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Effect of Structural Variations of Non-ionic Surfactants on Micellar Properties and Solubilization: Surfactants with Semi-polar Hydrophobes

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Abstract—Novel non-ionic surfactants have been synthesized in which a polar group (either an ether or a keto group) has been introduced into the hydrocarbon chain of an octadecylpolyoxyethylene glycol monoether ($C_{18}E_n$) with an oxyethylene chain length, n, of 17–18 units. Light scattering studies have indicated aggregation numbers for these semi-polar surfactants in aqueous solution of between 55-65% of that of an unsubstituted octadecylpolyoxyethylene glycol monoether, $C_{18}E_{22}$. The solubilizing capacities of the semi-polar surfactant micelles for test compounds which were mainly solubilized at the polyoxyethylene/core interface were lower than those of $C_{18}E_{22}$ whilst solubilizates which exhibited a reasonable degree of solubility in both the interface and the micellar core showed an increased solubilization.

Previous studies (Arnarson & Elworthy 1980, 1981, 1982; Elworthy & Patel 1982) have reported that lengthening the alkyl chain of a series of n-alkylpolyoxyethylene glycol mono ether surfactants [general formula $C_mE_{1\cdot25m}$] above m = 16, although causing an increase in micellar size did not result in the enhanced solubilization of a range of drugs. The first surfactant of this series to exhibit a decreased solubilizing capacity ($C_{18}E_{22}$) was also the first to possess a hydrocarbon chain which was not fluid at the experimental temperature of 298K. Evidence from NMR (Elworthy & Patel 1984a), viscosity (Elworthy & Patel 1984b) and density (Patel & Elworthy 1984) studies suggests that, in an attempt to retain a fluid micellar core, some polyoxyethylene intrudes into the core in order to depress its melting point. This intrusion has the effect of diluting, in terms of the polyoxyethylene content, the polyoxyethylene/water region close to the micelle core, thus destroying the main locus of solubilization for most drugs. These studies have emphasized the importance of the fluid nature of the micelle core in determining the micellar properties and solubilising capacity.

It has previously been suggested (Patel et al 1981) that an alternative approach to increasing the solubilizing capacity would be the replacement of the hydrocarbon core with one of a more polar nature in order to promote solubilization in this region. In the present study we have examined how the introduction of a polar group (either an ether or keto group) into the hydrophobe of an octadecylpolyoxyethylene glycol mono ether surfactant affects the micellar properties and solubilization capacity of the surfactant. Furthermore, the introduction of the ether group will lower the melting point of the hydrophobe below that of the corresponding hydrocarbon and hence it should be possible to produce a liquid core without the necessity of intrusion and the consequent loss of solubilizing capacity.

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Materials and Methods

Materials

Synthetic surfactants. The novel surfactants synthesized in the study were $CH_3(CH_2)_{11}$ $O(CH_2)_5$ $(OCH_2CH_2)_{18}OH$ [$C_{18(e,6)}E_{18}$], CH_3 $(CH_2)_6O(CH_2)_{10}(OCH_2CH_2)_{17}OH$ [$C_{18(e,11)}E_{17}$] and $CH_3(CH_2)_5CO(CH_2)_{11}(OCH_2CH_2)_{18}$ [$C_{18(k,12)}E_{18}$]. In the designation used for these surfactants, e and k represent ether and keto groups, respectively, and the number following this letter specifies the position of the group in the chain. The hydrophobe is denoted as C_m, where m represents the number of atoms in the back bone. The hydrophile is denoted in the usual way as E_n, where n is the average number of oxyethylene units, E. The surfactants were synthesised in the following way.

The hydrophobe 6-oxaoctadecan-l-ol was prepared from l-bromododecane and a four molar excess of the monosodium salt of 1,5 pentanediol, by the Williamson ether synthesis. ll-Oxadecan-l-ol was prepared by reacting the mono-potassium salt of 1,10 decanediol with l-bromoheptane using dimethyl sulphoxide as a solvent. In both preparations, distillation followed by recrystallization from a water–methanol mixture yielded the desired product.

