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Inhalation characteristics and their effects on in vitro drug delivery from dry powder inhalers Part 3: the effect of flow increase rate (FIR) on the in vitro drug release from the Pulmicort 200 Turbuhaler

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Abstract

The efficacy of dry powder inhalers (DPIs) is usually related to peak inspiratory flow rate (PIFR) through the device. In this study, the effect of the acceleration in flow rate (flow increase rate: FIR) on the fine particle output from the Pulmicort 200 Turbuhaler is discussed. Inspiratory flow curves of 11 healthy volunteers were recorded during 'calm but deep' and 'fast and deep' inhalation, respectively, both as a function of air flow resistance. Thereby, attained FIRs were calculated for the section of the flow curve between 20 and 30 l/min (FIR_{20-30}). Mean values for an air flow resistance similar to that of the Turbuhaler were approximately 2 l/s^2 during calm but deep and 10 l/s^2 during fast and deep inhalation. In vitro fine particle output from the Turbuhaler was studied with a four stage cascade impactor. This output increased between 1 and 5 l/s^2 but appeared to be constant at higher FIR_{20-30}-values. The output was also found to be independent of PIFR when compared at the same FIR_{20-30}. Maximum output could therefore already be obtained at 40 l/min for FIR_{20-30} greater than 5 l/s^2, which could easily be achieved by the healthy volunteers. © 1997 Elsevier Science B.V.

Keywords: Asthma; COPD; Pulmicort Turbuhaler; Cascade impactor; In vitro deposition; PIFR; Flow increase rate (FIR)

1. Introduction

Dry powder inhalers (DPIs) derive the necessary energy for emptying of the dose system and powder disintegration from the inspiratory air

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Table 1
Studies presenting fine particle output from Turbuhaler as a percentage of (ND) nominal dose or (LC) label claim for terbutaline sulphate and budesonide

Study	Size fraction (μm)	Fines	30 (l/min)	60 (l/min)
Terbutaline sulphate				
Wetterlin, 1988	Not specified	ND	20.1	
Newman et al., 1989	<5.5	ND		35.6
Borgström et al., 1993	<5.5	—		31.7
Malton et al., 1995	0.4–5.8	LC	8.3	
Malton et al., 1995	0.8–6.2	LC		25.8
Ifversen et al., 1995	<5	ND	11	44
Prime et al., 1996	Not specified	LC	8	26
Budesonide				
Borgström et al., 1994	<6	—		27.3
Fuller, 1995	<6	LC	9.8	52.0
Olsson et al., 1995	<5	ND		45
Prime et al., 1996	Not specified	LC	6	18
De Boer et al., 1996a	<6.8	ND	19.6	39.1

stream. Fine particle output from most marketed DPIs is therefore dependent upon the inspiratory flow curve. Peak inspiratory flow rate (PIFR) is widely considered as the most characteristic parameter of the flow curve in this respect. PIFR is also related to the site of deposition in the respiratory tract. For these reasons, PIFR is generally recorded as the circumstantial parameter for in vitro and in vivo deposition studies on DPIs.

In spite of careful monitoring of this flow parameter, different in vitro deposition studies may result in different amounts of fine particles released from the same type of inhaler at the same PIFR. Table 1 summarizes studies presenting fine particle outputs from the Turbuhaler at two different flow rates for two different drugs. For each drug and flow rate minimum and maximum fine particle fractions differ approximately by a factor 2 or even more. Although the size fractions are not exactly the same, they are not likely to be responsible for these differences in result. Nor are possible batch variations (for the powder formulation).

In vitro deposition studies suggest that there are two different types of relationships between fine particle release and PIFR. Some DPIs, seem to produce a flow rate dependent output of fines. Other devices seem to deliver a more or less constant fraction of the dose as fine drug particles over a wide range of PIFRs. Various authors referred to the consistent fractions of fine particles obtained with the Diskhaler and Diskus compared with a flow dependent output from the Turbuhaler (Fuller, 1995; Ifversen et al., 1995; Malton et al., 1995; Prime et al., 1996). It has been shown that the maximum fine particle yield from Turbuhaler and Spinhaler may be twice as high as that from Diskus and Diskhaler (De Boer et al., 1996b).

Differences in inhaler design and especially in powder properties may be used to explain the different fine particle yields from different commercial DPIs at the same PIFR. However, they cannot explain the different amounts of fine particles released from the same DPI for the same drug at the same PIFR, as shown for the Turbuhaler (Table 1).

