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Fractal morphology of drug aggregates in aerosol propellant suspensions

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Abstract

The study and formulation of drug suspensions in aerosol propellants is frequently hampered by lack of information concerning the structure and properties of the aggregated drug particles in suspension. We describe apparatus for the photomicrographic study of aggregates in suspension of volatile liquids, and apply this technique to measure the fractal properties of the drug aggregates. The boundary fractal dimensions of such flocs indicate that the model drugs studied (lactose and salbutamol sulphate) aggregate by a diffusion limited cluster-cluster mechanism in the absence of surfactants. However in the presence of Span 80, a typical surfactant used in aerosol systems, the morphology of the aggregates is significantly altered. The tenuous convoluted flocs become more compact and spherical. This is characterized by a reduction in the boundary fractal dimension, suggesting that considerable floc rearrangement occurs during aggregation. This implies that the surfactant reduces bonding forces between drug particles, allowing dynamic changes in floc structure.

Keywords: Fractal; Aerosol; Metered dose inhaler; Flocculation; Chlorofluorocarbon

1. Introduction

Solid micronized drugs are frequently suspended in volatile liquid propellants of low dielectric constant for use as aerosol delivery systems for inhalation therapy. Such suspensions are usually flocculated, and it is widely recognized that the operation and reliability of metered dose inhaler aerosols (MDIs) is related to the dispersion of the drug in its suspending propellant. The difficulty of characterizing such systems has limited previous work to bulk measures of flocculation such as sediment height or rheology (Sidhu, 1993; Sidhu et al., 1993). We have now developed techniques to allow the size and structure of individual flocs to be measured, using microscopy in a high pressure liquid cell, suitable for all the commonly used aerosol propellants. In particular we have characterized the fractal nature of the flocs, which describes the porosity of the floc structure and compactness of the aggregate, and is closely linked to the mechanism of aggregation.

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2. Fractal dimension and particle aggregation

The fractal dimension as defined by Mandelbrot (1983) extends the familiar concept of integral dimensions to embrace non-integral dimensions, and thereby account more accurately for the scaling behaviour of the more rugged shapes found in nature, in particular the boundaries of aggregate particles. The scaling behaviour of a particle boundary is characterized by looking at the boundary length at various resolutions. This is normally done using a yardstick of decreasing size to cover the boundary, the decrease in size corresponding to an increase in resolution. If we use circles of radius r to cover the boundary then for smooth Euclidian curves the number of circles n required to cover the boundary obeys the relationship:

$$n(r) \propto r^{-1} \quad (1)$$

However, most particles have a more rugged morphology and since their boundaries are more convoluted, examination at higher resolutions reveals further detail and Eq. 1 must be replaced by a power law equation after Peitgen and Saupe (1988):

$$n(r) \propto r^{-D} \quad (2)$$

where D is termed the fractal dimension, and characterizes the rate at which additional detail appears as the resolution is increased. Regular geometric fractal objects, such as the triadic Koch curve, are termed 'self similar', in other words, increases in resolution reveal more and more detail ad infinitum. Aggregates of real particles are however normally only 'statistically self similar' (Peitgen and Saupe, 1988) and they show fractal behaviour over only a limited range of resolution, the lower limit being set by the size of the individual particles that make up the aggregate.

The perimeter of a simple shape such as a circle has a fractal dimension of 1, a more rugged curve which fills more of the plane has a non-integral value somewhere between 1 (a line) and 2 (a plane). This allows the morphology of the aggregate to be characterized in terms of its space filling ability. Extensive computer modelling studies of particle aggregation have shown that the fractal dimension is dependent on the aggregation mechanism, and so provides insight into interparticle forces and dynamics (Meakin, 1988).

