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Development of a systematic theory of suspension inhalation aerosols. II. Aggregates of monodisperse particles nebulized in polydisperse droplets

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Summary

Using the previously developed statistical framework to study the aggregation of primary drug particles in droplets formed on nebulization of suspensions, we have computed the expected size distributions of clusters of monodisperse primary drug particles obtained after drying of log-normally distributed polydisperse aerosol droplet sprays. In systems with a high ratio of droplet to primary particle diameters and relatively high average number of particles per droplet, the cluster size distributions were found to be essentially log-normal with the same geometric standard deviations as the droplets, and the mass median (aerodynamic) diameters were accurately predictable on the basis of assumption of uniform distribution of the solid throughout the liquid phase. In systems where the average number of primary particles per droplet was less than one, the cluster size distributions showed markedly non-linear behaviour on log-normal probability graphs. However, the mass median (aerodynamic) diameters could be still predicted quite reliably assuming uniform distribution of the solid among the fraction of the droplets expected to be occupied by the solid particles (i.e. excluding the empty droplets from the calculations). When the ratio of the droplet to primary particles was small and the concentration of the suspension was high, the size distributions of the aggregates deviated markedly from the log-normal function, particularly when the droplet sprays were narrowly distributed. Calculation of the mass median (aerodynamic) diameters and geometric standard deviations using the uniform distribution assumption could lead to grossly erroneous results in these systems. The reason for this behaviour is that (i) spherical particles cannot fill space completely and (ii) a significant portion of the log-normally distributed droplets is too small to accommodate the number of primary particles which would be computed for these droplets on purely statistical grounds. This 'exclusion' effect, however, becomes marked only at high concentrations which are beyond the range used in current therapeutic aerosols and outside the regions of validity of some of the assumptions of the present theory. Thus, assuming uniform distribution of solid in the droplets of aerosol sprays, it is possible to estimate the significance of formation of solid aggregates arising for purely statistical reasons (i.e. without taking into account any forces of attraction causing flocculation or coagulation). Outside the regions of validity of the assumption of uniform distribution, the full computational model developed in this paper has to be used to find the median size and the shape of the distribution of the solid clusters.

Introduction

Nebulization of suspensions of drug particles is a very common mode of drug delivery into the human respiratory tract. Typically, the primary

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drug particles have a narrow size distribution with a mass median aerodynamic diameter around 2–3 μm; their concentration is usually in the range $(3 \times 10^{-2}$ to 3% v/v and, on nebulization, they are contained in droplets whose initial mass median diameter is probably 30–40 μm (the basis for these estimates was reviewed in the first paper in this series (Gonda, 1985)). After evaporation of the carrier liquid, the deposition of the drug aerosol in the respiratory tract depends on the aerodynamic behaviour of the resulting drug particles which may be significantly different from the primary drug particles. There could be several reasons (Gonda, 1985) for such behaviour: in the previous paper, we dealt specifically with one of the reasons, namely the situation when large monodisperse droplets of propellant could hold more than one primary drug particle and, on evaporation of the propellant, these particles formed an aggregate (or 'cluster'). Clearly, the aerodynamic diameter of such an aggregate would be greater than that of a single particle. We wish to extend this simple picture, which ignores so far any other causes of aggregation or modified aerodynamic behaviour, to the more realistic model of monodisperse primary drug particles distributed in polydisperse droplets. We have noted previously (Gonda & Chan, 1985) that, over a narrow but reasonable range of formulation parameters, it may be possible to predict an approximate aerodynamic size distribution of the drug aggregates on the assumption that the drug is uniformly distributed in the droplets. In other words, the predicted distribution would be the same as that obtained for a drug completely soluble in the volatile propellant. The present communication investigates the validity of this approximation over a much wider range of formulation parameters.

Theory

We treat a suspension of monodisperse particles with equivalent sphere volume diameters d_e, dispersed in a volatile propellant at a % v/v concentration c. On nebulization, a droplet spray is formed with a size distribution $p(D)$, D being the diameter of individual droplets. The probability $P(k, D)$ that k primary particles are found in a droplet of diameter D is given by the Poisson expression (Raabe, 1968):

$$P(k, D) = \frac{\exp(-n)n^k}{k!} \quad k = 0, 1, \ldots, \infty \qquad (1)$$

where $n = n(D)$ is the average number of particles per droplet of diameter D. The probability that k particles can be found in a droplet of any size is:

$$P'(k) = \int_{D_{min}}^{D_{max}} P(k, D) \cdot p(D) dD \qquad (2)$$

If $p(D)$ is the experimentally determined initial distribution of the droplets after nebulization of the suspension, then D_{min} and D_{max} are dictated by the size ranges of the measuring device. The sum of the probabilities is then

