



Flow early in the inspiratory manoeuvre affects the aerosol particle size distribution from a Turbuhaler

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Several *in vitro* and *in vivo* studies have emphasized the importance of generating a high inspiratory flow when using a dry powder inhaler. Little attention has been paid to the influence of the inspiratory flow profile on the particle size distribution contained in aerosols generated by these devices. The internal volume of a device such as the Turbuhaler is small compared with a vital capacity breath and it is possible that all the powder has been drawn from the device before peak inspiratory flow has been achieved, particularly if the time to peak inspiratory flow is prolonged. A series of experiments were performed to assess the effect of different flow profiles through the Turbuhaler, each with a peak flow of 60 l min^{-1} .

A $400 \mu\text{g}$ budesonide Turbuhaler was enclosed in a chamber allowing air to pass unimpeded through the dosing channels and entrainment ports. A large three-way tap was used to blow powder from the device across a Malvern Mastersizer laser particle sizer which produced a profile of the particle size distribution within the aerosol. The rate of increase in flow through the Turbuhaler was determined by the rate at which the three-way tap was turned, and recorded by means of a pneumotachograph.

The rate of increase in flow was found to significantly affect the particle size distribution within the aerosol. Failure to attain a flow of 30 l min^{-1} before 150 ml of air had passed through the device resulted in the aerosol volume median diameter increasing from less than $6.6 \mu\text{m}$ to greater than $45.3 \mu\text{m}$.

These results indicate that flow during the initial part of the inspiratory effort may be important in determining the characteristics of the aerosol generated by a dry powder inhaler. With more sophisticated equipment, it might be possible to explore the relationship between flow profile and particle size distribution generated by dry powder devices in more detail.

RESPIR. MED. (1997) 91, 624–628

Introduction

Currently available dry powder inhalers (DPIs) require energy, imparted by the inspiratory effort of the patient, to disaggregate the powder into particles small enough to be inhaled. Clinical (1–5) and radiolabelled deposition (6) studies have indicated that drug delivery to the lungs, from a variety of dry powder inhalers, is enhanced as the peak inspiratory flow increases. These findings are consistent with the results from *in vitro* studies which have indicated that disaggregation of the micronized powder within a dry

powder inhaler, such as the Turbuhaler, increases as the peak flow through the device increases, resulting in a greater proportion of ‘respirable’ particles (7). This increase in ‘respirable’ dose results in improved delivery of drug to the lungs despite the high inspiratory flows which would normally act to reduce delivery of drug to the lower respiratory tract.

When inhaling through a Turbuhaler, it is likely that all the powder is drawn from the device by the time the first 100–200 ml have been inhaled (8). Hence, the powder may have passed through the spiral disaggregation channels and have left the device before peak inspiratory flow has been achieved. The acceleration applied to particles within the device, and the resultant velocity of those particles as they pass through the spiral disaggregation channels, will vary depending upon the inspiratory flow profile of the inspiratory manoeuvre. Therefore, it is

Received 20 December 1995 and accepted in revised form 5 December 1996.

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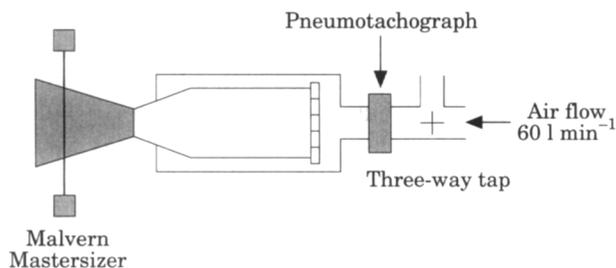


FIG. 1. Experimental set up illustrated. A large three-way tap permitted air to be directed through the Turbuhaler, directing the resultant aerosol across the laser of the Malvern particle sizer. The rate of increase in flow was determined by the rate of opening of the three-way tap.

entirely possible that the degree of disaggregation will depend more on the inhalation flow profile than the final flow achieved.

In order to address this issue, a Malvern Mastersizer laser particle sizer was used to assess the effect of altering the rate of increase in flow on the particle size distribution generated by a Turbuhaler.

