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AN *IN VITRO* TECHNIQUE FOR CALCULATING THE REGIONAL DOSAGES OF DRUGS DELIVERED BY AN ULTRASONIC NEBULIZER

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Abstract—This study describes an *in vitro* technique for calculating the dosages of drug delivered to the different regions of the human lung by an ultrasonic nebulizer. The technique uses phase Doppler anemometry to measure particle sizes. Tidal breathing is simulated with a reciprocating pump. Inhalation is divided into an interval in which the sizes of the particles are nearly independent of the relative humidity (RH) of the inlet ambient air and a second interval in which the particles have evaporated. The numerical hygroscopic lung deposition model of Stapleton, Finlay, and Zuberbuhler (*J. Aerosol Med.* 7, 325, 1994) is used to calculate the regional dosages. The methodology is applied to the DeVilbiss Aerosonic® ultrasonic nebulizer for 2.5 ml nebules of 1 mg ml^{-1} Ventolin®. The dosage of drug delivered to the extrathoracic, bronchial, and pulmonary regions is 0.42, 0.10, and 0.22 mg, respectively, at an inlet RH of 95% and 20°C. The corresponding values for RH = 3% are 0.39, 0.097, and 0.22 mg.

1. INTRODUCTION

One way to deliver aerosol particles for nebulizer therapy is through the use of an ultrasonic nebulizer. The advantages of these types of nebulizers are that they are quiet, reusable, and do not require a source of compressed air. The disadvantages are that they are expensive and that they may be unable to nebulize certain suspensions and proteins properly.

In an ultrasonic nebulizer, the aerosol particles are produced by the high-frequency oscillations of a piezoelectric crystal that atomizes the drug solution. In some units, a fan blows the particles out of the nebulizer, while in other units the aerosol particles are removed from the nebulizer when the patient inhales.

Compared to jet nebulizers, there is little previous research on ultrasonic nebulizers in the archival literature. Most previous work concentrates on measuring the particle size distribution produced by the ultrasonic nebulizer and the total mass nebulized (cf. e.g. Newman *et al.*, 1987; Smaldone *et al.*, 1988; Dennis *et al.*, 1990; and Riedler and Robertson 1994).

O'Doherty *et al.* (1992) and Thomas *et al.* (1993) describe *in vitro* radiolabelled measurements of drug delivery during a simulation of mechanical ventilation of a patient. They studied the effects of breathing pattern, nebulizer fill volume, and size of the aerosol storage chamber and concluded that ultrasonic nebulizers are of value for aerosol therapy of mechanically ventilated patients.

To the authors' knowledge, there has not been any previous work on using a lung deposition model to calculate the dosage of drugs that can be delivered by an ultrasonic nebulizer. In this study, an *in vitro* numerical technique is described to calculate the regional dosages of drugs that can be delivered by an ultrasonic nebulizer. The technique is applied to a DeVilbiss ultrasonic nebulizer for tidal breathing of a normal subject.

2. METHODOLOGY

The ultrasonic nebulizer used in this study was the DeVilbiss Aerosonic® (Model 5000, DeVilbiss Health Care (Canada) Inc., Barrie, ON, Canada). Three different units were tested to examine inter-nebulizer variation. Single-dose nebules of Ventolin® (DIN 00897345,

Glaxo Canada, Inc., Mississauga, ON, Canada) which contain 2.5 mg of salbutamol sulphate solution dissolved in 2.5 ml of normal saline were used as the test solution. Suspensions may not be reliably nebulized by an ultrasonic nebulizer since the capillary waves produced by the piezoelectric crystal may not entrain the suspended particles and the liquid may be preferentially nebulized.

A sketch of the nebulizer is shown in Fig. 1. The nebulizer is a hand-held unit about 13 cm high and 5 cm in diameter and is attached to the power unit by a flexible power cord. The nebulizer solution is added to the nebulizer bowl and a piezoelectric crystal atomizes the solution with high-frequency vibrations of 2.25 MHz. The mean diameter of the droplets is proportional to the wavelength λ of the standing capillary waves generated by the piezoelectric crystal, where

$$\lambda = \left(\frac{8\pi\gamma}{\rho f^2}\right)^{1/3} \tag{1}$$

and γ is the surface tension of the liquid, ρ is the density of the liquid and f is the frequency of the crystal vibrations (Mercer, 1981).

The nebulizer produces aerosol particles continuously and the particles accumulate in the nebulizer dome until they are inhaled by the patient. During inhalation, ambient air is drawn through the inlet valve and the air–aerosol mixture leaves the nebulizer through the mouthpiece. During exhalation, the inlet valve closes and an outlet valve on the mouthpiece opens so that no air flows through the nebulizer.

A reciprocating pump with a tidal volume of 1.25 ℓ and a speed of 17.6 cycles per minute was constructed to simulate the breathing of the patient. The motion of the piston was controlled by a cam with a cardioid profile which resulted in the flow pattern shown in Fig. 2. The values of tidal volume and inspiration flow rate for the pump are similar to those observed by Rudolf *et al.* (1990) for healthy subjects.

The relative humidity (RH) of the incoming air was controlled with the humidity chamber described by Prokop *et al.* (1994). Briefly, a stream of pressurized air was divided into two streams, one of which was humidified by bubbling it through water, and the other of which was dehumidified by passing it through desiccant granules. By mixing these two streams in appropriate ratios, a wide range of humidities can be produced. The ultrasonic nebulizer was tested at inlet relative humidities of 3% and of 95% at 20°C.

