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The Effect of Surfactant and Solid Phase Concentration on Drug Aggregates in Model Aerosol Propellent Suspensions

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Abstract

The effect of increasing solid phase concentration on the morphology and flocculation rate of model aerosol suspensions has been investigated. Suspensions of micronized salbutamol sulphate and lactose in trichlorotrifluoroethane (P113) were studied under conditions of increasing shear stress. By use of image analysis techniques, measurement of aggregate size, fractal dimension and rate of aggregation was performed. The effect of the surfactant sorbitan monooleate on morphology and flocculation rate was also studied.

Increased solid phase concentration caused an increase in the rate of aggregation and average aggregate size at a given value of shear stress. Surfactant addition retarded the aggregation rate, and caused a shift from a diffusion-limited cluster aggregation to a reaction-limited cluster aggregation mechanism. The aggregate profiles showed a corresponding change from rugged and crenellated without surfactant, to increasingly smooth and Euclidian with increasing surfactant concentration. The morphological changes were characterized by a decrease in the average boundary fractal dimension which also correlated well with the corresponding reduction in aggregation rate.

Since the signing of the Montreal Protocol in 1986, the changeover from chlorofluorocarbon (CFC) to non chlorine-containing propellants is becoming a pressing issue in the field of inhalation technology. In particular the shift to use of chlorine-free propellants in metered-dose inhalers (MDI's), used for the treatment of respiratory disorders, has associated difficulties. The therapeutic drug administered by the MDI is normally a finely micronized polar solid; it therefore has a tendency to form a flocculated suspension in low-polarity CFC propellants, such as those in current use. For optimum MDI performance the drug should be delivered in a uniform dose of the correct size range to allow penetration of the lung. A stable, well-dispersed suspension, or easily dispersible suspension, is required to meet these criteria. Non-ionic surfactants such as lecithin, oleic acid or sorbitan tri- and mono-oleate (Span 85 and Span 80 respectively) are therefore normally added to stabilize the formulation. Unfortunately these surfactants are insoluble in the proposed chlorine-free alternative propellants such as 1,1,1,2-tetrafluoroethane (P134a), since they are more polar in nature (Byron et al 1994) than the CFC mixtures they are intended to replace.

The re-formulation of MDI suspensions is currently reliant on predominantly macroscopic techniques such as measurement of sediment ratios, respirable fractions and flocculation times. In this paper we present a complementary microscopic technique that looks at the size and morphology of individual aggregates in suspension under conditions of increasing shear stress. In particular we have investigated the effect of surfactant and solid phase concentration on the size, morphology and aggregation kinetics of model suspensions in CFC propellants.

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Materials and Methods

Rheometer

Model suspensions of either lactose or salbutamol sulphate in 1,1,2-trichlorotrifluorethane (P113) were used to study aggregation behaviour. All measurements were taken using a modified Deer rheometer (Integrated Petronic Instruments, London, UK) that allowed imaging of suspensions under conditions of variable shear stress. The configuration and validation of the apparatus is described in detail elsewhere (Bower et al 1995).

Aggregation rate measurements

Measurement of the rate of flocculation in model suspensions of the materials mentioned above is hindered by either gravitational settling or creaming, since the densities of solid and liquid are unequal. This makes aggregate size difficult to determine since it is hard to resolve individual particles within the uniform sediment, or cream layer formed. To avoid this problem the suspension was subjected to a continuously variable shear stress in a rheometer, which kept the flocs in suspension, as well as providing a controllable means of applying a small shear field.

