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The use of isothermal titration calorimetry to assess the solubility enhancement of simvastatin by a range of surfactants

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Abstract

Surfactants are commonly used to increase the solubility of poorly water soluble drugs but the interactions between drug and surfactant can be complex and quantitative relationships can be hard to derive. One approach is to quantify the thermodynamics of interaction and relate these parameters to known solubility or dissolution rate enhancement data. Isothermal titration calorimetry (ITC) was used to measure the enthalpy and free energy of transfer of a model drug (simvastatin) to a number of surfactant (SDS, HTAB, SDCH and Brij 35) micelles. These data were then compared with the solubility enhancements determined for each surfactant using HPLC assays. As expected, there was correlation between the free energy of transfer for the drug to each surfactant and the solubility enhancement of that surfactant. Although the data set is limited, the results suggest that ITC screening of a range of surfactants against a poorly water soluble drug may allow the selection of the best potential solubilising surfactants.

Keywords: Isothermal titration calorimetry (ITC); Solubility enhancement; Surfactants; Simvastatin; Free energy of transfer

1. Introduction

The Noyes–Whitney equation predicts that dissolution rate will increase with an increase in solubility. Surfactants can be used to increase the solubility of poorly water soluble drugs, usually by incorporation of the drug into a hydrophobic micellar core. However, an increase in solubility does not necessarily ensure an increase in dissolution rate. In some instances the dissolution rate can fall, even though solubility has increased [1,2] while in other cases the dissolution rate can be improved with no apparent change in solubility [3–6]. These empirical observations show that drug–surfactant interactions are complex and make it difficult to predict the likely effect of a surfactant on the solubility and dissolution rate of a drug.

A better understanding of drug–surfactant interactions can be obtained from thermodynamic data. One approach is to use isothermal titration calorimetry (ITC), wherein the enthalpy of interaction is measured directly as a surfactant solution is titrated into a suspension or solution of drug. ITC has been used in this way to study the interactions between oleic acid and Span 85 with crystalline and partially amorphous salbutamol sulphate [7]. However, such data can be complex and difficult to interpret as they contain components from many processes, including surfactant dilution, drug dilution, surfactant adsorption, drug dissolution and drug solubilisation, some of which will occur over extended (possibly longer than the experimental measurement) time periods.

The effects of much of this complexity can be mitigated by studying the interactions between materials that are already solvated. This does not allow the direct measurement of dissolution rates or quantification of solubility enhancement but does allow a quantitative measurement of the enthalpy of interaction between the drug and the surfactant, which can then be correlated with data from other studies (such as dissolution or solubility studies for instance). The use of ITC to measure the critical micellar concentration (cmc) of surfactants is well accepted and there are many published studies of the interaction of surfactants with other solutes [8–11]. However, there is little data regarding the interactions between surfactants and pharmaceuticals in solution, despite the widespread use of surfactants in pharmaceutical formulations.

In this work ITC was used to study the interactions between simvastatin and a number of surfactants (sodium dodecyl sul-

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phate, SDS, hexadecyl trimethylammonium bromide, HTAB, sodium deoxycholate, SDCH and polyoxyethylene 23 lauryl ether, Brij 35). The data were correlated with solubility enhancement factors calculated by HPLC analysis. Simvastatin was selected for study as a model of a poorly water soluble drug ($1.1 \pm 0.13\,\mu g\,mL^{-1}$, by HPLC, this work). The surfactants were chosen because they represent a typical selection of compounds that might be selected in a pharmaceutical screen for solubility enhancement.

2. Materials and methods

Simvastatin was donated by Merck Sharpe and Dohme Ltd. (Herts, UK). Sodium dodecyl sulphate, acetonitrile and the buffer components were purchased from BDH Chemicals. Hexadecyl trimethylammonium bromide, sodium deoxycholate and polyoxyethylene 23 lauryl ether were purchased from Sigma. All chemicals were used as received. Buffer (pH 7.0 0.01 M phosphate buffer), surfactant and drug solutions were prepared using AnalaR water (BDH Chemicals).

2.1. Solubility measurements

Solutions for solubility measurements were prepared by dissolving an excess of simvastatin in surfactant solution (10 mL) and agitating in an orbital mixer for 24 h at 25 °C. After filtration through a 0.2 μm Millipore filter, simvastatin was assayed by HPLC using a Hewlett Packard 1090 workstation with an auto sampler and auto integrator. The column employed was a C_{18}-ODS (Octadecylsilane) Pertisil 5 μm (Hichrom Ltd.). A UV detector set at 238 nm recorded the simvastatin peak. The mobile phase was a 58:42 mixture of acetonitrile and water, both HPLC grade, set at a flow rate of $1.5\,mL\,min^{-1}$. The detector was calibrated with a range of simvastatin solutions from 0.7 to $60\,\mu g\,mL^{-1}$ and a linear response was observed. Experiments were repeated in triplicate.

