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Introduction
New Liquid Aerosol Generators
Devices That Create an Aerosol by Forcing Liquids Through Nozzles
The Respimat
- Respimat Deposition Studies
- Respimat Clinical Studies
- Challenges for Respimat
The AERx System
- AERx Deposition Studies
- AERx Clinical Trials: Systemic Drugs
- AERx Clinical Trials: Pulmonary Delivery for Lung Disease
- Challenges for the AERx System

Summary

Over the past few decades, aerosol delivery devices have been relatively inefficient, wasteful, and difficult for patients to use. These drawbacks have been tolerated because the drugs available for inhalation have wide therapeutic margins and steep dose-response curves at low doses. Recently several forces have converged to drive innovation in the aerosol device industry: the ban on chlorofluorocarbon propellants in metered-dose inhalers, the need for more user-friendly devices, and the invention of expensive inhalable therapies for topical and systemic lung delivery. Numerous devices are in development to improve the efficiency, ease of use, and reproducibility of aerosol delivery to the lung, including systems that force liquid through a nozzle to form the aerosol cloud. The Respimat is a novel, compact, propellant-free, multi-dose inhaler that employs a spring to push drug solution through a nozzle, which generates a slow-moving aerosol. Deposition studies show that the Respimat can deliver 39–44% of a dose to the lungs. Clinical asthma and chronic obstructive pulmonary disease trials with bronchodilators show that the Respimat is 2–8 times as effective as a metered-dose inhaler. Respimat has been tested with bronchodilators and inhaled corticosteroids. The AERx device uses sophisticated electronics to deliver aerosol from a single-dose blister, using an integral, disposable nozzle array. The electronics control dose expression and titration, timing of aerosol generation with the breath, and provide feedback for proper inhalation technique. Lung deposition ranges from 50 to 80% of the loaded dose, with remarkable reproducibility. AERx has been tested with a variety of drugs, for both topical and systemic delivery, including rhDNase (dornase alfa), insulin, and opioids. These novel devices face competition from other technologies as well as financial and regulatory hurdles, but they both offer a marked improvement in the efficiency of pulmonary drug delivery. Key words: nebulizer, nebulization, aerosol, AERx, Respimat.

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Introduction

For the past half century the devices available for the delivery of aerosolized drugs to the lung have included pressurized metered-dose inhalers (pMDIs), jet and ultrasonic nebulizers, and dry powder inhalers (DPIs). Each of these systems has benefits and drawbacks with respect to the type of drug used and the target patient population. The well-recognized inefficiencies of these devices have not been of concern until recently, since most of the aerosolized drugs for topical lung delivery (i.e., bronchodilators and anti-inflammatory agents) are inexpensive and have wide therapeutic margins. However, over the past decade there have been many driving forces for the innovation of new inhalable drug formulations and devices to deliver them.

First, the ban on chlorofluorocarbon (CFC) (to preserve the upper atmosphere’s ozone layer) has required pharmaceutical companies to seek alternative propellants. The pMDI has for decades been one of the most commonly prescribed delivery methods for asthma and chronic obstructive pulmonary disease (COPD) drugs, so the ban on CFC is a major driving force for change in the industry. The basic design of the pMDI is almost 50 years old, with few modifications until recently. The pMDI was a landmark innovation that has had tremendous impact on inhaled drug delivery, though the problems with its use are well known. The pMDI is relatively difficult to teach and to use and requires synchronization of actuation and inhalation to achieve successful lung deposition. Pressurized MDIs produce high-velocity particles that impact in the oropharynx and cause adverse effects. Drug delivery to the lung with CFC pMDIs is only 5–20% of the label dose, even with good technique. Children under a few years old are incapable of mastering the pMDI technique. To overcome these difficulties, several companies designed spacers and valved holding chambers to reduce oropharyngeal deposition and improve coordination. The competition between the companies that manufacture spacers led to a huge body of literature arguing the merits of the various devices, leading to confusion among clinicians and patients.

