SOLUBILISATION OF DRUGS IN NONIONIC SURFACTANTS

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Nonionic surfactants can provide an attractive way of presenting otherwise insoluble drugs in aqueous solution. An increase in solubilising capacity with an increase in micellar size was observed for ionic surfactants (e.g. Klevens 1950) but not with nonionic surfactants whose hydrocarbon chains are larger than that present in cetomacrogol. (e.g. Arnarson and Elworthy 1981). A knowledge of the site of solubilisation within the micelle is useful in understanding the factors governing the solubilising capacity of the surfactant. One of the possible methods of studying this is to measure the solubilities of drugs in water, n-hexadecane and dimethoxytetra-ethylene glycol (DMTG). DMTG was chosen to represent the local environment of dehydrated polyoxyethylene (PEG).

Solubilities were determined, at 25°C, by shaking excess drug and solvent in sealed ampoules for 2 days, followed by clarification by centrifugation, dilution and measurement of the UV absorbance, at λ max, of the samples. Extinction coefficients ($E^{1\%}_{1cm}$) were obtained by measuring the absorbance, against an appropriate blank, of solutions of known concentration of the solubilisate in the dilution medium (absolute alcohol).

Table: Solubilities of test compounds in various solvents at 25°C.

Solubilisate	log P^{α}	solubility g/100g solution		
		water	n-hexadecane	DMTG
Azobenzene	3.82	4.7×10^{-4}	12.3	33.5
Phenylbutazone	3.25	3.4×10^{-3}	3.4×10^{-1}	16.7
Cortisone acetate	2.37	2.8×10^{-3}	3.5×10^{-4}	2.0
Tolbutamide	2.34	1.1×10^{-2}	2.2×10^{-3}	18.1
Menaphthone	2.20	1.6×10^{-2}	1.5	10.3
Griseofulvin	2.18	9.7×10^{-4}	3.9×10^{-4}	2.2
Betamethasone	1.99	7.6×10^{-3}	2.0×10^{-4}	9.7×10^{-1}

α P - partition coefficient n-octanol/water (Arnarson and Elworthy 1980).

Apart from azobenzene, menaphthone, and phenylbutazone, the drugs have a lower solubility in n-hexadecane than in water. In every case solubility is highest in DMTG. The differences in solubility reflect, in general, the differences in dielectric constants (or polarity) of the solvents and the solubilisates.

Calculations show that in micelles of $C_{16}E_{20}$ [polyoxyethylene (20) glycol monohexadecyl ether] the hydrocarbon core accounts for less than 0.1% of the total solubility observed for the steroids, tolbutamide and griseofulvin. For azobenzene, the core accounts for about half of the total solubilisation. Excluding azobenzene, solubilisation must occur in the PEG mantle of the micelle.

The solubility of griseofulvin in PEG/water mixtures was shown (Elworthy and Lipscomb 1968) to increase exponentially with PEG concentration. A similar behaviour for the other test compounds is expected, based on their relative solubilities in DMTG and water. The locus of solubilisation for all compounds except possibly azobenzene must therefore be the relatively dehydrated PEG region close to the core. A similar conclusion was previously reached for griseofulvin (Elworthy and Lipscomb 1968) and some steroids (Barry and El Eini 1976).

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