A Microcalorimetric Investigation of the Interaction of Surfactants with Crystalline and Partially Crystalline Salbutamol Sulphate in a Model Inhalation Aerosol System

Peter M. Blackett[1] and Graham Buckton[1,2]

Received May 2, 1995; accepted July 25, 1995

Purpose. The purpose of the work is to study the adsorption of Oleic acid and Span 85 (materials frequently used in aerosols as surfactants) onto partially amorphous and essentially crystalline salbutamol sulphate, attempting to understand the behaviour of metered dose inhalers (MDIs) and observing whether there were any differences in adsorption behaviour and if this could be related to the surface properties of the powder.
Methods. Isothermal titration microcalorimetry was the principal technique used to measure the adsorption behaviour of surfactants to salbutamol sulphate. A Malvern particle size analyzer was also employed to provide size data on the interactions between the surfactant and powder suspensions.
Results. The calorimetric data revealed that surfactant adsorption to the crystalline micronised powder (78% RH and aged dry sample) produced significant exotherms, whereas adsorption to the partially amorphous micronised powder resulted in small heat responses. The differences in adsorption behaviour to the partially crystalline and crystalline surfaces resulted in changes in aggregation behaviour.
Conclusions. The stability of MDIs varies depending on the water content, crystallinity and surface composition of the powder. The advantages of using isothermal titration microcalorimetry to evaluate this surface behaviour in such difficult systems was demonstrated.

KEY WORDS: microcalorimetry; surfactants; aerosols; salbutamol sulphate.

INTRODUCTION

Dispersions of solids in liquids of low dielectric constant are used in many industries (such as paints, printing, coatings, lubrication and pharmaceutical), but the understanding of such systems is less well advanced than that for aqueous suspensions (1). One use of non-polar suspensions is in medicinal aerosols where drugs are suspended in chlorofluorocarbons (CFCs; currently being replaced by similar non-polar liquids (2,3)). In such systems the drug must be micronised (2–8 μm in size) if it is to be inhaled into the lung. Thus medical aerosols combine the need to have accurate control on the suspension properties of solids (which may be reasonably polar) in a liquid which is non-polar, with the need for micronisation of the drug. A further consideration is the small number of toxicologically acceptable surfactant stabilisers.

Any high energy process, such as micronisation, can cause significant disruption to crystalline materials, such that their surfaces (being the area which was exposed to the processing stress) are believed to become disordered (4–8). The amount of crystalline material which will become amorphous is related to the nature of the solid and the energetics of the stress applied. Equally, the ability of a material to recover from the stress, i.e. to form the thermodynamically stable crystalline state, will depend upon the nature of the material, the environment to which it is exposed and the length of time after processing. Salbutamol sulphate is a drug which is used in inhalation therapy in a micronised form. It is a relatively polar material (9) which can exist in an amorphous form, and which is known to recrystallise in the presence of air when the relative humidity (RH) is greater than 50% (at a rate which is dependent upon the RH and the mass of sample that is stored in one container (4,10)). Furthermore, the changes in crystallinity induced during different processing stages can be shown to affect the rate of crystal growth in inhalation aerosols (11). Thus, salbutamol sulphate is a material which may be susceptible to changes in crystallinity during processing and subsequent storage, but which must on every occasion be uniformly suspended in a non-polar liquid if it is to achieve reproducible dosing to a patient. It is probable that the surface energy of a solid will be different depending upon whether it is in the crystalline or the amorphous form (due to freedom of rotation of molecules in the amorphous form which can minimise interfacial energies). The interaction between the solid and other phases (in this case a surfactant and the liquid) will depend upon the surface energy of the solid. This study is designed to probe the influence of changes in crystallinity using a model inhalation system. By necessity the suspension must be liquid at room temperature, so the model of propellant 113 is being used.

