Nebulizers That Use a Vibrating Mesh or Plate with Multiple Apertures to Generate Aerosol

Rajiv Dhand MD

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Summary

Several electronic nebulizer devices that use a vibrating mesh or plate with multiple apertures to generate a fine-particle, low-velocity aerosol have been marketed or will shortly become available for clinical use. These devices have a high efficiency of delivering aerosol to the lung, such that the nominal dose of drugs to be administered could be substantially reduced. Moreover, the volume of drug solution left in these new devices when the nebulization has ceased is negligible, so there is potential to improve the cost-effectiveness of administering expensive medications. Because these devices nebulize at a faster rate than conventional jet or ultrasonic nebulizers, the duration of each treatment could be shortened. These devices efficiently nebulize solutions and suspensions; they have been successfully used for aerosolizing insulin, other proteins and peptides, and fragments of DNA. They could be employed for a wide variety of clinical applications, including the delivery of aerosols for systemic therapy and gene transfer. These devices have overcome many of the limitations associated with conventional jet and ultrasonic nebulizers, and they offer the versatility to modify the aerosol characteristics according to the clinical application for which they are employed. With these devices clinicians will be able to precisely control drug delivery to the respiratory tract. **Key words:** nebulization, nebulizer, aerosol, vibrating mesh, vibrating plate.  [Respir Care 2002;47(12):1406–1416]
Introduction

Nebulizers convert liquids into aerosol particles for deposition in the lower respiratory tract. A pneumatic (jet) nebulizer uses the energy provided by compressed gas flow to generate an aerosol, whereas an ultrasonic nebulizer uses electricity to vibrate a piezoelectric crystal at high frequency. Standing waves are generated when the high-frequency vibrations are focused onto the surface of the medication solution. Liquid droplets break off from the wave crest to form an aerosol.

For several decades nebulizers have been employed to deliver medications via inhalation. Indications for aerosol therapy, however, are rapidly expanding. In the not-so-distant future, aerosols could be used to deliver drugs to the respiratory tract for systemic effects and to deliver genes to the respiratory tract. There is a need for better technology to improve the efficiency, precision, and consistency of aerosol deposition in the lung, to use new formulations, and to allow efficient aerosolization of suspensions and drugs with high lipid solubility. In addition, there needs to be a concerted effort to protect respiratory therapists and other health care workers from occupational exposure to aerosolized drugs.

This review discusses several new devices that have in common the ability to aerosolize a drug solution by using a vibrating mesh or plate with multiple apertures. These devices offer important advances in our ability to deliver aerosolized drugs to the respiratory tract.

Design Features of Aerosol Generators That Use a Vibrating Mesh or Plate with Multiple Apertures to Generate Aerosol

Several manufacturers (Aerogen, Mountain View, California; Optron, Vernon Hills, Illinois; and ODEM, Royston, Hertfordshire, United Kingdom) have developed the technology that uses a vibrating mesh or plate with multiple apertures to produce a liquid aerosol. Table 1 lists the devices that have been developed or are under development.

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Some features are common to all the devices that use a vibrating mesh or plate with multiple apertures to generate aerosol. These devices generate aerosols with a high fine particle fraction, and they have a significantly higher efficiency of delivering drugs to the respiratory tract than do conventional jet or ultrasonic nebulizers. The aerosol is generated as a fine mist and no baffling system is required in these devices. Other features of these devices are that they are portable, battery-operated (operation with alternating current is optional in some devices), and they efficiently aerosolize solutions and suspensions with minimal dead volume (volume of liquid remaining in the nebulizer at the end of nebulization). Some of these devices are breath-actuated, thereby limiting the amount of aerosol released into the ambient air.

Aerogen’s Aerosol Generator

Aerogen’s aerosol generator consists of a vibrational element and a domed aperture plate. The ceramic vibrational element expands and contracts when electrical current is applied to it. This convection and expansion produces an upward and downward movement in the domed aperture plate (Fig. 1). The aperture plate has up to 1,000 tapered holes, which are electroformed in a sheet. The wider portion of the hole is toward the medication, and the narrower end is toward the atmosphere. The medication is placed in a reservoir above the domed aperture plate. During operation, upward and downward movement (by a few microns) of the aperture plate creates a micro-pumping action that extrudes the medication through the holes to produce an aerosol. Particle size, flow, and fine particle fraction are functions of the aperture hole exit diameter. The size of the holes in the aperture plate and, in turn, the size of the aerosol particles can be modified for specific clinical applications.

The devices that incorporate the Aerogen aerosol generator (Fig. 2) can be battery-operated, so they are portab-
ble. These devices nebulize at 0.3–0.6 mL/min, generally requiring less time for drug delivery than conventional nebulizers. Because they do not require any compressed gas flow or high-energy vibration, their operation is relatively quiet. Another important advantage is that the dead volume is minimal. In fact, the aerosol generator can aerosolize almost down to the very last drop of liquid, whereas the dead volume in conventional jet or ultrasonic nebulizers is 0.3–1 mL. Some of Aerogen’s devices are designed to operate in any orientation, including inverted. Aerogen’s aerosol generator efficiently nebulizes suspensions, proteins, and peptides. Because the energy required for nebulization is applied to the vibrational element in the aerosol generator rather than to the fluid, temperature increase in the fluid is minimized, which minimizes the risk of denaturing proteins or peptides or reducing the activity of antibiotics.

