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Mini review

Dry powder inhalers (DPIs)—A review of device reliability and innovation

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ABSTRACT

A wide range of dry powder inhaler (DPI) devices are currently available on the market to deliver drugs into lungs with a view to maximise drug delivery with low variability. DPIs also face numerous clinical challenges, particularly related to variable patient factors such as age, clinical condition and inspiratory flow. Due to the drug formulation and the design of devices, different DPIs do not show the same performance and manufacturers are taking a variety of device design approaches. The characteristics of an ideal DPI, recent innovations in powder formulation and device design are not universally reliable in terms of dose variability, clinical efficacy, user friendliness and economy. This mini review examines whether device reliability is more important than innovation. This study enables a comparison of the relative merits of optimising existing DPIs or seeking to develop novel devices.

1. Introduction

Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. DPIs have a number of advantages over other methods of pulmonary drug delivery, for example, direct delivery of drug into the deep lungs utilizing the patient's respiration and are increasingly being explored as a mechanism for the delivery of systemic drugs. Successful delivery of drugs into the deep lungs depends on the integration between powder formulations and the device performance (Peart and Clarke, 2001). Licensing and marketing approval requires that current DPIs demonstrate *in vitro* performance and *in vivo* efficacy and reliability. However, questions remain about the ability to interchange DPIs and the effects of different clinical states and patient characteristics.

Dry powders for inhalation are formulated either as loose agglomerates of micronised drug particles with aerodynamic particle sizes of less than 5 μm or as carrier-based interactive mixtures with micronised drug particles adhered onto the surface of large lactose carriers (Hersey, 1975). For topical respiratory drug delivery, a particle size of 2–5 μm yields optimal benefit, whereas for systemic effects particle size of less than 2 μm is needed for drug deposition in the small peripheral airways. Particles greater than 5 μm may also result in systemic effects due to impaction in the throat (i.e., oropharyngeal delivery) and oral absorption (Newman and Clarke, 1983; Byron, 1986; Hickey, 1992; Bisgaard, 1996). The powder formulation is aerosolized through a DPI device, where the drug particles are separated from the carrier (from drug–carrier mixtures) or deagglomerates drug particles, and the dose is delivered into the patient's deep lungs. In these systems, particle size and flow property, formulation, drug–carrier adhesion, respiratory flow rate and design of DPI devices extensively influence the performance (Hickey and Concessio, 1997).

Since the inception of the first DPI Spinhaler® (Aventis), device technology has continued to grow and a lot of devices are now currently available on the market; however, no devices have shown remarkable efficiency in delivering drugs from the formulation. Researchers are searching ways to improve the efficiency of drug delivery from DPI by changing formulation technology, designing drugs and carriers and designing new devices. Currently, a large number of DPI devices are on the market, a significant number are awaiting Food and Drug Administration (FDA) approval, some are under development and a large number have been patented and/or applied for patent and have not been perfected. Therefore, the aim of this paper is to determine whether device reliability is more important than innovation. This question can be interpreted in a number of ways. Some may define innovation as the development of an entirely novel system for dry powder inhalation. Others would suggest that it can also mean improvements in existing devices. Therefore, innovation and improvements in device reliability may not be mutually exclusive. For the purposes of this discussion the question has been interpreted as meaning 'should our research efforts focus on optimising existing DPIs or pursuing the development of novel DPIs?'

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This paper discusses factors for consideration in the design of DPIs, limitations in current DPIs, the characteristics of an ideal DPI and recent innovations in powder formulation and inhalation devices. This discussion enables a comparison of the relative merits of optimising existing DPIs or seeking to develop novel devices.

2. Dry powder inhalers

The aerosolization or inhalation of medicaments by humans has been used since late the 1950s and since 1956, the pressurised metered dose inhaler (pMDI) become the most commonly used device to deliver inhaled asthma drugs (Freedman, 1956); however, with the advancement of science and technology, pulmonary delivery of drugs has become the route of choice after the introduction of the DPI in 1967 (Altounyan, 1967; Bell et al., 1971). Inhalation therapy, or pulmonary drug delivery, via pMDIs, DPIs or nebulisers, is the preferred method of treating patients with asthma (Kirk, 1986; Byron and Patton, 1994; Sheth, 2002). The clinical features of nebulisers, pMDIs and DPIs have recently been compared and pulmonary drug delivery is increasingly becoming a target for systemic drug delivery as a result of its inherent convenience, ability to administer drugs with poor oral availability, and the large surface area of lungs and long residence times associated with peripheral lung deposition (Byron and Patton, 1994; Patton, 1996; Cochrane et al., 2000; Groneberg et al., 2003).

DPIs represent the most rapidly expanding field in pulmonary drug delivery in recent years, largely as a result of the perceived limitations in pMDIs and nebulisers (Hickey et al., 1994). Unlike pMDIs, DPIs avoid problems inherent in the use of propellant gases and the need for coordination of inhalation and actuation (Hickey et al., 1994). DPIs are also very portable, patient friendly, easy to use and do not require spacers (Geller, 2005). DPIs are subject to strict pharmaceutical and manufacturing standards by regulatory bodies, the most challenging of which is the demonstration of device reliability in terms of delivered dose uniformity (Newman and Busse, 2002).

2.1. Development of an ideal DPI

The inhalation device is important in achieving adequate delivery of inhaled drug to lungs. The device should be easy to use, inexpensive and portable. The device must provide an environment where the drug can maintain its physicochemical stability and produce reproducible drug dosing. The device should be designed to deliver high fine particle fraction (FPF) of drugs from the formulations (Srichana et al., 1998). However, devices with higher resistance, need a higher inspiratory force by the patients to achieve the desired air flow. This could be difficult for patients with severe asthma and for children and infants. Therefore, a balance between these two factors is necessary to achieve the desired therapeutic effect from DPI formulations.