At the end of each minute of nebulization, the nebulizer was weighed and the concentration of the solution remaining in the nebulizer was measured with a freezing point depression osmometer (μOSMETTE model 5004, Precision Systems, Inc., Natick, MA, U.S.A.). The run was arbitrarily terminated at the end of the minute in which there was at least a 15 s pause in nebulization due to an insufficient amount of drug solution on the piezoelectric crystal. This resulted in a total nebulization period of 6 min at an inlet of 3% and 8 min at an inlet RH of 95%.

Using the set-up shown in Fig. 3, a phase Doppler anemometer (PDA) (Dantec Electronics Inc., Mahwah, NJ, U.S.A.) measured the particle-size distribution and the number of

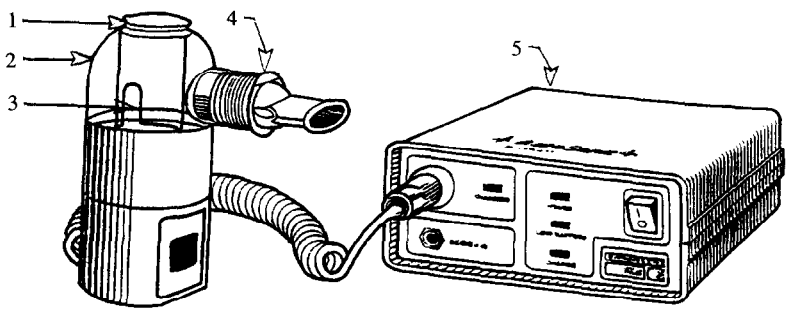

Fig. 1. A sketch of the Aerosonic nebulizer is shown: (1) inlet valve; (2) nebulizer dome; (3) baffles; (4) mouthpiece and outlet valve; (5) power supply.

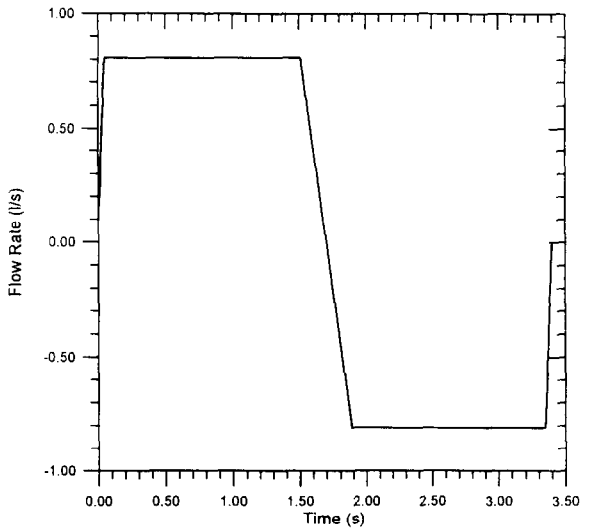

Fig. 2. The flow rate produced by the reciprocating pump to simulate tidal breathing. Inhalation is the first half of the cycle.

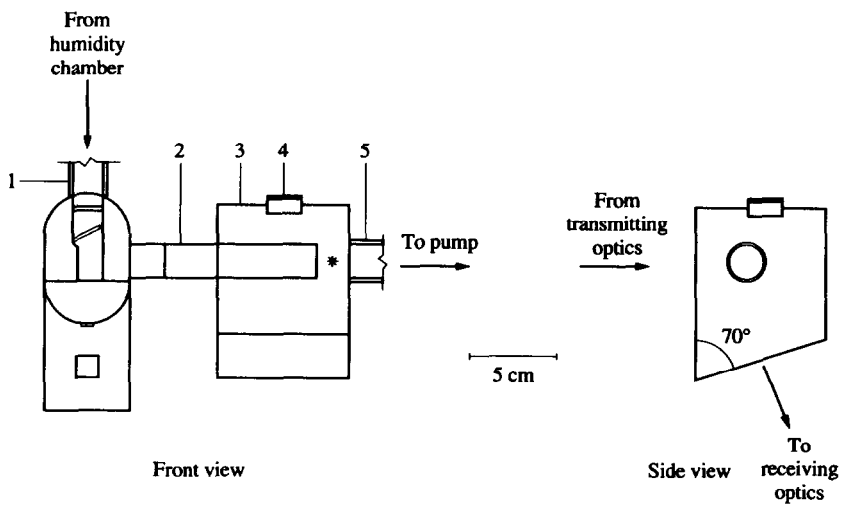

Fig. 3. A sketch of the measurement box is shown: (1) inlet hose; (2) glass tube; (3) measurement box; (4) exhaust valve; (5) outlet hose. The side view shows only the measurement box. *Corresponds to the point at which the particle-size distribution was measured.

particles per cubic centimetre leaving the nebulizer. Since some particles may not have been counted due to the optical depth of the aerosol cloud, the nebulized mass and concentration data was used to correct the measured particle number concentrations (Stapleton *et al.*, 1994).

To make the connection between the nebulizer and the pump without obtaining incorrect PDA readings due to refraction of the laser beams or receiving signal, a glass box was constructed with one corner meeting at a 70° angle as shown in Fig. 3. Since the scattering angle of the receiving optics of the PDA system was 110° away from the plane of the transmitting optics, the sides of the box were parallel with the PDA optics. The accuracy of the system was confirmed by measuring the diameter of 4.2 μm polystyrene spheres. The measured diameter was 4.25 $\pm$ 0.14 μm, which was within the 4% accuracy quoted for the PDA system.

