Pharmacy

General factors influencing drug delivery to the lung

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The first devices to be developed for the delivery of bronchodilators and corticosteroids for the treatment of asthma were the pressurised metered dose inhalers (pMDIs). While pMDIs are viewed as patient friendly, they are associated with some serious disadvantages, such as considerable oropharyngeal deposition (due to the speed of delivery of the dose) and poor patient co-ordination of inhalation and activation. This has resulted in the development of alternative systems, such as the dry powder inhaler (DPI). However, DPIs also have problems, as there are difficulties in handling, measuring and metering fine particles. New devices, such as the Easi-breathe® and Diskus® inhalers, are now being introduced to overcome some of these problems. The ideal device is one that will produce a large proportion of respirable particles in the emitted dose. It must also deliver precise and uniform doses of drug to the patient. Further innovations are required to achieve these goals.

Introduction

When Dr Mark Everard, Consultant Paediatrician at Sheffield Children’s Hospital, addressed the symposium ‘A Question of Asthma’ at the British Pharmaceutical Conference last year, he observed that the dose of a drug reaching the lung bore little relation to the nominal or prescribed dose. The lowest apparently effective dose should, therefore, be used. However, it would be preferable to be able to improve the clinical outcome by improving the precision of the administered drug dose. To achieve this, three interacting factors must be considered: the patient, the formulation, and the device.

The device must accurately meter the drug dose. Since this dose must be satisfactorily delivered during the inspiratory process, the total entrainment of the drug is also important. Finally, all the particles in the delivered dose must be of an appropriate size for deposition.

Pressurised Metered Dose Inhalers (pMDIs)

pMDIs have various advantages, including high market appeal and the energy within the formulation (i.e. the propellant which creates the respirable particles). They are portable and unobtrusive. However, these devices are also associated with some serious disadvantages. As the particles are produced by internal energy they travel very fast, resulting in impaction in the oropharynx and reducing the dose reaching the lung. Furthermore, pMDIs cannot be used for large drug doses. Another disadvantage is poor patient co-ordination (see below). In addition, formulation with non-chlorofluorocarbon (non-CFC) propellants (hydrofluoroalkane; HFA) has also proved to be difficult. For example, some HFA formulations of beclomethasone dipropionate (BDP) use ethanol to solubilise the drug and the end process is atomisation of a solution rather than a suspension stabilised by surfactants (as in most CFC pMDIs). The mean particle size is <2 µm, whereas established CFC formulations (in which the particle size is determined primarily by the extent to which the active ingredient can be milled) have an average particle size of 3 to 4 µm.
TABLE 1. Incidence of patient misuse of pMDIs

<table>
<thead>
<tr>
<th>Reason</th>
<th>Incorrect use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remove cap</td>
<td>7</td>
</tr>
<tr>
<td>Shake inhaler</td>
<td>43</td>
</tr>
<tr>
<td>Breathe out</td>
<td>29</td>
</tr>
<tr>
<td>Position in mouth</td>
<td>29</td>
</tr>
<tr>
<td>Slow inhalation</td>
<td>64</td>
</tr>
<tr>
<td>Actuate at start</td>
<td>57</td>
</tr>
<tr>
<td>Continue to inhale</td>
<td>46</td>
</tr>
<tr>
<td>Hold breath</td>
<td>43</td>
</tr>
<tr>
<td>Exhale slowly</td>
<td>5</td>
</tr>
</tbody>
</table>

These new formulations also produce a very different particle size distribution, with the result that only 50 or even 25 μg of BDP is required compared with 100 μg from conventional pMDIs. In addition, because of the larger proportion of small particles in the HFA BDP formulation, around 20% of the dose from the new formulation is exhaled and there is high alveolar exposure, which does not occur with conventional pMDIs.

Clinicians are very familiar with patient misuse of pMDIs (Table 1). Indeed, many hours are spent counselling patients how to use these devices correctly. While this has resulted in formal, consultative, advisory counselling activities, which will improve the situation with pMDIs, the question of incorrect use remains a problem. Misuse is being addressed with new devices, such as the Easi-Breathe™ inhaler. The aim of this device is to improve the co-ordination between dose generation, which is an intrinsic part of the device, and the inspiration process.

A different principle is used in the Spacehaler®. This device captures large, fast-moving particles within a modified actuator, giving a smaller dose of slow-moving, deeply respirable particles.

Although such developments will help to sustain the future place of pMDIs, the intrinsic disadvantages of these devices have stimulated the development of alternative systems.

Dry powder inhalers (DPIs)

One of the difficulties facing the development of formulations for powder systems is that drugs that are fine enough to deposit within the lung are very difficult to handle, measure and meter. Consequently, such drugs have to go through an aggregation process, which usually involves binding the drug to a carrier, such as lactose. As the material passes through the device during inhalation, a proportion of the drug de-aggregates to create respirable particles (Fig. 1). This proportion is typically quite low (around 10–20%), and there is still significant oropharyngeal deposition, because most of the drug remains associated with large carrier particles. However, DPIs do have one intrinsic advantage in that the de-aggregation process is generated by patient inspiration. There is, therefore, natural co-ordination between generation of the aerosol cloud and inspiration, but the quality of the cloud will depend on the patient.

Some early, but important, work on the delivery of sodium cromoglycate in volunteers using a

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**Fig. 1.** De-aggregation of drug from carrier by passage through a dispersion device to produce the 'dispersed' aerosol. Only a proportion of the drug + carrier is de-aggregated to create respirable particles.
Spinhaler® demonstrated that the dose of drug delivered to the lung is much higher with greater peak inspiratory flow rates (1). Using a Turbuhaler®, Pedersen et al. (2) studied the delivery of terbutaline (250 µg) in children using different inspiration rates. This study showed that clinical response improved as the inspiration rate (and presumably the number of respirable particles) increased. (Fig. 2).

