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# Effect of an external resistance to airflow on the inspiratory flow curve

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**Abstract**

Inhalation is a convenient way to deliver drugs to the respiratory tract in the treatment of respiratory diseases. For dry powder inhalers (DPI's), the principle of operation is to use the patient-generated inspiratory flow as energy source for emptying of the dose system and the delivery of fine drug particles into the respiratory tract. Resistance to airflow of the inhaler device is a major determinant for the inspiratory flow profile through the dry powder inhaler that can be generated by the patient. Therefore, resistance to airflow is one of the design parameters for DPI's, that could be used to control the inspiratory flow profile, and is one of the parameters to optimise particle deposition in the airways. In this study the effect of resistance to airflow on different parameters of the inspiratory flow curves as generated by healthy subjects, asthmatics and COPD patients was determined. As a result of increased resistance to airflow, the peak inspiratory flow (PIF), the flow increase rate (FIR) and the inhaled volume to reach PIF is decreased. On the other hand, the total inhalation time as well as the 80% dwell time is increased. In general, tuning of the resistance to airflow in the design of a dry powder inhaler may improve the drug deposition in the respiratory tract. 

*Keywords:* Dry powder inhaler; Resistance to airflow; Inspiratory flow curve; Pulmonary drug delivery; Peak inspiratory flow; Flow increase rate

## 1. Introduction

Inhalation is a convenient way to deliver drugs to the respiratory tract in the treatment of respira-

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tory diseases. Different types of devices, such as pressurised metered dose inhalers (p-MDI's), nebulizers or dry powder inhalers (DPI's) are used for the pulmonary delivery of drugs.

The generation of fine particles, by nebulization or disintegration of agglomerates, and the delivery of fine drug particles in the inspiratory airflow, requires an energy source. In case of p-MDI's and nebulizers an external energy source is used. Either the propellant or pressurised air is used as energy source to generate the fine particle cloud, which can be taken up by the inspiratory airflow for further transport into the respiratory tract.

For DPI's, the principle of operation is to use the patients generated inspiratory flow as energy source. After activation of the dose system, the patient's inspiratory flow controls the disintegration of the powder formulation, followed by delivery and deposition of fine drug particles into the respiratory tract. Therefore, the inspiratory flow profile is one of the major determinants for DPI performance (Clark and Bailey, 1996). The inspiratory flow profile as generated by different patients is variable and depends on the patient's inhalation performance. The shape of the inspiratory flow curve can be characterised by several parameters (Olsson and Asking, 1994a,b; de Boer et al., 1997a). The important parameters are the peak inspiratory flow (PIF); acceleration in inspiratory flow rate, the so-called flow increase rate (FIR); total inhalation time; time needed to reach PIF (time to PIF); the inspiratory volume to reach PIF; and the time over which a certain flow through the inhaler can be maintained, the so-called dwell time (DT). The relevance of each of these parameter depends on the type of DPI.

In general, the resistance to airflow of a device restricts the inspiratory flow through the DPI that can be generated by the patient, and it is a major determinant for the inspiratory flow profile. The 'target inspiratory flow rate' varies with inhaler design and is also a function of the resistance to airflow of the device. Drug delivery to the lung is greater for high resistance DPI's, which disintegrate the powder to a greater extent within the device than low resistance devices, which rely solely on the patient to disintegrate the powder by a rapid inhalation manoeuvre (Dolovich, 1995). Fine particle output of the device depends on the generated flow profile and the powder formulation used in the device. Therefore, for each combination of an inhaler device and a powder formulation, an optimal flow profile exists at which the highest amount of fine particles is deposited into the respiratory tract. Unfortunately, the shape of this optimal flow curve may be complex, resulting in complicated inhalation-instructions (Newman et al., 1994). For instance, a flow curve with a steep increase towards peak inspiratory flow (high FIR) and a gradual decrease towards the end of inhalation, requires a rapid change in effort during one single inhalation manoeuvre. Theoretically, more than one change in effort might be desirable. Since many patients are unable to follow even simple inhalation-instructions (van der Palen et al., 1997), complex breathing patterns might be impossible for a patient to exercise, even after extended practice. For this reason, it is clear that difficult inhalation-instructions will diminish the chance of a successful therapy. Therefore, they should be avoided. One option to solve this problem is to enforce the desired breathing pattern as much as possible by the inhaler device. The use of resistance to airflow is a possibility to control the inspiratory flow profile, and is one of the methods to optimise the performance of the dry powder inhaler.