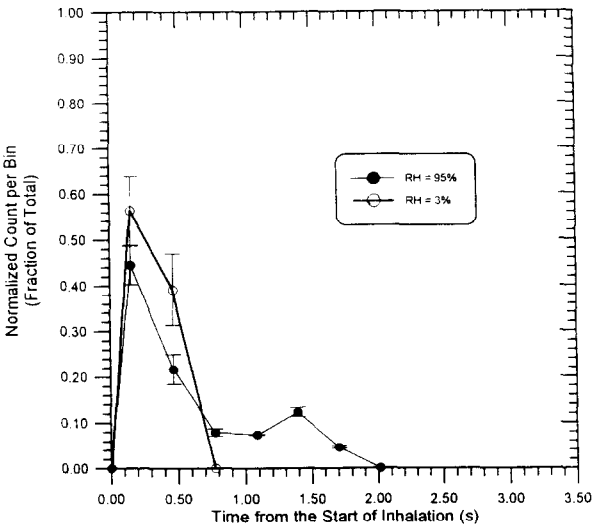

Fig. 4. The normalized particle count per temporal bin is shown as a function of time within the breathing cycle. The data was normalized by dividing by the total count for the measurement period and was averaged over the entire nebulization period. The value for each temporal bin was plotted at the midpoint of the bin. Each data point is the mean for three runs ± standard errors.

In order to examine the variation in the particle size distribution during inhalation, the data were analysed with a temporal ensemble averaging procedure. At the start of every minute of nebulization, the particles were measured over ten breathing cycles for each of three runs. Each particle was classified into temporal bins according to its arrival time. For each temporal bin, the particles were subsequently classified by diameter into 1 μm size bins to determine the associated mass median diameter (MMD) and geometric standard deviation (GSD). The temporal bin width used in this study was 0.3 s since smaller bin widths resulted in inconsistent MMDs due to an insufficient number of particles.

Figure 4 shows the number of particles leaving the nebulizer as a function of time from the beginning of inhalation. The inhalation phase of the breathing cycle occurs from 0.0 to 1.74 s in the figure. Since no particles are removed during exhalation, the particles accumulate within the nebulizer and the particle number concentration in the initial bolus is high. Once the particles that were produced during exhalation are removed, the number of particles leaving the nebulizer per unit time is equal to the rate of particle production.

Figure 5 shows that the MMD of the particles in the initial bolus is different than the remaining particles. Since the particle number concentrations vary with time, a different amount of evaporation is required per particle to come to equilibrium with the surrounding phase. Figure 6 shows the volume of the particles leaving the nebulizer during the breathing cycle. The volume contained in the initial bolus is significantly higher than the remaining portion of the cycle due to the higher particle count and larger MMD during this interval.

The variation in output during the breathing cycle can be approximated by dividing the inhalation phase of the breathing cycle into two consecutive intervals. The first interval, Interval 1, covers the first 0.6 s of the breathing cycle and consists of the particles in the initial bolus. The particles in Interval 1 are assumed to be the "true size" of the particles produced by the nebulizer; this assumption is justified in Section 2.4. The second interval, Interval 2, consists solely of particles that are produced during the period from 0.6 to 1.74 s from the start of inhalation.

As shown in Fig. 5, the particles in Interval 2 are smaller than in Interval 1 due to evaporation from the surfaces of the particles when they mix with ambient air during inhalation. At an ambient RH of 3%, the PDA system does not measure any particles in Interval 2. Since the detection limit of the PDA system is 0.5 μm, it is therefore assumed that at 3% ambient RH, the particles in Interval 2 are the dry crystals of salt and drug that

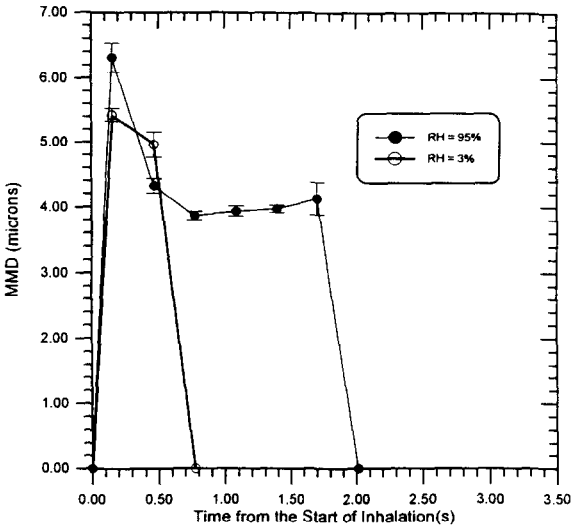

Fig. 5. The MMD of the particles measured by the PDA system is shown as a function of time within the breathing cycle. Each data point is the mean for three runs ± standard errors.

