Rheology of Model Aerosol Suspensions

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Abstract—The rheological properties of model aerosol suspensions at phase fractions of less than 5% w/v (phase ratio of 0.05) were investigated. The rheological profiles of lactose in chloroform, lactose in trichlorofluoromethane (Propellent 11, P11), and salbutamol sulphate in P11 have been investigated in the presence and absence of lecithin, a phospholipid surface-active agent. The relative viscosities of these disperse systems correlated with the increasing disperse phase fractions and the addition of surfactant was found to reduce these viscosities to a relative viscosity of aproximately 1·0. The results suggest that the relative viscosity is a useful indicator of flocculation in these systems, and may be valuable in formulation development.

Aerosol suspensions for metered dose inhalers are inherently unstable systems. Flocculation of the dispersed phase readily occurs in the non-aqueous propellents (Hickey et al 1988). Surfactants, such as lecithin or the non-ionic surfactant, Span 85, may be added to deflocculate these systems. Although a deflocculated dispersion has a slow settling time, a densely packed sediment may be produced which is difficult to redisperse. A flocculated system has a rapid settling time but the sediment may be redispersible on agitation. A weakly flocculated system is ideal for aerosol delivery since shear forces generated by agitation result in floc rupture, thereby providing a uniform system for metering, but the flocs reform so as to produce a sediment which is redispersible.

At present, techniques to produce this weakly flocculated state rely mainly on experience and visual observation (Ranucci et al 1987). It is often difficult to judge the dispersion quality, especially when the disperse phase fraction is high and phase separation is poor. A quantitative technique is required to assess flocculation and to optimize the quantity of surfactant required to produce a weakly flocculated suspension. In order to assess this, an investigation into the rheological properties of model aerosol dispersions was undertaken. A concentric cylinder rheometer was used in preference to a cone and plate device, since propellent loss through evaporation was considerable and losses were minimized when using the concentric cylinder arrangement.

Light-diffraction techniques were considered for the study of these systems, but were unsuitable due to the high absorbance of the concentrated suspensions, which made scattering measurements difficult due to low signals and multiple scattering. Turbidity changes, which we have previously used in submicron aqueous systems (Washington & Davis 1987), were ambiguous since the particle size of the suspended material was such that the extinction of the particles was not simply related to aggregation.

A number of workers have previously used rheological techniques to study aggregating suspensions (Papir & Krieger 1970; Doroszkowski & Lambourne 1978; Fowkes & Pugh 1984; Green & Parfitt 1987). These systems have all

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contained relatively large phase fractions of dispersed materials (20–50%). To date the technique does not appear to have been used for the study of aerosol suspensions, possibly due to the technical difficulties of performing rheology at low temperatures. There is also little information on the rheology of disperse systems containing low phase fractions of solid. In this paper we present rheological profiles of model aerosol suspensions containing disperse phase fractions of 0·01–0·05% lactose in chloroform as a model system, and salbutamol sulphate in Propellent 11, and discuss these in terms of the flocculation behaviour of the systems.

Materials and Methods

Lactose BP (Lactochem Ltd, Cheshire) was micronized to a mean particle size of 3·4 μm (measured by Malvern 2600 diffraction sizer) and suspended in reagent grade chloroform (May and Baker Ltd, Dagenham, UK). Dispersion was achieved by ultrasonication of the suspension with a sonic probe (Dawe Instruments, UK) for about 5 s. The viscosity of the dispersion was measured in a Deer rheometer (Integrated Petronic Instruments Ltd, London, UK), which is a concentric cylinder instrument. A gap of 1 mm between the cup and rotating cylinder was used and the angle at the base was approximately 5°. To avoid sedimentation of the suspension in the rheometer, the viscosity was measured rapidly after filling (within 1 min to allow equilibration) and subsequent measurements were made after re-agitating the suspension with a small concentric stirrer, any overflow being made up with fresh suspension. At random intervals the suspension was completely replaced with fresh material. This provided data of good consistency; the effects of sedimentation (erratic increases in viscosity) could be observed if the suspension was allowed to stand for more than 5 min.

