Chapter 6

Effect of Peak Inspiratory Flow and Flow Increase Rate on *In Vitro* Drug Deposition from Four Dry Powder Inhaler Devices


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Abstract

Several *in vitro* as well as *in vivo* studies have emphasised the importance of generating a particular peak inspiratory flow (PIF) when using a dry powder inhaler (DPI). But also other parameters, such as the flow increase rate (FIR20-80%), may affect the performance of this type of inhaler devices. In the present study both the effect of PIF and the FIR20-80% on the fine particle output from four corticosteroid DPI’s was investigated. For the *in vitro* evaluation of the inhaler performance a four stage cascade impactor method is used, with a controllable inspiratory flow profile. The range of PIF and the FIR20-80% values were based on previous *in vivo* experiments, having physiological relevance. From the four investigated devices, the fine particle output from the Turbuhaler is the most sensitive to PIF and FIR20-80%. However, this device also had the highest fine particle output; more than 50% of the nominal dose at 60 l·min⁻¹ and a FIR20-80% of 7.5 l·s⁻². The fine particle output for the Diskhaler, Diskus and Cyclohaler also vary with PIF and the FIR20-80%, although variations are relatively small. The maximum fine particle output for the Diskhaler is 23%, for the Diskus 33% and for the Cyclohaler 29% of the nominal dose. For all four tested inhalers it should be recommended to patients to inhale forcefully and deeply through the DPI’s to obtain the highest fine particle output.
6.1 Introduction

The cornerstone of modern asthma treatment is inhalation therapy with corticosteroids. The amount of deposited fine particles in the target area, the lower respiratory tract, is important. Little information is available on the fine particle output of the inhaled dose of corticosteroids from different inhalers. Dry powder inhalers are described as breath-actuated drug delivery systems, which are widely used in the treatment of pulmonary diseases. Available DPI’s have different designs, which amongst other things results in different resistances to airflow during inhalation. Therefore, with the same inhalation performance different inhalation profiles have been obtained through the different inhaler devices (chapter 2, chapter 3, and chapter 4). Fine particle output of the device depends on the generated flow profile, the inhaler design, and the used powder formulation. It may therefore be expected that for each inhaler device in combination with a particular drug formulation an optimal flow profile exists at which the highest amount of fine particles is generated.

DPI’s can be categorised in two major groups, single dose and multi-dose inhalers. The multi-dose inhalers are divided in two different types of design: the reservoir systems and the multiple unit-dose inhalers. An example for the reservoir system is Turbuhaler (figure 6.1). In this type of inhaler, the powder formulation is stored in a container from which a single dose is measured volumetrically with a special dose-metering unit. Accurate dose metering for this type of inhaler requires careful manipulation of the device at the moment of patient use. In the multiple unit-dose inhaler, single doses are filled by the manufacturer into suitable dose compartments, such as blisters. Examples are Diskhaler (figure 6.1), having the blisters on a disk (Rotadisk), and Diskus (figure 6.1) with the blisters on a long strip. Before inhalation, a single blister is either perforated or the cover foil is peeled off the blister foil in order to gain access to one single dose.

Single dose inhalers are characterised by use of individual (sealed) dose compartments,
usually capsules, that have to be placed into the inhaler by the patient. Capsule cap and body must be separated before inhalation or the capsule has to be pierced at both ends, as for the Cyclocaps for Cyclohaler (figure 6.1).

![Turbuhaler](AstraZeneca)  ![Diskhaler](GlaxoWellcome)  ![Diskus](GlaxoWellcome)  ![Cyclohaler](Pharbita)

*Figure 6.1: Dry powder inhaler devices used for in vitro deposition study.*

For the many available DPI’s, two different types of powder formulations are currently applied. So-called spherical pellets are used in the Turbuhaler. In this type of formulation, the micronised drug particles are agglomerated into much larger units without binder agent and subsequently spheronised into a free flowing powder. The formulation does not contain coarser carrier crystals. Pellets can disintegrate rather completely during inhalation into much smaller agglomerates or even primary particles that have the required size range for deep penetration into the respiratory tract. The Rotadisk for Diskhaler, the blisters in Diskus and the Cyclocaps for Cyclohaler are filled with adhesive mixtures. This type of formulation consists of relatively large carrier crystals, mostly $\alpha$-lactose monohydrate, carrying the micronised drug particles distributed over their surface. During inhalation, the drug particles have to be released from the carrier crystals to enter the lower respiratory tract. The fraction of drug not detached may cause local side effects, like candidiasis, in the upper respiratory tract (mouth and throat) where the larger particles are deposited.