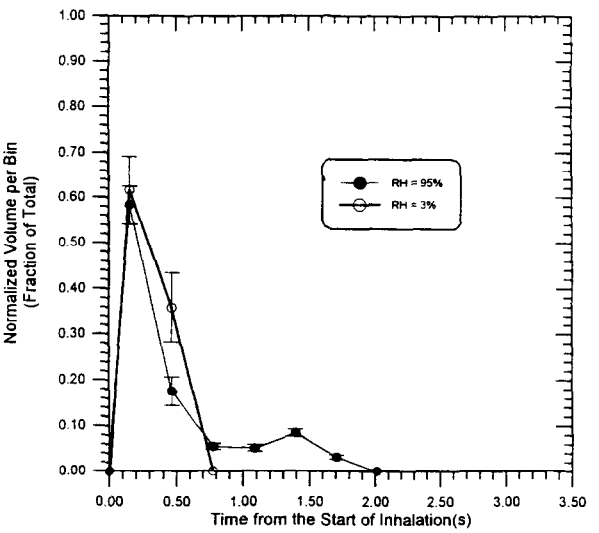

Fig. 6. The normalized volume contained within the particles per temporal bin is shown as a function of time within the breathing cycle. The data was normalized in the same manner as Fig. 3. Each data point is the mean for three runs ± standard errors.

remain when all of the water evaporates from the particles. Ferron and Soderholm (1990) showed that the time required for the size of liquid droplets considered here to evaporate completely at very low RH is on the order of 0.01 s. Therefore, the particles can be expected to evaporate prior to reaching the PDA measurement location. Since the behavior of the particles in Interval 2 is dependent on the inlet RH, separate calculation procedures were developed to determine the amount of drug leaving the nebulizer for high ambient RH versus low ambient RH.

2.1. *Calculation procedure for high ambient RH*

For a control volume consisting of the nebulizer dome, the mass leaving the nebulizer during 1 min, m, must be equal to

$$m = m_\ell + m_v + m_s, \tag{2}$$

where, for the given minute, m_ℓ is the mass of water leaving in liquid particles, m_v is the mass leaving as water vapour, and m_s is the mass leaving as dissolved solids (i.e., salt and drug) in the liquid droplets.

The variation in nebulizer output with time can be approximated by considering m_ℓ and m_s to be the sum of values associated with the two intervals described earlier, i.e.

$$m_\ell = m_{\ell 1} + m_{\ell 2}, \tag{3}$$

$$m_s = m_{s1} + m_{s2}, \tag{4}$$

where 1 and 2 refer to Interval 1 and Interval 2, respectively.

The total mass leaving the nebulizer in the minute, m, is obtained by weighing the nebulizer at the start and end of each minute. The remaining five quantities (i.e., m_v, $m_{\ell 1}$, $m_{\ell 2}$, m_{s1}, and m_{s2}) are unknown and must be calculated.

The concentration of the solution at the end of each minute, C_f, is equal to

$$C_f = \frac{\rho_\ell(m_{s,\text{initial}} - \sum m_s)}{m_{\ell,\text{initial}} - \sum m_\ell - m_v}. \tag{5}$$

Here ρ_ℓ is the density of the liquid, $m_{s,\text{initial}}$ is the known mass of solids contained in the drug nebules, and $m_{\ell,\text{initial}}$ is the known mass of liquid continued in the drug nebules. The summation is carried out from the start of the nebulization period up to the end of the current minute. By substituting equation (2) into equation (5) and noting that m_s is several orders of magnitude smaller than m_ℓ and m_v, equation (4) can be approximated as

$$C_f = \frac{\rho_\ell(m_{s,\text{initial}} - \sum m_s)}{m_{\ell,\text{initial}} - \sum m}. \tag{6}$$

Thus, the mass of solids, m_s, can be calculated by measuring m and C_f.

The particles in Interval 1 are assumed to have the same solute concentration as the average concentration remaining in the nebulizer. Stapleton and Finlay (1995) showed that this assumption is valid provided that there is minimal evaporation of the particles and sufficient recirculation of the fluid within the nebulizer. The minimal evaporation of the particles in Interval 1 is demonstrated later in Section 2.4. The fluid in the nebulizer recirculates at least five times per minute since it runs dry in about 10 s if the nebulizer dome is removed. Thus,

$$C_1 = \frac{\rho_\ell m_{s1}}{m_{\ell 1}}, \tag{7}$$

where C_1 is the measured average concentration of the nebulizer solution for the minute. Equation (7) neglects the volume of dissolved solids which is reasonable for the concentrations considered here.

A similar equation can be written for the concentration, C_2, of the liquid droplets in Interval 2:

$$C_2 = \frac{\rho_\ell m_{s2}}{m_{\ell 2}}. \tag{8}$$

However, because the particles in Interval 2 have undergone evaporation, C_2 is not known since we cannot assume that C_2 is the same as the nebulizer solution concentration. However, if the particles in Interval 2 are in equilibrium with the surrounding phase, then they must have same solute concentration. This assumption is justified later in Section 2.4.

To summarize the above discussion, the total mass leaving in the minute, m, the total mass of solids leaving in the minute, m_s, and the concentration within the particles of Interval 1, C_1, can be considered to be known. If the mass leaving as water vapour, m_v, was known, equation (2) could be used to determine m_ℓ. Using equation (3) and the ratio of $m_{\ell 1}/m_{\ell 2}$ (which is obtained by making a plot of the volume data for the current minute of nebulization in the manner of Fig. 5 and taking the ratio of the areas in Intervals 1 and 2) the values of $m_{\ell 1}$ and $m_{\ell 2}$ could be determined. Equation (7) could then be solved for the

unknown m_{s1}, and m_{s2} could be calculated from (4). Thus, all five of the required parameters (i.e., m_v, $m_{\ell 1}$, $m_{\ell 2}$, m_{s1}, and m_{s2}) would be known. Note that this calculation requires an iterative solution since the five required parameters are related by coupled nonlinear equations.

