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Inhalation characteristics and their effects on in vitro drug delivery from dry powder inhalers Part 1. Inhalation characteristics, work of breathing and volunteers' preference in dependence of the inhaler resistance

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Abstract

A test inhaler with exchangeable air flow resistances encompassing the range of commercial DPIs has been used to study the inspiratory flow curves of 39 healthy adult volunteers. A strong increase in mean Peak Inspiratory Flow Rate (PIFR) has been obtained with decreasing inhaler resistance, varying between 160 l/min for a resistance equivalent to the Rotahaler and 50 l/min for the simulated Inhalator Ingelheim at maximum inspiratory effort. The volunteers experienced on average 55% of maximum effort as comfortable (expressed in PIFR) and gave preference (82%) to relative high air flow resistances in the range of $0.4–0.9 \times 10^5$ ($N^{0.5} \cdot s \cdot m^{-4}$). It has been calculated that the real amount of work of breathing does not increase with increasing air flow resistance at comfortable inspiration mode. At maximum inspiration, the amount of work performed through a high resistance inhaler (1.5×10^5) is approx. 70% of that through a low resistance device (0.4×10^5). The calculated mean PIFR of 62 l/min at maximum effort through an air flow resistance of 0.9×10^5, equivalent to the Turbuhaler, is in good agreement with PIFR-values of 68.5 vs. 59 l/min from two other studies with asthmatic patients through this device. It has, therefore, been concluded that the flow curves of healthy volunteers may be used to predict the range of PIFRs for asthmatics through the same air flow resistances.

Keywords: Asthma; Dry powder inhalers; Peak inspiratory flow rate; Preferable inhaler resistance; Work of breathing; Inspiration mode; Inspiration force

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Abbreviations: AFR, average flow rate during inspiration; %AFR, average flow rate in percentage of peak inspiratory flow rate; dP, differential pressure drop across the (test) inhaler; dP_{max}, maximum pressure drop across the (test) inhaler, corresponding with peak inspiratory flow rate (PIFR); DPI, dry powder inhaler; MDI, metered dose inhaler; $PEFR_M$, measured peak expiratory flow rate; $PEFR_C$, calculated (predicted) peak expiratory flow rate; %PEFR, measured peak expiratory flow rate in percentage of predicted; PIFR, peak inspiratory flow rate; $PIFR_F$, mean peak inspiratory flow rate of female volunteers; $PIFR_M$, mean peak inspiratory flow rate of male volunteers; $\%PIFR_{F/M}$, mean peak inspiratory flow rate of female volunteers in percentage of mean peak inspiratory flow rate of male volunteers; $PIFR_{TBH}$, peak inspiratory flow rate as generated through the Turbuhaler; R, specific inhaler resistance to air flow; t, inspiration time; t_{PIFR}, time necessary to obtain peak inspiratory flow rate; t_{TOT}, total duration of inspiration; V_{tot}, total volume inspired during inhalation; W_B, work of breathing; Φ, volumetric flow rate

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1. Introduction

The factors affecting lung deposition of inhaled aerosols are well documented (e.g. Kirk, 1986; Morén, 1987; Vidgrén, 1994). The efficacies of both metered dose inhalers (MDIs) and dry powder inhalers (DPIs) are largely defined by their droplet and particle generation during inhalation. A relevant difference between both types of inhalation systems in this respect is, that droplet generation by MDIs is not dependent of inspiratory flow rate. Drug particle release from DPIs on the contrary is both actuated and controlled by the patient's inspiratory flow. This provides the advantage of automatic coordination between drug delivery and inhalation on the one side, but makes the efficacy of DPIs strongly dependent on patient's performance on the other. The latter may be considered disadvantageous, as inhalation is a highly variable energy source (Olsson and Asking, 1994b). Marketed DPIs show a variety of constructions for both the dose system and the powder disintegration facilities. As a consequence, they are different with respect to efficiency in utilizing the available energy (Olsson and Asking, 1994a). Local flow constrictions may be applied in order to increase local air velocities (or turbulencies) for enhanced entrainment and improved powder disintegration. Flow constrictions also increase the total inhaler resistance to air flow, and therefore influence not only the necessary but also the possible range of flow rates attained by the patient.

The volumetric flow rate (Φ) through an inhaler may be calculated from its linear relationship with the square root of the generated pressure drop across the device ($\sqrt{dP}$), using the reciprocal specific inhaler resistance (R) as the constant for proportionality. Clark and Hollingworth (1992) stated that the importance of the inhaler resistance is not the volumetric flow rate at a particular pressure drop, but rather its relationship to the flow rates and pressure drops attained by patients. They concluded that the flow rate range over which inhalers of a particular specific resistance should be tested (in vitro) is defined by the maximum flow rate through this resistance as obtained from maximum inspiratory effort. They also noticed that patient comfort is an important factor, and suggested therefore that a typical user flow rate would be the comfortable effort curve. Richard and Saunders (1993) shaded this recommendation by suggesting that the performance of dry powder inhalers should be assessed at comparable pressure drops producing clinically relevant inspiratory flow rates for each device. This clinically relevant inspiratory flow rate for a particular DPI may be considerably lower than the maximum flow rate.

Olsson and Asking (1994b) stated that, ideally, test flow rates should reflect the likely inspiratory flows attained by asthmatic patients inhaling from the devices under test. They concluded that there is a need for a relationship able to translate a patient's inspiratory force into flow rates through devices differing in their air flow resistance. The authors multiplied the air flow resistance with the PIFR raised to the power 2.4, in order to obtain a characteristic parameter K, named inspiratory force. This parameter proved to be invariant with the air flow resistance for individual flow curves from ten healthy subjects inhaling at maximum effort through a series of flow constrictions. Also when applying their relationship on data obtained from a group of 100 asthmatic patients, K was approximately independent of the air flow resistance at constant inspiration mode. The empirical relation is rather a useful mathematical tool for comparing the performance of different (groups of) patients or human volunteers, but it does not provide information regarding the real amount of work accomplished for different types of DPIs at comparable effort.