For determination of the aggregation rate the suspension was subjected to a shear stress sufficient to ensure that all aggregates were strongly disrupted (for suspensions of low solid phase concentration $4\,N\,m^{-2}$ was sufficient) and only individual particles and small aggregates were present. The applied shear stress was then instantaneously reduced to $2{\cdot}5\,N\,m^{-2}$ and images then captured every 4 s. The lower value of shear stress was chosen to maximize the number of

aggregates of a reasonable size per image to optimize the measurement precision. Rapid reduction of the applied shear stress gave a reproducibly decaying shear field by utilizing the electromagnetic braking effect of the induction motor driving the rheometer. As soon as the applied shear stress was reduced, floc size increased as particle aggregation was no longer disrupted by the applied shear stress. The captured images were then analysed to determine the average aggregate size. The data from this procedure enabled a graph of aggregate size vs time to be plotted. To calculate the initial rate of size increase of the aggregates, the first five data points were then fitted with a third-order polynomial, since this gave a good approximation of the aggregate growth at small times. Calculation of the growth rate was then readily obtained from the first differential of this polynomial with respect to time. The initial rate was not sensitive to the order of the polynomial used.

Materials

Model suspensions of 0·08% w/w lactose or 0·04% w/w salbutamol sulphate in 1,1,2-trichlorotrifluoroethane (Propellant 113, Aldrich Chemical Co. Ltd.) were dispersed by ultrasonication (Decon FS100 sonic bath) for 10 min before use. The lactose and salbutamol used in these studies were milled to a volume mean diameter of ~3 μm (Malvern 2600 diffraction sizer) by fluid-energy milling. The surfactant sorbitan monooleate (Span 80) was purchased from Sigma and dissolved in the propellant before addition of the solid phase.

Results

Size with increasing shear stress

To study solid phase concentration effects, the proportion of micronized lactose in P113 suspensions was varied and the average aggregate size measured at constant shear stress. The aggregates formed at higher solid phase concentrations required higher shear stress to disperse, and the average size at a given shear stress increased with increasing disperse phase fraction. Fig. 1 shows the effect of increasing the amount of lactose in suspension on the size/shear relationships.

A similar trend was found with suspensions of salbutamol sulphate in P113 (Fig. 2). Salbutamol is less dense than lactose and has a higher phase volume; therefore the solid-phase concentrations used had to be reduced relative to those of lactose to avoid formation of a continuous floc network. This was undesirable since the formation of one continuous aggregate made it impossible to resolve discrete aggregates for measurement. Even with this reduction of concentration the average size of the salbutamol aggregates was larger than that of the equivalent lactose aggregates at the same shear stress. The increase in the aggregate size was most pronounced at shear stresses below 1 N m^{-2}; above this value increasing the proportion of solid caused a much smaller size increase.

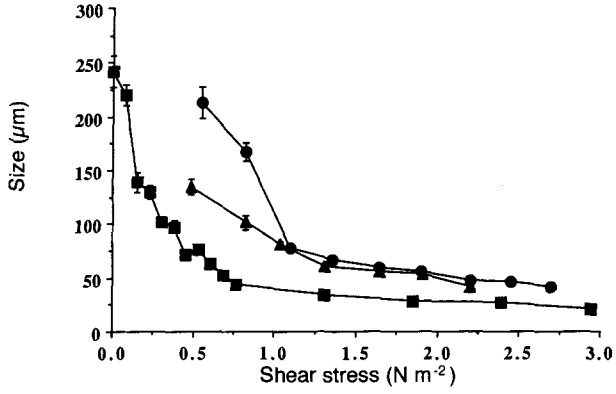

FIG. 2. Effect of increasing shear stress on average size of salbutamol sulphate aggregates in P113; (■) 0·04% w/w, (▲) 0·08% w/w, (●) 0·10% w/w salbutamol sulphate.

