J. Pharm. Pharmacol. 1996, 48: 337–341
Received February 3, 1995
Accepted September 5, 1995

Characterization of Surfactant Effect on Aggregates in Model Aerosol Propellent Suspensions

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Abstract

A novel technique of rheometry combined with image analysis to study model aerosol suspensions used in inhalation technology has been used. The role of surfactants in the stability and aggregation of such suspensions was also investigated.

Addition of increasing concentrations of sorbitan monooleate (Span 80) to suspensions of micronized polar solids in model CFC suspensions caused marked changes in aggregate morphology and suspension stability. The aggregate behaviour was characterized in a modified constant stress rheometer by use of image analysis techniques, allowing the measurement of particle size, elongation and fractal dimension as a function of shear stress.

This method was used to study the effect of Span 80 on suspensions of lactose and salbutamol sulphate in P113. Lactose suspensions showed a gradual reduction in aggregate size, and more spherical structure, with increasing surfactant concentration. Salbutamol sulphate suspensions displayed a more prominent transition from an aggregated state to a weakly aggregated state at 0·02% w/w surfactant. Both suspensions were disaggregated by shear, the resulting fractal properties of the aggregates in shear demonstrating the increased particle mobility caused by the surfactant.

There is considerable interest in the behaviour and characterization of suspensions of fine-particles in liquid media, particularly in the field of inhalation technology where it is directly related to the performance of metered-dose inhalers. Such systems predominantly contain solid micronized drugs in suspensions of low boiling point chlorofluorocarbons (CFCs) which act as both suspending medium and propellent. It is important that the suspended drug particles are within the respirable range of ~5–10 μm for the inhaler to be effective; suspension homogeneity and redispersibility are therefore important since these systems are usually flocculated. To overcome the problem of flocculation, suspensions are stabilized by the addition of low HLB value surfactants, typically oleic acid, lecithin, sorbitan trioleate or sorbitan monooleate (Span 85 and Span 80).

Existing methods for the study of flocculated or aggregated suspensions are predominantly macroscopic, relying on the measurement of bulk properties of the mixture; for example, standard methods of assessing suspension stability include measurement of sediment height and flocculation time, both of which are empirical, giving a qualitative description of the suspension. The use of conventional rheometry to study the nature of flocculated systems has also been investigated (Sidhu et al 1993a), but is only useful for suspensions with a higher solid-phase concentration than is normally encountered in real metered-dose inhalers. Such studies allow the viscosity of the suspension as a function of shear stress to be determined; information about aggregate shape and size can only be inferred after a theoretical model system has been assumed (Mills & Snabre 1988).

The concept of a boundary fractal dimension is useful for characterizing aggregate structure, since the aggregates encountered in these systems have rugged non-Euclidian profiles that show statistical self similarity (Peitgen & Saupe 1988). By comparison with theoretical models of particle aggregation, the fractal dimension also yields information about the aggregation mechanism. Previous work using a high-pressure microscopy cell to study model non-aqueous suspensions has shown that the aggregates formed have fractal dimensions that compare well with cluster-cluster aggregation theory (Meakin 1983). Comparison of aggregates formed in suspensions of propellants with those formed in model propellant substitutes shows a relative insensitivity to variations in CFC composition (Bower et al 1995a) suggesting that the same fundamental aggregation mechanism is occurring in different suspending media. However, addition of a stabilizing surfactant modifies the aggregation mechanism, causing marked changes in aggregate morphology which may be characterized by the fractal dimension.

In this paper we combined rheometry and image analysis to observe the behaviour of such aggregated suspensions when subjected to shear forces. The effect of stabilizing surfactants on the shear behaviour of the suspensions is also investigated. Development of techniques to study surfactant effects is of particular relevance for the change-over to chlorine free propellants (HFCs) since the Span surfactants are incompatible with the more polar (Byron et al 1994) alternatives such as 1,1,1,2-tetrafluoroethane (P134a).

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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). The configuration was concentric-cylinder geometry, the sample being placed in the temperature-controlled cup and the bob lowered into the sample. An induction drive linked to a calibrated control enabled a controlled torque to be applied to the bob. To allow direct viewing of the particulate suspension, the original stainless-steel cup and bob were replaced by concentric glass cylinders of similar dimensions. Shear stress applied to the sample was continuously adjustable up to a maximum of $\sim 10\,N\,m^{-2}$.

