AEROSOLS

S P Newman, Nottingham, UK

Abstract

The inhaled route is used to deliver drugs as aerosols for the maintenance therapy of asthma, chronic obstructive pulmonary disease, and other conditions. The deposition of aerosol particles in the respiratory tract is an important prerequisite to obtaining a good clinical effect. Generally, inhaler devices should deliver particles smaller than approximately 5 μm in diameter in order to enter the lungs. A variety of inhaler devices are available for inhalation therapy. Pressurized metered dose inhalers (pMDIs) have been widely used for 50 years, but many patients have problems using them correctly. They are currently being reformulated with ozone-friendly propellants. Breath-actuated inhalers and spacer attachments may be useful supplements to pMDIs for some patients. Dry powder inhalers (DPIs) are easier to use correctly than pMDIs, and they do not require propellants. Many pharmaceutical companies seem to be prioritizing DPIs above pMDI reformulation, and they are also preferred by many patients. Nebulizers continue to be used widely, but the limitations of jet and ultrasonic nebulizers have led to the development of novel systems, sometimes involving vibrating meshes. Finally, a new class of inhalers (soft mist inhalers) is emerging, composed of multidose devices containing liquid formulations, some of which could challenge pMDIs and DPIs in the portable inhaler market.

Inhaled Drug Delivery

The pulmonary route may be used to deliver drugs for the maintenance therapy of some lung diseases, most notably asthma and chronic obstructive pulmonary disease (COPD). Drugs are also given by inhalation to treat other chest problems, including respiratory tract infections in cystic fibrosis. In addition, it is hoped that inhaled drugs intended to have a systemic action in the body (e.g., insulin) will soon be marketed. The potential benefits of the inhaled route have long been recognized, but the importance of good quality inhaler devices that deliver drugs reliably to the lungs has only been appreciated during the past 25 years.

Aerosol Properties

An understanding of aerosol properties and aerosol deposition is an important prerequisite for optimizing inhalation therapy. Drugs are given by inhalation as aerosols of solid particles or liquid droplets, but for simplicity the term 'particle' may be used to describe both solid and liquid dispersions. The most important property of an aerosol particle is its size, and this is best expressed as the aerodynamic diameter, which also takes into account particle density and shape. For spherical particles, aerodynamic diameter (D_a) and physical diameter (D_p) are related by the formula $D_a = D_p\sqrt{\rho}$, where ρ is the specific gravity of the material from which the particles are made. In practice, aerosol particles are seldom spherical; for instance, micronized drug particles are often highly irregular in shape.

Aerosol systems found in medicine are usually heterodisperse, indicating that the particles in a particular spray or cloud have a wide range of sizes. Monodisperse aerosols, in which all the particles have approximately the same size, are not normally found in pharmaceutical products, although they can be made using specialized equipment. It is preferable to describe the mass or volume distribution of an aerosol rather than the distribution of particles by number since many small particles may contain much less drug than a few large particles. In practice, particle size spectra from inhaler devices often approximate to log-normal distributions. The mass median aerodynamic diameter (MMAD) may be used to express the average aerosol size. This diameter is such that half the aerosol mass is contained in larger particles and half in smaller particles. The spread of particle sizes may be expressed as a geometric standard deviation (GSD), a dimensionless quantity. A perfectly monodisperse aerosol has a GSD of 1. A typical pharmaceutical aerosol may contain particles ranging in size from <0.5 to >10 μm, with an MMAD of 3–4 μm and a GSD of 2.0–2.5.

As explained later, deposition of aerosols depends critically on particle size. The fraction of the aerosol mass contained in particles <5 μm in diameter is usually termed the respirable fraction or fine particle fraction (FPF). These are the particles with the greatest likelihood of reaching the lungs in adults, although even smaller particles may be needed for drug therapies in small children. In adults, particles <3 μm in diameter are needed in order to deliver drugs to the alveolated regions – for instance, to deliver inhaled α_1 antitrypsin to the alveoli of patients with emphysema.

