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Review

Developing an efficient and reliable dry powder inhaler for pulmonary drug delivery – A review for multidisciplinary researchers

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ABSTRACT

Pulmonary drug delivery is the focus of much research and development because of its great potential to produce maximum therapeutic benefit. Among the available options the dry powder inhaler (DPI) is the preferred device for the treatment of an increasingly diverse number of diseases. However, as drug delivery from a DPI involves a complicated set of physical processes and the integration of drug formulations, device design and patient usage, the engineering development of this medical technology is proving to be a great challenge. Currently there is large range of devices that are either available on the market or under development, however, none exhibit superior clinical efficacy. A major concern is the inter- and intra-patient variability of the drug dosage delivered to the deep lungs. The extent of variability depends on the drug formulation, the device design and the patient's inhalation profile. This article reviews recent advances in DPI technology and presents the key factors which motivate and constrain the successful engineering of a universal, patient-independent DPI that is capable of efficient, reliable and repeatable drug delivery. A strong emphasis is placed on the physical processes of drug powder aerosolisation, deagglomeration, and dispersion and on the engineering of formulations and inhalers that can optimise these processes.

Contents

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1. Introduction

There is rapid expansion in the use of respiratory drug delivery technologies [1,2] utilising dry powder aerosol systems for the treatment of local and systemic disorders. While much effort has been expended in designing, manufacturing and marketing novel, user-friendly and affordable devices which are widely used, such devices continue to exhibit sub-optimum performance (i.e. the drug dispersion from currently available devices and formulations varies from 12% to 40% of the load dose [3,4]). Not only do current devices result in incomplete delivery of drugs, more concerning is the large variability in the delivered dosage (the fine particle fraction or FPF) from one use to the next or from one patient to another. At present a large number of dry powder inhalers (DPIs) are available on the market with a varying degree of demonstrated delivery efficiency [5]. The performance of a DPI system is governed by a combination of factors including the physicochemical properties of the powder formulation, the design of the device's dose metering systems, and the physical mechanisms (e.g. turbulence, shear and/or impactions) used to aerosolise, deagglomerate, disperse and deposit the drug powders in the deep lungs. The existence and intensity of these physical mechanisms is determined by the design of the device and the inhalation profile of the patient while their impact on the powders is largely a function of the properties of the formulation. It has been demonstrated by computational fluid dynamics (CFD) that small changes in device design can affect inhaler performance [6,7]. Also, variations in the morphology of drug powders can determine the behaviour of such powders when used in a DPI [8].

There is debate about the best approach for improving DPI system performance [9]; whether it is best to change the physicochemical properties of the drug powder formulation [10,11], or to vary the device design [6,12]. To this we might add improved patient training [13] and compliance with regulatory frameworks and pharmacopoeial specifications as steps towards system performance improvements. The most recent initiatives to adopt a quality by design (QBD) ethos [14,15], is stimulating this debate. It is possible, at least in principle, to individually and combinatorially optimise the design of the device and the drug powder formulation. However, optimisation of the complete DPI system (formulation, device and usage) is very difficult because of the essentially random variability in a user's inhalation profile, and their skill in using and caring for their device. Therefore, it is apparent that any design philosophy should optimise practical system performance rather than pursuing technically ideal inhalers that are difficult to use. With this view of how DPI system design should proceed there is an immediate need to identify the main engineering factors that both motivate and constrain the successful development of a universal, patient-independent DPI device that is capable of efficient, reliable and repeatable drug delivery with maximum therapeutic benefit.

The remainder of the article is organised as follows. In the next section (Section 2) we review the fundamental mechanisms of DPI drug delivery, the performance of existing and under development devices and the major limitations of some DPI devices. Section 3 discusses ambitions for systemic drug delivery via DPIs and the additional emphasis this gives to improve engineering of DPI systems. In Section 4 we discuss the key factors to consider in the development of new DPIs; namely, the ability to engineer the drug powder formulations, patient variability, the availability of modern engineering enabling technologies such as computational fluid dynamics and advanced experimental diagnostics, and the need for regulatory and pharmacopoeial compliance. Finally we make conclusions in Section 5.

2. Review of DPI technologies

2.1. Physical mechanisms of DPI drug delivery

The delivery of dry powder drugs to the lungs involves a number of complex and inter-related physical processes. The key processes are powder aerosolisation (or fluidisation), deagglomeration of active drug particles from larger carriers and/or drug-only agglomerates, dispersion and transport of the drug aerosols through the airways, and deposition. The effectiveness of these processes in delivering maximum and repeatable dose delivery is dependent on the properties of the powder formulation, the design of the device and the strength of the patient's inspiratory air flow. In this review article we concentrate on the processes within the DPI device itself. A detailed review of the fluid mechanics of aerosol transport in the airways is provided by Golshahi and Finlay [16] and is not discussed in depth here.

Aerosolisation requires an aerodynamic force that is sufficient to overcome the weight of the powder particles. This force can be increased by increasing the air velocity either by the patient inhaling at a greater rate of by directing the flow through a nozzle, venturi or contraction while incurring a pressure drop. Either method requires greater effort by the patient. Aerosolisation of a single powder particle in isolation can also be improved by reducing its aerodynamic diameter. This can be done in a number of ways. The most obvious is a reduction in the geometric diameter (while keeping particle density constant), although this will increase particle cohesive forces resulting in greater agglomeration and possibly reduced propensity for the bulk formulation to be aerosolised. The aerodynamic diameter can also be reduced independently of the geometric diameter by reducing the particle density (e.g. by introducing porosity) or by increasing the particle shape factor (e.g. by using needle-shaped particles) [17].

The drug powders are formulated as either interactive mixtures of micron sized actives (<5 μm) that adhere to larger carrier particles such as lactose, or as drug-only agglomerates (Fig. 1). The primary purpose of adding carrier particles is to reduce the propensity of the fine drug particles to exist as strongly cohesive agglomerates and to increase the flowability of powders prior to aerosolisation. Agglomeration occurs naturally due to the cohesive forces between small and irregularly shaped particles, whereas the interactive mixtures are produced by adding carrier particles to drug particles in such as way that the cohesive drug agglomerates are broken and are replaced by weaker adhesions between the carrier and multiple active particles. In practice, when carrier particles are introduced not all agglomerates are broken and the interactive mixture will consist of some drug-only agglomerates. Types of powder mixtures and methods for producing them are discussed in more detail by Hersey [18] and physicochemical properties of drug powders and their variability are explored by Telko and Hickey [17]. Once aerosolised the powders must be deagglomerated to a size that is sufficiently small for deposition in the alveolar region of the lungs. Lung deposition requires an aerodynamic diameter typically less than 5 μm. Particles with a larger aerodynamic diameter are deposited in the upper airways from

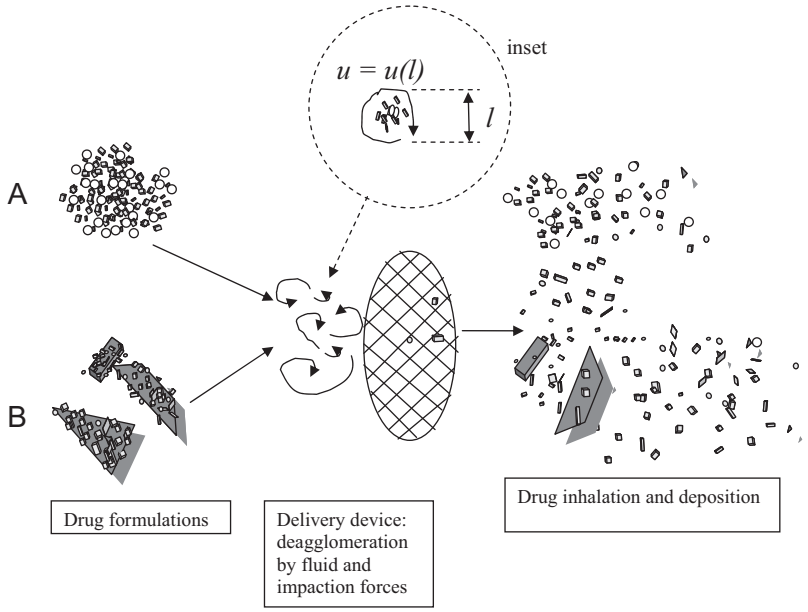

Fig. 1. Schematic diagram of DPI formulations and dispersion process: A. Drug-only formulation (drug agglomerates); B. Carrier-based formulation.

where they are swallowed or expelled, whereas particles with a smaller aerodynamic diameter are often exhaled or deposited by Brownian diffusion upstream of the alveoli. Powder deagglomeration and dispersion occur due to fluid dynamic shear which may be enhanced by turbulence. These mechanisms of particle deagglomeration are explained with reference to Fig. 1. Here two types of currently available DPI formulations i.e., (A) formulation containing only drug particle agglomerates, and (B) formulation containing drug carrier mixture, where small drug particles are adhered on the large carrier surface, have been presented. Once aerosolised the agglomerates may be subjected to fluid forces and impaction forces or a combination of both. The former are comprised of fluid shear (i.e. velocity gradients across the agglomerates) and sudden accelerations due to drag forces in a flow of varying velocity. These fluid forces are enhanced by turbulence as shown in the inset in Fig. 1. The turbulent eddies of the carrier air have a range of length and time scales and the velocity is thus a function of the eddy size. The eddy velocity decreases at smaller length scales but not as quickly as the length scale itself decreases; thus turbulent shear forces are greater at the smallest sizes. The magnitude and frequency of the turbulent shear at the size of the agglomerate will determine whether deagglomeration occurs. Further discussions on turbulent shear forces are found in Section 4.3.1.3. Sudden accelerations due to fluid drag are likely to be small since the powder density is usually much larger than the fluid density (up to three orders of magnitude) and the response time of agglomerates due fluctuations in the air velocity will be long. Collisions with the device or with other particles also result in sudden acceleration (in this case deceleration) of the agglomerates and these can be large enough to result in breakage.

Careful device design can improve the deagglomeration and dispersion potential of the flow. Currently available DPIs employ rotating impellers, turbulence/impaction grids, cyclone and reverse-cyclone flow paths, and pressure drop devices such as contractions or orifices, nozzles and venturis. The design of some DPI devices with the mechanism of particle dispersion has been produced in Fig. 2. Fig. 2A shows the mechanism of drug dispersion from Spinhaler in which a single-dose capsule containing drug formulation is fitted into an impeller, which rotates during inspiration. It is important to note that the rotation speed and thus rate of aerosolisation and dispersion varies according to the patient's inspiratory force and breathing cycle. Fig. 2B demonstrates the mechanism of drug dispersion from Rotahaler. After twisting the Rotahaler, the capsules breaks into two pieces i.e., the body containing the dose falls into the device and the cap is retained in the entry port of the device. Due to the patient's inhalation, the portion of the capsule containing the drug powder experiences rotational motion in the airstream, which causes deagglomeration/dislodgement of particles after impacting on the turbulence grid for dispersion. Fig. 2C demonstrates the mechanism of drug dispersion from a sophisticated device Turbuhaler. Initially the dose of drug powder is metered into small conical cavities by twisting a grip at the base of the device. Upon inhalation by patients, air is ducted through the cavities and the drug particles pass through the turbular pathway where impaction occurs. Fig. 2D demonstrates the dispersion of powders from a rotary planar device known as Easyhaler. This is a multiple dose reservoir type of inhaler, which can hold up to 200 doses. After pushing down the overcap of the device rotates the metering helical blade, which removes a dose of powder drugs that aerosolised and dispersed during inhalation. Aerolizer (Fig. 2E) is another capsule containing device. With the aid of two pins the capsule is pierced. Upon inhalation the drug powders experience high velocity collisions between powder particles and the grid which also generates more energetic turbulence. Diskus, a multi-unit dose inhaler (Fig. 2F), contains factory prepared unit dose drug powders in sealed blister, which is pierced by lifting the mouthpiece lid and the powders are dispersed by the turbulent shear upon inspiration. The performance of some specific inhalers using a variety of the above mentioned deagglomeration mechanisms is discussed in Section 2.2.

2.2. Performance of existing and developmental DPI designs

There are four main types of DPI system as shown in Fig. 3. The single-unit dose inhaler requires the patient to load a single hard gelatine capsule containing the powder formulation into the device before each use (Fig. 3A). This is a very common type of DPI device currently available on market. Fig. 3B shows a device containing a pre-metered amount of a single dose that is discarded after use. Multi-unit devices deliver individual doses from pre-metered replaceable blisters, disks, dimples or tubes (Fig. 3C). Multiple dose reservoir inhalers as shown in Fig. 3D contain a bulk amount of

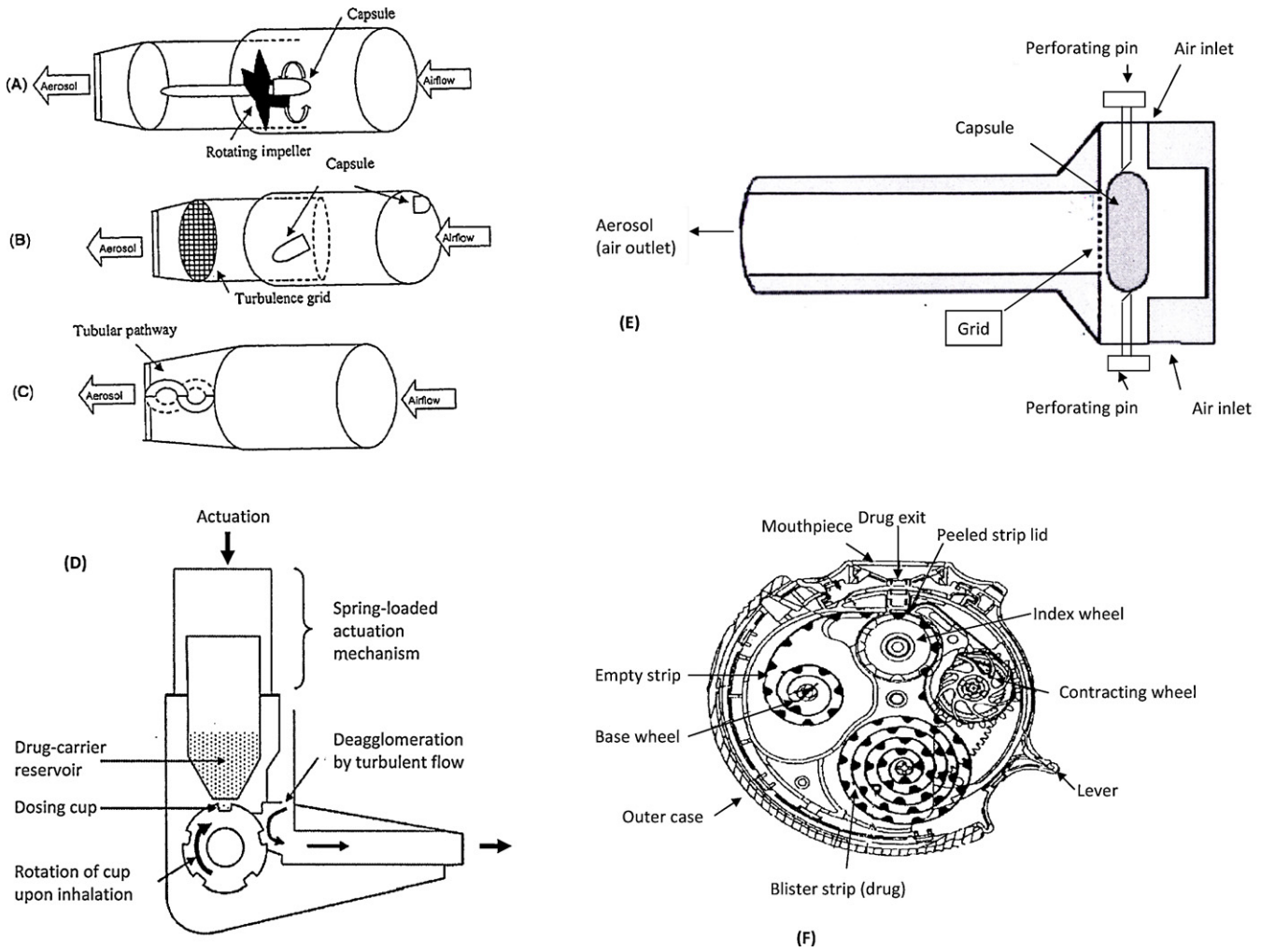

Fig. 2. Different types of DPI devices and some mechanisms for drug deagglomeration and dispersion (adapted from [208–210]). A. Spinhaler, B. Rotahaler, C. Turbuhaler, D. Easyhaler, E. Aerolizer and F. Diskus inhaler.

drug powder in the device with a built in mechanism to meter a single dose from the bulk and individual doses are delivered with each actuation. The multi-unit inhalers (Fig. 3C) are likely to ensure greater dosage control and chemical stability of the formulation than multiple dose types (Fig. 3D); however, the former are more expensive than the latter.