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 onset of the patient’s inspiratory flow starts entrainment of the powder from the dose system, and the disintegration of the powder formulation. Delivery and deposition of fine drug particles into the respiratory tract will follow. The generated inspiratory flow curve is one of the major determinants for DPI performance\(^1\). The inspiratory flow as generated by different patients is variable and depends on the patient's inhalation performances. As shown in chapter 2, the shape of the inspiratory flow curve can be characterised by several parameters. The important parameters are the peak
inspiratory flow rate (PIF); acceleration in inspiratory flow rate, the so-called flow increase rate ($FIR_{20-80\%}$); total inhalation time; time needed to reach PIF (time to PIF); the inspiratory volume to reach PIF; and the time during which a certain flow through the inhaler can be maintained, the so-called dwell time ($DT_{80\%}$).

PIF is often the only flow parameter that is controlled adequately when the in vitro performance of DPI’s is determined. For inhalers with large volume of drug and carrier powder, the total inhalation time is important. On the other hand, recent studies\(^1\)\(^-\)\(^4\) show that also other parameters of the inspiratory flow curve, such as the flow increase rate (FIR), may be important for the evaluation of inhaler performance.

In each of the studies FIR is differently defined. Everard et al.\(^4\) defined FIR (s\(^{-1}\)) as flow after 150 ml of inhaled volume. Burnell et al.\(^3\) defined FIR (l·min\(^{-1}\)·s\(^{-1}\)) as flow acceleration during dose emission. De Boer et al.\(^2\) defined FIR (l·s\(^{-2}\)) as flow increase rate from 30 to 40 l·min\(^{-1}\). In the presented study a more general applicable definition of flow increase rate is used. The flow increase rate (l·s\(^{-2}\)) is defined as the mean acceleration in airflow from 20% to 80% of the peak inspiratory flow ($FIR_{20-80\%}$). The change in slope at the start of inhalation as well as near PIF is large and may therefore dominate average FIR values from start to PIF. In the definition of $FIR_{20-80\%}$ these parts of the curve are excluded. This definition allows a reproducible measurement of FIR in a broad range of resistances to airflow.

In the present study the effects of both the PIF and the $FIR_{20-80\%}$ on the in vitro drug deposition from four corticosteroid DPI’s (figure 6.1) were investigated. A range of PIF-values as well as $FIR_{20-80\%}$-values was defined, based on the inspiratory flow curves that were measured in an earlier study (chapter 3 and chapter 4) in healthy subjects, asthmatics and COPD patients. For the in vitro evaluation of the inhaler performance a four stage cascade impactor was used. The impactor classifies the drug particles from the inhaler into size fractions that are relevant to lung deposition. The fractions retained from the 3\(^{rd}\) and 4\(^{th}\) impactor stages are considered to be the fine particles that are likely to enter the target area in the lower respiratory tract\(^5\).

### 6.2 Materials and Methods

For this study, three types of multi-dose DPI’s and one single-dose DPI with corticosteroid formulations were used. The inhalers were Pulmicort Turbuhaler, containing 200 doses of 200 µg budesonide per nominal dose; Flixotide Diskhaler, with Flixotide Rotadisks (4-doses), containing 250 µg fluticasone propionate per nominal dose; Flixotide Diskus, containing 60 doses of 250 µg fluticasone propionate; and the Cyclohaler, with budesonide Cyclocaps, containing 200 µg budesonide per nominal dose. To complete the whole study, several devices of the same inhaler type were necessary. In order to exclude batch variation, the different inhalers of the same type were derived from the same batch (first listed batch number in table 6.1). Some additional inhalers from other batches were used for the
examination of batch to batch variation, and the influence of drug load on the carrier crystals. All inhalers were provided by a community pharmacy.

