Expert Opinion

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Dry powder inhalers for pulmonary drug delivery

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The pulmonary route is an interesting route for drug administration, both for effective local therapy (asthma, chronic obstructive pulmonary disease or cystic fibrosis) and for the systemic administration of drugs (e.g., peptides and proteins). Well-designed dry powder inhalers are highly efficient systems for pulmonary drug delivery. However, they are also complicated systems, the the performance of which relies on many aspects, including the design of the inhaler (e.g., resistance to air flow and the used de-agglomeration principle to generate the inhalation aerosol), the powder formulation and the air flow generated by the patient. The technical background of these aspects, and how they may be tuned in order to obtain desired performance profiles, is reviewed. In light of the technical background, new developments and possibilities for further improvements are discussed.

Keywords: adhesion, aerosol, asthma, cohesion, COPD, cystic fibrosis, de-agglomeration, devices, dry powder inhaler, flow-rate dependency, lung deposition, particle engineering, peptides, powder formulation, proteins, pulmonary drug administration, size distribution, systemic drug administration, vaccines

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1. Introduction

The respiratory tract is one of the oldest routes used for the administration of drugs. Dry and wet aerosols (including steam), gas and smoke have all been inhaled for medical purposes. Since the second half of the twentieth century, inhaler technology has diverged rapidly along three different pathways. The widespread introduction of electric pumps enabled more continuous air flows through jet nebulisers, which, in combination with the use of baffles, reduced the size distribution in the aerosol substantially, thereby increasing lung deposition. Portable jet nebulisers evolved in a great variety of devices, and ultrasonic nebulisers were introduced in the 1960s. The first metered-dose inhaler (MDI), utilising chorofluorocarbon (CFC) propellants, became available in 1956 (Medihaler®, Riker Pharmaceuticals [now 3M Pharmaceuticals]) and nearly 15 years later (1970), the first dry powder inhaler/DPI (Spinhaler®, Aventis) reached the market [1,2]. Technologies from various disciplines have been applied in these device developments, which were strongly stimulated by the increased occurrence of asthma and chronic obstructive pulmonary disease (COPD). The expectation that the pulmonary route can also be used for systemic administration has challenged the inhalation specialists, particularly in the past decade, to achieve a better controlled and more reproducible peripheral (deep) lung deposition of the drug [3]. Pulmonary drug delivery is of particular interest for drugs with poor-to-no bioavailability when administered via the oral route, such as peptides and smaller proteins which can pass the alveolar membrane [4-8]. In addition, drugs with a poor and irreproducible bioavailability because of first-pass metabolism in the intestinal wall or liver, and drugs for which a rapid onset of action is desired, are considered interesting drug candidates (e.g., morphine) for this route of administration [9,10].

With regard to DPIs, two other important stimuli have specifically increased the interest in this dosage form and driven the technology forward. The first stimulus came from the Montreal protocol in 1987, calling for signatory countries to phase out the production of CFC propellants by 1 January 1996, in order to stop depletion of the ozone layer. Replacement of CFC-driven MDIs by DPIs was one of the strategies to reach this goal. A more recent stimulus came from the advice not to use nebulisers for severe acute respiratory syndrome patients as their use could be one of the transmission causes of the disease [11].

DPIs are complex systems and their performance depends on many aspects. The most important technical aspects to take into account when designing and evaluating DPIs are:

- the design of the inhaler with a special emphasis on the powder de-agglomeration principle applied to generate the aerosol, and the moment at which the dose-containing aerosol will be released
- the dry powder formulation used in the inhaler
- the air flow that is generated by the patient through the inhaler and resultant fluid and particle dynamics thereof in the respiratory tract

These different aspects cannot be considered separately, but should be evaluated in their mutual relationship. The evaluation of DPIs is further complicated by a number of drug- and disease-specific aspects such as the dose of the drug (amount of powder to be aerosolised), the target area in the lung and the ease of use for the patient. All these different aspects should also be taken into account in their individual context when new developments are evaluated.

In this review a brief introduction to the technical aspects of DPIs and their relations to the various applications of DPIs will be given. In light of these technical aspects, new developments and strategies will be reviewed, discussed and evaluated, as it is this technical background in relation to the desired therapeutic effect that determines the value of the innovations in DPI design. Lung physiology, as such will not be further discussed in this review. The well-known lung model of Weibel [12] is used when describing fluid and particle dynamics in the lung and reference is made to a recent review for a description of cell types in the lung and absorption mechanisms [4,5].

2. The target area for drug deposition in the lung

The desired site of deposition should be the starting point for every DPI development. However, the target area may vary with the disease and drug to be administered. When local effects are desired, receptor densities may be indicative for the preferred site of drug deposition. However, when systemic absorption is desired, differences in membrane permeability and clearing mechanisms may be decisive. The most important diseases for which local effects in the airways are desired are asthma and COPD, but, in addition, most inhalation therapies in cystic fibrosis (CF) aim at a local effect in the respiratory tract.

Inflammation in asthma is present throughout the lungs [13], but asthma is associated particularly with lymphocytes and eosinophil cells. The highest numbers of eosinophils were found in the walls of non-respiratory bronchioles (with diameters < 2 mm) [14-16], but an increased infiltration of eosinophil cells, particularly in the larger airways (diameter > 2 mm), has also been reported [17]. This has led to discussions about whether central or peripheral inflammation is more important [18,19]. Both viewpoints are in disagreement with the observation that an increased recruitment of eosinophils with increased asthma severity occurs in all airway size groups [20]. Inhalation steroids are the cornerstone in asthma therapy and their molecular action occurs at intracellular glucocorticoid receptors, which can be found in most cell types [21]. This may explain why distribution of inhaled steroids throughout the airways is often recommended [22], although it has also been assumed that the small airways comprise the optimal site for corticosteroids in asthma treatment [23]. Bronchodilators (β_2-agonists) in asthma and COPD, such as salbutamol and formoterol, interact with β_2-adrenoceptors, which are also located on a variety of cells, including smooth muscle and epithelial cells. The concentration of β-receptors throughout the lungs varies. Places of highest density differ between studies and vary from central lung [24] to small airways [14] and the alveoli [25]. Moreover, starting in the bronchioles, there is a gradual decrease in the ratio of β_2- to β_1-receptor type with decreasing airway diameter [26]. β_2-Agonist deposition in the alveoli is considered to result in reduced bronchodilatation because of the lack of smooth muscle in this region [14]. Muscarine receptors exist almost exclusively in the larger (proximal) airways [24,27].

The pulmonary complications in CF begin in the small peripheral airways and progress to the development of widespread bronchiectasis, which is most marked in the upper lobes [28,29]. This explains why the bronchial lumen [30-33,201] and the smaller bronchioles [28,33] have both been considered as the target area for inhaled antibiotics in CF. More recently, it has been described that the inflammatory process is much more severe in the peripheral than in the central airways [34], which indicates the need for substantial peripheral deposition.

The preferred site of delivery for drugs that are inhaled to be systemically absorbed depends largely on the molecular weight of the drugs, although there is still an ongoing debate over which molecular weight substances can be absorbed from what part of the lung (which is not the subject of this review). A few general statements regarding the knowledge on pulmonary drug absorption in man can be made. Smaller drugs (≤ 4 kDa) may be absorbed from both airways and alveoli. Therefore, the site of deposition will not be very critical as long as the drug reaches the airways. However, macromolecular drugs (up to ~ 30 kDa) can only pass the alveolar

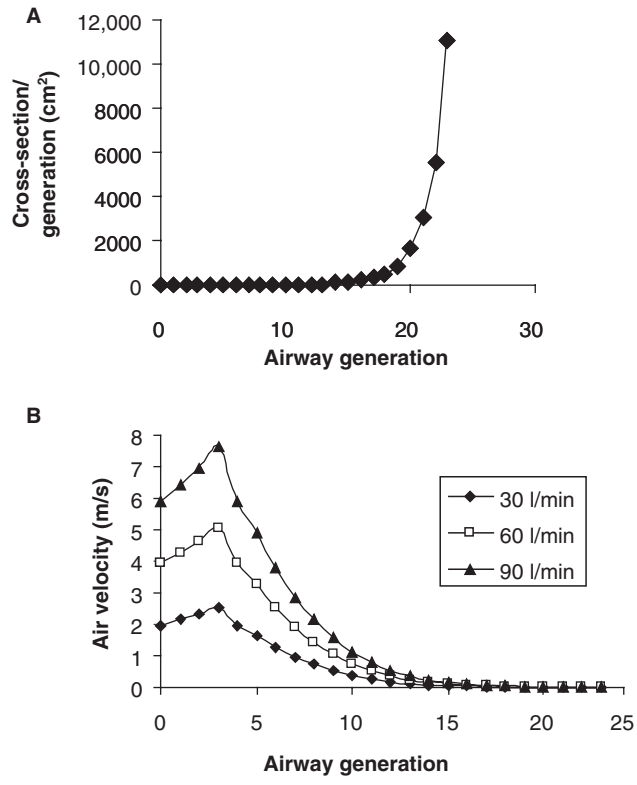

Figure 1. Cross-section for air flow as function of airway generation (A) and air velocity (at three different inspiratory flow rates) as function of airway generation (B).