**Omnron’s Vibrating Mesh Technology**

The Omron technology incorporates a piezoelectric crystal that vibrates at a high-frequency when electrical current is applied. The vibration of the crystal is transmitted to a transducer horn that is in contact with the liquid to be aerosolized (Figs. 3–5). Vibration of the transducer horn causes upward and downward movement of the mesh plate, and the liquid passes through the apertures in the plate to form an aerosol. The mesh plate consists of numerous (up to 6,000) tapered holes, each approximately 3 μm in diameter. These holes amplify the vibration of the transducer horn throughout the medication and reduce the amount of power required to generate the aerosol. Using a low frequency of vibration with a mesh plate containing numerous minute holes allows efficient generation of a fine-particle mist.

The Omron devices are battery-operated and alternating-current-powered, produce a low-velocity aerosol, and require no propellant or compressor. They are portable and can produce an aerosol in almost any orientation.

**ODEM’s TouchSpray Technology**

ODEM’s TouchSpray technology employs a perforate membrane that vibrates at high frequency against a body of liquid. The vibration source is a piezoelectric actuator, which is activated by a simple electronic drive circuit. The perforate membrane is a wafer-thin plate of stainless steel with many laser-drilled holes. The actuator and the perforate membrane form the TouchSpray atomization head, which is in contact with the liquid to be aerosolized (Fig. 6). Liquid jets are created as an inertial response to the vibration of the perforate membrane. Surface tension and hydrodynamic effects then cause these jets to break up to produce streams of precisely controlled droplets. This stream has a low velocity, and the atomization head can generate an aerosol in any orientation.
The TouchSpray inhaler devices can efficiently aerosolize a wide range of liquids and particulate suspensions. With these devices the particle size and flow of the aerosol can be precisely controlled.

Characteristics of Devices

Aerogen Devices

Aeroneb Portable Nebulizer System. The Aeroneb Portable Nebulizer System is a simple, compact, silent nebulizer that delivers a fine-particle, low-velocity aerosol. The Aeroneb system is designed for use by ambulatory patients and for delivering nebulizer treatments in the hospital. Alternating current, alkaline batteries, or a car adapter can power the Aeroneb. This device does not require any propellants or a compressor system, and it can operate in a variety of orientations. Figure 2 shows a model of the Aeroneb.

Aerodose Inhaler. The Aerodose Inhaler is a small, hand-held inhaler that uses Aerogen’s aerosol generator. This device is powered by 4 AAA batteries, does not require an external power source, and is breath-actuated. An inhalation sensor detects inspiratory flow above a threshold of approximately 10 L/min and synchronizes aerosol generation with inspiration. The sensor signals to terminate aerosolization when inspiratory flow falls below the threshold for actuation. Indicator lights on the device flash when the inhaler is turned on and is ready for operation. During inhalation the lights remain lit without flashing. Once the dose has been aerosolized, the indicator light shuts off. There is also a red light that indicates low batteries. When the batteries reach a very low level, the red light glows continuously, at which point the batteries need to be replaced immediately. Approximately 30 min of aerosol delivery time can be expected from a new set of batteries. A bypass button at the rear of the power supply can be used to trigger aerosolization to test the device or during cleaning.

The physical size and shape of the device is similar to that of a metered-dose inhaler (MDI). The velocity of the aerosol emitted from the Aerodose Inhaler is only about one tenth that of an MDI aerosol. The low-velocity aerosol produced by the Aerodose Inhaler is more easily entrained into the patient’s inspired air than the high-velocity aerosol emitted from an MDI. The lower aerosol velocity reduces oropharyngeal deposition of drug particles. Single-dose nebulifer’s standard bronchodilator solutions can be used with this device. It usually takes less than 2 or 3 minutes to deliver a bronchodilator treatment with the Aerodose Inhaler.
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Aeroneb Professional Nebulizer System (Aeroneb Pro). The Aeroneb Pro is a novel system designed for use during mechanical ventilation. The Aeroneb Pro is connected in the inspiratory limb of the ventilator circuit and generates aerosol continuously (see Fig. 2). It can be adapted to generate aerosol only during inspiration. The power for generating the aerosol comes from an alternating current outlet or from a rechargeable battery pack within the device.

Aeroneb Insulin Inhaler. The Aeroneb Insulin Inhaler is a small device, about the size of a cellular telephone. It has a rechargeable battery in a single unit that can fit into a pants pocket (see Fig. 2). It contains a cartridge of liquid insulin that contains approximately a 1-week supply. The patient dials in the pre-meal dose with an insulin pen-type mechanism that can provide 1-unit increments of insulin dose. The liquid insulin is rapidly aerosolized into small particles by the aerosol generator and inhaled into the lungs in a few breaths. The insulin deposits in the lung and is then absorbed into the bloodstream.