For an ideal DPI a number of characteristics are important for device reliability, clinical efficacy and patient acceptance. These include:

- a device which is simple to use, convenient to carry, contains multiple doses, protects the drug from moisture and has a indicator (audiovisual) of doses remaining (Ashurst et al., 2000; Sheth, 2002; Helen, 2001; Newman, 2004; Hickey and Crowder, 2007);
- dose delivery which is accurate and uniform over a wide range of inspiratory flow rates (Ashurst et al., 2000; Sheth, 2002; Newman, 2004; Chrystyn, 2006);
- consistent dose delivery throughout the life of the inhaler and consistency of dose when compared to other similar inhalers (Ashurst et al., 2000; Newman and Busse, 2002);
- optimal particle size of drug for deep lung delivery (Clark, 1995);
- suitability for a wide range of drugs and doses (Newman, 2004);
- minimum adhesion between drug formulation and devices (Byron, 2004);
- product stability in the device(Clark, 1995; Ashurst et al., 2000; Byron, 2004; Newman, 2004);
- cost-effectiveness (Clark, 1995; Bisgaard, 1996); and
- feedback mechanism to inform the patient of dose administration (Ashurst et al., 2000; Newman, 2004).

No DPIs achieve all of these ideal characteristics; however, considerable research is being conducted to improve their performance characteristics where necessary. Some of these ideal characteristics are more important than others and will require different levels of improvement and/or innovation. Furthermore, others are influenced by the need for patient education in the proper use and storage of their DPI.

2.2. Considerations in the development of DPIs

For DPIs and other inhalers the dose received by the patient is dependent on four interrelated factors (Atkins, 2005; Hess, 2005; Chan, 2006):

1. the properties of the drug formulation, particularly powder flow, particle size and drug–carrier interaction;
2. the performance of the inhaler device, including aerosol generation and delivery;
3. correct inhalation technique for deposition in the lungs; and
4. the inspiratory flow rate.

The optimisation of the drug formulation is often dependent upon the type of device used and as such they are often formulated together (Newman and Busse, 2002; Atkins, 2005). Therefore, the inhaler–drug combination is generally considered a unique medication whose *in vitro* performance and *in vivo* efficacy must be demonstrated (de Boer et al., 1996; Borgstrom et al., 2005; Sato et al., 2005; Rosenstock et al., 2007). For example, lung deposition of budesonide (1000 μg) delivered via a Turbuhaler® was 2.2-fold higher than that of fluticasone propionate (1000 μg) via Diskus®. The systemic bioavailability of budesonide via Turbuhaler® was 3-fold higher than fluticasone via Diskus®; however, similar plasma cortisol suppression was observed in both cases (Thorson et al., 2001). In another study, inhalation of fluticasone propionate (250 μg) delivered via Diskus® inhaler and budesonide (600 μg) delivered via Turbuhaler® in patients with asthma has been conducted and fluticasone propionate produced similar effect compared to that of budesonide (Backman et al., 2001). Higher lung deposition (31.0%) of budesonide (800 μg) via a Turbuhaler® was also observed while compared with that of fluticasone (750 μg) deposition (8%) via a Diskus® inhaler (Agertoft and Pederson, 2003). *In vitro* and *in vivo* performances of a new device Swinghaler®, a multi-dose inhaler device has been evaluated for procaterol and budesonide, and Swinghaler® showed an equivalent plasma concentration of budesonide as that using the Turbuhaler® (Sato et al., 2005). Using a new device both *in vitro* and *in vivo* delivery of a tailor made placebo powder and insulin, was carried out and more than 50% lung deposition of powders was observed (Rosenstock et al., 2007). There are many factors that affect the quality of device, formulation, and drug delivery pattern from different devices. Therefore, well-defined *in vitro* and *in vivo* studies may help select best inhalers to achieve maximum therapeutic benefits.

Clinical effectiveness of a DPI is also influenced by drug factors such as potency, pharmacokinetics, safety and efficacy, patient factors (such as disease severity and age), inhalation technique and compliance (Kelly, 2002). Similar levels of clinical effectiveness of different DPIs, particularly for asthma, have been demonstrated through randomised controlled trials. However, this is sometimes questioned in real-life where patient factors are more variable (Thomas and Williams, 2005). Despite this, patient factors can be harmonised to a certain extent, particularly factors such as inhalation technique and compliance. Evidence has shown that a patient's pattern of inhalation can be changed with education so as to improve the performance of the DPI (Kelly, 2002; Smith and Parry-Billings, 2003; Hess, 2005).

2.3. Current dry powder inhalers on the market

The inhaler device is very important in successful development of DPI products. Presently, over 20 DPI devices are available on the market and more than 25 are in development, but no device meets all of the requirements of an ideal DPI device mentioned in Section 2.1. A list of current DPI devices with delivery mechanism has been presented in Table 1. Photographs of some currently available devices are presented in Fig. 1.

There is a wide range of DPI devices, single or multiple dose devices, breath activated and power driven, are available in the market (Table 1); however, the development of novel devices with new designs continues because the design of device affects DPI performance (Coates et al., 2004). Currently, based on the design, DPI devices may be classified into three broad categories, i.e., the first generation DPIs, the second generation DPIs and the third generation DPIs. The first generation DPIs were breath activated single unit dose (capsule), i.e., the Spinhaler® and Rotahaler® and the drug delivery issues were related to particle size and deagglomeration of drug–carrier agglomerates or drug–carrier mixtures delivered by patient's inspiratory flow. The second generation of DPIs use better technology, i.e., multi-dose DPIs (they measure the dose from

Fig. 1. Photographs of some currently available DPI devices: (A) Aerolizer™, (B) Easyhaler™, (C) Turbohaler™, (D) Diskhaler™, (E) Novolizer™, (F) Rotahaler™, (G) Clickhaler™, (H) MAGhaler™, (I) Spinhaler™, (J) Handihaler™ (*Source*: Photograph of some devices are taken in the laboratory; and from the web: http://images.google.com.au/inages).