Particle size distributions of aerosols intended for pulmonary delivery may be quantified by several methods. The approach favored within the pharmaceutical industry is the cascade impactor, through which the aerosol is drawn by a vacuum pump, and particles of different sizes are collected on a series of stages. Each stage can be washed out with a solvent

so that the amount of drug associated with different size bands may be quantified by an analytical technique. Supplementary particle size data may be provided by optical methods, the best known of which is laser diffraction. This involves passing the aerosol cloud through a laser beam, and the angle of diffraction of the laser light is inversely proportional to particle size. It is important to remember that these *in vitro* measurements are undertaken primarily for purposes of quality control and product release, and they may not predict accurately drug delivery to the lungs *in vivo*.

Deposition of Pharmaceutical Aerosols

Several mechanisms cause aerosol particles to deposit in the respiratory tract, but the two most important ones relating to pharmaceutical aerosols are inertial impaction and gravitational sedimentation.

Inertial impaction takes place mainly in the oropharynx and at the bifurcations between major airways, when the aerosol particle has too much inertia to follow the air stream as it changes direction. The probability of inertial impaction occurring is proportional to D_a^2Q, where Q is the inhaled flow rate. Deposition in central lung regions may be enhanced by the effects of air turbulence, especially at fast inhaled flow rates. Gravitational sedimentation takes place mainly in smaller conducting airways and in the alveoli, when particles settle onto the airway surface under gravity either during slow steady breathing or during breath-holding. The probability of gravitational sedimentation occurring is proportional to D_a^2T, where T is the residence time of the particle in the airways. A third deposition mechanism (Brownian diffusion) is also important for aerosol particles $<1\,\mu m$ in diameter, which may be pushed in a random direction toward airway walls by collisions with gas molecules. Some particles (especially those $<1\,\mu m$ in diameter) are not deposited, and after inhalation they are simply exhaled.

In addition to particle size, the patient's inhalation also plays a major part in determining the site of aerosol deposition. The inhaled flow rate is particularly important, with slow inhalation usually being recommended in order to reduce impaction losses in the oropharynx. Deep inhalation and a period of breath-holding help to increase gravitational sedimentation in the peripheral parts of the lungs. For most pharmaceutical aerosols, lung deposition is enhanced by a combination of aerosol particles $<5\,\mu m$ in diameter and a slow inhaled flow rate ($20–30\,l\,min^{-1}$). As will be explained later, there is an exception to this rule for dry powder inhalers, where faster inhalation may preferable. Particles are filtered efficiently from the inhaled air by the nasal passages, so wherever practicable it is better to deliver an inhaled aerosol via a mouthpiece (with mouth breathing) than via a face mask (with nose breathing).

The airways of the patient who inhales the aerosol particles also determine the site and extent of deposition in two major ways. First, random variations in airway geometry between different individuals will lead to random variations in the deposition pattern. Hence, for aerosols delivered from any inhaler device, considerable intersubject variability of deposition is to be expected. Second, in patients with asthma, COPD, and other obstructive conditions, the airways may be narrowed by bronchospasm, inflammation, and mucus hypersecretion so that aerosol particles may deposit preferentially in the larger airways of the lungs, with less deposition in the peripheral airways.

Both electrostatic charge and humidity affect aerosol deposition in a variety of ways. The most striking effect of humidity is that dry particles composed of water-soluble materials are likely to absorb water when they enter the respiratory tract and, hence, to increase in size.

The deposition of pharmaceutical aerosols may be quantified by radionuclide imaging (gamma scintigraphy, single photon emission computed tomography (SPECT), and positron emission tomography (PET)). SPECT and PET are three-dimensional imaging methods and provide information about the distribution pattern within the lungs. However, PET is relatively complex and is probably not practical for use on a regular basis. Certain pharmacokinetic methods are also useful for assessing delivery of some drugs to the lungs. For instance, the plasma or urinary concentrations of albuterol in the first 30 min after inhalation are considered to result solely from pulmonary absorption.

Pressurized Metered Dose Inhalers

The pressurized metered dose inhaler (pMDI) has been the backbone of inhalation therapy for asthma for approximately 50 years, since its introduction by 3 M Riker Laboratories in 1956. Patients and physicians recognized the convenience of the pMDI, which contains 100–200 doses in a small portable device that is immediately ready for use (**Figure 1**). The pMDI consists of an aluminum can mounted in a plastic actuator. Individual doses (25–100 µl) are delivered as a spray via a sophisticated metering valve. The drug is usually a micronized suspension of drug particles but may be a solution dissolved in propellants, ethanol, or another excipient as a co-solvent.

