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Current Therapies and Technological Advances in Aqueous Aerosol Drug Delivery

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Recent advances in aerosolization technology have led to renewed interest in pulmonary delivery of a variety of drugs. Pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) have experienced success in recent years; however, many limitations are presented by formulation difficulties, inefficient delivery, and complex device designs. Simplification of the formulation process as well as adaptability of new devices has led many in the pharmaceutical industry to reconsider aerosolization in an aqueous carrier. In the acute care setting, breath-enhanced air-jet nebulizers are controlling and minimizing the amount of wasted medication, while producing a high percentage of respirable droplets. Vibrating mesh nebulizers offer advantages in higher respirable fractions (RFs) and slower velocity aerosols when compared with air-jet nebulizers. Vibrating mesh nebulizers incorporating formulation and patient adaptive components provide improvements to continuous nebulization technology by generating aerosol only when it is most likely to reach the deep lung. Novel innovations in generation of liquid aerosols are now being adapted for propellant-free pulmonary drug delivery to achieve unprecedented control over dose delivered and are leading the way for the adaptation of systemic drugs for delivery via the pulmonary route. Devices designed for the metered dose delivery of insulin, morphine, sildenafil, triptans, and various peptides are all currently under investigation for pulmonary delivery to treat nonrespiratory diseases. Although these devices are currently still in clinical testing (with the exception of the Respimat®), metered dose liquid inhalers (MDLIs) have already shown superior outcomes to current pulmonary and systemic delivery methods.

Keywords nebulization; vibrating mesh; metered dose liquid inhaler; pulmonary aerosol; improved deposition

INTRODUCTION

Liquid aerosol inhalation has been an accepted means of drug delivery since the beginning of modern pharmaceutical therapy. Beginning with the development of the first nebulizer in the early 20th century (Dessanges, 2001), aerosol-generating devices have continued to progress to provide higher efficiencies, lower variability, and better patient compliance. Aerosol delivery is used in almost every stage of health care: acute, long-term, and home health care, each of which demands variations on liquid aerosol generation method. While trying to adapt to patient needs in a multitude of settings, pulmonary delivery devices are constantly being improved and modified to create aerosols that effectively traverse the human airway. Extensive work has been reported using in vitro methods to characterize aerosols (Gurses & Smaldone, 2003), model the human airway (Burnell et al., 2007; Finlay & Martin, 2007; Mitsakou, Helmis, & Housiadas, 2005; Schuepp et al., 2005), and predict how effectively a device might perform in a clinical setting (Nikander, Denyer, Smith, & Wollmer, 2001).

Compact devices designed for ambulatory patients in the home heath field have been dominated in recent years by two types of devices: pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). Whereas these methods of pulmonary delivery have seen considerable success, recent technological innovations have lead to renewed interest in aqueous aerosol drug delivery (Lange & Finlay, 2006; Smaldone, 2006). New technology involving liquid aerosolization has been focused predominately on delivery of a precisely metered dose to the deep lung (Schuster et al., 1998), which may fill a well-known need for devices capable of delivery of systemic drugs via the pulmonary route (Sanjar & Matthews, 2001). Aqueous aerosol delivery devices can also greatly simplify the formulation process and allow for new pulmonary therapies to be implemented more readily. Devices for aqueous aerosol generation seen in currently marketed products can be classified into four main categories: air-jet nebulizers, vibrating nebulizers, "smart" nebulizers, and metered dose liquid inhalers (MDLIs). The goal of this article is to review fundamental concepts of aerosol generation (Figure 1) (Dalby, Spallek, & Voshaar, 2004; O'Callaghan & Barry, 1997), current problems in pulmonary delivery, and next generation devices in each of these categories.

AIR-JET NEBULIZERS

Traditionally, aqueous aerosols produced by jet nebulization have been used for pulmonary drug delivery to nonambulatory patients in an acute care or home care setting. Patients who

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experience acute respiratory distress are unable to synchronize device actuation with breathing patterns, or require high doses to the lungs often benefit most from jet nebulization treatments rather than alternative pulmonary therapies. In many cases, however, these devices are quite cumbersome and require professional assistance, additional tubing and mouth pieces, and compressed air and/or oxygen sources. Additionally, most nebulizers have been proven to be highly variable between different formulations (Hess, Fisher, Williams, Pooler, & Kacmarek, 1996; Smith, Denyer, & Kendrick, 1995) and inefficient (Leung, Louca, & Coates, 2004), leading to wasted drug and unknown lung deposition levels. For most nebulizers, only about 10% of the total reservoir dose will actually reach the lung (Zainudin, Biddiscombe, Tolfree, Short, & Spiro, 1990). For these reasons, the majority of new formulations for pulmonary delivery developed over the past 20 years have been designed for administration with formulation-specific pMDI and DPI devices. These devices have allowed for greater control over aerosol characteristics and total delivered dose by integrating formulation with device design.

Although inefficient in comparison with other pulmonary delivery devices, jet nebulizers remain an effective mode of treatment for many new formulations. In investigating a new pulmonary formulation for clinical efficacy, formulation parameters are greatly simplified when nebulization is chosen as the method of aerosolization. As a result, many new pulmonary treatments in both laboratory and clinical settings use jet nebulization (Kohler, Sollich, Schuster-Wonka, & Huhnerbein, 2003; Koshkina, Golunski, Roberts, Gilbert, & Knight, 2004; Lentz, Anchordoquy, & Lengsfeld, 2006). Difficulties encountered in the formulation and aerosolization processes result in many therapies that cannot be delivered with pMDIs or DPIs for risk of damaging the therapeutic moiety. Antibiotics, mucolytics, β2-agonists, liposomal formulations (Elhissi & Taylor, 2005), and recombinant products such as Pulmozyme® (dornase alfa) Inhalation Solution are recommended for nebulization because of the superior stability afforded by this method of aerosolization (Anderson, 2001; McCallion, Taylor, Bridges, Thomas, & Taylor, 1996). Additionally, Lentz et al. have shown that further mechanical stability can be added to gene therapies designed for jet nebulization by the complexation of DNA with cationic agents (Lentz, Worden, Anchordoquy, & Lengsfeld, 2005). Vibrating mesh nebulizers have also been used for pulmonary gene delivery due to the reduction of mechanical shear as well as minimization of the concentration effect (Lynch, Behan, & Birkinshaw, 2007). Formulation limitations imposed by other delivery technologies, particularly in chlorofluorocarbon (CFC) containing pMDIs, have resulted in increased use of jet nebulization in Europe and many other countries (Waldrep, 1998).