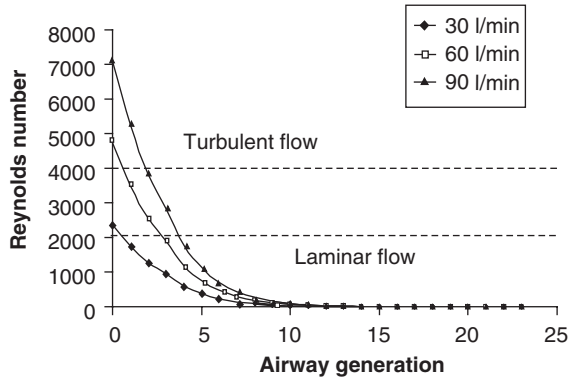

Figure 2. Reynolds number as function of airway number at three different inspiratory flow rates.

membrane, which is explained by the large surface area (≤ 125 m^2) and high permeability of this part of the lung [4,5,35]. Absorption of larger molecules has been reported (mostly in animals), but, in general, highly variable bioavailabilities of ≤ 5% have been found. For example, no significant systemic absorption of inhaled dornase alpha (molecular weight of 32 kDa) has been described. For the pulmonary delivery of vaccines, the target site has not yet been investigated. LiCalsi *et al.* [36] described CD46 receptors for the measles vaccine as present in nearly all cells in the pulmonary tract. However, it is unclear what the target site for other vaccines will be.

3. Fluid dynamics and particle dynamics in the respiratory tract

Once the different target areas for the inhalation drugs are designated, the question of how to reach these targets arises. For inhalation drugs, the particle dynamics as they are determined by the particles' physical properties and the fluid dynamics in the respiratory tract, determine the site of deposition.

One of the most frequently cited lung models to explain the principles of aerosol delivery to the respiratory tract is that of Weibel [12,37,38]. The model distinguishes 23 subsequent bifurcations of the airways, starting at the trachea (generation 0) with a diameter of 18 mm (for adults) that decreases to 0.41 mm in the alveolar sac (generation 23). As a result of bifurcation of each airway, the number of airways increases from 1 (trachea) to 2^{23} (8.388.608 alveolar sacs). As a consequence the cumulative cross-section for air flow increases exponentially with each generation (Figure 1A), after an initial small decrease from trachea to lobar bronchus. This occurs despite a decreasing diameter of the individual airways in each generation (by a factor 44 over the total airways). From the cumulative cross-section, the air velocity in each airway generation can be estimated as function of the inspiratory flow rate (Figure 1B). Different divisions between airway regions have been made, for example, upper and central (> 2 mm) versus peripheral (< 2 mm) airways [39,40]; conducting (generation 0 – 11), transitional (12 – 16) and respiratory (17 – 23) airways [41]; and tracheobronchial region (generations 0 – 16) versus alveolar (pulmonary) region (generations 17 – 23) [37]. Owing to their relatively small total cross-sectional area, the upper and central airways (generation 0 – 4) account for ~ 90% of total airway resistance [39].

The relevance of the Reynolds number to fluid mechanics and particle deposition in the human lungs has been described previously [42]. As a result of the exponentially decreasing air velocity from the lobar bronchus towards the alveoli, and the decreasing airway diameter in the same direction, the Reynolds number decreases rapidly from ≥ 4000 (at flow rates ≥ 60 l/min) in the trachea (turbulent flow) to values far < 2000 (laminar flow), starting at a low generation number (Figure 2). However, local turbulence at the bifurcations and at constrictions also occur in the smaller airways. Furthermore, local regions of back flow are present at the bifurcations during inhalation, which may contribute to the aerosol deposition [42].

Particle penetration and deposition in the lung are determined by the aerodynamic behaviour of the particles in the inhaled air stream, which constantly changes its velocity and

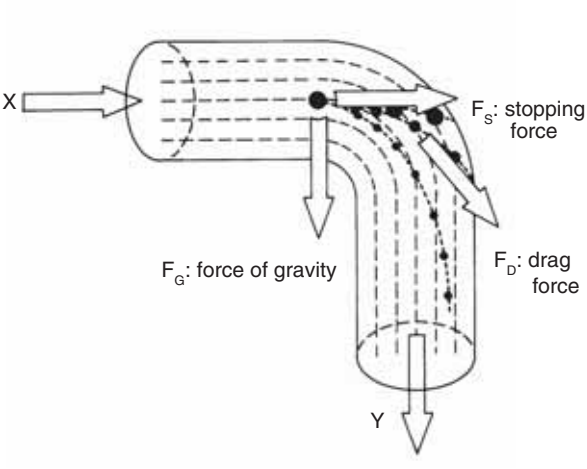

Figure 3. Forces acting on an airborne particle in a bent airway duct.

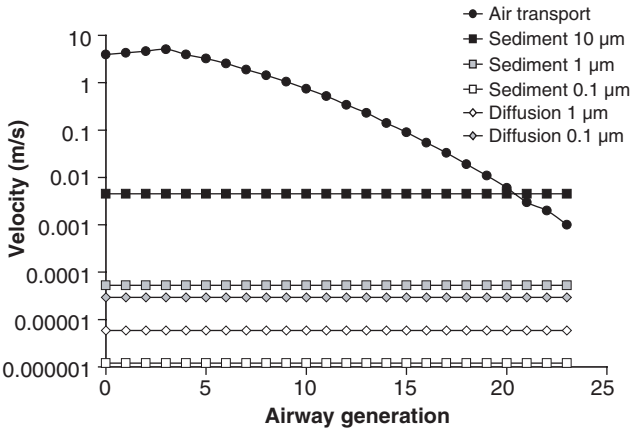

Figure 4. Particle velocity in different airway generations of the human respiratory tract (Weibel model) as the result of air transport, sedimentation and diffusion.

direction in the respiratory tract. Penetration of the particles into the lung is the first step. Penetration into the peripheral parts of the lung is only possible when the particle is able to pass the different bends in the airways, starting with the throat, followed by the different bifurcations.

Three different forces act on airborne particles passing a bend in an airway duct: the force of gravity (F_G); the drag or resistance force of the air (F_D); and a stopping or inertial force (F_S), as shown in Figure 3. The force of gravity is constantly acting on all particles in a field of gravity. The magnitude of the force ($F_G = m{\cdot}g$) is proportional to the mass (m), and thus to the third power of the particle diameter (d), but independent of the particle velocity (g is the acceleration of gravity). The F_D acting on aerosol particles (when frictional forces are much larger than inertial forces) is proportional to the particle diameter, to the first power and particle velocity relative to the velocity of the air. Different expressions can be given to the F_S, all of which relate to particle momentum (product of particle mass and particle velocity). Frequently, the stopping distance (S), or inertial range, is also used. This is the distance necessary to reduce the initial particle velocity (U_0) to zero by the action of the F_D.

A large stopping distance (high particle mass, high velocity or both) relative to the drag force tends to bring the particle in contact with the airway wall by inertial deposition. A relatively high drag force may conduct the particle into the next airway generation. However, it is difficult to predict whether a particle with known velocity and mass will really impact on the airway wall in a certain bifurcation simply because the streamlines of the air cannot be assessed properly and the particle may have different starting positions in the airway duct. In addition, there exists uncertainty about the precise shape and cross-section of the airway duct, the angle of bifurcation, the presence, size and shape of local flow constrictions, the effect of back flows, and so on. In general, particles > 5 µm have a high collision probability in the throat at a moderate flow rate of 60 l/min, whereas particles < 5 µm may be transported into the trachea.

Once a particle has passed the throat and upper airways, it should be deposited on the wall of the airways or alveoli. The action of the force of gravity results in a stationary particle settling velocity (U_{TS}), which could lead to contact with the wall of an airway duct by sedimentation. As air velocity decreases with increasing airway number, the ratio of settling velocity to air transport velocity increases and sedimentation becomes more important. In the deep lung, into which no large particles can enter and where the air practically stands still, diffusion by Brownian motion gains importance, particularly for particles in the submicron range. The magnitude of the particle velocity by air transport, sedimentation and diffusion in different airway generations is given in Figure 4 for spherical particles (three different diameters) with a density of 1.5 g/cm^3, which are inhaled at 60 l/min. The Brownian motion is represented by a linear velocity, which is a simplification as this motion randomly changes in all directions.

