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COMMUNICATIONS

Solubility of diazepam and prazepam in aqueous non-ionic surfactants

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The solubility of diazepam and prazepam in aqueous polyoxyethylen-10-dodecanol, polyoxyethylen-23-dodecanol and polyoxyethylen-20-hexadecanol, has been determined at 25·0 °C. Diazepam seems to achieve a higher micellar penetration than prazepam, in spite of an expected smaller hydrophobic character. Thermodynamic interpretation of the micellar solutions is carried out using the regular solutions approach. A surfactant-independent relation between solubilities of both drugs has been derived.

Micellar aggregates may modify physicochemical properties of the system in which they are present (Lindman & Wennerstrom 1980). In particular, one of the properties that may be affected by them, is the capacity of the system to solubilize organic species (Elworthy et al 1968). This increased solubility is one of the more interesting micellar properties from a biological viewpoint (Mukerjee 1980).

In this work, a comparative study has been carried out on the solubilization of two 1,4-benzodiazepines, diazepam and prazepam, in aqueous non-ionic surfactant solutions, to determine solubility thermodynamic parameters for these two drugs in the micellar phase, and to attempt to elucidate whether the small difference of such molecules provoke a different solubility capacity of micellar core and mantle.

Materials and methods

Materials. The surfactants used were of the general formula C_n-$[EO]_m$-OH, where C is a linear alkyl chain with n methyl and methylene groups, and EO stands for oxyethylene [$-CH_2-CH_2O-$], with a number m of these groups. Polyoxyethylen-10-dodecanol, polyoxyethylen-23-dodecanol, Brij 35, and polyoxyethylen-20-hexadecanol, Brij 58 (Sigma Chemical Co.) were used as received. Diazepam (Prodes, m.p. 125–126 °C) was recrystallized from acetone–light petroleum (1 : 1), and prazepam (Substancia-Parke Davis, m.p. 145–146 °C), was recrystallized from methanol (Merck Index 1976).

Solubility experiments. An excess of drug was added to aqueous solutions with different surfactant concentrations. The adjusted pH was maintained at a value of 10·3 by adding the necessary volume of a diluted aqueous sodium hydroxide solution, to guarantee that only the non-ionized species were present (Clifford & Smith 1974). The temperature was always 25·0 ± 0·1 °C. Equilibrium was established after successive spectrophotometric determinations of drug concentrations at different time intervals. Samples were filtered through 1 μm filters, diluted with aqueous surfactant solutions of the same concentration and pH, and assayed for solubilizate content.

Assay. Diazepam and prazepam were assayed by ultraviolet absorption spectrophotometry. Surfactants did not interfere with the assay. Appropriate blanks were used. The Beer-Lambert law applied in all cases. The following spectrophotometric parameters were obtained: diazepam, ε_{253} = 19 600 ± 800 litre mol^{-1} cm^{-1}; prazepam, ε_{255} = 14 800 ± 300 litre mol^{-1} cm^{-1}.

Results and discussion

Drug solubility values, S_t, in aqueous solution of polyoxyethylen-10-dodecanol (up to $2{\cdot}0 \times 10^{-2}$ M), Brij 35 (up to $1{\cdot}9 \times 10^{-2}$ M), and Brij 58 (up to $2{\cdot}9 \times 10^{-3}$ M), with different surfactant concentrations, (D − cmc), are shown in Fig. 1 (diazepam), and Fig. 2 (prazepam). Each value is the average of at least three determinations which agree within 2%. Solublities in water, S_w, were 0·232 ± 0·006 and 0·0280 ± 0·0010 mM, for diazepam and prazepam, respectively.

Solubility dependence with surfactant concentration of these drugs appears to be remarkably linear above the corresponding cmc. The cmc values determined in this laboratory were: 6×10^{-5} M for polyoxyethylen-10-dodecanol, 8×10^{-5} M for Brij 35 and 4×10^{-6} M for Brij 58, in accordance with literature values (Rosen 1978). Below the cmc, solubility experiments gave the same values as in the absence of surfactants. These facts may be represented by the following equation:

$$S_t = S_w + \frac{x_m}{1 - x_m}(D - \text{cmc}) \qquad (1)$$

* Correspondence.

which is a simple expression of the solubilizate molar fraction in the micellar phase, x_m. Linear least squares treatment of experimental data gave good fits to equation 1. Results for best values of the solubility in the micellar phase, expressed in molar fractions, are presented in Table 1.

