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Inhalation characteristics and their effects on in vitro drug delivery from dry powder inhalers Part 2: Effect of peak flow rate (PIFR) and inspiration time on the in vitro drug release from three different types of commercial dry powder inhalers

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Abstract

Three commercial dry powder inhalers with completely different dosing and powder disintegration principles were evaluated in an in vitro deposition study. A four-stage cascade impactor was used for the range of flow rates between 20 and 60 l/min. Turbuhaler, Diskhaler and Spinhaler showed increasing amounts of drug discharged from the dose system with increasing peak inspiratory flow rate (PIFR). Only for the Spinhaler, was discharge influenced by total inspiration time as well. All three inhalers also showed improved powder disintegration with increasing PIFR. Highest fine particle yield was obtained from the Turbuhaler, reaching a maximum of 35–40% of the nominal dose at flow rates of 50–60 l/min. In comparison, less than 10% of the nominal dose from the Spinhaler and on average 23% from the Diskhaler were released as fine drug particles at 60 l/min. From the work of inspiration involved, it has been concluded that a short and fast inspiration through the Turbuhaler gives an optimal result from fine particle output and from efficiency point of view.

Keywords: Asthma; COPD; Dry powder inhalers; Cascade impactor; Work of inspiration; In vitro deposition; Peak flow rate (PIFR); Inspiration time

1. Introduction

Dry powder inhalers (DPIs) are breath controlled drug delivery systems. Both the discharge

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from the dose system and the degree of powder disintegration depend on the generated inspiratory flow through the device. Sumby et al. (1992) and Matthys (1994) consider a flow rate of 60 l/min as the optimal respectively ideal for DPIs. Vidgrén (1994) also refers to inspiratory flow rates in general of 60 l/min or more for obtaining good effect from DPIs.

The few available in vitro studies on commercial DPIs in this respect all relate delivered dose and fine particle output to the applied inspiratory peak flow rate (PIFR). Holmann et al. (1989) examined the required flow rate for complete discharge of the dose system. They found great differences between the different types of DPIs used for their study. Required flow rates varied between 24 l/min for the Turbuhaler and more than 96–120 l/min for the Spinhaler. Bell et al. (1971) showed at a flow rate of 60 l/min, that the degree of emptying of the hard gelatin capsules by the Spinhaler depends strongly on mean particle size and thus on the flow properties of the lactose fractions used.

Vidgren et al. (1988) found a higher in vitro fine particle output from the ISF-inhaler than from the Spinhaler for two different types of formulation for disodium cromoglycate (DSCG) at 60 l/min. From impactor data given by Bell et al. (1971), a particle size fraction < 5.5 μm from the Spinhaler at 60 l/min of 23.9% can be calculated. This is of the same order of magnitude as the respirable fraction from the Turbuhaler at only 28.3 l/min given by Wetterlin (1988), being 20.3% on average for four different batches of terbutaline sulphate. Zanen et al. (1992) showed that the size fraction < 5 μm for salbutamol from the Cyclohaler is more or less constant between 40 and 80 l/min, but the size fraction 5–7 μm increases with increasing flow rate.

It is difficult to compare the results from different studies with each other as the percentages given refer to different fractions of the dose, sometimes being total mouthpiece release (Bell et al., 1971) and sometimes total recovery (Vidgren et al., 1988). Still, the results from various studies suggest that fine particle output from a DPI increases with increasing flow rate. There also seem to be considerable differences in fine particle yields between different types of DPIs at the same flow rate. So, the necessary (peak) flow rate for sufficient powder disintegration may not be the same for different DPI-designs.

In the first part of this study (De Boer et al., 1996) it was shown that the attainable PIFR through DPIs strongly increases with decreasing air flow resistance at the same inspiration mode. Mean PIFRs of 39 healthy volunteers generated at maximum effort have been summarized in Table 1. For the high resistance Turbuhaler ($R = 0.9 \times 10^5$ $N^{0.5}.s.m^{-4}$) maximum PIFR (on average 60 l/min) is considerably lower than maximum PIFR through the low resistance Spinhaler (mean PIFR of 137 l/min at $R = 0.35 \times 10^5.s.m^{-4}$).

It is rather obvious that the necessary PIFR for good drug delivery from a DPI should be within the range of attainable PIFRs for the same device. Higher flow rates may promote fine particle generation, but it has been recognized that they are rather disadvantageous from deposition point of view (Newman and Pavia, 1985; Vidgrén, 1994). The optimum inspiratory conditions must therefore be balanced between fine particle generation and the losses of these particles due to oropharyngeal deposition. Both are increasing with increasing inspiratory flow rate though in different manners. For this study, PIFR has been confined to the 60 l/min referred to by various authors as being 'ideal'.