Table 1
Current DPI devices available in the market

Device	DPI type	Company	Delivery method	Drugs	Diseases
First generation: breath actuated single unit dose					
Spinhaler	Single dose	Aventis	Capsule	SC	Asthma
Rotahaler	Single dose	GlaxoSmithKline	Capsule	SS, BDP, SS + BDP	Asthma
Inhalator	Single dose	Boehringer-Ingeheim	Capsule	Fenoterol	Asthma
Cyclohaler	Single dose	Pharmachemie	Capsule	SS, BDP, IB, BUD	Asthma
Handihaler	Single dose	Boehringer-Ingeheim	Capsule	Tiotropium	COPD
Aerolizer	Single dose	Novartis	Capsule	Fomoterol	Asthma
FlowCaps	Single unit dose	Hovione	Capsule	NA	Asthma
TwinCaps	Single dose	Hovione	Capsule	Neuraminidase inhibitors	Influenza
Second generation DPIs: breath actuated multi-unit, multiple dose					
Turbohaler	Multi-dose	Astra Zeneca	Reservoir	SS, TS, BUD	Asthma
Diskhaler	Multi-unit dose	GlaxoSmithKline	Blister package	SX, BDP, FP, zanamivir	Asthma, Influenza
Diskus/Accuhaler	Multi-unit dose	GlaxoSmithKline	Strip pack	SS, SX, FP, SX + FP	Asthma
Aerohaler	Multi-unit dose	Boehringer-Ingeheim	-	IB	Asthma
Easyhaler	Multiple dose	Orion Pharma	Reservoir	SS, BDP	Asthma
Ultrahaler	Multiple dose	Aventis	Reservoir		
Pulvinal	Multiple dose	Chiesi	Reservoir	SS, BDP	Asthma
Novolizer	Multiple dose	ASTA	Reservoir Cartridge	BUD	Asthma, COPD
MAGhaler	Multiple dose	Boehringer-Ingeheim	Reservoir	SS	Asthma
Taifun	Multiple unit dose	LAB Pharma	Reservoir	SS	Asthma
Eclipse	Multiple unit dose	Aventis	Capsule	Sodium chromoglycate	Asthma
Clickhaler	Multiple dose	Innoveta Biomed	Reservoir	SS, BDP	Asthma,
Asmanex Twisthaler	Multiple dose	Schering-Plough Corporation	Reservoir	MF	Asthma
Third generation DPIs: active device					
Exubera	Single dose	Pfizer	Blister	Insulin	Diabetic
Airmax	Multi-dose	Norton Healthcare	Reservoir	Formoterol, BUD	Asthma, COPD

MF: mometasone furoate, SS: salbutamol sulphate, SX: salmeterol xinafoate, FP: fluticasone propionate, BUD: budesonide, TS: terbutaline sulphate, F: fenoterol, formoterol, IB: ipratopium bromide, Ti: triotpium, SC: sodium cromoglycate, BDP: beclomethasone dipropinate, EFD: eformoterol fumarate dihydrate.

a powder reservoir) or multi-unit dose (they disperse individual doses which are premetered into blisters, disks, dimples, tubes and strip by the manufacturers) and multi-unit dose devices are likely to ensure the reproducibility of the formulation compared to that of multi-dose reservoir. All DPIs devices have some essential components incorporated with the device such as drug holder, the air inlet, the deagglomeration compartment, and the mouthpiece. The design of DPIs is developed in such a way that the device should induce sufficient turbulence and particle–particle collisions to detached drug particles from the carrier surface (interactive mixtures) or deagglomerates particles from large agglomerates of drugs only. The majority of DPI devices are primed by pressing (Rotahaler®), sliding (Spinhaler®), rotating (Twisthaler®) or piercing (Handihaler®) to prepare the dose for fluidization with tangential flow of air during patient inspiration. The fluidised powder is then passed through a screen (incorporated within the device), which deagglomerates particles for deep lung delivery. Nevertheless, lung deposition from these inhalers varies from 12 to 40% (Steckel and Muller, 1997; Dunbar, 2002; Hickey, 2004; DiNunzio et al., 2007). The third generation DPIs, also known as active devices, which employ compressed gas or motor driven impellers or use electronic vibration (Crowder et al., 2001; Young et al., 2004; Brown et al., 2004) to disperse drug from the formulation. These devices are more sophisticated but user-friendly. Due to the presence of an energy source, active devices enable respiratory force independent dosing precision and reproducible aerosol production. The very first approved active device (Exubera®, Pfizer) with compressed air to aerosolise drug formulation for DPI insulin delivery was until recently available on market. This DPI with insulin was anticipated to be cost effective compared to that of insulin injection. However, this large and clumsy device has failed to achieve recognition of physicians and patients. While passive inhalation is commonly used in DPIs designed for topical respiratory drug delivery, active dispersion mechanisms (i.e., where the device inputs the energy) are considered desirable for drugs intended for systemic action which have to penetrate more deeply into the lungs (Schultz et al., 1992; Hil, 1994). The efficiency of breath actuated DPI devices depends on the patient's inspiratory force, whereas, the powder dispersion from active DPIs is limited to the physical or electrical mechanism (vibration, compressed air, impact force and impellers available in the device (Crowder et al., 2001; Young et al., 2004; Brown et al., 2004); however, active DPIs are useful for aged people.

There are design differences in these devices including the presence of grids, baffles, constrictions, diameter and length of inhalation channel, positioning of mouthpiece, and orientation of inclination of device (Timsina et al., 1994). As mentioned before, single- or multi-unit dose devices have individual pre-metered doses sealed in the device, whereas in reservoir devices the patient dispenses the dose at each use. Single-dose and multi-unit dose inhalers are more effective than multi-dose reservoir devices as they ensure dose consistency and avoid the effects of moisture in the powder reservoir (Steckel and Muller, 1997). Another advantage of unit and multi-unit dose devices is the isolation of each dose, which facilitates storage stability. Some multi-dose reservoir types of devices are lacking dose uniformity during inhalation and stability of formulations, if it is not protected from environmental degradation. However, they are more complex due to the need to reload the device with a new cartridge/pack and patients (especially in the aged population) need appropriate education to operate the device. Therefore, they are generally less favoured than multi-dose reservoir designs. An intensive patient education would help improve compliance. The majority of devices on the market and in development are multi-dose reservoir designs, largely as a result of their relatively lower cost and ease of use. However, dosing uniformity and storage stability is difficult when powders are delivered from a bulk powder.