The hydrophobe, 12-oxooctadecan-l-ol was prepared in a multi-stage synthesis using 12-hydroxyoctadecanoic acid as the starting material. Technical grade 12-hydroxyoctadecanoic acid was first purified by extraction with light petroleum (b.p. 40–60°C), then oxidized using the method of Sandborn (1929) and the resulting oxo acid converted into the ethyl ester according to the method of Leonard & Goode (1950). The ethyl ester was reduced to the alcohol using lithium aluminium hydride, following protection of the free oxo group by conversion into the corresponding ketal. The free oxo group was reformed after reduction by alkaline hydrolysis of the ketal to give the desired product.

The final stage in the preparation of all the novel semi-polar surfactants was the condensation and polymerization

of ethylene oxide with the hydroxyl group of the hydrophobe, using sodium metal as the catalyst. Purification was by the method of Longman (1978). The surfactants were shown to contain no glycols or starting alcohols by TLC on silica. Elemental analysis, MS, IR and NMR spectra for all products were consistent with the expected structure. The sample of $C_{18}E_{22}$ was that of Patel (1982).

Solvents and solubilizates. The hydrophobe, $C_{18(e,6)}$, was methoxylated for use in solubility studies according to the method of Johnstone & Rose (1979) and purified by distillation.

The following solubilizates were used as received, azobenzene (BDH), cortisone acetate (ICI Pharmaceuticals), betamethazone, griseofulvin and phenylbutazone (Glaxo).

Methods

Light scattering measurements. Total intensity light scattering measurements were made at 298K ± 0·1K using a Fica 42 000 photogoniodiffusometer at the incident wavelength of 546 nm. Solutions were clarified by ultra filtration through 0·1 μm Millipore filters until the ratio of intensities at scattering angles of 30° and 150° did not exceed 1·10. Specific refractive index increments were measured at 546 nm by differential refractometry yielding values of 0·132, 0·129 and 0·145 $dm^3\ mol^{-1}$ for $C_{18(e,11)}E_{17}$, $C_{18(e,6)}E_{18}$ and $C_{18(k,12)}E_{18}$, respectively.

Viscometric measurements. Viscosity measurements were made at 298 K ± 0·05 K using a suspended-level viscometer. Solutions were previously filtered through 0·22 μm Millipore filters.

Density measurements. The densities of the aqueous surfactant solutions were measured at 298 K ± 0·01 K using a digital densimeter (Anton Parr Model DMA 02C).

Cloud point determination. Surfactant solutions, in the concentration range $0\text{-}3 \times 10^{-2}$ mol dm^{-3}, were heated at a rate of 1 K min^{-1} and observed visually for the appearance of clouding. All solutions remained clear up to 373K in the presence and absence of the solubilizates over the concentration range studied.

Solubilization studies. The solubilities of five test compounds at 289K were determined in 2% w/w solutions of the novel semi-polar surfactants, using the method of Arnarson & Elworthy (1980).

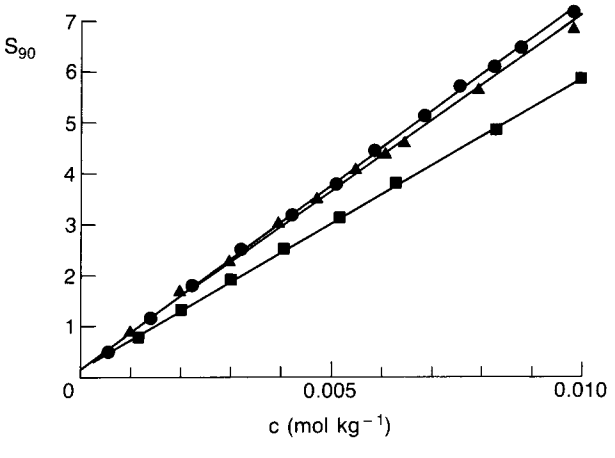

FIG. 1. Variation of light scattering intensity, S_{90}, with micellar concentration, c, for ■, $C_{18(e,6)}E_{18}$, ▲, $C_{18(e,11)}E_{17}$, and ●, $C_{18(k,12)}E_{18}$ at 298K.

