Delivery Options and Devices for Aerosolized Therapeutics*

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Although inhalation is one of the oldest modes of drug delivery, it is currently receiving renewed attention. Prior to 1987, aerosolized therapeutics were delivered via systems that relied on chlorofluorocarbon propellant systems. The subsequent ban on all nonmedical uses of these inert gases stimulated pharmaceutical companies to investigate other propellant systems. Two hydrofluoroalkanes were effective. However, in some instances, the change in propellant required reformulation of the drugs to be delivered. In some cases, bioequivalence could be achieved at lower doses with reduced toxicity. Pressurized metered-dose inhalers (pMDIs) have been used to deliver many types of inhaled therapeutics since the 1960s. Their major limitation is that drug delivery and effectiveness are affected by patient factors, including coordination difficulties and problems related to breathing and breath holding in patients with airway disease. Dry-powder inhalers are being developed to deliver powdered formulations of drugs such as bronchodilators and anti-inflammatory drugs for the treatment of asthma and COPD, and, eventually, proteins, peptides, recombinant products, and gene therapeutics. These devices have been proven to be as efficient as pMDIs in clinical trials. In some cases, they deliver a greater amount of the drug to the lungs. Percentages of the emitted dose deposited in the lungs range from 15 to 40% with the current generation of these devices. Finally, metered-dose liquid inhalers also are under development. Drug deposition in the lung with devices that are currently being tested ranges from 30 to 80% of the emitted dose. The choice of delivery system depends on the effective dose, drug deposition, patient ability, patient acceptance, and cost. Patient education in the correct use of each device is essential to maximize the therapeutic benefit.

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Abbreviations: CFC = chlorofluorocarbon; DPI = dry powder inhaler; HFA = hydrofluoroalkane; MDLI = metered-dose liquid dose inhaler; pMDI = pressurized metered-dose inhaler

*From the University of Arkansas for Medical Sciences, Little Rock, AR. Dr. Anderson is an investigator or subinvestigator for AstraZeneca Pharmaceuticals; Boehringer Ingelheim Pharmaceuticals; GlaxoSmithKline, TAP Holdings, 3M Pharmaceuticals; St. Paul, MN; required reformulation as the ban, many pharmaceutical companies began to investigate other formulations and delivery systems for inhaled therapeutics. Two propellants that were found to be effective substitutes for CFCs were the hydrofluorokanes (HFAs), HFA 134a and HFA 227.

The substitution of HFA propellants for CFC propellants changed the properties of some of the drugs delivered by CFC propellant systems and required reformulation of the drugs. In general, the HFA-propelled systems deliver a softer spray and alter the taste of the drug. HFA-propelled beclomethasone, recently available in the United States for the treatment of asthma (QVAR; 3M Pharmaceuticals; St. Paul, MN), required reformulation as a solution rather than a suspension for delivery via the HFA propellant. The reformulation resulted in an increase in the fine-particle fraction and also reduced the velocity with which particles exit the pressurized metered-dose inhaler (pMDI). These changes caused increased drug delivery to the lungs and reduced deposition in the oropharynx. As a result, the same degree of asthma control could be obtained with half of the beclomethasone dose. Figure 2 shows radiolabeled lung scans of a healthy individual who inhaled equal doses of either HFA-propelled or CFC-propelled beclomethasone. It can be seen that HFA-propelled formulations achieved greater lung deposition. The improved drug deposition was of sufficient magnitude that the actual drug dose could be reduced by 50%. Thus, the change from CFC to HFA propellant and the subsequent reformulation of beclomethasone as a solution produced equivalent pharmacokinetics at half the dose. Toxicity and adrenal suppression were equal at equal doses. Figure 3 shows that an equivalent pharmacokinetic effect could be obtained with 200 μg HFA-propelled beclomethasone or 400 μg CFC-propelled beclomethasone. HFA-propelled alfentanil, which is available both in the United States and Canada, appears to be bioequivalent to the CFC-propelled formulation at the same dose.

Dry-Powder Inhalers

In addition to researching new propellants following the ban on CFCs, pharmaceutical companies also began to
develop inhalable drugs in new forms such as dry powders. This was not entirely new territory. Dry-powder inhalers (DPIs) such as the AeroHaler (Abbott Laboratories; Abbott Park, IL) (Fig 4), which was used principally for aerosolizing penicillin, had been in existence for > 50 years. Clinical trials of these devices have shown them to be equal to pMDIs; some studies have suggested that lower drug doses may be comparably as effective when administered with a DPI device.