MATERIALS AND METHODS

Materials

In this work, we have studied the adsorption of both oleic acid and Span 85 (materials which have frequently been used in inhalation aerosols as surfactants) to micronised salbutamol sulphate. The micronised drug was investigated in three conditions, one of which was stored at 0% RH immediately after micronisation until it was studied (subsequently described as the "fresh sample"). A crystalline sample of micronised salbutamol was prepared by spreading a thin layer of the fresh sample (such that particle-particle contact was minimised) and then equilibrated in an atmosphere of 78% RH for 72 hours in order to allow recrystallisation of any processing induced disorder (10) (described as the "78% RH sample"). The third form was obtained by taking the 78% RH sample and returning to storage at 0% RH for at least 24 hours before further investigation ("aged dry sample").

The relative crystallinity of the different samples was assessed by isothermal microcalorimetry in which the powder was exposed to humid air and any recrystallisation event recorded (see Ref. 4 for method).

[1] Centre for Materials Science, School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX.
[2] To whom correspondence should be addressed.

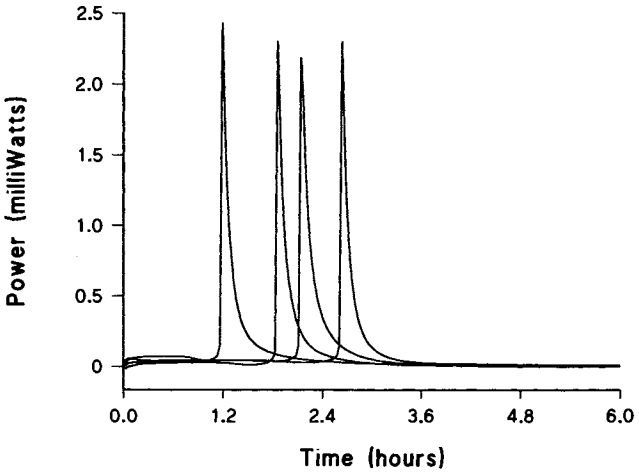

Fig. 1. The recrystallisation responses of micronised salbutamol sulphate at four relative humidities (75%, 65%, 58% and 54% RH) determined by batch isothermal microcalorimetry.

Methods

Adsorption of surfactant (Span 85 and oleic acid) onto the powders in the presence of liquid propellant was followed using a perfusion-titration cell in an isothermal microcalorimeter (Thermal Activity Monitor, Thermometric). A suspension of 50 mg of powder in 3 ml of the non-polar liquid (Arcton 113, which is 1,1,2-tri-chloro-tri-fluoro-ethane) was equilibrated in the calorimetric cell, and then lowered into the measuring position of the microcalorimeter. The sample was stirred continually with an *in situ* turbine whilst being titrated with a solution of surfactant (0.55 M Oleic acid, 0.37 M Span 85) in Arcton 113. Sequential 20 µl injections were made at fifteen intervals of one hour. After each injection, the heat output was recorded as power as a function of time. The calorimetric response was calibrated chemically with reference to the reaction of Ba^{2+} and macrocyclic 18-crown-6-ether in water, the results were in excellent agreement with literature values (12) (measured = -31.28 ± 0.29 kJ mol^{-1}; literature value = -31.42 ± 0.20 kJ mol^{-1}).

RESULTS AND DISCUSSION

Assessment of the Degree of Crystallinity of the Samples

The fresh sample (i.e. that which had been stored at 0% RH since micronisation) gave a response for recrystallisation in the microcalorimeter, (i.e. was partially amorphous), whilst the crystalline sample[3] showed no such response (showing it to be greater than 99.7% crystalline using the sensitivity limits which have been demonstrated for this technique (13)). The data in Figure 1 are for a recrystallisation of the amorphous content of the fresh salbutamol sulphate at four different humidities. The area under the curve in each case was identical within experimental error, giving a mean value of 9.9 mJ/mg for the recrystallisation event. The recrystallisation of amorphous[1] spray dried salbutamol (10) yielded a recrystallisation event of 26.2 mJ/mg, thus the fresh sample investigated here is 38% amorphous. It can be seen that the micronisation process has induced significant disorder, which has not been able to recover due to storage in dry conditions.