Methods

IN VITRO EXPERIMENTS

These experiments, carried out to assess particle size distribution and dose delivered, utilized a 'spaceship' (Astra Draco, Sweden). This simple device encloses the Turbuhaler such that air can flow unimpeded through the dosing channels and entrainment ports and out through the mouth piece. A large three-way tap permitted compressed air to be directed through the 'spaceship' and hence Turbuhaler as required (Fig. 1). A flow of 60 l min^{-1} , calibrated using a rotameter (Fischer & Porter Ltd, U.K.), was used for all experiments. The flow profile through the Turbuhaler could be altered by the rate at which the three-way tap was turned from closed to fully open. Flow through the 'spaceship' was measured using a Fleisch no. 2 pneumotachograph (PK Morgan Ltd, Chatham, U.K.) Data was collected and analysed using Labdat and Anadat programmes (RHT infodat, Montreal, Canada).

Particle sizing was performed using a Malvern Mastersizer X (Malvern Instruments Ltd, U.K.) Turbuhalers were placed in a 'spaceship' and then blown across the path of the laser particle sizer. This approach to particle sizing aerosols generated by the Turbuhaler has been used in previous studies (9–12).

A series of experiments were performed in which the rate at which the flow increased was varied from rapid (peak flow achieved within 0.35 s) to slow (peak

flow achieved within 3 s). Since it has been suggested that it is the first 100–200 ml of volume passing through the device that are important (8), the flow through the Turbuhaler was quantified after 150 ml had passed through it. The flow at 150 ml was then plotted against the volume median diameter (VMD) for that particular run.

When using the Malvern particle sizer, data is collected as volume data and a VMD can be derived. Fifty percent of the total aerosol volume is contained in particles greater than this size and 50% of the total volume is in particles with a diameter less than this value. A mass median aerosol diameter can be calculated from this value if all particles have the same diameter. Results in this study was presented as VMD as the large aggregated particles are likely to have a different density to those of the small disaggregated particles.

IN VIVO STUDY

Ten healthy adult subjects, four males and six females, aged 24–51 years, inhaled through a Turbuhaler on two occasions. On one occasion, they inhaled with maximum inspiratory effort, and on the other they aimed for a peak inspiratory flow of 30 l min^{-1} . A visual display of their inspiratory flow permitted them to aim for this preset value. Flow through the 'spaceship' was measured using a Fleisch no. 2 pneumotachograph, and data were collected and analysed using Labdat and Anadat programmes. For each run, the inspiratory flow at 150 ml inhaled volume was calculated.

Results

IN VITRO STUDY

Flow at 150 ml volume plotted against VMD obtained for the individual runs ($n=13$) is shown in Fig. 2.

The six experiments are shown in Figs 3 and 4. The flow profiles are shown in Fig. 3. These are typical of those obtained for rapid (1), intermediate (2–5) and slow (6) increases in flow. The corresponding particle size distribution are shown in Fig. 4. The calculated aerosol volume median diameters for the six experiments were (1) $3.9 \mu\text{m}$; (2) $5.0 \mu\text{m}$; (3) $6.6 \mu\text{m}$; (4) $45.3 \mu\text{m}$; (5) $89.3 \mu\text{m}$ and (6) $100 \mu\text{m}$.

IN VIVO STUDY

When aiming for maximum inspiratory flow, the inspiratory flow when the inhaled volume reached 150 ml ranged from 54 to 73 l min^{-1} (median 58 l

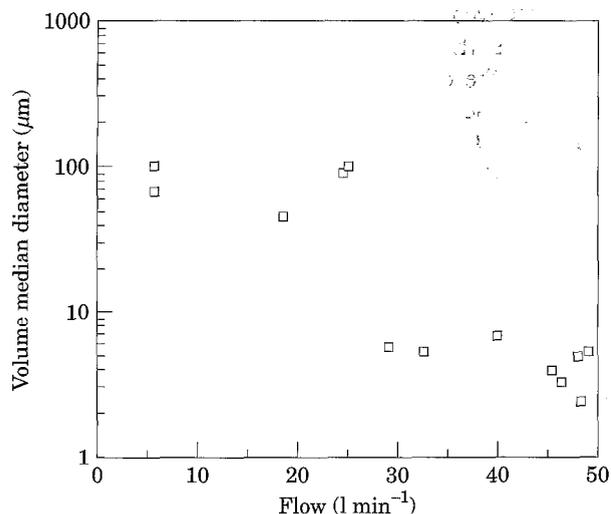


FIG. 2. Volume median diameter obtained at different flows. Flow was measured after 150 ml of air had passed through the Turbuhaler.

