The ideal inhaler: design and characteristics to improve outcomes

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Summary Inhalation therapy is likely to continue to dominate asthma treatment. The pressurised metered dose inhaler (pMDI) accounts for most of the inhaler market world-wide, but is inefficient and difficult to use. Dry powder inhalers (DPIs) have several advantages over MDIs. They are breath-activated, easy and convenient to use and environmentally friendly. The Turbuhaler® is the most widely used DPI, offering good deposition with sufficient inspiratory flow, but it provides no confirmation of dosing, exhibits high dose variation, has a high intrinsic resistance, and inspiratory flow profile-dependent drug deposition. The Novolizer® (VIATRIS, Frankfurt, Germany) is a new DPI which has several characteristics of an ‘ideal’ inhaler. It is convenient and easy to use, demonstrate and teach, provides accurate and consistent drug delivery and provides patients with feedback of dose taken. The Novolizer® is a promising new delivery system for inhalation therapy.

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INTRODUCTION

The goals of asthma therapy are to minimise exacerbations, to alleviate symptoms and to control inflammation. Successful management depends on adequate delivery of medication, particularly controller therapy, to target sites within the lung. However, most patients cannot use their inhalers correctly, and many are non-compliant with their treatment regimens. There are several reasons why patients do not comply with therapy. In order to facilitate compliance we should keep treatments simple, persuade patients of treatment effectiveness, minimise dosing regimens, but most important of all, ensure that patients can use their inhalers correctly. Delivery of drugs by inhalation has dominated asthma therapy for more than 30 years, and will likely continue to do so for the next 10–15 years. It is essential that we identify all of the characteristics of an inhaler device that could optimise delivery of drug, not just to the large but also to the small airways.

MDIs versus DPIs

Pressurised metered-dose inhalers (pMDIs) have been the dominant means of delivery of drug to the lungs for the last 30 years, and world-wide, they still constitute more than 80% of the global market. However, they have a number of disadvantages both in terms of effectiveness and usability. The most prescribed MDIs are inefficient and are not user friendly. Typically, they deliver only about 1/3 of the amount of drug to the lungs compared with the newer dry powder inhalers (DPIs). Table 1 summarises several studies which investigated lung deposition achieved with pMDIs and with DPIs.

Abbreviations: CFC, chlorofluorocarbon; DPI, dry powder inhaler; HFA, hydrofluoroalkane; pMDI, pressurised metered dose inhaler

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Results for MDIs showed that between 8–16% of the metered dose was deposited in the lungs. DPIs fared slightly better. The old fashioned Spinhaler\(^\text{R}\) showed lung deposition rates between 7% and 20% compared to approximately 12% for the Diskhaler\(^\text{R}\) (GlaxoSmithKline, UK), which was one of the early DPIs. Most of the deposition studies have been done with the Turbuhaler\(^\text{R}\) (AstraZeneca, UK) which deposits between 10% and 30% of the metered dose into the lungs. A new DPI, the Novolizer\(^\text{R}\) (VIATRIS, Frankfurt, Germany) shows lung deposition of 32%.

MDIs require good co-ordination between dose activation and inhalation in order to ensure correct inhalation and deposition of the drug into the bronchial tree. Misuse of pMDIs, which is mainly due to poor co-ordination, is frequent and associated with poorer asthma control in inhaled corticosteroid-treated patients with asthma.\(^3\) Pressurised MDIs also require an optimal inspiratory flow, a full inspiration from functional residual capacity and a breath hold of at least 6 s.\(^4\) Therefore, correct use of these inhalers requires intensive training by the physician and regular technique re-testing may also be necessary.\(^5\) For example, some MDIs require shaking before use in order to thoroughly mix drug and propellant; users often forget this which makes drug delivery unreliable. As many as 90% of patients cannot use their MDI correctly.\(^6\) Common mistakes include failure to continuously inhale slowly after activation of the inhaler, failure to exhale fully before the inhalation,\(^7,8\) activation the inhaler before inhalation or at the end of inhalation and concluding inhaler activation while holding breath.\(^8,9\)

