Dry Powder Inhalers: An Overview

Paul J Atkins PhD

Dry powder inhalers (DPIs) are a widely accepted inhaled delivery dosage form, particularly in Europe, where they currently are used by a large number of patients for the delivery of medications to treat asthma and chronic obstructive pulmonary disease. The acceptance of DPIs in the United States after the slow uptake following the introduction of the Serevent Diskus in the late 1990s has been driven in large part by the enormous success in recent years of the Advair Diskus. This combination of 2 well-accepted drugs in a convenient and simple-to-use device has created an accepted standard in pulmonary delivery and disease treatment that only a few years ago could not have been anticipated. The DPI offers good patient convenience, particularly for combination therapies, and also better compliance. The design and development of any powder drug-delivery system is a highly complex task. Optimization of the choice of formulation when matched with device geometry is key. The use of particle engineering to create a formulation matched to a simple device is being explored, as is the development of active powder devices in which the device inputs the energy, making it simpler for patients to receive the correct dose. Patient interface issues are also critically important. However, one of the most important factors in pulmonary delivery from a DPI is the requirement for a good-quality aerosol, in terms of the aerosol's aerodynamic particle size, and its potential to consistently achieve the desired lung deposition in vivo. *Key words: dry powder inhaler, DPI, lactose, aerosol, asthma, bronchodilator, chronic obstructive pulmonary disease, COPD, corticosteroids, drug delivery.* [Respir Care 2005;50(10):1304–1312. © 2005 Daedalus Enterprises]

Introduction

The most frequent use of inhalation therapy is for the treatment of obstructive airway diseases, including asthma and chronic obstructive pulmonary disease, using drugs such as short-acting and long-acting β agonists, corticosteroids, and anti-cholinergic agents. Traditionally, these agents have been delivered via pressurized metered-dose inhaler (MDI). However, in recent years, dry powder inhalers (DPIs) have gained wider use, particularly in the United States, partly because of the introduction of the

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first combination of a long-acting β agonist (salmeterol) and a corticosteroid (fluticasone propionate) in a convenient multi-dose DPI (Advair Diskus, GlaxoSmithKline, Research Triangle Park, North Carolina).[1]

Key to all inhalation dosage forms (either MDI or DPI) is the need to generate the optimum "respirable dose" (particles < 5.0 μm) of a therapeutic agent that will reach the site of action (ie, the lung). This is a critical performance feature in the rational design and selection of a pulmonary delivery system. Historically, MDIs have achieved lung deposition of 5–15% of the delivered dose. Current DPIs have similar efficiency, but they have a number of advantages over MDIs, including the fact that they are breath-actuated and therefore require less coordination than a conventional press-and-breathe MDI. Furthermore, they do not contain chlorofluorocarbon propellants, which have been implicated in atmospheric ozone depletion[2] and are being phased out. In addition, the more recently developed multi-dose DPIs have either a dose counter or indicator that tells the patient how much medication remains in the inhaler, which is another feature that differentiates DPIs from currently available MDIs.

DPIs do, however, suffer from some inherent disadvantages, including the fact that they require moderate inspiratory effort to draw the formulation from the device; some patients are not capable of such effort. Furthermore, there is only a limited number of drugs available in a multi-dose format, with some drugs being available only in unit-dose formats. These unit-dose devices are perceived as complex and confusing for patients.[3] In a recent review, Frijlink and De Boer claimed that "well designed DPIs are highly efficient systems for pulmonary drug delivery. However, they are also complicated systems, the performance of which relies on many aspects, including design. . . , powder formulation, and airflow generated by the patient."[4] This paper will review the currently available DPIs, focusing primarily on the United States market, evaluate the key performance variables of these DPIs, including patient preferences, and provide some insights into potential future developments of DPIs for the delivery of agents to treat respiratory diseases and systemic diseases.