Development of a DPI into a successful concept includes design, optimisation and tuning of each of the three principal inhaler parts: the powder formulation, the dose system, and the powder disintegration principle by which primary drug particles are generated during inhalation. The disintegration mechanism applied in the design of a DPI mainly determines the resistance to airflow of a DPI. However, for an optimal tuning of the resistance to airflow of a DPI, the effectiveness of the disintegration mechanism should, in a certain range, be independent to the total resistance to airflow of the device. Bypass airflow or sheath flow can be used for tuning the overall resistance to airflow of the device without influencing the disintegration efficiency dramatically (Lerk and de Boer, 1995; de Boer et al., 1997b).

Increasing resistance to airflow in the design of a DPI generally reduces the velocity of inhaled powder particles. Reduced velocity reduces the inertial impaction of the particles in the throat. In vivo studies show that reduced velocity of the inhaled powdered drug particles increases lung deposition and decreases the oropharyngeal deposition (Svartengren et al., 1995).

In this study the influence of resistance to airflow on the different characteristics of the inspiratory flow curves as generated by healthy subjects, asthmatics and COPD patients was determined. As inhalation through a DPI is in fact inhalation through an external resistance to airflow, the effect of inhalation through DPI's (of different designs) on the inspiratory flow curve can be simulated by inhalation through simple orifices having the same resistance to airflow as these DPI's (Fig. 1) (Clark and Hollingworth, 1993). The used orifice disks cover the range of resistances to airflow of commercially available DPI's (Fig. 2). It has to be recognised that the relationship between the orifice diameter and the resistance to airflow presented in Fig. 2 is only valid for the specific type of orifice disks used for this study. Minor changes in inlet and outlet geometry (Fig. 1) may change this relationship. Therefore, the projection of the marketed inhalers on this relationship has no other meaning than to visualise their relative differences and to show that the resistance to airflow increases exponentially with decreasing effective cross section for airflow through an inhaler.

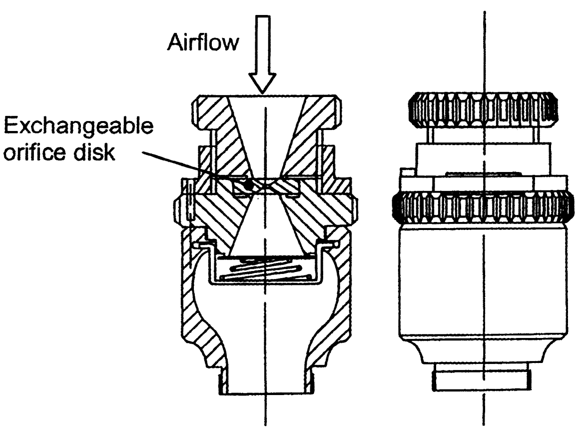


Fig. 1. Cross section and side view of the housing for the external resistance to airflow. Six different exchangeable orifice disks were used, with diameter increasing from 3 to 8 mm ($R_3$–$R_8$).

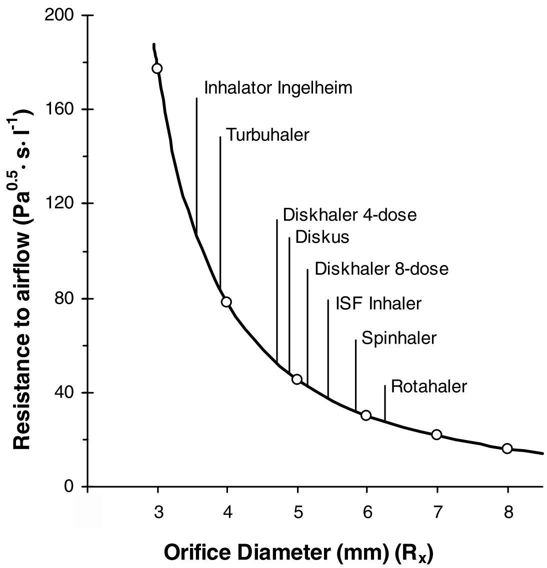


Fig. 2. Relationship between resistance to airflow and the orifice diameter (o = orifice disk, denoted as $R_x$). Resistance to airflow of commercial available DPI's are also indicated.