Borgström et al. (3) investigated the clinical relevance of the variability in dose produced from the Turbuhaler®. The variability of the emitted dose was much higher with the Turbuhaler® than with the pMDI (Table 2), which produces very precise doses. Despite this, the Turbuhaler® resulted in much higher pulmonary availability than the pMDI (19.5 vs 6.3% of nominal dose). Thus, the basic principle of generating the aerosol cloud by the inspiration profoundly affected the clinical efficacy of the two devices. Unlike the pressurised system, the DPI is therefore capable of important refinement. This study also showed that there were improvements in intra- and inter-patient variability with the powder inhaler compared with the pMDI (3), arising from the co-ordination of dose generation and inspiration.

Early examples of powder inhalers include the Spinhaler®, Rotahaler® and Berotec® inhaler. The simple pre-metered DPI, such as the Spinhaler®, uses a capsule. While such devices have some advantages, such as good dose uniformity, compact size, dose protection, no dose size limitation (20–30 mg can be given, if necessary) and low cost, they are not very patient friendly.

An important development in the use of powder inhalers is the reservoir DPI, for example, the Turbuhaler®. Reservoir DPIs are much closer in concept to pMDIs. However, reservoir DPIs also have disadvantages, including problems with dose uniformity, complexity and cost. They are also moisture sensitive and are generally dose limited by the size of the reservoir.

There is, therefore, an interesting balance between pre-metered and reservoir dry powder systems, and the best aspects of both have been incorporated in the Diskus® (the Accuhaler® in the UK and some other countries). This device maintains the advantages of the pre-metered system while incorporating multiple doses. One important aspect of DPIs is dose protection. It is extremely difficult to protect powders in device reservoirs as they are particularly susceptible to humidity, but the Diskus® has overcome this problem, the doses being factory dispensed in sealed blisters.

The ideal inhaler

The ideal inhaler is a device in which at least 80% of the emitted dose consists of respirable particles. It must also deliver precise and uniform doses of the drug to the patient.

Formulation

In refining a formulation, process conditions, carrier size, drug:carrier ratio, and tertiary components can

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**Table 2. Insulin bioavailability is dependent on regional deposition in the lung.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species (number)</th>
<th>Penetration index (P:C)</th>
<th>t&lt;sub&gt;max&lt;/sub&gt;(min)</th>
<th>F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colthorpe et al. (4)</td>
<td>Rabbit (4)</td>
<td>0.3</td>
<td>11</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.5</td>
<td>12</td>
<td>57</td>
</tr>
<tr>
<td>Pillai et al. (5)</td>
<td>Rhesus monkey (6)</td>
<td>1.6</td>
<td>10–20</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.1</td>
<td>10 20</td>
<td>Approx. 100</td>
</tr>
</tbody>
</table>

Abbreviations: P=peripheral; C=central; t<sub>max</sub>=time to maximum plasma concentration; F=bioavailability.
be altered, and surfaces modified. A recent example is the ‘passivation’ of a carrier substrate surface. The theory of adhesion of small particles to large particles suggests that there are areas of high and low activity, and in this case, leucine is added as an adhesion-modifying tertiary component. This greatly enhances the ability of the energy from the patient’s inspiration to displace active drug particles, thus increasing the effective dose.

There may, however, be limitations in the way in which formulations can be improved to generate efficient devices. There may be a future for DPIs in which the energy for de-aggregation is built into the device. One of the most advanced devices of this type is the Dura Spir@ inhaler, which uses electronic/mechanical means to generate the cloud and co-ordinate inspiration with operation.

Drug
Clearly, the drug is a very important factor influencing delivery to the lung. Its size, surface morphology and adhesiveness can be controlled by refined fluid energy milling, spray drying and other novel techniques. The method by which fine particles are produced for pulmonary delivery is a major limitation of the efficacy of formulations and devices. Nevertheless, the range of techniques available offer different methods for producing particles of appropriate sizes and surface characteristics. As a result, much remains to be achieved with DPIs before their full contribution to pulmonary delivery is realised; this contrasts with pMDIs, which appear to be more fully developed. It will be interesting to see if this proves to be the case, particularly as new HFA formulations are introduced.

Other devices
Alternative device technologies are also being developed. It is generally accepted that it is easier to sub-divide a liquid than a solid into very fine particles. Traditionally, this has been achieved using nebulisers, which have their own place in clinical practice. Nebulisers have the advantage that the particles are entrained at the speed of respiration, resulting in efficient delivery. However, many uncertainties surround the performance of nebulisers and at present, fine particle dose is determined by the particular nebuliser and its operation. Further key developments are anticipated.

One such development is the AER@ dosage form, which nebulises a liquid by forcing it, under pressure, through an array of fine holes to produce a fine spray with a carefully controlled particle size. The Bineb® device uses a similar process. At present, most effective systemic delivery using the pulmonary route, based on new technologies, are being derived from nebuliser systems. Studies with such innovations have shown the importance of regional deposition and distribution pattern, i.e. penetration index, the ratio of peripheral to central deposition (Table 2). Finer particles result in much deeper lung penetration, as reflected by the change in the penetration index (4,5). Comparison of blood levels after pulmonary delivery with those following either subcutaneous or intravenous administration showed that systemic availability depended on the penetration index and that almost total systemic availability was possible. This suggests that if the precision of pulmonary delivery is radically improved, greater exploitation of the concept of targeting drugs to the lung becomes possible.

References