The key DPI design parameters, which influence the effective dispersion of drug from the formulation include the geometry and the length of device mouthpiece [19,20], the air flow rate and the sizing of the air inlet and other flow accelerators [21,22], the shape, size and positioning of the drug capsule or other drug dispensing insertions [23], and the geometry and sizing of flow straighteners and turbulence generating meshes [20] or other adornments to alter the direction and velocity of the fluid or particles. Failure of the drug powders to deagglomerate can lead to a high rate of device and upper respiratory tract impactions and is a major contributing factor to the observed low percentage of particles reaching the lungs [24]. Therefore the effect of design changes on the deagglomeration potential of the flow is of great interest and is a central theme of the papers cited above. As mentioned above the deagglomeration potential increases with mean and turbulent flow shear and the intensity (frequency and speed) of impactions. A number of methods are employed in existing DPIs to enhance these quantities [25,26]. Turbulence generating meshes are employed in some DPIs such as the single-unit devices Spinhaler® and Rotahaler®. In the Spinhaler (Fig. 2A) the capsule is mounted so that it spins when air flows over it and this assists full aerosolisation of the drug. The fluid dynamic mechanisms in this device are discussed in some detail in Section 4.3 in the context of computational fluid dynamics modelling. *In vitro* trials indicate that dispersed FPF is relatively independent of the inhalation flow rate although there is still more variability than can be achieved with some metered multiple dose devices such as Easyhaler® [27,28]. Deagglomeration in some second-generation, multiple dose devices such as Easyhaler® and Turbuhaler® is achieved by directing the flow through a narrow mouthpiece channel to generate strong turbulent shear while the Clickhaler® (another multiple dose device) utilises high particle velocity directed at internal impaction surfaces. In vitro trials for salbutamol formulation [27,28] indicate that Easyhaler® demonstrates lower sensitivity to air flow rate in the 30–60 L/min range (25–30% FPF emitted) than the Turbuhaler® although the latter device achieves much higher FPF emitted at 60 L/min (40%). Turbuhaler is also much more variable in its performance than is Easyhaler [27–29]. Clickhaler® performs similarly to Easyhaler with relatively low variability and low sensitivity of the FPF over a wide range of flow rates [30]. While the investigations cited above all contribute to accumulated knowledge of DPIs it is difficult (perhaps impossible) to use the information contained in those publications to compare the performances between devices because the cited drug dispersion studies have not been undertaken using the same formulations at the same experimental conditions. We return to this theme later.

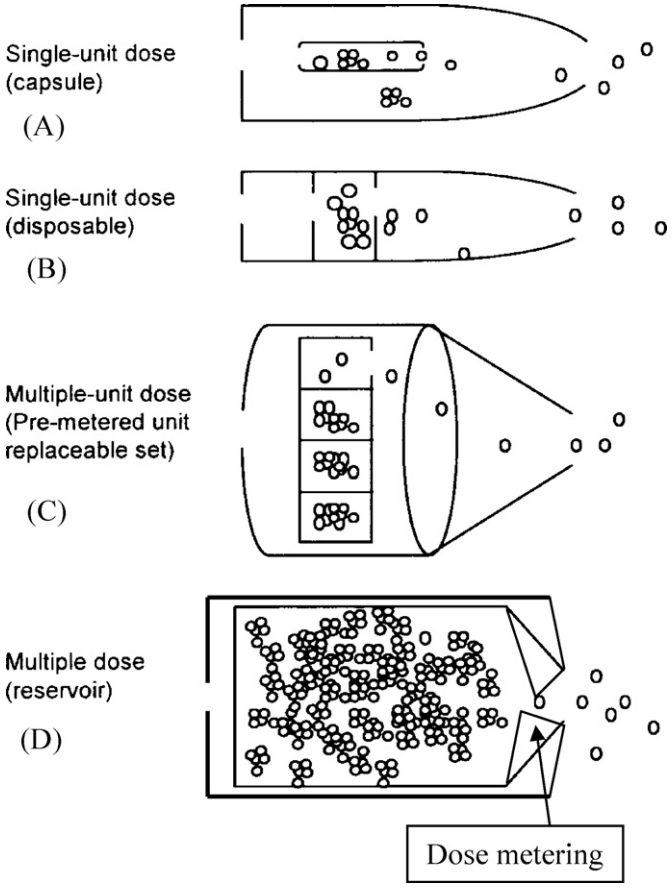

Fig. 3. Different types of doses available in DPI formulations (modified from [211]).

Many novel devices currently under development have features designed to specifically enhance deagglomeration of the drug powders. Adler et al. [31] developed a mesh-based DPI device containing a breath-driven rotor which repeatedly beats the mesh causing agitation/vibration, resulting in better deagglomeration of the drug powders. However, no further details on the formulation and FPF of the dispersed drug from this device are available. Another new device uses a cyclone chamber coupled with a fine sieving mesh to enhance the deagglomeration potential [32]. Experiments show that FPF of ciprofloxacin and budesonide are 69.7% and 50.5%, respectively, for a flow rate 60 L/min. Using the same formulation of budesonide, the marketed Turbuhaler dispersed 34.5% drug at the same flow rate. Upon aerosolisation the agglomerates exit from the cyclone with a particle motion tangential to the fine mesh surface, which is claimed to cause the increased deagglomeration. Using reverse-cyclone technology, Needham et al. [33] developed a new passive device, 3 M Conix™ (Fig. 4), for efficient deagglomeration of particles and this device showed higher FPF albuterol sulphate compared with a currently available DPI device, Accuhaler. The reverse flow in the device produces high velocities providing the energy required for deagglomeration through turbulent shear, particle–particle and particle–wall impactions. Another modern device, the AirMax, has a cyclone separator and produces consistent dose emission and a high FPF (50%) of formoterol [34]; however, the tests also reveal that the efficiency is dependent on the patient's inspiratory flow rate.

All currently available DPIs are passive devices which rely solely on the inspiratory force of the patient to disperse the drug powders. However, each inhaler device has a different air flow resistance and a threshold inspiratory force is required to achieve the correct flow rate to aerosolise, deagglomerate and disperse the powder

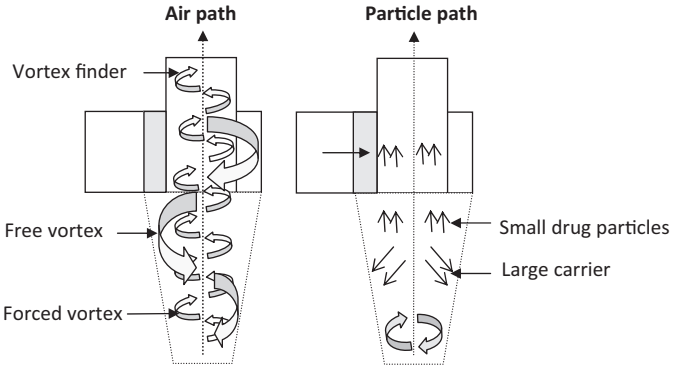

Fig. 4. The reverse flow cyclone mechanism of deagglomeration process. Adapted from [33].

formulation and to achieve an effective therapeutic response [35,36]. For example, Spinhaler and Rotahaler are both very low resistance, single-unit dose DPIs. Very high flow rates (from 90 to 120 L/min) are required to produce only moderate lung deposited FPF for Rotacaps 400 formulation (Budesonide) of about 17% and 20% for Spinhaler and Rotahaler, respectively [37,38]. Diskus and Accuhaler are found to be low to moderate resistance multi-unit dose devices with a pressure drop of about 4 or 5 times greater than that of Spinhaler achieving 50% higher FPF over flow rates of 30–90 L/min for the same powder formulation [37]. Turbuhaler is a high resistance device with a pressure drop of about 10 times the Spinhaler [37,39]. Patients with severely impaired lung function and young children may find it difficult to generate sufficient inspiratory force and for them high device resistance may not always lead to high FPF deposition in the lungs [36]. Therefore it is common to compare the performance of two different devices at the same pressure drop (i.e. for the same patient effort) even though the drug formulation and the flow rate are quite different. At a comfortable inspiratory effort of 3.9 kPa the flow rate through the Spinhaler is 105 L/min while only 63 L/min for the Turbuhaler. For these conditions the Spinhaler produces approximately double the lung deposited FPF than Turbuhaler during in vitro trials with eformoterol fumarate dehydrate formulation [38]. In another example the lung deposited FPF of budesonide via the Jethaler and Novolizer is 62.0% and 72.0%, respectively, for the same observed pressure drop of 4 kPa [40].

The above mentioned device adornments, which are designed to increase the deagglomeration and dispersion potential of the flow by increasing shear, turbulence and impactions, also increase the resistance and hence pressure drop across the device. The pressure drop also increases with flow rate. Device pressure drop is an important factor for parameterising the FPF deposited in the lungs; it is generally expected that higher FPF correlates with higher device pressure drop [37]. As previously mentioned, it may be difficult for some patients with impaired lung functions, especially elderly patients and children, to produce that required inspiratory force [36]. To allow for lower patient inspiratory force yet achieve effective drug delivery, active devices with an inspiration-actuated integrated energy source such as compressed gas, motor driven impeller or electronic vibration are under investigation [41,42]. It is hoped that active devices could enable FFP delivery that is independent of the patients inhalation profile. Despite their promise active devices also tend to have complicated designs and are more expensive than passive devices. The very first approved active device (Exubera®, Pfizer) used compressed air for insulin delivery. However, due to its awkward design and high cost the Exubera® inhaler was not taken-up by physicians and patients and production was discontinued. Another active device is the Aspirair® (not yet approved) which employs an air flow-sensor triggered

compressed air energy source and a vortex separation chamber to breakup agglomerates and improve FPF lung delivery [43].

From the above discussion, it is clear that a large number of variables are associated with the performance of DPI devices, which significantly affected the drug dispersion from various drug formulations. It is very difficult to compare the performances of different DPIs (which have different design, resistance, mechanism of drug dispersion) without investigating their performances using the same drug formulation and same inspiratory force in a controlled environment. There is no comprehensive information (or data with limited information/access) on the comparative studies based on the performance of various devices. Therefore, it is extremely difficult to make a straightforward comparison on the performances of various devices; however, this section may be considered as an example of the performances of some commonly used DPI devices. This theme is taken-up again in Section 4.4 in the context of regulatory and pharmacpoeial compliance.

2.3. Limitations of currently available devices

The FPF deposited in the lung from currently available inhalers varies from 9% to 78.7% (see Table 1). One of the major reasons for this wide variability and generally low lung deposition may be due to insufficient deagglomeration of the powders [24]. This is caused by formulations with strong cohesive forces, device designs which do not enhance fluid–particle interactions such as turbulent shear or which do not enhance agglomerate impactions, and also by the inability of the patient to achieve sufficient inspiratory force. In addition, different devices have been investigated using different drug formulations, which have different physicochemical properties, which might affect the deagglomeration/aerosolisation behaviours. Moreover, device tests may have been operated at different flow rates that affect the dispersion of drugs from the formulation. Therefore, it is very difficult to produce straightforward comparison in the performances of various devices. These issues are discussed in detail above in Sections 2.1 and 2.2. Now we discuss some other design limitations of existing DPIs which are mainly concerned with convenience and ease of use, but which can also lead to variable and incomplete drug delivery.

DPIs are of great interest partly due to the perceived simplicity of their use relative to pressurised metered dose inhalers (pMDIs). However, correct usage of some first-generation, single-unit dose DPIs such as Spinhaler (formerly Aerolizer), Rotahaler and Handihaler requires a sequence of steps that may not be easy for children or elderly patients with diminished dexterity. A new capsule is loaded into the device before each use, the device is then primed by breaking the capsule, and then, depending on the patient's breathing profile, the inhalation process must be continued or repeated until the capsule is emptied. Most devices are opaque (apart from the multiple dose Pulvinal) and it is not obvious if the dose has been correctly administered. In addition the capsules may not always protect the formulation against atmospheric humidity [26].

The second-generation multi-unit devices were developed as more convenient alternatives to single-unit devices although they also have their limitations. The earlier version of the multi-unit dose DPI, Diskhaler (four–eight blisters), is complicated to use. It is recommended that blisters containing the drug formulation must be changed frequently and the device needs to be cleaned to avoid microbial growth before refilling. Furthermore, the device has only a 3 months lifetime which is not cost effective. The later version of Diskhaler is the Diskus inhaler, containing 60 doses on a foil blister strip. It is more sophisticated compared to its predecessor, however it is not refillable, the mouthpiece is not user-friendly and, due to the complex design, the production cost is high. Further, the Diskus has a low resistance and sometimes the loaded dose is not completely emptied upon inspiration [44].

The multiple dose (reservoir type) DPIs such as Turbuhaler, Easyhaler and Clickhaler contain the drug formulations in a reservoir within the device thus avoiding the inconvenience of loading a capsule immediately before use. A metering system is often fitted and a measured dose is primed into the air flow-path just before inhalation. As the drugs are stored within the device the design must ensure protection against atmospheric humidity and the three above mentioned devices achieve that. However, a consequence of this is that most multiple dose devices are not refillable and this increases the cost of medication. Even though multiple dose DPIs are protected against the exposure effects of atmospheric humidity, the temperature and humidity at the time of use may affect performance including dose variation. The FPF of Turbuhaler for turbutaline sulphate formulation falls from 20% to 7% at 30 °C and 72% relative humidity and to nearly zero at 5 °C [45]. It is thought that condensation on the walls of the device is to blame. Another complaint against multiple dose DPIs is a lack of feedback to the user to show that the correct dose has been delivered and to continuously show how many doses remain. Some user-friendly multiple dose devices such as AirMax™ and Novolizer® have been developed more recently with specific design features including dose counters. The Novolizer has the advantage of being refillable through use of a cartridge reservoir with up to 200 single doses and has been shown to deliver consistent FPF even at high temperature and humidity [46]. This device is found to deliver 32% of the emitted dose to the lung at high inspiratory flow rate (99 L/min) however there is sensitivity of the FPF to flow rate [47,48]. We note that many other multi-unit and multiple dose passive devices are not completely free from the limitations mentioned above.

3. Delivery of drug for systemic effects

For decades pulmonary drug delivery, either via pMDIs or DPIs, has been used in the topical treatment of respiratory tract diseases such as asthma. With advances in nanotechnology and the development of aerosol drug formulations capable of passing into the blood stream there is growing interest in extending the use of DPIs for the delivery of drugs for systemic diseases [49–51]. Some examples are discussed here.

The bioavailability of levonorgestrel has been investigated using both pulmonary and oral routes [52]. It is revealed that the pulmonary delivery of the drug produces effective drug plasma concentrations over a prolonged period of 16–60 h with reduced side effects compared to oral delivery. Valle et al. [53] compare disposition of levofloxacin in isolated rat lungs by inhalation and bolus injection. Overhoff et al. [54] tested deep lung delivery of fentanyl citrate with the TAIFUN® dry powder inhaler for the management of breakthrough cancer pains. FPF of 27.6% and 30.6% were achieved for 100 and 200 μg doses, respectively, with a rapid onset of action (t_{max} = 1 min). In another rapid onset test, inhaled levodopa for the treatment of Parkinson's disease showed a therapeutic effect within 10 min [55]. Using the DPI technique, respiratory delivery of other potent drugs such as insulin [56], antibiotics [57,58], drugs for neurological disorders like Parkinson's disease [59], antituberculosis [60], antihypertensive nifedipine [61], anticoagulant heparin [62], drugs for sexual dysfunction [63], opioids and fentanyl for cancer pain [64–66], and delivery of atropine sulphate nanoparticle as an antidote for organophosphorus poisoning with better bioavailability [67] have been investigated. DPI formulations of measles vaccine [68], mucosal vaccination for influenza virus [69], malarial vaccine [70], and siRNA [71] have all been investigated with significant success.

