

The Inhalation of Drugs: Advantages and Problems

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Inhalation is a very old method of drug delivery, and in the 20th century it became a mainstay of respiratory care, known as aerosol therapy. Use of inhaled epinephrine for relief of asthma was reported as early as 1929, in England. An early version of a dry powder inhaler (DPI) was the Aerohalor, used to administer penicillin dust to treat respiratory infections. In the 1950s, the Wright nebulizer was the precursor of the modern hand-held jet-venturi nebulizer. In 1956, the first metered-dose inhaler (MDI) was approved for clinical use, followed by the SpinHaler DPI for cromolyn sodium in 1971. The scientific basis for aerosol therapy developed relatively late, following the 1974 Sugarloaf Conference on the scientific basis of respiratory therapy. Early data on the drug-delivery efficiency of the common aerosol delivery devices (MDI, DPI, and nebulizer) showed lung deposition of approximately 10–15% of the total, nominal dose. Despite problems with low lung deposition with all of the early devices, evidence accumulated that supported the advantages of the inhalation route over other drug-administration routes. Inhaled drugs are localized to the target organ, which generally allows for a lower dose than is necessary with systemic delivery (oral or injection), and thus fewer and less severe adverse effects. The 3 types of aerosol device (MDI, DPI, and nebulizer) can be clinically equivalent. It may be necessary to increase the number of MDI puffs to achieve results equivalent to the larger nominal dose from a nebulizer. Design and lung-deposition improvement of MDIs, DPIs, and nebulizers are exemplified by the new hydrofluoroalkane-propelled MDI formulation of beclomethasone, the metered-dose liquid-spray Respimat, and the DPI system of the Spiros. Differences among aerosol delivery devices create challenges to patient use and caregiver instruction. Potential improvements in aerosol delivery include better standardization of function and patient use, greater reliability, and reduction of drug loss. *Key words:* aerosol, metered-dose inhaler, dry powder inhaler, nebulizer, MDI, DPI. [Respir Care 2005;50(3):367–382. © 2005 Daedalus Enterprises]

Introduction: The Inhalation of Drugs for Respiratory Disease

The use of inhaled and aerosolized medications for treatment of diseases of the respiratory tract has a long history in medical therapy. Inhalation therapy for asthma and other

complaints had a traditional place in Ayurvedic medicine, whose origins date back 4,000 years.¹ In 17th-century Ayurvedic literature there are instructions for smoking an anticholinergic preparation from the *Datura* group of herbs for asthma or cough with dyspnea.¹ Inhaled *Datura* for asthma was recorded in 1802 in Britain, and in 1797 a Philadelphia physician, Samuel Cooper, experimented with *Datura stramonium* preparations.¹ Asthma cigarettes (Fig. 1) (which contained stramonium leaves and had atropine-like effects), along with powders and cigars, were widely used in the 19th century as “fuming asthma remedies.”^{1,2} Medications have also been added to boiling water to allow inhalation.

Muers reports that the word “nebuliser” was defined in 1874 as “an instrument for converting a liquid into a fine spray, especially for medical purposes.”³ Seeger’s fire-powered steam nebulizer was advertised in *Geo. Tiemann*

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Fig. 1. Methods of inhaling formulations of stramonium, an atropine-like compound with anticholinergic effects, used in the 19th century.

and Co's Surgical Instruments Catalogue in New York in 1876.³ After the turn of the 20th century, newly discovered and isolated preparations of epinephrine and ephedrine began to supplant use of atropine-like substances such as stramonium.¹

Origins of Modern Aerosol Therapy

In 1929, in England, Camps evaluated and recommended use of epinephrine via inhalation, and described "spraying it into the tracheobronchial tract."⁴ In a 1948 publication, Benson and Perlman described the "spray method for administering epinephrine" as originating "with certain relatively obscure individuals in the Pacific Northwest" of the United States.⁵ They state that these individuals "appear not to have contributed to the regular medical journals, but have formed companies to produce a racemic brand of epinephrine and a fine nebulizer for administration."

Benson and Perlman⁵ kept a record of 2,236 asthma patients in their practice, and reported that 48 of 648 users of oral spray epinephrine were fatalities (7.4%), while only 22 of 1,588 non-users were fatalities (1.4%). Although not acknowledged by those authors, their results were early evidence that inhaled β agonists alone will not control the sometimes fatal pulmonary inflammation of asthma. Their work presaged the subsequent debate over the potentially harmful effects of inhaled β_2 agonists in asthma almost 50 years later.⁶ The kit sold for inhaling epinephrine consisted of a bottle of 1:50 solution of racemic epinephrine and an all-glass nebulizer, which in all likelihood was the DeVilbiss No. 40 glass nebulizer (Fig. 2A), introduced for treatment of asthma in the 1930s.^{3,5}

The first real precursor to the modern T-piece plastic hand-held pneumatic nebulizer was the 1950s Wright neb-

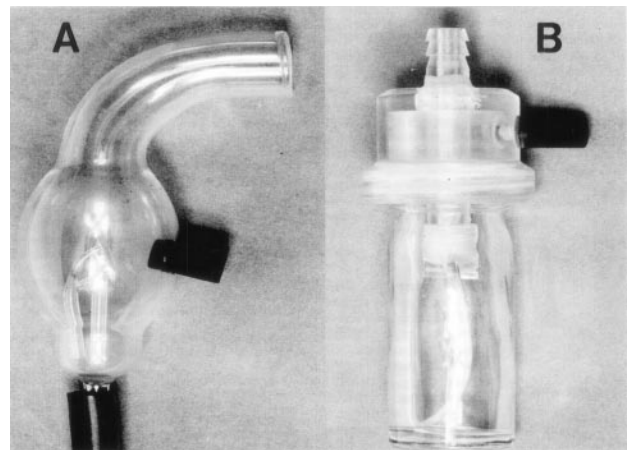


Fig. 2. A: The DeVilbiss No. 40 glass squeeze-bulb nebulizer. B: The Wright jet-venturi nebulizer, introduced in the late 1950s.

ulizer (see Fig. 2B), made of Perspex, a shatter-resistant plastic used for fighter-plane canopies.³ This device used a combination of gas flow, precise venturi orifices, and baffles to produce aerosol particles more in the fine particle range of 1–5 μm . The earlier DeVilbiss glass nebulizer and hand-bulb atomizers generated a wide range of particle sizes, and many of the particles were too large to reach the lower airways.³

In 1944, Bryson et al published work on the introduction of nebulized penicillin for treatment of respiratory infection.⁷ They described a mist formed by oxygen or air forced through aqueous solutions of the drug. Shortly thereafter, in 1949, Krasno and Rhoads described the inhalation of penicillin dust for management of respiratory infections, particularly sinusitis.⁸ Their inhalation device, known as the Aerohalor (Fig. 3), was produced by Abbott Laboratories. This was actually the first dry powder inhaler (DPI), and it used small cartridges of powdered penicillin

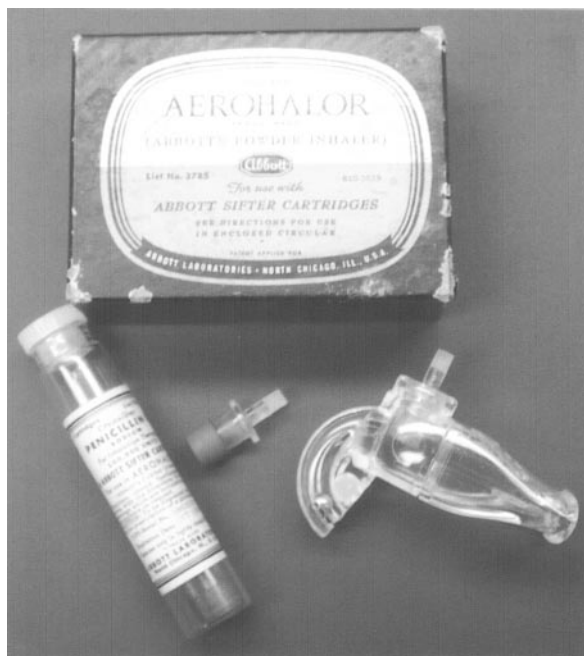


Fig. 3. The Aerohalor was an early dry powder inhaler, reported by Krasno and Rhoads,⁸ used for inhalation of penicillin dust to treat respiratory infections. (From Reference 2, with permission.)

that fit into a rather modern-appearing clear plastic inhaler.^{2,8} The advantages of aerosol drug delivery noted by Krasno and Rhoads remain those seen with aerosol therapy today: simplicity, low cost, little need for manipulation or instruction, no pain of injection, sustained localized action, and less local irritation than liquid nebulized penicillin.⁸

Development of Modern Aerosol Delivery Devices

One of the most interesting stories of drug-device implementation is the origin of the metered-dose inhaler (MDI), as described by Charles G Thiel.⁹ Thiel worked for Riker Laboratories, a subsidiary of Rexall Drugs and the company that developed the MDI. In 1955, Susie, a 13-year-old asthmatic, struggled with her squeeze-bulb nebulizer, and asked her father why she couldn't get her inhaled medicine from a spray can, in the way in which hairspray is packaged. Susie was the daughter of George Maison, then President of Riker Laboratories. Apparently her father had also been frustrated with the fragile, easily breakable glass-bulb nebulizers. In the spring of 1955, a propellant ("FREON," a trademark name for a certain mixture of chlorofluorocarbons 12 and 114), a metering valve, a glass vial device, and drug formulations of isoproterenol and epinephrine were investigated and assembled. In June of 1955, a clinical trial was conducted at the Long Beach, California, Veterans Administration Hospital by a Dr Karr.