6.2.1 Inhaler specific resistance to airflow

Inhaler specific resistance to airflow was calculated as the slope in the linear relationship between the square root of pressure drops and flow rate (6-8). The experimental set-up (figure 6.2) consists of a thermal mass flow meter (Brooks, The Netherlands, model 5863S (range up to 2.5 l·min⁻¹)), a flow controller (Festo, Germany, Drossel-Rückschlagventil type 3720 GR-½) and a coupling flange for the inhaler device. Pressure drop across the inhaler device was recorded with a differential pressure gauge (HBM, Germany, type PD1 (range 100 kPa)) connected to a computer. Inspiratory flow was generated by using partial vacuum, provided by a vacuum pump (Leybold, USA, model Sogevac SV 40). Inhaler specific resistance to airflow was used in the cascade impactor analysis to calculate the volumetric flow rate through the inhaler device from the recorded pressure drop.

![Figure 6.2: Experimental set-up for the measurement of relationship between pressure drop and flow rate for the different dry powder inhalers.](image)

6.2.2 Cascade impactor analysis

Cascade impactor analysis with the selected inhaler types was performed at different flow increase rates and different flow rates. To obtain flow profiles, with the desired flow increase rates and flow rates, special experimental set-ups were used (figure 6.3 and figure 6.4). The pressure against time profiles were recorded with a computer. From the recordings, the PIF and FIR₂₀⁻₈₀% values were calculated.

For the measurement of dry powder inhaler performance, two identical four-stage cascade impactors (Lenz Labor Instruments, The Netherlands, Fisons type) with dry bent inlet tubes were used for the flow rates up to 60 l·min⁻¹. For flow rates above 60 l·min⁻¹ a cascade impactor with a modified 4th stage was used (9). The modified 4th stage had a lower resistance to airflow and, therefore, analyses with higher flow rates were possible. The size distribution of the fines derived from the 3rd and 4th stages of both impactors varied with the flow rate, because the cut-off diameter of the 2nd stage as well as the collection efficiency of the 4th
stage depends on the flow rate. Fine particle losses as the result of incomplete collection efficiency can not be assessed accurately, although it is known that these losses are less substantial for the modified impactor than for the standard device. The cut-off diameters of the 2nd stage with 50% collection efficiency can be calculated as function of particle density and the inspiratory flow rate. Within the range of applied flow rates, the theoretical upper class limit of the fine particle fraction decreases from 12.4 µm at 30 l·min⁻¹ to 7.6 µm at 80 l·min⁻¹ for spherical pellets with a true density of 1.5 g·cm⁻³. This implies that the fine particle fraction is considerably narrower at 80 l·min⁻¹ than at 30 l·min⁻¹. For this reason, the obtained fine particle mass fractions, also referred to as fine particle output, derived from the 3rd and 4th stages are not expressed in terms of aerodynamic particle diameter, but they have been calculated as percentage of the nominal dose, the so-called label claim. The mass fractions collected on the 3rd and 4th stage are considered to be most relevant for deposition in the lower respiratory tract.

For the cascade impactor analysis, a coupling flange with exchangeable rubber seal was mounted on the inlet tube for holding the inhalers during testing (figure 6.3). From this coupling flange, a tube connection was made to a differential pressure gauge. The required flow rate through the dry powder inhalers during cascade impactor analysis was obtained by adjusting the corresponding pressure drops across the device with a flow controller. The inspiration time was controlled with a time controlled solenoid valve (Honeywell, Minneapolis, USA, Lucifer 7000 series) and was set for 3 seconds.

\[ \text{Figure 6.3: Experimental set-up for standard cascade impactor analysis} \]

\[ (FIR_{20-80\%} = 2.3 \text{ l·s}^{-2}) \]

Reduced flow increase rate \( (FIR_{20-80\%} = 1.2 \text{ l·s}^{-2}) \) was obtained by introducing a buffer volume.