Alternatives to the CFC pMDI include other propellants, such as hydrofluoroalkane (HFA), new DPIs, and the recently developed propellant-free liquid systems. The HFA pMDIs have been redesigned to solve some of the problems with the CFC devices. The plume has a slower velocity, there is no “cold front” effect, and the last few doses in the canister are delivered more consistently. Some of the inhaled corticosteroids are soluble in the HFA propellant/excipient mixture and have been engineered to deliver small-particle aerosols (average droplet size of only 1 μm), which improves lung deposition and decreases throat deposition. Other HFA formulations have particle size characteristics similar to their inefficient CFC counterparts. Like CFC pMDIs, HFA pMDIs require synchronization of the actuation and the inspiratory effort, so holding chambers may be necessary for some patients. DPIs are also available for many medications and come in single-dose and multiple-dose formats. DPIs are breath-actuated and rely on the patient’s inspiratory effort to deaggregate the powder into fine particles that can be deposited in the lung. DPI deposition efficiency is in the range of approximately 12–37%, depending on the device, the formulation, and the patient. Since a stronger inspiratory effort is required with current DPIs, there is substantial oropharyngeal deposition. The difficulties with pMDIs and DPIs are partly responsible for the development of propellant-free liquid aerosol systems.

Aerosol Generators That Force Liquids Through Nozzles

Another force driving innovation of new aerosol technology is the recognition that existing devices are either inefficient, difficult to use, or have poor precision (high intra-subject and inter-subject variability). In addition to the above-described problems with pMDIs and DPIs, jet and ultrasonic nebulizers waste drug by having large dead volumes (i.e., medication remaining in the nebulizer after nebulization has ceased), by nebulizing during exhalation, and by forming polydisperse aerosols that have a high percentage of droplets too large to reach the lung. With most of the available systems the patient is not guided or prompted to breathe in an appropriate or consistent fashion, which increases variability of lung deposition. Drugs with large therapeutic windows, such as anti-inflammatory agents, β2 agonists, and anticholinergics, can be clinically effective even when delivered by inefficient devices, but more recent medications and novel therapies in development, including gene therapies, are too expensive to tolerate substantial waste.

Nebulizers are the most time-consuming method of aerosol delivery. Patients with cystic fibrosis (CF) and other chronic lung diseases may have numerous aerosol medications to use, which may take up to 2 hours daily. New user-friendly devices that reduce treatment time may improve patient compliance with therapy and thus improve outcomes and quality of life.

Finally, the need for novel device development has been fueled by the invention of innovative liquid formulations and modifications of older formulations designed to use...
Aerosol Generators That Force Liquids Through Nozzles

the large absorptive surface of the peripheral lung as a portal for systemic drug delivery. These therapies include peptides, proteins, small molecules, hormones, and liposome/drug suspensions. Many of these agents have a very narrow therapeutic index and require a marked improvement in efficiency and precision of dosing to the distal lung. DPIs with drugs reformulated into easily dispersible powders with improved aerodynamic properties have been used for systemic drug delivery via inhalation (eg, by Inhale Therapeutics). However, for most novel drugs, liquid formulations are used as a starting point for development. Many formulations have already been used as parenteral solutions or suspensions, with known storage and stability variables. The aerosol characteristics of an aqueous compound are mostly controlled by the device design, not by the inhalation pattern. Feasibility studies to demonstrate the usefulness of inhaling a compound can proceed more quickly with liquid formulations. The new devices must optimize aerosol delivery to the peripheral lung, which maximizes the absorption of drug into the bloodstream and minimizes drug loss by mucociliary transport. Also, the intra-subject and inter-subject variability of pharmacokinetic variables should be comparable to those of conventional methods.

The new aerosol systems developed for systemic drug delivery are so efficient that many have been modified for use with topical airway drugs as well. Improved design features of the new devices include smaller device size to improve portability, a flow sensor to match bolus drug delivery to the breathing pattern, and features that guide the patient to inhale at the proper flow rate. These improvements should improve dosing reliability and patient acceptance.

New Liquid Aerosol Generators

Some of the recently introduced devices are improved versions of jet nebulizer technology. For example, the AeroEclipse (Monaghan Medical, Syracuse, New York) is a compressor-driven, breath-actuated nebulizer. The breath actuation is controlled by a mechanical spring device and helps minimize drug waste during exhalation. The Halo-Lite (Profile Therapeutics, West Sussex, United Kingdom) is also a breath-actuated nebulizer; it uses adaptive aerosol delivery to electronically monitor the patient's breathing pattern, then delivers a pulse of aerosol to the first 50% of each inhalation. A pre-set dose is delivered with each button push of the Halo-Lite system. The AKITA (InAMed, München-Gauting, Germany) delivery system incorporates conventional jet nebulizers, but directs the patient to take slow, deep breaths and only delivers aerosol during inhalation. These devices match drug output to the patient's respiratory pattern, may increase lung dose, and minimize drug waste during exhalation, breath-holding, coughing, or talking. However, they do have substantial dead volume.