The aim of this study is to prove that PIFR is not the only characteristic parameter for the performance of DPIs. This first part characterizes inhalation profiles, relates the work of breathing to both the inhaler resistance and mode of inhalation, and reports volunteers' preference for specific air flow resistance. In the next part, the effect of inhalation mode on the in vitro drug delivery from three different types of commercial dry powder inhalers will be discussed.

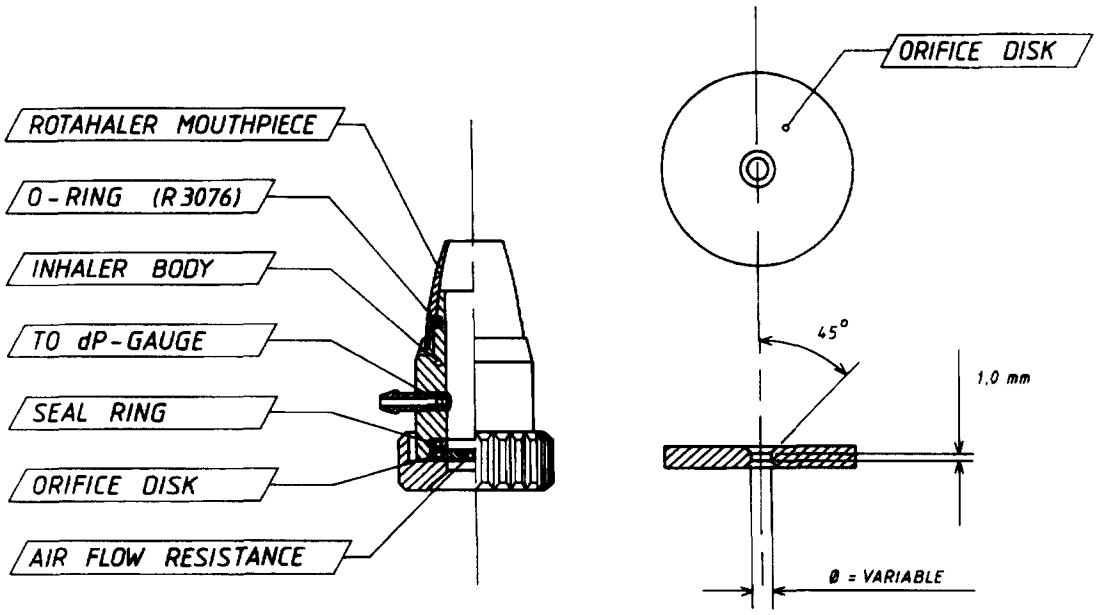

Fig. 1. Test inhaler with exchangeable orifice disks as air flow resistances, varying in diameter between 2 and 8 mm.

2. Methods

Fig. 1 presents the test inhaler with adjustable air flow resistances that has been used for recording the inspiratory flow curves of healthy volunteers. The inhaler consisted of a cylindrical housing with a Rotahaler mouthpiece and exchangeable orifice disks. Cylindrical bores in the orifice disks with the in- and outstream over angles of 45° varied in diameter between 2 and 8 mm with intervals of 1 mm.

Fig. 2a shows the experimental arrangement for measuring the volumetric air flow as a function of the pressure drop across both the test inhaler combinations and different types of commercial DPIs (calibration). The arrangement consisted of a single stage rotary vacuum pump (Edwards, U.K., type E1M40 with a capacity of 42.5 $m^3 \cdot h^{-1}$), a thermal mass flow meter (MFM: Brooks, The Netherlands, model 5812N-1394 with a measuring range of 150 l_N/min), a flow controller and a coupling flange with exchangeable seal ring for the inhalers.

Pressure drops across the inhalers have been recorded with a differential pressure gauge (dP: HBM, Germany, type PD1 with a measuring range of 1 bar in combination with HBM Messkonverter MC2A). The figure illustrates the test inhaler alone, as well as in an in-line arrangement with the flow head of a Vitalograph (discontinuous lines). Underpressure was created by the rotary pump and flow rates through the (test) inhalers were increased with intervals of 15 l/min from 15 to 90 l/min.

Pressure drops across the test inhalers as generated by the healthy volunteers were recorded against inspiration time, using the arrangement shown in Fig. 2b. The measuring system consisted of the test inhaler (Fig. 1), the differential pressure gauge and a portable computer with a DAS-1401 card for the A-D conversion (Keithley Instruments, The Netherlands) having a conversion time of 25 ms. The data were collected in data arrays for subsequent calculations, using a Viewdac data acquisition program (Keithley Instruments). The volunteers were asked to perform their instructed inhalation exercise after hearing a signal at the start of the data acquisition period of 20 s. The software allowed immediate visualization of the recorded curves for a quick check on usefulness.

