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Size analysis of metered suspension pressurized aerosols with the Quantimet 720†

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A method is described for particle sizing of pressurized metered suspension aerosols by collection in a settling drum followed by microscopic evaluation of the slides with a Quantimet 720 automatic image analyser. The method gives satisfactory representation of the distribution of particles settling to the drum base, and demonstrates the excellent stability and reproducibility between and within aerosol packs for two widely used inhalation products. There is much drug deposition of somewhat finer size distribution on the wall of the drum than on the drum base. In spite of this wall loss, the method gives only slightly higher results for the weight and number mean diameters, than when both wall and base distributions are considered. The Quantimet was found to be suitable for particle sizing salbutamol used in preparing aerosol products.

The deposition of inhaled aerosol particles in the lung, essential for effective inhalation therapy of bronchial asthma, depends markedly on the aerosol particle size. During normal respiration particles with an aerodynamic diameter of 1–2 μm have the highest probability of deep lung deposition, the fraction deposited depending on the tidal volume and the period of the respiratory cycle (Hatch & Gross, 1964; Task Group Report, 1966; Stuart, 1973; Heyder, Armbruster & others, 1975). The aerodynamic diameter is defined as the diameter of a unit density sphere of the same settling velocity as the particle considered, regardless of its shape and density (Hatch & Gross, 1964).

It is essential to design and manufacture metered dose inhalation aerosols delivering an adequate and reasonably constant fraction of the dose of drug within the required small particle range. The present report is concerned with metered suspension products, in which the insoluble microfine drug is suspended in propellant. These products give stable particles after the initial rapid drying (ignoring possible humidity effects) but the metered discharge is difficult to sample as it is very brief and produces a high velocity concentrated polydisperse cloud.

Fisher (1956), Tarpley (1957) and Kanig (1963) have discussed the particle sizing of pressurized aerosols, while the problems of sizing the input drug and emitted spray of metered aerosols have been discussed by Porush, Thiel & Young (1960); Bell (1967); Grim, Portnoff & others (1968); Polli, Grim & others (1969). However, of the methods applicable, air sedimentation has been usefully applied to metered and non-metered aerosols by rapid assessment of the settling rate under turbulent conditions with a light-scattering detector (Dimmick, Hatch & Ng, 1958; Vos & Thompson, 1974), or by selective size sampling (Tarpley, 1957). Optical methods can determine particle sizes directly in the aerosol cloud but for polydisperse aerosols severe sampling and dilution problems occur. Fisher (1956) used a light scattering detector with a dilution system. Laser holography gives good resolution but due to anticipated sampling problems is probably more suitable for studying the rapid changes occurring soon after emission. Centrifugal air sedimentation and horizontal elutriation appear to be applicable but apparently have not been used for metered aerosols. The major methods used are indirect sizing by inertial impaction (Hallworth & Andrews, 1976) or sedimentation, and direct sizing by microscopy.

Several workers have described microscopic methods for sizing solution type aerosols from pressure packs. The methods have some relevance for the suspension type. The spray is allowed to settle down a cylinder on to slides, which can be evaluated with a semi-automatic size analyser either from enlarged photomicrographs or directly (Lefebvre & Tregan, 1965a, b; Rance, 1972). Dixon (1966) sprayed pressurized solution aerosols upwards through a port into a large drum and sized the sedimented droplets on coated slides. Good correlation was found with a cascade impactor. The C.S.M.A. method (1971) for insecticide aerosols uses a wind tunnel to impact the droplets on to a non-

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wettable rotating slide, for microscopic sizing. Corrections are applied for uneven sampling of different sizes of droplets.

We describe a method based on that of Dixon (1966), which we have used extensively, originally with manual microscopy and more recently with automatic image analysis.

MATERIALS AND METHODS

Aerosols

These were suspension products which emit two hundred doses, each containing the drug dispersed in 85 mg of fluorochlorohydorcarbon propellant. Most of the experiments were conducted with normal products which deliver either beclomethasone dipropionate (BDP) 50 μg or salbutamol 100 μg in each metered dose. They were fired through a standard (Allen & Hanburys Ltd) oral adaptor which contains the atomizing nozzle. The same adaptor was used throughout each experiment.