It is evident that there is expanding interest in the pulmonary delivery of various drugs for the management of various systemic disorders. Current DPI devices have large inter-user and intra-user

Table 1
Lung deposition of drugs from some commercially available DPI devices.

Device	DPI type	Drugs	Flow (L/min)	% FPF	References
Rotahaler	Single dose	Salbutamol	–	9.1	[212]
		SCG	–	9.0	[213]
Spinhaler	Single dose	SCG	–	10.0	[214]
		SCG		14.2	[215]
Diskhaler	Multi-unit dose	Salbutamol	–	11.4	[216]
Easyhaler	Multiple dose	Salbutamol	–	24.0	[217]
Pulvinal	Multiple dose	Salbutamol	27.8	11.7	[218]
		Salbutamol	46	14.1	
Turbuhaler	Multiple dose	Terbutaline	57	26.9	[219]
		Terbutaline	–	20.8	[220]
		Nedocromil	60	19.0–22.0	[221]
Ultrahaler	Multiple dose	Nedocromil	40	15.0–15.8	[222]
		Nedocromil	60	18.6–20.8	
		Budesonide	52	32.0	[223]
		Budesonide	65	29.1	[224]
		Budesonide	36	14.8	[225]
Novolizer	Multiple dose	Budesonide	54	19.9	[226]
		Budesonide	65	25.0	
		Budesonide	99	32.1	
		Budesonide	–	72.0	[40]
Handihaler	Single	Tiotropium	20	16.3	[227]
		Tiotropium	28.3	21.8	
		Tiotropium	40	23.4	
		Tiotropium	50	25.3	
		Tiotropium	60	24.3	
Taifun	Multi-unit dose	Budesonide	15	29.6	[228]
		Fentanyl	30	27.6–30.6	[54]
		Fentanyl	30	34.3	
MAGhaler	Multiple dose	Salbutamol	30	21.1	[229]
		Salbutamol	60	26.4	
Jethaler	Single unit	Budesonide	–	62.0	[40]
AIR	Single dose	Placebo powder	38	51.0	[230]
New DPI	Single	Ciprofloxacin	60	78.7	[32]
New DPI	Single	Budesonide	60	66.9	[32]
Genuair	Multi dose	Aclidinum	90	30	[231]

SCG: sodium chromoglycate.

variability and while this can often be tolerated for drugs with broad therapeutic windows, it is unacceptable for potent systemic drugs. Thus the development of new DPI formulations to deliver potent drugs (proteins, peptides, vaccines, chemotherapeutics, etc.) for systemic effects is promising; however, much tighter FPF delivery control is required to minimize unwanted side effects as well as costs.

4. Key factors for engineering a new DPI device

As the preceding sections indicate, the development of an optimised and universal DPI system is an ongoing process. The key factors which motivate and constrain the achievement of that goal are: (i) the ability to engineer the drug powder formulations; (ii) patient variability; (iii) the availability of modern engineering enabling technologies such as computational fluid dynamics and advanced experimental diagnostics; and (iv) the need for regulatory and pharmacopoeial compliance. In the remainder of this section we review these topics in detail.

4.1. Engineered drug formulations

The effective delivery of drugs from inhaler devices depends not only on the design of the device but also on the drug formulation. The composition of the drug formulation is an important factor that controls the physical delivery mechanisms and the physicochemical properties of the formulation can be engineered to improve the effectiveness of drug delivery [72,73]. The effective dispersion of drug particles from the formulation depends on the characteristics of the particles including morphology [8,74], surface area [75,76], particle size [77] and size distribution [78,79], density [56], and adhesion/cohesion forces [80–84]. In the following sub-sections the effects of some of these characteristics on the delivery of powders from a DPI are discussed in detail.

4.1.1. Morphology of particles

Surface morphology in DPI formulations affects the cohesive/adhesive properties and thus the agglomeration and deagglomeration processes. The presence of surface asperities is likely to affect the contact area and interaction forces between particles. For example, particles with corrugated surfaces are found to have improved dispersibility due to a reduction in the attractive forces between individual particles [85,86]. The surface roughness of lactose carriers in DPI formulations is found to affect the FPF of drugs [80,87] and the modification of surface morphology by a surface coating technique can result in greater delivered FPF [75,88–90]. The fundamental physics of particle morphology effects on formulation flowability, agglomeration and deagglomeration, compactability etc. requires additional research to explain the observed FDF delivery from a DPI.

4.1.2. Carrier particles

As previously discussed the drug powders are formulated as either agglomerates of micronized active drugs or as interactive

mixtures containing inactive, larger excipients/carriers. Although lactose is the most commonly used excipient in carrier mediated DPI formulations, alternative sugars such as sorbitol, mannitol, glucose, maltitio, xylitol, trehalose, etc. have also been investigated for use [91–93]. Here we discuss carrier particle shape and size.

Although the effect of carrier particle shape on the dispersion of drugs from the DPI formulation is not fully understood but it is known that the attractive forces between drug and carrier particles can be shape dependent [94,95]. In fact most commonly used particles for DPI formulations have irregular shapes. Elongated [96,97], needle-like [98], porous and wrinkled particles [99] have all resulted in increased FPF of various drugs. Recently, a DPI formulation of budesonide drug particles mixed with pollen-shaped hydroxyapatite carrier showed improved dispersibility of drug particles due to reduction in particle interactions [100,101]. Zeng et al. [78,97] observe increased FPF of salbutamol sulphate when elongated rather than spherical lactose carrier particles are used. Certainly surface shape effects agglomeration strength but the authors also argue that the outcome is influenced by a change in the aerodynamic diameter of the agglomerates. Due to their larger shape factor, elongated particles have a smaller aerodynamic diameter than do spherical particles and thus agglomerations of active drug particles and elongated carriers remain aerosolised for a longer time, and greater distance along the inhalation path, and deagglomeration is enhanced.

The literature on the effect of intrinsic carrier particle size gives mixed reports. Several studies have found an increase in FPF with decreasing carrier size. For example, increased respirable fraction of salbutamol sulphate [78,102], terbutaline [102], disodium chromoglycate [103] and budesonide [104] occurred with decreased carrier size. The authors suggest that smaller agglomerates see more intense shear in the turbulent airstreams thus leading to more effective deagglomeration, however, the dependence on carrier size is not mentioned. It is also suggested that the larger carriers, which correspond to a greater aerodynamic diameter, result in a greater fraction of the formulation being deposited on the device walls. In twin-stage impinger tests Braun et al. [103] find greater late stage deposition of disodium cromoglycate for smaller sized carriers and conclude that this is due to a greater disturbance of the agglomerates with the increasing carrier particle number density. In another study, the opposite trend is revealed, with formulations containing 90–125 μm sized carriers producing a higher drug dispersion than the same formulation with 38–75 μm carriers, and it is argued that this is due to the lower inter-particle forces among the larger sized particles [105]. Similarly, a higher respirable fraction of terbutaline sulphate was obtained from a formulation containing coarse lactose (53–105 μm) than the same drug containing fine lactose carriers with intrinsic size less than 53 μm for tests using the Rotahaler at 60 L/min [106]; however, the reason behind this is unclear. Increased respirable fractions of spray dried mannitol and recombinant human granulocyte-colony stimulating factor rHG-CSF/mannitol particles from large carriers (90–125 μm) of poly ethylene glycol (PEG) compared with that of smaller carriers (38–75 μm) were observed due to lower inter-particle forces among the large carrier particles [105]. Very recently, an increase in carrier size resulted in an increase in aerosolisation behaviour of insulin loaded PLGA microparticles mixed with mannitol carrier with a size range between 25 and 167 μm [107]. The authors conclude that the use of larger particles of mannitol carrier with a lower carrier/microcapsule ratio leads to higher dispersion of the drug due to increase flowability.

While some studies listed above conclude that a decrease in carrier size increases drug dispersion, there were some studies that indicated a contrary view. However, the complete reasons for the observed effects are not clear. It is likely that a decrease in nominal carrier particle size corresponds to an increased fraction of fine incipients. Thus the effect may be related, not so much to carrier size per se, but to the presence of fine excipients. In the publications listed in the previous paragraph the concentration of fine excipients within the formulation is not reported, and likely was not known or controlled. To address this issue, Islam et al. [77,108] demonstrated a decantation method for the size separation of lactose carrier particles, where fine lactose (<5.0 μm) was removed (not completely) from the large carriers and no significant differences in the FPF of salmeterol xinafoate with various decanted lactose carrier size within a range of 45–190 μm was observed; however, the wet decanting process caused a significant decrease in dispersion of SX. Interestingly, FPFs of SX were found to revert very close to their original values after the addition of fine lactose (<5.0 μm) to the decanted carriers. Thus the presence of fine lactose associated with large carriers or added as an excipient, played a key role in the drug dispersion process in this study. Similar observations are made by Louey et al. [73] in *in vitro* trials using salbutamol sulphate with various lactose carriers. It was found that a distribution of small and large carriers is required for increased FPF with maximum drug deposition achieved for a carrier particle distribution of approximately 10% fines and 90% coarse particles.

The addition of ternary components like magnesium stearate and leucine [105,108–110] has also lead to improve drug dispersion by reducing the cohesive forces between drug particles. The addition of 10% fine sugars (lactose, glucose, mannitol and sorbitol) in the interactive mixtures of salmeterol xinafoate and coarse carriers demonstrated that fine sugars played an important role in the detachment of the drug from the large carriers [111].

4.1.3. Formulations with nanoparticles

Nanotechnology is a rapidly growing field which has a wide range of application for drug delivery and therapeutics. Even though particles less than 1 μm have challenging dispersion behaviour due to the strength of the inter-particle forces, nanoparticles have raised considerable interest for researchers of pulmonary drug delivery [51,61,112–114]. The advantages of nano-sized particles in DPI drug formulations include their rapid absorption in the epithelium cells [115] and avoidance of the mucociliary clearance [116]. Nano-agglomerates have low aerodynamic diameter due to their relatively small size (micron sized) and often hollow morphology. Thus, provided that the strong adhesive forces are broken nanoparticles are readily deposited in the deep lungs. This is supported by recent research on a formulation containing carrier lactose and salbutamol sulphate nanoparticles, which demonstrated a two–three-fold increase in total lung deposition compared to a formulation containing the same drug as micronized form [112]. Some researchers have investigated various drug formulations with soluble excipients and claim that the rapid re-dispersion into the primary nanoparticles can improve therapeutic performance [117,118]. Lung delivery of insulin loaded chitosan nanoparticles [119], nanoparticles of calcitonin [120], 5-fluorouracil (5-FU) [113], elcatonin coated with chitosan [121,122], liposome [123,124], cyclodextrin [125,126], and rifampicin loaded PLGA nanoparticles [127] have all been investigated with significant success. Drug-loaded biodegradable polymer nanoparticles have been investigated for controlled, targeted and prolonged drug delivery [128,129]. These studies have extended the opportunities for polymer scientists and nanomedicine scientists to study the application of biodegradable polymers nanoparticles in the lung delivery of various drugs. Moreover, microencapsulated nanoparticle dry powders of various vaccines [70,130–134], have been investigated with promising outcome. Chotosan based nanoparticles of ovalbumin [135] and hepatitis B [136] preparations produced significantly higher immunity compared to that of conventional alum-adsorbed vaccines. Therefore, immunologist may extend their research in lung delivery of vaccines, which have

been found to be effective with very low dose in the management of various immunological disorders.

4.1.4. Some advanced formulation technology

To increase the delivered FPF a number of other novel powder formulations have been researched such as those with surface modified particles [137], and dry coating by mechanofusion of actives [138], and supercritically produced micronized powders [139,140]. The use of engineered powder particles is rapidly growing. Recently, a carrier-free L-leucine coated salbutamol sulphate formulation was developed [141]. The tests indicate that the FPF decreases with increasing surface roughness, while the smoother surfaces achievable with the L-leucine coating result in 47% FPF delivered from the Easyhaler, which is 3–4 times higher than other common micronized drug powders from the same device. Using PulmoSphere technology (an emulsion-based spray drying process), it is possible to create porous particles with a sponge-like morphology [142]. A formulation of budesonide (PulmoSphere) powders, delivered at both high and low flow rates from the Eclipse DPI yield a two-fold higher deposition compared to formulations containing pelletized particles delivered from the Turbuhaler at 60 L/min [143]. A DPI formulation of tobramycin (PulmoSphere) showed 34% lung deposition compared to a nebulized (5% deposition) formulation [142]. In addition, the DPI formulation produced higher peak drug concentration (0.6 mg/mL) compared to that of nebulized formulation (0.28 mg/mL) [142]. Similar outcome of tobramycin powders was also observed by others [57]. Another powder, insulin Technosphere (MannKind Corp., Valencia, CA, USA), containing fumeryl diketopiperazine as a carrier, provides rapid onset of action upon inhalation [144,145]. The size of this powder particle is 2–3 μm and they have high porosity and large surface area to achieve the rapid absorption (15 min) upon pulmonary delivery.

4.2. Patient variability

4.2.1. Inhalation profile dependence

To ensure effective drug delivery into the deep lungs, a certain inspiratory force from a patient is essential in order to overcome the device resistance and to produce a flow rate through the device that is sufficient to aerosolise, deagglomerate and disperse the drug powders. Patients with severe asthma or chronic obstructive pulmonary disorder (COPD) or elderly or very young patients may not be able to produce the required inspiratory force thus increasing intra-patient and inter-patient variability of drug delivery. The main limitation with existing DPIs, in this regard, is that FPF deposited in the lungs is often sensitive to the flow rate [27,28,146] and this is primarily due to the variable extent of powder deagglomeration [82,108,147]. As previously mentioned the Turbuhaler, a high pressure drop device, demonstrates significant sensitivity of the emitted FPF to flow rate, increasing from approximately 23% at 30 L/min to 40% at 60 L/min. However, studies have shown that some patients, including young asthmatic children [148] and patients with COPD [149], cannot even achieve a peak inspiratory flow of 30 L/min through a Turbuhaler. Nor is there conclusive evidence to show that low resistance DPIs, per se, have superior performance. The Spinhaler (formerly Aerolizer) is a very low resistance device that provides quite low FPF of salbutamol but with strong variability between 30 and 60 L/min and then fairly constant FPF up to 90 L/min whereas Rotahaler with similar resistance shows monatonic increase in FPF over the same range of flow rates [37]. In another study Aerolizer produced a much higher respirable FPF of formoterol formulation at high flow rates than the non-proprietary single-dose capsule inhaler, Ratiopharm, despite similarities in the resistances of the two devices [150]. The situation is the same for some medium resistance DPIs. Diskhaler and Cyclohaler have nearly identical pressure drop yet Diskhaler delivers near double the FPF of Rotacaps 400 formulation with strong sensitivity up to 90 L/min than the Diskhaler which shows very little change in FPF between 60 and 90 L/min.

An ideal inhalation profile of a child may not be the same as that for an adult patient yet the majority of currently available inhaler devices have been designed without considering the inhalation profiles of children, who are seriously prone to inhalation error. Furthermore, as the computational modelling of Ruth et al. [151] shows the fraction of drug particles that passes through the lungs of a small child is low and it is concluded that variation in lung physiology as well as inhalation profile is the cause. Therefore the developer of a new device should take into account the differences in the inhalation profile and lung morphology between adults and children of various ages. In this light, a recent patent by Charles et al. [152] gives details of a spacer fitted to a single-use, disposable DPI which provides a containment volume to hold the aerosolised powders while the patient uses their natural, untrained inhalation profile. Such devices may be quite useful for children or other situations (e.g. aid and emergency situations) where communication of the inhalation method is problematic. We note, however, that no further details or comparative studies are available and it further research is needed to demonstrate that there is not significant amounts of deposition of drugs within the spacer volume.

The situation described in this subsection obviously makes effective treatment for a range of patients with a range of inhalation profiles and lung physiology difficult to manage. It is therefore imperative to minimize the flow rate sensitivity to completely aerosolise, deagglomerate and disperse the drug so that as broad a group as possible from the patient demographic can attain maximum therapeutic benefit. In addition to effective treatment it is also a safety issue that will be ever more important especially with the pulmonary delivery of potent systemic drugs as discussed below.

