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A microcalorimetric study of surfactant aggregation and surfactant-drug interaction in a model inhalation aerosol system

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Abstract

Two surfactants, oleic acid and Span 85, have been diluted from concentrated solution in Arcton 113 by gradual titration into Arcton 113 in a titration cell of an isothermal microcalorimeter. The heat of dilution responses revealed areas of interest in which it can be assumed that the state of aggregation of the surfactants changes. These points are at concentrations of approx. 0.3 and 0.7% w/v for oleic acid and at 0.8% w/v for Span 85. The experiments were repeated with salbutamol base suspended in Arcton 113, such that the adsorption of surfactant to the drug could be investigated. For both surfactants the results when drug was present were significantly different from those when drug was absent (dilution only). For oleic acid the data with drug were more exothermic and for Span 85 they were more endothermic, indicating different thermodynamics of adsorption for the two surfactants. For both surfactants there were break points in the adsorption data at concentrations corresponding to the break points in the dilution data. It can be concluded that the adsorption process is highly dependent upon the structure of surfactant in solution. For both surfactants the critical concentration was at or just below the value of 1% that has been found to be an effective surfactant loading for the production of inhalation aerosols. This data provides an explanation for the practical observation on surfactant use and demonstrates that microcalorimetry is a valuable technique for studies on these difficult systems.

Keywords: Isothermal microcalorimetry; Salbutamol; Metered dose inhaler; Adsorption; Oleic acid; Span 85; Critical micelle concentration

1. Introduction

The use of surfactants is common place in many pharmaceutical and industrial processes. The aggregation behaviour of surfactants in aqueous solution is comparatively well understood, although a lot of fundamental work on the subject is still being undertaken. The knowledge of phase behaviour of surfactants in non-polar solvents is, by comparison, still in its infancy. In part, the problem with studies of phase behaviour of surfactants in non-aqueous fluids is that measurements on the system tend to be harder to obtain than for aqueous fluids. For example, the adsorption of surfactants to the liquid-vapour interface is easily measured for water based systems by the use of surface tension measurements, however, the surface tension of non-aqueous fluids is already so low that differences due to

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additives are often insignificant, even if substantial adsorption occurs at the liquid-vapour interface.

The use of non-aqueous suspensions for inhalation aerosols remains an important means of drug delivery and will continue to be so even when chlorofluorocarbon propellants are replaced. However, little is known about the role of surfactants in stabilising these suspension systems, which as noted above is due to the poor level of understanding of the nature of non-polar suspensions. There have been a few studies on electrophoretic properties in model aerosols (e.g., Sidhu et al., 1993; Sanstrom et al., 1994), however, it is acknowledged that such experiments are difficult to perform. It is extremely difficult to obtain adsorption isotherms for surfactant onto drug particles in chlorofluorocarbon liquids as their high volatility makes the measurement of small changes in concentration problematic. In order to investigate the role of surfactants in such non-aqueous suspensions it would be valuable to develop more non-invasive sensitive experimental methods. One approach to the study of these systems has been proposed by Craig and Taylor (1994) which was the use of dielectric spectroscopy. In the current study, however, an alternative approach to such investigation is considered, that of isothermal titration microcalorimetry.

2. Materials and methods

2.1. Materials

Micronised salbutamol base (a gift from 3M Health Care), was stored in a desiccator at 0% relative humidity (RH) prior to use. Arcton 113 (Romil Chemicals) was used as a model non-polar non-aqueous phase, as it is a liquid at room temperature. Oleic acid (Aldrich) was stored in a refrigerator before use. Span 85 (Aldrich) was used as supplied.