Early jet nebulizer designs of the 1940s, constructed of glass and operated by compressing a hand bulb, incorporated the same basic principles that are still used in jet nebulization today (Dessanges, 2001). The driving force of current air-jet nebulizers is based on negative pressure created by high-velocity gas, drawing liquid from the reservoir up to a narrow opening (called a Venturi), through which the compressed air enters the nebulizer. This fundamental principle of jet nebulization, called the Bernoulli effect, ultimately results in the aerosolization of the formulation. Bernoulli's principle is described in the equation below:

$$P + 0.5\,\rho v^2 + \rho g h = \text{constant} \quad (1)$$

where P is the pressure in the tube, ρ is the gas or liquid density, v is the gas or liquid velocity, g is the gravitational acceleration, and h is the height above a reference level. Nebulizer design improvements such as aerosol-conserving reservoirs (Corcoran, Dauber, Chigier, & Iacono, 2002), large particle reducing baffles, and breath-enhanced aerosol production (Leung et al., 2004) have led to higher nebulizer outputs, larger fine particle fraction (FPF), and less formulation wasted during the expiratory maneuver, respectively. Breath-enhanced nebulizers use the negative pressure created by a patient's inspiration to further reduce pressure in the nebulizer head and increase aerosol production. The Pari LC® Star (Pari GmbH, Starnberg, Germany) and the AeroEclipse II® BAN (Trudell Medical International, London, Canada) are examples of breath-enhanced nebulizers, producing aerosols in high respirable fractions (RFs) and limiting the amount of aerosol lost to the outside environment. When compared, it was found that the Pari LC® Star produces a higher rate of deposition (0.093 mg/min) at a given breathing rate, whereas the AeroEclipse® ensures a more efficient drug deposition (58.9% of total dose was deposited in lung) (Leung et al., 2004). High-velocity air entrainment leads to enhanced aerosol production, as well as assisting with aerosolization of more viscous formulations. Highly viscous dextrose solution for treatment of cystic fibrosis was nebulized more rapidly with the Pari LC® (breath enhanced) than with ultrasonic or closed-head nebulizers (Warren H. Finlay, Lange, King, & Speert, 2000). In comparison with other breath-enhanced jet nebulizers (not including the AeroEclipse®), the Pari LC® has been shown to have higher efficiency (Ho, Kwong, O'Drowsky, & Coates, 2001).

Nebulizers are unique from other pulmonary delivery methods in that they are exempt from strict regulatory guidelines (Silkstone, Dennis, Pieron, & Chrystyn, 2002). This allows for fast approval of new technologies; however, benchmarks for comparison are not well defined, and clinical outcomes may vary greatly between different nebulizer/formulation combinations. None et al. have proposed a residual gravimetric method that will accurately measure total aerosol output (None et al., 2004). Other in vitro studies have used a human throat model to attempt to compare aerosol deposition (Burnell et al., 2007; DeHaan & Finlay, 2001); however, there is no universally accepted model or method for comparison outside of these studies. Burnell and coworkers found that

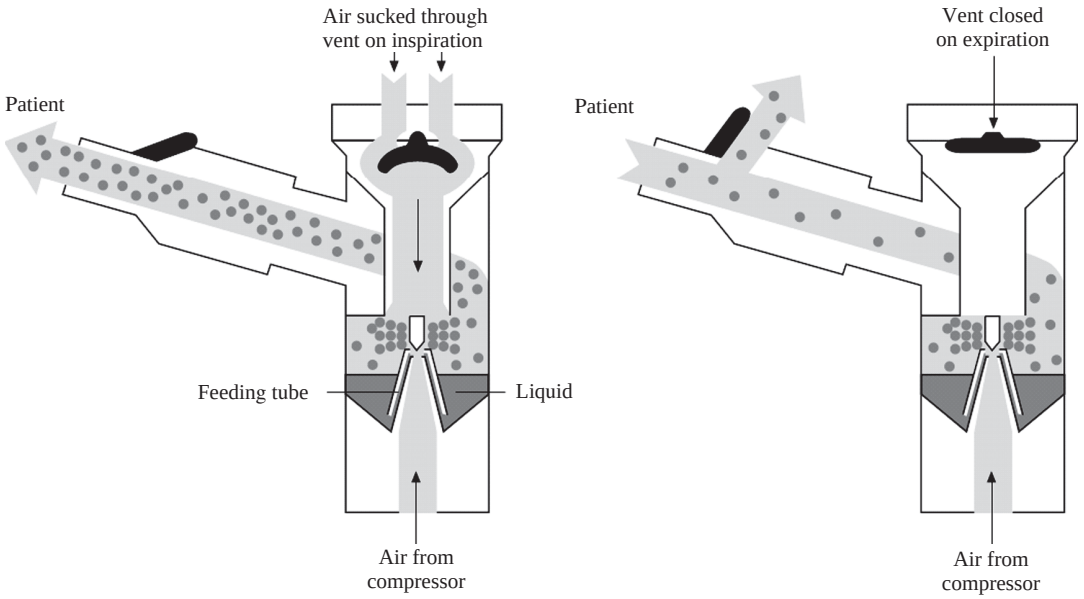

FIGURE 1. An example of the breath-enhanced mechanism used in the Pari LC® Star (Reprinted with permission from O'Callaghan, C., & Barry, P. W. (1997). The Science of nebulised drug delivered. *Thorax, 52*, 31–44).

throat volume, which may vary between models and patients alike, plays a large role in drug deposition. In Europe an effort to standardize in vitro characterization of nebulizers has been established in the European Standard for Nebulizers (CEN) (BS EN 2001). Continued standardization of analytical and characterization methods of traditional nebulizers is needed to optimize treatments and reduce therapeutic variability. Revisions in hospital dosing protocols are also essential as less wasteful, higher output nebulizers are incorporated into daily treatments of respiratory patients.

VIBRATING MESH NEBULIZERS

In addition to jet nebulization, aerosols may also be generated using ultrasonic devices. By incorporating a piezoelectric crystal vibrating at high frequencies (1–3 MHz), ultrasonic nebulizers produce a therapeutic aerosol mist of respirable droplets. Traditional ultrasonic aerosol production is described mathematically by capillary wave theory (Mercer, 1981) and cavitation theory. Briefly, the capillary theory describes aerosol formation as capillary waves form on the fluid surface. As the amplitude of the waves reaches a threshold, the crest begins to break off into small, airborne droplets. In cavitation theory, the implosion of small surface bubbles causes hydraulic shocks which create aerosolized droplets (Taylor & McCallion, 1997). Although high outputs are attainable with ultrasonic nebulization, there are many limitations when compared with jet nebulization. Residual formulation due to "dead" volume, inability to aerosolize viscous solutions, settling of suspensions, and degradation of heat-sensitive materials are some of the common problems encountered with traditional ultrasonic nebulizers (Taylor & McCallion, 1997).

Recent adaptations of ultrasonic devices for pulmonary delivery have led to the development of micropump technology for aerosol production, commonly referred to as vibrating mesh nebulization. This technology allows for the production of high RF, low velocity aerosols by adapting a vibrating piezoelectric crystal to a laser-bored mesh plate. Oscillation of the mesh plate pumps fluid from the small volume reservoir through thousands of tapered holes, producing primary aerosol droplets in the respirable range (1–5 μm in diameter). The Aeroneb® Pro (Aerogen Inc., Galway, Ireland) is a currently marketed vibrating mesh nebulizer that has been tested for multiple formulations/therapies. The Aeroneb® has been shown to effectively aerosolize recombinant adeno-associated virus (Wilson, Simmons, & Uster, 2003), liposomal salbutamol sulfate (Elhissi, Faizi, Naji, Gill, & Taylor, 2007), insulin (Shaw, 2004), and other moieties that are prone to degradation from heat or shear produced by harsher nebulization methods. When compared with liposomal aerosols produced by an air-jet nebulizer (Pari LC®), an adapted Aeroneb® Pro demonstrated high output rates, shorter nebulization time, and 44% more drug entrapment in multilamellar liposomes after aerosolization (Elhissi et al., 2007). Clinically, vibrating mesh nebulization has shown improvements over other modalities. In clinical studies involving ventilation, the Aeroneb® Pro was used in-line with a ventilated infant and, due to negligible additional flow input, showed no negative effects on ventilator function (Smith, 2004). Additional studies have shown that the ability to nebulize very small volumes (as low at 0.5 mL) and simultaneously deliver humidification to ventilated patients give added value to vibrating mesh nebulizers in ventilated patients (Bartram, 2005). It should be noted, however, that circuit