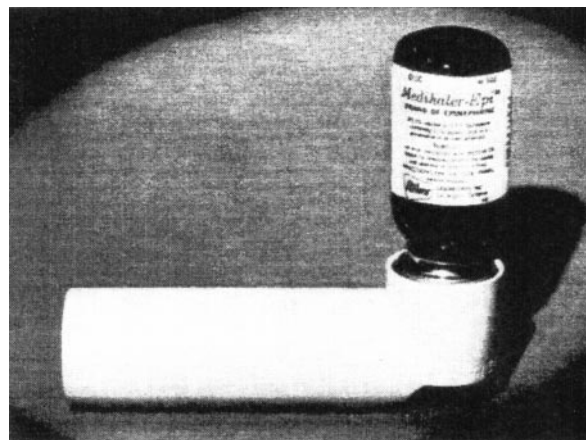


Fig. 4. The Medihaler-Epi was the original metered-dose inhaler for epinephrine. (From Reference 9, with permission.)

The New Drug Application was filed on January 12, 1956, and consisted of a file only 13 mm thick—unheard of in today's new-drug-submission-and-testing system. The drug-delivery device was approved by the Food and Drug Administration on March 9, 1956, and the Medihaler-Iso and the Medihaler-Epi were launched later that month. It is even more interesting that the original MDI of Medihaler-Epi (Fig. 4) differs very little from the appearance and even function of current MDI devices. Following the release of the MDI, a DPI (the SpinHaler) for delivery of the anti-asthmatic drug cromolyn sodium was developed and approved. The article by Bell et al,¹⁰ describing and evaluating the SpinHaler, gave the following rationale for the new device:

It is not generally realized that, with the pressurized aerosol. . . the administration of medication requires coordination of activation with the inspiratory cycle of respiration if variation in the quantity and site of drug deposition in the airways is to be minimized.¹⁰

Bell et al¹⁰ noted a primary problem for optimal use of MDIs, namely, the difficulty for patients in activating the MDI while simultaneously beginning a slow deep inhalation. Because it was a breath-actuated device, the SpinHaler relied on the force of a patient's inspiratory flow to spin a small plastic propeller, thereby creating turbulent airflow through the device, and disaggregating drug powder from its carrier lactose particles (Fig. 5),¹¹ which created a fine powder suitable for penetration to the lower airways. The SpinHaler was breath-actuated, so it eliminated the need to coordinate device actuation with patient inhalation (which is critical to effective MDI use).

The problem of coordinating inhalation with MDI-actuation, along with the high loss of drug in the oropharynx, which contributes to systemic adverse effects, ultimately

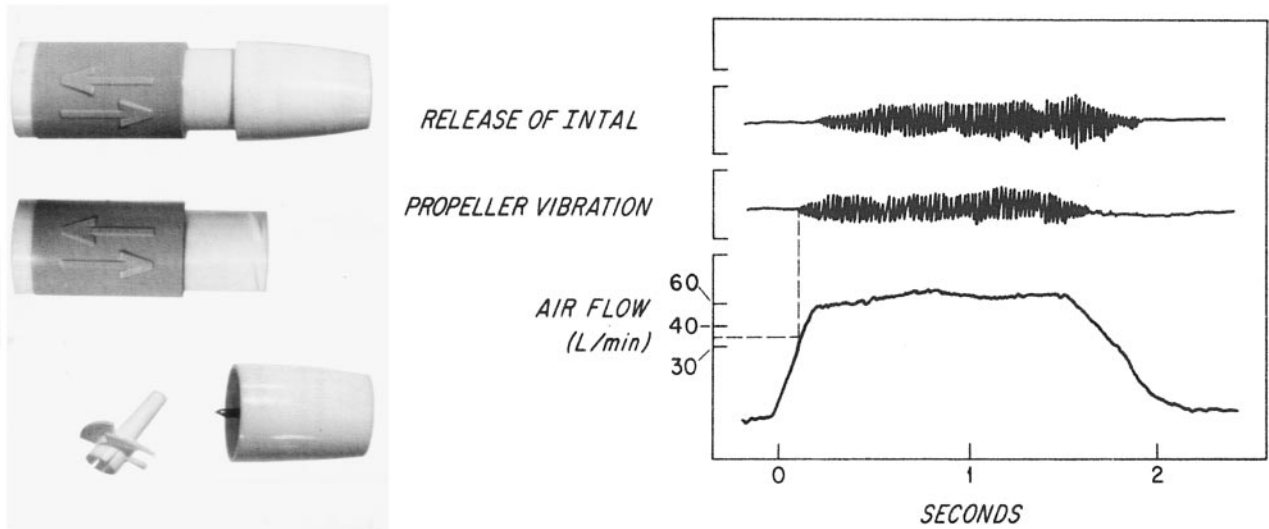


Fig. 5. The SpinHaler, a dry powder inhaler to deliver cromolyn sodium, reported in 1971 by Bell et al.¹⁰ (Based on data from Reference 11.)

led to the development of spacer devices (add-on tubes with no valves) and holding chambers (extension tubes with 1-way inspiratory valves to contain the aerosol). This distinction in terminology between “spacer” and “holding chamber” is based on a presentation of Dr Myrna Dolovich at the Drug Information Association meeting on spacer devices in 1995.¹²

In 1976, an early breath-actuated MDI system was developed to simplify the coordination of actuation and inhalation, but the device required almost 50 L/min of inspiratory airflow to operate.¹³ In 1978, Folke Morén investigated the effect of spacer tube design on delivery of pressurized MDI aerosols.¹⁴ Newman et al had also noted that a high proportion of the fast-moving and larger MDI aerosol particles deposit in the oropharynx, not in the lungs.¹⁵ In 1981, Newman et al examined the deposition of MDI aerosol, using small (10-cm long) and large (750-mL) “extension” devices.¹⁶ Their results showed unchanged alveolar deposition, but initial oropharyngeal deposition was reduced from 82% with the MDI alone to 57% with the large-volume pear-shaped spacer.

In 1982, at the conference of the American Association for Respiratory Care, held in New Orleans, Louisiana, Dr Martin Tobin graphically described the lack of patient coordination in using MDIs, and introduced the InspirEase drug delivery system for MDIs (Fig. 6).¹⁷ The advantages of this spacer device were its relatively small size, collapsibility, the presence of an airflow signal to warn of too high an inspiratory flow, the separation of MDI-actuation from inspiration, and reduced oropharyngeal drug loss. The disadvantages were cost of an additional device to use an MDI, and the need to assemble the device. In fact, the original version required 2 different mouthpieces with MDI nozzle receptacles, to match different MDI drug canisters.

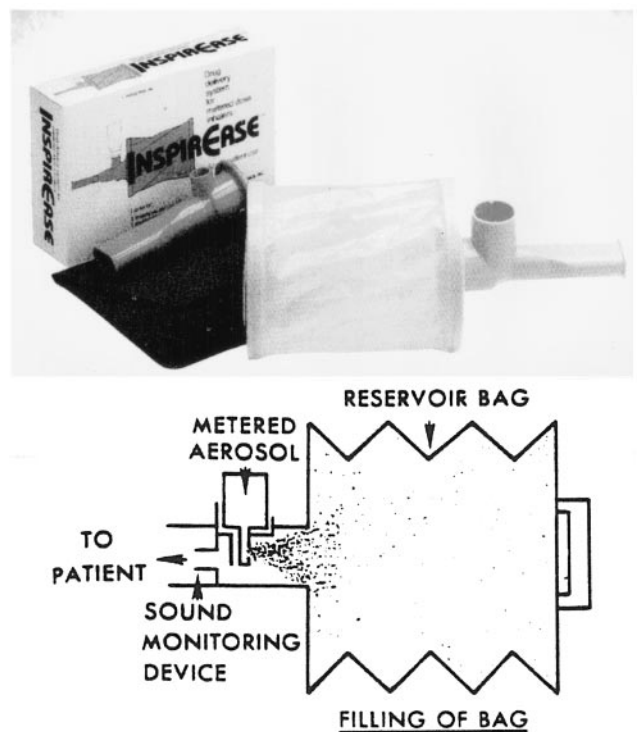


Fig. 6. The InspirEase, an early spacer system to facilitate use of metered-dose inhalers and reduce oropharyngeal aerosol deposition.