It is therefore expected that there is another important, but yet uncontrolled, flow parameter being responsible for these differences. The aim of this study was to investigate the effect of the steepness of (a part of) the upward slope of the inhalation curve on the performance of the Turbuhaler. This parameter is referred to as the flow increase rate (FIR). The Turbuhaler has been

selected for this study because of its specific design. From in vitro evaluation of the Turbuhaler at flow rates between 20 and 60 l/min, it was concluded that there is a discrepancy between the necessary flow rate for discharge of the dose system and the flow rate required for the high fine particle output from this device (De Boer et al., 1996a). For the present study, discharge of the dose system and fine particle output from the mouthpiece have been measured at flow rates up to (and including) 100 l/min. These new results have been depicted in Fig. 1a,b. Fig. 1a shows fine particle output and discharge from the dose system as percentage of nominal dose, whereas in Fig. 1b both fractions are expressed in percentage of what is attained at maximum (at approximately 100 l/min). From Fig. 1b it can be seen that the majority of the dose (> 70%) is already released at 20 l/min. Fine particle output reaches the same level at 40–50 l/min and near-maximum (> 90%) first at 60 l/min.

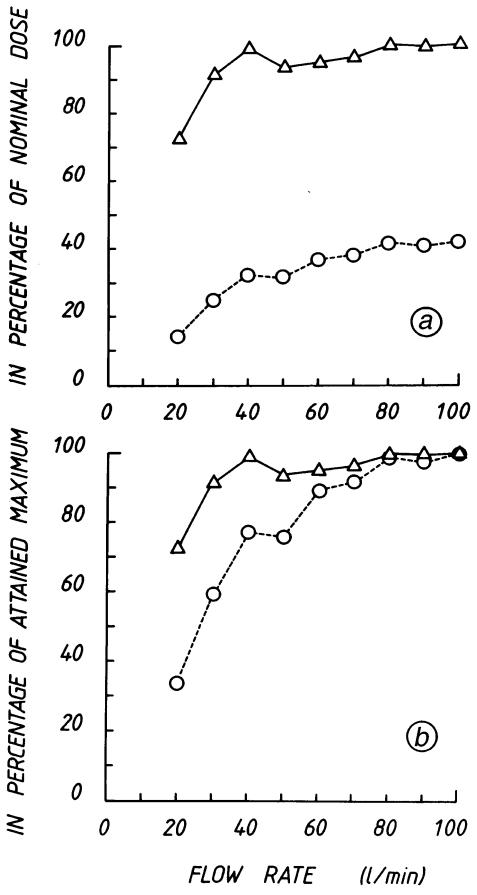

Fig. 1. Discharge from the dose system (△) and fine particle emission from the mouthpiece (○) for the Pulmicort 200 Turbuhaler as function of inspiratory flow rate, in percentage of nominal dose (a) and in percentage of attained maximum (b) from 'standard' cascade impactor analysis.

2. Theory

2.1. Turbuhaler: design and function

The Turbuhaler has two distinct regions for dose measuring and powder disintegration (Wetterlin, 1988). Entrainment of the dose from the powder holes in the dose measuring disk is the result of a certain pressure drop across these holes. This threshold pressure drop for dose release corresponds to a total flow rate through the device of approximately 20 l/min (Fig. 1). After entrainment from the dose system, the powder is transported towards the mouthpiece where disintegration takes place. This conveyance by the inspiratory air stream involves a certain travelling time for the dose inside the inhaler device. Discharge from the dose system generally occurs at a position on the upward slope of the inspiratory curve, since PIFR is usually higher than 20 l/min. During the short travelling time inside the inhaler device, total flow rate therefore increases. As a result, disintegration in the mouthpiece is performed at a higher flow rate than discharge of the dose system. The higher the flow increase rate, the higher the flow rate will be during disintegration and the more fine drug particles will be released.

2.2. Inspiratory flow curves through Turbuhaler

In order to obtain near-maximum fine particle output from the Turbuhaler in vitro under usual conditions, total flow rate through the device should be increased from approximately 20 l/min to 60 l/min during dose transport inside the inhaler (Fig. 1). Attained mean PIFR-values through the Turbuhaler from various studies, following instructions aiming at forceful inhalation, are generally between 55 and 70 l/min (Table 2).