4.2.2. Training

An effective treatment becomes unsuccessful if the patient does not understand the need for self management of diseases. Patient adherence and compliance is important in achieving success in the treatment of various diseases. This is especially the case for treatment using complicated DPI systems. To achieve maximum patient compliance, training is required in both the use and care of DPIs and, furthermore, designers should ensure that the devices are easy and convenient to use. Currently this is not the case. It has been demonstrated that around 31% of patients using common and popular DPIs use them incorrectly while that figure increases to 42% for patients over 60 years of age [153]. The specific details of the incorrect use are, however, not elaborated on. In another study, van der Palen et al. [154] quantified usage statistics for asthma treatment via Turbuhaler, Diskhaler, Cyclohaler, Rotahaler and Inhaler Ingelheim. It was found that patients using only the Diskhaler made the fewest errors and that the percentage of patients who make no errors decreases from 71% to 61% if multiple devices are prescribed for them to use. Similar investigation can be found in other articles [13,155]. Lavorini et al. [13] reviewed the literature on the usage of DPIs by patients with asthma and COPD revealing between 4% and 94% of patients use their devices incorrectly with the most common errors being failure to exhale before and hold breath after inhalation, failure to inhale with sufficient force, and incorrect priming and positioning of the device. The authors also emphasise that the inability of patients to properly use their device is due to insufficient instructions from their medical practitioners and the device manufacturers. Most of the currently available devices are not ideal from a user's perspective and consistent dispersion of drugs for all types of patients is challenging. The increasing number of inhaler devices with limited efficiency and variability for different inhalation techniques causes many patients to use their prescribed

inhalers incorrectly. Surprisingly, a large number of healthcare professionals are not proficient users of DPIs themselves [156] and consequently their patients tend to receive less instruction and are also less proficient users.

Proper training of health care professional and patients in the use of various devices is essential. Also during the training session the practitioner should assess the patient's ability. Subsequent feedback to the manufacturers will accelerate the development of more user-friendly devices. To avoid confusion physicians should limit their selection to a small number of inhalers whose operating principles are fully known to them. Pharmacists are also in a good position to provide patient training due to their more frequent contact with patients. Of course, improvement of disease management could be achieved by the development of a new universal DPI device, which is easy to use correctly, thereby ensuring more successful drug delivery with limited training.

4.3. Engineering enabling technologies

In this section we discuss the application of engineering enabling technologies for improving the scientific knowledge of DPI systems which has, at least in some cases, lead to improve DPI system design concepts. We start with computational fluid dynamics, giving a considerable introduction to the basic concepts, followed by a review of CFD applications to DPIs and some critical comments on analyses that have been made based on the turbulent shear. The following subsection discussed advanced experimental diagnostic methods with specific attention to research involving atomic force microscopy, inverse gas chromatography, velocimetry and laser diffraction. We end our discussion of engineering enabling technologies with a subsection on cross-disciplinary research and make reference to other research fields where collaborations between modellers and experimentalists has resulted in rapid advances.

4.3.1. Computational fluid dynamics

4.3.1.1. Basic concepts. Computational fluid dynamics (CFD) is a useful tool, used in a wide range of engineering and scientific fields, which may provide significant benefits in designing a new and universal DPI device. The CFD should model the physical flow phenomena as much as is possible given current understanding and computational resources. In this section we start with an overview of general CFD capabilities starting from the most sophisticated and working down to the practical forms for DPI design. This is followed in the next subsection by a detailed review of applications of CFD for the design of DPIs.

The most complete CFD model applied to drug aerosol dispersion would numerically solve the governing continuity, momentum (Navier Stokes) and energy equations for the continuous air phase and the transport of the discrete drug powder phase as it undergoes aerolisation, deagglomeration, dispersion and deposition. The continuous phase flow is normally subject to turbulent motions whose scales range from the largest, energy containing eddies corresponding to the macro length scale of the flows (e.g. the size of the DPI) down to the Kolmogorov scales where the turbulence is dissipated by molecular viscosity. A direct numerical simulation (DNS), whereby all turbulent scales are resolved computationally, is the most accurate approach, but due to the huge cost DNS is normally limited to low Reynolds number flows and is applied in order to gain fundamental insights on flow phenomena and turbulence structure or to validate other, simpler models [157,158]. For practical applications, two alternative modelling approaches are employed. The cheapest and most commonly used approach for drug aerosol modelling [19–23,159–164] (and more generally also) is to solve the Reynolds averaged Navier Stokes (RANS) equations whereby the statistical mean of the fluid velocity field is modelled. RANS approaches for turbulent flow are relatively simple, computationally inexpensive, can be simplified by invoking two-dimensional, symmetric and steady-state assumptions, are incorporated in all commercial codes and have been tuned for a wide range of flow conditions. The Reynolds averaging of the transport equations introduces additional turbulent stress terms whose closure is typically via a two-equation eddy viscosity model [159–163] or a transported turbulent shear stress model [19–23,161,164].

The processes of drug powder aerosolisation, deagglomeration, dispersion and deposition within a DPI and respiratory tract are inherently transient and furthermore those processes are either enhanced or attenuated by immersion of the powders in the unsteady air flow. In a RANS setting these particle–fluid interactions are not resolved but rather they are modelled at the particle locations using the known mean quantities. The alternative approach, with a computational cost betweens DNS and RANS, is large eddy simulation (LES), whereby the large energy containing turbulent eddies are resolved while modelling is required for the small dissipative scales only. A number of studies [165,166] of particle deposition within the respiratory tract have employed LES and it is claimed that this extension has resulted in improved predictions of particle wall impaction and deposition [165]. To our knowledge, there has not yet been any application of LES to simulate the flow within a DPI although given its use for studying complex, internal and multiphase flows in other fields (e.g. see Ref. [167]) this step would likely be beneficial.

Before aerosolisation within a DPI the drug powder formulation exists as polydispersed and irregular-shaped agglomerates. On inhalation the agglomerates are accelerated from rest by aerodynamic forces. Once airborne the agglomerates are dispersed by the turbulent flow and deagglomerate under the enhancing effects of shear stresses applied by the air (particle–fluid interactions) and impactions (particle–wall and particle–particle interactions). Much of the literature reports on application of commercial CFD software using standard Reynolds averaged turbulence closures for the continuous phase and Lagrangian tracking of representative powder particles using a range of available methods [168]. In these modelling efforts the particle size distribution is generally polydispersed but it is also static and does not change with time. There is as yet very little in the way of fundamental models to account for deagglomeration by any of the mechanisms (e.g. high turbulent shear, impactions, etc.). Recently a number of researchers have attempted to model the mechanics of drug powder deagglomeration more directly using discrete element methods (DEM) [169–171]. Here the translational and rotational motions of individual particles, which may be part of a larger agglomerate, are determined by the forces applied to them due to their immersion in the continuous phase (fluid–particle interactions), due to collisions with each other and the walls of the device, and due to van der Waals attractive forces. Computational cost is an inhibiting factor however, and the DEM literature cited is applied to single agglomerates only containing up to 4000 individual particles [169].

4.3.1.2. Use of CFD for DPI design. A series of concurrent experimental in vitro and CFD studies by Coates and co-workers at the University of Sydney [19–23] have investigated the effects of varying the key design parameters of an Aerosolizer DPI. The CFD is used to explain the experimentally observed changes in the DPI performance (characterised by the FPF deposited in stages 3 and 4 and the filter of a multistage liquid impinger). The computational solution of the Reynolds averaged transport equations for the continuous phase is validated against laser doppler velocimetry experimental data [20]. At the same time the CFD results provide information that is not experimentally observable such as turbulent kinetic energy, shear rate and particle–device impactions. The latter is modelled in Lagrangian fashion using a relatively small number of particles

(up to 10,000) with a static size distribution. Particular attention is given to how design changes impact on the deagglomeration potential of the flow field. Although powder deagglomeration is not explicitly modelled, the CFD is used to provide a fundamental description of the deagglomeration potential of the flow. While it is noted that the intensity of particle–particle impactions could also be important, the CFD modelling does not cover that level of detail. Some of the findings of this coupled experimental/CFD work are reviewed below.

Experiments reveal that variations in the design of the grid structure upstream of the Aerosolizer mouthpiece can have a significant effect on performance, with an approximate five-fold increase (our guess) in grid voidage leading to a reduction in FPF as a fraction of the loaded mass from 57% to 44% while as a fraction of the mass emitted from the device (i.e. released into the mouthpiece) there is no discernable change [20]. While grid structure design changes have a big effect on performance, it is also observed that a four-fold reduction in mouthpiece length has no significant effect on either the loaded or emitted FPF measures [20]. The CFD indicates that while there is little observable sensitivity of averaged turbulent kinetic energy within the DPI with increased voidage of grid structure, there is a significant decrease in the integral scale shear or, in other words, a reduction in the aerodynamic shear stresses at the scale of the largest turbulent eddies in the flow. Presumably this results in diminished breakup of powder agglomerates leading to a lower FPF relative to the loaded mass. While the CFD confirms the rather obvious idea that increased grid structure voidage will result in fewer particle–grid impactions, it also suggests that a less obtrusive grid structure does not straighten the flow as much as a fine grid structure resulting in greater tangential velocities in the mouthpiece and, because of particle inertia, more particle–mouthpiece impactions. The authors hypothesise that with reduced grid voidage the greater deagglomeration potential due to particle–grid impactions is offset by the diminished deagglomeration potential due to their being fewer particle–mouthpiece impactions and that this explains the insignificant variation in FPF as a fraction of the emitted mass. However, as the CFD analysis does not quantify the relative importance of the deagglomeration mechanisms one could alternatively suggest that the turbulent shear is the dominant deagglomeration mechanism and that the deagglomeration potential of impactions (both particle–grid and particle–mouthpiece) is less significant. Moreover, the insignificant variation in FPF relative to load and emitted masses with changes to the mouthpiece length reported in [20], despite a presumably corresponding variation in particle–mouthpiece impactions (not reported) seems to support this view that strain rate is the controlling mechanism. An earlier experimental study by Voss and Finlay [172] also supports the view that particle impactions are a less effective deagglomeration mechanism. The authors further conclude that while turbulence has a definite effect it may not be the only or even the dominant deagglomeration mechanism. A very recent coupled experimental/CFD publication by Wong et al. [164] indicates that the mechanism for deagglomeration may depend on the characteristics of the powder formulation. While Voss and Finlay [172] performed experiments on interactive formulations consisting of small drug particles attached to much larger carrier particles to conclude on the dominant effect of turbulent strain over impactions, Wong et al. arrived at the opposite conclusion for drug-only agglomerated formulations.

The impact of integral scale turbulent shear and particle–device impactions on the Aerosolizer DPI performance is further explored by Coates and co-workers by making variations to the DPI air inlet size [22], the flow rate [21,22], the design of the powder capsule [23] and the mouthpiece geometry [19]. While the CFD once again reveals that these relatively simple design changes can enhance the deagglomeration potential of the device by increasing the turbulent shear and the intensity of particle–device impactions, the experimental observations also point to other factors which must be considered in order to improve the FPF. Two noteworthy conclusions are the existence of an optimal flow rate and the importance of having a short flow development time relative to the device emptying time. For the standard Aerosolizer design it is observed experimentally that there is an optimum flow rate of about 65 L/min at which FPF as a fraction of loaded mass is about 40%. That FPF is reduced for lower and higher flow rates in the range 30–120 L/min [21]. CFD shows that while integral scale strain rate and particle–device impaction intensity monotonically increase with the flow rate, both of which enhance deagglomeration potential, so too does the impaction frequency in the throat of the test rig and this tends reduce the FPF referenced against both the loaded and emitted masses. The optimum flow rate is therefore determined by balance of the deagglomeration and hence FPF enhancing mechanisms of strain rate and to a lesser extent particle–device impaction intensity and the FPF diminishing mechanism of throat deposition. Adjustments to the air inlet size for a given flow rate also modifies the DPI performance in a complicated way [22]. A reduction in air inlet size leads to increase turbulence and higher impaction velocities which enhance deagglomeration and lead to an increase in FPF for the low flow rate tests (30 and 45 L/min). However at higher flow rates (60 and 90 L/min) the performance diminishes as the area of the air inlet is decreased. The CFD reveals that at these higher flow rates an area reduction increases turbulence and impaction velocities which is consistent with CFD observations of the lower flow rates. However due to increase resistance to flow a reduction in the air inlet size leads to a longer time taken for the flow inside the device to reach its peak rate. If that flow development time is of the order of the time taken to clear the device of the powder (as is the case for flow rates greater than 60 L/min) then the powder experiences a much lower average turbulence and velocity and deagglomeration potential is not as high as the nominal (i.e. once developed) flow rate conditions would suggest.

The latest DEM publication with favourable comparison with experiments investigates the effect of the particle–device impact angle on deagglomeration within a model impaction throat [171]. Significant sensitivity is observed and was found to be dependent on flow rate. While increasing the impact angle from 15 to 90° increases the FPF for flow rates below 120 L/min for higher flow rate throat wall deposition is increased when the angle is increased beyond 45° and dispersion performance diminishes. This is generally in keeping with earlier observations of Coates et al. [21].

Similar concurrent in vitro experimental and CFD research on spray aerosol inhaler design variations have been conducted by Longest and Hindle [162,163]. While there are similarities between spray and dry powder inhalers there are also significant differences in the physics with the former requiring consideration of droplet evaporation and possibly condensation while deagglomeration is a major consideration in the latter. The spray inhaler work reports that the intensity of turbulence and diameter of device mouthpiece were (in common to powder inhalers) found to directly influence dispersion and deposition but while increasing turbulence intensity improves DPI performance due to enhance deagglomeration potential it is found to increase device mouthpiece deposition and retention in a prototype spray inhaler and therefore diminish the effective delivery to the lungs [162]. Flow recirculation near the nozzle region of a Respimat Soft Mist inhaler also increases device wall deposition [163]. All of these results are important contributors to understanding pulmonary drug delivery and for designing better inhaler devices in future.

4.3.1.3. A comment on turbulent shear. The use of the integral scale turbulent shear by Coates et al. [19–23] to quantify the

deagglomeration potential of a flow (in fact, the authors use an approximation given by the ratio of the large-scale turbulent kinetic energy and eddy dissipation) needs some clarification. Certainly the large-scale turbulent eddies, which scale with the size of the device (e.g. its diameter), have the highest characteristic velocities and generate the turbulent kinetic energy of the flow but despite this it is not obvious that the large-scale eddies are the most dominant scales leading to deagglomeration. We expand on this below.

The characteristic velocity, u, of an eddy of size l which is significantly greater than the Kolmogorov scale is a function of the eddy dissipation and length, scaling as $u \sim (\varepsilon l)^{1/3}$ (a pictorial view of an agglomerate in a turbulent eddy is given in Fig. 1). Whereas the turbulent shear scales as $u/l \sim \varepsilon^{1/3} l^{-2/3}$. So, although the eddy velocity decreases for smaller l the turbulent shear in fact increases. At the Kolmogorov length scale the viscosity, ν, dissipates the turbulent kinetic energy. The Kolmogorov scale shear is given by $\left(\varepsilon/\nu\right)^{1/2}$. From this simple scaling introduced above it is possible to make some general comments about deagglomeration due to turbulent motions. The acceleration of an agglomerate will be largely determined by its path through the large-scale turbulent eddies since they have the greatest eddy velocity. A sudden accelerating force could result in the breakup of an agglomerate [173] but this process probably has more in common with impaction than with deagglomeration due to fluid shear. The fluid shear results from two sources: firstly, surface shear resulting from the different fluid and particle velocities; and secondly, body shear resulting from an agglomerate straddling a turbulent eddy and being subject to a moment about some internal fulcrum. Both types of shear are enhanced by increasing levels of flow turbulence, but the former is dominated by the large-scale turbulent eddies while the latter is dominated by eddies of the size of the agglomerate. If the agglomerate is sub-Kolmogorov sized then it will experience the maximum body shear but at the same time its small size means that the differential velocity between the fluid and the particle is small and thus surface shear will be less important.

