RESPIRATORY MEDICINE

REVIEW

Evolution of dry powder inhaler design, formulation, and performance

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Abstract Many companies are now prioritizing the development of dry powder inhalers (DPIs) above pressurized formulations of asthma drugs. A well-designed DPI and an appropriate powder formulation can optimize the effectiveness of inhaled drug therapy. A DPI must be able to deliver medications effectively for most patients, and an ideal inhaler would provide a dose that does not vary with inspiratory flow rate. Recent regulatory guidelines, among which the U.S.FDA draft guidance is the most stringent, demand consistent dose delivery from an inhaler throughout its life and consistency of doses from one inhaler to another. However, the properties of free micronized powders often interfere with drug handling and with drug delivery, reducing dose consistency. Recent advances in formulation technology can increase lung dose and reduce its variability. While a perfect DPI may never exist, both device and formulation technology are evolving to rectify perceived deficiencies in earlier systems.

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INTRODUCTION

Effective inhalation therapy, using pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs), is the cornerstone of asthma management. Inhaled corticosteroids are recommended for maintenance therapy in all patients with persistent asthma, while short-acting inhaled β_2-agonists are the primary rescue medications in intermittent as well as persistent asthma (1). Effective inhaled corticosteroid therapy will reduce airway inflammation and hyperresponsiveness, improve lung function, and decrease symptoms. Since the 1960s, the pMDI has been the predominant device for delivering inhaled asthma drugs. Because of environmental concerns and inherent design limitations in pMDIs, there has been interest in developing alternative ways to deliver inhaled drugs. One of the alternatives to the pMDI is the breath-actuated DPI, which does not require any propellants. This review examines the design and performance characteristics of some of the available DPIs. The DPI and its formulations are evolving so that the DPI could become the system of choice in many therapeutic situations.

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INHALER DESIGN AND THE GOALS OF ASTHMA MANAGEMENT

Effectiveness and compliance

Although inhaled bronchodilators and corticosteroids are effective in the treatment of asthma, the incorrect use of an inhaler by patients can lead to poor compliance and treatment failure (2). A properly designed inhaler containing an appropriate formulation can increase adherence and achieve the desired therapeutic effects (3) and may also allow a reduction in dosing frequency (4).

A healthcare provider's ability to demonstrate the operation of the inhaler and a patient's capacity to use it are functions of the design of the inhaler and its inherent ease of use. The degree of comfort and satisfaction the patient experiences with the inhaler is a significant determinant of compliance. It is important that the inhaler be unobtrusive, durable, easy to hold and operate, and cost effective (5). Most portable asthma inhalers contain

multiple doses, and some type of dose counter is desirable for self-management to prevent the use of an empty inhaler and to allow the patient to order refills in a timely manner, as well as allowing the health care provider to monitor a patient's compliance with therapy.

Stable and predictable therapeutic responses require a consistent dose delivery from an inhaler throughout its life and consistency of doses from one inhaler to another. Recognizing this, specifications for inhaler dose uniformity have been defined by regulatory bodies, including the European Pharmacopoeia (EP) (6) and the U.S. Food and Drug Administration (FDA) (7).

Safety

It is also important that any delivery system minimizes systemic drug exposure, especially to corticosteroids, particularly because of concern over the potential for corticosteroids to contribute to systemic side effects, including osteoporosis in the elderly, suppression of growth in children, and suppression of adrenal activity at any age (8). To minimize systemic exposure, a corticosteroid should be delivered to its target, usually assumed to be the conducting airways, in the lowest possible dose to achieve the desired effects. It has been suggested that inhalers should minimize delivery of particles $<1.1\ \mu m$ in size, which could contribute to systemic exposure after deposition into the capillary-rich alveolar airspaces (9). It is also desirable for the corticosteroid to have low oral bioavailability since part of the administered dose will be swallowed. Ideally, inhalers should minimize oropharyngeal deposition since local side effects associated with inhalation of corticosteroids can include oral candidiasis and dysphonia (10).

LIMITATIONS OF PMDIS

Propellant

The pMDI is currently the most common inhaler for asthma drug delivery and until recently has contained a suspension or solution of drug in one or more pressurized chlorofluorocarbon (CFC) propellants (11). Stratospheric ozone depletion has been attributed in part to degradation products of CFCs, and more than 140 nations signed the Montreal Protocol in 1987 to control and phase out any chemical compounds responsible for ozone loss. This agreement created the opportunity and motivation to develop new inhaler technology that would significantly improve the delivery of aerosol drugs to the respiratory tract. Alternative propellants for pMDIs [hydrofluoroalkanes (HFAs)] are being introduced, but these substances also have the potential to cause environmental problems (12).