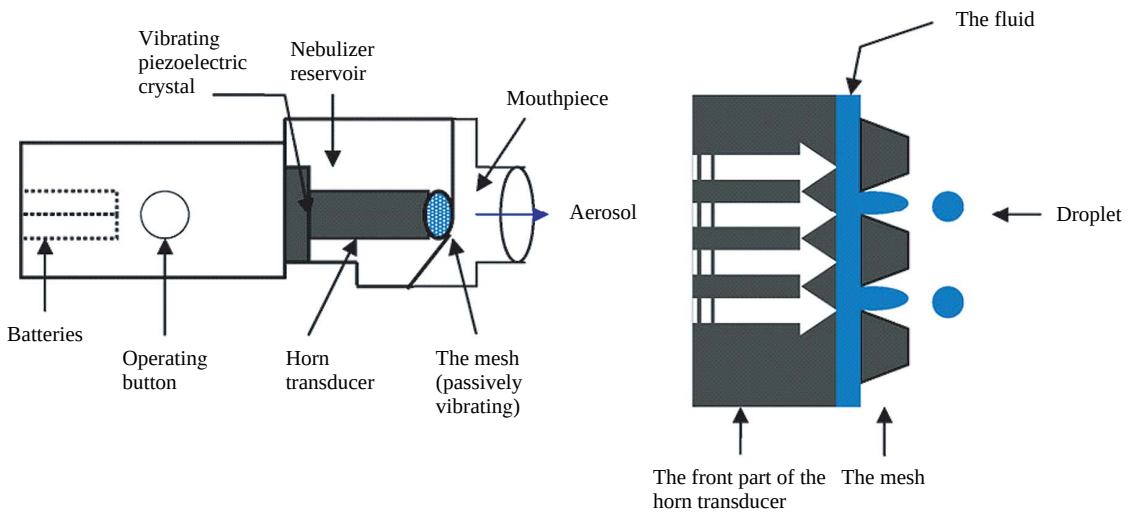

FIGURE 2. A diagram of the Omron Micro*Air*®, a hand-held passively vibrating mesh nebulizer (Reprinted with permission from Ghazanfari et al., 2007).

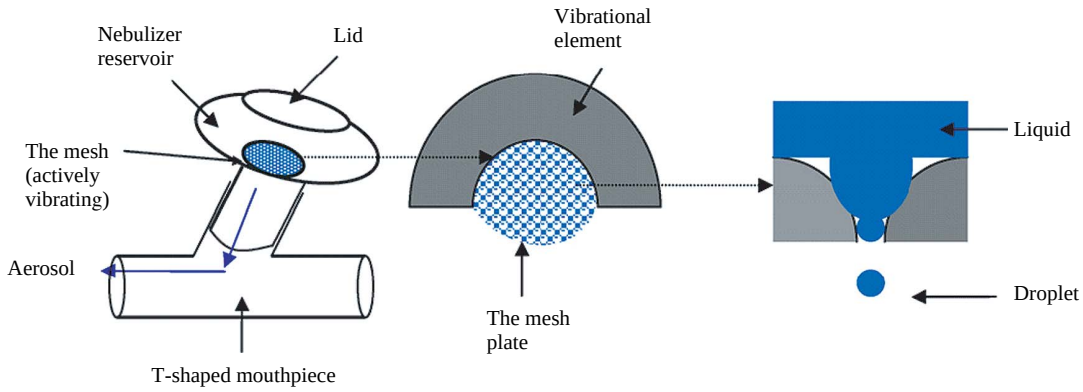

FIGURE 3. A diagram of the Aeroneb® Pro, an active vibrating mesh nebulizer (Reprinted with permission from Ghazanfari et al., 2007).

dimensions and ventilator settings will affect nebulizer performance in a ventilator circuit (Pedersen, Handlos, Heslet, & Kristensen, 2006). Passively vibrating mesh nebulizers, such as the Omron Micro*Air*® VMT (Omron Healthcare, Bannockburn, IL, USA), incorporate the same aerosolization concept; however, the ultrasonic vibrations are passively conducted through a thin layer of fluid to the mesh plate. Fluid viscosity has been shown to significantly affect passively vibrating mesh nebulizers due to the lower vibratory energy of the mesh (Figure 2 and 3) (Ghazanfari, Elhissi, Ding, & Taylor, 2007).

In general, it is important to consider formulation changes, ambient temperatures, and in vitro assessment methods in the characterization of an aerosol. When characterizing aerosolization of albuterol with the Omron Micro*Air*®, a next generation impactor (NGI) showed that 55–61% of the droplets emitted were in the RF range (<5 μm diameter) (Waldrep, Berlinski, & Dhand, 2007). Formulation characteristics have been shown to have a significant effect of both passive and active vibrating mesh nebulizers. Specifically, increases in fluid viscosity and solution ion concentration resulted in smaller droplet size and increased FPF. At extreme viscosities (2.75 cP), the Omron Micro*Air*® ceased aerosol production, whereas the Aeroneb® showed discontinuous aerosol production (Ghazanfari et al., 2007). As with any method of aqueous aerosolization, defining aerosol characteristics of a specific formulation and concentration in conjunction with a given nebulizer device is essential in determining total dose available to the patient.

SMART NEBULIZERS

As the range of new formulations intended for pulmonary delivery continues to broaden, the need for better control over delivered dose, especially with expensive or potentially toxic drugs, grows in importance. Continuous air-jet nebulization will waste from 60 to 70% of a formulation by dosing during exhalation. Breath-assisted nebulizers waste less; however,

nebulization occurring at the end of inspiration will most likely not reach the lung. Breathing patterns (i.e., minute volume) have a large influence over drug deposition in the lung and have been studied thoroughly in simulated lung models to determine human lung deposition before clinical trials (Nikander, Denyer, Everard, & Smaldone, 2000; Roth, Lange, & Finlay, 2003). Studies have shown that variability exists between breathing patterns of subjects receiving an aerosol treatment. Furthermore, as the aerosol treatment progresses, intrasubject breathing patterns continue to change as duration of inhalation becomes longer and tidal volume increases (Roth et al., 2003). This is an expected physiological response to most bronchodilator therapies. In light of these observations, it becomes evident that a method of aerosol production is needed that is not only efficient and of high RF, but that will deliver the aerosol at the most effective times during patient inspiration while actively adapting to changes in breathing patterns. By incorporating the benefits of vibrating mesh nebulization with "smart" devices, more accurate and reproducible pulmonary delivery may be achieved.

The I-neb™ Adaptive Aerosol Delivery (AAD®) System (Respironics, Murrysvile, PA, USA) is designed for high accuracy, low variability lung delivery by considering patient breathing pattern, formulation characteristics, and nebulizer function (McGuire, 2006). By monitoring peak flow of a patient's first three inhalations, the I-neb™ determines the duration of aerosol production needed to target the beginning of a breath. By aerosolizing only during the first half of inspiration, sufficient time is allowed for droplets to navigate the bronchial tree and reach the deep lung. Recalculation of the targeted aerosolization time with each subsequent breath is also enabled with this device to account for changing breathing patterns during the course of a treatment. Formulation-specific device function through AAD® Disc™ technology and deep lung deposition through patient feedback are also possible with this device, allowing optimization of operating parameters (Denyer, Nikander, & Smith, 2004). In preclinical testing, eight simulated breathing patterns were tested for an expected dose of 250 μL. Results showed a mean dose of 234.1 μL with a relative standard deviation (RSD) of 14.8% (Potter, Prince, Dyche, Hatley, & Smith, 2005), demonstrating nebulizer precision regardless of breathing pattern. Other studies have shown that vibrating mesh aerosolization incorporated in this device creates small respirable droplets with a FPF of 82% (Van Dyke & Nikander, 2007). In conjunction with dosing improvements, a study on patient compliance to dosing regimen has also shown positive results. In a double-blind study involving 125 asthmatic children and their parents, 82.5% both adhered to the dosing regimen and complied with nebulizer instructions (Nikander, Arheden, Denyer, & Cobos, 2003). Through advanced aerosolization technology, continuously adaptive breath coordination, and improved patient interfaces, the I-neb™ enables delivery of precise lung doses without the assistance of a health care professional.