$$\sum_{k=0}^{\infty} P'(k) = 1$$

If, however, $p(D)$ is an assumed function defined in the range $0 \leqslant D \leqslant \infty$, it is usual to put $D_{max} = \infty$; it is also necessary to ensure in such theoretical modelling that the diameter of the smallest droplet, D_{min}, is sufficiently large for the droplet to be able to accommodate the cluster of k particles (Callingham, 1980; Gonda, 1985; Gonda and Chan, 1985). In this situation when $D_{min} > 0$ it is found that $\sum_{k=0}^{\infty} P'(k) < 1$ and the probabilities $P'(k)$ must be renormalized:

$$P(k) = \frac{P'(k)}{\sum_{k=0}^{\infty} P'(k)} \qquad (3)$$

Then, clearly, these renormalized probabilities obey the summation condition

$$\sum_{k=0}^{\infty} P(k) = 1 \qquad (4)$$

For experimentally determined $p(D)$, or when $D_{min} = 0$, we have, of course,

$$P'(k) = P(k).$$

The total number of droplets, n_T, formed from a volume V of a suspension is

$$n_T = V/\bar{V}_D \tag{5}$$

where $\bar{V}_D$ is the average volume of a droplet. The total number of droplets containing aggregates of i particles, $n(i)$, is obtained by multiplying the probability of finding such an aggregate in a droplet of any size by the total number of droplets:

$$n(i) = P(i)n_T = P(i)V/\bar{V}_D \tag{6}$$

The mass of an aggregate of i primary drug particles is $m(i)$; the fraction of the total drug mass contained in aggregates of i drug particles is thus

$$F(i) = \frac{m(i)P(i)V/\bar{V}_D}{NgV} \tag{7}$$

where N is the number of primary particles per unit volume of suspension, g is the mass of a primary particle and the aggregate mass is

$$m(i) = ig \tag{8}$$

Eqn. 7 can be rewritten as

$$F(i) = \frac{igP(i)}{Ng\bar{V}_D} = \frac{iP(i)}{\bar{V}_D N} = \frac{iP(i)}{\bar{n}} \tag{9}$$

since the average number of particles per droplet, $\bar{n}$, is equal to the average volume of droplet $\bar{V}_D$ times the number concentration of particles, N:

$$\bar{n} = \bar{V}_D N \tag{10}$$

($\bar{n}$ is in fact the number of particles to be found in a droplet whose volume is equal to the arithmetic average droplet volume). Eqn. 9 is identical to that derived previously for monodisperse droplets (Gonda, 1985), with a proper definition of $\bar{V}_D$ as the average droplet volume (Eqn. 5). The cumulative mass distribution, $M(i)$, as a function of i is then calculated as shown before (Gonda, 1985; Gonda and Chan, 1985):

$$M(i) = \frac{1}{\bar{n}} \sum_{k=1}^{i} kP(k) \tag{11}$$

In order to compute the cumulative mass as a function of 'size', it is necessary to make certain assumptions about the shape of the aggregates. We shall assume the same model as in our previous papers, namely that the aggregates are adequately described as being spherical. It can be shown then (Gonda, 1985) that the equivalent sphere volume diameter $d_e(i)$ and the aerodynamic diameter $d_{ae}(i)$ of an aggregate of i particles are, respectively,

$$d_e(i) = d_e(1)\sqrt[3]{i/f(i)} \tag{12}$$

$$d_{ae}(i) = d_{ae}(1)\sqrt[3]{i/f(i)}\sqrt{K(1)f(i)/K(i)} \tag{13}$$

where $f(i)$ = fraction of volume occupied by the solid; $K(1)$ and $K(i)$ are the dynamic shape factors (Hinds, 1982) for the primary particle and for a spherical aggregate of i such particles, respectively.

The above equations enable us to calculate the cumulative mass distribution $M(i)$ as a function of the equivalent sphere volume diameter $d_e(i)$, or the aerodynamic diameter $d_{ae}(i)$. The model is now in a form which is testable experimentally: $M(i)$ can be obtained from the formulation parameters and $P(k)$'s. The latter can be computed from the experimentally determined $p(D)$ using Eqn. 2. $d_e(i)$ or $d_{ae}(i)$ can be both measured, approximate values of $K(1)$ and $K(i)$ are available in the literature (Hinds, 1982) and $f(i)$ can be deduced, e.g. from microscopic examination of the aggregates.

However, if we wish to carry out a computational investigation, it is necessary to make the model more specific; e.g. the following assumptions can be made (Gonda, 1985; Gonda and Chan, 1985): (1) the primary drug particles are nearly spherical; (2) the aggregates are close-packed hexagonal structures; (3) the droplet size distribution can be described adequately by the log-normal probability function.