Other new devices create aerosol by way of a porous membrane that vibrates at ultrasonic frequencies. Examples include Aeroneb, Aerodose (Aerogen, Mountain View, California), the Omron ultrasonic nebulizer (Omron, Tokyo, Japan), and the eFlow (PAR, Starnberg, Germany). Electrostatic aerosol generators, such as that under development at BattellePharma (Columbus, Ohio), create a nearly monodisperse, low-velocity aerosol from a liquid. These new-generation devices are discussed in the other reviews in this issue of Respiratory Care. The remainder of this review discusses the Respimat and AERx, 2 new devices that produce an aerosol by forcing liquids through nozzles.

Devices That Create an Aerosol by Forcing Liquids Through Nozzles

The technique of forcing liquid through a nozzle to create an aerosol is not new. In the late 19th century, antiseptics were nebulized by this method to treat tuberculosis. In the early 1900s Ephraim used adrenaline in a perfume atomizer to treat asthma and laryngeal edema. Nasal spray bottles also use systems that force the drug suspension through a nozzle. In his contribution to this Journal Conference published in the previous issue of Respiratory Care, Dr MacIntyre described a new type of aerosol generator: a multi-channel catheter that passes through an endotracheal tube and generates the aerosol at the catheter tip, within the trachea.

The Respimat

The Respimat (Boehringer Ingelheim, Ingelheim am Rhein, Germany) is a novel, propellant-free, hand-held, multi-dose inhaler that has the convenience of a pMDI but offers better particle characteristics and ease of use (Fig. 1). Application for regulatory approval of the Respimat will be submitted in Germany and other countries soon. The Respimat generates a slow-moving aerosol ("soft mist") from a metered dose of drug, using the mechanical power of a spring. The qualities of the aerosol produced are not dependent on propellants or inspiratory effort (unlike pMDIs and DPIs, respectively). The Respimat does not require a spacer, battery, or outside electric power source. The liquid in the cartridge is a solution, not a suspension, so no shaking is required. The Respimat is reusable for the life of 3 replacement cartridges.

Figure 2 shows a diagram of the Respimat. The patient primes the device by rotating the base 180 degrees, which
Aerosol Generators That Force Liquids Through Nozzles

Respiratorv: md

(1) compresses the spring, thereby storing energy for actuation, and (2) lowers the capillary tube by a precise distance, to draw up a metered dose into the pumping chamber. The volume of the dose is 11–15 μL, depending on the drug. A non-return valve prevents the drug from returning to the cartridge. The patient then inhales slowly from the mouthpiece and pushes the dose-release button, which unleashes the tension in the spring and forces the drug through a nozzle system called a “uniblock.”

The uniblock (Fig. 3) measures approximately 2 × 2.5 mm and consists of a silicone wafer sandwiched to a glass plate. A photolithographic technique is used to etch filter channels into the silicone. Two small, opposing channels at a carefully controlled angle form the exit of the uniblock, such that the 2 converging jets of liquid impact and form a soft mist (see Fig. 3b).

So far, the drugs studied with the Respinmat have been those commonly used for asthma and COPD. The bronchodilators fenoterol and ipratropium bromide are aqueous drug solutions contained in multi-dose cartridges. The corticosteroid flunisolide is dissolved in 96% ethanol. The fine particle fraction produced by the latest version of Respinmat is about 66% with the aqueous solutions and 81% with the ethanol solutions, which is higher than that of corresponding CFC pMDIs.

The aerosol velocity from the Respinmat is about one fifth of that from a CFC pMDI. The duration of aerosol generation is about 1.2 seconds for aqueous solutions and 1.6 seconds for ethanol solutions. Though the Respinmat requires synchronization of inspiration with actuation, the low velocity of the aerosol allows even poorly coordinated patients to capture the aerosol with a slow, deep inspiration.

Respinmat Deposition Studies

Gamma scintigraphy is a method for assessing lung deposition of inhaled drugs. Scintigraphic studies have been carried out for the Respinmat with fenoterol (a β₂ agonist, not available in the United States) and flunisolide. These studies were done with healthy volunteers and compared Respinmat to a pMDI with and without a holding chamber. A randomized, 3-way crossover study was performed to compare fenoterol deposition with Respinmat, pMDI, and pMDI with an Aerocamber. Lung deposition values were 39.2 ± 12.7%, 11.0 ± 4.9%, and 9.9 ± 3.4% of the nominal dose, respectively. The Respinmat showed less oropharyngeal deposition than the pMDI (37.1 vs 71.7%), but the pMDI plus AeroChamber had the lowest oropharyngeal deposition (3.6%).

