value of 13.59 (cal/ml)$^{1/2}$. On a mol solubilizate/mol surfactant basis, $C_{22}OE_{24}$ with the highest solubility parameter δ_0 has a better solubilizing capacity in most cases than the other two surfactants, i.e., the most hydrophilic surfactant was the most efficient. An exception to this rule was observed in the case of steroids (Tables 4 and 5), a fact which may be attributed to their specific molecular structure. The thermodynamic parameters controlling the process of solubilization of steroids by long-chain polyoxyethylene surfactants were reported by Barry and El Eini (1976). The standard free energy change, $-\Delta G_s^o$, decreased with increasing hydrophilic chain length indicating that solubilizing efficiency was greater for the more hydrophobic surfactants. The decrease in $-\Delta G_s^o$ was explained by considering micellar hydration, the water trapped by the polyoxyethylene chain mesh physically hinders incorporation of steroid molecules and since hydration increases with hydrophilic chain length, steroid solubilization efficiency decreases (Barry and El Eini, 1976). In order to reach a general conclusion about the usefulness of the solubility parameter concept as a prediction index of solubilization capacity, more solubilization data must be analyzed. In addition, a more accurate expression incorporating the molar volume of solubilizate is now in progress.

Comparison of solubility parameters calculated for $C_{22}OE_{24}$ and $C_{22}OE_{21}$ shows the profound effect of the *cis*-double bond introduced into the former surfactant. The large difference of 1.11 (cal/ml)$^{1/2}$ in δ_0 can be mainly attributed to the double bond present in $C_{22}OE_{24}$ since the 3 extra oxyethylene units would lead to only a very small increment in δ_0 (Table 1).

The application of the solubility parameter concept to surfactant behaviour in aqueous solutions together with the CMC–solubility parameter correlations presented in this study provide an initiation for the generalized use of this concept in pharmaceutical research problems involving non-ionic surfactants.

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