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Advancements in Dry Powder Delivery to the Lung

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The dry powder inhaler (DPI) has become widely known as a very attractive platform for drug delivery. Many patients have traditionally used DPIs to treat asthma and chronic obstructive pulmonary disease. Recently, the development of new DPIs for delivering therapeutic proteins such as insulin has been accelerated by patient demands, and innovative research. The current market for DPIs has over 20 devices presently in use, and many devices under development for delivering a variety of therapeutic agents. DPIs are recognized as suitable alternatives to pressurized metered dose inhalers for some patients, but the performance of DPI devices may vary according to a given patient's physiological condition. This variation can be associated with the necessary powder dispersion mechanism of each device. As such, much interest has focused on the development of efficient powder dispersion mechanisms, as this effectively minimizes the influence of interpatient variability. This article reviews DPI devices currently available, advantages of newly developed devices, outlines some requirements for future device design.

Keywords carrier particles; powder dispersion; passive inhalation devices; mechanical inhalation devices

INTRODUCTION

Drug delivery to the lung has changed dramatically in recent years. Commercialization of the pressurized metered dose inhaler (pMDI), containing a chlorofluorocarbon (CFC) propellant, began as a convenient system for asthma management in the 1950s. The pMDI has become the most popular device for out-patient inhalation therapy, with its worldwide production exceeding 300 million per year (McDonald & Martin, 2000; Vaswani & Creticos, 1998). However, concerns have often been highlighted over potential drawbacks of pMDI devices: an altogether environmentally incompatible propellant, harmful effects of freons to patients; and perhaps of most concern is the extensive oropharyngeal deposition of the active pharmaceutical ingredient (API) included in the device (Hendeles, Colice, & Meyer, 2007; Molina & Rowland, 1974; Newman, 1990; Oenbrink, 1993). Because the contribution to ozone depletion of CFC was initially hypothesized by Molena and Rowland (1974), pharmaceutical companies were forced to find alternative propellants (Dolovich, 1999a; Lewis, 2007). As a result hydrofluoroalkane (HFA)-based and propellant-free pMDIs were developed as a way to replace CFCs (Acerbi, Brambilla, & Kottakis, 2007; Dalby, Spallek, & Voshaar, 2004; Leach, Davison, & Boudreau, 1998; Zeidler & Corren, 2004). This replacement strategy has not been altogether successful because of several setbacks, including potency, manufacturing cost increase, and reformulation difficulty amongst others (Brambilla et al., 1999; Peart, Magyer, & Byron, 1998).

Problems with the pMDI performance and operational restrictions have spurred the exploration of dry powder systems. As a consequence, many dry powder inhaler (DPI) devices have emerged and a number of them have been introduced onto the market. Since the first single-dose DPI product, new the Spinhaler® (Sanofi-Aventis, Holmes Chapel, UK) (formerly Fisons, Loughborough, UK), appeared on the market, the devices have made remarkable progress in various aspects such as dose-metering, dose-dispensing, and aerosolization systems for dry powder particles (Ashurst, Malton, Prime, & Sumby, 2000; Labiris & Dolovich, 2003b; Smith & Parry-Billings, 2003; Smyth & Hickey, 2005). Additionally, attempts have been made to deliver peptides and proteins (e.g., insulin) via pulmonary route using novel inhalation devices such as Exubra® (Nektar therapeutics, San Carlos, CA, USA), Spiro® (Dura Pharmaceuticals, San Diego, CA, USA), and AIR™ (Alkermes Cambridge, MA, USA).

This review therefore focuses on notable progresses in dry powder formulation, and delivery devices, which are now commercially available or in currently under development.

Delivery of Peptides and Proteins

The pulmonary route of administration has many potential advantages for the delivery of macromolecules compared with other administration routes. This is because the lungs have a large surface area for absorption, high permeability through a thin membrane, the membrane is smaller than that of the gastrointestinal tract (Labiris & Dolovich, 2003a; Patton, 1996, 1997), few proteases for degredation of the API (Labiris &

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Dolovich, 2003a), no first-pass hepatic clearance/metabolism (Labiris & Dolovich, 2003a), and the reported excellent bioavailability for some molecules (Patton, 1997; Patton, Bukar, & Nagarajan, 1999). Therefore, the idea of delivering a therapeutic peptide or protein, such as insulin, or growth hormone via pulmonary route has been addressed by many research groups and pharmaceutical companies (Bindra & Cedalu, 2002; Mandal, 2005; Patton, 2005; Shoyele & Slowey, 2006; Valente, Langer, Stone, & Edwards, 2003). In particular, research into inhaled insulin has increased because of the potential of improved patient care and compliance for individuals suffering from diabetes.

Insulin is a protein with a molecular weight of 5.7 KDa. It has been considered as a candidate for non-invasive delivery since its discovery (Mandal, 2005; Valente et al., 2003). Considering the various routes for non-invasive delivery of insulin, the major problem for oral and nasal administration is a low and variable bioavailability, as it is reported that insulin has difficulty passing through the respective epithelial membranes because of its large molecular weight (Mayer, Zhang, & DiMarchi, 2007; Patton et al., 1999). The only available route of administration for insulin for an out-patient has been through subcutaneous (SC) injection (American Diabetes Association, 2003). Delivery of insulin via pulmonary route promises to provide many advantages to patients due to alleviate their suffering from painful injection (Cappelleri, Cefalu, Rosenstock, Kourides, & Gerber, 2002; Cramer, Okikawa, Bellaire, & Clauson, 2003; Ellis, Gemperline, & Garg, 2007).

Inhaled insulin first entered clinical human trials in the mid-1990s. Since then, the commercial potential and technical challenges of an inhaled insulin product have grown (Bindra & Cedalu, 2002; Mandal, 2005; Patton, 2005; Valente et al., 2003).

