

Performance Comparison of Nebulizer Designs: Constant-Output, Breath-Enhanced, and Dosimetric

Joseph L Rau PhD RRT FAARC, Arzu Ari MSc CRT CPFT, and Ruben D Restrepo MD RRT

INTRODUCTION: Design differences among pneumatically powered, small-volume nebulizers affect drug disposition (percentage of the dose delivered to the patient, lost to deposition in the equipment, and lost via exhalation to ambient air) and thus affect drug availability and efficacy. **OBJECTIVE:** Evaluate in vitro the dose disposition with 5 nebulizer models, of 3 types (constant-output, breath-enhanced, and dosimetric), using simulated normal, adult breathing. **METHODS:** We compared 5 nebulizer models: 2 constant-output (Misty-Neb and SideStream), 1 breath-enhanced (Pari LCD), and 2 dosimetric (Circulaire and AeroEclipse). Each nebulizer was filled with a 3-mL unit-dose of albuterol sulfate and powered by oxygen at 8 L/min. The nebulizers were connected to an induction throat, connected to a breathing simulator. We measured (1) inhaled drug (subdivided into mass deposited in the induction throat and mass deposited in the filter at the distal end of the induction throat), (2) exhaled drug (lost to the ambient air), (3) drug lost to deposition in the apparatus, and (4) drug left in the unit-dose bottle. The duration of nebulization (until sputter) was measured with a stopwatch. All drug amounts were analyzed via spectrophotometry and expressed as a percentage of the total dose. **RESULTS:** The mean \pm SD inhaled drug percentages were: Misty-Neb $17.2 \pm 0.4\%$, SideStream $15.8 \pm 2.8\%$, Pari LCD $15.2 \pm 4.2\%$, Circulaire $8.7 \pm 1.0\%$, and AeroEclipse $38.7 \pm 1.3\%$. The mean \pm SD percentages of drug lost to the ambient air were: Misty-Neb $26.8 \pm 0.7\%$, SideStream $17.3 \pm 0.4\%$, Pari LCD $18.3 \pm 0.8\%$, Circulaire $12.3 \pm 0.8\%$, and AeroEclipse $6.6 \pm 3.3\%$. The mean \pm SD percentages of drug lost to deposition in the apparatus were: Misty-Neb $52.3 \pm 0.6\%$, SideStream $63.4 \pm 3.0\%$, Pari LCD $62.5 \pm 4.0\%$, Circulaire $75.8 \pm 0.5\%$, and AeroEclipse $51.0 \pm 2.1\%$. Duration of nebulization was shortest with the Circulaire and longest with the AeroEclipse ($p < 0.05$ via 1-way analysis of variance). **CONCLUSIONS:** The nebulizers we tested differ significantly in overall drug disposition. The dosimetric AeroEclipse provided the largest inhaled drug mass and the lowest loss to ambient air, with the test conditions we used. *Key words: nebulizers; aerosols, drug therapy; drug administration, inhalation; respiratory drug administration.* [Respir Care 2004;49(2):174–179. © 2004 Daedalus Enterprises]

Introduction

Gas-powered jet nebulizers are commonly used for delivering medications in the clinical and home-care settings.

Joseph L Rau PhD RRT FAARC, Arzu Ari MSc CRT CPFT, and Ruben D Restrepo MD RRT are affiliated with Cardiopulmonary Care Sciences, Georgia State University, Atlanta, Georgia.

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Correspondence: Joseph L Rau PhD RRT FAARC, Cardiopulmonary Care Sciences, MSC 8R0319, Georgia State University, 33 Gilmer Street SE, Unit 8, Atlanta GA 30303. E-mail: jrau@gsu.edu.