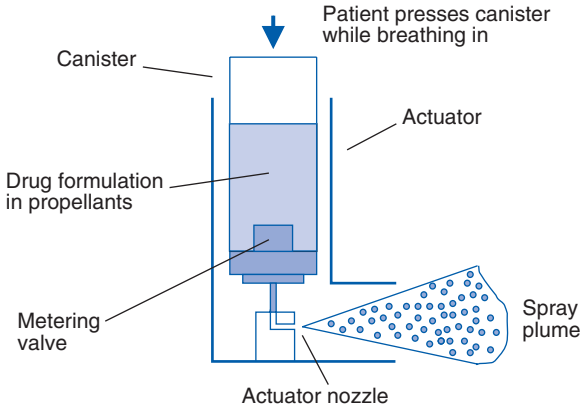

Figure 1 Design and operation of a typical pressurized metered dose inhaler.

The best known pMDI therapies include the β-agonists albuterol, terbutaline, and salmeterol and the glucocorticosteroids beclomethasone dipropionate, budesonide, and fluticasone propionate.

Successful pMDI therapy is highly dependent on the patient's inhalation technique, and patient education about their use is essential. In most pMDI products, it is necessary for the patient to press the pMDI at the same time as inhaling. Failure to do this is sometimes described as poor coordination or hand–lung dyscoordination, and it is probably the most important problem patients have with pMDIs. A second major problem using pMDIs is the so-called cold Freon effect, where the patient stops inhaling when the cold propellant spray is felt on the back of the throat. Freon is one of the trade names of chlorofluorocarbon (CFC) propellants. In order to optimize lung deposition from pMDIs, patients also need to inhale slowly and deeply and to hold the breath for several seconds. Even with perfect inhalation technique, no more than 10–20% of the dose from a CFC pMDI is deposited in the lungs, with the majority of the dose being deposited in the oropharynx. However, the lung dose will vary from product to product according to the nature of the formulation and the diameter of the actuator orifice.

Until recently, all pMDIs were formulated in CFC propellants, giving the pMDI an internal pressure of approximately 300 kPa (3 atm) and a spray velocity at the nozzle exceeding $30\,m\,s^{-1}$. However, it is possible to reduce the spray velocity by modifications to the actuator design, for instance, in the Spacehaler device (formerly known as Gentlehaler). During the past few years, the pharmaceutical industry has been forced to start reformulating pMDIs in non-CFC propellants, consisting of one of two hydrofluoroalkanes (HFA-134a or HFA-227). This challenge arose following the discovery that the degradation of CFCs damages stratospheric ozone and has proved to be a major stimulus to the development of novel inhaler technologies. The switch to HFA-powered pMDIs is in progress and will take several more years to complete. In the meantime, CFCs have been granted an essential-use exemption in pMDIs under the Montreal Protocol of 1987, reflecting their importance to the well-being of society. HFAs are greenhouse gases, and despite the fact that their contribution to global warming is small, this issue could restrict their future use.

The development of novel HFA pMDI formulations has not been a simple manner, owing to a range of technical factors and the need to demonstrate clinical efficacy and safety for the reformulated products. Individual companies have adopted one of two strategies. One strategy involves making a product that is bioequivalent with the CFC pMDI that is to be replaced so that the HFA pMDI can be used in exactly the same doses as the CFC pMDI. The alternative strategy is to make a product that deposits drug in the lungs more efficiently than a CFC pMDI. This usually involves formulating a corticosteroid product as a solution, enabling a very small particle size to be achieved as the propellant evaporates. With such a product, it is also possible to reduce the spray velocity and to deposit up to half the dose in the patient's lung, with greatly reduced oropharyngeal deposition, so that asthma control may be achieved using only a fraction of the CFC pMDI dose. A formulation of beclomethasone dipropionate (Qvar) was the first of these products to reach the market, and several similar products are either already marketed or in development.

Breath-actuated pMDIs may be helpful in patients with poor coordination, who cannot actuate the pMDI at the same time as inhaling. These devices contain triggering mechanisms that are operated by the patient's inhalation via the mouthpiece. However, it is unlikely that breath-actuated pMDIs confer any additional benefit on patients who can use a conventional pMDI successfully.

pMDIs with Spacer Devices

Spacer devices are widely used with pMDIs. These vary greatly in size and shape, with volumes of commercially available models ranging from 50 to 750 ml. The concept of a spacer is to place some distance between the point at which the aerosol is generated and the patient's mouth, allowing the propellant to evaporate and the rapidly moving aerosol cloud to slow down before it is inhaled (**Figure 2**). The most successful spacers have a one-way valve in

Figure 2 pMDI connected to a large volume spacer device.