2.2. Calorimetric measurements

Calorimetric data were recorded at 25 °C with a 2277 TAM (Thermometric AB, Järfälla, Sweden) equipped with a titration unit. Surfactant solution was loaded into the syringe and a saturated solution of simvastatin ($1.1\,\mu g\,mL^{-1}$, 3 mL) was loaded into the sample ampoule. An equivalent volume of water/buffer was used as a reference. The cannula delivering the surfactant solution was set to be just below the surface of the drug solution. The pump was programmed to deliver 25 aliquots (10 μL) of surfactant solution (at a rate of $1.5\,mL\,min^{-1}$), at 45 min intervals. The amplifier was set to 30 μW and the system was calibrated by the electrical substitution method before each experiment. Data (1 point every 10 s) were collected with the dedicated software package Digitam 4.1. Blank experiments were performed by titrating water into water, buffer into buffer and water or buffer into simvastatin solution. All returned negligible heat-outputs. The surfactant solutions were characterised by titrating surfactant into water or buffer. The experimental data were integrated with Origin (Microcal Software Inc., USA). Note that the TAM registers exothermic events with positive power values; the integrated data were thus inverted in sign to produce the enthalpy values recorded below. Experiments were conducted in triplicate.

2.3. Solubility measurements

The solubility of simvastatin in water, and in a range of surfactant solutions, was determined using HPLC following 24 h incubation. Incubation for longer time periods did not result in an increase in drug concentration. Simvastatin is administered in the form of a lactone prodrug which undergoes hydrolysis to form the active hydroxyl acid following administration. This process is catalysed in vivo by cytochrome P450; analysis of a simvastatin solution prepared in water after several days by HPLC showed no detectable quantity of the hydroxyl acid and so it was assumed that the extent of this conversion was negligible over the course of the solubility experiments.

To compare the improvement in solubility across the range of surfactants, a solubility enhancement factor, K^*, was determined. Assuming micellisation can be described by a phase separation model, this is easily achieved by fitting the solubility data to Eq. (1) [12];

$$\frac{S_{surf}}{S_{water}} = 1 + K^* C_{surf} \quad (1)$$

where S_{surf} is the solubility of simvastatin in a solution of surfactant of concentration C_{surf} and S_{water} is the solubility of simvastatin in water. Hence a plot of the normalised solubility (S_{surf}/S_{water}) versus the molar surfactant concentration should result in a straight line of slope K^*. Since the phase separation model treats micelles and monomers as distinct phases, and assumes a constant aggregation number, n, it is possible to obtain the number of simvastatin molecules solubilised per surfactant micelle if n is known, by application of Eq. (2) [12];

$$N = \frac{S}{C_{surf} - cmc} n \quad (2)$$

where N is the number of molecules of simvastatin solubilised per surfactant micelle, cmc is the critical micellar concentration of the surfactant and S is the slope of a plot of solubility of drug versus surfactant concentration. This was possible only for SDS ($n = 58$) [13] and SDCH ($n = 6$) [14] because these were the only two of the study surfactants for which values of n were available from the literature. Knowledge of K^* allows the calculation of the free energy of solubilisation, $\Delta_s G$, by [15,16];

$$\Delta_s G = -RT \ln K^* \quad (3)$$

where R is the universal gas constant and T is the absolute temperature.

3. Results

3.1. Solubility enhancement of the surfactants

The values of K^* are given in Table 1. There was an improvement in the solubility of the drug with all the surfactants, post

Table 1
Solubility enhancement factors for SDS, HTAB, SDCH and Brij 35

Surfactant	K^* ($\times 10^3$ M^{-1})
SDS	102
HTAB	89
SDCH	24
Brij 35	56

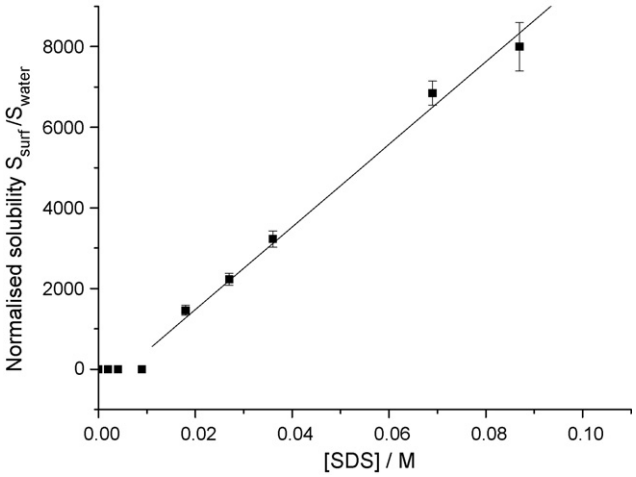

Fig. 1. Solubility enhancement curve for simvastatin in aqueous SDS solutions.