## 2. Material and methods

### 2.1. Methods

Inspiratory flow volume curves were recorded with the orifice disks connected to a pneumotachograph (Jaeger, Würzburg, Germany) as an *add-on* device (Fig. 1). Six different exchangeable orifice disks were used, with diameters increasing from 3 to 8 mm ($R_3$–$R_8$) (Fig. 2). The different orifice disks are denoted as $R_x$, in which $x$ indicates the orifice diameter. When no external resistance to airflow was applied (unloaded inhalation), the results obtained are denoted with $R_S$. All recorded flow volume curves were corrected for changes in gas density in the pneumotachograph.

Inhalation characteristics were measured during inhalation through three out of the six available external resistances to airflow. The orifice disks were applied in random order.

Inspiratory flow volume curves were measured with the inhalation-instruction to inhale forcefully and deeply during a maximal inhalation. During the measurements all subjects were seated, wore a nose clip and carried out their maximal inspiratory manoeuvres from residual volume (RV) up to total lung capacity (TLC). From a series of five measurements through one orifice disk, the three highest flow values were taken if their variation was within 10%. If the last measurement was the highest of all three, additional measurements were performed. Each effort was displayed on a monitor, and the subjects were coached to improve their effort.

## 2.2. Study subjects

Twenty-five healthy subjects and 50 patients volunteered for the study, which was approved by the medical ethics committee of the University Hospital Groningen. The healthy subjects were without any respiratory symptoms according to the MRC-ECSC questionnaire (Minette, 1989). Inclusion criteria for patients were a doctor's diagnosis of asthma (30 patients) or COPD (20 patients). Demographic and lung function data of the participants are given in Table 1. No drugs were administered during the tests. All measurements of dynamic lung function were obtained during a single visit to the pulmonary out-patient clinic. Unloaded spirometry measurements were performed followed by the measurement of inspiratory flow volume curves through the external resistances to airflow. Subjects were allowed to practice inhalation through the external resistance to airflow, before the actual measurement.

## 2.3. Analysis

In all in vivo analyses, except for the flow against time curves, the results of the three groups of subjects are pooled and given as a mean result.

### 2.3.1. Resistance to airflow

Specific resistances to airflow ($R$), for the different orifice disks and DPI's, are determined in vitro, by calculating the slopes of the linear relationships between the square root of pressure drop ($\Delta p$) against the volumetric flow rate ($\Phi$), according to Eq. (1) (Clark and Hollingworth, 1993):

$$\sqrt{\Delta p} = R \cdot \Phi \qquad (1)$$

The good linear correlation's between the square root of pressure drop and the volumetric flow rate obtained from calibration, show that Eq. (1) is valid for all types of inhalers and orifice disks in this study. Even complex devices can be characterised with the simple proportionality constant $R$, defined as specific resistance to airflow. They also confirm that a simple orifice disk as used in this study (Fig. 1) can represent such devices.

### 2.3.2. Total inhalation time

Total inhalation time is calculated from the onset of inhalation at RV to TLC. Fig. 3 shows a

Table 1
Demographic and lung function data of the participants

| | Healthy | Asthma | COPD |
|---|---|---|---|
| | $n = 25$ (15m/10f) | $n = 30$ (11m/19f) | $n = 20$ (13m/7f) |
| | Mean ± S.D. | Mean ± S.D. | Mean ± S.D. |
| Age (years) | 34 ± 13.1 | 39 ± 14.6 | 57 ± 5.3 |
| Smokers/ex-smokers/never | 2/6/17 | 5/9/16 | 2/14/4 |
| PEF (%pred) | 110.5 ± 20.6 | 94.7 ± 22.4 | 87.7 ± 30.0 |
| $FEV_1$ (%pred) | 106.7 ± 12.8 | 89.5 ± 21.0 | 77.3 ± 27.0 |
| $PIF_{RS}$ (l/s) | 6.58 ± 1.52 | 5.96 ± 1.61 | 5.60 ± 1.86 |
| $FIV_1$ (l) | 4.86 ± 0.89 | 3.96 ± 1.17 | 3.87 ± 0.97 |