2.2. Method

A suspension of salbutamol base in 3 ml Arcton was equilibrated in a stainless steel perfusion-titration cell of an isothermal microcalorimeter (Thermal Activity Monitor, Thermometric) at 298.15 K. The filled titration vessel was inserted stepwise down the channel of the microcalorimeter using three equilibrium positions, equilibrating at the first two stages for 5 min and at the last for 10 min. The vessel was finally located in the measuring site of the calorimeter where it remained until a stable baseline was established after 1 h. The liquid was constantly stirred by the in situ turbine (engineered in our laboratories). The surfactant was dissolved in Arcton 113 (0.55 or 1.13 M for oleic acid; 0.37 M for Span 85) and then injected from a 500 μl gas-tight motor driven Hamilton syringe (1750 LT) controlled via the computer system in 20 μl aliqouts. The permanently affixed needle of the syringe was soldered to a 1 m stainless-steel cannula, the other end of which was positioned such that it was secured just above the surface of the liquid in the titration vessel. For each titration experiment, about 15 injections were made at time intervals of 1 h. Blank experiments were undertaken to allow a correction for the heat changes associated with the dilution of the surfactant. The heat change for each addition was measured as power as a function of time. From the corrected results of the calorimetric titration, values for the enthalpy change in mJ were calculated.

The reliability of the calorimeter was checked using the test calibration reaction of Ba^{2+} and macrocyclic 18-crown-6 ether in water at 298.15 K suggested by Briggner and Wadsö (1991). An enthalpy value ($\Delta H°$) of -31.28 ± 0.29 kJ mol^{-1} was obtained, which was in excellent agreement with the literature value of -31.42 ± 0.20 kJ mol^{-1}. All experimental data reported are means of triplicate determinations.

3. Results

3.1. Oleic acid

The data for the addition of oleic acid (0.55 M in Arcton 113) to Arcton 113 are shown in Fig. 1. Fig. 1 shows two break points in the cumulative

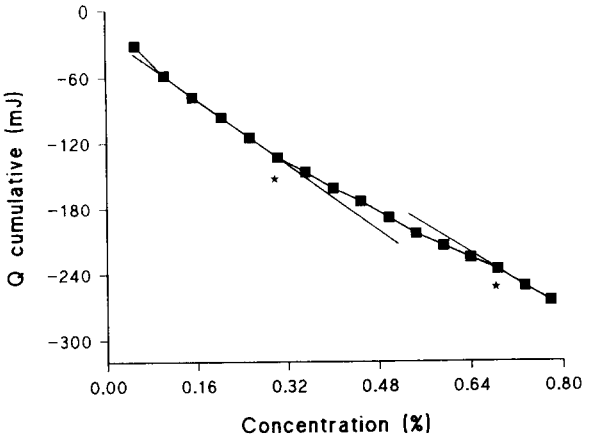

Fig. 1. Cumulative titration plot for the addition of 0.55 M oleic acid to Arcton (3 ml). The x-axis represents the percentage concentration of surfactant in the calorimeter cell after each addition of the concentrated surfactant solution; the y-axis represents the sum of the heat output for each individual addition in mJ. * Marks concentrations of interest.

heat relationship. One break point is at a concentration of approx. 0.3% oleic acid and the other is a minor deviation from linearity as the concentration approaches ca 0.7%. Fig. 2 shows the results for injecting a more concentrated solution of oleic acid (1.13 M) into Arcton. These data whilst obviously having only a few data points at the low concentration regions support those presented in Fig. 1, demonstrating a break in the relationship

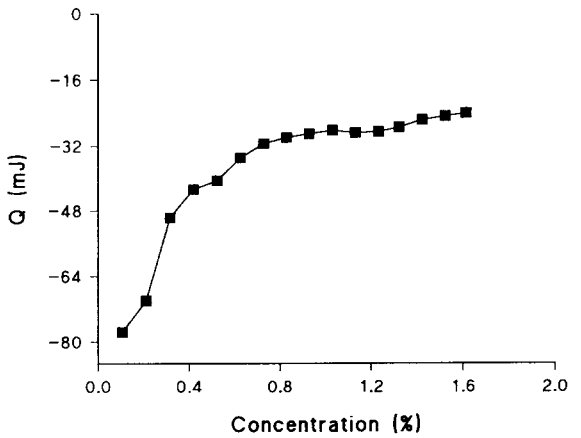

Fig. 2. Titration plot for the addition of 1.13 M oleic acid to Arcton (3 ml).