Diffusion-limited aggregation (DLA) is one of the simplest mechanisms modelled by Witten and Sander (1981), whereby particles are allowed to diffuse randomly about a geometric lattice until they collide with a central particle, to which they adhere on contact. Particles are normally added one at a time, and the resulting structures resemble tenuous dendrites emanating from a central point. The sticking probability in such models is usually set to 100%, but can be varied to examine the influence of adherence and particle mobility on the fractal morphology, a lower sticking probability causing a reduction in fractal dimension as the aggregate becomes more compact. Models of this type are very sensitive to the underlying lattice structure, producing aggregates whose shape reflects the underlying lattice symmetry. This property is rarely observed in real systems, which show no preferential directions of movement. The boundary fractal dimension of DLA clusters grown in two dimensions is around 1.71. This model is, however, applicable only to those processes where aggregation is directed towards a particular centre, for example, on a surface, as in electrodeposition.

Cluster-cluster aggregation is a more realistic theoretical model of particle suspension aggregation than DLA, since the diffusing particles are now allowed to stick to each other to form clusters. Clusters are allowed to diffuse and adhere to each other, so there is no preferential centre for aggregation. The sticking probability, which determines whether or not encounters between particles or clusters will be successful, can be varied to simulate the effects of different interaction forces between clusters, or different rates of aggregation. The fractal dimension of two-dimensional aggregates formed in computer models of such processes is 1.45 (Meakin, 1988). The lower D value suggests that the aggregates are more compact and possibly more difficult to re-disperse than more tenuous aggregates.

2.1. Practical applications of fractal characterization

Although a relatively new technique, the use of fractal dimension to characterise fine particles is of increasing application. In the mining industry it is used to describe ores, mineral grains and the cracks which will facilitate mineral liberation; in the metallurgical industry where it is important to characterise the fine powder grains used in sintering, and in electrochemical processes. It offers an elegant means to describe the change in particle profiles of material undergoing any form of milling or polishing process, and is likely to prove useful in the pharmaceutical industry for describing the flow and packing behaviour of powders used in tableting (Kaye, 1989). Farin et al. (1985) and other workers have used fractal dimension to characterise proteins, porous materials and aggregates. Colloidal gold aggregates (Weitz and Oliveria, 1983), polystyrene latex and silica particle aggregates (Zhou and Chu, 1991) and even galactic clusters (Mills, 1987) have all been subjects of fractal analysis.

2.2. Measurement of fractal dimension from two-dimensional images

By using progressively smaller yardsticks of length r to measure the length of the particle boundary a series of increasing perimeter estimates may be obtained. If $n(r)$ steps are required to traverse the boundary, the estimate of the length of the perimeter is given by:

$$\text{length} = r \cdot n(r) \tag{3}$$

From Eq. 2 we know that $n(r)$ scales as r^{-D}, so we have:

$$\text{length} \propto r^{1-D} \tag{4}$$

Taking logarithms on both sides yields:

$$\ln(\text{length}) = (1 - D) \cdot \ln(r) + \ln(F) \tag{5}$$

where F is a constant of proportionality. A ln-ln plot ('Richardson plot') of the perimeter estimate against the yardstick size r thus yields the boundary fractal dimension from the slope.

The measurement of the boundary length by such a yardstick method is computationally difficult. However, a simpler method was described by Flook (1978), by use of the 'dilation' facility available on most image analysis packages. This takes each pixel and replaces its value with the maximum value of its nearest eight neighbours. This covers the boundary with objects of increasing size (the structuring elements), which has the effect of dilating the boundary. By applying successive dilations to the image every boundary pixel is replaced by increasingly larger structuring elements, thus obscuring more detail, which is equivalent to decreasing the resolution of observation. The perimeter length estimate for any particular resolution is then obtained by dividing the area of the dilated boundary by the diameter of the structuring element.