The above considerations do not necessarily contradict the outcomes of the analysis of Coates et al. Obviously an increase in integral scale turbulent shear will correspond to an increase in small scale turbulent shear although the magnitudes at the integral and micro scales are very different. There are contested views about what are the dominant mechanisms resulting in deagglomeration within a DPI. It seems that only fundamental research examining each mechanism in isolation and in combination will resolve the argument. Along this line a detailed analysis of turbulence interactions with agglomerates is required. Certainly there is significant progress in other types of two-phase flows (e.g. breakup of sprays [174] and suspended particles [175]). We advance this discussion a bit more in Section 4.3.3 in the context of cross-disciplinary research.

4.3.2. Advanced experimental diagnostics

The other arm of science besides modelling (discussed in previous subsection), and which certainly predates computational modelling, is experimental diagnostics performed in the laboratory. In the field of dry powder inhaler research a number of advanced diagnostical methods are commonly applied: these include scanning electron microscopy (SEM) for visualisation of the formulation structure including particle morphology and agglomeration geometry [176–180]; atomic force microscopy (AFM) to determine the single contact point adhesive/cohesive forces between individual powder particles [177–179,181–184], inverse gas chromatography (IGC) to determine surface energy characteristics of bulk powder formulations [179,185,186], X-ray diffraction (XRD) to determine crystal structure and formulation composition [179,187,188], and high-speed photography for direct visualisation of deagglomeration [189] or used in combination with laser diffraction to get "in flight" real-time, particle size distributions [176,190,191] and particle image velocimetry (PIV) [20,192] or laser doppler velocimetry [193] for air velocity and related quantities. Critical reviews of some of these technologies and the advances they have brought about in our understanding of DPI systems are available in the literature [179,194] and we do not repeat that here. Instead we focus on only a few of the diagnostic methods (namely AFM, IGC, laser diffraction and LDV/PIV) which can be used to quantitatively analyse powder dispersion and deagglomeration. These methods have great potential in combined experimental and modelling research; a topic that is discussed in some detail in the next subsection.

4.3.2.1. AFM and IGC. Deagglomeration of powders occurs when the external forces (e.g. rapid acceleration due to impaction or fluid shear) overcome the adhesive/cohesive forces between particles. These forces are the van der Waals force, capillary force and electrostatic force. AFM quantifies the force required for one contact point between particles to be broken; which of course is the most basic process of deagglomeration. AFM data is therefore the starting point for any fundamental study of breakage. The forces of attraction between particles are dynamic and various AFM studies have shown how the forces vary with particle size, particle shape [195] and extent of surface roughness [179,184], the contact area [80,181], relative humidity [177,178,183,184] and particle core composition [184] or coating composition [182]. While AFM is very good for analysing the microscale it is of course the mesoscale (i.e. the bulk powders) which are more complicated due to multipoint contacts with multiple other particles. Furthermore, the permutations of these contact arrangements and of the contact surface area are countless and vary with agglomerate and bulk power packing structure, powder composition, temperature and relative humidity. For quantifying bulk powder adhesive/cohesive forces IGC is popular. Inter-particle forces are not measured directly but rather surface energy and surface acid/base properties which are linked to the adhesive/cohesive forces are determined. The interparticulate interactions in the powder, influenced by the surface energies [196], of the individual components in the mixture, affect the dispersibility of powder. IGC is applied to the analysis of bulk powders and it is very useful as a fast, accurate and non-distructive method for measuring surface energy of various powders [197,198]. Some early pharmaceutical powder cohesion studies using IGC are reviewed by Grimsey et al. [186]. Recently, some studies demonstrated the relationship between the powder dispersibility and surface energy [199,84]. For example, decreased FPF of salbutamol sulphate from the mixture of lactose with increased dispersive surface energy of powders was observed [199]. However, Traini et al. demonstrated an inverse relationship between the surface energies of four different lactose polymorphs and FPF of the same drug from the interactive mixtures with those lactose powders [84]; whereas, negative relationship was found between the dispersive surface energy of spray dried and milled lactose and the dispersion of budesonide [200]. A more recent study by Davies et al. [185] has used a combination of AFM and IGC to investigate the surface energy and intrinsic mechanical properties of drug (budesonide) particles, which help preformulation of DPI formulation for better dispersion. Therefore both AFM and IGC studies are important in studying particulate interactions for improving DPI technology.

4.3.2.2. Velocimetry. The impaction and fluid shear processes within a DPI which lead to dispersion and deagglomeration are highly unsteady and non-linear and vary both temporally and spatially (thus some researchers use CFD as described in the previous subsection). Unlike methods such as hot-wire anemometry,

the LDV and PIV methods of measuring the flow velocity are non-invasive and do not affect the flow velocity. In velocimetry methods the flow is seeded with small particles as glass, polystyrene, aluminium or oil droplets that move with the flow and which scatter light produced by a laser. LDV is a point measurement method; the Eulerian flow speed is derived from the change in wavelength between the incident and reflected light. PIV, on the other hand, provides vector information; high-speed photography captures the particles at small time increments and the directional distance travelled divided by the time gives the velocity. By imaging two orthogonal planes and making use of continuity it is possible to obtain the three-dimensional velocity. Although LDV and PIV are commonly applied in many fields of fluid mechanics research there are relatively few inhaler applications although a number of publications are available [20,172,192,193]. Coates et al. [20] use LDV of the flow at the exit of an Aerolizer inhaler to validate their CFD modelling (see Section 4.3.1 for detailed discussion). A comparison is made between the experimental and CFD predicted mean axial velocity. Higher moments (e.g. mean square) can also be obtained by LDV and, although not available in that work, would be useful for validation of the CFD modelled velocity within a DPI. Voss and Finlay [172] perform LDV on the flow in a specially designed deagglomeration rig consisting of a circular pipe with controllable levels of turbulence and an insertable impact mesh. They explore the relative importance of shear and impaction mechanisms of deagglomeration. Root mean square velocity measurements are reported at various stages in the deagglomeration rig and this is correlated with the extent of deagglomeration which is measured in an inertial cascade impactor. Mendes et al. [193] did detailed LDV analysis of the flow in a transparent twin-stage impinger and combined the observed mean velocities with a stochastic particle dispersion model to study trajectories, mass fluxes and deposition. Han et al. [192] used PIV to obtain the velocity within an optically transpared Spiros inhaler mouthpiece that was machined from transparent sapphire crystal. The mouthpiece is designed with tangential jets to induce a rotational flow that acts as a sheath to prevent drug deposition in the mouthpiece. The author's PIV analysis shows, however, that there is in fact increased likelihood of deposition where the jets interact with the drug laden core flow prior to development of the rotational sheath. Some brief suggestions are also made about improving the design.

Although velocimetry in DPIs is a relatively immature field that has been used to investigate only basic velocity statistics within limited regions of the devices there is a potential for extracting rich data including the turbulent shear rate (which contributes to deagglomeration). Some initial steps have been taken towards this end. Voss and Finlay [172] correlated the extent of deagglomeration with the root mean square of turbulent velocity fluctuations but did not determine the fine scale shear. The issue of course is that being dominant at the smallest Kolmogorov length scales (typically of the order of 1–10 μm in a DPI) it is difficult to have sufficient PIV resolution to obtain the shear correctly. It is not yet possible to resolve such a fine scale; some recent PIV measurements of two-phase flow have obtained resolutions down to 60 μm in a limited region of a flow where the Kolmogorov scale was 110 μm [201]. Although respirable drug powders are much smaller, carrier particles are typically of the order of 100 μm in size. Therefore fundamental information on the turbulent shear rate at that scale is currently possible and may be of use for studying primary breakup of the small drug actives from the much larger carrier particles. As with direct numerical simulation the limiting factor on fine scale PIV is the computational power that is available and it may still be some time before the small scale turbulence information is investigated for practical DPIs although studies of a fundamental nature (e.g. deagglomeration within a canonical jet configuration) would be of value to improving our understanding of the key processes involved and also for validation of computational models.

4.3.2.3. Laser diffraction. Particle size and size distribution of micronized drug powders and their subsequent dispersion behaviour can be obtained using the laser diffraction method, which uses the theory of Mie scattering. Laser light is focussed at the particle cloud and the light is scattered at an angle that is dependent on the size of the particles; smaller particles scatter the light at bigger angles than do larger particles. Generally, assumptions are made that the particles are spherical and that the dispersion is dilute enough for there to be no re-scattering (i.e. the photodetectors receive the light directly from the initial particle). Corrections must be made for laser diffraction of dense dispersions where re-scattering will be significant. The advantage of laser diffraction is that it can generate time resolved "in flight" information about the particle size distribution unlike alternative sizing methods such as inertial cascade impactors. Particle size and size distributions can be determined using a small amount of sample. A series of recent papers by Behara et al. have investigated the laser diffraction approach for DPI systems [176,190,191] to study the particle size and size distribution in real life situation and relate the deagglomareation and aerosolisation pattern of highly cohesive powder agglomerates dispersed from the DPI devices. The outcome their studies have found the laser diffraction technique to be useful in understanding the kinetics of powder aerosolisation form different DPI devices.

4.3.3. Cross-disciplinary research

The preceding sections of this review article have highlighted the enormous research and development efforts surrounding the development of DPI systems in areas as diverse as pharmaceutical and medical sciences, nanotechnology, materials science and engineering, fluid dynamics, spectroscopy and laser diagnostics. Yet despite this effort the existence of reliable and universal DPIs remains lacking. There is a clear need for an organised and continuous international collaborative effort between researchers across the many disciplines involved; and certainly this is happening to some degree already. Here we focus on just one cross-disciplinary research area – computational fluid dynamics/advanced experimental diagnostics – due to the natural fit between those disciplines and the obvious benefit organised collaboration would have to both fields. We cite an exemplar of such a collaboration within a different field of research and suggest some advances that could be expected in the DPI research field if a similar collaborative effort was instigated. We also briefly give requirements and examples of model problems that could be investigated as part of a concerted cross-disciplinary research effort.

CFD and experimental diagnostics have a natural affinity. CFD is predictive and can be used to aid the design of new and novel DPIs but as direct numerical solution is not possible for practical CFD applications modelling is required for the turbulent processes and these models and their numerical solutions require validation. Experimental diagnostics do not require external validation and provide solid data for further analysis but they are not in themselves predictive, and while experiments certainly can aid aspects of DPI design full diagnostic imaging of the processes within a DPI is not yet possible. A number of examples are available in the literature from researchers using combined CFD and advanced experimental diagnostics and in previous sections we have already reviewed the contributions by Coates et al. at the University of Sydney (e.g. Ref. [20] and other references to that research team given in Section 4.3.1), and Mendes et al. [193] at the Universidade de Lisboa.

This review article has put a strong focus on the processes associated with aerosolisation, deagglomeration and dispersion.

As already discussed these processes are complicated due to their non-linearity and occurrence at very small scales. To truly understand these we require information on the material properties and their inter-particle attractive forces (e.g. from SEM, AFM and/or IGC). We require information on the velocity and turbulent structure of the carrier air (e.g. from LDV and/or PIV). We also require data on the size distribution of the powders within the turbulent air flow (e.g. from "in-flight" laser diffraction). Lastly (at least in this simple list) we need CFD for quantifying and visualising the physics that cannot be experimentally observed and for investigating new and novel DPI designs. While some such cross-disciplinary research exists already it seems that a more coordinated international collaboration would be of benefit. This conclusion is reached based on the personal experience of the second author who has for some years been involved in just such a cross-disciplinary, international collaboration in the field of turbulent combustion; another complex, non-linear system that is dominated by small scale processes. This collaboration is under the auspices of the International Workshop on Measurement and Computation of Turbulent Nonpremixed Flames (TNF Workshop http://www.sandia.gov/TNF/abstract.html). This workshop brings together scientists and engineers in fields as varied as chemical kinetics, laser/PIV/LDV diagnostics and computational fluid dynamics with the objectives of establishing an archive of well-documented flame cases, of providing a common basis for collaborative comparison of measured and modelled data, and of identifying future research priorities. The workshop meets biennially and has a published set of proceedings. Even a cursory review of the workshop proceedings (at the above listed website) will indicate that great progress has resulted in both the CFD and experimental diagnostics fields as a result of the coordinated international collaboration.

The nomination of DPI-like test cases would be an important first step for such an international collaboration if instigated in the DPI research community. The test cases should foremost be of practical importance to real DPI processes. Secondly the test cases should isolate the physics (e.g. deagglomeration by shear, deagglomeration by impaction, aerosolisation, dispersion, etc.) so that observations can be confidently attributed to those isolated phenomena. Additionally the test cases should, as much as possible, suit the requirements of experimentalists and CFD modellers. For example, the test cases should use apparatus that is optically transparent for laser and photo imaging. Also the modellers need unambiguous boundary conditions, for example the inflow air velocities and powder fluxes for be fully prescribed. Such conditions and other requirements of modellers and experimentalists only come about as a result of extensive cooperation between the two. We note that the L-leucine turbulent deagglomeration study by Raula et al. [180] which specifically eliminates deagglomeration by wall collision as an example of test case that could (with modifications to include the above mentioned requirements) be studied by both experimentalists and modellers. Similarly the DEM modelling of agglomerate wall impactions in the absence of fluid interaction forces by Tong et al. [170] could also for the basis of another test case. Both these examples have carefully isolated specific physics and conclusions were confidently made in that knowledge.

4.4. Regulatory and pharmacpoeial compliance

DPIs are subjected to strict pharmaceutical and manufacturing standards by regulatory bodies and the most challenging issue is the demonstration of delivered dose uniformity [202], which, as already illustrated, is lacking in currently available devices. It is technically challenging to ensure effective product testing procedures. The performance of inhaled products is characterised by testing dose uniformity and aerodynamic particle size distribution to ensure the reproducibility of delivered dose, which is not straightforward. No precise guidelines are available in any official compilation for developing new formulations or devices. The Committee for Proprietary Medicinal Products (CPMP) states that the minimum delivered dose uniformity from a device should be the mean $\pm$ 20% of the nominal content per actuation [203]. It also states that the uniformity of the delivered dose should be determined for a fixed pressure drop of 4.0 kPa as this represents a uniform patient inhalation force which is otherwise very variable in the population. As previously noted the delivery efficiency of different devices containing various drug formulations is very variable. To ensure that testing methods and conditions are not adding to this variability it is critical that there is a high degree of device, method and formulation quality control during testing. Current European Pharmacopoeial requirements are practiced wherever possible as the FDA guidelines [204] are still in draft form. Both FDA and CPMP guidelines on DPI products came into existence in 1998 and have not been updated since.

Very recently, the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) stated that the influence of particle size and size distribution on the bioavailability of orally inhaled and nasal drug products (OINDP) should be considered [205]. However, it is a complex and time consuming process to correlate between particle size or size distribution of inhaled products and bioavailability. In addition, the usefulness of risk assessment and management is emphasised because of the complex interactions between drug formulations, delivery device designs and patient usage. The major pharmacopoeias are working through the International Conference on Harmonisation (ICH) to ensure the reproducibility and accuracy of delivered dose under test conditions which imitate patient practice.

From the above discussion, it is revealed that compendia and regulations focus mainly on the delivered dose uniformity and particle size distribution, which determines the consistency of delivery. However, no guideline on the lower limit of FPF of a drug delivered or emitted from a device is specified. It may be that new devices can deliver consistency over a range of usage conditions and the correct size distribution yet the delivered FPF is low [27,28]. Clarification of minimum FPF would be most useful to device designers.

Investigation is still ongoing to ensure the quality of products by appropriate techniques although certain aspects of instrument assembly, operation and data presentation create a dilemma. Most pharmacopoeia limit the performance testing of OINDPs to quality assessment due to the complexity of aerosol dosage forms. In vitro drug dispersion using a cascade impactor (CI) is not a straightforward method in predicting the pulmonary dose accurately and more detailed studies on the suitability of CI for assessing differences in the regional deposition are required to establish in vitro to in vivo correlations [206,207]. For testing with a CI the flow rate is critical since it affects the size of particles collected at each stage. The best methods for describing stage mass deposition and representation of particle size data obtained from each stage is still uncertain. In addition, there is a lack of agreement on the appropriate statistical methods for the assessment of in vitro results. Due to the complexity of inhaled products, which are directly associated with drug formulation, delivery device and inspiratory force, it is difficult to establish standard specifications for quality assessment. Pharmaceutical industries may take a step to have completed understanding of the requirements for a universal DPI device and corresponding drug formulations and unique performance assessment of the delivery system. Effective testing protocols which distinguish the unique features of a delivery system can be used to improve understanding in the development of an efficient new device.