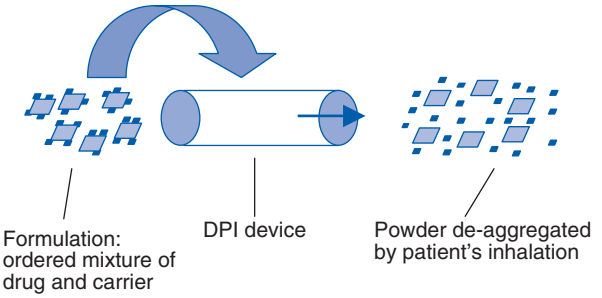

Figure 3 Principle of operation of a dry powder inhaler (DPI). The formulation most frequently consists of an ordered mixture of micronized drug and carrier lactose, which is de-aggregated by the patient's inhalation through the device.

the mouthpiece, which allows the pMDI to be actuated into the spacer, with a brief pause before the patient inhales so that it is not necessary to actuate and inhale simultaneously. Some spacers function effectively if the patient takes a series of relaxed tidal breaths from the device immediately after actuating a dose. Spacers reduce oropharyngeal deposition of drug and may increase lung deposition, but the majority of the dose is often deposited on the walls of the spacer. This may allow the reduction of the total body burden of inhaled corticosteroids compared with a standard pMDI. Large volume spacers, such as the Volumatic and Nebuhaler, have a well-accepted role in hospital emergency rooms for treating acute asthmatic attacks. Specially designed spacers with a volume of 200–300 ml are available for treating young children.

Most spacer devices are made of plastic, which may acquire a static charge during handling. This results in a suspended aerosol cloud being attracted to the spacer walls, with a marked reduction in the dose available for inhalation. Specific handling and washing techniques are usually recommended, and at least one lightweight metal spacer is available that is not susceptible to the effects of static charge. With correct use, including control over electrostatic charge effects, large volume (>500 ml) spacer devices may deposit more than 30% of the dose from a CFC pMDI in the patient's lungs.

Dry Powder Inhalers

Dry powder inhalers (DPIs) have been available commercially since approximately 1970, although the earliest prototypes were described several decades earlier. DPIs contain a powder formulation, which most frequently consists of an ordered mixture of micronized drug (<5 μm in diameter) and larger carrier lactose particles that are required to improve powder flow properties. The patient's inhalation through the device is used to disperse the powder and to ensure that some of the dose is carried into the lungs (Figure 3). An alternative type of formulation used in some DPIs consists either of micronized drug particles alone loosely aggregated into small spherules or of cospheronized drug and lactose.

DPIs are basically of three types: (1) unit-dose devices, in which an individual dose in a gelatin capsule or blister is loaded by the patient immediately before use; (2) multiple unit-dose devices, which contain a series of blisters or capsules; and (3) reservoir devices, in which powder is metered from a storage unit by the patient before inhalation. Unit-dose devices, including Spinhaler and Rotahaler, were the only DPIs available until the mid-1980s. Patients generally find multiple unit-dose devices, such as the Diskus (Accuhaler), and reservoir DPIs, such as the Turbuhaler, to be more convenient than unit-dose DPIs since they provide several weeks' treatment. DPIs tend to deposit a greater fraction of the dose in the lungs compared with CFC pMDIs, but in practice lung deposition varies widely between devices (Figure 4). Powder formulations are susceptible to the effects of moisture, and protecting the formulation against these effects is an important part of DPI design.