Binding strength of aggregates

Figs 1 and 2 show that suspensions of 0·08% w/w lactose and 0·04% w/w salbutamol had similar aggregate sizes of around 40 μm at a shear stress of 1 N m^{-2}. To determine which aggregates had the higher binding strength, both suspensions were subjected to higher shear stress. Fig. 3 shows the size variation with increasing shear for the two suspensions; up to a stress of ~3 N m^{-2} the aggregates showed a similar size/shear relationship. The salbutamol aggregates were reduced to a minimum size of around 8 μm by a shear stress of 4 N m^{-2}. No size measurement was

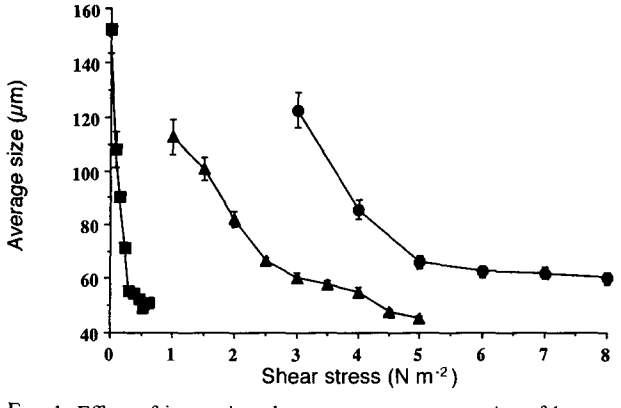

FIG. 1. Effect of increasing shear stress on average size of lactose aggregates in P113; (■) 0·08% w/w, (▲) 0·16% w/w, (●) 0·24% w/w lactose.

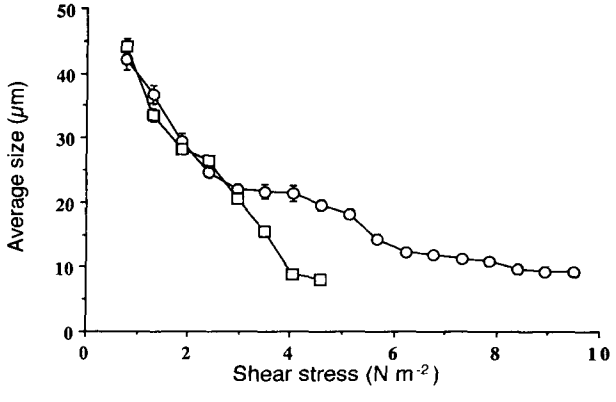

FIG. 3. Effect of higher shear stress on average aggregate size in 0·04% w/w salbutamol sulphate (□) and 0·08% w/w lactose (○) suspensions in P113.

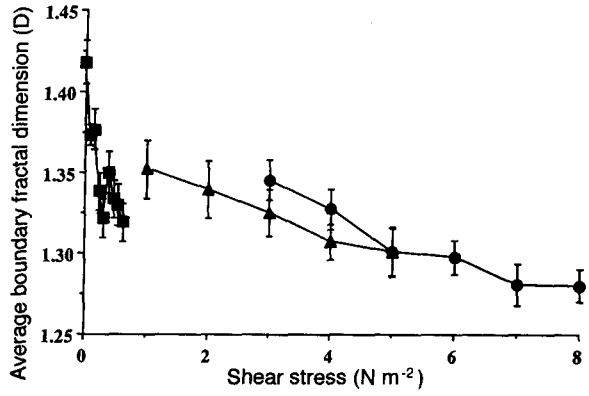

FIG. 4. Effect of increasing shear stress on lactose aggregate morphology in P113 suspensions; (■) 0·08% w/w, (▲) 0·16% w/w, (●) 0·24% w/w lactose.

possible at higher shear rates since the combination of high rotational velocity and number of particles increased the light scattering to such an extent that individual aggregates could not be clearly resolved. A shear stress of 8 N m^{-2} was needed to achieve the same size reduction of the lactose aggregates, indicating the greater binding strength of lactose compared to salbutamol.

Morphology with increasing shear stress

Fig. 4 shows the variation of the average boundary fractal dimension of lactose aggregates as a function of shear stress. At a solid phase concentration of 0·08% w/w the aggregates were compacted, and there was a consequent smoothing of the boundary by shear stresses below 1 N m^{-2}, as indicated by the reduction of boundary fractal dimension from 1·42 to 1·32. As the concentration of lactose was increased, progressively higher shear stress was required to achieve the same reduction in fractal dimension: 3 N m^{-2} at 0.16% w/w and 4 N m^{-2} at 0·24% w/w lactose.

