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Development of a systematic theory of suspension inhalation aerosols. I. A framework to study the effects of aggregation on the aerodynamic behaviour of drug particles

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Summary

When a suspension of drug particles is nebulized, the number of particles in a droplet depends on its size and on the relative sizes of the particles and the concentration of the suspension. Therefore, the drug particle size distribution after aerosolization is, in general, different from the distribution of the primary particles. The dry drug particles left after the evaporation of the propellant from a droplet form a cluster (aggregate). The average number of particles in such an aggregate and the variance of this number is calculated from the Poisson probability distribution function. Further progress is made under the following simplifying assumptions: (1) both the primary drug particles and the droplets are monodisperse; (2) the primary drug particles and the clusters are spherical; and (3) a particular model of packing of particles into aggregates can be adopted. The cumulative mass distribution of the drug as a function of the number of drug particles/cluster, equivalent volume and aerodynamic diameters are computed for a specific model. The ranges of concentration and ratios of droplet/particle diameters where aggregation is likely to affect significantly the aerodynamic behaviour of the drug, are outlined. The theoretical calculations are in qualitative agreement with the available experimental evidence for currently used therapeutic suspension inhalation aerosols. It is suggested that the

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treatment presented here may be developed into a predictive tool for formulation of aerosols with desired aerodynamic features.

Introduction

The purpose of this work is to attempt to develop a framework which would link the fundamental properties of a suspension of drug particles in a propellant (or carrier liquid) to those physical characteristics of the nebulized product which are ultimately important for therapeutic efficacy. Thus, the present paper is concerned with the basic relationship between the concentration and size of the droplets and the primary solid non-volatile drug particles on the one hand, and the size distribution of the drug after nebulization and subsequent evaporation of the volatile components from the droplets of aerosol on the other hand.

When a suspension of solid particles in a liquid medium is nebulized, the number of particles per droplet will depend on the relative size of the droplets and particles, and the concentration of the suspension (Raabe, 1968). Thus, 'empty' droplets, or droplets containing one or several drug particles are possible, as observed experimentally (Callingham, 1980; Morén, 1982; Raabe, 1968). After evaporation of the volatile components, one therefore does not regenerate the original size distribution of the primary drug particles, except when the suspension is extremely dilute and the droplets are not much larger than the drug particles. There may be, of course, other reasons for the difference between the primary drug particle and the 'dried' aerosol size distributions, e.g.: (1) the suspended particles may undergo the processes of coagulation, or partial dissolution and Ostwald ripening (Florence and Attwood, 1981 and refs. therein) prior to aerosol generation; and (2) non-volatile excipients form droplets of 'residues' (i.e. formation of inactive aerosol particles or droplets from 'empty' droplets) and they will also increase the volume of the drug particles after the 'drying' process (Morén, 1982). Some of these factors will be treated in detail in future papers but they will be neglected in the present work. Here, the 'primary drug particle size distribution' stands for the distribution of distinct drug particles which exists in the generating device immediately prior to nebulization. We have some evidence (Ashurst and Gonda, unpublished results) that drug particles stabilized by secondary minimum flocculation (Florence and Attwood, 1981) can be regarded as such distinct entities. Presumably, the forces present during the evaporation of the propellant are sufficient to break-up the flocs held in a shallow potential energy minimum. Deflocculated suspensions (Florence and Attwood, 1981) with slow sedimentation or 'creaming' should also yield distinct primary drug particles.

The present treatment considers mainly the model in which the drug particles and the initial aerosol droplets containing them are monodisperse. The polydispersity of the latter can be incorporated readily into the treatment (Raabe, 1968) as outlined below. Micronized drug powders for inhalation aerosols have usually a relatively small degree of polydispersity (geometric standard deviation typically 2 or less (Newman, 1984 and refs. therein)), and therefore the assumption about their monodispersity does not appear to be too restrictive. At any rate, the theory could be extended to polydisperse primary drug powders but the ensuing treatment would result in some loss of clarity.

Finally, the examples presented to illustrate the theory are based on spherical shapes of primary drug particles and their aggregates. As the theories to account for the aerodynamic behaviour of non-spherical particles in different flow regimes are still under development (Dahneke, 1982; Gonda, 1985; Kasper, 1982a and b), it is felt that only results for spherical shapes have sufficient general validity at present.

Theory

Consider a total mass G of non-volatile monodisperse solid particles suspended in a volatile liquid. If the total volume of the suspension is V, the % w/v concentration C of the solid is:

$$C = \frac{G}{V} \cdot 100 \tag{1}$$

and the % v/v concentration c is, for particle density ρ

$$c = \frac{G}{\rho V} \cdot 100 \tag{2}$$

The average number concentration N can be calculated from the weight of an individual particle, g, as:

$$N = \frac{G}{gV} \tag{3}$$

The volume V_D of an individual droplet (assuming that it is a perfect sphere) of diameter D is:

$$V_D = \frac{\Pi}{6} \cdot D^3 \tag{4}$$

Thus, the average number of particles per droplet, n, is from Eqns. 3 and 4

$$n = V_D N = \frac{\Pi}{6} \cdot D^3 \cdot \frac{G}{gV} \tag{5}$$

The mass g of an individual drug particle can be expressed in terms of an equivalent volume sphere diameter d_e:

