

REVIEW ARTICLE

The Diskus™: a review of its position among dry powder inhaler devices

H. Chrystyn

OnlineOpen: This article is available free online at www.blackwell-synergy.com

Department of Clinical Pharmacy, School of Pharmacy, University of Bradford, Bradford, UK

Correspondence to:

H. Chrystyn,
Department of Clinical Pharmacy, School of Pharmacy, University of Bradford, Bradford BD7 1DP, UK
Tel.: + 44 1274 233495
Fax: + 44 1274 236490
Email: h.chrystyn@brad.ac.uk

Disclosures

The author has been a consultant to and received grants to attend conferences and educational meetings from numerous companies in the Pharmaceutical Industry that market inhaled products including GlaxoSmithKline. The author's research group has also received funds from many of these pharmaceutical companies to carry out research. The author has no personal shares with any pharmaceutical company.

SUMMARY

The use of dry powder inhalers (DPIs) to administer treatments for respiratory diseases has increased significantly in recent years. There is now a wide range of DPIs available that vary considerably in design, required operational techniques, output characteristics and drug delivery across a range of inhalation patterns. Different patient populations may find individual types of DPI easier to use correctly than others and selecting the right DPI for particular patient requirements will improve compliance with therapy. For example, some DPIs offer a greater resistance against inspirational flow rate than others which affects the total emitted dose and also fine particle mass of the aerosol released. An individual patient may therefore receive different amounts of drug when inhaling from different DPIs. Therefore, it is important that the prescriber is fully aware of the characteristics of the different types of DPI, so that he or she can prescribe the device that is most appropriate to an individual patient's needs. This review explores the characteristics of currently available DPIs and evaluates their efficacy and patient acceptability. The differences in output characteristics, ease of use and patient preferences between available devices is shown to affect treatment efficacy and patient compliance with therapy. Changing the DPI prescribed to a patient to a cheaper or generic device may therefore adversely affect disease control and thereby increase the cost of treatment.

Introduction

The benefits of inhaled therapy for the treatment of lung diseases have been recognised for many years. In comparison with oral or parenteral formulations, minute but therapeutic doses of drug are delivered topically into the airways causing local effects within the lung. Unwanted systemic effects are minimised as the medication acts with maximum pulmonary specificity together with a rapid onset and duration of action. Consequently, aerosol formulations of bronchodilators and corticosteroids are the mainstay of modern treatment for asthma and chronic obstructive pulmonary disease (COPD). Central to the success of inhaled treatment has been the availability of efficient aerosol delivery systems or 'inhalers'. To provide consistent clinical control, an appropriate inhaler should satisfy the criteria that are described in Figure 1.

The pressurised metered dose inhaler (pMDI) was first introduced 50 years ago for the delivery of bronchodilators (1). It was readily accepted by patients and soon formulated to contain other classes of

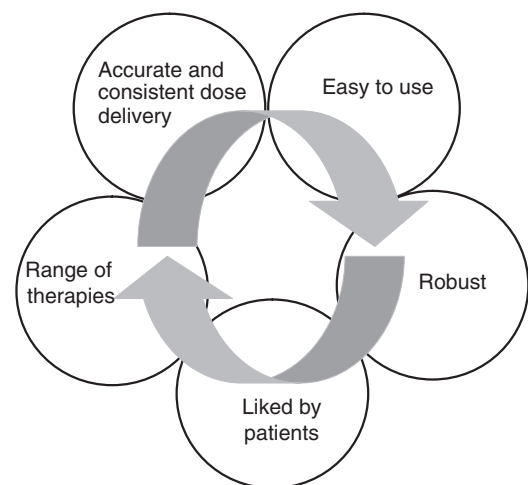
Review Criteria

The information presented in this review has been sourced from published literature. In particular, the review has focussed on comparative studies that have measured in vitro aerosol output characteristics of different types of dry powder inhaler, and also clinical studies that have assessed ease of handling and patient preferences for different dry powder inhalers.

Message for the Clinic

Different types of dry powder inhaler have different output and handling characteristics. Therefore, it is important to select the best DPI for any given patient, based on aerosol delivery, ease of handling and patient preference because these factors directly affect treatment compliance and therefore disease control. Substituting a patient's preferred DPI for a cheaper, generic device may prove to be a false economy and deleteriously influence treatment efficacy and patient outcomes.

asthma medications. It was particularly useful for the administration of corticosteroids which hitherto had been administered orally. Because of the large doses needed for oral administration, corticosteroid treatment for asthma was associated with an unacceptably

**Figure 1** Criteria for an ideal inhaler

high adverse event profile (2). As a result of the availability of inhaled formulations, with the introduction of beclometasone dipropionate in 1972, inhaled corticosteroids are now part of the cornerstone of asthma treatment. Virtually every class of inhaled drug is now formulated as a pMDI. This small and unobtrusive device remains the most commonly used inhalation device worldwide (3), with estimates of annual production in excess of 800 million units (4). A significant factor in its enduring popularity is its advantage of being cheap and relatively simple to manufacture on a large commercial scale and also the availability of a range of drugs that can be formulated for pMDIs.

In addition to pMDIs, dry powder inhalers (DPIs) have been available since 1967. The SpinhalerTM (Aventis) was first introduced for the delivery of sodium cromoglycate (5). It was developed because it was not possible for a pMDI to accommodate the large (20 mg) required dose of sodium cromoglycate for each administration. To deliver a dose of such magnitude, this aerosol delivery system comprised an inhaler which was supplied with separate capsules. Each gelatin capsule contained a single dose of drug, which was placed inside the inhaler before each use and the empty capsule was discarded. Presentation of the formulation in a capsule also provided protection from moisture ingress. This is essential to maintain good powder flow and ensure that the drug particles have the potential to be deposited in the lungs during normal patient use. The SpinhalerTM was regarded as inconvenient to use because of the number of steps required to administer each dose. Nevertheless, this type of system is still widely used especially when protection of the drug formulation from moisture is important, for example the recent introduction of tiotropium in the HandihalerTM (Boehringer-Ingelheim) device.

A DPI has some distinct advantages over pMDIs for the delivery of inhaled drugs to two particular groups of patients. Many children and elderly patients have difficulty using a pMDI correctly, because of the high velocity at which each dose is released and, therefore have problems following the inhalation technique recommended in the Patient Information Leaflet. Extensive training is required to achieve correct use of a pMDI. To deliver the drug effectively into the lung, the patient must actuate the pMDI as they start to inhale. This requires a high degree of 'hand/lung' co-ordination and failure to achieve this often results in reduced effectiveness of treatment and poor disease control (6,7). Because the SpinhalerTM required inspiratory effort to draw the medication from the device, drug was only released while the patient inhaled. Therefore, the issue of

'hand-lung' co-ordination was resolved. However, this problem has been substituted by another problem that affects all DPIs. To ensure that the dose emitted from a DPI contains drug particles that have the greatest potential to be delivered to the conducting airways, it is necessary for the patient to generate adequate inspiratory effort. The faster the inspiration rate through the DPI (and hence acceleration), the better is the quality of the emitted dose for lung deposition. This applies to all DPIs, but for some the effect is minimal, whereas other DPIs show significant flow-dependent dose emission, which may result in erratic dose emission and in turn compromise consistent disease control. The latter problem could be overcome by recommending adjustable maintenance dosing regimens to a patient's management plan.

Concurrent with the introduction of DPIs was a growing environmental concern that the chlorofluorocarbon propellants used in pMDIs were causing irreparable damage to the ozone layer in the atmosphere (8). The pharmaceutical industry was therefore committed to the development of non-chlorofluorocarbons (CFC) propellants for use in pMDIs and also DPIs that required no propellant at all. The reformulation to change the propellant used in pMDIs to those based on hydrofluoroalkanes, in place of CFC was not easy and some difficulties still remain. Consequently, other DPIs began to appear on the market. The first such DPIs were similar to the SpinhalerTM, for example salbutamol (9) and beclometasone dipropionate (10) delivered via the RotahalerTM (GlaxoSmithKline) and ipratropium bromide delivered by the AerohalerTM (Boehringer-Ingelheim) (11). Dose emission from some of these DPIs was less than that from the corresponding pMDI and therefore the recommended doses from the DPIs were double those from a pMDI.

Gradually, a new generation of novel DPIs became available with extensively different designs, operating characteristics and improved drug delivery to the lung. Some devices contained a reservoir of drug such as the TurbuhalerTM (Astra Zeneca), ClickhalerTM (Innovata Biomed) and EasyhalerTM (Orion), while other devices had individually sealed unit doses of drug, such as the DiskhalerTM (GlaxoSmithKline) and DiskusTM (GlaxoSmithKline) (otherwise known as the AccuhalerTM in the UK). Some DPIs, such as the ClickhalerTM and EasyhalerTM were designed to resemble pMDIs as closely as possible while other devices, such as DiskusTM, were designed to facilitate easy use and patient acceptability. Other refinements such as integral dose counters to enable patients and their healthcareers to monitor their inhaler use have also been incorporated into the design of some DPIs. The importance of

protecting the formulation, especially for those designed on the reservoir concept has also been considered.