As with the size measurements it was not possible to calculate data points at low shear for the 0·16 and 0·24% w/w lactose concentrations due to aggregate gelation. Similarly D values for 0·08% w/w lactose aggregates could not be measured at shear stresses above 1 N m^{-2} since the aggregates were too small to provide a sufficient number of boundary points.

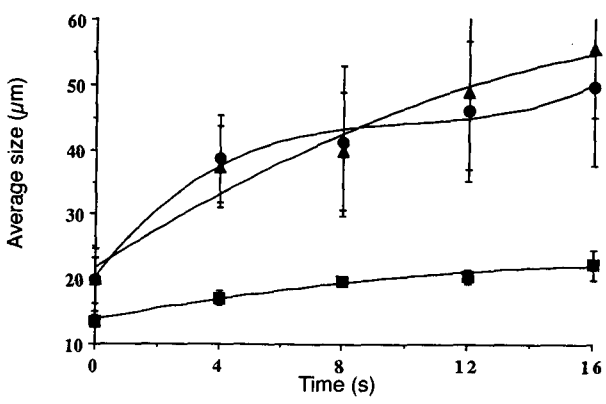

FIG. 5. Average size of lactose aggregates in P113 after reduction in applied shear stress at t = 0. (■) 0·08% w/w, (▲) 0·16% w/w, (●) 0·24% w/w lactose. The solid lines are third order polynomials.

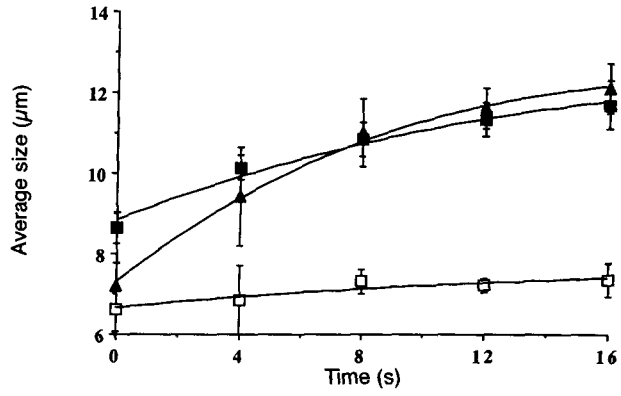

FIG. 6. Average size of salbutamol sulphate aggregates in P113 after reduction in applied shear stress at t = 0. (■) 0·04% w/w, (▲) 0·08% w/w salbutamol and (□) 0·04% w/w salbutamol sulphate + 0·05% w/w Span 80. The solid lines are third order polynomials.

Aggregation rate

Fig. 5 shows the size increase with time of lactose aggregates in the rapid shear reduction experiment. Increasing the proportion of lactose in the suspension increased the initial aggregation rate from 1·3 to 6·4 μm s^{-1} for 0·08 and 0·24% w/w lactose in P113, respectively. Fig. 6 is a similar plot for salbutamol sulphate suspensions. The aggregation rates of salbutamol were much slower relative to lactose suspensions; this can be seen initially from the aggregate size vs time; 0·08% w/w lactose aggregates had an average size of ~50 μm after 16 s, 0·08% w/w salbutamol aggregates had an average size of only ~12 μm. The calculated rates of size increase 0·04 and 0·08% w/w salbutamol in P113 were 0·3 and 0·6 μm s^{-1} respectively. All rates of increase are quoted as the rate of increase of the projected area equivalent diameter of the aggregate.

The lower data set in Fig. 6 shows the effect of addition of 0·05% w/w Span 80 to the 0·08% w/w salbutamol suspension. It is clear that surfactant addition reduced the aggregation rate considerably, to a measured rate of 0·08 μm s^{-1}.