Subsequently in 1983, Dolovich et al reported the clinical evaluation of a simple “demand inhalation MDI aerosol delivery system,” which was the early version of the AeroChamber from Monaghan Medical Corporation.¹⁸ This was a true holding chamber; that is, the chamber contained a 1-way inspiratory valve, so that aerosol was released

Table 1. Recommended Aerosol Studies, Listed in Order of Priority, From the 1974 Sugarloaf Conference on the Scientific Basis of Respiratory Therapy

1. Determine regional deposition of nonhygroscopic stable aerosols, in both normal subjects and in patients with COPD
2. Determine the effect of water vapor in patients with COPD
3. Determine the physicochemical properties of bronchial secretions
4. Conduct studies on bronchodilators
5. Conduct studies on corticosteroids

COPD = chronic obstructive pulmonary disease

only when the patient inhaled from the chamber. Throat deposition (as measured with an aerosol radiolabeled with technetium) was reduced from 65% with the MDI alone to 6.5% with the AeroChamber, in bronchitic subjects. The AeroChamber, a 145-mL cylinder, incorporated a rubberized opening into which fit the MDI's mouthpiece actuator (or "boot") regardless of MDI actuator shape. There was no need for different nozzle receptacles to accommodate different MDI drug nozzles. A vibrating reed warned users of excessive inspiratory airflow.

The Need for Scientific Evidence With Inhaled Drug Delivery

In the early 1970s there was little scientific or clinical evidence on the increasingly widespread and popular use of inhaled aerosols, especially with nebulization of a variety of agents. On May 2–4, 1974, a landmark conference was held in Philadelphia, Pennsylvania, examining the scientific basis of respiratory therapy. The conference came to be called the "Sugarloaf Conference," because of the site where it was held, and its proceedings were published in the December 1974 supplement of *American Review of Respiratory Disease*. The final report on aerosol therapy noted that there was a need for mathematical models of pulmonary distribution of aerosols, "with actual studies of deposition using various breathing patterns."¹⁹ The report called for studies with both normal subjects and patients with chronic obstructive pulmonary disease. There was a call to determine "output characteristics of aerosol-producing devices," including mass median diameter and dose delivered. Table 1 lists the recommended studies, in order of priority.

The 1974 Sugarloaf Conference was followed 5 years later by the 1979 Conference on the Scientific Basis of In-Hospital Respiratory Therapy. The final report on aerosol and humidity therapy again noted problems, including: difficulty in estimating or measuring the dose of a drug given via aerosol; lack of adequate information on particle-size distributions produced by aerosol generators and nebulizers; failure of different nebulizers to provide a re-

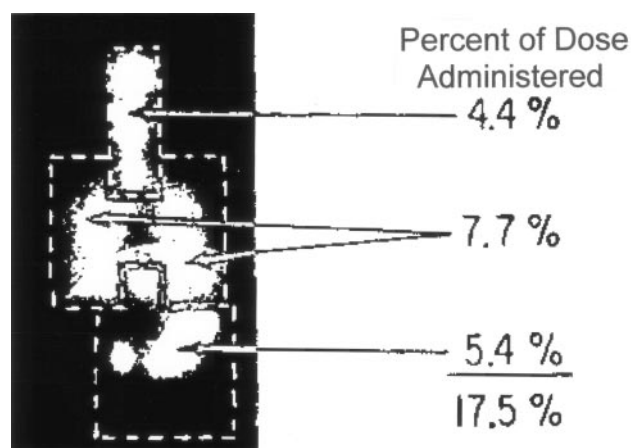


Fig. 7. Anterior scintigram showing distribution of radiolabeled aerosol in the respiratory tract and stomach. The aerosol was delivered by an intermittent positive-pressure breathing device with a jet nebulizer. The lung deposition was 7.7%. (From Reference 21, with permission.)

producable dose; patients' difficulty with MDIs in releasing the proper dose at the correct time; and the possibility that aerosol generators and nebulizers can be contaminated and act as sources of nosocomial infection.²⁰

Early Data on Modern Aerosol Devices

Even before the 1974 Sugarloaf Conference, there were studies that began to provide scientific data and raise critical questions about aerosol therapies. In 1973, Irwin Ziment published an article in *RESPIRATORY CARE*, entitled "Why Are They Saying Bad Things About IPPB?" [intermittent positive-pressure breathing] He offered his own unpublished data that with IPPB only 7.7% of radiolabeled saline was deposited in the lungs of a normal volunteer (Fig. 7).²¹ Although Ziment was concerned more with IPPB therapy than nebulizer therapy in that article, his data supported the trend calling for quantitative scientific measurement of aerosol therapy, which was seen in the Sugarloaf Conference the following year.

Further scientific evidence on aerosol therapy began to accumulate in the literature after the 1980 publication of the proceedings of the second conference on respiratory therapy. Stephen Newman et al published their classic and oft-referenced study on the disposition of aerosol drug from a pressurized MDI.¹⁵ Their measurement of 8.8% lung-deposition of the total MDI dose was similar to Ziment's data from 1973 for IPPB/nebulizer delivery. In the study by Newman et al, 80% of MDI drug was lost to the oropharynx, and 9.8% was retained in the MDI mouthpiece-actuator (Fig. 8). These early studies began to alert clinicians to the relative inefficiency of aerosol delivery devices.

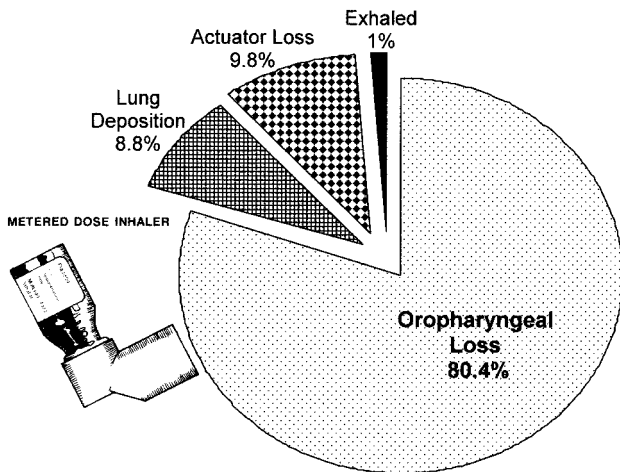


Fig. 8. Distribution of radiolabeled aerosol in the human respiratory tract, delivered via metered-dose inhaler with no add-on or spacer device. (Based on data from Reference 15.)

The study I mentioned above, by Dolovich et al,¹⁸ concerning the early AeroChamber, showed that the large throat loss of drug from an MDI was reduced 10-fold with use of a valved holding chamber (Fig. 9). However, lung deposition was almost identical for the MDI alone (8.7%) versus the MDI with holding chamber (9.0%).¹⁸ An often overlooked aspect of that study is the improvement in *peripheral* lung deposition and the more uniform lung deposition with use of the holding chamber by the normal subjects, although this was not seen with the chronic bronchitis subjects. Newman et al dramatically showed the transposition of aerosol loss in the throat using the MDI alone (> 80%) with loss in the chamber using a spacer device (approximately 76%), based on ventilation scans using radiolabeled aerosol (Fig. 10).²² That study also noted that good technique with the MDI delivered 11.2% of the total dose to the lungs, and use of a spacer device increased this to 14.8%, which was a statistically significant difference, but may not be clinically important. Their data indicated that the spacer increased lung deposition for patients with poor MDI technique.

Data also became available that indicated that lung deposition with a nebulizer was roughly the same as that with an MDI. The classic study by Lewis and Fleming examined the disposition of radiolabeled albumin in saline, in volunteers using an Inspiron Mini-Neb, and found that 12% of the total dose reached the lungs (Fig. 11).²³ This was not very different from the 9% lung-deposition that Newman et al had found with an MDI.¹⁵ In their study, Lewis and Fleming contrasted the disposition of the total aerosol dose using the nebulizer with the MDI data from Newman et al. Although lung deposition was approximately the same with the 2 types of aerosol device, the largest loss of aerosol drug with the MDI was in the oropharynx (80%), whereas with the nebulizer, 66% of the

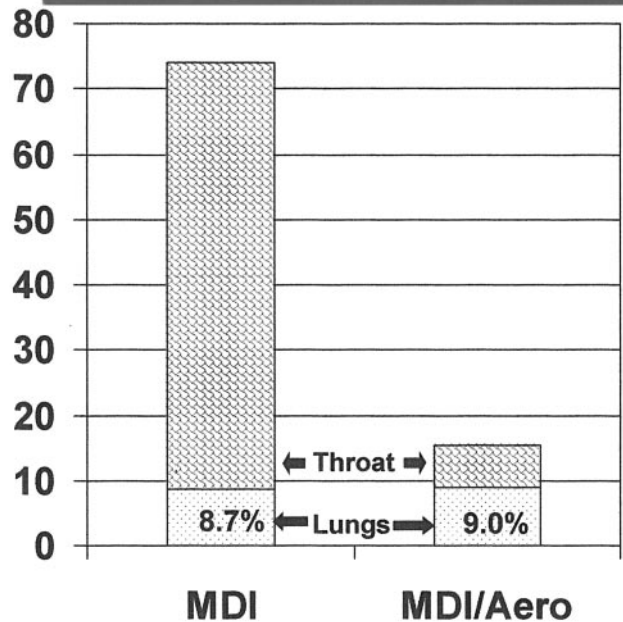
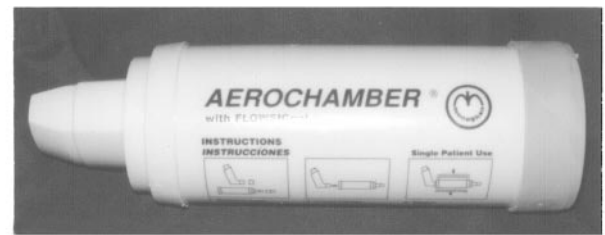


Fig. 9. Difference in throat deposition of drug from a metered-dose inhaler (MDI) with and without a breath-actuated valved holding chamber (AeroChamber). (Based on data from Reference 18. Photograph courtesy of Monaghan Medical.)

loss was in the device itself. A relatively large percentage (20%) of the aerosol was lost to the ambient air, which is not surprising, given the nebulizer's open-T-shape design and constant output of aerosol.