To ensure effective drug delivery into the lower airway of lungs the inspiratory flow rate must be sufficient to produce adequate turbulent air flow in any devices so that adequate aerosol cloud of the aerosolised fine particles. Therefore, a balance between the design of an inhaler device, drug formulation, and the inspiratory flow rate of patient is required (Steckel and Muller, 1997; Srichana et al., 1998). According to Ashurst et al. (2000), in order for new DPI designs to establish their own place in the market they should show advantages over existing devices. It is generally very difficult to compare devices because they often deliver different medications. Numerous research articles and review papers have been published demonstrating designs and performances of various devices and the readers are referred to those papers for further details (Newman, 2004; Chrystyn, 2006; Dalby et al., 2007). A large number of new devices with various designs and various types of drug delivery mechanisms have been developed; however, none of them showed superficial efficiency in delivering drugs into the deep lungs. Market is rapidly expanding and a large number of novel devices are in development with limited published data and some of them will be approved in the near future (Table 2).

2.4. Limitations in the reliability of existing DPIs

The respiratory pattern of patients during aerosol intake may influence the deposition of inhaled particles, because the mean flow rates of particles in each region of the airways is governed by the breathing volume and frequency of breathing (Byron, 1986; Gonda, 1990; Martonen and Katz, 1993). The main limitation with existing DPIs is that delivery of the drug is often dependent upon inspiratory flow rates for effective delivery of the drug powder (Ganderton and Kasem, 1992; de Boer et al., 1996; Hickey and Concessio, 1997) and deagglomeration of drug particles (Lucas et al., 1998; Zeng et al., 1998; Louey and Stewart, 2002; Islam et al., 2004; Adi et al., 2006). For example, some DPIs require inspiratory flow of $\geq$30 L/min to effectively deagglomerate the powder (de Boer et al., 1996). However as discussed above, the breath actuation characteristic of DPIs is also thought to be one of their main strengths and drug delivery can also be influenced by the rate of increase in inspiratory air flow (Newman and Busse, 2002).

The majority of passive DPIs are less efficient at lower flow rates (<30 L/min) so that optimal lung deposition will only occur if the patient is able to achieve a sufficiently rapid and deep inhalation (Sheth, 2002). Low-resistance passive DPIs are generally less dependent on flow rate than high-resistance devices. Inspiratory flow rate was found to play the most important role in determining the dispersion of salbutamol sulphate aerosolized from a Rotahaler® (Steckel and Muller, 1997; Srichana et al., 1998; Zeng et al., 2000). A flow rate of 60 L/min has been reported to be advantageous for effective delivery of drugs from Turbuhaler® (de Boer et al., 1996) and patients can achieve sufficient inspiratory effort to deagglomerate and aerosolise the dose (Li and Edwards, 1997). Increased inspiratory flow rate may help increase the deposition of particles in the upper airways. Slow inhalation rate increases the number of particles to reach in the peripheral region of the respiratory tract by impaction. A slow inhalation rate (25 L/min) with breath holding showed maximal deposition of terbutaline sulphate compared to the faster rate (80 L/min) of inhalation (Newman et al., 1981). However, some DPIs such as the Clickhaler® (Nantel et al., 1999) and the Easyhaler® (Palander et al., 2000; Tarsin et al., 2004) have showed uniform delivery of doses independent of flow rate compared to that of Turbuhaler® (Newhouse et al., 1999). Conversely, the active devices are designed to deliver drugs independent of the

Table 2
Future/next generation DPIs (approved or in development stage)

Device	Type	Company	Delivery type	Drug	Disease
Aspirair/active	Multiple dose	Vectura	Powder	Apomorphine hydrochloride	Erectile dysfunction
Omnihaler/active	Single dose	Innoveta Biomeds Ltd.	–	–	–
Actispire/active	Single dose	Britania	Powder	Pumactant	–
NEXT™ DPI	Multi-unit dose	Chiesi	Reservoir	–	Asthma/COPD
DirectHaler	Once daily unit dose	Direct-Haler	Pre-metered	–	Asthma/COPD
Taifun	Multiple dose	Focus Inhalation	Reservoir	Fentanyl	Cancer pain
JAGO	Multi-dose	SkyPharma	Reservoir	SS	Asthma
Airmax	Multi-dose	Norton Healthcare	Reservoir	Formoterol, Budesonide	Asthma
Turbospin	Single dose	PH & T	Capsule	–	Asthma
AIR	Single dose	Alkermes	Capsule	Placebo powders	–
MicroDose/electronic breath activated	Single/Multiple unit dose	MicroDose Technologies/3M	Powder in blister	Insulin, beta agonists, cortic-steroids	Multi purpose
Cyclovent	Multi-dose	Pharmachemie	Reservoir	Opioids (Morphine)	Dyspnoea and pain
Dispohaler	Multi-dose	AC Pharma			
CONIX ONE	Single dose	Cambridge Consultant	Foil seal	Vaccines, antiasthmatic drugs	Avian flue, COPD
Microhaler/passive	Single unit dose	Harris Pharmaceutical	Capsule	Sodium chromoglycate	Asthma
Technohaler/passive	Multi unit dose	Innoveta Biomed Ltd.	Blister	–	Asthma
Spiros/breath activated active	Multi unit dose	Dura	Blister	Albuterol sulphate	Asthma
Bulkhaler/passive	Multi-unit dose	Asta Medica	Reservoir	–	Asthma
Miat-Haler/passive	Multi-unit dose	MiatSpA	Reservoir	Formoterol, fluticasone, budesonide	Asthma, COPD
Prohaler	Multi-unit dose	Valois	Blister	–	Asthma
Otsuka DPI/breath actuated	–	Otsuka Pharmaceutical Co. Ltd.	Compact Cake	–	Asthma
Acu-Breath	Multi-dose	Respirics	Powder	Fluticasone propionate	
MF-DPI	Multi-unit dose/passive		Reservoir	MF	Asthma
Swinhaler	Multi-dose	Otsuka Pharmaceutical Co. Ltd.	Powder	Procaterol, budesonide	Asthma
Pfeiffer/active	Single dose	Pfeiffer GmbH	–	–	–
Certihaler/breath actuated	Multi-dose	Novartis Pharma/Skye Pharma	Powder	Formoterol	Asthma

Dash line (–) indicates information is not available.

patient's inspiration but powder dispersion is dependent on the physical or electrical mechanisms.

