The clinical relevance of dry powder inhaler performance for drug delivery

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KEYWORDS
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Summary
Background: Although understanding of the scientific basis of aerosol therapy with dry powder inhalers (DPIs) has increased, some misconceptions still persist. These include the beliefs that high resistance inhalers are unsuitable for some patients, that extra fine (<1.0 μm) particles improve peripheral lung deposition and that inhalers with flow rate-independent fine particle fractions (FPFs) produce a more consistent delivered dose to the lungs.

Objectives: This article aims to clarify the complex inter-relationships between inhaler design and resistance, inspiratory flow rate (IFR), FPF, lung deposition and clinical outcomes, as a better understanding may result in a better choice of DPI for individual patients.

Methods: The various factors that determine the delivery of drug particles into the lungs are reviewed. These include aerodynamic particle size distribution, the inspiratory manoeuvre, airway geometry and the three basic principles that determine the site and extent of deposition: inertial impaction, sedimentation and diffusion. DPIs are classed as either dependent or independent of inspiratory flow rate and vary in their internal resistance to inspiration. The effects of these characteristics on drug deposition in the airways are described using data from studies directly comparing currently available inhaler devices.

Results: Clinical experience shows that most patients can use a high resistance DPI effectively, even during exacerbations. Particles in the aerodynamic size range from 1.5–5 μm are shown to be optimal, as particles <1.0 μm are very likely to be exhaled again while those >5 μm may impact on the oropharynx. For DPIs with a constant FPF at all flow rates, less of the delivered dose reaches the central and peripheral lung when the flow rate increases, risking under-dosing of the required medication. In contrast, flow rate-dependent inhalers increase their FPF output at higher flow rates, which compensates for the greater impaction on the upper airways as flow rate increases.

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Conclusions: The technical characteristics of different inhalers and the delivery and deposition of the fine particle dose to the lungs may be important additional considerations to help the physician to select the most appropriate device for the individual patient to optimise their treatment.

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Introduction

The mainstay of asthma and COPD treatment is via the inhaled route, medication given either to control inflammation (inhaled corticosteroids [ICS]) or to prevent or reverse bronchoconstriction (β₂-agonist or muscarinic antagonist bronchodilators) [1]. A key advantage of the inhaled route of administration is that lower doses of the required drug can be delivered directly to the site of action, resulting in a rapid clinical response with lower potential for risk of systemic adverse effects compared with other routes of administration [2,3].

Increased understanding of the scientific basis of aerosol therapy has led to the development and introduction of many new inhaler devices, including nebulisers, pressurised metered-dose inhalers (pMDIs) and, particularly, dry powder inhalers (DPIs) [3–5]. Approaches including Adaptive Aerosol Delivery (AAD) [6], the AKITA® inhalation system (Activaero, Germany), which controls the breathing manoeuvre [7] and mist inhalers [8], have utilised and exploited new insights into the relationships between factors such as delivered dose, aerosol particle size, inspiratory flow rate (IFR), lung deposition and clinical effects. These insights have also led to a greater awareness of the importance of choice of DPI to suit the individual patient.

Despite these advances in scientific understanding, a number of misconceptions about inhalers have proved very persistent. These include the belief that the optimal flow rate or pressure drop to operate a DPI is 60 L/min or 4 kPa, irrespective of the inhaler design. Other misconceptions include the role of the inhaler’s internal resistance, the belief that extra fine particles (mass median aerodynamic diameter [MMAD] <1 μm) give improved peripheral lung deposition and the belief that inhalers with flow rate independent particle size distribution produce a more consistent delivered dose to the lungs. However, it is becoming to begin to more widely understood that there is no unique IFR nor pressure drop for optimal use of DPIs. It has also become accepted that higher resistance DPIs can be used effectively, both by COPD patients and by children with an asthma exacerbation, and that they can have several advantages with respect to lung deposition [9–13]. Furthermore, there are good theoretical arguments (with experimental support) to question the benefit of extra fine (<1 μm) particles and flow rate independent aerosol delivery [14]. And finally, lung deposition is not always improved by inhaling faster or more forcefully [15].