Deposition of flunisolide was compared with the Respinmat and a pMDI with an Inhaçart spacer. Lung deposition was 44.6 ± 7.9% with Respinmat and 26.4 ± 6.2% with the pMDI plus spacer. Oropharyngeal deposition was 26.2% and 31.2%, respectively. In a prior study, with a pMDI without a spacer, the flunisolide lung deposition was 15.3 ± 5.1%, with oropharyngeal deposition of 66.9%. Thus the Respinmat reduced oropharyngeal deposition, eliminated the need for a spacer device, and increased lung deposition, compared with either MDI or pMDI with holding chamber.

Respinmat Clinical Studies

Though they can be used to compare device performance, in vitro and deposition studies are not enough to prove that one device/drug combination is superior to another in the clinical setting. Therefore, several clinical trials with asthma and COPD patients were performed to compare the Respinmat to a CFC pMDI. The studies using bronchodilators had the premise that lower doses with the Respinmat would be equivalent to higher doses with the pMDI. VanNoord et al. studied 62 stable adult asthmatics, using a single dose of fenoterol from either the Respinmat (range 12.5–200 μg per dose) or CFC pMDI (100 or 200 μg per dose). The forced expiratory volume in the first second (FEV₁) response was measured over a 6-hour period. This dose-ranging study showed that the 12.5 and 25 μg doses with the Respinmat were therapeutically equivalent to the 100 μg dose with the pMDI. All Respinmat doses were therapeutically equivalent to the 200 μg dose. A similar study by Goldberg et al. examined the bronchodilator response with a single dose of a formulation containing fenoterol and ipratropium bromide. That study showed that the Respinmat had a log-linear dose-response relationship, as in the vanNoord study. It also showed that the bronchodilators administered with the Respinmat were...
therapeutically similar to the pMDI at one quarter to one eighth the dose. Pharmacokinetic analysis also showed a 2-fold greater systemic availability with the Respimat than with the pMDI. As in most studies, there was a high intersubject variability in FEV\textsubscript{1} response. The safety profiles were similar between therapeutically equivalent doses.

Other studies with the combination of fenoterol and ipratropium bromide via the Respimat with asthmatics using cumulative doses (simulating doses used during acute exacerbations) have shown similar results. A study of 43 adult asthma patients showed that cumulative doses from the Respimat produced therapeutic equivalence at half the dose of the pMDI.\textsuperscript{13} There was no paradoxical bronchospasm with repeated doses in either device in that study. A pediatric study of 461 asthmatic children between the ages of 5 and 15 showed a similar relationship with single doses of drug.\textsuperscript{15} Subjects were treated for 4 weeks with fenoterol and ipratropium bromide via the Respimat or pMDI plus Aerochamber. The FEV\textsubscript{1} response on the final study day showed that the Respimat was twice as effective as the pMDI with holding chamber.

Clinical trials have also been performed with COPD patients with either ipratropium bromide alone or in combination with fenoterol. In each case the findings were similar to those of the asthma studies; that is, the Respimat was as effective at half the dose of the pMDI. Safety profiles were also similar between devices.\textsuperscript{16-18}

**Challenges for Respimat**

The Respimat has solved many of the problems of pMDIs, DPIs, and nebulizers. It is small, portable, and does not require a power source. It produces a slow-moving cloud with a high proportion of fine particles, which reduces mouth and throat deposition and allows a higher proportion of the emitted dose to be delivered to the lungs. It is also propellant-free and thus does not contribute to ozone depletion or global warming.

However, the Respimat still requires a degree of hand/breath synchronization. The patient must be inhaling when the device is activated, though with the Respimat the "soft mist" is produced over a longer period of time than a pMDI, making it easier for the patient to capture the aerosol during inspiration. The Respimat will have competition from DPI and HFA pMDI preparations of the same or similar drug combinations. The budesonide Turbuhaler can deposit up to 35\% of the nominal dose in the lung.\textsuperscript{19} The newer HFA pMDI beclomethasone has been shown to deposit more than 50\% of the initial dose in the lung.\textsuperscript{2} The introduction of a new aerosol delivery technology in the United States may face stiff competition from devices that are already familiar to physicians and patients.