This arrangement allowed the sample to be observed under conditions of increasing shear using a CCD colour video camera, continuous illumination being provided by transmitted light from a high power LED used to strobe the sample. The camera was then linked to a monochrome monitor to provide real-time images, and to a frame-grabber card in the Macintosh, to allow capture of colour or greyscale images for analysis. The construction and validation of this apparatus has been described in detail elsewhere (Bower et al 1995b).

Materials

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. The lactose and salbutamol used in these studies were milled to a volume mean diameter of $\sim 3\,\mu m$ (Malvern 2600 diffraction sizer) by fluid-energy milling. The surfactant sorbitan monooleate (Span 80) was purchased from Sigma.

Results

Effect of increasing concentrations of Span 80

Aggregate size. Fig. 1 shows the effect of increasing concentrations of surfactant on model suspensions of 0·04% micronized salbutamol sulphate and 0·08% micronized lactose in P113. The salbutamol sulphate being less dense, had a larger phase volume than lactose, and so less concentrated suspensions were necessary to facilitate discrete aggregate observation. The data were obtained under extremely low shear stress, sufficient only to prevent settling or creaming without significant aggregate disruption. Aggregate size was measured using the mean Ferets diameter (defined as the longest dimension of the particle) calculated from the ellipse of best fit of 500 aggregates at each surfactant concentration.

The concentration of surfactant used represents a range from 0–75% surfactant to solid phase ratio in each case, but behaviour for the two solids is notably different. Addition of increasing amounts of surfactant to lactose suspensions caused a monotonic reduction in aggregate size over the entire range of concentrations studied. In contrast, the salbutamol suspensions showed an obvious discontinuity as the surfactant concentration reached 0·02% w/w (50% surfactant/solid), following which aggregate size decreased abruptly, to a value closer to the individual particle size. Lower surfactant concentrations than 0·02% w/w had a much less marked effect on the suspension stability, causing only a slight decrease in the average size of aggregates.

Aggregate morphology. Surfactant addition not only decreased the average size, but also altered the aggregate shape, which became more compact and spherical. The data in Fig. 2 supports this observation; the elongation and boundary fractal dimension of lactose aggregates both tended to unity as the surfactant concentration was increased. The decrease in fractal dimension was due to smoothing of the aggregate boundary as the morphology became more Euclidian. Salbutamol sulphate suspensions (Fig. 3) showed the same trend with increasing surfactant concentration. Both elongation and fractal dimension showed little change below concentrations of 0·02% w/w; at higher surfactant concentrations a more pronounced change in aggregate size and fractal dimension occurred. The extreme size reduction at higher surfactant additions made calculation of fractal dimension impractical, since the boundary was vanishingly small and consequently the number of data points was limited. Calculation of the

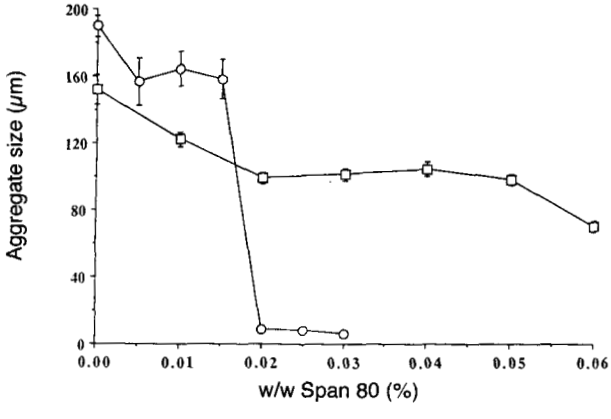

FIG. 1. Effect of increasing the surfactant (Span 80) concentration on the average aggregate size of 0·08% w/w lactose (□) and 0·04% w/w salbutamol sulphate (○) suspensions in P113.

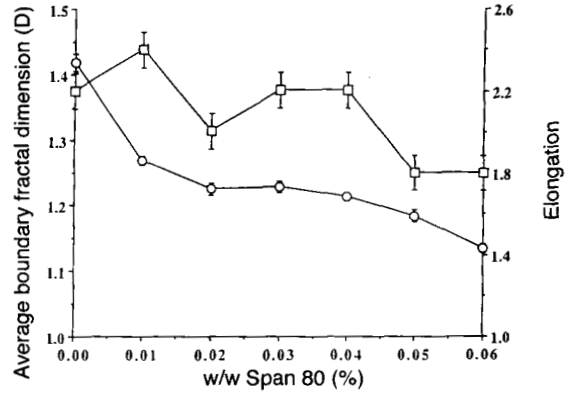

FIG. 2. Effect of increasing surfactant concentration on average boundary fractal dimension (○) and elongation (□) of 0·08% w/w lactose aggregates in P113.