Table 1. Solubility of diazepam and prazepam in different aqueous surfactant solutions expressed as molar fractions, at 25·0 °C.

Surfactant	$10^3 x_m$ (exp.) Diazepam	Prazepam	$10^3 x_m$ (calc.)* Prazepam
$C_{12}[EO]_{10}OH$	66·7 ± 1·2	23·5 ± 1·1	23·7
$C_{12}[EO]_{23}OH$	95·5 ± 1·4	31·7 ± 0·8	31·4
$C_{16}[EO]_{20}OH$	119 ± 2·2	40·6 ± 1·0	40·6

* See text.

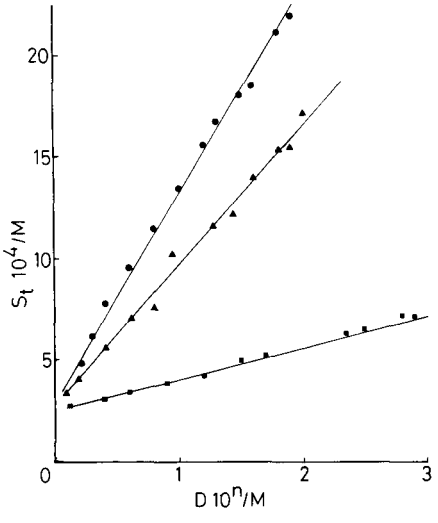

FIG. 1. Solubility of diazepam in aqueous surfactant solutions vs surfactant concentration: polyoxyethylen-10-dodecanol (n = 2, ▲); polyoxyethylen-23-dodecanol (n = 2, ●) and polyoxyethylen-20-hexadecanol (n = 3, ■). Full lines are calculated according to equation 1 and Table 1.

Some qualitative observations may be extracted from the results. Micellar solubility increases when increasing both hydrocarbon and polyoxyethylene chain lengths. However, the hydrocarbon core seems to have more solubility capacity than the polyoxyethylene mantle. On the other hand, according to experimental conditions, an equilibrium is established among three phases: solid drug (s), aqueous solution (w) and micellar solution (m). At equilibrium, the drug reaches equal chemical potentials in all the three phases:

$$\mu_s = \mu_w = \mu_m \qquad (2)$$

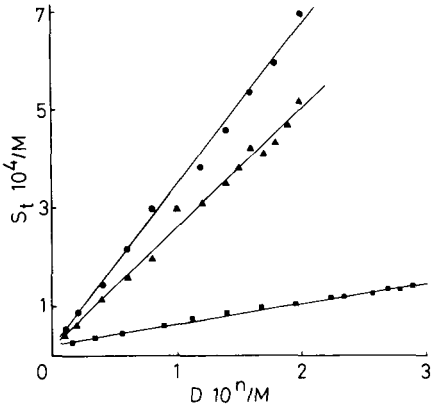

FIG. 2. Solubility of prazepam in aqueous surfactant solutions vs surfactant concentration: polyoxyethylen-10-dodecanol (n = 2, ▲); polyoxyethylen-23-dodecanol (n = 2, ●) and polyoxyethylen-20-hexadecanol (n = 3, ■). Full lines are calculated according to equation 1 and Table 1.

For such a three-phase system (solid, aqueous and micellar) with three components (drug, water and surfactant), only two degrees of freedom are specified by the Gibbs Phase Rule. In this case, as the pressure, p, and temperature, T, are fixed, the system is therefore invariant; so, the drug concentrations in the aqueous and micellar phases are also fixed, and correspond to limit solubilities.