Table 2
Studies presenting attained PIFRs through the Turbuhaler by adult asthmatic patients (A) and healthy volunteers (H) for instructions aiming at forceful, deep and fast inspiration, respectively or inhalation at 60 l/min

Study	Subjects	Mean age (years)	PIFR (l/min)	Range
Engel et al., 1989	28 A	41	—	39–105[a]
Newman et al., 1989	10 A	21–76	56	45–70
Engel et al., 1990	101 A	43.5	59	25–93
Hill et al., 1991	29 A	38	—	45–105
Brown et al., 1992	99 A	41.8	60	26–103
Borgström et al., 1992	6 H	37	55	45–66
Borgström et al., 1993	8 H	21	58	49–66
Borgström et al., 1994	10 H	32	57	52–61
Timsina et al., 1994	31 H	—	69	33–102[b]
Brown et al., 1995	99 A	42	60	26–105[c]
De Boer et al., 1996c	11 H	33	62	46–82
Meijer et al., 1996	30 A	31	68	30–118

[a] Data derived from graphic presentation.
[b] Range reproduced from Timsina et al., 1993.
[c] Adults with acute exacerbations of asthma.

In previous work it was reported that both average PIFR and FIR (up to peak flow rate) decrease with increasing air flow resistance in a study with healthy volunteers (De Boer et al., 1995). It was found that there is a fairly good (and more or less linear) relationship between PIFR and FIR, if the instruction is the same for all resistances. Fifty-five to seventy litres per minute can be considered as a moderate peak flow rate and taking the observed proportionality between PIFR and FIR in mind, it could be expected that FIR through Turbuhaler on average is not extremely high. This is especially true when the instruction is aiming for a deep and forceful inhalation only and not referring to a fast inspiratory manoeuvre as well. Therefore, a recorded PIFR of 60 l/min, may not be a guarantee for disintegration at a flow rate of 60 l/min. The complete dose may have been discharged from the mouthpiece before PIFR has been achieved.

This is elucidated in Fig. 2a,b, showing each a different type of inspiratory flow curve, however with the same PIFR. Both Figs. suggest that entrainment of the dose occurs at a flow rate of 20 l/min (positions A in the bottom Figs.). Subsequently, the powder is transported through the inhaler over a distance of approximately 30 mm before the mouthpiece is entered (top graphs). If inhalation is slow (Fig. 2a) with low average flow increase rate up to PIFR, flow rate during travelling time towards mouthpiece may be increased to approximately 30 l/min (position B in bottom graph). At this flow rate, disintegration in the mouthpiece is still insufficient (Fig. 1). At high average FIR up to peak flow (Fig. 2b), travelling time inside the inhaler device will be shorter (top graph). But in spite of this, total flow rate through

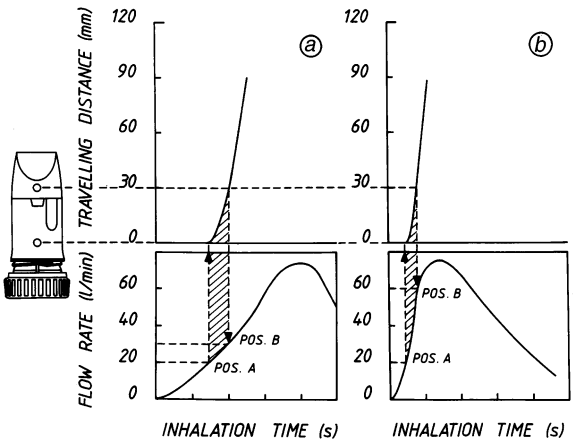

Fig. 2. Examples of flow curves with different flow increase rates (FIR), but the same peak inspiratory flow rate (PIFR), with projection of the corresponding travelling times for the powder through the Turbuhaler on the upward slopes.

the mouthpiece will be higher (position B at 60 l/min in the bottom graph). In the example of Fig. 2b, fine particle output will be higher and PIFR will be a better parameter from the flow curve in relation to the output.

2.3. Definition of FIR

Average flow increase rate up to peak flow rate (FIR_{PIFR}) may not be a good parameter for the Turbuhaler, as the steepness of the flow curve rapidly changes at the start of inhalation as well as near PIFR. It has been calculated that, in particular, the change in slope over approximately the last 10% of the upward curve may dominate average FIR_{PIFR}. More controlling is the part of the inspiratory flow curve between the flow rate initiating discharge of the dose system and the flow rate necessary for adequate powder disintegration.