Despite the many recent advances and innovations, inhalation therapy is also still associated with poor adherence and many patients have low levels of ability/dexterity or poor breath-to-hand co-ordination and so use their inhaler device incorrectly/ineffectively [16,17]. Even with training, there is a high potential for handling errors, particularly when patients are prescribed different types of inhaler concurrently [18]. Patients also develop strong preferences for specific types of inhalers [19–23], which can have an impact on adherence, particularly if they are switched to a different inhaler type [24]. Switching inhaler device, particularly if the decision is made without consultation, is not recommended [25]. Care should also be taken even when switching among the same type of inhaler — for example a DPI — because different levels of asthma control are achieved even when delivering the same drug [26].

In an effort to reduce the impact of inevitable handling errors, research has been done to produce inhalers that are less dependent on the user for delivery of the optimum dose [27]. In this regard, the performance and specific design characteristics of a DPI, such as the delivered particle size distribution and their internal resistance, have been shown to be important from a clinical perspective, in that they can be modified to minimise the influence of the patient’s IFR on the deposition pattern and dose [3,4,16].

The aerosol particle size distribution is known to be one of the main factors influencing the deposition pattern of a drug in the lungs. Historically, the optimal aerodynamic particle size range for deposition in the lung was thought to be <5 μm. The mass fraction of the dose emitted in this size range by a particular inhaler is often referred to as the fine particle fraction (FPF) [28]. The factors determining the FPF generated by a DPI are complex and interrelated [29].

The aims of this article are to clarify the complex interplay between inhaler design and resistance, inspiratory flow manoeuvre, FPF and lung deposition, and to highlight the clinical relevance of this interplay, in terms of effectiveness and outcomes.

Particle size matters

Aerodynamic particle size distribution, in combination with the inspiratory manoeuvre and airway geometry, determines the penetration of drug particles into the airways and deposition on the walls of the airways — and this determines the dose delivered to the target site [13,16,30–33]. Three basic principles are the main determinants of the site and extent of deposition — inertial impaction, sedimentation and (to a lesser extent) diffusion (Fig. 1) [29,30,34]. Particles that are not deposited are exhaled again.

At higher IFRs, most particles >5 μm in diameter will impact on the oropharynx and in the first airway bifurcation. Particles deposited on the oropharynx will be
swallowed, potentially contributing to a reduction in efficacy and local oropharyngeal or systemic effects. This was demonstrated by Usmani and colleagues in a randomised, double-blind, placebo-controlled clinical efficacy study in 12 patients with stable mild-to-moderate asthma quantifying deposition with salbutamol aerosols of different particle size (either 1.5, 3 or 6 μm MMAD) at two different flow rates (31 or 67 L/min) [35]. The study demonstrated that deposition fractions of smaller particles (1.5 and 3 μm) in the central and peripheral airways are much higher than those of larger (6 μm) particles, particularly at the higher IFR (Fig. 2) [35]. By extrapolation of data from this study, it can be derived that particles of ≤1 μm have a greater than 40% chance of being exhaled again (both flow rates) due to their low settling velocity, in spite of a short breath-hold period. Bronchodilation (measured as change in forced expiratory volume in 1 s [FEV1]) following administration of salbutamol significantly decreased with particle size at the higher IFR [35]. Bronchodilation with the 1.5 μm particles was unaffected by IFR. Oropharyngeal deposition increased for all particle sizes at the higher IFR, but this was significantly greater for the larger particles (p < 0.001). These findings highlight the dynamic interaction between FPF and IFR and show that this translates into clinical outcomes, i.e. decreased lung deposition and increased oropharyngeal deposition with the higher IFR for large particle sizes results in a reduced bronchodilator effect (Fig. 3) [35]. The Usmani study used monodisperse aerosols (geometric standard deviation < 1.22) and similar effects may be expected for aerosols from DPIs with the same MMAD, although they may have slightly wider size distributions.

