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The twin impinger: a simple device for assessing the delivery of drugs from metered dose pressurized aerosol inhalers

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The development is described of the twin impinger, a two-stage separation device for assessing the drug delivery from metered dose inhalers and other oral inhalation delivery devices. The discharged aerosol is fractionated by firing through a simulated oropharynx and then through an impinger stage of defined aerodynamic particle size cut-off characteristics. The fine (pulmonary) fraction which penetrates is collected by a lower impinger. It is demonstrated that this device is able to assess individually the fine particle delivery of both components of two-drug aerosols. Formulations showing undue agglomeration or serious crystal growth of drug are readily detected. The twin impinger is shown to be a valuable device for routine quality assessment of aerosols during product development, stability testing and for quality assurance and comparison of commercial products.

A variety of methods has been described for assessing the fine particle 'pulmonary' fraction of the aerosolized dose discharged from metered dose inhalers (Bell 1967; Bell et al 1973; Hallworth & Andrews 1976; Hallworth & Hamilton 1976). The two basic approaches are: direct measurement of the dose fraction which penetrates through a simplified model upper respiratory tract; and measurement of the aerosol cloud particle size distribution to enable calculation of the likely deposition behaviour. Optical sizing methods based on microscopy (Hallworth & Hamilton 1976) or settling rates in stirred clouds (Porush et al 1960) are slow. Unfortunately, particle counters based on light scattering (Davies et al 1980a, b) do not determine aerodynamic sizes, the relevant particle size parameter which controls their behaviour in the respiratory tract; those which do measure aerodynamic sizes require extreme aerosol cloud dilution and thus present more severe problems for representative sampling (Agarwal et al 1982; Hiller et al 1978, 1980). All these optical methods (with the possible exception of microscopy) are unable to distinguish drug particles from foreign or excipient particles or from other drugs in combination drug products. More importantly, they do not assess or account for oropharyngeal deposition, a factor that exerts a major effect on airway deposition; thus, in such methods, sampling of the important aerosol fraction passing to the lower airways is possibly unrealistic and non-representative.

In contrast, the cascade impactor method can determine specifically the aerodynamic size distribution of one or more drug components. This may be based on sampling the metered dose following actuation, either through a throat or directly into a large chamber (Bell et al 1973; Hallworth & Andrews 1976; Nilsson et al 1977). However, although valuable, such methods are slow and tedious. For routine use there is a need for a simpler but reproducible method. Simple two-stage inertial separation devices that divide the aerosol into a coarse oropharyngeal fraction and a fine pulmonary fraction could meet this need. This was recognized in the devices of Kirk (1972) and Sciarra & Cutie (1978), each of which used a branching throat/upper airway system coupled to a fine particle filter. The value of two-stage separators for assessing the respirable fraction of atmospheric dust aerosols has long been recognized (Hatch & Gross 1964).

We now describe the development of the twin impinger, a device for assessing powder and metered dose inhalers and its use for evaluating the latter. Its value for the quality control of metered dose inhalers has been recognized by the British Pharmacopoeia, which will include the twin impinger in the 1988 Edition under the term 'Glass Impinger'.

DEVELOPMENT

The basic concept of the twin impinger was a simplified device to simulate the performance of the multistage liquid impinger (MLI) developed by May (1966). This glass cascade impinger, in which the aerosol particles impinge on to liquid surfaces due to their inertia in a deflected airstream, had proved

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valuable for assessing both metered dose inhalers (Bell et al 1973; Hallworth & Andrews 1976) and powder inhalers (Bell et al 1971; Hallworth 1977). To enable correct functioning of most powder inhalers, a high airflow (60 L min^{-1}) version was used fitted with an inlet throat, an extra stage for large particle capture (May 1966) and a fine terminal filter.

