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Size analysis of suspension inhalation aerosols by inertial separation methods†

G. W. HALLWORTH* AND U. G. ANDREWS

Pharmaceutical Research Department, Allen and Hanburys Research Ltd., Ware, Herts, U.K.

The particle size distribution of beclomethasone dipropionate (BDP) aerosols delivered from pressurized metered dose suspension inhalers has been measured with three cascaded inertial separation instruments, the Casella Cascade Impactor, Multistage Liquid Impinger and Cascade Centripeter. Various methods for collecting the emitted aerosol before measurement have been examined. A bent glass tubular 'throat', used as a simulated oro-pharynx, collects 35–60 % of the emitted dose by impingement of the wet spray cone in the throat. The aerosol passing through the throat has a similar but somewhat finer size distribution to that collected by firing directly into a large flask. The three cascaded instruments give similar results which in the Multistage Liquid Impinger also resemble those given by a salbutamol inhaler. The mass fraction (35–60%) emitted from the oral adaptor which is of a size capable of deep lung penetration (<4 μm) is much higher than the fraction (10–16%) found in the lungs of dogs after inhalation of aerosol. The size distributions resemble those determined by microscopy and are expressed as aerodynamic sizes, thus showing that the particles approximate to unit density spheres. The performance of two simpler devices, Kirk's apparatus and the Harwell size selective air sampler are also assessed, the latter shows some promise for the simple evaluation of the respirable fraction of inhalation aerosols.

The problems of sampling and measuring the particle size distribution of suspension type metered dose inhalation aerosols have been discussed by Hallworth & Hamilton (1976), who also described an automatic microscopic method. A widely used instrument, the cascade impactor (May, 1945), dynamically fractionates the aerosol cloud into size fractions. In each stage of such an instrument, the aerosol in an airstream at a standard volumetric flow rate passes through a jet of a width that gives the required velocity and then impinges on a plate where it is deflected through 90°. Large particles of sufficient inertia are impacted on the plate whereas finer particles are impacted on the subsequent stages which have progressively finer jets and thus impart higher velocities (Fig. 1).

The method has several inherent advantages; total sampling reduces sampling errors, the mass fractions are given directly in terms of equivalent aerodynamic diameters, if the device is suitably calibrated, and determination of the total emitted dose is in itself a useful quality control feature.

Grim, Portnoff & others (1968) have described the use of the American Battelle round jet cascade impactor for quality control and formulation studies of dexamethasone sodium phosphate metered aerosols. The instrument has also been used for assessing the undesirable fine particle inhalable fraction of cosmetic aerosols (Sciarra, McGinley & Izzo, 1969; Sciarra & Adelman, 1971). Solution and suspension type metered isoprenaline aerosols have been compared with a multistage liquid impinger (MLI), which is a 'wet-stage' cascade impactor (Bell, Brown & Glasby, 1973).

More empirical 'tortuous airway' devices have been used to compare the likely respiratory penetrability of aerosols, without determining particle sizes (Kirk, 1972) or with poorly defined size cut-off characteristics (Karig, Peck & Sperandio, 1973).

We have used various inertial separation devices to measure beclomethasone dipropionate and salbutamol metered dose aerosols.

MATERIALS AND METHODS

The aerosol packs deliver up to 200 doses of beclomethasone dipropionate (BDP) (50 μg) or salbutamol (100 μg). The weight fractions measured are based on the total dose emitted from the oral actuator, which itself removes about 5–10% of the dose leaving the atomizing nozzle.

Each instrument is calibrated in terms of unit density spheres and cut-off sizes of each impaction stage represent the effective cut-off diameter (ECD), the size at which 50% of the particles of that size pass the stage (Mercer, 1963; 1964; Soole, 1971). The results are expressed in terms of equivalent aerodynamic diameters, defined as the size of a unit density

* Correspondence.

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sphere which assumes the same terminal settling velocity as the particle considered, regardless of its shape and density. The manufacturers' calibrations were used for the Casella, Centripeter and S.S.E. Sampler, whereas the MLI has been calibrated with a polydisperse dibutyl phthalate aerosol (Bell & others, 1973). The instrument arrangements and sampling systems are shown in Fig. 1. The calibrations and wall losses (deposition on surfaces other than the slides) are summarized in Table 1.

The air flow in each instrument was set initially with a Rotameter type of flow gauge coupled to the inlet orifice and it was then controlled with a critical flow orifice (Druett, 1955) reamed to give the correct inlet flow for the particular instrument. To verify that there were no leaks and to monitor the flow during measurement, a mercury manometer was coupled to the instrument outlet.

The drug fractions were washed out of the oral adaptor and each stage of the sizing instruments with

