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# Effects of structural variations of non-ionic surfactants on micellar properties and solubilization: surfactants based on erucyl and behenyl ($C_{22}$) alcohols

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Studies on erucyl alcohol ethoxylated with 24 units and on behenyl alcohol ethoxylated with 21 ethylene oxide units gave values of $10{\cdot}2 \times 10^3$ and $25{\cdot}4 \times 10^3$ for the micellar weights, 74 and 203 for the aggregation number, and 134 and 106 moles water $mole^{-1}$ surfactant for the micellar hydration, respectively. The solubilization of azobenzene, cortisone acetate, griseofulvin, sulphadiazine, phenylbutazone, betamethasone, tolbutamide, and menaphthone was studied in 2% solutions of the above surfactants, and in cetomacrogol. Excluding sulphadiazine, a linear relationship was found between moles solubilized/mole surfactant, and (log P)/molar volume of solubilizate.

Although non-ionic surfactants are more physiologically tolerable than ionics, their solubilizing capacity is lower than that of the ionics (Elworthy & Treon 1967). New non-ionic surfactants with greater solubilizing capacity would be useful in solving formulation problems, particularly for insoluble intravenous anaesthetics. We have examined how variations in the chemical structure of non-ionics affects their micellar properties, in the hope that this will lead to new surfactants with increased solubilizing capacity.

For ionic surfactants, increase of hydrocarbon chain length, with the attendant increase in micellar size, is the principal method of increasing the amount of material solubilized e.g. Klevens (1950) showed that 0·139 moles ethylbenzene was solubilized per mole of potassium octanoate, while 1·26 moles was taken up per mole of potassium hexadecanoate. For non-ionic surfactants evidence for this effect is not so clear (Elworthy et al 1968), but increasing the hydrocarbon chain length is a logical starting point for the investigation, and we report results on two non-ionics containing 22 atoms in the hydrocarbon chain, compared with the C16 chains in surfactants normally used.

Because of the complex nature of the non-ionic micelle, the theoretical interpretation of solubilization data is extremely difficult. The micelle can be considered as a series of regions (hydrocarbon, polyoxyethylene, polyoxyethylene/water), and formal expressions written for the total amount solubilized in terms of the volume of each region, and the solubility of a drug in each. As yet it is impossible to determine the volumes and compositions of the regions, so a semi-quantitative approach to the interpretation has been attempted. Some comments on the relationship of micellar structure to solubilization have been made by Nishikido (1977), Barry & El Eini (1976), while Tomida et al (1978) have related log P to the log of the distribution coefficient of solubilizate between micelles and water.

* Correspondence.

## MATERIALS AND METHODS

### *Materials*

Cortisone acetate, griseofulvin, sulphadiazine, phenylbutazone, betamethasone, tolbutamide, and menaphthone were of B.P. quality. Azobenzene (BDH) had a m.p. 342K (Pollock & Stevens 1965a, give m.p. 341K). Water was distilled from a seasoned still.

Behenyl alcohol (BDH, 1-docosanol) was fractionally distilled, treated with hot methanolic KOH, the methanol removed, and the resulting solid extracted with chloroform. After filtration, the solution was washed twice with water, and the chloroform removed. The resulting solid had m.p. 343K (Pollock & Stevens 1965a, give 344) and -OH value 169·5 (theoretical 171·8 by the method of Jenkins et al 1967). Erucyl alcohol (docos-13-ene-1-ol) was treated in the cold with absolute methanol and conc. hydrochloric acid, followed by vacuum distillation to give the methyl ester, which was reduced with lithium aluminium hydride (e.g. Vogel 1978). The product was dissolved in ethanol and passed down a column of Amberlite IRA-400 (BDH) to remove unreacted ester. After removing

the ethanol and drying, the product has m.p. 307–308K (Pollock & Stevens 1965b, give 308), -OH value 171·8 (theoretical 172·8), and iodine number 74·7 (theoretical 75·0). The alcohols were ethoxylated by ICI Organics Division. The number of ethylene oxide units added were determined by the method of Crooks et al (1974), and also from the -OH value. Polyoxyethylene-1-docosane ether (abbreviated to $BE_{21}$) had 20·8 from the two methods: polyoxyethylene-1-docosyl-13-ene-ether had 25·0 and 22·2 units respectively (abbreviated to $ErE_{24}$).