In a more recent study, published in 1994, Newman et al measured total drug disposition with a DPI, the SpinHaler.²⁴ Lung deposition was 13% when volunteers achieved an inspiratory flow of 120 L/min (Fig. 12). Not surprisingly, since the DPI is "powered" by inspiratory flow, a lower flow rate of 60 L/min resulted in a lung deposition of only 6%—less than half of that with the higher flow rate.

Figure 13 combines data from these well-done, landmark studies into one graph that shows the disposition of aerosol drug with MDI, MDI-with-spacer, small-volume nebulizer (SVN), and DPI (SpinHaler). Figure 13 shows that these studies indicate lung deposition in the 10–15% range for all the aerosol device types, although oropharyngeal loss, device loss, and exhalation loss differ markedly among the devices. The data clearly show that among these devices there was no important difference in effi-

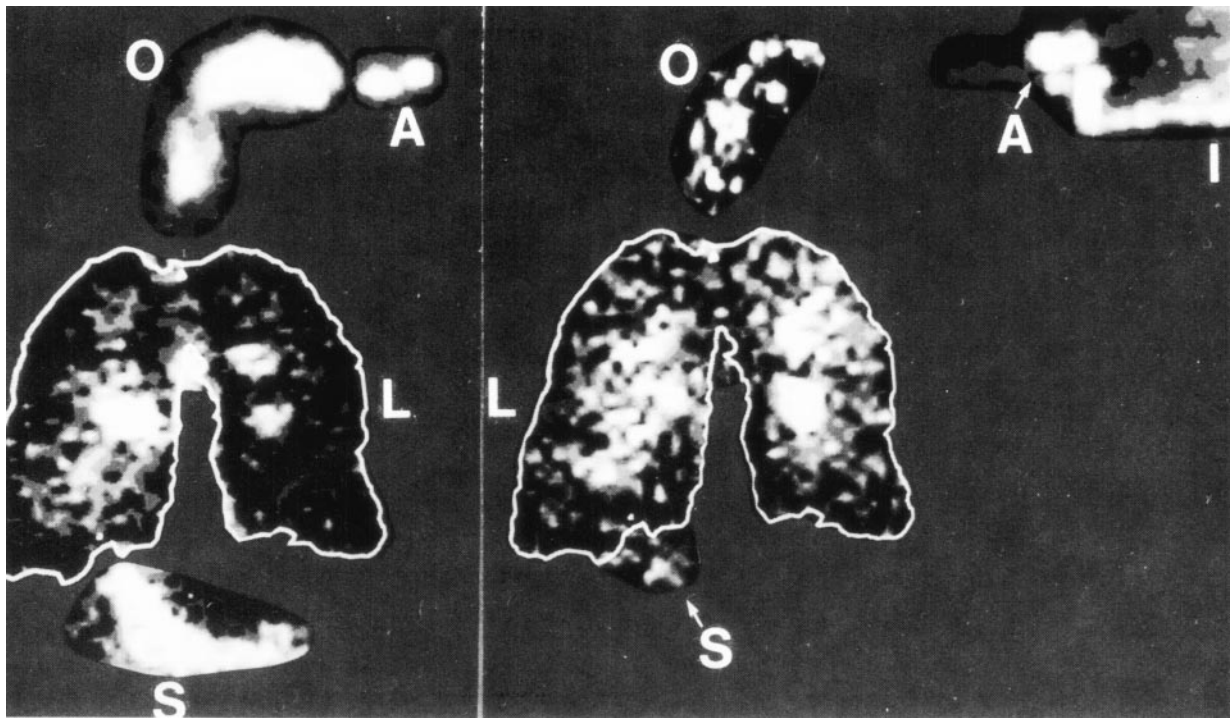


Fig. 10. Patterns of radioaerosol distribution from a metered-dose inhaler alone (left) and a metered-dose inhaler with the InspirEase spacer (right). A = actuator. O = oropharynx. L = lungs. S = stomach. I = InspirEase. (From Reference 22, with permission.)

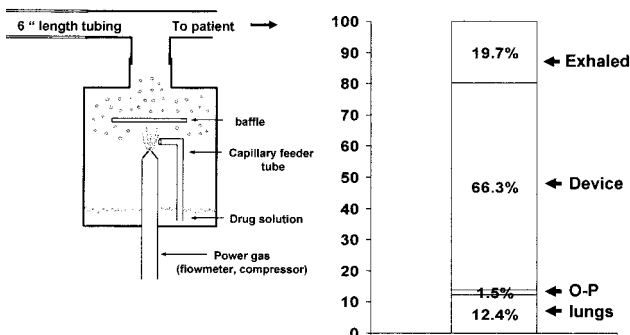


Fig. 11. Left: Schematic of a generic constant-output jet nebulizer. Right: Drug disposition with the Inspiron Mini-Neb, measured with radiolabeled albumin suspended in saline. O-P = oropharyngeal. (Based on data from Reference 23.)

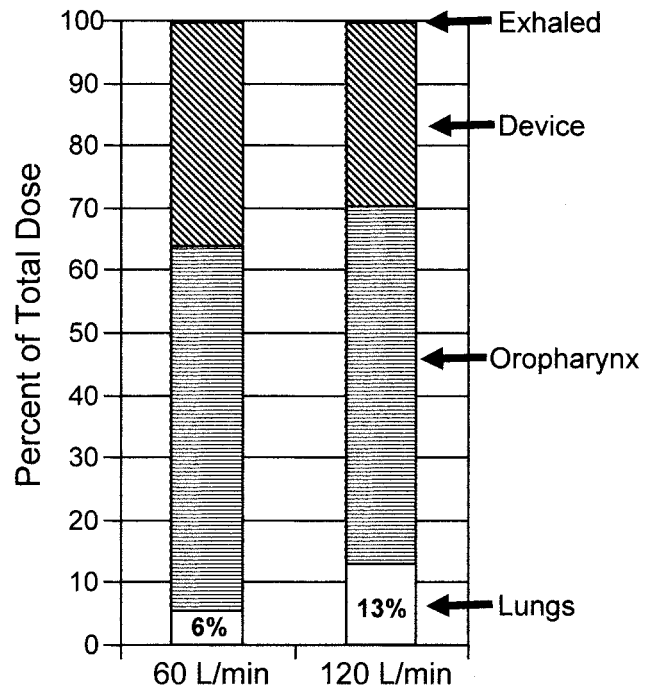


Fig. 12. Drug disposition of cromolyn sodium from the SpinHaler at inspiratory flows of 60 L/min and 120 L/min. (Based on data from Reference 24.)

ciency—if efficiency is interpreted as the percentage of total dose that reaches the lung.

Advantages to Administering Drugs as Aerosols

Given the problems with patient use of different aerosol devices and the relatively low fraction of total dose that reaches the lungs, critics could certainly argue against the use of inhaled aerosol drug therapy. It is unquestionably faster and possibly simpler to take a pill than to use an MDI, a nebulizer, or a DPI. Nonetheless, there are advan-

tages to aerosol inhalation for treating airways diseases (Table 2). Inhaled aerosol therapy allows placing the drug

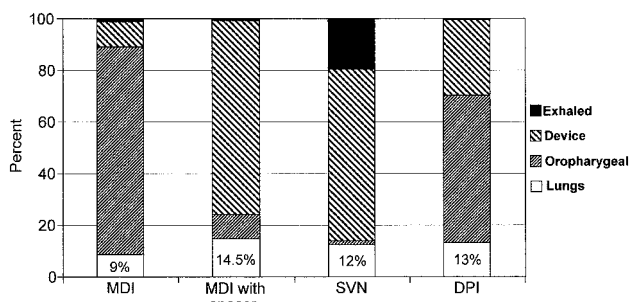


Fig. 13. Summary of drug disposition from the major types of aerosol delivery devices in clinical use. MDI = metered-dose inhaler. SVN = small-volume nebulizer. DPI = dry powder inhaler. (Data from multiple studies: MDI alone - Reference 15; MDI with spacer device - Reference 22; SVN - Reference 23; DPI - Reference 24.)