Each sample was subjected to a range of shear stresses between 15 and 410 mN m^{-2} and the shear rate was measured. Studies on lactose in chloroform were carried out under room conditions at a controlled temperature of 20 ± 0.5°C. The viscosity of the continuous phase was measured over the same shear stress range. The relative viscosity was calculated from the shear rate of the suspension
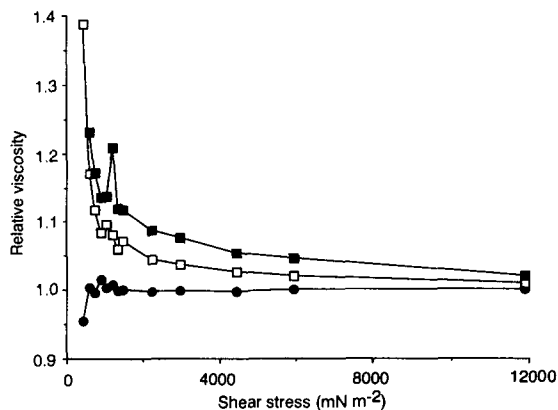
Fig. 1. Relative viscosity of lactose in chloroform containing no surfactant. ● 1% lactose, □ 3% lactose, ■ 5% lactose.

relative to the shear rate of the continuous phase alone, at each shear stress.

The effect of a surfactant was investigated by the addition of egg lecithin containing 80% phosphatidylcholine (Ovothin 180, Lucas Meyer, Hamburg, Germany) to the lactose suspensions. The lecithin was dissolved in chloroform and then added to the appropriate quantity of lactose, before dispersion with the sonic probe. The relative viscosities of 1, 3 and 5% w/v lactose in chloroform in the presence of 0·5% w/v lecithin were measured relative to the viscosity of 0·05% lecithin in chloroform.

Model aerosol suspensions investigated were lactose in trichlorofluoromethane (Propellent 11 or P11) (ICI, Macclesfield, UK), and micronized salbutamol sulphate (kindly provided by 3M Health Care Ltd) in P11. Each suspension was prepared as previously described except that dispersion was achieved by shearing the suspension for 3 min with a Silverson mixer (Silverson Machines Ltd, Waterside, Chesham, UK) fitted with a high shear head.

Owing to the volatile nature of P11, rheological measurements of suspensions containing this material as the continuous phase were carried out at a temperature of $-12 \pm 1°C$ and at a relative humidity of $-20°C$ dew point. The rheometer was cooled to low temperatures by circulating

Fig. 3. Relative viscosity of lactose in P11 containing no surfactant. ● 1% lactose, □ 3% lactose, ■ 5% lactose.

a cooling fluid via an Endocal ULT 95DD refrigerated circulating bath (Neslab Instruments Inc., Hewington, NH, USA).

Results

Fig. 1 shows how the relative viscosities of lactose in chloroform suspensions vary with the applied shear stress. The relative viscosity is high at low shear rates and is followed by a region of shear thinning and finally a region where the viscosity is independent of shear stress. Each suspension follows a similar rheological profile. This profile is attributable to the changes in suspension structure which result from the applied shear stress.

As expected from the Einstein equation (Einstein 1905, 1906) the relative viscosity is proportional to the phase fraction of solid in the suspension. Fig. 1 shows that the suspension containing 5% w/v lactose exhibits the highest relative viscosities at each shear stress, whereas the 1% w/v lactose suspension displays the lowest relative viscosities of the three dispersions investigated. At high shear rates, the difference between the three suspensions is not significant,
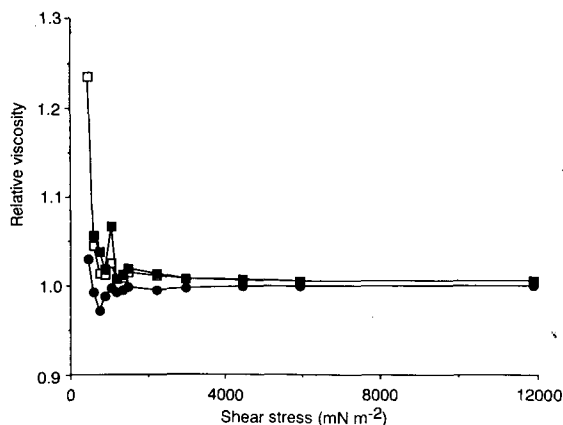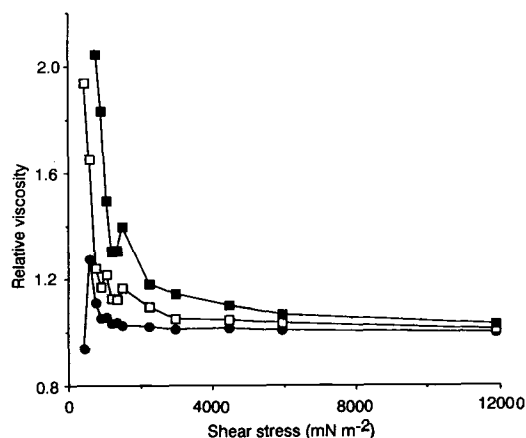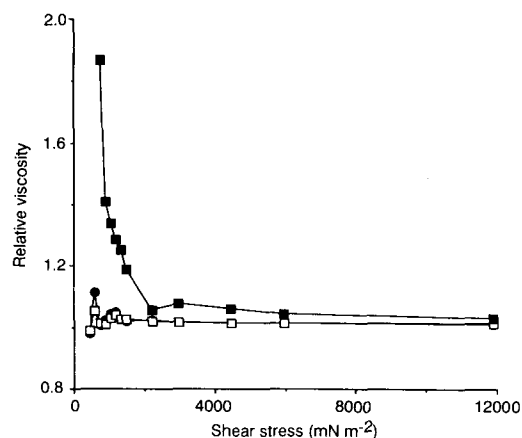