For the standard cascade impactor analysis, the FIR_{20-80\%} is approximately 2.3 l·s⁻². Reduced FIR_{20-80\%} is obtained by introducing a volume buffer of 1 litre in the system (figure 6.3). The capillary on the 4th stage in the cascade impactor limits the flow increase rate for the standard
cascade impactor analysis. Higher \( \text{FIR}_{20-80\%} \) is obtained by introducing a small pre-inhalation partial vacuum in the cascade impactor before the start of the actual inhalation (figure 6.4). That way the initial pressure drop across the DPI increased. The \( \text{FIR}_{20-80\%} \) was accurately controlled with the speed adjustable three-way valve and the amount of partial vacuum in the system (appendix, figure 6.10). For the cascade impactor analysis with increased \( \text{FIR}_{20-80\%} \), the inhalers were placed in a specially designed closed inhaler adapter, with exchangeable inhaler housings for the different types of DPI’s (appendix, figure 6.11). In the pre-inhalation situation, the partial vacuum in the cascade impactor system was adjusted with flow controller 4 (figure 6.4). To start the inhalation through the cascade impactor, the speed adjustable three-way valve changed direction by activating the time controlled valves. Both valves were synchronised with the same timer. The speed of the three-way valve was controlled by the flow rate of pressurised air, which was adjusted by flow controller 1. With the speed of changing the flow direction in the three-way valve as well as the amount of pre-inhalation partial vacuum in system the \( \text{FIR}_{20-80\%} \) rate could be controlled. Flow controllers 3 and 5 were used to adjust the PIF through the inhaler system.

![Figure 6.4: Experimental set-up for cascade impactor analysis for higher flow increase rates. (Pre-inhalation situation)](image)

For each cascade impactor analysis, 2000 µg of active compound (based on nominal dose) was inhaled in the cascade impactor. Therefore, each cascade impactor result is the mean of a series of ten successive inhalations for the Turbuhaler and Cyclohaler, both with 200 µg per nominal dose. For the Diskhaler and the Diskus, both with 250 µg per nominal dose, eight successive inhalations were used per cascade impactor analysis. For the Turbuhaler, containing 200 doses, only the doses 10-180 from each device was used in order to avoid inaccuracies from incomplete dose measuring.
Fractions deposited in the cascade impactor and accumulated in the inhaler devices, were dissolved in pure ethanol. For the Diskhaler, blister residues were also analysed. Accumulation and waste of dose in the inhaler device is difficult to measure. Especially in the multi-dose inhalers as Turbuhaler and Diskus, because in both inhalers the dose system cannot be rinsed without affecting the remaining doses. For the Turbuhaler it is possible to measure the mouthpiece accumulation by simple reassembling and rinsing of the mouthpiece. For the Diskhaler, waste in the Rotadisk, and mouthpiece accumulation can be measured by rinsing the Rotadisk and the mouthpiece after the admission of all inhalations into the cascade impactor. For the Cyclohaler it is possible to measure the mouthpiece accumulation by rinsing the inhaler, but with our measurement method it is not possible to measure the remaining drug in the Cyclocaps. All drug solutions of fractions collected from the Diskhaler, Diskus and Cyclohaler were treated in a centrifuge (3000 rpm. for 5 min.) in order to precipitate the lactose carrier crystals. Analysis was performed by UV absorption at 243.7 nm for budesonide, and 236.6 nm for fluticasone propionate, using a PU 8720 UV/VIS Spectrophotometer (Philips, The Netherlands).