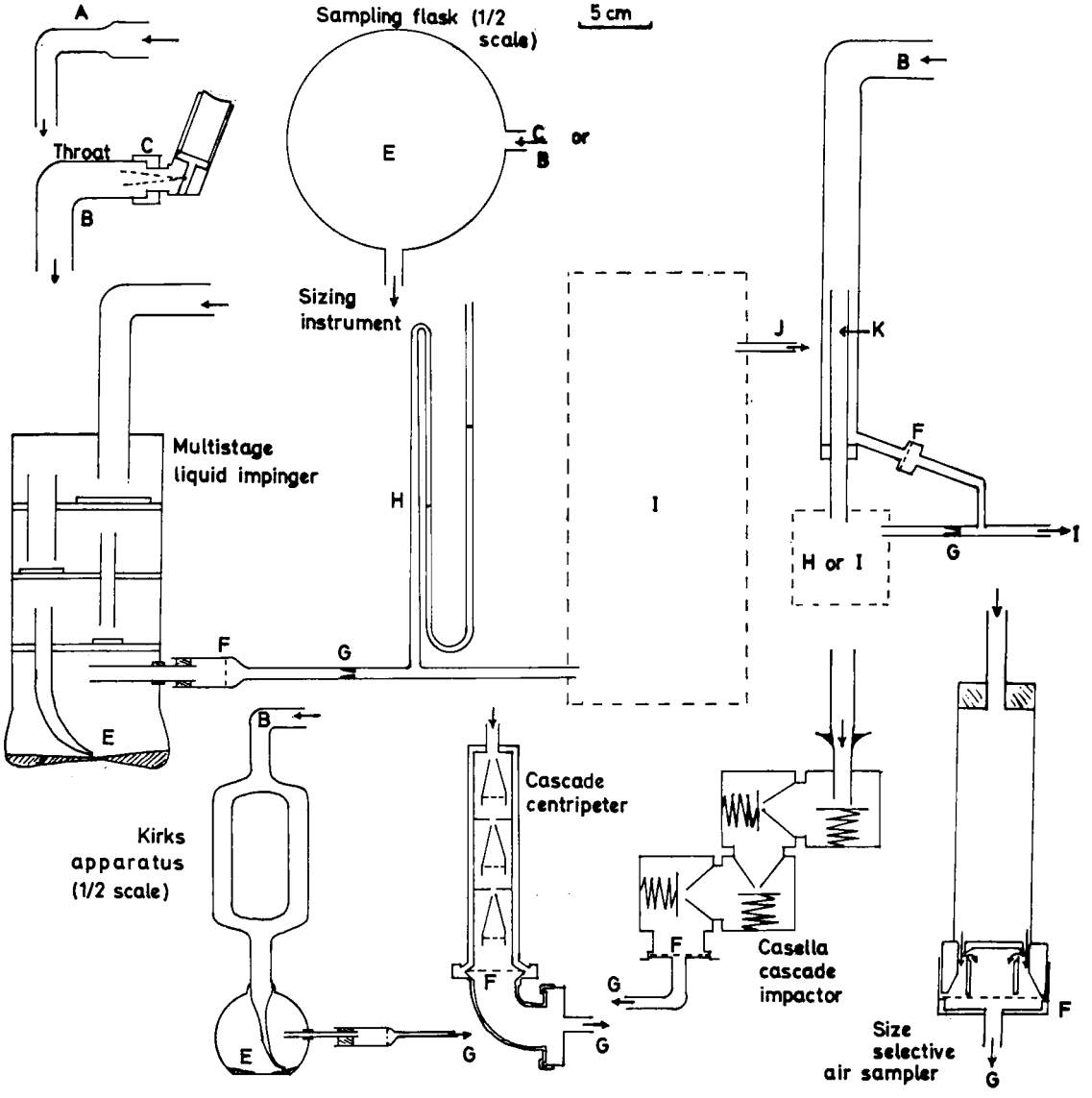

FIG. 1. A Constricted glass throat for Casella or Centripeter. B Normal glass throat (2·5 cm bore, 16 cm total length). C Moulded socket to receive oral adaptor. With metered dose inhaler in its oral adaptor, E Liquid impinger. F Whatman GF/A high efficiency glass fibre filter. G Critical flow orifice. H Mercury manometer. I 10 litre vacuum chamber to minimise pressure fluctuations. J To vacuum pump. K Isokinetic probe.

Table 1. *Calibration constants and wall losses of the Cascade Centripeter. Casella Cascade Impactor and Multistage Liquid Impinger.* Results as % collection efficiency[b].

	Cascade Centripeter			Multistage Liquid Impinger			Casella Cascade Impactor			
Stage	ECD[a] (μm)	Aerosol J[c]	K	ECD[a] (μm)	Aerosol B	Dibutyl phthalate aerosol	ECD[a] (μm)	Aerosol F	H	I
1	12·5	47·0	24·4	12·6 (14·3)	43·8	28·7	12·4			
2	3·8	83·3	49·6	7·4 (9·6)	43·8	61·8	3·9			
3	1·4	74·4	62·9	3·8 (5·8)	38·7	73·9	1·5			
4				1·0 (1·4)			0·4			
filter		84·8	81·4							
All stages								84·8[d]	79·6	82·8

[a] Effective cut-off size for 50% collection efficiency. The MLI calibration in brackets was measured on inserted plates and thus does not include the chamber wall losses.

[b] Collection efficiency is $\frac{\text{drug collected on the impaction plate or filter}}{\text{total drug in the whole chamber including the plate}} \times 100$

[c] J, K etc. refer to the metered aerosol experiments indicated in Tables 2, 3 & 4.

[d] The Casella total wall losses are calculated from the difference between the total drug recovery and the total emitted dose, as it is difficult to measure wall losses directly.

methanol and measured by chemical analysis. BDP was reacted with isoniazid and the yellow colour determined spectrophotometrically at 410 nm. Salbutamol was measured by a modification of the British Pharmaceutical Codex assay for salbutamol inhalation. Duplicate measurements were made in each experiment.

Casella Cascade Impactor (C. F. Casella & Co Ltd). This is a slit jet impactor with four stages and a final filter (May, 1945), operating at 17·5 l min^{-1} airflow. The slides were thinly coated with an adhesive 80/20 semi-solid mixture of soft paraffin/liquid paraffin. The bell-shaped inlet orifice was used uppermost, into which was cemented the tapered end of a 1·35 cm bore stainless steel tube.