Fig. 2. Relative viscosity of lactose (1–5%) in chloroform containing lecithin (0·5%). ● 1% lactose, □ 3% lactose, ■ 5% lactose.

Fig. 4. Relative viscosity of lactose (1–5%) in P11 containing lecithin (0·5%). ● 1% lactose, □ 3% lactose, ■ 5% lactose.
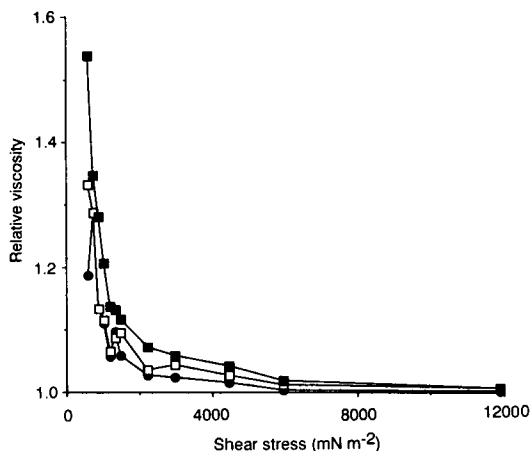
FIG. 5. Relative viscosity of salbutamol (1–5%) in P11 containing no surfactant. ● 1% lactose, □ 3% lactose, ■ 5% lactose.
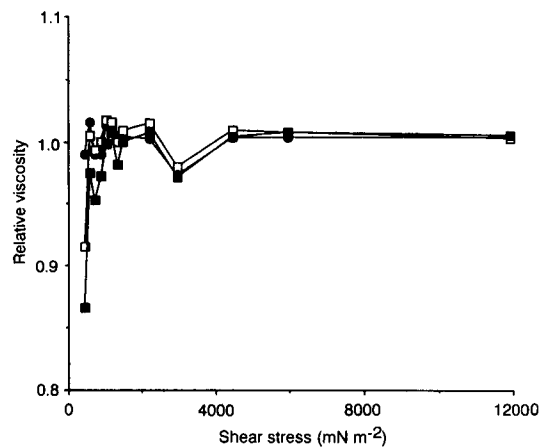

FIG. 6. Relative viscosity of salbutamol (1–5%) in P11 containing lecithin (0·5%). ● 1% lactose, □ 3% lactose, ■ 5% lactose.

but at low shear rates, there is a considerable difference in the relative viscosities of the different formulations.

The effect of the addition of lecithin is shown in Fig. 2. The relative viscosities of each suspension have been dramatically reduced relative to the suspensions containing no surfactant, and are almost independent of shear stress.

Lactose exhibits a rheological profile in P11 (Fig. 3), which is similar to its profile in chloroform. The highest relative viscosities are obtained with the 5% w/v dispersion and the lowest with the 1%, as observed in Fig. 1 and as predicted by the Einstein equation (although we should note that this only strictly applies to non-interacting systems).

