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Slower dissolution rates of sulphamerazine in aqueous sodium dodecyl sulphate solutions than in water

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Abstract

The solubility of sulphamerazine in 0.1 M sodium dodecyl sulphate solution (SDS) was found to be 2.8-times that in water (at standard reporting conditions). The thermodynamics of transfer to the micelle were indicative of a spontaneous, enthalpy-driven, process. Contact angle and surface energy data revealed a favoured interaction between drug and SDS micelles, however, the dissolution rate of the drug into SDS decreased with increasing SDS concentration. The activation thermodynamics revealed a slight activation barrier to solubilisation. Apparent diffusion coefficients were calculated from initial dissolution rates from rotating disks, with different rotating speeds. The greatly reduced diffusion coefficient in the presence of micelles was taken as an explanation for the reduced rate of dissolution. The changes in solubility and diffusion rate have been considered in terms of the Noyes-Whitney equation, to show the combined effect on dissolution rate is as seen, i.e., reduced dissolution rate, despite the increased solubility. Care should be taken before assuming that an SDS solution is an appropriate medium for improving dissolution test data for poorly soluble drugs.

Keywords: Dissolution; Sodium dodecyl sulphate; Wettability; Surface energy; Thermodynamics; Sulphamerazine

1. Introduction

It is extremely important to understand factors which affect dissolution rates of drugs if in vitro dissolution test data are to be interpreted correctly and if factors which affect absorption in vivo are to be understood.

Surfactants are known to improve wetting of solids and thus aid dissolution, furthermore, at concentrations above their critical micelle concentrations, they can solubilise poorly soluble materials into their hydrophobic cores and so increase the apparent solubility. In this study the dissolution and solubility of sulphamerazine are investigated in some detail, as we had previously observed that the dissolution rate actually decreased in the presence of surfactant, compared with that in water.

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2. Background theory

The inter-relationships of physico-chemical properties are often viewed in a simplistic manner, which can lead to general conclusions being held as absolute facts. For example it is a general fact that a solid will dissolve more rapidly in a solution in which it is more soluble. This observation is in keeping with the Noyes-Whitney equation:

$$dm/dt = [Da/h](C_s - c) \quad (1)$$

where dm/dt is the dissolution rate (rate of change of mass in solution with time), D is the diffusion coefficient, a is the surface area, h is the diffusion layer thickness, C_s is the equilibrium solubility and c is the concentration in solution at time t. From Eq. 1 it can be seen that a higher equilibrium solubility will indeed result in a faster dissolution rate. It is quite usual for the dissolution rate to be influenced by solubility, as the extent of variability in pharmaceutical systems is greatest in the solubility term. For example, the surface area of pharmaceuticals may vary between about 100 to a little over 1000 $m^2\ kg^{-1}$ (i.e., about 1 order of magnitude). The diffusion coefficient is related to the inverse of molecular weight, the values of which vary only marginally for most pharmaceuticals (ca 200–500). The solubilities of pharmaceuticals, however, vary from micrograms to in excess of 50 mg ml^{-1} (i.e., about 4 orders of magnitude) and hence are a major impact on drug dissolution.

The Noyes-Whitney equation does not specifically deal with wettability, however, this is partially covered by the surface area term, as poorly wetted surfaces will have a lower area of contact than those which are well wetted by the liquid.

3. Methods

The material (from Sigma) studied was sulphamerazine. Sodium dodecyl sulphate (SDS) was used as received from BDH. SDS was used in solution of 0.1 M, unless otherwise stated. Water was double distilled (checked as having a surface tension of 72.6 mN m^{-1}), the other liquids used were bromonaphthalene (Fisons) and ethylene glycol (BDH, Analar).

3.1. Contact angle studies

Contact angles were measured using a Cahn DCA, with rectangular compacts of the drug substances (200 mg of powder, 2 × 1 cm, at 6×10^5 kN m^{-2}). The method was as recorded by Mall et al. (1995). At least six replicate plates were used for each experiment. Three test liquids, bromonaphthalene, water and ethylene glycol were used to calculate the surface energies of the sulphamerazine as described and presented elsewhere (Mall et al., 1995). The contact angles for aqueous SDS solutions of different concentration were also measured.