Powder Inhalers Today

Today there are essentially 2 types of DPI: those in which the drug is packaged into discrete individual doses (in a gelatin capsule or a foil-foil blister) and those that contain a reservoir of drug from which doses are metered out.[5] Both are now widely available around the world and are gaining broad acceptance as suitable alternatives to MDIs. There is clearly considerable interest in these devices, because they do not require chlorofluorocarbon propellant to disperse the drug and are therefore ozone-friendly. Furthermore, DPIs obviate coordination of actuation and inspiration (a limitation of MDIs) because DPIs are essentially breath-actuated. However, this breath-actuation is also one of their disadvantages. Some DPIs require inspiratory flow of $\geq$ 60 L/min to effectively de-aggregate the powder,[6,7] which cannot always be achieved by all asthmatic patients, particularly infants. All the currently available DPIs suffer from this potential drawback and can be characterized as "passive" inhalers (ie, the patient provides the energy to suck the drug from the device). This has prompted several companies to evaluate ways of providing energy in the inhaler, which is leading to the development of several "active" DPIs, although none of these are currently available commercially.

Unit-Dose Devices

With a single-dose DPI, a powder-containing capsule is placed in a holder inside the DPI, the capsule is opened within the device, and then the powder is inhaled. The spent capsule must be discarded after use and a new capsule inserted for the next dose. The concept of the first capsule-based device (the Spinhaler) was first described in the early 1970s, by Bell and colleagues,[8] who had developed this device for the administration of powdered sodium cromoglycate. Briefly, the drug mixture, which often includes a bulk carrier to aid powder flow, is pre-filled into a hard gelatin capsule and loaded into the device. After activation of the device, which pierces the capsule, the patient inhales the dose, which is dispensed from the vibrating capsule by means of inspired air. This product is no longer available in the United States.

A similar DPI (Rotahaler, GlaxoSmithKline), which has also been available for many years, delivers albuterol. With the Rotahaler, the drug mixture is also in a hard capsule. The capsule is inserted into the device, broken open inside the device, and the powder is inhaled through a screened tube (Fig. 1).[9,10] Again, this product is no longer available in the United States.

Although these single-dose devices have performed well in clinical use for many years, the main criticism of them is the cumbersome nature of loading the capsule, which might not be easily accomplished by a patient who is undergoing an asthma attack and requires immediate delivery of the drug. This is clearly very relevant for devices that deliver short-acting bronchodilators. In addition, elderly patients may not have the manual dexterity to accomplish all the necessary maneuvers to take the capsule from the package, load it, and pierce the capsule in the device. However, despite the perception that unit-dose devices are not patient-friendly and are not easy to use, several introductions of single-dose DPIs have occurred over the last few years using similar designs (eg, Foradil Aerolizer, made by Novartis/Schering-Plough, and Spiriva HandiHaler, made by Boehringer Ingelheim/Pfizer).[11,12]

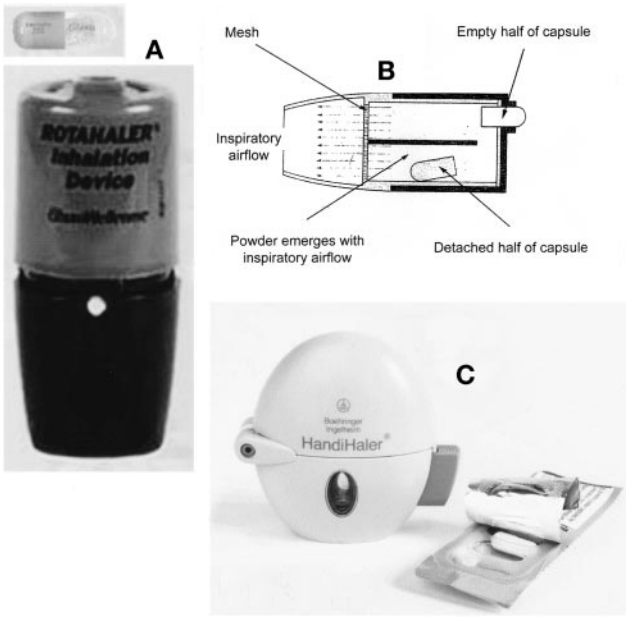

Fig. 1. Examples of unit-dose dry powder inhalers (DPIs). A: Rotahaler and Rotacap (contains albuterol). B: Diagram of Rotahaler. C: Spiriva Handihaler. (Diagram from Reference 10, with permission. Photograph C courtesy of Boehringer Ingelheim/Pfizer.)