Any traces of catalyst and polyoxyethylene glycol were removed by dissolving 10 g surfactant in 50 ml of a mixture of 75% chloroform and 25% 60–80° C light petroleum, and washing with three 50 ml portions of water. The organic layer was evaporated to dryness and the residue recrystallized from ether. The sample of cetomacrogol used (Macarthys) was treated similarly. It contained 19·6 ethylene oxide units from the n.m.r. method, and 20·2 from the -OH determination (abbreviated to $C_{16}E_{20}$).

*Light scattering measurements*

Measurements were made at 303K (all physical properties were measured at this temperature), with a Fica 42000 photogoniodiffusiometer (A.R.L. Ltd.) at 546 nm. Solutions were clarified by filtering through 0·22 $\mu$m Millipore filters, and refractive index increments were measured at 546 nm using a differential refractometer.

*Density measurements*

Densities of surfactants were determined by displacement using 80–100 °C light petroleum saturated with surfactant. Densities of solubilizates were found by flotation in potassium iodide solutions of known density (West 1976).

*Viscosity measurements*

After filtration of solutions through a no. 3 sintered glass filter, viscosities relative to water were measured in a size A Ostwald viscometer.

*Solubilization measurements*

Powdered drug and 2% surfactant solution were sealed in ampoules, which were inverted 5 times each minute in a thermostat. After clarification by centrifugation, and dilution with a suitable ethanol-water mixture, samples were assayed by u.v. spectroscopy. Equilibrium was attained after 48 h, and samples were checked at 72 and 96 h. E (1%, 1 cm) values were obtained in exactly the same solvent system used for dilution. Where necessary, the solubility of drugs in pure water was determined by the same technique.

*Critical micelle concentrations (cmc)*

Azobenzene was added to dilute solutions of the surfactants, which were treated as described for the solubilization measurements. Optical densities were measured at 322 nm, and the cmc read from the intersection of two straight lines on a graph of optical density vs concentration.

## RESULTS AND DISCUSSION

*Micellar structure*

Light scattering results are given in Fig. 1(b) as plots of $c/S_{90}$ vs c, where $S_{90}$ is the scatter at 90° to the incident beam from a solution of concentration, c. Dissymmetry values ($Z_{450}$) were in the range 1·00–1·05. Micellar weights were calculated from the

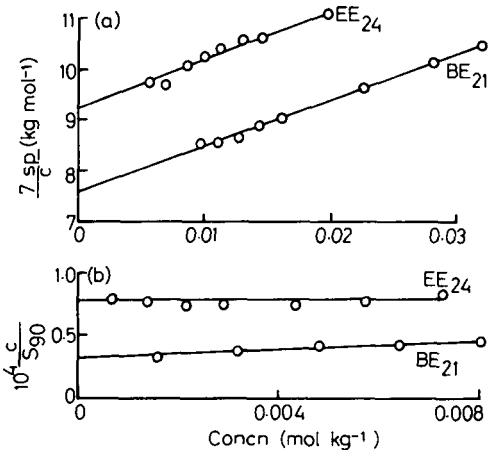


FIG. 1. (a) reduced viscosity against concentration for $ErE_{24}$ and $BE_{21}$.
(b) Concentration/scattering ratio against concentration for $ErE_{24}$ and $BE_{21}$.