Other formulation issues in pMDIs

In addition to using CFC propellants, other drawbacks of pMDIs are related to aerosol formulation and generation. Pressurized MDIs may contain surfactants, such as oleic acid, that could pose a risk of inducing bronchospasm in patients suffering from advanced airway hyperreactivity (13). Also, the large size (14) and high velocity (15) of many droplets leaving the pMDI nozzle produce extensive oropharyngeal deposition (up to 90% of the dose), although this can be reduced by using a spacer or add-on device (16).

Ease of use

Patient misuse of pMDIs continues to be problematic. Correct use of a pMDI is difficult and leads to a large proportion of patient errors (17). Even healthcare professionals demonstrate poor knowledge of the use of pMDIs (18), and therefore it is not surprising that patients also have trouble using these inhalers correctly. Breath-actuated pMDIs (e.g., Autohaler™ [3M] and Easibreathe™ [IVAX]) can help to minimize patient coordination problems (19).

ASPECTS OF DPI DESIGN

Formulation of powders for inhalation

Drugs delivered by DPIs are formulated as either pure drug or mixed with an inactive excipient. The budesonide preparation for use in the Turbuhaler® DPI (AstraZeneca) is an example of a pure drug powder formulation. Powder blends contain micronized particles of the drug with an excipient, usually lactose, which may be micronized, but which more often comprises larger "carrier" particles.

While the optimal therapeutic particle size distribution for an inhaled dry powder asthma medication is generally considered to be $<5\ \mu m$, or possibly $1-5\ \mu m$ (9), particles this small are typically not free flowing. Cohesion and static charge interfere with drug handling during manufacture and with inhaler filling, can reduce uniformity in metering individual doses, and can cause drug retention within the device. The use of excipients can help to improve dose uniformity, partly because a larger mass of powder is generally easier to meter accurately. Under specific manufacturing conditions, the micronized particles can be combined to form stabilized agglomerates with controlled uniformity and hardness. For example, a novel DPI (Twisthaler®, Schering-Plough) uses agglomerates of the corticosteroid mometasone furoate and lactose, stabilized to the appropriate hardness and size for handling and metering (20).

Agglomerates of drug particles, or of drug and lactose, must be deagglomerated by shear forces during

inhalation, producing fine particles which are carried by the airflow into the lungs. Particles $< 5\,\mu m$ in size can be distributed deep into the smaller airways (21) and this penetration correlates with good clinical response (22,23).

DPI design issues

The design of a DPI must be coordinated with the formulation of the drug. Inhaler design, particularly the geometry of the mouthpiece, is critical for patients to produce an airflow sufficient to lift the drug from the dose chamber or capsule, break up the agglomerates in a turbulent airstream, and deliver a dose to the lungs as therapeutically effective fine particles (24). The airflow generated by inhalation directly determines particle velocity and hence the ease with which particles are deagglomerated.

The materials used in the construction of DPIs (25) and characteristics of the formulation (26–28) affect electrostatic charge accumulation. Some formulations, as well as inhaler materials, accumulate and retain electrostatic charge more strongly than others, and this will affect both drug retention within these inhalers as well as delivered aerosol behavior.

Airflow rate, inhaler resistance, and aerosol delivery

The intrinsic resistance to airflow through a DPI is a fixed property that determines the airflow rate through the inhaler in response to the inspiratory effort of the patient. Each inhaler has a unique resistance and current inhalers have a wide range of resistance values (29). The peak inspiratory flow rate (PIFR, measured in l/min) influences the efficiency of the inhaler in lifting particles of the drug formulation from the drug chamber or capsule, and it will also affect the efficiency of deagglomeration of the particles and the amount of drug reaching into the lungs (30,31). Ironically, a major advantage of DPIs (breath-actuation) is closely linked to a significant disadvantage, namely that patients have to inhale through most DPIs with full inspiratory effort in order to optimize drug delivery (32). A reduction in inspiratory effort, and hence in PIFR through the device, is likely to result in a lower delivery of "respirable" particles from the device and a reduction in the quantity of drug deposited in the lungs (32). A patient's inhalation effort will generate a higher PIFR through an inhaler with a low airflow resistance than through an inhaler with a high airflow resistance. In high-resistance DPIs, interpatient variability in PIFR may be reduced compared to that through low-resistance devices, leading to more reproducible drug delivery (33). However, fine particle production is a function of specific inhaler design, not simply airflow rate through the inhaler, and neither inhaler airflow resistance nor PIFR alone can predict how efficiently a DPI will deliver a drug to the lungs.