3. Materials and methods

Suspensions of micronized lactose and salbutamol sulphate (VMD (volume mean diameter) = 3.5 μm by Malvern 2600 sizer) were prepared in propellant blends ranging from 10% w/w trichlorofluoromethane (P11) to 10% dichlorodifluoromethane (P12) or 100% of the novel propellant 1,1,1,2-tetrafluoroethane (P134a) (all donated by 3M Health Care, Loughborough) in polyethylene terephthalate (PET) vials; the vials were sealed with non-metered valves using a crimping tool. The vials were then sonicated for 15 min in a sonic bath to ensure dispersal of any aggregates. Span 80 (sorbitan monooleate; Sigma Chemical Co.) was used as the surfactant additive and was dissolved in the propellant prior to sealing the vials. Sediment heights were measured to ± 1 mm using a travelling microscope.

To facilitate observation of the aggregates a custom-made pressure cell was used (Fig. 1). The cell consisted of a stainless-steel chamber with non-metered aerosol valves at either end to allow charging from PET vials with non-metering valves by use of a teflon transfer tube. The valves were easily removable to allow cleaning of any residue from the chamber after each measurement. Cleaning was performed by rinsing with distilled

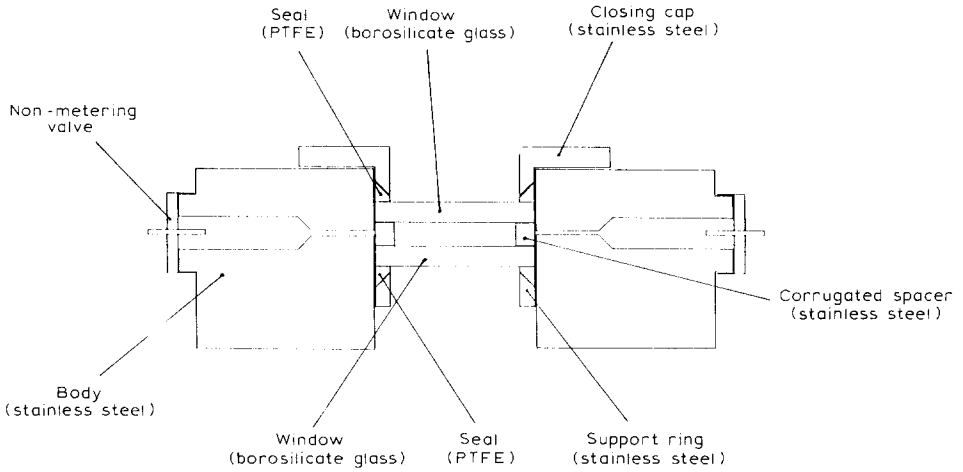

Fig. 1. Schematic diagram of the high-pressure microscopy cell.

water to remove the polar solids, then soaking and rinsing first in acetone, then dichloromethane before drying for 20 min in a oven to ensure that no water was left in the cell.

Two pyrex windows separated by a 0.5 mm spacing ring in the centre of the chamber allowed observation of the aggregates in situ using an Olympus CH-2 optical microscope (Olympus Optical Co. (UK) Ltd) with CCD camera (CV-790PAC). Image capture was by Quickimage 24 video frame grabber card and software (Mass Microsystems) running on a Macintosh IIci computer. This apparatus enabled capture of 384 × 288 pixel 8-bit grey scale or 24-bit colour images.

The raw images were processed using IPlab Spectrum image analysis software (Signal Analytics Corp.), removing any unwanted aggregate pieces to leave only the aggregate of interest. The image was then thresholded and the boundary obtained by subtracting an eroded version of the image from the original. Calculation of fractal dimension was by an IPLab command script which implemented the dilation method described above.

4. Results

To validate the software, the boundary fractal of a test object was first measured. The object was the triadic Koch island (Fig. 2), which has a known fractal dimension of 1.2618. This was generated using the program FRACTINT on an IBM PC. The corresponding Richardson plot is shown, and provided a fractal dimension of 1.26 ± 0.01.

