Dry Powder Inhaler Formulation

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SUMMARY

A drug product combines pharmacologic activity with pharmaceutical properties. Desirable performance characteristics are physical and chemical stability, ease of processing, accurate and reproducible delivery to the target organ, and availability at the site of action. For the dry powder inhaler (DPI), these goals can be met with a suitable powder formulation, an efficient metering system, and a carefully selected device. This review focuses on the DPI formulation and development process. Most DPI formulations consist of micronized drug blended with larger carrier particles, which enhance flow, reduce aggregation, and aid in dispersion. A combination of intrinsic physicochemical properties, particle size, shape, surface area, and morphology affects the forces of interaction and aerodynamic properties, which in turn determine fluidization, dispersion, delivery to the lungs, and deposition in the peripheral airways. When a DPI is actuated, the formulation is fluidized and enters the patient's airways. Under the influence of inspiratory airflow, the drug particles separate from the carrier particles and are carried deep into the lungs, while the larger carrier particles impact on the oropharyngeal surfaces and are cleared. If the cohesive forces acting on the powder are too strong, the shear of the airflow may not be sufficient to separate the drug from the carrier particles, which results in low deposition efficiency. Advances in understanding of

aerosol and solid state physics and interfacial chemistry are moving formulation development from an empirical activity to a fundamental scientific foundation. *Key words: dry powder inhaler, DPI, formulation development, particles, physico-chemical properties, drug delivery.* [Respir Care 2005; 50(9):1209–1227. © 2005 Daedalus Enterprises]

INTRODUCTION

Formulation development encompasses an array of processes in which an active pharmaceutical ingredient is incorporated into a drug product. While biological activity is a prerequisite for a successful dosage form, it is not the sole determinant. Factors such as stability, processibility, delivery, and availability to the target organ contribute to an efficacious pharmaceutical system. Optimization of these factors is a key development task, and the final product is often a compromise between pharmaceutical and practical (ie, economic/engineering) considerations. Formulation development is challenging because molecules with pharmacologic activity often display poor physicochemical properties. In fact, the same molecular characteristics that confer pharmacologic activity (eg, high receptor affinity) frequently limit a compound's pharmaceutical utility, making it difficult or even unsuitable for delivery.[1,2] This is particularly true for many of the compounds that are identified by high-throughput screening methods.[2,3]

Development of pharmaceuticals for inhalation is a particular challenge, as it involves the preparation of a formulation and the selection of a device for aerosol dispersion. The lungs have lower buffering capacity than other delivery sites (eg, the gastrointestinal tract or the blood), which limits the range of excipients that could enhance delivery outcomes. An additional variable, unique to pulmonary delivery, is the patient, both in terms of inhalation mode and respiratory-tract anatomy and physiology.[4] There are many more ways to administer an inhaled aerosol than there are to swallow a tablet. Variability in delivered dose to an individual or a population of patients can be substantial.[5,6] Consequently, reproducible therapeutic effect is difficult to assure.

Treating respiratory diseases with inhalers requires delivering sufficient drug to the lungs to bring about a therapeutic response. For optimal efficacy, drug administration must be reliable, reproducible, and convenient. This goal can be achieved by a combination of formulation, metering, and inhaler design strategies.[7] The technical and clinical aspects of device design and selection have been extensively reviewed elsewhere.[8–10] The following discussion outlines the design of dry powder inhaler (DPI) formulations to achieve the delivery goals. Formulation development and characterization strategies and processing methods will be discussed, with emphasis on their effect on stability, manufacturing feasibility, delivery, and bioavailability. To that end, an understanding of dry powder physics and surface chemistry is essential. The text focuses on broad concepts and examples, with only sparing use of equations.

DRY POWDER INHALERS

Development of the DPI

Inhaled drug delivery systems can be divided into 3 principal categories: pressurized metered-dose inhalers (pMDIs), DPIs, and nebulizers, each class with its unique strengths and weaknesses. This classification is based on the physical states of dispersed-phase and continuous medium, and within each class further differentiation is based on metering, means of dispersion, or design. Nebulizers are distinctly different from both pMDIs and DPIs, in that the drug is dissolved or suspended in a polar liquid, usually water. Nebulizers are used mostly in hospital and ambulatory care settings and are not typically used for chronic-disease management because they are larger and less convenient, and the aerosol is delivered continuously over an extended period of time. pMDIs and DPIs are bolus drug delivery devices that contain solid drug, suspended or dissolved in a nonpolar volatile propellant or in a dry powder mix (DPI) that is fluidized when the patient inhales. The clinical performance of the various types of inhalation devices has been thoroughly examined in many clinical trials, which have been reviewed by Barry and O'Callaghan,[10] and more recently by Dolovich et al.[8] Those authors concluded that none of the devices are clinically

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Table 1. Dry Powder Inhalers Versus Metered-Dose Inhalers

Advantages of the Dry Powder Inhaler
Environmental sustainability, propellant-free design
Little or no patient coordination required
Formulation stability
Disadvantages of the Dry Powder Inhaler
Deposition efficiency dependent on patient's inspiratory airflow
Potential for dose uniformity problems
Development and manufacture more complex/expensive

(Adapted from Reference 18.)

superior and that device selection should be guided by other factors, such as convenience, cost, and patient preference.

First approved in 1956, the pMDI was the first modern inhaler device.[11] With a global market share of about 80%, the pMDI remains the most widely used device.[12] The development of DPIs has been motivated by the desire for alternatives to pMDIs, to reduce emission of ozone-depleting and greenhouse gases (chlorofluorocarbons and hydrofluoroalkanes, respectively) that are used as propellants, and to facilitate the delivery of macromolecules and products of biotechnology. Concurrently, DPIs proved successful in addressing other device and formulation-related shortcomings of the pMDI. DPIs are easier to use, more stable and efficient systems. Because a pMDI is pressurized, it emits the dose at high velocity, which makes premature deposition in the oropharynx more likely.[13,14] Thus, pMDIs require careful coordination of actuation and inhalation. Despite enhancements to their design (eg, use of spacers),[15] incorrect use of pMDIs is still a prevalent problem; Giraud and Roche found that poor coordination of actuation and inhalation caused decreased asthma control in a substantial proportion of patients treated with corticosteroid pMDIs.[16] Since DPIs are activated by the patient's inspiratory airflow, they require little or no coordination of actuation and inhalation. This has frequently resulted in better lung delivery than was achieved with comparable pMDIs.[17]

Since DPIs are typically formulated as one-phase, solid-particle blends, they are also preferred from a stability and processing standpoint.[18] Dry powders are at a lower energy state, which reduces the rate of chemical degradation and the likelihood of reaction with contact surfaces. By contrast, pMDI formulations, which include propellant and cosolvents, may extract organic compounds from the device components.[19] Table 1 summarizes the main advantages and disadvantages of the DPI (versus the pMDI). For more detail on the evolution of aerosol delivery devices, excellent reviews are available.[11,20]

The development of several new DPI devices, which have been reviewed elsewhere,[18,21–23] and the commercial success of the bronchodilator-corticosteroid combination product Advair (GlaxoSmithKline, Research Triangle Park, North Carolina) have further stimulated interest in and development of DPIs.[7]

Principles of Operation

Figure 1 shows the principles of DPI design. Most DPIs contain micronized drug blended with larger carrier particles, which prevents aggregation and helps flow. The important role these carrier particles play is discussed later in this article. The dispersion of a dry powder aerosol is conducted from a static powder bed. To generate the aerosol, the particles have to be moved. Movement can be brought about by several mechanisms. Passive inhalers employ the patient's inspiratory flow. When the patient activates the DPI and inhales, airflow through the device creates shear and turbulence; air is introduced into the powder bed and the static powder blend is fluidized and enters the patient's airways. There, the drug particles separate from the carrier particles and are carried deep into the lungs, while the larger carrier particles impact in the oropharynx and are cleared. Thus, deposition into the lungs is determined by the patient's variable inspiratory airflow.[24–26] Inadequate drug/carrier separation is one of the main explanations for the low deposition efficiency encountered with DPIs.[27] Dose uniformity is a challenge in the performance of DPIs. This is a greater concern with powders than with liquids because of the size and discrete nature of the particulates.

Various dispersion mechanisms have been adopted for DPIs.[22] While most DPIs are breath-activated, relying on inhalation for aerosol generation, several power-assisted devices (pneumatic, impact force, and vibratory) have been developed or are currently under development. These devices are being considered for the delivery of systemically active drugs that have narrow therapeutic windows.[28] It is important to note that these "active" inhalers are not subject to the same limitations as passive inhalers and have a different advantage/disadvantage profile. Moreover, it has been suggested that if shear and turbulence could be standardized by using a dispersion mechanism that is independent of the patient's breath, high delivery efficiency and reproducibility might be achieved. Thus, an active inhaler might provide formulation-independent delivery.[29] There are no commercially available active-dispersion DPIs. Therefore, in the interest of brevity, these devices are not discussed here; the reader is instead referred to other literature.[28–30]

Powder and Aerosol Physics/Physicochemical Characterization

The character of particulate systems is central to the performance of DPIs. Powders present unique design chal-

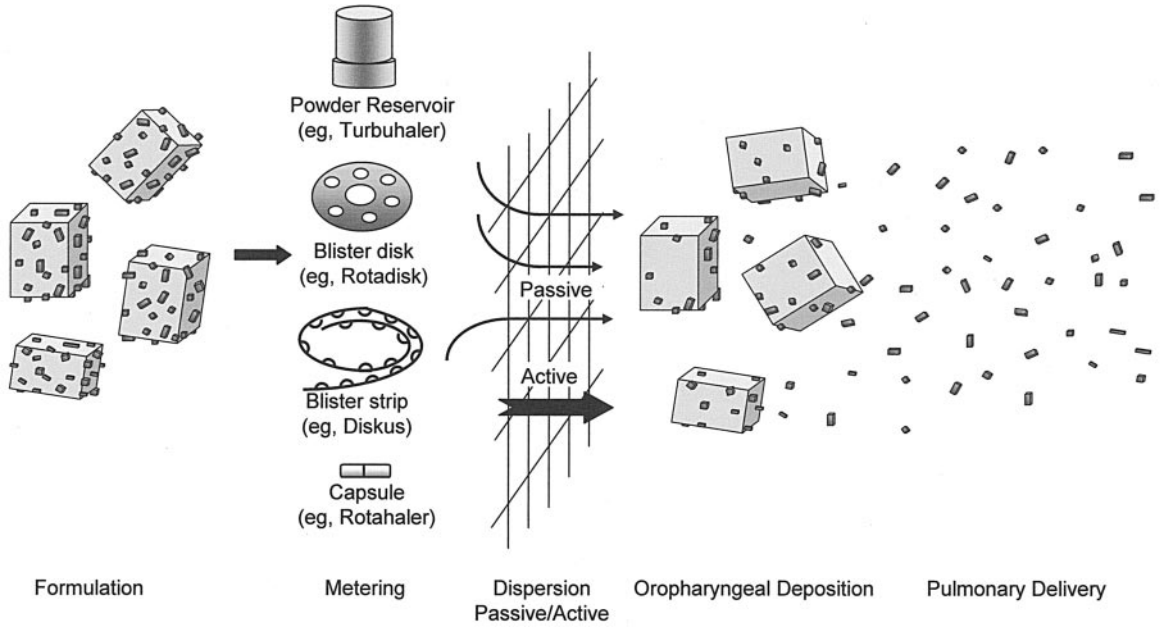

Fig. 1. Principle of dry powder inhaler design. The formulation typically consists of micronized drug blended with larger carrier particles, dispensed by a metering system. An active or passive dispersion system entrains the particles into the patient's airways, where drug particles separate from the carrier particles and are carried into the lung.

lenges. Powders are 2-phase gas-solid systems. When powders are static, they behave as solids; when they flow, they resemble liquids, easily assuming the shape of the containing vessel.[31] When a powder is dispersed in air, as is the case after actuation of a DPI, in many ways it conforms to its carrier gas (unlike gases or vapors, pharmaceutical powders are nonequilibrium systems). Whereas gas and liquid behavior is understood and accurately predicted by equations derived from first principles, physical equations governing powders are often empirical or rely on assumptions that are only approximations to real systems, such as homogeneity in size and shape of particles. As a consequence, equations describing the behavior of solids are less predictive than their fluid counterparts. The reader is referred to texts on multiphase flow phenomena.[32–36]

Powder properties can vary widely. Powder features, such as the physicochemical properties and morphology of its constituent particles and the distribution of particle sizes, contribute to variability. Unlike liquid solutions or gas mixtures, powders are never completely homogeneous (at primary particulate scale) and segregation by size, which is a function of external forces, is always a potential problem. The aerodynamic behavior, which has a profound effect on the disposition of drug from a DPI, is particularly sensitive to powder properties.