Omron Devices

NE-U03. In the NE-U03 (see Fig. 3) the vibration of the piezoelectric crystal produces rapid movement of a transducer horn within the medication cup. The liquid medication passes through the hollow center of the transducer horn and through the mesh plate. The movement of the transducer causes vibration of the ceramic plate; springs attached to the ceramic plate prevent it from breaking. The liquid passes through the holes in the vibrating mesh plate to form an aerosol. The frequency of the current applied to the piezoelectric crystal is much lower than that employed in standard ultrasonic nebulizers, making electricity from a wall outlet unnecessary (but optional). The NE-U03 can operate for 5 hours on a set of 4 AA batteries. The energy is applied to the transducer horn rather than to the liquid medication, which minimizes the risk of denaturing the drug by heating during nebulizer operation. Similar to Aerogen's aerosol generator, the NE-U03 can nebulize solutions and suspensions almost down to the last drop of...
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Fig. 4. Omron's NE-U22 nebulizer. A: Mechanism by which aerosol is generated. The liquid to be aerosolized is placed in the medication bottle, which is covered with a mesh plate containing several hundred electroplated apertures. Applied electrical current causes the piezoelectric crystal to vibrate, the vibration is transmitted to a transducer horn, and the transducer horn transmits the vibration to the liquid, which forces the liquid through the apertures in the mesh plate. B: A model of the assembled device. (Courtesy of Omron, Vernon Hills, Illinois.)

liquid, so that the dead volume is negligible. It is also position-independent in its operation.

NE-U22. Currently the NE-U22 (see Figs. 4 and 5) is marketed only in Japan. A medication bottle is connected to a transducer horn, and high-frequency vibration of the piezoelectric crystal is transmitted to the transducer horn. The vibration of the horn pushes the liquid medication through apertures in the mesh plate above it. Unlike the NE-U03, the NE-U22 has a metal alloy mesh plate in which the holes are produced by electroplating, thereby making the mesh plate more stable, biocompatible, durable, and resistant to corrosion. In contrast to the NE-U03, the metal end of the tapered holes in the NE-U22 is toward the medication, and the wider end is toward the atmosphere. The NE-U22 uses more energy than the NE-U03, but the frequency of vibration is considerably less than that employed in standard ultrasonic nebulizers. The NE-U22 also nebulizes down to the last drop, such that dead volume is negligible. The aerosolization head on the NE-U22 can be disconnected for cleaning.

In conventional nebulizers, diluents are added to the drug solution to increase the volume of solution to be aerosolized, because up to 1 mL of solution may remain in the nebulizer. Because the Omron NE-U03 and the NE-U22 can aerosolize with as little as 0.2 mL of solution, the need for diluent is eliminated.

ODEM TouchSpray Inhaler Devices

The ODEM TouchSpray Inhaler devices are under development, in partnership with various pharmaceutical companies. These devices are small, simple to use, portable, have low power consumption, and they can be custom designed for various clinical applications. They are configured for single-dose or multi-dose drug delivery, and their high rate of aerosol flow allows treatments to be completed in a few breaths. Some of these devices will incorporate features such as breath-actuation and compliance monitoring. Figure 6 shows a concept model of a device incorporating ODEM's TouchSpray technology.

PARI eFlow

The eFlow incorporates the TouchSpray atomization head (see Fig. 6). The eFlow is a small, portable, and silent device that is highly efficient for nebulizing solutions and suspensions. The nebulizer produces an aerosol with a high fine particle fraction and an output of up to 0.5 mL/min.8 Aerosol is delivered continuously via tidal breathing. The eFlow is expected to be available for clinical use within the next year.

Comparison of Vibrating Mesh/Plate Devices and Conventional Jet and Ultrasonic Nebulizers

In Vitro Comparisons of Efficiency in Aerosolizing Solutions

Several investigators have compared the performance of vibrating mesh/plate aerosol devices and conventional jet and ultrasonic nebulizers.

Using an adult breathing pattern, the Acroneb system was shown to aerosolize albuterol solution (0.083%) at a flow of 0.41 mL/min, compared to 0.20–0.36 mL/min with various jet nebulizers, such as the PARI LC Plus, DeVilbiss 800, Allegiance Air Life MistyNeb, and Saltex
Labs 8900. With the Aeroneb system the volume median diameter (VMD) ranged from 4.1 to 5.9 \( \mu \)m, corresponding to a mass median aerodynamic diameter (MMAD) of 1.4 – 2.8 \( \mu \)m and a fine particle fraction of 60–70%. Those values compared favorably with the particle sizes generated by the conventional jet nebulizers. The mass of albuterol in the fine particle fraction with the various nebulizers ranged from 0.1 to 0.34 mg, corresponding to 3.9–13.5% of the nominal dose. The fine particle fraction delivered with the Aeroneb System was comparable to that produced by the breath-enhanced PARI LC Plus nebulizer and was higher than that delivered by the DeVilbiss 800, Allegiance Air Life MistyNeb, and Salter Labs 8900.