In order to determine m_v, we use the following equation:

$$m_v = (C_{w,outlet} - C_{w,inlet})(V_t)(B), \tag{9}$$

where $C_{w,inlet}$ and $C_{w,outlet}$ are the concentration of water in $g\,cm^{-3}$ in the air at the nebulizer inlet and outlet, V_t is the tidal volume, and B is the breathing frequency in cycles min^{-1}. The values of $C_{w,inlet}$ and $C_{w,outlet}$ are obtained from the empirical Antoine equation (Reid *et al.*, 1977)

$$C_w = 363.8\ RH\ e^{(-4943/T_a)}, \tag{10}$$

where T_a is the air temperature in K. The air temperature at the inlet and outlet of the nebulizer are measured with a thermocouple which is shielded to avoid particle impaction and the associated evaporative cooling. The inlet temperature is held fixed at 20°C. The inlet RH is measured with a hygrometer (Fisher Scientific, Ottawa, ON, Canada) that has a quoted accuracy of $\pm$ 3%. The outlet RH is calculated based on the assumption that the particles exiting the nebulizer are in equilibrium with the surrounding phase so that

$$RH_{outlet} = \frac{M_s/M_w - (m_s/m_w)(i-1)}{M_s/M_w + m_s/m_w}. \tag{11}$$

Here M_s is the effective value of the molecular weight of the solids, M_w is the molecular weight of water and i is the effective van't Hoff factor of the solids (Glasstone and Lewis, 1971). The van't Hoff factor accounts for the non-ideality of solute dissociation so that the molality of the solution can be calculated from the masses of solute and solvent. Note that the equilibrium RH for Intervals 1 and 2 of inhalation must be calculated separately since the concentration of salt and drug within the particles is different.

The iterative method of solving equations (7)–(11) begins by selecting an initial value of m_v and then following the procedure described above, assuming m_v to be known. The value of C_2 is calculated from equation (8) so that equation (11) can be used to calculate the equilibrium RH in this region. A new value of m_v is then calculated from equations (8) and (9) and this value is used in equation (2) to begin the next iteration. The iterative process is repeated until convergence. For a tolerance $\varepsilon = 0.001$, roughly 10 iterations were required.

2.2. *Calculation procedure for low ambient RH*

As discussed earlier, the particles in Interval 2 at the inlet RH of 3% evaporate completely. At an intermediate RH, the smallest particles may have evaporated completely while the largest particles may have only partially evaporated and the amount of drug within each particle depends on the particles size and particle trajectory.

However, if the particles do evaporate completely, $m_{\ell 2}$ is equal to zero and the conservation of mass equation for a given minute reduces to

$$m = m_{\ell 1} + m_{s1} + m_{s2} + m_v. \tag{12}$$

The total mass, m, is obtained by weighing the nebulizer at the start and end of each minute so that the unknown quantities are m_v, $m_{\ell 1}$, m_{s1}, m_{s2}.

Equations (4), (6), and (7) are still applicable at the low inlet RH. However, one more equation is required to calculate all four unknown quantities. As will be shown in Section 3.1, the dead volume remaining in the nebulizer is the same for both inlet humidities. We assume that the particles exiting the nebulizer in Interval 2 evaporate completely at the low inlet RH and that the rate of particle production by the nebulizer is independent of the inlet RH. Therefore, the mass of water vapour at the 3% inlet RT would be approximately equal to the sum of the water vapour present in the air for the 95% inlet RH plus the water

content of the particles in Interval 2 that evaporate completely:

$$(m_{v,\text{total}})|_{RH=3\%} \approx (m_{v,\text{total}} + m_{\ell 2,\text{ total}})|_{RH=95\%}. \tag{13}$$

Here the subscript *total* denotes the total value leaving over the entire nebulization period. To determine the mass of water vapour leaving the nebulizer in a given minute, equation (13) is scaled by the mass m leaving in the given minute, i.e.:

$$m_v = \left(\frac{m}{m_{\text{total}}}\right) m_{v,\text{total}}, \tag{14}$$

where all values in equation (14) are for the inlet RH of 3%. Unlike the high humidity case, iteration is not necessary to determine the unknown quantities.

Since the detection limit of the PDA system is 0.5 μm, the diameters of the evaporated particles in Interval 2 are too small to be measured (see Fig. 3) and are therefore calculated. This was accomplished by assuming that the particles in the measured size distribution of Interval 1 evaporate completely. If the volume of the solute in the particles in Interval 1 is ignored, the diameter of a particle in Interval 2 is equal to

$$d_2 = \left(\frac{C_{\text{salt}}}{\rho_{\text{salt}}}\right)^{1/3} d_1, \tag{15}$$

where C_{salt} is the concentration of salt in the particles in Interval 1, ρ_{salt} is the density of the salt, and d_1 and d_2 are the diameters in Intervals 1 and 2, respectively.

2.3. *Deposition model*

Once the above calculations are completed, the amount of drug within each particle is known for both regions. The particle sizes measured by the PDA system are assigned to the appropriate interval by the particle arrival time and the size distribution for the dry crystals at the low inlet humidity are computed. This data is then input into the numerical lung deposition model of Stapleton *et al.* (1994), including the modifications of Finlay and Stapleton (1995) and the non-ideal solution behaviour of Cinkotai (1971) for the NaCl component of the vapour pressure reduction.

Briefly, the numerical model uses the Weibel A lung (scaled for a TLC of 3000 cm^3) for the geometry of the respiratory tract with an additional extrathoracic region to model the mouth, larynx, and pharynx. The hygroscopic growth of the aerosol particles is computed at each generation of the lung by solving the equations governing the coupled heat and mass transfer between the aerosol particles and the surrounding continuous phase. Unlike previous models, this deposition model accounts for the effects of the droplet evaporation and condensation on the humidity and temperature of the air in the airways. The importance of accounting for these effects is demonstrated by Finlay and Stapleton (1995) and Eisner *et al.* (1990).