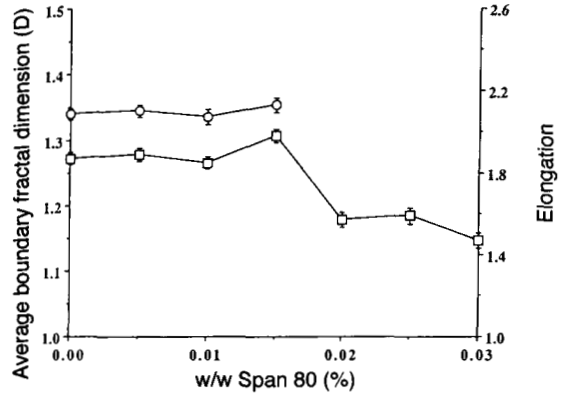

FIG. 3. Effect of increasing surfactant concentration on average boundary fractal dimension (○) and elongation (□) of 0·04% w/w salbutamol sulphate aggregates in P113.

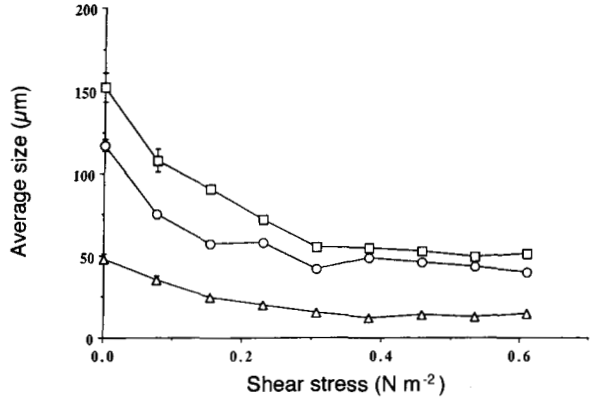

FIG. 5. Size variation of 0·08% w/w lactose in P113 with increasing shear, with; 0% w/w (○), 0·03% w/w (□) and 0·06% w/w Span 80.

average elongation was still possible however, and showed that as with lactose suspensions, morphology became more spherical with increasing quantities of surfactant present.

Effect of shear stress

Salbutamol sulphate suspensions. To investigate the behaviour of the suspension under shear stress, three suspensions of 0·04% w/w salbutamol sulphate were used: the first with no surfactant, the second with 0·015% w/w Span 80 and the third with 0·03% w/w Span 80. Fig. 4 shows the variation of average aggregate size with increasing shear stress for all three suspensions. With 0 and 0·015% w/w Span 80 the aggregate size was reduced in a monotonic manner; only slight shear stresses were needed to cause disruption. The surfactant concentration of 0·015% w/w had negligible effect on the suspension stability and interparticle binding strength; aggregates in this suspension showed an almost identical size/shear relationship to the surfactant-free suspension. The sudden increase in stability at surfactant concentrations above 0·02% w/w apparent in Figs 1 and 3 was also evident in the size/shear data of Fig. 4; the average size of the 0·03% w/w Span 80 aggregates again approached the constituent particle size at all values of shear stress.

Lactose. Suspensions of 0·08% w/w micronized lactose in P113 with equivalent surfactant/solid phase ratios to the salbutamol sulphate suspensions were observed under increasing shear stress. The surfactant had a less dramatic effect on the stability of the lactose suspensions than the salbutamol suspensions. In particular, the rapid transition from flocculated to stable behaviour at 50% surfactant/solid ratio was not observed. Surfactant effect on lactose suspensions was of a more gradual transition from flocculated to stable, making it possible to observe the intermediate effect of surfactant on aggregate morphology as the suspension approached stability. Low concentrations of Span 80 increased stability, reducing aggregate size relative to surfactant free suspension aggregates over the entire shear stress range studied. Fig. 5 shows the effect of shear on the size of lactose aggregates in the absence and presence of Span 80. A minimal shear of 0·2 N m^{-2} was required to cause reduction of aggregate size to around half of the initial value. At higher shear stress the average size tended to an equilibrium value of about 50 μm for the surfactant free suspension, and progressively lower asymptotes with the addition of increasing amounts of surfactant.