$$g = \frac{\Pi}{6} \cdot d_e^3 \cdot \rho \tag{6}$$

Combining this expression with the previous one and Eqn. 2, we obtain:

$$n = \left(\frac{D}{d_e}\right)^3 \cdot \frac{c}{100} \tag{7}$$

This expression relates the average number of drug particles per droplet to the volumetric concentration of the solid and the relative sizes of the droplet and the drug particle. The actual number of drug particles per droplet would approach n only if the particles were distributed uniformly throughout the droplets. In fact, the distribution of drug particles in droplets follows a probabilistic course. It is customary to assume that the probability P(k) that k particles will be contained in a droplet obeys the Poisson distribution function (Raabe, 1968):

$$P(k) = \frac{e^{-n} n^k}{k!}, \ k = 0, 1 \ldots \infty \tag{8}$$

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

It may be worth remembering that for $k > 10$, the Poisson distribution can be approximated quite adequately by the normal distribution (Green and Margerison, 1978), and this property could be exploited when dealing with concentrated suspensions as, e.g. in spray-drying. The validity of the Poisson distribution for dilute suspensions was shown by Raabe (1968).

If the droplets were polydisperse, the probability P(k) would be also a function of the droplet diameter D, through the dependence of n on D (Eqn. 7). The probability that k particles would be found in droplets of any size could be calculated then from (Raabe, 1968):

$$P(k) = \int_0^{\infty} \frac{e^{-n} n^k}{k!} \cdot p(D) \, dD \tag{9}$$

where p(D) stands for the droplet size distribution function. Eqn. 9 carries an inherent assumption, namely that any droplet could accommodate an arbitrarily large number of solid particles, and it is therefore invalid for concentrated suspensions with overlapping droplet and drug size distributions. It is possible to set-up a statistical model which excludes the possibility that the volume of drug particles per droplet exceeds the volume of the droplet (Callingham, 1980). It will be shown below, however, that this 'crowding' effect can be ignored for most practical formulations of inhalation aerosols.

The problem which is of more direct interest to us is the average number of primary drug particles per droplet, n_D. This is obtained from n divided by the fraction of drug-containing droplets. That is, we have to exclude 'empty' droplets from Eqn. 7. With the help of Eqn. 8, we can calculate n_D as:

$$n_D = \frac{n}{\sum_{k=1}^{\infty} P(k)} = \frac{n}{1 - P(O)} = \frac{n}{1 - e^{-n}} \tag{10}$$

The variance σ^2 of n_D, can be derived as (Appendix I):

$$\sigma^2 = n^2 + n - \frac{n^2}{1 - e^{-n}} \tag{11}$$

Although the average number of drug particles per aggregate, n_D, and its variance σ^2 (Eqns. 10 and 11) are quite informative, a more detailed insight into the distribution of the drug mass among the aggregates may be obtained by the following considerations: the mass of an aggregate containing $k = i$ primary drug particles is m(i)

$$m(i) = i \cdot g \tag{12}$$

Since the probability of having i primary drug particles per droplet is P(i), the number of droplets containing this size of aggregates is given by (the total number of droplets, V/V_D) × P(i). These droplets will contain a total drug mass $(V/V_D) \times P(i) \times m(i)$. The fraction F(i) of the total drug mass $G = NgV$ (Eqn. 3) contained in aggregates having i particles per aggregate is therefore (c.f. Eqns. 5 and 11):

$$F(i) = \frac{VP(i)m(i)}{V_D NgV} = \frac{P(i)ig}{V_D Ng} = \frac{iP(i)}{n} \tag{13}$$

The cumulative mass distribution M(i) as a function of i is therefore:

$$M(i) = \frac{1}{n} \sum_{k=1}^{i} kP(k) \tag{14}$$

M(i) for $i = 1, 2 \ldots \infty$ can be computed by summation of the terms kP(k) where P(k) is the Poisson probability function given by Eqn. 8.

However, it is customary to express M as a dependence on the 'particle' size, rather than as a function of the number of primary particles per aggregate. The equivalent volume of an aggregate of i drug particles is:

$$V_e(i) = \frac{\Pi}{6} \cdot d_e^3(i) = \alpha(i) d_e^3 \tag{15}$$

where $\alpha(i)$ is a (static) volume shape factor (Allen, 1975). Eqn. 15 therefore relates the equivalent volume diameter of the aggregate of i particles $d_e(i)$ to the equivalent volume diameter of an individual drug particle d_e. Clearly, for spherical primary particles,

$$\alpha(1) = \frac{\Pi}{6} \tag{16}$$

For $i \geqslant 2$, $\alpha(i)$ depends on the geometric arrangement of the primary drug particles in the aggregate. This problem, for aggregates of spherical particles, has been reviewed by Davies (1979) and more recently by Kasper (1982a). In order to proceed further, it is necessary to consider a specific model for α. Let us suppose, for example, that the aggregates are in the form of porous spherical clusters. The sphere which envelopes the cluster has a diameter $d_e(i)$. Its 'equivalent' volume is:

$$V_e(i) = \frac{\Pi}{6} \cdot d_e^3 i/f(i) = \frac{\Pi}{6} \cdot d_e^3(i) = \alpha(i) d_e^3 \tag{17}$$

where f(i) is the fraction of the total volume occupied by the solid. Thus:

$$\alpha(i) = \frac{\Pi}{6} \cdot i/f(i) \tag{18}$$

and, from Eqns. 15 and 18, we obtain:

$$\frac{d_e(i)}{d_e} = \sqrt[3]{\frac{6}{\Pi} \cdot \alpha(i)} = \sqrt[3]{i/f(i)} \tag{19}$$