Deposition rates with MDIs depend on inhalation technique.\(^9\) MDIs can be used with a spacer device to improve drug deposition in the lungs, but this device is very bulky. However, use of an MDI without a spacer device results in high deposition of the therapeutic agent in the mouth and pharynx.\(^10\) It is worth noting that there are significant differences in dose output from different combinations of MDIs and spacers.\(^11\) In addition, MDIs require priming if they haven’t been used for a lengthy period of time, have no inhalation control mechanism or dose counter and contain propellants which are not environmentally friendly (e.g. chlorofluorocarbons, CFCs). These are being phased out due to their depletion of atmospheric ozone layers.\(^12\) The replacement for CFCs, hydrofluoroalkanes (HFAs), do not destroy ozone layers, but are known to be up to 2000 times more potent greenhouse gases than carbon dioxide. Lubricants and CFCs in MDIs may cause bronchoconstriction\(^13\) and can blast the back

### Table 1 Summary of studies which investigated lung deposition achieved with pressurised metered dose inhalers and dry powder inhalers.

<table>
<thead>
<tr>
<th>Device</th>
<th>Substance</th>
<th>Lung deposition (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metered dose inhalers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDI</td>
<td>Terbutaline</td>
<td>9.1</td>
<td>Borgstrom and Nilsson(^\text{26})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.7</td>
<td>Newman et al.(^\text{27})</td>
</tr>
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<td></td>
<td></td>
<td>8.2</td>
<td>Borgstrom et al.(^\text{28})</td>
</tr>
<tr>
<td>MDI</td>
<td>Budesonide</td>
<td>15.0</td>
<td>Thorsson et al.(^\text{14})</td>
</tr>
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<td><strong>Dry powder inhalers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinhaler(^\text{R})</td>
<td>DSGC</td>
<td>10</td>
<td>Richards et al.(^\text{29})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.2</td>
<td>Neale et al.(^\text{30})</td>
</tr>
<tr>
<td>Rotahaler(^\text{R})</td>
<td>DSGC</td>
<td>9.0</td>
<td>Vidgren et al.(^\text{31})</td>
</tr>
<tr>
<td></td>
<td>Salbutamol</td>
<td>9.1</td>
<td>Zainudin et al.(^\text{32})</td>
</tr>
<tr>
<td>Easyhaler(^\text{R})</td>
<td>Salbutamol</td>
<td>24.0</td>
<td>Vidgren et al.(^\text{33})</td>
</tr>
<tr>
<td>Diskhaler(^\text{R})</td>
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<td>11.4</td>
<td>Melchor et al.(^\text{34})</td>
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<td></td>
<td></td>
<td>58</td>
<td>19.0–22.0</td>
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<tr>
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<td>32</td>
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<td></td>
<td></td>
<td>36</td>
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<td></td>
<td></td>
<td>58.1</td>
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</tr>
<tr>
<td>Novolizer(^\text{R})</td>
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<td>45</td>
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<td>25.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>32.1</td>
</tr>
</tbody>
</table>

DSCG: disodium chromoglycate; PIF: peak inspiratory flow; MDI: metered dose inhaler.
of the throat stopping the patient from inhaling (the 'cold freon' effect).

DPIs, as a class of delivery device, have numerous advantages over pMDIs. They are breath activated, precluding the need for the patient to coordinate actuation with inhalation. This assists the effective drug delivery to the lungs. Indeed, Thorsson and colleagues\textsuperscript{14} showed that in healthy volunteers lung deposition of budesonide through the Turbuhaler\textsuperscript{16} was over twice that through a pMDI (32\% versus 15\% respectively) (Fig. 1). This result suggests that the same degree of asthma control can be achieved with a lower dose of budesonide using the Turbuhaler\textsuperscript{16}, thus reducing the risk of unwanted systemic effects. Agertoft and Pedersen\textsuperscript{15} showed that DPIs are more effective than pMDIs for the treatment of asthma. Budesonide delivered through the Turbuhaler\textsuperscript{16} produced equivalent clinical improvement compared to double the dose of budesonide delivered through the Nebuhaler\textsuperscript{16} in children with perennial asthma (Fig. 2), indicating that the dose of budesonide should be reduced when patients are switched from Nebuhaler\textsuperscript{16} to Turbuhaler\textsuperscript{16} treatment.\textsuperscript{15}