Assumptions 1 and 2 which were justified in the first paper in this series lead to the following numerical values (Gonda, 1985):
(i) the volume fractions occupied by the solid in aggregates are

$$f(1) = 1;\ f(i) = 0.741 \text{ for } i \geq 2 \tag{14}$$

(ii) the dynamic shape factors for the aggregates are

$$K(1) = 1,\ K(2) = 1.02 \text{ and } K(i) = 1.10 \text{ for } i \geq 3 \tag{15}$$

(iii) $D_{\min}$, the lower integration limit in Eqn. 2, is calculated as follows: the minimum volume of a droplet containing a spherical aggregate of i particles, $V_{\min}$, must be at least equal to the volume of the aggregate, i.e.,

$$V_{\min} = \frac{\pi}{6} D_{\min}^3 = \frac{\pi}{6} d_e^3(1) \frac{i}{f(i)} \tag{16}$$

Therefore

$$D_{\min} = d_e(1) \sqrt[3]{\frac{i}{f(i)}} \tag{17}$$

Assumption 3 above, i.e., that the droplet size distribution can be approximated by a log-normal probability function, can be justified on empirical grounds (Hinds, 1982). Thus, the distribution at the moment of generation can be characterized by a mass median diameter of the droplets MMD_D, and a geometric standard deviation σ_D. The count median diameter CMD_D is then (Hinds, 1982)

$$CMD_D = MMD_D \exp\left[-3(\ln \sigma_D)^2\right] \tag{18}$$

and the diameter of a droplet of average volume is (Hinds, 1982)

$$\overline{D} = CMD_D \exp\left[1.5(\ln \sigma_D)^2\right] \tag{19}$$

The average droplet volume is (c.f. Eqns. 5 and 10)

$$\overline{V}_D = \frac{\pi}{6} \overline{D}^3 = \bar{n}/N \tag{20}$$

Therefore, the average number of particles per droplet, $\bar{n}$, is

$$\bar{n} = N \frac{\pi}{6} \overline{D}^3 \tag{21}$$

If we express the number concentration N in terms of the % v/v concentration c

$$N = \frac{6c}{100\pi \left[d_e(1)\right]^3} \tag{22}$$

and substitute for $\overline{D}$ in Eqn. 20 from Eqns. 18 and 19, we get

$$\bar{n} = \frac{c}{100} \left[\frac{MMD_D}{d_e(1)}\right]^3 \exp\left[-4.5(\ln \sigma_D)^2\right] \tag{23}$$

Therefore, $\bar{n}$ can be calculated from the basic properties of the droplet size distribution (MMD, σ_D), primary particle size [$d_e(1)$] and the suspension concentration (c), so that $M(i)$ can be obtained according to Eqn. 11. If a population of droplets with a log normal distribution with initial parameters MMD_D and σ_D containing non-volatile solutes evaporates, the resulting dry particles have the same geometric standard deviation σ_d as the droplets and their mass median diameter is proportional to MMD_D and the cube root of their concentration (see the Appendix). The uniform distribution model for nebulized suspensions (Gonda, 1985; Gonda and Chan, 1985) would predict similarly that the geometric standard deviation of the aggregates $\sigma_d = \sigma_D$, and that the mass median diameter of the dry aggregates, MMD_d, corresponds to the diameter of the aggregate which contains the number of particles n_{MMD}, expected in a droplet of median mass. I.e.

$$\begin{aligned} n_{MMD} &= (\text{vol. of a droplet of median mass}) \times \\ &\quad (\%\text{v/v concentration})/(\text{vol. of a primary particle}) \\ &= \frac{\pi}{6} (MMD_D)^3 \frac{c}{100} \Big/ \left[\frac{\pi}{6} d_e^3(1)\right] \\ &= \left[MMD_D/d_e(1)\right]^3 \frac{c}{100} \end{aligned} \tag{24}$$

The n_{MMD} calculated from this equation can be converted to the corresponding mass median diameters MMD_d, or mass median aerodynamic diameters, $MMAD_d$ of the dry aggregates using Eqns. 12 or 13 with $i = n_{MMD}$, $d_e(i) = MMD_d$ and $d_{ae}(i) = MMAD_d$; for non-integer values of n_{MMD}, linear interpolation between two successive values of i can be carried out (Gonda, 1985).

Intuitively, we would expect the uniform distribution model to work satisfactorily for relatively concentrated nebulized suspensions. In dilute systems, the probability of obtaining empty droplets is high, and a better estimate of the mass median (aerodynamic) diameter of the aggregate, MMD_d (or $MMAD_d$) may be obtained by excluding the empty droplets from the considerations. The average number of primary drug particles $n'(D)$ in drug-containing droplets of diameter D can be deduced from Eqn. 1 (Gonda, 1985) as

$$n'(D) = \frac{n(D)}{\sum_{k=1}^{\infty} P(k, D)} = \frac{n(D)}{\sum_{k=0}^{\infty} P(k, D) - P(0, D)} = \frac{n(D)}{1 - P(0, D)} = \frac{n(D)}{1 - e^{-n(D)}} \qquad (25)$$