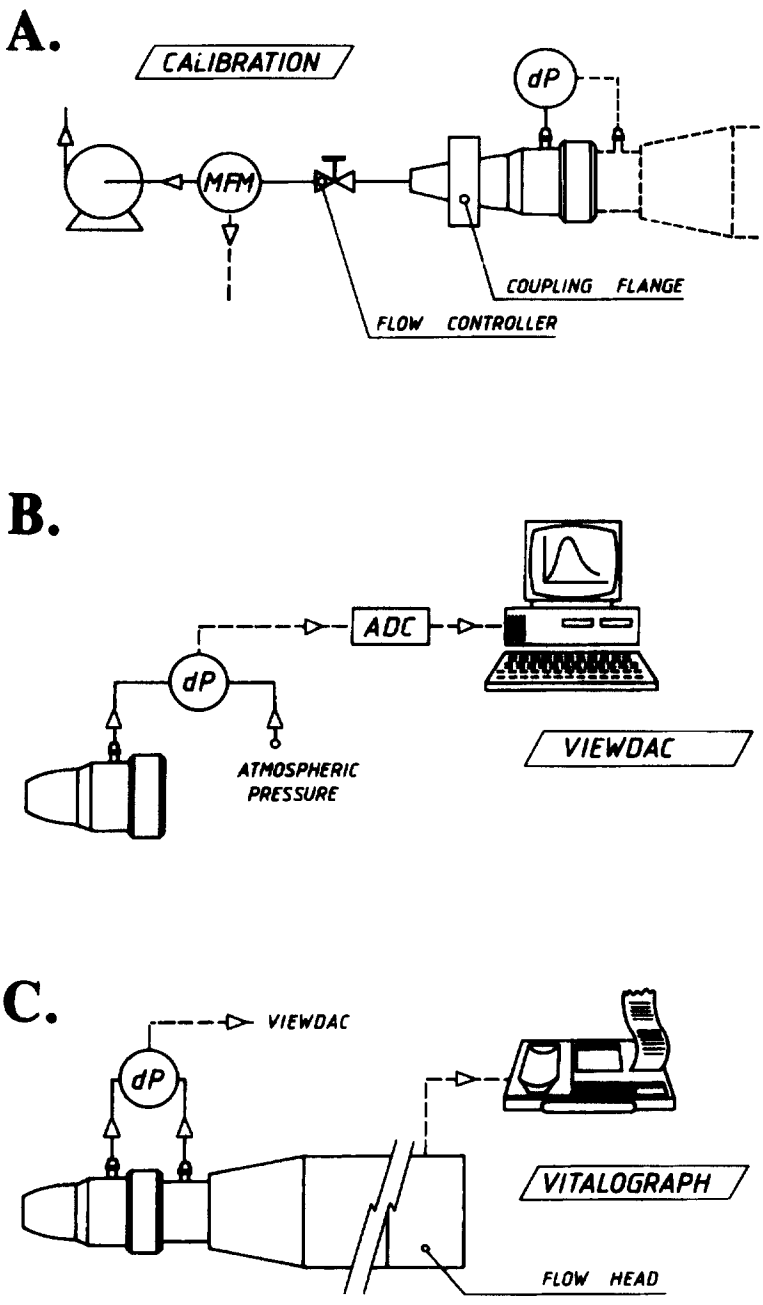

Fig. 2. Experimental arrangement (a) for flow rate versus pressure drop calibration of the test inhaler combinations: the discontinuous lines complete the in-line arrangement with the Vitalograph flowhead, (b) during recording of the flow curves of the healthy volunteers, and (c) during in-line recording of the flow curves through the simulated Turbuhaler with the Viewdac and Vitalograph. MFM is (thermal) mass flow meter; dP is differential pressure gauge.

2.1. Inhalation protocols

Healthy volunteers were briefly introduced to the working principle of breath actuated dry powder inhalers. The need for such introduction was concluded from a previous pilot study where volunteers received no introduction at all, yielding irrelevant flow recordings with respect to flow rate, inspiration time, etc.

2.1.1. Study 1: recording of the comfortable inspiration mode and selection of the preferable air flow resistance

The healthy volunteers were allowed to experience inhalation through either one of the orifice disks 3, 5 or 7 mm of the test inhaler given in random order. After a short practice period, the volunteers performed three successive inspirations for recording through each disk in a comfortable mode without seeing their results on the screen. The volunteers were then asked to choose their preferable air flow resistance. The possibility of retrial was given in cases of doubt.

Using the same procedure, the volunteers were next invited to refine upon their choice between the selected orifice disk and two neighbouring disks, differing now only 1 mm in diameter from their preference from the first series (e.g. disks 4, 5 and 6 mm, if 5 was the preferable disk from the first series of 3, 5 and 7 mm). If necessary, the volunteers were allowed to re-inspire through (one of) the disks from the first series. Their definite choice was finally noted as their preferable air flow resistance.

2.1.2. Study 2: recording of the inspiratory flow curves at maximum effort

Nearly the same procedure as described for study 1 has been used to record the inspiratory flow curves through the orifice disks 3, 5 and 7 mm at maximum effort. However, now the volunteers were allowed to see the results on the screen while conducting at least three forceful inspirations, and were challenged to improve each time on their previous performance.

2.1.3. Study 3: comparison of healthy volunteers with asthma patients

A Vitalograph Compact (Vitalograph Ltd., U.K.) was used in an in-line arrangement with the Viewdac system (Fig. 2c) for recording of the PIFR of 11 healthy volunteers (selected at random from the group of 39) generated through orifice disk number 4. The Vitalograph was calibrated on a standardized air volume before each recording. The test inhaler with orifice disk 4 mm was used, having an air flow resistance in the in-line arrangement of 0.94×10^5 $N^{0.5} \cdot s \cdot m^{-4}$, which is of the same order of magnitude as that for the Turbuhaler ($0.85–0.9 \times 10^5$ without flow-head). The volunteers were invited to carry out three successive inspirations through the test inhaler combination at maximum effort, and their performance was recorded simultaneously with both measuring systems for comparison with each other as well as with data from literature for asthmatic patients.

2.2. Characterization of the healthy volunteers

A Wright Peak Flow Meter (Clement Clarke International Ltd., U.K., cat. no. 3103001) has been used to measure the peak expiratory flow rate ($PEFR_M$) of the 41 healthy volunteers entering this study. The measured values were compared with their predicted values ($PEFR_C$) from the regression equations of Nunn and Gregg (1989). Only 39 volunteers with a mean $PEFR_M > 80\%$ of $PEFR_C$ were accepted for data processing.

2.3. Calculations

Specific air flow resistances (R in $N^{0.5} \cdot s \cdot m^{-4}$) were calculated as the reciprocal slopes of the linear relationships between the volumetric flow rate (Φ in m^3/s) and the square root of the pressure drop across the (test) inhaler ($\sqrt{dP}$ in $N^{0.5} \cdot m^{-1}$).

Using these specific air flow resistances, the pressure drop versus time recordings from studies 1–3 could be transferred into flow curves. Typical flow curves are shown in Fig. 3.

For each of the recordings, the maximum in obtained pressure drop (dP_{max}) and the correspondent peak inspiratory flow rate (PIFR) has been derived, as well as the time to reach this maximum (t_{PIFR}) and the total inspiration time (t_{TOT}).

Total volume inspired (V_{TOT}), has been calculated as the product of the flow rate (Φ) and inspiration time (t), using the equation

$$V_{TOT} = \frac{1}{R} \cdot \sum_{i=1}^{n} \left(\frac{dP_n + dP_{n-1}}{2} \right)^{0.5} \cdot (t_n - t_{n-1})$$

where $t_n - t_{n-1}$ is the conversion constant of 0.025 s.