Fink et al compared the performance of the Aeroneb Pro and 2 small-volume jet nebulizers (MistyNeb and Vix-One). The ability to deliver 2.5 mg of 0.083% albuterol sulfate solution was tested in a simulated pediatric patient receiving mechanical ventilation with high-frequency oscillation. The Aeroneb Pro delivered 3 times more albuterol to the distal end of the endotracheal tube than the conventional small-volume nebulizers. In contrast to the Aeroneb Pro, the gas flow used to operate the jet nebulizers required a change in ventilator variables, and refilling the jet nebulizers required interruption of ventilation.

The Aeroneb Pro was compared with the Siemens Ultra Nebulizer 145 (SUN 145) in a model of adult mechanical ventilation. The output from the SUN 145 was influenced by medication volume and by the air flow through the device (at 6, 30, and 60 L/min), with the highest output being observed at 60 L/min (Fig. 7). The output from the Aeroneb Pro remained stable at various medication volumes and air flow rates. In contrast to the SUN 145, the Aeroneb Pro aerosolized the solution even in the inverted position (with the reservoir above the aerosol generator...
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![Graph A: Aerosol Volume vs Medication Volume](image)

**Fig. 7.** A: Effect of gas flow rate and medication volume on the output of aerosol by the Aeroneb Pro (AN Pro) and Siemens Ultra Nebulizer 145 (SUN 145) ultrasonic nebulizer. The gas flow rate and medication volume influence the output from the ultrasonic nebulizer. The highest output was achieved with a flow of 60 L/min and medication volume between 2 and 4 mL. In contrast, aerosol output from the Aeroneb Pro was not influenced by those factors. B: Solution temperature change during operation of the Aeroneb Pro and SUN 145. Solution temperature change during 20 minutes of operation with the Aeroneb Pro was significantly less than that with the SUN 145 (p < 0.01). (Adapted from Reference 11.)

and at a higher level than the connection to the ventilator circuit). The dead volume was 0.2–0.4 mL in the Aeroneb Pro versus 0.8–1.2 mL in the SUN 145.11 Though both systems delivered comparable amounts of aerosol to the distal end of the endotracheal tube during mechanical ventilation, heat generation in the medication reservoir over 20 min was significantly lower in the Aeroneb Pro (2 ± 1°C) than in the SUN 145 (24 ± 3°C) (see Fig. 7).11

In another investigation the Aeroneb Pro was compared with the Siemens SUN 145, the Puritan Bennett ultrasonic EasyNeb, and 2 jet nebulizers (AirLife Misty Neb and Salter Labs 8900).12 Each nebulizer was placed in the inspiratory limb of a heated, humidified ventilator circuit. A Puritan Bennett 760 ventilator provided controlled mechanical ventilation, using adult ventilator settings. Each nebulizer was filled with 3 mL of albuterol sulfate solution (0.083%), and the aerosol was collected by an absolute filter con-

ected to the end of an endotracheal tube (8.0 mm inner diameter). Drug delivery with the SUN 145 and Aeroneb Pro was more than 4-fold higher than that with the jet nebulizers.12 Furthermore, the efficiency of the Aeroneb Pro in delivering aerosol to the distal end of the endotracheal tube improved to approximately 40% of the nominal dose when a device producing a finer aerosol was used in conjunction with 0.5 mL of albuterol solution placed in the nebulizer.12 This improvement in the efficiency of the Aeroneb Pro was attributed in part to the ability of the device to aerosolize the solution almost to the last drop, so that dead volume was negligible.12

Using a simulated adult breathing pattern, the amount of drug delivered to filters by the Aerodose Inhaler was compared to that by the PARI LC Plus.13 Aerosol particle size distribution from the Aerodose Inhaler (VMD ± geometric standard deviation = 4.3 ± 2.1 μm) was comparable to that from the PARI LC Plus (4.8 ± 2.3). Because the Aerodose Inhaler is breath-actuated and has a very low dead volume (< 5 μL), the nominal dose required in the Aerodose Inhaler to achieve comparable drug delivery was one fifth of the nominal dose in the PARI LC Plus.13 Moreover, the treatment time was less with the Aerodose Inhaler (≤ 2.5 min) than with the PARI LC Plus (approximately 10 min).13 Thus, use of the Aerodose Inhaler in place of the PARI LC Plus could reduce the nominal dose and treatment time without compromising drug delivery and clinical response.

The NE-U03 and NE-U22 have also been shown to produce aerosols with the majority of particles in the fine particle fraction (MMAD < 4.7 μm). These devices can aerosolize up to 70% of the volume of solution placed in the nebulizer.14 With ODEM’s TouchSpray, altering the diameter and geometry of the perforations in the membrane modifies the characteristics of the aerosol.15 The TouchSpray devices produce aerosols with MMAD of 2.1 or 2.7 μm, with > 80% of the particles in the aerosol being < 5 μm.15

In Vitro Comparisons of Efficiency in Aerosolizing Suspensions

A simulated pediatric breathing pattern was employed to test delivery of drug suspensions with the Aerodose Inhaler and the PARI LC Plus.16 Budesonide suspension contains irregularly shaped drug particles with mass median sizes of 2.2–2.9 μm suspended in an aqueous medium (0.25 mg/mL). With equal amounts (2 mL) of budesonide suspension, the dose in the fine particle fraction was approximately 3-fold higher with the Aerodose Inhaler,16 mainly because of its finer particle size and lower dead volume.