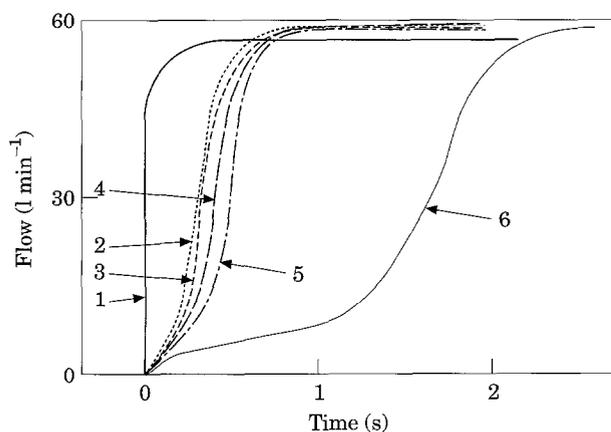


FIG. 3. Flow profiles from six experiments. Particle size distributions measured during each experiment are shown in Fig. 4.

min^{-1}). When aiming for 30 l min^{-1} inspiratory flows at 150 ml were in the range $21\text{--}36 \text{ l min}^{-1}$ with two subjects obtaining values $<30 \text{ l min}^{-1}$.

Discussion

These results suggest that the particle size distribution from the Turbuhaler is not entirely dependent on the peak inspiratory flow but is influenced to a large extent by the flow achieved early in the inspiratory effort. Indeed, it appears that the flow achieved within the first 150 l min^{-1} inhaled is more important than the peak flow, providing this is greater or equal than 30 l min^{-1} .

Figure 2 suggests that there is a relatively modest change in aerosol characteristics as flow at 150 ml

volume falls towards 30 l min^{-1} , but between 29 and 25 l min^{-1} there is a major change in the characteristics of the aerosol generated with a large increase in VMD. The small but noticeable trend of a fall in VMD as the flow falls toward 30 l min^{-1} may well be reflected in the relative dose reaching the lung. From Figs 2-4, it appears that the characteristics of aerosols generated by the Turbuhaler alter as the rate of increase in flow decreases from rapid, as illustrated by flow profile in Fig. 3(a), to less rapid as in Fig. 3(b) and (c). A much greater change then occurs as the rate of increase in flow falls further, as shown in Fig. 3(d) and (e).

It is of interest that clinical studies have found similar results with relatively little change in performance as the flow increases above 30 l min^{-1} , but a sudden fall in effectiveness of the device below this level. Pedersen *et al.* found that the bronchodilator response in children using a Turbuhaler was unaltered as inspiratory flow fell from 60 to 30 l min^{-1} but then dropped significantly as flow fell further to 22 l min^{-1} (4). Engel *et al.* found that reducing inspiratory flows from greater than 80 l min^{-1} to 34 l min^{-1} in adults had no obvious effect on the degree of bronchodilation achieved using a terbutaline Turbuhaler and produced only slightly lower plasma terbutaline levels (13).

The magnitude of the change in volume mediated diameter observed between profiles '3' and '4' is such that it would result in a very large fall in the lung dose achieved. As noted earlier, laser particle sizing has been used previously for dry powder inhalers (9-12) and although there may be a small effect on the mass median diameter calculated from the volume median diameter if there is a change in particle density, as is the case for disaggregated and spheronized particles, any such differences are minimal compared with the magnitude of the observed changes. The 'spaceship' has been specifically designed to ensure that airflow through the entrainment channels and dosing channels is unimpeded and hence follows the normal pattern of flow when in clinical use.

This study suggests that flows of 30 l min^{-1} should be achieved early during inhalation. The healthy adults inhaling to maximal PIF all achieved flows at 150 ml well in excess of this figure, but when inhaling to an artificially low PIF of 30 l min^{-1} , some individuals will fail to achieve this value by 150 ml. One recent deposition study in adult subjects using the Turbuhaler found a drug delivery to the lungs using a PIF of 58 l min^{-1} was approximately double that at 34 l min^{-1} . Subjects were required to achieve PIF within 1 s and it is possible that the results obtained from subjects when inhaling at the lower PIF were

