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In vitro assessments of inhaler performance are important in product development and quality control, but are not, as such, good predictors of performance *in vivo*. It is, however, possible to modify *in vitro* techniques so that they more closely resemble the *in vivo* situation. Measurements of fine-particle dose (defined as the amount of drug with an aerodynamic diameter less than 5 µm) by cascade impactor have shown that the measured fine-particle dose *in vitro* is highly dependent on the geometry of the inlet to the impactor, the fine-particle dose being considerably lower when the cast of a human throat (an "anatomical throat") is used than when a standard glass inlet is used. This difference is, however, less with a dry-powder inhaler such as Turbuhaler[®] than with a pressurized metered-dose inhaler (pMDI). Furthermore, there is a good correlation between fine-particle dose measured *in vitro* and *in vivo* lung deposition, provided that an anatomically correct inlet is used for the *in vitro* determination. Studies in children have shown that the degree of lung deposition of budesonide, delivered via Turbuhaler, is of the same order of size as the *in vitro* fine-particle dose. No comparable data are available for pMDIs; however, since children are smaller than adults, it is likely that differences in lung deposition between Turbuhaler and pMDIs are probably greater in children than in adults.

In vitro assessments of inhaler performance are primarily designed to characterize aerosol formulations during product development, and to ensure consistent product quality, rather than to predict how the device will perform when used by a patient. *In vivo*, delivery is influenced by numerous factors, including the anatomy of the oropharynx and patient compliance, and inhaler performance, evaluated

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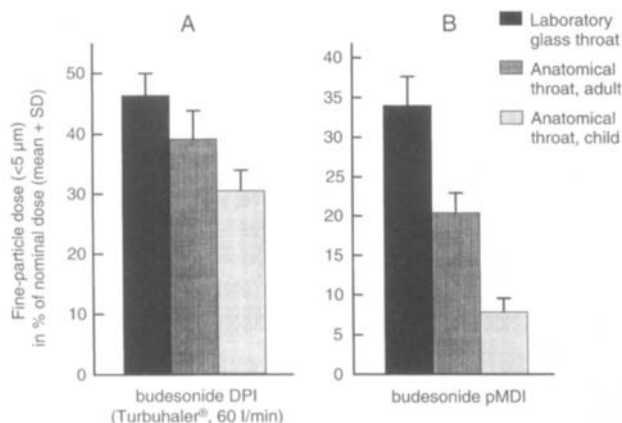


Figure 1. Proportion of nominal dose of budesonide, delivered via pressurized metered-dose inhaler or Turbuhaler, to Anderson impactor through three types of inlet throat (6).

in vivo, shows greater variability than when measured *in vitro*. For this reason, *in vitro* techniques are not good predictors of *in vivo* performance. It is, however, possible to modify *in vitro* techniques so that they more closely mimic the *in vivo* situation. Recent studies, using such “*ex vivo*” measurements of fine-particle dose, have shown that there is a good correlation between fine-particle dose *ex vivo* and lung deposition *in vivo*.

Measuring fine-particle dose *ex vivo*

Inhaler performance can be assessed *in vitro* by means of a cascade impactor, which measures the proportion of particles of different sizes released in the aerosol under controlled conditions (1). Such devices consist of an inlet throat which typically bends through 90° and leads into a chamber containing a series of partitioned stages. Upon discharge from the inhaler, drug particles collect on these stages according to their size; large particles tend to collect on the upper stages, whereas smaller particles travel further through the impactor. Thus, the cascade impactor resembles the human lung, where large particles tend to be deposited in the oropharynx and large airways, whereas small particles tend to be deposited in the peripheral airways (2–4). Particles with diameters below approximately 5 µm tend to be deposited preferentially in the more peripheral airways and alveoli (4); hence, in interpreting *in vitro* data, fine-particle dose has generally been defined as the proportion of particles with diameters below 5 µm.

Although cascade impactors provide useful information about the proportion of particles of different sizes in the generated aerosol, it is not clear whether the deposition of

particles in the glass throat accurately reflects that in the human throat. The use of casts of human throats (“anatomical throats”) provides a means of reproducing the *in vivo* situation more accurately (5). Several studies have compared the fine-particle dose of inhaled corticosteroids when measured by cascade impaction with either standard glass inlets or anatomical throats (6, 7). In one study, the fine-particle dose of budesonide, delivered via pressurized metered-dose inhaler (pMDI), was markedly reduced when an anatomical throat was used, compared with a standard glass throat, and a still greater reduction was seen when the cast of a child’s throat was used (Fig. 1B). In contrast, when budesonide was delivered via a dry-powder inhaler (DPI: Turbuhaler®), the reduction in fine-particle dose seen when an anatomical throat was used was considerably smaller than with a pMDI (Fig. 1A). Similar results were obtained with fluticasone delivered via pMDI or Diskhaler®.