At each generation of the lung, each particle is assumed to travel at the mean flow velocity. The hygroscopic change in size of a particle is computed from the rate of mass transfer due to the diffusion of water, which is governed by the difference in vapour pressure of the particle solution and the surrounding air (cf. Ferron and Soderholm, 1990). The change in temperature of a particle is computed from the rate of latent heat transfer due to the hygroscopic change in size and the rate of conduction between the particles and the surroundings (cf. Ferron and Soderholm, 1990).

The probability of deposition for each particle size due to impaction, sedimentation, and diffusion are calculated to determine the fraction of particles that deposit in the current lung generation. The deposition probabilities are calculated from the semi-empirical equations for a stable particle given by Ferron *et al.* (1988), with the extrathoracic deposition probabilities given by Rudolf *et al.* (1990) and James *et al.* (1991). These equations are summarized by Stapleton *et al.* (1994).

2.4. *Validation of the assumptions*

Two assumptions are made in the above methodology which clearly require justification:

(1) the particles are in equilibrium with the surrounding phase upon exiting the nebulizer; and

(2) the particles in the initial bolus associated with Interval 1 have not evaporated significantly.

If assumption (1) is true, the diameters of the particles should be independent of time once they have exited the nebulizer. The sizes of particles were measured with and without a 22 cm glass tube extension between the nebulizer and the measurement point and a Student's t-test was used to compare the two distributions. The results of the comparison are summarized in Table 1. They show that there is no statistically significant difference between the two distributions which indicates that the particles are in equilibrium with the surrounding air.

Assumption (2) (i.e. that the particles in Interval 1 have not evaporated significantly) was validated by comparing the particle-size distributions in Interval 1 for 3% inlet RH versus 95% inlet RH. The MMD and geometric standard deviation (GSD) of all the particles in Intervals 1 and 2 are summarized in Table 2. The data for Interval 2 at the inlet RH of 3% was obtained by performing the calculations outlined above. Since this comparison yielded a p-value of 0.897, we can conclude that the sizes of the particles in Interval 1 are independent of the inlet RH.

Additional validation of both of the assumptions was completed by calculating the equilibrium particle sizes at the inlet RH of 95% with the computer model of Finlay and Stapleton (1995). During stabilization, a particle in Interval 1 with an initial size equal to the MMD in this interval shrinks to 99.4% of its initial size, while a particle with an initial size of the Interval 2 MMD shrinks to 95.8% of its initial size. These amounts of particle shrinkage are significantly smaller than those calculated for a single particle by Ferron and Soderholm (1990) because of the particles' influence on the surrounding RH and the large number of particles per unit volume. Consequently, the amount of evaporation per particle is so small that the particles are essentially at equilibrium when they are produced and the amount of particle shrinkage in Interval 1 is negligible.

Table 1. p-Values for comparing the particle-size distributions with and without a 22 cm extension tube are shown for each minute of nebulizer

Time (min)	Inlet RH = 3%	Inlet RH = 95%
1	0.963	0.877
2	0.864	0.925
3	0.798	0.962
4	0.936	0.989
5	0.971	0.917
6	0.910	0.853
7	—	0.759
8	—	0.786

Table 2. The MMD and GSD are shown for each interval of the breathing cycle for the inlet RH of 3 and 95%

Interval	MMD (μm)	GSD
Interval 1, RH = 3%	5.198 ± 0.231	1.727 ± 0.038
Interval 2, RH = 3%	0.915 ± 0.015	1.721 ± 0.021
Interval 1, RH = 95%	5.324 ± 0.232	1.805 ± 0.049
Interval 2, RH = 95%	3.978 ± 0.266	1.700 ± 0.117

Note: All particles within each interval were pooled and the MMD and GSD were calculated for the interval distribution. The values are the means for three runs of 10 breathing cycles ± standard error.

3. RESULTS

3.1. *Nebulizer output*

The values obtained from the calculation procedures outlined in the methodology are summarized in Table 3.

3.2. *Variation of the particle-size distribution over the nebulization period*

Although the nebulizer output varies during a breathing cycle, it was found to vary little from one minute to the next during the nebulization period. In particular, at each inlet RH, when the particle-size distributions were averaged over the entire nebulization period and the size distribution for each minute was then compared to this average distribution, no statistically significant variation was found. At an inlet RH of 3%, the average p-value was 0.879 ± 0.023 and 0.897 ± 0.025 at an inlet RH of 95%.

3.3. *Inter-nebulizer variation of nebulizer output*

A comparison of three different units was made to evaluate the variation in inter-nebulizer performance. Three runs were completed for each unit and the particle-size distribution and nebulized mass was compared. The data are summarized in Table 4. No statistically significant variation in performance was found: the average p-value for the particle-size distribution comparison was 0.901 ± 0.021 and the average p-value for the total nebulized mass comparison was 0.392 ± 0.060.

3.4. *Regional dosages*

The dosage of salbutamol sulphate delivered to the extrathoracic, bronchial, and pulmonary regions of the respiratory tract are summarized in Table 5.