An ideal inhaler would provide a dose to the airways that did not vary with inspiratory flow rate. The performance of DPIs will depend not only upon the PIFR generated through the device, but also upon the rate of increase in flow, or "rise time" to peak airflow rate (34). Measurements of inspiratory flow profiles of patients with persistent asthma made using a DPI with moderately high airflow resistance (35) suggest that patients with a range of asthma severity can use these inhalers. The inspiratory flow profiles of adults with mild-to-moderate and severe asthma (Fig. 1) allowed comparison of inspiratory flow rate, rise time (defined by the time between 10 and 30 l/min), and duration of inhalation. Adults with severe asthma produced mean PIFRs (> 57 l/min) and rise times (< 300 ms) that were similar to those of adults with mild-to-moderate asthma, although patients with mild-to-moderate asthma generally showed longer durations of inhalation. Thus, even patients with relatively severe asthma appeared to be able to generate the rise times and PIFRs needed to operate the DPI and receive an optimal dose. Those patients who were tested approximately 3 months later showed similar rise times and peak flow rates to those recorded immediately after training (36). Therefore, with proper training, patients appeared to remember and perform appropriate inhalation techniques over long periods of time.

EXAMPLES OF DPI DESIGN

A number of DPIs have been used to deliver inhaled drug formulations, and many more are in development. In

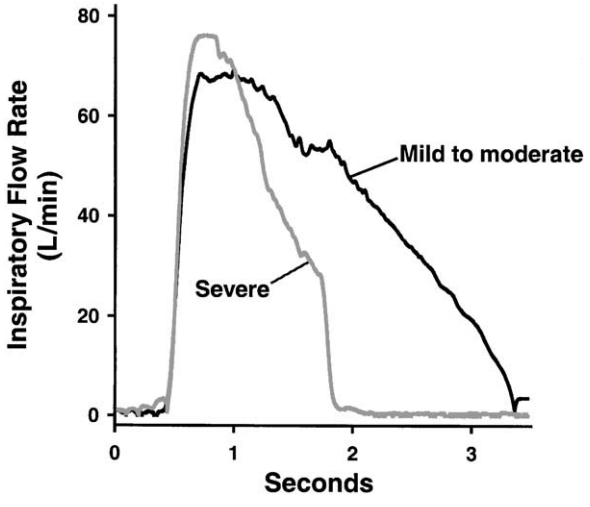

Fig. 1. Examples of inspiratory flow rates produced by adults with mild-to-moderate persistent asthma and severe asthma. Data were taken with a model of the Twisthaler®, and are representative of the preliminary findings of Kenyon *et al.* (35).

Table I, "passive" or breath-actuated DPIs are listed. There are also several "active" devices, where the powder is dispersed by some mechanism other than the patient's inhalation, for instance, an internal supply of compressed air (37, 38). DPIs listed in Table I are divided into several categories. In "single-dose" devices, individual doses are provided, usually in gelatin capsules, and have to be loaded into the inhaler before use. "Multiple unit dose" inhalers contain a number of individually packaged doses, either as multiple gelatin capsules or in blisters. In "multidose" devices, drug is stored in a bulk powder reservoir, from which individual doses are metered. Table 2 lists some examples of formulations and dose ranges from a variety of DPIs. Multidose devices incorporating powder reservoirs are generally capable of delivering more than 100 metered doses, providing a level of convenience equivalent to a pMDI. Multiple unit dose devices may offer other advantages in terms of more accurate metering of individual doses and better protection against ingress of moisture, but are generally more expensive to produce.

Single-dose devices

While single-dose devices are reusable, they are inconvenient because an individual dose has to be loaded into the device each time it is used. The Spinhaler® (Aventis) was developed to deliver sodium cromoglycate in individual gelatin capsules. The patient inserts a capsule onto a propeller seated inside the inhalation channel, and the capsule is pierced by two needles that are actuated by a sliding cam arrangement. When the patient inhales strongly through the mouthpiece, the propeller turns and vibrates, dispensing the drug as an aerosol (39). The Rotahaler® (GlaxoSmithKline) has been used to deliver salbutamol and beclomethasone dipropionate. With this inhaler, a capsule is loaded and a twist motion causes the two halves of the capsule to separate and release the powder. When the patient inhales, the drug is drawn through a grid and exits the inhaler (40).

Other DPIs intended for purposes other than delivering asthma drugs may look very different. The Inhance™ DPI (Inhale Therapeutic Systems) is a totally unique single-dose device for delivering inhaled peptides and proteins, which are intended to be absorbed via the lungs into the systemic circulation. The patient loads an individual blister into the device, and the powder is dispersed by compressed air into a chamber mounted on top. By enabling the patient to inhale a fine particle aerosol slowly and deeply, conditions for delivering drug into the alveolated regions of the lungs are optimized (41).