Multistage liquid impinger. This is an all-glass round jet cascade impactor with wet sintered glass impaction plates and a final liquid impinger stage (May, 1966). The largest size was constructed with an additional stage with a 13 μm cut-off size (May, 1966; Bell & others, 1973) and used at 60 litre min^{-1} airflow. To enable wall losses to be measured in each chamber, as the glass impaction plates are not removable, these were covered with adhesive coated, close-fitting thin metal discs inserted through side slots and the drug was analysed separately on these discs and on the chamber walls. When used in this manner, different calibrations were used.

The calibration was measured with a polydisperse dibutyl phthalate aerosol (Bell & others, 1973) by sampling on the inserted impaction plates and also with the MLI used in its normal manner, with total chamber recoveries. Both calibrations were close to predicted values for all the impaction stages (May, 1966, 1975a).

Cascade Centripeter (Bird & Tole Ltd). This device is not an impactor, but separates the aerosol by particle inertia in each stage by directing the airflow through a hole to the feather edged orifice of a conical nozzle, for collection on a filter. It thus has the advantage that it is not easily overloaded (Hounam & Sherwood, 1965).

High flow size selective environmental sampler. ('SSE sampler') (Bird & Tole, Ltd). This device relies on inertial separation caused by deflection of 40% of the airflow, (35 litre min^{-1}) inwards through an annular slot. 'Pulmonary' and 'nasopharyngeal' deposition fractions are collected on a filter (Task Group on Lung Dynamics, 1966) and the wall losses are small (Stevens & Churchill, 1973.)

Kirk's apparatus. This is a simple simulated respiratory airway consisting of a glass tubular throat and tortuous 'bronchi' lined with moist agar, with a final efficient filter as the 'lung', and operates at 16 litres min^{-1} (Kirk, 1972). In the present work, the final particle trap is a liquid impinger and filter, resembling those of the MLI to enable an airflow of 60 litre min^{-1} to be used. The distribution of a polydisperse dibutyl phthalate aerosol (as for the

MLI calibration) was measured throughout the apparatus.

Sampling. Two possible sources of error in sizing depend on the dimensions of the aerosol collecting chamber. These are the effect of 'gas surge' of the aerosol discharge, which could decrease the effective cut-off size of the first one or two stages of the cascade impactor, and the extent of particle drying and deposition in the collecting chamber before the aerosol enters the cascade impactor. We have adopted two main methods of sampling, a large chamber (5 litre round flask) to give minimum inlet deposition and to eliminate any gas surge, and a throat to simulate the clinical situation. For the first approach, a 0·5 or 1 litre round flask (Sciarra & others, 1969) gave moderate (25%) deposition but some droplet impaction on the opposing face. A horizontal long (20 cm) cylindrical chamber of 5 cm diameter gave about 30% deposition.

From mouth-rinsing experiments it is known that some 43 % of the dose emitted from metered bronchodilator and steroid aerosols is deposited in the human oro-pharynx (Paterson, Conolly & others, 1968; unpublished observations). To simulate this loss we used an unlined 2·5 cm bore glass throat with a sweeping bend (Fig. 1) (Kirk, 1972; Bell & others, 1973). A shaped oro-pharynx of human dimensions with a moist agar lining gave similar (40–45%) deposition, so the simple throat was adopted. For all inlet systems a close-fitting socket was fitted to the oral adaptor to ensure accurate centering of the actuator mouthpiece. In some experiments on measuring devices which operate at a lower airflow than 60 litre min^{-1} (Casella, Centripeter and SSE Sampler), a constant airflow of 60 litre min^{-1} was passed through the throat to match the MLI inlet conditions, and a suitable knife-edged isokinetic probe below the throat was used to deliver a fraction of the airstream at the appropriate airflow to each instrument (Fig. 1). Analysis of the fraction diverted from the instrument confirmed correct splitting of the airflow. The experimental variation of deposition in the throat was measured during multiple experiments with Kirk's apparatus (Table 6) and the effects of eliminating the 'bronchi' and varying the airflow in the throat were also studied (Table 7). The regional disposition of drug deposition in the throat was examined briefly (Table 7).

RESULTS

The MLI (Multistage Liquid Impinger) results are summarized in Table 2 and Fig. 2. When used in the normal manner, with methanol (for BDP) or water (for salbutamol) in all the chambers, and collecting the aerosol in a throat, similar results were given by BDP and salbutamol. The results resemble those of Bell & others (1973) for isoprenaline metered aerosols measured in an MLI. A BDP inhaler prepared with coarser drug (mean mass diameter 12 μm) gave similar throat deposition (54%), but as expected

Table 2. *Multistage Liquid Impinger—BDP (50 μg dose^{-1}) and salbutamol (100 μg dose^{-1}) inhalers.*

Location	Exp.	μg of drug per metered dose (mean of 2 determinations each on 30 doses) A	B	C	D	E
Filter		1·4 6·0%[a]	1·7 6·7%	1·0 4·0%	0·9 2·6%	1·5 3·7%
Stage 4		18·4 76·7%	19·0 66·0%	17·3 70·8%	23·0 63·5%	30·8 76·5%
Stage 3		1·6 6·7%	2·0 8·0%	4·7 19·3%	9·0 24·6%	5·8 13·6%
Stage 2		1·4 5·9%	1·2 4·6%	1·0 4·0%	2·5 6·9%	1·7 4·2%
Stage 1		1·1 4·7%	1·2 4·7%	0·5 1·9%	0·9 2·4%	0·8 2·0%
5 litre flask				1·0 3·8%	5·7 13·5%	
Throat		19·3 44·6%[b]	13·2 29·8%[b]	20·0 44·0%[b]		35·8 47·1%[b]
oral adaptor		5·0 10·4%[c]	5·0 13·8%[c]	4·9 9·8%[c]	5·3 11·6%[c]	4·5 5·4%
Total recovery		48·3	48·3	50·4	47·4	80·7