Over the past few years nebulizer design changes have created nebulizer categories, termed constant-output, breath-enhanced, and dosimetric.¹ Constant-output nebulizers are the traditional T-piece nebulizers that generate aerosol constantly, during the inhalation, exhalation, and breath-hold. With constant-output nebulizers some of the aerosol is lost during exhalation, which causes release of aerosol to the ambient air through the expiratory limb of the T-piece.^{2–4} Constant-output nebulizers have been criticized as unreliable and inefficient, because a low percentage of the dose reaches the patient.^{5–7} A length of large-bore tubing is usually attached to the expiratory side of the constant-output nebulizer T-piece, to reduce drug loss and increase the inhaled amount.^{8–9}

Breath-enhanced nebulizers are designed to allow release of more aerosol during inhalation, when ambient air

is drawn through the nebulizer.⁹ During exhalation, gas flow through the nebulizer falls back to the power-gas flow only, exhaled gas is routed out the expiratory valve in the mouthpiece, and aerosol is contained in the nebulizer chamber. Examples of breath-enhanced nebulizers include Pari LC Plus and Pari LCD. Coates et al¹⁰ and Dennis¹¹ found better drug output with breath-enhanced nebulizers.

Dosimetric nebulizers release aerosol only during inhalation.¹ The Circulaire represented an early attempt to convert a constant-output nebulizer to a dosimetric device, by attachment of a storage bag with a 1-way valve in the mouthpiece connector.^{12,13} A recently introduced nebulizer, the AeroEclipse, has a breath-actuated valve that triggers aerosol generation only during inhalation, eliminating the need for a storage bag or reservoir.

Theoretically, both breath-enhanced and dosimetric nebulizers would have reduced or no aerosol loss during exhalation. However, although there may be reduced exhalation loss of aerosol, does the emitted drug amount in fact increase, or is there a shift in the location of lost aerosol, from exhaled/ambient to device? With the Circulaire does the storage of aerosol increase or decrease the inhaled drug? We found no studies of all 3 categories of nebulizer, including the Circulaire, using the same set of realistic breathing conditions¹⁴ and that characterized the total drug disposition, including emitted drug, device loss, and exhaled/ambient drug loss. The purpose of the present study was to evaluate *in vitro* the total drug disposition of constant-output, breath-enhanced, and dosimetric nebulizers, using simulated normal adult breathing.

Methods

Study Design

The nebulizer brands tested were AirLife Misty-Neb (Allegiance Healthcare, McGaw Park, Illinois), AirLife SideStream (Allegiance Healthcare, McGaw Park, Illinois), Circulaire (Westmed, Tucson, Arizona), Pari LCD (PARI Respiratory Equipment, Monterey, California), and AeroEclipse (Monaghan Medical, Plattsburgh, New York). The Misty-Neb and SideStream are traditional constant-output nebulizers. The Pari LCD is a breath-enhanced nebulizer. The Circulaire and AeroEclipse were considered dosimetric devices, based on Dennis's definition.¹ The Circulaire was tested with the supplied nebulizer. Figure 1 shows the principle of operation of each nebulizer brand tested.

Three of each of the 5 nebulizer brands were tested, using a simulated normal adult breathing pattern. Each device nebulized a unit-dose of albuterol sulfate solution, 2.5-mg base equivalent (Proventil, Schering, Kenilworth, New Jersey), with a 3 mL total fill volume. No additional diluent was added to any nebulizer. All the nebulizers were powered by 50-psi oxygen at 8 L/min.

Lung Model

The nebulizers were connected to a breathing simulator (Series 1101, Hans Rudolph, Kansas City, Missouri), which provides a complete breathing cycle with both inhalation and exhalation phases. Tidal volume was set at 600 mL, inhalation flow at 30 L/min, and respiratory rate at 12 breaths/min, giving a 1:3 inspiratory-expiratory ratio. Figure 2 shows the equipment configuration. An induction port (throat) (Thermo Andersen, Franklin, Massachusetts), as described in the United States Pharmacopeia (USP) for use with cascade impactor testing,¹⁵ was placed between the nebulizer outlet and the breathing simulator. The throat, which has a diameter of approximately 19 mm and a right angle, was used as a simple geometric analogue of the upper airway, to allow inertial impaction of larger aerosol particles. This allowed a standardized basis for comparison of inhaled aerosol from each nebulizer tested. A filter (2-way nonconductive anesthesia filter, Baxter Healthcare, Deerfield, Illinois) was attached to the distal end of the throat, between the throat and the breathing simulator. We defined the total inhaled drug mass as the amount in the throat plus the filter.