at approx. 0.3 and 0.7% oleic acid as well as showing that at concentrations above 0.8% oleic acid the heat output for each subsequent addition was essentially identical. As with all thermal methods, interpretation of these breaks in the relationship can only be hypothesised, but it is very probable that the concentrations of 0.3 and 0.7% represent points of phase change in the solution, due to variation in solvation and aggregation of the surfactants. One of the inflection points may well be a critical micelle concentration (CMC) and the other could be a lower order aggregation (such as the formation of dimers) or the formation of a higher order surfactant aggregate structure (depending on whether the first or the second inflection point corresponds to the critical micelle concentration). The change in behaviour at 0.8% (Fig. 2) can be regarded as being the conclusion of the change that is occurring at 0.7% (Fig. 1) and can reasonably be assumed to be a point where no further change in structure occurs in the solution, after which the subsequent responses are reproducible heats of dilution.

The observed heat changes are heats of dilution of the surfactant from a concentrated solution to a dilute solution. The endothermic results are indicative of a disfavoured process, which must be entropically driven.

The data for the addition of surfactant to a liquid with suspended salbutamol (Fig. 3) are very different from those reported in Fig. 1 and 2. Fig. 3 was obtained by subtracting the responses for surfactant addition to Arcton (taken to be a blank response) from the responses obtained when the surfactant was added to Arcton with salbutamol present. Fig. 3 shows that the presence of salbutamol causes the data to switch from modest endotherms to exotherms. Thus, there is an enthalpic driving force for the adsorption of surfactant to the drug. The data in Fig. 3 also show two distinct break points, one at about 0.3% and the other at approx. 0.7%. These break points are at the same concentration as were seen in Fig. 1 and 2 and demonstrate that the extent of surfactant aggregation is important in determining the interaction between the surfactant and the drug. The peak between 0.3% and 0.8% (Fig. 3) demonstrates a stronger enthalpic driving force for ad-

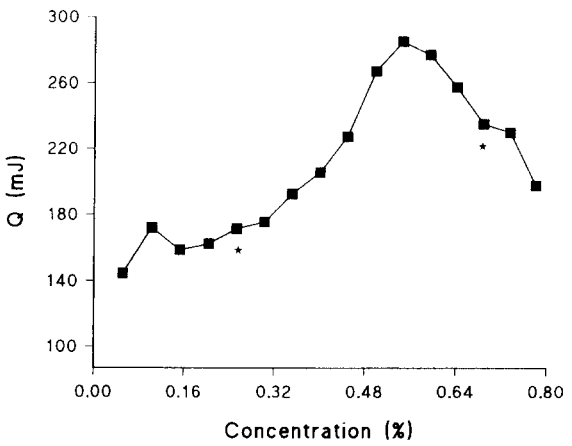

Fig. 3. Titration plot for the addition of 0.55 M oleic acid to salbutamol base suspended in Arcton (3 ml), corrected for dilution effects by subtracting the responses without drug present from each data point obtained in the presence of the drug. * Identifies concentrations of interest.

sorption in this region. This is shown more clearly by presenting the data from Fig. 3 as cumulative heat as a function of concentration (Fig. 4) for which it can be seen that a steeper gradient is obtained between the critical concentrations of 0.3 and 0.7%.

It would be advantageous to characterise fully the system thermodynamically, for which it would be necessary to determine a free energy change

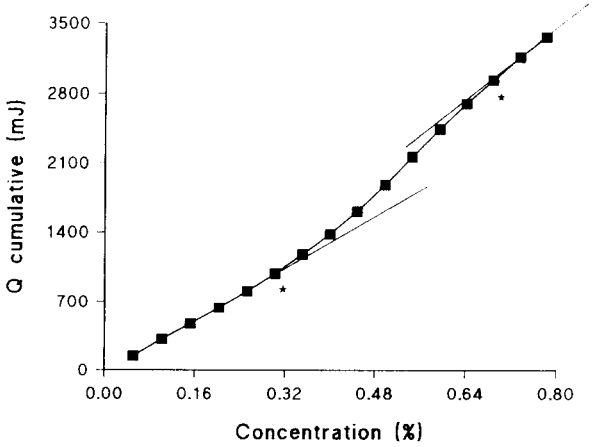

Fig. 4. Titration data for the addition of 0.55 M oleic acid to salbutamol presented as cumulative heat. * Identifies concentrations of interest.

and thus a value for the entropy change. However,the data clearly demonstrate that there is an advantage in studying such systems by isothermal microcalorimetry as a greater understanding of the interactions that occur can be obtained.