Table 2. Advantages of the Inhalation Route of Administration With Aerosolized Drugs in Treating Pulmonary Diseases

Aerosol doses are generally smaller than systemic doses. For example, the oral dose of albuterol is 2–4 mg, whereas the inhaled dose is 0.2 mg (via MDI) to 2.5 mg (via SVN).

Onset of effect is faster with inhalation than with oral administration. For example, the onset of effect with oral albuterol is about 30 min, whereas inhaled albuterol takes effect within about 5 min.

The drug is delivered directly to the target organ (lung), with minimized systemic exposure.

Systemic adverse effects are less severe and less frequent with inhalation than with systemic drug delivery (injection or oral) (eg, less muscle tremor and tachycardia with β_2 -agonists; less hypothalamic-pituitary-adrenal suppression with corticosteroids).

Inhaled drug therapy is painless and relatively comfortable.

MDI = metered-dose inhaler
SVN = small-volume nebulizer
COPD = chronic obstructive pulmonary disease

directly in the target organ, which reduces systemic exposure. This advantage is lost with the oral or parenteral (injection) route.

Dulfano and Glass examined the effect of terbutaline on pulmonary function with the subcutaneous route, the oral route (tablets), and the aerosol route.²⁵ The quickest and largest response in forced expiratory volume in the first second (FEV_1) was with the inhaled route, followed by the subcutaneous route (Fig. 14). The slowest onset and smallest effect was seen with the oral route. In fact, a larger change in FEV_1 occurred with 0.75 mg of inhaled terbutaline than with a 5.0-mg oral dose.

Grimwood et al found similar results. Both nebulized and inhaled-powder preparations of albuterol caused larger improvements in peak expiratory flow than did oral albuterol tablets.²⁶ In that study, the nominal (starting) dose of albuterol via nebulizer and via oral tablet was 4 mg, whereas the powder inhalation nominal dose (from a Rotahaler

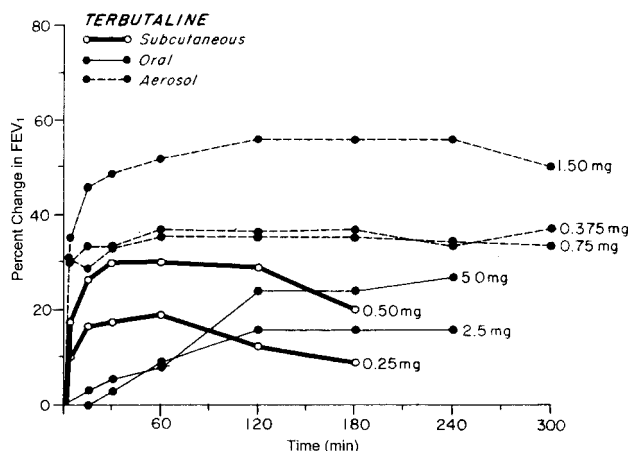


Fig. 14. Changes in forced expiratory volume in the first second (FEV_1) with 3 different routes of administration for the bronchodilator terbutaline. Lower inhaled drug doses resulted in larger clinical response, measured by FEV_1 . The aerosol was from a metered-dose inhaler. (From Reference 25, with permission.)

DPI) was only 400 μg —one tenth of the nebulizer or oral dose. The DPI had a stronger effect on peak expiratory flow than did the oral route, but the DPI's effect was less than the nebulizer's effect, almost certainly because of the lower DPI nominal dose. The DPI's duration of action declined below that of the oral dose. Grimwood et al showed that different starting doses in aerosol devices can give different effects. If the 3 types of aerosol device studied (MDI, SVN, and DPI) are all equally efficient in delivering 10–15% of the nominal dose to the lungs, then it is the starting dose and not the type of device alone that can determine clinical response.

Because the inhalation route puts the drug directly into the lung, there should be lower systemic drug levels and therefore less adverse effect. Thiringer and Svedmyr compared dose-response effects with terbutaline given intravenously versus as an aerosol on lung function (FEV_1), heart rate, blood pressure, and skeletal muscle tremor.²⁷ Table 3 shows that the cumulative highest dose of 0.34 mg terbutaline given via infusion resulted in greater adverse effects than did the cumulative 8.0-mg dose given via inhalation—a dose almost 24 times larger. All the differences in adverse effects between the infused and inhaled routes were significant, except for muscle-tremor changes.

Are Aerosol Devices Equivalent?

Measurements of aerosol disposition with the different types of aerosol devices in use have shed light on comparative performance. As seen previously in Figure 13, all of the aerosol devices in common use prior to the 1990s delivered around 10–15% of the total starting dose to the lungs, so the MDI, MDI-with-spacer, SVN, and the DPI

Table 3. Comparison of Adverse Effects With Infused Versus Inhaled Terbutaline in Patients With Asthma*

	Infusion (0.34 mg)	Inhalation (8.0 mg)
Heart rate (beats/min)	25 ± 3	-0.7 ± 2.2
Systolic blood pressure (mmHg)	8 ± 6	-4 ± 4
Diastolic blood pressure (mmHg)	-17.1 ± 1	-3 ± 1
Tremor ratio†	1.2 ± 0.45	0.2 ± 0.03

*The changes listed are with the highest cumulative dose of terbutaline with each administration route.

†The tremor ratio is the change over baseline. (Based on data in Reference 27)

Table 4. Differences in Nominal (Starting) Doses Between MDI and Nebulizer Formulations for 4 Different Drugs

	MDI*	Nebulizer	Ratio (Nebulizer to MDI)
Metaproterenol (mg)	1.3	15	11.5
Albuterol (mg)	0.2	2.5	12.5
Ipratropium (µg)	40	500	12.5
Cromolyn sodium (mg)	1.6	20	12.5

*MDI (metered-dose inhaler) recommended dose

MDI dose/actuation: metaproterenol 0.65 mg; albuterol 90 µg; ipratropium 18 µg; cromolyn sodium 800 µg

are equally efficient. However, it is often overlooked that the starting, nominal dose in different types of device is not the same. Table 4 lists the nominal dose differences between MDIs and nebulizers for 4 different inhaled drugs. The nominal nebulizer dose is usually 11–12 times larger than the MDI dose. If MDIs and nebulizers both deliver 10–15% of the starting dose to the lung, then 11–12 times more drug reaches the lung with a nebulizer than with an MDI, all other factors being held constant, and assuming correct use of the devices. It is little wonder that anecdotally many clinicians have considered nebulizers more effective than MDIs, especially in emergency use. However, Mestitz et al clearly showed that the lower-dose MDI can achieve as much clinical effect as the higher-dose nebulizer, by increasing the number of MDI puffs (Fig. 15).²⁸ In that study, 5 MDI puffs (1.25 mg) of terbutaline had the same FEV₁ effect as a 2.5-mg nebulizer dose of terbutaline. Because the MDI nominal dose is usually lower than the corresponding nebulizer dose, it is often necessary to increase the number of MDI actuations to achieve clinical results equivalent to a nebulizer.

Perhaps the clearest demonstration of the equivalence of MDIs, nebulizers, and DPIs was provided by Zainudin et al.²⁹ Their study was unique in loading the *same* nominal dose of 400 µg of albuterol into an MDI, a nebulizer, and a DPI. As seen in Figure 16, the lung deposition was nearly identical among the 3 devices. The change in FEV₁

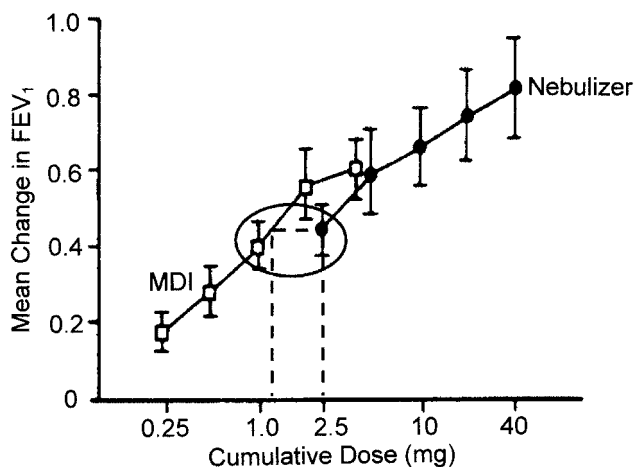


Fig. 15. Mean change in forced expiratory volume in the first second (FEV₁) versus cumulative dose of terbutaline from a metered-dose inhaler (MDI) or from a jet nebulizer. More puffs from the MDI (250 µg per puff) were required to give equivalent responses to that from the larger 2.5-mg nebulizer dose. (From Reference 28, with permission.)