Crystallinity and Polymorphism

Many pure organic substances, including most drugs, are crystalline. A crystal is a solid in which the molecules or ions are arranged in an ordered, repeating pattern (the unit cell) extending in 3 spatial dimensions. Crystalline systems are defined by the intermolecular spacing (ie, bond lengths and bond angles) of the unit cell, which can be determined by x-ray diffraction.[37] There are 7 crystal classes, which yield 14 distinct lattice structures.[38] The arrangement of molecules into crystals is governed by noncovalent interactions, including hydrogen bonding, van der Waals forces, π-π stacking, and electrostatic interactions.[39]

Nearly one third of all drugs are known to display polymorphism,[40] which is the ability of a solid to exist in more than one crystal from. A prominent example of a polymorphic pharmaceutical is carbamazepine, which has 4 known polymorphs, one of which was discovered almost 30 years after identification of the first polymorphs.[41] Determination of the polymorphic forms of a drug is an important part of the formulation-development process, because polymorphic forms are not equivalent. Different polymorphs are at different energy states and thus have different properties, including stability, solubility, and even bioavailability.[38] Identification of all polymorphs of a drug also has important economic implications, because a separate patent can be granted for each polymorph.[40]

It is also possible to generate a noncrystalline solid. In most cases this involves cooling a fluid so rapidly that its molecules lose mobility before assuming their lattice positions. A noncrystalline material is considered amorphous because it lacks long-range order. Amorphous materials have higher Gibbs free energies than crystals; thermodynamic laws predict that, in the long-term, materials seek to

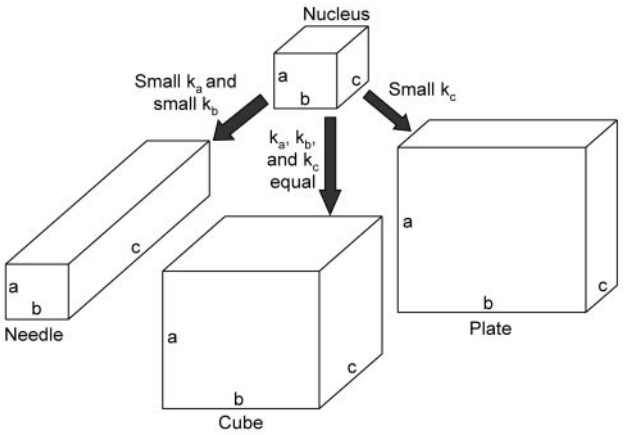

Fig. 2. Crystal habit. Inhibition of growth in one of more spatial directions (k_a, k_b, and k_c) results in particles with plate or needle morphology.

minimize their free energies by transitioning to lower energy states (eg, crystallization). Whether this will occur at a timescale that need be of concern to the pharmaceutical scientist is governed by the chemical kinetics of the system.

Different polymorphs can be discerned in terms of various physicochemical properties. Polymorphs usually differ in density, melting point, solubility, and hygroscopicity. The most stable polymorph frequently has the highest density, highest melting point, and lowest solubility. Discriminating analytical methods to characterize polymorphs include x-ray diffraction and thermal analysis, such as differential scanning calorimetry.[38] To reduce the risk of transformation during processing or storage, the most stable polymorph is typically selected for development, provided its other properties are manageable.

While crystallinity refers to the geometry of the unit cell, crystal habit describes the morphology of particles, which can vary independently of the crystal lattice structure if crystal growth rates (during precipitation) vary in some dimension (Fig. 2).[42] Crystal habit is important because particle shape affects aerodynamic behavior and, thus, lung deposition. Crystallization and crystal habit are influenced by various factors, including identity of solvent,[43,44] impurities present during crystallization,[45] and processing variables such as temperature, pH, solution volume, and viscosity.[46]

Some compounds will spontaneously incorporate solvent molecules into the lattice structure upon crystallization or storage at certain conditions. This phenomenon has been referred to as pseudopolymorphism, and is relevant for many drugs that exist as solvates or hydrates.[47] It is important to understand the conditions that will result in hydration, because, as with true polymorphs, hydrates differ in their physicochemical properties.

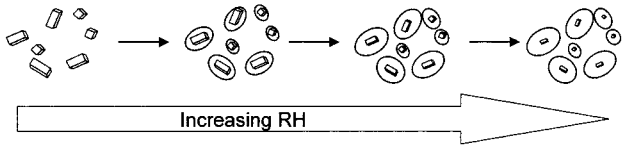

Fig. 3. Hygroscopic growth. Particles absorb moisture as they traverse the humid environment of the airways, resulting in increased particle size.

Knowledge of crystallization and polymorphism is still unfolding, and the ability to predict polymorphism remains imperfect. In most solids, a large number of different intermolecular interactions are possible, but few are actually observed.[48] The difficulties involved in crystallization are illustrated by several reported cases of "disappearing polymorphs." These cases were characterized by difficulty in resynthesis of a polymorph after initial synthesis, despite seemingly identical procedure and conditions.[49] Controlling crystallization is at the heart of "particle engineering," which is a term that is used with increasing frequency in the pharmaceutical and chemical literature. Control over the crystallization process could yield particles with precisely engineered morphology; co-crystallization (inclusion of functional impurities into the crystal) could then become a formulation strategy, resulting in "supramolecular pharmaceutics."[47]

Moisture Content and Hygroscopicity

Hygroscopicity is the intrinsic tendency of a material to take on moisture from its surroundings. The hygroscopicity is affected by the crystallinity of the material and the morphology of the particles. Hygroscopic drugs present a greater risk of physical and chemical instability. Moisture uptake and loss due to changes in relative humidity can result in local dissolution and recrystallization, leading to irreversible aggregation through solid bridge formation,[22] which can adversely affect aerosol generation and lung deposition.[50] Hygroscopicity can also alter the adhesive and cohesive properties, or, in more extreme situations, substantially increase particle size.[51] Hygroscopic growth (Fig. 3) involves the uptake of moisture, which will reach equilibrium in droplets as a function of the water activity of the solution formed and the surrounding atmosphere of water vapor; the Kelvin-Gibbs equation describes the phenomenon involved.[52] Hygroscopic growth has implications for the equilibrium moisture content of the particles in the dosage form prior to aerosol generation; it can cause chemical or physical instability of the product. For aerosols, the physical instability is more important, because agglomeration may be irreversible and lead to an inability to generate aerosol particles of respirable size. As aerosol particles enter the lungs, they experience a high-humidity

environment (99.5% relative humidity at 37°C). Although they may not reach equilibrium during transit, susceptible aerosol particles may be subject to hygroscopic growth, which increases particle dimensions and affects lung deposition.[53] Hygroscopic growth can be prevented by coating the drug particles with hydrophobic films.[52] However, no such approach has been successfully implemented in a marketed formulation.

The equilibrium moisture content of a drug and excipient must be determined over a range of relative humidities, so that storage conditions can be defined and other protective measures considered. Excipients that modify the hygroscopic properties of a drug may need to be considered.

Particle Size

Particle size is the single most important design variable of a DPI formulation. Methods for determining particle size and distribution use various geometric features or physicochemical properties.[54] Among these, aerodynamic diameter is the most relevant to lung delivery and ultimately to therapeutic effect. There is substantial literature from the fields of industrial hygiene, environmental and occupational medicine, and pharmaceutical sciences that links aerodynamic size and size distribution to the probability of deposition in specific lung sites. The statistical basis for these relationships in terms of variability in airways geometry and lung physiology, both between individuals and within an individual, has been sufficient to allow the development of semi-empirical models correlating particle size with lung deposition.[55]

Aerodynamic Diameter and Dynamic Shape Factor

Aerodynamic diameter is the most appropriate measure of aerosol particle size, because it relates to particle dynamic behavior and describes the main mechanisms of aerosol deposition; both gravitational settling and inertial impaction depend on aerodynamic diameter. To reach the peripheral airways, where drug is most efficiently absorbed, particles need to be in the 1–5 μm aerodynamic diameter range.[56] Particles larger than 5 μm usually deposit in the oral cavity or pharynx, from which they are easily cleared. In contrast, particles smaller than 0.5 μm may not deposit at all, since they move by Brownian motion and settle very slowly. Moreover, they are inefficient, as a 0.5-μm sphere delivers only 0.1% of the mass that a 5-μm sphere carries into the lungs. In a series of studies, the optimal particle size of aerosol particles was examined for several different therapeutic agents in patients with different disease states. Although some differences due to patient lung function were noted, the optimal size was always in this 1–5 μm range.[57–60]

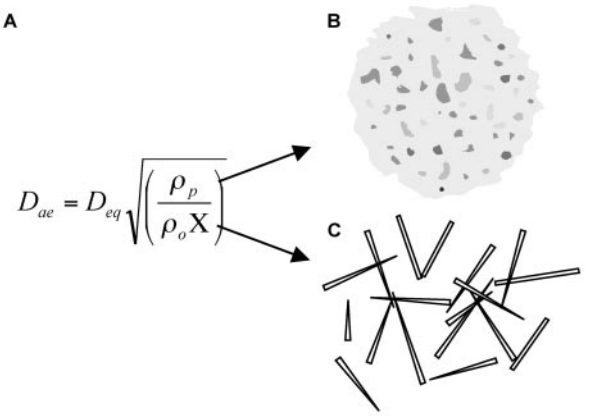

Fig. 4. Strategies for altering the aerodynamic diameter. A: Aerodynamic diameter equation. B: Large, low-density porous particles. C: Needle-shaped particles. Particles in both B and C are expected to have aerodynamic diameters smaller than their size would suggest. D_{ae} = aerodynamic diameter. D_{eq} = unit density of equivalent volume sphere. ρ_p = particle density. ρ_o = unit density. X = dynamic shape factor.

The aerodynamic diameter, D_{ae}, is defined by the diameter of an equivalent volume sphere of unit density D_{eq} with the same terminal settling velocity as the actual particle. For particles larger than 1 μm, the following expression describes the relationship between these dimensions.

$$D_{ae} = D_{eq}\sqrt{\left(\frac{\rho_p}{\rho_o X}\right)}$$

where ρ_p and ρ_o are particle and unit densities, and χ is the dynamic shape factor. Pharmaceutical powders are rarely spherical, and shape factors are dimensionless measures of the deviation from sphericity. The dynamic shape factor is the ratio of the actual resistance force experienced by the nonspherical falling particle to the resistance force experienced by a sphere having the same volume.[61] Dynamic shape factors are determined either experimentally or using more complex models that are beyond the scope of this paper. A very thorough review of this concept, with values for common shapes, is provided by Hinds.[61]

The above equation merits closer examination. As discussed, it is the aerodynamic diameter that determines lung disposition, irrespective of geometric particle size (to a certain point). The aerodynamic diameter can be decreased by decreasing the particle size, decreasing particle density, or increasing the dynamic shape factor. This concept is shown graphically in Figure 4, and is discussed in more detail below. All 3 of these approaches have been applied.