Systems (airflow in throat etc. 60 l min^{-1} in all cases).
A BDP inhaler 50 μg dose, fired through throat, with methanol on MLI stages.
B BDP inhaler 50 μg dose, fired through throat, coated aluminium plates on stages, plates analysed.
C BDP inhaler 50 μg dose, fired through throat into a 5 litre flask—methanol on stages.
D BDP inhaler 50 μg dose, fired directly into a 5 litre flask—methanol on stages.
E Salbutamol inhaler 100 μg dose, fired into throat—water on stages.
[a] Expressed as % of the total dose entering the MLI.
[b] Expressed as % of the total dose leaving the oral adaptor mouthpiece.
[c] Expressed as % of the total dose leaving the oral adaptor nozzle.

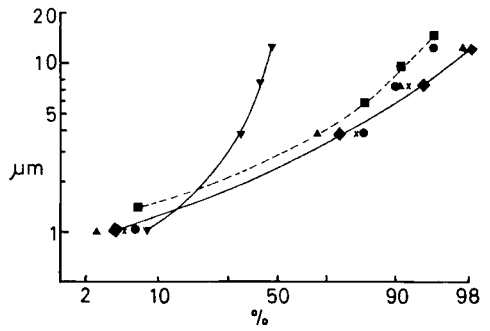

FIG. 2. Size distribution of beclomethasone dipropionate and salbutamol aerosols measured in the MLI. BDP aerosol sampled through: ● throat; ◆ throat to flask; ■ throat, measured on plates only; ▲ flask; ▼ coarse aerosol through throat. × throat.
Salbutamol aerosol + throat. y axis—Particle diameter (μm) log scale. x axis— % undersize by weight (probability).

gave a much coarser aerosol than the normal product made with micronized drug (Fig. 2).

The Casella Cascade Impactor results for BDP aerosols are summarized in Table 3 and Fig. 3. The Casella is the only one of the three cascaded sizing instruments used which measures particles below

Table 3. *Casella Cascade Impactor—BDP inhalers 50 μg dose^{-1}.*

Location	μg of drug per metered dose (mean of 2 determinations each measured on 30 doses) Exp. F	G[e]	H	I
Filter	0·8	1·8	1·3	1·6
	6·9%[a]	9·6%	11·8%	5·7%
Stage 4	1·3	2·4	1·3	2·5
	10·8%	12·6%	11·5%	9·0%
Stage 3	5·5	7·4	5·1	10·9
	44·7%	39·3%	44·5%	39·2%
Stage 2	4·3	6·7	3·6	12·0
	34·9%	35·5%	31·4%	43·0%
Stage 1	0·3	0·6	0·1	0·9
	2·7%	3·0%	1·0%	3·1%
Isokinetic probe		2·9		
5 litre flask			0·8	6·6
			2·3%[b]	15·6%[b]
Throat	24·3	14·8	26·7	
	53·2%[b]	35·3%[b]	63·0%[b]	
Oral adaptor	3·7	4·1	5·6	3·7
	7·5%[c]	8·9%[c]	12·2%[c]	8·0%[c]
Total recovery[d]	41·9	37·4	36·6	38·1

Systems

F Firing through a throat with a constriction before the bend (Fig. 1) at 17·5 litre min^{-1} airflow.
G Firing through a throat at 60 litre min^{-1} and then sampled with an isokinetic probe.
H Firing through a throat at 17·5 litre min^{-1} and then into a 5 litre flask.
I Firing into a 5 litre flask at 17·5 litre min^{-1}.

Notes

[a] Expressed as % of the total dose entering the Casella.
[b] Expressed as % of the total dose leaving the oral adaptor mouthpiece with allowance for estimated losses in the Casella.
[c] Expressed as % of the total dose leaving the oral adaptor nozzle, with allowance for estimated losses in the Casella.
[d] The total recovery ignores the wall losses in the Casella.
[e] Stage recoveries are corrected for aerosol diverted from the Casella.

1 μm. Curvature at the bottom of the graphs (Fig. 3) strongly suggests that 'slippage' occurred on the instrument stage 4 impaction plate (ECD = 0·4 μm) the high jet velocity (7700 cm s^{-1}) causing impacted particles to be blown off the slide. This overloading phenomenon did not occur with dibutyl phthalate aerosol at a high stage loading (5 mg) but it is well

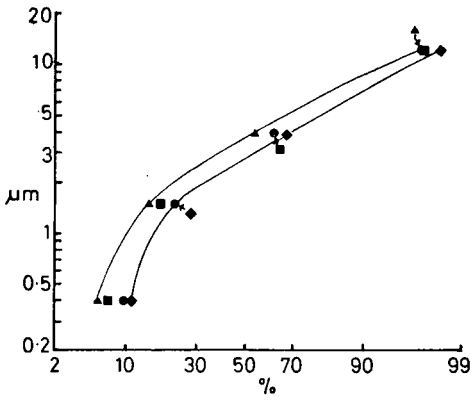

FIG. 3. Size distribution of beclomethasone dipropionate aerosols in the Casella Cascade Impactor sampled through: ● throat at 60 litres min^{-1} to probe; ◆ throat to flask; ■ throat with constriction; ▲ flask. y axis—Particle diameter (μm) log scale. x axis—% undersize by weight (probability scale).

known that solid aerosol particles are much more prone to this effect than liquid aerosol particles (Lundgren, 1967; May 1975a, b). Use of the paraffin coating and reducing the aerosol doses from 30 to 10 did not reduce this effect. De-aggregation in the 4th jet is an alternative possible explanation.