The optimum inspiratory conditions for drug deposition are not determined by PIFR alone however. The effects of other inspiratory flow parameters, such as total inspiration time and flow increase rate (FIR) may be considerable, dependent upon the specific DPI design. Very

Table 1
PIFR in l/min at maximum inspiratory effort through commercial dry powder inhalers attained by 39 healthy volunteers

DPI	Mean	Range
Rotahaler	161	76–220
Spinhaler	137	64–187
ISF inhaler (Cyclohaler)	126	58–171
Diskhaler	109	48–148
Turbuhaler	59	25–83
Inhalator Ingelheim	50	24–71

little attention has been paid to these parameters so far. Also inhaler accumulations (in the mouthpiece) and residues (in the dose system) have not been reported in detail.

The aim of this and following studies is therefore to assess the required inspiration curves for optimal fine particle outputs from commercial DPIs that show completely different designs. In this part, delivered dose, fine drug particle fraction, inhaler losses and residues will be evaluated as a function of the inspiratory flow rate and of total inspiration time for the Turbuhaler, Diskhaler and Spinhaler. The ranges were confined to 0.5–2 × 3 s for the inspiration time, and 20–60 l/min for the flow rate. In one of the next parts of this series, fine particle generation at flow rates > 60 l/min will be discussed.

2. Materials and methods

Dry powder inhalers used for this study were Turbuhaler Pulmicort, containing 200 μg budesonide per nominal dose, Diskhaler (with Becotide Rotadisks, containing 200 μg beclomethasone dipropionate (BDP) per nominal dose) and Spinhaler (with Lomudal Spincaps, containing 20 mg DSCG per nominal dose). In order to complete the whole study, several devices had to be used for each type of inhaler, all derived from the same batch.

2.1. Accuracy of dose weighing

Accurate mean weights of the contents of capsules and blisters were obtained by weighing 30 individual cartridges before and after complete removal of the drug formulation. Before measuring the tare weights, inner capsule respectively blister walls were wiped clean with pressurized nitrogen gas. Mean anhydrous drug contents in the hydrous DSCG-formulation for Lomudal, respectively BDP containing adhesive mixture for Becotide were calculated from content uniformity testing of 30 individual doses. A correction was made for BDP fractions adhering onto blister walls. For this analysis, the brown overprint on the aluminium blister foil was removed completely before opening and rinsing the blisters with ethanol. For the accuracy of dose measuring by the Pulmicort Turbuhaler, a special mini-impinger was constructed. The apparatus allowed complete removal of (30) individual doses directly from the dosing disk of a slightly modified Turbuhaler, with complete recovery of the removed dose.

2.2. Cascade impactor analysis (CIA)

Two identical four-stage cascade impactors with a dry bent inlet tube were used for the study (Lenz Labor Instruments, The Netherlands). The approximate cut-off diameters at 60 l/min for budesonide are 13 μm for the first, 7 μm for the second and 3 μm for the third stage. Mass fractions derived from individual stages have not been expressed in terms of (aerodynamic) particle diameter, but referred to by stage numbers, as the cut-off diameters of the different stages vary with the type of drug (slightly) and flow rate. The mass fractions collected on the 3rd and 4th stage are considered to be most relevant for deposition in the lower respiratory tract.

A coupling flange with exchangeable rubber seal was mounted on the inlet tube for holding the inhalers during inspiration. From this coupling flange, a tube connection was made to a differential pressure gauge (type PD1 with Meßkonverter MC2A, Hottinger Baldwin Messtechnik, Germany). Flow rate versus pressure drop relationships were recorded for the individual inhalers, using a thermal mass flow meter Brooks, model 5812N (Brooks Instrument, The Netherlands). The required flow rate through the DPIs during CIA was obtained by adjusting the corresponding pressure drops across the devices. The pressure drops were recorded against inspiration time with a Gould EasyGraf TA240 (Simac Electronics, The Netherlands). The recordings were not only used for a check upon correct PIFR adjustment, but also for calculation of the flow increase rates during the experiments.

Each cascade impactor result given, is the mean of two series of 10 successive inspirations, except for Lomudal were each result is the mean of two series of five doses. Mean flow increase rate up to 90% of the adjusted peak flow ($FIR_{0.9PIFR}$) was

approx. 2 l/s^2 for the whole range of flow rates between 20–60 l/min. For the inspiration time of 3 s, flow rate intervals were 10 l/min. For the inspiration times of 0.5, 1.5 and 2 × 3 s, only the flow rates 20, 40 and 60 l/min were applied. For the Pulmicort Turbuhalers, containing 200 doses, only the doses 10–150 from each device were used.

Fractions separated in the cascade impactor and accumulated in the inhalers were dissolved in pure ethanol for budesonide and BDP. Fractions DSCG were dissolved in demineralized water. For the Diskhaler, blister residues were also analysed. All drug solutions from collected fractions of BDP were treated in a centrifuge (3000 rev./min for 5 min) in order to precipitate the lactose carrier crystals. Analysis was performed by UV absorption at 243.7 nm for budesonide, 239.2 nm for BDP and 328 nm for DSCG respectively, using a PU 8720 UV/VIS Spectrophotometer (Philips, The Netherlands). All mass fractions have been expressed in percentages of the nominal anhydrous dose (label claim).

