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Solution and adsorption behaviour of lecithin surfactants in CFC suspensions: a light scattering study in aerosol propellants

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Abstract

The behaviour of the lecithin Epikuron 200 was studied in solution in a chlorofluorocarbon (CFC) aerosol propellant (P113) using light scattering to determine the micellar structure as a function of temperature. At room temperature Epikuron 200 formed micelles with a radius of approximately 25 nm. The radius increased with decreasing temperature until a phase boundary was reached at 15–16°C, below which the micellar radius increased rapidly to 150–250 nm. This was accompanied by a large increase in the viscosity and turbidity of the solution. We consider that this behaviour is due to the formation of large wormlike micelles similar to those reported for lecithin in cyclohexane. The adsorption of Epikuron 200 on salbutamol sulphate was measured over this temperature range. The adsorbed amount of Epikuron 200 increased with decreasing temperature, and the hemimicelle concentration decreased rapidly at a temperature corresponding to the threshold for the formation of wormlike micelles. It is likely that these structures do form in CFC-MDI systems (particularly during cold-fill formulation), and that the structure of the adsorbed surfactant layer changes at low temperature. This may have implications for the formulation of stable aerosol suspensions.

Keywords: Aerosol; Metered dose inhaler; Lecithin; Hemimicelle; Light scattering; Wormlike micelle

1. Introduction

The metered dose inhaler (MDI) is one of the most popular methods for delivering drugs directly to the lungs via the inhaled route. In suspension formulations the drug is finely divided by fluid energy milling and suspended in the liquefied propellant, so that a reproducible dose is administered when the valve ejects a metered volume of the suspension.

In order for the device to operate correctly it is important that the drug is suspended uniformly in the propellant, in a state which is easily dispersed by the shear forces generated as the propellant

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vaporises. In order to achieve such a suspension it may be necessary to incorporate a propellant-soluble surfactant in the mixture, or the particles will form tightly bound aggregates due to attractive Van der Waals forces between them. A number of surfactants are in common use, with one of the most popular being lecithin, which is a complex mixture of phospholipids derived from egg yolk or soya beans.

The behaviour of lecithin in aqueous systems is well-understood; its colloid chemistry has been studied for many years, since it forms vesicular systems which can be used as model cell membranes. Its behaviour as a surfactant and emulsifier has also been widely investigated since it is one of the few materials which can be used as a surfactant in large volume parenterals, and is used for the preparation of intravenous fat emulsions (Washington, 1990). However, in non-aqueous systems its behaviour is much less well understood. Previous zeta potential measurements from this group (Sidhu et al., 1993) established that it behaves as a charge-stabilising surfactant in lactose and salbutamol dispersions, despite the low dielectric constant of the propellant.

We had previously observed that lecithins dissolved in aerosol propellants displayed a range of unusual behaviour, in particular becoming turbid and viscous at low temperatures. In this paper we wished to study the solution-phase state of lecithin in an aerosol propellant using light scattering, and the effects of the behaviour in solution on the adsorption on a typical micronised drug (salbutamol sulphate). This was performed over a range of temperatures, since it is often necessary to chill the propellant when the cold-fill method is used to prepare the MDI suspensions. In order to do this we had to devise methods whereby the light scattering of the solution could be measured under pressure and over a temperature range 10–25°C.

2. Experimental section

2.1. Materials

Salbutamol sulphate (micronised by fluid energy milling) and propellant 113 were supplied by 3M Health Care, UK. Lecithin E200 was obtained from Lucas–Meyer (Hamburg) and stored frozen under nitrogen until required. Epikuron 200 is a purified lecithin consisting of approximately 95% phosphatidylcholine with a relatively low level of acidic phospholipids; in aqueous media it is considered to be too weakly charged to be a powerful emulsifier but is widely used in CFC-MDI formulations.

2.2. Absorption measurements

Absorption of Epikuron 200 on salbutamol sulphate was measured as described previously (Washington, 1990). Briefly, suspensions of salbutamol sulphate containing lecithin were equilibrated in sealed containers, filtered, and the supernatant assayed for unadsorbed lecithin using Stewart's colorimetric assay (Stewart, 1980).