It was soon apparent that to reduce analytical time a simpler high airflow device suitable for use with both metered dose inhalers and powder inhalations was necessary. The twin impinger was evolved as a glass two-stage separator in which the upper portion (stage 1) represented the throat and stages 1 and 2 of the MLI, whilst the lower portion (stage 2) represented stages 3, 4 and the filter of the MLI. An impinger was preferred to a filter for stage 2 to avoid problems of drug recovery and, in the case of powder inhalations, possible blockage of the filter.

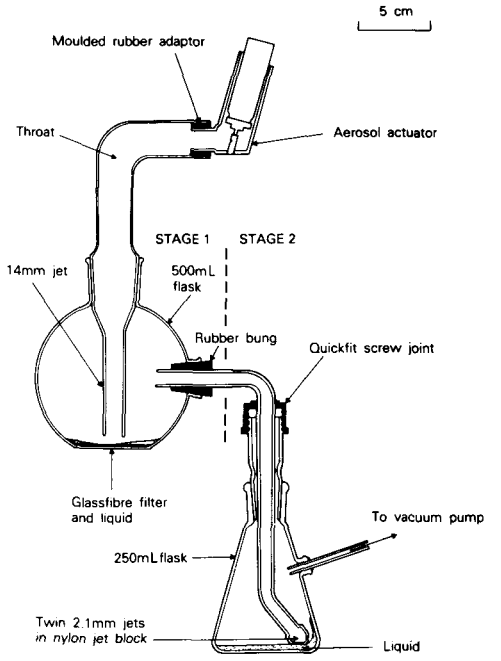

FIG. 1. Diagrammatic representation of the twin impinger, type I.

The original (type I) model (Fig. 1) was described briefly by Hallworth et al (1978). It operated normally at 60 L min^{-1} airflow and was used extensively for product development and quality control of both metered dose inhalers and powder inhalations. The alternative of a direct simplification of the MLI merely by elimination of certain stages was considered likely to present problems in construction and use. However, to improve dimensional reproducibility, interchangeability of components and simplicity of use, a revised type II version of the twin impinger (Fig. 2) was developed subsequently (construction details are available from the authors). The major changes are: (a) replacement of the tubular MLI-type glass throat with one based on a small flask; (b) a stage 1 impinger which uses direct impingement into liquid rather than onto a wet filter disc; (c) a vertical four-jet stage 2 impinger to replace the twin-jet rotary swirl action type; (d) increased use of Quickfit joints to simplify assembly.

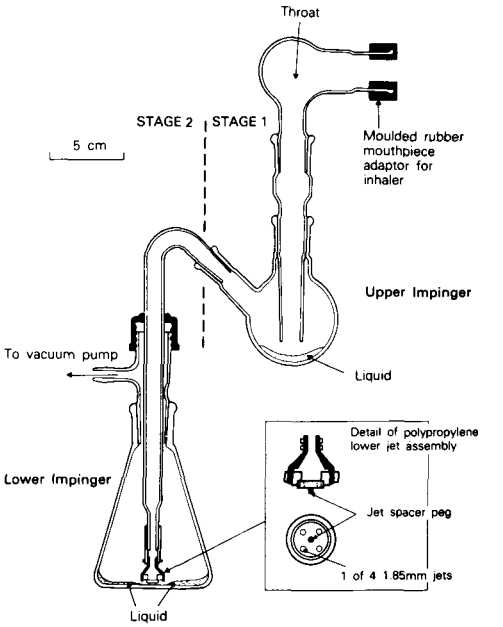

FIG. 2. Diagrammatic representation of the twin impinger, type II.

The new throat has a Quickfit inlet of improved dimensional reproducibility and has a moulded rubber adaptor for the inhaler mouthpiece which gives a good air seal with improved location and centring of the inhaler. The exit cone was preferable to a socket, since this caused drug deposition in the joint. The size of flask used for the throat and the length of its inlet were selected to give similar deposition with metered dose inhalers to the original tubular design. The throat can be separated from the upper impinger if separate throat deposition is to be evaluated. The upper impinger uses vertical impingement of the airstream into liquid to form a vortex (or pocket), which has several advantages over the previous wet filter system. It allows smaller quanti-

ties of liquid to be used without excessive evaporational loss, and drug removal is simplified.