In order to assess the behaviour of surfactant adsorption onto salbutamol in the model non-polar non-aqueous phase (Arcton), particle size studies using the Malvern Series 2000 instrument were undertaken. The particle sizes of salbutamol base suspensions in Arcton are shown in Fig. 5. It is not possible to express the data in Fig. 5 in relation to a concentration of surfactant in solution, in part this is due to the fact that Arcton is volatile thus concentration was subject to variability. There are other reasons why the Malvern data cannot be directly related to the calorimetric study, which are the amount of suspended drug had to be altered in the Malvern cell in order to optimise the sizing process, furthermore, the stirring in the Malvern cell was different from that in the calorimeter cell. The size data are thus a guide to behaviour only. The salbutamol base was found to give multi-modal size distributions, which cannot readily be expressed numerically. The calorimetric response shows a large exotherm when oleic acid is added to salbutamol in Arcton 113. Such an exotherm is typical of the formation of physical bonds, such as adsorption processes, rather than being indicative of the breaking of bonds. This is in keeping with the observed size distributions (Fig. 5) which show the total size distribution remaining largely unchanged, but with the distribution splitting into more focused sub-distributions as more surfactant is added.

3.2. Span 85

The calorimetric data for the addition of Span 85 to Arcton 113 show endotherms (Fig. 6), with an inflection point in the region of 0.8% surfactant [1]. As argued in section 3.1, this point may well relate to a change in structure for the surfac-

[1] Data were also obtained for the dilution of a less concentrated solution of Span (0.11 M), but as no significant break points were seen these data are not presented.

tant in solution, such as a critical micelle concentration. A break at this concentration is totally in keeping with the observation by Craig and Taylor (1994) that properties of these solutions changed at approx. 1%.

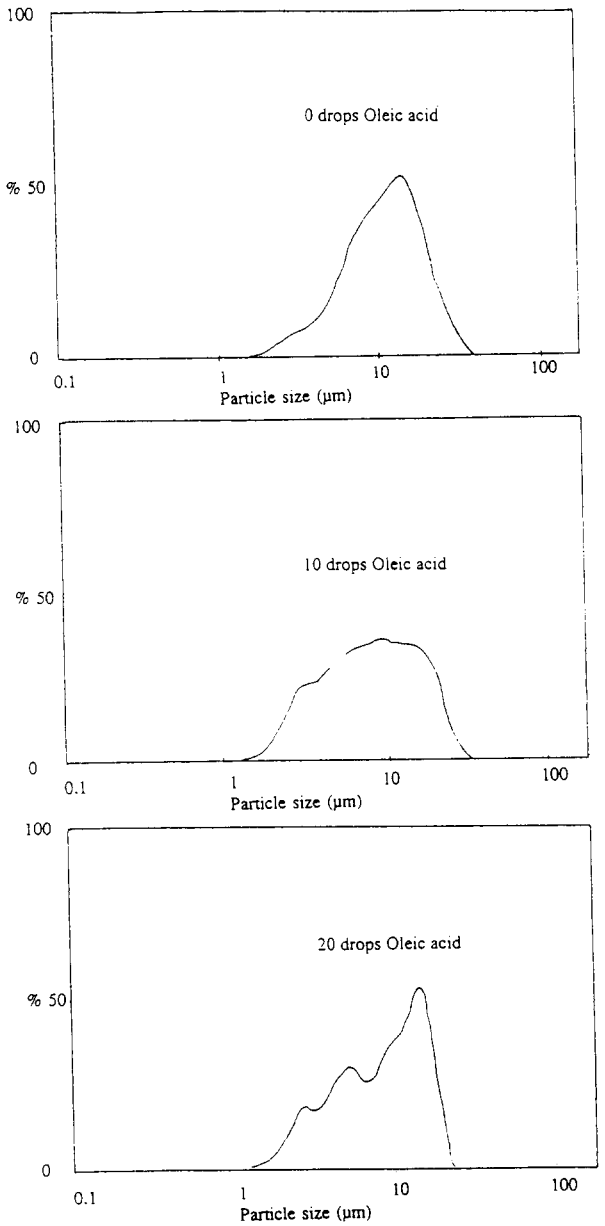

Fig. 5. Change in particle size distribution for salbutamol base in Arcton 113 upon addition of 10 and 20 drops of oleic acid.