Like the I-neb™ AAD®, the eFlow® (Pari Pharma, Munich, Germany) produces high RF aerosols using vibrating mesh technology (TouchSpray™) and precision dosing through patient feedback options, as well as formulation-/dose-specific settings. Operating continuously, the eFlow® requires only 2–3 min to complete most treatments; however, efficiencies are lower when compared with delivery using the I-neb™ because aerosol is produced continuously and more drug is wasted. As with other vibration mesh nebulizers, the eFlow® aerosolization method is well suited for easily degraded formulations such as liposomal suspensions (Wagner, Vorauer-Uhl, & Katinger, 2006).

METERED DOSE LIQUID INHALERS

A new generation of unit dose aerosol delivery devices is currently in development and clinical trials, incorporating novel aerosol production technology through mechanical and electromechanical means (Hindle, 2004). Methods of metered dose delivery used by pMDI have been shown to be inefficient, achieving only 20 and 50% deposition in CFC-propelled and hydrofluoroalkane (HFA)-propelled pMDIs, respectively (Dalby et al., 2004). The majority of drug containing aerosol is lost due to high velocities and poor breath/actuation coordination, resulting in impaction on the oropharynx (Newman, Pavia, Moren, Sheahan, & Clarke, 1981). By avoiding incorporation of a volatile propellant, MDLIs allow for greater formulation freedom while producing accurately dosed, slow velocity aerosols. MDLIs show great potential not only in local pulmonary delivery, but also as a method of aerosol generation of drugs intended for systemic therapy.

AERx®

The AERx® pulmonary delivery platform by Aradigm (Hayward, CA, USA) is built around a microprocessor controlled hand-held device that delivers a unit bolus dose by extruding a drug-containing solution through small laser-drilled holes. The extruded jets of fluid will break up into droplets when appropriate pressure, surface tension, and pore diameter are present (Schuster, Rubsamen, Lloyd, & Lloyd, 1997). Each unit dose is packaged in a disposable strip with the nozzle built in.

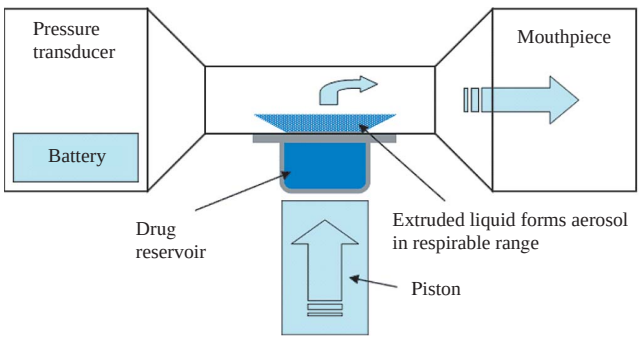

FIGURE 4. A schematic of the AERx® pulmonary dosing system.

The nozzle pore size, aerosol production rate, required patient flow rate, and integrated patient instruction may be changed depending on the treatment desired (Deshpande et al., 2005; Schuster et al., 1998). The slow-velocity aerosol produced has a narrow droplet size distribution; 90% of the droplets are within the 2–3 μm diameter range, contributing to the high-deposition efficiency of this device. In a γ-scintigraphic study evaluating the dosing efficiencies of the AERx® and a microprocessor controlled pMDI (SmartMist), Farr and colleagues found that 53.3% (CV, 10%) of solubilized ^{99m}Tc-DTPA in the blister achieved lung deposition when delivered by the AERx® system (Farr et al., 2000). Owing to slower aerosol velocity and high FPF, AERx® dosing resulted in only 6.9% of the total dose in the oropharynx and stomach as compared with 42% dosed with a pMDI. In comparison, the pMDI showed poor lung deposition and reproducibility at 21.7 and 31%, respectively.

Development of a noninvasive alternative to subcutaneous insulin injection has been a hot topic for some time in the pharmaceutical industry. Pulmonary delivery has received much of the attention in this area as the most promising route of delivery due to the ability to quickly and noninvasively produce systemic therapeutic levels. The proprietary inhaled-insulin product, Exubera® (Pfizer Inc., New York, NY, USA), has experienced some difficulty in the marketplace due to cost of production, lack of dosing flexibility, and concerns regarding long-term risks associated with pulmonary insulin (Wollmer, Pieber, Gall, & Brunton, 2007). Preliminary results of intensive pulmonary insulin therapy with the AERx® Insulin Diabetes Management System (iDMS) have been promising. In a 12-week proof-of-concept trial where AERx® iDMS was compared with subcutaneous injection in patients with type 2 diabetes, Hermansen et al. found no significant difference in patient lung function after standard pulmonary function tests (PFTs) (Hermansen, Ronnemaa, Petersen, Bellaire, & Adamson, 2004). Additionally, no difference was seen in the number of major hypoglycemic events between the two groups. Relative to the subcutaneous compartment, it has been shown that the lungs are more immunotolerant, suggesting that long-term pulmonary administration may be safe (Laube, 2001). Clinical trials are currently underway to insure the long-term safety of pulmonary insulin delivery via the AERx®. Pharmacokinetic properties of inhaled insulin incorporating this technology in other studies have showed peak serum levels, and the subsequent therapeutic response is achieved more quickly with pulmonary insulin as compared with traditional subcutaneous injection (Farr et al., 2000). The time to maximum serum concentration (T_{max}) for inhaled insulin occurred in 7–20 min; however, subcutaneous insulin did not reach maximum serum levels until 50–60 min after administration. Interestingly, this study also found that drug diffusion from the lung to the blood stream can be enhanced by the forced pulmonary maneuvers involved in PFTs performed up to 30 min after initial dose. More investigation is needed to study the effects of deep breathing on lung pharmacokinetic profiles of inhaled small molecules. Many theorize that stretching of intracellular junctions in pulmonary epithelium during deep inspiration is the mechanism driving enhanced absorption. This phenomenon may prove problematic in reducing intersubject blood level variability and therapeutic effect. Other studies dosing insulin via the AERx® have found intrasubject variability when compared with subcutaneous injection when PFT was performed 6 h after the initial dose of inhaled insulin (Kapitza, Hompesch, Scharling, & Heise, 2004). In asthmatic patients, lower forced expiatory volume (FEV) and forced vital capacity (FVC) were also shown to reduce serum insulin levels (Henry et al., 2003). Airway inflammation and obstruction effecting airway dynamics promote droplet deposition in proximal airways, rather than in the targeted distal airway. This, as well as abnormal blood flow and secretion levels, results in less efficient dosing and reduced systemic levels for patients with asthma.