6.2.3 Carrier residue analysis

After the disintegration of an adhesive mixture, a fraction of the active material will still be attached to the carrier crystals, the so-called carrier residue. The carrier residue as a function of drug load on the carrier crystals can be measured with a specially designed test inhaler device\(^\text{(11)}\). The test inhaler has a cyclone based disintegration principle that can withhold larger carrier particles. The withheld carrier particles were analysed upon adhering drug particles after inhalation, the so-called carrier residue. The percentage carrier residue is the active compound still attached to the carrier particles in the cyclone chamber at the end of the inhalation cycle expressed as the percentage of the nominal dose. For each carrier residue analysis, 2000 µg of active compound (based on nominal dose) was inhaled. For the comparison of the powder formulation from the Rotadisk and the Diskus, the amount of carrier crystals at each inhalation was kept constant. Therefore, eight inhalations each with the content of one blister from a Rotadisk were carried out (25 mg lactose carrier crystals). For the Diskus, four inhalations each with the contents of two blisters were carried out (2×12.5 mg lactose carrier crystals). After each inhalation, the carrier crystals were retained from the cyclone chamber. The total carrier residue was collected and analysed. The inhalation conditions for the test inhaler were set at an inhalation time of 3 seconds at 40 l·min\(^{-1}\).
6.3 Results and discussion

6.3.1 Inhaler specific resistance to airflow

The inhaler specific resistances to airflow are presented in table 6.1. The highest resistance to airflow is found for the Turbuhaler, while the lowest resistance to airflow is found for the Cyclohaler.

**Table 6.1: Characteristics of used inhaler devices**

<table>
<thead>
<tr>
<th>Inhaler device</th>
<th>Resistance to airflow</th>
<th>Batch numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turbuhaler Pulmicort 200 (AstraZeneca)</td>
<td>81.7 Pa$^{0.5}$·s·l$^{-1}$</td>
<td>03-2000 98C24-A ZC 991</td>
</tr>
<tr>
<td>Diskhaler Flixotide 250 (GlaxoWellcome)</td>
<td>52.5 Pa$^{0.5}$·s·l$^{-1}$</td>
<td>Diskhaler: 98 06 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rotadisk 250: 98 07 02/1 Jul-00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rotadisk 250: 99G 21/2 Jul-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rotadisk 500: 99H 25/2 Aug-2001</td>
</tr>
<tr>
<td>Diskus Flixotide 250 (GlaxoWellcome)</td>
<td>50.1 Pa$^{0.5}$·s·l$^{-1}$</td>
<td>99C 28 B Sep-00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99G 26 E Jan-01</td>
</tr>
<tr>
<td>Cyclohaler Budesonide 200 (Pharbita)</td>
<td>34.3 Pa$^{0.5}$·s·l$^{-1}$</td>
<td>Cyclohaler: 99-04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclocaps: 01 2001 2F 0170 98 A 06</td>
</tr>
</tbody>
</table>

6.3.2 Cascade impactor analysis

Typical flow rate against inhalation time curves for cascade impactor analyses at standard flow increase rate and at higher flow increase rate are given in figure 6.5.

![Flow rate against Inhalation time curves](image)

*Figure 6.5: Typical flow rate against inhalation time curves for cascade impactor analysis at a FIR$^{20-80\%}$ of 2.3 l·s$^{-2}$ and at a higher FIR$^{20-80\%}$ of 8 l·s$^{-2}$."

In figure 6.6 and figure 6.7 the retained drug fractions from the cascade impactor analysis as percentage of the nominal dose are given for the four investigated DPI’s. Figure 6.6 shows the results of the standard cascade impactor analysis at different inspiratory flow rates. The total
length of the bars represents the total drug recoveries for the analyses. Figure 6.7 shows the results of the comparable analyses at a higher flow increase rate. The total drug recovery is relatively constant at increasing inspiratory flow rate and flow increase rate for the different inhaler devices. However, the percentages collected from the different stages change. For the Turbuhaler the fine particle output increases with increasing inspiratory flow rate (figure 6.6). At higher FIR\textsubscript{20-80%} an identical trend is found (figure 6.7). Moreover, the fine particle output at the various flow rates is increased compared to the lower FIR\textsubscript{20-80%} (figure 6.6 and figure 6.7).