Unfortunately, earlier attempts to scale the Porton pre-impinger (May & Druett 1953) to an airflow of 60 L min^{-1} failed, as the higher airflow caused severe rippling and excessive turbulence in the liquid. The pre-impinger, which gives a reproducibly shaped liquid vortex by tangential impingement of air on the liquid surface, showed good particle size separation and was promising for screening inhalation systems at low airflow rates (Tarpley 1957). The present system provides a consistent liquid vortex and jet-liquid surface spacing provided that the appropriate liquid and its volume are used for a particular airflow and jet size. The 45° upward link tube prevents inadvertent transfer of liquid from stage 1 to stage 2.

The new stage 2 impinger eliminates the previous difficulty of obtaining a consistent rotary swirl action, which required critical positioning of the jet housing. The lower impinger broadly resembles the Porton impinger, which is an efficient fine particle trap (May & Harper 1957), but uses four 1·85 mm diameter jets rather than a single one. Multiple jets reduced the vacuum required to about 30 mm mercury at 60 L min^{-1} airflow (vacuum being proportional to $N^{-\frac{3}{4}}$ where N is the number of jets, May 1975), which reduced leakage problems and the size of the vacuum pump. The high position of the lower flask outlet was essential to minimize losses of fine spray and methanol; the latter distils and climbs up the flask.

CALIBRATION

To assess the particle size cut-off characteristics of stage 1 of both types of twin impinger, the deposition of various sizes of aerosolized monodispersed dye particles was measured in the upper and lower stages and, in some cases, separately in the oropharynx section. Comparative measurements were made on stages 2, 3 and 4 of the MLI. Methylene blue spherical particles were generated from methanolic solutions in a spinning top atomizer and dried in a 150 cm long air tunnel; their density was assumed to be 1·1 g cm^{-1} (O'Connor 1973). The dried particles were sized microscopically with a Quantimet 720 image analyser before and after each experiment. The geometric standard deviation of the mass size distributions was generally 1·05 to 1·10 but sometimes up to about 1·20. Both twin impingers were fitted with a type 1 tubular throat and water (5 mL stage 1 and 20 mL stage 2) was used for impingement. The dye fractions were measured colorimetrically at 644 nm. Particles above 20 μm were generated similarly from xylene solutions of Oil Orange dye (Du Pont) in dioctyl sebacate. These dried to non-volatile droplets (May 1975) which were sized microscopically after collection on magnesia-coated slides (May 1950). The measurements were all made at 18–22 °C; the impaction behaviour is insensitive to temperature differences of a few degrees.

The calibration results are shown in Fig. 3 and some derived approximate impaction parameters are shown in Table 1. These simplify comparisons between the cut-off behaviour of the impingers and with published data on impactors. Dimensionless impaction parameters (Stk) were calculated from equation 1 (Table 1) based on the stage 1 jet size (Raabe 1975). The Stokes-Cunningham slip correction factor was omitted from equation 1 as this is small for particles above 1 μm. The Stk values corresponding to particular percentage deposition levels (e.g. 50%, 90%) were obtained from graphs of log percentage deposition against Stk (probability scale).

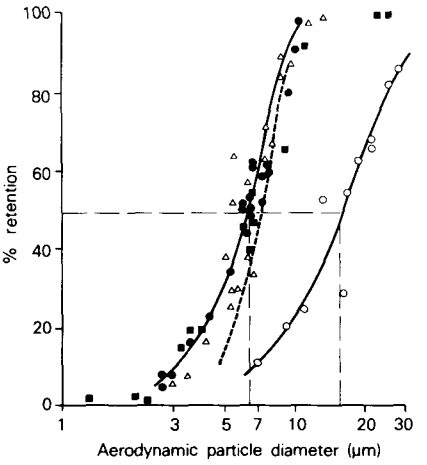

FIG. 3. Calibration curves for impingers. Key: △ twin impinger type I, ● twin impinger type II, ■ MLI (stages 2–4), - - - - MLI (May's adjusted data), ○ throat only (TI type II/MLI type).