Dry powder inhalers have now an established role in inhalation therapy. It is estimated that in 2004 approximately 113 million DPIs were dispensed worldwide (12). As the number of different types of DPIs on the market continues to increase, particularly with the advent of generic DPIs, the prescriber may experience some uncertainty in the selection of the optimal inhalation device for any given patient. This may be compounded by recent suggestions that because pMDIs are, in general, cheaper than DPIs, they should be prescribed as first-line treatments for all patients (13,14). Furthermore, it has been proposed that it is acceptable to switch patients from more expensive DPIs to pMDIs or generic DPIs without compromising treatment efficacy in asthmatic patients (14). However, the interchangeability of DPIs has been doubted (15).

Characteristics and performance of dry powder inhalers

The range of DPIs that are currently available falls into three device categories: single-unit dose inhalers in which each dose is loaded into the device before use; multi-dose reservoir inhalers in which a bulk supply of drug is preloaded into the device and multi-unit dose inhalers in which several single doses are individually sealed and discharged each time the device is actuated. Table 1 summarises the more common DPIs that fall into the three categories. In recent years, there has been a dramatic increase in the number of patent applications for new DPIs and it is anticipated that many more will be introduced in the future. Furthermore, attention has recently focussed on using the pulmonary route to deliver active compounds into the systemic circulation. For example, a DPI formulation of insulin (Exubera, Pfizer in collaboration with Nektar Therapeutics) will soon be available.

Single-unit dose devices

In single-unit dose devices, such as Spinhaler™, Rotahaler™ and Handihaler™, the drug, which is formulated as a micronised powder in a lactose excipient, is supplied in individual single-dose gelatin capsules which must be inserted into the inhaler before use. In the Spinhaler™, the capsule is placed into a holder located on top of a propeller. The walls of the capsule are pierced by two spears when the patient primes the device by sliding a cam, while in the Rotahaler™ the capsule is severed by a twisting action. Once the capsule has been broken, the patient

inhales through the device causing the propeller to turn and vibrate dispersing the powder into the inspired airstream (5,16). After use, the remains of the gelatin capsule must be removed from the inhaler before the next capsule can be placed in the device. Consequently, devices such as these are inconvenient to use and have largely been superseded by multi-dose DPIs. However, a single-unit DPI, the Handihaler™, has recently been developed for the delivery of tiotropium to patients with COPD (17). The use of the Handihaler™ has been shown to be associated with a significantly high and age-related error rate, because of the complexity of its operation (18). In addition, the Handihaler™ has a high internal resistance and many COPD patients have problems achieving an adequate inhalation rate to emit the required dose to be deposited in the airways (19,20). As patients with COPD are generally older than asthmatics, the use of simpler multi-unit dose DPIs, which are easy to use and in which inhalation flow rate has minimal effect on dosage emission and ease, such as Diskus™, may well be beneficial in this population, (21,22) as well as those with asthma.

Multi-dose reservoir devices

Multi-dose DPIs, by definition, contain more than one dose of drug. There are two types of multi-dose DPI, reservoir and multi-unit dose devices. Multi-dose reservoir devices contain a bulk supply of drug from which individual doses are released with each actuation. The first such inhaler to be developed was the Turbuhaler™ (23) which is used to deliver β_2 -agonists and corticosteroids separately and in combination. The drug located within this inhaler is formulated as a pellet of a soft aggregate of micronised drug which may be formulated with or without any additional lactose excipient. To release a dose of drug, the patient twists the base of the device resulting in a dose of drug being shaved off the pellet while holding the inhaler in a vertical position. It is essential that this orientation is used when dose metering all reservoir DPIs, because they rely on gravity to fill the dose metering cup. The dose is then dispersed by turbulent airflow as the patient inhales through the device. This turbulent airflow creates the energy to disperse particles in the emitted dose that are small enough to have a high possibility of depositing in the conducting airways.

Other multi-dose reservoir devices have become available in recent years including the Easyhaler™ (24), Clickhaler™ (25) and Twisthaler™ (Schering-Plough) (26). The design of new multi-dose reservoir DPIs has focussed on minimising the flow-dependent dose emission that occurs with the Turbuhaler™. Also, attention has been directed to the protection of

Table 1 Examples of commercially available dry powder inhaler

DPI type	Device name	Company	Drugs available
Single-unit dose	Aerolizer TM	Novartis	Formoterol
	Cyclohaler TM	Pharmachemie	Salbutamol BDP Budesonide Ipratropium bromide
	Rotahaler TM	GlaxoSmithKline	Salbutamol BDP Salbutamol + BDP
	Spinhaler TM	Aventis	Sodium cromoglycate
	Inhalator TM	Boehringer-Ingelheim	Fenoterol
	Handihaler TM	Boehringer-Ingelheim	Tiotropium
Multi-dose reservoir	Clickhaler TM	Innovata Biomed/ML Labs Celltech	Salbutamol BDP
	Easyhaler TM	Orion Pharma	Salbutamol BDP
	Pulvinal TM	Chiesi	Salbutamol BDP
	Turbuhaler TM	Astra Zeneca	Salbutamol Terbutaline Formoterol Budesonide Formoterol/BUD
	Twisthaler TM	Schering-Plough	Mometasone
	Novolizer TM	ASTA Medica	Budesonide
Multi-unit dose	Aerohaler TM	Boehringer-Ingelheim	Ipratropium bromide Fenoterol
	Diskhaler TM	GlaxoSmithKline	Salbutamol* Salmeterol BDP FP
	Diskus TM /Accuhaler TM	GlaxoSmithKline	Salbutamol Salmeterol FP Salmeterol + FP

*Recently discontinued. BDP, beclometasone dipropionate; BUD, budesonide; FP, fluticasone propionate.

the formulation from moisture ingress during routine storage and patient use. For example, the EasyhalerTM has a protective case and the hopper is designed, so that it is impossible for the patient to blow into it. Furthermore, all multi-dose reservoir DPIs are packaged with a protective wrapper to prevent moisture ingress prior to dispensing and patient use. The majority of this type of DPIs are disposable and cannot be refilled with additional drug. However, the NovolizerTM (ASTA Medica) is rechargeable and designed to be used with cartridges that contain 200 doses of drug (27).

Multi-unit dose devices

Multi-unit dose DPIs utilise individually prepared and sealed doses of drug. The first such DPI was the

AerohalerTM which contained six unit dose capsules as a magazine, each delivering one dose of drug. The device was used to deliver fenoterol and ipratropium bromide and was very similar in design to single-unit dose inhalers. The DiskhalerTM is used in conjunction with refill RotadisksTM which house four or eight sealed blisters containing drug and lactose excipient (28). Excipients such as lactose improve dose uniformity by increasing the mass of powder for each dose thereby improving the accuracy of dose metering and minimising the effect of inhalation flow-dependent dose emission. The sealed blisters offer a high degree of protection against environmental factors such as humidity and because the pre-metered doses of drug are factory prepared and separately packaged, dose uniformity is assured. The

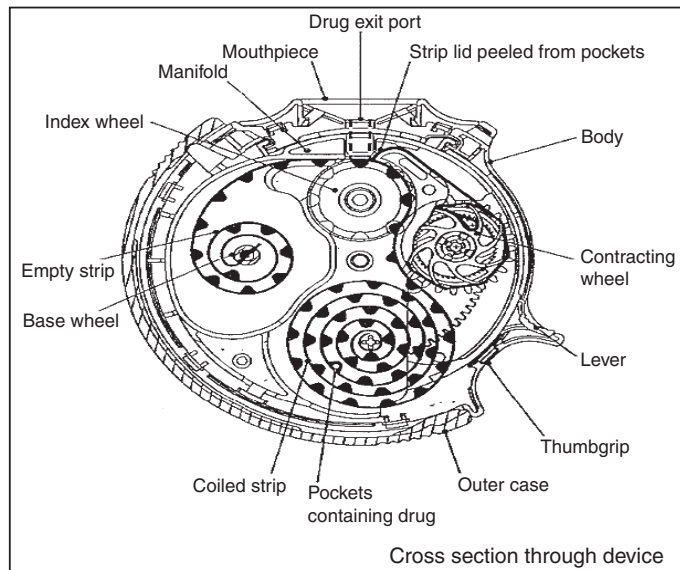
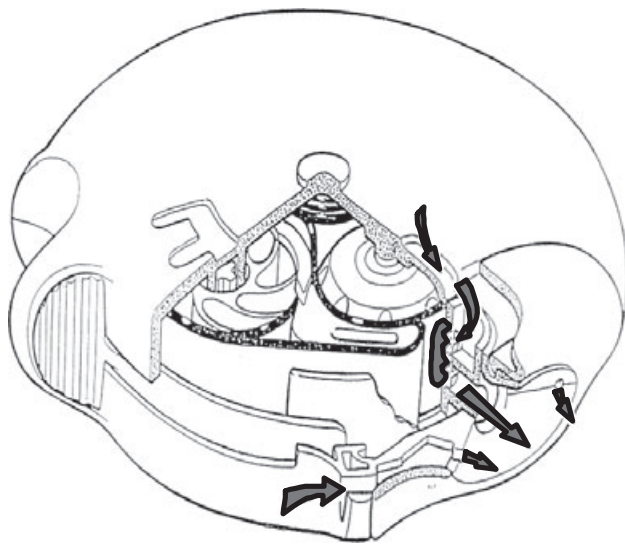


Figure 2 The Diskus inhaler

patient operates the Diskhaler™ by lifting the mouthpiece lid which causes a blister in the Rotadisk™ to be pierced and the dose to be released as the patient inhales through the device. The Diskus™ or Accuhaler™, shown in Figure 2, was developed to enable the sealed dose uniformity achieved in the Diskhaler™ to be combined with a larger number of doses. Furthermore, the Diskus™ was designed to simplify use by providing up to 1 month's medication in one device without the need to manually replace spent cartridges or capsules. The Diskus™ houses a coiled strip of 60 double foil-wrapped individual doses. The patient operates the inhaler by sliding a lever which moves the next dose-containing blister into place. A ratchet within the inhaler causes the device to click when the next dose is properly positioned. Priming the device in this way simultaneously peels the two layers of foil apart exposing the dose ready for inhalation. The Diskus™ also incorporates a dose counter, which enables the patient to monitor the number of doses remaining in the device, and also has an integral outer case which serves to keep the device dust free and also resets the lever ready for the next dose.