Although, historically, the optimal aerodynamic particle size range for deposition in the lung was thought to be < 5 μm, basic physics, deposition modelling and also in vivo deposition studies (e.g. Usmani et al. [35]) indicate that particles smaller than 1.0 μm are undesirable because of their extremely low settling velocity [29]. Because the settling velocity increases with the square of the particle radius, this means that particles smaller than 1 μm have a low likelihood of reaching the lung, even at high flow rates.

Figure 1 Dominant particle deposition mechanisms in the respiratory tract and effect of particle size on the likelihood of particle penetration and deposition in the airways.

Figure 2 Effect of different inspiratory flow rates (31 or 67 L/min) on lung deposition for three different sizes of particle (1.5, 3.0 or 6.0 μm). Adapted from Usmani et al. (2005) [35].

Figure 3 Clinical effects of relationship between inspiratory flow rate (slow [31 L/min] and fast [67 L/min]) and particle size for monodisperse salbutamol aerosols in 12 patients with stable mild-to-moderate asthma [35]. FEV1, forced expiratory volume in 1 s; ns, not significant.
diameter, the probability of deposition by sedimentation increases rapidly when the particle diameter is increased. For 1.5 μm particles, the time to travel the same distance by falling is 2.25 times shorter than that for 1 μm particles. Also, the chance of inertial deposition in the larger airways increases with increasing diameter, but for particles of approximately 1.5 μm, the oropharyngeal deposition is still low and widely flow rate independent [35]. Therefore, particles of 1.5 μm are more appropriate than <1.0 μm particles and the optimal size range for inhalation seems to be 1.5–5 μm rather than <5 μm.

Drug distribution and concentration in the whole lung

For aerosols from DPIs a reasonably equal distribution (1:1:1) of the total lung dose has been found between the upper (conducting), intermediate (transitional) and lower (peripheral) airways [33,36]. Usmani et al. reported comparable lung distributions for 1.5–3 μm particles inhaled at 30–67 L/min: about two-thirds of total lung dose was deposited in the central plus intermediate and one-third in the peripheral airways (Fig. 2) [35]. This seems to be in fair agreement with the lung distribution from DPIs, although the definitions for central, intermediate and peripheral lung may have been different. However, due to the exponential increase in airway surface area towards the alveoli, so that over 95% of lung surface area is within peripheral airways, the actual concentration for a given dose of drug is significantly higher in the conducting airways than the respiratory airways [33,37]. Differences in average concentration between the conducting and peripheral airways for a 1:1:1 deposition ratio may approach a factor of 100. Deviations from the 1:1:1 ratio in the deposition pattern do not really level out this extreme concentration difference. Even for a ratio of 1:2:3 in favour of a much higher peripheral deposition, which is difficult to achieve in practice with pMDIs and DPIs, the average concentration difference between conducting and peripheral airways is still a factor >30. At the clinical level, this may be highly relevant for drugs that need to particularly target the smaller airways, like corticosteroids, or that need to be more evenly distributed over the entire lung, like antibiotics. Only for bronchodilators has this concentration gradient been considered less relevant so far. Although β₂-agonists and anticholinergics target autonomic receptors on the airway smooth muscle of large and small airways [38], cholinergic activity of the lung is most pronounced in the large airways [39]. Additionally, the amount of smooth muscle gradually decreases from the bronchioles towards the alveoli. Therefore, targeting the larger airways with bronchodilators has been the objective until now. However, several studies are currently underway to investigate the contribution of small airways to asthma and COPD. Recently, it has been proposed that muscarinic receptors may have a much greater role in the pathophysiology of obstructive airway diseases than previously thought [40]. Drugs like tiotropium may potentially inhibit airway inflammation and remodelling [41], whereas for aclidinium an important role in inhibiting fibroblast–myofibroblast transition has been reported, which is a key step in peribronchiolar fibrosis formation [42]. For these reasons, and also to achieve the desired synergistic effect with ICS, achieving high drug concentrations in the central and peripheral lung may become a future challenge for anticholinergic bronchodilators too. However, a balance must be achieved on particle size, because any drug capable of reaching the alveoli is more likely to be absorbed into the circulation and increase the potential for adverse systemic effects [29].