![Figure 6.6: Amount of drug deposited on the four different impactor stages, inlet tube and mouthpiece as a percentage of the nominal dose at different PIF's at a standard FIR\textsubscript{20-80%} of 2.3 l·s\textsuperscript{-2} for the Turbuhaler, Diskhaler, Diskus and Cyclohaler. For the Diskhaler, also the remaining amount of drug in the Rotadisk was measured.](image)

For the Diskhaler an increase in the 1\textsuperscript{st} stage deposition is found at increasing flow rates. This can be explained with a decreasing amount of drugs remaining in the Rotadisk and the mouthpiece. The total amount of drug found on the 1\textsuperscript{st} stage for the Diskhaler, Diskus and Cyclohaler are relatively high compared to the Turbuhaler. This is a consequence of the presence of large lactose carrier crystals in the drug formulation of the Diskhaler, Diskus and Cyclohaler. Since, larger particles are deposited on the 1\textsuperscript{st} stage of the cascade impactor, the high amount of 1\textsuperscript{st} stage deposition is considered to be the fraction of the drug that was not released from the carrier particles.

The drug accumulation in the mouthpiece is different for all four types of DPI’s. Differences in accumulation are also related to the way of analyses of the four mouthpieces. For the
Turbuhaler, the total mouthpiece was disconnected from the inhaler and analysed. For the Diskhaler and the Cyclohaler, the mouthpiece was rinsed with ethanol. For the Diskus, analysis of mouthpiece accumulation was difficult. With a brush the mouthpiece was cleaned and the removed particles were analysed. The Turbuhaler has a construction in which the mouthpiece is the major disintegration system of the inhaler. A relatively high number of drug particles make contact with the inner walls of the mouthpiece. Since fine particles are sensitive to accumulation due to Van der Waals forces and electrostatic charges, a relatively high mouthpiece accumulation could be expected for the Turbuhaler.\(^8\) In the design of the other inhalers, the mouthpiece is a less important design parameter for the disintegration of the drug formulation. Additionally, the large carrier particles in the drug formulation may sweep previously accumulated drug particles from the walls of the mouthpiece, which reduces the mouthpiece deposition. Inlet tube and 1\(^{st}\) stage deposition are a measure for the mouth and throat deposition. Deposition of corticosteroids in the throat is responsible for local side effects as dysphonia (hoarse voice), sore throat, and oropharyngeal candidiasis. Reduction of drug deposition in this region might help to reduce these local side effects.\(^{12}\)

The total drug deposition on the 3\(^{rd}\) and 4\(^{th}\) stage of the cascade impactor is a measure for the fine particle output from the DPI and represents the respirable fraction that can enter the lower respiratory tract. The fine particle output from the four investigated DPI’s as a function of

\[\text{Figure 6.7: Amount of drug deposited on the four different impactor stages, inlet tube and mouthpiece as a percentage of the nominal dose at different PIF's and a higher FIR}_{20-80}\%\] of 8 l·s\(^{-2}\) for the Turbuhaler, Diskhaler, Diskus and Cyclohaler. For the Diskhaler, also the remained amount of drug in the Rotadisk was measured.
both the \( \text{FIR}_{20-80\%} \) and the PIF through the inhaler is presented as contour plots in figure 6.8. As demonstrated in the contour plots the fine particle output pattern (isofines) is different for the four types of investigated DPI’s. For all four DPI’s a slight decrease in fine particle output is found at flow rates above 60 l·min\(^{-1}\). This decrease is not expected and is considered to be an artefact introduced by the cascade impactor method. At increasing flow rate, the collection efficiency for the finest particles decreases.

![Contour plots](image-url)

**Figure 6.8:** Contour plots for the relationship between PIF through the inhalers, the \( \text{FIR}_{20-80\%} \) and the fine particle output as a percentage of the nominal dose, for the Turbuhaler, Diskhaler, Diskus and Cyclohaler. Contour lines indicate the isofines levels.
The fine particle output from the Turbuhaler depends on both the PIF and the FIR_{20-80%}. The optimal fine particle output is found at a PIF near 60 l·min^{-1} and a FIR_{20-80%} near 7.5 l·s^{-2}. In this area, a fine particle output above 50% of the nominal dose is found. For an optimal inhaler performance of Turbuhaler it is therefore important that patients inhale forcefully and deeply. This is also demonstrated in *in vivo* experiments in literature^{13}. As demonstrated in chapter 3, the actual generated mean PIF, by volunteers and patients, through a resistance to airflow (R4) comparable with that of the Turbuhaler, is about 70 l·min^{-1} and the mean FIR_{20-80%} is found at 7.6 l·s^{-2}, which fits in the area of optimal fine particle output.