A Richardson plot for a typical salbutamol sulphate aggregate in P11/P12 blend is shown in Fig. 3, with a fractal dimension of 1.30 ± 0.01. The gradient of the graph was taken over the linear section of the plot; this involved neglecting the first few points which correspond to the highest resolution data. These data were at the limit of resolution of the capture and display medium, since both the CCD camera and the images cap-

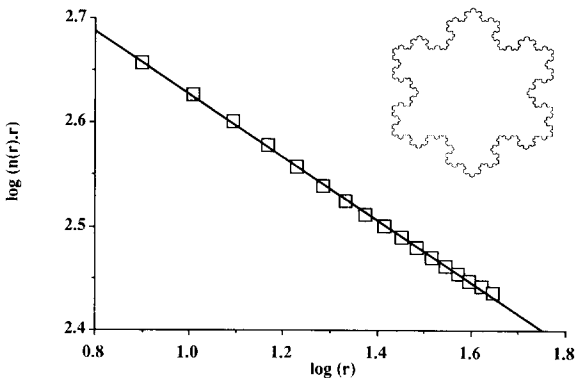

Fig. 2. Richardson plot for a triadic Koch island ($r^2 = 0.999$). Inset: triadic Koch island.

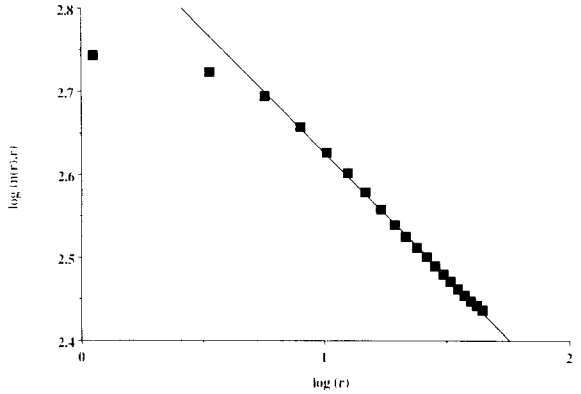

Fig. 3. Richardson plot for a typical aggregate of salbutamol sulphate in P11/P12 blend.

tured have a finite resolution determined by the number of pixels in each case, and the ultimate size of the drug particles.

Fig. 4 shows the fractal dimension of lactose and salbutamol flocs as a function of propellant composition in P11/P12 blends. The values obtained were independent of propellant concentration, with a mean value of 1.38 ± 0.04 for suspensions containing 1.0% w/w lactose and 1.40 ± 0.03 for 0.35% w/w lactose. The fractal dimension of salbutamol sulphate aggregates as a function of propellant composition again showed little variation with propellant blend with an average D value of 1.41 ± 0.03 for 0.1% salbutamol sulphate in P11/P12 suspensions. It was not possible to study more concentrated salbutamol sulphate suspensions, since the flocs were extended and images of isolated flocs could not be obtained.

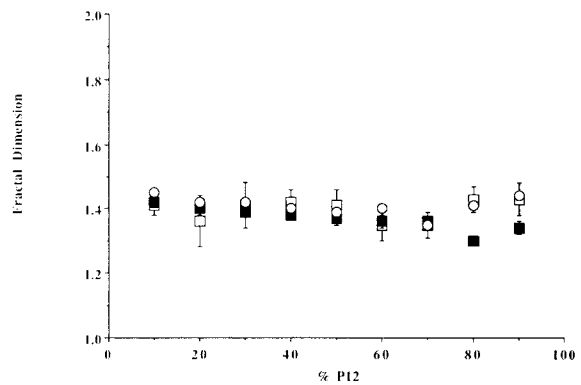

Fig. 4. Boundary fractal dimension of lactose flocs in P11/P12 propellant blends. (■) 1% w/w lactose, (□) 0.35% w/w lactose, (○) 0.1% w/w salbutamol sulphate.