Perhaps the largest challenge for Respimat is that there has been growing concern regarding the use of preservatives in drug formulations. Multi-dose liquid formulations need preservatives, and Respimat is a multi-dose device.
Aqueous Respimat solutions are preserved with benzalkonium chloride and ethylenediaminetetraacetic acid (EDTA), which have been implicated in causing paradoxical bronchoconstriction in asthmatics. The inhalable steroid used in Respimat is preserved and stabilized with 96% ethanol, which has also been implicated in causing bronchospasm. Even so, studies with the Respimat and asthmatic patients with substantial bronchial hyperactivity have shown it to be well tolerated. The dose of benzalkonium chloride inhaled with several puffs of an aqueous Respimat solution is still considerably lower than that in some of the available nebulizer preparations in the United States. However, there has been increased interest in banning preservatives from inhaled drugs. The current regulatory environment favors sterile, unit-dose drugs without preservatives, so the Respimat may face this hurdle in the United States.

The AERx System

The AERx (Aradigm, Hayward, California) is an electronic microprocessor-controlled device designed to pro-
Aerosol Generators That Force Liquids Through Nozzles

![Diagram of AERx system]

Table 1. Therapeutic Agents Delivered by the AERx System

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rhDNase = recombinant human deoxyribonuclease (deoxyribonuclease)
IL = interleukin

Pulmonary device, including peptides, proteins, hormones, and small molecules.

With the AERx the drug is contained in a single-use, multi-layer, laminated dose blister that consists of a drug reservoir and a burstable-seal layer with a slot that directs drug through a nozzle array (Figure 5A). The nozzle consists of a number of small laser-drilled holes approximately 1 μm in diameter. Since the nozzle array is incorporated in the dose blister, it is used only once, thus avoiding clogging issues, which improves the reproducibility and reliability of aerosol production. Each dose blister holds approximately 45 μL of liquid. In the case of higher dose requirements, the dose blisters can be manufactured in a strip so that after one dose is inhaled the next one is automatically loaded.

The AERx incorporates sophisticated technology to deliver aerosol during a pre-set portion of inspiration and only when conditions are ideal (Fig. 6). The dose blister is inserted into the strip guide, which advances it to the extrusion mechanism. The blister is held by a clamp that seals the perimeter to ensure a controlled release of drug. The blister is positioned above a piston mechanism driven by an electrical motor, which is capable of up to 50,000 actuations over the life of the device. A temperature controller heats the air to control temperature and relative humidity. This reduces the aerosol particle size variability that can be caused by ambient air conditions.

A pressure-sensing system located near the temperature controller measures the inspiratory flow and inhaled volume. The patient is guided to inhale at the desired flow rate by visual feedback from a display. When the AERx senses the proper flow rate, the motor/cam/piston assembly mechanically pressurizes the blister dose and extrudes the drug through the nozzle array. The aerosol produced is entrained in the inspired air (Fig. 7). The display screen then prompts the patient to hold the breath for a count of

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5–10 seconds. The dose is expressed over approximately 1.5 seconds. More than 90% of the particles are between 1 and 3 μm. The aerosol is nearly monodisperse, with a geometric standard deviation ranging from 1.2 to 1.5 μm, depending on the drug and device prototype. These characteristics of the AERx are ideal to achieve low oropharyngeal deposition and high peripheral lung deposition. The motor in the AERx also has a position-sensing system that allows increments of a dose blister to be administered. For example, the patient can set the AERx to deliver one-unit increments of insulin, allowing accurate dose titration by the patient. The nozzle array design and the timing of aerosol release can be changed to target the central lung regions for topical airway applications. By controlling the conditions of dose expression and managing the inhalation and delivery process, the AERx can provide the level of dose reproducibility that is required for a drug with a narrow therapeutic index.

**AERx Deposition Studies**

Gamma scintigraphy studies with normal volunteers and asthmatics have shown deposition efficiency of 50–80% with various AERx prototypes. The electronics that monitor the patient inhalation profile prior to dosing are similar to those of an earlier device, the SmartMist, developed by Aradigm, which provided reproducible actuation of a pMDI at a pre-programmed point during inspiration. A study with normal human subjects compared lung deposition with the SmartMist pMDI and the AERx. The SmartMist’s average deposition fraction was 21.7% (well above a typical CFC pMDI), and the AERx averaged 53.3%. The pMDI produced a high-velocity aerosol with throat deposition of 42%, versus only 6.9% with the AERx. In another study, a radiolabeled protein was delivered with the AERx device or a ventic nebulizer (the PARI LC Star) to 4 asthma patients. The AERx averaged 80% lung dose.
AERx Clinical Trials: Systemic Drugs

