Technological and practical challenges of dry powder inhalers and formulations ☆

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ABSTRACT

In the 50 years following the introduction of the first dry powder inhaler to the market, several developments have occurred. Multiple-unit dose and multi-dose devices have been introduced, but first generation capsule inhalers are still widely used for new formulations. Many new particle engineering techniques have been developed and considerable effort has been put in understanding the mechanisms that control particle interaction and powder dispersion during inhalation. Yet, several misconceptions about optimal inhaler performance manage to survive in modern literature. It is, for example still widely believed that a flow rate independent fine particle fraction contributes to an inhalation performance independent therapy, that dry powder inhalers perform best at 4 kPa (or 60 L/min) and that a high resistance device cannot be operated correctly by patients with reduced lung function. Nevertheless, there seems to be a great future for dry powder inhalation. Many new areas of interest for dry powder inhalation are explored and with the assistance of new techniques like computational fluid dynamics and emerging particle engineering technologies, this is likely to result in a new generation of inhaler devices and formulations, that will enable the introduction of new therapies based on inhaled medicines.

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Contents

1. Introduction

Therapeutic drug administration by inhalation covers a period of more than 4000 years and finds its origin in India and the Middle East [1].In the second half of the twentieth century, inhaler technology rapidly developed along three different pathways. The availability of electric pumps gave a boost to the development of jet nebulisers, whereas the evolution of chlorofluorocarbon propellants for military purposes in the interbellum between World War I and II enabled the development of pressurised metered dose inhalers (pMDIs) for therapeutic applications, of which the first one (Medihaler®, Riker) reached the market in 1956 [1]. Simultaneously, the possibilities for dry powder dispersion were explored and not much later one of the first (capsule based) dry powder inhalers (DPI: Spinhaler®, Fisons) became commercially available in 1971 [2,3]. In the past three decades all three types of pulmonary administration devices evolved and diversified rapidly into a huge variety of different concepts with specific pros and cons for a large number of different inhaled drugs. The development of DPIs was stimulated particularly by the Montreal Protocol (1987) on substances that deplete the ozone layer [4,5] and in the past decennium there is an increased awareness that DPIs may have the best potential for several new areas of interest for pulmonary administration [6–10].

The development and use of DPIs have originally been focused on diseases like asthma and COPD. The pulmonary route for these applications provides direct access to the site of action and has the advantage of a rapid onset of action. This reduces the total dose to be given substantially compared to oral administration, for a drug like salbutamol even by a factor of 10 to 20 [11]. Inhaled corticosteroids (ICS), bronchodilators (beta$_2$-agonists and muscarinic receptor antagonists) or combinations of these drugs are nearly all given in low doses varying from a few to a few hundred micrograms with an exception for cromolyn sodium in the Spinhaler®, which is administered in the milligram range [12]. Several capsule based DPIs followed the Spinhaler® [13–17] before other single dose compartments were considered suitable too. A concept with four or eight blisters on a disk [18] was presented as successor of the capsule based Rotahaler® and only a few years later followed a concept with 60 blisters on a long strip [19,20]. With these introductions an extension with multiple unit dose DPIs was made to the single dose DPIs which increased the patient's comfort. Roughly in the same decade a first multi-dose DPI (Turbuhaler®, AstraZeneca) was developed [21] which contains 200 doses in a supply chamber. In contrast with pre-filled capsule and blister inhalers, such DPIs have a dose measuring mechanism that has to be operated by the patient. By design, and due to the required safety measures that prevent double dosing and moisture uptake by the drug formulation and indicate the number of doses left in the device, multi-dose DPIs are generally more complex than single dose DPIs. Other examples of currently marketed multi-dose DPIs for anti-asthma and COPD drugs are Novolizer® (Meda) [22], Genuair® (Almirall) [23], Easyhaler® (Orion) [24], Clickhaler® (MSD) [25], Nexthaler® (Chiesi) [26] and Twisthaler® (MSD) [27].

Next to the developments in DPI design and formulation, an increasing interest in new therapeutic areas of interest for dry powder drug delivery can be observed. Examples are antibiotic therapies against infectious diseases which start and develop in the lungs (e.g. in bronchiectasis, tuberculosis (TB) and cystic fibrosis (CF)), vaccination programmes against viral diseases (e.g. influenza and measles), systemically acting drugs that cannot effectively be delivered via the oral route (e.g. like insulin for diabetic patients or levodopa for Parkinson patients in an off-period) or drugs that need a rapid onset of action, like fentanyl. The effective local targeting that is obtained by pulmonary administration allows for a reduction of the total dose to be given, without decreasing the drug concentrations at the site of action (e.g. for antibiotics). This reduces the adverse systemic side effects for which many antibiotics are notorious. Dry powder inhalation is much more convenient than classic jet nebulisation for this application as it reduces the time for administration of a dose considerably [28]. Dry powders are in general also more stable than aqueous drug solutions and do not require cold chain storage or reconstitution of powders into solutions for nebulisation. This is particularly of importance for antibiotic therapies or vaccination programmes in tropical developing countries where cold chain transport and storage may be problematic. Vaccination is mostly a once-only administration for which re-usable nebulisers are not the most appropriate devices [29]. Disposable nebulisers can be used, but their performance for the drug solution to be administered is often uncertain, whereas they still need electricity (from the mains or batteries) or pressurised air to be operated. Disposable DPIs are much easier to use in this respect and additionally DPIs are registered combinations with the drug formulation which guarantees a better drug delivery to the site of action.

Many of the new areas of interest for pulmonary drug administration require a change from low dose to high dose drugs for which different formulation types are needed than adhesive mixtures. High drug contents may increase the influence of the physico-chemical drug properties on the behaviour of the powder formulation during inhalation and frequently particle engineering techniques are needed to obtain well dispersible powders. The literature contains abundant formulation studies for inhaled drugs and vaccines, but surprisingly very little attention is given to improvement of the inhaler design for these new applications. Nearly all newly developed formulations in the literature are optimised for existing DPIs that were developed for the administration of low dose drugs processed into adhesive mixtures. Therefore, the greatest challenge for future dry powder inhalation applications may lie in designing well integrated device-formulation systems that enable one to achieve a good balance between the three major types of forces that govern pulmonary drug delivery. Fig. 1 shows this balance. The interparticulate forces in the powder formulation, the dispersion forces generated by the inhaler during inhalation and the deposition forces in the human respiratory tract, together determine the success of the pulmonary administration. Many newly developed drug formulations or formulation-device combinations require relatively high flow rates of 60 L/min or more through the inhalers to generate dispersion forces

Interparticulate forces in the powder formulation

Dispersion forces generated by the DPI

Deposition forces in the respiratory tract
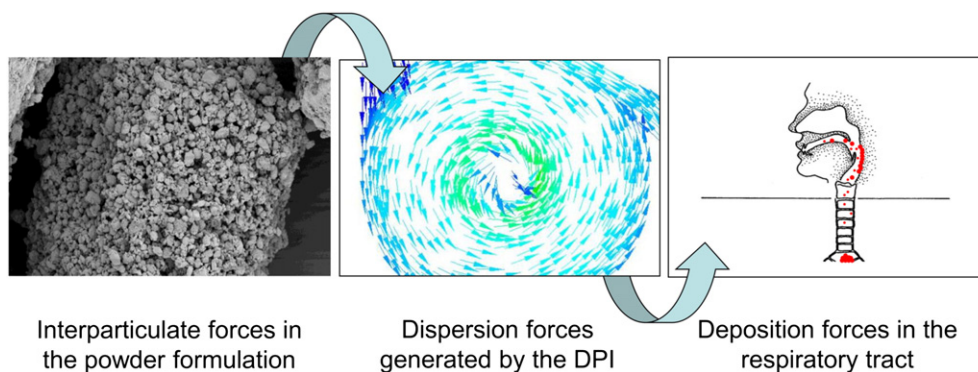
Fig. 1. Desired balance for optimal DPI therapy between the interparticulate forces in the powder formulation, the dispersion forces generated by the inhaler and the deposition forces in the respiratory tract during inhalation.

that are sufficiently high for producing an adequate aerosol for inhalation [30]. However, the use of such high flow rates results in a decreased central and peripheral lung deposition [31]. With the use of more effective inhalers (regarding powder dispersion efficiency), not only the flow rate for effective dispersion can be reduced to increase total lung deposition, dispersion may also become less dependent on the interparticulate forces that govern the powder properties (Fig. 1). Many other challenges for dry powder inhalation exist and they will be reviewed and discussed in this manuscript.