Fine-Particle Fraction

"Fine-particle fraction" is the percentage of particles in the fine-particle range (1–5 μm). "Fine-particle mass" is

the total mass of the particles that are in the fine-particle range.[62] The fine-particle component of aerosols is usually defined as the percentage of particles that are smaller than 5 μm aerodynamic diameter, or, in the case of certain particle-sizing instruments, a cut-off diameter that is close to 5 μm. Quite often this may be in the 6–7 μm range. The danger of adopting these values as definitive measures of equivalency is associated with the effect of particle size on deposition.[63] This is considered more later in this article.

Polydispersity

For drug delivery it is the convention to consider the mass associated with each particle size as the frequency term in the distribution, since this relates directly to dose. Conventional statistical properties apply to populations of particles (ie, mode, mean, and median). It is usual to define the central tendency of numbers of aerosol particles by the mass median aerodynamic diameter, which reflects the particle size that divides the distribution in half as a function of mass. Monomodal distributions may conform to log-normal mathematical interpretation, in which case the breadth of the distribution can be expressed in terms of the geometric standard deviation, which is usually derived by dividing the particle size at the 84th percentile by the median size, to achieve a dimensionless number greater than 1.

When considering particle size, the degree of polydispersity (ie, the range of particle sizes around the mode) is also important. The simplest and preferred system exhibits a single mode. However, many pharmaceutical aerosols will exhibit more than one mode. It is conceivable that 2 completely different aerosol distributions (eg, small median size with narrow distribution or large median size with broad distribution) could give exactly the same fine-particle fraction. However, within the fine-particle fraction, the aerosol would exhibit different sizes, leading to differences in regional lung deposition, resulting in variations in therapeutic effect. Thus, degree of dispersity is an important consideration for both quality and efficacy of pharmaceutical aerosols.[64] The nature of the aerosol distribution must be established accurately if its implications for deposition and efficacy are to be understood.

Another consideration relates to the standard DPI formulation, which is frequently bimodal, because it contains micronized drug and substantially larger carrier particles. Recognizing the potential for multimodal distributions is important to the application of statistical methods to the interpretation of the data. Traditional methods of data interpretation (eg, log-normal mathematical fits to distributions[65]) may be superseded by other mathematical approaches[66] or nonlinear curve-fitting using calibration data.[67]

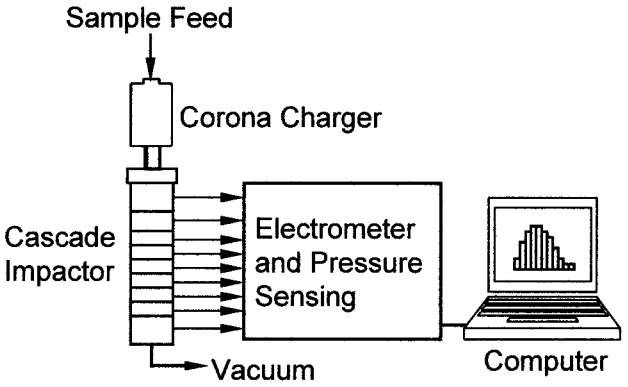

Fig. 5. The electrical low-pressure impactor. (Courtesy of Dekati Ltd, Tampere, Finland.)

Particle Sizing Techniques

Several techniques are available for determining particle size distributions; they have been described in depth elsewhere[65] and will be covered briefly here. The aerosol sizing techniques can be classified as (1) inertial methods, (2) light-scattering methods, or (3) imaging methods.

Cascade Impactor. Cascade impactors,[68,69] including multi-stage liquid impingers, are the most widely used instruments for sizing aerosols; they are recommended by both the United States and the European pharmacopeias. Their utility stems from the fact that they directly measure aerodynamic size, rather than equivalent volume diameter (based on cross-sectional area) like the other methods. The theory of cascade impactor operation has been described in depth elsewhere.[70] Briefly, cascade impactors contain several stages, with orifices of decreasing size, stacked on top of each other. When the aerosol is drawn through the impactor, the particles deposit on different stages, based on their inertia. After each run, the impactor is disassembled and the mass of particles deposited on each stage is determined, mostly via analytical methods (dissolution in solvent, followed by chromatography or ultraviolet absorbance). A cut-off diameter is associated with each stage of the impactor. This diameter varies with airflow, so the impactor must be calibrated for different flow rates. This airflow dependence allows investigation of the effect of different inspiratory flow rates on deposition.

The electrical low-pressure impactor[71] (Figure 5) is a rather recent modification of the cascade impactor. Particles passing through the electrical low-pressure impactor are charged before traversing the cascade of stages. Their impact on the stages produces an electrical current that is detected and converted into particle-size data that can be interpreted immediately. The utility of the electrical low-pressure impactor has been demonstrated in the sizing of particles in diesel engine exhaust[71–76] and other combus-

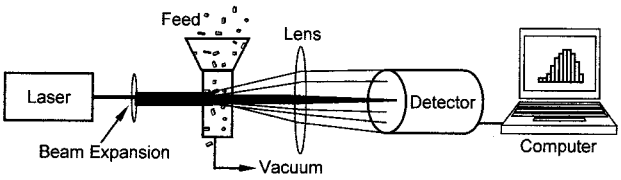

Fig. 6. Particle sizing via laser-light scattering.

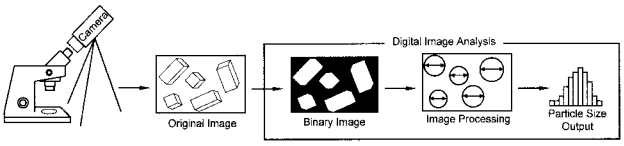

Fig. 7. Particle sizing via digital image analysis.

tion processes.[77] A limitation of the electrical low-pressure impactor is that it is not suitable for particles larger than 20 μm, so it cannot be used to size carrier particles, which limits its utility for sizing pharmaceutical aerosols. Based on a PubMed search, reference to electrical low-pressure impactors in medical/pharmaceutical journals is limited to a single publication, in which an electrical low-pressure impactor was used for sizing sub-micron size pMDI particles.[78] However, the electrical low-pressure impactor has great potential to simplify the aerosol sizing process and is likely to make an impact in the field in the future.

Light Scattering and Laser Diffraction. Light-scattering methods, especially laser-light-scattering, are quite commonplace in formulation development. The operating principle of laser-light scattering is depicted in Figure 6. An expanded laser beam is passed through a sample that is being drawn through a measuring zone. Different size particles diffract the light at different angles. A computer algorithm, which differs between manufacturers, interprets the diffraction pattern and calculates a particle size distribution. The algorithms are based on Fraunhofer or Mie theory, from which the particle sizes are determined. Since the algorithms differ among the different instruments, comparisons are difficult, particularly for the majority of pharmaceutical particles, which deviate from sphericity.

Image Analysis. The last method that is of importance in sizing particles is image analysis; it is illustrated schematically in Figure 7. An example of this method consists of taking digital images of particle samples, converting them to binary data, designating the key dimension, and deriving particle-size data. The analyst can perform the steps individually or use an automated piece of equipment that samples particles and produces particle-size-distribution data. The software differs, so conversion from binary data to particle size can produce different results. However, this technique is very powerful in that it has the capability to account for the shape of the particles, though the images are only 2-dimensional representations of 3-dimensional particles. Another limitation of this approach is low capacity. Since individual particles are imaged, it takes considerably more time than the other techniques.

While light-scattering and imaging methods are very useful in the characterization of raw materials (eg, drug particles or excipient particles alone), cascade impaction is more useful in determining the fine-particle fraction, so it is a better measure of the performance of the formulation rather than the raw materials. The different methods complement each other. In the early stages of the formulation-development process it is not uncommon to use all methods at your disposal until good process control has been established or a methodology has been developed that is robust enough to describe all desired features.

Surface Area and Morphology

Particle surfaces are important elements in particle interactions, stability, and ease of dispersion. Since aerosol particles are small, the total surface area of a powder is very large. A large surface area renders the particles subject to greater potential for charging and moisture uptake. In addition, the size of the particles renders them more susceptible to the influence of van der Waals forces.

Forces of Interaction

Particle separation is the most important performance characteristic for effective aerosol generation. To separate particles, specific forces of interaction must be overcome. There are 4 major forces of interaction between particles: mechanical interlocking due to surface asperities, capillary forces from the presence of water, electrostatics arising from the insulating nature of the material, and van der Waals forces from the fundamental electromagnetic nature of matter. Much has been written on the subject of particle interactions, both from a solid state physics[79] and a therapeutic aerosol[80] standpoint.

On a large scale, physical interactions are barriers to aerosol generation. In this case, mechanical interlocking due to surface features or roughness is a prominent mechanism preventing particle dispersion. Temperature and humidity cycling, or poor drying may also result in solid bridging, through crystallization/recrystallization phenomena at the particle surfaces.[81] The presence of moisture, even in small quantities, will also bring about capillary forces.[79] The magnitude of these forces is related to the diameter of the pores between particles and the interfacial tension due to hydrogen bonding of water. Controlling moisture content will aid in reducing capillary forces, but care must be taken to avoid increasing the surface charge of the particles. The origins of the electrostatic charge are

atmospheric ionization, chemical composition, contact with charged objects, and triboelectric charging from motion. Electrostatic charging is difficult to study and control. Since most pharmaceutical powders are poor conductors, electrostatic charge plays a role in their dispersion. Electrostatic forces are reciprocally but not linearly related to capillary forces in magnitude. Attempts have been made to modify the electrostatic charges of carrier particles to affect drug deposition.[82] The strong forces (mechanical, capillary, and electrostatic) act in a background of weak electromagnetic van der Waals forces, which relate to the influence of point charges at a distance and can be derived from the Lennard Jones potential.[83,84] It is possible to manipulate van der Waals forces by reducing particle contact area or increasing the distance between particles. Low-density, high-porosity particles achieve the goal of reducing van der Waals forces.[85]

The forces of interaction between pharmaceutical powders are difficult to characterize and control because of heterogeneity in particle composition and physicochemical characteristics. Consequently, it is difficult to consider each of the forces independently or to apply rigid controls. Various methods can be used to study particles, and specifications can be placed on key features that may be responsible for particle interactions, such as crystallinity, presence of impurities, surface asperities, roughness, moisture content, density, size, and distribution.

Surface Morphology

Surface area is not solely determined by particle size and shape; the surface morphology also contributes to surface area: corrugated (ie, rough) particles have more surface area than smooth particles that occupy the same volume. Thus, particle morphology can also be exploited for DPI formulation design.[86–88] By creating drug particles with specific morphology or by selecting (modifying) carrier particles to obtain specific surface morphology, the interparticulate forces can be modulated to enhance lung deposition. Ideally, the contact area and thus the forces should be adjusted to a level that provides enough adhesion between drug and carrier to provide a stable formulation, yet allows easy separation upon inhalation. Carrier-particle surface morphology affected the fine-particle fraction in several studies.[27,88–93] However, the influence of surface corrugation on the fine-particle fraction has not been firmly established. Smooth-surface lactose carrier particles have been shown to increase the fine-particle fraction and dispersibility of micronized drug,[27] while other studies showed that corrugated carrier particles increased the fine-particle fraction.[90–93] These results appear contradictory, but both may be correct, since the surface force balance depends on several variables, not simply surface structure.

Surface Area and Morphology Measurements

Since surface area is highly correlated with particle interactions, measurements must be obtained as part of the DPI formulation development effort. Determining the powder surface area involves measuring the volume of gas adsorbed to the powder surface at a given pressure. Several models have been developed to describe gas-solid adsorption behavior, the most prominent one being the Brunauer, Emmett, and Teller equation.[94] Over the last few decades, new techniques for studying surfaces have emerged or have been borrowed from other scientific disciplines. Two particularly noteworthy examples are inverse gas chromatography and atomic force microscopy.