Figure 4 clearly shows that only for relatively large particles (10 µm), the terminal settling (sedimentation) velocity can exceed the air transport velocity. This occurs in the respiratory zone, however, where such large particles do not exist because they have already been removed from the air stream by inertial impaction in the upper airways. On the basis of the Weibel model, it can be calculated that it takes only 1.3 s for a particle to travel from generation 15 to 23 at a constant flow rate of 60 l/min. For these airway generations, the diameter decreases from 0.65 (generation 15) to 0.41 mm (generation 23), meaning that the mean distance to travel for a particle from the central axis of the airway duct to its wall is only 0.27 mm. At the particle velocities for sedimentation and diffusion given in Figure 4, it takes a 1 µm particle 5.0 s and 44.9 s, by sedimentation and diffusion, respectively, to complete this distance, whereas a 0.1 µm particle requires 9.0 s by

diffusion (assuming linear movement). All times are longer than the 2.6 s (2 × 1.3) residence time in generations 15 and 23, suggesting that only particles that are already near the wall of an airway duct do have sufficient time to be captured by sedimentation or diffusion.

The above calculations only indicate orders of magnitude because flow rate (air transport velocity) varies during inhalation, whereas local turbulence may effectively remove small particles from a position near the wall of an airway duct. Neither does diffusion result in a linear particle movement, and as a result of all that, sedimentation and diffusion have a rather poor collection efficiency. The calculations suggest that the deposition efficiency by diffusion and sedimentation can be increased by reducing the air transport velocity (inspiratory flow rate) or by a breath hold between inhalation and expiration. Both increase the residence time in the alveolar region. An increase in the air transport velocity also changes the ratio of stopping force to drag force or to force of gravity. This shifts the cut-off of aerosol particles of all sizes to lower airway numbers (airways with larger diameter). The many attempts to model the airway deposition of aerosol particles are based on similar considerations, as given above [40,43-46]. Such computations yield valuable information about the preferable aerodynamic diameter of the aerosol. However, absolute predictions on the magnitude and site of the deposition, based on these models, are still hard to make.

4. The desired aerodynamic size distribution of the drug particles in the aerosol

The preferred size distribution of the drug-containing aerosol is strongly related to the desired site of deposition and the inhalation manoeuvre, as can be concluded from the previous paragraphs. However, the desired site of deposition is just one of the parameters that determines the preferred particle size of an inhalation aerosol. The different parameters that should be balanced when the desired particle size distribution is established are:

- the target area in the lung, taking account of the patient's lung morphology and anatomy
- the presumed inhalation manoeuvre
- the occurrence and severity of side effects
- the efficiency of powder de-agglomeration during inhalation

The preferred range for the aerodynamic size distribution of an inhalation drug can be estimated from mathematical models predicting lung deposition, from *in vivo* deposition (scintigraphic) studies, or from clinical effect studies combined with pharmacokinetic methods. The numerical deposition probability values obtained from computations are arguable because of the many assumptions and simplifications, but the influence of relevant parameters and the effects of changes therein can be studied. For example, it has been calculated that increasing the inspiratory flow rate from 12 to 60 l/min is quite dramatic for 5 µm particles [47]. At the lower flow rate, the deposition probability for sedimentation in the respiratory region with a peak in generation 18 is nearly 5 times as high as the probability for inertial impaction in the conducting zone with a minor peak in generation 4. At 40 l/min, both probability peaks are of the same magnitude, and at 60 l/min the deposition by inertial impaction around airway 4 is twice as high as that by sedimentation in airway 18. As may be expected from the relevance of the residence time in the airway to the deposition probability expressions for sedimentation and diffusion, there is a great effect of breath hold on the deposition in the respiratory zone. Increasing the breath hold period from 0 to 10 s increases the fractional deposition (probability) of 1 µm particles in generation 18 by a factor of 8. Therefore, it has been concluded that lung deposition is more sensitive to particle residence time than to inspiratory flow rate [44].

Side effects should also be considered when determining the particle size distribution of the aerosol. For corticosteroids, hoarseness and oropharyngeal candidiasis are known to be the result of upper throat deposition. This may occur when large particles are used [48]. On the other hand, increased alveolar deposition of much smaller particles may cause an increase in systemic adverse drug reactions. This was confirmed by Weda *et al.* [49,50], who found that, in the case of salbutamol, an increase in fine particle fraction (FPF) (at the same inspiratory flow manoeuvre) does not improve lung function, but does increase the adverse side effects (decrease of serum potassium level).

The final parameter to be considered is the efficiency of the powder de-agglomeration principle used in the inhaler. Drugs used in dry powder formulations frequently have mass median diameters of 1 – 2 µm, based on the observation that not all drug particles are released as primary entities from the DPI. Moreover, drug particle size in dry powder formulations affects the efficacy with which particles can be detached from carrier crystals during inhalation. By slightly increasing the primary drug particle size, even within this narrow range, the detached mass fraction of the drug can be increased substantially, particularly for inhalers with poor de-agglomeration efficiency [51].

To summarise the conclusions from the many studies performed on the particle size of inhalation aerosols, it can be stated that the optimal aerodynamic diameter for DPIs that are operated at inspiratory peak flow rates of 30 – 150 l/min, lies somewhere in the range of 1 – 5 µm. Distribution throughout the lungs, as has been recommended for inhaled corticosteroids, may benefit from a somewhat wider distribution.

However, if the distribution is too wide, and the target area is primarily in the central and small airways (as for β_2-agonists), adverse systemic side effects may be obtained from particles that are deposited in the alveolar region and in the throat, from which they can enter the systemic circulation. Improved targeting at a particular deposition site and a reduction in adverse

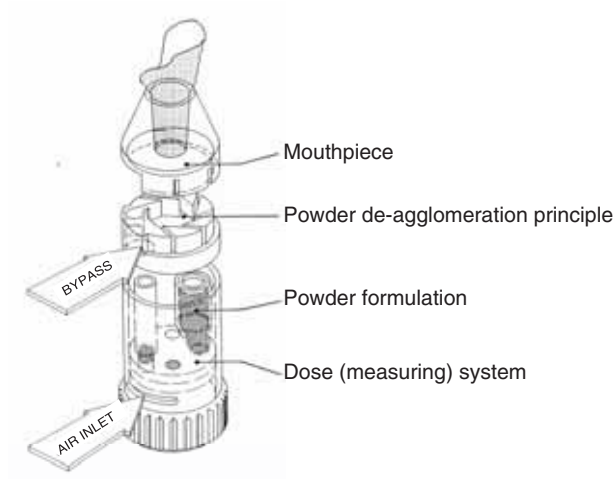

Figure 5. Primary functional design elements of a dry powder inhaler.

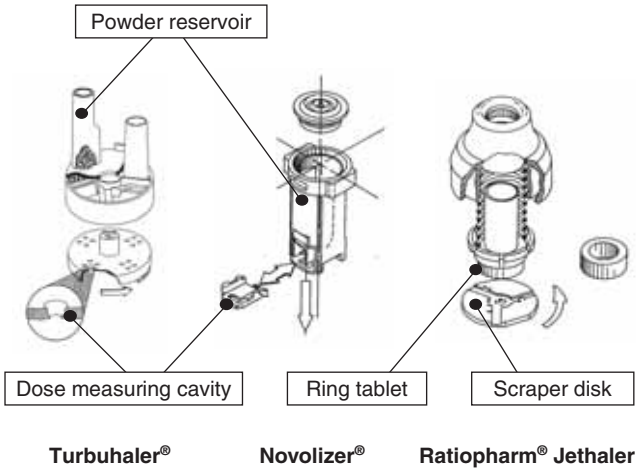

Figure 6. Different multi-dose reservoir and metering principles applied in dry powder inhalers.

side effects, are two arguments to use narrow size distributions or even monodisperse particles instead of polydisperse aerosols [52-54]. However, as may be clear from the deposition calculations, this only makes sense when the inspiratory manoeuvre can be controlled within quite narrow limits for the flow rate and the inhaled volume [53]. Even then, the preferable particle size may differ considerable for different patient groups and age categories. Without breath control, or in the case of extreme pulmonary morphology and/or anatomy (as with small children), deposition of monodisperse aerosols may substantially be outside the target area. Therefore, a somewhat wider size distribution is likely to increase the therapeutic efficacy in all patients.

5. Basic design and functional elements of a dry powder inhaler

From a design viewpoint, the primary inhaler parts in Figure 5 are the same for all types of devices on the market and many in development. They consist of a powder formulation, a dose mechanism containing (or measuring) a single drug dose, a powder de-agglomeration principle dispersing the powder into the inhaled air stream, and the inhaler's mouthpiece. Many types of secondary inhaler parts are applied to fulfil a large variety of functions. They are mostly added for safety, ease of handling, signalling to the patient and moisture protection of the drug formulation.

The dose mechanisms may consist of capsules or blisters containing pre-weight unit doses of inhalation powder. Many different capsule/blister piercing or opening mechanisms have been developed to gain access to the powder during inhalation. In most of the examples, discharge of the capsule/blister and powder dispersion into the inspiratory air stream occur simultaneously. Only some recently developed capsule and blister inhalers apply additional powder de-agglomeration means to increase the FPF; for example, Eclipse™ (Aventis) and Spiros® (Dura Pharmaceuticals, now part of Elan Pharmaceuticals) [55].