2. Demands on performance of DPIs and their formulations

Pulmonary drug administration will only result in an effective and safe therapy when the inhaler is able to reproducibly deliver a high fine particle dose to the site of action (receptor, infection, absorption site) in the respiratory tract. Additionally for an effective therapy, correct inhaler use and good adherence to the therapy are needed. The inhaler design and powder formulation determine to a large extent whether these prerequisites can be met.

2.1. Consistency of delivered dose

Firstly, the dose containing or measuring principle has to deliver a consistent amount of the formulation to the airstream. This depends not only on the weighing into the dose cavity or container, but also on an effective discharge of the compartment during inhalation. For peripheral deposition the discharge has to be within the first 1 to 1.5 L of inhaled air. This may be impossible for high drug doses in capsules for which the rate and degree of emptying mostly depends on the flow properties and size distribution of the powder formulation [12,32]. Emptying of the spinning, vibrating or rotating capsules during inhalation is mostly through small holes or slits in the capsule wall and the mass flow rate is limited by the number and diameter of the holes. Therefore, capsule inhalers generally have longer emission times than DPIs making use of open blisters or dose measuring mechanisms that go with drug supply containers. For the recently introduced TOBI® Podhaler (Novartis) two inhalations per capsule are recommended, and if necessary a third one, to ensure that the entire capsule contents is released [33]. Dose measuring mechanisms combined with drug supply containers have to prevent that double or incorrect dosing is possible, and that the patient will stop using the inhaler when the multi-dose drug compartment is empty. A good dose counter is needed which indicates the number of doses left in the device. When the drug formulation is hygroscopic, good moisture protection in well sealed compartments is needed, to prevent the occurrence of capillary forces by liquid films between particles [8]. Moisture may be a risk for the chemical stability of the product, but it also influences the dispersibility of the powder, especially when the drug compartments are subjected to humidity and temperature changes and the capillary forces progress into solid bridges.

### 2.2. Consistency of delivered fine particle dose

As a next step in the inhalation process the entrained powder mass from the dose cavity has to be dispersed effectively at the attainable range of flow rates through the inhaler and inhaler retention has to be low and preferably highly consistent to ensure consistency of the delivered dose. The nature and differences in efficiency of various types of dispersion forces, like drag and lift forces from the moving air, shear forces and impaction forces generated in the inhalers, have been explained and discussed before as well as how they can be generated by different dispersion principles [10,34,35]. Not only the efficiency of the dispersion forces, but also the duration of powder exposure to these forces determines to what extent the drug particles can be redispersed from the formulation. Circulation in whirl or classifier chambers may be extended to generate higher fine particle fractions (FPFs), but at the same time this will increase the emission time of the drug too. This requires adequate balancing during development between these various parameters to obtain an optimised inhaler performance. Moreover, these variables will also depend to a large extent on the powder properties too.

As the last step in the inhalation process, the generated aerosol has to be transported by the inhaled air stream into the respiratory tract and be deposited on the site of action. It is well recognised that transport, losses in the oropharynx plus first bifurcations and deposition in the target area all depend on both the aerodynamic particle size distribution and the flow rate with which the aerosol is inhaled [36–39]. Yet, some persistent misconceptions and false expectations exist in this respect and they will be discussed hereafter as they are all related to the inhaler design.

2.3. Misconceptions

2.3.1. Regarding the optimal flow rate or pressure drop

One of the most widespread fallacies is that all DPIs perform best at 4 kPa or 60 L/min [40]. However, various comparative in vitro evaluation studies have shown that this is incorrect. Fig. 2 compares the FPFs <5 μm as function of the pressure drop for a number of currently marketed inhalers, showing that most well designed inhalers deliver about the same FPF in the order of magnitude of 20 to 30% of the label claim (which is still low after over 40 years of development) at relatively low pressure drops of 2–3 kPa. These pressure drops correspond with a wide range of different flow rates depending on the inhaler resistance to air flow. Fig. 2 also shows that DPIs fall into two different categories: those who deliver approximately the same FPF at all flow rates and those producing higher FPFs when the flow rate is increased. This difference in flow rate dependency relates to another essential aspect of DPI performance around which many misconceptions exist.
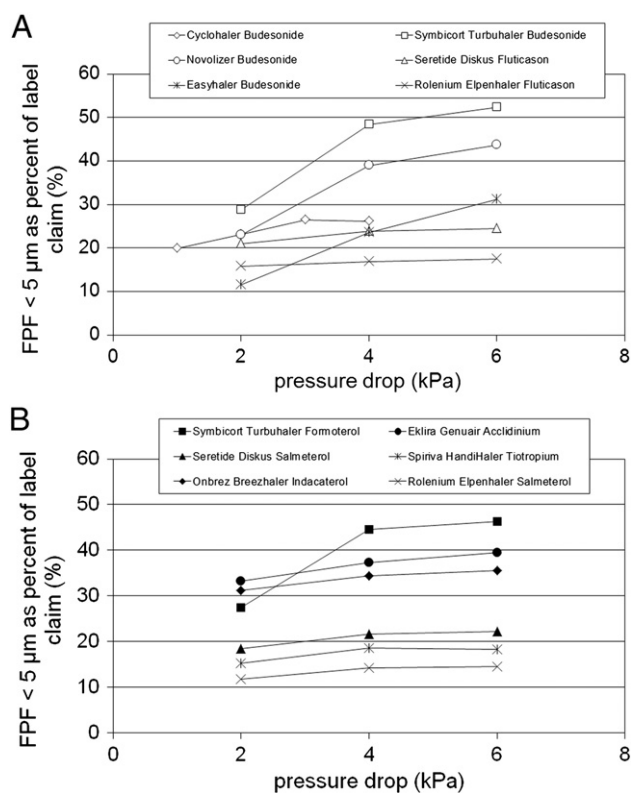
Fig. 2. FPF < 5 μm as function of the pressure drop across the DPIs for a number of marketed DPIs. A is for corticosteroid (ICS) monotherapy inhalers or ICS from combination therapy devices; B is for beta₂-agonists and anti-cholinergics.
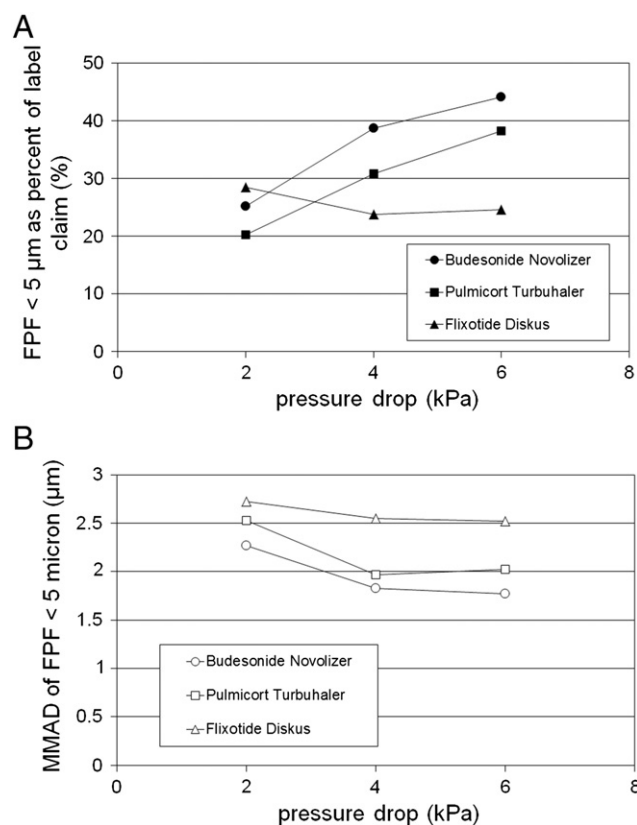
Fig. 3. Comparison of FPF < 5 μm from 3 monotherapy ICS DPIs as function of the pressure drop across the inhalers (A) and the MMADs of these FPFs (B).