2.3. Design of PCS pressure cell

In order to perform the light scattering measurements in volatile solvents we devised and built the cell shown in Fig. 1. It consists of a standard 1-cm OD quartz cylindrical cell which is bonded using epoxy resin into a stainless steel flange; the upper part of the flange carries a conventional non-metering valve through which the cell can be filled. A viton O-ring seal between the two halves of the flange ensures that the epoxy joint (which carries the pressure load) is not exposed to propellant. The lower end of the tube is epoxied into a stainless steel end cap which serves to support the flat bottom of the tube against the pressure load. The cell was tested to 14 bar by filing with propellant 12 and immersing in a water bath at 40°C for 30 min.

2.4. Light scattering measurements

Light scattering measurements were performed using a Malvern 4700 photon correlation spectrometer equipped with a 120 mW air-cooled

argon laser and 64 channel correlator. Samples of lecithin dissolved in propellant were filled into the pressure cell and the temperature was controlled to ± 1°C using a water recirculator (Grant Instruments) attached to the PCS cell bath. Angle scans were gathered over the range 10–140°. Since the instrument alignment is critical when performing angle scans, scattering from toluene was regularly measured to confirm proper operation of the instrument.

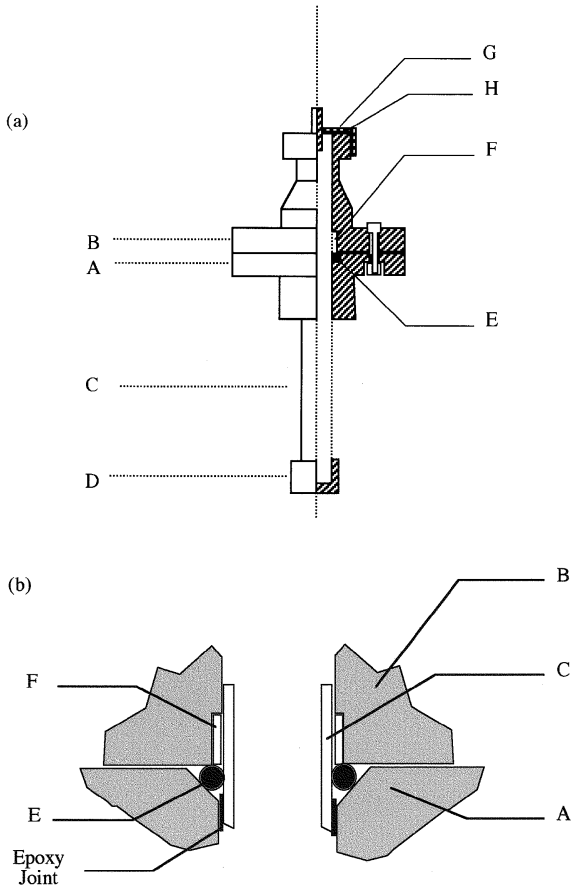

Fig. 1. Diagram of pressurised light scattering cell. (a) complete cell; (b) detail of seal. A, Lower flange; B, Upper flange; C, Cylindrical quartz cell; D, Cell end cap; E, Main seal (Viton); F, Softening ring (PTFE); G, Inlet valve; H, Valve seal.

2.5. Data analysis

A number of models are available for data fitting depending on the form of the scattering object. The normal justification for selecting a specific structural model is that it provides a better fit than other models. However this may not always be appropriate since a complex model with a large number of variable parameters will often give a better fit than a simple model, even though it may be physically incorrect. In the present studies we chose the Guinier model (Brasher and Kaler, 1996); this allows us to extract a radius of gyration whose value depends on the shape of the structure. In this model the scattering intensity $I(Q)$ scattered from spheres is given by:

$$\mathrm{Ln}(I(Q)) = -Q^2R_g^2/3 + K$$

$$Q = (4\pi/\lambda)\sin\theta/2$$

where R_g is the radius of gyration and K is a constant. If the particles are rods, the scattering intensity is given by:

$$\mathrm{Ln}(Q\ I(Q)) = -Q^2R_c^2/2 + K$$

Where R_c is the cross-sectional radius of gyration, which is related to the cylindrical radius R by:

$$R_c = \sqrt{2}R$$

3. Results

Fig. 2 shows the scattering plots from lecithin in P113 at 25°C as a function of lecithin concentration in the range 0.1–0.5% w/v. Fig. 3 shows the values of R_g as a function of lecithin concentration assuming that the micelle is spherical. R_g increased from 10 nm in 0.1% lecithin solution to 33 nm in 0.5% solution.