Opioid analgesics, including morphine and fentanyl (Mather et al., 1998), have been investigated for the systemic treatment of severe pain using Aradgim's technology. Oral dosing is the accepted method of patient-controlled anesthesia (PCA) once the patient has left the acute care setting; however, the time it takes for a therapeutic concentration to be reached by oral delivery is dependent on parameters such as gastrointestinal absorption and gastric emptying time. Pulmonary delivery allows for nearly immediate maximum serum concentrations. When compared with 4-mg intravenous morphine, three inhalations (6.6 mg) using the AERx® pain management system provided similar analgesic levels in postoperative patients (Thipphawong et al., 2003). Pharmacokinetic plasma profiles of inhaled morphine have proved to be reproducible, with peak blood concentration occurring almost instantaneously (T_{max} = 2.7 min) (Ward et al., 1997).

Localized treatments are also being investigated for use with the AERx® for treatment of pulmonary diseases. Ciprofloxican, hydroxychloroquine, and recombinant human deoxyribonuclease (rhDNase) have shown potential for delivery in an aqueous aerosol carrier bolus dose to treat chronic lung infection, asthma, and cystic fibrosis, respectively. In a clinical study, delivery of a rhDNase bolus to 16 subjects diagnosed with cystic fibrosis provided significant improvements in FEV after dosing 0.45 mg three times daily for 15 days (Geller et al., 2003). Traditional nebulization of this drug provides delivery efficiencies ranging from 10 to 20%, whereas the AERx® delivery system can been show to deliver at least 50% of loaded drug. Other investigations into using this device for liposomal delivery (Deshpande et al., 2002), poorly soluble drugs (Okumu et al., 2002), and high-dose therapies (Cipolla et al., 2000) have also been investigated.

Respimat®

Of the new technologies for propellant-free metered aerosol production, the Respimat® Soft Mist™ Inhaler (SMI) (Boehringer Ingelheim, Ingelheim, Germany) has been the first

to be approved for market. After completion of clinical trials, ipratropium bromide/fenoterol hydrobromide (IB/FEN) for treatment of asthma and chronic obstructive pulmonary disease (COPD) was approved for market with the Respimat® SMI™. Phase II and III trials investigated multiple dosing regimens for efficacy and safety and demonstrated that the same therapeutic outcomes seen with this formulation in pMDIs can be achieved in a reduced dose delivered with the Respimat® SMI (Kassner, Hodder, & Bateman, 2004). Specifically, improvements in patient forced expiratory volume were nearly identical when dosed with the Respimat® SMI at 20/50 μg IB/FEN as with a pMDI at 40/100 μg IB/FEN. Similar outcomes were also seen when a quarter of the pMDI dose was delivered with the Respimat® (Kilfeather et al., 2004). Since its approval, this product has given patients the benefit of a more efficient method of pulmonary delivery to treat asthma and COPD without the use of a spacer.

Soft mist inhalation offers several advantages over current metered dose inhalation therapies including easier patient coordination, less oropharyngeal deposition, and formulation simplification without the use of ozone depleting propellants (Newman, Brown, Steed, Reader, & Kladders, 1998; Voshaar et al., 2006). Spacers, commonly used to slow down high-velocity pMDI aerosols, are not necessary or recommended for use with this, or any, MDLI device because of the unique method of aerosolization used. In this device aerosolization occurs when two liquid jets of formulation collide to produce a slow-velocity mist containing a FPF of 65–80% (Dalby et al., 2004) able to achieve a twofold-to-fourfold reduction in oropharyngeal impaction when compared with a pMDI (Pitcairn, Reader, Pavia, & Newman, 2005). Potential energy stored in a compressed spring supplies required force for multiple actuations. Dose delivered has been shown to remain uniform over several actuations (Figure 5) (Spallek, Hochrainer, & Wachtel, 2002). In a randomized four-way crossover study comparing radiolabeled budesonide delivery via a MDLI (Respimat®), DPI (Turbuhaler®), and pMDI (Becloforte®), the Respimat® produced the highest whole-lung levels (51.6% of total dose) after a single dose when compared with levels achieved by the Turbuhaler® (28.5%) and the Becloforte® (8.9%) (Pitcairn et al., 2005). All patients were trained previously on each inhalation device, so improper patient use can be assumed to have a limited effect on the results. Still, 82.2% of the total pMDI dose was found to impact the oropharnyx, compared with only 19.3% of the Respimat® dose. Reliance on patient inspiratory flow rate to aerosolize powdered drug and lower FPF were main contributing factors to a lower overall deposition in the Turbuhaler®.

A low-velocity aerosol plume has been remarked by many as a key factor in successful pulmonary dose delivery (Dhand, 2005; O'Callaghan & Wright, 2002). Thorough characterization of aerosol velocity and duration was conducted by Hochainer et al. for comparison of the aerosol generated by the Respimat® to that of CFC- and HFA-propelled MDIs. A video recording method, laser light diffraction, and a rotating disc method used in plume characterization found the velocity and duration of the Respimat® aerosol to be 0.8 m/s and 1.5 s, respectively. Aerosol velocities produced by pMDIs ranged from 2.0 to 8.4 m/s, whereas the plume duration lasted a maximum of only 0.36 s (Hochrainer et al., 2005). Low-velocity aerosols also have been shown to have the added benefit of limiting ocular and facial deposition when unintended activation occurs (Newman et al., 2007). By producing a slow, standing aerosol, patient/device coordination becomes less important and use of a spacer device becomes unnecessary.

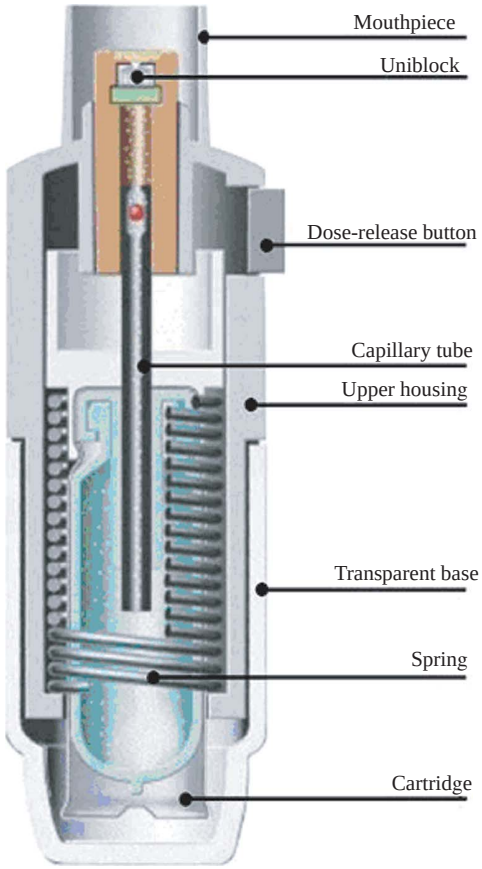

FIGURE 5. A schematic of the Respimat® Soft Mist™ Inhaler (Reprinted with permission from Spallek et al., 2002).