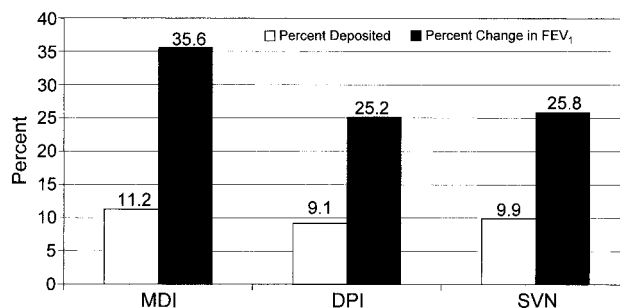


Fig. 16. Lung deposition (white bars) and percent change in forced expiratory volume in the first second (FEV₁, black bars) with metered-dose inhaler (MDI), dry powder inhaler (DPI), and small-volume nebulizer (SVN), each using the same nominal dose of 400 µg of albuterol. (Based on data from Reference 29.)

was somewhat higher for the MDI, and the authors attributed that difference to patient variability. Nonetheless, such results suggest that we should expect similar clinical results with similar starting doses. In comparing aerosol therapies, Mestitz et al stated that the clinical effect “is a reflection of the dose of bronchodilator administered and not the mode of administration.”²⁸

Raimondi et al clinically compared MDI-with-holding-chamber, SVN, and DPI in emergency-department treatment of 27 adult asthmatics whose FEV₁ was < 30% of predicted. They administered 400 µg of albuterol via MDI-with-holding-chamber and via DPI (Rotahaler), and 5 mg via nebulizer.³⁰ Despite the larger nominal dose with the nebulizer, there were no differences in FEV₁ response over 6 hours, or in other clinical variables, including numbers discharged and admitted.

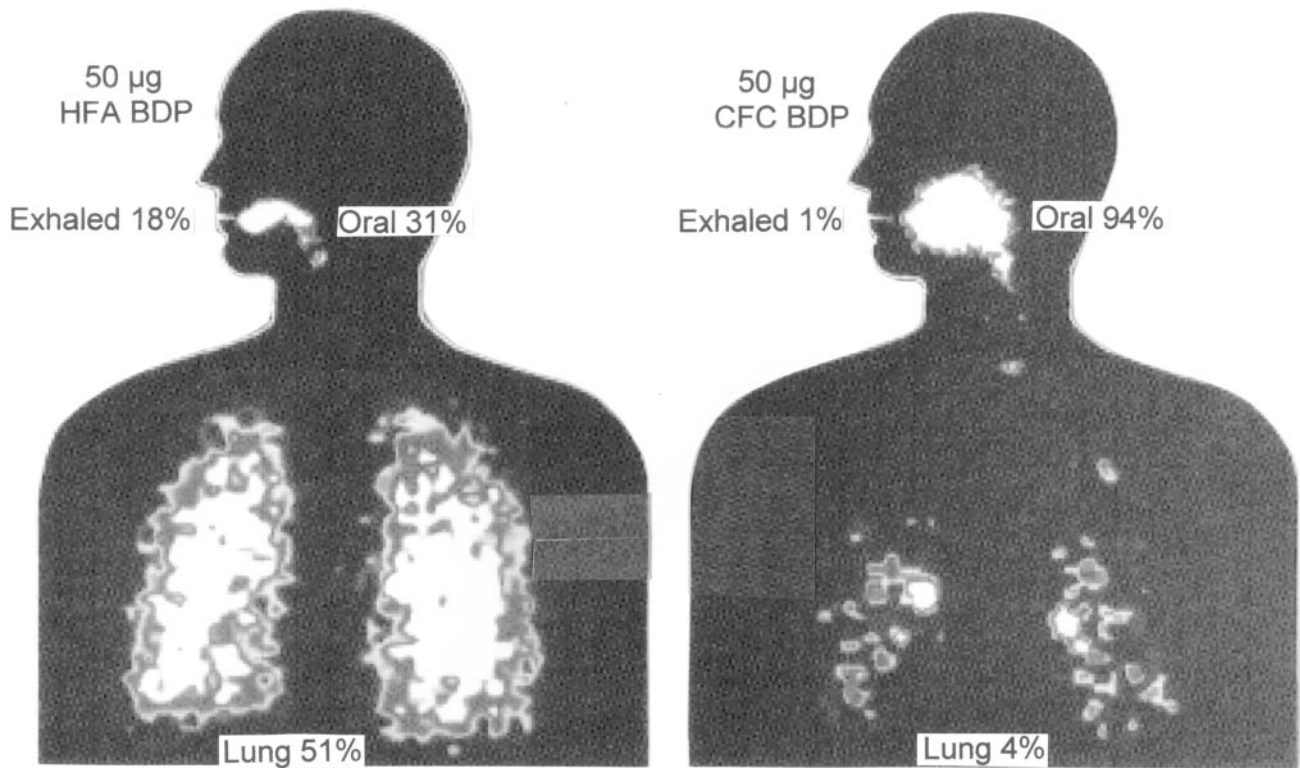


Fig. 17. Deposition in the human respiratory tract with the hydrofluoroalkane (HFA) formulation and the chlorofluorocarbon (CFC) formulation of beclomethasone dipropionate (BDP). Lung deposition was better with HFA-BDP because of the ultrafine particle distribution of the HFA aerosol. (Adapted from Reference 36, with permission.)

Changes in Aerosol Delivery Systems Beginning in the 1990s

In 1987 the Montreal Protocol, which banned the use of chlorofluorocarbons (CFCs, often known by the brand name FREON) as pressurized propellants and refrigerants, catalyzed a number of changes in aerosol delivery systems.^{31,32} That signal event, agreed to by the United States among others, stimulated a fresh look at the technology of aerosol generators. The use of CFCs in MDIs was exempted under the Protocol as an “essential use,” until suitable alternatives for aerosol drug delivery could be developed. Hydrofluoroalkanes (HFA), which have similar physical and chemical properties to CFCs, offered a replacement propellant for MDIs. Attention focused on 2 HFAs in particular: first HFA 134a, and then HFA 227. The need to replace CFC-propelled MDI formulations resulted in new aerosol drugs being released as DPI formulations (eg, formoterol [Foradil Aerolizer] and tiotropium [Spiriva HandiHaler]), and in a virtual explosion of nebulizer technology changes. This is at least partially because transitioning MDI drug formulations from CFC to new propellants has been more difficult than expected.

Development of HFA MDI Formulations

At present there are only 2 drugs that have HFA-MDI formulations in the United States, namely albuterol and beclomethasone dipropionate, both of which use HFA 134a propellant. The HFA albuterol formulation was designed to be equivalent (in dose released and clinical effect) to the previous CFC MDI.^{33,34} However, the development of HFA-beclomethasone resulted in a redesign of the entire MDI metering-valve system and an improved particle size distribution.^{35,36} Lung deposition with the new formulation is in the 50–60% range (Fig. 17). There are other HFA MDI drug formulations in various stages of development or approval, including the short-acting β_2 agonist levalbuterol and the corticosteroid ciclesonide.

Although the HFAs have similar physicochemical properties to the CFCs they have replaced, they also differ in some physical properties. In particular, HFAs have high polarity, which results in poor solvation of previously used surfactants or excipients such as oleic acid, lecithin, or sorbitan trioleate. These differences have necessitated re-engineering of MDI valves and seals, drug formulations (solutions instead of suspensions), and MDI manufacturing processes, such as that seen with HFA-beclomethasone.³⁷

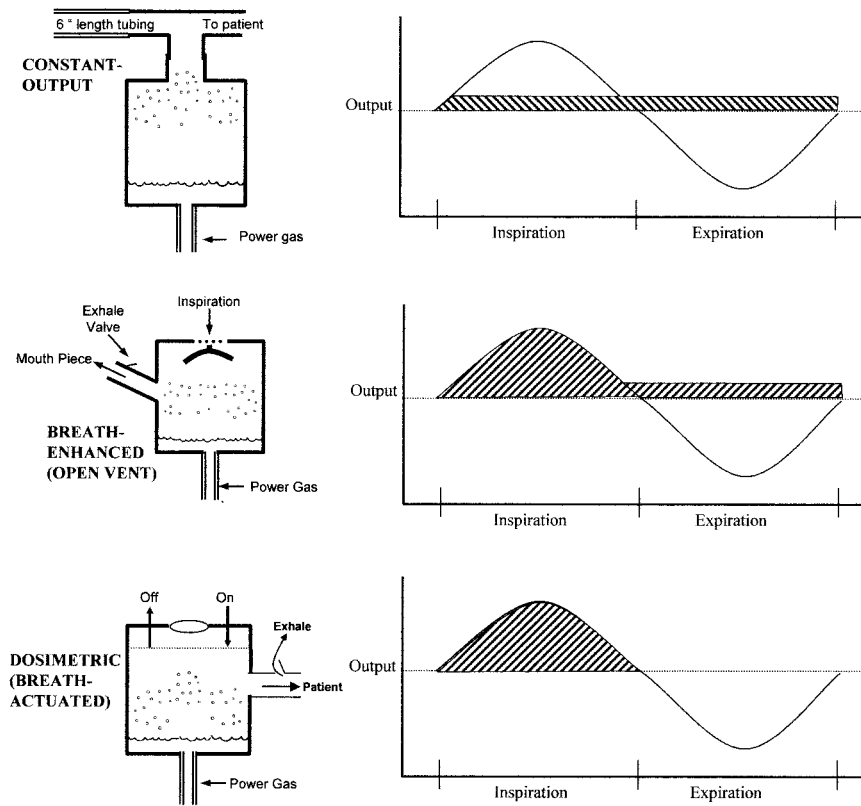


Fig. 18. Conceptual illustration of the development of nebulizer designs, from constant-output, to breath-enhanced, to dosimetric. The sine wave indicates the breathing pattern. The hatched areas indicate the period of aerosol generation. Based on a concept introduced by Dennis.⁴¹ (From Reference 40, with permission.)