2.3.2. Regarding the requirements for a patient independent therapy

Too often it is still thought that a flow rate independent FPF guarantees a more consistent therapy than a flow rate dependent FPF [40,41]. However, basic equations to describe particle dynamics, like impaction parameters, indicate that the chance of particle impaction in the upper respiratory tract, where the particle velocity is high, increases proportionally with the particle velocity and thus, the flow rate through the same inhaler [39]. Deposition modelling studies for monosized particles show that this increased impaction propensity results in a shift in deposition over the entire airways. However, the shift towards larger airways for larger particles is most pronounced for the upper respiratory tract where inertial impaction dominates deposition [42]. These theoretical effects are confirmed by in vivo deposition studies [31]. The shift in deposition is the reason why DPIs with a constant FPF output should not be used at higher pressure drops than the pressure drop at which the plateau value for FPF is achieved, which for many DPIs is already at 2 to 3 kPa (Fig. 2). Any further increase in pressure drop will result in more drug loss in the larger airways, including the oropharynx, and this will be at the cost of central and peripheral lung deposition. For DPIs delivering higher FPFs at higher flow rates, the shift in deposition may (at least partly) be compensated by a higher FPF, or a lower mass median aerodynamic diameter (MMAD) of the aerosol. This principle of compensation with a higher and finer aerosol has in vivo been confirmed for the budesonide Novolizer® [43] of which the FPF < 5 μm and the MMAD of this fraction are compared with those from the Flixotide® Diskus® and Pulmicort® Turbuhaler® in Fig. 3. To which extent and over which range of flow rates this compensation is obtained depends on the changes in FPF and in the lung deposition pattern, both with the flow rate, relative to each other. The challenge for future DPI developments is to limit the range of attainable flow rates through the device and to balance changes in FPF with changes in deposition pattern according to the force balance principle shown in Fig. 1.

2.3.3. Regarding the inhaler resistance

Resistance to airflow is a further essential property of inhalers which needs serious attention in design and development. DPI resistance is a direct consequence of its design and inhalers with more powerful dispersion principles tend to have higher resistances. To create turbulence or to generate impaction forces, the DPI needs narrow air passageways, flow obstructions or swirl, vortex or classifier chambers. These do not only increase the resistance, but also make dispersion more dependent on the flow rate. A misapprehension is that high resistance DPIs require a high flow rate or considerable inspiratory effort to be operated correctly, which would be a reason not to prescribe such inhalers for patients with severe COPD [40,44]. Fig. 2 shows that high pressure drops and thus, high flow rates through high resistance DPIs, may not be needed. Medium or medium–high resistance DPIs according to the definitions of the ERS/ISAM task force [45], like the Turbuhaler® and Novolizer®, perform probably best regarding lung deposition in the range of pressure drops between 2 and 4 kPa. It has been shown that even severe COPD patients are capable of generating such pressure drops [46]. It has also been shown that it becomes easier to achieve a high pressure drop when the resistance is higher and this is independent of the disease or severity of the disease. Therefore, the inspiratory effort is not a good argument to deny patients with inspiratory restrictions to use a high resistance DPI and in practice excellent results can be obtained with high and medium–high resistance DPIs [47]. A further major advantage of high resistance DPIs is that they reduce the flow rate and this favours central and peripheral lung deposition. Not being able to use a high resistance device effectively may have other reasons, like the inhalation of a (too) low volume as a result of the relatively low flow rate through high resistance DPIs in combination with dyspnea. In this respect there exists a great challenge for future studies in discriminating between what patients (with impaired breathing) consider less comfortable and what they are unable to perform. A better understanding may lead to better future DPI design regarding resistance.

2.3.4. Regarding the role of extra fine particles

A recent DPI development is the marketing of a multi-dose DPI delivering extra fine particles with MMAD < 1.5 µm [26]. The expectation from this development is that it enables a better targeting of the central and small airways compared to conventional DPIs. This expectation is based on the comparison between chlorofluorocarbon (CFC) and hydrofluorocarbons (HFA) containing pMDIs with the same drug. From this comparison it was concluded that much lower doses are needed from HFA pMDIs compared to CFC pMDIs to achieve the same clinical effect [48]. The improvement is contributed to the much smaller particles delivered by HFA pMDIs, having a MMAD of 1.1–1.5 µm versus 3.5–4.0 µm from the CFC holding pMDIs, which facilitates higher deposition in the peripheral lung from the HFA pMDI. However, another even more substantial difference between both types of pMDIs is their plume velocity, which (without valved holding chamber) causes approx. 90% oropharyngeal deposition from CFC containing pMDIs versus 30% from HFA devices [49]. The corresponding doses delivered to the lung are 10% and 70% and it may be expected that a seven-fold lung dose gives a better clinical effect in spite of a lower deposition efficiency for the smaller particles (Fig. 4). In Fig. 4, the mass fraction exhaled for monodisperse particles as function of the particle diameter is presented [31]. The trends measured for 1.5; 3 and 6 µm particles (two different flow rates) are extrapolated to 1 µm particles (red markers) and they are compared with the settling time needed to fall a distance equal to the diameter of a respiratory bronchiole (0.43 mm). The fair match between both relationships seems to indicate that the extrapolated data points have a realistic value. With this inefficient deposition for small particles in mind, the expectation that DPIs producing extra fine aerosols will give improved clinical effect too compared to conventional DPIs, may be false considering that not only the particle size distribution, but also the flow rate with which the aerosol is delivered is important. Such fine aerosols contain substantial particle mass fractions <1 µm for which the deposition efficiency by sedimentation is low and aerosols with MMADs in the range between 2 and 2.5 µm delivered at a relatively low flow rate from a high resistance DPI are expected to give similar or even higher lung deposition.

2.4. Inhaler use and adherence to therapy

No matter how good the DPI design and its in vitro performance are, the efficacy of the therapy for which it is used may entirely depend on the patient's compliance with the instructions and adherence to the therapy. Robustness, ease of handling and convenience are prerequisites for correct inhaler use and different studies have suggested that considerable differences in the occurrence of incorrect inhaler technique exist between different inhaler types [50]. Different studies also have different outcomes however, and the data compared by Lavorini et al. (2008) [51] show that overall taken (26 studies included)
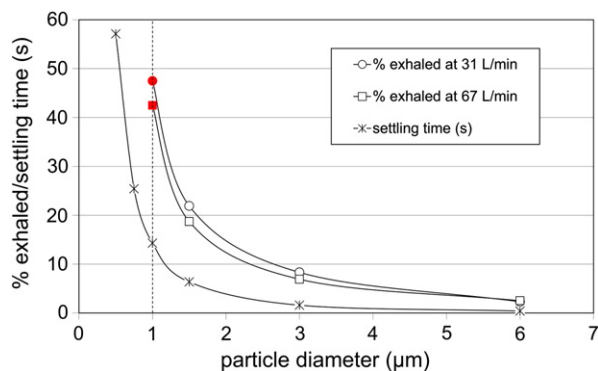