It has already been discussed that the majority of the dose is released from the Turbuhaler at 20–30 l/min and that fine particle output reaches near-maximum first at 60 l/min. Therefore, FIR between 20 and 60 l/min seems to be a better tool. There are practical reasons however, as to why FIR was calculated for an even smaller part of the inspiratory curve between 20 and 30 l/min (FIR_{20-30}). Calculation of FIR between 20 and 60 l/min would have ruled out all experiments performed at flow rates less than 60 l/min. Since the rising part of the inspiratory curve shows a certain extent of linearity between approximately 20 and 80% of PIFR, it may be expected that FIR_{20-30} is characteristic for a much larger section of the upward curve. In addition to that, near-maximum fine particle output in vitro from Turbuhaler at 60 l/min (Fig. 1) has been obtained with restricted flow increase rates. From recordings of the flow curves during normal cascade impactor analysis, moderate FIR_{20-30}-values of 2.3, 3.5 and 4.3 l/s^2 were calculated at PIFRs of 40, 50 and 60 l/min, respectively. So, from increasing the FIR during cascade impactor analysis, a decrease in necessary PIFR for near-maximum fine particle output could be expected.

3. Materials and methods

Pulmicort 200 Turbuhalers used for this study were derived from three different batches (9SC09-A/VC652, 95H30-A/VH706 and 95I19-A/VI712). From the first two batches, more than one device has been used. The first ten, as well as the last 50 doses from each device were wasted.

3.1. Recording of inspiratory flow curves

A test inhaler with exchangeable air flow resistances was used for recording the inspiratory flow curves attained by healthy volunteers. The test inhaler as well as the additional measuring equipment and the calibration arrangement have been described previously (De Boer et al., 1996c). A slightly modified inhaler design was used for this study. The inhaler consisted of exchangeable tubes with different flow constrictions instead of orifice disks. Generated flow curves were recorded on a thermal recorder (Gould EasyGraf TA240, Simac Electronics BV, Veldhoven, Netherlands) for a high time resolution. Eleven healthy volunteers (three females) participated in this study, their age ranging from 22 to 51 with a mean of 34 years. All volunteers performed several inhalations through each of the air flow resistances according to two different instructions, but only the first attempts for both instructions were used for calculation of the attained FIRs.

3.2. Cascade impactor analysis

The cascade impactor, flow diagram and procedures used for measuring of the in vitro drug deposition from the Turbuhaler have been described by De Boer et al., 1996a.

In order to vary flow increase rate, two additional flow diagrams were applied (Fig. 3(a,b)). Reduced FIRs (compared with the standard procedures) could be achieved by incorporating a dead volume of 1 l in the flow diagram between the 3-way valve with bypass and the cascade impactor (Fig. 3(a)). In addition, an exchangeable capillary was used on the low pressure side of this volume for tuning the required FIR-value at all flow rates within the range of 40–60 l/min.

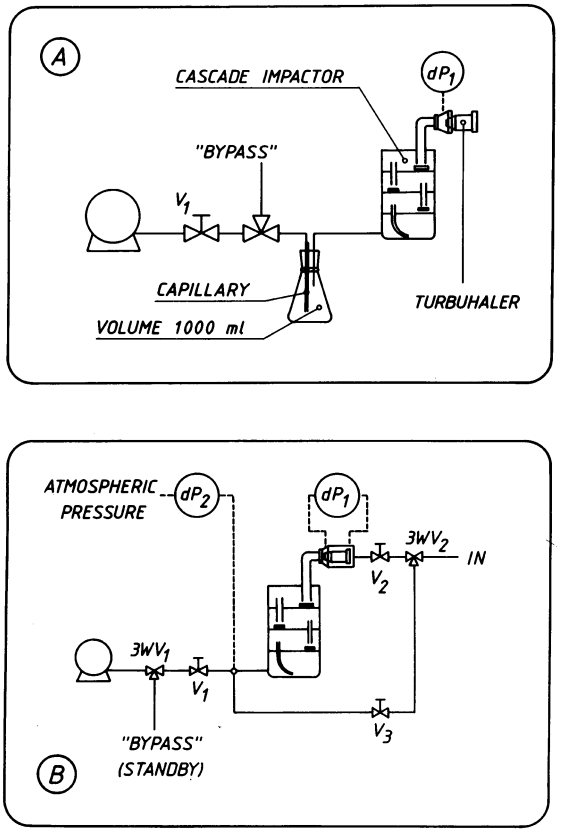

Fig. 3. Flow diagrams with the cascade impactor for reduced (a) and increased (b) FIR.