Rayleigh equation. The cmc's were found to be $6·9 \times 10^{-7}$ mol kg$^{-1}$ and $8·7 \times 10^{-6}$ mol kg$^{-1}$ for $BE_{21}$ and $ErE_{24}$ respectively. Since the lowest concentrations used in the light scattering and viscosity measurements exceed the cmc by a factor of ca $10^3$, no corrections were made, apart from the normal subtraction of solvent scattering from solution scattering. The cmc's are not of prime interest in the work, but they are lower than that of cetomacrogol ($5·2 \times 10^{-5}$ m kg$^{-1}$, Elworthy 1960). This is because of the longer hydrocarbon chain present in the $ErE_{24}$ and $BE_{21}$ surfactants.

Using the equation for the intrinsic viscosity (Tanford 1961) where $\nu$ is the shape factor, $\bar{v}$ is the

$$(\eta) = \nu(\bar{v} + w v_1^0)$$

partial specific volume of solute $v_1^0$ is the specific volume of solvent, and w is the micellar hydration, w was calculated on the assumption that the micelles were spherical. Macfarlane (1970) showed by a combination of hydrodynamic measurements that cetomacrogol did form spherical micelles, having an intrinsic viscosity of 9·22 kg mol$^{-1}$. As values of this property for $BE_{21}$ was 7·60 and for $ErE_{24}$, 9·23 kg mol$^{-1}$, Fig. 1(a), the assumption of sphericity does not seem unreasonable.

The three surfactants listed in Table 1 were chosen to have approximately the same ratio of ethylene oxide units/number of carbon atoms in the hydrocarbon chain. This ratio is 1·25, 0·95, and 1·09 for $C_{16}E_{20}$, $BE_{21}$ and $ErE_{24}$ respectively. It is difficult to achieve greater similarity because of difficulties in controlling the polymerization process by which they are made.

As expected, increasing the hydrocarbon chain length from $C_{16}$ in $C_{16}E_{20}$ to $C_{22}$ in $BE_{21}$ produces a marked increase in micellar size. It is surprising that $BE_{21}$ is water soluble. Shinoda et al (1976) have shown a correlation between the melting points of alkanoic acids, and the Krafft points of their sodium salts in water. In general ionic surfactants with hydrocarbon chain lengths of $C_{16}$ or greater are insoluble at 298K. The introduction of branches lowers both melting point and Krafft point. Presumably this behaviour is because the hydrocarbon chains need to be in the liquid state for normal micellization to occur. Schick et al (1962) have reported data on water soluble octadecanol ethoxylates, and the compound $BE_{21}$ is also water-soluble. The melting point of docosan-1-ol is 344 and that of docosane 317K (Pollock & Stevens 1965b), hence other factors must operate to depress the melting points of the hydrocarbon chains, when these are long. It may be that a few ethylene oxide units are intruded into the core and have this effect. This is consistent with the unexpectedly low value of the micellar hydration found for $BE_{21}$ (Table 1); if a few ethylene oxide units are in the core then less are available to be hydrated in the polyoxyethylene-water region of the micelle. Tanford(1972) pointed out on geometrical grounds that micelles should be ellipsoidal rather than spherical. This is at variance with Macfarlane's (1970) careful hydrodynamic study of cetomacrogol. However, intrusion of some ethylene oxide into the micelle core could result in the formation of a spherical micelle, which has been suggested for Triton X100 by Robson & Dennis (1977).

The $ErE_{24}$ surfactant forms micelles which are only one third of the size of those formed by the straight chain $BE_{21}$, showing the profound effect of the cis double bond. There is no systematic study on the effects of branching long chains or the presence of double bonds on non-ionic micellar structure in the literature. Clearly the packing in the micelle of a V-shaped hydrocarbon chain, which has a much shorter distance between the extremities of the V than the distance between the extremities of a regularly arranged saturated $C_{22}$ chain, is very different from the packing of the straight chain analogue. The micellar size of $ErE_{24}$ is close to that of cetomacrogol. Erucyl alcohol has a melting point of 307K (Pollock & Stevens 1965b) i.e. it is a much more liquid chain than its saturated analogue, and polyoxyethylene intrusion effects may not be as great as those occurring with $BE_{21}$.