The Foradil device has been poorly accepted since its introduction. This may be related to the need to store the capsules refrigerated. With the recently introduced Spiriva Handihaler it is too early to evaluate the degree of patient acceptance of this device, although it is complex and requires at least 7 distinct steps to deliver the dose. For some patients, 2 inhalations are required to completely empty the capsule and achieve the therapeutic dose, which adds to the degree of complexity for the patient when using this device. Furthermore, there have been recent reports[3] of patients ingesting the capsules instead of placing the capsule in the device and inhaling the contents. This is clearly not desirable.

Multi-Dose Devices

Given the inherent limitations of single-dose devices, in the past decade or so there has been considerable focus on developing multi-dose DPIs. The development of multi-dose DPIs was pioneered by the AB Draco company (now a division of AstraZeneca), with their Turbuhaler.[13] This device was truly the first metered-dose powder delivery system. The drug formulation is contained within a storage reservoir and can be dispensed into the dosing chamber by a simple back-and-forth twisting action on the base of the device. The device is capable of working at a moderate flow rate and also delivers carrier-free particles as well as lactose-based formulations.[14] Although the Turbuhaler is widely available in Europe and Canada, and has been used to deliver both β agonists (formoterol, terbutaline) and combinations (formoterol and budesonide), in the United States this device is only available to deliver the inhaled corticosteroid budesonide (Pulmicort Turbuhaler).[15]

One of the drawbacks for the Turbuhaler, which may have contributed to its limited acceptance in the United States, is its variable delivery at different flow rates.[5,16] This has also been the major criticism of several recently developed reservoir-type DPIs[17] and may limit their introduction into the United States. It is, however, important to note that Schering-Plough recently announced approval of their reservoir DPI for the delivery of the inhaled corticosteroid mometasone (Asmanex Twisthaler).[18]

To address issues associated with multiple dosing and consistent dose-to-dose delivery, in the late 1980s Glaxo developed the Diskhaler,[19] which was used to deliver a range of drugs, including albuterol, beclomethasone, salmeterol, fluticasone, and the anti-viral agent zanamivir. This device uses a circular disk that contains either 4 or 8 powder doses, which typically would be sufficient drug for 1–2 days of treatment; the empty disk is then discarded and a new disk is inserted in the device. The doses are maintained in separate aluminum blister reservoirs until just before inspiration. On priming the device, the aluminum blister is pierced and its contents drop into the dosing chamber. This device had limited commercial success, primarily because it held only a few doses per disk and was perceived as very cumbersome to load (Fig. 2).[20] It was used in the United States for the delivery of fluticasone propionate to pediatric patients, although the product has now been withdrawn. It was also used (in a modified form) to deliver the anti-influenza agent zanamivir, although, again, the use was not widespread.

Further improvements in patient convenience and ease of use were incorporated into the next generation of multi-dose DPI, called the Diskus. This product was introduced in the late 1990s. Initially it delivered salmeterol or fluticasone, but in 2001 a version was released that contains a combination salmeterol-plus-fluticasone formulation (Advair Diskus). This is a true multi-dose device; it contains 60 doses (one month's therapy) in a foil-foil aluminum strip that is indexed, and the dose blister is only opened just prior to patient inspiration (Fig. 3).[20,21] Consistent performance,[5] broad patient acceptance,[22,23] and the growing use of combination therapy (long-acting β agonist plus inhaled corticosteroid) for asthma have allowed the Diskus to become the accepted standard multi-dose powder delivery device (Fig. 4).