3.2. Rotating disk initial dissolution rates

Rotating disk initial dissolution rates were measured using rotating disks of powder compacts. These were made in stainless steel cylinders, which were directly attached to a stirrer system, leaving a constant surface area of compact exposed to the dissolution fluid. The disks were of 1.3 cm diameter, and the powders were compacted using a force of 1×10^4 N for 1 min. The disks were rotated at 100 rpm in either distilled water or 0.1 M SDS in water (1000 ml). The experiment was repeated at four different temperatures (25, 30, 37 and 42°C), each with three replicates for each drug. The drug release was monitored by UV spectroscopy at 258 nm.

The rotating disk initial dissolution rate constants (k) were determined from the initial linear portion of a plot of drug released as a function of time. Arrhenius plots were constructed ($\ln k$ as a function of $1/T$), the gradients of which were used to determine values for the activation energy (E) of the process, which in turn was used to calculate the enthalpy of activation ($\Delta H^{\neq}$), as

$$\Delta H^{\neq} = E - RT \quad (2)$$

(R = gas constant).

By use of a conventional Arrhenius plot, the entropy of activation ($\Delta S^{\neq}$) was calculated from the intercept (where the intercept on the y-axis is $\ln A$, with A being the collision number). The free energy of activation ($\Delta G^{\neq}$) was then calculated from:

$$\Delta G = \Delta H - T\Delta S \quad (3)$$

Rotating disk initial dissolution rate studies were also undertaken at 37°C at stirring rates of 50, 130 and 150 rpm and at 37°C at 100 rpm in aqueous SDS solutions of 0, 6.9×10^{-4}, 3.46×10^{-3}, 6.93×10^{-3}, 3.463×10^{-2} and 6.925×10^{-2} mol dm^{-3}. The CMC was assessed by measuring surface tension as a function of SDS concentration at pH 7.1 (the measured pH of sulphamerazine in aqueous solution) and was found to be 1.47×10^{-2} mol dm^{-3}).

3.3. Solubility studies

The solubility was measured in water and in water containing SDS micelles. This was undertaken at 25, 30, 37 and 42°C. The procedure was as reported previously (Mall et al., 1995).

4. Results and discussion

4.1. Solubilities

The normalised solubility of sulphamerazine (i.e., solubility in SDS/solubility in water), is shown in Fig. 1 as a function of SDS concentration. It can be seen that there is an exponential relationship, with the solubility of drug increasing 2.8-fold when the SDS concentration reaches

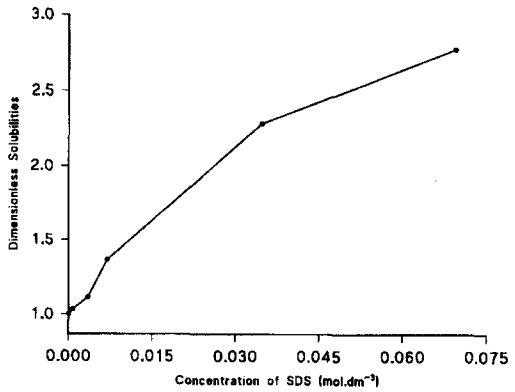

Fig. 1. The normalised solubility of sulfamerazine (i.e., solubility in SDS/solubility in water) as a function of SDS concentration.

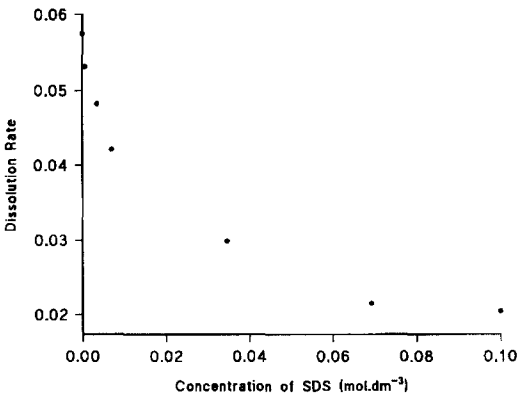

Fig. 2. RDIDR (%w/v $min^{-1} \times 10^4$) as a function of concentration of SDS in the dissolution fluid.

6.925×10^{-2} mol dm^{-3}. This equates to a substantial increase in equilibrium solubility in the presence of SDS and by the Noyes-Whitney equation (Eq. 1) this would expect to be mirrored by a similar increase in dissolution rate.