Fig. 4. Comparison of the particle fraction exhaled (for monodisperse particles) and the time needed for a particle to travel a distance (0.43 mm) equal to the diameter of a respiratory bronchiole by sedimentation at stationary settling velocity. Exhalation data are derived from Usmani et al. [31] and extrapolated to 1 µm particles.

differences in percentages of patients with incorrect inhaler technique between various inhalers are relatively small. A major complicating factor in comparing the outcomes of different studies is the fact that the criteria for incorrect use were different. Some score lists contained criteria that are at least arguable, like generating insufficient flow rate through high resistance inhalers without knowing what flow rate is really needed for good fine particle dose delivery with these devices. This explains why error percentages may vary extremely between studies for the same inhaler, e.g. between 4 and 94% adequate use for the Turbuhaler® [51]. Some of the errors made have no relation with the inhaler design, like forgetting to exhale before dose inhalation (most frequent error), exhaling through the device and keeping no breath hold following dose inhalation and they can therefore, not be prevented by designing better devices. Incorrect inhaler technique may further be influenced by patient-related determinants, like age, gender and education level of the patient [52] and instructor [53]. Particularly patients using different devices for their therapy are more prone to perform incorrect inhalation techniques [50] and this offers opportunities for improvement of new therapies as against TB, which involve a large number of different drugs (e.g. antibiotics). If such drugs become all available in the same inhaler device, the efficiency of the drug administration and adherence to the therapy may be significantly better than when different devices are to be used. Also inconvenience and hygienic aspects may be causes of poor adherence. DPIs should be small, preferably silent, have an ergonomic design and prevent severe inhaler pollution or powder waste. Keeping re-usable DPIs in air tight containers with a desiccant compartment may seem a good solution for hygroscopic drugs, but could become fatal for good inhaler performance when patient compliance is insufficient [33]. Compliance also benefits from good feedback signalling to the patient. Seeing, tasting and/or hearing that the inhaler is operated correctly may contribute to the patient's confidence in the therapy and this will stimulate adherence and compliance. A further aspect known to influence adherence is the dose frequency. Some long acting bronchodilators (LABAs and LAMAs) need to be taken only once daily. Whether this is really an advantage can be questioned, because forgetting to take a dose may have serious consequences for the therapy, much greater than for drugs that have to be taken twice daily [54]. Dose frequency has no relation to inhaler or formulation design however, and will therefore not further be discussed in this manuscript.

3. The technical design of DPIs

Basically, a well designed DPI consists of a number of primary and secondary functional parts and for each of the primary functional parts different solutions can be chosen. They are a suitable powder formulation for the drug, a pre-filled single dose compartment or multi-dose container with a measuring mechanism for the powder formulation, a powder dispersion principle and a housing for all parts. Secondary features can include several ways of signalling to the patient for correct use regarding correct dose activation and inhalation and for the number of doses left in the inhaler. They may also be measures for protection against moisture uptake by the formulation in multi-dose devices or against exhalation through the inhaler. Good signalling to the patient is one of the most recent developments in DPI technique and it was first introduced with the marketing of the Novolizer® [55].

3.1. Dry powder inhalation formulations

Micronised drug particles in the microgram range cannot be measured and administered accurately and they have to be processed into a suitable, mostly free flowing, formulation for inhalation. The two basic powder formulations for low dose anti-asthma and COPD drugs are soft spherical agglomerates and adhesive mixtures (Fig. 5). Soft pellets are more appropriate for high dose drugs (mg-range). Since the drug content of adhesive mixtures is limited by the drug containing
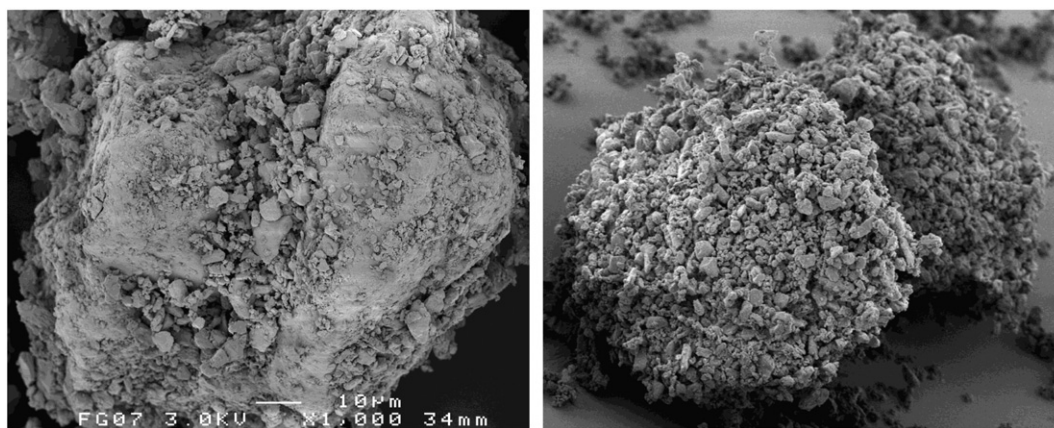
Fig. 5. Scanning electron micrographs of an adhesive mixture (left) and soft spherical pellet (right). The adhesive mixture is from the Rolenium Elpenhaler; the pellet formulation from the Pulmicort® Turbuhaler®.

capacity of the carrier surface this type of formulation is more suitable for low drug doses (µg-range) [56]. Of the currently marketed originator devices, only the Turbuhaler® contains so-called soft (spherical) pellet formulations [21,57] with or without micronised lactose as filler agent depending on the dose weight to be measured. Although the pellets have excellent dispersion behaviour in the Turbuhaler®, their use puts great demands on the production process and the accuracy of the dose measuring mechanism in the inhaler. For these reasons, and also because of a relatively low mechanical stability of the soft pellet formulations [58], nearly all other inhalers for low dose anti-asthma and COPD drugs make use of adhesive mixtures. In such mixtures, originally referred to as ordered mixtures, the micronised drugs are mixed with coarse carrier crystals which act as host particles carrying the drug particles on their surface [59]. For adhesive mixtures, many variables exist which vary from the type and size distribution of the lactose carrier and the drug content in the mixture to the blending conditions during preparation of the mixture. All these variables influence the flow properties and dispersion performance of the formulation during inhalation and by that, the (consistency of) delivered dose and fine particle dose. The state of the art regarding adhesive mixtures, as well as various particle engineering techniques for high dose drugs, will be discussed more in detail in paragraph 4 'the technical design of dry powder inhalation formulations'.

3.2. Dose measuring systems

For the dose (measuring) system, different options are possible. Next to capsules and blisters, other pre-loaded dose systems have been proposed [13] and a variety of measuring mechanisms is used in combination with drug reservoir containers in multi-dose inhalers [21,27,41,60–62]. There may be incompatibilities between the drug formulation and dose system however, which emphasises the need for an integrated development. For instance, formulations with lower mechanical instability (e.g. soft spherical pellets or adhesive mixtures with high drug content or weakened interaction forces introduced by the use of so-called force control agents) are preferably not used in drug containers with an excess of volume, as subjection of the inhaler to violent movements (e.g. dropping) may break-up the powder in such containers and deteriorate the flow properties and jeopardize dose consistency. Coarse carrier size fractions may be less favourable or unsuitable for capsule inhalers as they cannot pass the perforations in the capsule wall [12,32]. When moisture sensitive drug formulations are processed in multi-dose reservoir DPIs good protection against water uptake from the ambient air is needed [63,64].