COMMERCIALLY AVAILABLE DPI DEVICES

DPIs are designed to impart energy into the powder formulation to overcome gravitational and electrostatic forces; this disrupts the aggregates formed by interparticulate forces, so that particles may be inhaled and deposited in the lung at their primary particle size (Voss & Finlay, 2002). The overall performances of DPI systems are influenced by several factors including design of the powder formulation, the dose-metering systems, and the mechanism used to disperse the powder as an aerosol (Dunbar, Hickey, & Holzner, 1998; Peart & Clarke, 2001). Therefore, powder formulation–device combinations must be optimized to generate aerosolized drug, which have an appropriate particle size distribution and concentration to ensure optimal deposition and dose in the desired region of the lung. Additionally, in order to minimize interpatient variability in terms of anatomy, physiology, ability to use devices correctly, and variable disease state, development of patient-independent devices could also potentially be considered.

DPIs in common use today are breath-actuated or passive devices. Those patient-driven passive devices have the advantage that drug release is automatically coordinated with patient's inhalation. Ironically, the advantage of this passive system raises many problems because the devices currently available have different air flow resistance that govern patient's inspiratory flow rate (Tarsin, Pearson, Assi, & Chrystyn, 2006; Tiddens et al., 2006). To generate a therapeutically effective amount of drug aerosol particles, a certain inspiratory effort from a patient is required (Breeders, Molema, Vermue, & Folgering, 2001; Cegla, 2004; De Boer, Winter, & Lerk, 1996). However, this requirement may be difficult for some patients with asthma, chronic obstructive pulmonary disease (COPD), or in elderly patients and young children (Sarinas, et al., 1998; Stanescu, Veriter, & Van de Woestijne, 2000; Tiddens et al., 2006). In addition, the amount of lung deposition for an inhaled drug in an individual patient's lungs is variable, depending on the overall inspiratory flow rate the patient can generate at a given time. Several studies have shown that dosing performance of passive dry powder devices in terms of total dose or fine particle dose emitted from the device is dependent on patient inspiratory flow rate (Steckel & Muller, 1997; Tarsin et al., 2006). Table 1 lists performance of some selected marketed devices (Ashurst et al., 2000; Borgstrom, Bondesson, Moren, Trofast, & Newman, 1994; Chrystyn, 2006;

TABLE 1
The Performance Features of Selected Passive Devices

Device	Drug	Carrier	Type	Inhalation	Deposition (%)	Reference
Rotahaler	Sodium cromoglycate	Lactose	S (C)	60 L/min	6.2	Vidgren et al. (1988)
Spinhaler	Sodium cromoglycate	Lactose	S (C)	60–120 L/min	5.5–13.1	Newman et al. (1994)
Diskhaler	Salbutamol	Lactose	M (B)	—	11%	Melchor et al. (1993)
Turbuhaler	Budesonide	Free	M (R)	35–60 L/min	14.8–27.7	Borgstrom et al. (1994)
Pulvinal	Salbutamol	Lactose	M (R)	28–46 L/min	11.7–28.9	Pitcairn et al. (1994)
Easyhaler	Salbutamol	Lactose	M (R)	28.5–65 L/min	25–35	Vidgren et al. (1995) and Crystyn et al. (2006)
Clickhaler	Budesonide	Lactose	M (R)	35–65 L/min	30.8	Warren et al. (1998) and Newhouse et al. (1999)

S, Single-dose; M, Multidose; B, Blister; R, Resevoir; C, Capsule.

Melchor, Biddiscombe, Mak, Short, & Spiro, 1993; Newman, Hollingworth, & Clark, 1994; Newhouse, Nantel, Chambers, Pratt, & Parry-Billings, 1999; Pitcairn, Lunghetti, Ventura, & Newman, 1994; Smith & Parry-Billings, 2003; Vidgren, Karkkainen, Karjalainen, Nuutinen, & Paronen, 1988; Vidgren et al., 1995; Warren & Taylor, 1998).

Particles within the aerodynamic size range of 1–5 μm are effectively delivered to alveoli region by sedimentation (Labiris & Dolovich, 2003a). However, because of their small particle size, manufactured drugs for inhalation are extremely adhesive and cohesive. To minimize the interparticulate forces caused between those small particles, almost all dry powder formulations contain carrier materials such as lactose (Smyth & Hickey, 2005). From the viewpoint of dose metering, carrier formulations are to be preferred (with the carrier acting as a diluent). But these carriers can markedly affect the aerosolization properties of the powder (Smyth & Hickey, 2005; Tobyn, Staniforth, Morton, Harmer, & Newton, 2004; Young, Price, Tobyn, Buttrum, & Dey, 2003). In practice, several early developed devices such as the Spinhaler®, and the Rotahaler® (GlaxoSmithKliene, RTP, NC, USA) have both demonstrated very low distribution of desired respirable-sized particles and lung deposition (~10%) (Newman et al., 1994; Vidgren et al., 1988). In general, this poor performance could be attributed to the incomplete de-agglomeration of small particles from larger carrier particles because of interparticulate forces (Saint-Lorant, Leterme, Gayot, & Flament, 2007; Steckel, Markefka, TeWierik, & Kammelar, 2004).