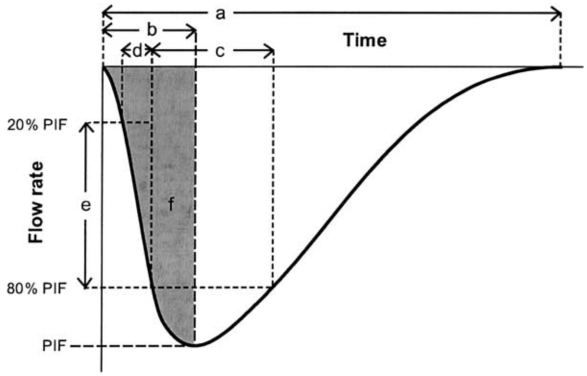


Fig. 3. Schematic presentation of the analysis parameters. ($a$ = total inhalation time; $b$ = time to PIF; $c$ = 80% dwell time ($DT_{80\%}$); $d = \Delta$ time between 20 and 80% PIF; $e = \Delta$ flow between 20 and 80% PIF; $f$ = inhaled volume at PIF).

schematic presentation of the analysis parameters. Total inhalation time is given by time segment *a*.

### 2.3.3. Time to PIF

Time to PIF is defined as the time between the onset of inhalation at residual volume and the moment of reaching the peak inspiratory flow (PIF). In Fig. 3, time to PIF is given by time segment *b*.

### 2.3.4. 80% Dwell time ($DT_{80\%}$)

The elapsed time over which a flow of 80% or more of PIF was achieved is defined as the 80% dwell time ($DT_{80\%}$). In Fig. 3, $DT_{80\%}$ is given by time segment *c*.

### 2.3.5. Flow increase rate ($FIR_{20-80\%}$)

Flow increase rate (FIR) is the acceleration in airflow. In this study, FIR is calculated as the average FIR from 20 to 80% of $PIF_{Rx}$ ($FIR_{20-80\%}$ ($l\ s^{-2}$)). In Fig. 3, $FIR_{20-80\%}$ ($l\ s^{-2}$) is calculated as the ratio of $\Delta$ (flow 20% of PIF and 80% of PIF) (flow segment $e$) to $\Delta$ (time 20% of PIF and 80% of PIF) (time segment $d$), or $e/d$.

### 2.3.6. Volume as $\%VC_{in}$ to PIF

For each curve the inhaled volume to reach PIF is calculated as percentage of the total inhaled volume ($VC_{in}$). Therefore, the inhaled volume to PIF, given in Fig. 3 by the area under the curve indicated with *f*, is divided by the total inhaled volume (total area under the curve).

## 3. Results

The impact of an external resistance to airflow on the inspiratory flow curve through inhaler device is shown in the Figs. 4–7.

In Fig. 4 the mean inspiratory flow rate against time curves through two different resistances to airflow, $R_4$ and $R_7$, are presented. In this graph, different lines represent the healthy subjects (solid line), asthmatics (dashed dot line) and COPD patients (dashed line). It is clear that an increased resistance to airflow ($R_4$) decreases the inspiratory flow, but increases the total inhalation time.

Peak inspiratory flow rate decreases with increasing resistance (Fig. 5, white bars) from 5.98 $l\ s^{-1}$ for the unloaded inhalation ($R_S$) to 0.53 $l\ s^{-1}$ for $R_3$. The flow increase rate is related to the peak inspiratory flow. Decrease in $FIR_{20-80\%}$ is observed from 47.8 $l\ s^{-2}$ for the unloaded inhalation ($R_S$) to 1.69 $l\ s^{-2}$ for $R_3$ (Fig. 5, black bars). Next to the effect of resistance to airflow on the PIF-value, also the time to PIF and the inhaled volume at PIF are changed when different resistances are used. Time to PIF is doubled from 0.31 s for $R_S$ to 0.67 s for $R_3$ (Fig. 6, white bars). In contrast, the inhaled volume to PIF as percentage of $VC_{in}$ is decreased from 34.5% for the unloaded inhalation ($R_S$) to 9.4% of total volume for $R_3$ (Fig. 6, black bars). As shown in Fig. 7, increasing resistance to airflow increases the total inhalation time. The unloaded inhalation ($R_S$) has duration

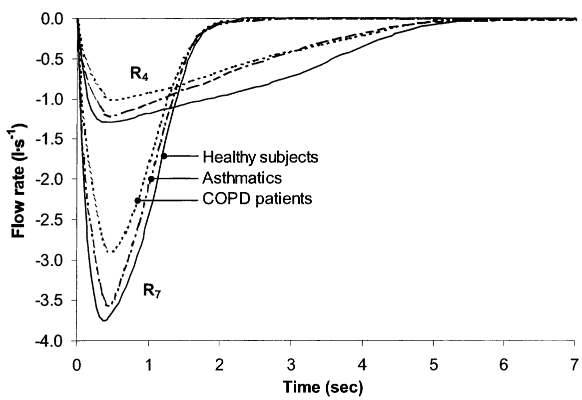


Fig. 4. Flow against time curve through resistance to airflow $R_4$ and $R_7$ for healthy subjects (solid line), asthmatics (dashed dot line) and COPD patients (dashed line).