The cut-off curves are characterized in Table 1 by the impaction parameters for 50% retention ($Stk^{0.5}$) and the two ratios $Stk^{0.7}/Stk^{0.3}$ and $Stk^{0.9}/Stk^{0.1}$. These ratios indicate, respectively, the slope in the central region (30–70% deposition) of the impaction curves and the overall behaviour as combined slope and tailing towards the extremes (10–90% deposition). Both these ratios are greater than those shown from 'sharp' impactors but are also dependent on the monodispersity of the test aerosols (Jaenicke &

Table 1. Impaction characteristics for various impingers.

Impinger	Stage	d_{50} (μm) (a)	$Stk^{0.5}_{50}$ (b)	X (c)	$Stk^{0.5}_{70}/Stk^{0.5}_{30}$	$Stk^{0.5}_{90}/Stk^{0.5}_{10}$	W (cm)	F (min^{-1})
Twin impinger Type I	Total stage 1	6·4	0·486	30·0	1·24	1·6	1·46	60
	Stage 1 minus throat	6·8	—	—	1·22	—	1·46	60
Twin impinger Type II	Total stage 1	6·4	0·486	30·0	1·30	1·7	1·46	60
	Stage 1 minus throat	7·0	0·530	32·7	1·32	—	1·46	60
—	Tubular throat (as T1/I & ML1)	16	0·510	31·4	1·37	—	2·5	60
Multistage	I	7·0	0·478	29·5	1·20	1·54	1·5	60
Liquid impinger [d]	II	3·9	0·458	30·2	1·22	1·58	1·0	60
Porton Pre-impinger [e]		4·0	0·410	25·0	1·16	1·5	0·65	11

[a] d_{50} is the effective aerodynamic resistance diameter (cm) (i.e. the particle size for 50% retention of unit density spheres of equivalent settling rate in air).

[b] Stk_{50} is the dimensionless impaction parameter for 50% retention.

$$Stk \quad \frac{\rho^* U_0 D_{ar}^2}{9 \mu W} \quad \text{(eqn 1)}$$

D_{ar} = aerodynamic resistance diameter (cm)
ρ^* = standardizing particle density (exactly 1 g cm^{-3}) (Raabe 1976)
U_0 = jet mean velocity (cm s^{-1})
μ = air viscosity = $1{\cdot}82 \times 10^{-4}$ poise
W = jet diameter (cm)

[c] $d_{50} = X\,(W^3/F)^{1/2}$ (eqn 2), where d_{50} is in μm and F is the volumetric flow rate through the jet (L min^{-1}).

[d] Data of May (1966) corrected to a flow rate of 60 L min^{-1} and unit particle density, measured without a throat.

[e] Data of May & Druett (1953); similar impaction parameters were found by them for various flow rates up to 39 L min^{-1}, with various jet sizes.

Blifford 1974; May 1975). To achieve adequate monodispersity for more critical assessment would require extreme modification of the spinning disc equipment and technique (Mitchell 1984), whilst suitable latex spheres in the large sizes required were not available. The twin impingers both show relatively large retention of 3–5 μm particles by the tailing of the lower end of the impaction curves. There is less tailing of the upper curves, presumably partly because of significant overlap with the throat impaction curve.

The 14 mm standard stage 1 jet has an effective (mean) aerodynamic particle cut-off size of 6·4 μm at an airflow rate (F) of 60 L min^{-1}. The effect of changes in F or jet size (W) on d_{50} can be calculated from the simplified impaction equation (equation 2, Table 1) which shows $d_{50} \propto F^{-0.5}$ and $W^{1.5}$. The constant X value of 30 has not been verified experimentally for alternative values of F and W, but should be satisfactory provided that the liquid vortex shape and jet-liquid spacing are kept similar to the standard conditions, by adjustment of the liquid volume where necessary (May & Druett 1953).