Factors That Impact Performance and Patient Acceptance

Currently available DPIs are all passive systems, meaning that the patient must provide the energy to disperse the

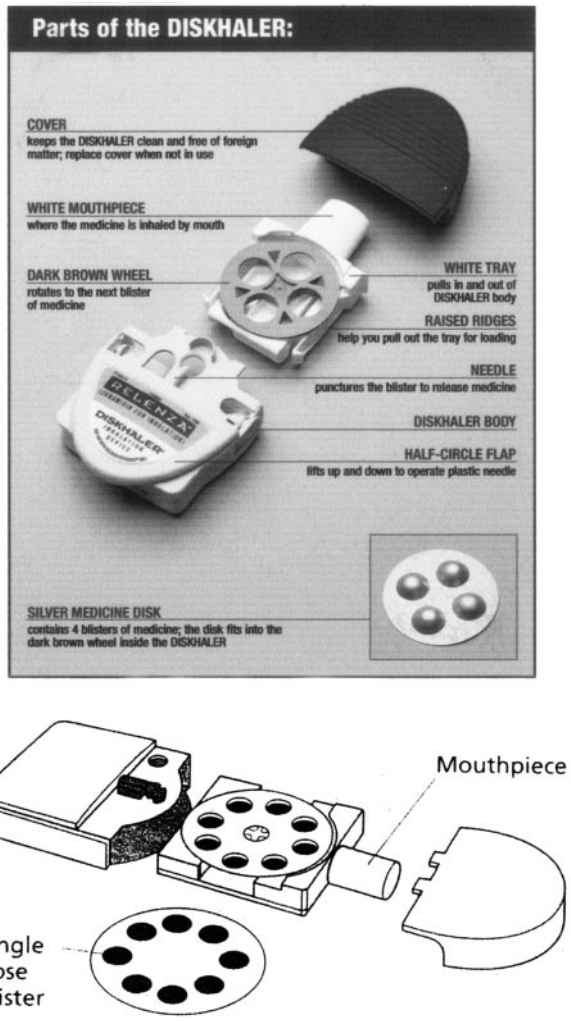

Fig. 2. Relenza Diskhaler. (Photograph courtesy of GlaxoSmithKline. Diagram from Reference 20, with permission.)

powder from the device. The performance of these devices depends on both the formulation and the geometry of the air path in the device. Thus, frequently these delivery systems tend to be compound-specific and, without substantial re-formulation efforts, are not used to deliver other compounds. Typical formulations in DPIs are either drug alone (eg, budesonide in the Turbuhaler) or drug blended with a carrier, typically lactose (eg, formoterol in the Foradil Aerolizer). The requirement for specific DPI formulations is addressed in Hickey's contribution to this Journal Conference,[24] but I will make some general observations regarding current DPI products.

The particle size distribution, both in vitro and, more importantly, in vivo, depends on the patient's ability to pull a certain airflow through the device to create the shear force that disperses the particles. In general, a higher shear leads to a higher percentage of smaller particles, which may be beneficial, depending on the drug being delivered.

Table 1. Resistance of 5 Dry Powder Inhalers

Inhaler	Manufacturer	Resistance (H_2O/L/s)
Rotahaler	GlaxoSmithKline	0.015
Spinhaler	Sanofi-Aventis	0.016
Diskhaler/Diskus	GlaxoSmithKline	0.032
HandiHaler	Boehringer Ingelheim	0.042
Turbuhaler	AstraZeneca	0.044

(Adapted from Reference 4.)

Table 1 shows that there are important differences in resistance among the DPIs, and this difference in resistance causes differences in drug delivery efficiency between these devices.

The patient labeling for DPIs reveals some interesting statistics. For example, with the Spiriva Handihaler,[12] the powder is delivered at a flow as low as 20 L/min. However, when tested under standardized in vitro conditions, the HandiHaler delivers a mean of only 10.4 μg (or 58% of the nominal dose) when tested at a flow of 39 L/min for 3.1 s (for a total of 2 L of inspired volume). For patients with chronic obstructive pulmonary disease (mean forced expiratory volume in the first second 1.02 L, 37.6% of predicted), their median peak inspiratory flow through the HandiHaler was only 30.0 L/min (range 20.4–45.6 L/min). That relatively low flow impacts the amount of drug the patient receives, and the patient instructions include a provision for a second inhalation if all the powder has not been evacuated from the capsule.