Alternatively, multi-dose reservoir systems may be used. Examples of these systems are shown in Figure 6. Individual doses can be isolated by volumetric measurement of powder into well-defined orifices in a disk (e.g., Turbuhaler®, AstraZeneca) or a cavity in a slide (e.g., Novolizer®, Viatris). The measuring compartments are filled from the powder bulk reservoirs mainly through the action of gravity. This requires the inhaler be kept in an upright position. In some special cases, forced metering is applied, for example by conducting compressed air through the powder bed in the bulk reservoir (e.g., Airmax™, Ivax Corporation) [56]. In general, multi-dose systems require certain properties of the powder formulation regarding flowability and homogeneity.

An exception to this general concept is the Ratiopharm® Jethaler (Ratiopharm) (Figure 6), which has a ring compact of the drug–excipient mixture, from which small amounts are grated with a scraper disk during inhalation [57]. The concept is the same as that of the Ultrahaler® (Aventis) [58], and appears to have a poor dose reproducibility [59].

The de-agglomeration principle is one of the most important parts of the inhaler, as to a large extent it determines the de-agglomeration efficiency and thereby the lung deposition of the drug. The de-agglomeration principle should break-up spherical pellets into primary drug entities, or detach drug particles from the carrier crystals in adhesive mixtures or nucleus agglomerates during inhalation. Its objective is to generate an aerosol that contains drug particles in the aerodynamic size range of 1 – 5 µm that can enter the target area for deposition.

During inhalation, the adhesive forces that exist between the drug and carrier particles in adhesive mixtures, or the cohesive forces between drug particles in spherical pellets,

Table 1. Different principles for powder de-agglomeration that do not operate in conjunction with the dose system as used in dry powder inhalers.

Dispersion principle	Example(s)
Aerosol passage through narrow passages (e.g., venturi tubes)	Easyhaler® (Orion Pharma) [208]
Aerosol conducted against impact bodies (baffles, plates, internal inhaler surfaces)	Clickhaler® (Innovata Biomed) [66] Skyehaler™ (SkyePharma)*
Aerosol conducted through specifically shaped (discharge) channels or channels with (helical) inserts	Turbuhaler® (AstraZeneca) [65] Twisthaler® (Schering-Plough Corporation) [67] Directhaler™ (Direct-Haler AS)*
Circulation, whirl or cyclone chambers (with or without control of residence time)	Pulvinal® (Chiesi) [68] Airmax™ (Ivax Corporation) [56] Novolizer® (Viatris) [209] Taifun® (Focus Inhalation) [69]
Pressurised air or vacuum chambers	Inhance™ (Nektar Therapeutics) [210] Aspirair™ (Vectura)*
Battery-powered (impellor) systems	Spiros® (Dura Pharmaceuticals, now part of Elan Pharmaceuticals) [55]
Miscellaneous	Ratiopharm® Jethaler (Ratiopharm) [70] Ultrahaler™ (Aventis) [58] Eclipse™ (Aventis)*

*No reference has been found in which a proper description of the working principle is given.

have to be overcome in order to aerosolise primary drug particles. Different de-agglomeration principles use different forces to generate the aerosol. Clearly, the more efficient the force is, the higher the FPF will be.

Friction forces may result in high internal shear forces for spherical pellets (and, therefore, be effective for this type of formulation). However, friction forces cannot get hold of particles in carrier surface discontinuities in adhesive mixtures, as is also the case for drag and lift forces in turbulent airflows. Such forces are not even effective in removing drug particles attached to smooth crystal planes, as micronised particles are mainly present in the stationary boundary layer. Therefore, these forces are much lower than the adhesive forces in the mixture, and will result in poor FPFs [37,60]. Most effective are inertial (e.g., vibratory, centrifugal or impaction) forces, because their magnitude is proportional to the third power of the drug particle diameter (drag and lift forces only to the first or second power of the diameter). The efficiency of inertial forces is not necessarily negatively influenced by high carrier particle rugosities. Moreover, different technical means can be applied to sustain the action of such forces, such as whirl, circulation or cyclone chambers. Generated inertial forces (such as drag forces) may act in all directions. Obviously, detachment occurs only when (a component of) the inertial force is of sufficient magnitude, in an opposite direction to the adhesive force.

Powder de-agglomeration systems that are applied in DPIs vary considerably in their principle of operation. Classification is often into breath-operated systems, utilising the kinetic energy of the inspiratory air flow, and principles using auxiliary energy, such as electromechanical means and pressurised air. It is inherent in breath-operated de-agglomeration principles that the efficacy of drug particle detachment increases with increasing inspiratory flow rate through the inhaler. The effect is more pronounced when the kinetic energy of the air flow is utilised more efficiently. In contrast, battery- and pressurised air-operated DPIs perform virtually independent of the inhalation manoeuvre in terms of de-agglomeration efficiency, but they are much more complex in design and, therefore, expensive and prone to failure (e.g., in case of flat batteries). This makes them inappropriate as disposable devices.

The breath-operated systems can be divided into different categories. For many DPI designs using, for example, hard gelatine capsules or blisters as the dose system, powder de-agglomeration is connected with emptying of the dose system [61,62,202,203]. All, or part, of the inspiratory flow rate is directed through the dose compartment, in order to entrain the powder while dispersing the particles by turbulent shear or by collision forces. Neither of these systems produces a high fine particle dose, particularly because the time during which the powder is subjected to the disruptive forces is quite short. In other capsule inhalers, the capsules are set to a particular motion to discharge and disperse the powder [63,204,205], or a special flow pattern inside the capsule is created [64].

Categories of de-agglomeration principles that do not operate in conjunction with the dose system, with their most well known or characteristic representative(s), are summarised in Table 1. The category of miscellaneous principles includes ring compacts of the drug and excipient, from which small amounts are grated during inhalation (e.g., the Jethaler and Ultrahaler), a powder capsule with propellants [65], a battery driven piston tapping drug from a tape [206], a woven cloth from which drug is removed during inhalation with pressurised air [207], a circulation chamber with grinding balls

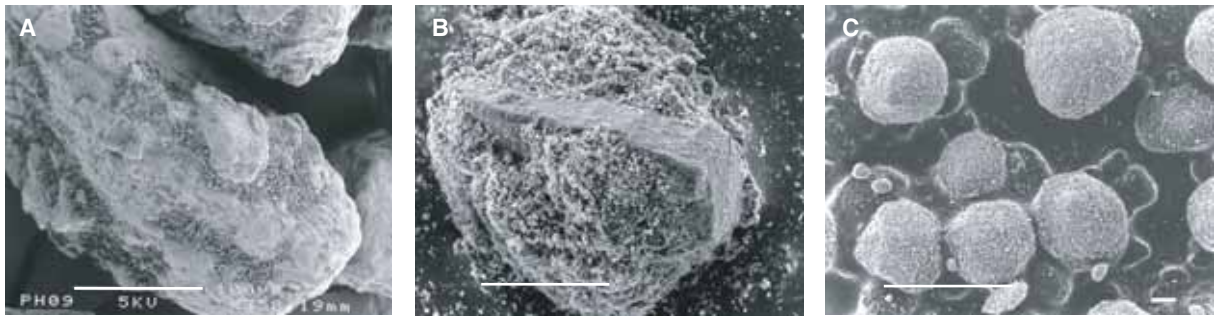

Figure 7. Scanning electron micrographs of an adhesive mixture (A), a nucleus agglomerate (B) and a spherical pellet type of formulation (C). Scale bar in A and B is 100 µm, in C 500 µm.

(Eclipse) and many other systems. Only some devices from the categories 'miscellaneous' and 'circulation, whirl and cyclone' chambers have the ability to sustain the action of the separation forces over a certain time period. They all make use of inertial forces and are consequently the most effective types of de-agglomeration principles. Recent developments have led to the introduction of devices with battery-powered (e.g., Spiros) or pressurised air facilitated de-agglomeration principles (e.g., Inhance™ DPI [Nektar Therapeutics] and Aspirair™ [Vectura]). De-agglomeration by these inhalers is independent of the patient's inhalation effort. In the Spiros system the powder is dispersed by a mechanically-driven impeller to form the aerosol. In the Inhance, an air flow (generated from manually compressed air) through the powder-containing blister is used to disperse the powder into a holding chamber similar to the aerosol from an MDI in a spacer chamber. The inhalation of the aerosol can occur subsequently from this chamber.

The mouthpiece of the inhaler may not seem to be a primary design element, but it can be used to add certain functionality's to the inhaler. The mouthpiece may have bypass channels to control the resistance to air flow, and the bypass flows can be arranged such that they constitute a co-axial sheath of clean air around the aerosol cloud. This reduces deposition of drug in the mouth from back flows. Mouthpiece design is also relevant to the shape of the released aerosol cloud. A strongly diverging cloud increases mouth deposition, although it can be favourable for adhesive mixtures when deposition of the carrier crystals is directed to the mouth instead of the throat (to reduce local side effects).