DPIs also do not contain environmentally unfriendly propellants and do not produce a cold sensation on inhalation. Additionally, patients often express a preference for DPIs. For example, in elderly patients breath-activated inhalers are used correctly and are preferred by patients over conventional MDIs.\textsuperscript{16}

\textbf{Figure 1} Distribution of budesonide deposition delivered by the Turbuhaler\textsuperscript{16} or pressurised metered dose inhaler in healthy volunteers. Reprinted with permission from: Thorsson L, Edsbacker S, Conradson TB. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler. Eur Respir J 1994, 7:1839–1844. GI: gastrointestinal.

\textbf{Figure 2} Efficacy of budesonide delivered by Nebuhaler\textsuperscript{16} or Turbuhaler\textsuperscript{16} in children with perennial asthma ($n = 240$). Reprinted with permission from Agertoft L, Pedersen SE. Budesonide administered via Turbuhaler\textsuperscript{16} and a nebulator. Ugeskr Laeger 1994, 156:4134–4137.
The ideal inhaler

Disadvantages of specific DPIs

There are several DPIs currently on the market or being developed by the pharmaceutical industry. These devices are divided into single dose devices, multiple unit dose devices or multidose devices. The Spinhaler® and Aerolizer® (Novartis) are single dose devices. Doses are individually loaded into gelatine capsules or blisters, each of which is loaded into the inhaler immediately before use. The Diskhaler® and Diskus® (GlaxoSmithKline) are examples of multiple unit dose devices as they contain a series of capsules or blisters. With multidose or reservoir devices the drug is metered from a reservoir of freely flowing powder (e.g. Novolizer®, Turbuhaler®). Although DPIs, as a class of delivery devices, offer both the patient and physician several advantages over pMDIs, individually they do have some limitations of design, cost-effectiveness and user-friendliness.

Single unit dose devices

The Aerolizer® is a modern day Spinhaler®. Limitations of this device include the fact that there is no feedback on deposition. Additionally, high inspiratory flow must be achieved to generate a fine particle fraction. For each inhalation a new capsule needs to be inserted into the device, which does allow for dose counting but is not very convenient, and the inhalation process must be repeated until the capsule is empty. This may give rise to high dose variability. The Aerolizer® is approved for only 50 capsules, and high temperatures can soften capsules making them difficult to perforate.

Multiple unit dose devices

The Diskhaler® was the forerunner of the Diskus®, and is still used to some degree in the UK, although it is complicated to use. An inherent design flaw of this early multiple unit dose device is that blisters must be frequently changed and the device cleaned before refilling. In addition, the device can be used for only 3 months, so it is not very cost-effective. The Diskus® overcame some of these problems, but it contains only 60 doses. It is a more sophisticated device, but unlike the Diskhaler® it is not refillable. In some cases the metered dose is not completely emptied as the patient is not able to inspire fully. The mouthpiece is also not user-friendly, and it is costly to produce because of the level of complexity.

Multidose devices

The Turbuhaler® is the most frequently prescribed DPI as it offers good deposition with sufficient inspiratory flow. However, it does have some disadvantages. For example, there is no feedback to the patient that medication has been successfully delivered. The patient does not taste, smell or even feel the delivered particles of the dose that is inhaled. There is no inhalation control mechanism, the dose counter is limited, there is high dose to dose and device to device variation, and the device is not refillable. The Turbuhaler® also has a high intrinsic resistance, requiring a relatively high inspiratory flow of 60 l/min for optimal drug delivery. This may not be achievable, especially in younger children, elderly patients and other patients with a low peak inspiratory flow rate. Finally, the particle size inhaled is very much dependent on the patients’ inspiratory flow rate, and the amount of drug released from the device is reduced under conditions of high humidity.

The Novolizer®: an ideal inhaler?

Users’ dissatisfaction with pMDIs has led to the concept of an ‘ideal’ inhaler. Discussions with asthma patients (or their parents, in the case of children) and healthcare professionals have led to the following characteristics being drawn up for the ‘ideal’ inhaler: accurate and consistent in effective drug delivery; easy and convenient to use; easy to teach, learn and remember how to use correctly; capable of delivering a range of drugs; accurate dose counter; patient feedback of dose taken; convenient to carry; robust; visually appealing to the patient; easily identifiable in terms of the drug/strength contained in the inhaler; and propellant-free.