Specific examples of the above expression will be discussed under Results. In general, information about f(i) may be gained from microscopic examination of deposits of the sprayed product, and d_e can be obtained from the microscopic dimensions and shape of the primary particle, or by a volume-dependent particle sizing method such as the Coulter Counter (Gonda et al., 1982; Polli et al., 1969). With this information, it is then possible to make 'predictive' calculations of the cumulative mass distribution M(i) vs 'size' $d_e(i)$ for various values of n, i.e. the suspension concentration, c, and the ratio of the droplet and primary drug particle size D/d_e (Eqn. 7). Since c and D/d_e can be varied by the formulator (Polli et al., 1969), these calculations can aid in the design of a product with a satisfactory drug mass distribution.

Finally, it is appropriate to consider the relationship between the aerodynamic behaviour of the primary drug particles and the 'ultimate' product. The aerodynamic diameter of an individual particle, d_{ae}, of density ρ is (Raabe, 1976; Hinds, 1982):

$$d_{ae} = d_e \sqrt{\frac{\rho C_e}{\rho_0 C_{ae} K}} \tag{20}$$

where ρ_0 is unit density (e.g. 1 g/cm^3), C_e and C_{ae} are slip correction factors for d_e and d_{ae} (for details, see Raabe, 1976) and K is the dynamic shape factor. A similar formula is valid for an aggregate of i primary particles with all the parameters (except for ρ_0) being a function of the index i. The composite particle which is an aggregate of primary particles plus the 'excluded' volume occupied by air, and not by the solid, has the apparent density $\rho(i)$. Neglecting the mass of air in the 'excluded' volume, the mass of this cluster is (Eqns. 6 and 12):

$$m(i) = ig = i \cdot \frac{\Pi}{6} \cdot d_e^3 \cdot \rho \tag{21}$$

and its volume is $V_e(i)$ (Eqn. 15). Thus,

$$\rho(i) = \frac{i \cdot \frac{\Pi}{6} \cdot d_e^3 \cdot \rho}{V_e(i)} = \frac{\Pi}{6} \cdot \frac{i\rho}{\alpha(i)} \tag{22}$$

Adopting the model of porous spherical clusters for $\alpha(i)$ (Eqn. 18), we obtain:

$$\rho(i) = \rho f(i) \tag{23}$$

Further, $d_e(i)$ can be expressed from Eqn. 19, so that the aerodynamic diameter of the cluster becomes:

$$d_{ae}(i) = d_e \sqrt[3]{\frac{6}{\Pi} \cdot \alpha(i)} \sqrt{\frac{\Pi}{6} \cdot \frac{i\rho}{\rho_0 \alpha(i)} \cdot \frac{C_e(i)}{C_{ae}(i)} \cdot \frac{1}{K(i)}} \tag{24}$$

The volume shape factor $\alpha(i)$ has been discussed already. The ratio of the slip factors $C_e(i)$ and $C_{ae}(i)$ can be put equal to 1 for drug particles of the size typically present in inhalation aerosols (Raabe, 1976). The dynamic shape factors K(i) for aggregates of spherical particles are available in literature (Davies, 1979; Hinds, 1982). If we further assume the particular form of $\alpha(i)$ given by Eqn. 18, $d_{ae}(i)$ becomes:

$$d_{ae}(i) = d_e \sqrt[3]{\frac{i}{f(i)}} \sqrt{\frac{\rho}{\rho_0} \cdot \frac{f(i)}{K(i)}} \tag{25}$$

Thus, the combination of Eqns. 20 and 25 gives the relationship between the aerodynamic diameters of a spherical cluster and the primary drug particle:

$$d_{ae}(i) = d_{ae} \sqrt[3]{\frac{i}{f(i)}} \cdot \sqrt{\frac{Kf(i)}{K(i)}} \tag{26}$$

This expression facilitates the calculation of the cumulative mass distribution M(i) (Eqn. 14) as a function of the aerodynamic diameter up to the cluster of $k = i$ primary drug particles. It requires: (1) the knowledge of the aerodynamic diameter of an individual particle which can be either measured directly, or calculated from the density and the dimensions of the particle (Gonda et al., 1982; Hinds, 1982); and (2) adoption of a model for the geometric arrangement of the particles in the cluster in order to estimate the values of $\alpha(i)$ and K(i) (Appendix II). The dynamic shape factor K for individual nearly-spherical or cubic particles is approximately equal to 1 (Hinds, 1982). The theories for irregularly shaped and elongated particles are being developed (Dahneke, 1982; Gonda, 1985; Kasper 1982a and b). The drug mass median aerodynamic diameter of the sprayed product can be predicted then from the plot of M(i) vs $d_{ae}(i)$ (Byron et al., 1977).