Fig. 4 shows Guinier plots for lecithin at 0.5% concentration in P113 as a function of temperature in the range 13–25°C. As the temperature was increased, the absolute scattering intensity and R_c both increased gradually up to a critical temperature of 15–16°C. At this point the solution underwent a phase change to a viscous sys-

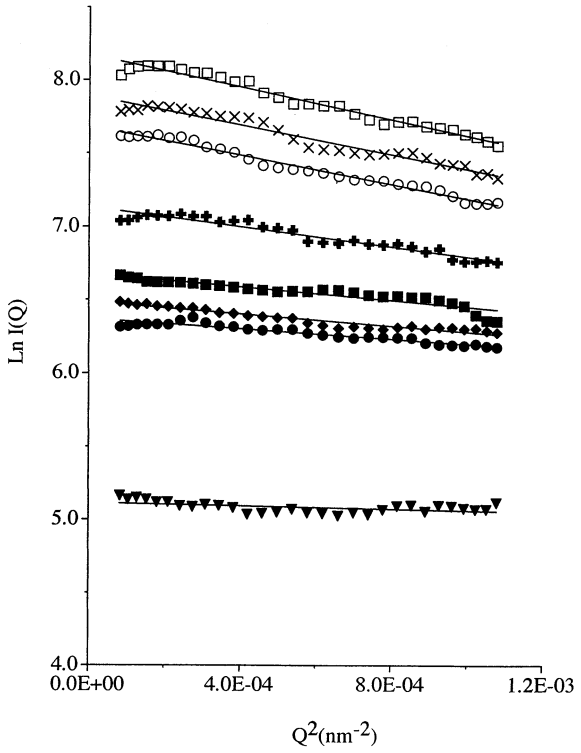

Fig. 2. Guinier plots for Epikuron 200 in propellant 113 at 25°C as a function of concentration. ▼ 0.1%, ● 0.2%, ◆ 0.25%, ■ 0.3%, + 0.35%, ○ 0.4%, X 0.45%, □ 0.5%.

tem and the character of the scattering changed significantly. The micellar radius increased rapidly from 24 nm at 24°C to 243 nm at 13°C.

Fig. 5 shows the adsorption of lecithin on micronised salbutamol sulphate from P113 over the temperature range 5–25°C, using the methods and assays previously described by us (Malik et al., 1999). The adsorbed amount increases with decreasing temperature. The corresponding hemimicelle concentrations (Fig. 6) decrease rapidly with decreasing temperature by nearly an order of magnitude over the temperature range 5–25°C.

4. Discussion

At room temperature the radius of the micelles is typical to that of a small inverse micellar system. At this temperature the shape is probably spherical or ellipsoidal, but since the micelles are much smaller than the wavelength of light it is not possible to distinguish between these structures, and the value of R_g obtained is either that for a sphere or an average value for an ellipsoid. In this region the Guinier sphere model is a good fit for the data, and there is no apparent influence of a structure factor, suggesting that the micelles are relatively non-interacting.

As the lecithin passes through the phase boundary the micellar radius increases dramatically. The turbidity of the solution indicates that structures are forming which are comparable in size to the wavelength of light. The Guinier plots become strongly curved, suggesting that scattering is occurring from different structures on a range of length scales. The initial slope of the Guinier plot increases to 150–200 nm, but as we explain below, it is unlikely that this is due to the formation of spherical micelles, but rather to their elon-

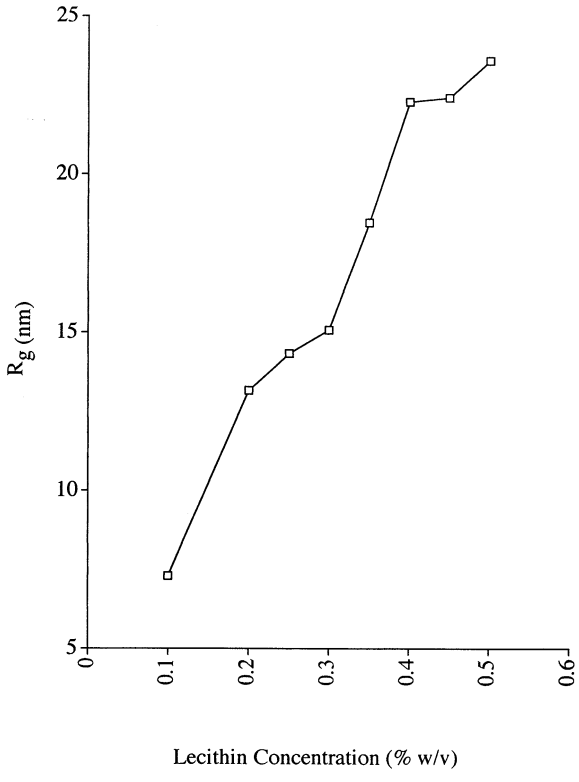

Fig. 3. Radius of gyration for Epikuron 200 in propellant 113 at 25°C as a function of concentration.