Mystic®

A unique concept of producing an aerosol through electrohydrodynamic disruption has led to the development of the Mystic® (Battelle, Columbus, OH). After passing through a capillary, the liquid formulation forms a conical shape due to the electrical field. At the crest of the liquid conical, electrically excited droplets aerosolize. The result is the production of fine respirable mist with an electrical charge that is subsequently neutralized. This method of aerosolization is not new in spray technology (Cloupeau & Prunet-Foch, 1989) but has only recently been adapted for pharmaceutical applications. Initial

TABLE 1
Current Products Used for Pulmonary Drug Delivery Through Liquid Aerosolization

	Product	Manufacturer	Characteristics	References
	AERx®	Aradigm	Metered dose, slow aerosol, extruded aerosol	Schuster, Rubsamen, Lloyd, & Lloyd, 1997; Schuster et al., 1998; Farr et al., 2000; Hermansen, Ronnemaa, Petersen, Bellaire, & Adamson, 2004
Metered Dose Liquid Inhalers	Respimat® SMI	Boehringer-Ingelheim	Metered dose, slow mist inhalation, spring loaded	Newman et al., 1998; Dalby, Spallek, & Voshaar, 2004; Hochrainer et al., 2005
	Mystic®	BattellePharma	Metered dose, slow aerosol, EHD aerosol	Zimlich et al., 2000; Hindle, 2004; Williams, 2007
"Smart" Nebulizers	eFlow®	Pari	Active vibrating mesh, adjustable output	Wagner, Vorauer-Uhl, & Katinger, 2006
	I-neb™ AAD®	Respironics	Adaptive aerosol delivery, programmable operation, passive vibrating mesh	Roth, Lange, & Finlay, 2003; Nikander, Arheden, Denyer, & Cobos, 2003; McGuire, 2006
Vibrating Mesh Nebulizers	Micro*Air*®	Omron Healthcare	Passive vibrating mesh, handheld	Newman & Gee-Turner, 2005
	Aeroneb®	Aerogen	Active vibrating mesh, ventilator eompatible	Taylor & McCallion, 1997; Ghazanfari et al., 2007; Elhissi, Faizi, Naji, Gill, & Taylor, 2007
Air-jet Nebulizers	Aeroeclipse®	Trudell	Breath-actuated aerosol	Leung, Louca, & Coates, 2004
	LC® Star	Pari	Breath-enhanced aerosol	Ho, Kwong, O'Drowsky, & Coates, 2001; None et al., 2004; Kohler, Sollich, Schuster-Wonka, & Huhnerbein, 2003

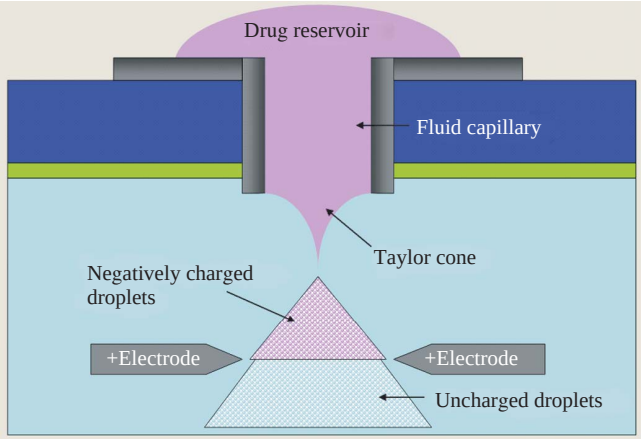

FIGURE 6. A schematic of the electrohydrodynamic aerosol generation mechanism in the Mystic® EHD.

device designs include the ability for multiple dosing (approximately 200) and an actuation cycle lasting 2 s (Zimlich et al., 2000). In a phase I clinical study, the proportion of the total emitted dose (for an intended dose of 400 μg) to reach the lung was 78%. While not much information is published regarding studies conducted with this device, the claim of a nearly monodisperse aerosol cloud and superior deep lung deposition in in vivo tests (Williams, 2007) provides promise for this product's future.

CONCLUSION

Current developments in technologies for aqueous aerosol production are leading the way for exciting new developments in pulmonary drug delivery. Patients in both clinical and ambulatory settings will benefit from shorter treatment times, less frequent dosing, and more patient compliant devices. By achieving greater control over dose delivered to the deep lung and increasing device efficiencies, the foundation has been laid for improved therapies for current formulations and the further adaptation of the pulmonary route for systemic delivery of drugs.

REFERENCES

Anderson, P. J. (2001). Delivery options and devices for aerosolized therapeutics. *Chest*, *120*(S3), 89S–93S.

Bartram, P. (2005). Use of a micropump nebulizer for aerosolized medication delivery in a ventilated infant. *Neonatal Intensive Care*, *18*(1), 14.

Burnell, P. K. P., Asking, L., Borgstrom, L., Nichols, S. C., Olsson, B., & Prime, D., et al. (2007). Studies of the human oropharyngeal airspaces using

magnetic resonance imaging IV – the oropharyngeal retention effect for four inhalation delivery systems. *J. Aerosol. Med., 20*(3), 269–281.

Cipolla, D., Boyd, B., Evans, R., Warren, S., Taylor, G., & Farr, S. (2000). Bolus administration of INS365: Studying the feasibility of delivering high dose drugs using the AERX pulmonary delivery system. *Respir. Drug Deliv., 7*, 231–239.

Cloupeau, M., & Prunet-Foch, B. (1989). Electrostatic spraying of liquids in cone-jet mode. *J. Electron., 22*, 135–159.

Corcoran, T. E., Dauber, J. H., Chigier, N., & Iacono, A. T. (2002). Improving drug delivery from medical nebulizers: The effects of increased nebulizer flow rates and reservoirs. *J. Aerosol Med., 15*(3), 271–282.

Dalby, R. N., Spallek, M., & Voshaar, T. (2004). A review of the development of respimat soft mist inhaler. *Int. J. Pharm., 283*, 1–9.

DeHaan, W. H., & Finlay, W. H. (2001). In vitro monodisperse aerosol deposition in a mouth and throat with six different inhalation devices. *J. Aerosol Med., 14*(3), 361–367.

Denyer, J., Nikander, K., & Smith, N. J. (2004). Adaptive aerosol delviery (AAD) technology. *Expert Opinion Drug Deliv., 1*(1), 165–176.

Deshpande, D. S., Blanchard, J. D., Schuster, J., Fairbanks, D., Hobbs, C., & Beihn, R., et al. (2005). Gamma scintigraphic evaluation of a miniaturized AERx pulmonary delivery system for aerosol delivery to anesthetized animals using a positive pressure ventilation system. *J. Aerosol Med., 18*(1), 34–44.

Deshpande, D., Blanchard, J., Srinivasan, S., Fairbanks, D., Fujimoto, J., & Sawa, T., et al. (2002). Aerosolization of lipoplexes using AERx pulmonary delivery system. *AAPS PharmSci, 4*(3), 1–10.

Dessanges, J. F. (2001). A history of nebulization. *J. Aerosol Med., 14*, 65–71.

Dhand, R. (2005). Aerosol plumes: Slow and steady wins the race. *J. Aerosol Med., 18*(3), 261–263.

Elhissi, A. M. A., Faizi, M., Naji, W. F., Gill, H. S., & Taylor, K. M. G. (2007). Physical stability and aerosol properties of liposomes delivered using an air-jet nebulizer and a novel micropump device with large mesh apertures. *Int. J. Pharm., 334*, 62–70.

Elhissi, A. M. A., & Taylor, K. M. G. (2005). Delivery of liposomes generated from proliposomes using air-jet, ultrasonic, and vibrating-mesh nebulisers. *J. Drug Deliv. Sci. Technol., 15*(4), 261–265.

Farr, S., Warren, S., Lloyd, P., Okikawa, J., Schuster, J., & Rowe, A., et al. (2000). Comparison of in vitro and in vivo efficiencies of a novel unit-dose liquid aerosol generator and a pressurized metered dose inhaler. *Int. J. Pharm., 198*, 63–70.