Results and Discussion

Calculations were carried out for the ratios $(D/d_e) = 2$–10 and % v/v concentrations $c = 0.001$–5%, thus covering the range of $n = 8 \times 10^{-5}$–50 (Eqn. 7). It was assumed that the aggregates of primary particles would form clusters enveloped by a sphere with equivalent volume diameter given by Eqn. 19. The hexagonal close-packing model was selected, i.e. $f(i) = 0.741$ for $i \geqslant 2$. With this choice of f(i), K(i) was taken to be $K(i) = 1.10$ for $i \geqslant 3$, and $K(i) = 1.02$ for $i = 2$ (see Appendix II for justification of the model and the numerical values), and for $i = 1$, $K(1) = 1$ (spherical primary particles) and, of course, $f(1) = 1$. The assumption that the equivalent volume of the largest cluster does not exceed the total volume of the droplet was checked by calculation of the maximum number of primary particles k_{max} that a droplet could accommodate:
From Eqns. 4 and 17:

$$V_e(k_{max}) = \frac{\Pi}{6} \cdot d_e^3 \cdot \frac{k_{max}}{f(k_{max})} = \frac{\Pi}{6} \cdot D^3 \tag{27}$$

Thus

$$k_{max} = \left(\frac{D}{d_e}\right)^2 \cdot f(k_{max}) = 0.741 \cdot \left(\frac{D}{d_e}\right)^3 \tag{28}$$

The computer programme rejected the calculations whenever k_{max} turned out to be smaller than the i value corresponding to 99.99% of cumulative mass of the drug (Eqn. 14). This rejection criterium is quite arbitrary, of course, but it does put a realistic limit on the calculations.

It is instructive to look initially at equivalent volume and aerodynamic diameters of the aggregates (Eqns. 19 and AII.2) as a function of the number of particles in the aggregate according to this model (Table 1). It is apparent that more than 4 primary particles are required to form an aggregate with an aerodynamic diameter 50% greater than the d_{ae} of a primary particle, and over 10 particles/aggregate cause an increase of $d_{ae}(i)$ by a factor of 2 or more. The reason for the slow increase of $d_{ae}(i)$ is its cube-root dependence on i (Eqn. AII.2). Following from this, we may conclude

TABLE 1

RELATIVE EQUIVALENT VOLUME AND AERODYNAMIC DIAMETERS OF SPHERICAL CLUSTERS OF SPHERICAL PARTICLES AS A FUNCTION OF THE NUMBER OF PRIMARY PARTICLES/AGGREGATE

i	$d_e(i)/d_e$ [a]	$d_{ae}(i)/d_{ae}$ [b]
1	1	1
2	1.39	1.19
3	1.59	1.31
4	1.75	1.44
5	1.89	1.55
6	2.01	1.65
7	2.11	1.74
8	2.21	1.81
9	2.30	1.89
10	2.38	1.95
11	2.46	2.02
12	2.53	2.08
13	2.60	2.13
14	2.66	2.19
15	2.73	2.24
16	2.78	2.29
17	2.84	2.33
18	2.90	2.38
19	2.95	2.42
20	3.00	2.46
30	3.43	2.82
40	3.78	3.10

[a] Eqn. 19. [b] Eqn. AII.2.

that significant changes ($> 50\%$) in the aerodynamic behaviour of aggregates as compared to the primary particles occur only if the aggregates contain more than four particles. The likelihood of forming a substantial number of such aggregates is indicated by the average number of particles/aggregate, n_D (Eqn. 10) and its variance (Eqn. 11), or standard deviation σ. Both n_D and σ depend on n, i.e. the ratio of the droplet and primary particle diameters, and the volumetric concentration of the suspended substance. Fig. 1 shows n_D vs n, with the σ values (vertical lines) at a number of discrete points. Clearly, aggregates containing four or more particles are unlikely until $n > 3$. For example, if the ratio of the droplet to particle diameter is $D/d_e \sim 5$, then the likelihood of aggregates of four or more particles becomes significant at $c > 2.5\%$. For $D/d_e \sim 10$, however, this treatment indicates that already at $c \sim 0.3\%$, a number of particles will form aggregates of four or more, i.e. they form clusters with aerodynamic diameters 50% or greater than the primary particles.

As n increases, both n_D and σ^2 approach n. Thus, for $n = 4$, $n_D = 4.07$ and $\sigma^2 = 3.7$, and for $n = 8$, $n_D = 8.00$ and $\sigma^2 = 7.98$. Clearly, when the average number of particles per droplet (including empty droplets) exceeds 4, the average aggregate size (n_D) becomes approximately equal to the value that one would expect on the