The fine particle output for the Diskhaler, Diskus, and Cyclohaler also depends on the PIF through the inhaler, although variations are relatively small. Both the Diskus and the Cyclohaler show dependence of the fine particle output to the FIR_{20-80%}. The maximal fine particle output is 23% for the Diskhaler, 33% for the Diskus and 29% for the Cyclohaler. Based on the fact that the cut-off value change at increasing flow rate, as discussed in section 6.2.2, the fine particle output of all four inhaler devices might even have a greater dependence on the PIF and the FIR_{20-80%} than shown in figure 6.8.

The difference in fine particle output between the Diskhaler and the Diskus is remarkable, because the Diskus is designed to be equal to the Diskhaler^{14}. Small differences in the design of the disintegration systems in the Diskus and Diskhaler might result in an increased fine particle output from the Diskus. However, the main difference between both DPI’s is the powder formulation. The used powder formulation in both inhalers is an adhesive mixture of relatively large \( \alpha \)-lactose monohydrate crystals, carrying the micronised drug particles on their surface. A single dose in the Rotadisk for the Diskhaler consists of 25 mg lactose carrier particles, whereas a dose for the Diskus consists of 12.5 mg lactose carrier particles. The drug load on the surface of the lactose carrier particles is therefore about 1\% for the Rotadisk in the Diskhaler, and about 2\% for the Diskus. It is known that the detachment of the drug particles from the lactose carrier crystals during inhalation may be influenced by the drug load. It is also known that the drug-to-carrier interaction may vary considerably from batch to batch for the same type of marketed lactose. Effect of drug load on fine particle output was measured with a special designed cyclone type test inhaler device^{11}, in which the large carrier particles are withdrawn in the inhaler, whereas only the fine particles are emitted. The amount of not detached drug from the carrier, the so-called carrier residue, was determined for the powder formulations of the Rotadisk, as well as the Diskus. In the Rotadisk, a 38.7\% carrier residue was found, and for the Diskus, with a higher drug load, a 26.3\% carrier residue was found. This difference in carrier residue is probably one of the reasons of the difference in fine particle output between both inhalers. Rotadisk containing 500 \( \mu \)g fluticasone propionate have also a drug load of 2\%, which is comparable to the drug load in the Diskus. Therefore, cascade impactor analyses with Rotadisk 500 are performed (figure 6.9) for comparison. This resulted in a fine particle output of 21.6\%, at 60 l·min^{-1},
The carrier residue is decreased, compared to the 250 µg Rotadisk. But the fine particle output is not increased to the level as found for the Diskus, with the same drug load on the carrier crystals. Additionally, cascade impactor analyses with the Diskus and the Diskhaler from another batch are carried out. The results in figure 6.9 show different fine particle outputs for the two batches of the Diskhaler and Diskus, respectively. The difference between the Diskhaler and the Diskus is only 5% for the batches used for the additional experiments (figure 6.9), compared to 10% for the batches used for figure 6.8. This confirms a batch to batch variation in powder formulation. Since it is found that the fine particle output from the Diskus is higher than for the Diskhaler, for both batches, it seems reasonable to assume that there also exits an effect of inhaler design on fine particle output. The first stage deposition in figure 6.9 and the obtained carrier residues are in good agreement. It shows that the fraction not detached decreases with increasing drug load. However, a lower carrier residue does not guarantee a higher fine particle output, as there may be a shift from 3rd and 4th stage deposition towards mouthpiece, inlet tube and blister accumulation (figure 6.9).