As indicated, the energy source for de-agglomeration in most DPIs is the shear force associated with a patient's inspiratory flow rate and volume; when a patient's inspiratory air flow pulls particles though a specific de-agglomeration zone in a given device, where fine drug particles may be separated by air turbulence. The particle de-agglomeration capacity of devices varies considerably. For instance, both the Easyhaler® (Orion Pharma, Espoo, Finland) and the Clickhaler® (ML Laboratories PLC, Albanes, UK), which are comparably modern devices, maximize their particle separation by changing the dimensions of the airflow path, and by use of an impaction body, respectively (Chrystyn, 2006; Parry-Billings et al., 1999; Smith & Parry-Billings, 2003). As a result, the fine particle fraction (FPF), and the lung deposition ratio of drug particles are enhanced; compared with those of older devices such as the Spinhaler® and the Rotahaler® (Chrystyn, 2006; Warren & Taylor, 1998). Figure 1 indicates how this separation occurs during inhalation.

The dose-metering and powder-dispensing mechanisms are also very important for the construction and function of a given device along with particle de-agglomeration process [the FDA recommend the submission of a detailed packaging description along with performance and stability data (Guidance for Industry, 1998)].

Accurate dose metering and consistent powder dispensing are directly related to dose reproducibility, and both are essential for maintaining a good therapeutic regimen. Reservoir devices are commonly used because they have relatively simple designs that are cheaper to produce than factory-metered

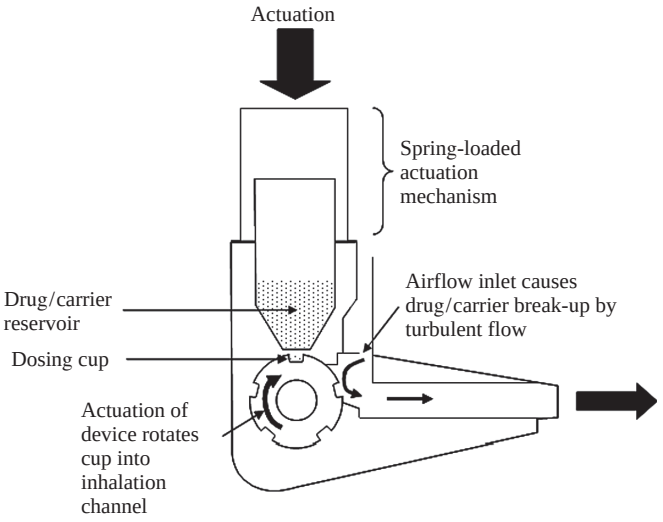

FIGURE 1. Schematic diagram to indicate how fine particles are generated during inhalation using the Easyhaler® device.

devices (e.g., blister, capsule), but have some drawbacks such as dose variability and poor environmental protection (i.e., humidity, temperature) (Borgstrom, Asking, & Lipniunas, 2005; Maggi, Bruni, & Conte, 1999; Meakin, Cainey, & Woodcock, 1993). Several studies have proposed new dose-metering and dispensing methods to improve those drawbacks. The Clickhaler® consists of a hopper reservoir of powder and a dimpled metering cone for dispensing single doses (Newhouse et al., 1999; Smith & Parry-Billings, 2003; Thibert, Parry-Billings, & Shott, 2002). Figure 2 shows schematic diagram of metering cone design of the Clickhaler®, demonstrating a more consistent and flow-rate-independent delivery system (Newhouse et al., 1999). In the Pulvinal® device (Chiesi Pharmaceuticals

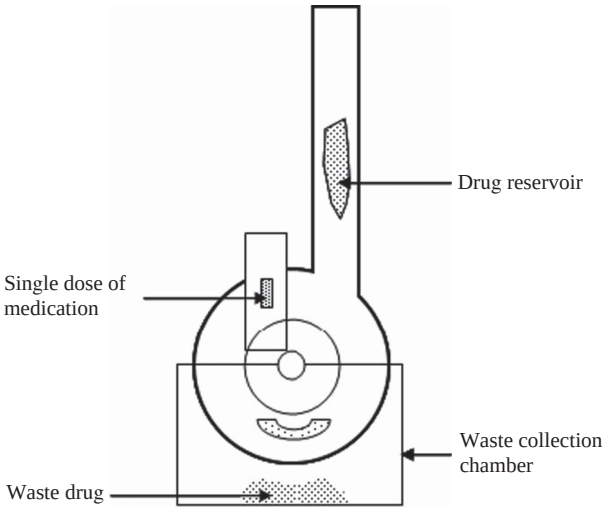

FIGURE 2. Schematic diagram of the metering cone design of the Clickhaler® device.

TABLE 2
Required Characteristics for an Ideal Dry Powder Inhaler (DPI) Device

1. Effective dose
   a. Effective dose-metering method
   b. Consistent dose dispensing
2. Efficient powder dispersion
   a. Maximize particle de-agglomeration
   b. Development of an appropriate separation mechanism
   c. Minimize patient dependency
   d. Ideally, consistent lung deposition across wide flow rate range
3. Achieve good environmental protection
4. Optimized design for new chemical entities and formulations
   a. Large porous particles
   b. Peptide/Protein (e.g., Insulin)
5. Easy to use
   a. Reusable, compact, portable
   b. Dose counter

This table modified from Ashurst et al. (2000).

Ltd., Parma, Italy), bulk powder is protected from the humidity by silica capsule in reservoir (Pitcairn et al., 1994; Smith & Parry-Billings, 2003).

Although passive devices have progressed in their construction and performance, the various systems still face several problems. Table 2 lists the requirements for the development of ideal devices. The development of ideal inhalation systems has been accelerated by an increasing demand from patients, and the advent of new technologies that may be able to meet many of these demands.