Focussing discussion on the thermodynamic behaviour of the solubilizate in the micellar phase, its chemical potential is given by:

$$\mu_m = \mu_m^\theta(T,p) + RT \ln x_m f_m \qquad (3)$$

where $\mu_m^\theta(T,p)$ represents the standard state chemical potential at infinite dilution, and f_m is the corresponding activity coefficient. Combination of equations 2 and 3 allow an expression for the free energy change of solubilizate transfer from solid to micellar phases, as:

$$\Delta G_{m/s} = \mu_m^\theta - \mu_s = -RT \ln x_m f_m \qquad (4)$$

It is possible to interpret the activity coefficient of the drug in the micelle, f_m, through the thermodynamic regular solutions approach (Guggenheim 1967), which has been applied with some success to micellar solutions (Mukerjee 1971):

$$\ln f_m = (1 - x_m)^2 \, w/RT \qquad (5)$$

Because of the close structural similarities between diazepam and prazepam, it is reasonable to assume that the drug-micelle interaction processes involve the same energy parameter, w, and that the solid-micelle transfer free energies may also be related through the following simple expression:

$$\Delta G_{m/s}(\text{prazepam}) - \Delta G_{m/s}(\text{diazepam}) = C \qquad (6)$$

where C stands for a surfactant chain length independent free energy, that would just correspond to the transfer of the structural group in which both molecules differ.

A simultaneous non-linear least squares fit with respect to the equations 4, 5 and 6 of the diazepam vs prazepam x_m experimental data, using a grid search method (Bevington 1969), may be carried out, giving w/RT = 2·2 and C/RT = 0·85 as the best fitting parameters. In Table 1, the calculated x_m values for prazepam starting from the diazepam data, and following the aforementioned procedure are also shown. The calculated solubilities fit the experimental data well within the experimental error margin.

This result may confirm, in a first approximation, that micellar solubilization data can agree with the simple model of non-ideality provided by the regular solutions approach. The procedure allows the prediction of the solubility of prazepam/diazepam in an n-alkyl-polyoxyethylene non-ionic surfactant aqueous solution, provided the solubility of one of them is known.

The moderately high positive value of the w parameter may be in accordance with a reputed high degree of inmiscibility between micellar and drug components, as the low solubility values obtained seem to indicate (Guggenheim 1967). The free energy transfer from the solid to the micellar phases of the cyclopropyl radical of prazepam, C = 2·1 kJ mol^{-1}, is also in the range of other established values (Tanford 1980).

The approach described suggests that micellar solutions may be amenable to analysis in terms of bulk thermodynamic concepts, and that generalizations of solubilization results in series of homologous surfactants and/or chemical compounds are possible.

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Preparation of single bilayer liposomes by an electrocapillary emulsification method

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The single bilayer liposomes have been prepared by an electrocapillary emulsification technique based on interfacial fluctuation in the absence of surfactant. Electron microscopy showed the liposome to be a unilamellar vesicle with a size generally in the range 60–120 nm.

Electrocapillary emulsification is based on interfacial tension between two phases in contact with each other when under the influence of a potential difference. When a potential difference higher than the critical voltage of emulsification is applied to an oil/water interface, the interfacial tension is reduced almost to zero and spontaneous emulsification occurs, due to the interfacial fluctuation, in the absence of surfactant or in the presence of a very small amount (Watanabe et al 1978).

The emulsions formed are monodisperse and stable, the average particle radius being less than 0·1 μm. Arakawa & Kondo (1980, 1981) reported that poly-(N^{α},N^{ε}-1-lysinediylterephthaloyl)(PPL) microcapsules containing sheep erythrocyte haemolysate were prepared by an interfacial polymerization technique using electrocapillary emulsification as the means of producing very fine haemolysate droplets for encapsulation.

Liposomes consist of concentric closed lipid bilayers alternating with aqueous compartments. The liposomal suspension forms liquid crystal dispersions, the droplets being very stable. We have developed a novel method for liposome production based on the electrocapillary technique.

Materials and method

Fig. 1 shows the schematic diagram of the apparatus for electrocapillary emulsification. The oil phase (dichloromethane, A) in the glass syringe (D) is injected into the aqueous phase (B) by means of an electrically driven

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