Sampling

The method uses a much smaller diameter collecting drum (Fig. 1) than that of Dixon (1966), and the particles are collected on four clean uncoated glass slides at exact locations on the drum base. The can is shaken by hand initially and before each dose is fired through the actuator into the drum port. To prevent undue cooling of the pack, the doses are fired intermittently to give six doses in each minute.

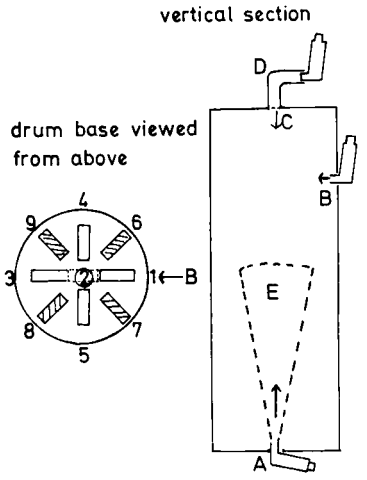

FIG. 1. The aerosol settling drum. A, B, and C are the 'bottom', 'side' and 'top' firing positions of the oral actuator. D is a glass 'throat' 2·5 cm bore and 14 cm in length. E is the approximate position of the emitted aerosol cone. The 'normal' slides are at positions 1, 3, 4 and 5. The 'outer set' = slides 6, 7, 8 and 9. Internal dimensions: diameter 28·1 cm; height 75·3 cm; base area (S_b) 620 cm^2; side wall area (S_w) 6647 cm^2; volume (V) 46 700 cm^3 (0·047 m^3); S_w/S_b = 10·72; S_w/V = 0·1423.

Normally doses are fired upwards through the bottom port of the drum when it is essential that on each return (filling) stroke of the aerosol valve the pack is moved to the valve-down position to ensure correct filling of the metering chamber. Because of this, the alternative side and top entry drum firing positions (Fig. 1) have also been evaluated, as these allow for firing the inhaler in the normal valve-down position. The 'top-firing' position uses a simulated oropharynx or 'throat' of 2·5 cm bore to assess the effect on size distribution of the considerable deposition which occurs clinically in this region.

Size distributions on the slides in the normal positions and in extra positions on the drum base (Fig. 1) were individually and collectively computed for all firing methods. For all methods the number of doses was adjusted (usually 10–30 doses) to give a suitable particle concentration on the slides. The firing was done in a room controlled at 30° ± 2°, the port was closed and the drum left undisturbed overnight to allow complete settling of the particles. Comparative sampling experiments were done with a drum of larger diameter (47 cm, similar height) and in the normal drum at 20°.

Size analysis of micronized salbutamol used in the inhalers was achieved with the Quantimet after dispersing the drug ultrasonically in liquid paraffin containing a surfactant (Span 85) before slide preparation (Table 2). BDP dispersed in this manner gave inadequate optical contrast for detection with the present optical system.

Wall losses and slide uniformity

For all three firing positions the wall losses were assessed by analysing BDP on the base of the drum. The method of analysis involved reaction with isoniazid and hydrochloric acid in chloroform and spectroscopic measurement of the resulting yellow colour at 410 mm in comparison with a blank and standard. The side wall losses were obtained by calculation from the known metered dose, as direct measurement of wall deposition was invalidated by the interference from trace contamination from the drum. Sampling of particles was also done at timed intervals on slides attached to the inner wall of the drum at various heights, and simultaneously on the drum base, to check the size distribution and rate of deposition of particles on the sides and base of the drum.

Particle size analysis of the slides

Manual microscopy was replaced with a Quantimet 720 instrument (Cambridge Instruments Ltd) (Fisher, 1971), essentially a television type scanner coupled to an image analysing computer. The maximum chord lengths of the particles scanned in one direction are automatically recorded in eight size classes.