Work of inspiration (Nm) during inspiration was calculated as the product of pressure drop across the inhaler (dP in N/m^2), volumetric flow rate (Φ_v in m^3/s) and inspiration time (t in s).

2.3. Scanning electron micrographs

Scanning electron micrographs of two different types of powder formulation were made using a JSM 35C microscope (JEOL, Japan). The powders were scattered on a thin film of a two-component epoxy resin and coated with a gold layer of approx. 300 Å. Acceleration voltage during observation was 15 kV.

3. Results and discussion

3.1. Inhaler design and powder formulation

Fig. 1 shows the different DPI-concepts used for this study. All three concepts may be described in terms of a dose system and a mouthpiece region. During inhalation, the powder has to be entrained from the dose system by the

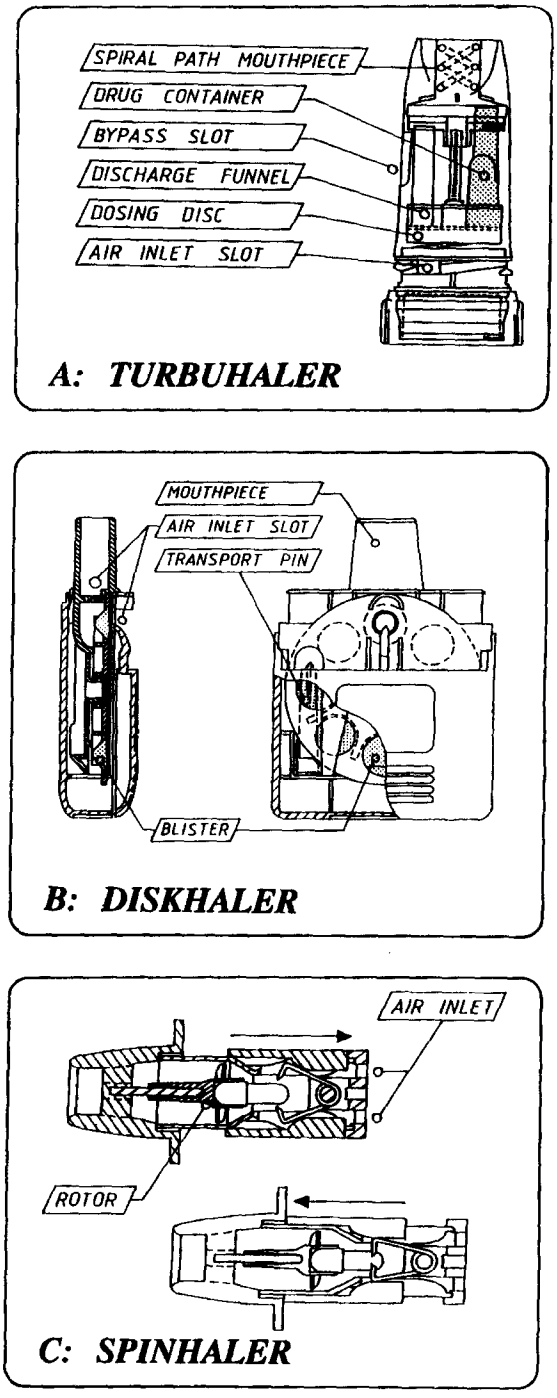

Fig. 1. Functional parts of the Turbuhaler, Diskhaler and Spinhaler.

inspiratory air stream and to be conveyed towards the mouthpiece region. In this region powder disintegration occurs in order to promote the emission of primary drug particles from the device. As a consequence of incomplete discharge from the dose system and accumulations especially inside the mouthpiece region, there may be considerable differences between the weighed dose, the entrained dose and the emitted dose, respectively.

The Turbuhaler (Fig. 1a) is a multi-dose device bearing its supply of pure drug for 200 doses in a small container. Fig. 2 depicts the measuring system of the Turbuhaler in more detail. The construction consists basically of successive scrapers forcing the drug compound into groups of bores in a dosing disk during rotation of the disk against these scrapers (Wetterlin, 1988). For the multi-dose Diskhaler (Fig. 1b), individual doses are stored in blisters that are arranged in a tangential pathway on a disk (see Sumby et al., 1993 for the four-dose Serevent Diskhaler). The Becotide Rotadisks for this study consisted of eight blisters per disk. The Spinhaler (Fig. 1c) is a so-called single-dose DPI: individual capsules filled with drug compound are inserted in the inhaler device and pierced before emptying during inhalation (Bell et al., 1971).