Despite these well-recognised limitations, the importance of device reliability and drug deposition depends somewhat on the drug's physicochemical properties and the clinical indication. There is some debate about the importance of better drug deposition in patients with asthma but little about the need for improved deposition deep into the lung for treatment of systemic disease. Despite this, device performance should be assessed over a range of flow rates to account for all possible patients and clinical circumstances.

2.5. Recent innovations in DPIs (in development)

As previously mentioned DPIs are an expanding area of interest of pharmaceutical companies and are seen as the most promising mechanism for pulmonary drug delivery (Chan, 2006). There are two general approaches to improving the performance characteristics of DPIs: develop a better device or a better powder. A list of DPI devices or parts of devices, which are in development, is presented in Table 2.

The majority of recent research has focused on developing new devices along with powder formulations in the pursuit of enhanced dose uniformity and flow independent delivery (Chan, 2006). However, recent advances in DPI devices have also seen the development of active devices (mentioned before) which provide energy to assist the patient receive the correct dose (Atkins, 2005; Hickey and Crowder, 2007). Active DPIs attempt to overcome the dependence upon inspiratory flow which many of today's passive devices demonstrate. Active DPIs overcome problems associated with dependence upon inspiratory air flow via a number of techniques including: priming the device with a bolus of compressed air, the use of high frequency piezoelectric vibrators, and battery-powered motors (Newman, 2004; Hickey and Crowder, 2007). For example, an active device (not yet approved) the Aspirair®, utilizes a vortex separation chamber and compressed air source that is triggered by an airflow sensor to degglomerate drug particle agglomerates and improve lung delivery of drugs (Tobyn et al., 2004a,b).

More recently, the development of a novel DPI device, NEXT™ (Fig. 2A), a multi-unit dose device has been reported (Brambilla et al., 2006). It has been designed in such a way that can provide accurate dose metering and protection of drugs from environment, easy to use and cost effective to manufacture. The figure shows a reservoir which metered powder into a dosing cup is incorporated with the device. Another chamber helps compact the powder into the cup during dosing and the drug compact is deagglomerated during inhalation. Recently, de Boer et al. (2006) described the use of a passive, novel disposable inhaler (Twincer®) with what they have called 'multiple air classifier technology' for the delivery of moisture sensitive high powder doses. The powder drug in blister

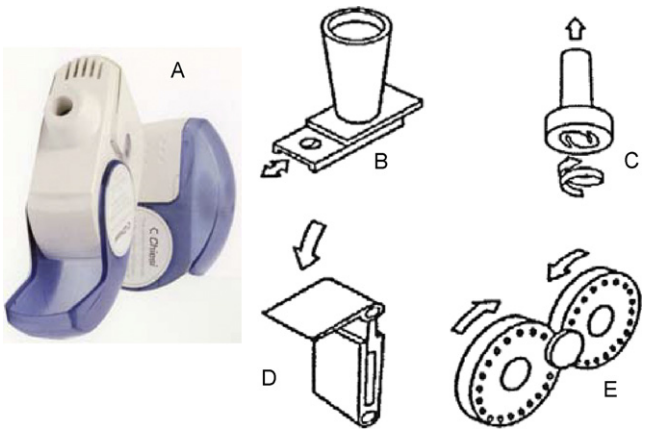

Fig. 2. Different components of a next generation DPI device: (A) NEXT™ DPI (open and ready for inhalation); (B) dose metering; (C) powder de-agglomeration device; (D) breath actuation, and (E) dose counting (*Source*: Brambilla et al., 2006).

is aerosolized (powder flow divides between parallel classifiers) by the tangential air flow during inhalation (de Boer et al., 2006). Another novel DPI device, Microdose™ (Beth et al., 2004), a breath actuated and piezo-electronic driven device has been developed. The drug powder, enclosed in blister, which protects drug from the environment, is aerosolised by patient inspiratory force. Just before taking the drug, blister is pierced and the patient takes a breath by which airflow sensor turns on the piezo vibrator which vibrates at high frequency to deagglomerate the particles of powder and aerosolised through the airstream by the inspiratory flow. More than 25 chemical compounds including insulin, other proteins and peptides, short and long acting β-agonist, corticosteroids and anti-cholinergic drugs and FPF were found to be 50–70% and 70–90% for crystalline powders and spray dried powders, respectively. This device could be an ideal inhaler if the dosing counter is incorporated with it. Photographs of some DPI devices under development for future are presented in Fig. 2.

Using the combination of drug formulation and DPI design technology, another novel DPI device, AIR™ has been demonstrated (DeLong et al., 2005); however, drug delivery mechanism has not been revealed. Using this device, delivery of a tailor made placebo powder and insulin showed more than 50% lung deposition (Rosenstock et al., 2007). Recently, a promising DPI device Prohaler™ (Valois), a breath activated device with dose counter dispenses drug from blister pack containing individual doses. This multi-unit device incorporates with audiovisual feedback system which helps patient ease of use and control and is ideal for patient with asthma and chronic obstructive pulmonary disease (COPD); however, no data is available. There has been a lot of innovations in the development of novel devices and drug formulations but unfortunately very limited information is provided or published. For the purpose of this review article, the authors will focus mainly on the innovation and reliability of novel DPI systems.