Flow rate: dependence or independence?

DPIs fall into two main classes — according to whether their FPF output is dependent on, or independent of, the user’s IFR [13,16,29,30]. Fig. 4 shows that the percentage of ICS fine particles <5 μm from the (Pulmicort® and Symbicort®) Turbuhaler® and the (Budelan®) Novilizer® inhaler increases at higher IFR, while for the (Seretide®) Diskus®, budesonide Cyclohaler® and (Rolenum®) Elpenhaler®, the percentage is relatively unchanged at different IFRs. It has to be borne in mind that pharmaceutical companies may use different definitions for their label claims, which blurs any performance comparison between devices. Some companies take the weighed drug amount as reference for their label claim whereas others base their label claim instead on the average drug mass released from the mouthpiece.

Whilst an inhaler that produces a consistent percentage of FPF <5 μm independent of the IFR of the patient may appear at first sight to be the best way to ensure reproducible lung deposition, the reality is quite the opposite. An IFR-dependent inhaler produces an increased FPF <5 μm at
higher IFR — thus compensating for the shift in deposition towards larger airways due to increased inertial impaction in the oropharynx and first airway bifurcation [29,30,33,36,43–48], which otherwise reduces deposition in the peripheral respiratory airways of the lung at higher IFRs. The compensation should ensure that a relatively constant dose is delivered to where it is needed in the lung regardless of IFR. An example of the difference in lung deposition between constant and IFR-dependent FPF is given in Fig. 5 for a comparison between the Diskus® and Novolizer®. Based on the data from an in vitro deposition study and by making use of deposition probability equations for particles in the delivered size range, the proportions of this FPF that are deposited in the upper airways and central plus peripheral airways, respectively, can be assessed, as a function of the inspiratory flow rate [30].

IFR-independent inhalers, such as the Diskus®, produce a constant percentage of FPF over a wide range of IFRs, but, at higher IFRs, significantly reduced amounts of the constant fine particle dose actually reach the peripheral airways. The decrease in computed dose reaching the peripheral airways with this IFR-independent inhaler is from 6.7% to 2.2% (Fig. 5A) [30]. Clinically, this means that patients with higher or variable IFRs using IFR-independent inhalers risk under-dosing, particularly with ICS therapies, which, unlike the fast-acting bronchodilators, do not give immediate response feedback to the patient so that they can tell whether their inhalation was insufficient and repeat the procedure if necessary [49]. In contrast, with increasing percentage FPF at higher IFR, the computed peripheral lung dose from the Novolizer® varies from 6.3% to 10.8% (Fig. 5B). These computed values are in good agreement with the data from a lung deposition study in healthy volunteers with radiolabeled budesonide aerosols from the Novolizer® yielding peripheral lung depositions of 6.5% (at 45 L/min), 7.8% (60 L/min) and 8.5% (90 L/min), respectively [36].

**Meeting resistance**

Drugs for inhalation by DPI in the treatment of asthma and COPD therapy are supplied in one of two forms, either as a so-called adhesive mixture or as soft spherical agglomerates, referred to as pellet formulation (Fig. 6). In adhesive mixture formulations, the micronised drug particles are distributed over the surface of coarse carrier particles by natural adhesion. Pellet formulations may consist of pure

![Figure 5](image1.png)

(A) Flow-rate independent inhalers such as Diskus® provide a decreasing dose to the central and peripheral airways as air flow rates (pressure drops) increase, whereas (B) flow-rate dependent inhalers such as Novolizer® maintain their lung deposited dose as air flow rates (and pressure drops) increase [29,30,47].