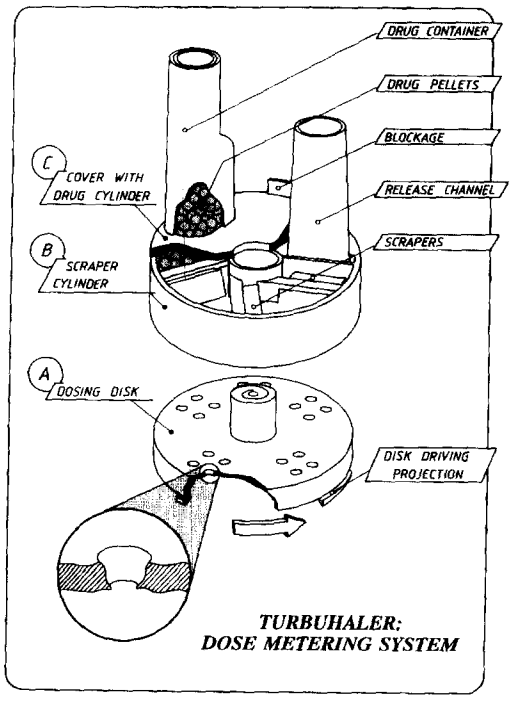

Fig. 2. Dose measuring system of the Turbuhaler.

Only two different types of powder formulations are applied for the DPIs described above. Fig. 3a shows a spherical pellet type of formulation. The example given is DSCG in Lomudal for the Spinhaler. Although budesonide pellets for the Turbuhaler are of the same principle, considerable differences in pellet size distribution may occur between the different types of drug, as well as between different batches of the same drug. The pellets of the high dose DSCG in the Spincaps are supposed to stay intact until release from the capsule. The budesonide pellets are distorted during scraping into the bores of the dosing disk. Further disintegration into primary particles is promoted by the spiral path mouthpiece of the Turbuhaler during inhalation of the dose. The blisters of the Becotide Rotadisks are filled with an adhesive mixture, as shown in Fig. 3b. This type of formulation consists of relatively large α-lactose monohydrate crystals, carrying the micronized beclomethasone dipropionate (BDP) particles on their surface.

3.2. Discharge from the dose system

The effect of inspiratory flow rate and inspiration time on the discharge from the dose systems of the three different DPIs is presented in Fig. 4a–c. All data were calculated as total recoveries from cascade impactor analysis, including corrections for inhaler accumulations and depositions in the inlet tube to the cascade impactor. Fig. 4a shows that the dose entrainment from the Pulmicort Turbuhaler slightly improves with increasing flow rate within the range 20–60 l/min for all four inspiration times. Inter-device variations (for the same batch) make it difficult to decide whether there is really a significant effect of inspiration time. The Diskhaler (Fig. 2b) shows a much stronger effect of flow rate on discharge from the dose system. On average 20–25% of the nominal dose is still not yet released from the Becotide blister at 60 l/min. As for the Turbuhaler, the

Fig. 3. Scanning electron micrographs of Lomudal spherical pellets (a) and Becotide adhesive mixture (b) at a microscopic magnification of 300 ×: the bars represent 100 μm.

effect of inspiration time on the entrainment from the dose system seems to be negligible. The effect of flow rate for the Spinhaler (Fig. 2c) is of the same order of magnitude as that for the Turbuhaler. The effect of inspiration time on the other hand, is evident for this type of DPI. After 0.5 s of inspiration time, only a fraction of the dose is discharged from the capsules compared to the longer inspiration times. Explanations for these differences in behaviour can be found in the different designs for the dose systems. There may be an effect from the type of powder formulation as well.

Discharge of the volumetrically measured amount of drug from the bores in the dosing disk of the Turbuhaler is rather a consequence of a certain pressure difference across the powder mass than of a partial flow rate through these bores.

Once the threshold pressure drop for lifting has been generated by the patient, entrainment of the dose occurs more or less instantaneously. This threshold value for lifting may vary slightly from dose to dose or even from bore to bore (for the same dose) however, as a consequence of observed incomplete filling of bores. Inhomogeneities in the powder bed influence cohesion forces and total adhesion force between the powder mass and the inner walls of the bores. Not all bores are therefore emptied or emptied completely at the same moment. At lower flow rates, corresponding pressure drops across the bores are of the same order of magnitude as the mean threshold value for lifting. As soon as only part of the dose is discharged, the pressure drop across the dose disk decreases immediately towards a level being insufficient for lifting of the remaining drug fractions. Only at higher flow rates, will a further increase in pressure drop to values beyond the threshold for lifting follow a temporary pressure drop at discharge. Entrainment at higher flow rates is therefore more complete (Fig. 4a).