Under standard in vitro test conditions, Advair Diskus[1] delivers 93 μg, 233 μg, and 465 μg of fluticasone propionate and 45 μg of salmeterol base per blister from the 100/50 μg, 250/50 μg, and 500/50 μg products, respectively, when tested at a flow of 60 L/min for 2 seconds. In contrast to the HandiHaler, adult patients with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in the first second 20–30% of predicted) achieved mean peak inspiratory flow of 82.4 L/min (range 46.1–115.3 L/min) through the Diskus. Furthermore, adolescents (n = 13, age 12–17 years) and adults (n = 17, age 18–50 years) with asthma inhaling maximally through the Diskus had a mean peak inspiratory flow of 122.2 L/min (range 81.6–152.1 L/min). Among pediatric patients with asthma inhaling maximally through the Diskus, mean peak inspiratory flow was 75.5 L/min (range 9.0–104.8 L/min) among the 4-year-old patient set (n = 20) and 107.3 L/min (range 82.8–125.6 L/min) among the 8-year-old patient set (n = 20).[1]

Thus, it is important that physicians recognize that these devices will deliver different amounts of drug to different patients, and the lung delivery depends on patient factors,

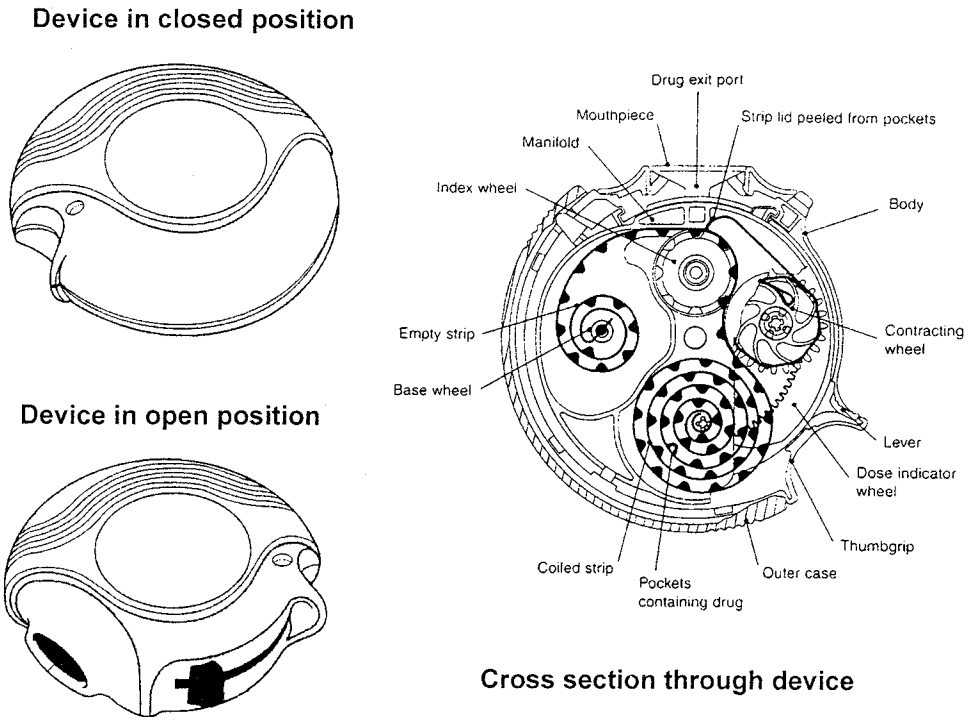

Fig. 3. Schematic of the Diskus powder inhaler. (From Reference 20, with permission.)

Fig. 4. Serevent Diskus (left) and Advair Diskus (right) powder inhalers. (Courtesy of GlaxoSmithKline.)

such as inspiratory flow, patient inhalation technique, and device resistance.