Specifically, for $D = MMD_D$, we have

$$n'_{MMD} = \frac{n_{MMD}}{1 - e^{-n_{MMD}}}$$

where

$$n_{MMD} \equiv n(MMD) \text{ and } n'_{MMD} \equiv n'(MMD). \qquad (26)$$

Results and Discussion

Previous studies (Gonda, 1985; Gonda and Chan, 1985) showed that the size distributions of the aggregates calculated according to the above computational model conformed well to the log-normal probability function which is frequently employed to approximate particle size data (Hinds, 1982). For these reasons, we have again plotted the computed values of the cumulative mass fraction (undersize), $100 \times M(i)$, on a probability scale against the relative aerodynamic diameter $d_{ae}(i)/d_{ae}(1)$ (Eqn. 13) on a logarithmic scale (all such plots in this paper show also the scale in units of $d_e(i)/d_e(1)$ (Eqn. 12) for the reader interested in equivalent sphere volume diameters). The ratio R_1, of the mass median aerodynamic diameters of the cluster, $MMAD_d$, to the aerodynamic diameter of the primary drug particle, $d_{ae}(1)$, was obtained, where possible, from the graphs as the interpolated value at $M(i) = 50\%$. Where the $100 \times M(i)$ plot started above 50%, of course, $MMD_d/d_{ae}(1) = 1$ since $MMD_d = d_{ae}(1)$ is the minimum value for the 'aggregate' size that would be measured in practice. Fig. 1 shows the results for $c = 0.5$–2% v/v, $MMD_D/d_e(1) = 10$ and 15 and $\sigma_D = 1.01$–2. Over the range that would be normally accessible in experiments ($100 \times M(i) \cong$ 10–90%), the graphs appear reasonably linear, i.e., suggesting logarithmic-normal size distribution of the aggregates; their geometric standard deviation, σ_d, was estimated from (Hinds, 1982; Martin et al., 1983)

$$\sigma_d = \frac{d_{ae}(i) \text{ at } [100 \times M(i) = 84\%]}{MMAD_d} \qquad (27)$$

Where this procedure could not be followed because the cumulative computed values did not reach 84% (see the results below), the formula, (Hinds, 1982; Martin et al., 1983) was used

$$\sigma_d = \frac{MMAD_d}{d_{ae}(i) \text{ at } [100 \times M(i) = 16\%]} \qquad (28)$$

Table 1 shows that the values of σ_d for the systems in Fig. 1 are very well approximated by the geometric standard deviations of the droplets, σ_D. This indicates that the uniform distribution model might represent these systems well. In order to test this possibility, the relative ratio, R_2, of the mass median aerodynamic diameter of the aggregates, $MMAD_d$, to $d_{ae}(1)$ was also calculated according

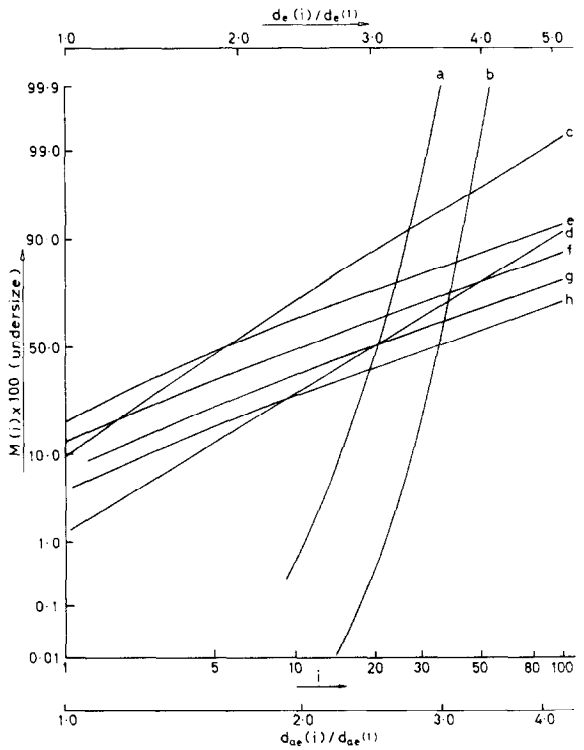

Fig. 1. Percentage cumulative mass fraction (undersize) $M(i) \times 100$, against the number of primary particles per cluster, i, and the relative equivalent volume and aerodynamic diameters, $d_e(i)/d_e(1)$ and $d_{ae}(i)/d_{ae}(1)$, respectively. The formulation parameters for the curves are given in Table 1.