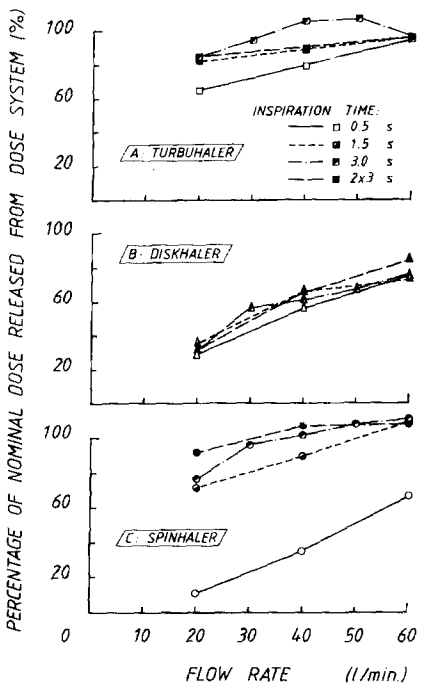

Fig. 4. Drug amounts discharged from the dose systems as a percentage of the nominal dose, as a function of flow rate and inspiration time.

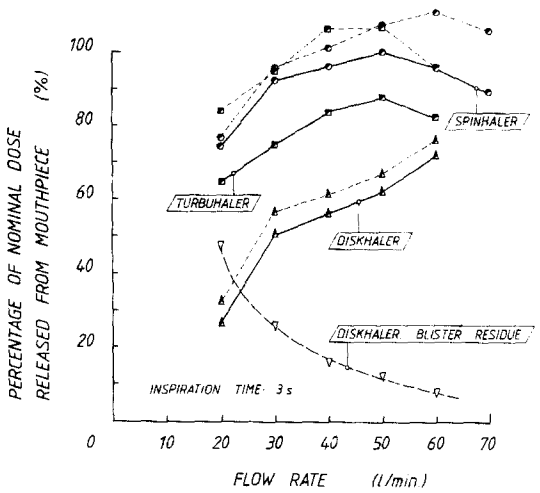

Fig. 5. Delivered doses by the DPIs at an inspiration time of 3 s. The discontinuous lines represent the amounts discharged from the dose systems (derived from Fig. 4); the dotted line shows the blister residue for the Diskhaler. All amounts are expressed as a percentage of the nominal dose.

The design of the Diskhaler (Fig. 1b) is rather different from that of the Turbuhaler. Blisters, containing one single dose each, have to be perforated at both sides prior to inhalation. During inhalation, part of the inspiratory flow passes through the holes in the blister foils for entrainment of the dose. The powder stream is then mixed with a bypass flow, entering the mouthpiece channel through two opposite holes (Sumby et al., 1993). In this mixing zone, a turbulent air flow is created by which the powder agglomerates are disintegrated. The results in Fig. 4b prove that powder release from the blister is incomplete at flow rates < 60 l/min. In this range of flow rates, partial powder flow is insufficient for entrainment of total powder mass. It is rather disadvantageous in this respect that part of the powder is forced into the periphery of the blister during perforation. This peripheral powder fraction is sheltered from the inspiratory air stream by deformed fragments of the pierced soft blister foil. Total flow rates > 60 l/min are necessary for complete entrainment, as shown in Fig. 5, presenting blister residues for the Diskhaler as a function of total flow rate. As for the Turbuhaler, it was observed

that the accessible part of the dose is entrained almost instantaneously. These observations are confirmed by the results in Fig. 4b, showing that there is hardly any effect of inhalation time.

For the Spinhaler, a Spincap (hard gelatin capsule) containing one single dose of 20 mg of Lomudal is placed in a holder connected to the rotor inside the device. The Spincap is subsequently perforated in the body part at two positions facing each other. As a consequence of the special tapered bearing of the rotor (Bell et al., 1971), the pierced end of the capsule wiggles during rotation with greatest amplitude at the site of the perforations. Therefore the dose is conveyed along the capsule walls towards these perforations and the capsule is discharged by the centrifugal force acting on the powder. Discharge rate depends on the flow properties of the drug formulation (soft spherical pellets for Lomudal) and the rotation speed of the capsule. It may therefore not be surprising that the dose release results for the Spinhaler in Fig. 4c show a dependence on both the flow rate and inspiration time. Flow rates < 50–60 l/min seem to be insufficient for complete emptying, even at relatively long inspiration times of 3–6 s. It was observed that the position of the Spinhaler during inhalation is of great effect on the discharge from the Spincaps: when the inhaler is kept in a more or less vertical position, the percentage released is even lower than the data shown in Fig. 4c.

3.3. Delivered dose (mouthpiece release)

The amount of drug discharged from the dose system of the three DPIs does not equal the amount of drug delivered to the respiratory tract (mouthpiece release). Losses occur inside the inhaler, partly due to waste directly from the dose system even before inhalation and partly as a result of accumulation of primary drug particles in the mouthpiece region during inhalation. Fig. 5 shows the differences for the range of flow rates between 20 and 60 l/min at the inspiration time of 3 s. In this figure, the discontinuous lines represent the percentages released from the dose system, whereas the continuous lines show the percentages of the dose delivered. The incomplete discharge from the Rotadisks is reflected by the measured blister residues (percentage of drug in the adhesive mixture tapped out of the blister after inhalation).