The thermodynamic functions for solution of sulphamerazine in water and micellar SDS solution have been calculated from a van't Hoff relationship of measured solubility as a function of temperature (Mall et al., 1995). These allow the calculation of the thermodynamic functions for the transfer between the water and the micelles, which were: $\Delta H_{sol}^{trans} = -16.1$ kJ mol^{-1}; $\Delta G_{sol}^{trans} = -3.1$ kJ mol^{-1}; $\Delta S_{sol}^{trans} = -43.7$ J mol^{-1} K^{-1} (these three terms being the enthalpy, free energy and entropy of transfer from the solubility data, respectively). The negative value for the free energy is indicative of a favoured overall process (i.e., thermodynamically spontaneous). The negative values for enthalpy and entropy change demonstrate that the driving force is enthalpic, this being dominant despite the disfavoured imposition of order.

4.2. Rotating disk initial dissolution rate studies (RDIDR)

4.2.1. As a function of SDS concentration

The RDIDR as a function of SDS concentration (100 rpm 37°C) is shown in Fig. 2, from which it can be seen that the rate falls with increasing SDS concentration. A plateau is

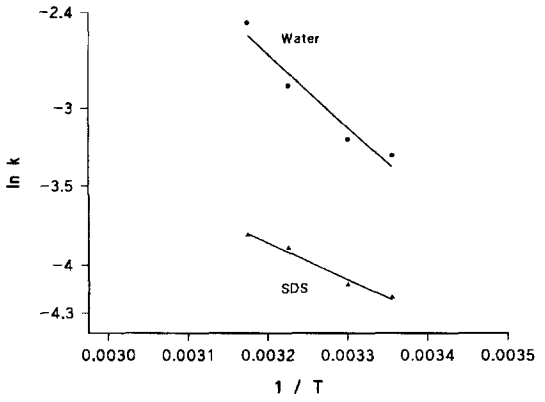

Fig. 3. Arrhenius relationships for ln RDIDR (k) as a function of reciprocal absolute temperature in water and 0.1 M SDS.

reached for the higher SDS concentrations, but the onset of this plateau is well above the CMC.

4.2.2. As a function of temperature

The effect of temperature on RDIDR is shown in the Arrhenius relationship in Fig. 3, where it can be seen that at each temperature the RDIDR is lower in the presence of SDS than without, but in both cases the rate increases with increasing temperature. The thermodynamics of activation (see Eqs. 2 and 3) are shown in Table 1, together with the calculated thermodynamics of transfer.

The data in Table 1 are indicative of a process with an enthalpic driving force, but a disfavoured entropy of transfer, which combine to yield a small positive free energy of transfer. It is clear (from the equilibrium solubility data) that the transfer to the SDS micelle is indeed spontaneous, however, the rate data demonstrate an activation barrier which must be overcome prior to solubilisation.

Table 1
The thermodynamics of activation calculated from the temperature dependence of the RDIDR (as shown in Fig. 3)

	Water	SDS	Transfer
$\Delta G^{\neq}$ (kJ mol^{-1})	96.7	99.6	2.9
$\Delta H^{\neq}$ (kJ mol^{-1})	38.3	19.0	−19.2
$\Delta S^{\neq}$ (J mol^{-1} K^{-1})	−188.5	−260.0	−71.5

4.2.3. As a function of stirring speed

The rate data as a function of stirring rate are given in Table 2. After converting the rotational speed to radians$^{0.5}$, the data in the presence of SDS show a linear relationship (r = 0.994) with an intercept of zero (within error) and a gradient of 6.62×10^{-3}. The data for dissolution in water shows a moderate correlation (r = 0.964) with an intercept at −0.117 on the y-axis and a gradient of 0.059.