6. The powder formulation

The powder formulation is another core element in the DPI. In general, the micronised drug is formulated into a powder mixture to improve processing and/or dose measuring. Due to their size distribution (~ 1 – 5 µm), inhalation drugs are extremely co- and adhesive. They tend to stick together (agglomerate) and to (inhaler) surfaces with which they make contact primarily by Van der Waals forces. Doses are given in a wide range, varying between only a few µgs (e.g., formoterol fumarate) to several 10s or 100s of mgs (e.g., tobramycin), and, particularly the lower doses, cannot be measured in a reproducible way without using dilutent excipients. The excipient can either be micronised to (approximately) the same size distribution as the drug, or consist of larger crystals (or agglomerates) that act as a carrier for the drug. Three different formulation types exist: spherical pellets, adhesive mixtures and nucleus agglomerates. In Figure 7, scanning electron micrographs of these different formulation types are shown.

Spherical pellets consist of pure micronised drug or mixtures of micronised drug and miconised excipient [211]. Spherical pellets are produced by controlled agglomeration (without adding binder excipient) and subsequent spheronisation of the agglomerates to spheres in an approximate size range of 200 –2000 µm. The porosity of such pellets is quite high (generally 60 – 80%) and their mechanical stability is low. As a result, they are distorted on impact [71], which is intentional and advantageous during inhalation, but also occurs when, for example, the inhaler is dropped. This may influence the dose-measuring accuracy and the dispersibility of the powder.

In adhesive mixtures (carrier type formulations) drug particles are distributed (homogeneously) over the total surface area of generally much larger carrier crystals when drug and carrier are mixed together, and attached to this surface primarily by Van der Waals forces. Carrier excipients in adhesive mixtures generally consist of special size fractions of α-lactose monohydrate. Occasionally, other lactose modifications (β-monohydrate or spray dried) have been proposed [72,212]. When the drug is distributed in multi-particulate layers around carrier particles, nucleus agglomerates are formed [213]. Pellet size and carrier size distribution have been selected to obtain good flow properties, which is a requisite for reproducible dose measuring.

The interaction between the micronised drug and carrier particles has received a lot of attention in the literature. The number of studies on this subject is high and could fill a review on their own. In this review, only a few aspects relevant to the performance of the powder formulations in DPIs are discussed. The adhesion forces between carrier particles and drug particles consist mainly of Van der Waals forces

(molecular forces), Coulombic forces (tribocharge) and capillary forces (moisture). Van der Waals forces are the most dominant forces determining adhesion or cohesion in inhalation powders. Compared with Coulombic and capillary forces, Van der Waals forces are generally lower, which is favourable from the viewpoint of dispersion during inhalation. Moreover, they can be controlled to a certain extent, and are more constant over longer periods.

In the past 15 years, investigations into adhesive mixtures (formerly named ordered or interactive mixtures) have focussed on their application in DPIs. For inhalation, an optimum is desired between homogeneity, stability and drug particle detachment during inhalation, meaning that the adhesive forces have to be strong enough for processing (and storage) of the powder, but weak enough to be overcome by the removal forces generated during the inhalation manoeuvre. Variables that have been investigated are the effects of electrostatic charge [73], changing the moisture content [74,75] and modifying the carrier surface rugosity [76]. Optimisation of adhesive mixtures for inhalation has also frequently been found in selecting and defining special carrier size fractions [214], but the choice in this respect is limited because of the requirements for powder flowability, which are the reason for adhesive mixture preparation.

Until quite recently, nearly all investigations into adhesive mixtures for inhalation have focussed on exploring, characterising and controlling the carrier surface properties, and measuring the adhesive forces between drug and carrier, using methods such as centrifugal techniques [77,78] and atomic force microscopy [75]. Mixing theories were developed based on the assumption that competition exists during mixing between cohesion (drug–drug interaction) and adhesion (drug–carrier interaction), and that the equilibrium between them at any moment during the mixing process is uncertain. It has also been postulated that the equilibrium can be driven in a certain direction by modifying the carrier surface properties [79]. A lot of attention is given to so-called 'active sites' on the carrier surface, onto which drug particles are attached with higher adhesive forces than to other sites. The term 'active site' has been used for a multitude of phenomena, including: surface irregularities (pores, clefts, cavities, lattice discontinuities); surface rugosity (coalesced or granular structures); adhering fines; amorphous spots; water of adsorption and impurities (i.e., water soluble protein residues, salts, decomposition products, riboflavin, urea). Investigations were undertaken to modify and control (e.g., by corrosion processes and recrystallisation and/or granulation) or to characterise the surface rugosity of carrier crystals (e.g., by permeametry and nitrogen adsorption). Rugosity has been classified into microscale (irregularities on smooth crystal surfaces) and macroscale (granular structures), and in most studies it has been concluded that either a microrugosity is favourable [76], or rugosity should not exceed a certain value [215]. However, in most of these studies, the effects of carrier payload, mixing conditions and type and magnitude of the removal forces during inhalation were ignored or not regarded relevant to the investigated drug-to-carrier interaction in relation to the carrier rugosity.

De Boer *et al.* [80] and Dickhoff *et al.* [81] showed that carrier bulk properties, under certain circumstances, may be more relevant than carrier surface properties to the drug adhesion, the carrier particles and the drug distribution. They concluded that the effects of carrier bulk properties and mixing conditions have been underestimated. So-called (inertial and frictional) press-on forces during mixing are capable of increasing the adhesive forces between drug and carrier, thereby affecting the FPF that is generated during inhalation [82,83]. Such press-on forces occur during the mixing process when a drug particle is, for example, squeezed between colliding carrier particles. As a result of the impact force, the adhesion force between the drug and carrier particle may increase due to decreased contact distance between drug and carrier, or increased contact surface. Factors that influence the magnitude and efficacy of press-on forces include the size and surface rugosity of the carrier particles, the type of mixing process, batch size and mixing time and the drug load in the formulation.

A multitude of techniques have been applied to improve the performance of powder formulations for inhalation. The most important developments are:

- The application of force control agents. Through the addition of micronised ternary excipients, such as isoleucine or magnesium stearate, the adhesive forces between the carrier and drug are decreased, mainly because the micronised excipient and drug compete for the active sites [84-86,216]. On the other hand, the use of magnesium stearate for inhalation raises questions related to safety.
- Supercritical fluid technology is applied to improve polymorphic purity and surface properties of the drug substance, which can reduce the adhesive forces between drug and carrier [87-89].
- Large porous particles are particles with a high porositiy. Such particles have a low density, which changes the ratio between their aerodynamic and geometric diameter. They have been produced for several reasons; the most important are the improved de-agglomeration of the powder and the improved aerodynamic behaviour in the airways. However, they are also of interest because of reduced phagocytosis of the deposited particles in the alveoli. Removal by the macrophages does not occur, which prolongs their stay in the alveolar region, opening possibilities to produce depot slow-release preparations for inhalation. [90,91]. In another approach, smaller porous particles (3 – 5 µm) have been used to improve de-agglomeration and lung deposition [92].
- Next to supercritical fluid technology, other particle processing technologies are applied to produce designer particles (including large porous particles) such as spray drying, spray freeze drying and (co-)spray drying of drugs and excipients. Such drying techniques can be used to incorporate unstable drugs, such as proteins, in to stabilising matrices. For example, various sugar or polyol

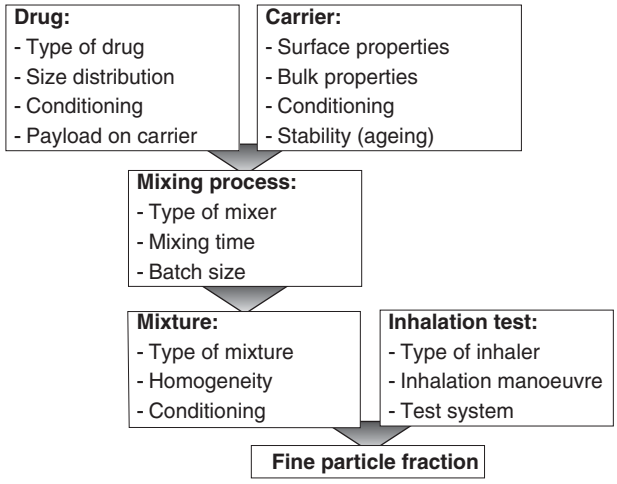

Figure 8. Scheme of variables that affect the adhesion and de-agglomeration forces and thereby the aerosol generation in a dry powder inhaler. Adapted from [83].

glasses have been applied to stabilise proteins in the dry state [93-96]. On the other hand, it was shown that for a decapeptide (e.g., cetrorelix) less advanced formulations could be used to design a formulation that still produced high FPFs, provided an effective de-agglomeration principle was used and sufficient moisture protection was given [97,98].