Inverse Gas Chromatography. Inverse gas chromatography is a technique for studying solids via gas chromatography. The technique has been used by physical chemists and chemical engineers for characterizing polymers since the 1960s, but its use in the study of pharmaceuticals appears to be rather new, with the first references in the pharmaceutical literature only dating back to the mid-1990s.[95] The theory and applications of inverse gas chromatography have been described in detail elsewhere.[96,97] Figure 8 shows the principle of inverse gas chromatography. A sample of powder is packed into a gas-chromatography column, and the retention time and elution peak shape are studied for a series of well-characterized nonpolar and polar gases. The technique appears to be of particular utility for DPI formulation work, because it requires only small samples for analysis, and it is nondestructive, fast, and information rich. It has been used to measure surface area and surface energy,[98,99] as well as to study small changes in surface characteristics caused by processing.[100] It may even detect minor batch-to-batch product variations that could not be detected with other techniques.[95]

Atomic Force Microscopy. Atomic force microscopy is a form of scanning probe microscopy that was first developed in 1986.[101] Unlike optical microscopes, scanning probe systems are not limited by diffraction because they do not use lenses; so they can image surfaces with near-atomic resolution. Figure 9 shows the principles of operation. Atomic force microscopy works by measuring height, with the probing tip placed in contact with the surface of the sample (contact mode atomic force microscopy) or very close to the surface of the sample (noncontact and tapping mode atomic force microscopy). The probing tip is attached to an elastic cantilever that is deflected proportionally to the force experienced by the tip. The atomic force microscope raster-scans the sample, producing a matrix of data points, from which quantitative height and roughness measurements can be extracted.[102]

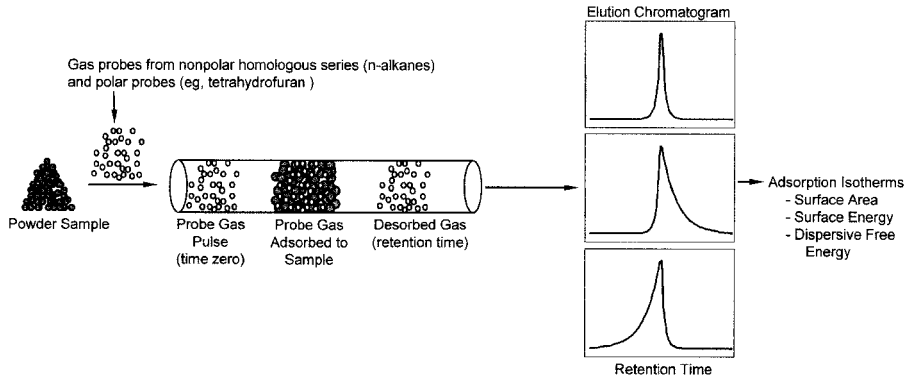

Fig. 8. Principle of inverse gas chromatography.

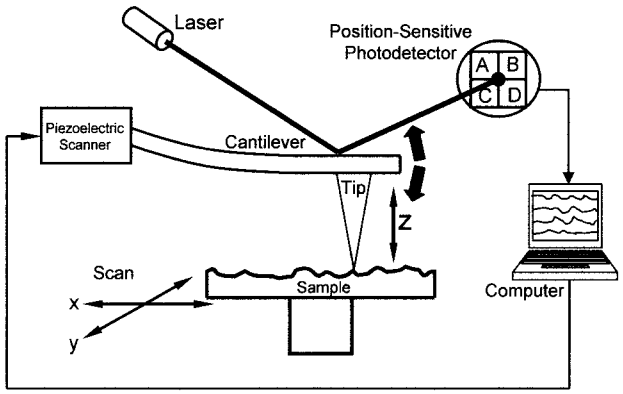

Fig. 9. Principle of atomic force microscopy.

Much like inverse gas chromatography, atomic force microscopy was first used extensively in other industries (particularly the semiconductor industry), before being applied to the characterization of pharmaceuticals. Tapping mode atomic force microscopy effectively images crystals of various organic compounds, including drugs (cimetidine[103] and felodipine[104]), and the adhesional properties of carrier-particle lactose.[105–109] Atomic force microscopy has also been used to observe and monitor the crystallization of lactose[110] and the effect of mechanical processing on the powder surface.[111]

Atomic force microscopy and inverse gas chromatography have been presented because they represent new approaches to formulation optimization, based on surface functionality. A more comprehensive review of techniques to characterize particle morphology, including Fourier, fractal and chaos analysis, and stochastic and percolation models has been published elsewhere.[112]

DRUG PROPERTIES AND MANUFACTURE

The Active Pharmaceutical Ingredient

The respiratory tract is both the therapeutic target and the route for delivery. It is an attractive delivery route because it does not subject drugs to the same harsh conditions they may experience in the gastrointestinal tract (ie, pH and enzyme levels),[113] yet it is noninvasive and convenient. Bioavailability for proteins and other macromolecules is greater than in any other noninvasive delivery route.[114,115] For these reasons, oral inhalation is increasingly being explored for the delivery of systemically active drugs, including therapeutic proteins, such as recombinant human granulocyte colony stimulating factor,[116] insulin,[117–119] drugs to treat bone disorders,[120] and vaccines.[121] Systemically active drugs need to be absorbed into the circulation, so they should be delivered to the alveoli, from which absorption is most efficient. Absorption through the alveolar-vascular membranes can take place via transcellular diffusion, paracellular diffusion (through tight junctions), and transcellular vesicular transport. The absorption mechanism depends on the drug.

Pulmonary drug delivery is also the most effective way of treating diseases of the airways. The majority of pulmonary drugs on the market are pharmaceuticals to treat obstructive airway ailments, such as asthma and chronic obstructive pulmonary disease. Most of these drugs fall into one of 3 therapeutic categories:

1. β_2 adrenergic agonists
2. Corticosteroids and cromones
3. Anticholinergics

Tronde et al found that of 34 inhaled drugs commercially available in 2001 (including anesthetics, but excluding lung surfactant preparations and macromolecules), 12 compounds were β_2 agonists and 6 compounds were corticosteroids.[122] The chemistry and pharmacology of these molecules have been reviewed elsewhere.[123] For effective delivery, it is important to understand the pharmacology of the drug so that the correct physiology can be targeted. Unlike systemically active drugs, the 3 drug classes above need not be absorbed into the circulation to exert their pharmacologic activity. Most β receptors are located in the alveoli.[124] Anticholinergics target muscarinic receptors, which are moderately distributed throughout the airways

Table 2. Mean Physicochemical Properties of Marketed Small-Molecule Drugs for Oral Inhalation

Physicochemical Property	10th to 90th Percentile
Logarithm of octanol/water distribution coefficient (cLogD) (pH 7.4)	−6.3–3.8
Molecular weight (Da)	225–482
Polar surface area (Å^2)	65–178
Logarithm of octanol/water partition coefficient (cLogP)	−1.0–4.1
Hydrogen bond donors	2–6
Hydrogen bond acceptors	4–11

(Adapted from Reference 122.)

and periphery. The trachea is more densely populated with M_3 muscarinic receptors than β receptors.[125] Corticosteroids target inflammatory cells, which are located throughout the airways and alveoli.[124] With respect to receptor distribution, it is not clear which receptors must be targeted for maximum therapeutic effect.

In contrast to the oral route, for which various structure-bioavailability relationships have been developed[3,126–129] and applied to the screening of drug candidates, the structure-bioavailability relationship for inhaled drugs remains largely unexplored. One notable exception is the publication by Tronde et al, in which the authors examined marketed inhaled pharmaceuticals for physicochemical similarities and studied their absorption.[122] The range of physicochemical properties of these 34 small-molecule therapeutic agents incorporated in oral inhalation products in 2001 are listed in Table 2.

Since the number of drugs is small, it is hard to establish guidelines, such as Lipinski's "Rule of Five," which is one of the prominent structure-absorption relationships for orally-active compounds.[3] As shown in Table 2, most properties examined varied widely or were closely linked to the respective drug category. No extremes were noted for any of the properties, but it was noted that inhaled drugs were generally more polar than oral drugs. Several drugs that showed poor oral permeability were well absorbed in the lung. Absorption appeared to be mostly related to the polar surface area of the molecule, but, overall, Tronde et al concluded that the range of physicochemical properties acceptable for respiratory delivery was wider than for orally administered drugs. Tronde et al did not, however, consider active transport, which plays a role with several inhaled drugs.[122]

Given the wide range of physicochemical properties that make a drug suitable for pulmonary absorption (compared to orally administered drugs), there is nonetheless one critical requirement a drug must meet to qualify for respiratory delivery; this requirement is potency. Current inhalation devices limit the quantity of drug that can be delivered to the lungs in a single dose to a few milligrams. Thus, in order to be considered for inhalation therapy, drugs need to be therapeutically effective in the microgram or milligram range. With the development of new inhalers, this quantity is likely to increase in the future; however, potency will continue to be a limiting factor. Moreover, it is questionable whether the lungs are able to manage large single doses administered chronically. Anatomically, the lungs have evolved to prevent entry of airborne particulates. This limits the use of particularly large molecules and explains the success of receptor agonists and endogenous or endogenous-like compounds such as cromones.

The evolution of combination-therapy from a single inhaler (eg, corticosteroid plus long-acting β_2 agonist[130]) has brought about new formulation challenges. In designing combination-therapy inhalers, one must also consider drug-drug interaction, whether chemical, pharmacokinetic, or pharmacodynamic in nature, in addition to the other developmental aspects.[131]

Active Pharmaceutical Ingredient Preparation

The final steps of bulk drug manufacture are crystallization from solution, filtration, and drying. Typically, the drug particle size is not well controlled during these steps. To create particles in the respirable size range (< 5 μm in diameter), the drug particle size must be reduced in a separate unit operation. There are several options for reducing the particle size, and it may be necessary to evaluate several methods to find the one that works best for the specific drug. The first size-reduction technique the formulation scientist will typically turn to is milling. There are many different mills, but only a few are able to mill powder to the required particle size range of 2–5 μm. The 3 main types of mills used in Active Pharmaceutical Ingredient manufacture are fluid-energy mills, such as the jet mill; high-peripheral-speed mills, such as the pin-mill; and the ball mill. The basic designs are shown in Figure 10; more in-depth discussion of their operation, with detailed illustrations, capacity, and performance, is provided elsewhere.[54] Mechanical processing, such as milling, has been shown to affect the crystallinity of the material;[111] this effect must be considered.

Jet milling[132] (or air-attrition milling) is the most useful technique; it reduces particle size via high-velocity particle-particle collisions. Unmilled particles are introduced into the milling chamber. High-pressure nitrogen is fed through nozzles and accelerates the solid particles to sonic velocities. The particles collide and fracture. While flying around the mill, larger particles are subjected to a higher centrifugal forces and are forced to the outer perimeter of the chamber. Small particles exit the mill through the central discharge stream. Depending on the nitrogen pressure

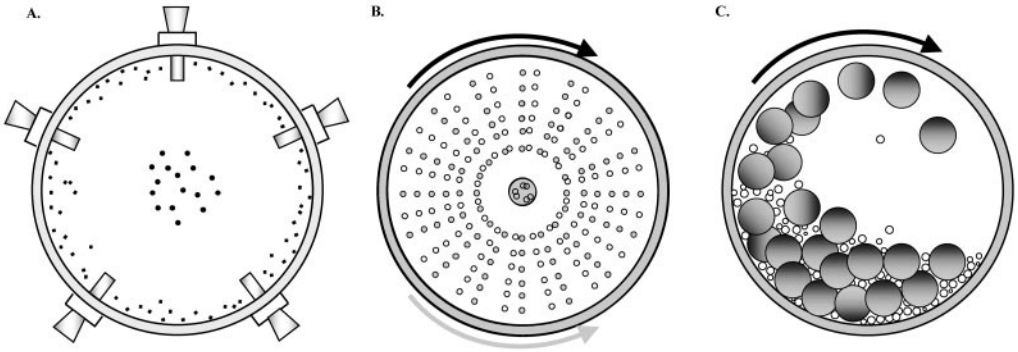

Fig. 10. Micronization. Cross-sections of 3 mills commonly used to create micron-size particles. A: Jet mill. B: Pin mill. C: Ball mill.

and powder feed rate, particles down to 1 μm in diameter can be produced.