By the end of 2004, at least 16 DPIs had been marketed in different areas of the world for asthma and COPD therapy, involving a range of unit-dose, multiple unit-dose, and reservoir systems. A further 20–30 DPIs were also known to be in development. The anticipated expansion of the generics market for inhaled asthma and COPD drugs is likely to result in a number of these novel DPIs reaching the market. It is interesting to note that the major pharmaceutical companies with an interest in inhaled asthma and COPD drugs appear to be prioritizing the DPI over reformulated HFA pMDIs products. In particular,

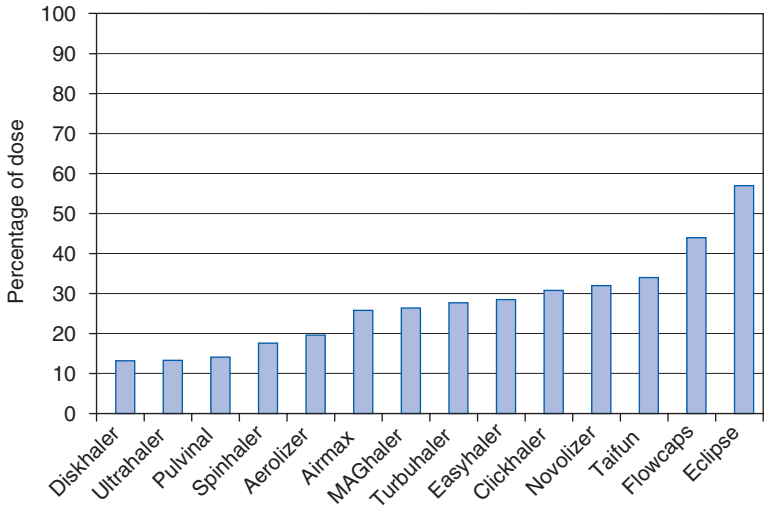

Figure 4 Mean percentage of the dose deposited in the lungs from 14 dry powder inhalers (DPIs), obtained in scintigraphic studies. The high lung deposition from the Flowcaps and Eclipse DPIs probably reflects the properties of the formulation as much as the DPI.

combination products in DPIs containing a long-acting β-agonist and a corticosteroid (e.g., Advair Diskus and Symbicort Turbuhaler) have been very successful. However, DPIs tend to be more expensive than pMDIs, and this may limit their use, especially in developing countries.

DPIs have two major advantages over pMDIs. First, they do not contain propellants. Second, all currently marketed models are breath-actuated, and patients find them easier to use correctly than pMDIs. However, this second advantage is closely linked to a disadvantage. In order to disperse the powder as efficiently as possible, and hence to maximize lung deposition, it may be necessary for patients to inhale as forcefully as possible via the DPI, and some patients may be either unable or unwilling to do this. All DPIs exhibit some degree of inhaled flow rate dependence, with forceful (fast) inhalation tending to give higher lung deposition than more gentle (slow) inhalation. For instance, in the Turbuhaler DPI, a reduction in peak inhaled flow rate from 60 to 30 l min^{-1} was shown to result in a reduction in lung deposition from 27% to 14% of the dose. In this respect, DPIs present a paradox since fast inhalation per se is generally associated with enhanced deposition in the oropharynx, as described previously. Low inspiratory effort through a DPI may result in a reduced emitted dose and poor particle deaggregation.

The actual magnitude of the peak inhaled flow rate associated with forceful inhalation will vary between devices from <30 to >100 l min^{-1}, according to the resistance to airflow of each device. Not only the peak inhaled flow rate achieved through the DPI but also the time taken to reach the peak flow will determine how efficiently particles are deaggregated. In practice, it seems that almost all patients with stable asthma or COPD can inhale sufficiently well via DPIs to benefit from them.

Several so-called active DPIs have been developed, in which the powder is dispersed by some mechanism other than the patient's inhalation – for instance, by an internal source of compressed air or by a fan driven by an electric motor. These active DPIs are generally more complex than breath-actuated DPIs and may come to be used primarily for therapies that require very efficient and reproducible targeting of drugs to specific lung regions, such as inhaled peptides for systemic therapy.

Sophisticated formulations for use in DPIs are also in development. These include drug/lactose blends, in which the surface of the lactose particles has been smoothed in order to aid dispersion, or particles made by processes other than micronization. For instance, a spray-dried formulation of the antibiotic tobramycin is under development for the treatment and prevention of respiratory tract infections in patients with cystic fibrosis, consisting of low-density spherical particles that disperse efficiently with minimal inspiratory effort. An advantage of these sophisticated formulations is that often they can be delivered efficiently to the lungs using very simple and inexpensive DPI devices.

Nebulizers

Drugs may often be formulated as solutions in water or ethanol, and they may be delivered by nebulizers

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.