*Solubilization*

The group of insoluble materials chosen as a test screen for evaluation of the solubilizing power of surfactants, vary in molecular mass from 172 to 403, and also vary widely in structure; they represent a fairly severe screen. Comparison of results for $BE_{21}$ and $C_{16}E_{20}$ (Table 2) shows that although $BE_{21}$ forms micelles 2·5 times larger than those of $C_{16}E_{20}$, its solubilizing ability is in most cases the worse of

Table 1. Micellar properties of $C_{16}E_{20}$ and $BE_{21}$, $ErE_{24}$.

| Surfactant | M × $10^{-3}$ | n | dn/dm kg mol$^{-1}$ | $\rho$ kg m$^{-3}$ | $(\eta)$ kg mol$^{-1}$ | w |
|---|---|---|---|---|---|---|
| $C_{16}E_{20}$ (1) | 101 | 83 | 0·161 | 1143 | 9·22 | 143 |
| $BE_{21}$ | 254 | 203 | 0·173 | 1119 | 7·60 | 106 |
| $ErE_{24}$ | 102 | 74 | 0·185 | 1090 | 9·23 | 134 |

1. Data from Elworthy (1960).
M = micellar mass. n = aggregation number. dn/dm = specific refractive index increment. $\rho$ = density. Micellar hydration, w, in moles $H_2O$ mole$^{-1}$ micellar surfactant.

Table 2. Solubilization results.

| | | Surfactants $C_{16}E_{20}$ | | $BE_{21}$ | | $ErE_{24}$ | |
|---|---|---|---|---|---|---|---|
| | | Amount solubilized $10^2$ g $g^{-1}$ | $10^2$ mol $mol^{-1}$ | $10^2$ g $g^{-1}$ | $10^2$ mol $mol^{-1}$ | $10^2$ g $g^{-1}$ | $10^2$ mol $mol^{-1}$ |
| Azobenzene | (A) | 5·37 | 33·4 | 2·60 | 17·9 | 5·76 | 43·7 |
| Cortisone acetate | (C) | 0·63 | 1·8 | 0·84 | 2·6 | 0·48 | 1·6 |
| Griseofulvin | (G) | 0·95 | 3·0 | 0·62 | 2·2 | 0·83 | 3·3 |
| Sulphadiazine | (S) | −0·04 | −0·2 | 0·22 | 1·1 | 0·19 | 1·0 |
| Phenylbutazone | (P) | 1·74 | 6·4 | 1·12 | 4·5 | 1·86 | 8·4 |
| Betamethasone | (B) | 1·39 | 4·0 | 1·73 | 5·5 | 1·22 | 4·3 |
| Tolbutamide | (T) | 2·26 | 9·5 | 1·33 | 6·2 | 2·39 | 12·2 |
| Menaphthone | (M) | 3·08 | 20·3 | 1·32 | 9·6 | 3·11 | 24·9 |

the two. This surprising result, runs contrary to behaviour in the ionic series and is being investigated. Micelles of $ErE_{24}$ are close in size to those of $C_{16}E_{20}$, and the amounts of solubilizates taken up in $ErE_{24}$ are often more than in $C_{16}E_{20}$, and the amounts of solubilizates taken up in $ErE_{24}$ are often more than in $C_{16}E_{20}$. It is apparent that the nature of the interior of non-ionic micelles is not as simple as has been supposed; this in turn gives difficulty in interpreting results.