A pin mill uses mechanical impact to grind material, both by particle-particle and particle-solid collisions. A pin mill is equipped with a series of concentrically mounted pins located on a spinning rotor and stationary stator plate. Powder is fed to the milling chamber and transported through the milling chamber by centrifugal force. Milled product is collected from the bottom. The pin mill can produce 1-μm particles,[133] but not as small as the jet mill. On the other hand, the pin mill's power consumption is lower than that of the jet mill.

The ball mill[134] is essentially a rotating cylinder loaded with drug and "milling media" (ie, balls that grind the drug between each other as they tumble inside the mill). The size and material of the milling media can be varied. Ball milling is very slow and the process is poorly scalable, which is why tumbling-ball mills are used only in the laboratory.

Other techniques for making micron-size particles involve direct particle formation from solution. Two noteworthy approaches for controlling particle size are spray-drying and supercritical fluid crystallization. These techniques are distinctly different from milling, in that the particles are built up (ie, particle size is increased), whereas particle size is decreased during milling. In spray-drying,[135,136] the drug is dissolved in water or solvent and sprayed as fine mist into a heated expansion chamber. The droplets dry, leaving behind tiny particles of drug that are collected at the bottom of the chamber. Compared to milling, spray-drying can produce more spherical particles; however, spray-dried particles are mostly amorphous.[137]

A supercritical fluid is a single phase with liquid-like density and gas-like transport properties. Supercritical fluids exhibit pressure-tunable solubility, which makes them well-suited for recrystallization operations. Several techniques have emerged that use supercritical fluids, most notably CO_2 or propane, as solvents (eg, rapid expansion of supercritical solutions[138]) or as antisolvents (eg, solution-enhanced dispersion by supercritical fluids[139]), for the formation of small particles. Schiavone et al noted that solution-enhanced dispersion by supercritical fluids yielded smoother budesonide particles, with less surface area than milled drug, which resulted in higher emitted dose with the Turbospin (PH&T, Milan, Italy).[140] Particle engineering with supercritical fluids is the subject of intense research in the pharmaceutical industry; excellent reviews on this topic have been published.[141]

For each technique it is important to consider the effect it has on the drug. Spray-drying and supercritical fluid methods offer more flexibility and the possibility of morphology control in addition to size control, but they may often yield only amorphous material or an undesired polymorph. Milling remains the process of choice for micronizing drug, because it is simpler, more predictable, easier to scale up, and less expensive. However, spray-drying, supercritical fluid, and a few other techniques remain alternatives for the formulator to consider when milling does not produce the desired results.

FORMULATION

The particle size distribution affects the deposition of drug in the respiratory tract. However, before drug can be delivered to the lungs, drug particles must leave the DPI and separate from each other and from other components in the formulation. Thus, a DPI formulation must undergo flow, fluidization, and deaggregation. However, micron-size particles, particularly those resulting from high-energy operations such as jet milling, have high surface areas and surface energies, which result in poor flow and a high tendency to aggregate. Formulation strategies aim at alleviating these problems.

Excipients

One way to improve the nonpharmacologic properties of a drug is through the addition of excipients. In general, excipients are used to enhance the physical or chemical stability of the active pharmaceutical ingredient, its me-

chanical properties, and/or its pharmaceutical properties, such as dissolution and permeation. In DPI formulations, excipients function first and foremost as carrier particles. Usually, no more than a few milligrams of drug need to be delivered, and excipients provide bulk, which improves handling, dispensing, and metering of the drug. Excipients also reduce drug cohesiveness by occupying the high-energy sites of the drug particles.

The primary function of the lungs is respiration. To fulfill this purpose, the lungs have a large surface area and thin membranes. Unlike the gastrointestinal tract, the lungs have limited buffering capacity. Many compounds that could enhance drug delivery outcomes also have the potential to irritate or injure the lungs. Consequently, the array of potential excipients is limited to compounds that are endogenous to the lung and can easily be metabolized or cleared.

Currently, lactose is the only excipient used in DPIs marketed in the United States. The reasons for this are as much historical as they are physicochemical/pharmaceutical in nature. Lactose had long been used as an excipient in oral dosage forms before being deployed in DPIs. It had an established safety and stability profile, manufacturing process with tight controls over purity and physical properties, and was available and inexpensive. Lactose is highly crystalline and has the smooth surfaces and satisfactory flow properties desirable for a DPI carrier particle.[7] Lactose is less hygroscopic than other sugars. Lactose is quite versatile; several manufacturers offer excipient-grade lactose of various sizes and morphologies. One drawback of lactose is that it is a reducing sugar, which makes it incompatible with drugs that have primary amine moieties.[142]

Other sugars, such as mannitol,[143,144] have been shown to be feasible alternatives to lactose, and it is expected that these sugars will eventually find their way into approved products. Glucose is already used in DPIs in Europe. Phospholipids, such as phosphatidyl choline and cholesterol, have also been used in experimental liposomal formulations.[145,146] Several other materials have been included in experimental DPI formulations, with various objectives and varying success.[147–149]

Excipients can makes up over 99% of the product by weight, making them crucial determinants of overall DPI performance. Despite the apparent lack of choices, the excipient must be carefully selected; physicochemical properties such as size and morphology profoundly affect the performance of the formulation.[99,150–153] The adhesive forces must be carefully considered; inadequate separation of drug and carrier is the main reason for deposition problems. The formulator may also choose to modify the excipient before combining it with the drug. It should also be noted that excipients are not always required; the Pulmicort (budesonide) Turbuhaler (AstraZeneca, Wilmington, Delaware) is an example of an excipient-free formulation.

Large Porous Particles

Porous or hollow particles exhibit very different equivalent volume diameters from their aerodynamic diameters, because of the density terms, as described by the Stokes equation. Particles can be made in the respirable aerodynamic diameter range, even as their geometric particle size is on the order of 20 μm.[85] This offers some important advantages in the dispersion of these particles, due to the reduced van der Waals forces, which reduces their tendency to aggregate and makes them more responsive to shear in an airflow path. However, there is a limit to how much such an approach can be used, because the peripheral airways of the lungs are very small. Consequently, beyond a particular geometric size, penetration to the periphery would not be possible. In addition, low-density particles carry little mass in a unit volume. Therefore, the limits on dose delivery must be considered carefully. With these caveats, for potent, low-dose drugs these particles can be excellent delivery systems.

Agglomerates

Loose agglomerates have been used as a means of stabilizing powder aerosols, so that, upon the introduction of energy from the patient's breath or some active source, they readily disperse into small particles for inhalation. These agglomerates can consist of particles of disparate sizes, as is the case when drug is prepared with large carrier particles, or particles of similar sizes prepared by unique methods of formation that result in ease of dispersion (Turbuhaler[154,155] and Twisthaler[156] formulations). Figure 11 shows an example of such an approach, in which agglomerates of needle-like particles disintegrate into respirable fine crystals at an airflow rate of 30–60 L/min (similar to inhalation flow rate).[157]

PHARMACEUTICAL PROCESSING

The processes involved in powder formulation have been extensively reviewed in the pharmaceutical technology/engineering literature.[158] After drug and excipient(s) have individually been brought to their desired forms, they are combined in the blending process. The importance of the blending process can be easily overlooked. However, it is a critical step in the manufacture of a DPI product and is in fact subject to substantial optimization work during development. When mixing powders with different properties, particle sizes, and ratios, as is the case with DPI formulations, inadequate mixing can cause poor dose uniformity. In many cases, inadequate mixing cannot be overcome simply by increasing the mixing time. Mixer selection, rotation speed, capacity, and fill level are all subject to optimization, as they can all affect the blend homoge-

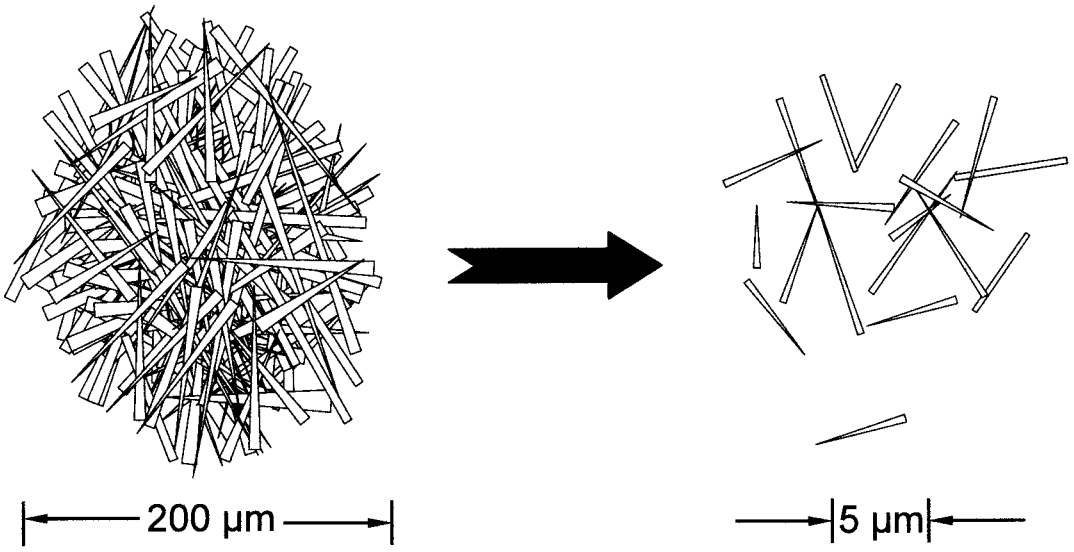

Fig. 11. Loose agglomerates.

neity.[159,160] Blending conditions also affect the interparticulate forces, which are a primary determinant of the fine-particle fraction.[161] Different powders may have different mixing requirements, depending on the forces present between the various particles.[162] For low concentration (drug-carrier ratio) blends, geometric dilutions are necessary preblending steps.[42] The flow properties of the components of the powder blend will play an important role in the efficiency of blending and, ultimately, in aerosol dispersion. Powder flow properties have been studied for some time, and methods have been adopted for their characterization, including bulk and tapped density and angle of repose.[163–165]

Powder sampling is an important prerequisite for accurate characterization. Blending validation is an important activity required by good manufacturing practices in the United States Code of Federal Regulations. However, taking blend samples at different times to determine the uniformity of the blend is associated with several difficulties.[166] New techniques are emerging that can determine the blend homogeneity without removal of samples from the mixer; techniques such as near-infrared and Fourier transform-infrared analysis can determine blend uniformity by nondestructive acquisition of infrared spectra.[167–169]

After the formulation has been blended, it is filled into capsules, multi-dose blisters, or reservoirs for use with the inhaler device. The filling process is automated and depends on the nature of the metering system.