Up to now, the list of excipients that are used in marketed DPIs is short. It actually consists only of lactose which is the carrier used in almost all DPIs, and glucose as (micronised) diluent in spherical pellets. However, to produce large porous particles, special excipients, such as dipalmitoyl phosphatidylcholine, are used [99], whereas for the stabilisation of proteins sugars or polyols, such as inulin, mannitol or trehalose are applied [94,95,100]. Sugars and polyols, such as mannitol or maltitol, have been investigated as alternative drug carriers [101]. Recent research also focuses on the development of slow-release formulations for pulmonary administration. Various approaches have been investigated in this respect, such as coating of the particles with poly(lactic acid) or the use of particles that consist of polymer matrices such as poly(DL-lactide-co-glycolide) or hydroxypropyl cellulose (HPC). HPC is interesting as it not only decreases the rate of drug release, but also retards mucociliary clearance, thereby prolonging the residence time in the airways [102-105].

7. Balancing between adhesive and removal forces

The FPF generated by a DPI following inhalation is always the result of the magnitude of the generated de-agglomeration forces relative to the magnitude of the adhesive forces in the formulation. Balancing between the adhesive forces in the mixture and the separation forces generated by the de-agglomeration principle during inhalation has the objective to obtain maximal powder homogeneity and stability on the one hand, and a high and reproducible FPF during inhalation on the other. For achievement of a good balance, adequate understanding of the drug–carrier interaction forces in the adhesive mixture is desired. Unfortunately, not all properties of the carrier and drug can be fully controlled. Small variations in size distribution, shape and impurities are inevitable. Moreover, conditions during storage and mixing of the starting materials cannot always be controlled to the extreme, and they will contribute to the variation in adhesive forces. Finally, the inhalation manoeuvre may vary, whereas different types of inhalers, generating different types of de-agglomeration forces, are used. In Figure 8, a scheme containing the most relevant variables to be taken into account when inhaler performance is evaluated is presented.

In an attempt to improve the understanding of the experimental results from studies where different variables were varied, a so-called force distribution concept was introduced [106]. This concept improves the understanding of the complex effects of mixing and inhalation parameters on the size distributions of adhesion and de-agglomeration forces, respectively, as well as their relevance to the aerosol generation. The concept includes the fact that the amount of drug not detached from the carrier (the carrier particles being retained in a classifier type of inhaler for analysis) during inhalation is used to show the occurrence (and magnitude) of changes in the size distributions of these forces, by varying certain powder formulation or inhalation parameters.

8. The performance of currently marketed dry powder inhalers

The inhaler design and inspiratory flow manoeuvre are the major determinants for DPI performance. A scheme of variables (and their interactions) that may affect the inhaler performance is presented (Figure 9). The flow manoeuvre is largely determined by the air flow resistance of the DPI (the inhalation effort generated by the patient is another determinant, but this parameter cannot be controlled by the DPI design and will, therefore, not be further discussed). The air flow resistances found for different DPIs vary significantly, as is shown in Table 2. In general, the resistance to air flow of DPIs is quite high compared with nebulisers and MDIs. This is a consequence of the design, which has elements of flow constriction to increase the kinetic energy of the air flow through the inhaler. Local pressure drops or high air velocities are necessary for adequate dose entrainment and powder de-agglomeration.

A high air flow resistance is favourable from a lung deposition point of view because it reduces the velocity of the aerosol particles in the respiratory tract, thereby increasing deep lung penetration. It has been postulated that a high air flow resistance requires a high work of inspiration (inspiratory effort) to operate the DPI correctly [61], but calculation of the amount of work reveals that this supposition in not true [107]. Nearly twice as much work is done when a dose is

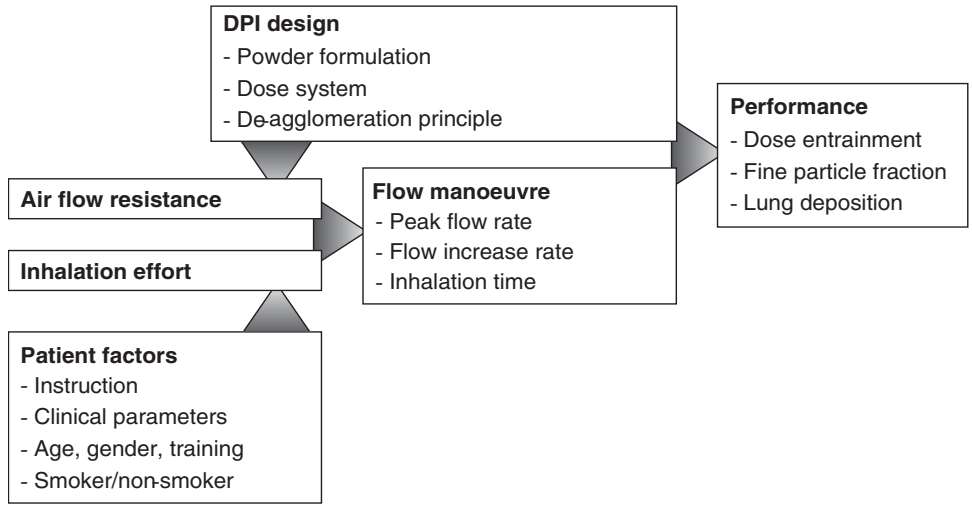

Figure 9. Scheme of the major variables and interactions in DPI performance.
DPI: Dry powder inhaler.

Table 2. Air flow resistances of some marketed dry powder inhalers ($kPa^{0.5}$·min/l_N).

Inhaler	Resistance
Rotahaler® (GlaxoSmithKline)	0.015
Spinhaler® (Aventis)	0.016
ISF inhaler (e.g., Cyclohaler®; Pharmachemie)*	0.019
Novolizer® (Viatris)	0.028‡
Diskhaler® (GlaxoSmithKline) (8-dose becotide)	0.032
Diskus® (GlaxoSmithKline)	0.034
Ratiopharm® Jethaler (Ratiopharm)	0.036
Handihaler® (Boehringer Ingelheim Pharmaceuticals)	0.042
Turbuhaler® (AstraZeneca)	0.043
Inhalator® (Boehringer Ingelheim Pharmaceuticals)	0.051 – 0.062§

*Also: Aerolizer™ (Novartis Pharmaceuticals Corporation) and Ciba-Geigy's Foradil® (Novartis Pharmaceuticals Corporation) inhaler. ‡Average value after valve switching. §Range, depending on capsule position.

inhaled (at maximal effort) from a low resistance DPI. A similar trend, although not so extreme, was observed at comfortable inhalation. The reason is the exponential increase in flow rate with decreasing air flow resistance, which has much greater effect in the computations for the amount of work than the decrease in pressure drop across the inhaler or the total inhalation time.

The preferences of patients and healthy volunteers for resistance have been studied, with different outcomes. Andersen *et al.* [108] reported highest preference for a low resistance (0.015 $kPa^{0.5}$min/l) by asthmatics and COPD patients, and Clark and Hollingworth [109] noticed that resistances > 0.032 $kPa^{0.5}$min/l are uncomfortable for healthy volunteers. In contrast, 82% of the healthy volunteers in another study gave preference to a moderate (or high) resistance of 0.021 – 0.047 $kPa^{0.5}$min/l [107]. The conflicting aspects of patient preference (moderate to low resistance) and lung penetration (high resistance) find an optimal solution in inhalers with an intermediate resistance (~ 0.030 $kPa^{0.5}$min/l).

Different methods are available for evaluation of DPI performance. *In vitro* dose collection and deposition methods (e.g., inertial cascade impactors) have been widely used to characterise DPIs with respect to the consistency of the delivered dose, the fine particle dose and the FPF (which is an indication for the de-agglomeration efficiency). More recently, the use of laser diffraction techniques was added to the methods that can be used to investigate DPI performance [110].

In the literature, different aspects of performance are presented and discussed in terms of FPF, delivered dose, inhaler accumulation, flow rate sensitivity and moisture protection by the inhaler [111-124]. Most frequently investigated devices are the ISF inhaler (a capsule inhaler) and the Turbuhaler (a multi dose reservoir inhaler). Several studies with the Turbuhaler have been reviewed [111]. These studies reported FPF's at 60 l/min in the range of 18 – 52% of the dose. The difference in results, however, reflects the poor reproducibility of the test procedures rather than that of the inhaler itself. In addition, different methods were used in these studies to express (either as fraction of delivered dose or of label claim) or to define FPF (with respect to size distribution). Studies with the ISF inhaler showed similar differences in FPF at the same flow rate for different types of drug and drug formulation [114,115]. Furthermore, it could be shown that storage of drug formulations in hard gelatine capsules at higher relative humidities may have a dramatic effect on FPF [115,116].

Environmental conditions are also known to affect the performance and stability of DPIs. This is mostly related to changes in the adhesion forces between drug and carrier

particles that are caused by changes in humidity. An increased humidity may increase the adhesion forces by a rise in the capillary forces between drug and carrier [117,118]. Therefore, adequate moisture protection of the powder is required.