Results and Discussion

Micellar structure

Fig. 1 shows the variation of light scattering intensity at 90°, S_{90}, relative to that from a calibrated standard, with micellar concentration, c, for the three surfactants in aqueous solution. Micellar concentrations were calculated using the critical micelle concentrations (CMC) of the surfactants as found from surface tension measurements (Lawrence 1985). The $S_{90}-c$ plots were linear for all systems. The weight average micellar weight, M, and aggregation number, N, as calculated from the Debye equation are given in Table 1, together with results obtained for $C_{18}E_{22}$ (Elworthy & Patel 1982), the polyoxyethylene n-alkyl ether with the equivalent hydrophobic chain length. Because of the problems associated with the control of the polymerization process by which the surfactants were synthesized, the semi-polar surfactants all contained a lower oxyethylene content than is required for strict comparison with $C_{18}E_{22}$. However, data of Arnarson & Elworthy (1981) have shown that for long chain length polyoxyethylene n-alkyl ether surfactants, the influence of the degree of polymerization on the micelle size is slight, providing that the n/m ratio is within the range 1·0–1·5. Consequently this discrepancy was not thought to invalidate conclusions drawn from comparisons with this compound.

Table 1 shows that the semi-polar surfactants have aggregation numbers of the order of 55–65% of that of $C_{18}E_{22}$. Since the experimental aggregation number of $C_{18}E_{22}$ (N = 111) is in close agreement with a value of 113 predicted from a linear regression fit of N against m for other members of the polyoxyethylene n-alkyl ether surfactants with a n/m ratio in the range 1·0–1·5 (Arnarson & Elworthy 1981), there is little reason to doubt the reliability of this value. A reduction in aggregation number was also reported (Patel 1982) following the incorporation of a *cis* double bond into the hydrocarbon chain of $C_{18}E_{22}$. Since there was no change in the polarity of the hydrophobe, this reduction of micellar

Table 1. Micellar properties at 298 K.

Surfactant	M $\times 10^{-4}$	N	$[\eta]$	K_H	δ (g/g)	ω	R_{obs} (nm)	R_{calc} (nm)
$C_{18(e,6)}E_{18}$	6·0	61	4·58	4·5	0·85	2·91	3·55	5·21
$C_{18(e,11)}E_{17}$	7·1	70	6·02	2·4	1·38	4·55	4·06	5·13
$C_{18(k,12)}E_{18}$	6·7	62	8·53	1·2	2·11	7·12	4·37	5·23
$C_{18}E_{22}$ [a]	13·8	111	8·00	1·5	1·67	5·23	5·22	6·39

[a] From Elworthy & Patel (1982)

M = micellar mass, N = aggregation number, $[\eta]$ = intrinsic viscosity, K_H = Huggins constant, δ = micellar hydration in g of H_2O g^{-1} micellar surfactant, ω = number of water molecules per ether linkage, R_{obs} and R_{calc} are the observed and calculated hydrodynamic micellar radii.

size was attributed solely to the geometric constraints of packing a 'V' shaped chain (due to the *cis* double bond) into the micellar core. Replacement of the double bond by a polar dihydroxy group restored some of the rotational freedom around the bond causing an increase of aggregation number. The aggregation number, however, remained below that of $C_{18}E_{22}$ due to the presence of this polar group. It is difficult with the semi-polar surfactants of this study, to distinguish the respective contributions to the micelle size reduction of increased polarity of the hydrophobe and the geometric constraints on packing resulting from the introduction of the ether and keto groups.