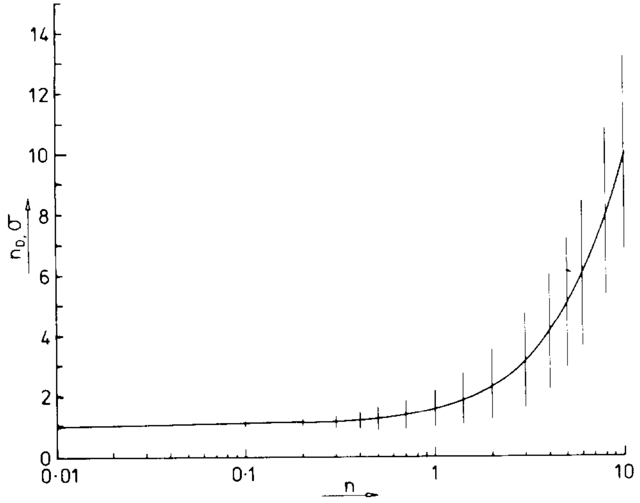

Fig. 1. The dependence of the average number of primary drug particles per cluster, n_D, on the average number of drug particles per droplet (including empty droplets), n. The square-root of variance of n_D, σ, is shown by the vertical lines.

basis of a uniform, homogeneous distribution of particles. However, the increasing value of σ^2 (which also approaches n) shows that, at the same time, there is an increase in the polydispersity of the aggregates, in terms of distribution of the number of particles/cluster.

Further insight into the nature of the changes caused by aggregation is obtained by studying the cumulative mass fraction of the clusters M(i) as a function of their diameters. In practice, one would expect that the size distribution of an aerosol conforms to the logarithmic-normal probability distribution function. Accordingly, representative results are shown in Fig. 2 where $d_{ae}(i)/d_{ae}$ and $d_e(i)/d_e$ are plotted on logarithmic scales while the % cumulative mass fraction (undersize) $100 \times M(i)$ is on normal probability scale. The number of primary particles per cluster is also shown. All plots appear reasonably linear over the range that would be accessible in experiments ($100 \times M(i) \simeq 10$–99%). As explained above, the value of n_D, and therefore n, controls the significance of aggregation. For instance, curve h in Fig. 2 corresponds to c = 3% and $D/d_e = 10$. Table 2 shows that in this case $n = n_D = 30$. It is clear from Fig. 2 that MMAD, the mass median aerodynamic diameter [the aerodynamic diameter above, or below, which 50% of the mass of the aerosol resides, i.e. $d_{ae}(i)/d_{ae}$ at $M(i) = 50\%$] is also at $i \simeq 30$. This gives $\text{MMAD}/d_{ae} \simeq 2.8$. Thus, high concentration of suspended primary particles coupled with a large ratio of the droplet to primary particle diameters leads eventually to a substantial increase in the mass median aerodynamic diameter. However, there does not appear to be a corresponding marked increase in the polydispersity of the aerodynamic diameters of the aerosol. This is in sharp contrast to the 'polydispersity' of the number of primary particles per cluster. The explanation for this apparent discrepancy lies in the fact that the aerodynamic diameter of a cluster depends only weakly on the

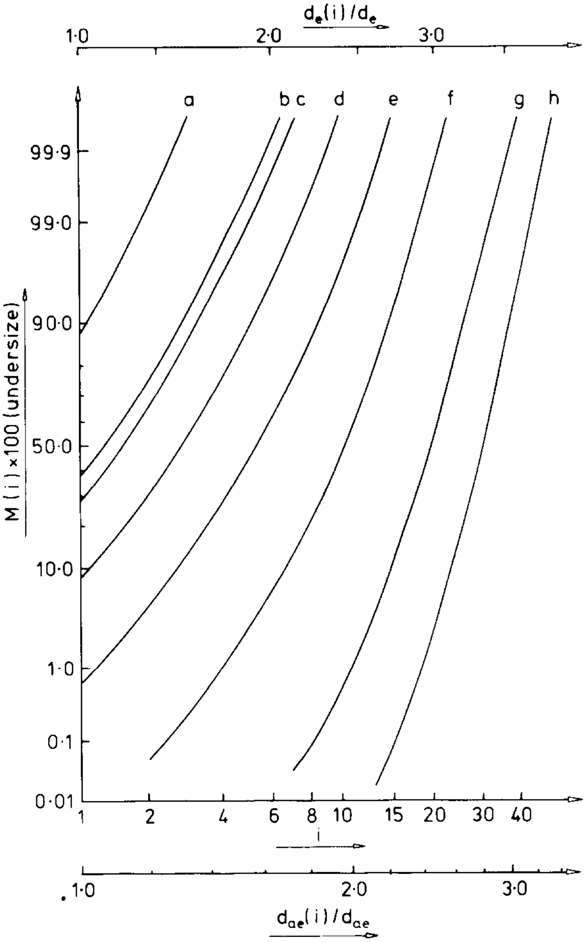

Fig. 2. % cumulative mass fraction (undersize), M(i)×100, against the number of primary particles per cluster, i, and the relative equivalent volume and aerodynamic diameters, $d_e(i)/d_e$ and $d_{ae}(i)/d_{ae}$, respectively. The values of the % volumetric concentrations c and the ratios of droplet to primary particle diameters, D/d_e, are: a 0.1, 5; b 0.1, 10; c 1, 5; d 2, 5; e 0.5, 10; f 1, 10; g 2, 10; h 3, 10.