However, due to the complex physiology of the respiratory tract, it is difficult to ensure consistency on dose delivery from a device and this will surely remain as a subject of future debate.

5. Conclusions

In this review article we have comprehensively discussed critical issues associated with the development of DPI systems. We have discussed four key factors which motivate and constrain the engineering of a universal DPI which is able to deliver maximum and repeatable drug delivery and which could be used for both local and systemic drug treatments. The first factor is the ability to engineer the physicochemical properties of the drug formulations (i.e., powder production methods, particle forces, dispersion behaviour etc.) which can provide enhanced aerosolisation, deagglomeration and dispersion during delivery and improved therapeutic effect upon deposition in the lungs. The second factor to consider is the sensitivity of DPI performance to patient usage. This is expected to be overcome by a device design which enables delivery of the correct dose over a wide range of inhalation profiles. Modern engineering enabling technologies, particularly computational fluid dynamics and advanced experimental diagnostic methods, are the third key factor to consider for realising a universal DPI design. CFD can offer fundamental insights into the physical processes which take place within a DPI and the respiratory tract and provide a level of flow detail that is not possible or is too expensive to observe in the laboratory. Already computational modelling is improving DPI design but in general it requires validation and that is where advanced experimental diagnostics come. We have specifically reviewed some of the contributions made using AFM, IGC, velocimetry methods and laser diffraction. Additionally the importance of a coordinated collaborative research effort among practitioners of the various engineering enabling technologies is emphasised along with some brief discussion of example model problems. Finally, regulatory and pharmacopoeial compliance is a factor that will continue to constrain DPI development to ensure safety but these can also serve the functions of coordinating multidisciplinary research and testing efforts and in guiding and advising on best practice. Given the potential for improved treatment for a range of conditions and the obvious financial incentives, research and development can be expected to expand within medical, pharmaceutical and engineering research institutions and industries to develop DPI device with universal design, which is independent of patient inspiratory force and that can deliver a consistent and reproducible dose into the lungs with patient compliance.

Conflict of interest

There are no conflicts of interest to the author's knowledge.

References

[1] Patton JS. Pulmonary drug delivery comes of age: the outlook for 2005 & beyond. Drug Deliv Technol 2005;5(44):6–9.
[2] PRWEB. Global pulmonary drug delivery technologies market. http://wwwstrategyrcom/Pulmonary_Drug_Delivery_Technologies_Market_Reportasp. Accessed 51011; 2010.
[3] DiNunzio JC, McGinity JW, Williams III RO. A review of development & design technology for next-generation dry powder inhalers. Drug Deliv Technol 2007;7:22, 6, 8–30, 2–4.
[4] Hickey AJ. Pharmaceutical inhalation aerosol powder dispersion – an unbalancing act. Am Pharm Rev 2003;6:106–10.
[5] Islam N, Gladki E. Dry powder inhalers (DPIs) – a review of device reliability and innovation. Int J Pharm 2008;360:1–11.
[6] Coates MS, Chan H-K, Fletcher David F, Chiou H. Influence of mouthpiece geometry on the aerosol delivery performance of a dry powder inhaler. Pharm Res 2007;24:1450–6.
[7] Coates MS, Chan H-K, Fletcher David F, Raper Judy A. Influence of air flow on the performance of a dry powder inhaler using computational and experimental analyses. Pharm Res 2005;22:1445–53.
[8] Adi H, Traini D, Chan H-K, Young PM. The influence of drug morphology on the aerosolisation efficiency of dry powder inhaler formulations. J Pharm Sci 2008;97:2780–8.
[9] Dunbar CA, Hickey AJ, Holzner P. Dispersion and characterization of pharmaceutical dry powder aerosols. Kona 1998;16:7–45.
[10] Clarke MJ, Tobyn MJ, Staniforth JN. Physicochemical factors governing the performance of nedocromil sodium as a dry powder aerosol. J Pharm Sci 2000;89:1160–9.
[11] Corrigan DO, Corrigan OI, Healy AM. Physicochemical and in vitro deposition properties of salbutamol sulphate/ipratropium bromide and salbutamol sulphate/excipient spray dried mixtures for use in dry powder inhalers. Int J Pharm 2006;322:22–30.
[12] Coates MS, Fletcher DF, Chan H-K, Raper Judy A. Effect of design on the performance of a dry powder inhaler using computational fluid dynamics Part 1: grid structure and mouthpiece length. J Pharm Sci 2004;93:2863–76.
[13] Lavorini F, Magnan A, Dubus Jean C, Voshaar T, Corbetta L, Broeders M, et al. Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. Respir Med 2008;102:593–604.
[14] Bowles N, Cahill E, Haeberlin B, Jones C, Mett I, Mitchell JP, et al. Application of quality by design to inhalation products. RDD Europe 2007; Available at http://wwwrddonlinecom, 2007; 1 pp. 61–70.
[15] FDA. Pharmaceutical CGMPs for the 21st century – a risk-based approach. Available at http://wwwfdagov/cder/gmp/gmo2004/GMP_finalreport2004htm; 2004.
[16] Golshahi L, Finlay WH. Recent advances in understanding gas and aerosol transport in the lungs: application to predictions of regional deposition. Adv Transport Phenom 2009;1:1–30.
[17] Telko MJ, Hickey AJ. Dry powder inhaler formulation. Respir Care 2005;50:1209–27.
[18] Hersey JA. Ordered mixing: a new concept in powder mixing practice. Powder Technol 1975;11:41–4.
[19] Coates MS, Chan H, Fletcher DF, Raper JA. Influence of mouthpiece geometry on the aerosol delivery performance of a dry powder inhaler. Pharm Res 2007;24:1450–6.
[20] Coates MS, Fletcher DF, Chan H, Raper JA. Effect of design on the performance of a dry powder inhaler using computational fluid dynamics. Part 1: grid structure and mouthpiece length. J Pharm Sci 2004;93:2863–76.
[21] Coates MS, Chan H, Fletcher DF, Raper JA. Influence of air flow on the performance of a dry powder inhaler using computational and experimental analysises. Pharm Res 2005;22:1445–53.
[22] Coates MS, Chan H, Fletcher DF, Raper JA. Effect of design on the performance of a dry powder inhaler using computational fluid dynamics. Part 2: air Inlet Size. J Pharm Sci 2006;95:1382–92.
[23] Coates MS, Fletcher DF, Chan H, Raper JA. The role of capsule on the performance of a dry powder inhaler using computational and experimental analyses. Pharm Res 2005;22:923–32.
[24] Finlay WH, Martin AR. Modelling of aerosol deposition with interface devices. J Aerosol Med 2007;20:S19–28.
[25] Frijlink HW, Boer AHD. Dry powder inhalers for pulmonary drug delivery. Expert Opin Drug Deliv 2004;1:67–86.
[26] Smith IJ, Parry-Billings M. The inhalers of the future? A review of dry powder devices on the market today. Pulmon Pharmacol Ther 2003;16:79–95.
[27] Palander A, Mattila T, Karhu M, Muttonen E. In vitro comparison of three salbutamol-containing multidose dry powder inhalers. Clin Drug Invest 2000;20:25–33.
[28] Chrystyn H. Closer to an 'ideal inhaler' with the Easyhaler: an innovative dry powder inhaler. Clin Drug Invest 2006;26:175–83.
[29] Hindle M, Byron PR. Dose emissions from marketed dry powder inhalers. Int J Pharm 1995;116:169–77.
[30] Barrowcliffe J, McGlynn P, Ratcliffe S, Sewell M, Sheikh S, Walters M. Beclomethasone dipropionate (BDP) Clickhaler; in vitro performance of a steroid novel dry powder inhaler. Proc Drug Deliv 1997;8:125–8.
[31] Adler D, Kritzman A, Genosar A, Slutski A. Dry powder inhaler. Application: WO. Israel: Aespironics Ltd; 2009.
[32] Wang ZL, Grgic B, Finlay WH. A dry powder inhaler with reduced mouth-throat deposition. J Aerosol Med 2006;19:168–74.
[33] Needham M, Fradley G, Cocks AP. Investigating the efficiency of reverse cyclone technlogy for drug delivery. Respir Deliv Drug 2010;2:369–72.
[34] Zeng XM, Jones S, O'Leary D, Phelan M, Colledge J. Delivery of formoterol from a novel multi-dose inhaler Airmax. Respir Med 2002;96:397–403.
[35] Clark AR, Hollingworth AM. The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers – implications for in vitro testing. J Aerosol Med 1993;6:99–110.
[36] Tiddens HA, Geller DE, Challoner P, Speirs RJ, Kesser KC, Overbeek SE, et al. Effect of dry powder inhaler resistance on the inspiratory flow rates and volumes of cystic fibrosis patients of six years and older. J Aerosol Med 2006;19:456–65.
[37] Srichana T, Martin GP, Marriott C. Dry powder inhalers: the influence of device resistance and powder formulation on drug and lactose deposition in vitro. Eur J Pharm Sci 1998;7:73–80.

[38] Chew NY, Chan HK. In vitro aerosol performance and dose uniformity between the Foradile Aerolizer and the Oxis Turbuhaler. J Aerosol Med 2001;14:495–501.
[39] Munzel U, Marschall K, Fyrnys B, Wedel M. Variability of fine particle dose and lung deposition of budesonide delivered through two multidose dry powder inhalers. Curr Med Res Opin 2005;21:827–33.
[40] de Boer AH, Gjaltema D, Hagedoorn P, Frijlink HW. Comparative in vitro performance evaluation of the Novopulmon 200 Novolizer and Budesonid-ratiopharm Jethaler: two novel budesonide dry powder inhalers. Pharmazie 2004;59:692–9.
[41] Brown BAS, Rasmussen JA, Becker DP, Friend DR. A piezo-electronic inhaler for local & systemic applications. Drug Deliv Technol 2004;4:90–3.
[42] Crowder T, Hickey A. Powder specific active dispersion for generation of pharmaceutical aerosols. Int J Pharm 2006;327:65–72.
[43] Tobyn M, Staniforth JN, Morton D, Harmer Q, Newton ME. Active and intelligent inhaler device development. Int J Pharm 2004;277:31–7.
[44] Virchow JC, Crompton GK, Dal Negro R, Pedersen S, Magnan A, Seidenberg J, et al. Importance of inhaler devices in the management of airway disease. Respir Med 2008;102:10–9.
[45] Meakin BJ, Cainey JM, Woodcock PM. Simulated 'in-use' and 'mis-use' aspects of the delivery of terbutaline sulfate from Bricanyl Turbohaler dry powder inhalers. Int J Pharm 1995;119:103–8.
[46] Fyrnys B, Stang N, Wolf-Heuss E. Stability and performance characteristics of a budesonide powder for inhalation with a novel dry powder inhaler device. Curr Opin Pulm Med 2001;7:S7–11.
[47] Newman SP, Hirst PH, Pitcairn GR. Scintigraphic evaluation of lung deposition with a novel inhaler device. Curr Opin Pulm Med 2001;7(Suppl. 1): S12–4.
[48] Fenton C, Keating GM, Plosker GL. Novolizer: a multidose dry powder inhaler. Drugs 2003;63:2437–45.
[49] Hassan MS, Lau R. Effect of particle formulation on dry powder inhalation efficiency. Curr Pharm Des 2010;16:2377–87.
[50] Smutney CC, Adamo B, Polidoro JM, Kinsey PS, Overfield D, Sahi CR, et al. Dry powder drug delivery system for pulmonary inhalation to treat endocrine diseases. Application: US. USA: Mannkind Corporation; 2010. p. 57pp, Cont-in-part of U S No 484,137.
[51] Cheow WS, Hadinoto K. Preparations of dry-powder therapeutic nanoparticle aerosols for inhaled drug delivery. J Aerosol Res 2010;25:155–65.
[52] Shahiwala A, Misra A. Pulmonary absorption of liposomal levonorgestrel. AAPS PharmSciTech 2004;5.
[53] Valle MJdJ, Gonzalez Lopez F, Sanchez Navarro A. Pulmonary versus systemic delivery of levofloxacin. Pulmon Pharmacol Ther 2008;21:298–303.
[54] Overhoff KA, Clayborough R, Crowley M. Review of the TAIFUN multidose dry powder inhaler technology. Drug Dev Ind Pharm 2008;34:960–5.
[55] Wright T, Morgan FG, Main MJ. Pulmonary inhalation of levodopa containing compositions in the treatment of Parkinson's disease and other central nervous system disorders. Application: GB. UK: Vectura Group PLC; 2009. p. 44 pp.
[56] Edwards DA, Hanes J, Caponetti G, Hrkach J, Ben-Jebria A, Eskew ML, et al. Large porous particles for pulmonary drug delivery. Science 1997;276:1868–71.
[57] Geller David E, Konstan Michael W, Smith J, Noonberg Sarah B, Conrad C. Novel tobramycin inhalation powder in cystic fibrosis subjects: pharmacokinetics and safety. Pediatr Pulmonol 2007;42:307–13.
[58] Hickey Anthony J, Lu D, Ashley Elizabeth D, Stout J. Inhaled azithromycin therapy. J Aerosol Med 2006;19:54–60.
[59] Stoessl AJ. Potential therapeutic targets for Parkinson's disease. Expert Opin Ther Targets 2008;12:425–36.
[60] Anon. Method of and apparatus for effecting delivery of fine powders. IP Com J 2008;8(1B):13.
[61] Plumley C, Gorman EM, El-Gendy N, Bybee CR, Munson EJ, Berkland C. Nifedipine nanoparticle agglomeration as a dry powder aerosol formulation strategy. Int J Pharm 2009;369:136–43.
[62] Rawat A, Majumder QH, Ahsan F. Inhalable large porous microspheres of low molecular weight heparin: in vitro and in vivo evaluation. J Control Release 2008;128:224–32.
[63] Cheatham WW, Leone-Bay A, Grant M, Fog PB, Diamond DC. Pulmonary delivery of inhibitors of phosphodiesterase type 5. Application: WO. USA: Mannkind Corporation; 2006. p. 23 pp.
[64] Farr SJ, Otulana BA. Pulmonary delivery of opioids as pain therapeutics. Adv Drug Deliv Rev 2006;58:1076–88.
[65] Fleischer W, Reimer K, Leyendecker P. Opioids for the treatment of the chronic obstructive pulmonary disease. Application: EP. Luxembourg: Euro-Celtique S. A.; 2005, 24 pp.
[66] Kleinstreuer C, Zhang Z, Donohue JF. Targeted drug-aerosol delivery in the human respiratory system. Ann Rev Biomed Eng 2008;10:195–220.
[67] Ali R, Jain GK, Iqbal Z, Talegaonkar S, Pandit P, Sule S, et al. Development and clinical trial of nano-atropine sulfate dry powder inhaler as a novel organophosphorous poisoning antidote. Nanomed 2009;5:55–63.
[68] LiCalsi C, Maniaci MJ, Christensen T, Phillips E, Ward GH, Witham C. A powder formulation of measles vaccine for aerosol delivery. Vaccine 2001;19:2629–36.
[69] Edwards DA, Sung J, Pulliam B, Wehrenberg-Klee E, Schwartz E, Dreyfuss P, et al. Pulmonary delivery of malarial vaccine in the form of particulates. Application: WO:. USA: President and Fellows of Harvard College; 2005. p. 25 pp.
[70] Smith DJ, Bot S, Dellamary L, Bot A. Evaluation of novel aerosol formulations designed for mucosal vaccination against influenza virus. Vaccine 2003;21:2805–12.
[71] Brito L, Chen D, Ge Q, Treco D. Dry powder compositions for RNA influenza therapeutics. Application: US. USA: Nastech Pharmaceutical Company Inc.; 2007. p. 29 pp.
[72] Hickey AJ, Concessio NM, Oort VM, Platz RM. Factors influencing the dispersion of dry powders as aerosols. Pharm Technol 1994;(August):58–84.
[73] Louey MD, Razia S, Stewart PJ. Influence of physico-chemical carrier properties on the in vitro aerosol deposition from interactive mixtures. Int J Pharm 2003;252:87–98.
[74] Telko Martin J, Hickey Anthony J. Dry powder inhaler formulation. Respir Care 2005;50:1209–27.
[75] Young PM, Cocconi D, Colombo P, Bettini R, Price R, Steele DF, et al. Characterization of a surface modified dry powder inhalation carrier prepared by particle smoothing. J Pharm Pharmacol 2002;54:1339–44.
[76] Zeng X-M, Martin GP, Marriott C, Pritchard J. Lactose as a carrier in dry powder formulations: the influence of surface characteristics on drug delivery. J Pharm Sci 2001;90:1424–34.
[77] Islam N, Stewart P, Larson I, Hartley P. Effect of carrier size on the dispersion of salmeterol xinafoate from interactive mixtures. J Pharm Sci 2004;93:1030–8.
[78] Zeng XM, Martin GP, Marriott C, Pritchard J. The effects of carrier size and morphology on the dispersion of salbutamol sulfate after aerosolization at different flow rates. J Pharm Pharmacol 2000;52:1211–21.
[79] Zeng XM, Martin GP, Tee S-K, Ghoush AA, Marriott C. Effects of particle size and adding sequence of fine lactose on the deposition of salbutamol sulfate from a dry powder formulation. Int J Pharm 1999;182:133–44.
[80] Islam N, Stewart P, Larson I, Hartley P. Surface roughness contribution to the adhesion force distribution of salmeterol xinafoate on lactose carriers by atomic force microscopy. J Pharm Sci 2005;94:1500–11.
[81] Louey MD, Mulvaney P, Stewart PJ. Characterization of adhesional properties of lactose carriers using atomic force microscopy. J Pharm Biomed Anal 2001;25:559–67.
[82] Louey MD, Stewart PJ. Particle interactions involved in aerosol dispersion of ternary interactive mixtures. Pharm Res 2002;19:1524–31.
[83] Podczeck F, Newton JM, James MB. The adhesion force of micronized salmeterol xinafoate particles to pharmaceutically relevant surface materials. J Phys D: Appl Phys 1996;29:1878–84.
[84] Traini D, Young PM, Thielmann F, Acharya M. The influence of lactose pseudopolymorphic form on salbutamol sulfate-lactose interactions in dry powder inhaler formulations. Drug Dev Ind Pharm 2008;34:992–1001.
[85] Adi S, Adi H, Tang P, Traini D, Chan H.-k., Young PM. Micro-particle corrugation, adhesion and inhalation aerosol efficiency. Eur J Pharm Sci 2008;35:12–8.
[86] Chew NYK, Chan H-K. Use of solid corrugated particles to enhance powder aerosol performance. Pharm Res 2001;18:1570–7.
[87] Donovan MJ, Smyth HDC. Influence of size and surface roughness of large lactose carrier particles in dry powder inhaler formulations. Int J Pharm 2010;402:1–9.
[88] Kawashima Y, Serigano T, Hino T, Yamamoto H, Takeuchi H. Effect of surface morphology of carrier lactose on dry powder inhalation property of pranlukast hydrate. Int J Pharm 1998;172:179–88.
[89] Kawashima Y, Serigano T, Hino T, Yamamoto H, Takeuchi H. Design of inhalation dry powder of pranlukast hydrate to improve dispersibility by the surface modification with light anhydrous silicic acid (AEROSIL 200). Int J Pharm 1998;173:243–51.
[90] Kawashima Y, Serigano T, Hino T, Yamamoto H, Takeuchi H. A new powder design method to improve inhalation efficiency of pranlukast hydrate dry powder aerosols by surface modification with hydroxypropylmethyl cellulose phthalate nanospheres. Pharm Res 1998;15:1748–52.
[91] Steckel H, Bolzen N. Alternative sugars as potential carriers for dry powder inhalations. Int J Pharm 2004;270:297–306.
[92] Amaro MI, Tajber L, Corrigan OI, Healy AM. Design of experiment to study the effect of spray dryer operating variables on sugar powders intended for inhalation. J Pharm Pharmacol 2010;62:1413–4.
[93] Minne A, Boireau H, Horta MJ, Vanbever R. Optimization of the aerosolization properties of an inhalation dry powder based on selection of excipients. Eur J Pharm Biopharm 2008;70:839–44.
[94] Mullins ME, Michaels LP, Menon V, Locke B, Ranade MB. Effect of geometry on particle adhesion. Aerosol Sci Technol 1992;17:105–18.
[95] Crowder TM, Louey MD, Sethuraman VV, Smyth HDC, Hickey AJ. An odyssey in inhaler formulation and design. Pharm Technol North Am 2001;25: 99–113.
[96] Larhrib H, Martin GP, Marriott C, Prime D. The influence of carrier and drug morphology on drug delivery from dry powder formulations. Int J Pharm 2003;257:283–96.
[97] Zeng XM, Martin GP, Marriott C, Pritchard J. The influence of carrier morphology on drug delivery by dry powder inhalers. Int J Pharm 2000;200: 93–106.
[98] Ikegami K, Kawashima Y, Takeuchi H, Yamamoto H, Isshiki N, Momose D-i., et al. Improved inhalation behavior of steroid KSR-592 in vitro with Jethaler? By polymorphic transformation to needle-like crystals (beta-Form). Pharm Res 2002;19:1439–45.
[99] Chew NYK, Tang P, Chan H-K, Raper JA. How much particle surface corrugation is sufficient to improve aerosol performance of powders? Pharm Res 2005;22:148–52.