A Reichert Zetopan microscope was used with transmitted light at a magnification up to 200×. The dry mounted particles are particularly easy to detect automatically as they give good optical contrast.

The size analysis was based on B.S. 3406 part 4. The computed geometric mean diameter by weight (d) and by number (dgn) and their polydispersity values (the geometric standard deviation σ_g) agreed well with results from log probability graphs, and the size distributions were log normal.

RESULTS AND DISCUSSION

The results show that the standard upwards firing position and the other two firing positions each give uniform particle distribution between the four slides (Table 1) which are probably log normal; there is little difference in sampling on the inner and outer regions of the drum base. The side entry and bottom entry methods give similar average results, although in the former method the proximal slides 1 and 2 collect more large particles. This method also tends to cause impaction of some large droplets on the opposing side of the drum which is apparent on slides on the walls and from the rather higher mass wall deposition (Table 4). The top firing 'throat' method gives a finer size distribution and 42% deposition in the throat. A similar proportion of the aerosol passing the throat is deposited on the drum walls compared with the base-firing method. This throat deposition has been investigated in more detail by Hallworth & Andrews (1976).

Generally there was excellent uniformity of weight size distribution between inhalers. Tables 2 and 3 show that manual and automatic sizing give similar results. Those for the Quantimet on eighteen batches of micronized salbutamol, and the aerosols made from these (Table 2), each show excellent uniformity (the results on the drug are those reported by Hallworth & Barnes, 1974). As expected for such uniformity of size between the batches of drug, there is no correlation between the drug particle size and the corresponding aerosol size. There is appreciable aggregation of the original drug, the peak of the frequency distribution by weight of the aerosols

Table 1. *The effect of slide position and drum entry position on the weight particle size distribution.*

	Beclomethasone dipropionate aerosol						Salbutamol aerosol			
	Bottom entry		Top entry with throat		Side entry		Bottom entry		Side entry	
	d(μm)	σ_g	d(μm)	σ_g	d(μm)	σ_g	d(μm)	σ_g	d(μm)	σ_g
Mean of (Slide positions 1–9 (Fig. 1))	5·55	1·66	4·31	1·58	5·66	1·58	6·21	1·70	6·59	1·71
s.d.	0·371	0·116	0·187	0·062	0·401	0·074	0·765	0·090	0·814	0·131
Mean of normal set (Slide positions 1, 3, 4, 5)	5·49	1·66	4·40	1·61	5·74	1·60	6·42	1·71	7·00	1·78
s.d. of normal set	0·415	0·114	0·243	0·067	0·422	0·079	1·01	0·116	1·07	0·139
Mean of outer set (Slide positions 6, 7, 8, 9)	5·61	1·66	4·24	1·54	5·41	1·54	6·00	1·69	6·25	1·66
s.d. of outer set	0·375	0·136	0·123	0·045	0·177	0·022	0·489	0·071	0·479	0·113
Computed from pooled total results	5·55	1·68	4·30	1·58	5·67	1·60	6·29	1·74	6·63	1·74

'd' is the geometric mean particle size by weight, σ_g is the geometric standard deviation.

Table 2. *The uniformity of particle size (A) of micronized salbutamol (18 batches) and (B) salbutamol inhaler (16 batches) by the Quantimet method, and correlation with manual microscopy.*

	Salbutamol inhaler				A		B	
	Man.		Auto		Mean	Over-all s.d.	Mean	Over-all s.d.
d(μm)	6·6[a]	7·0[b]	6·7[a]	6·0[b]	2·00	0·20	6·58	0·610
σ_g	1·9	1·7	1·6	1·5	1·59	0·10	1·68	0·044

[a] and [b] refer to two different batches, which were on stability tests and measured by both methods on the same day.

but it is essential to consider how accurately these results represent the size distribution of the spray emitted into the drum, and how well this in turn reflects the clinical inhalation situation.