Increased FIRs could be achieved by creating a certain underpressure in the cascade impactor before leading the air stream through this apparatus. The applied flow diagram is depicted in Fig. 3(b). Three different flow controllers (V_1–V_3) were used in this diagram, as well as a bypass circuit from a 3-way valve ($3WV_2$). The Turbuhaler was placed in a housing and the combination was calibrated separately for each of the individual devices used for this study. In the position of 3-way valve $3WV_2$ for bypass flow, flow controller V_3 enabled adjustment of the necessary underpressure in the cascade impactor (monitored with differential pressure gauge dP_2). In the position of 3-way valve $3WV_2$ for flow through the cascade impactor, flow controller V_2 was used to adjust the required peak flow rate through the Turbuhaler (monitored with differential pressure gauge dP_1). Flow controller V_1 appeared to be necessary for levelling out the overshoot in flow rate. Applied underpressures in the cascade impactor prior to the inhalations were in the range between 1 and 0.8×10^5 Pa.

Flow curves during adjustment procedures and cascade impactor analysis were recorded with the thermal Gould recorder for calculation of the attained FIR-values.

4. Results and discussion

4.1. FIR_{20-30}-values attained by healthy volunteers through Turbuhaler

In order to estimate the range of FIRs to be applied for this study, volunteers were asked to perform (A) a calm but deep inhalation and (B) a deep inhalation in order to attain PIFR as fast as possible through the test inhaler. For both inhalation modes through each of the air flow resistances FIR_{20-30}-values were calculated. Average

Table 3
FIR_{20-30} and PIFR attained by 11 healthy volunteers dependent on air flow resistance according to two different instructions

Resistance ($10^5 N^{0.5} . s . m^{-4}$)	FIR_{20-30} (l/s^2)	PIFR (l/s^2)
Instruction A: calm but deep inhalation		
0.29	6.91 (1.52--16.70)	2.03
0.42	7.26 (0.98--33.40)	1.43
0.70	2.37 (0.51--8.35)	0.88
TBH	2.08	0.74
1.14	1.79 (0.13--5.57)	0.60
Instruction B: fast and deep inhalation		
0.29	14.68 (4.18--33.40)	2.81
0.42	15.31 (4.18--33.40)	2.02
0.70	13.53 (2.78--33.40)	1.22
TBH	10.22	1.00
1.14	6.91 (1.19--16.70)	0.78

Turbuhaler (TBH) with air flow resistance 0.806×10^5 calculated arithmetically.

values (and ranges) are depicted in Table 3. The results show that average FIR decreases with increasing air flow resistance. Also smallest average PIFR-values were attained through the highest air flow resistances. Compared with instruction A, instruction B yielded higher average PIFR-values as well as higher average FIRs. For individual flow recordings however, no consistent correlation was observed between FIR and PIFR.

The Turbuhaler used for the in vitro evaluation experiments exhibited an air flow resistance of 0.81×10^5 ($N^{0.5} \cdot s \cdot m^{-4}$). Flow increase rates have not actually been recorded through the Turbuhaler itself, but were derived arithmetically from the values obtained for the neighbouring air flow resistances of the test inhaler (TBH in Table 3). The order of magnitude for FIR_{20-30} resulting from calm but deep inhalation is 2 l/s^2. Fast and deep inhalation (instruction B) yielded a much higher average value of 10 l/s^2, which is more than twice as high as FIR during normal cascade impactor analysis at 60 l/min with the unmodified flow diagram.

4.2. The effect of FIR on fine particle output from the Turbuhaler

Cascade impactor analyses were performed for the range of FIR_{20-30}-values between 0.5 and 20 l/s^2. Flow rates (PIFRs) were 40, 50 and 60 l/min, respectively. Fig. 4 presents the fine particle output from Turbuhaler as a function of FIR_{20-30}. Each symbol represents the mean of two series of ten inhalations. Individual devices used for the study are marked with different symbols; different flow rates are not indicated. Fig. 4 shows that fine particle output (3rd + 4th stage deposition) increases with increasing FIR_{20-30}. The effect of this flow parameter on fine particle output is remarkable, especially within the range of attainable FIR_{20-30}-values between approximately 1 and 5 l/s^2. Within this range, fine particle output almost redoubles.