The average flow rate (AFR) has been calculated as the quotient of V_{TOT} and t_{TOT}.

The work of breathing (W_B) has been calculated as the product of generated pressure drop (dP), volumetric flow rate (Φ) and inspiration time (t), equivalent with the previous equation for V_{TOT} after substituting the power 0.5 by 1.5. By expressing the time in seconds (s), the flow rate in cubic meters per second (m^3/s) and the pressure drop in N/m^2, the required dimension of Nm for work is obtained. The 'work of breathing' is herewith defined as the gross result of patient's 'inspiratory effort'.

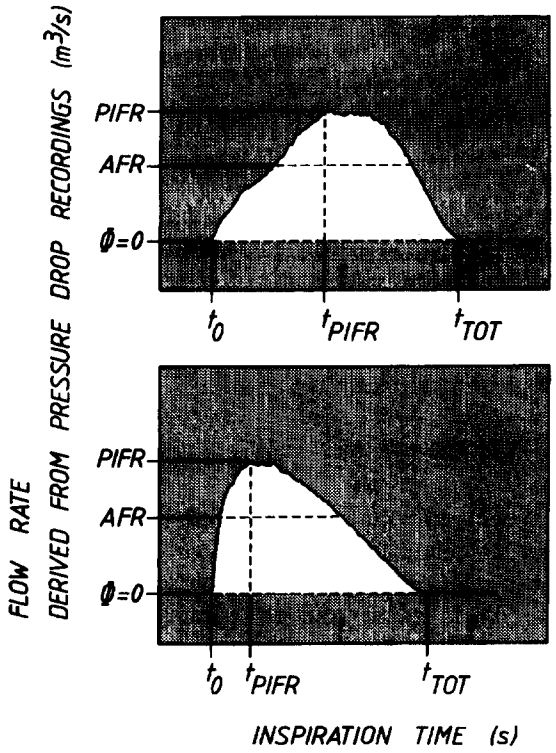

Fig. 3. Typical flow curves calculated from pressure drop recordings versus inspiration time.

3. Results and discussion

3.1. Air flow resistances

Fig. 4 presents the linear relationships between volumetric flow rate and square root of the pressure drop measured for six different types of commercial DPIs. All plots represent the mean of several devices. The inhalers using hard gelatin capsules as dose system, have been tested with empty capsules inserted. The results show that the tested commercial DPIs may roughly be divided into two groups with respect to air flow resistance. For the Inhalator Ingelheim, considerable differences in pressure drop at the same flow rate between individual calibration series were observed.

Similar linear relationships were obtained for the orifice disks of the test inhaler. Their specific air flow resistances, calculated as reciprocal slopes of these relationships, are plotted in Fig. 5 against the orifice diameter. It should be noted that the resistance values relate only to these particularly shaped orifices, and not necessarily to other flow constrictions having the same diameter. The range of equivalent diameters for the commercial inhalers were estimated by projecting their resistances derived from Fig. 4 onto this curve. From the projection it may be concluded that the orifices with diameters between 4 and 7 mm roughly cover the range of commercial DPIs. The flow curves through the orifice disks within this range are therefore a good measure for the flow curves to be expected through commercial DPIs.

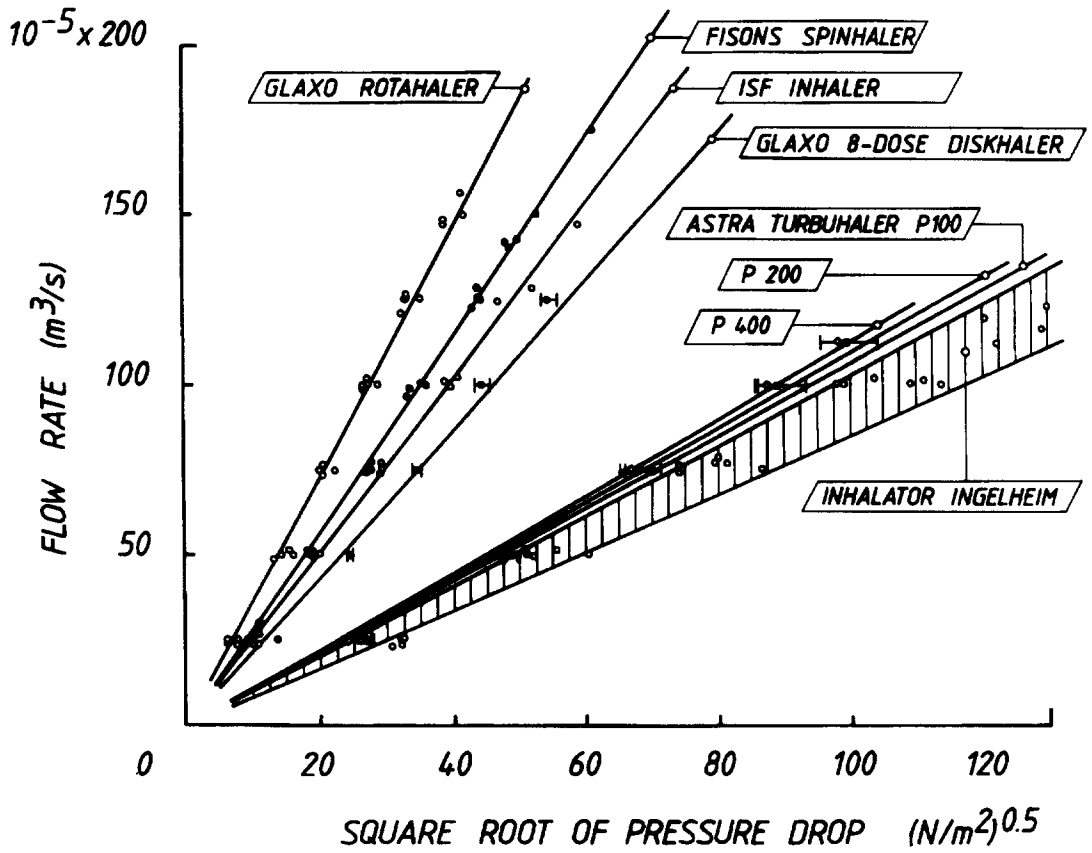

Fig. 4. Linear relationships between volumetric flow rate and square root of pressure drop across six different types of commercial DPIs.