Two factors which could give incorrect sampling must be considered, these are, coagulation and wall losses on the sides of the drum. The relative rates of these processes must be assessed in relation to the rate of gravitational settling to the drum base. These aspects have been reviewed by Green & Lane (1957) and Fuchs (1964a), while an extensive analysis by

Table 3. *Examples of the particle size stability of inhalation aerosols measured by Quantimet 720 and by manual microscopy.* Results as geometric mean particle size by weight and the geometric standard deviation (σ_g).

Storage temperature (°C)	Storage time (months)	Experimental BDP steroid inhaler ref. 1194		BDP Steroid inhaler ref. 1230		BDP Steroid inhaler ref. 1389		Experimental salbutamol inhaler ref. 1316	
		Manual microscopy		Quantimet		Quantimet		Quantimet	
		d(μm)	σ_g	d(μm)	σ_g	d(μm)	σ_g	d(μm)	σ_g
—	0	—	—	—	—	5·7	1·8	5·8	1·6
4°	12	—	—	—	—	—	—	6·4	1·7
20°	3	7·3	2·0	6·5*	1·9*	6·5	1·7	5·3	1·7
	6	5·9	1·7	—	—	7·1	1·6	—	—
	12	5·8	1·8	6·2	1·7	5·2	1·6	5·5	1·5
30°	6	—	1·8	—	—	—	—	—	—
	12	6·6	—	5·7	1·6	6·1	1·7	—	—
	24	—	—	—	—	—	—	5·9	1·8
37°	3	6·5	1·9	6·0*	1·7*	6·3	1·7	—	—
	6	6·6	1·8	—	—	6·1	1·5	—	—
	12	6·0	1·7	5·5	1·6	5·9	1·7	—	—
	24	—	—	—	—	—	—	4·8	1·5
20°/37°† cycle	1	5·5	1·7	6·4*	1·8*	—	—	—	—
	3	7·5	1·9	8·9*	1·8*	—	—	6·4	1·7
	6	—	—	—	—	7·1	1·6	—	—
	Overall mean	6·4	1·8			6·2	1·7	5·7	1·6
	Standard deviation	0·61	0·11			0·62	0·09	0·58	0·11

* These samples were measured by manual microscopy. †These were cycled alternately day and night at 37° and 20° respectively.

is about 3 μm diameter, but only 1·5 μm for the drug.

The excellent uniformity of particle size distribution through the dose range of two steroid (BDP) inhalers is shown in Fig. 2.

The method has proved useful for comparing products and stability testing and has the advantage that increased agglomeration or crystal size are readily apparent. The normal slide sampling method gives a reliable indication of the size distribution of particles settling on the base of the collecting drum, Gillespie & Langstroth (1951) shows the effects of forced convection in a drum on the behaviour of ammonium chloride aerosols of 0·3–2 μm particle diameter.

Analysis of the present system is complicated because there is inevitably turbulence in the drum during the 6 min period of intermittent firing of the doses, and doubtless this turbulence persists for a significant time after dosing. Even in temperature controlled drums, small thermal gradients cause convective mixing so that particles tend to be homo-

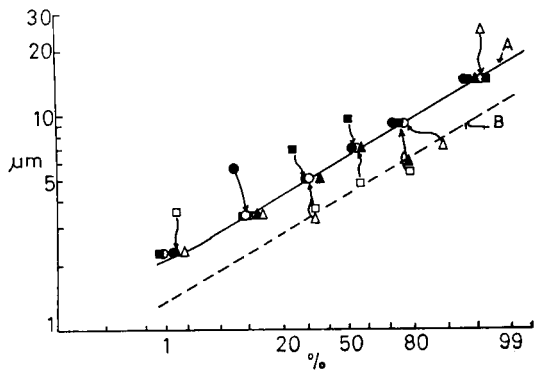

FIG. 2. Uniformity of particle size distribution of beclomethasone dipropionate aerosol through the dosage range of the pack. Open symbols = can 1. closed symbols = can 2.