[100] Hassan MS, Lau R. Inhalation performance of pollen-shape carrier in dry powder formulation with different drug mixing ratios: comparison with lactose carrier. Int J Pharm 2010;386:6–14.
[101] Hassan MS, Lau R. Feasibility study of pollen-shape drug carriers in dry powder inhalation. J Pharm Sci 2010;99:1309–21.
[102] Kassem NM, Ho KKl, Ganderton D. The effect of air flow and carrier size on the characteristics of an inspirable cloud. J Pharm Pharmacol 1989;41:14.
[103] Braun MA, Oschmann R, Schmidt PC. Influence of excipients and storage humidity on the deposition of disodium cromoglycate (DSCG) in the twin impinger. Int J Pharm 1996;135:53–62.
[104] Steckel H, Mueller BW. In vitro evaluation of dry powder inhalers II: influence of carrier particle size and concentration on in vitro deposition. Int J Pharm 1997;154:31–7.
[105] French DL, Edwards DA, Niven RW. The influence of formulation on emission, deaggregation and deposition of dry powders for inhalation. J Aerosol Sci 1996;27:769–83.
[106] Byron PR, Jashnani R. Efficiency of aerosolization from dry powder blends of terbutaline sulphate and lactose NF with different particle size distributions. Pharm Res 1990;7:S81.
[107] Hamishehkar H, Emami J, Najafabadi AR, Gilani K, Minaiyan M, Mahdavi H, et al. Influence of carrier particle size, carrier ratio and addition of fine ternary particles on the dry powder inhalation performance of insulin-loaded PLGA microcapsules. Powder Technol 2010;201:289–95.
[108] Islam N, Stewart P, Larson I, Hartley P. Lactose surface modification by decantation: are drug-fine lactose ratios the key to better dispersion of salmeterol xinafoate from lactose-interactive mixtures? Pharm Res 2004;21:492–9.
[109] Guchardi R, Frei M, John E, Kaerger JS. Influence of fine lactose and magnesium stearate on low dose dry powder inhaler formulations. Int J Pharm 2008;348:10–7.
[110] Staniforth JN. Improvements in dry powder inhaler performance: surface passivation effects. Drug Deliv Lungs 1996;VII:86–9.
[111] Adi H, Larson I, Stewart PJ. Adhesion and redistribution of salmeterol xinafoate particles in sugar-based mixtures for inhalation. Int J Pharm 2007;337:229–38.
[112] Bhavna, Ahmad FJ, Mittal G, Jain GK, Malhotra G, Khar RK, et al. Nano-salbutamol dry powder inhalation: a new approach for treating broncho-constrictive conditions. Eur J Pharm Biopharm 2009;71:282–91.
[113] Kalantarian P, Rouholamini AN, Haririan I, Vatanara A, Yamini Y, Darabi M, et al. Preparation of 5-fluorouracil nanoparticles by supercritical antisolvents for pulmonary delivery. Int J Nanomed 2010;5:763–70.
[114] Zhang Y, Zhu J, Tang Y, Chen X, Yang Y. The preparation and application of pulmonary surfactant nanoparticles as absorption enhancers in insulin dry powder delivery. Drug Dev Ind Pharm 2009;35:1059–65.
[115] Huang M, Ma Z, Khor E, Lim L-Y. Uptake of FITC-Chitosan nanoparticles by A549 cells. Pharm Res 2002;19:1488–94.
[116] Chono S, Tanino T, Seki T, Morimoto K. Influence of particle size on drug delivery to rat alveolar macrophages following pulmonary administration of ciprofloxacin incorporated into liposomes. J Drug Target 2006;14:557–66.
[117] Kho K, Hadinoto K. Effects of excipient formulation on the morphology and aqueous re-dispersibility of dry-powder silica nano-aggregates. Colloids Surf A 2010;359:71–81.
[118] Kho K, Hadinoto K. Aqueous re-dispersibility characterization of spray-dried hollow spherical silica nano-aggregates. Powder Technol 2010;198: 354–63.
[119] Grenha A, Seijo B, Remunan-Lopez C. Microencapsulated chitosan nanoparticles for lung protein delivery. Eur J Pharm Sci 2005;25:427–37.
[120] Kawashima Y, Takeuchi H, Yamamoto H, Mimura K. Powdered polymeric nanoparticulate system to improve pulmonary delivery of calcitonin with dry powder inhalation. Proc Inter Symp Controlled Release Bioactive Mater 2000;27th:229–30.
[121] Yamamoto H, Kuno Y, Sugimoto S, Takeuchi H, Kawashima Y. Surface-modified PLGA nanosphere with chitosan improved pulmonary delivery of calcitonin by mucoadhesion and opening of the intercellular tight junctions. J Control Release 2005;102:373–81.
[122] Tozuka Y, Takeuchi H. Fine particle design and preparations for pulmonary drug delivery. Drug Deliv Syst 2008;23:467–73.
[123] Desai TR, Li D, Finlay WH, Wong JP. Determination of surface free energy of interactive dry powder liposome formulations using capillary penetration technique. Colloids Surf B Biointerfaces 2001;22:107–13.
[124] Lu D, Hickey Anthony J. Liposomal dry powders as aerosols for pulmonary delivery of proteins. AAPS PharmSciTech 2005;6:E641–8.
[125] Matilainen L, Jaervinen K, Toropainen T, Naesi E, Auriola S, Jaervinen T, et al. In vitro evaluation of the effect of cyclodextrin complexation on pulmonary deposition of a peptide, cyclosporin A. Int J Pharm 2006;318:41–8.
[126] Ungaro F, d'Emmanuele di Villa Bianca R, Giovino C, Miro A, Sorrentino R, Quaglia F, et al. Insulin-loaded PLGA/cyclodextrin large porous particles with improved aerosolization properties: in vivo deposition and hypoglycaemic activity after delivery to rat lungs. J Control Release 2009;135:25–34.
[127] Sung JC, Padilla DJ, Garcia-Contreras L, VerBerkmoes JL, Durbin D, Peloquin CA, et al. Formulation and pharmacokinetics of self-assembled rifampicin nanoparticle systems for pulmonary delivery. Pharm Res 2009;26:1847–55.
[128] Edwards DA, Chen D, Wang J, Ben-Jebria A. Controlled-release inhalation aerosols respiratory drug delivery VI: biological, pharmaceutical, clinical and regulatory issues relating to optimized drug delivery by aerosol. In: The international symposium. 1998. p. 187–92.
[129] Shoyele SA. Controlling the release of proteins/peptides via the pulmonary route. Methods Mol Biol 2008;437:141–8.
[130] Sievers RE. Dry powder aerosol vaccine and antibiotics delivery development to reduce risks of deaths in developing countries. In: Abstract of Papers, 238th ACS National Meeting: PRES-008. 2009.
[131] Kersten G, Hirschberg H. Needle-free vaccine delivery. Expert Opin Drug Deliv 2007;4:459–74.
[132] Laube Beth L. The expanding role of aerosols in systemic drug delivery, gene therapy, and vaccination. Respir Care 2005;50:1161–76.
[133] Wee JLK, Scheerlinck JPY, Snibson KJ, Edwards S, Pearse M, Quinn C, et al. Pulmonary delivery of ISCOMATRIX influenza vaccine induces both systemic and mucosal immunity with antigen dose sparing. Mucosal Immunol 2008;1:489–96.
[134] Sluetter B, Soema PC, Ding Z, Verheul R, Hennink W, Jiskoot W. Conjugation of ovalbumin to trimethyl chitosan improves immunogenicity of the antigen. J Control Release 2010;143:207–14.
[135] Sluetter B, Bal S, Keijzer C, Mallants R, Hagenaars N, Que I, et al. Nasal vaccination with N-trimethyl chitosan and PLGA based nanoparticles: nanoparticle characteristics determine quality and strength of the antibody response in mice against the encapsulated antigen. Vaccine 2010;28:6282–91.
[136] Prego C, Paolicelli P, Diaz B, Vicente S, Sanchez A, Gonzalez-Fernandez A, et al. Chitosan-based nanoparticles for improving immunization against hepatitis B infection. Vaccine 2010;28:2607–14.
[137] Morton D. Dry powder inhaler formulations comprising surface-modified particles with anti-adherent additives. Application: WO:. UK: Vectura Limited; 2006. p. 63 pp.
[138] Zhou QT, Qu L, Larson I, Stewart PJ, Morton DAV. Improving aerosolization of drug powders by reducing powder intrinsic cohesion via a mechanical dry coating approach. Int J Pharm 2010;394:50–9.
[139] Shekunov BY, Feeley JC, Chow AHL, Tong HHY, York P. Physical properties of supercritically-processed and micronised powders for respiratory drug delivery. Kona 2002;20:178–87.
[140] Shekunov BY, Feeley JC, Chow AHL, Tong HHY, York P. Aerosolisation behaviour of micronised and supercritically-processed powders. J Aerosol Sci 2003;34:553–68.
[141] Raula J, Laehde A, Kauppinen EI. Aerosolization behavior of carrier-free L-leucine coated salbutamol sulphate powders. Int J Pharm 2009;365:18–25.
[142] Newhouse MT, Hirst PH, Duddu SP, Walter YH, Tarara TE, Clark AR, et al. Inhalation of a dry powder tobramycin PulmoSphere formulation in healthy volunteers. Chest 2003;124:360–6.
[143] Duddu SP, Sisk SA, Walter YH, Tarara TE, Trimble KR, Clark AR, et al. Improved lung delivery from a passive dry powder inhaler using an engineered pulmosphere? Powder Pharm Res 2002;19:689–95.
[144] Richardson PC, Boss AH. Technosphere insulin technology. Diabetes Technol Ther 2007;9:S65–72.
[145] Schatz H. Inhaled insulin and the dream of a needle-free insulin application. Exp Clin Endocrinol Diabetes 2004;112:285–7.
[146] Hickey AJ, Concessio NM. Descriptors of irregular particle morphology and powder properties. Adv Drug Deliv Rev 1997;26:29–39.
[147] Lucas P, Anderson K, Staniforth JN. Protein deposition from dry powder inhalers: fine particle multiplets as performance modifiers. Pharm Res 1998;15:562–9.
[148] Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. Arch Dis Child 1990;65:308–10.
[149] Al-Showair Raid AM, Tarsin Walid Y, Assi Khaled H, Pearson Stanley B, Chrystyn H. Can all patients with COPD use the correct inhalation flow with all inhalers and does training help? Respir Med 2007;101:2395–401.
[150] Criee CP, Meyer T, Petro W, Sommerer K, Zeising P. In vitro comparison of two delivery devices for administering formoterol: foradil P and formoterol ratiopharm single-dose capsule inhaler. J Aerosol Med 2006;19:466–72.
[151] Underwood R, Dufour F, Davies G, Pocock A, Gupta S. Using computer modelling to investigate the effect of inhaler design and patient variation in the deposition of particles in the upper airway of paediatric patient. J Aerosol Med Pulmon Drug Deliv 2009;22(3):294.
[152] Charles DS, Joel DK, Lea C, Powel KG. Development of a disposable dry powder delivery device platform. Respir Drug Deliv 2008;2:405–8.
[153] Wieshammer S, Dreyhaupt J. Dry powder inhalers: which factors determine the frequency of handling errors? Respiration 2008;75:18–25.
[154] van der Palen J, Klein JJ, van Herwaarden CL, Zielhuis GA, Seydel ER. Multiple inhalers confuse asthma patients. Eur Respir J 1999;14:1034–7.
[155] Molimard M, Raherison C, Lignot S, Depont F, Abouelfath A, Moore N. Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care. J Aerosol Med 2003;16:249–54.
[156] Self Timothy H, Arnold Lori B, Czosnowski Lauren M, Swanson Joseph M, Swanson H. Inadequate skill of healthcare professionals in using asthma inhalation devices. J Asthma 2007;44:593–8.
[157] Crowe CT, Troutt TR, Chung JN. Numerical models for two-phase turbulent flows. Annu Rev Fluid Mech 1996;28:11–43.
[158] Balachandar S, Eaton JK. Turbulent dispersed multiphase flow. Annu Rev Fluid Mech 2010;42:111–33.
[159] Farkas A, Balashazy I, Sxocs K. Characterization of regional and local deposition of inhaled aerosol drugs in the respiratory system by computational fluid and particle dynamics methods. J Aerosol Med 2006;19:329–43.
[160] Zhang Y, Chia TL, Finlay WH. Experimental measurement and numerical study of particle deposition in highly idealized mouth-throat models. Aerosol Sci Technol 2006;40:361–72.