cmc. The solubility increase was linear with surfactant concentration for all the surfactants except SDS, Fig. 1 (R^2, 0.9958). The non-linearity observed for SDS suggests that as well as an effect of increasing numbers of micelles, there are changes in the solubilising capacity of the surfactant micelles as a function of concentration. It has been shown that at high SDS concentrations there is micelle growth [17] which may lead to changes in the number of drug molecules that can be solubilised. Similar effects have been noted for the solubilisation of griseofulvin in mixed micelles of sodium cholate and phosphatidylcholine [18] and for the solubilisation of phenobarbital in sodium paraffin sulfonate [19]. Hence, we note that the value of K^* given in Table 1 should be treated with caution, since the model assumed does not strictly apply in this case. The number of drug molecules solubilised per surfactant micelle was 15 for SDS and 0.4 for SDCH. It is perhaps not so surprising that the bile salt is such a poor solubiliser; bile salt micelles are small and rigid in nature because their hydrocarbon core is not as fluid as a simple surfactant leading to poor drug packing [20]. The $\Delta_s G$ values, calculated by application of Eq. (3), are presented in Table 2.

Table 2
Gibbs free energies of solubilisation for simvastatin in the four surfactants, calculated by application of Eq. (3), and the solubility enhancement factors

Surfactant	$\Delta_s G$ (kJ mol^{-1})	K^* ($\times 10^3$ M^{-1})
SDS	−28.4 ± 0.1	95 ± 4.9
HTAB	−28.2 ± 0.3	88 ± 10.7
SDCH	−24.9 ± 0.2	23 ± 1.1
Brij 35	−27.1 ± 0.05	56 ± 1.2

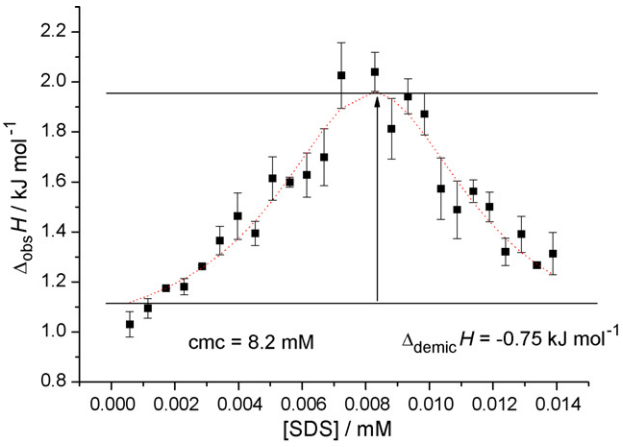

Fig. 2. Enthalpy per injection vs. concentration of SDS in the calorimetric ampoule for dilution of SDS into water.

3.2. Interactions between simvastatin and the surfactants by ITC

The analysis of a classical (i.e. two-state) surfactant cmc using ITC is as follows; the concentration of the titrant solution is selected to ensure that the surfactant is above its cmc. If the concentration of surfactant achieved in the sample ampoule following the first injection is much lower than the cmc then it is assumed that there is complete demicellisation of the surfactant and the measured power comprises components from the enthalpy of demicellisation ($\Delta_{demic}H$) and the enthalpy of dilution ($\Delta_{dil}H$). This statement holds true for all successive injections until the concentration of surfactant in the ampoule approaches the cmc, at which point total demicellisation cannot be assured and the measured power reduces. After the cmc has been reached in the sample ampoule the power change per injection is constant and reflects only $\Delta_{dil}H$. Thus, a plot of power per injection versus concentration yields an S-shaped isotherm with plateaux before and after the cmc. The peak maximum of the first-derivative of the isotherm gives the cmc while the difference in heat between the plateaux gives $\Delta_{demic}H$ (which is equal and opposite to the enthalpy of micellisation, $\Delta_{mic}H$). Further discussions of this type of analysis, and practical examples, are provided by Loh et al. [11].

3.2.1. Dilution of SDS into water or buffer

The integral values of each peak for the dilution of SDS solution (0.09 M) into water, normalised for the number of moles of SDS, are plotted in Fig. 2. It is immediately apparent that the behaviour shown does not follow the ideal case described above, although it is easy to determine the cmc of SDS from the peak maximum. The value returned (8.1 ± 0.2 mM) compares very well with literature data (Table 3). The enthalpy of micellisation was determined to equal 0.75 ± 0.02 kJ mol^{-1}, indicating micellisation of SDS in water is entropically driven. Again, this value shows reasonable agreement with literature data (Table 3).