3.2. Characteristics of the volunteers

The demographic data of the selected 39 adult volunteers are presented in Table 1. These volunteers showed mean expiratory flow rates ($PEFR_M$) within the range of 83–129% of their predicted values ($PEFR_C$), based upon age, length and sex.

3.3. Inspiratory flow characteristics

The mean peak inspiratory flow rates (PIFR) generated by the volunteers during inspiration through the different orifice disks are plotted in Fig. 6 against the specific air flow resistances of the disks for both comfortable (Study 1: symbol ○) and maximum effort (Study 2: symbol △). Closed symbols represent the mean values: minimum and maximum PIFR obtained for each air flow resistance at both inspiration modes are indicated with open symbols. The commercial DPIs have been marked again upon the air flow resistance scale.

The profiles in Fig. 6 show a steep increase with decreasing inhaler resistance for both inhalation modes, especially below 0.5×10^5 $N^{0.5} \cdot s \cdot m^{-4}$. At maximum effort, the PIFR values through the orifice disk correspondent with the Rotahaler (with lowest air flow resistance) varied between approx. 80 and 230 l/min with a mean of 161. The range of peak flow rates through the air flow resistance equivalent to the Inhalator Ingelheim (with highest resistance) was confined to only 25–70 l/min with a mean of 50. At comfortable inhalation mode, the PIFR values were found to

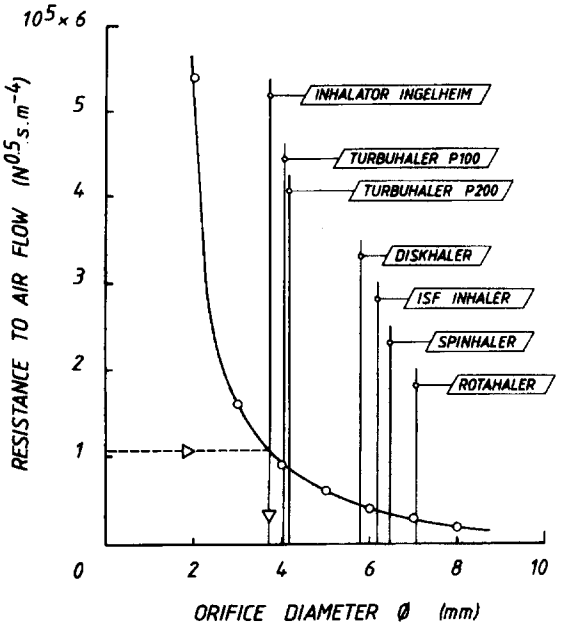

Fig. 5. Specific air flow resistance versus orifice diameter of the test inhaler; the calculated air flow resistances of commercial DPIs are projected on the relationship yielding equivalent diameters.

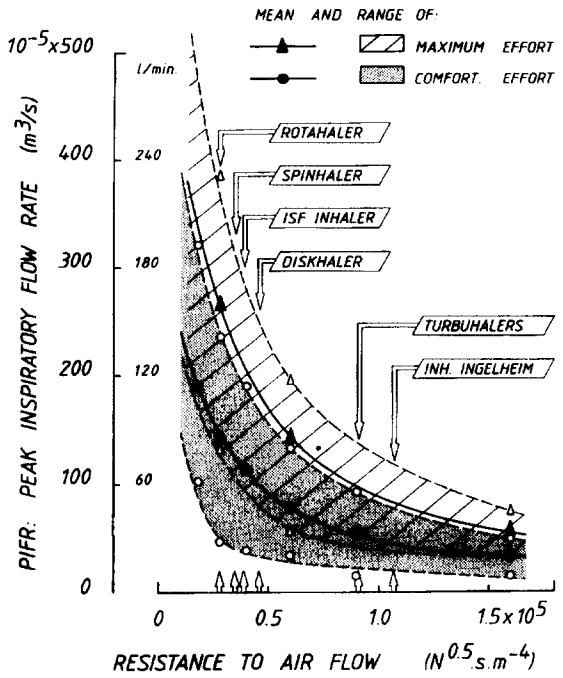

Fig. 6. Mean PIFR (closed symbols) versus air flow resistance at comfortable (○) and maximum (△) inspiration mode. The open symbols mark the maximum and minimum values obtained.

be much lower, on average about 60% of the PIFR obtained at maximum effort, showing mean values of 85 l/min and 25 l/min at the Rotahaler and Inhalator Ingelheim resistances, respectively. The relative spread in PIFR values, expressed as the ratio between maximum and minimum PIFR for each air flow resistance, seems to be independent of the resistance, but the spread at comfortable inspiration mode (4.2) is considerably higher than that at maximum effort (2.8). This suggests that the spread in primary drug particle release from PIFR-controlled DPIs may decrease with increasing effort.

Table 1
Characteristics of the 39 adult healthy volunteers

	Mean	S.D.	Max	Min
Age (years)	31.9	11.8	56	20
Height (m)	1.79	0.08	1.94	1.64
%PEFR	103.3	12.1	129	83
Male/Female = 25:14				

%PEFR is peak expiratory flow rate in percentage of predicted.

The data presented in Fig. 6 are in good agreement with the results reported by Clark and Hollingworth (1992). They found for healthy volunteers at comfortable inspiration mean PIFR values through the Rotahaler and Inhalator Ingelheim of 79 and 29 l/min, respectively. At maximum inspiratory effort, they calculated mean PIFR values through the same DPIs of 185 and 58 l/min. It is to be noted that these authors defined comfortable inspiration as the effort necessary to generate 60 l/min through the Spinhaler and asked the volunteers to use the same effort through the test device. In our study, we allowed the volunteers to define their own comfortable mode.