Generally the trend in development of new DPIs is to mimic aspects of traditional devices while improving drug delivery, ease of use, and drug formulation (Newman, 2004). Application of spacers (Everard et al., 1996; Bisgaard, 1998) and other add-on devices (Matida et al., 2004) to improve the performance of existing DPIs has been demonstrated. For example, using a nonelectrostatic spacer to a commercial multi-dose dry powder inhaler Turbohaler® showed high fine particles in the aerosol of budesonide compared to that of Turbohaler® only (Bisgaard, 1998). The addition of a spacer with Turbohaler® was found to reduce the non-respirable portion of the dose (Everard et al., 1996). Recently, the particle deposition of terbutaline sulphate via a new add-on spacer with Turbohaler has been demonstrated and the delivery of particles with the spacers has been found to increase 47% compared to the experiments without the spacer (Matida et al., 2004). These approaches generally result in more rapid development timeframes and reduced cost.

2.6. Some future inhalers (patent review)

Recently, a large number of new DPI devices (breath actuated or active/applied energy system) with extended technology (accurate dose reproducibility with product stability) are patented or applied for patent (Table 3); however, drug delivery data are not accessible or very limited data are available for the readers. Researchers continue to gain more knowledge on how the design of the inhaler mouthpiece, air inlet, and drug release mechanism can impact on the dispersion of the fine drug particles into the deep lung. These systems have been investigated both in academic and industrial settings. Recently, Zhu et al. (2007), have developed

Table 3
Future/next generation DPI device (patented/applied for patent)

Device	Patent no.	Delivery type	Company	Ref./Company
DPI/passive	US Pat. Appl. US 2008035143	Reservoir	USA	Sievers et al. (2008)
DPI	PCT Int. Appl. WO 2008001132	Single dose, capsule	Brintech International Limited, UK	Chawla and Paul (2008)
Cyclone DPI	Britt. UK Pat. Appl., GB 2439204; WO 2007144614	–	Cambrdge Consultant Ltd., UK	Smith and Harris (2007)
Hinged Cyclone DPI	Britt. UK Pat. Appl., GB 2439205; WO 2007144607	Multi-unit blister pack	Cambrdge Consultant Ltd., UK	Smyth and Truman (2007)
Simple Inhaler	PCT Int. Appl., WO 2007132217	Multi-unit cartridge	Hovione Inter AG, Switzerland	Villax et al. (2007)
DPI	PCT Int. Appl., WO 200712928	Single doge blister strips	Greece	Pentafragas (2007)
DPI	PCT Int. Appl., WO 2007144659	Single dose, capsule	Cipla Limited, India	Malhotra and Lulla (2007)
DPI[a]	US Pat. Appl Publ., US 2007235029; WO 2007115395	Multi-unit dose/blister, carrier free drugs	China	Zhu et al. (2007)
New DPI	PCT Int. Appl., WO 2007073302	Powder	Astrazeneca AB, Sweded	Dagsland (2007)
DPI/breath actuated	Indian Pat. Appl., IN 2006KO00144	Single dose capsule	India	Sengupta (2007)
DPI	PCT Int. Appl., WO 2007093310	Powder, deagglomeration mechanism	Jagotec AG, Switzerland	Muller and Egginman (2007)
DPI/breath actuated	Britt. UK Pat. Appl., GB 2433247; WO 2007096667	Multi-dose, reservoir with timing control	UK	Li (2007)
DPI/breath actuated	PCT Int. Appl., WO 2007098870	Single dose, capsule	Germany	Eslve and Kreim (2007)
DPI	CN 200710020974	Single unit dose, powder	China	Chen (2007a)
DPI	CN 200710020975	Single unit dose, capsul	China	Chen (2007b)
DPI/active	PCT Int. Appl., WO 2007103152	Single dose powder/multiple dose, blister	Stc. Unm, USA	Smyth and Truman (2007)
DPI for moisture sensitive drugs	US Pat. Appl. Publ. WO 2007037748, US 2007068524	Powder	Microdrug AG, Switzerland	Nilsson and Holaster (2007)
DPI	Indian Pat. Appl., IN 2004MU00520	Single unit/disk	Sun Pharma. Industries Ltd., India	Satish et al. (2007)
DPI	PCT Int. Appl., WO 2006GB03803 20061012	Unit dose, powder/tryptan	Innovata Biomed Ltd., GB	Lucking and Martin (2007)
DPI	Published	Single dose/powder	–	Wang et al. (2006)
DPI/active	Published	Single dose/two drug in separate chambers	Oriel Therapeutics	Timothy et al. (2006)

[a] Indicates carrier free formulation and the FPF of drugs (not disclosed) from this device is 80%.

a new DPI device, that can deliver carrier free ultrafine powdered (<5 μm) drug packed into blisters. The air stream goes through the blister and fluidizes the medicament (after piercing the blister), deagglomerates and finally disperses by shear force. This device incorporate with the rotating multi-dose blister, which can hold up to 60 doses, and it has higher drug loading capability in small volumes, compared to those of most current dry powder inhalers. It has been mentioned that the fine particle fraction (<4.7 μm) of a drug aerosolised via this device was 80%; however, the type of drug, flow rate, etc., are not disclosed. This invention looks very promising and may be considered as one of the best inhalers in the world and an indication that device reliability and innovation works together.

2.7. Trends in developing innovative dry powder inhalers

As previously mentioned most of the recent research has focused on inhaler devices rather than powder formulations. Furthermore, the concept of powder interaction with the device as well as the influence on powder dispersion has generally been poorly understood. Recently, computational fluid dynamics has enhanced understanding of the impact of inhaler design on powder dispersion and deposition and has demonstrated that small variations in the device design can produce significant variations in performance (Coates et al., 2004; Chan, 2006). For example, active DPIs have been designed specifically for patients, or for clinical situations in which patients cannot generate sufficient inspiratory effort, and are being explored for systemic drug delivery. Variability in drug delivery due to insufficient inspiratory flow is often not a major problem for asthma drugs but it would probably be unsatisfactory for novel drugs such as inhaled proteins and macromolecules.