Several DPIs are available in the United States at present, but a greater number of more sophisticated DPI devices are currently available in Europe. They have a more stable aerosol and are activated and driven by inspiratory flow. Their efficiency may vary according to inspiratory flow rate as many are designed to maximize drug delivery at a relatively high inspiratory flow rate. Thus, young children or patients with severely compromised airways or pulmonary exacerbations may have difficulty using DPI devices. It is also important for the clinician to be aware that patients are not able to sense drug delivery with these devices and, thus, may not realize that they are receiving the medication.

Two DPIs in common use in the United States are the Diskus (Glaxo SmithKline Inc; Research Triangle Park, NC) and the Turbuhaler (Astra Zeneca Pharmaceuticals; Wilmington, DE). Currently, salmeterol and the combination of salmeterol and fluticasone are available for delivery via the Diskus. Drug dose is stable over flow rates ranging between 30 and 90 L/min. The Diskus inhaler contains multiple doses of the drug sealed in blister packs.
which confers better protection against moisture. This device is recommended for use in patients ≥ 4 years of age for salmeterol and ≥ 12 years for the combination of salmeterol and fluticasone.

The Turbuhaler, which has been available in Europe for a number of years, has a drug reservoir. Each dose is sheared off by a cocking mechanism. Use of this device results in relatively high drug deposition in the lung, particularly in comparison with a pMDI. The device output also is somewhat flow-dependent. It is optimally operated at an inspiratory flow rate of 60 L/min. The Turbuhaler is recommended for patients ≥ 6 years of age. Currently, in the United States, it is available for use with budesonide. In Europe, it also is used to deliver other bronchodilators and steroids.

**DPIs Currently in Development**

A large number of increasingly effective and sophisticated DPIs are currently in development in the United States, Canada, and Europe. Figure 5 shows the Spiros, currently under development by Dura Pharmaceuticals (San Diego, CA). It is a small (approximately 6 x 10 cm), handheld, breath-actuated, battery-assisted device that contains 30 doses in a rotating cassette. When the patient initiates a breath, a twin-bladed impeller aerosolizes the drug. It is optimally operated at 15 L/min. The fact that it is operated at such a low flow rate makes it advantageous for use in pediatric patients and in those persons with severe airflow obstruction or in those who suffer from periodic pulmonary exacerbations that increase airflow obstruction. The disposable device has a life span of 1,500 actuations.

The Clickhaler (ML Laboratories; Leicestershire, UK) (Fig 6) is a multidose reservoir device that also is breath-actuated. It is effective at flow rates from 15 to 60 L/min.

Inhale Therapeutics Systems (San Carlos, CA) has developed a DPI primarily for use with inhaled insulin. It generates compressed air to release powder into a holding chamber. Other DPIs under development include the EasyHaler from Finland (Orion Farmos; Kuopio, Finland), the UltraHaler from Fisons (Loughborough, United Kingdom), and the Pulvinal from Chiesi (Parma, Italy).

**Drug Deposition in the Lung With DPIs**

The percentage of the emitted dose that is deposited in the lung varies among the different DPI devices (Fig 7). Lung deposition with the TurbuHaler is approximately 25%, and it is 15% with the Diskus DPI. The Spiros DPI delivers approximately 40% of the emitted dose to the lungs. DPIs thus represent a significant improvement over pMDIs, which deliver approximately 10% of the emitted drug dose.

For most DPIs, drug deposition is greater at higher flow rates (Fig 8). However, the Spiros DPI is an exception as it is meant to operate optimally at 15 L/min. At 15 L/min, drug deposition is approximately 40%. It decreases if the patient breathes faster.
from different DPIs at two different inspiratory flow rates (IFRs). Most DPIs deliver lower amounts of aerosol to the lungs at less than the optimal flow rates. From Dolovich.9

Figure 8. Lung deposition, as a percentage of the emitted dose, from different DPIs at two different inspiratory flow rates (IFRs). Most DPIs deliver lower amounts of aerosol to the lungs at less than the optimal flow rates. From Dolovich.9

### CHOICE OF DELIVERY SYSTEM

pMDIs, DPIs, and nebulizers all have advantages and disadvantages. The pMDI is inexpensive and convenient but requires patient coordination to operate effectively. Most pMDIs still use CFC propellant systems.

### NEBULIZER

Air-jet and ultrasonic nebulizers are non-propellant-based alternatives for the delivery of inhaled therapeutics that predate metered-dose inhalers. These devices do not require a coordinated breathing maneuver or a strong inspiratory effort, and so they have received substantial use by pediatric, elderly, and hospitalized patient populations. In particular, the simple nebulization of a fast-acting bronchodilator is an effective way to treat an acute bronchospasm attack without placing unreasonable demands on the distressed patient. Nebulizers also have been the only method available for delivering very high doses of some inhaled drugs, most notably antibiotics and mucolytics for the treatment of cystic fibrosis. In these special cases, the amount of drug that must be deposited in the airways to achieve efficacy far exceeds the payload capabilities of pMDIs and DPIs.