Some of the difficulties of quantitative interpretation of solubilization data were listed in the introduction to this paper. In the semi-quantitative treatment that follows it is assumed that the amount solubilized depends on an intensity factor (a 'fit' of the properties of the drug molecule to the properties of some part of the micelle), and a capacity factor (the volume of that part of the micelle in which solubilization occurs). Log P was used for the intensity factor. Although the size of the relevant part of the micelle is unknown, the capacity factor should be proportional to 1/Vm, where Vm is the molar volume. Data for the calculation of (log P)/Vm are given in Table 3, and the amount solubilized plotted against this function in Fig. 2. Excluding sulphadiazine, the other seven materials lie on a reasonably straight line with a correlation coefficient ($r^2$) = 0·948 for $C_{16}E_{20}$, and equation:

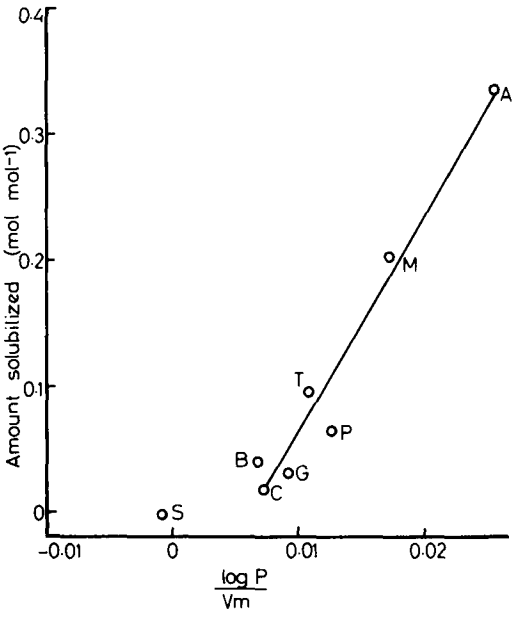


FIG. 2. Moles solubilizate/mole surfactant against (log P)/Vm $C_{16}E_{20}$. For key to abbreviations of drugs, see Table 2.

Table 3. Data for calculation of (log P)/Vm.

| Solubilizate[1] | A | C | G | S | P | B | T | M |
|---|---|---|---|---|---|---|---|---|
| log P[2] | 3·82 | 2·37 | 2·18 | −0·13 | 3·25 | 1·99 | 2·34 | 2·20 |
| $\rho$, kg $m^{-3}$ | 1221 | 1251 | 1489 | 1433 | 1201 | 1323 | 1248 | 1334 |

(1) Abbreviations for solubilizates as in Table 2.
(2) Values from Leo et al (1971), and from Taylor (private communication, 1979) for octanol/water partition coefficients.

mole solubilized/mole surfactant = $-0{\cdot}1053 + 17{\cdot}03$ (log P)/Vm.

For $BE_{21}$:
mole solubilized/mole surfactant = $-0{\cdot}0281 + 7{\cdot}63$ (log P)/Vm. $r^2 = 0{\cdot}876$.

For $ErE_{24}$
mole solubilized/mole surfactant = $-0{\cdot}1459 + 22{\cdot}44$ (log P)/Vm.$r^2 = 0{\cdot}956$.

As five experimental quantities (optical density of solubilized system, E (1%, 1 cm), water solubility, and density, and log P of drug) are needed to calculate a point for one solubilizate in Fig. 2, so combining five sets of experimental error, it is surprising that the correlation coefficients are as high as listed above. $BE_{21}$ has the lowest value of $r^2$, and in general solubilizes the smallest amounts of test materials. Sulphadiazine is the only substance with a negative value of log P. It therefore prefers to partition into water rather than into an organic phase. The observed values of its solubility in the surfactant solutions are nearly the same as its water solubility, within experimental error, and the observed results are small and either negative or positive. A negative log P should give a negative value for the amount solubilized, as the surfactant is occupying part of the solution, and an excluded volume effect is operating.

There are two inherent assumptions in the above treatment. Firstly, that the micellar aggregation number is not much affected by the presence of the solubilizates, otherwise the capacity factor might change on solubilization. Secondly, that all the materials are dissolved in the same region of the micelle, otherwise the use of log P as an intensity factor might not be correct for comparing different materials. It is to be expected that if a group of solubilizates which contained a group interacting with some other part of the micelle were studied, a different mole/mole vs (logP)/Vm plot might be obtained. Preliminary results indicate that this linear holds for eleven other non-ionic surfactants.

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