Performance of DPIs

As a result of the wide variation in design characteristics of the many DPIs available, their performance characteristics vary considerably and this may impact their suitability for use in different patient populations. Therefore, it is imperative that before prescribing a DPI for an individual patient, the characteristics of that DPI are known so that its

suitability can be assessed. The main factors described in Figure 1 that must be taken into account are summarised in Table 2.

Drug delivery

It is easy to assume that when an inhaler is actuated, the dose of drug delivered to the patient is the same as that cited on the package (label claim). However, this is not always the case. There are considerable differences in the proportions of the nominal dose (label claim) released from different DPIs which is defined as the total emitted dose (TED). European and American regulatory agencies have now put into place standards that specify output requirements in terms of the quantity and variability in the emitted doses from DPIs (29,30). These standards are designed to ensure consistent dosing from DPIs, both throughout the life of an individual DPI and also between inhalers of the same DPI make.

The TED is the term used to describe the quantity of drug that is released from an inhaler during a single actuation. Within the TED, therapeutic benefit is derived from the mass of drug particles that are small enough to reach the airways during inhalation. This parameter is described as the fine particle fraction (FPF) or fine particle mass (FPM) and refers to mass of particles released in an actuation that have an aerodynamic diameter of $< 5 \mu\text{m}$ (31). These particles have the greatest potential to be deposited on to the airways during an inhalation. Larger aerosol particles tend to deposit in the oropharynx and are swallowed.

Both the TED and FPF are measured in the laboratory using *in vitro* pharmacopoeial methods. Using

Table 2 Factors affecting dry powder inhaler use

Drug delivery	Consistent dose delivery throughout device life Dose reproducibility across range of temperatures and humidities High proportion of dose available for inhalation over a range of inspiratory flow rates Large fine particle mass in relation to total emitted dose (see section Drug delivery)
Ease of use	Low resistance of device to airflow during inhalation Small number of steps required to actuate device Low inhaler technique training requirements Low degree of manual dexterity required to use device
Patient preference	Appropriate size and low obtrusiveness Incorporation of a dose counter Positive reinforcement of dose delivery

these methods, it has been demonstrated that there is a wide variation in performance, in terms of TED and FPF, from the range of DPIs available as a result of intrinsic design differences. These design differences affect parameters such as the internal resistance of a device which in turn affects the flow rate achieved through the DPI. For example, when the TurbuhalerTM and DiskusTM were compared for the delivery of budesonide and fluticasone propionate respectively, the DiskusTM delivered 87–93% of the label claimed dose while the TurbuhalerTM delivered 40–58% (32).

Flow rate has been shown to directly affect the proportion of the nominal dose (TED) and also the FPF of the aerosol released from different types of DPI. This effect is more significant with some DPIs than others. For example, at a constant sampling flow rate (60 l/min), the FPF varied by 40% of the nominal dose in the TurbuhalerTM and < 10% with the SpinhalerTM (33). Furthermore, even within a particular type of DPI, flow rate directly affects both TED and FPF. For example, increasing the flow rate of air through a budesonide/formoterol TurbuhalerTM from 30 to 60 l/min and 90 l/min resulted in increases in the budesonide TED from 37.5% to 64.4% and 107.4% respectively (34), with similar increases in formoterol TED, as shown in Figure 3. Increases in FPM were also observed in parallel with flow rate. Similarly, the FPM of both drugs more than doubled when the flow rate was increased from 30 to 60 l/min. Figure 3 also highlights that intra-inhaler dose emission can also be erratic. However, this phenomenon was not found for the EasyhalerTM or the DiskusTM when studied at different flow rates (35) as shown in Figure 4. Large intra- and interinhaler dose emission differences could have clinical consequences in the bronchodilator treatment of asthma exacerbations. Also, because of the absence of immediate therapeutic feedback when inhaling corticosteroids,

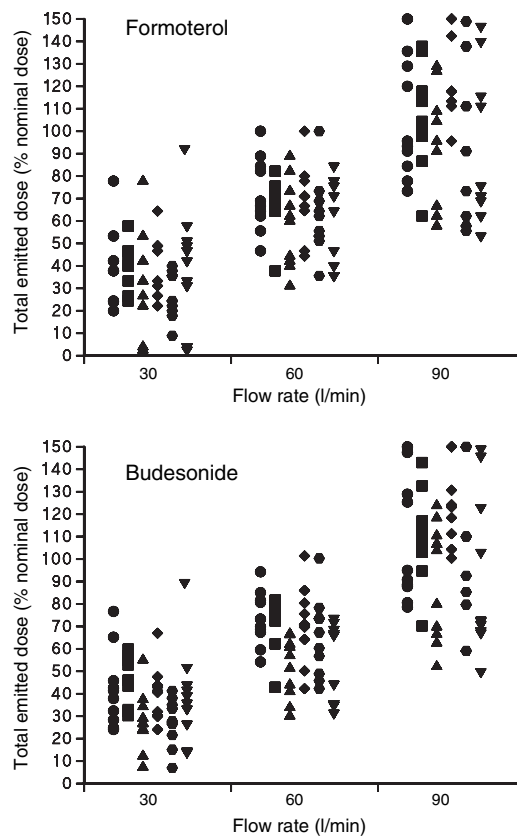


Figure 3 The amounts of budesonide and formoterol (expressed as a percentage of the labelled emitted dose) emitted from each dose of the six inhalers tested using *in vitro* inhalation flow rates of 30, 60 and 90 l/min (reproduced with permission)

these differences may also cause problems in achieving adequate asthma or COPD control. Therefore, it is important that a DPI should deliver a consistent dose irrespective of a patient's inspiratory flow rate.

The rationale for the presentation of drug as individually, factory-measured unit doses as supplied in

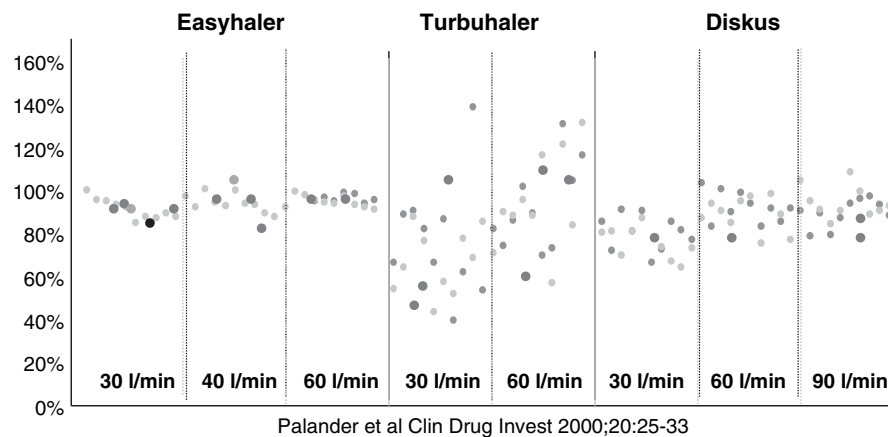


Figure 4 Uniformity of dose delivery from three salbutamol-containing multi-dose powder inhalers. Buventol Easyhaler[®] (200 µg/dose), Inspiryl Turbuhaler[®] (100 µg/dose) and Ventolin Diskus[®] (200 µg/dose) at different flow rates. The delivered dose is expressed as a percentage of the nominal labelled dose. Each data point represents a single-dose actuation (reproduced with permission)

the DiskusTM was to ensure a higher degree of dose consistency throughout the life of the device than that achieved in multi-dose reservoir devices (36). Consistent dosing from the DiskusTM has been found with salmeterol (37), fluticasone propionate (38) and the combination of both salmeterol and fluticasone propionate (39) and is therefore independent of the drug delivered. Figure 4 illustrates the minimal effect of inhalation flow rate on the dose emitted from the DiskusTM. Furthermore, multi-unit dose inhalers, such as DiskusTM have been shown to deliver more consistent doses across a wide range of sampling flow rates than the TurbuhalerTM reservoir multi-dose device (40,41,32).