In order to maintain its physical and chemical integrity and dispersibility, the product must be stored appropriately. Storage conditions, such as temperature and relative humidity profoundly effect DPI stability and performance,[170–173] so permissible storage conditions need to be determined. The requirements are regulated by the United States Food and Drug Administration, which provides a complete list of the testing requirements for DPI products,[174] summarized by Ashurst et al.[18]

SUMMARY

Interest in DPIs has increased in the last decade, in response to the need for alternatives to propellant-driven devices and new approaches to the delivery of potent new chemical entities of biological origin. The number of diseases that are being considered candidates for aerosol therapy has increased substantially. Until recently, asthma was the only clear example of a disease that could be treated via aerosol delivery to the lungs. We now consider it possible to treat not only asthma and chronic obstructive pulmonary diseases but also systemic disorders such as diabetes, cancer, neurological diseases (including pain), and other pulmonary diseases such as cystic fibrosis and pulmonary infectious diseases.

DPIs offer unique opportunities and unique challenges. The opportunity to use solid-state physics and chemistry to prepare stable, dispersible particles for aerosol delivery to the lungs is clear. The challenges relate to the unique formulation strategies required and the susceptibility of dry powders to forces of interaction caused by their surface and bulk energetics, which can inhibit their dispersion and limit aerosol delivery and, therefore, efficacy. In the foregoing sections the means of preparation of dry particles, the important features of these particles and the means of characterizing them have been outlined to indicate the success that pharmaceutical scientists are achieving in overcoming the barriers to the preparation of optimal DPI systems.

From a commercial standpoint, validation of the importance of DPIs has come from the success of three of the most recent additions to the available aerosol therapies in the United States. In the last few years, Advair/Seretide (salmeterol/fluticasone, GlaxoSmithKline), Foradil (formoterol, Novartis) and Spiriva (tiotropium, Boehringer Ingelheim) were introduced to the United States market. They represent a range of inhaler technologies, both old and new drugs, and therapies for 2 diseases, asthma and chronic obstructive pulmonary disease. The encroachment of DPI technologies on propellant-driven MDI technologies with respect to proportion of the global market for inhaled therapy has been important, and it is not clear that there is a limit to the proportion of the market that might ultimately be served by DPIs. However, it is clear that, for the foreseeable future, the market for DPIs will continue to increase. It is likely that as market equilibrium is approached, nebulizers and pMDIs will represent some portion of overall sales, as there are applications and demographic groups for which these devices offer important therapeutic advantages.

As a greater understanding of the science of pharmaceutical powder properties and their influence on performance is gained, it will be possible to adopt sophisticated technological approaches to solve the problems associated with efficient, reproducible, and efficacious aerosol drug delivery to achieve local and systemic pharmacologic effect.

REFERENCES

1. Di L, Kerns EH. Profiling drug-like properties in discovery research. Curr Opin Chem Biol 2003;7(3):402–408.
2. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods 2000;44(1): 235–249.
3. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 2001;46(1–3):3–26.
4. Timsina MP, Martin GP, Marriott C, et al. Drug-delivery to the respiratory-tract using dry powder inhalers. Int J Pharm 1994;101(1): 1–13.
5. Aswania O, Ritson S, Iqbal SM, Bhatt J, Rigby AS, Everard ML. Intra-subject variability in lung dose in healthy volunteers using five conventional portable inhalers. J Aerosol Med 2004;17(3):231–238.
6. Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. Chest 2000;117(2):542–550.
7. Smyth HD, Hickey AJ. Carriers in drug powder delivery: implications for inhalation system design. Am J Drug Deliv 2005;3(2)117–132.
8. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 2005;127(1): 335–371.
9. Atkins PJ, Crowder TM. The design and development of inhalation drug delivery systems. In: Hickey A. Pharmaceutical inhalation aerosol technology, 2nd ed. New York: Dekker; 2004.
10. Barry PW, O'Callaghan C. The influence of inhaler selection on efficacy of asthma therapies. Adv Drug Deliv Rev 2003;55(7):879–923.
11. Rau JL. The inhalation of drugs: advantages and problems. Respir Care 2005;50(3):367–382.
12. O'Connor BJ. The ideal inhaler: design and characteristics to improve outcomes. Respir Med 2004;98 Suppl A:S10–S16.
13. Newman SP, Clarke SW. Bronchodilator delivery from Gentlehaler, a new low-velocity pressurized aerosol inhaler. Chest 1993;103(5): 1442–1446.
14. Ganderton D. General factors influencing drug delivery to the lung. Respir Med 1997;91 Suppl A:13–16.
15. Newman SP, Newhouse MT. Effect of add-on devices for aerosol drug delivery: deposition studies and clinical aspects. J Aerosol Med 1996;9(1):55–70.
16. Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. Eur Respir J 2002;19(2): 246–251.
17. Borgstrom L, Derom E, Stahl E, Wahlin-Boll E, Pauwels R. The inhalation device influences lung deposition and bronchodilating effect of terbutaline. Am J Respir Crit Care Med 1996;153(5):1636–1640.
18. Ashurst II, Malton A, Prime D, Sumby B. Latest advances in the development of dry powder inhalers. Pharm Sci Technol 2000;3(7): 246–256.
19. Norwood DL, Prime D, Downey BP, Creasey J, Sethi SK, Haywood P. Analysis of polycyclic aromatic hydrocarbons in metered dose inhaler drug formulations by isotope dilution gas chromatography/mass spectrometry. J Pharm Biomed Anal 1995;13(3):293–304.
20. Dalby R, Suman J. Inhalation therapy: technological milestones in asthma treatment. Adv Drug Deliv Rev 2003;55(7):779–791.
21. Newman SP, Busse WW. Evolution of dry powder inhaler design, formulation, and performance. Respir Med 2002;96(5):293–304.
22. Dunbar CA, Hickey AJ, Holzner P. Dispersion and characterization of pharmaceutical dry powder aerosols. Kona 1998;16:7–44.
23. Smith IJ, Parry-Billings M. The inhalers of the future? A review of dry powder devices on the market today. Pulm Pharmacol Ther 2003;16(2):79–95.
24. Newman S, Hollingworth A, Clark A. Effect of different modes of inhalation on drug delivery from a dry powder inhaler. Int J Pharma 1994;102(1):127–132.
25. Cegla UH. Pressure and inspiratory flow characteristics of dry powder inhalers. Respir Med 2004;98 Suppl A:S22–S28.
26. Dunbar CA, Morgan B, Van Oort M, Hickey AJ. A comparison of dry powder inhaler dose delivery characteristics using a power criterion. PDA J Pharm Sci Technol 2000;54(6):478–484.
27. Zeng XM, Martin AP, Marriott C, Pritchard J. The influence of carrier morphology on drug delivery by dry powder inhalers. Int J Pharm 2000;200(1):93–106.
28. Tobyn M, Staniforth JN, Morton D, Harmer Q, Newton ME. Active and intelligent inhaler device development. Int J Pharm 2004;277(1–2):31–37.
29. Crowder TM. Vibration technology for active dry-powder inhalers. Pharm Technol 2004;28:52–61.
30. Crowder TM, Louey MD, Sethuraman VV, Smyth HD, Hickey AJ. An odyssey in inhaler formulations and design. Pharm Technol 2001; 25:99–113.
31. Pell M, Dunson JB. Gas-solid operations and equipment. In: Green DW, editor. Perry's chemical engineers' handbook. New York: McGraw-Hill; 1999.

32. Crowe CT, Sommerfeld M, Tsuji Y. Multiphase flows with droplets and particles. Boca Raton, Florida: CRC Press; 1998.
33. Kreith F. Fluid mechanics. Boca Raton, Florida: CRC Press; 2000.
34. Gidaspow D. Multiphase flow and fluidization: continuum and kinetic theory descriptions. Boston: Academic Press; 1994.
35. Kolev NI. Multiphase flow dynamics. 2nd ed. Berlin: Springer; 2005.
36. Johnson RW. The handbook of fluid dynamics. Boca Raton, Florida: CRC Press; 1998.
37. Brittain H. Physical characterization of pharmaceutical solids. New York: Dekker; 1995.
38. Brittain H. Polymorphism in pharmaceutical solids. New York: Dekker; 1999.
39. Moulton B, Zaworotko MJ. From molecules to crystal engineering: supramolecular isomerism and polymorphism in network solids. Chem Rev 2001;101(6):1629–1658.
40. Henck JO, Griesser UJ, Burger A. Polymorphism of drug substances: an economic challenge. Pharmazeutische Industrie 1997;59(2):165–169.
41. Grzesiak AL, Lang M, Kim K, Matzger AJ. Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. J Pharm Sci 2003;92(11):2260–2271.
42. Cartensen JT. Pharmaceutics of solids and solid dosage forms. New York: Wiley-Interscience; 1989.
43. Garekani HA, Sadeghi F, Badiee A, Mostafa SA, Rajabi-Siahboomi AR. Crystal habit modifications of ibuprofen and their physicomechanical characteristics. Drug Dev Ind Pharm 2001;27(8):803–809.
44. Stoica C, Verwer P, Meekes H, et al. Understanding the effect of a solvent on the crystal habit. Crys Growth Design 2004;4(4):765–768.
45. Wood WML. A bad (crystal) habit: and how it was overcome. Powder Technology 2001;121:53–59.
46. Rodriguez-Hornedo N, Sinclair BD. Crystallization: significance in product development, processing, and performance. In: Swarbrick J, Boylan JC, editors. Encyclopedia of pharmaceutical technology. New York: Dekker; 2002.
47. Rodriguez-Spong B, Price CP, Jayasankar A, Matzger AJ, Rodriguez-Hornedo N. General principles of pharmaceutical solid polymorphism: a supramolecular perspective. Adv Drug Deliv Rev 2004; 56(3):241–274.
48. Desiraju GR. Chemistry beyond the molecule. Nature 2001; 412(6845):397–400.
49. Dunitz JD, Bernstein J. Disappearing polymorphs. Acc Chem Res 1995;28:193–200.
50. Braun MA, Oschmann R, Schmidt PC. Influence of excipients and storage humidity on the deposition of disodium cromoglycate (DSCG) in the Twin Impinger. Int J Pharm 1996;135:53–62.
51. Maggi L, Bruni R, Conte U. Influence of the moisture on the performance of a new dry powder inhaler. Int J Pharm 1999;177(1): 83–91.
52. Hickey AJ, Gonda I, Irwin WJ, Fildes FJ. Effect of hydrophobic coating on the behavior of a hygroscopic aerosol powder in an environment of controlled temperature and relative humidity. J Pharm Sci 1990;79(11):1009–1014.
53. Hickey AJ, Martonen TB. Behavior of hygroscopic pharmaceutical aerosols and the influence of hydrophobic additives. Pharm Res 1993;10(1):1–7.
54. Snow RH, Allen T, Ennis BJ, Litster JD. Size reduction and size enlargement. In: Perry RH, Green DW, editors. Perry's chemical engineers' handbook. New York: McGraw-Hill; 1999.
55. Rudolf G, Gebhart J, Heyder J, Schiller CF, Stahlhofen W. An empirical formula describing aerosol deposition in man for any particle-size. J Aerosol Sci 1986;17:350–355.
56. Bates DV, Fish BR, Hatch TF, Mercer TT, Morrow PE. Deposition and retention models for internal dosimetry of the human respiratory tract. Task group on lung dynamics. Health Phys 1966;12(2):173–207.
57. Zanen P, Go LT, Lammers JW. Optimal particle size for beta 2 agonist and anticholinergic aerosols in patients with severe airflow obstruction. Thorax 1996;51(10):977–980.
58. Zanen P, Go LT, Lammers JW. The optimal particle-size for beta-adrenergic aerosols in mild asthmatics. Int J Pharm 1994;107:211–217.
59. Zanen P, Go LT, Lammers JW. The optimal particle-size for parasympathicolytic aerosols in mild asthmatics. Int J Pharm 1995;114: 111–115.
60. Usmani OS, Biddiscombe MF, Nightingale JA, Underwood SR, Barnes PJ. Effects of bronchodilator particle size in asthmatic patients using monodisperse aerosols. J Appl Physiol 2003;95(5):2106–2112.
61. Hinds WC. Aerosol technology: properties, behavior, and measurement of airborne particles, 2nd ed. New York: Wiley; 1999.
62. Hickey AJ, Martonen TB, Yang Y. Theoretical relationship of lung deposition to the fine particle fraction of inhalation aerosols. Pharm Acta Helv 1996;71(3):185–190.
63. Martonen TB, Katz I, Fults K, Hickey AJ. Use of analytically defined estimates of aerosol respirable fraction to predict lung deposition patterns. Pharm Res 1992;9(12):1634–1639.
64. Chew NY, Chan HK. Effect of powder polydispersity on aerosol generation. J Pharm Pharm Sci 2002;5(2):162–168.
65. Hickey AJ. Methods of aerosol particle size characterization. In: Hickey AJ, editor. Pharmaceutical inhalation aerosol technology. New York: Dekker; 2004:345–384.
66. Dunbar CA, Hickey AJ. Evaluation of probability density functions to approximate particle size distributions of representative pharmaceutical aerosols. J Aerosol Sci 2000;31:813–831.
67. Raabe OG. A general method for fitting size distributions to multicomponent aerosol data using weighted least-squares. Environ Sci Technol 1978;12:1162–1167.
68. Marple VA, Olson BA, Santhanakrishnan K, Roberts DL, Mitchell JP, Hudson-Curtis BL. Next generation pharmaceutical impactor: a new impactor for pharmaceutical inhaler testing. Part III: Extension of archival calibration to 15 L/min. J Aerosol Med 2004;17(4):335–343.
69. Mitchell JP, Nagel MW. Cascade impactors for the size characterization of aerosols from medical inhalers: their uses and limitations. J Aerosol Med 2003;16(4):341–377.
70. Marple VA, Rubow KL, Olson BA. Inertial, gravitational, centrifugal, and thermal collection techniques. In: Baron PA, Willeke K, editors. Aerosol measurement: principles, techniques and applications. New York: Wiley Interscience; 2001:229–260.
71. Keskinen J, Pietarinen K, Lehtimaki M. Electrical low-pressure impactor. J Aerosol Sci 1992;23:353–360.
72. Lehmann U, Niemela V, Mohr M. New method for time-resolved diesel engine exhaust particle mass measurement. Environ Sci Technol 2004;38(21):5704–5711.
73. Van Gulijk C, Marijnissen JCM, Makkee M, et al. Measuring diesel soot with a scanning mobility particle sizer and an electrical low-pressure impactor: performance assessment with a model for fractal-like agglomerates. J Aerosol Sci 2004;35(5):633–655.
74. Maricq MM, Chase RE, Xu N, Podsiadlik DH. The effects of the catalytic converter and fuel sulfur level on motor vehicle particulate matter emissions: gasoline vehicles. Environ Sci Technol 2002;36(2): 276–282.
75. Brown JE, Clayton MJ, Harris DB, King FG Jr. Comparison of the particle size distribution of heavy-duty diesel exhaust using a dilution tailpipe sampler and an in-plume sampler during on-road operation. J Air Waste Manag Assoc 2000;50(8):1407–1416.
76. Holmen BA, Qu Y. Uncertainty in particle number modal analysis during transient operation of compressed natural gas, diesel, and