NOVEL DRY POWDER DEVICES

Mechanisms of Powder Dispersion

As indicated, during inhalation both adhesive and cohesive forces existing between the drug and the carrier must be overcome in order to generate respirable sized drug particles. As many studies have discussed, the influence of carrier on the performance of DPIs is very significant (Saint-Lorant et al., 2007; Steckel et al., 2004; Tobyn et al., 2004; Young et al., 2003). To successfully overcome those interparticulate forces, efficient powder dispersion mechanisms must be used. At present, the principal forces leading to powder de-agglomeration in inhalers can be divided into frictional forces, drag and lift forces, and internal forces (De Boer, Hagedoorn, Gjaltema, Goede, & Frijlink, 2003; Voss & Finlay, 2002). Those forces are all generated by patient's inspiratory efforts, and the detachment forces increase with increasing inspiratory flow rate through the inhaler. In an effort to minimize the dependence of a given device on the patient's ability to generate a high inspiratory flow rate, several new particle dispersion mechanisms have been developed. Among them, power-assisted active devices are expected to significantly improve the drawback of passive devices. In Table 3, different types of powder dispersion mechanisms are shown.

The Passive Mechanism of Dry Powder Dispersion

The Air Classifier Technology (ACT) is described as an efficient passive dispersion mechanism compared with other passive devices (De Boer, Hagedoorn, Gjaltema, Goede, & Frijlink, 2006b). Tangential air flow generated by a multi-channel classifier forms a cyclone in the device during inhalation. This is a leading mechanism for particle de-agglomeration. The passage of large carrier particles in the cyclone chamber is retarded because of centrifugal energy (De Boer et al., 2003).

Novolizer®. The Novolizer® (Viatris, Bad Homburg, Germany) uses the ACT as a powder dispersion mechanism (Part 3: De Boer et al., 2006a; Part 4: De Boer et al., 2006b). Several published studies have compared the clinical efficacy for in vitro and in vivo drug deposition of the Novolizer®, with other breath-actuated devices such as the Turbuhaler® (AstraZeneca, Lund, Sweden) (Fenton, Keating, & Plosker, 2003; Kohler, 2004; Newman et al., 2000). The Novolizer® delivered more drug to the lung, and the deposition of drug in the mouth and oropharynx was decreased compared with that of the Turbuhaler® (Newman et al., 2000). An average 32% of

TABLE 3
Particle Dispersion Techniques used in Selected Devices

Device	Developer	Technique	Type
Passive			
Novolizer®	Viatris	Air classifier	Multi dose (Reservoir)
AirMax™	Yamanouchi	Cyclone separator	Multi dose (Reservoir)
Taifun®	Leiras OY	Vortex chamber	Multi dose (Reservoir)
AIR®	Alkermes	Narrow passage	Single dose (Capsule)
Active			
Exubera®	Nektar therapeutics	Air pump	Multi dose (Blister)
Aspirair®	Vectura	Air chamber	Multi dose (–)
Spiros®	Dura Pharmaceutical	Battery powder	Multi dose (Disk well)
Jethaler®	RatioPharm GmbH	Mechanical cutter	Multi dose (Ring tablet)

the total emitted dose (TED) was delivered to the lung at an inspiratory flow rate of 99 L/min. However, the drug deposition ratio at different flow rates was still shown to be variable (Newman et al., 2000; Fenton et al., 2003).

AirMax™. The AirMax™ (Yamanouchi, Leiderdorp, Netherlands) has a cyclone separator. The cyclonic flow within the separator is also created by tangential air inlets such as a Novolizer® (Zeng, Jones, O'Leary, Phelan, & Colledge, 2002a). Figure 3A and 3B indicates the separator design aspects of both the Novolizer® and the AirMax™ devices. In vitro performance, using micronized formoterol blended with lactose, of the AirMax™ shows very consistent dose emission, and a high FPF generation of approximately 50% (Zeng et al., 2002a). Tests using either budesonide or salbutamol, on the FPF and TED from the AirMax™ also demonstrated significant improvement compared with that of the Tubuhaler® (Zeng et al., 2002b). Comparative scintigraphic studies of budesonide with AirMax™ and Tubuhaler devices support the results observed in vitro with the AirMax™ device; delivering more consistent amounts of drug to the lung at various flow rates (Hirst, Newman, Clark, & Hertog, 2002). Although the de-agglomeration of particles was significantly enhanced, and the variability is minimized compared to older devices, the overall performance of the device is still dependant on the flow rate generated by the patient like other passive devices (Zeng et al., 2002b).

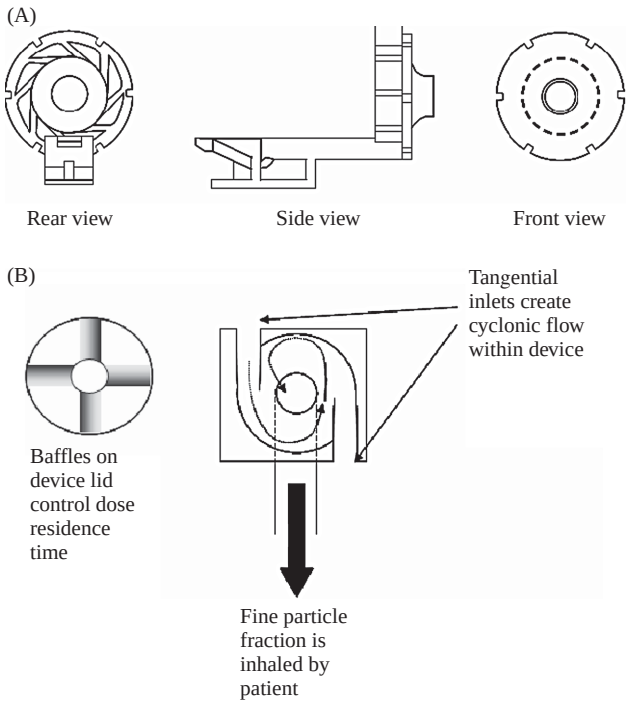

FIGURE 3. (A) Classifier concept with an integral powder channel in the Novolizer®, (B) Schematic diagram of the cyclone chamber in the AirMax™ device.