Numerous studies have shown that pMDIs with spacers are at least as effective, if not more so, than nebulizers, or are more effective in the hospital, in the emergency department, and at home. Nebulizers continue to be used with great frequency, although they are cumbersome, time-consuming, and relatively inefficient, because many clinicians believe them to be superior to pMDIs. It should be noted that certain drugs require a nebulizer for delivery. These include antibiotics and rhDNase (Pulmozyme [dornase alfa] Recombinant Inhalation Solution; Genentech, Inc; South San Francisco, CA). Nebulizers also may be necessary for the delivery of recombinant products and gene therapeutics. Except in those cases in which the type of therapeutic agent dictates the delivery system, the choice of delivery system depends first on clinical benefit. The efficiency of dose delivery, upper and lower respiratory tract drug deposition, and toxicity all must be considered. Cost also is an important consideration. Ease of use and convenience should be considered. The optimal delivery device is the one a given patient can and will use.

### PATIENT EDUCATION

**Metered-Dose Inhalers**

With both pMDIs and DPIs, drug delivery and efficacy are affected by patient factors. Numerous studies since the 1960s have demonstrated rates of incorrect pMDI use ranging from 12 to 90%. Patient problems may include difficulties with coordination, the inability to breathe sufficiently slowly for drug delivery, and difficulty in breath holding.

One way of improving drug delivery in patients who experience these types of problems using a pMDI is to use a spacer or holding chamber. The following are the three basic designs: the open tube; the holding chamber; and the reverse-flow design. The holding chamber design appears to function best for patients who are experiencing coordination difficulties. Coordination is still required for both the open tube and the reverse-flow design. Spacers and holding chambers decrease oropharyngeal deposition and improve drug delivery to the lungs in patients experiencing difficulties using a pMDI effectively. They are also important for decreasing oropharyngeal deposition of inhaled steroids.

Although package inserts recommend the regular washing of spacers and holding chambers, plastic spacers in particular often develop an electrostatic charge that may attract significant amounts of drug before it exits the spacer. Thus, with continued use, the drug coats the spacer, decreasing electrostatic charge, and an increasing dose is delivered to the patient. This problem can be exacerbated if the patient washes the device frequently and rubs it dry, increasing the electrostatic charge. Instead, patients should be instructed either to dry the device with an antistatic cloth or to rinse it in a weak detergent solution and let it air dry to avoid loss of drug in the spacer or chamber.

Patients often ask whether it is acceptable to actuate multiple puffs into a spacer prior to inhaling. They should be informed that even one additional puff into the spacer would decrease the amount of drug that is released. Only one puff should be actuated each time in order to avoid adversely affecting medication delivery.

**DPIs**

DPIs are used differently from pMDIs, and patients must be correctly instructed in their use. It is not necessary to shake the device. The dose must be loaded, and loading is position-sensitive. The device is held horizontally and placed on the lips; inhalation must be forceful and deep. It is necessary to hold the breath, to increase lung deposition by the settling of the drug particles. The patient should be instructed not to exhale through the DPI, as it must be kept dry.
**Future Delivery Systems**

Several new products are in the research-and-development pipeline. The Respimat (Fig 9), which is being tested by Boehringer Ingelheim Pharmaceuticals, Inc (Ridgefield, CT), is a metered-dose liquid inhaler (MDLI) that employs a multidose reservoir.\(^\text{11}\) It functions similarly to a pMDI, except that it delivers a stream of liquid. Like the pMDI, it is mechanically actuated and requires patient coordination for inhalation and effective drug delivery. Drug deposition in the lung with this particular device is approximately 30 to 40% of the emitted dose.\(^\text{12}\)

Another device currently being tested is the AER Pulmonary Drug Delivery System (Aradigm; Hayward, CA).\(^\text{13}\) It, too, is a MLDI with a multidose reservoir. It has been developed for topical drug delivery but also is being used with systemic drugs like insulin analog and hematopoietic drugs. The drug is contained in unit-dose blister packs. Delivery is computer-controlled. The liquid is extruded under pressure through a nozzle. Drug deposition in the lung is extremely high at approximately 80%. This fact would be particularly advantageous when choosing a delivery device for expensive medications such as gene therapeutics and recombinant products.

**Summary**

In summary, it is important for the clinician to be aware that dose efficacy, deposition, and toxicity all can be influenced by the drug formulation, the propellant, and/or the delivery device. Therefore, a familiar drug in a new formulation or delivered using a different device may not function as expected based on prior experience.

\[\text{Figure 9. The Respimat, an MLDI. From Zierenberg.}^\text{11}\]

**References**

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