Developments in Nebulizer Technology

There appears to be greater variety in the development of new nebulizer technology than in MDIs or DPIs in recent years. This development was comprehensively and critically reviewed in a conference on nebulizer technology held in Montreal in June 2002, the proceedings of which were published in the November and December 2002 issues of *RESPIRATORY CARE*.^{38,39} See those 2 issues for more detailed and complete descriptions of the newer technologies than can be presented here.

Nebulizers used in clinical care have evolved in design and operation (Fig. 18).⁴⁰ For years, disposable hand-held jet nebulizers have had an open-T-shape design and constant aerosol output (aerosol generation proceeds during both inhalation and exhalation).⁴¹ With that design there is a large exhaled loss (around 20%) and a large apparatus loss (60–70%).²³ An improvement in this design, in the late 1980s, was the breath-enhanced nebulizer (eg, Pari LC Plus), which has also been termed an “open-vent” nebulizer.⁴² Ambient air is entrained through a 1-way valve along with the power gas during inspiration, and exhalation is through a 1-way plastic flapper valve in the mouth-piece. Aerosol is generated during exhalation but is rela-

tively contained in the nebulizing chamber (see Fig. 18). It should be noted that there are important differences between the reusable and the disposable Pari models; the disposable model lacks the 1-way valves that enhance efficiency.

Theoretically, the most efficient nebulizer is a breath-actuated “dosimeter” that generates aerosol and makes it available only during inhalation (Fig. 18). An *in vitro* comparative study of representative nebulizers from each of the 3 categories described measured total drug disposition.⁴³ Figure 19 shows the aerosol-deposition results from the Misty-Neb (a constant-output nebulizer), the Pari LCD (a breath-enhanced nebulizer), and the Monaghan Aero-Eclipse (a dosimeter), which confirmed that the dosimetric design gave the highest available emitted aerosol drug mass with albuterol sulfate and reduced both apparatus loss and exhaled loss.

If a dosimetric nebulizer is defined as one that releases aerosol only during inhalation,⁴¹ then the recently marketed Medicator models from Healthline Medical are dosimetric. The Medicator employs a reservoir bag, 1-way inspiratory filter, and can add an exhalation filter (McPeck M, Healthline Medical, 2004, personal communication). The overall design is similar to that of the Circulaire.

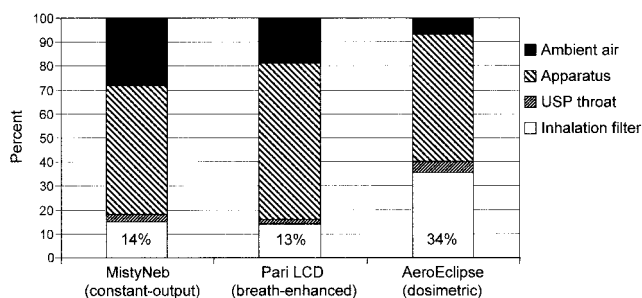


Fig. 19. In vitro disposition of albuterol with 3 types of nebulizer: constant-output (Misty-Neb), breath-enhanced (Pari LCD), and dosimetric (AeroEclipse). USP = United States Pharmacopoeia. (Based on data from Reference 43.)

Table 5. Categories of Technologies Used in Newer Nebulizers, With Examples of Devices

Modified piezoelectric (vibrating mesh or aperture plate)
- Aerogen nebulizers
- Omron NE-U03, U22
- Pari eFlow
High-pressure micro spray
- Boehringer Ingelheim RespiMat
- Aradigm AERx
Electrohydrodynamic
- BattellePharma Mystic

Another example of a dosimetric design is seen with “adaptive aerosol delivery,” represented originally by Medic Aid’s HaloLite nebulizer. This device is a “smart” nebulizer that senses the patient’s breathing pattern over several breaths, and then releases aerosol pulses during a predetermined portion of the inspiratory phase.^{44,45}

Table 5 summarizes other developments in nebulizer technology. Many of the devices listed as examples of the different aerosol-generation methods represent a convergence of features of the pressurized MDI with those of the liquid nebulizer. Myrna Dolovich, a well-respected aerosol scientist, has termed such devices “metered-dose liquid inhalers” because they mimic the action of an MDI by releasing a unit dose with 1–2 actuations, and they use a liquid spray.⁴⁶ An example of a metered-dose liquid inhaler is the RespiMat, made by Boehringer Ingelheim (Fig. 20),⁴⁷ which is not currently available in the United States. The RespiMat is propellant-free and generates a slow-moving aerosol, or “soft mist,” using a spring-loaded canister.⁴⁸ The canister contains multiple doses of a liquid drug solution, not a suspension (as do most MDIs). The device is about the size of an MDI, and is primed by twisting the base to compress the spring. The drug is emitted by depressing a dose-release button, and the spring tension forces the solution through a uniquely designed “uniblock” nozzle. Figure 20 also shows comparative lung

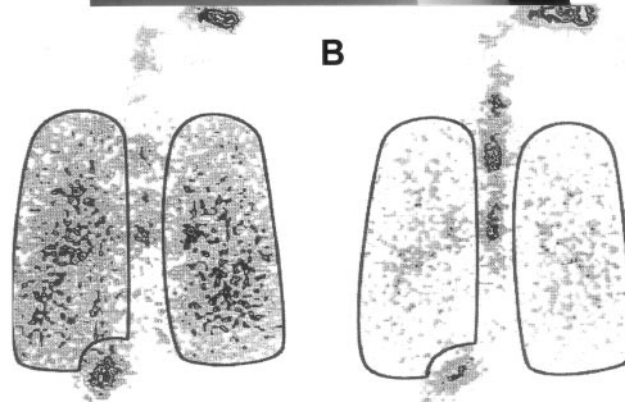
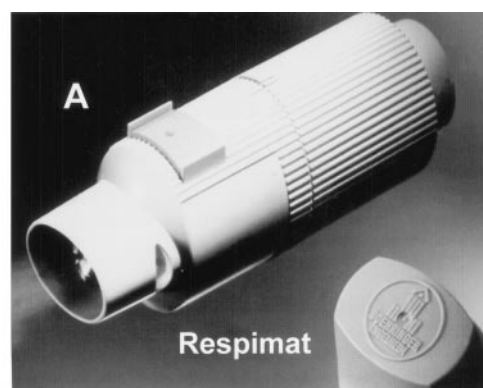


Fig. 20. A: The RespiMat, a “soft-mist” metered-dose liquid inhaler. B: Lung scintigraphy images showing respiratory-tract and stomach deposition of flunisolide from the RespiMat (left) and from a pressurized metered-dose inhaler with no spacer or holding chamber (right). (From Reference 47, with permission.)

scans of deposition with the RespiMat versus with an MDI with no spacer or holding chamber.⁴⁷

Developments in Dry Powder Inhaler Design

The aerosol-generation force in a DPI is inspiratory flow. Powder drug formulations are either in a pure form, such as that with budesonide in the Turbuhaler, or mixed with an inactive excipient such as lactose.⁴⁹ Finely milled powder particles (< 5 μm) do not flow freely, because they possess cohesive force and static charge. The micronized drug particles can be agglomerated with larger “carrier” particles of the excipient, to aid in particle separation.⁴⁹ To produce suitably small drug particles, the drug-excipient agglomerate must then be disaggregated by shear forces during an adequate inhalation. It is for this reason that DPIs require a relatively high inspiratory flow for drug delivery to the airways. The effect of lower inspiratory flow on drug delivery to the lung was previously seen in Figure 12.

Newman and Busse gave an excellent review of DPI design and formulation.⁴⁹ Figure 21 shows the DPIs cur-



Fig. 21. Dry powder inhaler devices currently available in the United States. From top left, clockwise: Diskhaler, Diskus, Aerolizer, Turbuhaler, HandiHaler.