In cascade impactor testing the throat is placed vertically, but in our experiments the throat was placed horizontally to prevent the inhalation filter from collecting drug that might condense on the throat wall and then drip onto the inhalation filter. The mouthpieces were removed from the 2 constant-output nebulizers (Misty-Neb and SideStream) and the T-piece was connected directly to the throat and the breathing simulator. A 15-cm length of large-bore corrugated tubing, as supplied by the nebulizer manufacturer, was attached to the exhalation outlet of the T-piece, and exhaled drug was collected by a filter at the end of the tubing (see Fig. 2).

The breath-enhanced Pari LCD, which is a disposable unit, has a nonvalved opening at the top of the chamber and open exhalation ports in the mouthpiece (see Fig. 1). With the Pari LCD we placed exhalation filters at the chamber top and at the outlet of a T-piece, which replaced the mouthpiece (see Fig. 2). The Circulaire contains a 1-way valve in the nebulizer T-piece, which directs aerosol toward the mouth. There is also an exhalation port with a size-adjustable opening between the 1-way inspiratory valve and the mouthpiece (see Fig. 1). An exhalation filter was attached to the exhalation port, with maximum opening; the T-piece assembly, without the mouthpiece, was attached to the throat and breathing simulator (see Fig. 2). The AeroEclipse has a 1-way exhalation flapper valve integrated into the mouthpiece assembly. An inhalation flow of approximately 6 L/min causes the spring-loaded valve to engage and generate aerosol (see Fig. 1). The mouthpiece was replaced with a T-piece, and an outwardly directed 1-way valve was added to the exhalation outlet of the T-piece so that inhalation flow came from the nebulizer and allowed breath-actuated triggering of the nebulizer (see Fig. 2).