Farr, S. J., McElduff, A., Mather, L. E., Okikawa, J., Ward, M. E., & Gonda, I., et al. (2000). Pulmonary insulin administration using the AERx® system: Physicological and physicochemical factors influencing insulin effectiveness in healthy fasting subjects. *Diabetes Technol. Ther., 2*, 185–197.

Finlay, W. H., Lange, C. F., King, M., & Speert, D. P. (2000). Lung delivery of aerosolized dextran. *Am. J. Respir. Crit. Care Med., 161*, 91–97.

Finlay, W. H., & Martin, A. R. (2007). Modeling of aerosol deposition with interface devices. *J. Aerosol Med., 20*(S1), S19–S28.

Geller, D., Thipphawong, J., Otulana, B., Caplan, D., Ericson, D., & Milgram, L., et al. (2003). Bolus inhalation of rhDNase with the AERx system in subjects with cystic fibrosis. *J. Aerosol Med., 16*(2), 175–182.

Ghazanfari, T., Elhissi, A. M. A., Ding, Z., & Taylor, K. M. G. (2007). The influence of fluid physicochemical properties on vibrating-mesh nebulization. *Int. J. Pharm., 339*, 103–111.

Gurses, B. K., & Smaldone, G. C. (2003). Effect of tubing depostion, breathing pattern, and temperature on aerosol mass distribution measured by cascade impactor. *J. Aerosol Med., 16*(4), 387 – 394.

Henry, R. R., Mudaliar, S. R. D., Howland, W. C., Chu, N., Kim, D., & An, B., et al. (2003). Inhaled insulin using the AERx insulin diabetes management system in healthy and asthmatic subjects. *Diabetes Care, 26*, 764–769.

Hermansen, K., Ronnemaa, T., Petersen, A. H., Bellaire, S., & Adamson, U. (2004). Intensive therapy with inhaled insulin via the AERx insulin diabetes management system. *Diabetes Care, 27*(1), 162–167.

Hess, D. R., Fisher, D., Williams, P., Pooler, S., & Kacmarek, R. M. (1996). Medication nebulizer performance. Effects of diluant volume. *Chest, 110*(2), 498–505.

Hindle, M. (2004). Soft mist inhalers: A review of current technology. *The Drug Delivery Companies Report* (Autumn/Winter), 31–34.

Ho, S. L., Kwong, W. T. J., O'Drowsky, L., & Coates, A. L. (2001). Evaluation of four breath-enhanced nebulizers for home use. *J. Aerosol Med., 14*(4), 467–475.

Hochrainer, D., Holz, H., Kreher, C., Scaffidi, L., Spallek, M., & Wachtel, H. (2005). Comparison of the aerosol velocity and spray duration of Respimat Soft Mist Inhaler and pressurized metered dose inhalers. *J. Aerosol Med., 18*(3), 273–282.

Kapitza, C., Hompesch, M., Scharling, B., & Heise, T. (2004). Intrasubject variability of inhaled insulin in type 1 diabetes: a comparison with subcutaneous insulin. *Diabetes Technol. Ther., 6*(4), 466–472.

Kassner, F., Hodder, R., & Bateman, E. D. (2004). A review of ipratropium bromide/fenoterol hydrobromide (Berodual) delivered Via Respimat Soft Mist Inhaler in patients with asthma and chronic obstructive pulmonary disease. *Drugs, 64*(15), 1671–1682.

Kilfeather, S. A., Pointz, H. H., Beck, E., Schmidt, P., Lee, A., & Bowen, I., et al. (2004). Improved delivery of ipratropium bromide/fenoterol from respimat soft mist inhaler in patients with COPD. *Respir. Med., 98*(5), 387–397.

Kohler, E., Sollich, V., Schuster-Wonka, R., & Huhnerbein, J. (2003). Lung deposition in cystic fibrosis patients using an ultrasonic or a jet nebulizer. *J. Aerosol Med., 16*(1), 37–46.

Koshkina, N. V., Golunski, E., Roberts, L. E., Gilbert, B. E., & Knight, V. (2004). Cyclosporin a aerosol improves the anticancer effect of paclitaxel aerosol in mice. *J. Aerosol Med., 17*(1), 7–14.

Lange, C. F., & Finlay, W. H. (2006). Liquid atomizing: Nebulizing and other methods of producing aerosols. *J. Aerosol Med., 19*(1), 28–35.

Laube, B. L. (2001). Treating diabetes with aerosolized insulin. *Chest, 120*(3), S99–S106.

Lentz, Y. K., Anchordoquy, T. J., & Lengsfeld, C. S. (2006). Rationale for the selection of an aerosol delivery system for gene delivery. *J. Aerosol Med., 19*(3), 372–384.

Lentz, Y. K., Worden, L. R., Anchordoquy, T. J., & Lengsfeld, C. S. (2005). Effect of jet nebulization on DNA: Identifying the dominant degradation mechanism and mitigation methods. *Aerosol Sci., 36*, 973–990.

Leung, K., Louca, E., & Coates, A. L. (2004). Comparison of breath-enhanced to breath-actuated nebulizers for rate, consistency, and efficiency. *Chest, 126*(5), 1619–1627.

Lynch, J., Behan, N., & Birkinshaw, C. (2007). Factors controlling particle size during nebulization of DNA-polycation complexes. *J. Aerosol Med., 20*(3), 257–268.

Mather, L. E., Woodhouse, A., Ward, M. E., Farr, S. J., Rubsamen, R., & Eltherington, L. G. (1998). Pulmonary administration of aerosolised fentanyl: Pharmacokinetic analysis of systemic delivery. *Br. J. Clin. Pharmacol., 46*, 37–43.

McCallion, O. N. M., Taylor, K. M. G., Bridges, P. A., Thomas, M., & Taylor, A. J. (1996). Jet nebulisers for pulmonary drug delivery. *Int. J. Pharm., 130*, 1–11.

McGuire, S. (2006). The I-neb adaptive aerosol delivery (AAD) system – a holistic approach to inhaled drug delivery including regulatory approval. *Drug Deliv. Rep., (Spring/Summer)*, 68–71.

Mercer, T. T. (1981). Production of therapeutic aerosols: Principles and techniques. *Chest, 80*(6 suppl), 813–818.

Mitsakou, C., Helmis, C., & Housiadas, C. (2005). Eulerian modeling of lung deposition with sectional representation of aerosol dynamics. *Aerosol Sci., 36*, 75–94.

Newman, S. P., Brown, J., Steed, K. P., Reader, S. J., & Kladders, H. (1998). Lung deposition of fenoterol and flunisolide delivered using a novel device for inhaled medicines: Comparison of Respimat with conventional metered-dose inhalers with and without spacer devices. *Chest, 113*, 957–963.

Newman, S., & Gee-Turner, A. (2005). The omron MicroAir vibrating mesh technology nebulizer, a 21st century approach to inhalation therapy. *J. Appl. Ther. Res., 5*(4), 29–33.

Newman, S. P., Pavia, D., Moren, F., Sheahan, N. F., & Clarke, S. W. (1981). Deposition of pressurised aerosols in the human respiratory tract. *Thorax, 36*, 52–55.

Newman, S. P., Steed, K. P., Phil, M., Reader, S. J., Pavia, D., & Sohal, A. K. (2007). An in vitro study to assess facial and ocular deposition from Respimat Soft Mist Inhaler. *J. Aerosol Med., 20*(1), 7–12.

Nikander, K., Arheden, L., Denyer, J., & Cobos, N. (2003). Parents' adherence with nebulizer treatment of their children when using an adaptive aerosol delivery (AAD) system. *J. Aerosol Med., 16*(3), 2003.