These studies show that the fine-particle dose measured *in vitro* is highly dependent on the geometry of the inlet throat. The influence of the inlet throat, however, varies according to the type of inhaler; DPIs are influenced to a lesser extent than pMDIs. The reason for this may relate to the characteristics of the aerosol cloud produced by the two inhaler types. With pMDIs, the output is large particles with a high initial velocity. These particles have ballistic properties, and a true aerosol is not formed until they have evaporated to form fine particles, and lost momentum. Hence, in a confined inlet throat, a high proportion of the generated particles will be deposited in the throat, and the measured fine-particle dose will be reduced accordingly. The aerosol produced by a pMDI is dynamic; the composition changes continuously and there are interactions between the aerosol and surrounding surfaces. In contrast, the aerosol produced by DPIs is stable and follows the inhaled air gently. As a result, the fine-particle dose delivered by such devices is less dependent on the geometry of the inlet throat. This would suggest that, *in vivo*, DPIs should be less influenced by the smaller oropharynx of children than pMDIs. This question will be further discussed below.

Comparing *in vitro* and *in vivo* performance

In order to compare inhaler performance *in vitro* and *in vivo*, it is necessary to know at what flow rate *in vitro* performance should be assessed. In order to mimic the *in vivo* situation, the flow through the inhaler should match the resistance to flow presented by the device (1). Studies in

Table 1. Conditions for measurement of lung deposition of salbutamol *in vivo* and fine-particle dose *in vitro*, for four different inhalers (11)

Inhaler	<i>In vitro</i>			<i>In vivo</i>	
	Peak flow (l/min)		Dose	Peak flow (l/min)	
	Weak	Moderate		Weak	Moderate
Turbuhaler	30	60	50 µg×6	34	62
Rotahaler	74	144	200 µg×3	72	142
Cyclohaler	55	107	200 µg×3	60	111
pMDI		28	100 µg×6		69

healthy volunteers have determined the effect of resistance on peak inspiratory flow (8, 9); hence, DPIs with different resistances can be compared at similar levels of inspiratory force rather than at a single, arbitrarily selected, flow rate. Thus, inhalers which offer a moderately high resistance (such as Turbuhaler) should be studied at relatively low flow rates, whereas inhalers offering lower resistance should be studied at relatively high flow rates. Studies have shown that the peak inspiratory flow through Turbuhaler is approximately 60–70 l/min in asthmatic children (10); hence, *in vitro* assessments of Turbuhaler performance have been carried out at such flow rates.

Olsson et al. have compared the lung deposition of salbutamol with the *in vitro* fine-particle dose for three DPIs (Turbuhaler, Rotahaler®, and Cyclohaler®) and pMDI (11). Lung deposition was measured in 11 healthy volunteers (six males, five females) by the charcoal-block technique. In this technique, a slurry of activated charcoal is given orally before each inhalation to inhibit gastrointestinal absorption of the drug (12). Salbutamol was given at doses of 300 µg via Turbuhaler and 600 µg via the other devices. With the DPIs, the drug was inhaled at two peak flows, corresponding to a weak and a moderately strong inhalation (Table 1); the flow rates used with Rotahaler and Cyclohaler were calculated from the inspiratory forces needed to achieve flow rates of 30 and 60 l/min with Turbuhaler. The pMDI was actuated at the beginning of a slow inhalation. Fine-particle dose *in vitro* was measured with either one (at flow rates below 75 l/min) or two Andersen Mark II cascade impactors, with either a normal glass throat inlet or an anatomical cast of an adult throat inlet. Lung deposition varied from approximately 3% of the nominal dose with Rotahaler at weak inspiratory flow rate to 23% with Turbuhaler at moderate flow rate (Table 2). Increasing the flow rate from weak to moderate levels was associated with an increase in lung deposition with all three DPIs, and a reduction in interindividual variation. The fine-particle dose *in vitro*,

Table 2. Lung deposition of salbutamol (percentage of nominal dose), delivered by three DPIs at weak and moderate inspiratory flow rates or pMDI, in healthy volunteers (11)

Inhaler	Inspiratory flow	Lung deposition		
		Mean	Range	CV* (%)
Turbuhaler	Moderate	23.2	17.7–32.7	22
	Weak	13.9	6.2–21.0	34
Rotahaler	Moderate	7.0	2.9–9.1	24
	Weak	3.4	1.9–6.1	42
Cyclohaler	Moderate	10.7	6.4–14.4	23
	Weak	7.0	1.8–11.9	55
pMDI	Slow	13.3	6.2–18.3	27

*Coefficient of variation.

measured with a standard glass inlet throat, was approximately 25–42% with Turbuhaler, 11–19% with Rotahaler and Cyclohaler, and 45% with the pMDI. Lower measurements were obtained when an anatomic throat inlet was used (Turbuhaler: 25–33%; Rotahaler and Cyclohaler: 9–15%; pMDI: 19.7%). The large influence of inlet geometry on the resulting fine-particle dose from pMDI should be noted. There was a moderate correlation between lung deposition and fine-particle dose when a normal glass inlet throat was used, and a better correlation when the anatomical throat was used (Fig. 2). This study shows, therefore, that the fine-particle dose measured *in vitro* can predict *in vivo* lung deposition, provided that an anatomically correct impactor inlet is used.