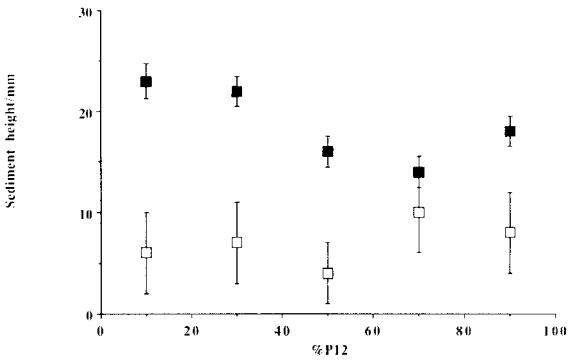

Fig. 5. Cream depths in lactose (1% (■)) and salbutamol sulphate (0.1% (□)) suspensions in P11/P12 blends.

The sediment heights as a function of propellant blend are shown in Fig. 5. Lactose showed a sediment height of 15–25 mm, with the highest density propellants showing the largest sediment depth, and a gradual decrease in the lighter propellant blends. In contrast, salbutamol sulphate formed a cream layer due to its lower density, and displayed no significant variation in cream depth with changes in propellant density.

The addition of the surfactant Span 80 was studied in the system 90% P11/10% P12/0.1% salbutamol, and had a dramatic effect on floc structure, the average Ferets diameter of the aggregates was reduced from approx. 500 μm to approx. 100 μm, and the flocs become much more rounded in appearance. A concentration of 0.25% Span 80 resulted in a D value of 1.07 ± 0.06, indicating a much more compact floc structure. Fig. 6 shows typical aggregates in the absence and presence of 1% Span 80. Fractal dimensions of surfactant-free systems, and those containing Span 80 are given in Table 1.

5. Discussion

The similarity of D values for both lactose and salbutamol in different propellant blends suggests that the same fundamental aggregation mecha-