The geometric constraints on packing of the semi-polar surfactants would be expected to be less than those caused by the introduction of a double bond. The ether bond angle is $110° \pm 0{\cdot}3°$ (Baggett 1979) which is similar to the C—C—C bond angle in alkanes ($112{\cdot}6° \pm 0{\cdot}2°$). Similarly the carbonyl bond angle lies in the range $121{\cdot}0° \pm 2{\cdot}0°$ and it also might be expected to have only a minimal effect on the mode of packing of the hydrophobe into the core. There is little doubt that the micelles of the semi-polar surfactants are spherical, the aggregation number being less than the maximum theoretical value of 117 for the formation of a spherical micelle from a surfactant containing a C18 chain (Tanford 1972). Hence the hydrophobic chain length within the micelles may be estimated by calculation of the volume of the spherical micellar core. From a knowledge of the micelle aggregation number and the density of comparable hydrophobes, values of core radii of between 1·97 and 2·07 nm may be calculated assuming the core to resemble a liquid droplet. These radii are less than the fully extended chain lengths of 2·25 nm for $C_{18(e,6)}$ E_{18} and $C_{18(e,11)}$ E_{17} and 2·26 nm for $C_{18(k,12)}$ E_{18} as calculated from bond angle measurements. These calculations suggest that the hydrophobic chains are bent within the micellar core. Such bending would introduce constraints on packing which, combined with the polarity associated with the ether and keto groups, could cause the reduction in aggregation number compared to the straight chain equivalent, $C_{18}E_{22}$.

An estimation of micellar hydration has been obtained from a combination of viscosity and density measurements. Fig. 2 shows plots of reduced specific viscosity as a function of micellar concentration. Intrinsic viscosities, $[\eta]$, and Huggins constants, K_H, were obtained by extrapolation of the reduced specific viscosity to zero micellar concentration, according to

$$\eta_{sp}/c = [\eta] + [\eta]^2 K_H c \quad (1)$$

The weight of water per unit weight of surfactant, δ, was determined from the deviation of $[\eta]$ from the theoretical value (2·5) for hard, uncharged spheres using,

$$[\eta] = 2{\cdot}5\ (\bar{V}_2 + \delta V_1^\circ) \quad (2)$$

where V_1° is the specific volume of pure solvent. The partial specific volume $\bar{V}_2$ ($mL g^{-1}$) of the surfactant monomer was calculated from

$$d_s = d + (1 + \bar{V}_2\, d)C \quad (3)$$

where d_s and d are the densities of solution and solvent respectively and C is the total surfactant concentration in g mL^{-1}. Hydration values are given in Table 1.

Although the cores of the surfactant micelles contain polar groups it is not thought that these would attract any significant amount of water, and the hydration calculated from Eqn 2 may be assumed to be associated with polyoxyethylene chains. Table 1 shows that the number of water molecules per ether linkage, ω, was in excess of the 2 molecules of water which may be hydrogen bonded to the ether oxygen of each oxyethylene group. This excess hydration may be accounted for by water molecules which are physically trapped in the interstices of the polyoxyethylene chains. Clearly any intrusion of these chains into the core will influence the extent of hydration. NMR measurements (Lawrence 1985) have shown that neither $C_{18(e,11)}$ E_{17} nor $C_{18(e,6)}$ E_{18} exhibit intrusion and in these systems all the oxyethylene chains are available for hydration. However, intrusion of some of the polyoxyethylene into the micelles of $C_{18(k,12)}$ E_{18} has been noted. Intrusion has two opposing effects on the hydration. It removes polyoxyethylene from the palisade layer into the core, leading to a decrease in hydration. This effect is however counteracted by an increase in the effective area per molecule at the core/mantle interface. Patel (1982) calculated that the intrusion of six polyoxyethylene groups into the micellar core of $C_{18}E_{22}$ caused the area per molecule at the interface to increase from 0·65 nm^2 to 0·98 nm^2. As a consequence it is possible to accommodate a larger amount of physically trapped water and hydration may increase. The high δ value for $C_{18(k,12)}$ E_{18} suggests that this latter effect predominates in this compound.