Multiple unit dose devices

The Aerohaler® (Boehringer Ingelheim) was the first DPI to hold more than one capsule; a six-capsule inhaler is currently available. This inhaler has been used to deliver fenoterol and ipratropium bromide. The magazine of capsules is loaded into position, allowing two needles to pierce a capsule. The patient's inspiration pulls air through the holes, vibrating the capsule and delivering the formulation into the airstream.

The Diskhaler® (GlaxoSmithKline) was the first inhaler to use drug formulations prepackaged into single-dose blisters in a multidose package (42). This inhaler has

Table I. Current and future "passive" (breath-actuated) dry powder inhalers (table modified from Parry-Billings (37) and Ashurst *et al.* (38))

	Single dose	Multiple unit dose	Multidose
Marketed	Spinhaler® (Aventis)[a] Rotahaler® (GSK) Aeroliser™ (Novartis)[c] Inhalator® (Boehringer) Eclipse (Aventis)	Diskhaler® (GSK) Diskus® (GSK)[b] Aerohaler® (Boehringer)[d]	Turbuhaler® (AstraZeneca) Easyhaler® (Orion) Novolizer® (ASTA Medica) Clickhaler® (IB) Pulvinal® (Chiesi)
In development	Turbospin (PH and T) AIR™ Inhaler (Alkermes)	Flowcaps® (Hovione) MicroDose DPI (MicroDose) Delsys DPI (Delsys) Technohaler® (IB)	Ultrahaler® (Aventis) Taifun® (Focus Inhalation) MAGhaler (Mundipharma) Cyclovent (Pharmachemie) Twisthaler® (Schering-Plough) Airmax (Yamanouchi) Dispohaler (AC Pharma) Jago DPI (Skyepharma)

[a] Formerly Fisons.
[b] Known as Accuhaler in UK.
[c] Also known as Cyclohaler (Pharmachemie) and Monohaler (Miat).
[d] Also known as Inhalator-M.
GSK: GlaxoSmithKline; IB: Innovata Biomed.

Table 2. Types of DPIs, formulations, and delivery systems

	Example formulations				
DPI	Drug	Formulation	Total dose weight	Dosing system	Doses
Spinhaler® (Aventis)	20 mg sodium cromoglycate	1: 1 sodium cromoglycate: lactose	40 mg	Capsule	1
Rotahaler® (GSK)	200 μg salbutamol	1:125 salbutamol: lactose	25 mg	Capsule	1
Inhalator® (Boehringer-Ingelheim)	200 μg fenoterol	1:24 fenoterol: glucose	5.0 mg	Capsule	1/6
Diskhaler® (GSK)	100 μg fluticasone propionate (FP)	1:250 FP: lactose	25 mg	Blister	4
Diskus®/Accuhaler® (GSK)	50 μg salmeterol	1:250 salmeterol: lactose	12.5 mg	Blister	60
Turbuhaler® (AstraZeneca)	200 μg budesonide	Budesonide alone	200 μg	Reservoir	200
Easyhaler® (Orion)	100 μg salbutamol sulfate	1:9.9 salbutamol sulfate: lactose	10 mg	Reservoir	200
Twisthaler® (Schering-Plough)	200 μg mometasone furoate (MF)	1:5.8 MF: lactose	1.36 mg	Reservoir	60
Novolizer® (ASTA Medica)	200 μg budesonide	1:56.5 budesonide: lactose	11.5 mg	Reservoir	200

GSK denotes GlaxoSmithKline.

been used to deliver a range of products, including salbutamol, salmeterol xinafoate, beclomethasone dipropionate, and fluticasone propionate. The inhaler uses refill disks, each of which contains four or eight blisters. When the lid of the Diskhaler is opened and closed, the disk rotates and a new blister is available to be pierced. When the patient inhales through the mouthpiece, the drug formulation is drawn from the blister and is dispersed as an aerosol into the respiratory tract.

The Diskus® or Accuhaler® (GlaxoSmithKline) has been used to deliver salbutamol, salmeterol xinafoate, fluticasone propionate, and a combination of fluticasone propionate and salmeterol xinafoate (Advair®/Seretide®). This inhaler uses a tape of 60 premetered blisters rather than a disk (43). Movement of a lever opens the tape, loads the drug into the inhalation channel, and decrements the dose counter. The patient's inspiration draws the formulation from the inhaler into the lungs.