3.3. Powder dispersion principles

Incompatibilities may also occur between the powder formulation and the dispersion principle. Many different dispersion principles seem theoretically possible. Yet, most of the currently marketed inhalers rely on relatively weak and less efficient drag and lift forces in turbulent air streams. Such dispersion principles require carrier materials with relatively smooth surfaces, which are mostly naturally present in relatively fine carriers [65] or obtained with carrier particle smoothing techniques [66–68]. They mostly benefit also from certain amounts of fine lactose particles in the mixture [32,69–71] although inconsistencies in this respect have been reported. Dispersion principles that generate inertial separation forces are by nature more effective and as a consequence, their performance depends less on the properties of the mixture [35,72]. They may, in contrast with dispersion systems relying on drag and lift forces, perform even better in combination with mixtures containing carriers with a relatively high surface rugosity and carriers which do not contain large quantities of fines [73]. This difference in demands for the carrier properties shows that general recommendations cannot be given and that an optimal carrier product for inhalation does not exist. Which carrier to use for adhesive mixtures depends on many factors, including the type of drug, the drug content in the mixture, the mixing conditions and particularly the dispersion principle of the inhaler. This again asks for well-designed integrated formulation-inhaler developments.

3.4. DPIs for high dose drugs

Demands on inhaler design for high dose drugs may be different from those for low drug dose formulations. Many high dose drugs (e.g. antibiotics) and also some excipients are highly hygroscopic [74, 75]. They also frequently have poor flow properties and this combination of properties makes them basically unsuitable for multi-dose DPIs with dose measuring systems. Good compatibility between the powder formulation and the dispersion principle for high dose drugs is even more important than for low dose drugs and particle engineering of the drug is often needed to achieve adequate dispersion. Avoiding the use of excipients in high dose drug formulations in order to minimise the powder mass inhaled may also require special technologies to keep the inhaler retention low, such as the use of sweeper crystals in circulation chambers or classifiers [76]. Not many high dose DPI developments are known up to now and most of them were reviewed very recently by Claus et al. [77]. An interesting approach is the use of a powder containing puck in the Orbital® disposable DPI which holds high drug doses up to 400 mg [78]. The puck releases the powder

by centrifugal force through one or more release rate controlling orifices into the de-agglomeration chamber in a number of subsequent inhalations.

3.5. The use of computational fluid dynamics

The design of new DPIs and studies on the performance of currently marketed DPIs can be supported by computational fluid dynamics (CFD) [79–82]. Modelling of the inhaler flow fields may yield information that helps understanding the dispersion behaviour of the devices and show what effect certain design modifications have on dispersion [83,84]. CFD may also teach one how to control the inhaler resistance, improve circulation in whirl and classifier chambers and to increase turbulence in dispersion zones [85,86]. By knowing the flow trajectories, predictions can also be made for particle behaviour and this may eventually lead to a better understanding of powder break-up and retention mechanisms in the inhaler. CFD simulations are expensive, time consuming and require considerable computational power, whereas the precise relationship between fluid and particle dynamics is complex and still partly uncertain due to several assumptions to be made. This may limit the use of this technique for modelling of the dispersion process and there is a great challenge in improving the models to simulate particle–particle interactions, powder break-up and retention behaviour. Further developments in the field of computational particle tracking could probably solve a number of these limitations.

3.6. Current state of the art

Currently over 60 different DPI designs can be found in the scientific literature and on the internet, however, not even half of them have reached the market so far and the ones that reached and stayed on the marked are all passive (breath-operated) devices. This number even excludes hundreds of concepts in the patent literature and some devices

primarily developed for local generic markets in Asian countries. The switch from branded to much cheaper generic inhalation medication under the pressure on healthcare budgets is a worldwide trend which is not limited to local markets and it is likely to result in the introduction of several new devices to the market in the near future [87]. Surprisingly, what seems to become also a trend is the use of relatively old capsule inhaler designs for new high-performance drug formulations [88–90]. Some devices, like the pulmonary delivery system used for Exubera® (inhaled insulin), have been commercially available only for a short period of time [91], whereas other developments, being presented as highly innovative with great potential, were stopped before they even reached the market, e.g. Spiros® (Dura) [92]. An overview of the most noteworthy inhaler designs of the past decades is presented in Table 1.

4. The technical design of dry powder inhalation formulations

Powder formulations for inhalation should contain the drug in the desired aerodynamic size distribution for deposition in the target area at the flow rate at which they are inhaled. The formulation has to facilitate reproducible dose measuring and good emptying of the dose compartment during inhalation. Furthermore, the formulation should be dispersed effectively into the inhaled air stream through the DPI during inhalation. Dispersion with most inhalers is rather incomplete and the size distribution of the aerosol may differ quite substantially from the primary particle size distribution of the drug particles. The functional demands require good flow properties of the formulation and control of the interparticulate forces in the powder. To achieve these requirements different types of formulations, with and without excipients, and special particle engineering techniques can be applied. It is the purpose of this paragraph to describe and comment on these formulations and techniques for which the best choice may depend on the drug dose,

Table 1
Some noteworthy DPI designs from the past two decades.

Inhaler	Company	Type	Details
Aeroshot	QuantumDesigns	Single dose	Caffeine inhaler (Dave Edwards)
Air2	Alkermes, now Civitas	Capsules	Renamed by Civitas into ARCUS™ for inhaled (high dose) levodopa
Aspirair®	Vectura	Single blisters	Pressurised air activated dispersion
Breezhaler®	Novartis	Capsules	Modification of the ISF inhaler for indacaterol en glycopyrronium
Clickhaler®	Merck, Mylan	Multi-dose	Inhaler for generic formulations
Conix™ DPI	3M	Cone shaped dose chamber	Disposable inhaler with reverse-flow cyclone action
Cricket™	MannKind	Single dose in cartridge	Single-use preloaded inhaler; disposable version of Dreamboat
DirectHaler™	DirectHale	Single dose caps	Single-use inhaler for pulmonary and nasal drug delivery
Diskhaler®	GSK	Multiple unit-dose	4 or 8 blisters on a disk
Diskus®	GSK	Multiple unit-dose	60 blisters on a tape
Dreamboat	MannKind	Single dose cartridges	New inhaler for inhaled Technosphere™ insulin Afrezza
Easyhaler®	Orion	Multi-dose	Inhaler for generic formulations
Ellipta®	GSK	Multiple unit-dose	Successor of Diskus for Breo (fluticason vilanterol combination)
Elpenhaler®	Elpen	Single duo blisters	Generic version of GSK's Seretide Diskus
Exubera® DPI	Pfizer	Single blisters	Active insulin inhaler with pressurised air aided dispersion into an aerosol chamber; withdrawn from the market
Genuair®	Almirall	Multi-dose	Second generation of the Novolizer® for aclidinium and aclidinium-formoterol
Gyrohaler®	Vectura	Multiple unit-dose	Generic inhaler targeting the Diskus market
HandiHaler®	Boehringer I	Capsules	Successor of the Inhalator Ingelheim
ISF inhaler®	Isf S.P.A.	Capsules	Also known as Aerolizer and Cyclohaler (Teva)
Jethaler®	Ratiopharm	Compressed powder ring with scraper	Similar to Ultrahaler (Sanofi-Avensis)
NEXThaler®	Chiesi	Multi-dose	Successor of Pulvinal, contains magnesium stearate for extra fine particle aerosol of BDP and formoterol
Novolizer®	Meda	Multi-dose	Generic DPI for budesonide, formoterol and salbutamol
TOBI® Podhaler	Novartis	Capsules	Also known as Turbospin (PH&T) and T-326 DPI (Nektar Therapeutics)
Skyehaler™	Skyefarma	Multi-dose	Inhaler for generic formulations
Spiromax®	Teva	Multi-dose	Previously referred to as Airmax (Norton Healthcare and Yamanouchi)
Spiros®	Dura	Multiple unit-dose	Battery driven dispersion (active DPI); development stopped
Taifun®	Leiras	Multi-dose	Generic DPI for budesonide
3M™ Taper DPI	3M	Multi-dose	120 doses on a microstructured carrier tape
TwinCaps®	Hovione	Capsules	Marketed (Japan) for Inavir
Twincer™	RUG, PureIMS	Single or double blisters	Disposable inhaler for high drug doses and vaccines (up to 50 mg in one inhalation)
Twisthaler®	Schering/MSD	Multi-dose	Asmanex (mometasone furoate) inhaler with hexagonal dispersion channel
Turbuhaler®	AstraZeneca	Multi-dose	The only ICS and bronchodilator inhaler with soft spherical pellets

drug properties and specific targeting or drug release goals and most of all, the type of inhaler used.