The hydrodynamic radius, R_{obs}, may be calculated from the viscosity data using

$$[\eta]M/N_A = 10\pi R_{obs}^3/3 \quad (4)$$

where N_A is the Avogadro constant. If the micelle is considered to be composed of a distinct core of radius R_c and surrounding mantle of width R_m then a hydrodynamic radius R_{calc} may be calculated from

$$R_{calc} = R_c + R_m \quad (5)$$

The assumption of a meander conformation for the polyoxyethylene chains with a value of 0·18 nm per oxyethylene unit (Birdi 1985) gives R_{calc} values consistently higher than those derived from experimental data (see Table 1). Our results clearly exclude the possibility of an extended zig-zag conformation of the chains since a value of 0·35 nm per oxyethylene

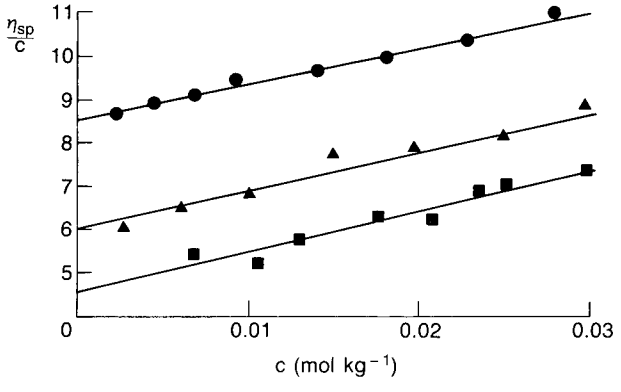

FIG. 2. Variation of reduced viscosity, η_{sp}/c with micellar concentration, c, for ■, $C_{18(e,6)}E_{18}$, ▲, $C_{18(e,11)}E_{17}$ and ●, $C_{18(k,12)}E_{18}$ at 298K.

Table 2. Solubilizing capacity (g g^{-1} of surfactant) and solubility (g g^{-1} of solvent) for test compounds in 2% surfactant solutions and in a series of solvents.

	Azobenzene	Phenyl-butazone	Griseo-fulvin	Beta-methasone	Cortisone Acetate
$C_{18(e,6)}E_{18}$	$5{\cdot}1\times10^{-2}$	$1{\cdot}7\times10^{-2}$	$0{\cdot}6\times10^{-2}$	$1{\cdot}5\times10^{-2}$	$0{\cdot}5\times10^{-2}$
$C_{18(e,11)}E_{17}$	$5{\cdot}0\times10^{-2}$	$1{\cdot}4\times10^{-2}$	$0{\cdot}7\times10^{-2}$	$1{\cdot}7\times10^{-2}$	$0{\cdot}4\times10^{-2}$
$C_{18(k,12)}E_{18}$	$5{\cdot}3\times10^{-2}$	$0{\cdot}9\times10^{-2}$	$0{\cdot}6\times10^{-2}$	$1{\cdot}2\times10^{-2}$	$0{\cdot}7\times10^{-2}$
$C_{18}E_{22}$ [a]	$4{\cdot}2\times10^{-2}$	$1{\cdot}1\times10^{-2}$	$0{\cdot}9\times10^{-2}$	$2{\cdot}1\times10^{-2}$	$0{\cdot}6\times10^{-2}$
Water [b]	$5{\cdot}0\times10^{-6}$	$3{\cdot}4\times10^{-5}$	$1{\cdot}0\times10^{-5}$	$7{\cdot}6\times10^{-5}$	$2{\cdot}8\times10^{-5}$
DMTG [b]	$3{\cdot}4\times10^{-1}$	$1{\cdot}7\times10^{-1}$	$2{\cdot}2\times10^{-2}$	$9{\cdot}7\times10^{-3}$	$2{\cdot}0\times10^{-2}$
n-hexadecane [b]	$1{\cdot}2\times10^{-1}$	$3{\cdot}4\times10^{-3}$	$3{\cdot}9\times10^{-6}$	$2{\cdot}0\times10^{-6}$	$3{\cdot}5\times10^{-6}$
$C_{18(e,6)}$	$1{\cdot}8\times10^{-1}$	$2{\cdot}6\times10^{-2}$	$1{\cdot}5\times10^{-4}$	$1{\cdot}0\times10^{-4}$	$5{\cdot}5\times10^{-4}$