Taifun®. The Taifun® device (Leiras OY, Turku, Finland) is a breath-actuated device which incorporates a vortex chamber. When air is passed through the vortex chamber, drug particles are separated from the carriers because of the generated air turbulence (Pitcairn, Lankinen, Seppala, & Newman, 2000). The Taifun® device has a high resistance to airflow, and drug delivery to the lungs is relatively independent of the inhalation flow compared with most other dry powder devices. Results for the Taifun® device have shown the mean lung deposition of budesonide to be between 34.3 and 29.6%, with a mean emitted dose from the device to be between 41.6 and 37.3% at 35.8 and 20.6 L/min, respectively (Pitcairn et al., 2000). These results contrast those observed in scintigraphic studies of some other devices, which demonstrate reduced lung deposition with reduced inspiratory effort for the Turbuhaler® or the Novolizer® (Borgstrom et al., 1994; Newman et al., 2000).

Active Mechanisms for Dry Powder Dispersion

Active devices, which have power-assisted powder dispersion systems, have been proposed to make up for potential variability displayed by passive devices as indicated above. Mechanical energy in the form of springs which can generate the compressed air or electrical energy battery storage systems have been used to generate the necessary separating forces for the particles. A possible advantage of this type of device is that achieving uniformity of dosage is less dependent on the patient's inspiration capability.

Exubera®. Exubera® (Nektar Therapeutics, San Carlos, CA, USA) was the first marketed insulin inhalation device. The device consisted of an air-pump-containing base, release unit, chamber, and mouthpiece. In this device, the main energy source for generating aerosol was compressed air. When the patient opened and closed an integrated handle pump, a fixed volume of air was drawn into the base chamber and compressed. Upon actuation, dry powder was dispersed from a blister to dosing chamber by vacuum force (generated when the previously formed compressed air passed though a precision jet-release unit). In contrast with other formulations within blister packs, which may contain a large carrier component such as lactose to facilitate dispersion, dry insulin powders for the Exubera® device did not contain any large carrier particles. Therefore, the energy generated was dissipated for efficient powder dispersal by drawing the drug from the dosage blister pack directly to the dosing chamber (instead of the energy being directed for drug particle separation from the large carrier particle). The in vitro performance, TED, and FPF have been examined at different flow rates (Harper et al., 2007). At an overall flow rate range of 5–56.6 L/min, the TED and fine powder were not significantly changed as a function varying the flow rate (Harper et al., 2007).

Aspirair™. The Aspirair™ device, currently under development by Vectura Ltd. (Chippenham, Wiltshire, UK) is primarily for use to obtain systemic concentrations, and for

conditions where the inspiratory power of the patient cannot be relied upon. This device has an air chamber as an energy source to disperse the powder and vortex chamber to generate a respirable "soft" aerosol (Figure 4) (De Boer et al., 2003; Morton & Staniforth, 2006). Release of compressed air inside the chamber is triggered by patient's inspiration effort, and the released air from the chamber passes through a blister containing the fine powder for inhalation. Finally, the dispersed powder flows into the vortex chamber and is effectively aerosolized by shear forces. In comparison with Exubera®, the Aspirair™ device uses both compressed air and a cyclone chamber instead of jet-release unit to make the overall aerosolization process more efficient. This cyclone chamber effectively disperses the powder and has a net effect of slowing down the air stream, so that aerosolized drug may be delivered directly to the patient through the mouthpiece [this negates the need for a large dose chamber like that seen in the Exubera® device (Morton & Staniforth, 2006)]. Inhaler performance testing indicates that almost 90% of a fine particle formulation containing amomorphine hydrochloride can be dispersed from the device at a flow rate of 60 L/min (Morton & Staniforth, 2006).

Spiro®. The Spiro® inhaler (Dura Pharmaceuticals) is a breath-actuated, multi-dose delivery device under development. In this device, patient's breath is utilized only for activating a battery-powered twin-blade impeller which subsequently generates a powder aerosol cloud. The impeller impacts the powder formulation to efficiently disperse the contents, and the dispersed drug particles may be inhaled during a patient's variable inspiration. This design offers consistent aerosol performance across a range of flow rates. Moreover, it is operable even at very low patient inspiration rates because battery power assists particle de-agglomeration of the powders (Nelson, Kemp, Bieler, Vaughan, & Hill, 1999; Warren, Taylor, Godfrey, Cote, & Hill, 1999). Device performance for APIs including insulin, albuterol sulfate, and bechlomethasone dipropionate (BDP) have been investigated (Nelson et al., 1999; Rave et al., 2004; Warren et al., 1999). A study investigating the delivery of BDP from Spiros® showed that the mean lung dose values were determined to be 40.5% at 15 L/min, 37.5% at 30 L/min, and 30.4% at 60 L/min (Warren et al., 1999). A noticeable result with a very high lung deposition value (~40%) is indicated at 15 L/min. For most passive devices, device performance such as fine powder fraction (FPF) and lung deposition is greater at a high flow rate (Dolovich, 1999b; O'Connor, 2004). However, Spiros® shows an optimal performance at a very low flow rate. This suggests that battery-driven power can effectively support a patient's weak inspiratory flow (useful for a wide range of specific patient populations with breathing difficulties).

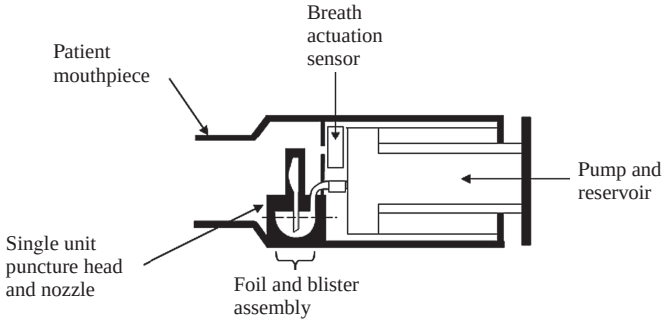

FIGURE 4. Cross-section of the Asirair™ device.