One of the key factors with DPIs is that the various DPIs require different techniques to achieve an appropriate therapeutic dose, unlike MDIs, with which, in general, the inhalation technique is the same. Thus, ease of use and clear, concise instructions are required. In a recent publication by Melani and colleagues,[25] some interesting observations were made linking patient-training with ease of use. In many device-handling studies the simple conclusions are that patients find device A better than device B, although often the criteria evaluated have been extremely subjective. In a recent study[26] conducted in Germany and Holland, it was shown that in elderly patients (mean age 60 years), approximately two thirds ($n = 254$) were able to use the Diskus successfully, without any problems, compared with less than 30% of the patients using HandiHaler. This is at-

tributable to the complex nature of the unit-dose system versus the simpler multi-dose system. In contrast, the study by Melani et al[25] showed that adherence to instructions was poorer with the Diskus and Turbuhaler than with another unit-dose device (the Aerolizer). Indeed, in that study, which examined over 1,400 patients in Italy, the authors concluded that adherence to correct inhaler use was similar across DPIs and, indeed, between the DPIs studied (Aerolizer, Turbuhaler, and Diskus) and an MDI. This was attributed in part to appropriate training prior to product use. Thus, one of the critical factors in ensuring that patients receive the appropriate medication from the currently available passive DPIs is the provision of appropriate training and device education by the health-care provider.

DPI Development

Historically, drug particles for inhalation have been produced by a milling (micronization) process that creates particles of 1.0–3.0 μm (this is absolutely necessary for inhalation). Of critical importance in the development of DPI products is the evaluation, optimization, and control of flow and dispersion (de-aggregation) characteristics of the formulation. These typically consist of micronized drug blended with a carrier (eg, lactose). The properties of these blends are a function of the principal adhesive forces that exist between particles, including van der Waals forces, electrostatic forces, and the surface tension of adsorbed liquid layers.[27] Particle size distribution of the drug and the excipient (lactose) are optimized during early formulation development studies to ensure consistent aerosol cloud formation during subsequent clinical evaluation.

The efficiency of dispersion of DPI aerosols, relative to the various geometric diameters of the particles, may also be an important factor. Specifically, dispersion requires the powder to overcome interparticulate forces that bind particles in bulk powder and to become entrained as single particles in the inhalatory air stream. Interparticulate forces are dominated by the van der Waals force for particles in the respiratory size range. All other factors being equal, the van der Waals force will decrease as the geometric particle size increases. Thus, in general terms, the probability of deposition in the deep lung is at odds with efficiency of dispersion for DPIs.

Environmental factors, especially temperature and humidity, are key factors that can impact DPI formulation stability and performance. The impact of these are studied in early development studies, and often the humidity effects negatively impact the formulation (particularly for lactose blends), making it more cohesive and therefore more difficult to disperse. This will be to some extent dependent on the device/formulation combination, and typically reservoir devices have a poorer ability to protect the formulation from moisture effects. Hence, many of the DPIs now available have secondary packing (a foil overwrap) to protect them from moisture effects until just prior to use.

Some years ago Brown[28] alluded to the complexities involved in the design and development of a DPI. In much the same way as for an MDI, the combination of formulation (drug and carrier), the way that it is presented to the device, and the design of the dosing device itself all contribute to the overall performance of the dosage form. The requirement to use micronized drug with small particles, to achieve good aerodynamic properties of the dispersed powder, is confounded by the need to develop formulations that fill easily and accurately.[29] It is also important that changes in the physical nature of the formulation on transportation and storage are studied and do not adversely affect the product performance.

The development of DPIs has traditionally linked a specific formulation to a particular device geometry that then creates a pneumatic dispersion of the powder to overcome the interparticulate forces and create the aerosol.[30] However, in the past decade, the notion of producing particles of a specific size, density, and morphology has evolved, and has the potential to lead to important advances in pulmonary drug delivery. This advance was recently reviewed by Peart and Clarke[31] and by Koushik and Kompella.[32] The underlying principle is that enhanced performance can be controlled by formulation changes (eg, generating highly porous particles with large geometric diameters but small aerodynamic diameters), an approach characterized as "particle engineering." These complex formulations are then coupled with a simple delivery device. This is clearly a subject of interest for formulation scientists as they strive to develop more efficient powder delivery systems.