Fig. 6 shows that the average boundary fractal dimension of aggregates showed a similar reduction with shear as shown by the aggregate sizes, but there was a marked difference in the behaviour of the suspension with 0·03% w/w surfactant present. Both suspensions showed a

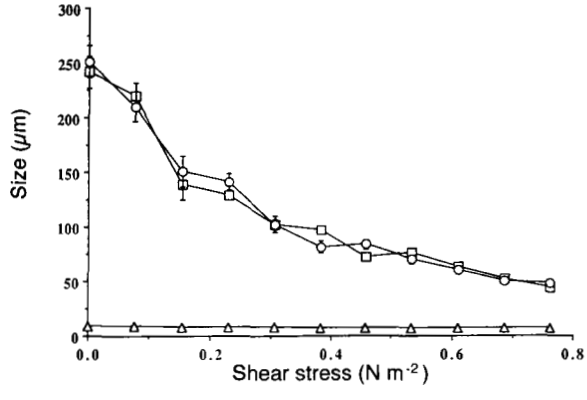

FIG. 4. Size variation of 0·04% w/w salbutamol sulphate in P113 under increasing shear stress, with; 0% (□), 0·015% (○) and 0·03% (△) w/w Span 80.

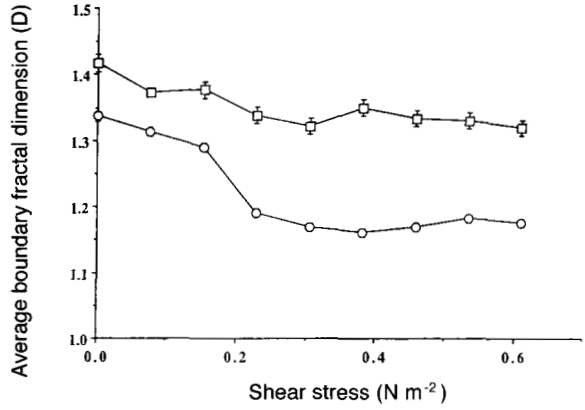

FIG. 6. Average boundary fractal dimension of 0·08% w/w lactose aggregates in P113 with (○) and without (□) 0·03% w/w Span 80.

decrease in average D with increasing shear stress indicating that compaction of the aggregates was occuring. The surfactant-free suspension aggregates showed a relatively small but uniform decrease in average D over the shear stress range studied. In contrast the aggregates formed with surfactant present showed a larger decrease in average D, with a sharp reduction around $0{\cdot}2\,N\,m^{-2}$ corresponding to the shear stress sufficient to halve the aggregate size. The overall morphology of the surfactant-free aggregates remained elliptical under increasing shear, in contrast to the tendency towards a spherical profile with increasing surfactant additions.

Aggregate size distribution. Fig. 7 shows the effect of surfactant on the size distribution of 500 aggregates in the lactose suspensions above under a typical shear stress of $0{\cdot}6\,N\,m^{-2}$. Without surfactant, the size distribution was broad, with a significant number of larger aggregates being formed. Addition of 0·03% w/w Span 80 made the distribution significantly narrower; 80% of the aggregates in this suspension had a size $\leq 20\,\mu m$. The average volume mean diameter (VMD) of aggregates was also decreased from $82 \pm 10\,\mu m$ without surfactant to $48 \pm 8\,\mu m$ in the presence of Span 80.

Discussion

Figs 1–3 illustrate how the aggregate size and morphology change when the interparticle forces are modified. As more surfactant is added the repulsive force between individual particles increases, effectively decreasing the sticking probability between colliding particles; aggregate sizes are therefore reduced. Decreasing the sticking probability below 100% changes the aggregation mechanism, since a particle colliding with an aggregate will now explore more possible sites of attachment. In terms of theoretical aggregation models the mechanism has shifted from diffusion limited cluster-cluster to reaction limited cluster-cluster. The morphology becomes more spherical with a less rugged profile and corresponding decreases in boundary fractal dimension and elongation, which tend to the Euclidian limit of unity. This observation is consistent with existing computer simulations of cluster-cluster aggregation (Kaye 1993; Robinson & Earnshaw 1993).

Surfactant-free suspensions of both lactose and salbutamol both showed similar behaviour when subjected to increasing shear stress. Aggregate size was rapidly reduced by low shear stresses of $<0{\cdot}3\,N\,m^{-2}$ indicating that flocs were only weakly bound together. At higher shear stress the size reduction was more gradual. Under conditions of zero shear, aggregation continued until all the suspended solid formed one continuous aggregate (gelation), hence slight agitation of the suspension was needed to obtain images of discrete aggregates. Measurement at precisely zero shear stress was therefore not practicable and so measurements at low applied shear stress should be treated with caution (as can be seen by the increased error at low shear in Figs 4 and 5). The rapid size decrease at shear stresses below $0{\cdot}3\,N\,m^{-2}$ corresponds to disruption of the few very large aggregates formed as the suspension approached gelation at low shear stress. The more gradual size decrease with shear stress above $\sim 0{\cdot}3\,N\,m^{-2}$ corresponds to disruption of aggregates from the now larger population of more polydisperse aggregates.