The ability of the NE-U22 to aerosolize budesonide suspension was also determined in vitro14 and its dead volume and distribution of particle sizes tend to be some-
what larger than that reported above with the Aerodose Inhaler. For example, the MMAD from the NE-U22 (using 2 mL of budesonide suspension) was 4.8 μm, and 30% of the volume remained in the filter, medication container, and vibrator after the treatment.14

Smart et al reported that both solutions and suspensions could be efficiently aerosolized with the TouchSpray and that the majority of particles were in the fine particle fraction.15 TouchSpray devices could be modified to produce aerosols of budesonide suspension (5 mg/mL) that had MMAD as low as 2.2 μm.15

Scintigraphic Evaluation of Pulmonary Deposition of Aerosol

Pulmonary deposition of inhalable tobramycin radiolabeled with technetium-99m diethyleneetriamine pentaacetic acid (99mTc-DTPA) was compared in 9 healthy subjects.17 On 2 separate days each subject received, in a randomized order, a standard label dose of 5 mL (300 mg) of radiolabeled tobramycin from either the PARI LC Plus Neb with Pulmo-Aide compressor or 1 mL (60 mg) of radiolabeled tobramycin from the Aerodose Inhaler. Gamma camera images of the lungs revealed that the PARI LC Plus nebulizer delivered 9.1 ± SD 2.2% of the nominal dose to the lungs, whereas the Aerodose delivered 35.4 ± 10.5% of the nominal dose. Despite using one fifth of the dose of tobramycin with the Aerodose Inhaler, the amount of drug deposited in the lung was similar (21.2 ± 6.3 mg with Aerodose vs 27.2 ± 6.7 mg with PARI LC Plus). Moreover, the nebulization time was reduced from approximately 20 min with the PARI LC Plus to approximately 6 min with the Aerodose Inhaler.17 That study supports earlier in vitro observations that the Aerodose Inhaler has a greater efficiency for drug delivery to the lung and that similar drug delivery could be achieved by decreasing the nominal dose to one fifth that employed in a conventional jet nebulizer.

With the TouchSpray device more than 80% of the liquid 99mTc-DTPA placed in the device could be delivered to the lung of a healthy volunteer.18

Clinical Evaluation of Devices

Concerns have been expressed about drug dose with new devices that have a much higher efficiency of delivering aerosol to the respiratory tract. Administering the standard dose of a drug with these devices might cause adverse effects. Clinical studies are needed to determine the appropriate drug doses with these devices.

A randomized, observer-blinded, cumulative-dose, 3-period crossover study was conducted with 24 patients with moderate to severe asthma (forced expiratory volume in the first second [FEV1] 30–70% of predicted, with ≥ 15% reversibility after albuterol inhalation).19 On separate days, patients received 4 doubling doses of albuterol with each of the study devices (62.25–498 μg with the Aerodose Inhaler; 312.5–2500 μg with the PARI LC Plus; and 100–800 μg with the Ventolin Evohaler MDI). Patients were randomized into 1 of 6 treatment sequences to receive all 3 inhalation treatments in a balanced crossover design. FEV1 increased by more than 300 mL or > 15% from baseline with all doses except the lowest dose from the Ventolin MDI. For all spirometric variables the dose-response curve for PARI LC Plus and Ventolin MDI were similar. In contrast, the Aerodose Inhaler produced bronchodilator efficacy comparable to the PARI LC Plus while using one fifth to one tenth of the nominal dose.19 No clinically relevant systemic effects were observed on plasma potassium level, heart rate, or QTc interval, even at the highest dose levels, with any of the devices or doses. Thus, with the Aerodose Inhaler the nominal dose of bronchodilator solution could be reduced by a factor of 1:5 or 1:10 (compared to the PARI LC Plus) without compromising bronchodilator efficacy or safety.

A prospective, randomized, investigator-blinded, 5-way crossover study compared the response to ipratropium bromide delivered via Aerodose Inhaler versus via PARI LC Plus in patients with stable chronic obstructive pulmonary disease.20 Response to ipratropium bromide solution (0.2%) with the Aerodose Inhaler (0.05; 0.1, and 0.2 mg) or placebo (0.9% saline) given via Aerodose Inhaler were compared with the standard dose of 0.5 mg delivered via PARI LC Plus. The area under the curve for FEV1 0–4 h (ie, during the 4 hours following administration) and peak change in FEV1 with 0.1 mg and 0.2 mg of ipratropium bromide with the Aerodose Inhaler were similar to those obtained with 0.5 mg of ipratropium bromide with the PARI LC Plus. The area under the curve for FEV1 0–4 h, and peak change in FEV1 in response to the 0.05 mg dose with the Aerodose Inhaler were lower than those with the PARI LC Plus.20 These findings lend further support to the view that the higher efficiency of lung delivery with the Aerodose Inhaler could allow substantial reduction of dose without compromising efficacy.