![Figure 6](image2.png)

Figure 6 Scanning electron micrographs of (A) adhesive mixture and (B) soft spherical agglomerates/pellets.
drug particles or a mixture of drug particles with a micronised excipient. In both examples, the excipient is usually lactose, which is used to dilute the drug and improve the flow properties to assist reproducible dosing to the patient. Adhesive mixtures and pellet formulations consist initially of particles that are too large to penetrate the patient. Adhesive mixtures and pellet formulations improve the flow properties to assist reproducible dosing to usually lactose, which is used to dilute the drug and frictional forces, which break down the pellet formulations into primary particles or detach drug particles from the carrier surface [30]. Optimal utilisation of the kinetic energy to generate de-agglomeration forces requires design features that largely determine the inhaler resistance to air flow. Such features can, for instance, be turbulent shear zones (creating drag and lift forces) or whirl and circulation chambers containing impact bodies. Inhalers with highly effective de-agglomeration principles are more likely to have a higher air flow resistance and provide greater lung deposition than those with a low internal resistance [16,37,50].

<table>
<thead>
<tr>
<th>Table 1A</th>
<th>Review of some corticosteroid (ICS) delivering DPs.</th>
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<tbody>
<tr>
<td>Inhaler</td>
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<td>FLU</td>
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<tr>
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<tr>
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<td>Foster NEXThaler</td>
<td>BDP</td>
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<tr>
<td>Asmanex Twisthaler</td>
<td>MOM</td>
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</table>

FPF as percent of label claim, unless stated otherwise.

<sup>a</sup> Defined as: high (IFR at 4 kPa < 45 L/min, medium/high (IFR at 4 kPa between 45 and 60 L/min); medium/low (IFR at 4 kPa between 60 and 80 L/min) and low (IFR at 4 kPa > 80 L/min). BUD, budesonide; BDP, beclomethasone (dipropionate); DPI, dry powder inhaler; FLU, fluticasone (propionate); FPF, fine particle fraction; ICS, inhaled corticosteroid, IFR, inspiratory flow rate; IND: indacaterol (maleate); SAL, salmeterol (xinafoate); TIO, tiotropium (bromide).

<table>
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<th>Table 1B</th>
<th>Review of some bronchodilator (BD) delivering DPs.</th>
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<td>Defined as % FPF</td>
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<tr>
<td>Spiriva HandiHaler</td>
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FPF as percent of label claim unless stated otherwise.

<sup>a</sup> Defined as: high (IFR at 4 kPa < 45 L/min, medium high (IFR at 4 kPa between 45 and 60 L/min); medium low (IFR at 4 kPa between 60 and 80 L/min) and low (IFR at 4 kPa > 80 L/min). ACC, aclidinium (bromide); BD, bronchodilator; DPI, dry powder inhaler; FOR, formoterol (fumarate dihydrate); FPF, fine particle fraction; GB, glycopyrronium (bromide); IFR, inspiratory flow rate; IND: indacaterol (maleate); SAL, salmeterol (xinafoate); TIO, tiotropium (bromide).
Generally, effective utilisation of the available energy for de-agglomeration results in an increasing FPF with increasing IFR. The clinical relevance of the internal resistance of an inhaler refers not only to a higher proportion of FPF dose achieved at the same inspiratory effort and a compensating increase in FPF at higher IFR. Resistance also has an impact on the site of deposition of drug particles in the respiratory tract. High-resistance inhalers reduce the maximal attainable flow rate, which equals the quotient of the square root of the pressure drop achieved (given in kPa) and the inhaler resistance (in kPa0.5 min L−1), thus reducing oropharyngeal deposition. Inhaling against a high resistance furthermore opens up the oropharynx and vocal cords, providing a wider passageway for the aerosol and increasing total lung dose [37].