In vitro techniques such as those described above provide valuable data that gives an indication of where an aerosol may deposit in the airways (42). However, FPF measured under laboratory conditions cannot be extrapolated into a direct measure of drug deposition (43). For example, most inertial impaction devices, such as cascade impactors described in the pharmacopoeial methods, sample aerosol from an inhaler by drawing air through the device at a constant sampling flow rate (usually 60 l/min, or the flow rate achieved at a pressure drop of 4 KPa). This is not representative of *in vivo* use. In practice, the magnitude of airflow passing through the DPI during use is variable and controlled by the patient's ability to inhale. An individual patient's inspiratory capacity is affected by several parameters including lung size, degree of airway obstruction that is present and their inspiratory musculature. In addition to these patient factors, the resistance of the inhaler itself affects the flow rate a patient can achieve when inhaling through

the device. Each type of DPI has its own resistance characteristics which are caused by the internal structure of the device and there is considerable variation in this parameter between available DPIs (44). The higher the internal resistance of a DPI, the lower the flow rate a patient can generate during inhalation at a given inspiratory pressure.

A modification of the aerosol sampling methodology used to obtain the TED and FPF measurements at variable flow rates has been developed. This technique, using the Electronic Lung, employs a variable sampling flow rate which is derived from *in vivo* recordings of patient breathing patterns. This *ex vivo* technique enables inhalation profiles from different patient groups to be recorded using a pressure-sensitive device. The recorded profiles are replayed via an electronic synthesiser which exactly copies the patient's inspiration through a sampling device while the aerosol is released from the DPI. Using this technique to simulate the breathing pattern of asthmatic children aged 4–8 years, the TED of fluticasone propionate via the DiskusTM was compared with that of budesonide delivered via the TurbuhalerTM (45). The results for TED were in general agreement with those obtained by pharmacopoeial methods and showed that 87–89% of the label claim was emitted from the DiskusTM compared with 56–62% from the TurbuhalerTM. However, while the TED from the DiskusTM was greater than that from the TurbuhalerTM, the FPF from the DiskusTM was slightly lower than that from the TurbuhalerTM (15–18% compared with 21–32% respectively). Overall, the results showed that DiskusTM delivered a more consistent dose across the varying inhalation patterns than the TurbuhalerTM (45).

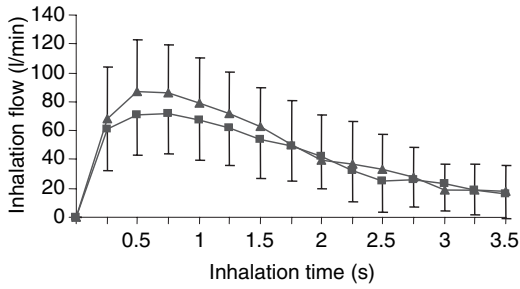


Figure 5 Mean (\pm SD) inhalation flow profile from the 20 severe asthmatics when they used a Diskus[®] (\blacktriangle) and Turbuhaler[®] (\blacksquare) (reproduced with permission)

Recently, this technique has been used to estimate the dose that severe asthmatics would receive when inhaling from a DiskusTM (containing 500 mcg fluticasone propionate with 50 mcg salmeterol) and a TurbuhalerTM (containing 200 mcg budesonide and 6 mcg formoterol) (46). Figure 5 illustrates the range of inspiratory flow rates generated by the patients through the two devices and shows that while that the effect of inhalation flow rate on the dose emitted from the Diskus was minimal, it had a significant effect on that released from the TurbuhalerTM. Figure 6 illustrates that there was an inverse relationship between inspiratory flow rate and mass median aerodynamic diameter (MMAD) of aerosol released from both DPIs. The change in the MMAD with inhalation flow rate was similar for both devices (46). This decrease in MMAD would counteract the greater potential for more central deposition of particles when using a faster inhalation flow rate.

Most DPIs are designed to be used by a spectrum of patients from children to the elderly people with a wide range of severities of asthma symptoms. This variety of patients inherently has different inhalation

capacities and therefore generates varying inspiratory flow rates. As small children have smaller inspiratory capacities than adults in terms of both flow rate and volume, DPIs are generally not advocated for children under the age of 6 years. However, DiskusTM operates at low flow rates and has been shown to be effective for use in children aged as young as 4 years (47). The TED and FPF released by some DPIs have been shown to vary considerably and be affected by differences in inspiratory flow rate (48,33,44). A study conducted to compare the delivery of SereotideTM via the DiskusTM inhaler with that of SymbicortTM via the TurbuhalerTM showed that while the output from the DiskusTM was consistent across a range of flow rates, the output from the TurbuhalerTM varied considerably across the same range. Therefore, delivery from the TurbuhalerTM was directly affected by the inspiratory flow rate of the patient (49). Similarly, the FPF of formoterol delivered via TurbuhalerTM was found to be more dependent on inspiratory flow rate than that of salmeterol delivered via DiskusTM (41). A study was conducted to measure the ability of asthmatic children and older COPD patients to generate adequate inspiratory flow through three different DPIs [DiskusTM, TurbuhalerTM and AerolizerTM (Novartis)]. The results showed that all patients could generate adequate flow through the DiskusTM. However, only 57% could generate adequate flow through the TurbuhalerTM and 21% through the AerolizerTM (50). A further study in children highlighted the problems that some may have to generate sufficient inspiratory effort to receive the required dose from a TurbuhalerTM and recommended that this device should not be prescribed to preschool age children (51).

The use of radio-labelled medications allows the *in vivo* deposition of the aerosol to be observed and

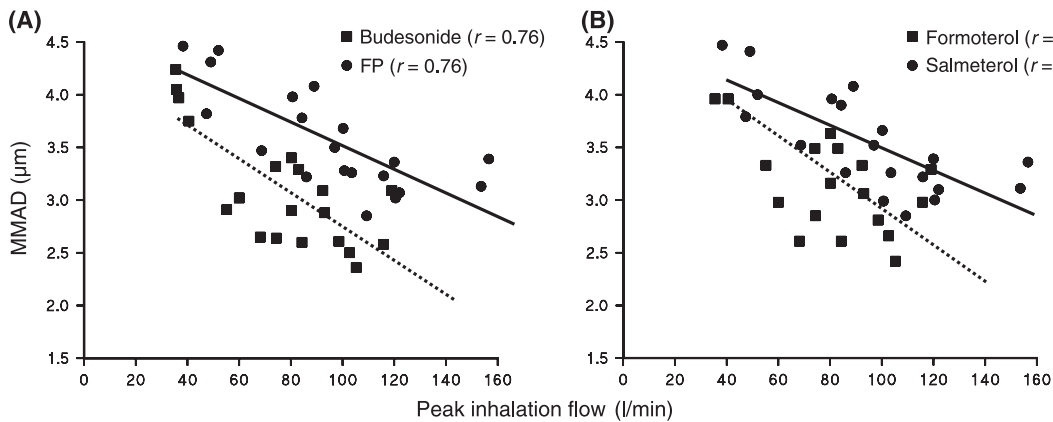


Figure 6 The mass median aerodynamic diameter with a peak inhalation flow (A) budesonide and fluticasone propionate and (B) formoterol and salmeterol (the continuous line represents the line of regression for fluticasone and salmeterol, the dashed line for budesonide and formoterol) (reproduced with permission). FP, fluticasone propionate

quantified using gamma-scintigraphic techniques. Using such methodologies, it has been possible to compare the lung delivery of inhaled medications delivered via different inhalers. For example, mean total lung deposition of 99 mTc-labelled salbutamol was calculated at 18% when delivered from a pMDI and 11% from a Diskhaler™ in asthmatic patients (52). Predictably, lung deposition was found to be higher in normal subjects without airflow obstruction, as illustrated by the study of Borgström et al. (53) who showed 27% and 28% lung deposition of 99 mTc-labelled terbutaline and budesonide respectively via the Turbuhaler™ when inhaled at approximately 60 l/min. However, this study also showed that lung deposition from the Turbuhaler™ was highly dependent on inspiratory flow rate and was halved to approximately 15% when the subject inhaled at 36 l/min. These *in vivo* studies highlight the *in vitro* and *ex vivo* results thereby showing the value of these laboratory methods to predict *in vivo* effects.

Just as tablet formulations of medications are subject to pharmaceutical deterioration when exposed to excessively high temperatures and humidity, the pharmaceutical performance of inhalers may also be adversely affected. The manufacturers of Diskus™ and Turbuhaler™ recommend in their Summary of Product Characteristics for Seretide™ and Symbicort™ respectively that they should not be stored at temperatures above 30 °C. Regulatory agencies require that inhalers should be tested for pharmaceutical stability over the long term (3 months) at 25 °C and 60% relative humidity (RH) and should also show short-term (1 month) stability at 40 °C and 75% RH.