Table 6. Classification of Dry Powder Inhalers, Based on Design and Function⁴⁹

	Drug(s)	Dose Container	Number of Doses
<u>Single-Dose Devices</u>			
SpinHaler*	cromolyn sodium	capsule	single
Rotahaler*	albuterol sulfate	capsule	single
Aerolizer	formoterol	capsule	single
HandiHaler	tiotropium	capsule	single
<u>Multiple Unit-Dose Devices</u>			
Diskhaler	fluticasone	blister cassette	4/cassette
	zanamivir	blister cassette	4/cassette
<u>Multiple-Dose Devices</u>			
Turbuhaler	budesonide	reservoir	200
Diskus	salmeterol	blister strip	60
	salmeterol/fluticasone	blister strip	60

*Withdrawn from the market

rently available in the United States. Table 6 shows a possible DPI classification system, based on their design features. Single-dose devices are best exemplified by the original SpinHaler, in which a gelatin capsule containing a single 20-mg dose of cromolyn sodium had to be inserted prior to inhalation. The SpinHaler and Rotahaler (albuterol) are no longer available in the United States, but the Aerolizer and the HandiHaler are examples of single unit-dose loading devices. The Diskhaler can deliver fluticasone, among other drugs, and uses refill disks that contain 4 or 8 unit-dose blisters. The disk

is replaced when all the doses have been used. Both the Diskus (salmeterol, or combined salmeterol and fluticasone) and the Turbuhaler (budesonide) contain a complete set of multiple doses for one prescribing period. The Diskus has a strip with unit-dose blisters. The Turbuhaler contains a reservoir of drug powder. The Turbuhaler is actuated by twisting the base back and forth, which drops the dose into the dispensing chamber for inhalation.

One example of a new DPI system is the Spiros, under development by Dura Pharmaceuticals, for inhalation of

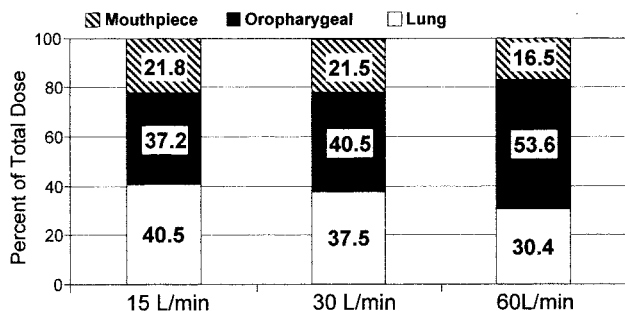
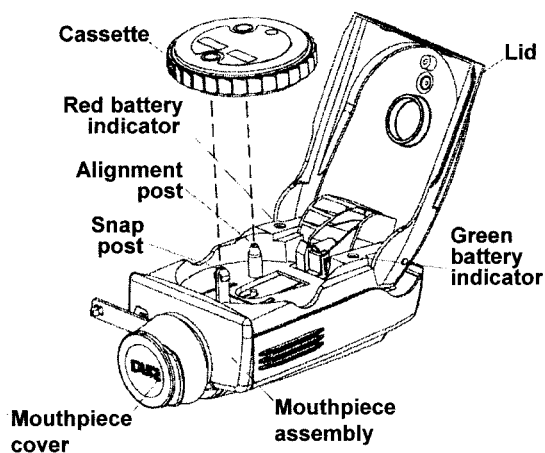


Fig. 22. The Spiros dry powder inhaler, which is in development, and the in vivo disposition of inhaled beclomethasone dipropionate at 3 different inspiratory flows. (Based on data from Reference 51.) (Diagram of Spiros from Reference 50, with permission.)

powdered albuterol sulfate (Fig. 22). The Spiros contains a removable circular multiple-dose cassette with 30 wells.⁵⁰ Each well contains a unit dose of micronized albuterol sulfate and lactose. A dose is loaded into the aerosolization chamber by opening the lid and then closing it. The aerosolization chamber contains an inspiration-actuated, battery-powered, twin-blade impeller, which generates the aerosol cloud. Ambient air is entrained through holes in the mouthpiece during inhalation. The system also contains an internal counting mechanism, and the DPI can be reused with replacement cassettes. This effort-assisted inhaler is designed to function more independently of the patient's inspiratory flow, in contrast with previous DPIs, which were highly dependent on inspiratory flow for disaggregation and adequate particle size. Figure 22 shows the effect of different inspiratory flows on the percent of total dose (of beclomethasone dipropionate) that reaches the lung.⁵¹ Another DPI that features active metering of the powder dose for inhalation along with a "cyclone separator" is the Airmax, which has been studied for delivery of both albuterol and budesonide.⁵²

Aerosol Therapy: Issues, Problems, and Challenges

By combining data from multiple sources and studies, it is possible to create a graphic comparison of aerosol de-

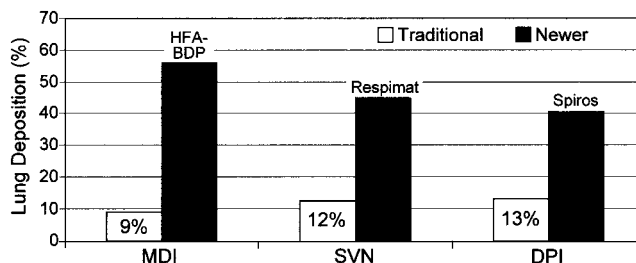


Fig. 23. Lung deposition, based on various studies, showing differences between traditional and newer devices. HFA-BDP = hydrofluoroalkane formulation of beclomethasone dipropionate. MDI = metered-dose inhaler. SVN = small-volume nebulizer. DPI = dry powder inhaler. Data for traditional devices: MDI - Reference 15; SVN - Reference 23; DPI - Reference 24. Data for newer devices: MDI - Reference 35; SVN - Reference 53; DPI - Reference 51.

livery to the lung from the 3 common types of aerosol device, between traditional (pre-1990s) and the newer devices just described. Figure 23 shows this comparison for an example of each of the 3 devices: the MDI with HFA-beclomethasone,³⁵ the RespiMat with flunisolide,⁵³ and the Spiros with beclomethasone.⁵¹ Although lung deposition has clearly increased with the newer generation of devices, it remains in the range of 40–50%. There is room for further increases in lung-delivery efficiency.

The recent development of aerosol delivery technology brings up several issues for researchers and clinicians, including cost and reimbursement, choice of a system from among multiple possibilities, problems with aerosol delivery of medications, and features of an ideal inhaler.

A complete discussion of cost analyses for aerosol devices is beyond the scope of this review. However, a statement by Dr Henry Milgrom, made with regard to the debate over costs with racemic albuterol versus single-isomer levalbuterol, is apropos:

It is the overall cost of patient care, and not merely the price of the drug [or device], that should be considered in any assessment of the cost of care of patients who use bronchodilators.⁵⁴

If a more expensive nebulizer reduces the number of treatments, exacerbations, hospital admissions, or duration of hospitalization, that nebulizer might be more cost-effective than a cheaper one. At the same time, manufacturers must strive to reduce all equipment costs where possible. It would be even more desirable to reduce hospitalizations and other expenses with a lower-cost, rather than a higher-cost, aerosol device.

Choosing an aerosol system from among the many becoming available will require selection criteria. Perhaps more expensive and more efficient devices should be used with either expensive or toxic drug therapy, where high

Table 7. Problems With Current Aerosol Delivery Systems

Lack of uniformity: 3 major device categories (metered-dose inhaler, small-volume nebulizer, and dry powder inhaler)
Need for ancillary equipment (eg, holding chamber or spacer) depending on age, coordination, or drug used
Ability to use the different device categories differs by age and disease
Each category of device requires a different breathing maneuver
Continuing low efficiency of lung deposition, contamination of ambient air, and drug loss

Table 8. Some Suggested Characteristics of an Ideal Aerosol Inhaler System

Dose reliability and reproducibility
High lung-deposition efficiency (target lung deposition of 100% of nominal dose)
Production of fine particles $\leq 5 \mu\text{m}$ diameter, with correspondingly low mass median diameter
Simple to use and handle
Short treatment time
Small size and easy to carry
Multiple-dose capability
Resistance to bacterial contamination
Durable
Cost-effective
No drug released to ambient-air
Efficient (small particle size, high lung deposition) for the specific drug being aerosolized
Liked by patients and health care personnel

(Based on information in Reference 40.)

lung delivery and little or no ambient contamination is most important. This will require discussion and guidance for clinicians.

Table 7 lists problems with aerosol delivery of medications. The variety of systems available is itself a problem, akin to the lack of standardization in railway track gauge early in the history of railroad construction. All 3 categories of device have differences, and there are different aerosol devices within each of the categories, particularly with the developments occurring in nebulizer technology. This is confusing to both patients and health care providers.⁵⁵ Age requirements for device use differ among the 3 categories, and ancillary equipment such as holding chambers and masks are needed for the very young. There are different breathing maneuvers for each of the 3 main types of device. A slow, deep inhalation is needed for optimal MDI use, whereas a rapid, forceful inhalation is required with a DPI. If we adopt a target of 100% lung-delivery of the nominal dose, even the newer systems remain far short of the goal. Also, aerosol-contamination of the environ-

ment or the caregiver is unacceptable, and exhaled or ambient loss of drug should be zero.

Table 8 lists some important characteristics for an ideal inhaler, based on my experience and reading of the literature. Though it may be difficult for manufacturers to devise the ideal aerosol system, such a list should be used as criteria to evaluate current and future inhaler devices. This list may be useful in stimulating further discussion on benchmarks for an ideal inhaler, and it should be viewed as only a starting point in guiding inhaler development rather than as a final and fixed list of features.

DEDICATION

Dedicated to the memory of Phil Kittredge, former editor of *RESPIRATORY CARE Journal*; thank you for demanding science in our profession.

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