trap-equipped diesel transit buses. Environ Sci Technol 2004;38(8): 2413–2423.
77. Jetter JJ, Guo Z, McBrian JA, Flynn MR. Characterization of emissions from burning incense. Sci Total Environ 2002;295(1–4):51–67.
78. Crampton M, Kinnersley R, Ayres J. Sub-micrometer particle production by pressurized metered dose inhalers. J Aerosol Med 2004; 17(1):33–42.
79. Israelachvili JN. Intermolecular and surface forces, 2nd ed. London: Academic Press; 1991.
80. Zeng XM, Martin GP, Marriott C. Particulate interactions in dry powder formulations of inhalation. New York: Taylor & Francis; 2001.
81. Crowder TM. A guide to pharmaceutical particulate science. Boca Raton, Florida: Interpharm Press/CRC; 2003.
82. Bennett FS, Carter PA, Rowley G, Dandiker Y. Modification of electrostatic charge on inhaled carrier lactose particles by addition of fine particles. Drug Dev Ind Pharm 1999;25(1):99–103.
83. Hickey AJ, Concessio NM, Van Oort MM, Platz RM. Factors influencing the dispersion of dry powders as aerosols. Pharm Tech 1994; 18:58–64.
84. Atkins P. Physical chemistry, 6th ed. New York: WH Freeman; 1998.
85. Edwards DA, Hanes J, Caponetti G, Hrkach J, Ben-Jebria A, Eskew ML, et al. Large porous particles for pulmonary drug delivery. Science 1997;276(5320):1868–1871.
86. Fults KA, Miller IF, Hickey AJ. Effect of particle morphology on emitted dose of fatty acid-treated disodium cromoglycate powder aerosols. Pharm Dev Technol 1997;2(1):67–79.
87. Hickey AJ, Fults AK, Pilliai RS. Use of particle morphology to influence the delivery of drug from dry powder aerosols. J Biopharm Sci 1992;3:107–113.
88. Young PM, Cocconi D, Colombo P, Bettini R, Price R, Steele DF, Tobyn MJ. Characterization of a surface modified dry powder inhalation carrier prepared by "particle smoothing". J Pharm Pharmacol 2002;54:1339–1344.
89. Zeng XM, Martin GP, Marriott C, Pritchard J. Lactose as a carrier in dry powder formulations: the influence of surface characteristics on drug delivery. J Pharm Sci 2001;90(9):1424–1434.
90. Chew NY, Chan HK. Use of solid corrugated particles to enhance powder aerosol performance. Pharm Res 2001;18(11):1570–1577.
91. Chew NY, Tang P, Chan HK, Raper JA. How much particle surface corrugation is sufficient to improve aerosol performance of powders? Pharm Res 2005;22(1):148–152.
92. Heng PW, Chan LW, Lim LT. Quantification of the surface morphologies of lactose carriers and their effect on the in vitro deposition of salbutamol sulphate. Chem Pharm Bull (Tokyo) 2000;48(3):393–398.
93. Chan LW, Lim LT, Heng PW. Immobilization of fine particles on lactose carrier by precision coating and its effect on the performance of dry powder formulations. J Pharm Sci 2003;92(5):975–984.
94. Brunauer S, Emmett PH, Teller E. Adsorption of gases in multimolecular layers. J Am Chem Soc 1938;60:309–319.
95. Ticehurst MD, York P, Rowe RC, Dwivedi SK. Characterization of surface properties of alpha-lactose with inverse gas chromatography, used to detect batch variation. Int J Pharm 1996;141:93–99.
96. Lloyd DR, Ward TC, Schreiber HP. Inverse gas chromatography: characterization of polymers and other materials. Washington, DC: American Chemical Society; 1989:391.
97. Conder JR, Young CL. Physicochemical measurement by gas chromatography. Chichester, New York: Wiley; 1979.
98. Grimsey IM, Feeley JC, York P. Analysis of the surface energy of pharmaceutical powders by inverse gas chromatography. J Pharm Sci 2002;91(2):571–583.
99. Cline D, Dalby R. Predicting the quality of powders for inhalation from surface energy and area. Pharm Res 2002;19(9):1274–1277.
100. Ohta M, Buckton G. Determination of the changes in surface energetics of cefditoren pivoxil as a consequence of processing induced disorder and equilibration to different relative humidities. Int J Pharm 2004;269(1):81–88.
101. Binnig G, Quate CF, Gerber C. Atomic force microscope. Phys Rev Lett 1986;56(9):930–933.
102. Luo XP, Silikas N, Allaf M, et al. AFM and SEM study of the effects of etching on IPS-Empress 2 (TM) dental ceramic. Surface Science 2001;491(3):388–394.
103. Danesh A, Chen X, Davies MC, Roberts CJ, Sanders GH, Tendler SJ. Polymorphic discrimination using atomic force microscopy: distinguishing between two polymorphs of the drug cimetidine. Langmuir 2000;16(2):866–870.
104. Trojak A, Kocevar K, Musevic I, Srcic S. Investigation of the felodipine glassy state by atomic force microscopy. Int J Pharm 2001;218(1–2):145–151.
105. Louey MD, Mulvaney P, Stewart PJ. Characterisation of adhesional properties of lactose carriers using atomic force microscopy. J Pharm Biomed Anal 2001;25(3–4):559–567.
106. Louey MD, Stewart PJ. Particle interactions involved in aerosol dispersion of ternary interactive mixtures. Pharm Res 2002;19(10): 1524–1531.
107. Eve JK, Patel N, Luk SY, Ebbens SJ, Robers CJ. A study of single drug particle adhesion interactions using atomic force microscopy. Int J Pharm 2002;238(1–2):17–27.
108. Hooton JC, German CS, Allen S, Davies MC, Roberts CJ, Tendler SJ, Williams P. Characterization of particle-interactions by atomic force microscopy: effect of contact area. Pharm Res 2003;20(3): 508–514.
109. Begat P, Morton DA, Staniforth JN, Price R. The cohesive-adhesive balances in dry powder inhaler formulations I: Direct quantification by atomic force microscopy. Pharm Res 2004;21(9):1591–1597.
110. Price R, Young PM. Visualization of the crystallization of lactose from the amorphous state. J Pharm Sci 2004;93(1):155–164.
111. Begat P, Young PM, Edge S, Kaerger JS, Price R. The effect of mechanical processing on surface stability of pharmaceutical powders: visualization by atomic force microscopy. J Pharm Sci 2003; 92(3):611–620.
112. Concessio NM, Hickey AJ. Descriptors of irregular particle morphology and powder properties. Adv Drug Deliv Rev 1997;26(1): 29–40.
113. Crooks PA, Damani LA. Drug application to the respiratory tract: metabolic and pharmacokinetic considerations. Respiratory Drug Delivery I 1990;1:61–90.
114. Patton JS, Platz MP. Pulmonary delivery of peptides and proteins for systemic action. Adv Drug Deliv Rev 1992;8:179–196.
115. Byron PR, Patton JS. Drug delivery via the respiratory tract. J Aerosol Med 1994;7:49–75.
116. Niven RW, Lott FD, Ip AY, Cribbs JM. Pulmonary delivery of powders and solutions containing recombinant human granulocyte colony-stimulating factor (rhG-CSF) to the rabbit. Pharm Res 1994; 11(8):1101–1109.
117. Cefalu WT. Concept, strategies, and feasibility of noninvasive insulin delivery. Diabetes Care 2004;27(1):239–246.
118. Owens DR, Zinman B, Bolli G. Alternative routes of insulin delivery. Diabet Med 2003;20(11):886–898.
119. Patton JS, Bukar J, Nagarajan S. Inhaled insulin. Adv Drug Deliv Rev 1999;35(2–3):235–247.
120. Patton JS. Pulmonary delivery of drugs for bone disorders. Adv Drug Deliv Rev 2000;42(3):239–248.
121. Roth Y, Chapnik JS, Cole P. Feasibility of aerosol vaccination in humans. Ann Otol Rhinol Laryngol 2003;112(3):264–270.