The Novolizer®, the multidose DPI from VIATRIS, is a breath-activated, refillable, multi-use inhalation device. Both 100 and 200 dose cartridges are available, and these are offered in sealed containers. It has an innovative design which combines simplicity of use with effective performance; which results in assured drug delivery. As the Novolizer® does not contain propellant it is an ecological and attractive alternative for the administration of a variety of drugs for inhalation. The Novolizer® closely meets the characteristics sought in an ‘ideal’ inhaler. In contrast, the Turbuhaler®, has several characteristics which provide uncertainty both for the patient and the healthcare professional.
The Novolizer® has several innovative features offering unique inhalation control and feedback which give it an advantage compared to other inhalers (Fig. 3). The Novolizer® has a multiple inhalation control system so that for the first time patients and doctors know that the prescribed drug has reached the lungs. The patient receives information as to whether the necessary flow has been achieved, and whether or not the powder has been released—visually and acoustically as well as by taste. Thus, the Novolizer® is easy to use and to teach, as it guides patients through the inhalation procedure. In contrast, the Turbuhaler® provides only limited feedback to the patient, and has a limited dose counter. A novel feature of the Novolizer® is a flow trigger valve system that releases the powder only after a certain flow rate has been achieved (35 l/min).23 This mechanism ensures sufficient drug delivery at the site(s) where it is needed. The Turbuhaler® does not confirm drug deposition as observed for the Novolizer®. The particle size emitted from the Turbuhaler® also depends upon the flow profile generated by the patient.19 In addition, the Novolizer® gives significantly greater lung deposition and less oropharyngeal deposition than the Turbuhaler® when both devices are used optimally with maximal inspiratory effort.2

The quality of the aerosol emitted from the Novolizer® is assured by a helix or cyclone in the mouthpiece.24 The Novolizer® delivers a precise and consistent dose over the cartridge lifetime independent of temperature and humidity, with minimal dosage variability between actuations.24 It is functionally reliable and hygienic in 'real-life' situations.25 This is not the case for the Turbuhaler®. If, for example, the Turbuhaler® is stored at 70% humidity, the amount of drug released from the device is reduced within 2 h and this reduction in dose lasts for up to 4 days.20 Even in the absence of high humidity conditions, there is a high dose to dose and device to device variation with the Turbuhaler®.18

Compared to other DPIs, the Novolizer® is characterised by low to medium airflow resistance and a smooth increase of pressure drop at higher flow rates during inhalation. This makes it easier for the patient to use the device for effective drug dispersion and deposition, and may thus improve compliance. Assuming a mean flow rate of 60 l/min during inhalation, patients have to overcome a resistance 2.5 times higher with the Turbuhaler® compared with the Novolizer®. Flow rates <60 l/min through the Turbuhaler® result in high oral and low lung drug deposition. The Novolizer® may be considered cost effective as it is robust (can be used every day for up to 1 year), is refillable, and

Figure 3 Innovative design features of the Novolizer® which make it an 'ideal' inhaler.
ensures deposition of therapeutic agent into the bronchial tree.

Conclusion

Asthma therapy is optimally given by inhalation. The inhaler device used to deliver this medication is one of the most important factors in asthma management decisions. The Novolizer™ is an innovative DPI with several of the characteristics sought in an ‘ideal’ inhaler, and overcomes many of the problems observed with other DPIs. It is safe, reliable, easy to use and carry, and ensures deposition of the drug into the lungs. The multiple control feedback mechanism gives unique confidence and reassurance that medication has been successfully delivered. These features, as well as patient satisfaction with the device are likely to improve compliance. The cyclone design ensures high quality aerosol release. The low resistance of the device, as well as the relative independence of particle size from flow rate, means that the Novolizer™ is also suitable for patients with more severe airflow obstruction. The Novolizer™ is a cost-effective device as it is refillable and is virtually impossible to use incorrectly. It is a real step forward in the development of DPIs and is a promising new delivery system for inhalation therapy.

References