A number of therapeutic agents have been used or considered for use with the AERx, for either systemic or topical use. Traditional delivery routes for systemic agents include oral, transmucosal (rectal, buccal, nasal), transdermal, intravenous, intramuscular, and subcutaneous. Some drugs are broken down in the gut, and some molecules are too large to be absorbed efficiently through the skin or mucosa. The large, absorptive, alveolar-capillary surface of the peripheral lung provides an attractive alternative to other delivery methods for large or small molecules. The advantage of inhaling systemically active agents, versus intravenous, intramuscular, or subcutaneous administration, is the elimination of injections. The advantages of inhalation over oral or transmucosal delivery are faster onset of action, precise dose titration, and high bioavailability. The 2 indications for which the AERx has been most studied are pain control with inhaled opioids (morphine and fentanyl) and diabetes treatment with inhaled insulin. Pharmacokinetic, pharmacodynamic, efficacy, and

compared to 33.6% with the PARI (Fig. 8). Even more impressive was the extremely low coefficient of variation with the AERx, which was only 3%, compared to 23% with the PARI. The reproducibility of lung delivery is far better with the AERx than with a pMDI, DPI, or nebulizer/compressor system.

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safety studies have been performed with these drugs delivered by the AERx device.

Early studies of nebulized opioid inhalation for dyspnea had mixed results, but there was good evidence of analgesia, as reviewed by Othulanta and Thippawong. The level of pain control with inhaled opioids was directly related to the efficiency of the nebulizer system. Bioavailability is very low with traditional nebulizer systems, but the AERx can produce small particles in a controlled inhalation to maximize systemic bioavailability. Pharmacokinetic studies with morphine or fentanyl with the AERx device in healthy volunteers have shown systemic bioavailability ranging from 59 to 95%. In one of these studies the in vitro measurements showed that the AERx had an emitted dose of 78% and a mass median aerodynamic diameter ± geometric standard deviation of 2.6 ± 1.3 μm. The 10 subjects in that study had a mean bioavailability of 75%, showing close agreement with the in vitro data. The pharmacokinetic profile of inhaled opioids with the AERx was similar to intravenous administration in each of these studies, with rapid peak serum levels and a short half-life (Fig. 9).

To date, over 120 patients have been treated with inhaled opioids with the AERx Pain Management System. Boyle et al used the AERx system to deliver fentanyl to patients with pain from advanced cancer, and showed good analgesia in all patients, with average pain control within 10 min of administration. A recent Phase 2 study with morphine showed greater and faster analgesia than immediate-release oral morphine in patients with breakthrough cancer pain. Two other studies of morphine delivered by the AERx to patients with orthopedic postoperative pain showed pain relief and onset of action comparable to intravenous morphine. The AERx Pain Management System’s safety features include patient identification keys and physician-set lockouts to prevent unauthorized access. These studies demonstrate the potential to control acute and breakthrough pain with opioid inhalation from a precise dosing system such as AERx.

Diabetes affects 150 million people worldwide. It has been demonstrated that tighter control of blood glucose levels in both type 1 and type 2 diabetes results in better long-term outcomes. However, better glycemia control means more insulin injections per day, which may be an inconvenience or burden to some patients. Therefore insulin inhalation has been investigated with new aerosol devices, including AERx. Data from healthy volunteers show faster insulin absorption via inhalation than via the subcutaneous route, but more insulin is required to achieve the same effect. Insulin is a large molecule, and not all the insulin deposited in the lung is absorbed. But inhaling deeply rather than with a shallow breath results in much faster absorption of insulin, perhaps because of better peripheral lung deposition. Kipnes et al reported insulin pharmacokinetic and pharmacodynamic responses after a standard meal in type 1 diabetics. The mean system efficiency relative to subcutaneous dosing was 16–17%, which is comparable to or better than other new aerosol systems. The time to peak insulin level was 41 min shorter than with subcutaneous administration. Thus, dosing just prior to a meal is possible with the AERx, whereas a subcutaneous dose must be given 30–40 min before a meal.