Multidose devices

The Turbuhaler® was the first DPI to dispense doses metered from a reservoir inside the inhaler (44). The device has been used to deliver formulations of terbutaline sulphate, formoterol, salbutamol or budesonide, or a combination of budesonide and formoterol (Symbicort®). When the patient activates the inhaler by twisting the base prior to inhalation, the Turbuhaler® reservoir system deposits a single dose of the drug into a series of holes in a dosing disk. The turbulence generated in spiral-formed channels in the mouthpiece during inhalation breaks up the agglomerates into fine particles, which are then inhaled into the lungs. Approximate dose counting is provided by the gradual appearance of a red band when 20 doses remain. Most Turbuhaler® formulations comprise soft aggregates of micronized drugs formed into pellets approximately 0.5 mm in diameter, without any excipients. The addition of a spring-operated spacer device has been suggested to make the Turbuhaler® easier for very young children to use (45).

The Easyhaler® (Orion) has been used to deliver salbutamol and BDP (46). The reservoir of this inhaler can hold up to 200 doses. Pushing down the overcap of the inhaler rotates the metering cylinder at the bottom of the reservoir, metering a dose of drug and lactose which is inhaled through the mouthpiece. The Clickhaler® (Innovata Biomed) has a broadly similar design, and has shown relative flow rate independence of both lung deposition (47) and bronchodilator response to salbutamol (48) over a range of inhaled flow rates. The Twisthaler® is relatively simple to use because removal of the cap over

the mouthpiece automatically meters a dose from the powder reservoir into a single-dose hole in the dose plate.

Most DPIs are disposable, but the Novolizer®, a multi-dose reservoir system from ASTA Medica, uses refill cartridges of up to 200 single doses of a drug/lactose blend (49). Formulations in DPIs range from low bulk density, freely flowing, powders which may be hard to meter accurately, to a compacted block where reproducible dosing should be easier to achieve, but where the powder may be harder to disperse (50). An intermediate solution is offered in the Airmax® DPI (Yamanouchi Europe) where air from a collapsing bellows is used to partially compress powder into the dosing chamber (51).

MORE SOPHISTICATED FORMULATIONS

Traditionally, most DPI formulations have comprised a blend of micronized drug particles and lactose carrier, or occasionally aggregates of pure drug particles. For these formulations, manufacturers have generally sought to optimize the performance of the system by optimizing the device, for instance ensuring that the design of the mouthpiece leads to airflow turbulence and hence effective deaggregation and a high fine particle dose. In reality, however, both the device and the formulation affect drug delivery, and there is increasing recognition of the benefits that can accrue from optimizing the formulation as well as, or perhaps instead of, the device.

Data from the University of London in the early 1990s showed that particle size distributions from DPIs could be manipulated by changes in the "rugosity" (surface roughness) of carrier particles (52). This concept was taken further by Staniforth *et al*. (53), who developed the process of "corrasion" to minimize the effect of high-energy binding sites on lactose particles, from which micronized drug particles could be difficult to remove (Powderhale™ formulations, Vectura). Improvements in particle dispersion have also been obtained using fine particle lactose (54), or fine particle lactose coupled with an additional excipient such as spray-dried leucine to modify the bulk density of the formulation (55).

The formulation in the Twisthaler® DPI uses a new approach to formulation with agglomerates of anhydrous mometasone furoate, a corticosteroid, and anhydrous lactose in a low weight ratio (1:5.8) (56). The agglomerates are manufactured as stabilized microcrystalline arrays of drug and excipient that allow ease in handling and accurate dose metering. Uniform delivery of mometasone furoate has been shown over a broad range of inspiratory flow rates and times (57,58).

In 1997 and 1998, Edwards *et al*. described large porous particles (59, 60), that have a bulk density of only about 0.1 g/cm^3. Owing to their low density, these particles have aerodynamic diameters only a fraction of their physical diameters so that they can penetrate deep into the lungs. As the number of contact surfaces between adjacent particles is reduced when the particles are large, the particles are readily dispersed in an inhaled airstream and can provide a relatively inhalation-effort- or flow-rate-independent performance. Similar considerations seem to apply to another porous particle system (PulmoSphere particles, Inhale). These and other formulations are listed in Table 3. Sophisticated formulations of this type have often proved effective in very simple DPIs (61,62) and this marks a definite trend wherein the formulation and not the device is being used to control drug delivery. Hence in a sense the wheel has come full circle, with greater attention now being given to optimizing the formulation than to optimizing the device for some pharmaceutical products, in some cases allowing companies to formulate their products in inexpensive single-dose DPIs. The inconvenience of loading a gelatin capsule into the device before use need not prove to be a limiting

Table 3. Novel dry powder formulations

Formulation	Company (if applicable)	Reference
Powderhale™ (Passcal)	Vectura	(53)
Fine particle excipients	—	(54)
		(55)
Large porous particles	Alkermes (AIR)	(59)
		(60)
PulmoSpheres™	Inhale (Alliance)	(61)
		(62)
SoliDose™	Elan (Quadrant)	(63)
SEDS™[a]	Inhale (BPD)[b]	(64)
Nanoparticles	Elan (NanoSystems)	(65)

[a] Solution-enhanced dispersion of supercritical fluids.
[b] Bradford Particle Design.