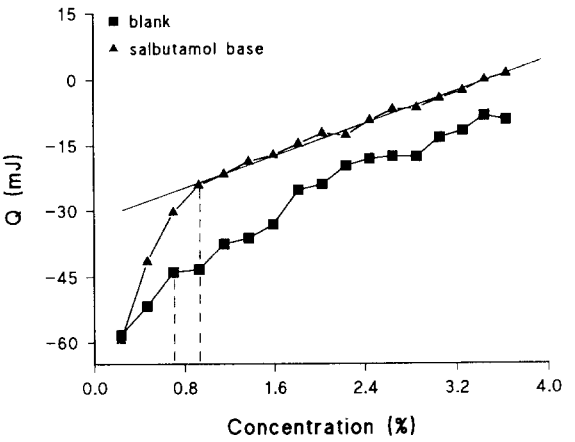

Fig. 6. Titration plot for the addition of Span 85 to Arcton 113 (squares) and for the addition in the presence of salbutamol base (triangles). Each data point represents the heat change associated with each sequential injection of surfactant to achieve the concentration shown on the x-axis.

The data for the addition of Span 85 to Arcton 113 with salbutamol base present are also shown in Fig. 6. The data reveal significant endotherms with a sharp break at a concentration of about 1%. The difference between the results in the presence of drug and for the dilution alone are shown in Fig. 7, where the break at around 1% is seen very clearly. This break at 1% will in reality be rather closer to the value of approx. 0.8% seen in the absence of drug (also in Fig. 6) as the equilibrium concentration of surfactant present will be lower than the concentrations plotted as a finite amount of surfactant will have adsorbed to the drug. As the quantity of adsorption cannot be quantified the correction cannot be applied to the plot. The fact that this break point so closely follows that observed in the dilution experiments and that seen by Craig and Taylor (1994) provides good evidence to link the aggregation behaviour of the surfactant to its interaction with the drug surface. The sizing data for the addition of Span 85 to the salbutamol suspension (Fig. 8) show a significant polarisation with sizes moving from an approximation to a normal distribution to two discrete groups, one with large size and the other small. There will be heat changes due to the

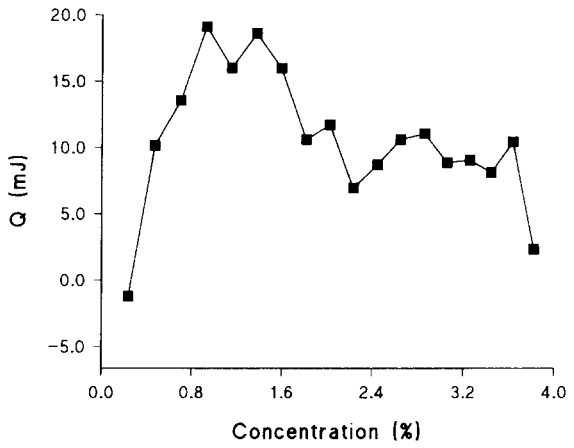

Fig. 7. Difference between the heat changes upon titration of Span 85 in the presence of salbutamol base and those seen for the dilution of the concentrated surfactant into Arcton 113.

aggregation and de-aggregation of the salbutamol which will contribute to the overall response (with de-aggregation and aggregation expected to be endothermic and exothermic respectively). Thus, the effect of particle size changes (being a composite of some de-aggregation and some aggregation) may make a rather small contribution to the overall heat change.

4. General discussion

The data for adding both oleic acid and Span 85 to Arcton, with and without salbutamol present, show that regions of interest in Fig. 1, 2 and 6 (where no drug is present) are mirrored by significant changes in Fig. 3, 4, 6 and 7 (where drug is present). Thus, for both surfactants there is a relationship between surfactant aggregation in solution and adsorption behaviour.