Adsorption Data

Oleic Acid

The cumulative responses for the adsorption of oleic acid onto the powder, in each case corrected for the blank response (dilution of the oleic acid solution into Arcton 113 with no solid present), are shown in Figure 2 (mean values ± SD, n = 3). It can be seen that there is a substantial difference between the response following the adsorption of the surfactant onto the three different samples. The calorimetric response is directly proportional to the enthalpy of the process(es) as well as the amount of material adsorbed. The amount of surfactant adsorbed cannot be readily quantified due to analytical difficulties with such volatile liquids. Thus, the values used to define surfactant concentration in the system with powder present are the amount of surfactant present, rather than the equilibrium concentration in solution. The correction of the calorimetric data obtained by subtracting the blank response will be slightly inaccurate, as the concentration of surfactant in solution in the presence of powder will, in reality, be reduced by an amount equal to that which has adsorbed (which consequently means the dilution response may be more similar to that seen for a slightly lower concentration of surfactant). However, this error in correction is expected to be small in comparison with the differences seen between the three samples (as the

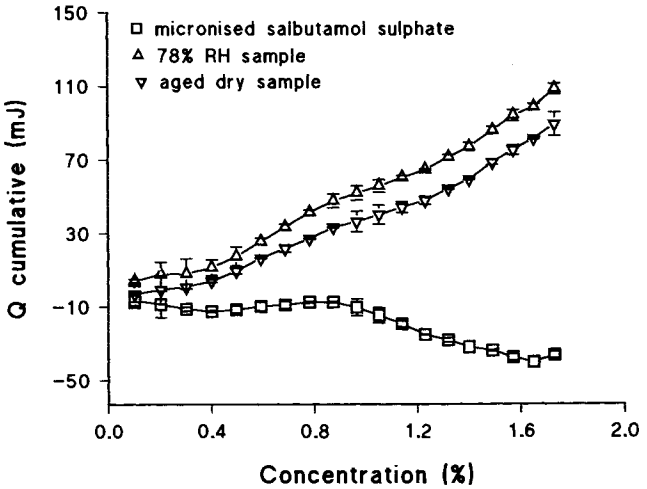

Fig. 2. The cumulative titration plot for the adsorption of 0.55 M oleic acid to micronised salbutamol sulphate, 78% RH salbutamol sulphate and aged dry salbutamol sulphate. [X-axis represents the percentage concentration of surfactant in the calorimeter cell after each addition of the concentrated surfactant solution. Y-axis represents the sum of the heat output for each individual addition in milliJoules (mJ)].

[3] The sample described as amorphous is one which has no crystallinity detectable by conventional experimental techniques (differential scanning calorimetry, powder X-ray diffraction). This in itself does not, however, prove the material to be amorphous, the best estimate of detection sensitivity would suggest that the sample is greater than 90% amorphous.

blank response for the addition of surfactant is relatively flat when plotted as cumulative heat as a function of concentration). Our hypothesis as to the reason for the large differences in calorimetric response between the three samples is that the amorphous sample yields data which are a composite for surfactant adsorption (exothermic) and subsequent particle de-aggregation (endothermic), giving a net small heat change which tends to a net endotherm as surfactant concentration increases.

The de-aggregation on addition of surfactant is shown by the size distributions (Figures 3 and 4), from which it