4.1. Particle preparation techniques

Different techniques are applied to obtain drug particles in the desired aerodynamic size range. Micronisation is mostly the standard for anti-asthma and COPD drugs. This so-called top-down manufacturing process can yield good control of the particle size distribution, but may have several disadvantages, like the creation of flat surfaces, local distortions of the crystal lattice (for crystalline materials) and charging of the particles or particle surfaces which all may affect the ad- and cohesiveness of the product [28,93,94]. Alternatively, various bottom-up techniques are available of which super critical fluid drying (SCF) and spray drying are mentioned frequently in the literature [95–98]. With these techniques, not only the size distribution can be controlled, but also to a certain extent the particle shape and (surface) morphology. This is of relevance since properties such as particle morphology, shape, density, (surface) porosity and smoothness are known to influence the bulk properties such as powder flow and dispersibility [28, 99,100]. SCF has particularly been explored for low dose anti-asthma and COPD drugs, but super-critical carbon dioxide drying of relatively high molecular thermo-labile protein based pharmaceuticals is also possible [101]. For stable, crystalline low dose drugs, spray drying may be less desirable, because this technique yields mostly particles in the amorphous state with increased moisture sensitivity and thus, reduced physical stability. For drugs like tobramycin, or aminoglycosides more in general, which are also highly hygroscopic in their crystalline modifications, spray drying does not have the disadvantage of reducing the physical stability of the product however. Spray drying may be either from solutions or from suspensions and co-spray drying with excipients (e.g. surfactants, lipids, volatile agents or carbohydrates) may result in a wide range of different particle structures and compositions to control release kinetics [102–105], increase pulmonary absorption and bioavailability [106,107] or improve the dispersion performance [28,108].

Several other ways of producing particles for inhalation have been explored and nearly all are bottom-up techniques. Different particle crystallisation or modification techniques have been described to control particle shape, modification and surface morphology. They include anti-solvent precipitation using ultrasound [109] or growth retarders and stabilizers [93,110]. Also the solid-state transformation of crystals from one modification into another [111], controlled spherical agglomeration in liquid [112] and confined liquid impinging from jets to produce elongated mannitol particles [113] have been explored. Spray-freeze dried particles mostly have excellent dispersion behaviour, but they are extremely voluminous (due to their high porosity) and allow only very small drug amounts to be measured in single dose compartments [114,115]. The technique has been combined with thermal ink-jet spraying for production of a carrier-free (low dose) salbutamol sulphate formulation [116]. Like spray-freeze drying, freeze drying is also a suitable technique to dry highly thermo-labile compounds, but this technique provides limited control over the particle size distribution and yields powders with very poor flow properties [117]. In contrast, micro-moulded PRINT particles (Liquidia Technologies) of drug or drug blended with excipients can be produced in a narrow size distribution by compression in micro-moulds with a variety of different shapes. This approach has recently reached the scale of cGMP-compliant production for preclinical and clinical productions [118].

4.1.1. Adhesive mixtures

Because of the cohesive and adhesive nature of the micron sized particles and the small quantities in which they are administered for anti-asthma and COPD drugs, formulation is required into powders that facilitate reproducible dose measuring. The types of formulations used for low dose drugs have already been mentioned in the Section 'The technical design of DPIs'. Most formulation studies in the literature regarding dry powder inhalation are about adhesive mixtures, because this is the most widely used type of formulation for low dose drugs. These studies aim to understand the complex mechanisms that control drug distribution over and adherence to the carrier surface and the dispersion behaviour during inhalation. They often focus on the influence of single variables thereon, like the surface properties of the carrier particles used [119], the presence of carrier (surface) fines [120], the carrier particle shape [121] or the effect of drug concentration in the blend [122]. So far this has not resulted in a more general understanding of these mechanisms, partially because several interactions between the variables and mechanisms exist [73]. Because of the poor understanding so far, recently a different approach has been presented which focuses primarily on the processes that occur during the mixing process [123]. These processes, governed by the inertial and frictional mixing forces, control (1) the size and (2) site distribution of the drug particles on the carrier surface as well as (3) the degree to which drug particles are pressed against each other and the carrier surface. The net result or balance of these three parameters can be explained in terms of size distributions for the adhesive and separation forces which determine the drug fraction that can be released from the carrier surface during inhalation. The primary challenges for such an approach are to develop and explore new techniques that enable one to measure drug particle size distribution in the mixture and the spatial distribution of the drug over the carrier surface as well as to investigate which of the variables of the starting materials and mixing process influence these three parameters most.

4.1.2. Carrier modification and dispersion aids in adhesive mixtures

Currently, a wide range of crystalline alpha lactose monohydrate types and sieve fractions are used as the carrier in inhalation formulations [124]. Because of the poorly controlled surface properties of this natural product and the batch-to-batch variation, there exists a great challenge in finding suitable alternative carrier products [125–128]. Other attempts to improve dispersion of lactose carrier based formulations are passivation of the active carrier sites in a ball mill [129], modulation of the carrier particle rugosity by wet-smoothing in a high-shear mixer [130] and reducing the interparticulate bonds between drug and carrier particles with the use of dispersion, or so-called force control agents (FCAs) like magnesium stearate [131–134]. The first DPIs containing such FCAs (NEXThaler®, Chiesi and Breezhaler®, Novartis) have recently reached the market [135,136] and some more are known to be launched on the short term. In the scientific literature no references can be found for the use of magnesium stearate in these two devices however, and the presence of finely divided insoluble materials in inhalation products may raise questions about the long term safety of the patients considering the great health risks related to fine particle inhalation [137].

4.1.3. Special types of adhesive mixtures

A special application of adhesive mixtures for high drug doses are the so-called supersaturated ordered mixtures or nucleus agglomerates [138]. This type of formulation differs from soft spherical pellets in that the pellets contain large lactose crystals as nuclei (Fig. 6). In practice, this type of formulation is of lower relevance for inhalation because such mixtures are mechanically highly unstable and they may exhibit a very low drug content uniformity [139]. A more promising special type of carrier based formulations are Technosphere® powders which are utilised by MannKind Corporation for pulmonary delivery of insulin [140,141]. Technosphere® technology makes use of self-assembling crystals of fumaryl diketopiperazine with a high specific surface area that are capable of absorbing high amounts of proteins and other substances for delivery to the deep lung. Also particles with effervescent activity to obtain an active release mechanism for the drug can be considered as a special application of carrier based formulations [142]. Soft spherical pellets are less thoroughly studied and the references to this type of formulation seem limited to one single study [56] and the patent literature (e.g. [57]).
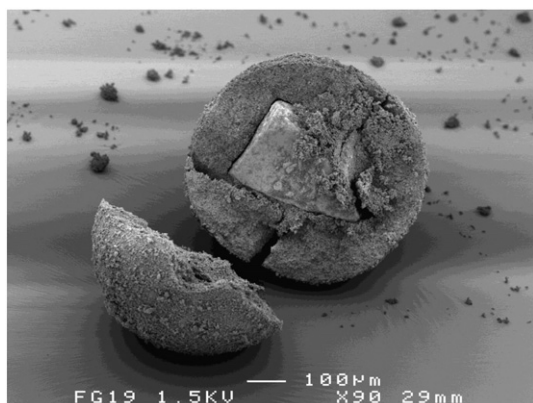
Fig. 6. Scanning electron micrograph of a broken nucleus agglomerate (supersaturated adhesive mixture).