Another study of type 1 diabetics showed a clear dose-response curve with the AERx system, and intra-subject variability similar to subcutaneous insulin administration, demonstrating the reliability and precision of dosing with the AERx. Finally, a recent 12-week study of 107 people with type 2 diabetes showed equivalent responses with short-acting insulin delivered thrice daily with meals either via inhalation with the AERx system or via the subcutaneous route. As with all the clinical trials with inhaled insulin, patients still required a nighttime subcutaneous dose of long-acting insulin. Therefore, the use of inhaled insulin with meals.
Aerosol Generators That Force Liquids Through Nozzles

![Graph: Plasma Morphine Concentration vs Time (minutes)]

**Fig. 9.** Pharmacokinetic profile of morphine delivered via AERx is similar to intravenous administration. (From Reference 28, with permission.)

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can result in tight glycemia control while reducing the number of injections to one per day.

**AERx Clinical Trials: Pulmonary Delivery for Lung Disease**

Most inexpensive asthma drugs with a wide therapeutic index may not require the dose precision and efficiency of the AERx. However, there are a number of expensive drugs available and in development that could be delivered topically with the AERx to treat lung disorders. Efficient and rapid aerosol delivery systems are needed for chronic disorders such as CF that require daily therapy with numerous inhaled drugs. And there will be more such drugs in the future.

One expensive biotechnology product used for CF is rhDNase (dornase alfa or Pulmozyme), which reduces sputum stickiness and thus aids in sputum clearance. Using a standard, approved nebulizer may take 10–15 min (per 2.5 mg dose) and deposit only 6–31% of the dose in the lung. A proof-of-concept study with the AERx and 16 CF patients with moderately severe lung disease showed that FEV₁ improvement averaged 9.9% after 2 weeks of daily bolus inhalation of rhDNase (1.35 mg in only 3 breaths). That was the first report of bolus inhalation of a protein used for topical airway application.

Another drug with potential for CF, chronic bronchitis, and COPD is INS-365, which is a uridine triphosphate analogue that binds the P2Y2 receptor in airway cells. Activation of the receptor triggers chloride secretion and increases ciliary beat frequency, which promotes airway clearance. It is thought that a high lung dose (about 10 mg) of INS-365 is necessary to be effective, making it a challenging drug to administer by bolus technique. The AERx dose blister can only hold 50 μL of fluid, which would necessitate a high concentration of drug in the blister. Fortunately, INS-365 is highly soluble. Though the viscosity is greater at higher concentrations, the AERx was able to deliver more than 10 mg INS-365 (240 mg/mL) in only 2 inhalations. Currently rhDNase and INS-365 are not being commercially developed for the AERx, but the latter studies demonstrate that the AERx can efficiently deliver such drugs to the airways.

**Challenges for the AERx System**

The AERx measures the inhaled flow briefly before aerosolizing a dose over about 1.5 seconds. Thus, to inhale a full dose from the blister a patient must have a minimum vital capacity of 1.5 L. This prohibits the use of the AERx with young children or older patients with restrictive or severe obstructive lung disease, so modifications will be necessary before those populations can benefit from the AERx.

Some drugs, such as anti-proteases and aminoglycosides, require a large lung dose to be effective. Since the
AERx dose form only holds 50 μL, it is not a viable option for some drugs that are not stable at high concentrations. Opioids delivered with the AERx provide pain relief similar to intravenous administration, with faster onset of action than oral or transmucosal administration. However, it is likely that the expense of the AERx Pain Management System will substantially exceed that of the other administration routes. Even if AERx is approved for morphine and fentanyl delivery, there is no guarantee that it will be reimbursed by third-party payors. The AERx also faces competition in the diabetes arena. Insulin pumps already provide strict glycemia control without multiple injections. A number of other insulin delivery systems are in development, including DPIs and liquid aerosol systems for inhalation, oral ingestion, and transmucosal methods. Regulatory concerns about the safety of inhaled insulin may delay approval long enough for other technologies to “catch up,” including islet cell transplantation, which may eliminate the need for insulin. This could be financially devastating for the companies investing considerable resources in inhalable insulin research. Nevertheless, there will be many inhalable therapeutics for both topical and systemic delivery that will require the efficiency and precision of devices such as AERx.

Summary

Aerosol delivery technology was stagnant until the past decade or so, when several forces ignited the fires of innovation in the industry. In the coming years we are likely to see several new drug/device products that will improve aerosol delivery efficiency and be much more user-friendly. The Respimat solves many of the problems with DPIs and pMDIs, by producing small particles in a slow-moving cloud. Because of its superior efficiency, Respimat can deliver asthma and COPD drugs at lower nominal doses while maintaining efficacy and safety. The AERx system can deliver a wide variety of liquid formulations for topical airway or systemic delivery. The dose accuracy and reproducibility of the AERx allow inhalation delivery of drugs that have narrow therapeutic windows. Both AERx and Respimat face regulatory, financial, and competition obstacles, but both technologies hold considerable promise to improve the lives of patients.