Fig. 4 shows that addition of a surfactant to the lactose/P11 system reduces the relative viscosities of the suspensions so that their profiles are almost indistinguishable. The 5% suspension shows some residual dependence of relative viscosity on shear stress. This may occur because there is insufficient surfactant to cover the entire surface of each lactose particle, therefore there is some structure in the system, possibly occurring through particle–particle contact at the locations where the surface is uncovered by surfactant. With the exception of this effect, the behaviour of lactose in both liquid systems (Figs 2, 4) is similar.

Salbutamol in P11 (Fig. 5) produced the characteristic rheological profile of flocculated systems as observed with the previous dispersions, in the absence of a surfactant. As with lactose, the 5% suspension exhibits the highest relative viscosities and the 1% suspension produces the lowest. However, the differences between the curves are not as clearly defined as with the lactose dispersions. The relative viscosities are lower than those observed in lactose–P11 suspensions, but comparable with those in lactose–chloroform dispersions. It is likely that the salbutamol–P11 interactions are responsible for the observed effects. These interactions may also be responsible for the smaller floc size which is visually observed in the salbutamol–P11 systems.

Fig. 6 shows relative viscosities of salbutamol–P11 dispersions in the presence of the surfactant. A dramatic reduction in the viscosities is observed and they are almost constant over the range of shear stresses applied. Considerable deviations occur at low shear stresses, especially for the

higher disperse phase fraction suspensions, probably as a result of poor flow of the suspension in the concentric cylinder of the rheometer. Creaming is a major problem in these systems, particularly at low shear stresses, when mixing does not occur throughout the bulk. The 5% salbutamol–P11 suspension does not produce the same rheological profile as the 5% lactose–P11 suspension (Fig. 4) in the presence of surfactant. It may be possible that the surfactant is able to cover the entire surface of the salbutamol particles, thereby preventing flocculation through interparticle contact. It is unfortunately not possible to test this hypothesis by calculation, despite a knowledge of the size distribution of the particles, because their irregular nature makes the surface area uncertain.

Discussion

The application of rheology to assess the presence of flocculation in model aerosol systems has been demonstrated. The results show that differences in disperse phase fraction lead to different rheological behaviour. A suspension containing a high disperse phase fraction exhibited a greater relative viscosity for a given shear stress than a similar suspension containing a low disperse phase fraction, in accordance with Einstein's law. A high phase fraction may produce a raised viscosity through an increase in the packing density of particles within a floc or via the number of links which must be broken to achieve fluid mobility.

Formulations containing surfactant displayed negligible floc structure, and exhibited relative viscosities close to unity. At the low disperse phase fractions studied, the presence of a surfactant reduced the apparent disperse phase fraction to its real proportion, thus resistance to fluid flow was reduced, resulting in lower relative viscosities. The presence of the surfactant at the particle surface is known to reduce floc formation (Sidhu et al 1990). Hence it may be inferred that the behaviour observed, for example in Fig. 1, was due to the presence of flocs and their subsequent breakdown on the application of shear forces. It is interesting to note that the relative viscosities of suspensions in the presence of lecithin were almost equal to unity, suggesting that the apparent

phase fraction occupied by the lactose particles was very small.

Particle–continuous phase interactions of lactose in P11 would be expected to be similar to those in chloroform. However, a major difference between the profiles was that the relative viscosities of lactose in P11 were much greater than the viscosities of lactose in chloroform suspensions. This difference may have been the result of changes in the lactose–continuous phase interactions, leading to changes in floc structure or binding energies. Changing the continuous phase resulted in differences in the particle–solvent and surfactant–solvent interactions, which were detected in the rheological profiles by observable changes in the relative viscosities. Hence rheology of systems at low disperse phase fractions is a sensitive technique for assessing dispersion quality.

Many theories have been proposed to relate non-Newtonian flow to structural breakdown in concentrated suspensions. The Einstein equation is well known. It relates viscosity of the continuous phase and the phase fraction of solid to the viscosity of the dispersion. However, it is only applicable for non-interacting particles (i.e. those which do not flocculate).

A number of theoretical approaches have been taken to relate the rheology of flocculated suspensions to their structure and bonding. Most of these make some assumption concerning the structure of the floc; thus Casson (1959) assumed that particles within a floc form long chains, while Adler & Mills (1979) assumed the floc to be a porous sphere. However, simple observation indicates that the flocs are not uniform in structure, and may be porous or irregular. Current theories of floc formation make use of fractal descriptions (Avnir 1989), and it seems likely that the application of fractal geometry to floc structure (Washington

et al 1991) and rheology will allow this area to be understood more thoroughly in the near future.

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