to the uniform distribution model from Eqn. 24 using the procedure explained in the text following that equation. It is evident from the excellent agreement between R_1 and R_2 in Table 1 that the uniform model is, indeed, a very reliable description of the situation for the range of the formulation parameters in Fig. 1. Substitution of the numerical values into Eqn. 24 in fact gives n_{MMD} in the range 5–33.75. For such large n_{MMD}, Eqn. 26 gives $n_{MMD} \cong n'_{MMD}$ because the probability of not finding a solid particle in a droplet size with the mass median MMD_D is very low. Furthermore, the ratio $MMD_D/d_e(1)$ is quite large for these systems, and therefore it is unlikely that there would be too many small droplets which could not accommodate enough solid particles. In other words, the integration limit $D_{\min} \cong 0$ in Eqn. 2 and the 'volume exclusion effect' (Callingham, 1980; Gonda, 1985) is not important in these systems. It is thus quite adequate for the purpose of estimation of MMD_d, $MMAD_d$, and σ_d to view the distribution of the solid in the same way as if though it was initially completely dissolved in the carrier liquid. So, $\sigma_d = \sigma_D$ and the median diameters are obtained simply from volumetric relationships, without the need for any computer modelling.

The situation is rather different, however, when

TABLE 1

Numerical relationships between the formulation parameters and the size distribution of the aerosol product for the systems in Fig. 1

Curve in Fig. 1	σ_D [1]	c [2]	$MMD_D/d_e(1)$ [3]	n_{MMD} [4]	R_1 [5]	R_2 [6]	σ_d [7]
a	1.01	2.0	10	20	2.45	2.46	1.08
b	1.01	1.0	15	33.75	2.94	2.93	1.06
c	1.5	0.5	10	5	1.61	1.55	1.5
d	1.5	2.0	10	20	2.47	2.46	1.5
e	2.0	0.5	10	5	1.61	1.55	1.9
f	2.0	1.0	10	10	2.02	1.95	1.9
g	2.0	2.0	10	20	2.47	2.46	2.0
h	2.0	1.0	15	33.75	2.95	2.93	1.9

[1] Geometric standard deviation of droplets.
[2] Percentage v/v concentration.
[3] Ratio of the mass median diameter of the droplets to the diameter of the primary particle.
[4] Average number of particles expected in a droplet of median mass (Eqn. 24).
[5] Ratio of the mass median aerodynamic diameter of the product to the aerodynamic diameter of the primary particle, obtained from the figure.
[6] Same as R_1, but calculated assuming uniform distribution (see text following Eqn. 24).
[7] Geometric standard deviation of the product obtained as explained in the text surrounding Eqns. 27 and 28.

the number of primary particles per droplet of mass median diameter n_{MMD} calculated from Eqn. 24 is less than 1. Examples of such formulations are given in Fig. 2 and Table 2; 'ideal' systems, i.e. truly log-normal distributions with geometric standard deviations $\sigma_d = 1.5$, 2.0 and 2.5 are shown for comparison as broken lines. For the same n_{MMD}, the greater the degree of polydispersity of droplets σ_D, the better is the geometric standard deviation of the aggregates σ_d approximated by σ_D (as evidenced, e.g., by the near parallelism of lines n and o with the broken line $\sigma_d = 2.5$); the agreement improves also as n_{MMD} becomes larger, as we would expect from the previous results in Fig. 1 and Table 1. In the very dilute systems (e.g. curves j and m), most occupied droplets have only one particle but there are finite, and observable, probabilities to find more than one particle per droplet in the large droplets. This leads to the long 'tails' of the cumulative mass $M(i)$ at high i which have slopes appropriate to σ_D. It should be noted, however, that when these 'long tails' are prominent, they contain only a small fraction of the total mass of particles (e.g. curves j and m have about 95 and 90%, respectively, of the mass in the form of individual particles). Effectively, these dilute systems are nearly monodisperse (Raabe, 1968). It is interesting to speculate about

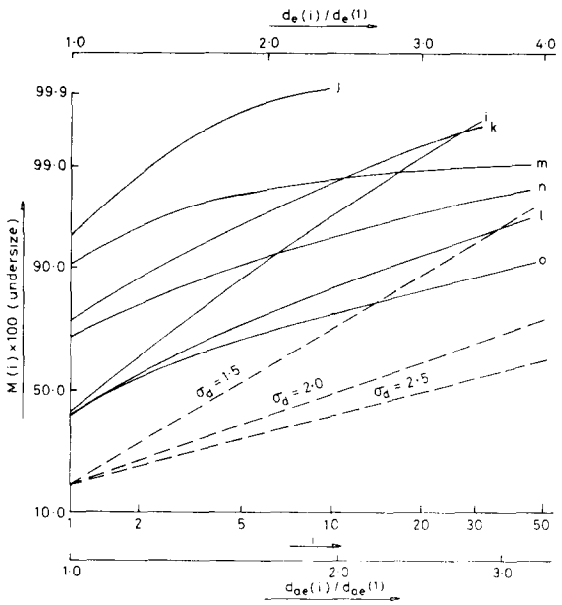

Fig. 2. See legend to Fig. 1 for explanations. The formulation parameters for the curves are given in Table 2. The broken lines show systems which would have geometric standard deviations as indicated.

the conclusion that one might arrive at if such distributions were observed experimentally: microscopic examination of the dry aerosol would reveal (correctly) that there are only a few large

TABLE 2

Numerical relationships between the formulation parameters and the relative mass median aerodynamic diameters of the products for the systems in Fig. 2.