Most drugs targeted for systemic action via pulmonary delivery are peptides and proteins, for example, insulin and vaccines (Edwards et al., 1997; Patton et al., 1999; Dilraj et al., 2000; Bennett et al., 2002). Gene therapy for cystic fibrosis is another area of active interest (Laube, 2005; Yvonne et al., 2006). Peptides and proteins are often formulated differently than conventional drugs used in DPIs. For example, the formulation of insulin covalently coupled with one or more hydrophilic polymer conjugate, i.e., polyethylene glycol (Patton et al., 2002), formulation of vaccine and particulate antigen comprised of a mixture of peptides or small molecular adjuvants (Friede and Aguado, 2005) for pulmonary delivery has been demonstrated. These formulations need devices which can efficiently delivered drugs in to the deep lungs and the use of devices optimised for the delivery of other drug formulations may not be suitable. Therefore, continued expansion on the development of devices that improve drug delivery to the deep lung has a high probability of success. The rationale for this is the potential to deliver dry powder formulations in different diseases like cystic fibrosis, lung cancers, influenza and diabetes.

2.8. Innovative powder formulations

Efficient delivery of drugs from DPIs depends not only on the device, but also on drug formulation and the formulation of a DPI involves the production of suitable powders for effective respiratory deposition as well as formulation of powders with or without excipients (Dolovich, 1992; Byron and Patton, 1994). Historically, drug particles for inhalation have been produced by milling (micronisation) process and are then blended with a carrier (e.g., lactose) to improve flow properties and dose uniformity (Timsina et al., 1994; French et al., 1996). Other carriers such as mannitol and trehalose (Stahl et al., 2002; Mao and Blair, 2004) have also been reported to use in the DPI formulations. The properties of such blends are a function of the principal adhesive forces that exist between the particles and the surface tension of the adsorbed moisture layers (Ibrahim et al., 2000). In carrier-mediated formulations, drug–carrier adhesion is likely to affect the dispersion of drugs aerosolised via inhaler devices (Podczeck, 1997; Louey and Stewart, 2002; Young et al., 2002; Islam et al., 2005); however, this review article deals with the DPI devices only.

Insufficiency of traditional methods of powder production has lead to the development of alternative techniques which produce powders of specific size, density and morphology and with less cohesion and adhesion (Hickey and Concessio, 1997). The dispersion of powder aerosols is also influenced by the geometric diameters of the particles which are generally at odds with the efficiency of deposition in the lungs (Hickey and Concessio, 1997). A number of alternative techniques, including specialised spray drying, ultrasound-assisted crystallisation and supercritical fluid technology, in situ method have also been demonstrated (York and Hanna, 1996; Steckel et al., 2003; Shekunov et al., 2003; Chow et al., 2007). Development of sustained released spray dried recombinant human insulin with hyaluronic acid is an exciting example of the formulation of proteins for DPIs (Surendrakumar et al., 2003). The underlying principle has been described as enhanced performance through particle engineering (Ostrander et al., 2000; Shekunov et al., 2003) and recent particle engineering has seen the development of highly porous particles with large geometric diameters but small aerodynamic diameters which by improving powder dispersion can improve efficacy of DPIs (Edwards et al., 1997, 1998). A number of novel powder formulations have been demonstrated such as Powderhale (Staniforth, 1996), porous particles (Edwards et al., 1997; Misra et al., 2006), PulmoSphere (Bot et al., 2000), SoliDose (Blair et al., 2000), nanoparticles (Ostrander et al., 2000), surface modified particles (Morton, 2006), engineered powder (Chet, 2007); however, still the efficiency of drug delivery did not reach to the target level.

Recently, respiratory delivery of proteins (Edwards et al., 1997; Chan, 2003), interleukins and oligonucleotides (Nyce et al., 2000), gene therapy and vaccination was reported elsewhere (Laube, 2005; Yvonne et al., 2006; Erin and James, 2006; de Swart et al., 2007; Dilraj et al., 2007). Inhalation of insulin from DPI formulation showed to increase systemic level of insulin and suppressed systemic glucose levels (Edwards et al., 1997; Patton et al., 1999; Graham and Ronald, 2006; Hussain et al., 2006; Thomas, 2006). Dry powder inhaler formulation of measles vaccine (de Swart et al., 2007; LiCalsi et al., 2001) and β-glucuronidase (Lu and Hickey, 2005) was also reported. Pulmonary delivery of erythritol-based powder form of Glucagon, a key regulatory element of glycogen metabolism has been demonstrated (Endo et al., 2005). Another study demonstrated that the bioavailability (66%) of inhaled calcitonin was more than double compared to that of the bioavailability (28%) of injected calcitonin (Banga, 2003). Pulmonary delivery of DPI for gentamicin (Crowther et al., 1999), colistin sulphate (Le Brun et al., 2002), and tobramycin sulphate (Newhouse et al., 2003) has been successfully investigated and inhaled delivery showed higher plasma concentrations compared to those achieved by nebulisation. The outcome of these investigations is indicative of expanding the DPI formulations for other drugs include protein-based compounds, biologics, for the treatment of systemic disorders.

3. The question of device reliability vs. innovation

Bryan (2005) recently posed the question of where should researchers focus their efforts in the development of delivery systems for pulmonary drug administration. It is clear that many pharmaceutical companies are asking this question and will continue to explore the options, particularly given the considerable size

of the existing and future potential markets. However, the major limitation for the development of a truly innovative product is cost and therefore Bryan provides a strong argument for improvements to existing designs (Bryan, 2005).