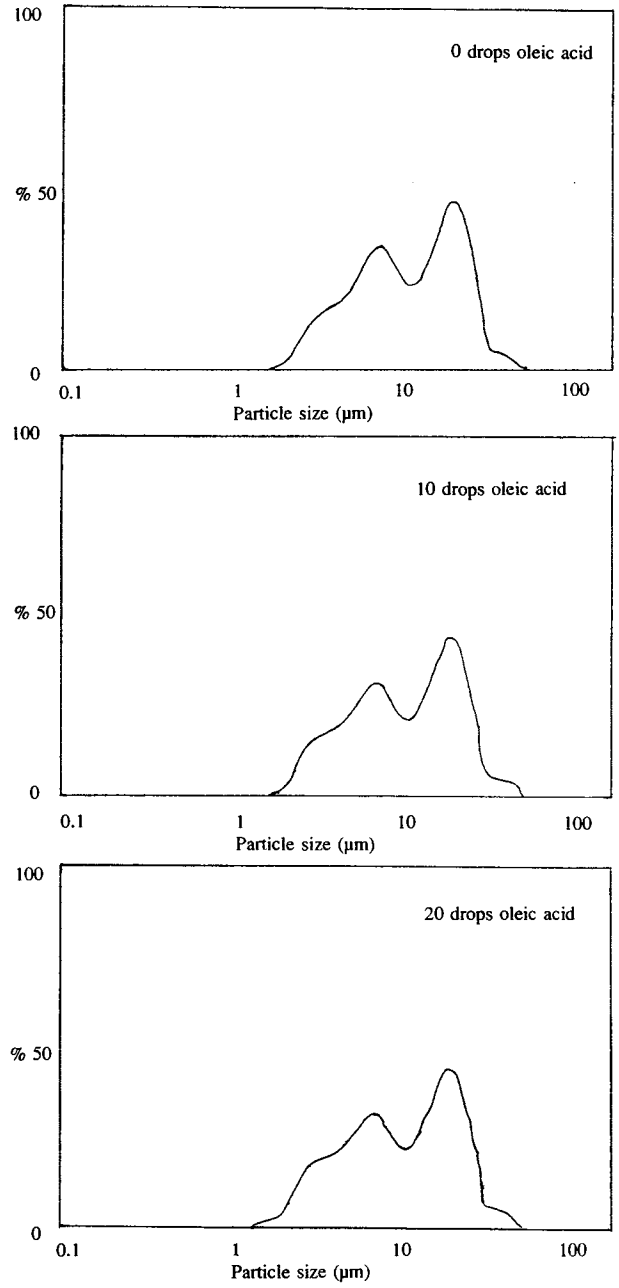

Fig. 3. The change in particle size distribution for 78% RH salbutamol sulphate in Arcton 113 upon addition of 10 and 20 drops of oleic acid. [Measured using a Malvern 2600c instrument fitted with a 63 mm lens. Y-axis represents the percentage population of particles].

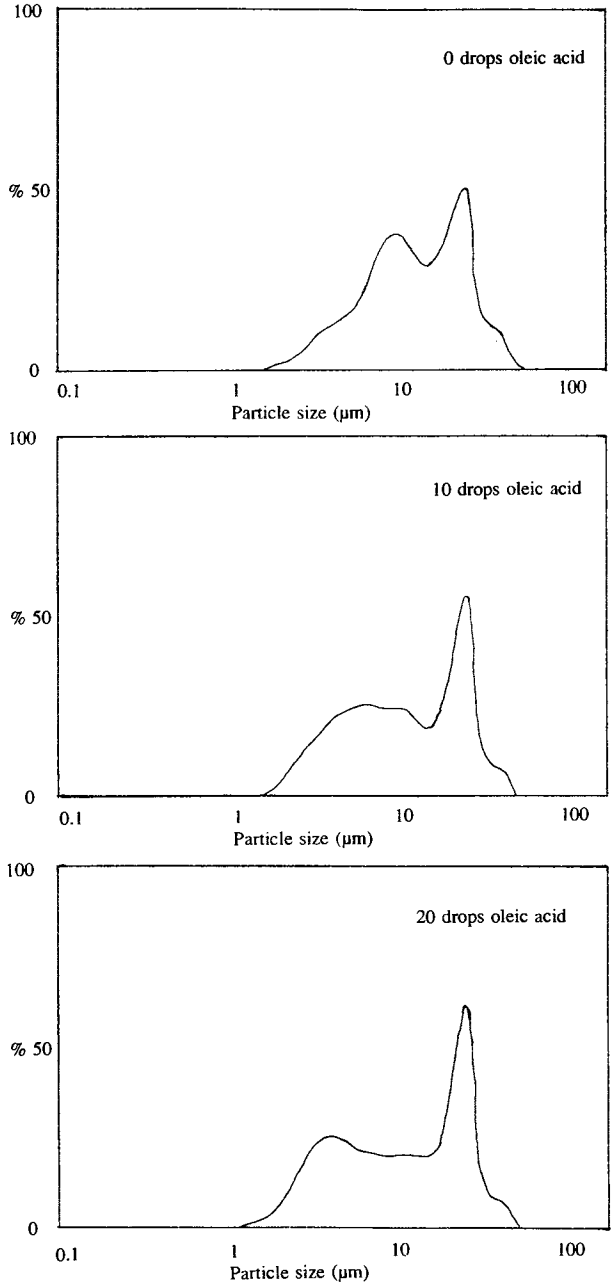

Fig. 4. The change in particle size distribution for aged dry salbutamol sulphate in Arcton 113 upon addition of 10 and 20 drops of Oleic acid. [Measured using a Malvern 2600c instrument fitted with a 63 mm lens. Y-axis represents the percentage population of particles].