122. Tronde A, Norden B, Marchner H, Wendel AK, Lennernas H, Bengtsson UH. Pulmonary absorption rate and bioavailability of drugs in vivo in rats: structure-absorption relationships and physicochemical profiling of inhaled drugs. J Pharm Sci 2003;92(6): 1216–1233.
123. Hickey AJ. Pulmonary drug delivery: pharmaceutical chemistry and aerosol technology. In: Wang B, Siahaan T, Soltero RA, editors. Drug delivery: principles and applications. Hoboken, New Jersey: Wiley Interscience; 2005:341–361.
124. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part I: physiological factors affecting therapeutic effectiveness of aerosolized medications. Br J Clin Pharmacol 2003;56(6):588–599.
125. Howarth PH. Why particle size should affect clinical response to inhaled therapy. J Aerosol Med 2001;14 Suppl 1:S27–S34.
126. Bergstrom CA, Strafford M, Lazorova L, Avdeef A, Luthman K, Artursson P. Absorption classification of oral drugs based on molecular surface properties. J Med Chem 2003;46(4):558–570.
127. Palm K, Luthman K, Ungell AL, Strandlund G, Artursson P. Correlation of drug absorption with molecular surface properties. J Pharm Sci 1996;85(1):32–39.
128. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem 2002;45(12):2615–2623.
129. Kerns EH, Di L. Pharmaceutical profiling in drug discovery. Drug Discov Today 2003;8(7):316–323.
130. Barnes PJ. A single inhaler for asthma? Am J Respir Crit Care Med 2005;171(2):95–96.
131. Suarez S, Hickey AJ. Drug properties affecting aerosol behavior. Respir Care 2000;45(6):652–666.
132. Cheng YS, Marshall TC, Henderson RF, Newton GJ. Use of a jet mill for dispersing dry powder for inhalation studies. Am Ind Hyg Assoc J 1985;46(8):449–454.
133. Drogemeier R, Leschonski K. Ultra fine grinding in a two stage rotor impact mill. International Journal of Mineral Processing 1996; 44(5):485–495.
134. Hu G, Otaki H, Watanuki K. Optimization of grinding performance of tumbling ball mill. International Journal Series C-Mechanical Systems Machine Elements and Manufacturing 2001;44:267–274.
135. Steckel H, Brandes HG. A novel spray-drying technique to produce low density particles for pulmonary delivery. Int J Pharm 2004; 278(1):187–195.
136. Chawla A, Taylor KMG, Newton JM, Holbrook P. Production of spray dried salbutamol sulfate for use in dry powder aerosol formulation. Int J Pharm 1994;108:233–240.
137. Vidgren MT, Vidgren PA, Paronen TP. Comparison of physical and inhalation properties of spray-dried and mechanically micronized disodium-cromoglycate. Int J Pharm 1987;35:139–144.
138. Debenedetti PG, Tom JW, Kwauk X, et al. Rapid expansion of supercritical solutions (RESS): fundamentals and applications. Fluid Phase Equilibria 1993;82:311–321.
139. Velaga SP, Berger R, Carlfors J. Supercritical fluids crystallization of budesonide and flunisolide. Pharm Res 2002;19(1):1564–1571.
140. Schiavone H, Palakodaty S, Clark A, York P, Tzannis ST. Evaluation of SCF-engineered particle-based lactose blends in passive dry powder inhalers. Int J Pharm 2004;281(102):55–66.
141. Jung J, Perrut M. Particle design using supercritical fluids: literature and patent survey. J Supercritical Fluids 2001;20:179–219.
142. Handbook of pharmaceutical excipients. 4 ed. Washington DC: American Pharmaceutical Association; 2003.
143. Steckel H, Bolzen N. Alternative sugars as potential carriers for dry powder inhalations. Int J Pharm 2004;270(1–2):297–306.
144. Tee SK, Marriott C, Zeng XM, Martin GP. The use of different sugars as fine and coarse carriers for aerosolised salbutamol sulphate. Int J Pharm 2000;208(1–2):111–123.
145. Shah SP, Misra A. Development of liposomal amphotericin B dry powder inhaler formulation. Drug Deliv 2004;11(4):247–253.
146. Joshi M, Misra AN. Pulmonary disposition of budesonide from liposomal dry powder inhaler. Methods Find Exp Clin Pharmacol 2001;23(10):531–536.
147. Kawashima Y, Serigano T, Hino T, et al. Design of inhalation dry powder of pranlukast hydrate to improve dispersibility by the surface modification with light anhydrous silicic acid (AEROSIL 200). Int J Pharm 1998;173:243–251.
148. Lucas P, Anderson K, Potter UJ, Staniforth JN. Enhancement of small particle size dry powder aerosol formulations using an ultra low density additive. Pharma Res 1999;16(10):1643–1647.
149. Kawashima Y, Serigano T, Hino T, Yamamoto H, Takeuchi H. A new powder design method to improve inhalation efficiency of pranlukast hydrate dry powder aerosols by surface modification with hydroxypropylmethylcellulose phthalate nanospheres. Pharm Res 1998;15(11):1748–1752.
150. Podczeck F. The relationship between physical properties of lactose monohydrate and the aerodynamic behaviour of adhered drug particles. Int J Pharm 1998;160:119–130.
151. Islam N, Stewart P, Larson I, Hartley P. Effect of carrier size on the dispersion of salmeterol xinafoate from interactive mixtures. J Pharm Sci 2004;93(4):1030–1038.
152. Chew NYK, Chan HK. The role of particle properties in pharmaceutical powder inhalation formulations. J Aerosol Med 2002;15(3): 325–330.
153. Sethuraman VV, Hickey AJ. Powder properties and their influence on dry powder inhaler delivery of an antitubercular drug. AAPS PharmSciTech 2002;3(4):E28.
154. Wetterlin KIL. Design and function of Turbuhaler. In: Newman SP, Moren F, Crompton GK, editors. A new concept in inhalation therapy. London: Medicom; 1987.
155. Wetterlin K. Turbuhaler: a new powder inhaler for administration of drugs to the airways. Pharm Res 1988;5(8):506–508.
156. Yang TT, Kenyon D. Use of an agglomerate formulation in a new multidose dry powder inhaler. In: Dalby RN, Byron PR, Farr SJ, editors. Respiratory drug delivery VII. Raleigh, North Carolina: Serentec Press; 2000:503–505.
157. Ikegami K, Kawashima Y, Takeuchi H, Yamamoto H, Mimura K, Momose D, Ouchi K. A new agglomerated KSR-592 beta-form crystal system for dry powder inhalation formulation to improve inhalation performance in vitro and in vivo. J Control Release 2003;88:23–33.
158. Hickey AJ, Ganderton D. Pharmaceutical Process Engineering. New York: Dekker; 2001.
159. Sudah OS, Coffin-Beach D, Muzzio FJ. Effects of blender rotational speed and discharge on the homogeneity of cohesive and free-flowing mixtures. Int J Pharm 2002;247(1–2):57–68.
160. Alexander A, Shinbrot T, Johnson B, Muzzio FJ. V-blender segregation patterns for free-flowing materials: effects of blender capacity and fill level. Int J Pharm 2004;269(1):19–28.
161. Iida K, Leuenberger H, Fueg LM, Muller-Walz R, Okamoto H, Danjo K. [Effect of mixing of fine carrier particles on dry powder inhalation property of salbutamol sulfate (SS)]. Yakugaku Zasshi [Journal of the Pharmaceutical Society of Japan] 2000;120(1):113–119. *(Article in Japanese)*
162. Staniforth JN, Rees JE, Lai FK, Hersey JA. Interparticle forces in binary and ternary ordered powder mixes. J Pharm Pharmacol 1982; 34(3):141–145.
163. Neumann BS. The flow properties of powders. In: Bean HS, Beckett AH, Carless JE, editors. Advances in pharmaceutical sciences. New York: Academic Press; 1967;181–221.

164. Thomson FM. Storage of particulate solids. In: Fayed ME, Otten L, editors. Handbook of powder science and technology. New York: Van Nostrand Reinhold; 1984;365–463.
165. Concessio NM, VanOort MM, Knowles MR, Hickey AJ. Pharmaceutical dry powder aerosols: correlation of powder properties with dose delivery and implications for pharmacodynamic effect. Pharm Res 1999;16(6):828–834.
166. Muzzio FJ, Robinson P, Wightman C, Brone D. Sampling practices in powder blending. Int J Pharm 1997;155:153–178.
167. Lee TH, Lin SY. Microspectroscopic FT-IR mapping system as a tool to assess blend homogeneity of drug-excipient mixtures. Eur J Pharm Sci 2004;23(2):117–122.
168. Lai CK, Holt D, Leung JC, Cooney GK, Raju, Hansen P. Real time and noninvasive monitoring of dry powder blend homogeneity. AIChE J 2001;47:2618–2622.
169. El-Hagrasy AS, Morris HR, D'Amico F, Lodder RA, Drennen JK 3rd. Near-infrared spectroscopy and imaging for the monitoring of powder blend homogeneity. J Pharm Sci 2001;90(9): 1298–1307.
170. Oyebola MT, Podczeck F, Barrett D. The influence of particle size and relative humidity of air on the shear properties of pharmaceutical powders. Eur J Pharm Sci 2004;23:S46–S46.
171. Podczeck F, Newton JM, James MB. The influence of constant and changing relative humidity of the air on the autoadhesion force between pharmaceutical powder particles. Int J Pharm 1996;145: 221–229.
172. Podczeck F, Newton JM, James MB. Variations in the adhesion force between a drug and carrier particles as a result of changes in the relative humidity of the air. Int J Pharm 1997;149:151–160.
173. Young PM, Price R, Tobyn MJ, Buttrum M, Dey F. The influence of relative humidity on the cohesion properties of micronized drugs used in inhalation therapy. J Pharm Sci 2004;93(3):753–761.
174. United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry. Metered-dose inhaler (MDI) and dry powder inhaler (DPI) drug products (draft). October, 1998. http://www.fda.gov/cder/guidance/2180dft.htm. Accessed June 20, 2005.

Discussion

Smaldone: I have seen very little deposition data on powders. Have any of these fluid dynamics and fluidized beds been correlated with deposition?

Hickey: The problem is with labeling the particles. The likely approach is to do deposition studies, and I think probably the best one so far has been the technetium-labeled carbon particles approach they've been using at Pharmaceutical Profiles.

Newman: We've got a lot of experience doing deposition studies with powder inhalers. Some of this goes back to the days when I was at the Royal Free Hospital in London. That experience was imported into Pharmaceutical Profiles in Nottingham, and we have tested a wide range of devices: single-dose, multi-dose, and so forth. Radiolabeling is certainly an issue, as it is in any scintigraphy study.

Basically, for blends you need to radiolabel the drug and then blend it with lactose. The best, most rigorous approach uses technegas, which involves nanoparticles of technetium loaded onto the surfaces of the drug particles. Then there's a validation program you have to carry out. We've got plenty of experience with that.

Hickey: I think we should do as many deposition studies as we can. The focus is usually on the combination of the device and the formulation, not independently.

Dhand: You showed us these data with the cubes. I've been mulling over Gerry's [Smaldone] point. We don't have much data on standardization or testing of powder inhalers, how to characterize the aerosols produced by these devices.

Hickey: The in vitro testing is very different for MDIs and DPIs. For DPIs you do need to take into account pressure drop and not simply flow rate. Even though we do particle sizing, when we do DPI testing and particle sizing at different flow rates, patients are going through an inspiratory cycle, which influences drug dispersion, particularly with passive inhalers. It's not clear to me that we have the best way of mimicking that yet, or even fixing on a pressure drop that might occur for a small volume of air through the device, that reflects patient inspiratory flow. That is somewhat problematic, because now you start to use sampling tools such as the cascade impactor in conditions they were not developed for, and so the particle-size measurements you get from them are no longer representative of particle size. It's obtained at some arbitrary inspiratory flow through the device. That, plus the fact that we don't have tools for dispersing aerosols in a uniform way, raises the number of issues we haven't addressed.

Dhand: How does that play out with regulatory agencies and people going in for marketing new devices? How do we compare one device with another device or formulation?

Hickey: You just hit on a key point. There is no such thing as a generic DPI right now, and nobody can conceive of one in regulatory terms. They can in scientific terms, which is based on performance, but from a regulatory perspective it would be so difficult to set the parameters for a generic DPI. Many people are trying to figure that out. In the mean time, the examples I gave of these studies that have given flow rates under fixed pressure-drop conditions are the standard for how we approach this. I think there will be other ways of doing this later on.