Table 3. A summary of the calculations

Quantity	Inlet RH = 3%	Inlet RH = 95%
Nebulization period (min)	6	8
m_{total} (g)	1.41 ± 0.018	1.38 ± 0.0358
$m_{\ell 1,total}$ (g)	0.607 ± 0.053	0.596 ± 0.251
$m_{\ell 2,total}$ (g)	—	0.218 ± 0.092
$m_{s1,total}$ (mg)	7.48 ± 0.651	6.63 ± 1.59
$m_{s2,total}$ (mg)	0.910 ± 0.111	3.71 ± 1.25
$m_{v,total}$ (g)	0.794 ± 0.078	0.565 ± 0.052
Outlet RH_1	$99.3\% \pm 0.030\%$	$99.4\% \pm 0.017\%$
Outlet RH_2	$43.0\% \pm 1.50\%$	$98.7\% \pm 0.452\%$
T_{final} (°C)	17.2 ± 0.8	22.8 ± 0.068
C_{final} (Relative to initial)	1.52 ± 0.037	1.31 ± 0.014
C_2/C_1	—	1.50 ± 0.136

Note: The subscript *total* denotes the total values over the nebulization period and the subscript *final* denotes the value obtained during the final minute of the nebulization period. The values are the means for three runs of 10 breathing cycles ± standard error.

Table 4. The nebulized mass and particles sizes obtained from three different units

	Unit 1	Unit 2	Unit 3
MMD (μm)	5.057 ± 0.054	5.360 ± 0.072	5.231 ± 0.092
GSD (μm)	1.750 ± 0.040	1.738 ± 0.018	1.758 ± 0.020
m_{total} (g)	1.41 ± 0.018	1.38 ± 0.012	1.34 ± 0.020

The particle sizes are the averages over the nebulization period and the masses are the total masses leaving the nebulizer over the nebulization period. Each unit was tested three times.

Table 5. Dosages of salbutamol sulphate delivered to the three regions of the respiratory tract

Dosage	Inlet RH = 3%	Inlet RH = 95%
Extrathoracic (mg)	0.39 ± 0.04	0.42 ± 0.06
Bronchial (mg)	0.097 ± 0.01	0.10 ± 0.02
Pulmonary (mg)	0.22 ± 0.03	0.22 ± 0.05
Total (mg)	0.71 ± 0.08	0.74 ± 0.13

4. DISCUSSION

4.1. *Nebulizer output*

There are several interesting results to note from Table 3. Although the nebulization times were different for the two humidities, the total mass nebulized is approximately the same. The final concentration of the nebulizer solution at the inlet RH of 95% is less than the value at the inlet RH of 3%. Therefore, since the dead volumes are roughly equal, the total mass of solids leaving the nebulizer must be different. As shown in Table 3, the total mass of solids leaving the nebulizer, $m_{s,total}$, is indeed greater for the inlet RH of 95%. Since the concentration of the particles in Interval 1 were assumed to be the same as the nebulizer solution, and $m_{\ell 1}$ is independent of inlet RH, the value of m_{s1} is lower at the 95% inlet RH. However, the value of m_{s2} is much higher at 95% inlet RH versus the inlet RH of 3%. A possible reason for this difference in m_{s2} between the two humidities is that the dry particles in Interval 2 at the low inlet RH become entrained in eddies within the nebulizer dome during inhalation so that fewer particles leave the nebulizer. Because the liquid droplets in Interval 2 at the high inlet RH have a much higher inertia, they may be less readily trapped in eddies in the nebulizer dome. This preferential concentration of certain particle size ranges in large-scale turbulent structures (i.e. eddies) is well-documented (Eaton and Fessler, 1994). Such a phenomenon may account for the fact that the mass of solids leaving the nebulizer in Interval 2 is higher for the droplets at 95% RH than for the dry crystals at 3% RH.

At the inlet RH of 95%, the temperature of the air exiting the nebulizer during the final minute is 2.8°C higher than the inlet temperature, while at the inlet RH of 3%, the exiting air temperature during the final minute of nebulization is 1.8°C lower than the inlet air temperature. The solution in the nebulizer is warmed by the action of the piezoelectric crystal, which in turn warms the outlet air. However, at very low RH, the amount of evaporation from the particles is sufficient to offset this warming, and the outlet air temperature decreases.

Note that there is a significant amount of mass leaving the nebulizer as water vapour. Riedler and Robertson (1994) studied the effect of tidal volume on the output of an ultrasonic nebulizer and found that the output increased linearly with tidal volume. However, they assumed that all mass left the nebulizer as aerosol particles. The increase in output may have been due to an increase in the amount of evaporation from the increase in tidal volume. Similarly, Dennis *et al.* (1990) came to the conclusion that all of the mass left the ultrasonic nebulizer as aerosol particles. However, they did not simulate tidal breathing to remove the particles from the nebulizer. Their study is roughly equivalent to analysing Interval 1 only of this study.

4.2. *Variation of delivered dosage with inlet RH*

From Table 4, it can be seen that the regional dosages obtained with the Aerosonic nebulizer are virtually independent of the inlet RH. Prokop *et al.* (1994) studied the influence of the inlet RH on the DeVilbiss Pulmo-Neb jet nebulizer and found that the regional dosages could vary by as much as 100% over the same range of inlet RH.

Therefore, this ultrasonic nebulizer is a more reliable method of obtaining a humidity-independent dosage of drug to the lungs.

The highest humidity used in this study was 95%. For drugs dissolved in isotonic saline solution and tested at humidities higher than 95%, the particles in Interval 2 can be expected to grow rather than shrink. Furthermore, since particle stabilization time increases with RH (Ferron and Soderholm, 1990) the particles may not be in equilibrium with their surroundings when they exit the nebulizer. Therefore, the procedures outlined here may not be applicable for humidities greater than about 95%.