should be noted that the prime particle sizes of all samples are similar (ca 3 μm), which is not surprising as the fresh sample was used to prepare the other two, but the states of aggregation vary. The recrystallised samples (78% RH and the aged dry material) however, do not readily disperse when the surfactant is added. The absence of an endothermic de-aggregation process in the 78% RH and the aged dry samples would explain the substantial difference in calorimetric response between these and the fresh material.

Thus, it can be hypothesised that the surfactant orientation differs during adsorption onto the fresh and the other

two samples, due to the difference in surface energy of the amorphous and crystalline surfaces. The changes in salbutamol surface energy will be due to the freedom of movement of molecules in the partially amorphous fresh sample allowing a minimisation of interfacial free energy. From the calorimetric adsorption data (Figure 2) it can be concluded that significant adsorption occurs to the recrystallised drug (78% RH and aged dry material), but this does not lead to de-aggregation (Figures 3 and 4). For the adsorption data onto the 78% RH sample, values are more exothermic showing that the presence of water on the crystalline surface alters the interaction with the surfactant, and furthermore, the particles with adsorbed water show almost no tendency to de-aggregate (Figure 4).

Span 85

The data for adsorption of Span 85 onto the fresh and aged dry samples of salbutamol sulphate (Figure 5) is similar to that observed for oleic acid (Figure 2). The only major difference is that the data for the 78% RH sample is more exothermic for Span 85 than for oleic acid. The particle sizing data for the 78% data (Figure 6) shows that the 78% RH sample, rather than de-aggregating upon addition of Span 85, actually results in a size increase. This further aggregation fits with the hypothesis presented above and would explain the larger exothermic response.

GENERAL DISCUSSION

It is known from practical experience that changes in milling and changes in water content affect the physical stability of inhalation aerosol systems. However, the difficulties encountered in studying such systems have resulted in a lack of experimental data appearing in the literature. For example, we cannot find any published adsorption isotherm data for surfactants onto solids in real or model inhalation aerosol suspensions. The data presented here are to the best of our knowledge the first study to show measurements of the surfactant adsorption process in a CFC and are consequently also the first to show adsorption onto physically different surfaces of the same chemical entity.

The difference in the responses demonstrate that changes in processing and storage history cause measurable changes in interfacial behaviour in non-aqueous suspensions. This provides a new approach to studies in this complex field and as such constitutes a significant stage towards the understanding of such systems.

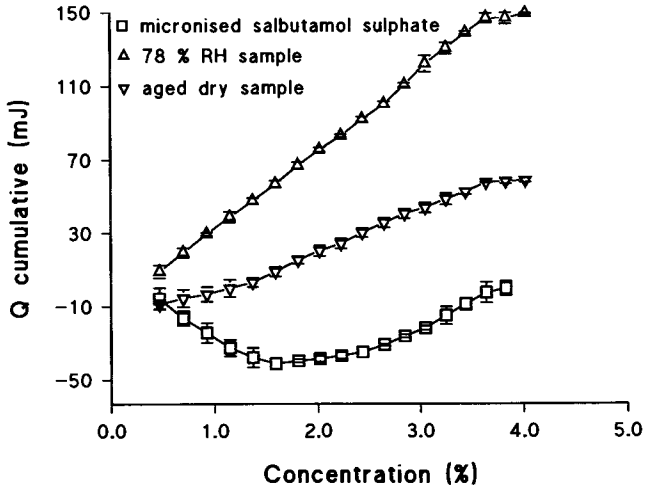

Fig. 5. The cumulative titration plot for the adsorption of 0.37 M Span 85 to micronised salbutamol sulphate, 78% RH salbutamol sulphate and aged dry salbutamol sulphate. [X-axis represents the percentage concentration of surfactant in the calorimeter cell after each addition of the concentrated surfactant solution. Y-axis represents the sum of the heat output for each individual addition in milliJoules (mJ)].