For the SDS data it is reasonable to estimate a diffusion coefficient by use of the equation of Levitch (1962):

$$\text{RDIDR} = 0.62\,\phi^{0.5}\,D^{2/3}\,v^{-1/6} \quad (4)$$

where ϕ is the rotational speed, D is the apparent diffusion coefficient and v is the kinematic viscosity. If the viscosity to the power of $-1/6$ is assumed to be approximately unity (which is reasonable given that a substantial change in v would be needed to alter $v^{-1/6}$ significantly), then the value of D can be determined as 8.9×10^{-6} cm^2 s^{-1}. This is a low value for D compared to those which have been reported in the literature for other systems, for example, 3.05×10^{-6} and 3.44×10^{-6} for betamethasone in water and 30 mM sodium taurocholate, respectively (Bakatselou et al., 1991), 3.01×10^{-6} cm^2 s^{-1} for betamethasone in sodium taurocholate/lecithin mixed micelles (Naylor et al., 1993). However, the value of D for Danazol in a sodium taurocholate/lecithin mixed micelle (Naylor et al., 1993) fell to as low as 2×10^{-8} cm^2 s^{-1}, indicating extremely low diffusivity compared to danazol in sodium taurocholate micelles which had a value of D similar to that which is reported here for sulphamerazine.

The data in the presence of water do not allow the calculation of an accurate diffusion coefficient, as the intercept is not zero and linearity is comparatively poor, however, as a guide the value of D which would be obtained from the gradient is 3×10^{-7} cm^2 s^{-1}, which (despite the reservations expressed) shows that the diffusivity is much more rapid for the free than the solubilised drug.

Table 2
The RDIDR as a function of stirring rate at 37°C in water and 0.1 M SDS in water (mean ± S.D., units %w/v $min^{-1} \times 10^4$)

	50 rpm	100 rpm	130 rpm	150 rpm
Water	$0.0255 \pm 1.3 \times 10^{-3}$	$0.0575 \pm 5.9 \times 10^{-3}$	$0.1009 \pm 1.3 \times 10^{-3}$	$0.1269 \pm 1.8 \times 10^{-3}$
0.1 M SDS	$0.0152 \pm 2 \times 10^{-4}$	$0.0204 \pm 9.6 \times 10^{-3}$	$0.0246 \pm 9 \times 10^{-4}$	$0.0262 \pm 2.8 \times 10^{-3}$

4.3. Contact angle and surface energy

4.3.1. Contact angles of SDS on the drug

Contact angles were measured for solutions of 6.9×10^{-4}, 3.46×10^{-3} and 6.93×10^{-3} mol dm^{-3} and were found to be: 64.6, 52.4 and 22.5° respectively. Solutions of SDS of 3.46×10^{-2} mol dm^{-3} concentrations and higher were all found to spread (zero contact angle) on the drug. The contact angles appear to approach zero as the CMC is reached.

4.3.2. Surface energy data derived from contact angles of pure liquids on the drug

Surface energy data have been described by dividing the total surface energy into contributions from Lewis acid-base (AB) and Lifshitz-van der Waals (LW) contributions (e.g., van Oss et al., 1987). For a liquid, once the surface tension is known, the γ^{LW} component of the surface energy can be found by contact angle (θ) measurement on an apolar surface (e.g., Teflon). The γ^{LW} component of the surface energy of solids can similarly be determined by contact angle measurement with apolar liquids for which $\gamma_L = \gamma^{LW}$.

Expressing the Young-Dupre' equation as

$$(1 + \cos\theta)\gamma_L = -\Delta G^{TOT} \quad (5)$$

and considering that

$$\Delta G^{TOT} = \Delta G^{LW} + \Delta G^{AB} \quad (6)$$

we obtain

$$(1 + \cos\theta)\gamma_L = -\Delta G^{LW} - \Delta G^{AB} \quad (7)$$

which becomes

$$(1 + \cos\theta)\gamma_L = 2(\sqrt{\gamma_S^{LW}\,\gamma_L^{LW}} + \sqrt{\gamma_S^{+}\,\gamma_L^{-}} + \sqrt{\gamma_S^{-}\,\gamma_L^{+}}) \quad (8)$$