There are substantial differences between the absolute values presented in Fig. 3 and 7, for the adsorption of the two different surfactants, which could relate to differences in the extent and thermodynamics of adsorption of the different surfactants to the same solid surface. A compounding factor is the fact that aggregation and de-aggregation behaviour can also contribute to this response. Given the similarities in the size distribution data (Fig. 5 and 8) it is unlikely that the differences are influenced in a major way by size changes.

The data for both surfactants indicate that adsorption is rapidly changing up to a critical

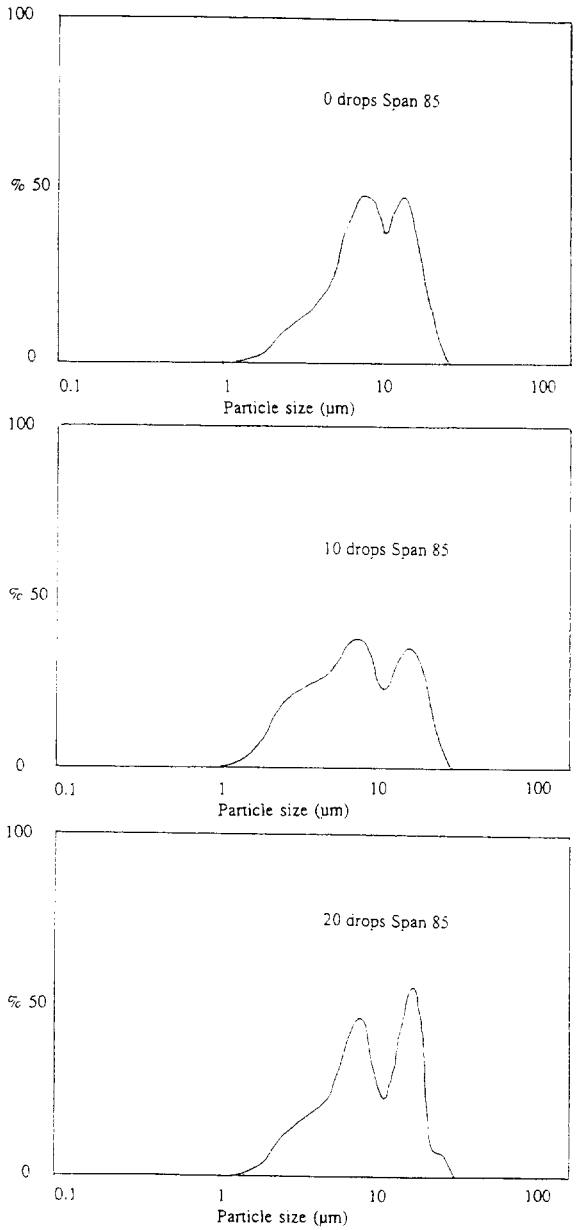

Fig. 8. Change in particle size distribution for salbutamol base in Arcton 113 upon addition of 10 and 20 drops of Span 85.

point (about 0.7% for oleic acid and 0.8% for Span 85). These data fit well with the practical observation that optimal surfactant concentrations for stabilising inhalation aerosols are in the region of 1%.

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References

Briggner, L.-E. and Wadsö, I., Test and calibration processes for microcalorimeters, with special reference to heat conduction instruments used with aqueous systems *J. Biochem. Biophys.*, 22 (1991) 101.

Craig, D.Q.M. and Taylor, K., The use of low frequency dielectric analysis in the characterisation of metered dose inhaler formulations. *Int. J. Pharm.*, 114 (1995) 129–133.

Sandstrom, K.B., Eriksson, P.M. and Rosenholm, J.B., Electrophoretic mobility of salbutamol drug powder in mixed propellant solvent. *J. Pharm. Sci.*, 83 (1994) 1380–1385.

Sidhu, B.K., Washington, C., Davis, S.S. and Prewell, T.S., Electrophoretic properties of lactose and salbutamol sulphate suspensions in halogenated solvents *Langmuir*, 9 (1993) 839–843.