Curve in Fig. 2	σ_D	c	n_{MMD}	n'_{MMD} [1]	R_1	R'_2 [2]	σ_d [3]
i	1.5	0.1	1	1.582	1.08	1.11	1.4
j	2.0	0.001	0.01	1.005	1.00	1.00	–
k	2.0	0.01	0.1	1.051	1.00	1.01	–
l	2.0	0.1	1	1.582	1.10	1.11	1.8
m	2.5	0.001	0.01	1.005	1.00	1.00	–
n	2.5	0.01	0.1	1.051	1.00	1.01	–
o	2.5	0.1	1	1.582	1.10	1.11	2.5

The ratio of the median droplet size to the size of the primary particle, $MMD_D/d_e(1)$, is 10. Other explanations are in the footnotes to Table 1.

[1] Average number of primary particles expected in occupied droplets of median mass (Eqn. 26).

[2] R'_2 is calculated from n'_{MMD} (Eqn. 26), in contrast to R_2 in Table 1 which was obtained from n_{MMD} (Eqn. 24). See text for further details.

[3] The values of σ_d could not be calculated for many of the curves in Fig. 2 using Eqns. 27 or 28. Approximate σ_d can be estimated by comparison with the broken lines.

aggregates present, and that the size distribution is truncated at the lower end at the size of a primary particle. However, devices which fit indirect observations by a continuous curve and extrapolate it as a distribution function from 0 to infinity (as e.g. some light scattering and diffraction instruments) could erroneously predict the presence of a large fraction of particles smaller than the actual primary particles [the reader can imagine this by extrapolating the curves in Fig. 2 to the left toward $d_{ae}(i)/d_{ae}(1)$ less than 1].

Clearly, for $n_{MMD} < 1$, the values of R_2 calculated on the basis of the uniform distribution model from Eqn. 24 (see Table 2) would be meaningless since they would predict for many of the dilute suspension mass median (aerodynamic) diameters of the clusters smaller than those of the primary particles! In these circumstances, the empty droplets must be excluded from the calculation and Eqn. 26 is used instead of Eqn. 24 to obtain R_2' from n_{MMD} by the same procedure as that for obtaining R_2 from n_{MMD} (see text following Eqn. 24). Excellent agreement between the values of R_1 and R_2 can be seen in Table 2. Thus, the uniform distribution model is successful again when it is modified to exclude empty droplets from the calculation of the mass median aggregate size for systems with low average occupancy of median size droplets by the solid particles.

We suspected that the simple uniform distribution approximation may be also inadequate when the volume exclusion effects become important. The type of formulations which would be likely to fall in this category would be those which have a large number of relatively small droplets (low ratio $MMD_D/d_e(1)$ and, or, large σ_D) and a high probability of forming large aggregates (high concentration of the dispersed phase). It was deduced (Gonda, 1985) that in monodisperse droplet systems, the volume exclusion effects for the droplet to primary particle size ratio of 2 would become important at concentrations in excess of 60%. Such concentrated suspensions would be almost certainly outside the validity of assumptions invoked in the introduction. However, it is possible that in polydisperse droplet systems, the volume exclusions begins to operate at much lower concentrations because, for a sufficiently large σ_D, there would exist an appreciable number of droplets which would not accommodate even relatively small aggregates. These expectations were confirmed in the computations for the range of formulations presented in Fig. 3. Examination of the results showed appreciable differences between the uncorrected probabilities $P'(k)$ (Eqn. 2) and the renormalized probabilities $P(k)$ (Eqn. 3). These differences became apparent at a lower concentration when $\sigma_D = 2.0$ than when the droplets were monodisperse. Perhaps, the most prominent feature of these systems is the slow increase in the cumulative mass (undersize) when the aggregates become large. This leads to a long 'tail' in the graph. For example, the mass median aerodynamic diameter for $c = 10\%$, $\sigma_D = 2.0$, $MMD_D/d_e(1) = 2$ (curve s in Fig. 3) is 1.29 which corresponds to aggregates of 2–3 particles. Yet the cumulative mass up to 200 particles per aggregate adds up to only 82.3%. The presence of the 'flat' portion at high cumulative mass is indicative of the fact that