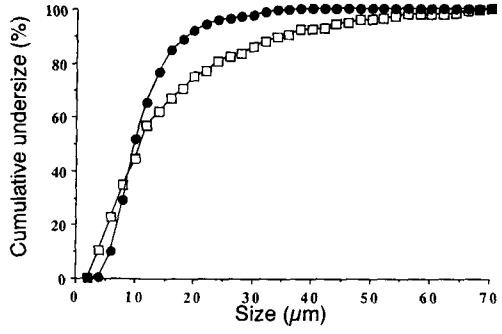

FIG. 7. Size distribution of 500 0·08% w/w lactose aggregates at $0{\cdot}6\,N\,m^{-2}$ with (●) and without (□) the presence of 0·03% w/w Span 80.

The addition of surfactant to the lactose suspension caused a significant size reduction over the entire range of shear stress (Fig. 5). This again suggests a reduction in the interparticle binding forces within the aggregate caused by surfactant. Salbutamol suspensions showed a significantly different behaviour, surfactants having little effect at concentrations below 0·02% w/w, and a powerful stabilizing effect at higher concentrations.

Several mechanisms may be suggested to explain these phenomena. Charge stabilization may be important in these systems; the low dielectric constant of the solvent ($\epsilon = 2{\cdot}41$ for P113) means that only a minimal number of charged species is required to give a high surface charge. However, suspensions in nonaqueous media are distinctly different from their aqueous counterparts. In dilute aqueous suspensions, the Debye-Huckel length is normally shorter than the average interparticle distance, so that an approaching particle experiences a pronounced field gradient. The Debye-Huckel length in nonaqueous systems is very long due to the low dielectric constant, and may exceed the interparticle separation. Under these conditions the approaching particles do not experience a field gradient, and so the stability is only weakly dependent on the surface charge; for stabilization the gradient of the electric field must be steep enough to provide adequate repulsive force between particles (Van der Hoevan & Lyklema 1992).

Lactose has a more negative zeta potential than salbutamol in P113 suspensions; addition of low HLB-value surfactants makes the zeta potential more positive in both cases (Sidhu et al 1993b). The increase in zeta potential is believed to be due to surfactant adsorption and screening of the surface charge by ions, arising from impurities in the surfactant. It seems reasonable to assume that the increased shielding of the surface charge collapses the double layer between the particles, and thus increases the field gradient sufficient to stabilize the suspension, and further that this occurs more rapidly with salbutamol than with lactose because of the more positive zeta potential of the former.

Alternatively stabilization may be due to steric repulsion of adsorbed surfactant molecules. In this case the magnitude of the interaction will be dependent on the adsorbed layer thickness, density and change in the Gibbs free energy by

the interaction between surfactant chains and solvent molecules. Adsorption of sorbitan trioleate onto salbutamol has been shown to produce multilayers of surfactant by hydrogen bonding of the sorbitan moiety. Surfactant adsorption to adsorbent was found to increase with increasing surfactant concentration and electrophilicity of the substrate (Clarke et al 1993). Using this theory one would expect the steric stabilization of lactose to be achieved more readily than that of salbutamol, lactose being the more electrophilic substrate. It is unclear why this effect was not observed in the present study.

The fractal dimension of aggregates in surfactant-containing suspensions showed a significant decrease relative to surfactant free suspensions, reflecting increased aggregate compaction and re-arrangement of the particles constituting the aggregate. Boundary fractal dimension measurements for surfactant-free suspensions of salbutamol and lactose again showed similar behaviour with a gradual decrease from ~1·43 to 1·30 in each case. This illustrates that even though some compaction was occurring, the aggregates retained most of their convoluted structure on disruption; i.e. aggregates were fractally broken. Fractal dimension measurements of aggregates in the salbutamol suspension with surfactant added also showed the same trend. The fractal dimension value of 1·43 for aggregates under low shear conditions agrees well with theoretical models of cluster-cluster growth mechanisms (Kolb et al 1983; Meakin 1988; Kaye 1993).

These studies demonstrate that the behaviour of aggregated suspensions in nonaqueous media is a complex function of composition; in particular surfactants increase particle mobility within flocs, and reduce interparticle binding forces, although their behaviour is also sensitively dependent on the nature of the solid substrate. The ongoing replacement of CFC propellants with environmentally acceptable alternatives will benefit from further detailed studies of these complex systems.

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