Conditions of high temperature and humidity have been shown in *in vitro* studies to negatively affect the efficacy of the Turbuhaler™ plastic reservoir device (54). The effect of hot and humid storage conditions on the FPF from the terbutaline Turbuhaler™ has been studied *in vitro*. It was found that there was considerable variation in output from the Turbuhaler™ over the range of test conditions and FPM was reduced to near zero when it was used at 5 °C (55). The Turbuhaler™ has been equipped with a detachable cap that forms a seal on the outlet of the inhaler when it is closed properly. This, of course, relies on the co-operation of the patient to put the lid firmly back on to the device after each use. In the Diskus™, each dose of drug is protected from the environment by moisture proof, sealed aluminium foil units, which are peeled back to expose each dose just as it is used. This has been shown to provide a high level of dose protection (37). In addition to the foil strip, the Diskus™ is also supplied

with an outer foil wrapper which provides extra protection from the environment during storage prior to use. A recent study showed that the FPF (but not TED) from the Diskus™ was shown to be reduced by 50% after 3 months of storage at high temperature and humidity (40 °C/75% RH), while that from the Turbuhaler™ was not affected to the same extent (56). However, in this study Diskus™ inhalers were used that had limited unexpired shelf life and no assurance was given regarding the storage conditions of these inhalers prior to their use in this study. Furthermore, the conditions of temperature and humidity under which the aerosol was sampled from the inhalers differed considerably from the conditions under which the inhalers had been stored. It is, therefore, difficult to assess whether the observed changes in FPM were due to the experimental conditions, ambient conditions during sampling or previous storage conditions of the inhalers.

Ease of use

Arguably, the most important criterion in the selection of a DPI is its ease of use. Even if a DPI is shown to have an excellent pharmaceutical performance in terms of drug output, if it is not used correctly then it can be rendered ineffective. The results of a recent survey conducted in 169 patients with asthma or COPD showed that patients rated 'ease of use during an attack' as the most important feature of an ideal inhaler (57). If patients cannot use an inhaler correctly, their treatment is compromised which may have extremely serious consequences.

Dry powder inhaler devices have an inherent advantage over pMDIs, because the dose of drug is only released from the inhaler as the patient inhales. Therefore, it is not necessary for the patient to coordinate inspiration with actuation of the device. However, it is still necessary for the patient to provide a sustained inspiration of adequate flow rate through the inhaler in order for the complete dose to be released. The inspiratory flow rate required for optimum delivery depends on the individual DPI and the ease with which a patient can generate this flow rate depends on the resistance of the individual DPI.

The diverse characteristics of patients who require inhaled medications are such that simplicity of operation is of paramount importance. One study assessed patients' use of their own DPI or pMDI and found that nearly 90% made at least one mistake in their inhalation technique (58). It is therefore imperative to provide training to patients so that they learn to use their DPIs correctly. It has been shown that effective training increases patients' ability to use a DPI correctly (57,59). Table 3 summarises the instructions for use of some popular DPIs (60).

Table 3 Instructions for dry powder inhaler use from Patient Information Leaflets (60)

Device	Loading dose	Preparation for inhaling the dose	Inhaling dose
Clickhaler™	Hold upright, shake, press	Breathe out as far as comfortable	Steadily and deeply
Diskhaler™	Insert disk, slide tray, pierce disk	Breathe out as far as comfortable	Suck in quickly and deeply
Diskus™	Open, slide	Breathe out as far as comfortable	Suck in quickly and deeply
Easyhaler™	Hold upright, shake, press	Breathe out	Strongly and deeply
Pulvinal™	Hold upright, press button, twist	Breathe out deeply	As quickly and deeply as possible
Turbuhaler™	Hold upright, twist base	Breathe out gently	Deeply and as hard as possible

It has been demonstrated that after a single instruction, 74% patients were able to use the Diskus™ correctly compared with only 32% patients who were able to use the Turbuhaler™ correctly after one instruction (61). After two training sessions, 99% patients could use the Diskus™ correctly and 88% patients used the Turbuhaler™ correctly. However, 12% of the patients studied required further training before they could operate the Turbuhaler™.

Many studies have highlighted the incorrect use of inhalers and have shown that some inhalers are easier to use than others. However, many such clinical studies require patients to have a good inhalation technique as an inclusion criterion. Therefore, real-life studies such as observational studies may be more relevant in evaluating DPI use. For example, an observational study in 3811 patients compared correct use of five types of inhaler (Aerolizer™, Autohaler™, Diskus™, Turbuhaler™ and MDI) (62). There were clear differences between devices in the percentage of patients who made at least one mistake during use. Fewer patients made a mistake when using the Diskus™ compared with the other devices. The percentage of patients who made errors that would result in ineffective dosing was also lowest when they used the Diskus™ (11%) and highest during use of the Turbuhaler™ (32%). Similar figures of incorrect use of the Turbuhaler™ have been found in other studies in adults and also in children (59,63–67). A study conducted in elderly patients with COPD demonstrated that patients made significantly fewer critical errors when they used the Diskus™ inhaler than when they used the single-unit dose Handihaler™ inhaler (22). DPIs may also be used to deliver other medications such as antiviral drugs to elderly patients who have not used any inhalers before. A study conducted to determine whether elderly people could use Relenza™ Diskhaler™ as effectively as Turbuhaler™ found that 74% of patients had difficulty to load and prime the Diskhaler™ compared with 43% of patients with difficulty using the Turbuhaler™ (68). Clearly, it is

important to maximise simplicity of use for elderly patients who are unfamiliar with inhaled therapy.

The design of a DPI is critical in facilitating correct use. It should be easy to hold by all patients including the elderly people who may have concomitant conditions such as arthritis that can affect manual dexterity. Similarly, a DPI should be easy to operate with a minimal number of required steps. The mouthpiece should be designed to be comfortable during use. Furthermore, the device should offer minimal resistance to airflow so that it is easy for the patient to inhale through the device. Some DPIs (e.g. Clickhaler™, Easyhaler™) have been designed to resemble pMDIs as closely as possible, in terms of size and unobtrusiveness. However, because the mode of operation of a DPI is so different from that of a pMDI, swapping a patient from a pMDI to such a DPI may cause confusion to the patient and result in incorrect use.

Several clinical studies have shown that the Diskus™ is easier to use than the Turbuhaler™ in elderly people, adult and paediatric patients (69–75). Similarly, the Diskus™ has been found to be easier to use than the Diskhaler™ (76,77).

Patient preference

Patient preference has been identified as the second most important consideration for device selection after ease of use (78). The recognition that patients have distinct personal preferences regarding the inhaler that they use and are able to make informed choices is particularly important in establishing an effective disease management partnership between the healthcare professional and the patient. Compliance with the treatment is improved when patient and physician work together to achieve effective disease control (79). Many studies have been conducted to establish patient preference for one device over others. The results show that there is enormous variation in preferred devices. Table 4 summarises the findings of some of the studies in which patient preference for one DPI over another was compared.

Table 4 Summary of studies to identify patient preference for dry powder inhalers

Comparisons	Comments	References
BDP Easyhaler™ vs. Diskhaler™	N = 185. Easyhaler™ rated more acceptable than Diskhaler™	Wettengel et al. (84)
Salmeterol or FP Diskus™ vs. Diskhaler™	Diskus™ preferred to Diskhaler™	Boulet et al. (77) Stallaert et al. (97)
Diskus™ vs. previous device	Diskus™ preferred to previous device (53% vs. Turbuhaler™, 82% vs. Diskhaler™, 83% vs. Rotahaler™; 92% vs. Spinhaler™)	Le Soeuf and Clay (98)
Diskus™ vs. Easyhaler™ vs. Turbuhaler™	Adult stable asthmatics scored Easyhaler™ 75 (of 90); Diskus™ 67 and Turbuhaler™ 65	Giner et al. (83)
Diskus™ vs. Handihaler™	67% COPD patients preferred Diskus™	Moore and Stone (21)
Diskus™ vs. Turbuhaler™	More patients prefer Diskus™ (60–82%) to Turbuhaler™ (8–18%). Turbuhaler™ preferred in one study (50% vs. 34%)	Luyt et al. (74) Arossa et al. (71) Chapman et al. (72) Serra-Batles et al. (57) Manjra et al. (99) van der Palen et al. (75)
Willingness to use Diskus™ vs. Turbuhaler™	More patients happy to be prescribed Diskus™ again (78–91%) than Turbuhaler™ (37–65%)	Backman et al. (70) Williams and Richard (100) Chapman et al. (72) Burdon et al. (73)

COPD, chronic obstructive pulmonary disease.

Although comparative studies are generally designed to show overall preference for one device over another, in reality patients may prefer certain features of one inhaler over those of another inhaler, but not necessarily other features. Therefore, studies have been conducted to identify the most important characteristics or features of an 'ideal' DPI for different groups of patient (80–83). The findings of these studies show that different groups of patients or parents have different priorities. For example, parents of children who administer the dose of medication to their child rated that it was more important to them to feel that the child had received the dose than it was for children or adults who self-administer the medication (83). Similarly, children stated that they preferred a small device that was easy to carry around, while this characteristic was not as important to adults or parents, and elderly patients may well wish for a larger device that is easier to see and hold. Clearly, different patient populations have different priorities and 'wish lists' for an ideal inhaler. A recent study set out to identify the 'wish list' among 250 patients with COPD (21). The three most important features of an ideal inhaler were being quick to use when needed, overall ease of use and having a counter to show how many doses remained in the device. The study found that the Diskus™ was

rated significantly higher than the Handihaler™ for each of these features.