Although an effect of FIR_{20-30} on fine particle output is clearly to be seen from Fig. 4, no unique correlationship has been obtained. An explanation for the scattering in data may come from a slight batch variation with respect to dose release

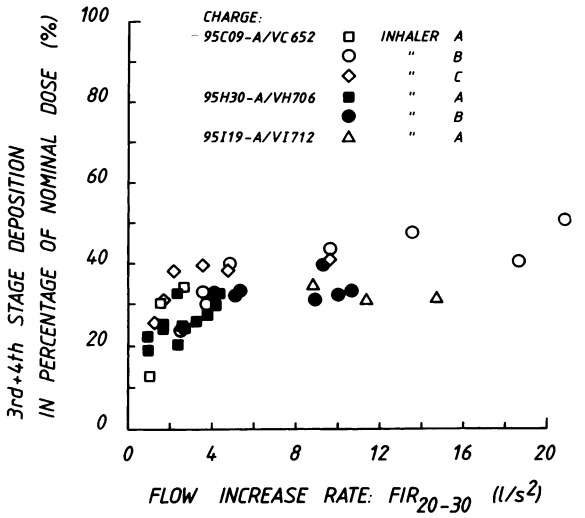

Fig. 4. Fine particle output from the Pulmicort 200 Turbuhaler as a function of flow increase rate between 20 and 30 l/min (FIR_{20-30}). Flow rates were varied between 40 and 60 l/min.

(Fig. 5). Also, a spread in mouthpiece and inlet tube accumulation has been observed (Fig. 6). In Fig. 5, the amount of drug released from the dose system is expressed as total recovery from cascade impactor analysis. The data spread considerably,

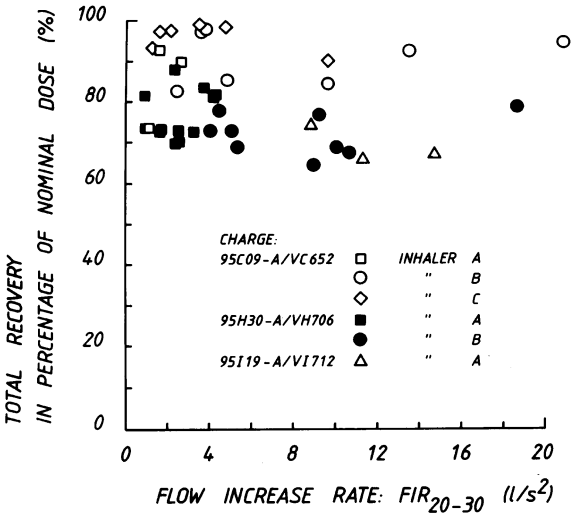

Fig. 5. Discharge from the dose system of the Pulmicort 200 Turbuhaler, expressed as total recovery from cascade impactor analysis, against FIR_{20-30} for the range of flow rates between 40 and 60 l/min.

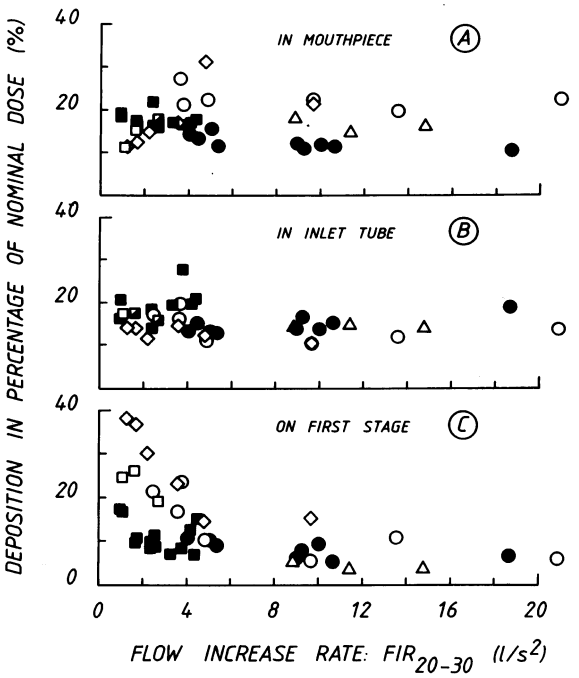

Fig. 6. Accumulation in the Turbuhaler's mouthpiece (A) and depositions in the inlet tube to the cascade impactor (B) and on the first impactor stage (C), respectively, as a function of FIR_{20-30}. Symbols refer to different devices (batches) as indicated in Fig. 4 and Fig. 5. Range of flow rates between 40 and 60 l/min.

although there seems to be no significant effect of FIR_{20-30} (slopes from linear regression: -0.29 to $+0.23$ for charge 95CO9-A and -0.88 to $+0.45$ for charge 95H30-A for the 95% confidence intervals ($CI_{95\%}$), respectively). The $CI_{95\%}$ for the interception with the y-axis confirm that there is a slight batch variation (87.2–95.8% for charge 95CO9-A vs. 71.3–80.1% for charge 95H20-A). Minute comparison of Figs. 4 and 5 leads to the conclusion that a lower amount of drug released from the dose system results in a lower amount of fine particles released from the inhaler's mouthpiece in the vast majority of cases. The spread of data in Fig. 4 could thus partly be explained by the variation in dose entrainment.