Thus by contact angle measurement with three different liquids (of which two must be polar) with known γ_L^{LW}, γ_L^{+} and γ_L^{-} values, the γ_S^{LW}, γ_S^{+} and γ_S^{-} of any solid can be determined by use of Eq. (8). Similarly, by contact angle measurement of a liquid on various solids (of which two must be polar) the γ_L^{LW}, γ_L^{+} and γ_L^{-} can be determined. For the specific case of an interaction between phases 1 and 2 in the presence of water (w) the full term for the free energy of adhesion would be (van Oss and Costanzo, 1992):

$$\begin{aligned}\Delta G_{1w2} = {} & (\sqrt{\gamma_1^{LW}} - \sqrt{\gamma_2^{LW}})^2 - \\ & (\sqrt{\gamma_1^{LW}} - \sqrt{\gamma_w^{LW}})^2 - \\ & (\sqrt{\gamma_2^{LW}} - \sqrt{\gamma_w^{LW}})^2 \\ & + 2[\sqrt{\gamma_w^{+}}\,(\sqrt{\gamma_1^{-}} + \sqrt{\gamma_2^{-}} - \sqrt{\gamma_w^{-}}) + \\ & \sqrt{\gamma_w^{-}}\,(\sqrt{\gamma_1^{+}} + \sqrt{\gamma_2^{+}} - \sqrt{\gamma_w^{+}}) - \\ & \sqrt{(\gamma_1^{+} \cdot \gamma_2^{-})} - \sqrt{(\gamma_1^{-} \cdot \gamma_2^{+})}]\end{aligned} \quad (9)$$

A negative value for the free energy of interaction will result in a net attraction between substances 1 and 2 immersed in water.

Using Eq. (9), it is possible to calculate that the free energy of adhesion of sulphamerazine to SDS tails in the presence of water is -84.1 mJ m^{-2}, and for the adhesion to the head group is -29.5 mJ m^{-2}. It follows that the interaction between both the head and tail groups of the surfactant and the drug is favoured in the presence of water, but that the interaction with the hydrophobic core is most strongly favoured. It can be expected from these data that the drug should readily solubilise into the micellar core.

4.4. General discussion

4.4.1. Some estimates of significance with respect to the Noyes-Whitney equation

As stated in the introduction it is generally

assumed that the influence of solubility of a drug on dissolution will be very significant, because the other factors vary over comparatively small ranges. In this example, however, it has been shown that the diffusivity may vary to a great extent between the water and SDS systems. To reconsider the Noyes-Whitney equation in relation to the data for this system, it can be seen (Table 2) that at 150 rpm the RDIDR with SDS present is a factor of 4.8 lower than that for water alone (the data at the highest rotational speed were selected so that the diffusion layer thickness term, h, would be minimised). The diffusivity for the drug in SDS was determined as 1.55×10^{-6} $cm^2\ s^{-1}$ which was a factor of 25 lower than the estimate of diffusivity of the drug in water alone. The increase in solubility due to SDS was by a factor of 2.8, thus adding these factors to Eq. (1):

$$(1/4.8)\ dm/dt = [(1/25)D\ (n)\ a/h]\ ((2.8)C_s - c) \quad (10)$$

(where n is an unknown factor for changes in a and h), by balancing these factors, n is equal to a little under 2. This factor can reasonably be explained by changes in contact angle affecting the apparent surface area (i.e., it is possible that only 50% of the compact made true contact with the water due to the high contact angle, but spreading occurred with high SDS concentrations), together with some uncertainty about the exact changes in magnitude for D. It follows that the reduced dissolution rate of the drug in SDS is in keeping with the changes in the terms of the Noyes-Whitney equation, where in this case the diffusivity has the largest influence.

It remains necessary to consider the ease of access of the drug to the core of a micelle. Here it can be shown that the process of solubilisation is favoured thermodynamically (as indicated by the free energy of adhesion obtained from contact angle/surface energy data estimates, and from the thermodynamics of transfer obtained from van't Hoff analysis of solubility data. There is, however, indication of a disfavoured activation step from the Arrhenius treatment of the rate data. These disfavoured thermodynamics of activation may well relate to difficulties in distribution of the solubilised drug into the bulk of the fluid, i.e., be a reflection of poor diffusivity of the swollen micelles with solubilised drug.

4.4.2. Implications for dissolution testing

The use of SDS as an additive to dissolution media is gaining in popularity in order to test poorly soluble drugs. It is generally true that increased solubility will result in increased dissolution rate, however, as shown above this is not always true. This situation is not limited to SDS systems, for example, Macheras and Reppas (1987) have shown slowing dissolution of dicumarol into solutions of proteins in which their solubilities were higher than for an aqueous control. It is, therefore, necessary to consider the data obtained from dissolution tests with great care when complex media are used in the test.

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