Nikander, K., Denyer, J., Everard, M., & Smaldone, G. C. (2000). Validation of a new breathing simulator generating and measuring inhaled aerosol with adult breathing patterns. *J. Aerosol Med., 13*(2), 139–146.

Nikander, K., Denyer, J., Smith, N., & Wollmer, P. (2001). Breathing patterns and aerosol delivery: Impact of regular human patterns, and sine and square waveforms on rate of delivery. *J. Aerosol Med., 14*(3), 327–333.

None, L. V., Grimbert, D., Bordenave, J., Benoit, G., Furet, Y., & Fauroux, B., et al. (2004). Residual gravimetric method to measure nebulizer output. *J. Aerosol Med., 17*(1), 63–71.

Okumu, F. W., Lee, R. Y., Blanchard, J. D., Queirolo, A., Woods, C. M., & Lloyd, P. M., et al. (2002). Evaluation of the AERx pulmonary delivery system for the systemic delivery of a poorly soluble selective D-1 agonist ABT-431. *Pharm. Res., 19*(7), 1009–1012.

O'Callaghan, C., & Barry, P. W. (1997). The science of nebulised drug delivery. *Thorax, 52*, 31–44.

O'Callaghan, C., & Wright, P. (2002). The metered dose inhaler. In C. Bisgaard, C. O'Callaghan, & G. C. Smaldone (Eds.), *Drug delivery to the lung* (pp. 337–370). New York: Marcel Dekker.

Pedersen, K. M., Handlos, V. N., Heslet, L., & Kristensen, G. (2006). Factors influencing the in vitro deposition of tobramycin aerosol: A comparison of an ultrasonic nebulizer and a high-frequency vibrating mesh nebulizer. *J. Aerosol Med., 19*(2), 175–183.

Pitcairn, G. R., Reader, S. J., Pavia, D., & Newman, S. P. (2005). Deposition of corticosteroid aerosol in the human lung by Respimat Soft Mist Inhaler compared to deposition by metered dose inhaler or Turbuhaler Dry Powder Inhaler. *J. Aerosol Med., 18*(3), 264–272.

Potter, R., Prince, I., Dyche, T., Hatley, R. H. M., & Smith, N. J. (2005). Abstracts from the international society for aerosols in medicine. *J. Aerosol Med., 18*(1), 112–113.

Roth, A. P., Lange, C. F., & Finlay, W. H. (2003). The effect of breathing pattern on nebulizer drug delivery. *J. Aerosol Med., 16*(3), 325–329.

Sanjar, S., & Matthews, J. (2001). Treating systemic diseases via the lung. *J. Aerosol Med., 14*(S1), S51–S58.

Schuepp, K. G., Jauernig, J., Janssens, H. M., Tiddens, H. A. W. M., Straub, D. A., & Stangl, R., et al. (2005). In vitro determination of the optimal particle size for nebulized aerosol delivery to infants. *J. Aerosol Med., 18*(2), 225–235.

Schuster, J., Farr, S., Cipolla, D., Wilbanks, T., Rosell, J., & Lloyd, P., et al. (1998). Design performance validation of a highly efficient and reproducible compact aerosol delivery system: AERx®. *Respir.Drug Deliv., 6*, 83–90.

Schuster, J., Rubsamen, R., Lloyd, P., & Lloyd, J. (1997). The AERx® aerosol delivery system. *Pharm. Res., 14*(3), 354–357.

Shaw, J. (2004). Aerogen impacts pulmonary drug delivery in the acute care setting. *Drug Deliv. Technol., 4*(6), 1–3.

Silkstone, V. L., Dennis, J. H., Pieron, C. A., & Chrystyn, H. (2002). An investigation of in vitro/in vivo correlations for salbutamol nebulized by eight systems. *J. Aerosol Med., 15*(3), 251–259.

Smaldone, G. C. (2006). Advances in aerosols: Adult respiratory disease. *J. Aerosol Med., 19*(1), 36–46.

Smith, K. (2004). The advantages of nebulization in the treatment of mechanically ventilated neonates. *Neonatal Intensive Care, 17*(3), 12–16.

Smith, E. C., Denyer, J., & Kendrick, A. H. (1995). Comparison of twenty-three nebulizer/compressor combinations in domiciliary use. *Eur. Respir. J., 8*, 1214–1221.

Spallek, M., Hochrainer, D., & Wachtel, H. (2002). Optimizing nozzles for soft mist inhalers. *Respir. Drug Deliv., 8*(2), 375–378.

Taylor, K. M. G., & McCallion, O. N. M. (1997). Ultrasonic nebulisers for pulmonary drug delivery. *Int. J. Pharm., 153*, 93–104.

Thipphawong, J. B., Babul, N., Morishige, R. J., Findlay, H. K., Reber, K. R., & Millward, G. J., et al. (2003). Analgesic efficacy of inhaled morphine in patients after bunionectomy surgery. *Anesthesiology, 99*(3), 693–700.

Van Dyke, R. E., & Nikander, K. (2007). Delivery of Iloprost inhalation solution with the HaloLite, Prodose, and I-neb adaptive aerosol delivery systems: An in vitro study. *Respir. Care, 52*(2), 184–190.

Voshaar, T., Lapidus, R., Maleki-Yazdi, R., Timmer, W., Rubin, E., & Lowe, L., et al. (2006). A randomised study of tiotropium Respimat Soft Mist Inhaler versus ipratropium pMDI in chronic obstructive pulmonary disease. *Thorax, 61*(S2), ii40.

Wagner, A., Vorauer-Uhl, K., & Katinger, H. (2006). Nebulization of liposomal rh-cu/zn-SOD with a novel vibrating membrane nebulizer. *J. Liposome Res., 16*, 113–125.

Waldrep, J. C. (1998). New aerosol drug delivery systems for the treatment of immune-mediated pulmonary diseases. *Drugs Today, 34*(6), 549–561.

Waldrep, J. C., Berlinski, A., & Dhand, R. (2007). Comparative analysis of methods to measure aerosols generated by a vibrating mesh nebulizer. *J. Aerosol Med., 20*(3), 310–319.

Ward, M. E., Woodhouse, A., Mather, L. E., Farr, S. J., Okikawa, J., & Lloyd, P., et al. (1997). Morphine pharmacokinetics after pulmonary administration from a novel aerosol delivery system. *Clinical. Pharmacol. Ther., 62*(6), 596–609.

Williams, L. (2007). Novel pulmonary delivery technology [electronic version]. *Pharma-Mag.*, 4–5.

Wilson, L., Simmons, R., & Uster, P. S. (2003). *Aerosol characteristics of adeno-associated viral vectors produced by an electronic micropump inhaler*, Poster presented at the Cystic Fibrosis Foundation Meeting.

Wollmer, Pieber, T. R., Gall, M., & Brunton, S. (2007). Delivering needle-free insulin using AERx iDMS technology. *Diabetes Technol. Ther., 9*(Suppl 1), S57–S63.

Zainudin, B. M. Z., Biddiscombe, M., Tolfree, S. E. J., Short, M., & Spiro, S. G. (1990). Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a pressurised metered dose inhaler, as a dry powder, and as a nebulised solution. *Thorax, 45*, 469–473.

Zimlich, W. C., Ding, J. Y., Busick, D. R., Moutvic, R. R., Placke, M. E., & Hirst, P. H., et al. (2000). The development of a novel electrohydrodynamic pulmonary drug delivery device. *Respir. Drug Deliv., 7*, 241–246.