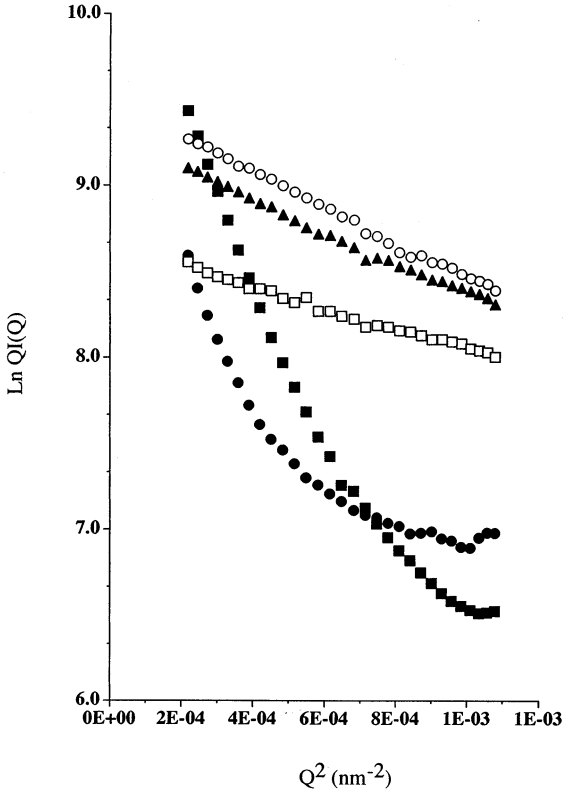

Fig. 4. Guinier plots for 0.5% Epikuron 200 in propellant 113 as a function of temperature. □ 24.8°C, ▲ 19.9°C, ○ 16.9°C, ● 14.9°C, ■ 13.0°C.

gation into cylinders. The slopes of the plots at higher Q are similar to those from the small micelles formed at higher temperatures, and probably represent the radius of the cylindrical structures. Unfortunately it was not possible to obtain an accurate value for R_g in this region owing to the limited Q range available. At lower Q the scattering originates from larger structures and is due to the extension along the rod axis. Schurtenberger et al. (1990), Schurtenberger (1996) have reported similar behaviour in solutions of soya lecithin in iso-octane and cyclohexane, and considers the rods to be flexible, so that the Guinier radius in this regime probably represents the radius of gyration of a flexible chain in much the same way as that of a polymer.

The extent of adsorption of lecithin on to solid salbutamol sulphate increased slightly with decreasing temperature. We have previously demonstrated that lecithins adsorb from propellant solution via inverse hemimicelle formation (Malik et al., 1999), and it is unlikely that the increase in adsorbed amount could be accommodated by the formation of multilayers, but is more probably due to an increased packing density at the interface. This implies that the strength of the interaction between lecithin and P113 decreases with increasing temperature, so that the interaction between the surfactant molecules increases, making the adsorbed layer more compact. The hemimicelle concentration is strongly temperature dependent and falls rapidly between 10 and 15°C. This is the temperature region in which the micellar structure also changes, so it is possible that this also corresponds to a change in the structure of the adsorbed micellar layer. In solution the