Table 4. Accuracy and reproducibility of dose emissions from some DPIs in vitro (data from Hindle and Byron (66))

Device	Drug	Mean (% label claim)	RSD (%)
Rotahaler®	Beclomethasone dipropionate	59.5	18.8
Rotahaler®	Salbutamol	62.7	16.1
Diskhaler®	Beclomethasone dipropionate	55.4	18.3
Diskhaler®	Salbutamol	52.0	23.3
Turbuhaler®	Terbutaline sulphate	62.5	13.7
Turbuhaler®	Budesonide	58.1	18.3
Spinhaler®	Sodium cromoglycate	100.2	7.6

The table shows the mean emitted dose expressed as a percentage of the stated label claim, and the relative standard deviation (RSD) of the emitted dose between devices. Data were obtained at a standardized flow rate of 60 l/min.

factor, especially for a drug that needs to be given no more frequently than once or twice daily. However, many of these sophisticated formulations may well find their main roles outside the field of asthma therapy, for instance, to deliver inhaled peptides and proteins.

IN VITRO MEASURES OF DPI DRUG DELIVERY

Dry powder inhalers have to meet specific standards for the average drug content of the emitted dose and dose uniformity. For instance, U.S. FDA draft guidance requires that 90% of inhalers tested must deliver active drug within 80–120% of the label claim, and that all inhalers tested must deliver 75–125% of label claim (7). A standard method is used to quantify the emitted dose from a DPI and its variability by collecting the discharge on a filter. By measuring the emitted dose from the inhaler and the retained dose on the inhaler itself, the metered dose and its variability can also be calculated. The emitted doses from several DPIs are shown in Table 4 from data collected by Hindle and Byron (66), suggesting first that some DPIs do not emit a dose consistent with the stated label claim, and second that the variability in emitted dose may be considerable.

Dose uniformity across a range of inspiratory flow rates ensures that the patient receives the desired dose of medication despite variations in inspiratory flow rate. The emitted doses of the Spinhaler®, Turbuhaler®,and Diskhaler® at different inhalation flow rates showed significant sensitivity of dose delivery to flow rate in all three inhalers (Fig. 2) (67). The Diskhaler® was the most sensitive to low flow rates, emitting $<30\%$ of the claimed label dose at 20 l/min. The fraction of dose delivered as particles finer than about 5 μm in diameter is usually called the "fine particle fraction" and is sometimes considered to be predictive of the amount of drug delivered to the lungs. Since most DPIs are breath actuated, fine particle fraction will decrease with a reduction in airflow rate through the device. Particle size distributions produced by DPIs can be measured with a cascade impactor (68,69), which separates airborne particles into size categories by trapping the particles on a series of discrete stages. The three most widely used cascade impactors are the Andersen sampler, multistage liquid impinger, and Marple-Miller impactor, although these three devices do not necessarily give identical results (70). Each cascade impactor is calibrated to operate at a specific airflow rate but may be modified to operate at different flow rates (71). In order to compare results between inhalers with differing resistances, current guidelines recommend testing DPIs at a fixed pressure drop of 4 kPa rather than at a fixed flow rate (68). Since none of the current instruments is considered ideal, an international consortium is currently developing an impactor optimized for use in the pharmaceutical environment (72).

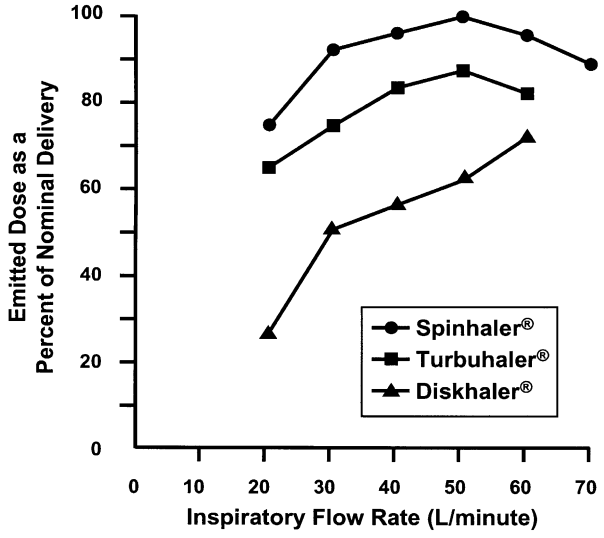

Fig. 2. Emitted dose as a percentage of claimed delivery of the Spinhaler®, Turbuhaler®, and Diskhaler® across a range of inhalation flow rates. Data adapted from de Boer *et al.* (67).