Although not the principal aim of this work, it is interesting to consider the reasons for the non-ideal behaviour of SDS. Fig. 3 shows the same data for the dilution of SDS into pH 7.0

Table 3
Literature values for the cmc and enthalpy of micellisation of SDS in water

$\Delta_{mic}H$ (kJ mol^{-1})	cmc (mM)	Reference
0.75	8.1	This work
0.68	8.1	[29]
−0.2	8.4	[24]
0.47	8.1	[45]
−0.21	8.3	[9]
−0.02	8.0	[32]
−0.4	8.1	[11]

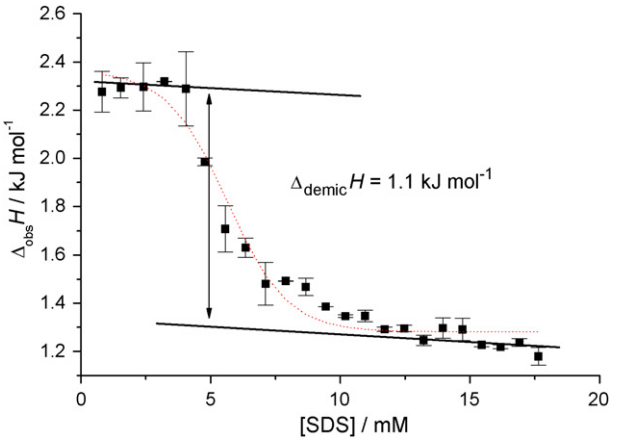

Fig. 3. Enthalpy per injection vs. concentration of SDS in the calorimetric ampoule for dilution of SDS into pH 7.0 phosphate buffer.

phosphate buffer. In this case it is clear that 'ideal' behaviour is observed, with a cmc of 5.2 ± 0.1 mM and an enthalpy of micellisation of -1.1 ± 0.04 kJ mol^{-1}.

In order to explain these differences, it is convenient to normalise the data shown in Figs. 2 and 3 relative to the initial enthalpy change ($\Delta_0 H$). This is analogous to plotting partial molar enthalpies, which reflect the differences between the observed enthalpies ($\Delta_{obs}H$) and the enthalpy change at infinite dilution ($\Delta_{inf}H$). The initial enthalpies were determined by extrapolating the fit lines shown in Figs. 2 and 3 to zero concentration with Origin (returning values of 1.09 and 2.35 kJ mol^{-1} for SDS dilution in water and buffer, respectively); Fig. 4 shows plots of ($\Delta_{obs}H - \Delta_0 H$) for SDS dilution into buffer and water.

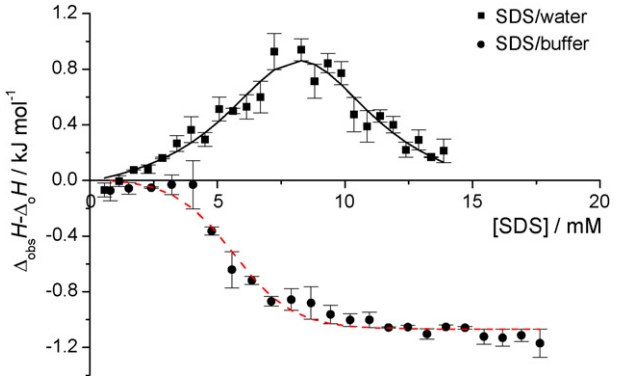

Fig. 4. ($\Delta_{obs}H - \Delta_0 H$) vs. SDS concentration for the dilution of SDS into water and SDS into buffer.

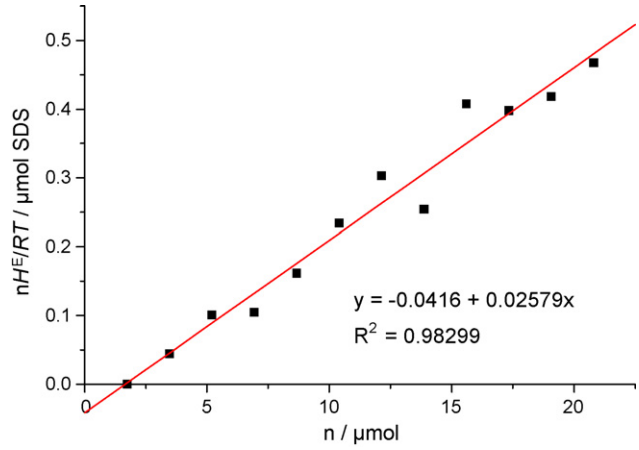

Fig. 5. nH^E/RT vs. n for the dilution of SDS into water.