The Centripeter results are shown in Table 4 and Fig. 4. Due to the high wall losses in stages 2 and 3 of monodisperse solid spherical particles, predominantly of particles 10–12 μm, O'Connor (1973) recommended increasing the recoveries on the filters of these stages by a 1·5 × correction factor. The present results are calculated on this basis and also by adding the wall losses measured concurrently (Table 1). The latter approach affects the first stage

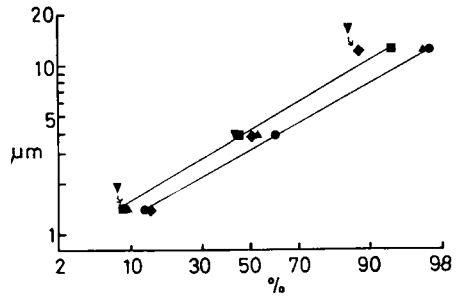

FIG. 4. Size distribution of beclomethasone dipropionate aerosols in the Cascade Centripeter 1·5 × stage corrections sampled through: ● throat at 60 litre min^{-1} with probe; ■ throat with constriction; ▲ flask. Corrected for measured losses: ◆ throat at 60 litres min^{-1} with probe; ▼ throat with constriction. y axis—Particle diameter (μm) log scale. x axis—% undersize by weight (probability scale).

Table 4. *Cascade Centripeter—BDP inhalers, 50 μg dose⁻¹.*

Location	μg of drug per metered dose (mean of 2 determinations each measured on 30 doses) Exp. J[a]	K[f]	L
Filter	1·3 (0·2)	3·4 (0·7)	3·0
	8·0%[c]	5·6%	8·1%
Stage 3	3·6 (3·0)	7·6 (2·2)	11·0
	35·9%	25·8%	44·9%
Stage 2	5·0 (3·7)	5·8 (2·8)	10·8
	49·1%	22·6%	44·3%
Stage 1	1·0 (1·5)	1·0 (1·5)	1·0
	6·4%	8·0%	2·7%
Throat	26·0	7·9	
	45·9%[d]	33·1%[d]	
5 litre flask			7·0
			21·3%[d]
Oral adaptor	5·3	1·9	4·7
	10·5%[e]	7·9%[e]	12·5%[e]
Total recovery[b]	50·5	49·3	53·5

Systems
J Fired into throat (Fig. 1) at 30 litre min⁻¹ airflow.
K Fired into throat at 60 litre min⁻¹ and then sampled with an isokinetic probe.
L Fired into a 5 litre flask at 30 litre min⁻¹.

Notes
[a] Wall losses shown in parentheses.
[b] Includes the measured wall losses.
[c] Expressed as % of total corrected dose entering the Centripeter, stage 2 and 3 recoveries are multiplied by 1·5 to compensate for losses (O'Connor, 1973).
[d] Expressed as % of total dose leaving the oral adaptor mouthpiece.
[e] Expressed as % of total dose leaving the oral adaptor nozzle.
[f] Stage recoveries are corrected for aerosol diverted from the Centripeter.

(12·5 μm) results appreciably but makes little difference at the smaller sizes (Fig. 4).

It can be seen from Table 1 that all three cascaded instruments have considerable wall losses. In the MLI the losses are high in the first three impaction stages but are low in the 4th (liquid impinger) stage, being confined to the inlet tube and jet. A different pattern of loss is shown by dibutyl phthalate aerosol (Table 1). Wall losses in the Casella are difficult to measure on each stage, but the total loss in the instrument shows that the losses must have been low in all impaction stages. From the results of Lundgren (1967) for solid dye particles the losses should be mainly of 5–8 μm particles and largely on stages 1 and 2. The effect of wall losses on the sizing results is probably small for the Casella and considerable for the Centripeter. In the MLI, BDP aerosol collected and measured on inserted impaction discs gave similar results to the usual measurements which include wall losses (Fig. 2), presumably because the wall losses were similar between the first three stages in this instrument.

In general, the three cascaded instruments gave similar results for a BDP inhaler and the different methods of collecting the aerosol before measurement had little effect on the size distribution curves, in spite of large differences in deposition in the collecting system.

The SSE sampler results with the BDP inhaler are shown in Table 5 for two different sampling

Table 5. *BDP inhaler in the Size Selective Air Sampler (30 × 50 μg doses).*

	Aerosol fired directly into a 5 litre flask[a]			Aerosol fired into throat and then passed through a 5 litre flask		
	μg dose⁻¹	%[b]	%[c]	μg dose⁻¹	%[b]	%[c]
Inner filter	7·3	15·4	19·0	9·0	14·5	30·8
Annular filter	31·2	66·0	81·0	15·7	32·6	69·2
Flask and inlet cylinder	8·8	18·6		0·5	1·0	
Throat				25·0	51·9	
Oral adaptor	5·0	9·7[d]		4·9	9·1[d]	
Total recovery	50·8			54·1		

[a] With both sampling systems, the aerosol from the flask passed down a wide vertical cylinder to the Air Sampler.
[b] Expressed as % of the total dose leaving the oral adaptor mouthpiece.
[c] Expressed as % of the total dose entering the Air Sampler.
[d] Expressed as % of the total dose leaving the oral adaptor nozzle.