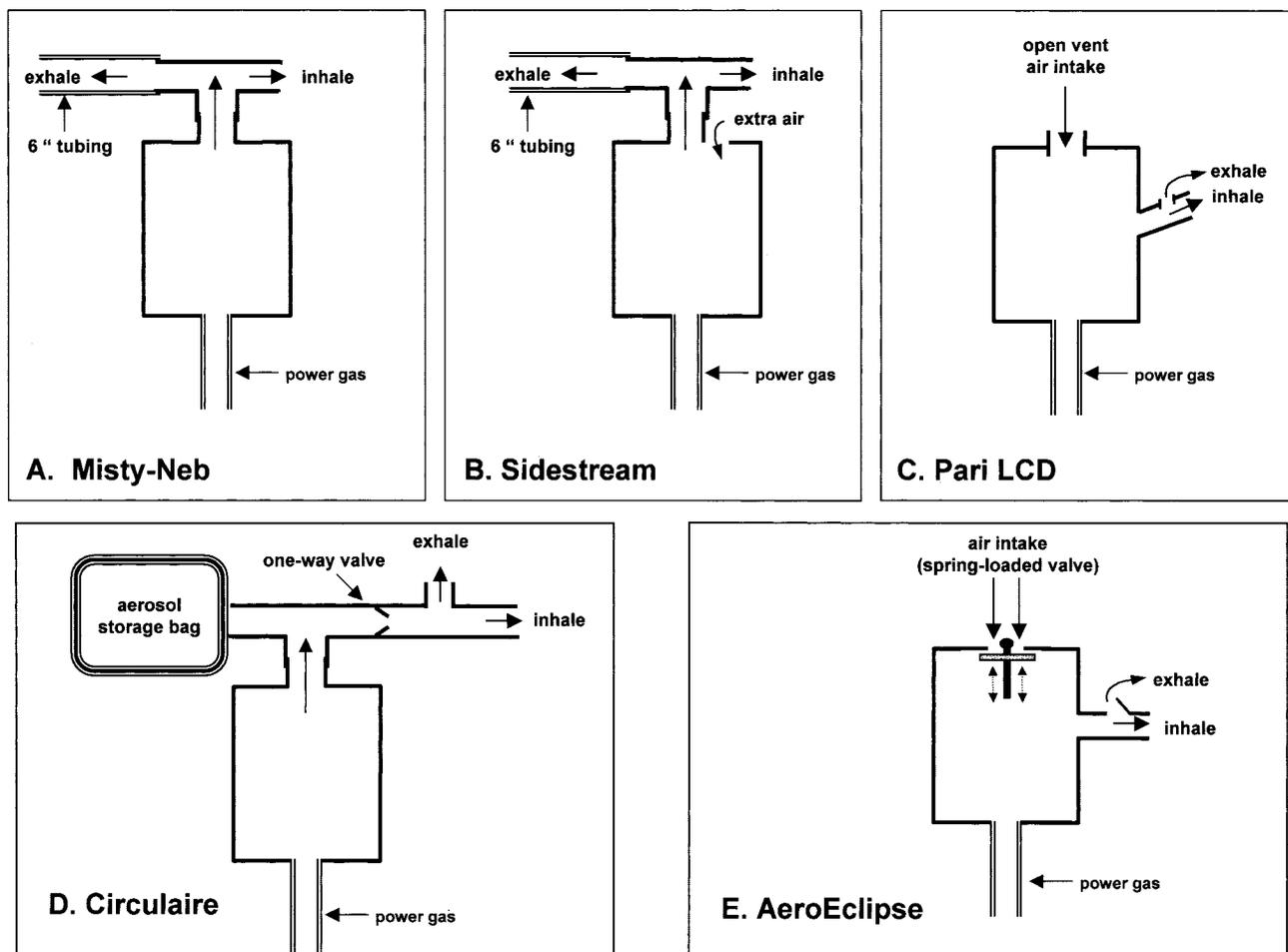


Fig. 1. Functional diagrams of the 5 nebulizer brands tested, illustrating principle of operation and patterns of gas flow during inhalation and exhalation.

Measurement of Drug

In each nebulizer trial the total aerosol drug mass was measured and consisted of the total inhaled drug mass, exhaled/ambient drug loss, and drug lost in the device. We also measured drug remaining in the unit-dose bottle. The total inhaled drug mass was divided into drug collected in the throat and drug from the collecting filter attached to the throat outlet. Exhaled drug was collected on a filter attached to the exhalation outlet of the nebulizer. The drug remaining in the nebulizer apparatus (including adapters, T-piece, and mouthpiece) was collected by washing, and analyzed. Each nebulizer was weighed empty, after filling, and at the end of nebulization, to calculate the volume left, as described by Coates et al.¹⁰ Solvent was added to the calculated volume, drug concentration was then determined by spectrophotometry, and the drug mass was calculated. Each nebulizer was operated until the onset of sputter, with no tapping of the nebulizer (as is usually done when

administering aerosol to a patient), and the time to sputter was recorded with a stopwatch. All drug amounts were analyzed via spectrophotometry (Beckman Instruments, Fullerton, California), at a wavelength of 276 nm. The solvent was 0.1 molar normal hydrochloric acid (JT Baker Company, Phillipsburg, New Jersey). Collecting filters were washed for 1 min with gentle agitation. Longer washing did not yield additional drug. Measurements with 2 filters in series verified that no drug was lost through the first filter. The spectrophotometer was calibrated prior to trials, using a holmium oxide filter (Beckman Instruments, Fullerton, California) to determine wavelength accuracy, and set to zero using the solvent alone before each analysis. A regression curve and prediction equation were developed from serial dilutions of known albuterol sulfate solution (Sigma, St Louis, Missouri). Concentrations of sample solutions, and thereby drug amounts of albuterol, were calculated from this known concentration/absorbance relationship.