![Figure 6.9: Comparison of the amount of drug deposited on the four different impactor stages, inlet tube, mouthpiece and Rotadisk as a percentage of the nominal dose for two batches of the Diskus 250 µg, two batches of the Diskhaler 250 µg and one batch of the Diskhaler 500 µg. Cascade Impactor analysis was performed at 60 l·min⁻¹ with a FIR₂₀-₈₀% of 6 l·s⁻².](image)

The results, as shown in figure 6.9, demonstrate a difference in fine particle output for the two batches of Diskus, as well as for the Diskhaler. The difference in fine particle output between both DPI’s of 10% of the nominal dose is now only 5% of the nominal dose (figure 6.9). As a
result of this comparison between the Diskhaler and the Diskus it might be concluded that the differences in fine particle output depend on the drug load on the carrier crystals, inhaler design parameters, as well as batch to batch variation in powder formulation.

Fine particle output from the spherical pellet type inhaler, the Turbuhaler, is higher compared to the adhesive mixture type inhalers as the Diskhaler, Diskus and Cyclohaler. These high differences in fine particle output are mainly the result of different inhaler designs, and used types of drug formulation. Break up forces, necessary for the disintegration of spherical pellets are generally more effective than the removal forces acting on the fine particles attached to the carrier crystals in adhesive mixtures.

It is shown that in vitro fine particle output depends on the shape of the inhalation curve, especially for DPI’s, which are sensitive to the FIR$_{20-80\%}$. The results may also explain the variation in fine particle output from the same type of DPI at the same PIF, as reported by various authors$^{2, 8, 15-20}$, due to the use of different FIR$_{20-80\%}$. For a reliable evaluation of deposition results for different DPI’s it is recommended to specify the inhalation curve not only by PIF through the inhaler, but also by FIR$_{20-80\%}$ and inhalation time used. These specifications should be given for in vitro as well as in vivo evaluation of DPI performance.

### 6.4 Conclusions

Dry powder inhaler performance depends on type of drug formulation, the peak inspiratory flow (PIF) as well as the flow increase rate (FIR$_{20-80\%}$). Therefore, DPI’s are better described as breath-controlled inhaler devices instead of breath-actuated inhaler devices. In this study, the inhaler performance of four corticosteroid DPI’s is investigated. The used ranges of PIF and FIR$_{20-80\%}$ values are based on attainable flow curves by healthy subjects, asthmatics and COPD patients (chapter 3 and chapter 4). The fine particle output of the Turbuhaler is the most sensitive to the PIF and the FIR$_{20-80\%}$. On the other hand, this type of inhaler also exhibits the highest fine particle output. The fine particle output for the Diskhaler, Diskus and Cyclohaler also varies with the PIF and the FIR$_{20-80\%}$, although variations are relative small.

Fine particle output from the different DPI’s depends on the inhaler design, as well as on the type of drug formulation. Because the fine particle output from DPI’s depends on several parameters of the inhalation curve, it is recommended to specify the inhalation curve more extensively by PIF through the inhaler, FIR$_{20-80\%}$, and inhalation time used.

There are large differences in fine particle output between the investigated DPI’s. These differences should be taken into account when changing the prescription of the inhaler device. For the tested inhalers it should be recommended to patients to inhale forcefully and deeply through the DPI to obtain the highest fine particle output.
6.5 Acknowledgements

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6.6 References


9. A.H. de Boer, H.W. Frijlink. Description of a modular inhaler adapter concept for (Sympatec) laser diffraction characterisation of the aerosol cloud emitted by inhalation systems. *Internal report (University of Groningen (RuG), Pharmaceutical Technology and Biopharmacy)* 1999;AH990601.CON.


6.7 Appendix to chapter 6: Technical drawings

Figure 6.10: Speed adjustable three-way valve for adjusting the flow increase rate during cascade impactor analysis with elevated flow increase rate.

Figure 6.11: Closed inhaler adapter for cascade impactor analysis at higher flow increase rate. Two inner housings are designed, one (top) for the Diskus and the other (bottom) for the Turbuhaler, Diskhaler or the Cyclohaler.