3.4. Waste and mouthpiece accumulation

Mouthpiece accumulations are shown in Fig. 6 for the inspiration time of 3 s for all DPIs and the other inspiration times for the Turbuhaler as well. Data for the other inspiration times are not given for the Spinhaler and the Diskhaler, because the accumulations for these two inhalers were more or less the same for all times (maximum and minimum values for the whole range of times depicted as spread).

Highest mouthpiece accumulations were found for the Turbuhaler at all flow rates within the range between 20 and 60 l/min. The much higher values compared with the other inhalers is not the result of inhaler design alone. A strong influence may be expected from the physico-chemical drug properties, the type of construction material(s) used and the (relatively high) number of primary particles passing through the mouthpiece. The differences between the different inspiration times are rather to be explained by a poor reproducibility in accumulation than by a time dependence. An effect of flow rate on mouthpiece accumula-

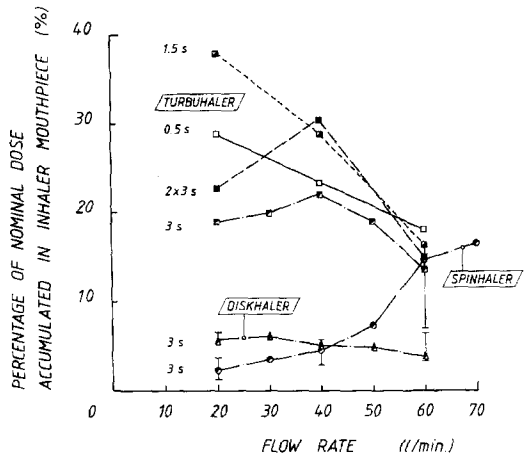

Fig. 6. Drug amounts accumulated in the inhaler mouthpiece channel as a percentage of the nominal dose. The lines for Spinhaler and Diskhaler represent an inspiration time of 3 s.

tion is also questionable. It seems reasonable to believe that re-entrainment of previously deposited drug particles increases with increasing air velocity in the mouthpiece channel. This is suggested by the results in Fig. 6. Other batches of Turbuhalers have shown slightly increasing accumulations with increasing flow rate however. In this respect, it must be realized that accumulation by adhesion onto surfaces exposed to an air stream is a random process, influenced by atmospheric conditions such as relative humidity of the air.

The Spinhaler (Fig. 6) shows a strong increase in mouthpiece accumulation between 40 and 60 l/min towards a value of the same order of magnitude as found for the Turbuhaler. This increase in inhaler accumulation explains the decrease in delivered dose from Fig. 5 for flow rates > 50 l/min.

Mouthpiece accumulation for the Diskhaler is very low and practically constant within the whole range of flow rates from 20–60 l/min. Delivered dose (Fig. 5) is therefore nearly the same as total recovery from CIA (Fig. 4b). An explanation for this extremely low mouthpiece accumulation for the Diskhaler may come from a sweeper action by the coarse carrier crystals and the relatively small total surface area of the mouthpiece channel.

Mouthpiece accumulations are disadvantageous because of possible microbiological growth and release of a high dose after (partial) detachment. Moreover, mouthpiece accumulations contribute to total inhaler pollution.

Waste of dose in the inhaler device (before inhalation) and residues in the dose systems (from incomplete entrainment) cannot simply be measured like mouthpiece accumulations. Especially for the Diskhaler, waste may be substantial as a result of adhesion onto different inhaler parts (e.g. the piercing pin), but the entire device cannot be rinsed after each dose administered. Neither can the dose system of the Turbuhaler be wetted in order to assess the residual dose. For this reason the weighed amounts of drug in respectively by the dose systems have been measured carefully (see Section 2), including the amount of drug adhering onto inner blister walls for the Rotadisks, as presented in Table 2. The residues in the dose systems (fractions not released during inhalation) have been calculated for Turbuhaler and Spinhaler as the differences between amounts weighed into (Table 2) and amounts discharged from (Fig. 4) the dose system. The residue in the Rotadisks is the sum of amount tapped out (7.8% at 60 l/min) and the amount rinsed from the blister walls (9.5% at 60 l/min). The results as a percentage of the nominal dose are given in Table 2, summarizing also the total inhaler accumulations at 60 l/min (3 s). Total inhaler accumulations for the Diskhaler includes other losses in the inhaler as well (being 13.7%), calculated as percentage weighed minus the sum of the known percentages for (a) delivered dose, (b) blister accumulation, (c) dose tapped out of the blister after inhalation and (d) mouthpiece accumulation respectively.