systems. Both sampling methods show that about 15% of the dose emitted from the oral adaptor should be deposited in the pulmonary region, based on the pulmonary deposition curves of the Task Group (1966). From the proportion of drug in the

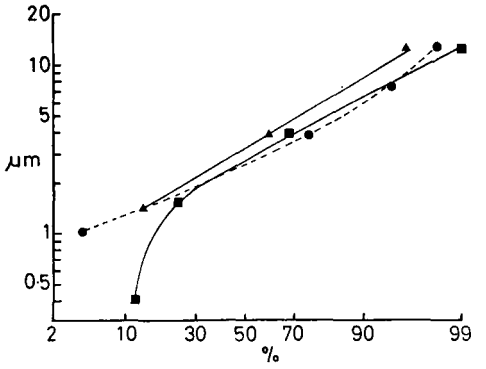

FIG. 5. Size distribution of BDP aerosols sampled through a throat into three sizing instruments. ● throat → flask in MLI ■ throat → flask in Casella Cascade Impactor. ▲ throat → probe in Cascade Centripeter (1·5 × stage corrections). y axis—Particle diameter (μm) log scale. x axis—% undersize by weight (probability scale).

sampler which deposited on the inner filter ('lung' fraction), it can be estimated from the graph of Stevens & Churchill (1973) that the mean mass diameter of aerosol entering the sampler is about 2·5 and 3·5 μm respectively when collected in a throat alone or when this is followed by a large flask.

The results on Kirk's apparatus (Table 6) are similar for various types of inhaler and show good reproducibility between individual BDP inhalers. About 43–50% of the dose emitted from the oral adaptor reaches the impinger 'deep lung' region, with little deposition in the 'bronchi', the results generally resembling those of Kirk (1972) for isoprenaline suspension inhalers. Calibration with dibutyl phthalate aerosol (as used for the MLI) gave effective cut-off sizes of 18, 13 and 1 um for the throat, 'bronchi' and impinger regions. It is expected, however, that the 'bronchi' would not have sharp size cut-off ability.

Table 6. *Inhalation metered aerosols in Kirk's apparatus.* I BDP inhaler 50 μg dose^{-1}; II experimental steroid inhaler 100 μg dose^{-1}; III salbutamol inhaler 100 μg dose^{-1}.

Region for deposition	I Mean deposit.[a] (%)	σ	II Mean deposit.[a] (%)	σ	III Fresh prod. %[b]	After 2 years at 20° %[b]
Oral adaptor	8·3	1·5	7·8	0·5	8·2	4·3
Throat	46·1 (50·2)	1·2	44·6 (48·4)	5·9	35·3	39·0
Bronchi	2·9 (3·2)	1·2	2·5 (2·7)	1·6	10·8	5·9
Impinger and filter[c]	42·6 (46·5)	5·1	44·9 (48·7)	4·1	45·6	50·8

[a] The depositions are the mean and standard deviation (σ) of determinations on nine separate packs, combinations of three cans with three different adaptors using 30 doses for each experiment. The depositions are % of total dose emitted from the nozzle, the results in parentheses are expressed on the dose emitted from the adaptor mouthpiece.
[b] The means of three separate packs.
[c] The filter collects particles < 1 μm, typically this was about 12% of the total sample.

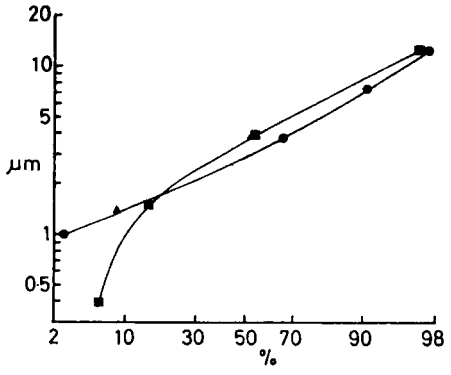

FIG. 6. Size distribution of BDP aerosols sampled through a large flask into three sizing instruments ● MLI. ■ Casella Cascade Impactor. ▲ Cascade Centripeter. y axis—Particle diameter (μm) log scale. x axis—% undersize by weight (probability scale).

The results in Table 7 show that deposition occurs by impingement of the aerosol spray in the tubular inlet part of the throat, and by inertial impaction on the bend of large wet droplets. Deposition falls with increasing airflow, particularly up to 17·5 litres min^{-1}, as a rapid airflow sweeps the wet aerosol along the throat and minimizes contact with the throat walls.

Table 7. *Deposition of BDP in a throat and the effect of airflow.* Each result is the mean of two determinations, each on 30 metered doses. The throat was 8 cm length, 2·5 cm bore, with a central sweeping 90° bend.

Effect of airflow on throat deposition		% of total dose leaving the oral adaptor		
airflow litres min^{-1}	Oral adaptor[c]	throat (oro-pharynx)	liquid[a] impinger	filter
0	20·2	87·7	11·4	1·7
17·5	9·2	51·1	43·3	5·6
30	6·7[b]	49·1[b]		
45	8·1	44·8	51·9	3·3
60	10·6	44·8	49·9	5·3
75	9·2[b]	39·0[b]		

[a] This resembles stage 4 of the MLI, with a 50% cut-off size of 1 μm.
[b] Calculated from the total emitted dose, impinger and filter not assayed.
[c] Expressed as % of total dose leaving the oral adoptor nozzle.

Site of deposition in throat

The deposition in throat, calculated as % of total dose leaving oral adaptor mouthpiece without extension tube (when the total throat deposition = 43·3%) was: first 3cm 12·8, 2nd 3cm 16·4, remainder including bend 14·1. When there was a 6 cm extension tube before the throat the total throat deposition was 35·0% and for the extension tube deposition was 25·8, for the first 6 cm of throat it was 7·4 and for the remainder 1·8.