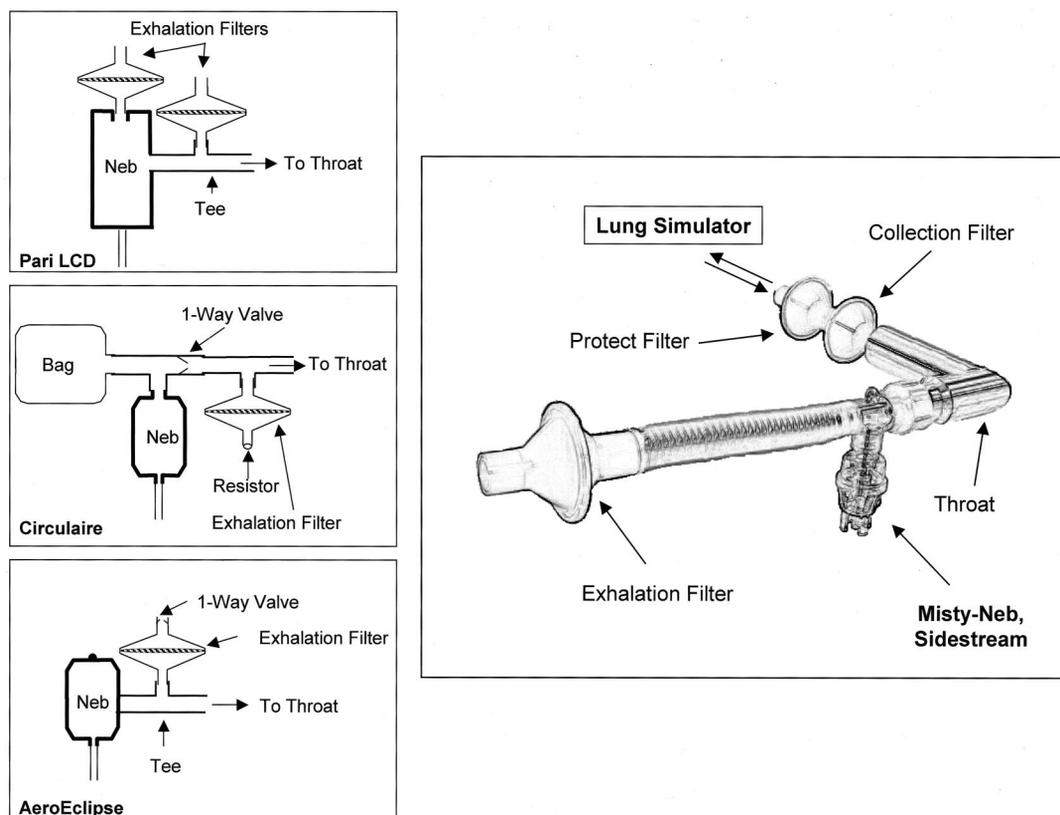


Fig. 2. Setup for nebulizer performance testing. Right Panel: Configuration for the constant-output nebulizers (Misty-Neb and SideStream). Left Panels: Configurations for the Pari LCD, Circulaire, and AeroEclipse. NEB = nebulizer. Tee = T-piece.

Data Analysis

Means and standard deviations were calculated for each component of the total drug mass and for time of nebulization. Differences between the total inhaled mass and the inhalation-filter mass (ie, total inhaled drug minus drug deposited in the throat) were compared with 1-way analysis of variance. Differences were considered statistically significant when $p < 0.05$. Multiple follow-up comparisons to identify differences among nebulizers were performed using Scheffé's S method.¹⁶ All statistical calculations were performed using commercially available software (SYSTAT 7.0, SPSS, Chicago, Illinois).

Results

Table 1 shows the dose disposition results, expressed as percentages of total drug recovered from the throat, inhalation filter, exhalation filter, nebulizer apparatus, and drug remaining in the unit-dose bottle. The mean \pm SD total drug mass of albuterol sulfate recovered from all sources and expressed as the base was 2.56 ± 0.09 mg, which corresponds well to the 2.5-mg nominal dose of the unit-dose albuterol nebulizer solution we used.

The percentage of total inhaled drug mass differed significantly (by 1-way analysis of variance) among the 5 nebulizer brands tested ($p = 0.0001$). Table 1 shows which groups of individual brands did not significantly differ from each other (homogeneous subsets), based on follow-up comparisons. The total inhaled drug obtained from the constant-output nebulizers, Misty-Neb and SideStream, was similar to that from the breath-enhanced Pari LCD, ranging from 15% to 17%. The 2 nebulizers considered dosimetric (Circulaire and AeroEclipse) differed from each other, and the Circulaire differed from the Misty-Neb. The inhaled drug mass from the Circulaire was approximately half that of the constant-output and breath-enhanced nebulizers, whereas the inhaled mass of the AeroEclipse was about 2.5 times greater than the constant-output and breath-enhanced nebulizers.

The inhalation filter mass differed significantly (by 1-way analysis of variance) among the 5 nebulizer brands ($p = 0.0001$). Table 1 shows groups of brands that did not significantly differ from each other, based on follow-up comparisons. The dosimetric nebulizers (Circulaire and AeroEclipse) had the least exhaled drug loss: approximately 7–12%. The duration of nebulization also differed significantly among the nebulizers ($p = 0.0001$).