Calibration of the stage 2 impinger was not attempted, but its ability to retain fine drug particles was verified as described below.

ASSESSMENT OF METERED DOSE INHALERS

Reproducibility of results on medicinal aerosols with a twin impinger type II

Suspension type metered dose inhalers were examined, containing beclomethasone dipropionate (Becotide, Glaxo) or salbutamol (Ventolin, Glaxo).

For each determination, 7 mL of methanol was placed in stage 1 and 30 mL in stage 2. These volumes were larger than those used for calibration to offset evaporational losses. Ten doses were discharged successively into the twin impinger at 5 s intervals with a continuous airflow of 60 L min^{-1}, the can being shaken before each actuation. The apparatus was rinsed out with methanol; the actuator washings included those from the inside and outside of the metering valve stem. Stage 1 washings included those from the rubber adaptor and stage 2 included those from the inside and outside of the stage 2 inlet tube assembly. The quantities of drug recovered separately from the actuator, stage 1 and stage 2, were determined by HPLC analysis and the mean results (for ten doses) were calculated as percentages of the total drug measured in each experiment. For each batch, measurements were made once each on the ten individual can units and ten times on a single can unit.

Table 2. Summarized results on an investigation of the reproducibility of the twin impinger type II for measuring beclomethasone dipropionate and salbutamol metered dose aerosols.

Inhaler		No. of can/valve units tested	No. of determinations on each can/valve unit	Actuator Mean	Actuator CV%	Stage 1 Mean	Stage 1 CV%	Stage 2 Mean	Stage 2 CV%
Beclomethasone dipropionate (50 μg/shot)	Batch A	1	10	14·4	12·8	38·8	10·2	46·7	10·3
		10	1	13·8	9·5	35·7	9·2	50·4	5·7
	Batch B	1	10	13·2	4·8	34·9	10·0	51·8	6·3
		10	1	17·1	19·8	28·3	7·6	54·5	4·7
Salbutamol (100 μg/shot)		1	10	13·3	14·0	31·00	9·0	55·5	5·2
		10	1	11·1	26·6	32·3	6·0	56·6	4·5

A 14 mm stage 1 jet was used with an airflow of 60 L min^{-1}.
The results are expressed as percentages of the total drug deposition in the actuator and twin impinger; CV% is the coefficient of variation.

The results are summarized in Table 2. No difference in behaviour was apparent between cans or within cans for each product, or between the batches. The stage 2 results are in broad agreement with the stability results for similar products obtained with the twin impinger type I (Table 3).

In separate experiments the escape of any salbutamol or beclomethasone dipropionate from stage 2 was checked for the appropriate aerosols by measuring the drug collected in a large membrane filter (of 0·4 μm pore size) fitted into the outlet. Only 1–2% of the total metered dose was recovered.

Comparison of twin impinger type I and the multistage liquid impinger

The twin impinger type I was used extensively to monitor the stability of various batches of both beclomethasone dipropionate and salbutamol inhalers following storage at various temperatures (Table 3). There was no positive evidence of a decrease in stage 2 deposition fraction in any batch, confirming the absence of any appreciable particle growth in the discharged aerosols. A strict comparison with the MLI was not undertaken. However, some earlier results obtained with three similar MLI models (Table 4) show comparable results when the total deposition on the lower stages (stages 3, 4 and filter) is compared with that in the theoretically equivalent stage 2 of the twin impinger (Table 2).

Table 3. Summarized stability results for different batches of beclomethasone dipropionate and salbutamol metered dose aerosols, as percentage stage 2 deposition in the type I twin impinger.