DISCUSSION

The most notable result is that the MLI, Casella and Centripeter instruments gave similar size distribution results, in spite of the wide differences in jet dimensions, jet velocity, volumetric airflow and the particle collection system. Similarly, in all these instruments the method of collecting the aerosol before measurement had little effect on the size distribution, in spite of large differences in the amount of deposition in the collecting system.

The 'gas surge' can be seen to propel the emitted aerosol at high velocity along at least 60 cm of a 2·5 cm diameter tube. It is caused by rapid evaporation of propellant before and after the atomizing nozzle to produce about 15 cm^3 of vapour from each metered dose of drug suspension. The gas velocity for continuous spraying aerosols of similar internal pressure and rather smaller nozzle is about 6000 cm s^{-1} near the nozzle, falling to 1100 cm s^{-1} at 10 cm distance, taking the maximum values at the centre of the spray cone (Rance, 1974). Although this gas surge could increase small particle deposition on the first and possibly second stages, in practice elimination of the surge by passing the aerosol leaving the collecting throat through a large expansion chamber (5 litre flask) before measurement had little effect on the results. A major reason is doubtless because the present type of aerosol is so closely dispersed it gives little deposition on the first stage of each instrument.

A throat (simulated oro-pharynx) probably represents the most realistic sampling condition for comparing with clinical performance. An airflow of 60 litre min^{-1} was used where possible as this is probably a reasonably attainable minimum inspirational flow for an asthmatic patient. The simple glass throat used collects a similar amount of deposition to the human oro-pharynx, so it was of interest to investigate if it has a fractionating effect on the size distribution. This has been assessed by comparing aerosols passing through a throat with those collected in a large flask, which gave minimal loss by deposition. The throat is more efficient at removing large particles than the flask, so that the throat delivers a somewhat finer aerosol. This result is seen for the three cascaded instruments when the airflow and throat design are standardized (Figs 2–4).

Calculation of throat impaction using the gas velocities of Rance (1974) and the impaction parameter ($\psi_{50\%}^{\frac{1}{2}}$) = 0·71; σ_g = 1·8) for a sweeping bend in a tube (Licht, 1972) shows that deposition due to inertial impaction at the bend should be 1, 50 and 90% respectively for 10, 20 and 24 μm spherical particles of unit density, assuming laminar flow and allowing for an airflow of 60 litres min^{-1} through the system. Clearly only large and mainly 'wet' particles should be impacted. The results in Table 7 show that most of the throat deposition is caused by impingement of the spray cone in the proximal parts of the tube. The airflow projects the cone further along the tube and allows more complete drying of wet droplets to occur and thus reduces the total deposition. Constriction of the throat before the bend caused increased deposition by increasing the cone impingement, even though the air velocity in the constricted region is matched to that in the normal throat of uniform bore.

Because the throat dimensions and airflow were known to affect total deposition and possibly could cause fractionation, in the early part of the work in some experiments the same airflow through a throat of constant dimensions was used with different instruments, necessitating the use of different isokinetic probes to deliver the appropriate airflow to the Casella and Centripeter. Subsequent experiments involved sampling through a 5 litre flask, which proved to be a useful 'low loss' collector removing only 13–21% of the dose. There is still some impaction on the opposing surface of the flask in spite of the large distance (25 cm) from the nozzle.

The reproducibility of the instruments (apart from Kirk's apparatus) has not been examined in detail. Their behaviour seems consistent and the individual measurements in each pair generally agreed well, execpt where the limit of accuracy of the assay methods was approached. Salbutamol inhalers have been examined less thoroughly, but the results show similar behaviour to BDP.

It is important that devices which are proposed for the characterization and quality control of inhalation aerosols should be tested with aerosols of varying size distribution, and which are of known clinical performance. The significance of the present results can be compared with those obtained on similar aerosols by automatic microscopy, following collection of the aerosol in a settling drum (Hallworth & Hamilton, 1976). The results in Table 8 in general show good agreement between the two approaches, although the present results only give a crude estimate of d_{aer} (aerodynamic mean diameter by weight) and σ_g (geometric standard deviation) due to the small number of points on the log d/probability graphs. The general agreement supports the validity of the assumption made by Hallworth & Hamilton (1976) that BDP aerosol particles approximate to unit density spheres and show no significant orientation when settling in air on a slide. The agreement between the two methods also indicates that little de-aggregation occurs in the jets of the present instruments, except possibly in the bottom stage of the Casella.

The present results show that as a proportion of the total aerosol mass from the oral adaptor 50–70% is less than 4 μm aerodynamic diameter, or 35–50% after the aerosol is passed through a throat. The latter results resemble those of Grim &

Table 8. *Comparison of the size distributions on an aerodynamic size basis of BDP aerosols measured by microscopy and by three inertial separation instruments by A, directly into settling drum; B, directly into 5 litre flask; C, through a throat (without air flow) into a settling drum; D, through a throat with air flow.*

	Measuring system	d_{aer}	d_{proj}	σ_g	% weight below d_{aer} of 4 μm
A[a]	microscopy	3·7[b]	5·5	1·7	56
B	CCI	3·6		1·9	56
	CC	3·6		1·9	56
	MLI	2·9		1·9[c]	69
C[a]	microscopy	2·9[b]	4·4	1·6	74
D	CCI	2·7[d]		2·0	72
	CC	3·2[e]		2·0	62
	MLI	2·5		1·8[c]	77
B	SSE Sampler	2·5[f]			
	SSE Sampler	3·5[f]			

d_{aer} is the mean aerodynamic diameter by weight (in μm) and σ_g is the geometric standard deviation.