number of particles it contains (Table 1). When the apparent geometric standard deviation σ_g is calculated from the curves in Fig. 2 as (Hinds, 1982; Martin et al., 1983):

$$\sigma_g \simeq \frac{d_{ae}(i) \text{ at } [100 \times M(i) = 84\%]}{\text{MMAD}}$$

it is found that all the aerosols in Table 2 would be still classed as 'monodisperse' ($\sigma_g < 1.22$) with respect to the distribution of their aerodynamic diameters (Fuchs and Sutugin, 1966). This is quite remarkable considering that some of the aerosols

TABLE 2

NUMERICAL RELATIONSHIPS BETWEEN THE FORMULATION VARIABLES AND THE SIZE DISTRIBUTION OF THE AEROSOL PRODUCT

c (% v/v) [a]	D/d_e [b]	n [c]	n_D [d]	σ [e]	$MMAD/d_{ae}$ [f]	σ_g [g]
0.001	10	0.01	1.005	0.007	1	–
0.01	10	0.10	1.05	0.07	1	–
0.1	5	0.125	1.06	0.09	1	–
0.1	10	1.0	1.58	0.65	1.07	1.17
0.5	10	5.0	5.03	2.2	1.59	1.13
1.0	5	1.25	1.75	0.79	1.12	1.16
1.0	10	10.0	10.0	3.2	1.98	1.10
2.0	5	2.5	2.72	1.4	1.30	1.15
2.0	10	20.0	20.0	4.5	2.46	1.07
3.0	10	30.0	30.0	5.5	2.81	1.06

[a] % volumetric concentration.

[b] Ratio of the droplet/primary drug particle size diameters.

[c] Average number of primary drug particles per droplet (including empty droplets, Eqn. 7).

[d] Average number of primary drug particles in a cluster (Eqn. 10).

[e] Standard deviation of n_D (Eqn. 11).

[f] Ratio of the mass median aerodynamic diameter of the product to the aerodynamic diameter of the primary particle, as obtained from Fig. 2.

[g] Geometric standard deviation of MMAD, obtained from Fig. 2.

are composed of aggregates containing an extensive range of primary particles per cluster.

Comparison of Fig. 2 and Table 2 shows that the value of $d_{ae}(i)$ which corresponds to n_D for a particular aerosol is an excellent predictor of MMAD. For example, curve c in Fig. 2 for $c = 1\%$ and $D/d_e = 5$ indicates $MMAD/d_{ae} = 1.12$. The value of n_D for this aerosol is 1.75 (Table 2). Interpolation of $d_{ae}(i)/d_{ae}$ from Table 1 between $i = 1$ and 2 gives $MMAD/d_{ae} = 1.14$ for $n_D = 1.75$. The slight disagreement between the two methods is probably more likely to be due to the inaccuracy of the graphical treatment rather than any 'real' differences.

As n is reduced towards 1, and lower, the clustering, if any, has no longer any appreciable effect on the aerodynamic behaviour in this model (Fig. 2 and Table 2). It should be emphasized again that this behaviour is determined solely by the value of n, irrespective of c and D/d_e which give rise to this value (Eqn. 7).

In the range and the model tested ($c = 0.001$–5%, $D/d_e = 2$–10, i.e. $n = 8 \times 10^{-5}$–50), the problem of the total volume of the cluster exceeding the volume of the droplet did not arise. This is understandable in view of the following: the minimum value of k_{max} (Eqn. 28) is 5.9 (for $D/d_e = 2$). Roughly speaking, therefore, the volume exclusion effect becomes important only at very low ratios of droplet/particle diameters and $n_D > 5$. The latter occurs when $n \geqslant 5$ (Fig. 1 and Table 2). When $D/d_e = 2$, it would be necessary to have $c = 62.5\%$ v/v to obtain $n = 5$ (Eqn. 7). Actually, it is found from the calculations of the cumulative mass fraction that more than 99.99% of the aerosol, by mass, would be in clusters containing less than 6 particles for $D/d_e = 2$, until c exceeds 5%. Thus, within the restrictions of the model in this section and $D/d_e \geqslant 2$, the droplets are sufficiently large, compared to the drug particles, to accommodate even the biggest clusters which are likely to be formed from up to 5% v/v concentration of the suspension.

