Dry Powder Inhaler Formulation

Martin J Telko and Anthony J Hickey PhD DSc

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-

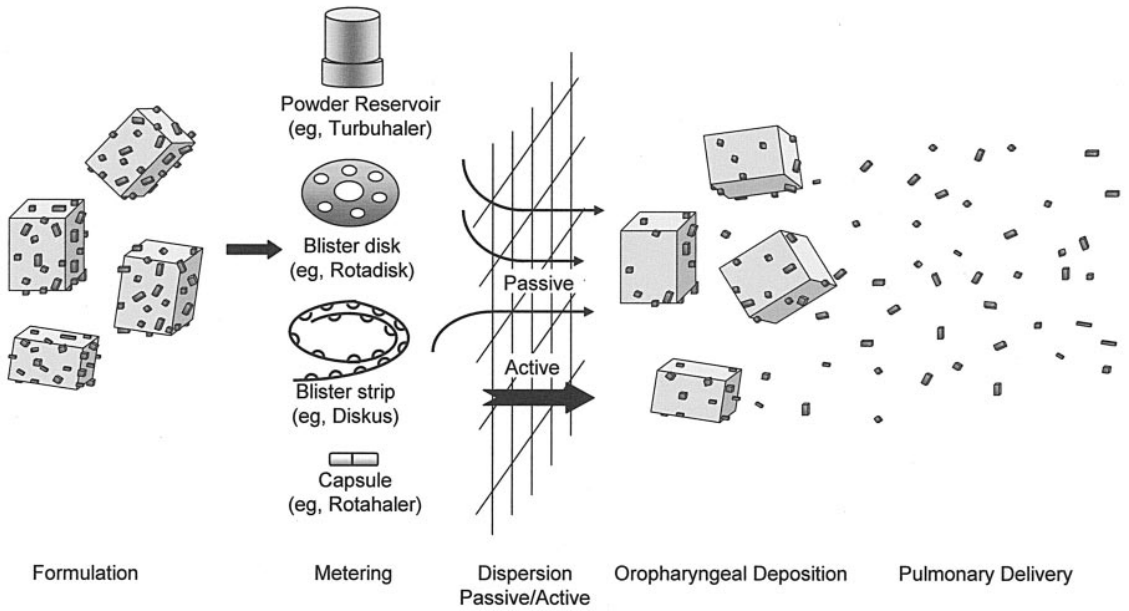

Fig. 1. Principle of dry powder inhaler design. The formulation typically consists of micronized drug blended with larger carrier particles, dispensed by a metering system. An active or passive dispersion system entrains the particles into the patient's airways, where drug particles separate from the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

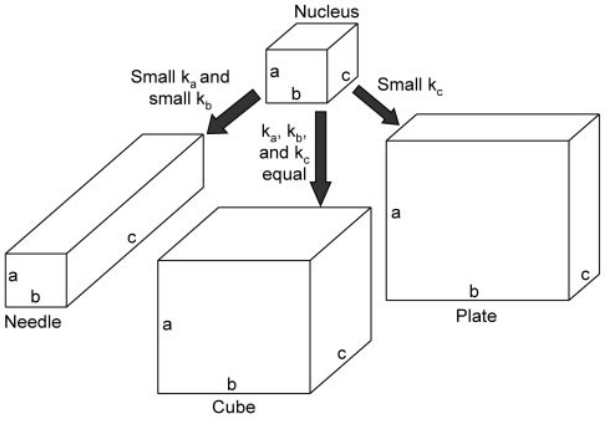

Fig. 2. Crystal habit. Inhibition of growth in one of more spatial directions (k_a, k_b, and k_c) results in particles with plate or needle morphology.

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.

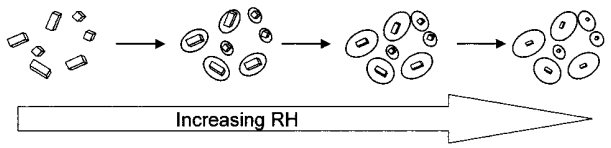

Fig. 3. Hygroscopic growth. Particles absorb moisture as they traverse the humid environment of the airways, resulting in increased particle size.

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

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