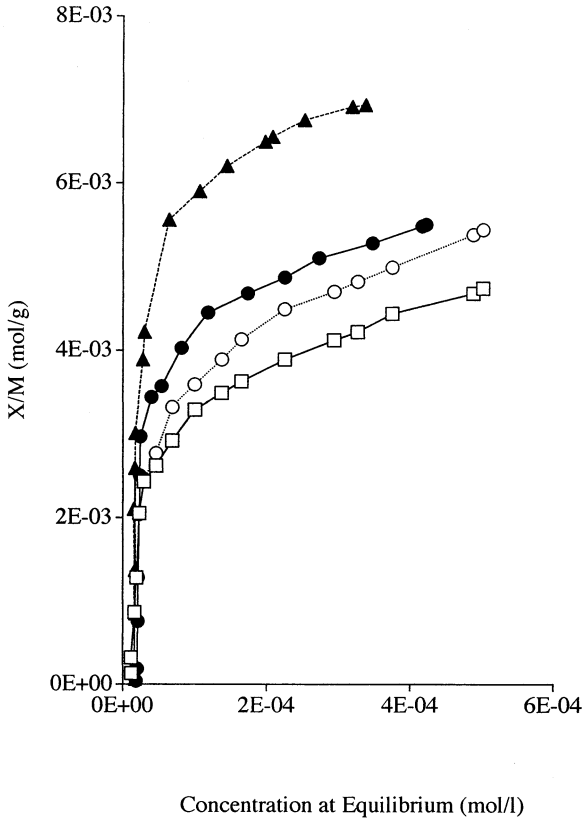

Fig. 5. Adsorption of Epikuron 200 on to micronised Salbutamol sulphate as a function of temperature. ▲ 5°C, ● 10°C, ○ 16°C, □ 25°C.

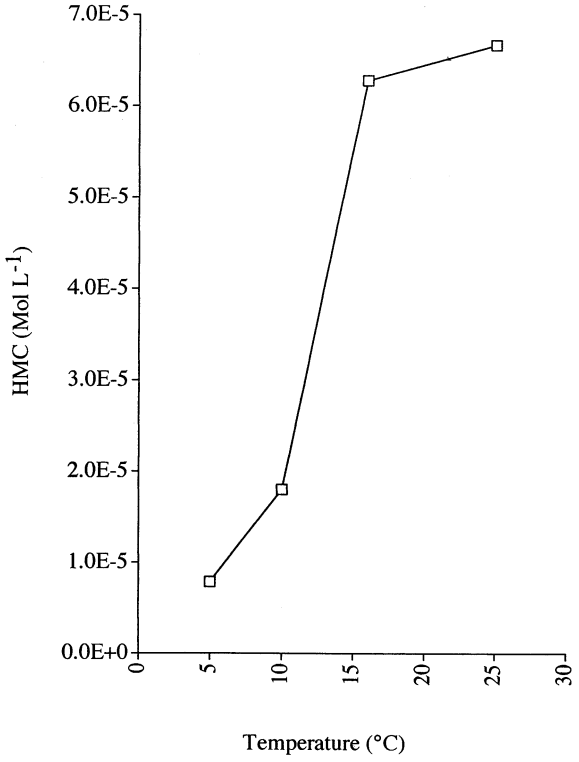

Fig. 6. Hemimicelle concentration of Epikuron 200 on micronised Salbutamol sulphate as a function of temperature.

relatively increased interactions between the lecithin molecules leads to the phase change to the cylindrical phase. This is not unreasonable as increased micellar aggregation cannot lead to a continuing increase in spherical radius without the formation of a central cavity. The micelles have no choice but to form a non-spherical structure, which can either be rodlike or laminar, depending on the packing, which is dictated by the relative geometries of the hydrophilic and hydrophobic portions of the surfactant (Clint, 1992).

There is an interesting analogy between the behaviour of lecithin in low dielectric solvents and the behaviour of many non-ionic species in aqueous solutions. Lecithins have HLB numbers of 8–14 depending on their exact composition; analogous poly(ethylene oxide) based non-ionics with a similar HLB range would include the well-studied Pluronic P85 and a number of analogous species of similar HLB. The interactions of poly(ethylene oxide) with water become weaker with 'increasing' temperature owing to the weakening of hydrogen bonds, which ultimately leads to precipitation at a cloud point temperature. However before the cloud point is reached, the micelles undergo a similar transition to a rodlike form with an increase in viscosity and turbidity (Mortensen and Pedersen, 1993; Schillen et al., 1994).

The formation of wormlike micelles in iso-octane was found to be sensitive to the concentration of water, and the micelles were able to absorb several moles of water per mole of lecithin (Scartazzini and Luisi, 1988). Evans et al. (1990) found that the micelle became increasingly ellipsoidal as the water fraction was increased. In the present studies we have not added water and the residual concentration of water in our samples was less than 1 ppm due to the extremely low solubility of water in P113. The lecithin/P113 solutions did not readily solubilise added water to form a single-phase system even after several days equilibration, although we hope to investigate the importance of water in future studies.

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