[a] From Hallworth & Hamilton (1976), measuring by automatic microscopy.

[b] Calculated assuming the particles approximate to unit density spheres.

[c] The MLI gave a curved log/probability graph, so the mean slope was estimated.

[d] Sampled through throat at 17·5 litre min^{-1} with back-up flask.

[e] Sampled through throat at 60 litre min^{-1} followed by isokinetic probe.

[f] Sampled through throat with back-up flask.

others (1968) and Bell & others (1973) on other types of inhalers. Particles below 4 μm are capable of penetrating into the deep lung (Stuart, 1973) but radioactive drug studies show that from BDP and salbutamol aerosols only about 10 and 16% respectively of the total emitted dose from the inhaler is deposited in the lungs of the dog (Martin, Hobson & others, 1971; Martin, Harrison & Tanner, 1973). Clearly many fine particles are not deposited in the lungs, this is also shown by evidence on well characterized spherical liquid particles during 'normal' breathing (Davies, 1973; Heyder, Armbruster & others, 1975). The particles tend to be exhaled before they are deposited by gravitational sedimentation, particularly if there is immediate exhalation following inhalation.

The control of airway resistance depends on the degree of muscular contraction of the larger conducting bronchioles, in which there is appreciable air velocity during respiration. The important site for deposition of bronchodilators such as salbutamol is likely to be in these larger bronchioles, whereas for optimal anti-inflammatory action of a steroid such as BDP it seems likely that additional deposition in the finer respiratory bronchioles would be necessary. It is difficult to establish experimentally the distribution of particles in the range 0·5–10 μm diameter in the various lung regions (Davies, 1973). It is not clear whether it is more appropriate to consider the total mass of fine particles entering the lung or their total number, a problem which is also common to considerations of particle toxicity (Hatch & Gross, 1964).

REFERENCES

Bell, J. H., Brown, K. & Glasby, J. (1973). *J. Pharm. Pharmac.*, **25**, *Suppl.*, 32P–36P.

Davies, C. N. (1973). 1st Congress of the Gesellschaft fur Aerosolforschung, at Bad Soden, October 1973. 'The Deposition of Aerosol in the Human lung'.

Druett, H. A. (1955). *Br. J. industr. Med.*, **12**, 65–70.

Grim, W. M., Portnoff, J. B., Testaino, F. A. & Toberman, R. O. (1968). *Aerosol Age*, **13**, (March), p 22 *et seq.*

Hallworth, G. W. & Hamilton, R. R. (1976). *J. Pharm. Pharmac.*, **28**, 890–897.

Hatch, T. F. & Gross, P. (1964). *Pulmonary deposition and retention of inhaled aerosols*, pp 170–172, New York and London: Academic Press.

Heyder, J., Armbruster, L., Gebhart, J., Grein, E. & Stahlhofen, W. (1975). *J. Aerosol Sci.*, **6**, 311–328.

Hounam, R. F. & Sherwood, R. J. (1965). *Am. ind. Hyg. Ass. J.*, **26**, 122–131.

Karig, A. W., Peck, G. E. & Sperandio, G. J. (1973). *J. pharm. Sci.*, **5**, 811–815.

Kirk, W. F. (1972). *Ibid.*, **61**, 262–264.

Licht, W. (1972). *J. Soc. cosmet. Chem.*, **23**, 657–678.

Lundgren, D. A. (1967). *J. Air Pollut. Control Ass.*, **17**, 225–228.

Martin, L. E., Hobson, J. C., Page, J. A. & Harrison, S. (1971). *Eur. J. Pharmac.*, **14**, 183–199.

Martin, L. E., Harrison, C. & Tanner, R. J. N. (1975). *Postgrad. med. J.*, **51**, (Suppl. 4), 11–20.

May, K. R. (1945). *J. Sci. Instr.*, **22**, 187–195.

May, K. R. (1966). *Bact. Rev.*, **30**, 559–570.

MAY, K. R. (1975a). *J. Aerosol Sci.*, **6**, 403–411.
MAY, K. R. (1975b). *Ibid.*, **6**, 413–419.
MERCER, T. T. (1963). *Ann. Occup. Hyg.*, **6**, 1–14.
MERCER, T. T. (1964). *Ann. Occup. Hyg.*, **7**, 115–124.
O'CONNOR, D. T. (1973). *Ibid.*, **16**, 119–125.
PATERSON, J. E., CONOLLY, M. E., DAVIES, D. S. & DOLLERY, C. T. (1968). *Lancet*, **2**, 426–429.
POLLI, G. P., GRIM, W. M., BACHER, F. A. & YUNKER, M. H. (1969). *J. pharm. Sci.*, **58**, 484–486.
RANCE, R. W. (1974). *J. Soc. cosmet. Chem.*, **25**, 545–561.
SCIARRA, J. J., MCGINLEY, P. & IZZO, L. (1969). *Ibid.*, **20**, 385–394.
SCIARRA, J. J. & ADELMAN, D. (1971). *Ibid.*, **22**, 867–877.
SOOLE, B. W. (1971). *J. Aerosol Sci.*, **2**, 1–14.
STEVENS, D. C. & CHURCHILL, W. L. (1973). *Ibid.*, **4**, 85–91.
STUART, B. O. (1973). *Archs intern. Med.*, **131**, 60–73.
TASK GROUP REPORT (1966). Task Group on Lung Dynamics of the International Commission on Radiological Protection, Health Phys., **12**, 173–207.