4.1.4. Spray drying techniques for improved dispersion, slow release or macrophage uptake

Particle engineering is frequently applied for high dose drugs (mg-range) which cannot be processed into adhesive mixtures as the carrier load would simply be too high. To reduce the cohesiveness of the powders, the number of contact points between the individual particles as well as the surface area per contact point can be reduced by preparing particles with a high (surface) porosity and/or a highly corrugated surface. This improves the flow properties and dispersibility of the powders, whereas the large powder quantity itself facilitates sufficient reproducibility of dose measuring. Particle engineering technologies may also be used for special reasons such as: to obtain particle growth during inhalation, sustained drug release, avoid clearance by macrophages or, in contrast, provoke the uptake by macrophages. The list of examples is almost endless and only a few examples are discussed for possible consequences and the challenges involved avoiding these consequences. Some of the techniques used may be very promising, but some are also harsh and impracticable [143]. One of the earliest reports in this respect was about the preparation of so-called large porous particles by a double-emulsion solvent evaporation technique [6,144]. Particles that are aerodynamically within the range from 1 to 5 μm, but geometrically larger due to a high internal porosity have the advantage of diminished clearance by macrophages in addition to improved dispersion. This elongates their residence time in the deep lung which makes them suitable for sustained drug release. Sustained release can also prevent fast systemic uptake of highly water soluble drugs or lower the number of doses needed. Such geometrically large particles can be produced by emulsion solvent evaporation or spray drying techniques [145,146] and may contain surfactants like distearoylphosphatidylcholine or biodegradable polymers such as polylactic or poly(lactic-co-glycolic) acid (PLA and PGLA respectively). Another application of emulsion based spray drying is PulmoSphere™ technology (Nektar Therapeutics) which has been explored originally for anti-asthma drugs like cromolyn sodium, salbutamol sulphate and formoterol fumarate [147], but is currently used for high dose antibiotics [88–90]. This technique does not produce large porous particles (geometric diameter < 5 μm), but particles with an open structure to improve dispersion behaviour. Different fluorocarbon-in-water emulsions (with different volatile agents and surfactants) may be used for this technique depending on the drug. Co-spray drying with excipients like leucine may result in corrugated particles with the desired improved dispersion behaviour [100]. The degree of corrugation can be controlled with the amount of leucine and the enrichment in leucine at the particle surface was found to slow down the water uptake of hygroscopic drugs, like Gentamycin. A special application of small insoluble (PLA or PLGA) particles is targeting of the macrophages [148]. Bacteria like *Mycobacterium tuberculosis* (*Mtb*) are known to survive effectively in alveolar phagocytes like macrophages and dendritic cells. Insoluble particles in a size range that can be taken up by the macrophages have to release their antibiotic content and eradicate the *Mtb* within the phagocytic cell. Finally, also inhalable liposomal particle formulations have been proposed for sustained drug release [149,150]. Sustained release particles may reduce the frequency of dose administration and contribute to a more constant therapy, providing that the drug concentrations needed at the site of action will become sufficiently high.

4.1.5. Some disadvantages of new particle preparation techniques

There may be disadvantages related to co-spray drying of high dose drugs with excipients which all have been described in detail before [151]. In brief, particles with a high porosity and also substantial amounts of excipients in the formulation increase the volume of powder to be inhaled. This may affect the number of inhalations per dose [88], which could reflect negatively on the adherence to therapy. For some excipients, like PLA and PLGA, the long term effects are still not completely known yet. An excess of lactic acid in the lungs may on the long term have an effect on myofibroblast differentiation [152]. Insoluble biopolymers may also accumulate when the rate of removal by macrophages or degradation does not keep pace with the rate of administration. The accumulation of surfactants bears the risk of disturbance of the delicate balance between tissue tension and the surface tension of the alveolar lining fluid. Such effects may not be noticeable in healthy volunteers, but could be a risk in patients with various lung diseases. Therefore, the aim should be to develop high dose pulmonary drug formulations preferably without excipients and to minimise the total inhaled mass and number of materials. If the complex particle engineering techniques and excipients are used only to improve dispersion, it is better to search for other solutions which are more simple, cheaper, possibly safer and do not increase the powder volumes and masses to be inhaled. Improved inhaler technology, particularly focussing on an improved dispersion efficiency, could be one of the solutions. For antibiotics, finding more potent drugs, using synergistic drug combinations and improving the targeting to the site of action are additional challenges. Better targeting of the peripheral lung has for instance been achieved by making drug formulations hygroscopic which leads to particle growth by moisture sorption in the highly humid environment of the respiratory tract. This growth, corresponding with an increase in mass, speeds up the stationary particle settling velocity. By delivering such particles in the submicron range to the lungs, substantial deposition in the oropharynx and upper tract can be avoided to the benefit of a high deposition fraction in the lower trachea-bronchial tree [153]. This so-called excipient enhanced growth (EEG) principle makes use of excipients like sodium chloride and mannitol. Reported drug: excipient mass ratios are 50:50 to 25:75 however, which seems to make the principle less appropriate for high dose drugs, but the EEG principle can also be utilised for drugs that are hygroscopic by nature.

5. Challenges for future developments

5.1. DPI design

Several challenges for the improvement of DPI and formulation design have already been given throughout this manuscript. One of the most important goals should be further improvement of the efficacy of dry powder inhalation. Fig. 7 shows that in spite of a gradual increase in the total lung deposition over the past decades from less than 10% to between 20 and 40% for currently marketed inhalers, still less than half the dose becomes available to the site of action (or site of absorption). In general, the performance of a DPI system can be improved by establishing a better balance between the three types of forces shown in Fig. 1. Most studies in the literature are about understanding and controlling the factors that determine the interparticulate forces in the powder (blend). They aim to improve the dispersion of the powder during inhalation [154–156]. The inhaler design as an important
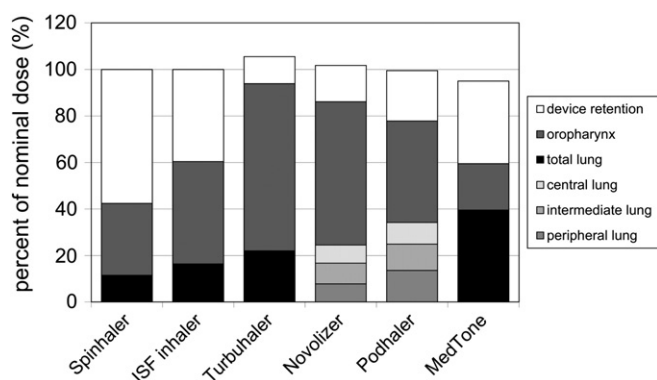
Fig. 7. Development of total lung deposition from DPIs (at approx. 60 L/min) in the past 45 years.
Data from radiolabelled deposition studies with Spinhaler® and ISF inhaler [24], Turbuhaler® [43,64,194], Novolizer® [43], TOBI® Podhaler [30] and MedTone, representing Dreamboat [141].

determinant in powder dispersion has grossly been neglected in many studies until quite recently [157,158]. Partly, this interest in device performance can be contributed to the introduction of new techniques like CFD [81,82]. However, still most studies focus on studying the performance of existing devices or investigating the effect of small design modifications thereon [80,83,84,159] as well as understanding the mechanisms of powder dispersion [86,160,161]. The design of new inhaler technology is hardly studied. Peer reviewed publications dealing with CFD-assisted new DPI developments are still not available although most pharmaceutical companies make use of this technique by now. With the availability of such new techniques in combination with an increased understanding of the mechanisms of powder dispersion, better integrated device-formulation development becomes possible. One of the challenges is to design optimally tuned combinations of the powder formulation and the dispersion principle. In this respect it is highly regrettable that still many consultancy agents or plastic manufacturers continue developing inhaler concepts for the market, initially not knowing for which types of formulation these concepts will be used. Part of the newly developed devices [162], or existing devices used for new powder formulations [28,30] are still low resistance capsule based DPIs. This has the disadvantage that powder properties need to be optimised with respect to both emptying of the capsules and good dispersion. If the drug formulation is an adhesive mixture, the carrier material providing best flow properties for discharge of the capsules may not always be the first choice from a dispersion viewpoint however. Moreover, the low airflow resistance of these capsule based DPIs will lead to very high flow rates which is at the cost of central and peripheral lung deposition (Fig. 1). Therefore, new developments should aim at limiting the flow rate to <50 L/min at 4 kPa. With the aid of CFD, this may not be too difficult.