The use of simulated inhalation profiles (73) or inlets to impactors that mimic the shape of the human upper airways (74) may provide *in vitro* data that more closely match the *in vivo* situation.

IN VIVO MEASURES OF DPI DRUG DELIVERY AND DISTRIBUTION IN THE LUNGS

Quantification of drug deposition *in vivo* from DPIs may be carried out using radionuclide imaging methods (75,76), or by certain pharmacokinetic techniques (77–79). Radionuclide imaging involves the addition of an appropriate gamma-ray-emitting radionuclide to the formulation, or occasionally into the structure of the drug molecule itself, and may be in two dimensions (gamma scintigraphy) or in three dimensions [single photon emission computed tomography (SPECT) or position emission tomography (PET)]. Whole lung deposition may be quantified for some drugs from drug excreted in a 48 h urine collection using the charcoal block pharmacokinetic method (77), and indices of lung deposition may be provided by the amount of drug appearing in the blood (78) or in the urine (79) within a few minutes of inhalation. Unlike radionuclide imaging, pharmacokinetic methods do not provide any data on the pattern of distribution within different lung regions.

Whole lung deposition data for a range of DPI products are listed in Table 5, and have ranged in various studies from about 5% of the metered dose to about 40%. Lung deposition is critically affected by the design of the device, the formulation, and the PIFR attained by the patient. In comparative studies, DPIs have often deposited more drug in the lungs than a CFC-based pMDI (89) and have been clinically effective in correspondingly lower doses (90). As expected, fast inhalation flow, involving maximal inspiratory effort, has usually deposited more drug in the lungs than slow inhalation flow, involving submaximal inspiratory effort. However, a number of devices, including some breath-actuated systems, appear to have deposition characteristics that are virtually inhalation-effort independent (47,85), which could make the devices concerned especially suitable for treating the very young, the elderly, and those with severe respiratory impairment. Scintigraphic images from one DPI with relatively effort-independent performance are shown in Fig. 3. The Spiros® DPI is unique amongst the devices listed in Table 5, as the powder is dispersed by an impeller blade, triggered by an electric motor, rather than by the patient's inhalation. Consequently, this device deposited drug more efficiently in the lungs with slow inhalation than with fast inhalation (87). Some companies

TABLE 5. Mean whole lung deposition of drugs from various DPIs, expressed as percent of metered or capsule dose.

Device	Drug	Inhalation	Deposition (%)	Reference
Rotahaler®	Sodium cromoglycate	Slow (60 l/min)	6.2	(30)
Spinhaler®	Sodium cromoglycate	Fast (120 l/min)	13.1	(80)
		Slow (60 l/min)	5.5	
Diskhaler®	Salbutamol	Not known	12.4	(81)
Turbuhaler®	Budesonide	Fast (58 l/min)	27.7	(82)
		Slow (36 l/min)	14.8	
Pulvinal®	Salbutamol	Fast (46 l/min)	14.1	(83)
		Slow (28 l/min)	11.7	
Easyhaler®	Salbutamol	Fast (60 l/min)	28.9	(46)
Ultrahaler®	Nedocromil sodium	Fast (75 l/min)	13.3	(84)
		Slow (42 l/min)	9.8	
Clickhaler®	Budesonide	35 – 65 l/min	30.8	(47)
Taifun®	Budesonide	Fast (36 l/min)	34.3	(85)
		Slow (21 l/min)	29.6	
Cyclohaler®	Asthma NCE[a]	Fast (98 l/min)	19.1	(86)
Spiros®	Budesonide	Slow (15 l/min)	40.5	(87)
		Fast (60 l/min)	30.4	
Novolizer®	Budesonide	Fast (99 l/min)	32.1[b]	(88)
		Slow (54 L/min)	19.9[b]	

Data are for gamma scintigraphic studies in healthy volunteers. There is no evidence that whole lung deposition differs significantly between healthy subjects and asthmatics who can inhale at the same PIFRs. Lung deposition data obtained by the charcoal block pharmacokinetic method are similar to those obtained by gamma scintigraphy.

[a] New chemical entity.

[b] Median values.