Fig. 6 shows that there are also variations in (a) mouthpiece and (b) inlet tube accumulations, although these variations in absolute sense are somewhat smaller than those found for dose release. An indirect parameter for powder disintegration could be the first stage deposition (Fig. 6c). First stage deposition represents the particles greater than 13 μm (for budesonide at 60 l/min), which are the particles that have not been disintegrated completely. As could be expected from the results in Fig. 4, first stage deposition decreases with increasing FIR_{20-30}.

In order to obtain a more unique relationship between fine particle output and FIR_{20-30}, a correction has been made for incomplete discharge of the dose system. The 3rd + 4th stage depositions from Fig. 4 have been extrapolated to 100% recovery, thereby using the data presented in Fig. 5. The corrected data have been plotted in Fig. 7, showing a much better correlation than Fig. 4. The spread left may be attributed to variations in mouthpiece and inlet tube accumulations. The corrected fine particle output ranges from slightly over 20% at lowest FIR_{20-30} to approximately 50% of the nominal dose at highest FIR_{20-30}-values. At FIR_{20-30} greater than 8 l/s^2, fine particle output becomes more or less constant. This seems logical, considering the fact that there must be a certain flow rate (corresponding with air velocity) through the mouthpiece at which powder disintegration becomes more or less complete. Conse-

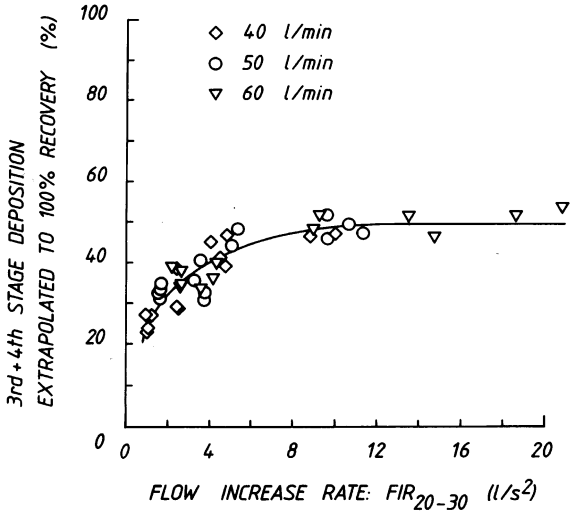

Fig. 7. Fine particle output form the Turbuhaler extrapolated to 100% recovery for the range of flow rates between 40 and 60 l/min. Different symbols refer to different flow rates.

quently, there is a minimum flow increase rate for establishing this flow rate (for maximum disintegration) during passage of the dose through the Turbuhaler from the dose system to the mouthpiece. Higher values than this threshold-value (of ~ 8 l/s^2) for FIR_{20-30} have no further effect on fine particle output. The existence of a threshold value for FIR_{20-30} (and flow rate) for maximum disintegration is confirmed by the results in Fig. 6(c): at FIR_{20-30} greater than 8 l/s^2, on average less than 7.5% of the dose is discharged as larger pellets from the inhaler. Practically, the relationship in Fig. 7 is well fitted by the logarithmic equation $\ln y = a + b/x$ (adjusted $R^2 = 0.78$). The $CI_{95\%}$ for the constant a are 3.90 and 3.99. Consequently, the maximum (corrected) fine particle output (at infinite FIR) lies between 49.4 and 54.1% of the nominal dose. In contrast with Fig. 4, the different symbols in Fig. 7 represent the three different flow rates applied. The data for each of the flow rates in Fig. 7 correlate with the same logarithmic equation as well: adjusted R^2-values are 0.82; 0.68 and 0.75 for 40; 50 and 60 l/min, respectively. Ninety-five percent confidence limits for the constant a of 3.83 and 3.99 (40 l/min); 3.88 and 4.05 (50 l/min) and 3.91 and 4.05 (60 l/min) indicate that maximum (corrected) fine particle output is independent of PIFR, between 46 and 57% of the nominal dose. But also at lower FIR-values, no significant differences are calculated between 40 and 60 l/min. This leads to the conclusion that FIR, rather than PIFR, is the relevant flow parameter for the Turbuhaler.