MicroDose. Vibration technique also been has used in aerosol powder-dispersion applications (Brwon, Rasmussen, Becker, & Friend, 2004; Crowder, 2004). A newly developed piezo-electronic inhaler, MicroDose (MicroDose Technologies, Inc., Monmouth Junction, NJ, USA) uses a piezo-vibrator to de-aggregate the drug powder packaged in aluminum blisters. The piezo-vibrator is automatically activated by built-in sensor which is detected by patient's inspiratory airflow. The jet created by piezo-vibrator effectively de-agglomerates powder and evacuates the powder from the blister pack (Brwon et al., 2004). The MicroDose device shows a consistent FPF (~80%) over wide flow rate range (15–60 L/min) (Brwon et al., 2004). Like a Dura's Spiros® device, the main driving force of MicroDose for activating device is battery-powered vibration energy. Thus, the device can be operated at very low patient inspiratory airflow.

Jethaler®. Mechanical forces have also been proposed as novel powder dispersion methods with the above-mentioned air pressure, and electrical energy techniques. The Jethaler® (RatioPharm GmbH, Ulm, Germany), formerly known as Maghaler®, has a "Mechanical Aerosol Generator" (Kunkel et al., 2003; Newman et al., 2002). Upon actuation, the active substance is milled from the pressed ring tablet by mechanical face-cutter and is available for inhalation in a micronized form. This ring tablet, which is compressed by radial isostatic technique (GGU GmbH, Braunschweig, Germany), contains higher amount of drug in the powder blend and uses a much finer lactose carrier instead of a coarse carrier (Newman et al., 2002). In a comparison of content uniformity testing using Novolizer® (Novopulmon®; budesonide) and the Jethaler® (Ratiopharm®; budesonide), a much higher proportion of budesonide was emitted from the Jethaler® device (De Boer, Gjaltema, Hagedoorn, & Frijlink, 2004).

In another study, investigating the use of salbutamol with the Jethaler®, distribution through the respiratory system was found to be largely independent of respiratory flow. In this study, 21.1% of the drug was shown to be delivered into the lung at 30 L/min with 26.4% delivered at 60 L/min (Newman et al., 2002). This is very encouraging when compared directly with a commercially available device such as the Easyhaler®, when the amount of delivered salbutamol is between 15 and 33% at a flow rate range 32 and 62 L/min, respectively (Vidgren et al., 1994).

Overall active devices are more independent of the inhalation maneuver in terms of FPF and uniform lung deposition. However, these types of devices may be much more complex in design, and therefore expensive and vulnerable to mechanical failure (Tobyn et al., 2004).

Dose Metering

Effective dose metering is an essential part of development of new dry powder devices. Drug particles for inhaled therapy may be stored in specific dose-sized containers (e.g., capsules or blister packs) with or without excipient, before aerosolization. Reservoir systems, on the other hand, can contain large amounts of bulk powder for multiple doses. Powder in this type of system is dispensed into a uniformly sized dosing cavity under gravity.

AirMax™

The AirMax™ device does not utilize gravity to meter, instead it employs an air pump to meter out a precise dose of medication. When the patient opens the mouthpiece cover the pump is activated. Activation of the pump exerts a constant air pressure on the powder in the drug reservoir (Zeng et al., 2002a, b). In performance tests, emitted masses of budesonide and formoterol from the AirMax™ were shown to be less variable than that of a conventional multidose dry powder device, the Turbuhaler® (Zeng et al., 2002a, b). Additionally, the emitted mass of drug demonstrated not to be significantly altered by mechanical forces such as shaking (Zeng et al., 2002b).

Ultrahaler™

The Ultrahaler™ (Sanofi-Aventis) and Jethaler® devices both ultilize unique dose-metering systems. The powder formulation for those two devices is formed into a powder compact or tablet (Figure 5) that is actively scraped during metering; in contrast, most reservoir type of devices require free flowing powder for volumetric dispensing (Newman et al., 2002; Pitcairn, Lim, Hollingworth, & Newman, 1997). This type of system can effectively protect the dry powder formulation from the environmental moisture, and demonstrates a highly reproducible dosing (Lim, Shah, Rohatagi, & Bell, 2006; Newman et al., 2002).

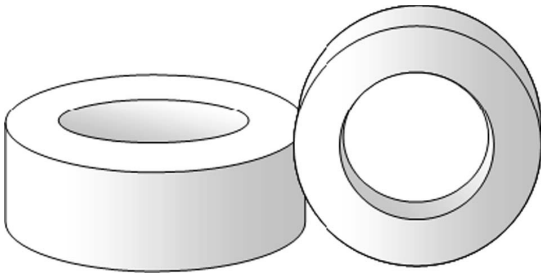

FIGURE 5. Diagram of the ring tablets for the Jethaler® device.

Humidity control inside the reservoir is also an important factor for correct dose metering (Borgstrom et al., 2005; Braun, Oschmann, & Schmidt, 1996; Mackin, Rowley, & Fletcher, 1997; Maggi et al., 1999; Meakin et al., 1993). Relative humidity (RH) has a significant influence on powder performance within drug-carrier formulations. At high humidity conditions, the electrostatic charge between drug and carrier is generally reduced by the increasing capillary force, evident as an adhesion force in lactose-blended formulations (Zeng, Martin, & Marriot, 2001). However, under low RH (i.e., <50% RH), capillary forces become less significant, and electrostatic force increases (Zeng et al., 2001). Therefore, balancing RH inside the reservoir must be considered to avoid strong electrostatic forces and subsequent high levels of adhesion between the drug and the carrier particles.