Interchangeability of DPI devices

The findings of some studies have suggested that clinical equivalence can be achieved when generic inhalers are substituted for other DPIs (84). However, such studies do not accurately reflect real-life situations and the effectiveness of inhaled medication to achieve disease control is the result of a combination of device design, pharmaceutical performance and patient behaviour.

The findings of this review have shown that there are wide differences between currently available DPIs in terms of pharmaceutical performance, ease of use and patient preference. It is clear that 'one inhaler does not fit all' and several factors should be taken into consideration when prescribing a dry powder inhaler device. However, two recent reviews have compared the clinical effectiveness of pMDIs with DPIs in the delivery of bronchodilators and corticosteroids in asthma (13,14). The conclusion of each review was that 'no evidence was found that alternative inhaler devices (DPIs, breath-actuated pMDI) are more effective than the pMDI for the delivery of β_2 -agonist or corticosteroids in asthma. pMDI remain the most cost-effective delivery devices'. In

some ways, the findings of these reviews are not surprising. This is because both reviews concentrated on the results of clinical studies in which patients were selected whose asthma symptoms were stable, and who demonstrated a good inhaler technique and were compliant with the dosing regimen of the study. Furthermore, the treatment periods in many of the studies cited were of short duration and because many of the studies were designed to show equivalence, doses were selected that were at the top of the dose-response curve. Consequently, many of the studies cited in these reviews demonstrated clinical equivalence between a standard pMDI and the alternative inhaler device.

The proportion of a dose of medication from a DPI that deposits in the lung during inhalation varies as a result of the device used, the drug delivered and the patient characteristics (85). A study was conducted in healthy volunteers that compared the lung deposition of ^{99m}Tc radio-labelled budesonide when delivered via ClickhalerTM and TurbuhalerTM. Lung deposition was assessed by the use of scintigraphy. The results showed that delivery of the budesonide to the lungs was directly affected by the device used and was significantly lower from the TurbuhalerTM (15.8%) compared with the ClickhalerTM (26.8%) ($p < 0.001$) (86). Similar findings were obtained when the deposition of sodium cromoglycate was compared from four different DPIs (87). Such differences in deposition have been shown to affect the safety profiles of inhaled corticosteroids. For example, in a 6-month study of children aged 5–10 years, delivery of budesonide via TurbuhalerTM was found to cause a significantly slower growth rate in these children than when the same drug was delivered via EasyhalerTM (88). Therefore, the pharmaceutical performance of a DPI, and consequent systemic absorption of the drug, has been shown to directly affect the safety profile of an inhaled medication. Similar differences in systemic absorption have been found when salbutamol was delivered from DiskusTM, TurbuhalerTM, Easi-breatheTM and DiskhalerTM (89). This therefore indicates that changing a delivery device can have adverse effects on both the safety and efficacy of an inhaled drug and that DPIs should not be regarded as interchangeable (15).

It is recognised that patient factors such as ease of use and patient preference directly affect treatment compliance. Therefore, if patients are switched from devices that they find simple to operate and like to use, then compliance with therapy may well deteriorate. This, in turn, will result in a loss of symptom control and consequent increases in morbidity and also healthcare costs. Furthermore, substitution of a familiar inhaler with a generic inhaler could confuse

the patient causing them to make additional appointments to see their doctor or nurse thereby negating any possible cost savings.

The availability of a DPI that can be used to deliver a range of drugs is important as patients become used to using a particular device effectively. The DiskusTM is available with salmeterol, fluticasone propionate and also the combination of both drugs at three different strengths. Analysis of prescribing habits, by managed care organisations in the USA, has shown that refill rates are higher when patients are prescribed combination inhalers compared with two separate inhalers each containing a single agent (90). Improving compliance with therapy regimens results in less reliever use, lower exacerbation rates and reduces the overall healthcare costs of respiratory disease (91).

Conclusions

National and international guidelines state that the aim of asthma management is to achieve optimal disease control (92–94). Poorly controlled asthma results in increased exacerbations of symptoms and resultant healthcare costs (95) and also negatively impacts quality of life (96). Poorly controlled COPD also results in an increased rate of disease progression, exacerbations requiring hospitalisation and ultimately mortality. Fundamental to achieving optimal disease control in both asthma and COPD is the provision of effective and reliable treatment. DPIs have become popular for the delivery of inhaled medications for both asthma and COPD. Improvements in technology and pharmaceutical science have facilitated the development of DPIs that are simple to use, provide consistent dosing of drug and are liked by patients. However, there are still wide variations in these properties among the different makes of DPI available. The prescriber must therefore ensure that the selection of a delivery device is appropriate for the individual patient needs. While it has been suggested that it is acceptable to swap a patient to the cheapest device available without compromising disease control, this is not supported by the clinical evidence that clearly demonstrates that there are wide differences between the quality of treatment delivered by different DPIs. The 'ideal' dry powder inhaler is the one that delivers consistent and reliable doses and is the one that the patient trusts, finds easy to use and prefers over others. While there is no single 'ideal' DPI that fulfils all those criteria for the entire spectrum of patients who use inhaled medications, the evidence suggests that multi-unit dose DPIs such as DiskusTM offer the most reliable and consistent pharmaceutical

performance, and are preferred by patients who rate them as the easiest to use.

Acknowledgement

Many thanks to Michelle Clay for help with the preparation of this manuscript.