In Fig. 6, the PIFR values have been presented without discriminating between sex. Table 2 presents the differences in male and female performance. The data show for the females at

Table 2
Mean peak inspiratory flow rates (PIFR) of Fig. 6 (in l/min) distinguished between sex as a function of specific resistance to air flow, at comfortable and maximum inspiratory effort, respectively

R ($N^{0.5} \cdot s \cdot m^{-4}$) $\times 10^5$	0.18	0.28	0.4	0.6	0.9	1.6	Mean
A. At comfortable inspiration							
$PIFR_M$	119	86	71	47	36	20	
$PIFR_F$	98	85	59	45	31	18	
$\%PIFR_{F/M}$	82	99	83	96	87	90	90
B. At maximum inspiration							
$PIFR_M$		175		92		36	
$PIFR_F$		132		74		30	
$\%PIFR_{F/M}$		76		80		87	81
C. $PIFR_{COMF}$ in percentage of $PIFR_{MAX}$							
Male		49		51		56	52
Female		64		61		61	62
Total		54		54		58	55

$PIFR_M$ is peak inspiratory flow rate for male, $PIFR_F$ is for female.
$\%PIFR_{F/M}$ is $PIFR_F$ in percentage of $PIFR_M$.

comfortable inspiration PIFR values of about 90% and at maximum inspiration of about 80% of the PIFR values as generated by the males. The higher percentage at comfortable inspiration, compared to maximum effort, suggests that there is a difference between male and female volunteers in the rather subjective judgment of what is comfortable inspiration. The female volunteers experienced approx. 62% of their maximum inspiratory force as comfortable, whereas the male volunteers qualified 52% of their full power as convenient.

PIFR is most widely referred to as the relevant parameter for primary drug particle release from DPIs. This probably finds its origin from in vitro experiments, where normally the fine particle yield is plotted against PIFR. It should be realized however, that dose transport and powder disintegration require energy (instead of flow), to be put in at the right moment and extended over the required time into sufficient amount. From this point of view it becomes obvious that other parameters, such as the air flow increase rate and total inspiration time, may be just as important. Air flow profiles generated for in vitro testing, may differ considerably from in vivo inhalation curves. Under in vitro conditions, the required flow rate is generally realized within tens of milliseconds and maintained constant during total inspiration time. In vivo inhalation curves are not perfect square functions and, in addition, they vary strongly in profile. Two typical inhalation profiles from the studies 1 and 2 are illustrated in Fig. 3, demonstrating a great difference in shape, especially with respect to the increase rate in air flow. The considerable variation in individual flow curves is also expressed by the high standard deviations listed in Table 3 for some parameters characterizing the inhalation profiles of the healthy volunteers. The table shows that the average flow rate (AFR) decreases with increasing inhaler resistance practically to the same extent as the PIFR. Hence, %AFR, expressed as AFR in percentage of PIFR, is indeed almost constant. As a result of the strong reduction in AFR with increasing air flow resistance, total volume inspired (V_{TOT}) decreases as well for both inhalation modes, this in spite of a found increase in total inhalation time (t_{TOT}) in the same direction. The mean time passed to reach the PIFR (t_{PIFR}) was found to be approx. 1 s at comfortable inspiration and only slightly shorter (on average 0.8 s) at maximum effort. The rather long mean t_{PIFR}, on average 40–50% of total inspiration time, points to a low mean increase rate in air flow, but the standard deviations show again that individual volunteers performed quite differently. At comfortable effort, t_{PIFR} was found to vary even between 0.2 s and 2.3 s for the same air flow

resistance. It has also been observed that a fast initial increase towards 75–90% of PIFR is often followed by a much slower increase towards 100% PIFR (bottom profile in Fig. 3). Borgström et al. (1992) reported similar t_{PIFR} values for inspirations through the Turbuhaler at a desired flow rate of 60 l/min with a mean of 0.6 s (S.D. = 0.3 s).

Different parameters may be of decisive influence on the fine particle yield from different commercial DPIs, mainly as a consequence of their differences in design. Considering the great variation in inhalation profiles at the same inhalation mode, expressed by the high standard deviations for all parameters (Table 3), it may be expected that the breath controlled fine particle output for a particular type of DPI is also strongly patient dependent. In the next parts of this series, the effects of some important flow parameters, next to PIFR, on the in vitro efficiency with respect to primary drug particle release will be reported and discussed.

Table 3
Mean inspiratory flow characteristics as a function of specific air flow resistance at comfortable and maximum inspiration, respectively

R ($N^{0.5} \cdot s \cdot m^{-4}$) $\times 10^5$	0.18	0.28	0.4	0.6	0.9	1.6
A. At comfortable inspiration						
PIFR	114	85	67	46	34	20
S.D.	41	31	25	16	12	6
AFR	85	64	48	34	25	15
%AFR	75	75	71	74	73	75
V_{TOT}	2.6	1.9	1.6	1.3	1.1	0.7
t_{TOT}	1.96	1.87	2.08	2.37	2.50	2.90
S.D.	0.45	0.56	0.64	0.92	1.01	1.41
t_{PIFR}	0.99	0.87	1.05	1.03	1.06	1.29
S.D.	0.51	0.41	0.48	0.47	0.49	0.70
B. At maximum inspiration						
PIFR		159		85		34
S.D.		39		16		6
AFR		109		58		24
%AFR		68		69		71
V_{TOT}		2.6		1.7		0.9
t_{TOT}		1.46		1.86		2.36
S.D.		0.46		0.56		1.42
t_{PIFR}		0.67		0.79		0.93
S.D.		0.34		0.38		0.47

t_{TOT} is total duration of inspiration (s).
t_{PIFR} is time necessary to reach PIFR (s).
PIFR is peak inspiratory flow rate (l/min).
AFR is average flow rate (l/min).
%AFR is AFR in percentage of PIFR.
V_{TOT} is total volume inspired (l).

3.4. Work of breathing

Sumby et al. (1992) concluded that inspiratory effort, expressed as the product of pressure drop and inspired volume, is a more meaningful parameter than the inspiratory flow to quote when assessing the potential ability of patients to use different breath operated devices. Moreover, the authors suggested an inspiratory flow rate of 60 l/min as being 'optimal' and concluded that a low resistance DPI, like Diskhaler, requires less than half the amount of work to be operated at this flow rate compared with a high resistance DPI, like Turbuhaler. In practice, however, inhalers are not operated at the same flow rate. Patients are generally instructed in terms of deep and powerful inhalation, independent of the type of DPI used. Therefore, dry powder inhalers are operated at the same inspiratory effort rather than at the same inspiratory air flow.