Fig. 4 shows that mixing of SDS into buffer occurs with approximately zero enthalpy (the first 5 data points) while the mixing of SDS into water shows a positive deviation from ideality. For a non-ideal process, the excess Gibbs free energy (G^E) is given by;

$$G^E = H^E - TS^E \quad (4)$$

where G^E, H^E and S^E are defined as the difference between the actual energy change observed (free energy, enthalpy and entropy, respectively) and the energy change of a hypothetically ideal solution (G^{id}, H^{id} and S^{id}) under the same conditions. Since S^E is zero it follows that $G^E = H^E$ and at a given temperature and pressure;

$$G_{obs} - G^{id} = G^E = H^E = nRT \ln \gamma_i \quad (5)$$

where n is the number of moles of solute and γ_i is the activity coefficient (a coefficient of 1 being ideal) [21]. Hence, a plot of nH^E/RT versus n should give a straight line of slope $\ln \gamma_i$. This plot, for SDS in water, is shown in Fig. 5; it can be seen that the data conform well to a linear model ($R^2 = 0.98$) and give a slope of 0.026 ± 0.002. This gives an activity coefficient of 1.026, very close to the value of 1.035 reported by Meagher et al. [22], and confirms the positive deviation from ideal behaviour noted for dilution of SDS into water. Similar positive deviations have also been observed by other workers for SDS into water [23,24] using calorimetry. It follows from Eq. (5) that $\Delta_{obs}G$ must be larger than ΔG^{id} and therefore the SDS monomers are less stable in water than the corresponding ideal solution.

Although it allows quantification of the activity coefficient, the above discussion does not explain why ideal behaviour is observed in the buffered system. The main differences between the buffer and water are the presence of a large number of common ions (Na^+) and the fact that in the buffer the pH remains constant. Measurements of the pHs of a range of SDS solutions in water showed there was no concentration dependent pH change (data not shown). The presence of the common ion is therefore the most likely cause for the observed difference in behaviour. The SDS molecules will dissociate to a large degree in water, forming dodecyl sulphate ions, but to a much lesser degree in buffer.

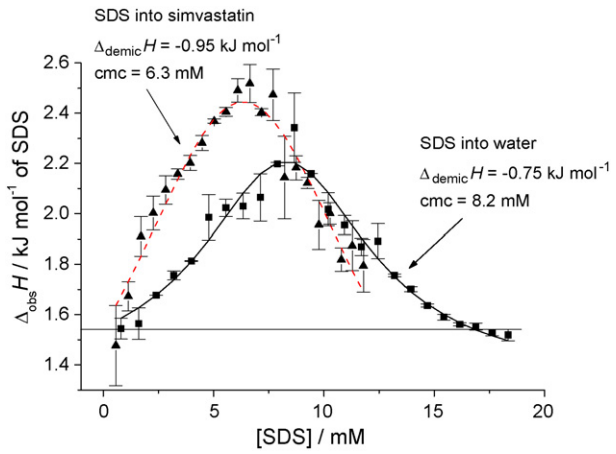

Fig. 6. Enthalpy per injection vs. concentration of SDS in the calorimetric ampoule for dilution of SDS into simvastatin solution and into water.

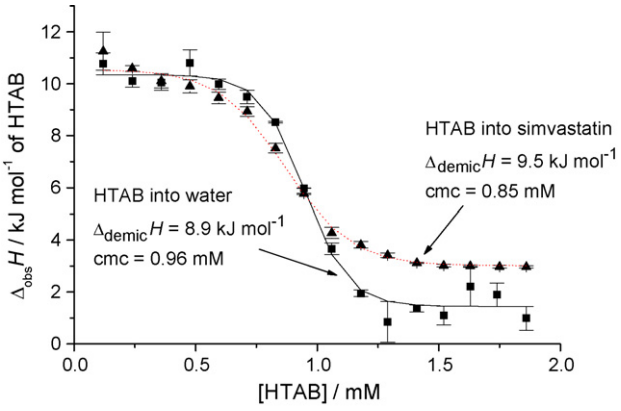

Fig. 7. Enthalpy per injection vs. concentration of HTAB in the calorimetric ampoule for dilution of HTAB into simvastatin solution and into water.

Mukerjee [25] stated that below the cmc, dodecyl sulphate ions form dimers by pair interaction between the alkyl chains. This argument was used by Birch and Hall [23] and Johnson et al. [24] to explain the positive deviation from ideality observed for the dilution of SDS into water. The formation of dimer pairs is also likely to be endothermic, which is tentatively supported by the net positive heat change observed in the calorimeter.

A further contribution to the observed heat change recorded by the calorimeter will be the enthalpy of dissociation of Na^+ from the SDS micelles. This value has been calculated by Ingram and Jones [26] to be 10.5 kJ mol^{-1}. Knowing the aggregation number of SDS micelles (58) [13] and the number of SDS molecules injected allows the contribution from this effect to be calculated (0.3 mJ per injection or 0.2 kJ mol^{-1} of total SDS injected). It appears that a combination of these two effects causes the positive deviation from ideality observed in the water system.