Taifun®

The Taifun® device has an advantage in terms of effective humidity control. This device was designed to maintain RH between 30 and 60% inside the API reservoir, achieved by the incorporation of a desiccant container (incorporating silica gel) within (Lehto & Lankinen, 2004). This double-barrier system controls RH inside the reservoir more effectively when compared with single-barrier system as with the Pulvinal® device (Lehto & Lankinen, 2004). In stability tests, the RH value was shown to be maintained between 27 and 60% for up to 330 days, and the powder reservoir also displayed a reversible sorption–desorption isotherm relative to environmental humidity (Lehto & Lankinen, 2004).

Recent Advances in Dry Powder Formulation Design

Therapeutic dry powder aerosols have classically been made with particle geometric diameters of less than 5 μm to achieve deep lung deposition (Labiris & Dolovich, 2003a). However, studies have indicated that large porous particles (>5 μm) which have low density are also good candidates for drug delivery via pulmonary route (Edwards et al., 1997). Some research has pointed toward good deposition efficiency of large porous particles (Ben-Jebria, Eskew, & Edwards, 2000; Dunbar et al., 2002; Edwards et al., 1997; Musante et al., 2002; Newhouse et al., 2003). The geometric diameter is related to the aerodynamic diameter for spherical particles as indicated in Equation 1, and as a result an aerodynamic particle size is present because of their low density (Edwards et al., 1997).

$$da = \rho^{1/2}\, d \quad (\rho\text{: density, } d\text{: geometirc diameter, } da\text{: aerodynamic diameter}) \tag{1}$$

Increasing the geometric diameter increases the dispersibility of the powder, making it possible to efficiently deliver a wide

range of doses using a simple device. In terms of powder de-agglomeration, these large particles do not require much energy input for generating an aerosol, because large porous particles aggregate less and de-aggregate easily under less shear force than smaller and non-porous particles. Therefore, the inhalation device used for this type of formulation generally has simpler and more compact features than other devices used for traditional dry powder formulations.

AIR®

The AIR® (Alkermes, Cambridge, MA, USA) inhaler is a representative example of this kind of small, simple device (Ellis et al., 2007; Muchmore, Silverman, de la Pena, & Tobian, 2007), Figure 6 shows the features of the AIR® device. The AIR® particle technology involves manufacture of relatively large, low-density drug particles containing insulin within an excipient matrix composed predominantly of natural lung surfactant dipalmitoyl phosphatidylcholine (DPPC) (Vanbever et al., 1999). Insulin particles pre-filled in a hard gelatin capsule are dispersed because of capsule's spin motion during inhalation (Ellis et al., 2007; Muchmore et al., 2007). In vivo drug delivery has been characterized by gamma scintigraphy, and in vitro testing has determined the emitted dose over a range of flow rates for the device (Delong et al., 2005). The mean lung deposition was shown to be 51% of TED across an inspiratory flow rate (12–86 L/min). Because of the particle characteristics, the amount of drug deposited into the lung has been demonstrated to be significantly higher than other breath-actuated devices. Additionally, this ratio was not variable overall at the tested flow rate range (Delong et al., 2005).

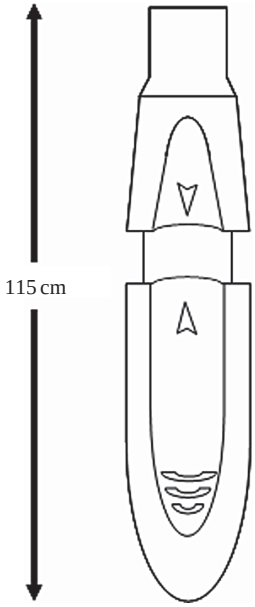

FIGURE 6. Diagram of the AIR® insulin inhaler device.

PulmoSphere®

PulmoSphere® (Nektar Therapeutic, San Carlos, CA, USA) formulations have been engineered to show improved powder flow and dispersibility relative to traditional micronized drug. These microparticles are manufactured by a spray-drying technique (Dellamary et al., 2000). The formulations have a porous surface structure like AIR® powder, with comparably small geometric particle size distributions. Each particle has sponge-like appearance, with a geometric diameter of about 4 μm and an aerodynamic diameter of about 1 μm (Figure 7A). Improved powder properties lead to increased delivery efficiency, and a reduction in the inspiratory flow rate-dependent deposition, as seen with traditional micronized drug powders delivered from passive devices (Duddu et al., 2002).

Technosphere®

Technosphere® (MannKind Corp., Valencia, CA, USA) inhalation powders were developed to deliver large peptides