Table 2
Comparison of weighed and delivered doses and losses as a percentage of the nominal dose at an inspiratory flow rate of 60 l/min (3 s)

	Turbuhaler	Diskhaler	Spinhaler
Weighed dose	117	107	117
Residue dose system	21	17	6
Total inhaler accumulation	14	18	15
Delivered dose	82	72	96

3.5. Fine particle output

Fig. 7a shows the fine particle output from the Turbuhaler as a function of flow rate and inspiration time. A strong increase with increasing flow rate has been found towards a maximum value of approx. 37.5% of the nominal dose for the range of flow rates between 20–60 l/min. The series at the inspiration time of 3 s suggest that this maximum may already be obtained at 50 l/min. The results for the Turbuhaler agree quite well with the claim of the manufacturer (Olsson, 1991), stating that a flow rate of 60 l/min already yields maximum fine particle output (< 6 μm) of approx. half the delivered dose (which is approx. 15–20% lower than the nominal dose due to

mouthpiece accumulations). As for the discharge from the dose system, an inspiration time dependence for the fine particle release from the Turbuhaler is rather arguable. Yet, a higher release from the dose system (Fig. 4a) corresponds with a higher fine particle output (Fig. 7a).

Fine particle detachment from the adhesive mixture in the Becotide Rotadisks increases with increasing flow rate as well for all inspiration times (Fig. 7b). But all values are lower than those found for the Turbuhaler for corresponding inspiratory conditions. It is surprising that the 3rd–4th stage deposition as a percentage of the release from the dose system (Fig. 4b) is more or less constant for the Diskhaler. The proportionality constant (25–30%) appeared not to be influenced by flow rate (within the range 20–60 l/min) nor by inspiration time, except for 0.5 s at 30 and 40 l/min. This suggests that the fine particle output approaches its maximum at 60 l/min, because discharge from the dose system is nearly at its maximum at this flow rate (Fig. 4a and Fig. 5).

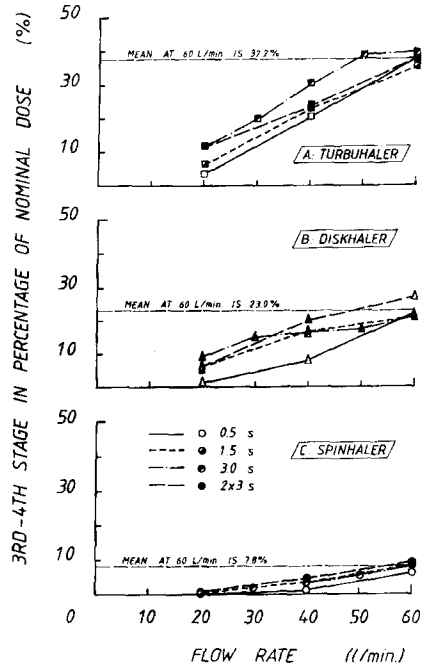

Fig. 7. Drug amounts derived from the 3rd and 4th impactor stage as a percentage of the nominal dose, as a function of flow rate and inspiration time.

Fine particle fractions from the Spinhaler (Fig. 7c) are much lower than those from both other devices at the same flow rate. At 60 l/min on average only 8% of the nominal dose is discharged as fine drug particles. Further improvement of fine particle generation at flow rates > 60 l/min may be expected for this type of DPI. But the fraction of fine particles delivered to the lower respiratory tract will not increase to the same extent as the fraction of particles released from the inhaler, as a result of increasing mouthpiece accumulation (Fig. 6) and increasing oropharyngeal deposition of the primary drug particles as well.

Differences in in vitro deposition from the different DPIs at the same inspiratory flow curve are primarily the result of different inhaler designs. But there may be a strong influence from the type of drug and drug formulation, as well as from the primary particle size distribution of the drug. Budesonide and BDP are micronized to somewhat smaller median mass diameter than DSCG. Removal forces for detachment of primary drug particles from carrier crystals in adhesive mixtures are generally higher than the forces necessary to break up spherical pellets. From this point of view the fine particle output from the Diskhaler at 60 l/min is quite good, especially when compared with that from the Spinhaler. There is also an effect of particle shape on deposition behaviour. Primary DSCG particles show a more plate-like shape than budesonide or BDP.

The fractions not disintegrated, derived from the first two impactor stages (Fig. 8), are complementary to the total fractions of fine particles. Highest deposition on 1st and 2nd stage has been found for the Spinhaler, corresponding with the lowest fine particle yield for this device. However, the strong decrease between 50 and 70 l/min contributes to an increased mouthpiece accumulation rather than to a higher output of fines. Dose fractions derived from the 1st–2nd stage are considerably lower for the Diskhaler and the Turbuhaler. The increase with increasing flow rate for the Diskhaler can be explained by improved emptying of the blisters. The fractions collected on the first two impactor stages are likely to be deposited in the oropharynx of patients, and should there-

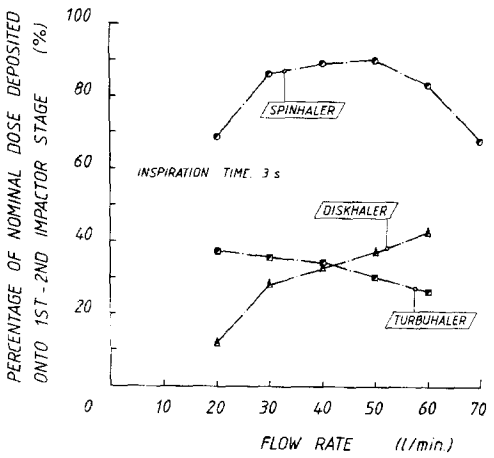

Fig. 8. Amounts of drug deposited on 1st and 2nd impactor stage as a percentage of the nominal dose at an inspiration time of 3 s.

fore be low in order to avoid local side effects and a contribution to the systemic effects.