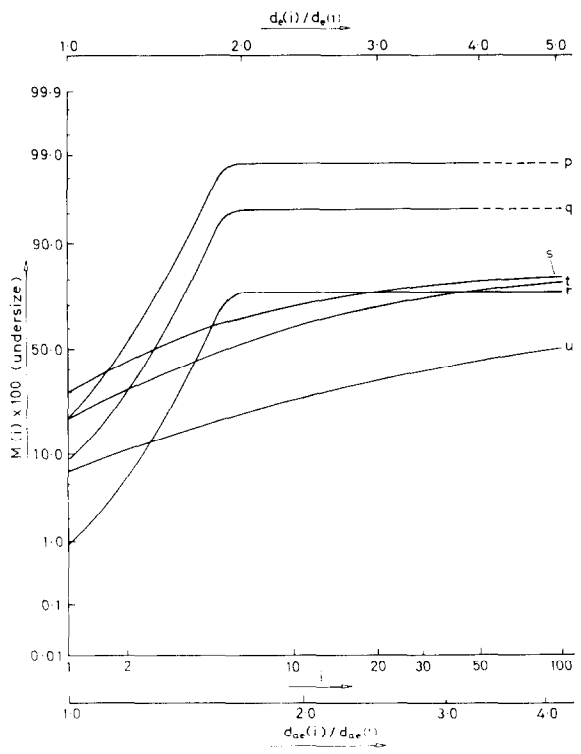

Fig. 3. See Legend to Fig. 1 for explanation. The formulation parameters for the curves are given in Table 3.

the size distribution could be no longer described as approximately log-normal. For the polydisperse systems in Fig. 3 ($\sigma_D = 2.0$), the values of σ_d could not be predicted accurately from σ_D and there are appreciable differences between the values of R_1 and R_2' (Table 3). Therefore the uniform distribution model would be a poor approximation of these systems, particularly if the droplets are polydisperse. The qualitative reasons for this behaviour may be summarized as follows: since the suspensions are relatively concentrated (c.f. Fig. 1 and Table 1), it would be expected on the basis of uniformity that each droplet should contain at least one solid particle. In the nearly monodisperse systems in Fig. 3 and Table 3 ($\sigma_D = 1.01$), this is possible. However, since $MMD_D/d_e(1)$ is only 2, the small droplets in the polydisperse systems cannot accommodate even single solid particles. Consequently, the unnormalized probability of finding a particle in a droplet of any size is less than what we would find in a monodisperse droplet system with $D/d_e(1) = 2$. When the same calculation is carried out for a greater aggregation number, an even bigger fraction of the droplets on the lower side of the droplet size distribution is incapable of accommodating these larger aggregates (c.f. the value of D_{min} in Eqn. 17 as a function of the aggregate number i). Thus, the probabilities of finding large aggregates are truncated by the exclusion of droplets of diameters less than D_{min}. This leads to the 'tailing' of the cumulative mass plots on the log-normal scales as shown in Fig. 3, i.e., the upper part of the calculated $M(i)$ falls below the expected plot for a log-normal distribution derived from the assumption of uniform distribution of the solid among the droplets. This effect is not important in the nearly monodisperse systems in Fig. 3 and Table 3 because more than 5 particles would be required to exceed D_{min} for the ratio $MMD_D/d_e(1) = 2$. Even the most concentrated suspension (curve r) has an average of 5 particles per droplet. The probability of finding droplets greater than the median size is low when $\sigma_D = 1.01$ and therefore the estimates of σ_D and R_2' from the uniform distribution model are quite reasonable (Table 3). Nevertheless, the curves p, q and r in Fig. 3 show that the small, but finite probability of droplets greater than the median sized ones leads to a long tail of low probability clusters with high aggregation numbers i.

Conclusions

Using purely probabilistic arguments, it was shown that suspended monodisperse drug particles would distribute themselves in log-normal droplets to give rise to distribution of 'clusters' after the carrier liquid evaporated. The cumulative mass distribution of the solid as a function of the cluster 'size' (number of primary particles per cluster) was computed according to a rigorous statistical model. The 'size' was also converted to

TABLE 3

Numerical relationships between the formulation parameters and the size distribution of the aerosol product for the systems in Fig. 3

Curve in Fig. 3	σ_D	c	n_{MMD}	n'_{MMD} [1]	R_1	R_2' [2]	σ_d
p	1.01	20.0	1.6	2.00	1.17	1.19	1.1
q	1.01	30.0	2.4	2.64	1.28	1.27	1.1
r	1.01	62.5	5.0	5.03	1.47	1.59	1.1
s	2.0	10.0	0.8	1.45	1.29	1.09	2.3
t	2.0	20.0	1.6	2.00	1.60	1.19	3.9
u	2.0	62.5	5.0	5.03	4.14	1.59	3.0

The ratio of the median droplet size to the size of the primary particle $MMD_D/d_e(1)$, is 2. Other explanations are in the footnotes to Table 1.

[1] average number of primary particles expected in occupied droplets of median mass (Eqn. 26).