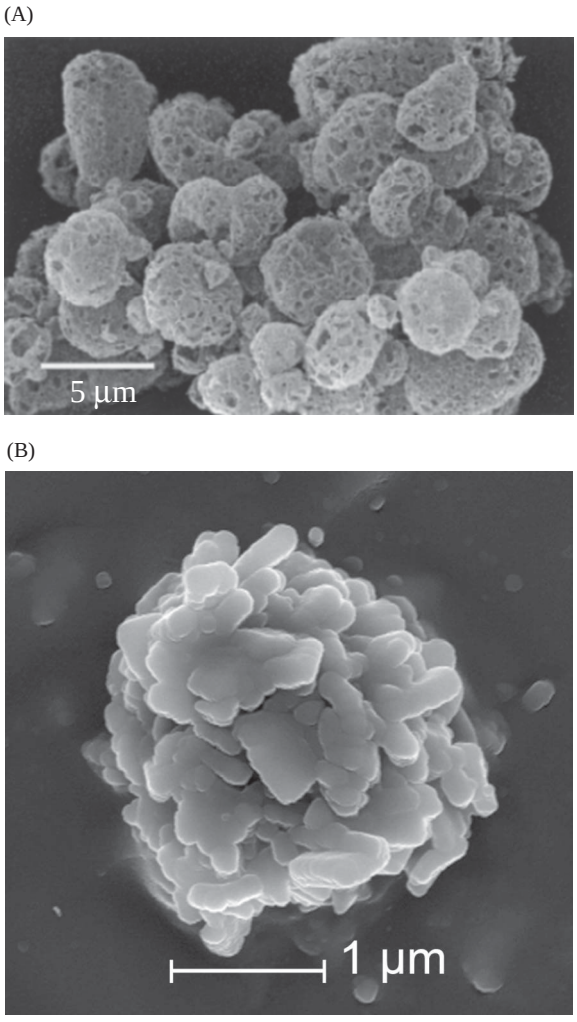

FIGURE 7. (A) Scanning electron microscopy image of a PulmoSphere® formulation, (B) Scanning electron microscopy image of Technosphere® particles.

via pulmonary route, having a size of 2–3 μm in diameter (Figure 7B). The formulations make use of fumaryl diketopiperazine (FDKP) as a carrier material, which can self-assemble into particles with a very large surface area and a high internal porosity (Richardson & Boss, 2007). These novel powder formulations can be delivered through the MedTone® DPI (Mannkind Corp.), which was specifically developed for use with the Technosphere® technology. The inhaler is a breath-actuated, single-dose device. A reusable cartridge containing powder is inserted into the dispersion chamber of the inhaler, and a patient self administers the drug by taking a deep breath (Richardson & Boss, 2007).

Recently, several other research groups have focused on the development of novel formulation designs for efficient powder delivery to the lung such as liposomes, and other engineered particles using various materials (chitosan, cyclodextrin, hyaluronic acid, etc.) (Cook, Pannu, & Kellaway, 2005; Corrigan, Healy, & Corrigan, 2006; Sebti et al., 2006). Relatively sophisticated formulation designs can effectively be delivered by very simple devices. The performances of these devices may be successfully controlled by the powder formulation properties. Hence, optimizing the formulation is another way of developing an efficient dry powder delivery system.

Patient Compliance

Convenience of use should be considered in parallel to the functional aspects in development of new delivery devices. To prevent side effects of inhaled drug because of incorrect operation by patients, certain delivery device requirements such as a dose counters, and dose-ready indicators should be incorporated into the device. In addition, more compact and simple designs are preferred for improved patient compliance (Moore & Stone, 2004). Several devices have been recently developed, such as AirMax™ and Novolizer® to incorporate more user friendly design features than older devices. Almost all devices have dose counters and dose-metering systems, and may be easily activated by simple patient operations, that is, pushing a button or opening a mouthpiece cover (Kohler, 2004; Muchmore et al., 2007; Newman et al., 2002; Richter, 2004; Zeng et al., 2002b). Additionally, a specific patient orientation for inhalation is not required in most cases, because of their unique features such as dose metering by pressurized air and customized formulation. The operating procedures of old and new devices are summarized in Table 4. These operations are vast improvements over variable patient activities, such as shaking or tapping to prime a device (Cochrane, Bala, Downs, Mauskopf, & Ben-Joseph, 2000; Moore & Stone, 2004). However, some active devices must ultimately have some degree of complexity in order to achieve their performance goals. For instance, Exubera® is actuated by very complicated mechanism and aerosol performance significantly decreases with a dwell time increase in the dosing chamber (Harper et al., 2007).

CONCLUSIONS

DPI delivery systems are increasingly likely to feature in future aspects of successful drug delivery; not only to treat asthma and COPD, but also to deliver a wider range of drugs intended both for local and for systemic applications. DPIs can successfully overcome many drawbacks of pMDIs; it is ultimately the patient inspiratory effort that generates aerosolized drug particles, instead of environmentally harmful propellants such as CFCs and or HFAs. All currently marketed DPI devices are patient-driven passive devices. In terms of drug

TABLE 4
Operational Requirements used for Selected Devices Prior to Inhalation

Device	Position	Opening	Priming
Turbuhaler®	Upright	Cap removal	Twisting base in one direction and back again Tapping the device Pressing the button on the mouthpiece
Pulvinal®	Upright	Cap removal	Twisting the body a half-turn anticlockwise and back again
Diskus®	—	Cap removal	Sliding the lever Shake inhaler
Clickhaler®	Upright	Cap removal	Pressing dose button Inset blister Lift a handle and back
Exubera®	—	Open dosing chamber	Press actuation button Rotate the mouthpiece Place the capsule
AIR®	—	Mouthpiece removal	Replace the mouthpiece
Novolizer®	Horizontal	Cap removal	Press the button
AirMax™	—	Open the cap	Open the cap

delivery, the development of these passive devices has made remarkable progress. However, the performance of passive devices to generate a fine aerodynamic particle fraction, and emitted dose may be changed by patient's inspiration force. Thus, device performance is directly related to the amount of inhaled drug. Minimization of patient variability has led to newly developed devices that adopt efficient aerosolization mechanisms. Active devices, having an independent energy source for powder dispersion (such as air pressure, battery, or mechanical grinders), demonstrate potential solutions for the drawbacks of passive devices. Also, the development of new enhanced formulation designs demonstrate better drug delivery efficiency and less variability than traditional microparticles for DPI devices. Finally, the intrinsic stability of dry powders my lead to increased delivery of delicate therapeutic proteins/peptides through the pulmonary route that may otherwise be degraded by other routes.

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