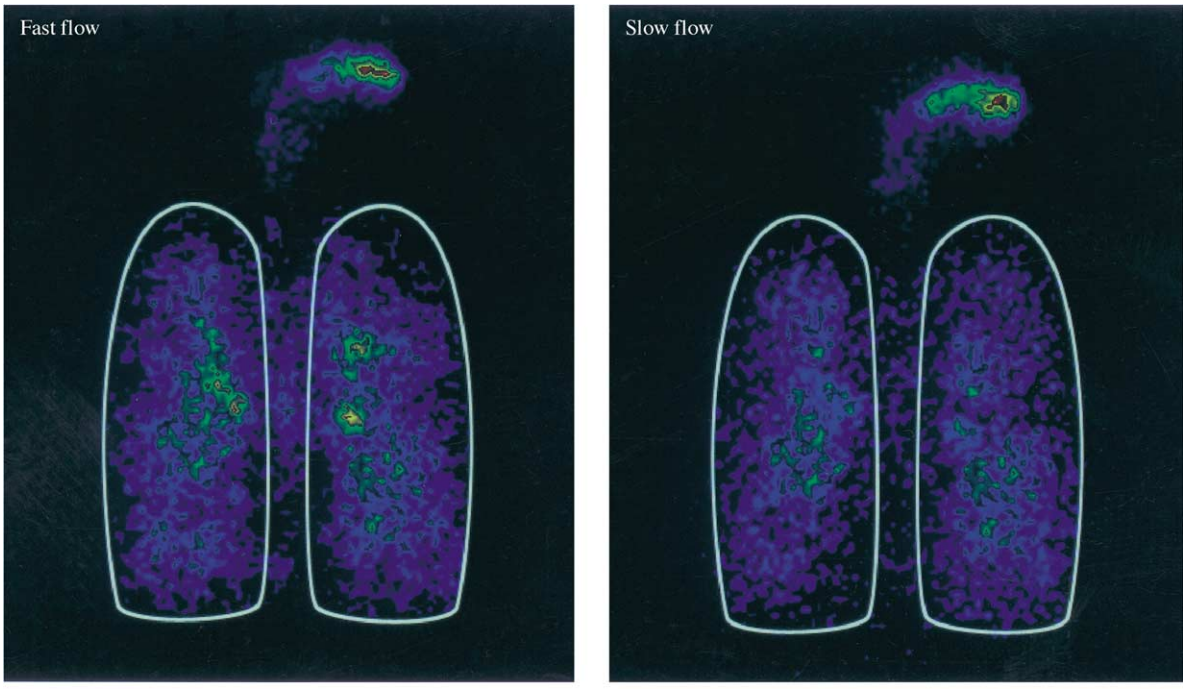

Fig. 3. Scintigraphic images showing the lung deposition from one DPI (Taifun) at fast and slow peak inhaled flow rates. This device was relatively flow-rate independent in performance (lung depositions 34 and 29% of the dose, respectively). Data from Pitcairn *et al.* (85). Reproduced from Newmann (76) with permission.

have used lung deposition studies to show comparability between their novel DPI and a well-established "gold standard" device, hence providing a rational basis for the selection of doses in subsequent pivotal clinical trials comparing the two devices (88).

In devices with a low airflow resistance, fast inhalation (maximal inspiratory effort) resulted in a PIFR through the device of 120 l/min, compared with values of only about 30 l/min for devices with very high airflow resistance. However, in terms of lung deposition, there is no evidence that devices with a high resistance to airflow are any more efficient or any less efficient than low-resistance devices. Each device must be treated on its merits, and attempts to predict the performance of one DPI based on the performance of another one with quite a different design have proved unreliable.

Table 6. Some characteristics of an ideal DPI, modified from Ashurst *et al.* (38)

Effective dosing	Uniform dose throughout the life of DPI
	Targeted, accurate, and reproducible delivery
	Generates full dose at low inspiratory flow rates
Efficient device	Design optimized by device and formulation innovation
	Compact, portable
	Cost effective
	Good moisture protection
Easy to use	Simple operation
	Easy for clinician to teach and for patient to learn
	Dose counter
	Mechanism to prevent multiple dosing
	Possible to sense dose on back of throat

CONCLUSION–APPROACHING THE IDEAL DPI

There is now clear evidence that many major players in inhaled drug delivery are prioritizing development of DPI products in preference to reformulation of pMDIs with HFA propellants. However, companies developing DPIs face many challenges, and must often make compromises. For instance, seeking solutions to technical problems associated with optimizing pharmaceutical performance may introduce incompatibilities with patient compliance issues. Multidose (reservoir) devices tend to target drug to the lungs more efficiently than multiple unit dose devices but tend to have poorer dose uniformity. While it is unlikely that an ideal DPI will ever appear, it is at least possible to list some of the characteristics of an ideal DPI (Table 6).

A range of DPIs is already marketed, and many others are in development. Not all new DPI devices and formulations will reach the market, but many of those that do are likely to have successfully addressed perceived limitations in earlier systems. As we go forward into the 21st century, DPI delivery systems are likely to contribute significantly to successful drug delivery by the inhaled route, not only to treat asthma, but also to deliver a wider range of drugs intended both for local and systemic applications.

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