Mean diam. by wt (d) in	Doses 5–65		Doses 80–140		Doses 140–200	
	○	●	□	■	△	▲
μm	6·4	6·7	6·5	6·6	6·3	6·2
σ_g	1·62	1·66	1·66	1·60	1·65	1·67

y axis—Particle diameter (μm) log scale. x axis—% undersize by weight (probability scale). A—projected area diameter. B—mean equivalent aerodynamic diameter.

geneously distributed throughout the drum except in a very thin stagnant surface layer (Fuchs, 1964b).

The probable extent of particle coagulation in the drum has been calculated for a 4 h settling period, assuming an initial particle concentration of 3400 cm^{-3} and alternative rate constants of $3{\cdot}3 \times 10^{-10}$ $cm^3 s^{-1}$ (K_1) and 8×10^{-10} $cm^3 s^{-1}$ (K_2). The reduction in particle number should be 4 and 13% respectively. K_1 is expected from Smoluchowski's theory and was found for slightly charged monodisperse aerosols (Devir, 1963), while K_2 was found for mildly stirred polydisperse powder aerosols (Gillespie & Langstroth, 1951). These estimates suggest that coagulation is unimportant in the present aerosols of low particle number, although it should be noted that bipolar electric charging of powder aerosols can give considerably higher K values (Gillespie & Langstroth, 1952). The aggregates seen in the present aerosols are almost certainly largely a result of incomplete dispersion during atomization of the drug suspension at the inhaler nozzle.

Table 4. *The mass distribution of beclomethasone dipropionate in the collecting drum for three different entrypositions of the aerosol.*

		drum entry position		
		Base	Side	Throat at top
	% on throat	—	—	41·7
	% on base	62·4	55·8	32·6
	% on walls	37·7	44·3	25·8†
base	outer area* / inner area	0·90	0·72	0·69

Each result is the mean of 2 determinations, expressed on the total drug (30 doses) emitted from the oral adaptor. The adaptor itself collected 4–7 % of the dose emitted from the nozzle. * The inner area was a circular foil disc with a diameter half that of the drum the results are expressed on equivalent areas. † Of the dose passing the throat, 53·3% was on the drum base.

Deposition of particles on the sides of the settling drum is caused largely by convective diffusion of particles to the walls and subsequent adhesion. Clearly the rate constant for this wall loss (βw) in relation to the gravitational settling rate affects sampling on the drum base. The settling rate is easily calculated for each size of particle, but βw is not predictable with any accuracy because widely varying results have been reported for the thickness (δ) of the stagnant wall layer on the drum wall to which βw is inversely proportional, (Fuchs, 1964c; Greenfield, Koontz & Hausknecht 1969; van der Vate, 1972). The effect of polydispersity on βw is also complex. We have therefore measured the size distributions of a BDP aerosol (Fig. 3) on the walls

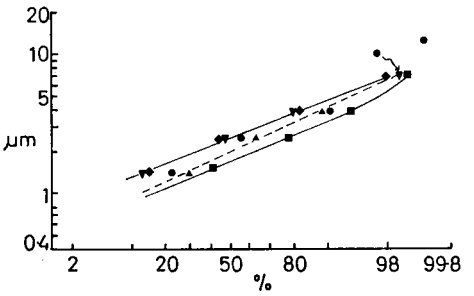

FIG. 3. The particle size distribution by number of beclomethasone dipropionate aerosol on the collecting drum base and walls, 1 and 4 h after emission. y axis—Particle diameter (μm) log scale. x axis—% undersize by number (probability scale).

	walls	base	base and walls
1 h	●	▼	---▲---
4 h	■	◆	

and base of the drum at intervals (1 and 4 h) to assess the ratio β_w/β_s for various particle sizes (Fig. 4).

The results show that the rate of wall deposition is always appreciable and is substantial after 1 h for small particles, when most of the larger particles have settled to the drum base. The βw values were similar to those of Gillespie & Langstroth (1951) for gentle stirring rates.