Product	Stage 2 mean	CV (%)	No. of measurements	Storage period (months)
Beclomethasone dipropionate	59·7	4·8	8	24
	51·2	8·4	16	12
	37·5	10·0	27	12
	42·7	8·9	8	12
Salbutamol	45·3	13·7	18	12
	48·3	16·6	18	12
	48·0	15·5	18	12
	50·6	15·3	18	12
	45·4	8·9	14	12
	57·7	8·4	16	6

A 14 mm stage 1 jet was used with an airflow of 60 L min^{-1}.
The results are calculated on the total drug deposited in the actuator and the twin impinger; CV% is the coefficient of variation.

Use of the twin impinger to assess two drug component aerosols and crystal growth

In common with cascade impactors, the twin impinger enables simultaneous sampling and separate chemical measurement of individual components in an aerosol cloud. For example, in a combination metered dose inhaler containing both a bronchodilator and a steroid, both drugs showed a stable stage 2 deposition fraction during storage (Fig. 4A). In

Table 4. Regional deposition of salbutamol metered dose aerosol (100 μg dose) in a multistage liquid impinger[a].

Region of MLI	Mean[b]	CV%
Throat	45·5	15·8
Throat, stage 1 and stage 2	52·3	16·2
Stage 3, stage 4 and filter	44·7	15·5

[a] Three multistage liquid impingers were tested, models A, B and C. The three models had a similar calibration, the d_{50} (effective aerodynamic mean cut-off sizes) being stage 1, 15·6 μm; stage 2, 7·0 μm; stage 3, 3·0 μm and stage 4, about 1 μm.
[b] Summarized results for 12 determinations, 3 in model A, 5 in model B and 4 in model C, expressed as percentages of the total drug recovered, each result based on 30 accumulated doses, measured by colorimetric assay.

contrast, in an experimental combination inhaler containing two bronchodilator drugs (A and salbutamol) component A gave very poor stage 2 results throughout storage, unlike the stable behaviour of salbutamol (Fig. 4B). This difference in behaviour

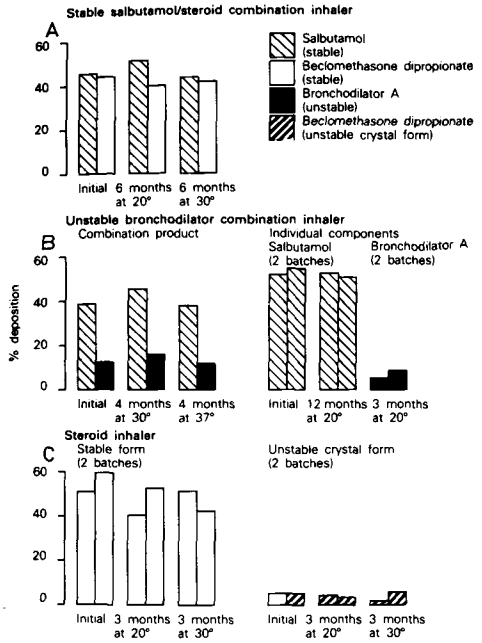

FIG. 4. Percentage stage 2 deposition for combination and steroid metered dose inhalers fired into a twin impinger, illustrating the relative stability of the drug components.

between the two components was also seen in inhalers containing either component singly (Fig. 4B). Subsequent work showed that component A was prone to severe agglomeration of the micronized drug during preparation of the inhalers, the effect depending on the exact preparative method.

The twin impinger has proved to be a sensitive method for revealing crystal growth in aerosols. Beclomethasone dipropionate inhaler gave stable stage 2 results of 40–60% (batches 1 and 2, Fig. 4C), whereas when the same steroid was incorporated as a different crystal form but of similar particle size distribution (batches 3 and 4), there were dramatically lower results both initially (after a four week settling period) and during storage. Alternative microscopic methods revealed the crystal growth in the sprayed aerosol but the twin impinger assessed the mass loss of fine aerosolized drug more accurately.