While in recent years the efficiency of DPIs has improved significantly, there is more progress to be made particularly with regards to the optimisation of both device and formulation, and the delivery of novel therapies (Newman, 2004). Optimisation of existing DPIs can be conducted through a variety of different mechanisms including improvements in drug formulation and device design and/or operation. In addition, factors controlling lung delivery of drugs from currently available devices are still unclear. However, it is often the case that the drug formulation and inhaler device need to be optimised together to ensure reliable and effective drug delivery. The design of a device needs to be coordinated with the drug formulations (i.e., powder in capsules, disks, bulk powders or agglomerates), so that the drugs are aerosolised during inhalation and deliver a dose to the lungs for achieving maximum therapeutic benefits (Pesson and Wire, 1989; Yang and Keynon, 2000). It is worthwhile to note that the materials used in the manufacture of devices and drug formulation affect the accumulation of electrostatic charge resulting in reducing the efficiency of drug delivery (Byron et al., 1997; Carter et al., 1998). Therefore, care should be taken when selecting materials for devices.

It is evident from the literature that much work is being done to investigate the parameters of device reliability and discover ways to improve the device and drug formulations to overcome existing limitations and improve the characteristics of DPIs. There is also a significant body of research being undertaken in the innovation of DPIs for the delivery of systemically targeted drug formulations, particularly proteins. Although most of these products are still in development they have a very promising future. This then suggests that there is a recognised need for both improvements in device reliability for existing DPIs (Bryan, 2005) and the development of innovative devices (Newman, 2004).

4. Discussions and conclusion

This review article sought to examine whether device reliability is more important than innovation. With the advancement of science and technology, this problem needs to be addressed in the changing world. Pulmonary drug delivery is a promising route of administration as it is non-invasive and helps patient compliance.

Despite appropriate standards of device reliability being a requirement for licensing and marketing of DPIs, there remain areas for improvement. Innovation and improvements in device reliability may not be mutually exclusive and neither is more important than the other. Until now, the cost of producing an inhaler economically, and with the necessary performance, has not been possible. In addition, there are many potential novel applications for DPIs for which device innovation will be necessary. The application of active DPI devices (the use of electrically driven dispersion) provides an opportunity to enhance the efficiency for the aged patients. According to the food and drug administration (FDA) it is recommended to add a necessary part like an integral dose counter as an active part of DPI device (CRER, 1998). With the advancing technology, the future DPI devices may add other features like dose reminder, audiovisual signals of dose delivery, measurement of flow rates during inhalation (Hickey and Crowder, 2007).

Along with the device design, there is a great concern about the interaction between formulation and device that has to be accounted during designing a new device. The effect of DPI formulation (type of lactose and physicochemical properties of drug), capsule material and inhalers on the charge and polarity of DPI aerosols have been demonstrated and the type of the charge acquired by the particle was dependent on the type of inhaler, carrier particle size and capsule shell used for a formulation (Telko and Hickey, 2005). Therefore, these factors should be considered for an ideal inhaler which is more reliable, efficient, user friendly and cost effective.

Most of the manufacturers and researchers are looking for novel efficient devices because in 2007, more than 20 new patent applications (Table 3) were filed for new designs of inhalers or parts of inhalers. Various studies have been conducted to compare the performance of DPIs; however, very limited number revealed insight into the mechanism of drug dispersion from the devices. Drug delivery mechanism is important to rational design of efficient inhaler with improved performance. With the changing technology, device development has progressed tremendously compared to that of novel DPI formulations. It is not clear whether the device engineering alone would solve inhaled drug delivery problems. Therefore, a link needs to be established between developing smart formulation and or smart device, which ensure efficient and reproducible delivery of drug from the powder formulation.

Pulmonary administration of medicaments is expanding with increasing rate of different diseases. In addition to asthma or COPD, some other DPI systems for mucolytics, antituberculosis, anticancer, antibiotics, drugs for sexual dysfunction, Augmentin® powder for otitis media, fentanyl for cancer pain, tobramycin (for cystic fibrosis long with infections related to chronic bronchitis and COPD), opioids for pain, interferons, alpha-1 antitrypsin, vaccines, gene therapy, and human growth hormone are in clinical development (Patton et al., 1999; Patton, 2005; Staniforth et al., 2006; Cheatham et al., 2006; Stephen and Babatunde, 2006; Chan et al., 2007). These studies reveal the promising future of DPIs in drug delivery and the application of DPI is expanding from pulmonary diseases to other disorders. Local and systemic delivery of different drugs for systemic chronic diseases needs to be focused more on using DPI formulations, which have a lot of potential. The DPI delivery systems are likely to contribute to successful drug delivery into the lungs not only to treat asthma, but also to deliver a wide range of therapeutic agents for pulmonary delivery. In future, very small amount of potent drugs like products of biotechnology will require smart devices that deliver drugs efficiently into the lower airway of lungs. Many devices mentioned in this review have yet to be commercialised; however, some of them will come to market in near future. Therefore, in combination with the increasing knowledge of DPI formulations and design of new devices, a step needs to be taken to develop more effective delivery system. The current trend in pulmonary drug delivery and potential benefits of this route, development of smart but reliable device will be continued to enhance deposition of drugs into deep lungs with a better patient compliance.

From the discussion it seems that neither is more important than the other, i.e., device reliability or innovation. Rather, the comparative importance of device reliability and innovation differs depending on specific circumstances. For example, one could argue strongly that for local delivery of drugs for conditions such as asthma, our continuing efforts are better placed in optimising existing devices and drug formulations rather than spending the considerable time and effort required to produce an innovative DPI. Alternatively, for systemic drug delivery via DPIs for conditions such as diabetes, cancer, CNS disorders and cystic fibrosis, there is considerably more demand and a stronger rational for innovative DPIs designed to optimise powder delivery and systemic therapeutic effects. The recent focus on the regulatory requirements means that it is essential for the inhalers to have minimal dependence on the patients inspiratory flow rates, reproducible aerosol performance to attain optimal performance. The future development of

DPI products may focus both on the inhaler device as well as the powder formulations for optimum therapeutic benefits. The delivery device may develop into a disposable device that will overcome the need for cleaning the device, concerns over product stability, and less expensive with improved patient compliance. Therefore, to realise the full potential of DPIs, at the lowest cost to both pharmaceutical companies and patients, innovation of new device with enhanced lung deposition and device reliability will play important roles in the future.

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