The goal of delivering micronized powders is a challenging one. Because of their very nature, these types of powders are highly cohesive. Their high inter-particulate forces make them difficult to de-aggregate: hence, the need for high inspiratory flow and turbulent airflow within DPIs. Inclusion of a carrier can aid in the de-aggregation process, but it can also lead to problems with absorption of atmospheric moisture. The alternative approach to achieving efficient dispersion of these highly cohesive powders is to provide an energy source for dispersion within the device itself, and a number of companies are pursuing this approach. An outline review of some of these approaches is provided below as part of a prediction of future DPI developments.

Future DPI Developments

The delivery of powdered medication for the treatment of lung ailments has been known for centuries, is well

Table 2. Aerosol-Dispersion Mechanisms of Dry Powder Inhalers

Mechanism	Inhaler	Manufacturer
Venturi effect	Easyhaler	Orion
Impact bodies	Clickhaler	Innovata Biomed (IB)
	CertiHaler	SkyePharma
Discharge channels	Turbuhaler	AstraZeneca
	Twisthaler	Schering Plough
Cyclone chambers	Pulvinal	Chiesi
	Airmax	Ivax
	Novolizer	Viatris
	Taifun	LAB International (formerly Focus Inhalation)
Pressurized air*	Inhance	Nektar
	Aspirair	Vectura
Battery powered*	(Inhaler names not yet released)	Microdose Technologies Oriel Therapeutics

*Active powder inhaler (Adapted from Reference 4.)

Fig. 5. Prototype of the Nektar PDS ("pulmonary delivery system") for Exubera. The device slides open and closed like a telescope, for compact carrying and portability. The patient opens the device, inserts the foil blister (which contains the powdered medicine), and pumps the handle, which compresses a small amount of air inside the device. When the patient pushes the button, the compressed air is released at high velocity, which aerosolizes the powder and sends the aerosol into the chamber, where it is a stationary cloud. The patient then inhales the aerosol from the chamber. The patient receives the medicine first, followed by a volume of air, which helps push the drug deep into the lung. (Courtesy of Nektar Therapeutics.)

documented,[33] and is addressed by Anderson in her contribution to this conference.[34] Despite this extensive history, and in part fuelled by a need for alternative pulmonary delivery methods, as the MDI is undergoing environmental challenge, innovative ways to deliver drugs to the lungs continue to be pursued today. As can be seen from the previous discussion, the goal of de-aggregating highly cohesive powder for delivery to the lung in a powdered form is a challenging one.[30] The small dose size required for many of these potent drugs is a confounding factor in developing optimal DPIs. Nevertheless, today it is estimated that annually approximately 100 million multi-dose DPIs are used, on a global basis. This compares with approximately 400 million MDIs. Most of the DPIs contain lactose-based formulations. There has been some concern raised about the use of lactose carriers in asthma patients who have lactose intolerance,[35] although the incidence of this is believed to be small.

As has been discussed by others,[4,30] there are only a limited number of mechanisms for dispersing powdered drugs (Table 2). Many of these devices are now available commercially, although only the Turbuhaler is currently available in the United States.

Much interest has been focused recently on developing delivery systems that de-aggregate the powder,[30–32] as this effectively minimizes formulation-development work. Some of these systems are extremely complex in operation and may prove difficult to achieve in everyday operations. In addition, some designs that have already been achieved (eg, Inhance device for the delivery of 1 mg or 3 mg of inhaled insulin, Nektar Therapeutics, San Carlos, California) are probably too bulky to be fully portable. Others are pursuing smaller and more compact options. A review of the full range of these delivery systems is beyond the scope of this paper, but there are a couple of subjects worth exploring.