DISCUSSION

The twin impinger has been shown to be a convenient and reliable means of distinguishing 'good' and 'poor' aerosols. Multi-stage devices give an actual size distribution and may therefore show greater discrimination for borderline cases, but at the expense of much more analytical effort. They are more suited to research on aerosol products, for comparison with clinical data or theoretical models of lung deposition, than for routine development or quality control purposes.

The deposition behaviour of metered dose inhalers in the throat portion of stage 1 appears to correspond to that in the human mouth and throat. This is seen by comparing the impinger throat dose fraction (about 40%) with that recoverable from mouth-washing experiments following inhalation from inhalers containing either isoprenaline sulphate, terbutaline sulphate or Teflon particles (Paterson et al 1968; Morén 1978; Newman et al 1981). Considerable extra-thoracic deposition also occurs in the region beyond the mouth, which is revealed by studies with gamma-labelled inhalers (Newman et al 1981) and which is not accessible to mouth-washing experiments. Much of this extra-thoracic deposition is probably caused by inertial impaction of dry drug particles or droplets of high momentum, either in the larynx or in 'hot spots' below the larynx (Martonen 1983; Schlesinger et al 1982). Such behaviour is mimicked in the twin impinger by impaction in the upper impinger. However, for the standard jet system employed here it is much less pronounced than in-vivo, judging by the lower deposition fraction revealed in the lungs by gamma-labelled aerosol studies compared with the impinger stage 2 deposition fraction (Newman et al 1981; Spiro et al 1984).

This raises the question of whether an upper impinger of reduced cut-off size should be used to give lower stage 2 deposition. However, this would not necessarily improve the discrimination of poor or borderline products and the reduced drug fraction could lead to significantly increased analytical errors. Furthermore, although finer particles (3–4 μm) have a greater probability of deposition in peripheral lung regions during steady-state breathing (Heyder 1982), which is perhaps advantageous clinically, this may not be true when inhaling from metered dose inhalers (Newman et al 1984). Similarly, the question of which airflow rate to use is debatable but changes from 60 L min^{-1} would not necessarily improve the value of the method or be clinically more realistic. Although impactors can be designed with sharper cut-off behaviour, this would not improve the simulation of upper airway behaviour, as the stage 1 impinger probably has sharper cut-off

characteristics than the human larynx with the large upper airways (Martonen 1983).

The use of a throat inlet is preferable to firing the inhaler into a chamber for particle size analysis which ignores the effect of impactional throat deposition on the fine particle inhaled fraction. Such deposition could be calculated from the momentum of the spray droplets but would require data on droplet density, size and velocity distributions at relevant flight distances, as well as the spray profile. Formulation constituents such as ethanol may increase throat deposition profoundly (Kirk 1972; Bell et al 1973).

Similar arguments favour a throat device for measuring powder inhalers, characterized by the deaggregation of powder agglomerates in the airflow (Hallworth 1977). It is advantageous analytically to use one device for the development and quality control of both metered dose inhalers and powder inhalations and this has been borne out by extensive use of the twin impinger. The potential of this and similar devices as a compendial quality control device for metered dose inhalers has been recognized by the British Pharmacopoeia, as the twin impinger will be included in the 1988 Edition.

A study of various commercial metered dose inhalers with the type II model demonstrated a wide range in stage 2 deposition between the products (Meakin & Stroud 1983). These results do not imply varying clinical efficacy of the products, as the metered dose of each one is normally selected during development to give the required clinical response. However, the magnitude of stage 2 results does indicate pharmaceutical quality (fine particle dispersion) and for products of a given drug implies their relative clinical efficacy. There is supporting clinical evidence from two studies on different bronchodilator drugs, where in each case relatively low stage 2 results were correlated with an inferior bronchodilator response in asthmatic patients, compared with the equivalent products giving higher stage 2 deposition (Padfield et al 1983; Parkkali 1983). The implications of this in terms of the equivalence of generic products remain to be seen.

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