References

- Freedman T. Medihaler therapy for bronchial asthma: a new type of aerosol therapy. *Postgrad Med J* 1956; **20**: 667–73.
- Brompton Hospital/MRC Collaborative trial. Double-blind trial comparing two dosage schedules of beclomethasone dipropionate aerosol in the treatment of chronic bronchial asthma. *Lancet* 1974; **2**: 303–7.
- Boyd G. The continued need for MDIs. *J Aerosol Med* 1995; **8** (Suppl. 1): S9–12.
- Ross DL, Gabrio BJ. Advances in metered dose inhaler technology with the development of a chlorofluorocarbon-free drug delivery system. *J Aerosol Med* 1999; **12**: 151–60.
- Bell JH, Hartley PS, Cox JSG. Dry powder aerosols 1: a new powder inhalation device. *J Pharm Sci* 1971; **10**: 1559–64.
- Amirav I, Goren A, Pawlowski NA. What do paediatricians know about the correct use of inhalers and spacer devices? *J Allergy Clin Immunol* 1994; **94**: 669–75.
- Cochrane GM, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. *Chest* 2000; **117**: 542–50.
- Noakes TJ. CFCs, their replacements and the ozone layer. *J Aerosol Med* 1995; **8** (Suppl. 1): S3–7.
- Hetzel M, Clark T. Comparison of salbutamol Rotahaler with conventional pressurized aerosol. *Clin Allergy* 1977; **7**: 563–8.
- Edmunds AT, McKenzie S, Tooley M, Godfrey S. A clinical comparison of beclomethasone dipropionate delivered by pressurized aerosol and as a powder from a Rotahaler. *Arch Dis Child* 1979; **54**: 233–5.
- Pakes GE, Brogden RN, Heel RC, Speight TM, Avery GS. Ipratropium bromide: a review of its pharmacological properties and therapeutic efficacy in asthma and chronic bronchitis. *Drugs* 1980; **20**: 237–66.
- Taylor A, Gustafsson P. Do all dry powder inhalers show the same pharmaceutical performance? *Int J Clin Pract* 2005; **59** (Suppl. 149): 7–12.
- Brocklebank D, Wright J, Cates C, on behalf of The National Health Technology Assessment Inhaler Review Group. Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering corticosteroids in asthma. *BMJ* 2001; **323**: 1–7.
- Ram FSF, Wright J, Brocklebank D, White JES, on behalf of The National Health Technology Assessment Inhaler Review Group. Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering β_2 -agonists bronchodilators in asthma. *BMJ* 2001; **323**: 1–7.
- Chrystyn H. Do patients show the same level of adherence with all dry powder inhalers? *Int J Clin Pract* 2005; **59**: 19–25.
- Hallworth GW. An improved design of powder inhaler. *Br J Clin Pharmacol* 1977; **4**: 689–90.
- Chodosh S, Flanders JS, Kesten S, Serby CW, Hochrainer D, Witek TJ. Effective delivery of particles with the Handihaler[®] dry powder inhalation system over a range of chronic obstructive pulmonary disease severity. *J Aerosol Med* 2001; **14**: 309–15.
- Dahl R, Backer V, Ollgard B et al. Assessment of patient performance of the Handihaler[®] compared with the metered dose inhaler four weeks after instruction. *Respir Med* 2003; **97**: 1126–33.
- Tarsin W, Al-Showair RAM, Corrado OJ, Pearson SB, Chrystyn H. Peak inhalation rates (PIFRs) of COPD patients when using a metered dose inhaler (MDI) and recently introduced dry powder inhalers (DPI). *Thorax* 2003; **58** (Suppl. 111): ii73.
- Al-Fadhl SA, Assi KH, Clark BJ, Chrystyn H. Tiotropium dose emission is influenced by the inhalation flow and the recommended two inhalations for each dose. *Eur Respir J* 2005; **26** (Suppl. 49): 125s–6.
- Moore AC, Stone S. Meeting the needs of patients with COPD: patients' preference for the Diskus compared with the Handihaler. *Int J Clin Pract* 2004; **58**: 444–50.
- Franks M, Briggs P. Use of a cognitive ergonomics approach to compare usability of a multidose dry powder inhaler and capsule dry powder inhaler: an open-label, randomized, controlled study. *Clin Ther* 2004; **26**: 1791–9.
- Wetterlin K. Turbuhaler: a new powder inhaler for administration of drugs to the airways. *Pharm Res* 1988; **5**: 506–8.
- Vidgren M, Silvasti M, Vidgren P, Sormunen H, Laurikainen K, Korhonen P. Easyhaler multiple dose powder inhaler – practical and effective alternative to the pressurized MDI. *Aerosol Sci Technol* 1995; **22**: 335–45.
- Warren S, Taylor G. Effect of inhalation flow profiles on the deposition of radiolabelled BDP from a novel dry powder inhaler (DPI. Clickhaler), a conventional metered dose inhaler (MDI), and MDI plus spacer. In: Dalby RN, Byron PR, Farr SJ, eds. *Respiratory Drug Delivery VI*. Buffalo Grove, IL: Interpharm Press, 1998: 453–5.
- Yang TT, Fan BJ, Kenyon D. Evaluation of the new mometasone furoate dry powder inhaler agglomerate formulation and deagglomeration during inhalation. *Chest* 2000; **118**: 98S.
- Berner B, Fyrnys B, de Boer A, Gottenhauer W, Wolf-Heuss E. Asta Medica multidose dry powder inhaler. In: Dalby RN, Byron PR, Farr SJ, eds. *Respiratory Drug Delivery VI*. Buffalo Grove, IL: Interpharm Press, 1998: 475–7.
- Sumby BS, Crucher KM, Smith IJ et al. Dose reliability of the Serevent Diskhaler system. *Pharm Tech Int* 1993; **5** (June): 20–7.
- European Pharmacopeia. *Preparations for Inhalation*. European Pharmacopeia Supplement, 2001; 2.9.18.
- FDA US. *Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products*, Chemistry, Manufacturing and Controls Documentation. US Dept of Health and Human Sciences, FDA Center for Drug Evaluation and Research (CDER), 1998; Rockville, US.
- Brain JD, Blanchard JD. Mechanisms of particle deposition and clearance. In: Moren F, Dolovich MB, Newhouse MT, Newman SP, eds. *Aerosols in Medicine: Principles, Diagnosis and Therapy*. Amsterdam: Elsevier, 1993: 351–74.
- Hill LS, Slater AL. A comparison of the performance of two modern multidose dry powder asthma inhalers. *Respir Med* 1998; **92**: 105–10.
- de Boer AH, Gjaltema D, Hagedoorn P. Inhalation characteristics and their effects on in vitro drug delivery from dry powder inhalers. Part 2: Effect of peak flow rate (PIFR) and inspiration time on the in vitro drug release from three different types of commercial dry powder inhalers. *Int J Pharm* 1996; **138**: 45–56.
- Tarsin W, Assi KH, Chrystyn H. In vitro and inter-inhaler flow rate-dependent dosage emission from a combination of budesonide and formoterol in a dry powder inhaler. *J Aerosol Med* 2004; **17**: 25–32.
- Palander A, Mattila T, Karka M, Muttonen E. In vitro comparison of three salbutamol-containing multidose dry powder inhalers. *Clin Drug Invest* 2000; **20**: 25–33.
- Fuller R. The Diskus[™]: a new multi-dose powder device – efficacy and comparison with Turbuhaler[™]. *J Aerosol Med* 1995; **8** (Suppl. 2): S11–7.
- Brindley A, Sumby BS, Smith IJ, Prime DA, Haywood PA, Grant AC. Design, manufacture and dose consistency of the Serevent Diskus inhaler. *Pharm Technol Eur Biopharm* 1995; **7**: 14–22.

- 38 Prime D, Slater AL, Haywood PA, Smith IJ. Assessing dose delivery from the Flioxotide Diskus inhaler – a multi-dose powder inhaler. *Pharm Tech Eur* 1996; **8**: 23–36.
- 39 Ashurst IC, Prime D, Haywood PA. Development of a dry powder inhaler device containing a combination of salmeterol and fluticasone propionate. *Eur Respir J* 1998; **12** (Suppl. 28): 93s.
- 40 Prime D, Parkes PA, Petchey L, Slater AL, Woodhouse RN. Evaluation of the pharmaceutical performance of two dry powder inhalers: a comparison of Diskus and Turbuhaler inhalers. *Am J Respir Crit Care Med* 1996; **153**: A62.
- 41 Malton A, Sumbly BS, Smith IJ. A comparison of in vitro drug delivery from two multidose powder inhalation devices. *Eur J Clin Res* 1995; **7**: 177–93.
- 42 Martonen TB, Katz I, Fufts K, Hickey AJ. Use of analytically defined estimates of aerosol respirable fraction to predict lung deposition patterns. *Pharm Res* 1992; **9**: 1634–9.
- 43 Newman SP. How well do in vitro particle size measurements predict drug delivery in vivo? *J Aerosol Med* 1998; **11** (Suppl. 1): S97–104.
- 44 Steckel H, Müller BW. In vitro evaluation of dry powder inhalers 1: drug deposition of commonly used devices. *Int J Pharm* 1997; **154**: 19–29.
- 45 Bisgaard H, Klug B, Sumbly BS, Burnell PKP. Fine particle mass from the Diskus inhaler and Turbuhaler in children with asthma. *Eur Respir J* 1998; **11**: 1111–5.
- 46 Tarsin WY, Pearson SB, Assi KH, Chrystyn H. Emitted dose estimates from Seretide Diskus and Symbicort Turbuhaler following inhalation by severe asthmatics. *Int J Pharm* 2006; **316**: 131–7.
- 47 Bracamonte T, Schauer U, Emeryk A, Godwood A, Balsara S. Efficacy and safety of salmeterol/fluticasone propionate combination delivered by the Diskus™ or pressurised metered dose inhaler in children with asthma. *Clin Drug Invest* 2005; **25**: 1–11.
- 48 Hindle M, Byron PR. Dose emissions from marketed dry powder inhalers. *Int J Pharm* 1995; **116**: 169–77.
- 49 Gustafsson P, Andersson H, Glad M. Comparison of total and fine drug particle mass generated from two dry powder inhalers (DPIs) by 4 year old children with asthma. *Eur Respir J* 2002; **20** (Suppl. 38): 429s.
- 50 Kokot M. Selection of a personal dry powder inhaler based on peak inspiratory flow measurements in selected groups of patients with bronchial obstruction. *Pol Merkur Lekarski* 2000; **9**: 672–6.
- 51 Pederson S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. *Arch Dis Child* 1990; **65**: 308–10.
- 52 Melchor R, Biddiscome MF, Mak VHF, Short MD, Spiro SG. Lung deposition patterns of directly labelled salbutamol in normal subjects and in patients with reversible airflow obstruction. *Thorax* 1993; **48**: 506–11.
- 53 Borgström L, Bondesson E, Moren F, Trofast E, Newman SP. Lung deposition of budesonide inhaled via Turbuhaler: a comparison with terbutaline sulphate in normal subjects. *Eur Respir J* 1994; **7**: 69–73.
- 54 Lindsay DA, Russell NL, Thompson JE et al. A multicentre comparison of the efficacy of terbutaline turbuhaler and salbutamol pressurized metered dose inhaler in hot, humid regions. *Eur Respir J* 1994; **7**: 342–5.
- 55 Meakin BJ, Cainey JM, Woodcock PM. Simulated 'in-use' and 'mis-use' aspects of the delivery of terbutaline sulphate from Bricanyl Turbuhaler™ dry powder inhalers. *Int J Pharm* 1995; **119**: 103–8.
- 56 Borgström L, Asking L, Lipniunas P. An in vivo and in vitro comparison of two powder inhalers following storage at hot/humid conditions. *J Aerosol Med* 2005; **18**: 304–10.
- 57 Serra-Batllés J, Plaza V, Badiola C, Morejon E. Patient perception and acceptability of multidose dry powder inhalers: A randomized crossover comparison of Diskus/Accuhaler with Turbuhaler. *J Aerosol Med* 2002; **15**: 59–64.
- 58 Van Beerendonk I, Mesters I, Mudde AN, Tan TD. Assessment of the inhalation technique in outpatients with asthma or chronic obstructive pulmonary disease using a metered dose inhaler or dry powder device. *J Asthma* 1998; **35**: 273–9.
- 59 Ferreira MB, Santos A, Clode MH, Carlos AGP. Turbutest in the training of asthmatic Turbuhaler users. *Allergy* 1999; **54**: 375–9.
- 60 Gustafsson P, Taylor A, Zanen P, Chrystyn H. Can patients use all dry powder inhalers equally well? *Int J Clin Pract* 2005; **59** (Suppl. 149): 13–8.
- 61 Clay MM, Huskisson SC, Jenkins MM. Ease of handling and clinical efficacy of a new multi-dose powder inhaler for the delivery of salmeterol in adult asthmatics. *Eur Respir J* 1994; **7** (Suppl. 18): 163s.
- 62 Molimard M, Raheison C, Lignot S et al. Assessment of handling of inhaler device in real life: an observational study in 3811 patients in primary care. *J Aerosol Med* 2003; **16**: 249–54.
- 63 Kaneko N, Narushima M, Tanaka K, Suzuki H. The efficacy of turbuhaler dry powder inhaler in Japanese asthma – measurement of peak inspiratory flow when using Turbuhaler. *Jpn J Allergol* 1996; **45**: 649–54.
- 64 Hawksworth GM, James L, Chrystyn H. Characterisation of the inspiratory manoeuvre when asthmatics inhale through a Turbuhaler pre- and post- counselling in a community pharmacy. *Respir Med* 2000; **94**: 501–4.
- 65 Cimas JE, Gonzalez Vazquez de Prada I, del Castillo Aravelo F. The validation of checklists for the inhalation technique for the pressurized cartridge and the Turbuhaler. *Arch Bronconeumol* 1999; **35**: 15–9.
- 66 Goren A, Noviski N, Avital A et al. Assessment of the ability of young children to use a powder inhaler device (Turbuhaler). *Ped Pulmonol* 1994; **18**: 77–80.
- 67 de Boeck K, Alifier M, Warnier G. Is the correct use of a dry powder inhaler (Turbuhaler) age dependent? *J Allergy Clin Immunol* 1999; **103**: 763–7.
- 68 Diggory P, Fernandez C, Humphrey A, Jones V, Murphy M. Comparison of elderly people's technique in using two dry powder inhalers to deliver zanamivir: randomised controlled trial. *BMJ* 2001; **322**: 1–4.
- 69 Burdon J, Bish R, Loder M, Walters EH. A comparison of fluticasone propionate 250 mcg bd via MDPI and budesonide 600 mcg bd via Turbuhaler in adult asthmatics. *Aust N Z J Med* 1997; **27**: 247.
- 70 Backman R, Baumgarten C, Sharma RK. Fluticasone propionate via Diskus inhaler at half the microgram dose of budesonide via Turbuhaler inhaler. *Clin Drug Invest* 2001; **21**: 735–43.
- 71 Arossa W, Fasolo A, Fina P. Patient perception of the Diskus inhaler: a comparison with the turbuhaler inhaler. *Eur Respir J* 1998; **12** (Suppl. 28): 41s.
- 72 Chapman KR, Balter MS, Boulet L-P et al. Handling of the multi-dose powder inhalers Diskus versus Turbuhaler in elderly asthmatics. *Am J Respir Crit Care Med* 1996; **153** (4 part 2): A61.
- 73 Burdon J, Droszcz W, Jones R, Marques A, Trowell S. Comparison of the efficacy and ease of handling of salmeterol xinafoate delivered via a new multi-dose powder inhaler and terbutaline sulphate delivered via a breath-actuated metered dose inhaler. *Eur Respir J* 1995; **8** (Suppl. 19): P1050.
- 74 Luyt D, Vermeulen J, Johnson L, Gomez E. A comparison of the ease of handling of the Diskus/Accuhaler inhaler and the turbuhaler inhaler in children aged 6–12 years with asthma. *J Aerosol Med Depos Clear Eff Lung* 1995; **8**: P144, 105.
- 75 van der Palen J, Klein JJ, Schildkamp AM. Comparison of the new multidose powder inhaler (Diskus/Accuhaler) and the Turbuhaler regarding preference and ease of use. *J Asthma* 1998; **35**: 147–52.
- 76 Gunawardena KA, Pleace KJ, Clay MM, Fuller RW. Salmeterol delivered from a new multi-dose powder inhaler (Diskus/Accuhaler inhaler) or Diskhaler inhaler in adult asthmatics. *Am J Respir Crit Care Med* 1994; **149** (4 part 2): A219.
- 77 Boulet LP, Cowie R, Johnston P, Krakovsky D, Mark S. Comparison of Diskus inhaler, a new multidose powder inhaler, with Diskhaler inhaler for the delivery of salmeterol to asthmatic patients. *J Asthma* 1995; **32**: 429–36.