5.2. Dry powder formulations

On the formulation site, several challenges still remain in spite of many years of effort put in the understanding of mechanisms of powder cohesion and dispersion. For adhesive mixtures some relevant variables, like moisture content or roughness have extensively been described, but there is insufficient knowledge of the mixture properties and the processes occurring during the mixing process that affect the final performance of the mixture. The extent to which particles de- and re-agglomerate and distribute over the carrier surface and to which the interparticulate forces are increased by inertial and frictional forces during blending are difficult to measure and require the introduction of new techniques. For high drug dose formulations the challenges are not so much related to getting a better understanding of the powder dispersion properties, because the particle engineering techniques that can

be applied to improve dispersion are well known. However, the low density particles obtained with these techniques also increase the volume of the powder to be inhaled, or, when substantial amounts of excipients are involved, also the powder mass to be administered may become too large. This increases the number of inhalations for a single dose [33] which is likely to influence the adherence to the therapy negatively. Besides, the long term effect of some of the excipients used is still uncertain [151]. Using less complex powder formulations and manufacturing techniques will also reduce production costs and make large scale antibiotic therapies and vaccination programmes in developing countries more feasible. In the light of the rapid global spread of multidrug-resistant and extensively drug-resistant TB and the risk of new outbreaks of bird flu and SARS, the challenge of making cheap, but effective inhaler technology for large scale antibiotic or antiviral therapies and vaccination programmes could well be the major challenges for the near future. Good dispersion of high dose drug formulations (particularly of the antibiotics) with minimum excipient content may require adaptation of the inhaler design to the physicochemical product properties, which again emphasises the need for integrated device-formulation development. Finally, total dose reduction can also be obtained by developing more potent drugs (e.g. antibiotics) or by using synergistic drug combinations. Only a few synergistic combinations have been reported so far [163,164] and there is a great challenge in finding more and developing dry powder inhalation systems for these combinations.

5.3. Pulmonary vaccination

The pulmonary administration of vaccines in large scale programmes may raise special challenges [29]. Vaccination is a once-only administration and if the vaccine delivery to the respiratory tract fails, there will be no, or insufficient protection. Because of the once-only aspect, disposable inhalers are preferred for this application, but it may be possible to use add-on devices with measuring equipment to record the entire inhalation manoeuvre. Monitoring of the inspiratory performance will give a good feedback to the health care professional and make sure whether sufficient protection is obtained or not, particularly if robust inhalers are used that perform well over a wide range of inspiratory efforts. A preference for disposable inhalers may also have other reasons, like the administration of hygroscopic formulations and pulmonary antibiotic administration for which bacterial resistance building in the device could be a risk. The number of disposable inhalers known in the public domain is still low however, whereas most of them are still in the development phase [165]. For the application of large scale vaccination there may be a future need for cheap but effective disposable DPIs with robust performance which can be connected to re-usable monitoring devices.

5.4. Special patient groups

The growing awareness that special inhalers may be needed for special patient groups like small children and the elderly has not resulted in the design of more appropriate devices for these groups yet. Most currently marketed DPIs are registered for children of six years and older due to a lack of clinical data for younger children. It has never been investigated systematically whether some of the children under six can use these DPIs too, or whether all children of six and more are indeed capable of understanding the instructions for use and have the ability to inhale correctly. Studies on dry powder inhalation in children so far focused either on how they operate specific DPIs [166–171], or on single inspiratory parameters like peak flow rate [172,173], and how these parameters are affected by the airflow resistance of the inhaler [174–177]. One of the greatest challenges for DPIs to be used by small children will be the delivery of the total dose in their much smaller inhaled volumes compared to adults [178]. Repeated inhalation of the same dose may be a solution for this problem, but this should not lead to exhalation through the device in between the inhalations. The

problems of DPI use by the elderly are largely the same as for children. They may have reduced inspiratory power and inadequate understanding of how to use an inhaler correctly and they often suffer from insufficient manual dexterity and hand strength [179]. Therefore, special DPI designs for small children, which are easy to operate, deliver the dose in lower inhaled volumes and produce appropriate aerosols at lower flow rates could also be suitable for use by elderly patients.

5.5. Target sites for inhaled drugs

The site of action may be different for different types of drugs. For anti-asthma and COPD drugs this depends on the distribution of specific receptors for the drug [180,181], the site of inflammation [182,183] or the presence of smooth muscle. Drugs administered via the pulmonary route for systemic action are mostly best (or exclusively) absorbed in the peripheral part of the lung and they have to be deposited in the most distal airways or even the alveoli [184]. For antibiotics against bacteria that are present in the entire lung, an equal drug concentration in the entire lung is desired. Underdosing part of the lungs with antibiotics may result in obtaining insufficient drug concentrations to reach their minimum inhibitory concentrations for the organisms to be eradicated and this has the risk of bacterial resistance building in these regions. Most studies with currently marketed DPIs show that very roughly one third of the total lung dose is deposited in the upper airways, one third in the central airways and one third in the peripheral lung [43, 185,186]. This, in combination with the exponentially increasing surface area of the airways from the trachea to the alveoli, results in drug concentration differences between the most extreme generations by more than a factor 100 [151,187]. Therefore, one of the greatest challenges for future DPI developments is to increase the peripheral deposition for these applications. A good approach for that could possibly be the already discussed excipient enhanced growth by moisture absorption of aerosol particles to increase their stationary settling velocity [153].

5.6. Patient preference

One aspect of inhaler design that has not been given attention in this review is patient preference for resistance and type of device. Many studies on the aspect of patient preference and acceptance are known, mostly performed in a comparative study between two or more different devices [188–191]. Unfortunately, different studies with the same inhalers produce inverse orders for preference. Like the studies on critical errors made during inhalation performance, this is mainly due to differences in questioning and rating of aspects like convenience of use, signalling to the patient, resistance and appearance. In contrast with critical error scores, preference scores may also be influenced by other factors, such as loyalty to the country in which the inhaler is produced or to the manufacturer of the DPI. Therefore, inhaler preference, although highly relevant to patient's adherence [192,193], is difficult to measure in an objective way and not very useful as a starting point for inhaler design.

6. Conclusions

Currently most studies on the development of new systems for dry powder inhalation focus on the drug formulation. Mechanisms of particle interaction, development of special formulations and particle engineering techniques to control these interactions aim to improve dispersion from the formulation side. Relatively little research effort is put in designing new devices with improved performance on aspects such as powder dispersion or inhaler resistance. Recent device studies that can be found in the literature investigate the operating principle of existing DPIs with CFD simulations, or the effect of design modifications on the performance of these inhalers.

There is an increasing awareness that good adherence to the therapy may be just as important as good inhaler performance. This results in

the development of secondary design features meant to give an adequate feedback to the patient on correct inhaler use. Considering that many future areas of interest for pulmonary drug administration may be found in antibiotic and antiviral therapy and in vaccination programmes for developing countries, the take home message for these applications should be to keep new developments simple and cheap yet effective and reliable. Well integrated formulation-device developments may be the key approach to achieve this goal. The greatest challenges in this respect are to obtain a high robustness and patient and inhalation flow independent performance, which is best realised with inhalers that have a flow rate dependent generation of the FPF, and improved targeting to the site of action or site of absorption.

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