In a number of studies, the effects of varying the inhalation flow rate on FPF have been investigated. These studies show that there are two basic types of such inhalers: those that perform in a flow rate-dependent manner and those that perform in a flow rate-independent way. Which one is the best mode to perform is the subject of debate (see Section 9). Unfortunately, many of the studies on FPF generation and flow rate dependency were designed in different ways, which makes comparisons between different studies difficult, particularly as some studies were designed in such a way as to show the device of the sponsor of the study in the best light.

Although it has been suggested that the Turbuhaler is sensitive to peak inspiratory flow rate (PIF) of 40 – 80 l/min [112], later studies proved that it is rather the flow increase rate (FIR) that determines the FPF of this device [110,113]. De Koning [124] was the first to investigate the effect of both PIF and FIR on more than one device and concluded that only the Turbuhaler is highly sensitive to FIR, producing a maximal (budesonide) FPF of 50% of the label claim at 60 l/min and 7.5 l/s^2, respectively. This study also confirmed that the maximal FPF from the (fluticason) Diskhaler® (GlaxoSmithKline) is only 23% (versus 33% for the fluticason Diskus® [GlaxoSmithKline]). Furthermore, it was also observed that the Diskus and Cyclohaler® (Pharmachemie) are slightly flow increase rate-dependent, which supports the idea that *in vitro* testing with simulated inhalation manoeuvres would yield a more realistic view of the performance of a DPI.

Selroos *et al.* [125] and Pauwels *et al.* [126] summarised the results from lung deposition (*in vivo*) studies using various devices, which showed that deposition not only varies strongly between devices, but also between studies with the same device and same drug-type. One of the reasons is the difference in inhalation manoeuvres, which cannot be controlled to the same extent as *in vitro*. In addition, the inter-subject variations with respect to lung morphology may be quite extreme. The total range of presented depositions has a span of 5.5 (for cromoglycate Spinhaler) – 32% (for budesonide Turbuhaler) of the label claim, and an arithmetic mean of 16.0 [125] and 16.2% [126], respectively, suggesting that there is still room for considerable improvement. In comparison, mean lung deposition from MDIs is 15.0% (ranging 7.2 – 6.2% [125]) and 12.3% (ranging 2.9 – 24.1% [125]). The extreme range of values for the same device tested with the same type of drug at approximately the same flow rate (e.g., Turbuhaler: 16.8 – 26.9% for terbutaline at 55 l/min, and 15 – 32% for budesonide at, on average, 44 l/min) indicates that lung deposition experiments may be useful in predicting ultimate clinical effects. However, they are not useful for device development, and they are time-consuming and expensive.

Many *in vitro* investigations of new devices were combined with *in vivo* deposition (scintigraphic) studies [127], or clinical effect studies. Some of these data have been compared [57], showing that the lung depositions of the new devices (in the range 13.6 – 41.5% of label claim) are generally higher than those from the first generation DPIs, with the exception of the Turbuhaler.

Finally, some studies have investigated the patient's acceptance/preference of a particular device [128,129]. Such studies could be very useful in designing a new inhaler device, if performed properly. In practice, they are merely inventories of opinions about one or two existing (competitive) devices, often based on questionable arguements, confirming the manufacturer's views on, and choices for, design, rather than bringing insight into the real desires and needs of the patient (or the physicians).

Several studies have been performed to evaluate recently developed DPIs with new drugs in new formulation types. Two large clinical studies were performed regarding the efficacy of inhaled insulin using Nektar's Inhance system (with insulin embedded in a polyol matrix). In both studies it was concluded that the efficacy and safety of the inhaled insulin were comparable with that of subcutaneously injected insulin [130,131]. This conclusion was confirmed by a Cochrane review on inhaled insulin [132]. Inhalation of porous particles (PulmoSpheres® [Nektar Therapeutics]) loaded with tobramycin was compared with the administration of a solution from a nebuliser. The improved aerosol properties of the dry powder compared with that from the nebuliser resulted in a ninefold improved pulmonary deposition [133]. Similar improvements were found by Le Brun *et al.* [134] when they tested an air classifier-type DPI with colistin [135] and compared its performance with that of a classic nebuliser.

9. Expert opinion

Many trends in the design and development of DPI and drug formulation can be observed, particularly from the patent literature. According to Ashurst *et al.* [1], > 30 DPIs were under development at the start of the year 2000 and, more recently, even higher numbers of inhalers in the pipeline are being reported by on the internet. Whether many of these new developments will result in significant improvements in dry powder inhalation therapy remains to be seen.

DPIs are complex delivery systems whoose performance is determined by a multitude of variables with complex interrelationships (Figure 9). The FPF remains the key parameter when DPI performance is considered. The quality of the starting materials, composition of the powder formulation, production process for this formulation, dosing system, deagglomeration principle and total device design are only some of the variables affecting FPF. Unfortunately, many of the current developments focus only on one or two individual aspects. It would be much better to integrate these different aspects during development to optimise the performance of the dry powder inhalation system, as proposed by De Boer *et al.* [106], in their formulation integrated DPI concept.

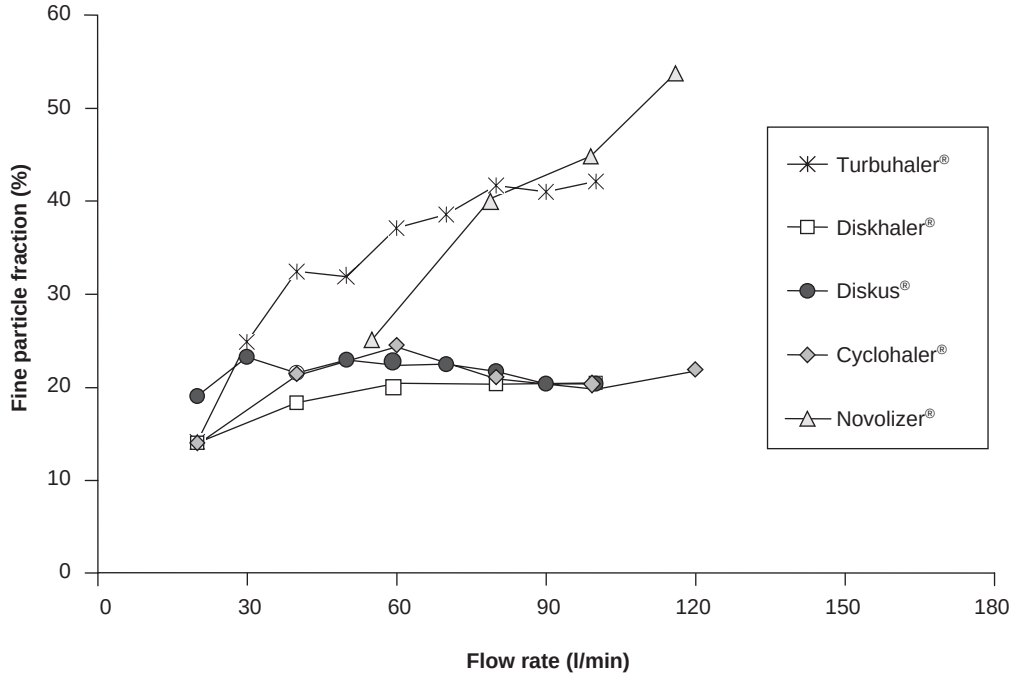

Figure 10. The effect of flow rate on the fine particle fraction (defined as amount deposited on third and fourth stage of the Fisons impactor, relative to label claim) generated from different corticoisteroid-containing inhalers (fluticasone for Diskus® [GlaxoSmithKline] and Diskhaler® [GlaxoSmithKline]; budesonide for the other inhalers).

Among the many variables in Figure 9, the adhesive forces in the powder and the de-agglomeration forces that create the aerosol are two of the most important. Many of the current particle engineering efforts aim to reduce the adhesive forces, whereas the efforts to improve de-agglomeration principles are rather scarce. It would be much better to focus on both and to create a balance between these two variables during development. It does not make sense to decrease adhesive forces in a powder when the de-agglomeration principle generates inadequate de-agglomeration forces. In that case, a more significant improvement can be obtained by changing the design of the de-agglomeration principle. Current developments in powder formulation (e.g., critical fluid technology, large porous particles, modified carrier surfaces) may improve aerosol generation by the already marketed inhalers. However, what their future value will be once inhalers with much more efficient de-agglomeration principles have been developed, is questionable. Improved de-agglomeration principles may also be necessary when special formulations are used that are more cohesive or adhesive than the currently used powders. Examples of these powders may come from the developments related to the systemic administration of proteins via the pulmonary route. When adhesive excipients (e.g., hygroscopic sugars) are, for example, necessary to produce stable powders, high de-agglomeration forces are necessary to generate an aerosol with sufficient penetration into the deep lung. So far, few inhaler designs with highly effective de-agglomeration principles have been described. Improved de-agglomeration principles may be developed through an optimised usage of the energy from the inspiratory air flow. This requires a delicate balancing between various aspects, such as the resistance to air flow, the inhalation time and the residence time of the powder in the de-agglomeration principle. An alternative way to improve powder de-agglomeration could be the use of external energy sources, such as pressurised air or electricity. However, battery-powered systems are vulnerable to failure (e.g., flat battery) and may be expensive.