Most inhalers deliver FPFs between 20% and 30% of the label claim at pressure drops between 2 and 4 kPa (Fig. 4A). For inhalers that deliver more or less the same amount of FPF over the entire range of attainable pressure drops (>2 kPa), higher pressure drops (corresponding with higher flow rates) are not desirable, because this is at the cost of total (in particular central and peripheral) lung deposition due to increased losses in the oropharynx at the higher flow rates. DPIs with IFR-independent FPF generation are frequently low-resistance devices, which facilitate the generation of higher IFRs. For instance, the increase in flow rate between 2 and 4 kPa through a high-resistance inhaler like the HandiHaler® is only from 28 to 39 L/min versus 57–106 L/min for the low-resistance Aerolizer®. In contrast, DPIs delivering a higher FPF with increasing IFR are frequently high-resistance devices. Fig. 4B compares the flow rates at which FPF <5 μm reaches the value of 25% of label claim for the inhalers presented in Fig. 4A. The difference is between 36.4 L/min for the medium/high-resistance Symbicort® Turbuhaler® and 82.2 L/min for the low-resistance Cyclohaler®. On the basis of the impact parameter (based on flow rate) as predictor for inertial impaction, this might give a 2.25 times higher chance of oropharyngeal impaction for the same particle size for the low-resistance device. For the Diskus®, Clickhaler® and Elpenhaler® FPF values of 25% of label claim were not obtained at any flow rate with the devices used to produce Fig. 4A. Attaining a pressure drop of 2–4 kPa — which is sufficient to operate most inhalers successfully and results in clinically effective drug delivery — is easier when using a high-resistance inhaler than when using a low-resistance device, independent of the type and severity of the disease [13,31,50]. Even during exacerbations of asthma and COPD, patients are able to achieve the required pressure drop and the performance of an inhaler with a higher resistance is less influenced by the underlying degree of bronchoconstriction than with a low-resistance inhaler [31]. Also, young children and adult patients with severely impaired lung function generate sufficiently high pressure drops to enable them to use IFR-dependent higher resistance inhalers such as the Turbuhaler® and Novolizer® effectively [13,31].

The ideal dry powder inhaler?

Determining the best inhaler is dependent on the circumstances and characteristics of each patient, so may vary in different clinical settings. However, based on the considerations discussed above and balancing the requirements of a broad range of patients, the ideal DPI device would have the following characteristics: a high and consistent IFR-dependent FPF (contributing to consistent central and peripheral lung deposition regardless of IFR) and a medium to high internal resistance to limit the IFR and minimise loss of the FPF dose in the oropharynx. In addition, the inhaler should be easy for patients to learn and maintain correct usage and small enough to be convenient to carry around or store, to minimise incorrect use and maximise adherence to the therapy [16]. Table 1 shows how some of the widely used inhalers measure up to these requirements. Originator devices like the Turbuhaler® and Novolizer® deliver a high FPF (1–3 μm) to the central and peripheral airways, where the medication being delivered (either bronchodilator or anti-inflammatory ICS) is generally most needed, up to 40% or more of the label claim at the flow rate corresponding with 6 kPa [29,30,33,43–46]. In contrast, some generic inhalers like the Elpenhaler® deliver more or less the same low FPF of <20% at all flow rates.

Conclusions

There are a growing number of dry powder inhalers available and these differ greatly in their design, technical characteristics and other individual features. Some inhalers have characteristics that mean they are likely to work for a variety of patients, which may provide a certain level of convenience for physicians. However, there are many factors to consider when selecting the optimal inhaler for patients with asthma or COPD. Apart from the type of drug inside the inhaler, the level of clinical evidence for its efficacy and safety, doctor and patient preferences, the technical characteristics of the different inhalers and the delivery and deposition of the fine particle dose to the lungs may be important additional considerations to help the physician to select the most appropriate device for the individual patient to optimise their treatment.

Conflict of interest statements

Pascal Demoly is a consultant and a speaker for Staller-genes, ALK, Circassia and Chiesi and was a speaker for Merck, AstraZeneca, Menarini and GlaxoSmithKline.

Paul Hagedoorn receives royalties from Almirall and Meda (Genuair and Novolizer sales) and is a speaker for AstraZeneca.

Anne de Boer receives royalties from Almirall and Meda (Genuair and Novolizer sales) and is a speaker for AstraZeneca.

Hendrik W. Frijlink’s employer has a royalty agreement regarding the Novolizer and the Genuair and he has been a speaker for AstraZeneca and Meda.

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