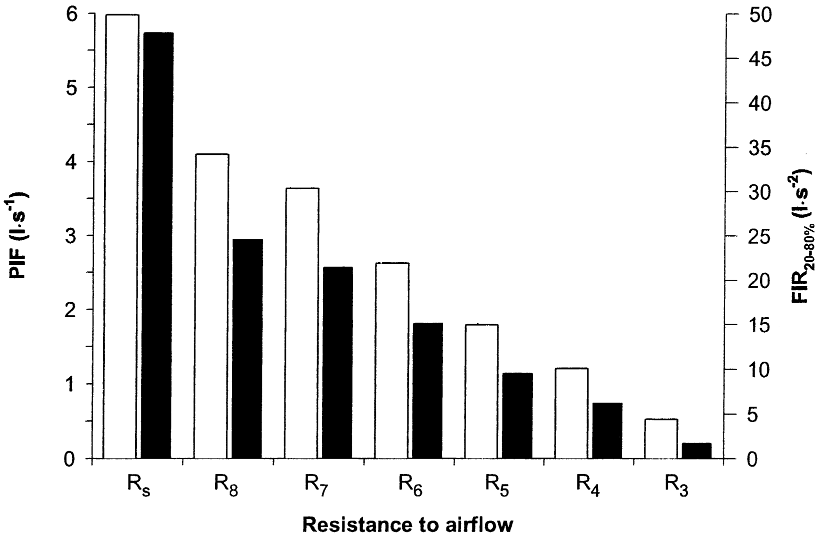


Fig. 5. PIF (l s$^{-1}$) (white bars) and flow increase rate (FIR$_{20-80\%}$) (l s$^{-2}$) (black bars) by maximal inhalation through different resistances to airflow.

of only 1.42 s. This total inhalation increases to 9.42 s for $R_3$ (Fig. 7, white bars). As a consequence of the decreased PIF and the increased total inhalation time, the inspiratory flow curve is less sharp at increasing resistance to airflow. Due to this change in shape of the inspiratory flow curve as shown in Fig. 4, the 80% dwell time increases with increasing resistance to airflow (Fig. 7, black bars). The 80% dwell time for the unloaded inhalation is only 0.45 s, while this is increased to 2.83 s for $R_3$.

## 4. Discussion

The introduction of a resistance to airflow in the inspiratory manoeuvre results in significant changes in the inspiratory flow curve. It was found that the differences between the three groups, the healthy subjects, asthmatics and COPD patients, are relatively small compared with the impact of resistance to airflow on the inspiratory flow curve (Fig. 4). Therefore, the results of the parameters are given as mean result for the three groups of subjects. Within the range of resistances to airflow of commercially available DPI's (Fig. 2), the most important and directly noticeable changes are the decrease in peak inspiratory flow and the increase in total inhalation time upon an increased resistance (Figs. 4, 5 and 7). By a maximal inspiratory manoeuvre, the total inhaled volume will not change by the use of an external resistance to airflow, the area under the curve of the flow time curve will be constant if different resistances to airflow are used. As a consequence the total inhalation time should increase by increased reduction of the peak inspiratory flow.

Considering the fine particle output pattern from dry powder inhalers, the first part of the inspiratory flow curve is of great importance, because discharge of the dose system, the disintegration and delivery of the fine particles into the airflow will mainly occur during this period of time.

The flow increase rate describes the acceleration in airflow, which is in some DPI's of importance for optimal disintegration. The flow increase rate is used in several studies for evaluation of DPI performance (Burnell et al., 1996; de Boer et al., 1997a; Everard et al., 1997). However, there is no general definition used for this parameter. The three previously named studies used a definition of FIR, which is only useful for the evaluated dry powder inhalers. The definition of Everard et al. (Everard et al., 1997) is even dimensionally incorrect ($s^{-1}$). The definitions used by Burnell et al. ($l\ min^{-1}\ s^{-1}$) (Burnell et al., 1996) and de Boer et al. ($l\ s^{-2}$) (de Boer et al., 1997a) are defined for specific measurements, or are useful for one inhaler device only. In our study a more general definition for the flow increase rate is used. We determined for each inspiratory flow curve, the flow increase rate from 20 to 80% of the peak inspiratory flow ($FIR_{20-80\%}$). During this part of the inspiratory flow curve, FIR does not depend on the highly variable onset of inhalation or on the strong decrease in acceleration near PIF. The resistance to airflow is a limitation for the peak inspiratory flow and is also a limitation for the maximal flow increase rate (Fig. 5). Therefore, the necessary FIR for optimal disintegration of the powder formulation should be within the possible range of FIR's for the resistance to airflow in the design of the inhaler device.