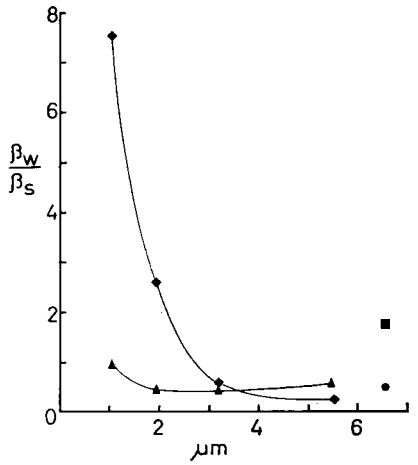

FIG. 4. The relative rates of particle deposition on the drum base and walls. x axis—Particle diameter (μm). ▲, ● 0–1 h, ◆, ■ 1–4 h after spraying. ● and ■ represent the mean rates for the particle size range 0·7–12·4 μm. β_w is the rate constant for diffusional wall loss. β_s is the rate constant for gravitational settling.

Apart from diffusive loss, there could be wall losses due to impaction of the large particles projected from the atomising nozzle but this effect is probably small in view of the insignificant change in drum base weight distribution when a very wide sampling drum was used, where less wall impaction is expected (Table 6).

Direct measurement of the effect of wall deposition on the weight size distributions determined on the drum base has proved difficult because of sampling problems, whereas the number distribution is much more easily established. The particle numbers are so low on wall microscope slides that high standard errors occur in the large particle sizes of the weight distribution. The problem has been minimized by extensive sampling of many slides over the drum walls. The weight distributions seemed similar at different drum heights, but marginally coarser towards the base, so all the wall results were pooled for calculation (Table 5). More accurate results were obtained by combining wall and base counts, with appropriate corrections for the relative areas measured and the total areas of the drum walls and base. The results (Table 5 and Fig. 5) show that as predicted the drum walls collect a finer size distribution than the base, nevertheless, the normal base results give a good estimate for both weight and number, with slightly high mean sizes in both cases. It is concluded that the normal 'base' sampling procedure is satisfactory for weight or number distributions. It would probably be impracticable and unnecessary for routine use to sample the drum walls in an attempt to increase the sampling accuracy.

Table 5. *The effect of particle deposition on the sampling drum walls on the size distributions measured on the drum base.*

Inhaler	Sampling position in drum	By weight d(μm)	By weight σg	By number dgn(μm)	By number σg
(a) Salbutamol	base	7·37	1·75	2·53	1·77
	walls	7·37[b]	1·99	2·24	1·61
	base + walls	7·32	1·84	2·38	1·70
b) BDP*	base	7·85	1·92	2·64	1·70
	walls	5·03†	2·01	1·81	1·49
	base + walls	6·31	1·88	2·06	1·62
(c) BDP	base	5·19	1·73	2·41	1·58
	walls	3·91	1·77	1·84	1·47
	base + walls	4·34	1·84	2·00	1·50

* BDP = beclomethasone dipropionate. In this batch the input drug was inadequately micronized, thus giving a coarser aerosol than normal. †The standard error in the largest size class was very high, so these results have a low accuracy. The results for (base and wall) have an acceptable standard error.

The results in Table 6 show that substantially correct number and weight size distributions are obtained after a 1 h settling period, in spite of the large numbers of fine particles which subsequently diffuse to the drum walls. Collection at 20° apparently