It should be observed that the impactor studies reported in this paper were all performed with a flow profile with a prolonged rise time. A buffer volume was interspaced between the pump and the impactor. This allowed the rise

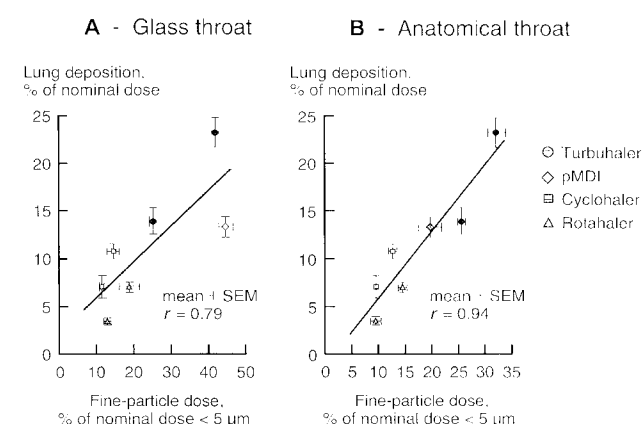
**Figure 2.** Correlation between lung deposition of salbutamol *in vivo* and fine-particle dose *in vitro* measured with glass inlet throat (A) or anatomical throat (B) (11).

Table 3. Lung deposition of budesonide in children with cystic fibrosis (13)

Age (years)	n	Lung deposition (%)	Oropharyngeal deposition (%)	Peripheral/central ratio	Peak inspiratory flow (l/min)
6–8	6	30 ± 9	70	1.8	42
9–12	6	24 ± 5	76	1.6	62
13–16	6	35 ± 8	65	1.5	64

time, defined as time to reach 90% of maximal value, to be adjusted to about 240 ms. This flow profile resembles the *in vivo* patient inhalation performance more closely than the traditional *in vitro* flow profile, which has a more step-like appearance.

Lung deposition in children

To date, few data have been published on lung deposition of inhaled drugs in children. In one study, Devadason et al. studied the lung deposition of budesonide, delivered via Turbuhaler, in 18 children, aged 6–16 years, with cystic fibrosis (13). The children received technetium-99 m (^{99m}Tc)-labeled budesonide, and anterior and posterior scans were obtained with a gamma camera. The proportions of the dose deposited in the lungs and oropharynx were calculated by analysis of the gamma camera scans. Peak inspiratory flow was measured by a spirometer attached to the inhaler. Deposition of budesonide in the lungs and oropharynx is shown in Table 3. The proportion of drug deposited in the lung, and the ratio of peripheral to central deposition, were similar irrespective of age. There was, however, a slight tendency for lung deposition to be higher in older children. This would be consistent with the larger size of the oropharynx in older children, which would result in less oropharyngeal deposition. In general, however, good lung deposition was achieved with Turbuhaler in children 6 years of age and over.

No corresponding data have been obtained with pMDIs in children. Studies in adults, however, have shown that the

lung deposition of budesonide pMDI *in vivo* is similar in numeric value to the fine-particle dose *in vitro*, measured with an anatomical throat inlet (7). However, as described above, both the fine-particle dose and *in vivo* lung deposition are markedly lower with pMDI than with Turbuhaler. *In vitro*, the fine-particle dose, measured with an anatomical cast of a child's throat, is approximately 5–10% with a pMDI, compared with approximately 30% with Turbuhaler. It therefore seems reasonable to speculate that *in vivo* lung deposition will be similar to these *in vitro* values. In addition, *in vitro*, the difference in fine-particle dose between pMDI and Turbuhaler is larger when the cast of a child's throat is used than when the cast of an adult throat is used. Thus, since children are smaller than adults, it is likely that differences in lung deposition between Turbuhaler and pMDI in children will be even greater than in adults.

Conclusions

In vitro measurements of inhaler performance have an important role to play in the development of drug-inhaler systems. However, extrapolation of *in vitro* techniques to the *in vivo* situation requires an appropriate experimental system, such as an impactor with anatomical throat as inlet. *In vitro* techniques can offer useful insights into inhaler performance in children; ultimately, however, the choice of device must depend on lung deposition *in vivo* and, finally, the elicited effect.

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