The time to reach the peak inspiratory flow (PIF) does increase with increasing resistance to airflow (Fig. 6). Time to PIF is twice as long for the highest resistance to airflow as for the lowest resistance to airflow in the study. On the other hand, the inhaled volume as $\%VC_{in}$ at the moment of PIF is for the highest resistance to airflow less than one third of the volume to PIF, as $\%VC_{in}$, for the lowest resistance to airflow in the study (Fig. 6). This could have consequences for inhalation through DPI's. It depends on the type of inhaler device, but in most DPI's the disintegration and delivery of the powdered drug particles occur in the first part of the inhalation, with the assumption that a maximum in released amount of drugs occurs near PIF. During inhalation through low resistance DPI's, about 30% of the total lung capacity is already used to reach the PIF. However, for high resistances, PIF is reached at less than 10% of $VC_{in}$. For this reason, when low resistance to airflow is used, a smaller inspiratory volume is left to transport the fine drug particles further into the respiratory tract. This means that exhaling to residual volume (RV) is more important for low resistance DPI's than for high resistance DPI's in order to ensure good transport of fine particles.

In some DPI designs, the delivery and disintegration of the powdered drug is not instantaneous, but takes some time. Therefore, the drug delivery from these DPI's requires a minimal level of inspiratory flow over a certain period of time. The ability to hold a certain flow for a particular

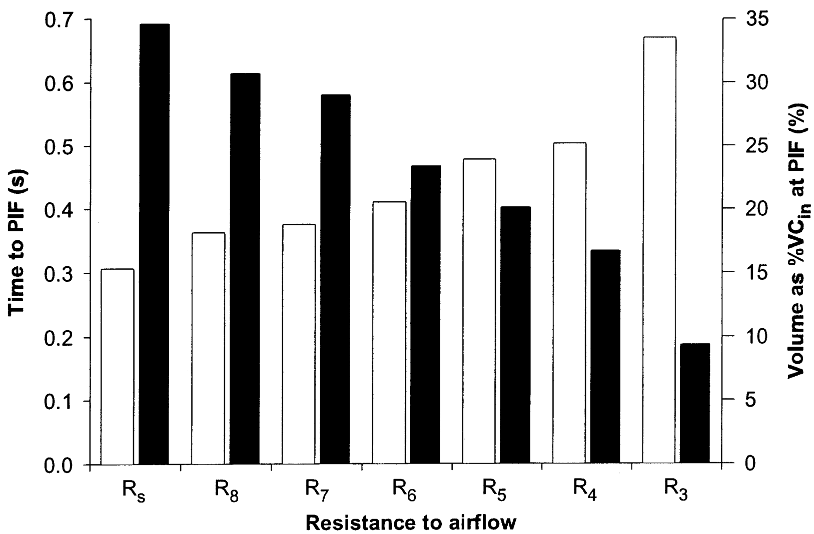


Fig. 6. Time to PIF (s) (white bars) and inhaled volume as $\%VC_{in}$ at PIF (%) (black bars) by maximal inhalation through different resistances to airflow.