- 78 Fletcher M, Hardy AJ, Karbal B, Walker SM. Effects of asthma training on inhaler device selection and utilisation in general practice. *Eur Respir J* 2004; **24** (Suppl. 48): 257s.
- 79 Everard ML. Inhaler devices in infants and children: challenges and solutions. *J Aerosol Med* 2004; **17**: 186–95.
- 80 Moore AC, Stone S. Patient preference for the Diskus over the Handihaler in patients with COPD. *Am J Respir Crit Care Med* 2003; **167**: A96.
- 81 Sharma RK, Edwards K, Hallett C, Fuller RW. Perception among paediatric patients of the Diskus inhaler, a novel multidose powder inhaler for use in the treatment of asthma. *Clin Drug Invest* 1996; **11**: 145–53.
- 82 Schlaeppli M, Edwards K, Fuller RW, Sharma R. Patient perception of the Diskus inhaler: a comparison with the Turbuhaler inhaler. *Br J Clin Pract* 1996; **50**: 14–9.
- 83 Giner J, Torrejón M, Ramos A et al. Patient preference in the choice of dry powder inhalers. *Arch Bronconeumol* 2004; **40**: 106–9.
- 84 Wettengel R, Laurikainen K, Silvasti M, Toivanen P, Sauter K. Therapeutic equivalence and acceptability of two multidose powder inhalers in the treatment of asthma. *Respiration* 2000; **67**: 77–82.
- 85 Bisgaard H. Drug delivery from inhaler devices. Lung deposition, clinical effect and cost-effectiveness vary. *Br Med J* 1996; **13**: 895–6.
- 86 Warren S, Taylor G, Smith J, Buck H, Parry-Billings M. Gamma scintigraphic evaluation of a novel budesonide dry powder inhaler using a validated radiolabeling technique. *J Aerosol Med* 2002; **15**: 15–25.
- 87 Vidgren M, Kärkkäinen A, Karjalainen P et al. Effect of powder inhaler design on drug deposition in the respiratory tract. *Int J Pharm* 1988; **42**: 211–6.
- 88 Vanto T, Hämäläinen KM, Vahteristo M, Wille S, Njå F, Hyldebrandt N. Comparison of two budesonide dry powder inhalers in the treatment of asthma in children. *J Aerosol Med* 2004; **17**: 15–24.
- 89 Aswania O, Ritson S, Iqbal SM et al. Intra-subject variability in lung dose in healthy volunteers using five conventional portable inhalers. *J Aerosol Med* 2004; **17**: 231–8.
- 90 Stoloff SW, Stempel DA, Meyer J, Stanford RH, Carranza-Rosenzweig JR. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *J Allergy Clin Immunol* 2004; **113**: 245–51.
- 91 Stempel DA, Stanford RH, Kim J, Chernicoff HO, Legoretta A. Asthma related ED/hospitalisation risk and asthma costs of fluticasone propionate/salmeterol in a single inhaler compared to fluticasone propionate and salmeterol in separate inhalers. *J Allergy Clin Immunol* 2004; **113**: S272.
- 92 GINA (Global Initiative for Asthma). *Pocket Guide for Asthma Management and Prevention*. <http://www.ginasthma.org> (accessed May 2007).
- 93 BTS/SIGN (British Thoracic Society/Scottish Intercollegiate Guidelines Network). British guideline on the management of asthma. *Thorax* 2003; **58** (Suppl. 1): i1–94, <http://www.brit-thoracic.org.uk/asthma-guide-download.html> (accessed April 2007).
- 94 National Institutes of Health, National Heart, Lung and Blood Institute. *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Institutes of Health, 2004.
- 95 Barnes PJ, Jonsson B, Klim JB. The costs of asthma. *Eur Respir J* 1996; **9**: 636–42.
- 96 Seemungal TA, Donaldson GC, Paul EA et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; **157**: 1418–22.
- 97 Staellaert RALM, Prins J, Greeffhorst APM et al. Evaluation of a new dry powder device, the Diskus/Accuhaler versus the Diskhaler inhaler for the delivery of fluticasone propionate in adult asthmatics. *J Aerosol Med Depos Clear Eff Lung* 1995; **8**(1): 140.
- 98 Le Soeuf P, Clay M. A multicentre study to evaluate ease of handling and patient preference for the Diskus/Accuhaler multi-dose dry powder inhaler. *ISAM Nov* 1994; abs 5.
- 99 Manjra AI, Mehra S, Zhang P, Mark S. Device handling comparison between Diskus (D) and Turbuhaler (TH) by paediatric patients and their parents. *Eur Respir J* 1998; **12** (Suppl 28): 86s.
- 100 Williams J, Richard KA. Ease of handling and clinical efficacy of fluticasone propionate Accuhaler/Diskus inhaler compared with Turbuhaler inhaler in paediatric patients. *Br J Clin Pract* 1997; **51**: 147–53.

Paper received November 2006, accepted February 2007