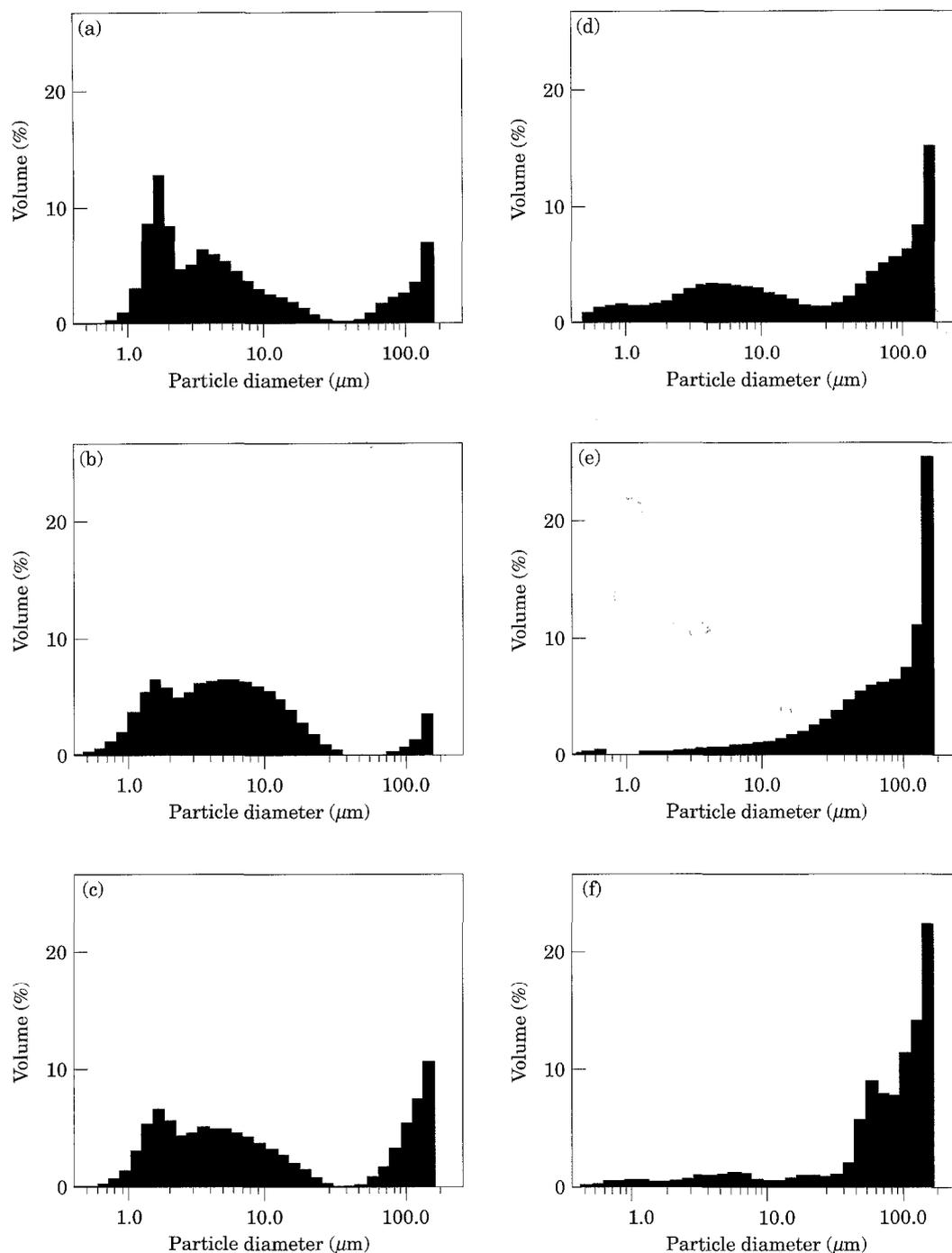


FIG. 4. Particle size distributions from six experiments obtained using Malvern Mastersizer. Experiments 1–6 correspond to flow profiles shown in Fig. 3.

adversely affected by attempting to achieve this artificially low PIF.

These results imply that when assessing these devices, close attention should be paid to both the peak inspiratory flow and the inspiratory flow profile or 'rise time'. With more sophisticated equipment it might be possible to explore the relationship between flow profile and particle size distribution

generated by dry powder devices in more detail. For instance it might be possible to increase flows for the first 100 or 200 ml of air passing through the device and then reduce the flow in order to define the critical volume at which all the powder has left the device.

More importantly, these results emphasize the importance of maximal inspiratory effort immediately

on commencing inspiration when using dry powder inhalers.

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