3.2.2. Dilution of SDS into a saturated simvastatin solution

Fig. 6 shows the integral values, normalised for concentration, for the dilution of SDS (0.09 M) into a saturated aqueous solution of simvastatin. Data for the dilution of SDS into water are included in Fig. 6 for comparison. The cmc of SDS is lowered in the presence of simvastatin to 6.3 ± 0.25 mM, while the enthalpy of micellisation increased slightly to 0.95 ± 0.04 kJ mol^{-1}. Again, this shows that SDS micellisation in the presence of simvastatin is entropically driven.

The Gibbs free energy of micellisation ($\Delta_{mic}G$) for the transfer of 1 mol of monomer to the micellar state for ionic surfactants is given by [27];

$$\Delta_{mic}G = (2 - \alpha)RT \ln X_{cmc} \quad (6)$$

where X_{cmc} is the cmc in mole fraction units and α is the degree of ionisation of the surfactant micelles ($\alpha = 0.85$ for SDS) [28]. Calculating the free energies for SDS micellisation in water and in simvastatin solution reveals that micellisation is slightly more favourable in simvastatin solution ($\Delta_{mic}G = -25.9 \pm 0.1$ kJ mol^{-1}) than in water ($\Delta_{mic}G = -25.2 \pm 0.1$ kJ mol^{-1}).

Although these values are close it is worth noting that the concentration of simvastatin in the ampoule is very small. Based on an aggregation number for SDS of 58 [13] it can be calculated that there are 5 SDS micelles for every one simvastatin molecule in the ampoule. Measurements of the solubility enhancement of simvastatin by SDS discussed above (Section 3.1) showed that one SDS micelle can solubilise 15 simvastatin molecules. These data might show a more marked difference if a suspension of simvastatin was used in the calorimetric ampoule, but this then introduces the complexity discussed earlier. The data clearly show, however, that there is a favourable interaction between the drug and the surfactant.

3.2.3. Dilution of HTAB, SDCH and Brij 35 in water

The remaining surfactants exhibited 'ideal' behaviour in water and were hence not studied in buffered solutions, because this would have unnecessarily increased the complexity of the solvent system. Fig. 7 shows the integral area per injection, normalised for concentration, for the titration of HTAB (50 mM) into water. The curve is seen to show a 'classical' cmc transition, the cmc itself being 0.96 ± 0.05 mM. This compares well with literature values by calorimetry of 0.96 mM [29] and surface tension of 0.92 mM [30]. The enthalpy of micellisation was found to be -8.9 ± 0.5 kJ mol^{-1}, again in good agreement with the literature values of -9.7 kJ mol^{-1} [31] and -8.2 kJ mol^{-1} [9].

Fig. 8 shows the 'classical' response obtained for the dilution of SDCH (0.24 M) into water. The transition is much broader than those seen for HTAB and Brij 35 (see below) and, consequently, the error in the cmc determined, 7.6 ± 0.3 mM, is much greater. This value is higher than that obtained by Paula et al. [32] of 5.5 mM using calorimetry and lower than that obtained by Roda et al. [33] of 10 mM using dye solubilisation and surface tension. As mentioned above, this transition broadening has been ascribed to pre-cmc aggregation [32]. It is known that bile salts form primary micelles below the main cmc, composed of between 2 and 10 monomers; as the concentration of bile salt is increased these primary micelles coalesce to form larger

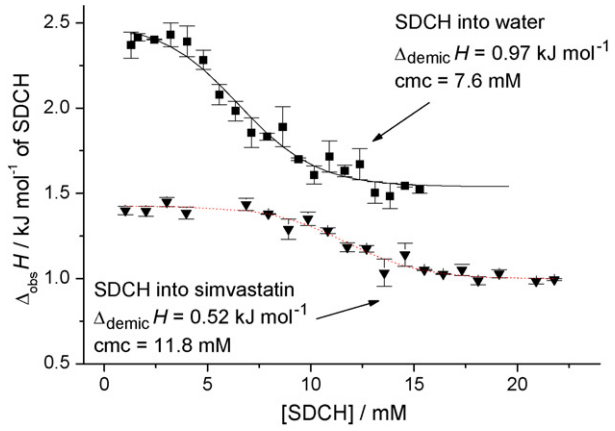

Fig. 8. Enthalpy per injection vs. concentration of SDCH in the calorimetric ampoule for dilution of SDCH into simvastatin solution and into water.