PERFORMANCE COMPARISON OF NEBULIZER DESIGNS

Table 1. Aerosol Deposition and Loss, and Nebulization Time With 5 Nebulizer Brands*

	Misty-Neb	SideStream	Pari LCD	Circulaire	AeroEclipse
Total inhaled (%)	17.2 ± 0.4†	15.8 ± 2.8†‡	15.2 ± 4.2†‡	8.7 ± 1.0‡	38.7 ± 1.3
Inhalation filter (%)	14.4 ± 0.5†§	14.7 ± 2.7†	13.3 ± 4.2†§	7.4 ± 1.0§	34.2 ± 1.3
Exhaled to ambient (%)	26.8 ± 0.7	17.3 ± 0.4	18.3 ± 0.8	12.3 ± 0.8	6.6 ± 3.1
Deposited in nebulizer apparatus (%)	52.3 ± 0.6	63.4 ± 3.0	62.5 ± 4.0	75.8 ± 0.5	51.0 ± 2.1
Remained in unit-dose bottle (%)	3.7 ± 1.1	3.6 ± 0.5	4.1 ± 0.6	3.0 ± 0.4	3.7 ± 0.6
Nebulization time (min)	11.9 ± 0.3	9.5 ± 0.1	8.4 ± 1.2	7.0 ± 0.5	14.4 ± 1.1

*The percent values represent percent of total dose. The inhalation filter percentage is a subset of the total inhaled percentage: specifically, the inhalation filter percentage equals the total inhaled minus the amount deposited in the throat. Subsets of nebulizer brands with no significant differences ($p < 0.05$) based on follow-up comparisons are indicated for total inhaled percentage and inhalation filter percentage. Nebulization time was until sputter.

†No significant difference between Misty-Neb, SideStream, and Pari LCD

‡No significant difference between SideStream, Pari LCD, and Circulaire

§No significant difference between Misty-Neb, Pari LCD, and Circulaire

Discussion

The focus of the present study was to measure drug disposition with different nebulizer design categories tested under the same conditions. We found differences among the nebulizers in total inhaled mass of aerosolized bronchodilator and in the location and amounts of aerosol drug lost to ambient air and to the nebulizer apparatus. Though the total inhaled drug mass was similar for the constant-output (Misty-Neb and SideStream) and the breath-enhanced (Pari LCD) nebulizers, the 2 dosimetric nebulizers differed in opposite directions. The Circulaire had the lowest and the AeroEclipse the highest inhaled mass of all the devices tested. We hypothesize that greater apparatus drug loss in the Circulaire's bag storage system accounts for the smaller inhaled mass. With the AeroEclipse the apparatus drug loss was similar to the Misty-Neb, but inhalation-only aerosol generation shifted aerosol from exhaled to inhaled. Both the Circulaire and the AeroEclipse lost less to the ambient air, as expected, based on their design and function. The Circulaire contains aerosol during the exhalation phase, and the AeroEclipse's breath-actuation limits aerosol generation to the inhalation phase. With breath-actuation, exhaled/ambient loss from the AeroEclipse was half that of the Circulaire.

We could find only 1 study, in the form of an abstract, by Hess et al, that tested the same nebulizers under a uniform set of breathing variables to allow direct comparison of nebulizer performance.¹⁷ Their study measured total nebulizer output of albuterol and calculated fine particle mass from particle size measurements. They did not measure exhaled or nebulizer apparatus drug loss. The fine particle mass output was greatest with the AeroEclipse and least with the Circulaire. The Pari LCD, SideStream, and Misty-Neb were intermediate between the AeroEclipse and Circulaire. That is the same order of output found in our study for total inhaled mass and for inhalation filter mass (total inhaled mass minus throat loss).