[a] From Elworthy & Patel (1982)
[b] From Patel et al (1981)

group (Birdi 1985) would greatly increase the difference between experimental and calculated values. A similar discrepancy between R_{calc} and R_{obs} was noted by Sato et al (1988) for a series of n-alkyloctaethylene glycol monoethers, C_mE_8, and was attributed to a possible intrusion of some of the oxyethylene chain into the core. Since, of the surfactants of Table 1, only $C_{18(k,12)}E_{18}$ and $C_{18}E_{22}$ have been shown to exhibit such intrusion, this is clearly not a valid explanation of the discrepancy noted in this study which is probably due to a slight contraction of the polyoxyethylene chains to a length smaller than that of the meander conformation.

Solubilization

The solubilizing capacities of 2% w/w solutions of the semi-polar surfactants for a series of test compounds are compared in Table 2 with those of $C_{18}E_{22}$. The solubilizing capacities were consistently lower than those of $C_{18}E_{22}$ for all solubilizates except azobenzene and phenylbutazone. Since there was not thought to be any intrusion of polyoxyethylene into the core of the semi-polar surfactants (with the exception of $C_{18(k,12)}E_{18}$), it was expected that there would be an increase in the solubilizing capacity when compared with the intruded micelles of $C_{18}E_{22}$. The reason why such an increase did not occur for all test compounds may be explained by consideration of the site of solubilization and the effect of the structural changes on the microenvironment at that site. The solubilities of the test compounds in one of the hydrophobes, ($C_{18(e,6)}$), were measured and compared with reported solubilities (Patel et al 1981) in n-hexadecane, in water and in dimethoxytetraethylene glycol (DMTG), which was chosen to represent the local environment of the dehydrated polyoxyethylene region close to the micellar core. In an attempt to simulate the conditions of the micelle core, the hydroxy groups of the hydrophobe $C_{18(e,6)}$ were capped with a methoxy group thus ensuring that effects due to these free hydroxy groups were avoided. The results, presented in Table 2, show a low solubility of griseofulvin, betamethasone and cortisone acetate in hexadecane and $C_{18(e,6)}$ when compared with their solubilities in DMTG. The main locus for solubilisation of these drugs might therefore be expected to be the polyoxyethylene region immediately surrounding the core. The remaining compounds, azobenzene and phenylbutazone, show similar solubilities in both DMTG and the $C_{18(e,6)}$ hydrophobe and might be expected to be partitioned between the core and the polyoxyethylene region. Any changes in the nature of the polyoxyethylene region might not therefore be expected to have such an influence on their solubilization. It is only these two compounds which are likely to be affected by changes in the nature of the core. In view of their higher solubilities in the $C_{18(e,6)}$ hydrophobe compared with hexadecane, some improvement of solubilization in the semi-polar micelles over that in the $C_{18}E_{22}$ might be expected, as was in fact seen in the solubilization results of Table 2.

The lower aggregation numbers of the semi-polar surfactants compared with $C_{18}E_{22}$ introduces changes in the area occupied by the monomer at the core/mantle interface. Areas per molecule at the hydrocarbon surface of 0·76, 0·79 and 0·83 nm^2 were determined for $C_{18(e,11)}$ E_{17}, $C_{18(e,6)}$ E_{18} and $C_{18(k,12)}$ E_{18}, respectively, compared with 0·67 nm^2 for $C_{18}E_{22}$ (Lawrence 1985). These larger areas per molecule effectively cause a reduction in the oxyethylene content at the solubilization site and a less favourable locus for solubilization. The reduction in solubilization capacity of the semi-polar micelles for those drugs (griseofulvin, betamethasone and cortisone acetate) which are mainly located at this site is therefore predictable.

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