The metering valves used in therapeutic aerosols deliver usually 25–100 μl of the propellant–excipients–drug mixture (Morén, 1978a). The nominal doses of drugs in this volume vary typically between 40 and 1000 μg (British National Formulary, 1981). For an order of magnitude estimate, we assume an average density of 1.3 $kg \cdot dm^{-3}$ for the drug particles (Gonda et al., 1982; Morén and Andersson, 1980). On this basis, the % volumetric concentration in currently available therapeutic suspension aerosols is in the range $c \simeq (3 \times 10^{-2}–3)\%$. There is, unfortunately, very little information about the initial size distribution of droplets of aerosols, immediately after their release from the pressurized cannisters. Morén and Andersson (1980) reported the results of pilot studies using holographic microscopy in which the initial mass median diameter of the droplets was found to be 36 μm. Since the primary drug particles are usually micronized to give a mass median diameter in the range suitable for bronchial and pulmonary delivery, i.e. around 2–3 μm (Gonda, 1981), the ratio of the droplet to primary particle diameters is likely to be about 10. These estimates suggest that aggregation affecting significantly the aerodynamics of drug particles is likely to occur with many practical formulations. It is possible, however, that during the initial rapid 'flashing' of the propellant, some further breaking-up of the droplets takes place. On the other hand, the size of the drug clusters will be increased by the presence of non-volatile excipients (Morén, 1982). This topic will be covered in a subsequent publication as well as other factors affecting the ultimate aerodynamic behaviour of the drug particles. Morén (1978a) has already presented some interesting experimental data on the effect of the propellant vapour pressure and metering volume on the deposition in the inhaler and the mouth. However, Morén's findings and subsequent work by Newman et al. (1982) reflect the dynamics of the droplets because the evaporation of the propellants in their experiments was almost certainly incomplete (Morén, 1978a; Newman et al., 1982). As it is likely that the proposed changes in the composition of the propellants and the new design of devices for administration of metered-dose aerosols will result in complete evaporation of the propellants prior to the entry to the patient's respiratory tract (Dolovich et al., 1983; Hidinger and Kjellman, 1984; Hidinger and Perk, 1981; Morén, 1978b; Newman et al., 1981; Pedersen, 1983), the present treatment seems to be pertinent both qualitatively and quantitatively.

Polli et al. (1969) investigated experimentally the dependence of the drug mass aerodynamic size distribution, after aerosolization of a steroid suspension, as a function of a number of formulation variables. They found that, in order to obtain approximately the same mass median aerodynamic diameter of the drug in the aerosol as the diameter of the primary particles, it was necessary to use high vapour pressure of the propellants. Unfortunately, their experiments did not distinguish between the effects of the propellant vapour pressure on the initial droplet size, and on the rate of evaporation. It is therefore possible that at lower propellant pressures, there was incomplete evaporation of the volatile components at the point of sampling (Morén, 1978a). Polli et al. (1969) also found that at drug concentrations 0.175 and 1.45 mg/g ($c \simeq 0.01$ and 0.1%), the drug mass median aerodynamic diameter was approximately twice as big as the diameter of the primary particles, and more than 10 × bigger when the concentration reached $c \simeq 2.5\%$. The experimentally observed increases in MMAD were greater than those that one would expect from the model calculations in this paper. There could be several reasons for this discrepancy: (1) the ratio of the droplet to primary particle diameters was much greater than 10. This is quite plausible because the drug particle mass median diameter was 1.4 μm whilst the initial droplet diameter was likely to be in excess of 30 μm (Morén and Andersson, 1980). (2) Flocculation of the drug particles in the suspension took place, and the spray orifice was less effective to break-up the agglomerates as the drug concentration in the suspension increased (Polli et al., 1969). (3) The present model does not take into account the polydispersity of the droplets (Raabe, 1968) and primary drug particles (Kasper, 1982a and b; Kops et al., 1974; Kops et al., 1975; Spurny et al., 1978), or the deviations from the spherical shape of the primary drug particles (Kasper, 1982a) and the clusters (Kasper, 1982a and b; Kops et al., 1974; Kops et al., 1975; Spurny et al., 1978; Stöber, 1972).

Finally, it should be pointed out that the dependence of the aerodynamic diameter of approximately spherical clusters on the cube-root of the number of particles per cluster (Eqns. 25, 26 and AII.2) is supported very well by experimental evidence: this is shown in the work of Stöber (1972) with nebulized aqueous suspensions of the latex particles, and in the investigations of Kops et al. (1974 and 1975) with clusters formed after coagulation of aerosols produced by the exploding wire technique.

Appendix I

Calculation of the variance of the average number of drug particles per aggregate

The variance σ^2 of n_D is defined as

$$\sigma^2 = \sum_{k=1}^{\infty} (k - n_D)^2 \cdot P(k) \tag{AI.1}$$

Substituting for n_D from Eqn. 10 and expanding Eqn. AI.1, we obtain

$$\sigma^2 = \sum_{k=1}^{\infty} \left[k^2 P(k) - 2k \frac{nP(k)}{1 - e^{-n}} + \left(\frac{n}{1 - e^{-n}} \right)^2 \cdot P(k) \right] \tag{AI.2}$$

The sum of the first term is (cf. Eqn. 8)

$$I = \sum_{k=1}^{\infty} k^2 P(k) = \sum_{k=1}^{\infty} k^2 \cdot \frac{e^{-n} n^k}{k!} = e^{-n} \sum_{k=1}^{\infty} \frac{k^2 n^k}{k!} = e^{-n} n \sum_{k=1}^{\infty} \frac{k n^{k-1}}{(k-1)!} \tag{AI.3}$$

Changing the index k to j = k − 1 and expanding gives

$$I = e^{-n} n \sum_{j=0}^{\infty} \left(\frac{jn^j}{j!} + \frac{n^j}{j!} \right) \tag{AI.4}$$