[161] Ball CG, Uddin M, Pollard A. High resolution turbulence modelling of airflow in an idealised human extra-thoracic airway. Comp Fluids 2008;37:943–64.
[162] Longest PW, Hindle M. Quantitative analysis and design of a spray aerosol inhaler Part 1: effects of dilution air inlets and flow paths. J Aerosol Med Pulmon Drug Deliv 2009;22:271–83.
[163] Longest PW, Hindle M. Evaluation of the respimat soft mist inhaler using a concurrent CFD and in vitro approach. J Aerosol Med Pulmon Drug Deliv 2009;22:99–112.
[164] Wong W, Fletcher DF, Traini D, Chan H, Crapper J, Young PM. Particle aerosolisation and break-up in dry powder inhalers 1: evaluation and modelling of venturi effects for agglomerated systems. Pharm Res 2010;27:1367–76.
[165] Matida EA, Finlay WH, Breuer M, Lange CF. Improving prediction of aerosol deposition in an idealized mouth using large-eddy simulation. J Aerosol Med 2006;19:290–300.
[166] Jin HH, Fan JR, Zeng MJ, Cen KF. Large eddy simulation of inhaled particle deposition within the human upper respiratory tract. Aerosol Sci 2007;38:257–68.
[167] Apte SV, Mahesh K, Gorokhovski M, Moin P. Stochastic modeling of atomizing spray in a complex swirl injector using large eddy simulation. P Combust Inst 2009;32:2257–66.
[168] Robinson RJ, Snyder P, Oldham MJ. Comparison of particle tracking algorithms in commercial CFD packages: sedimentation and diffusion. Inhal Toxicol 2007;19:517–31.
[169] Tong ZB, Yang RY, Chu KW, Yu AB, Adi S, Chan HK. Numerical study of the effects of particle size and polydispersity on the agglomerate dispersion in a cyclonic flow. Chem Eng J 2010;164:432–41.
[170] Tong ZB, Yang RY, Yu AB, Adi S, Chan HK. Numerical modelling of the breakage of loose agglomerates of fine particles. Powder Technol 2009;196:213–21.
[171] Adi S, Tong ZB, Kim HK, Yang R, Yu A. Impact angles as an alternative way to improve aerosolisation of powders for inhalation? Eur J Pharm Sci 2010;41:320–7.
[172] Voss A, Finlay WH. Deagglomeration of dry powder pharmaceutical aerosols. Int J Pharm 2002;248:39–50.
[173] Finlay WH. The mechanics of inhaled pharmaceutical aerosols: an introduction. London: Academic Press; 2001.
[174] Jones WP, Lettieri C. Large eddy simulation of spray atomization with stochastic modeling of breakup. Phys Fluids 2010;22:115106.
[175] Wang L, Vigil RD, Fox RO. CFD simulation of shear-induced aggregation and breakage in turbulent Taylor-Couette flow. J Colloid Interf Sci 2005;285:167–78.
[176] Behara SRB, Kippax P, McIntosh MP, Morton D, Larson I, Stewart P. Structural influence of cohesive mixtures of salbutamol sulphate and lactose on aerosolisation and de-agglomeration behaviour under dynamic conditions. Eur J Pharm Sci 2011;42:210–9.
[177] Berard V, Lesniewska E, Andres C, Pertuy D, Laroche C, Pourcelot Y. Dry powder inhaler: influence of humidity on topology and adhesion studied by AFM. Int J Pharm 2002;232:213–24.
[178] Harder C, Lesniewska E, Laroche C. Study of ageing of dry powder inhlaer and metered dose inhaler by atomic force micoscopy. Powder Technol 2011;208:252–9.
[179] Hickey AJ, Mansour HM, Telko MJ, Xu Z, Smythe HDC, Mulder T, et al. Physical characterization of component particules included in dry powder inhalers 1. Strategy review and static characteristics. J Pharm Sci 2007;96:1282–301.
[180] Raula J, Kurkela JA, Brown DP, Kauppinen EI. Study of the dispersion behaviour of L-leucine containing microparticles synthesized with an aerosol flow reactor method. Powder Technol 2007;177:125–32.
[181] Begat P, Morton DAV, Staniforth JN, Price R. The cohesive-adhesive balances in dry powder inhalar formulations 1: direct quantification by atomic force microscopy. Pharm Res 2004;21:1591–7.
[182] Paajanen M, Katainen J, Raula J, Kauppinen EI, Lahtinen J. Direct evidence on reduced adhesion of salbutamol sulphate particles due to L-leucine coating. Powder Technol 2009;192:6–11.
[183] Price R, Young PM, Edge S, Staniforth JN. The influence of relative humidity on particle interactions in carrier-based dry powder inhaler formulations. Int J Pharm 2002;246:47–59.
[184] Tsukada M, Iriea R, Yonemochi Y, Noda R, Kamiya H, Watanabe W, et al. Adhesion force measurement of a DPI size pharmaceutical particle by colloid probe atomic force microscopy. Powder Technol 2004;141:262–9.
[185] Davies M, Brindley A, Chen X, Marlow M, Doughty SW, Shrubb I, et al. Characterization of drug particle surface energetics and Young's modulus by atomic force microscopy and inverse gas chromotography. Pharm Res 2005;22:1158–66.
[186] Grimsey IM, Feeley JC, York P. Analysis of surface energy of pharmaceutical powders by inverse gas chromotography. J Pharm Sci 2002;91:571–83.
[187] Changsan M, Kim HK, Separovic F, Srichana T. Physicochemical characterization and stability of rifampicin liposome dry powder inhaler formulations for inhalers. J Pharm Sci 2009;98:628–39.
[188] Chawla A, Taylor KMG, Newton JM, Johnson MCR. Production of spray dried salbutamol sulphate for use in dry powder aerosol fomulation. Int J Pharm 1994;108:233–40.
[189] Shur J, Harris H, Jones MD, Kaerger JS, Price R. The role of fines in the modification of the fluidization and dispersion mechanism within dry powder inhaler formulations. Pharm Res 2008;25:1931–40.
[190] Behara SRB, Kippax P, Larson I, Morton DAV, Stewart P. Kinetics of emitted mass – a study with three dry powder inhaler devices. Chem Eng Sci 2011;66:5284–92.
[191] Behara SRB, Larson I, Kippax P, Morton DAV, Stewart P. An approach to characterising the cohesive behaviour of powders using a flow titration aerosolisation based methodology. Chem Eng Sci 2011;66:1640–8.
[192] Han R, Papadopoulos G, Greenspan BJ. Flow field measurement inside the mouthpiece of the Spiros inhaler using particle image velocimetry. Aerosol Sci Technol 2002;36:329–41.
[193] Mendes PJ, Sousa JMM, Pinto JF. Prediction of the deposition of dry powder aerosols. AAPS J 2009;11:186–94.
[194] Boer AHd, Chan HK, Price R. A critical review on lactose-based drug formulation and device studies for dry powder inhalation: which are relevant and what interactions to expect? Adv Drug Deliv Rev 2011, doi:10.1016/j.addr.2011.04.004.
[195] Louey MD, Mulvaney P, Stewart PJ. Characterisation of adhesional properties of lactose carriers using atomic force microscopy. J Pharm Biomed 2001;25:559–67.
[196] Mukhopadhyay P, Schreiber HP. Aspects of acid-base interactions use of inverse gas chromatography. Colloids Surf A 1995;100:47–71.
[197] Voelkel A. Inverse gas chromatography in characterization of surface. Chemom Intell Lab Syst 2004;72:205–7.
[198] Zhou Q, Denman JA, Gengenbach T, Das S, Qu L, Zhang H, et al. Characterization of the surface properties of a model pharmaceutical fine powder modified with a pharmaceutical lubricant to improve flow via a mechanical dry coating approach. J Pharm Sci 2011;100:3421–30.
[199] Thielmann F, Naderi M, Traini D, Young M. Impact of lactose polymorphism on salbutamol sulphate lactose interactions in DPI formulations. In: Dalby R, Byron P, Peart J, Suman J, Farr S, Young P, editors. Proc res drug delivery conf Scottsdale, Arizona. Boca Raton, Florida, USA: USA Davis Healthcare International Publishing; 2006. p. 793–5.
[200] Saleem I, Smyth H, Telko M. Prediction of dry powder inhaler formulation performance from surface energetics and blending dynamics. Drug Dev Ind Pharm 2008;34:1002–10.
[201] Tanaka T, Eaton JK. Sub-Kolmogorov resolution partical image velocimetry measurements of particle-laden forced turbulence. J Fluid Mech 2010;643:177–206.
[202] Newman SP, Busse WW. Evolution of dry powder inhaler design, formulation, and performance. Respir Med 2002;96:293–304.
[203] CPMP. Committee for proprietary medicinal products. The European Agency for Evaluation of Medicinal Products; 1998.
[204] CDER. Guidance for industry: metered dose inhaler (MDI) and dry powder inhaler (DPI) drug products. Food and Drug Administration (FDA), Rockville, MD; 1998.
[205] IPAC-RS. International pharmaceutical aerosol consortium on regulation and science; 2008.
[206] Mitchell J, Newman S, Chan H-K. In vitro and in vivo aspects of cascade impactor tests and inhaler performance: a review. AAPS PharmSciTech 2007;8:E110.
[207] Dunbar C, Mitchell J. Analysis of cascade impactor mass distributions. J Aerosol Med 2005;18:439–51.
[208] Chrystyn H. The Diskus: a review of its position among dry powder inhaler devices. Int J Clin Pract 2007;61:1022–36.
[209] Hickey AJ, Crowder TM. Next generation dry powder inhalation delivery systems. Lung Biol Health Dis 2007;221:445–60.
[210] Son Y-J, McConville JT. Advancements in dry powder delivery to the lung. Drug Dev Ind Pharm 2008;34:948–59.
[211] Daniher DI, Zhu J. Dry powder platform for pulmonary drug delivery. Particuology 2008;6:225–38.
[212] Zainudin BM, Biddiscombe M, Tolfree SE, Short M, Spiro SG. Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a pressurised metered dose inhaler, as a dry powder, and as a nebulised solution. Thorax 1990;45:469–73.
[213] Vidgren M, Paronen P, Vidgren P, Vainio P, Nuutinen J. In vivo evaluation of the new multiple dose powder inhaler and the Rotahaler using the gamma scintigraphy. Acta Pharm Nord 1990;2:3–10.
[214] Richards R, Dickson CR, Renwick AG, Lewis RA, Holgate ST. Absorption and disposition kinetics of cromolyn sodium and the influence of inhalation technique. J Pharmacol Exp Ther 1987;241:1028–32.
[215] Neale MG, Brown K, Hodder RW, Auty RM. The pharmacokinetics of sodium cromoglycate in man after intravenous and inhalation administration. Br J Clin Pharmacol 1986;22:373–82.
[216] Melchor R, Biddiscombe MF, Mak VH, Short MD, Spiro SG. Lung deposition patterns of directly labelled salbutamol in normal subjects and in patients with reversible airflow obstruction. Thorax 1993;48:506–11.
[217] Vidgren M, Arppe J, Vidgren P, Hyvarinen L, Vainio P, Silvasti M, et al. Pulmonary deposition and clinical response of 99mTc-labeled salbutamol delivered from a novel multiple dose powder inhaler. Pharm Res 1994;11:1320–4.
[218] Pitcairn G, Lunghetti G, Ventura P, Newman S. A comparison of the lung deposition of salbutamol inhaled from a new dry powder inhaler, at two inhaled flow rates. Int J Pharm 1994;102:11–8.
[219] Borgstrom L, Newman S, Weisz A, Moren F. Pulmonary deposition of inhaled terbutaline: comparison of scanning gamma camera and urinary excretion methods. J Pharm Sci 1992;81:753–5.
[220] Borgstrom L, Bengtsson T, Derom E, Pauwels R. Variability in lung deposition of inhaled drug, within and between asthmatic patients, with a pMDI and a dry powder inhaler, Turbuhaler. Int J Pharm 2000;193:227–30.

[221] Borgstrom L, Derom E, Stahl E, Wahlin-Boll E, Pauwels R. The inhalation device influences lung deposition and bronchodilating effect of terbutaline. Am J Respir Crit Care Med 1996;153:1636–40.
[222] Pitcairn GR, Lim J, Hollingworth A, Newman SP. Scintigraphic assessment of drug delivery from the Ultrahaler dry powder inhaler. J Aerosol Med 1997;10:295–306.
[223] Thorsson L, Edsbacker S. Lung deposition of budesonide from a pressurized metered-dose inhaler attached to a spacer. Eur Respir J 1998;12:1340–5.
[224] Wildhaber JH, Devadason SG, Wilson JM, Roller C, Lagana T, Borgstrom L, et al. Lung deposition of budesonide from Turbuhaler in asthmatic children. Eur J Pediatr 1998;157:1017–22.
[225] Borgstrom L, Bondesson E, Moren F, Trofast E, Newman SP. Lung deposition of budesonide inhaled via Turbuhaler: a comparison with terbutaline sulphate in normal subjects. Eur Respir J 1994;7:69–73.
[226] Newman SP, Pitcairn GR, Hirst PH, Bacon RE, O'Keefe E, Reiners M, et al. Scintigraphic comparison of budesonide deposition from two dry powder inhalers. Eur Respir J 2000;16:178–83.
[227] Chodosh S, Flanders JS, Kesten S, Serby CW, Hochrainer D, Witek Jr TJ. Effective delivery of particles with the HandiHaler dry powder inhalation system over a range of chronic obstructive pulmonary disease severity. J Aerosol Med 2001;14:309–15.
[228] Pitcairn GR, Lankinen T, Seppala OP, Newman SP. Pulmonary drug delivery from the Taifun dry powder inhaler is relatively independent of the patient's inspiratory effort. J Aerosol Med 2000;13:97–104.
[229] Newman S, Malik S, Hirst R, Pitcairn G, Heide A, Pabst J, et al. Lung deposition of salbutamol in healthy human subjects from the MAGhaler dry powder inhaler. Respir Med 2002;96:1026–32.
[230] DeLong M, Wright J, Dawson M, Meyer T, Sommerer K, Dunbar C. Dose delivery characteristics of the AIR pulmonary delivery system over a range of inspiratory flow rates. J Aerosol Med 2005;18:452–9.
[231] Newman SP, Sutton DJ, Segarra R, Lamarca R, de Miquel G. Lung deposition of aclidinium bromide from Genuair, a multidose dry powder inhaler. Respiration 2009;78:322–8.