It is clear that systems using external energy produce aerosols that are largely independent of the inhalation manoeuvre. Whether flow-independent aerosol generation (a constant FPF) is favourable, remains a matter of debate, both for the currently marketed inhalers and for the new systems under development. In Figure 10, the effect of inhalation flow rate on FPF (as a fraction of the labelled dose) of different marketed corticosteroid inhalers is shown. The figure clearly shows that three of the tested inhalers (Diskus, Diskhaler and Cyclohaler) generate FPFs that are independent of the inhalation air flow. In contrast, the Turbuhaler and Novolizer show a clear increase in FPF when higher inhalation flows are applied. It seems plausible to reason that flow rate-independent inhalers result in a more reproducible dosing and thus, in a more reproducible therapeutic effect. However, this line of reasoning neglects the fact that it is not FPF alone that determines the therapeutic efficacy. As explained previously, higher

velocities will result in an increased particle stopping distance. Therefore, increasing the flow rate shifts the deposition of particles of the same size towards higher airways. This effect will reduce the amount of drug that is able to pass deeper into the lung. As a consequence, a constant FPF at increasing flow rates results in a decrease of the amount of drug reaching the target area in the deep lung. When, on the other hand, FPF increases with increasing flow rate, the loss of drug in the upper airways may be compensated by the larger amount of drug in the aerosol. As a result of this compensation mechanism, the actual amount of drug that will enter the target area and become therapeutically effective is likely to be more reproducible for the flow rate-dependent inhalers. In this respect, an ideal DPI would generate an FPF attuned to the inhalation flow of the individual patient. A simplified option is to establish certain limits for the flow rate within which the DPI must be operated. Such a limit is the threshold value in the Novolizer that prevents use of the inhaler at flow rates that are insufficient for adequate dose entrainment and powder de-agglomeration. If the patient generates insufficient flow, the Novolizer cannot be operated. In addition, this device feedbacks to the patient about whether or not the inhalation flow has been adequate [136].

Air classifier technology [83,106] is one of the few examples which allows for balancing of adhesive and de-agglomeration forces. Classifier technology offers certain advantages for adhesive mixture de-agglomeration in comparison with other inhalers, such as the possibility to adjust the de-agglomeration efficiency. Changes in the design of the air classifier chamber alter the circulation pattern (and thereby impaction and shear forces) or the residence time of the powder in the classifier chamber. Dependent on the specific classifier design, additional spherical pellets can be disintegrated with high efficiency (up to 80 – 90%), without having severe drug accumulation in the classifier chamber (by using bypass channels creating an internal air barrier).

Balancing of the adhesive and cohesive forces in the powder formulation with the de-agglomeration forces, requires an understanding of the magnitude of these forces and the underlying mechanisms of de-agglomeration. Techniques and experimental methods are needed to investigate these different aspects. Until now, only few techniques have been available. For example, atomic force microscopy has been used to determine adhesive and cohesive forces, but the presented results vary strongly (up to a factor of 10^2) [118,137,138], which makes the relevance of these measurements questionable. Laser diffraction particle sizing is a newer technique that can be used to characterise the aerosol cloud. Although its application has been described, advanced measurements that could give better understanding of de-agglomeration mechanisms, such as time sliced measurements, have only scarcely been applied so far [139,140].

An important aspect of DPIs is of course their clinical efficacy. Numerous studies and reviews have been published to test clinical efficacy and compare the performance of DPIs with other inhalation devices. An overview of the studies published on this subject can be found in [141]. It should, however, be understood that most studies merely reflect the technical abilities of the specific DPI tested, or the intentions of the developers to design a system that is, for example, bioequivalent to a MDI or other DPI already on the market. Such studies do not indicate the potential of DPIs or try to find the limits of the system's capabilities. In this respect, papers on the use of DPIs in situations that are perceived as constrained are of greater interest [142]. The meta-analysis presented in [141] concluded that MDIs should preferentially be prescribed in asthma and COPD, as they have similar efficacy to breath-activated inhalers and DPIs and are cheaper. This conclusion was challenged by Barnes [143], who stated that DPIs are more cost-effective as they deposit more drug in the lung, improve compliance and result in more effective asthma control. In this respect, it should also be mentioned that, so far, the potential benefits have not been exploited, as many developments have been directed towards bioequivalency with originator products devices instead of improved devices.

The results of the *in vivo* studies performed so far show that there is still room for significant improvement regarding lung deposition. Reported values of, at maximum, 32% for locally acting drugs, and bioavailabilities of 10 – 15% for systemically-acting drugs are only a fraction of what should be possible based on theoretical calculations or results from studies using specifically-designed inhalation systems for research purposes. However, it should be realised that the limited bioavailability of macromolecules is not only caused by poor deposition, but also by metabolism occurring in the lung [144].

Special requirements that are necessary to improve therapy with locally-acting drugs or to improve the bioavailability of systemically acting drugs could involve stimuli to develop better DPIs. For example:

- Patients suffering from CF are treated with inhaled antibiotics. These drugs are given in high doses. These doses require new inhalers that are able to administer doses probably ≥ 100 mg of powder [145]. Such amounts would certainly require special de-agglomeration principles to generate an aerosol with the appropriate particle size. Moreover, this group of patients may require disposable inhalers as this could reduce the hazard of bacterial infection caused by a contaminated inhaler.
- On the other hand, many new drugs are highly potent, highly lipophilic materials that are given at a low dose. The reproducible administration of extremely low doses may also require special dosing and de-agglomeration technology. Furthermore, the poor water solubility of such drugs may require special techniques to dissolve the drug in the aqueous pulmonary fluids, as non-dissolved drug particles will not be absorbed into the systemic circulation.
- The feasibility of systemic administration of peptide or proteins by inhalation was shown in the insulin studies. This is very promising for other proteins, considering the small therapeutic window for this drug. However, its bioavailability is

still low. Other proteins may have different requirements, for example, with regard to stabilisation. This could require special protective measures for the powder (e.g., against moisture) or de-agglomeration principles.

- Slow-release products are interesting because a reduced administration frequency could improve patient compliance. However, even more important is the expectation that slow-release products could enable treatment options that are not yet possible. The most prominent example of such a possibility is the maintenance of the overnight insulin level in Type 1 diabetic patients. As no long-acting insulin for inhalation is available yet, even patients that use inhaled insulin (once it enters the market) may still need daily injections with long-acting insulin.
- The therapeutic efficacy of new inhalation therapies should be balanced with side effects. Side effects may be reduced by more specific targeting within the pulmonary tract. This may require narrower size distributions or monodisperse aerosols, as well as a better control of the patient's inhalation flow.
- Nebulisers were used to prove the feasibility of vaccination by inhalation of the measles vaccine [146]. For this application, no dry powder inhalation systems have been developed yet. Only a theoretical discussion has been published [36]. The development of such a DPI is quite a challenge as it requires an inhalable powder formulation for the vaccine. If appropriately formulated, such formulation could be more stable than a solution of the vaccine. In addition, for some other systemic therapies, for example analgesia with morphine, DPIs have not yet been developed.

Another aspect that may affect the development of DPIs in the future is the need for cost control in healthcare. This aspect has not been discussed in this review, but it is logical to assume that it requires the development of easy and cheap to produce inhalers that still meet the high requirements needed for advanced inhalation therapies.

Finally, it should be realised that DPIs are not the only systems that can be used for inhalation therapy. Advantages such as the potential ability to generate high FPFs and a relatively high lung deposition, fast and easy administration, the ability to prepare stable formulations (compared with solutions), and the fact that DPIs are breath-actuated and easily portable, justify their existence. However, DPIs are not the panacea for all existing problems in inhalation therapy. Specific advantages may be found for MDIs (e.g., inhalation flow-independent generation of aerosol, no effect of environmental conditions on performance) and nebulisers (e.g., formulation may consist of a simple aqueous solution of the drug), which, for certain specific applications (e.g., use in children $\leq$ 6 years), may make them more suitable than DPIs.

In conclusion, dry powder inhalation can be considered as an attractive drug delivery system, both for drugs that are to be administered for local therapy in the lung, as well as for drugs that act systemically and for which the lung is only a port of entry to the body. The possibility to administer proteins without injection remains a particularly attractive option. The systems used at present still require significant improvement in various areas. However, such improvements can only be obtained when a profound understanding of the powder formulation, inhaler design and functioning, aerodynamic behaviour of particles, and inspiratory flow manoeuvres of the patients exists. This requires further research both with regard to formulation and device as well as the experimental techniques and methods that provide relevant data when evaluating inhaler systems.

Disclaimer

HW Frijlink holds the chair in Pharmaceutical Technology and Biopharmacy. AH De Boer is research co-ordinator of the inhalation group within the department.

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