In order to calculate the work of breathing, defined as the product of pressure drop, volumetric flow rate and inspiration time, the generated pressure drops across the set of test inhalers have been recorded and plotted versus the air flow resistance in Fig. 7. The range of resistances for the commercial inhalers is shaded in the figure. The results confirm increasing pressure drops with increasing air flow resistances and demonstrate to be much higher (about 3 ×) at maximum effort than at comfortable inspiration. For both modes of inhalation the pressure drop seems to become constant, being approx. 8.5×10^3 Pa (85 mbar) at maximum inspiration. Apparently, this limit represents the maximum pressure drop healthy volunteers are able to generate (on average) when inspiring through a flow constriction. This result is in good agreement with the study of Clark and Hollingworth (1992) reporting a maximum of 80 mbar during inhalation 'as hard and as fast as possible'.

The calculated work of breathing is plotted in Fig. 8 again versus the air flow resistance. The

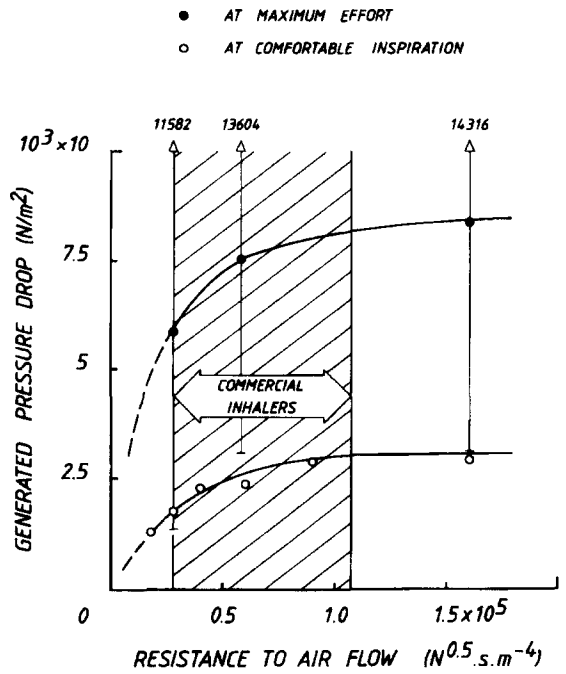

Fig. 7. Generated pressure drop as a function of air flow resistance at comfortable and maximum inspiration mode, respectively.

relationship indicates that about the same amount of work is put into action for all types of commercial inhalers when operated at comfortable inspiration. At maximum effort, which is the standard procedure, the amount of work of breathing even decreases with increasing resistance and shows to be 30% lower when inspiring through a low resistance DPI compared with a high resistance inhaler. This result proves that the conclusion of Sumby et al. (1992), stating that less than half the inspiratory effort is required to operate the Diskhaler compared with the Turbuhaler, is due to a misinterpretation. However, more interesting is the functional relationship between the amount of work of breathing and fine particle yield from a DPI, taking patient's comfort into account.

3.5. Preferable air flow resistance

During inspiration at comfortable effort (Study 1), the volunteers were asked to select the most comfortable air flow resistance as experienced

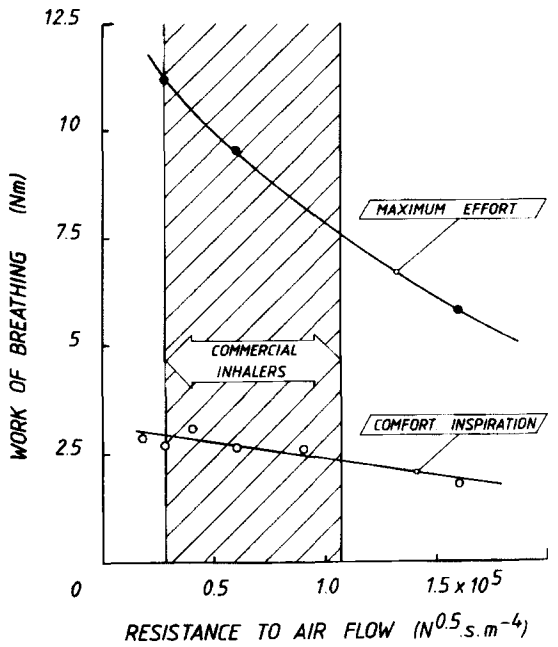

Fig. 8. Work of breathing as a function of air flow resistance at comfortable and maximum inspiration mode, respectively.

with the orifice disks 2–8, correspondent with air flow resistances of 5.4–0.18 $\times$ 10^5 $N^{0.5} \cdot s \cdot m^{-4}$. The obtained frequency distribution is given in

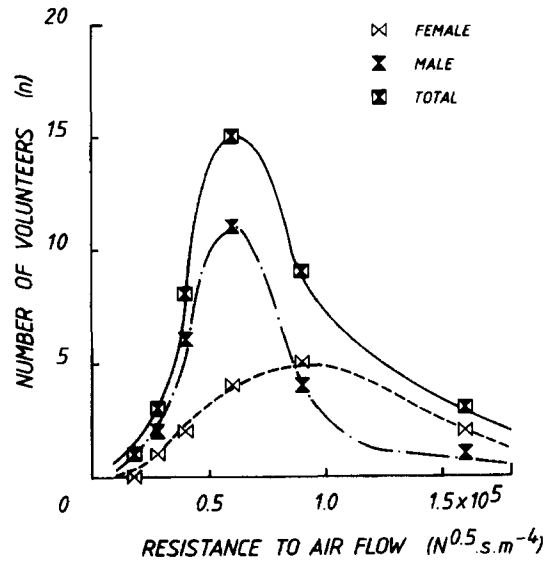

Fig. 9. Frequency distribution of the preference for air flow resistance from the 39 healthy adult volunteers of this study.