The present computer model uses the typical geometry of the lungs of a normal subject to calculate the dosages. It may be possible to use the same methodology to calculate the dosages delivered to diseased lungs by incorporating the associated changes in airway geometry when computing the deposition probabilities.

4.3. *Comparison of delivered dosage with a jet nebulizer*

Stapleton *et al.* (1994) showed that for a DeVilbiss Pulmo-Neb jet nebulizer running Ventolin nebules with a tapping protocol, 0.352 mg of drug is delivered to the respiratory tract at 26% RH and 23°C. This value is about half the values obtained in this study for the Aerosonic nebulizer. (The regional dosages obtained with the two types of nebulizers are different since the MMD of the aerosol obtained with the jet nebulizer was roughly twice that of the ultrasonic nebulizer.) The difference in total dosage can be explained by considering the ways these types of nebulizers perform during exhalation phase of the breathing cycle. Both types of nebulizer produce aerosol particles constantly. During exhalation with the usual jet nebulizer, the particles simply exit the nebulizer to the surroundings. During exhalation on the Aerosonic nebulizer, the patient either removes the mouthpiece from the mouth or the air is blown out through an exhaust valve in the mouthpiece if the patient maintains contact with the mouthpiece. Meanwhile, the generated aerosol particles accumulate within the nebulizer dome. Since the exhalation phase is about 43% of the total breathing cycle, this accounts for the large difference in drug delivery for the two types of nebulizers. It is reasonable to expect similar improvements in total dosage for any nebulizer that is equipped with inlet and outlet valves.

4.4. *Effect of dividing the inhalation phase into two intervals*

Another set of calculations were performed to determine the importance of dividing up the inhalation phase of the breathing cycle. The dosage of drug was calculated without separating the measured particles into the temporal bins and without dividing them into Intervals 1 and 2. In addition, the mass of solids leaving the nebulizer was evenly distributed among all of the particles measured by the PDA. This is equivalent to using the procedure for jet nebulizers developed by Stapleton *et al.* (1994). The regional dosages calculated in this manner were found to differ by no more than 10% from the results obtained by properly accounting for the temporal variation in the nebulizer output described in Section 2.

This result is somewhat surprising. However, it can be explained by noting that at the inlet RH of 3%, only 11% of the total amount of drug leaves the nebulizer in Interval 2 of the inhalation phase of the breathing cycle. Thus, although the jet nebulizer procedure of Stapleton *et al.* (1994) neglects these particles when used here, this does not have a significant effect on the predicted dosage. At the inlet RH of 95%, the two methods produce similar results because the particle MMDs differ by only 25% between Intervals 1 and 2 and the solution concentrations differ by 50%; thus the particles from the two regions do not undergo significant hygroscopic growth or shrinkage, and so they deposit in similar regions. If the particles had shrunk more significantly, the MMDs of the particles would have been significantly different, which would have caused a large difference in the deposition probabilities and the regional dosages. This difference would be compounded by the fact that the

difference in solution concentration would have been more significant, leading to different rates of hygroscopic growth in the respiratory tract.

Once the calculations are performed to determine the amount of mass leaving as dry crystals at low inlet RH and to calculate the degree of particle shrinkage at high inlet RH, one can determine if the division into the two regions is necessary. However, we know of no *a priori* method to determine if division of the inhalation phase into the regions is necessary.

5. CONCLUSIONS

The output from an ultrasonic nebulizer varies during the breathing cycle. This variation can be approximated by dividing the inhalation phase of the breathing cycle into two regions. Different calculation procedures are needed for the two cases of inlet RH considered (3 and 95%) to determine regional dosages *in vitro* using the lung deposition model of Stapleton *et al.* (1994) with the modifications of Finlay and Stapleton (1995). At a high inlet RH, the calculations account for the shrinkage of the particles due to inhalation of ambient air. At very low RH, the particles evaporate completely and leave the nebulizer as dry crystals of salt and drug.

The results show that the total dosage delivered by the ultrasonic nebulizer is approximately 50% higher than the dosage delivered by the DeVilbiss Pulmo-Neb jet nebulizer. Classical jet nebulizers lose drug from the mouthpiece during exhalation while no drug leaves an ultrasonic nebulizer during exhalation due to the inlet and outlet valves on the mouthpiece. The regional dosages are different due to a large difference in MMD between the two nebulizers. The calculation procedure used to examine the ultrasonic nebulizer used in this study might also be applied to other nebulizers that are equipped with inlet and outlet valves.

For the ultrasonic nebulizer used in this study, the predicted dosages are approximately the same whether or not the effects of temporal variation in output are included. At low inlet RH, this is explained for the Aerosonic nebulizer by the fact that only a small amount of mass leaves the nebulizer as dry salt/drug crystals so neglecting these particles does not introduce a significant error. At high inlet RH, this is due to the small amount of particle shrinkage for the Aerosonic nebulizer.

The predicted regional dosages of the Aerosonic nebulizer vary by less than 8% between the two extremes of 3 and 95% ambient RH. This is far less variation than that seen with the DeVilbiss Pulmo-Neb jet nebulizer, which varies by up to 100% in regional dosages delivered at these two humidities (Prokop *et al.*, 1994). This indicates that the ultrasonic nebulizer is a more reliable way of providing nearly humidity independent regional dosages.

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