Detached primary drug particles do not only deposit on the lower impactor stages and in the mouthpiece, but also in the bent inlet tube to the cascade impactor. Drug deposition in this tube is not so much the result of inertial impaction onto the inner walls at the position of the bend, but rather a consequence of the complex flow pattern directly beyond the mouthpiece. Deposition is mainly confined to this zone and there appeared to be no difference in adhesion between a straight and bent (dry) inlet tube. Accumulations in the inlet tube were found to be more or less constant within the range of flow rates between 20–60 l/min: on average 18% of the nominal dose for the Turbuhaler, 5% for the Diskhaler and 4% for the Spinhaler.

3.6. Fine particle output in relation to work of inspiration

The amounts of work of inspiration during cascade impactor analysis have been calculated and plotted against the fine particle outputs (3rd and 4th stage depositions) for the Turbuhaler for the whole ranges of exerted flow rates and inspiration times. The ratio between yield and corresponding amount of work might be considered as an inhaler efficiency. The curves in Fig. 9 suggest that increasing the inspiration time through this DPI is rather disadvantageous from inhaler efficiency point of view. At 60 l/min, maximum fine particle generation has already been achieved after 0.5 s. An increase in inspiration time does not result in an increase in fine particle yield, but only increases the amount of work that has been performed, thereby reducing the efficiency. Similar calculations will be presented for the Diskhaler and Spinhaler in one of the next parts of this series after maximum fine particle output has been obtained from these devices at flow rates >60 l/min.

The scale of the X-axis in Fig. 9 has little practical meaning as the inspiration curves during cascade impactor analysis exhibit constant peak flow rates during the practised inspiration times, except for very short inclination periods. A practical meaning can be obtained however by multiplying the scale by a factor 0.7–0.75, depending upon the inspiration mode. In the first part of this series (De Boer et al., 1996), it was calculated that the mean average flow rate (AFR) during inspira-

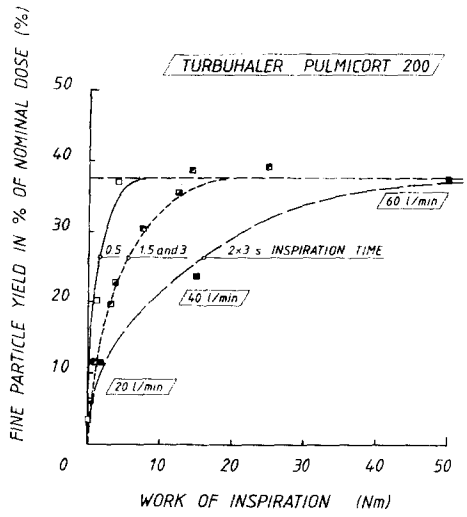

Fig. 9. Amounts of drug derived from the 3rd and 4th impactor stage as a percentage of the nominal dose against the work of inspiration for the Turbuhaler. The lines connect data obtained with the same inspiration time: along these lines in the direction of a higher yield, flow rate increases from 20 to 60 l/min.

tion through a flow resistance is 70% of mean PIFR at maximum mode, and 75% at comfortable inspiration. For this correction, it must be realized that 60 l/min through the Turbuhaler can only be obtained at maximum inspiration mode.

4. General conclusions

Three different DPIs were tested in the range of flow rates between 20–60 l/min at different inspiration times. The necessary flow rate (50–60 l/min) for maximum fine particle release from the Turbuhaler of approx. 37.5% of the nominal dose lies within this range, as does the attainable range of flow rates through this device. Higher flow rates through the Diskhaler and the Spinhaler are both possible and necessary for improving fine particle output from these devices, but with increasing flow rate, losses due to oropharyngeal deposition of fine drug particles will become more substantial.

The results from this study suggest that the instruction for all three DPIs should be to inhale at (sub)maximum effort. For the Turbuhaler, both maximum fine particle output and highest inhaler efficiency may already be obtained at the relatively short inspiration time of 0.5 s. For the Spinhaler, inhalation times > 1.5 s are necessary in the range of flow rates ≤ 70 l/min. Because it was shown in the first part of this series (De Boer et al., 1996) that inspiration at maximum effort cannot be continued over times of 1.5 s by all volunteers, it must be recommended to repeat inhalation through the Spinhaler at least once (using the same capsule).

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