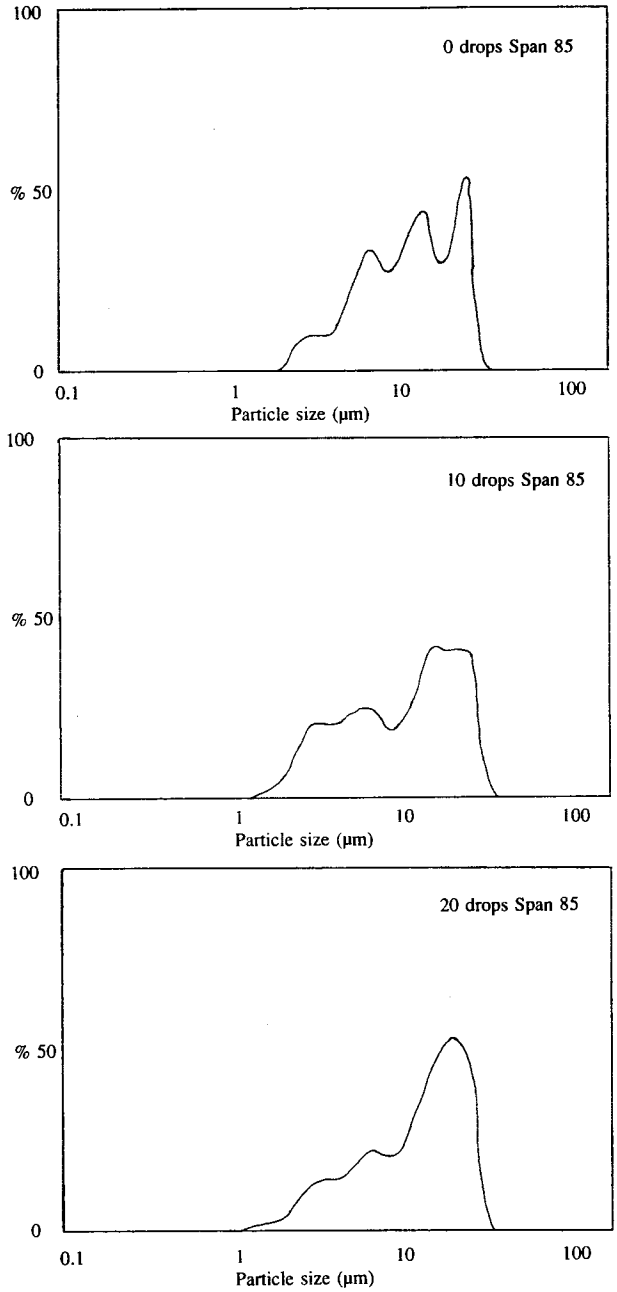

Fig. 6. The change in particle size distribution for 78% RH salbutamol sulphate in Arcton 113 upon addition of 10 and 20 drops of Span 85. [Measured using a Malvern 2600c instrument fitted with a 63 mm lens. Y-axis represents the percentage population of particles].

Both changes in powder crystallinity (due to process and storage changes) and changes in the level of water content of the powder had substantial impact on the nature of the surfactant-drug-liquid interactions. This was true both in the calorimetric data and in the sizing data.

CONCLUSIONS

Titration isothermal microcalorimetry offers a suitable way of probing the complex series of interactions which occur following liquid-surfactant-drug interaction in model inhalation aerosol systems. The possibility of measuring complex interactions in such difficult systems opens up the prospect of understanding and thus optimising such formulations. Whilst this work is for a non-polar model system (being the best model available which is liquid at room temperature) it can be envisaged that the effects of changes in powder crystallinity will be equally significant for other non-polar suspension systems.

ACKNOWLEDGMENTS

The authors wish to acknowledge the Wellcome Trust for funding the purchase of the microcalorimeter and for support to PMB. Thanks are also due to 3M Health Care for kindly donating micronised salbutamol sulphate.

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