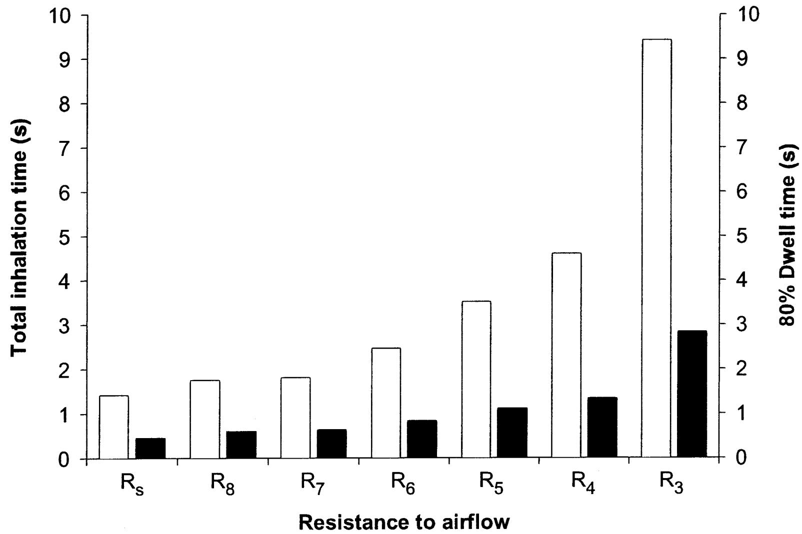


Fig. 7. Total inhalation time (s) (white bars) and 80% dwell time (s) (black bars) for the inhalation curves through different resistances to airflow.

time is given by the 80% dwell time (Fig. 7). The use of a low resistance to airflow generates a sharp inspiratory flow curve (Fig. 4), which results in a short 80% dwell time. For the high resistance to airflow, a broad smooth curve is generated, which results in a longer total inhalation time and also results in a longer 80% dwell time. Therefore, in DPI's with high resistance to airflow it is possible to sustain a certain inspiratory flow for a longer period of time, which improves the performance of the dry powder inhaler. Although the absolute duration of the 80% dwell time is increased for the high resistance to airflow, the ratio between the total inhalation time and 80% dwell time remains almost constant at 3:1 (Fig. 7). Fine tuning of the 80% dwell time is of great importance for those inhalers where a single dose capsule is used, or in those designs where the powder formulation is held for a longer period of time in a disintegration chamber (Lerk and de Boer, 1995; de Boer et al., 1997b).

An increase in resistance to airflow not only reduces inspiratory flow rate, but also reduces the velocity of inhaled powdered drug particles. In vivo studies show that reduced velocity of the inhaled powdered drug particles increases lung deposition and decreases the oropharyngeal deposition (Svartengren et al., 1995).

The resistance to airflow should be taken into consideration when new DPI's are designed, since the resistance enables the control over the inspiratory flow through the inhaler. Fine tuning of the inspiratory flow profile is possible with the introduction of a sheath flow, or a bypass airflow, especially in those inhaler designs where the powder disintegration and the fine particle output is, over a certain range, independent of the airflow through the device (Lerk and de Boer, 1995; de Boer et al., 1997b). On the one hand the total resistance to airflow of the device is adjusted, while on the other hand the resistance to airflow does not affect emptying of the dose system, disintegration, and fine particle output.

The choice of the resistance to airflow of the inhaler device depends on the disintegration concept used in the inhaler design. In designs where the dry powder formulation is only dispersed into the inspiratory airflow, a so-called non-specific disintegration system, the inspiratory flow, as energy source, is not used optimally. In this case, low total resistance to airflow of the inhaler device could be used. As a consequence of a non-specific disintegration system, the fine particle output is low. Due to the low resistance to airflow, larger variations in peak inspiratory flow are found. However, the fine particle output is more or less constant over a broad range of inspiratory flow at a low level (de Boer et al., 1996).

More specific disintegration systems use the inspiratory flow more optimally as energy source for disintegration and delivery of fine particles into the airflow. This usually results in an increased resistance to airflow of the disintegration system. Due to the inhaler design, the fine particle output more depends on patient's inspiratory performance. As a result, the fine particle output is more or less flow dependent. However, higher resistance to airflow limits the range of possible flow rates and due to the higher disintegration efficiency the fine particle output is higher compared with the non-specific disintegration systems (de Boer et al., 1996).

## 5. Conclusion

The profile of the inspiratory flow curve through an inhaler device depends on its resistance to airflow. The introduction of resistance to airflow in the design of a dry powder inhaler, affects the various parameters of the inspiratory flow profile differently. The peak inspiratory flow (PIF), the flow increase rate ($FIR_{20-80\%}$), and the inhaled volume as $\%VC_{in}$ at PIF decrease with increased resistance to airflow. On the other hand, time to PIF, the total inhalation time, and the 80% dwell time ($DT_{80\%}$) increase with increased resistance to airflow. Therefore, tuning of the resistance to airflow in the design of a dry powder inhaler is a tool to optimise the inspiratory flow curve through the inhaler device. This might improve the performance of the inhaler device.

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