A multi-dose reservoir device is now under review with the United States Food and Drug Administration for the delivery of formoterol (Foradil Certihaler, SkyePharma, San Diego, California; Novartis, East Hanover, New Jersey).[36] This would be a major advance, as it would provide a second long-acting β agonist in a multi-dose powder form. In addition, the first use of an active DPI is currently being sought for the delivery of pulmonary insulin (Exubera, Pfizer/Sanofi-Aventis, licensed from Nektar Therapeutics, Fig. 5). The device uses an air pump system that disperses the insulin powder into a spacer chamber, from which the patient can

then inhale. Approval of such a device will pave the way for future developments in this area, and many companies are seeking to follow the path that Nektar Therapeutics has pioneered. In our laboratories[37] we are working to use vibration to disperse powder efficiently and achieve consistent aerosol delivery. Others are using various different techniques. Details of these early development efforts have been extensively described.[4,31,32]

Summary

DPIs are a widely accepted inhaled delivery dosage form, particularly in Europe where they are currently used by an estimated 40% of patients to treat asthma and chronic obstructive pulmonary disease. Their use will continue to grow. The acceptance of DPIs in the United States, after the slow uptake following the introduction of Serevent Diskus in the late 1990s, has been driven in large part by the enormous success in recent years of Advair Diskus. This combination of 2 well-accepted drugs in a convenient and simple-to-use device has created an accepted standard in pulmonary delivery and disease treatment that only a few years ago could not have been anticipated. The DPI offers good patient convenience, particularly for combination therapies, and also better compliance. Adherence may be better, but only if there is sufficient effort put in place to clearly teach the correct use of the device.

The design and development of any powder drug delivery system is a highly complex task. Optimization of the choice of formulation when matched with device geometry is key. The use of particle engineering to create a formulation matched to a simple device is being explored, as well as the development of active powder devices that supply the energy, making it simpler for patients to receive the correct dose. Both of these avenues are being pursued by a number of companies and will result in further advances in DPI technology. Patient interface issues are also critically important. However, common to the development of all systems is an appreciation that one of the most important factors in pulmonary delivery from a DPI is the requirement for a good-quality aerosol (in terms of the aerodynamic particle size of the cloud generated) and its potential to consistently achieve the desired regional deposition in vivo. This has been the goal of many scientists over many years and we are still short of that goal. Today there is still no ideal DPI, unlike the MDI, which has been used ubiquitously. More work is required to ensure that DPIs are made available that are simple, easy to use, and independent of patient effort. Today, if we can make drugs on a chip, we should be able to make better DPIs!

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Discussion

Amato:* Do you think if Advair was introduced as an MDI, it would be as popular as the DPI is? Is its popularity related more to the device or to the drug?

Atkins: As to whether the device or the drug drives physician choice, I think it is usually the drug. I can tell you that, in France, with fluticasone at the same price per dose, patients preferred Diskus over HFA MDI, 65% to 35%. Another aspect is that some small percentage of the population, probably about 10% or less, will not be able to use Diskus or other DPIs. That doesn't answer your question directly, but I think there is probably a preference in some places for Diskus or other DPIs over MDI, but the MDI is going to be around for a while.

Smaldone: I think a lot of it has to do with the market. In the United States there was no heavy competition for the combination product. My answer to Mike's question would be that an MDI version of Advair probably would have been as popular. If you compare the Diskus against the MDI, the Diskus might win, but if the Diskus wasn't there, I don't think the company would have been any less successful with an MDI version.

MacIntyre: I was struck by Tony's [Hickey] comment during his presentation that there will probably not be generic DPIs. But you showed 2 devices that are being used as generic DPIs. Help me reconcile those 2 statements. Can you build a "generic" DPI and then find a product to disperse with it?

Hickey: It's a question of how you consider generic products to perform. If you do it based on performance, which is how the Europeans are looking at it, then it's possible. If you do it based on componentry equivalence, which is the way we look at it in the United States, it's absolutely impossible, because all these devices are different.

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