Fig. 7 shows the effect of Span 80 on 0·08% w/w lactose in P113 suspensions. As with the salbutamol suspension, the aggregation rate was decreased by increasing surfactant concentrations. The calculated aggregation rates for the

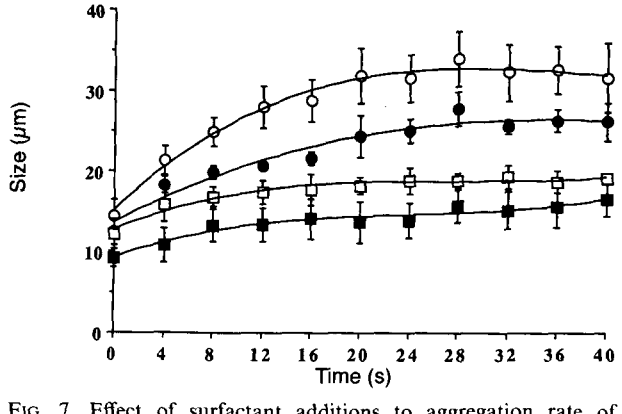

FIG. 7. Effect of surfactant additions to aggregation rate of 0·08% w/w lactose in P113; (○) 0% w/w, (●) 0·0004% w/w, (□) 0·0008% w/w and (■) 0·0010% w/w Span 80. The solid lines are third order polynomials.

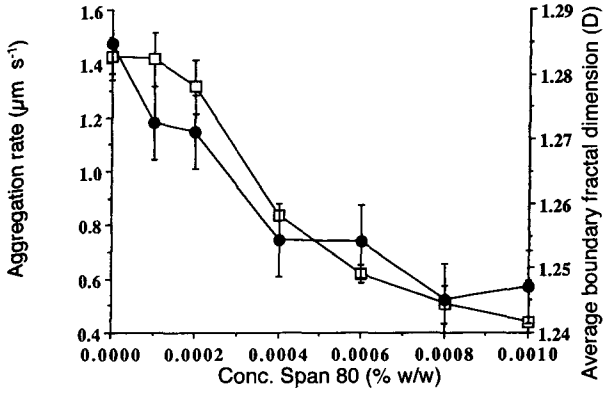

FIG. 8. The aggregation rate (□) of 0·08% w/w lactose in P113 with increasing concentrations of Span 80 and the average boundary fractal dimension (●) of the resulting aggregates.

various surfactant additions are summarized in Fig. 8, along with the average boundary fractal dimension of the aggregates in each suspension at a typical intermediate shear stress of $2{\cdot}2\,N\,m^{-2}$. The decrease in fractal dimension correlated well with the decrease in aggregation rate as the proportion of surfactant was increased.

Discussion

Solid-phase concentration effects

The results presented in Figs 1 and 2 indicate clearly that the solid phase concentration is an important factor in determining the behaviour of suspensions of polar solid in liquids of low dielectric constant. In such systems in the absence of shear, the equilibrium state involves flocculation of the solid material into large aggregates, and if the concentration is sufficiently large a single continuous aggregate will result, and so floc gelation occurs. When subjected to shear forces the system becomes a dynamic equilibrium between disruption and collision; aggregate size is reduced by shear, yielding many smaller aggregates, which may re-combine to form larger flocs which in turn are disrupted when they exceed a limiting size (Torres et al 1991). In this way an equilibrium aggregate size is maintained. Increasing the amount of solid matter present makes the probability of collision more likely; more collisions will mean an increase in the number of aggregates formed; assuming the sticking probability remains constant. If the shear stress remains constant the disruptive force is unchanged, so increasing the disperse phase fraction causes the equilibrium to be shifted towards aggregate formation rather than disruption. The average size of aggregates would therefore be expected to increase with the solid phase concentration as indeed Figs 1 and 2 show, as also demonstrated previously (Reich & Vold 1959; Thomas 1961; Michaels & Bolger 1962).