Aerosolization of Insulin

The ability to vary particle size distribution by altering the size of the plate’s aperture was investigated.21 Two types of Aerodose Inhaler, one with VMD of 3.5 μm and another with VMD of 4.5 μm, were selected. With the larger aerosol particle size the aerosolization rate of a commercial insulin formulation was higher, but the fine particle fraction was lower. That study demonstrated that the particle size distribution could be varied by changing the size of the aperture plate holes.21 Drug delivery to the respiratory tract could thus be precisely controlled by using different size aperture holes for different clinical applications.
Kapitza et al investigated the impact of particle size and aerosolization time with the Aerodose Inhaler on the metabolic effect of an inhaled insulin aerosol. They used Aerodose Inhalers that produced aerosols of 2 different particle sizes but both with MMAD < 3 μm. One of the inhalers produced a fine aerosol, whereas the other produced a very fine aerosol. Two different aerosolization times were employed (for either the first 2 s of a 5 s inhalation or for 4 s of a 5 s inhalation). Thirteen healthy volunteers were involved in a euglycemic glucose clamp study (180 min baseline, clamp level 5.0 mM/L, continuous intravenous insulin infusion 0.15 mU/kg/min). Each subject received 0.15 U/kg regular insulin on the first study day. On the following 4 study days, 1.5 U/kg of inhaled insulin was administered as a fine or very fine aerosol, using either 2-s or 4-s delivery times. Glucose infusion rates were measured for the subsequent 6 hours. Inhaled insulin had a faster onset of action (defined as time to half maximum action) than subcutaneous injection. Aerosolization time, but not differences in particle size distribution, significantly influenced the metabolic effect of inhaled insulin. The 4-second aerosolization time resulted in significantly higher maximum metabolic action, total metabolic activity, and relative biopotency than the 2-second aerosolization time. The metabolic effect of inhaled insulin was therefore changed by altering the aerosol particle size distribution and aerosolization time per breath. The highest relative biopotency was achieved with the combination of the very fine particle size and the 4-second aerosolization time. The ability to customize delivery by changing aerosol characteristics would allow rational selection of an optimal inhaler configuration in future studies.

ODEM's TouchSpray device can efficiently aerosolize human insulin (Velosulin, 100 U/mL) and bovine serum albumin (40 mg/mL) into fine particles with mean recovery rates > 90%.23

Aerosolization of Deoxyribonucleic Acid

Deoxyribonucleic acid (DNA) is substantially degraded during nebulization with conventional jet nebulizers. Smart et al determined whether ODEM's TouchSpray device could efficiently nebulize plasmid DNA. Two mammalian expression plasmids harvested from Escherichia coli DH5α strains (pRep5 and pCDNA-HEW) were tested. pRep5 is a circular plasmid DNA (11.0 kilobase pairs [kb]), whereas the pCDNA-HEW is a digested, linearized DNA segment (4.5 kb). Volumes of 300 μL pRep5 and pCDNA-HEW 1000 μL were aerosolized at concentrations ranging from 2.5 to 100 ng/μL. The particles in the aerosol generated were mostly in the fine particle fraction. Most (approximately 90%) of the circular pRep5 plasmid DNA molecules and approximately 50% of the pCDNA-HEW molecules were degraded during nebulization.25 Recovery of intact DNA was improved by either linearizing pRep5 or by using smaller fragments of pCDNA-HEW (1.5 kb vs 3 kb).26 More than 90% of the 1.5 kb linear pCDNA-HEW plasmid was recovered intact after aerosolization.23 The smaller and linearized DNA molecules may be more flexible and less easily degraded by the torsional stresses encountered during aerosolization.

Limitations/Drawbacks of Vibrating Plate/Mesh Devices

Obviously, at present clinical experience with routine use (or misuse) of these devices (that create aerosol with a vibrating mesh or plate with multiple apertures) by patients outside the setting of clinical trials is limited. However, most patients can be trained to use these new devices without difficulty. The cost of these devices is much higher than that of conventional jet nebulizers but may be lower than that of some ultrasonic nebulizers. The cost may vary but will probably be $200 to $300 for each device. That cost may decline as consumer demand increases. Concerns have also been expressed about blockage of the minute apertures with drug particles, particularly when suspensions are aerosolized. This problem may be more important for some devices than for others. Regular cleaning of the device needs emphasis. Because of the higher efficiency of drug delivery to the lung, the drug doses and volume of solution used need to be reduced to prevent adverse effects. The “all-purpose” nebulizer may become obsolete, with each new device being marketed with a specific drug. Manufacturers may not find it attractive to invest their resources in administering commonly used drugs, opting instead to deliver more expensive “designer” drugs with this new technology. Such an approach could limit the applications for this new technology.