From the definition of n

$$n = \sum_{j=0}^{\infty} jP(j) = \sum_{j=0}^{\infty} j \frac{e^{-n} n^j}{j!} = e^{-n} \sum_{j=0}^{\infty} \frac{jn^j}{j!} \tag{AI.5}$$

and from the identity

$$e^n = \sum_{j=0}^{\infty} \frac{n^j}{j!} \tag{AI.6}$$

it follows that Eqn. AI.4 can be recast as

$$I = e^{-n} n (e^n n + e^n) = n^2 + n \tag{AI.7}$$

The second term in Eqn. AI.3 is

$$II = -2 \sum_{k=1}^{\infty} \frac{nkP(k)}{1 - e^{-n}} = -\frac{2n}{1 - e^{-n}} \sum_{k=1}^{\infty} kP(k) \tag{AI.8}$$

Now (see Eqn. AI.5)

$$\sum_{k=1}^{\infty} kP(k) = \sum_{k=0}^{\infty} kP(k) = n \tag{AI.9}$$

Thus, Eqn. AI.8 becomes

$$II = -\frac{2n^2}{1 - e^{-n}} \tag{AI.10}$$

The last term in Eqn. AI.2 is

$$III = \sum_{k=1}^{\infty} \frac{n^2}{(1 - e^{-n})^2} \cdot P(k) = \frac{n^2}{(1 - e^{-n})^2} \sum_{k=1}^{\infty} P(k) = \frac{n^2}{(1 - e^{-n})^2} [1 - P(0)]$$

$$= \frac{n^2}{(1 - e^{-n})^2} (1 - e^{-n}) = \frac{n^2}{1 - e^{-n}} \tag{AI.11}$$

The variance (Eqn. AI.2) is the sum of (I + II + III), Eqns. AI.7, 10 and 11:

$$\sigma^2 = n^2 + n - \frac{2n^2}{1 - e^{-n}} + \frac{n^2}{1 - e^{-n}} = n^2 + n - \frac{n^2}{1 - e^{-n}} \tag{AI.12}$$

Appendix II

Stöber (1972) made detailed measurements of aerodynamic diameters of spherical and chain-like clusters of spherical latex particles. He defined the equivalent volume of a cluster of i primary latex spheres as

$$d_e(i) = d_e(1)i^{1/3} \tag{AII.1}$$

This definition was followed later by Kasper (1982a). However, it is different from the work of Davies (1979) and the present treatment (cf. Eqn. 19) because Eqn. AII.1 does not taken into account the volume of the cluster which is not occupied by the solid. Stöber (1972) then calculated the 'dynamic shape factors' K of the clusters from the experimental aerodynamic diameters and the equivalent volume diameters as given by Eqn. AII.1. By this method, he found K values of the spherical clusters to be significantly greater than 1. He suggested that the deviation of K's from the value of 1 for an ideal sphere was due to the fact that the cluster, indeed, contained spaces unoccupied by the solid. As discussed later by Kasper (1982a), Stöber's treatment of K's is in fact such that K can be interpreted essentially as a density correction factor. Davies (1979), however, re-calculated Stöber's results for spherical clusters, defining the equivalent volume diameter as in Eqn. 19 and assuming $f(i) = 0.741$ (hexagonal close packing of spheres). K's thus calculated were smaller than the values of Stöber (1972) but still significantly greater than 1. Davies proposed that the spherical clusters had a 'rough' surface and that the increased viscous drag, compared to a smooth sphere, caused K to be greater than 1. This was in contrast to the interpretation of Stöber (1972) who did not invoke the effect of surface roughness but, instead, suggested that the packing in the clusters was less dense than that predicted by the hexagonal arrangement.

However, it should be emphasized that despite these somewhat divergent opinions, it is still possible to predict the aerodynamic diameters of clusters of nearly spherical particles with a reasonable degree of accuracy: if we put $K = 1$ (the primary particle is assumed to be a smooth sphere), then from Eqn. 26

$$d_{ae}(i)/d_{ae} = i^{1/3} \cdot [f(i)]^{1/6} \cdot [K(i)]^{-1/2} \tag{AII.2}$$

$f(i)$ for hexagonal and cubic close packing is 0.741; it is 0.68 and 0.52 for body-centred cubic and simple cubic lattices, respectively (Atkins, 1978), and 0.61 for randomly packed spheres (Davies, 1979). Thus, provided the clusters are reasonably compact, the factor $[f(i)]^{1/6}$ in Eqn. AII.2 will vary between 0.897 and 0.951 depending on the packing assumed, the difference between the two extremes being about 6%. The values of $K(i)$ for $i > 2$ vary between 1.04 and 1.14 (Davies, 1979), giving rise to $[K(i)]^{-1/2}$ between 0.94 and 0.98. If we assume a constant $K(i) = 1.10$ for $i > 2$ (Davies, 1979; Stöber, 1972), then the error in $[K(i)]^{-1/2}$ is unlikely to be in excess of 3%.

For $i = 2$, identical result is obtained in Eqn. AII.2 with either $f(2) = 1$ and $K(2) = 1.12$, or $f(2) = 0.741$ and $K(2) = 1.02$ (Davies, 1979).

As mentioned in the main text, complications arise for non-spherical, and particularly chain-like clusters (Dahneke, 1982; Kasper, 1982a and b). Discussion of this problem is beyond the scope of the present article. However, in the absence of evidence of chain-like clusters of drug particles in therapeutic aerosols, the method proposed here can probably estimate the aerodynamic diameters of clusters within 10% accuracy.

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