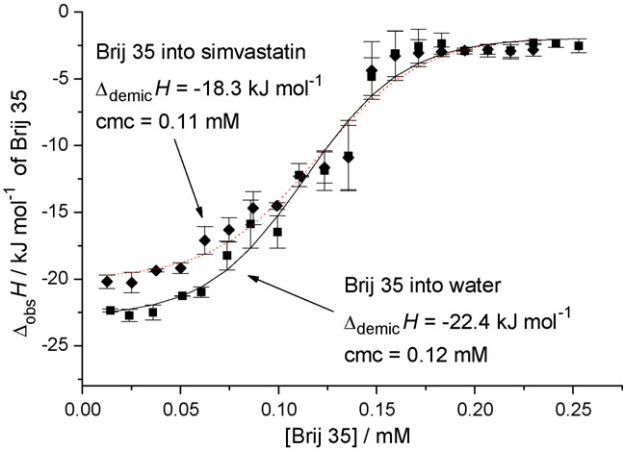

Fig. 9. Enthalpy per injection vs. concentration of Brij 35 in the calorimetric ampoule for dilution of Brij 35 into simvastatin solution and into water.

micelles [34,35]. It has been suggested that the term cmc should be replaced by 'noncritical multimer concentration' to define the range over which bile salt aggregation occurs [33]. The enthalpy of micellisation was found to be -0.97 ± 0.07 kJ mol^{-1} which compares well with the value of Birdi [36] of -0.92 kJ mol^{-1} but is less than that of Paula et al. [32] of -0.6 kJ mol^{-1}.

Fig. 9 shows the 'classical' response obtained for the dilution of Brij 35 (5.4 mM) into water. The cmc value obtained, 0.12 ± 0.007 mM, is slightly lower than that obtained by Woodhead et al. [37] of 0.18 mM using a similar calorimetric technique. There is, however, a range of values quoted for the cmc of Brij 35 in the literature (Table 4). It is stated that these discrepancies arise both from the polydisperse nature of

Table 4
Literature values for the cmc of Brij 35 in water

cmc (mM)	Technique	Reference
0.07	Surface tension	[39]
0.098	Surface tension	[24]
0.1	Surface tension	[46]
0.12	ITC	This work
0.18	ITC	[37]

Table 5
A summary of the free energies of micellisation, for all the surfactants, in water and simvastatin solution

Surfactant	$\Delta_{mic}G$ (kJ mol^{-1}) in simvastatin (1)	$\Delta_{mic}G$ (kJ mol^{-1}) in water (2)	$\Delta_{trans}G$ (kJ mol^{-1})
SDS	-25.9 ± 0.1	-25.2 ± 0.1	-0.7
HTAB	-31.9 ± 0.2	-31.5 ± 0.1	-0.6
SDCH	-33.9 ± 0.2	-35.7 ± 0.1	1.8
Brij 35	-32.5 ± 0.2	-32.3 ± 0.1	-0.2

Also shown are the calculated (1–2) free energies of transfer.

the commercial surfactant and from impurities remaining after manufacture [38]. Also, the cmc is very low which may mean that many of the determinations were recorded at or near the measuring limit of the instrument used. The enthalpy of micellisation, 22.4 ± 1.6 kJ mol^{-1} compares favourably with those of Becher and Trifeletti [39], 22.2 kJ mol^{-1}, and Woodhead et al. [37], 24.6 kJ mol^{-1}. The enthalpy of micellisation of this nonionic surfactant was of a much greater magnitude that those recorded for the ionic surfactants, which were also generally exothermic in nature. Olofsson [40] noted that for a series of polyoxyethylene dodecyl ethers the enthalpy of micellisation became more endothermic with an increasing number of ethylene oxide groups, because the hydrophilicity of the surfactants increases.

3.2.4. Dilution of HTAB, SDCH and Brij 35 into a saturated simvastatin solution

Fig. 7 shows the integral values, normalised for concentration, for the dilution of HTAB (50 mM) into a saturated aqueous solution of simvastatin. The cmc of HTAB is lowered in the presence of simvastatin to 0.85 ± 0.04 mM, while the enthalpy of micellisation increased slightly to -9.5 ± 0.1 kJ mol^{-1}. As in the case of SDS, the difference in enthalpy observed for titration into water and into simvastatin solution is not large, but this may reflect the small quantity of drug present. It is also noted that the transition is much broader in the presence of drug. Both phase separation and mass action models for polymer micellisation predict a narrow micellisation transition when the aggregation number is large. A similar phenomenon observed for SDCH was ascribed to aggregation prior to the cmc [32] and this may also be the case here.

The calculated free energies for HTAB micellisation in water and in simvastatin solution ($\alpha = 0.84$ for HTAB) [41] are given in Table 5.