Summary

Several electronic nebulizer devices that use a vibrating mesh or plate with multiple apertures to generate a fine-particle, low-velocity aerosol have been marketed or will shortly become available for clinical use. These devices have a high efficiency of delivering aerosol to the lung, such that the nominal dose of drugs to be administered could be substantially reduced. Moreover, the dead volume is negligible, so there is potential to improve the cost-effectiveness of administering expensive medications. Because these devices nebulize at a faster rate than conventional jet or ultrasonic nebulizers, the duration of each treatment could be shortened. These devices efficiently nebulize solutions and suspensions; they have been successfully used for aerosolizing insulin, other proteins and peptides, and fragments of DNA. These versatile and portable devices could be employed for a wide variety of
clinical applications, including the delivery of aerosols for systemic therapy and gene transfer.

Devices that use a vibrating mesh or plate with multiple apertures to generate an aerosol from a liquid medication have overcome many of the limitations associated with conventional jet and ultrasonic nebulizers. These devices have a high efficiency of delivering drugs to the respiratory tract and the versatility to modify the aerosol characteristics according to the clinical application for which they are employed. With these devices clinicians will be able to precisely control drug delivery to the respiratory tract.

ACKNOWLEDGEMENTS

My sincere thanks to Aerogen Inc, Terry O’Brien from Omron Inc, and Jonathan Smart from ODEM Ltd, for providing the information and graphics for this review. I am grateful to Lauren Elliott for her assistance with preparation and editing of the manuscript.

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domed aperture plate within the liquid. Because of that minimal movement very little energy is required and therefore very little heat is generated. With the Omron NE-U03 the energy requirement is very much lower. Standard ultrasonic nebulizers operate in the range of 1.5 MHz, whereas the NE-U03 operates at only 65 kHz. The NE-U22 requires more energy but it is still in the kilohertz range; I believe it’s about 135 kHz. Also, again, the energy is not directed toward the medication. In the case of the NE-U22, it’s the horn that vibrates, and that’s what moves the liquid through the mesh.

Smaldone: The older Omron devices were very sensitive to maintenance; there was a video (that was hard to follow) on how to clean it. The newer devices, I think, are more robust. So I’m wondering about clogging and cleaning. There are a lot of little holes in there.

Dhand: That is an excellent point. Obviously, if you’re using a suspension that contains larger particles, there will be a chance that the holes get clogged up. However, Jim [Fink] told me that with the Aerogen device they’ve not experienced that problem, and it might be that the pumping action itself is a cleaning action for the holes. Certainly when the devices come into clinical use we might find other problems, but with the in vitro and clinical testing that has not been a problem. In the devices we used with our patients with chronic obstructive pulmonary disease, we didn’t see that problem. The devices aerosolized very efficiently.

Fiel: I have a question about the reliability of some of these devices. Based on the range of solutions that might be used in routine practice, whether it be with proteins or not, are certain devices better than others in relation to reliability or the way they work? Whether it be the vibrating horn or some other technology or, as Gerry Smaldone pointed out, small particles, do you have a sense of one that might be better, at least theoretically, from your experience?

Dhand: I don’t have any personal experience with the Omron NE-U22, but I do have experience with the Aerogen device, and I believe that it will work well with suspensions, proteins, and even peptides.

Geller: Great presentation, Rajiv. I had some experience with the Omron MicroAir device. We measured laser particle size of around 7.5–8 microns MMAD. The device was engineered to be equivalent to older devices, not better than, in terms of respirable or fine particle dose. It nebulizes almost everything in the cup, but the particle size was much larger, so you end up with the same respirable dose.

Dhand: I think one of the changes they made was to the characteristics of the plate. The original device had a ceramic plate, and this one has an alloy, electroplated plate that will probably give a better and more uniform particle distribution.

Geller: We also did a “proof of concept” trial with TOBI [inhaled tobramycin solution] and showed that it took almost 100 mg of TOBI in the Aerodose versus 300 mg in the PARI LC Plus to get similar sputum and serum levels. That paper will be published in CHEST soon. One of the engineering problems encountered is that the Aerodose was not really meant to be used with tidal breathing. During the study the patients were tidal breathing, so one of the problems that occurred was that some of the tobramycin would get into the electronics of the device and gum it up. The device wasn’t reusable at that point. And that’s just one of the engineering issues that can be worked through over time (I hope) to make that device into a tidal breathing device. When you take a device that is meant to be used one way and try to use it in a different way, it might not always work.

Dhand: That’s a very valid point. Obviously, we don’t have all the answers right now. But certainly, we’re on the right track, and I believe these devices represent an important advance.

O’Riordan: How do they change the particle size for, say, insulin versus albuterol? Is that a function of the vibration frequency?

Dhand: No, it has to do with the size of the holes. You can vary the size of the holes and thereby the particle size.

Dolovich: Siemens came out with a nebulizer that was an integral part of their ventilator circuitry. They had a large-cup device and a small-cup device. The large cup was ineffective because the coupling was nonexistent for the fluid in the cup. Do you see any of these other devices being used in in-line ventilator circuits?

Dhand: I’m going to defer that question to Jim [Fink], because I think he did some testing with that device.