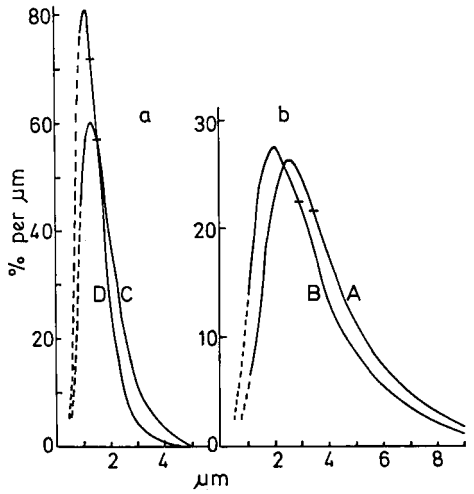

FIG. 5. Frequency particle size distributions of beclomethasone dipropionate aerosol as aerodynamic sizes, showing the effect of wall losses on sampling of the drum base. Derived from log probability graphs for inhaler (C) of Table 5. – – – extrapolated below the measured range. + mean size. A and C measured on the drum base. B and D measured from combined results on the drum base and walls. x axis—Equivalent aerodynamic particle size (μm) a—by number, b—by weight.

Table 6. *The effects of sampling time, drum size and temperature on the computed particle size distribution of beclomethasone dipropionate aerosols.*

		The effect of time of sampling (base sampling only)				
Time after firing doses (h)		1/2	1	2	4	7
By weight	d(μm)	7·5*	6·3	6·3	6·7	6·7
	σ_g	1·75	1·69	1·69	1·76	1·74
By number	d_{gn} (μm)	3·1	2·9	2·9	2·8	2·9
	σ_g	1·68	1·65	1·65	1·60	1·60

		The effect of drum size and temperature (base sampling only)				
		20°†	20°‡	Large drum†	Control†	Control‡
By weight	d(μm)	6·9	7·3	5·6	5·6	7·0
	σ_g	1·63	1·68	1·58	1·68	1·70
By number	d_{gn} (μm)	3·2	2·7	2·9	2·9	2·7
	σ_g	1·68	1·85	1·59	1·52	1·79

*The standard error exceeded 2% at the 7 or 12 μm size classes. †These measurements were made on the same aerosol pack in different drums, 100 doses collected in the large (47 cm diameter) drum. ‡These measurements were made on the same aerosol pack in different drums. The controls for † and ‡ were collected in the normal fashion, at 30°.

gives a slightly coarser and more polydisperse distribution that at 30°, but the reason for this difference is not apparent.

Throughout this work it has been assumed that all the particles counted consist of drug crystals or their agglomerates. In practice, the small proportion of oily surfactant in the drug suspension, the only other non-volatile additive, is also emitted in the aerosol spray. Some of this doubtless coats the drug particles and some can be seen as oily droplets. However, when the drug particles are focussed on the Quantimet screen the oily droplets have insufficient contrast to be detected by the instrument.

The clinical significance of the size distributions obtained by the present method are discussed elsewhere in comparison with dynamic flow methods of sizing (Hallworth & Andrews, 1976). However, it should be noted that the present method gives a size distribution in terms of the projected area diameters. Although the Quantimet acutally measures the longest horizontal chord length, clearly there will be random orientation of particles on the slides and thus the results express the projected area diameter. This is confirmed by the similarity given by the manual method, which measures by projected areas.

The projected area diameters can be converted to equivalent aerodynamic diameters (d_{aer}) by multiplying by 2/3, on the assumption that the particles are approximately spherical and of unit density. Although it is well known that dust aggregates can be very irregular in shape and of low density, Johnstone (1961) has shown that when aggregates are composed of solid particles of uniform size and shape their void space tends to be small and their effective density is close to that of the component particles. This situation applies almost certainly to the present aerosols, as the aggregates are approximately isodiametric and contain mostly small numbers of fairly regular particles of narrow particle size range. It is likely therefore that the 2/3 conversion is valid and also that little error is involved in assuming unit density, which is close to that of the component drugs.

An aerosol of BDP expressed in this way gave results plotted in Fig. 5, as frequency number and weight distributions derived from the size parameters in inhaler (C) in Table 5. These results also indicate the errors involved in ignoring the particles deposited on the drum walls. When corrected for wall losses those results on an aerodynamic size basis show that about 99% of the particles by number and 70% by weight are below 4 μg diameter and thus are capable of deep lung penetration. The total number in this size range is $5{\cdot}3 \times 10^6$ in each emitted dose of BDP inhaler and is approximately double for salbutamol.

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