REFERENCES

Discussion

Gomez: Since the AERx technique relies on forcing liquid through a 1-μm orifice, aren’t there issues of clogging? That may be one of the reasons the lung deposition is not as good as some of the other techniques that also yield monodisperse aerosol. You can achieve higher lung deposition if you have relatively narrow droplet size distributions. In principle the distribution should be very narrow with this device, but perhaps it isn’t because the droplets have to be generated through 1-μm orifices.

Geller: As I mentioned, the AERx does produce a fairly monodisperse aerosol. It’s a much smaller (GSP) distribution than a nebulizer, for example, though it’s probably not as monodisperse as the electrospray technology. But the AERx holes are laser drilled and they’re uniform in size. It’s a disposable, inexpensive blister. The nozzle array is just holes drilled into a film material, and they do get clogged after one use. I’ve seen a micrograph of a clogged nozzle. If you have to take 3 doses (that...
is, 3 dose blisters), they make a little cassette that automatically ejects the used one and loads the next. It’s not 100% deposition, but somewhere between 50 and 80% lung deposition of the nominal dose is great—a lot better than nebulizers.

**Dennis:** The design of the AERx device has taught me something very valuable. Aradigm put a lot of investment into their device, to control the temperature and the humidity of ambient air, and to ask the patient to inhale at a certain rate. I’ve talked with Igor Gonda [Aradigm research and development] about this, and I believe it’s true that the reason Aradigm did that is that they want to control the amount of evaporation in the aerosol bolus. The AERx has a 50 μL bolus that emits in 1 second into an air stream in which temperature and humidity are controlled. The Respimat only has a 15 μL bolus that emits in 1 second into roughly the same ambient air flow rate, but with no temperature or humidity control. So the Respimat cannot avoid a lot of variable aerosol evaporation and the resulting decrease in droplet size, which is dependent on the amount, humidity, and temperature of inhaled air.

To my knowledge, Boehringer has not addressed that at all. I haven’t seen anything in publication or during conference discussion. Even so, the device will undergo clinical trial, so this should prove its safety and efficacy for a specific application, though the variable evaporation will be important for generic application. There’s a message here to anybody who’s developing devices that emit a small bolus of liquid aerosol, which is that the amount of evaporation to ambient air will be as much as about 16–18 μL/L in dry air, so, with 50% humidity, evaporation will be about 8 μL of water from the aerosol droplets. If you have a small bolus volume of only 10–20 μL from a device releasing into a liter of air, that evaporation is going to seriously affect the particle size, and you’ll probably end up with either dry particles or very much concentrated particles.

**Geller:** I do have one comment. I forgot to mention that Aradigm (AERx) is developing a completely mechanical device as well. The electronics, obviously, are expensive, and there are some drugs that do not require the precision of the electronic version, so they are developing a mechanical device. I don’t know a lot about it, but it does not have a temperature controller, and I did see mention of one study that looked at temperature control versus no temperature control, and there was only a 5% difference in deposition. So the temperature control did help, but only by 5%.

**Fink:** Was there a difference in particle size?

**Geller:** It didn’t say.

**Fink:** The Respimat is a really cool device. We’ve been reading about it for years. Has it been released in Europe? Is there a plan to release it in the United States? What are the barriers?

**Geller:** Right now, neither AERx nor Respimat is available anywhere. I’m told that Respimat will go for application in Europe next year. There are some things in development that I’m probably not supposed to know about, so I can’t say. And I believe there is a move to market in the United States as well. I think the barrier is going to be the drug preservatives the device requires.

**Witek:** A couple of points about the Respimat Soft Mist Inhaler. It is being developed as an alternative to common metered-dose inhalers and dry powder inhalers. It is a pocket-sized, multi-dose device for the delivery of bronchodilators and other agents for COPD and asthma. With regard to the timelines, you’re right about the application in Europe, and the Phase III studies will be starting in the United States this year. Regarding your point about preservatives, I guess these are the balances we have. As Paracelsus said: It’s all in the dose. Respimat uses very low doses of preservative, and it will be seen in the clinical trials if the preservative is a problem. We’ve done some small-scale studies in which it appeared not to be, even in hypersensitive individuals.1–3

**REFERENCES**


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* James B Fink MSc, RRT FAARC, Aerogen, Mountain View, California.