The size of aggregates in Figs 1 and 2 show a rapid initial decrease followed by a more gradual decrease at higher shear stresses. This may be attributed to the instantaneous disruption of the few large aggregates present initially by liquid shear stress, which causes the rapid decrease in size. This creates a large number of aggregates of various sizes and therefore the additional mechanism of kinetic breakup by the shear due to collisions with other flocs (Sonntag & Russel 1985) becomes important. It is difficult to assign a single yield stress which defines the force required for aggregate disruption, since the shear experienced by flocs in suspension is unlikely to be equal to the applied shear stress. We may use the change of gradient in the shear/size graphs to give an order of magnitude estimate of the yield stress required to break the weak links between flocs by purely liquid shear stress. This gives values of around $0{\cdot}25$–$5{\cdot}0\,N\,m^{-2}$ for the lactose suspensions in Fig. 1 and around $0{\cdot}75$–$1{\cdot}25\,N\,m^{-2}$ for the salbutamol sulphate suspensions of Fig. 2. These values compare well with theoretically calculated Bingham yield values of around $0{\cdot}1$–$1\,N\,m^{-2}$ for theoretical aggregates by Bagster & Tomi (1974). An alternative interpretation is that increasing shear stresses cause progressively smaller flocs to be broken, and thus the rate of decrease of size reflects the distribution of floc sizes. Thus if there were few large aggregates, the shear would have to be relatively large to cause their disruption, while a distribution containing many larger flocs would be rapidly broken at lower shear stresses. It is evident that both binding strength and floc size contribute to the shape of the curves obtained, and it is unlikely that a more detailed discussion can be made until a theoretical model for the behaviour of aggregates in a shear field is employed.

Solid-phase polarity effect

Binding strength of aggregates is not expected to be a function of the solid-phase volume. However the nature of the suspended solid is expected to influence the strength of interparticle bonds. Fig. 3 illustrates the greater binding strength of lactose aggregates compared with salbutamol sulphate aggregates in the same suspending medium. This is believed to be due to the increased polarity of lactose relative to salbutamol sulphate. It is energetically favourable to remove a polar moiety from a non polar environment since it disrupts liquid-liquid interaction, which in this case is stronger than the liquid-surface interaction or the surface-surface interaction. The more polar the solid the more unfavourable the liquid-surface interaction becomes, so flocculation is increasingly favoured. It would appear that in liquids of low dielectric constant, such solvent forces are more important than the surface-surface forces which are predominant in more polar media such as water. We would therefore expect lactose to show a greater binding strength and aggregation rate than salbutamol, an observation confirmed by the studies of suspensions of the two materials.

Surfactant effect

The addition of surfactant further modifies interparticle forces and stabilizes the suspensions; this may be due to increased charge stabilization or steric stabilization of the solid particles (Heller & Pugh 1960; Pugh et al 1983). Increasing the repulsive forces reduces the rate of aggregation and allows particle re-arrangement once aggregates are formed. Aggregate morphology shows a transition from rugged and convoluted to smooth and Euclidian. In terms of theoretical aggregation models the mechanism undergoes a gradual transition from diffusion-limited to reaction-limited cluster aggregation as the sticking probability is decreased, a process other workers (Broide & Cohen 1990;

Elaissari & Pefferkorn 1991; Zhou & Chu 1991; Robinson & Earnshaw 1993) have described both theoretically and experimentally.

The fact that the morphological changes can be quantified by measuring the average boundary fractal dimension offers a potential method of studying the stability of solid suspensions; since the resultant aggregate morphology will be dependent on the strength of the repulsive interparticle forces, quantifying this may give an indication of the strength of such forces and consequently the effectiveness of the surfactant. The boundary fractal dimensions obtained in Fig. 8 for the surfactant free suspension are lower than the 1·44 expected for diffusion-limited cluster aggregation but this may be accounted for by compaction due to the applied shear stress of $2{\cdot}2\,N\,m^{-2}$.

Microscopic investigations such as these provide a useful addition to the current macroscopic techniques available for formulation of stable solid/liquid suspensions, and may be of particular relevance in inhalation technology for the shift away from CFC propellants.

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