Table 4
Characteristic data of adult healthy volunteers and asthmatic patients from three different studies referring to PIFR inspired through the Turbuhaler ($PIFR_{TBH}$ in l/min)

Reference volunteers	This study (1995)	Van der Mark et al. (1994)	Engel et al. (1990)
Volunteers	Healthy	Asthmatic	Asthmatic
No. of volunteers	11	30	101
Male/female	8:3	8:22	38:63
Age, mean	32.7	31	41.6
range	21–56	18–62	15–79
PEFR in % pred.			
mean	104	102	69
range	86–126	42–175	8–132
$PIFR_{TBH}$			
mean	62.0	68.5	59
range	46–82	55–92	25–93
Equipment	Vitalograph	Vitalograph	Monoghan 403

Fig. 9, showing highest preference (15%) for the resistance of 0.6×10^5. About 82% of the volunteers selected a disk from the range of air flow resistances between 0.4 and 0.9×10^5 $N^{0.5} \cdot s \cdot m^{-4}$ as being comfortable. It may, therefore, be concluded that there is a strong preference for DPIs with moderate to higher air flow resistances. Moreover, there seems to be little difference between male and female volunteers in this respect. The preferences expressed by the healthy volunteers in our study differ from the observation of Clark and Hollingworth (1992), who reported anecdotal evidence by unsolicited comments from their healthy volunteers, that resistances greater than about 0.6×10^5 $N^{0.5} \cdot s \cdot m^{-4}$ (in their units: 0.1 cm $H_2O^{0.5} \cdot min \cdot l^{-1}$) were 'uncomfortable'. Andersen and Hansen (1993) showed that from a group of 60 users of DPIs, nearly half the population (43%) gave preference to the Rotahaler ($R = 0.28 \times 10^5$), whereas only 10% considered the Turbuhaler (R = approx. $0.9 \times x\ 10^5$) as the most favourable device. These differences between the studies with respect to what is experienced as being comfortable may be attributed to different questioning. In our study, the healthy volunteers had to choose their 'preferable air flow resistance' whereas in the study of Andersen and Hansen (1993) the patients had to answer the question 'Which inhaler do you feel is the best to use?'. This includes other criteria for selection than air flow resistance only. We also noticed from preliminary pilot studies, that the habituation to a specific inhaler device (more specific to its air flow resistance) and the sequence of offering of the air flow resistances can have considerable influence on the results.

3.6. Comparison of healthy volunteers with asthmatic patients

One of the objects of this study was to compare the PIFR of healthy volunteers with the PIFR of asthmatic patients from other studies, generated through the Turbuhaler at the same inspiration mode. From the simultaneous recording with Viewdac and Vitalograph of the flow curves of the selected 11 volunteers through the simulated Turbuhaler, it was calculated that PIFR from Viewdac is on average 96.3% of PIFR from Vitalograph. It was, therefore, concluded that no corrections are necessary from equipment point of view when comparing data obtained with both different recording systems.

Table 4 summarizes some characteristic data of three different groups of volunteers and patients, including the PIFRs generated through the Turbuhaler ($PIFR_{TBH}$) vs. the correspondent test inhaler device. The data show about equal mean age and %PEFR for the healthy volunteers in our study and for asthmatic patients from a study by Van der Mark et al. (1994), but a higher mean age

and lower %PEFR for the group of athmatic patients in a study of Engel et al. (1990). In spite of the latter, all three groups of healthy volunteers and asthmatic patients generated about the same $PIFR_{TBH}$ values. This result seems to be in disagreement with literature presenting data from non-restricted inhalation, i.e. without air flow resistance, referred to as 'control' value. Timsina et al. (1994) reported a mean PIFR ('control' value) of 333 l/min for male and 214 l/min for female healthy volunteers, but only 200 l/min for asthma patients. Brown et al. (1991) measured a mean PIFR (control value) as low as 156 l/min for a group of 65 patients suffering from acute exacerbations of asthma. It may seem surprising that patients inspire (slightly) better through an air flow resistance than healthy volunteers (Van der Mark et al., 1994 versus this study). It must be realized however, that asthmatic patients are well trained to inhale through a flow resistance and have a strong motivation for obtaining maximum relief from their DPI, this in contrast with healthy volunteers. In general, studies dealing with the PIFR through DPIs are difficult to compare with each other, because of differences in inspiratory instructions and measuring techniques. Differences between individual studies seem to refer more to age and sex than to state of health, and differences between comparable groups of healthy and asthmatic volunteers with respect to mean PIFR seem to be smallest for the highest resistance inhalers. It is, therefore, concluded that inspiratory flow curves of healthy volunteers, through at least the higher flow resistances, may well be used to predict the performance of asthmatic patients.

4. General conclusions

Present marketed dry powder inhalers encompass a wide range of possible inspiratory flow rates due to differences in their air flow resistance. For the low resistance Rotahaler, a mean PIFR at maximum effort of 160 l/min was found, which is more than 3 × the mean peak flow through the high resistance Ingelheim Inhalator. Moreover, the healthy volunteers showed considerable variation in individual PIFR values and inhalation profiles. The variations in inhalation characteristics cause great uncertainty about drug delivery from DPIs, being breath controlled with respect to dose entrainment, powder disintegration and particle deposition in the respiratory tract.

The healthy volunteers in this study expressed a strong preference (82%) for the moderate to higher air flow resistances in the range of approx. 0.6 to 0.9 × 10^5 $N^{0.5} \cdot s \cdot m^{-4}$.

Insignificant differences were found between mean PIFR through the Turbuhaler for two groups of asthmatic patients and mean PIFR generated by healthy volunteers through an equivalent air flow resistance. Consequently, it has been concluded that the performance of healthy volunteers may be used to predict the possible range of flow rates through the same air flow resistance for asthmatic adults.

Finally, it has been demonstrated that the amount of work necessary to operate DPIs at the same effort does not increase with increasing air flow resistance, as suggested in literature. At maximum effort, even a decrease in the amount of work has been found with increasing air flow resistance. In the next part of this series, the relation between work of breathing and fine particle yield from in vitro deposition experiments will be presented for three different types of commercial DPIs.

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