There is a slight effect of flow rate on the cut-off diameters of the 2nd + 3rd impactor stages. Theoretically, the cut-off diameter (50% collection efficiency) for budesonide of the second stage of the used impactor type decreases from 7.6 μm at 40 l/min to 6.2 μm at 60 l/min ($Stk_{50} = 0.22$). In practice, the change in cut-off diameter is of minor influence on the result expressed in 3rd + 4th stage deposition, especially at flow rates greater than 40 l/min at which disintegration is mainly into primary drug particles. From particle size analysis with laser diffraction technique, it is known that at least 90% of the budesonide is less than 4 μm. This is considerably below the theoretical cut-off diameter of 6.2 micron for the second stage at 60 l/min. Nearly all primary particles, if not accumulated in the mouthpiece, inlet tube and connecting tubes between impactor stages, should therefore be deposited on the 3rd + 4th stage. This indeed is the case: less than 3% of the nominal dose has been found on the 2nd stage at all flow rates (40–60 l/min) and all FIR-values. The change in cut-off diameter (for the second stage between 40 and 60 l/min) does not cause a measurable shift in deposition of budesonide from the 3rd to the 2nd stage. Consequently, the cut-off diameter of the 2nd stage does not define the size fraction (for budesonide) collected on the 3rd + 4th stage.

The misconception that PIFR is the relevant flow parameter for the Turbuhaler is comprehensible, considering the proportionality between average FIR and PIFR both in vitro and in vivo. As a result, extremely high FIR-values are generally not obtained at low to moderate PIFRs. In this study, highest FIR generated during cascade impactor analysis at 40 l/min was 9 l/s^2. Yet, a high PIFR is no guarantee for a high FIR. Average FIR has been found to increase with average PIFR, but so does the spread in FIR, as shown in Table 3. FIR_{20-30}-values less than 2 l/s^2 were obtained at calm but deep inhalation (instruction A), even when using the lowest air flow resistance of 0.29×10^5 $N^{0.5} . s . m^{-4}$. This in spite of the high PIFR of 122 l/min attained through the same resistance. More in general and irrespective of air flow resistance and inhalation mode, FIR_{20-30}-values in this study varied between approximately 2 and 30 l/s^2 for individual flow curves with PIFRs all being greater than 100 l/min.

5. General conclusions

The so far assumed PIFR-dependence of the Turbuhaler is sometimes criticized as the major drawback of this type of DPI. When compared with most other marketed DPIs however, the Turbuhaler yields a competitive fine particle output of 20% of the nominal dose even under less favourable circumstances (low PIFR, corresponding with low FIR). By increasing the inspiratory flow rate (PIFR), fine particle output from com-

parable multi dose DPIs can either be improved (e.g. De Boer et al., 1996b for Spinhaler) or remains more or less constant (e.g. Malton et al., 1995 and Prime et al., 1996 for Fluticasone Diskus). In the first example, lung deposition is not likely to improve to the same extent as fine particle output from the DPI, because of an increasing inertial deposition in the upper respiratory tract. In the second example, approximately 20–25% of the nominal dose released as fines is the maximum at all flow rates. For the Turbuhaler, the percentage of fines released from the mouthpiece may be increased considerably even at low PIFR simply by optimizing the instruction to the patient. The correct inhalation manoeuvre should aim at a high FIR (from fast and deep inhalation) rather than at a high PIFR (from calm and deep inhalation). At FIR_{20-30} greater than 5 l/s^2, a PIFR of 40 l/min is sufficient for a fine particle yield of greater than 40% of the nominal dose.

On the other hand, a PIFR of 60 l/min through Turbuhaler in vivo does not guarantee this high fine particle output. This is of great importance for in vivo studies relating clinical effect or radiolabelled drug distribution in the respiratory tract to PIFR through this device. For in vivo studies it is therefore recommended to record the whole inspiratory flow curve.

The results of this study may also explain the differences in fine particle output from the Turbuhaler at the same flow rate as reported by various authors (Table 1). FIR through the Turbuhaler in line with a cascade impactor may vary strongly with pump capacity, total volume and total air flow resistance of the in vitro test diagram. So, comparing the in vitro results from Turbuhaler obtained at the same PIFR should be disapproved, unless other relevant flow parameters and (preferably standardized) testing conditions have been given as well.

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