Fig. 8 shows the integral values, normalised for concentration, for the dilution of SDCH (0.24 M) into a saturated aqueous solution of simvastatin. In contrast to the previous surfactants, the presence of simvastatin increases the observed cmc for SDCH to 11.8 ± 0.7 mM. Measurements of the free energy of adhesion between SDCH and simvastatin in water suggested that any interaction between the two would be only slightly favourable ($\Delta_{1w2}G = -1.7$ mJ m^2) [42]. Again in contrast to the previous surfactants, the enthalpy of micellisation becomes more endothermic in the presence of drug, decreasing to -0.52 ± 0.04 kJ mol^{-1}. The calculated free energies for SDCH micellisation in water and in simvastatin solution

Table 6
A summary of the micellisation enthalpies for the ionic surfactants in water and simvastatin solution and the calculated (1–2) enthalpies of transfer

Surfactant	$\Delta_{mic}H$ (kJ mol^{-1}) in simvastatin (1)	$\Delta_{mic}H$ (kJ mol^{-1}) in water (2)	(1)–(2) (kJ mol^{-1})
SDS	0.95 ± 0.04	0.75 ± 0.02	0.2
HTAB	−9.5 ± 0.1	−8.9 ± 0.5	−0.6
SDCH	−0.52 ± 0.04	−0.97 ± 0.07	0.5
Brij 35	18.3 ± 2.2	22.4 ± 1.6	−4.1

($\alpha = 0.38$ for SDCH) [43,44], shown in Table 5, reveals that micellisation is slightly less favourable in simvastatin solution than in water which is reflected in the increased cmc for this surfactant in the drug solution.

Fig. 9 shows the integral values, normalised for concentration, for the dilution of Brij 35 (5.4 mM) into a saturated aqueous solution of simvastatin. There was no difference in the cmc of the surfactant, within error, in the presence of drug, 0.11 ± 0.01 mM but the enthalpy of micellisation was less endothermic, 18.3 ± 2.2 kJ mol^{-1}. The calculated free energies for Brij 35 micellisation in water and in simvastatin solution ($\alpha = 1$ for non-ionic surfactants), Table 5, were almost identical.

3.3. Comparison of solubility enhancement and ITC data

The enthalpy data for the four surfactants are summarised in Table 6. The micellisation enthalpy comprises contributions from a number of events; apolar interactions (surfactant chain–surfactant chain, simvastatin–simvastatin and surfactant chain–simvastatin) and polar interactions (surfactant head group and simvastatin). The difference between $\Delta_{mic}H$ in the presence and absence of simvastatin should therefore relate only to simvastatin–surfactant events (assuming that simvastatin–simvastatin interactions can be ignored because of the low concentration of drug) and can be assumed to equal the enthalpy of transfer of simvastatin from solution into the micelle, $\Delta_{trans}H$. These values are shown in Table 6.

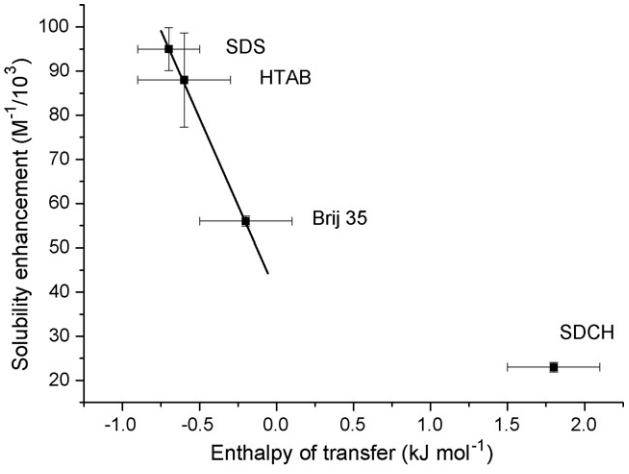

Fig. 10. A plot of the free energy of transfer of simvastatin into the surfactant micelles vs. the solubility enhancement; the data show a linear for those systems with a favourable free energy of transfer.

By the same argument, the difference between the free energies of micellisation in the presence and absence of surfactant represent the free energy of transfer of simvastatin from solution into the surfactant micelle. These data are summarised in Table 5.

Interestingly, a plot of the free energy of transfer versus the solubility enhancement suggests a linear relationship exists for those systems that show a favourable free energy of transfer, Fig. 10. Although the graph contains only a limited number of data points and further work with a wider range of ionic and non-ionic surfactants is needed, the preliminary data presented here suggest that measurement of the free energy of transfer of simvastatin into a surfactant micelle may allow the prediction of the likely solubility enhancement of that surfactant.

4. Summary

The aim of this work was to examine the potential role of isothermal titration calorimetric data in assessing the solubility enhancement of surfactants. This was achieved by studying the properties of a model hydrophobic drug with a small number of surfactants. Although the data set discussed is limited, the data appear to show that there is a potential use for ITC in this area, with a linear relationship being observed between the free energy of transfer for the drug to the surfactant and the solubility enhancement factor of that surfactant. This relationship is valid only when the free energy term is favourable. Clearly, further investigation is required with a wider range of drugs and surfactants, but this preliminary study suggests that isothermal titration calorimetry has the potential to assess the solubility enhancement of surfactants for poorly water soluble drugs.

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