Fink: The Aeroneb Pro is the application of the Aerogen aerosol generator technology designed for use with mechanical ventilation. Besides being relatively small and light, so that it can be placed closer to the patient in the ventilator circuit, the orifices in the aerosol generator are so small that it does not perceptibly leak gas when the nebulizer reservoir is open to the atmosphere. The Aerodose inhaler used in the TOBI study was an early version of our breath-actuated inhaler.

* Stanley B Fiel MD, MCP Hahnemann University, Philadelphia, Pennsylvania (discussant for Monaghan Trudell, Syracuse, New York)

* James B Fink MSc RRT FAARC, Aerogen, Mountain View, California.
which was designed for a deep breath and breath-hold maneuver, so that it needed to be “smoked” by the patient for use with tidal breathing. The newer version of the Aerodose inhaler can be used for deep breath or tidal breathing.

Maclntyre: We’ve heard 2 presentations in this conference about devices that improve lung deposition by 2 or 3 times over what we’re used to. Is it just because you’re making smaller particles and that the aerosol can be delivered with tidal breathing? Is that all there is to it? A better, cleaner, smaller aerosol cloud?

Dhand: Also a slower-moving cloud, more uniform particle size distribution, and with the Aerodose, I think the breathing-actuation is a very important part of it.

Smaldone: Nebulized drug delivery during tidal breathing has certain advantages, and the slow particle velocity is very important because it helps minimize oropharyngeal deposition. And the less the dead volume, the better the efficiency. To me the difference between the old technology and the new is the difference in dead volume. These mesh devices are one of the first attempts to minimize dead volume, although the non-nebulizer “squirters” such as AERs also have very small dead volume. Once you get rid of the dead volume, then all the advantages of nebulizers come out, in terms of their ability to deliver aerosol to the lung.

Gomez: I would point out that these nebulizers we’re discussing are all “ultrasonic” nebulizers, because they all operate above 20 kHz, even though the community seems to make some distinctions.

Fink: I’m not sure that everything that uses a piezoelectric ceramic element is best described as ultrasonic. The Aerogen technology runs at a lower frequency, does not generate heat, and uses a totally different mechanism to generate aerosol than do standard ultrasonic nebulizers. It seems that this is sufficient to merit a differentiating name for the principle mechanism of aerosol generation.

Gomez: I agree. They’re quite different. But both rely on ultrasonic excitation. Perhaps we should use a better-suited terminology to highlight the distinctions among the various types.

I was interested in that plate with the converging nozzles. Do you know how they make it? You seemed to indicate that it is of the vibrating-orifice type, which should produce strictly single-size droplets. If that’s so, why the spread in size distribution? Is it because the flow rates are not uniform across the single holes?

Fink: The Aerogen aperture plate is created through an electroplating process that allows us to build the funnel-shaped apertures with a specified exit diameter, depending on application. The diameter of the aerosol particle is directed only to the aperture exit diameter. The devices you referred to as monodisperse may use one aperture to produce aerosol. With approximately 1,000 apertures on a domed plate pumping aerosol, we tend to produce aerosols that are not quite monodisperse, with a geometric standard deviation of 1.9–2.0 μm rather than 1.4 μm.

Dennis: Gerry [Smaldone] said that we have increased efficiency because we have smaller dead volume (which is true)—and longer nebulization time; we need to train and educate people that a longer nebulization time isn’t necessarily bad; if a device becomes very efficient, then you can stop nebulization when the dose is right. We’re still nebulizing a standard ampule volume.

These devices also have the potential of much greater efficiency because they don’t waste aerosol to the environment. So for some of them you only get the aerosol inhalation. I think that’s as important as the small dead volume.

The third thing is that these devices don’t use compressed air. So if you’ve measured a standard particle size with the laser, that measure is really distance from the conditions when the patient inhales. The particle size measurement method should involve the inhalation system that will be used by the patient, so you inhale all these aerosols that are not being generated in a saturated cloud—they just come into being and are pulled into ambient air, and that ambient air will become saturated from water vapor drawn from the droplets. If you have a very small amount of emission from these devices, all the liquid will evaporate and you’ll end up with dry powder. So, traditionally, this could prove to be a very good avenue for producing dry powder inhalers.

On the down side, with devices that have variable output (it might be 30 or 50 or 100 mL/min) there will be various amounts of evaporation, so you lose control of particle size. Taking this observation further, the rate of total aerosol output ultimately controls particle size from bolt devices when they start getting down to low outputs, below 50 mL/min. If the bolt output is higher than about 50 μL, the evaporation doesn’t really matter, because it is minimal compared to the overall aerosol output. In any case, the way the patient uses the device must be taken into consideration in measuring particle size.

This is really a warning to users and manufacturers: that with variable output you’re going to have variable droplet size. One of the challenges to manufacturers is to overcome the technical difficulties and make devices that are not variable in output. I think there are technical difficulties in making all the devices right now, but these are being overcome—there are 3 or 4 separate company developments, so some of them are going to make it to market. I think these will be issues when they do come to market.