[2] R_2' is calculated from n'_{MMD} in a manner analogous to calculation of R_2 in Table 1 from n_{MMD}.

equivalent sphere volume, or aerodynamic diameters assuming sphericity of the primary particles and the clusters, and hexagonal close packing in the aggregates. The computer simulations predict that there would be a significant increase ($\geq 10\%$) in the drug mass median aerodynamic diameter as a result of such an 'aggregation' mechanism at suspension concentrations in excess of 0.1% v/v when the mass median diameter of the droplets is 10 times greater than the diameter of a primary particle. These findings are in agreement with the previous study carried out for monodisperse droplets and they should apply to the type of formulations currently in use (Gonda, 1985). Furthermore, it is shown that for the majority of realistic formulation parameters for therapeutic aerosols, it is possible to estimate the median size of the aggregates and their geometric standard deviation simply from volumetric relationships based on the assumption of uniform distribution of the 'solid' (i.e., usually the drug particles) in the carrier liquid (i.e. the propellant or any other liquid volatile components of the aerosol formulation).

At present, there are no detailed published data on simultaneous droplet and aggregate size analysis. Sakai et al. (1985) studied atomization of several relatively concentrated suspensions. Although they were primarily interested in the effect of suspension concentration on the droplet size, the authors concluded that their observations could be explained by a model in which the concentration of solid particles in each droplet was the same as the concentration in the suspension itself, i.e., their results were consistent with the uniform distribution theory.

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Glossary of Symbols

C	% v/v concentration of suspension
CMD_D	count median diameter of droplets
d	diameter of the solid particle after a droplet evaporated
$d_{ae}(i)$	aerodynamic diameter of an aggregate of i particles
$d_e(i)$	equivalent sphere volume diameter of an aggregate of i particles
D	diameter of a droplet
$\overline{D}$	diameter of a droplet of average volume
$D_{\max}$	upper integration limit for droplet size as given e.g. by the size range of the measuring device
$D_{\min}$	lower integration limit for droplet size as given e.g. by the size range of the measuring device
$f(i)$	volume fraction occupied by the solid in aggregates of i particles
$F(i)$	fraction of the total drug mass contained in aggregates of i drug particles
g	mass of a primary particle in suspension
i	number of particles in an aggregate
k	number of particles in a droplet
$K(i)$	dynamic shape factor for an aggregate of i particles
$m(i)$	mass of an aggregate of i particles
$M(i)$	cumulative mass distribution of aggregates as a function of i (i is the number of particles in an aggregate)
MMD_d	mass median diameter of dry aggregates
MMD_D	mass median diameter of droplets
$MMAD_d$	mass median aerodynamic diameter of the dry aggregates
$n = n(D)$	average number of particles per droplet of diameter D
$\bar{n}$	average number of particles per droplet of all sizes including empty droplets
$n'(D)$	average number of particles in drug-containing droplets of diameter D
$n(i)$	total number of droplets containing aggregates of i particles
$n_{MMD} =$ $n(MMD)$	number of particles in an aggregate expected to be formed from a droplet of median mass (including empty droplets in the median calculation)

n'_{MMD} = same as n_{MMD} except that empty droplets are excluded

n'_{MMD}

n_T total number of droplets formed from a volume V of a suspension

N number of primary particles per unit volume of suspension

$p(D)$ initial distribution of droplets after nebulization of the suspension

$P(i)$ probability of finding an aggregate of i particles in a droplet of any size

$P(k)$ renormalized $P'(k)$ to allow $D_{\min}$ to be sufficiently large to accomodate a cluster of k particles

$P(k, D)$ probability of finding k particles in a droplet of diameter D

$P'(k)$ probability of finding k particles in a droplet of any size

V volume of a suspension

$V_{\min}$ minimum volume of a droplet containing an aggregate of i particles

V_s volume of solid particles after the volatile components evaporated

$\bar{V}_d$ average droplet volume

σ_d geometric standard deviation of dry aggregates

σ_D geometric standard deviation of droplets

Appendix

Imagine a population of droplets with a log-normal distribution characterized by the parameters MMD_D and σ_D containing a non-volatile solute at a concentration c (% v/v). When the solvent evaporates, the remaining solid particle originating from the droplet of diameter D will have a volume V_s.

$$V_s = \frac{\pi d^3}{6} = \frac{\pi D^3}{6}\frac{c}{100} \qquad (A.1)$$

i.e., the solid particle will have a diameter

$$d = D\sqrt[3]{c/100} \qquad (A.2)$$

Since the same proportional relationship exists between all d's and all the diameters of the droplets from which the solid particles originated, the size distribution of the latter is simply shifted by a constant distance on the log-normal probability scale, i.e., it is parallel to the line for the size distribution of the droplets. It follows that the degrees of polydispersity for two parallel curves in such a graph are the same, i.e.,

$$\sigma_d = \sigma_D \qquad (A.3)$$

and

$$MMD_d = MMD_D\sqrt[3]{c/100} \qquad (A.4)$$

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