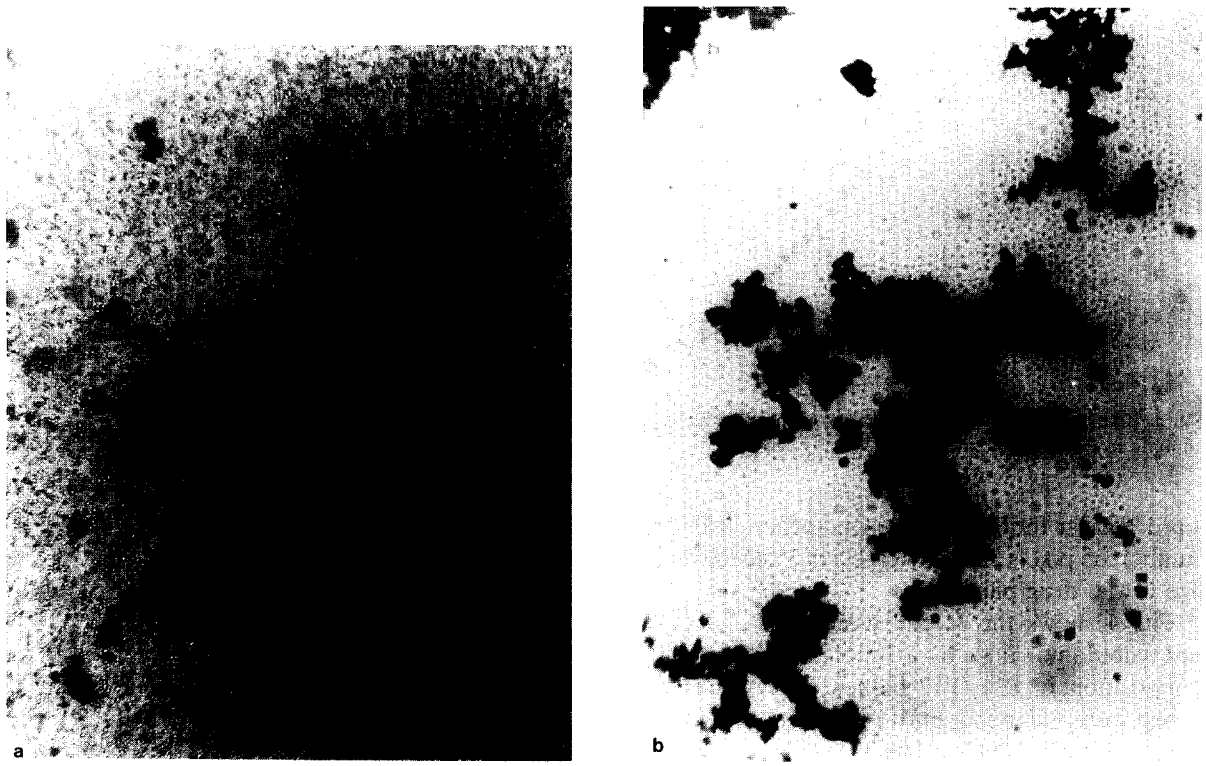

Fig. 6. Flocs of salbutamol sulphate (×100) in 10% P12, 90% P11, (a) in the presence of 1% Span 80, (b) without surfactant.

nism takes place in each case. A value of 1.45 for D is expected for a floc which is formed by diffusive cluster-cluster aggregation on a two-dimensional lattice; a significantly lower value suggests that post-flocculation rearrangement has occurred. The observed values of D in the absence of surfactants are close to this limit, suggesting that flocs of lactose or salbutamol do not rearrange or compact to a large extent after formation, and implying that the individual particles are strongly bonded into the floc network. However, the addition of surfactants results in flocs with a much lower fractal dimension, which in turn suggests that extensive rearrangement of particles occurs during floc formation. This is supported by the observation (Fig. 6) that a large number of unflocculated particles are also present in the suspensions. These observations are consistent with the hypothesis that the surfactants reduce the overall attractive force between the

Table 1
Fractal dimensions of lactose or salbutamol sulphate aggregatess in a range of media

System studied	Average fractal dimension
0.08% lactose in P113	1.43 ± 0.02
0.35% lactose in P11,12 blends	1.40 ± 0.04
1.0% lactose in P11,12 blends	1.38 ± 0.05
0.1% salbutamol in P11,12 blends	1.41 ± 0.02
0.1% salbutamol in P134a	1.40 ± 0.06
0.1% salbutamol in P11,12 with 0.25% Span 80	1.07 ± 0.01
0.1% salbutamol in P11,12 with 1.0% Span 80	1.16 ± 0.02

particles, allowing rearrangement and dynamic processes such as bound-free equilibria to become important.

Sediment heights have been widely used in the design of aerosol formulations (e.g., Cheever and Ulnicy, 1983). Unfortunately, the factors affecting sediment height are unclear; they appear to be related to a combination of floc structural features and density differences. The sediment heights observed in the present study confirm this interpretation; they show only minor variations with propellant density, although the lactose sediments do show to a small extent the expected increase in sediment volume as the density-matching condition is approached (P11 has a density of 1.48 g cm^{-3}, the highest propellant density studied, while the density of lactose is 1.59 g cm^{-3}). The fractal dimensions, however, show no such trend with propellant composition, indicating that they provide a more fundamental measure of floc structure. If the floc structure is independent of propellant composition in this series, then it is likely that the variations in sediment height are due to differences in floc packing in the sediment. Thus, studies of fractal structure allow the separation of structural and density contributions to the overall sediment height.

6. Conclusions

We have presented some preliminary data concerning the fractal nature of drug aggregates in aerosol propellant suspensions. The results show that, in the absence of surfactant, flocs are formed by a cluster-cluster aggregation mechanism, but that the addition of surfactants makes a significant change to the aggregation mechanism and floc structure. Studies of this type should be of some value in the formulation of drug suspension aerosols, and in particular may make a useful contribution to the problem of reformulating these systems in non-CFC propellants.

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