Other studies have measured drug output from one or several of the nebulizers tested in our study, using various breathing conditions. Our measurements of inhaled drug mass from the constant-output SideStream agree well with Dennis's *in vitro* research on the SideStream.¹¹ Devadason et al measured inhaled drug mass from a Pari LC, using volunteers and filter collection at the mouth.⁹ They found 19% for the total inhaled drug, which is higher than the 15% in our study of the Pari LCD with simulated breathing. That difference may be due to design differences among Pari models, notably between the Pari LC Plus, a nondisposable, reusable unit, and the Pari LCD, a disposable unit. The Pari LC Plus has a 1-way valve in the top of the nebulizer chamber, which allows ambient air to be entrained during inhalation, with no loss of aerosol on exhalation. The LCD has a simple opening with no valve in the top of the nebulizer chamber, and we observed visible loss of a small amount of aerosol through that opening during exhalation. The Pari LC Plus also has a 1-way flapper valve in the mouthpiece, whereas the Pari LCD has simple nonvalved openings on either side of the mouthpiece. Design differences may also account for the difference in exhaled loss between our study (18%) and the study by Dennis, who found approximately 11% exhaled loss with the Pari LC Plus.¹¹

Inhaled drug from a breath-enhanced nebulizer also increases or decreases as a function of inhalation flow.¹⁸ Measuring inhaled mass at a single flow with the Pari LCD, as we did, could be seen as limiting, but our peak inhalation flow corresponded to the highest uniform flow in a study by Knoch et al of the Pari IS-2; this was also the flow that gave the highest emitted drug mass in their study.¹⁸ The effect of variable flow or different inhalation waveforms (eg, uniform flow versus a sine waveform) with breath-enhanced nebulizers requires further investigation.

The Circulaire represents an adaptation of a constant-output nebulizer to create a dosimetric device, if we accept Dennis's definition of dosimetric as a nebulizer that re-

leases “aerosol only during the inhalation cycle” and that makes “all released aerosol available for patient inhalation.”¹¹ In an *in vitro* study of the Circulaire, using albuterol, Piper found an emitted drug mass of 0.32 ± 0.01 mg,¹³ which is approximately 13% of the nominal dose of 2.5 mg albuterol, compared to $8.7 \pm 0.99\%$ found in our study. That difference may be due to the fact that in Piper’s study emitted drug on inhalation was not directly measured but rather calculated based on intermittent sampling.

Measures of drug mass lost in the constant-output and breath-enhanced nebulizers have ranged between 55% and 66% in a number of studies.^{5,9,11,19,20} That range agrees well with the 52–63% apparatus loss we found for those types of nebulizers. Our measurement of drug remaining in the AeroEclipse (51%) was identical to that reported by Fink et al.²¹

A limitation in the present study was the use of the USP throat as a simple model of the upper respiratory tract, rather than measuring particle size distribution and the fine particle fraction. The USP throat was designed to capture the large and high-velocity aerosol particles emitted from a metered-dose inhaler, when testing at a constant flow of approximately 30 L/min. The throat has also been adopted by the USP as a model throat for testing dry powder inhalers,¹⁵ in the testing of which the flow varies through the throat, with the testing conditions prescribed in the USP, Chapter 601, on aerosols. With a dry powder inhaler there is no high-velocity, large-particle fraction, as there is with a metered-dose inhaler.¹⁵ The measurements of throat loss in our study do not represent a certain particle size nor provide an estimate of the fine particle mass that could reach the lower respiratory tract. Our use of the throat provides a standard model for the comparative evaluation of nebulizer designs. Based on the mechanism of inertial impaction, which is a function of particle mass and velocity, we would expect the model throat loss (the difference between the total inhaled mass and the inhalation filter mass) to be a very approximate measure of larger aerosol particles. Measurements of fine particle fractions have been reported elsewhere for the Misty-Neb,¹⁷ SideStream,^{11,17} Pari LC Plus,¹¹ Pari LCD,¹⁷ Circulaire,^{13,17} and AeroEclipse.¹⁷

Conclusions

Our results indicate that design differences among nebulizers affect drug disposition in inhaled mass, apparatus loss, and exhaled/ambient loss. Use of reservoir systems to store aerosol during the exhalation phase can cause large apparatus losses and thus decrease inhaled mass, whereas generating aerosol only during inhalation (ie, breath-actuated nebulization) increases inhaled mass and decreases ambient drug loss. Clinical comparisons are necessary to

determine if these differences substantially affect clinical outcomes.

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