Pergamon

J. Aerosol Sci., Vol. 26, No. 1, pp. 137–145, 1995
Elsevier Science Ltd
Printed in Great Britain

0021-8502(94)E0070-E

DETERMINING SOLUTION CONCENTRATION WITHIN AEROSOL DROPLETS OUTPUT BY JET NEBULIZERS

K. W. Stapleton and W. H. Finlay

Department of Mechanical Engineering, Rm. 4-9, Mechanical Engineering Bldg., University of Alberta, Edmonton, Alberta, Canada T6G 2G8

(*First received* 30 *August* 1993; *and in final form* 28 *March* 1994)

Abstract—The concentration of the solution within aerosol droplets exiting a jet nebulizer is determined by applying a control volume analysis to the air, water, and solute transport through the nebulizer. Measurements and calculations are made for the DeVilbiss Pulmo-Neb® disposable nebulizer delivering two unit dose nebules of Ventolin® (2.5 ml, 1 mg ml^{-1} salbutamol sulphate, 0.9% saline), and it is shown that the droplet solution concentration is closely approximated by the concentration of the solution remaining in the nebulizer's reservoir. By increasing the time the aerosol droplets have before contacting the ambient environment, it is shown that the droplets are in equilibrium as they exit the nebulizer, and therefore the concentration of the solution in the droplets is independent of droplet size.

INTRODUCTION

Recent models have made it possible to provide *in vitro* estimates of the deposition of hygroscopic aerosol droplets in the human respiratory tract (Martonen *et al.*, 1982; Persons *et al.*, 1987; Ferron *et al.*, 1988a, b). For an aerosol with predetermined size distribution, water and solute content, and solute chemistry, these models are in good agreement with experimental deposition data, and provide an expedient way of predicting the regional deposition of an aerosol (Stapleton *et al.*, 1994).

To use a hygroscopic deposition model to predict the dosage of medication delivered by a nebulizer to the respiratory tract, the size distribution and solution concentration within the aerosol droplets at the exit of the nebulizer are required. The size distribution and concentration measurements are input into the deposition model, and the aerosol growth and deposition can then be calculated as the aerosol moves through the respiratory tract (Stapleton *et al.*, 1994).

The output characteristics of jet nebulizers such as aerosol size distribution, nebulizer solution temperature, nebulizer solution concentration, and nebulization rate have been reviewed in the literature (Mercer *et al.*, 1968; Mercer, 1981; Clay *et al.*, 1983; Sterk *et al.*, 1984; Phipps and Gonda, 1990; Smye *et al.*, 1992; Langford and Allen, 1993) and statistical models of nebulizer performance have been presented (Smye *et al.*, 1991). However, the solution concentration of the aerosol droplets cannot be measured directly, and to the authors' knowledge, no procedure for determining droplet solution concentration for jet nebulizers has been reported. The goal of this paper is to provide such a methodology to facilitate the use of *in vitro* deposition models for predicting the regional deposition of aerosols produced by jet nebulizers.

THEORY

Conservation of mass dictates that during a given time period t, the change in mass of the solution in the nebulizer is given by

$$\Delta m_{neb} = m_{out} - m_{in}, \tag{1}$$

where m_{neb} is the mass of solution in the nebulizer, m_{in} is the mass of water vapour entering the nebulizer during time t, and m_{out} is the total mass leaving the nebulizer during time t and

is given by

$$m_{out} = m_s + m_l + m_v, \tag{2}$$

where m_s is the mass lost as solute, m_l is the mass lost as liquid water, and m_v is the mass lost as water vapour.

In equation (1), the change in total mass of solution in the nebulizer m_{neb} is easily measured by weighing the nebulizer during the nebulization session. The mass of water vapour entering the nebulizer m_{in} can be calculated knowing the temperature and relative humidity of the air with the equation

$$m_{in} = c_{w,in} Qt. \tag{3}$$

Here Q is the air flow rate through the nebulizer, and $c_{w,in}$ is the water vapour concentration in the air entering the nebulizer. The concentration of water vapour c_w is given by the Antoine equation (Reid *et al.*, 1977)

$$c_w = \mathrm{RH} \cdot 363.8 \exp\left(\frac{-4943}{273.15 + T_a}\right), \tag{4}$$

where T_a is the air temperature in Celsius, RH is the relative humidity of the air, and c_w is given in g/cm^3. To calculate $c_{w,in}$, the temperature and relative humidity of the ambient air entering the nebulizer are used in equation (4).

In equation (2), m_s is measured by collecting the aerosol droplets on a filter, then drying and weighing the collected solids; m_v is calculated in a similar way as m_{in}, but using the dry bulb temperature of the aerosol leaving the nebulizer as discussed in the next section.

Equations (1) and (2) can then be solved for m_l and the average solution concentration in the droplets c_{sp} is then given by

$$c_{sp} = \frac{m_s}{\left(\frac{(m_s + m_l)}{\rho}\right)}, \tag{5}$$

where ρ is the density of the solution and is given by (Ferron, 1977)

$$\rho = \frac{m_w + m_s}{m_w + \left(\frac{m_s}{\rho_s}\right)}, \tag{6}$$

where ρ_s is the density of the solid. For the Ventolin® solution tested here, the density of the solid ρ_s has been calculated as 2.07 g ml^{-1} (Stapleton *et al.*, 1994). The density of the solution varies between 1.0035 g ml^{-1} for a 0.01 g ml^{-1} solution of Ventolin® to 1.0043 g ml^{-1} for a solution that is 50% more concentrated. A constant value of 1.004 g ml^{-1} is assumed here to allow equations (1)–(5) to be solved without an iterative method.

Evaporation rates and stabilization times for hygroscopic droplets are strongly dependant on droplet size (Ferron and Soderholm, 1990), with smaller droplets having higher evaporation rates and shorter stabilization times. In a heterodisperse aerosol, this means the smaller droplets would have a different concentration than the larger droplets. However, droplets greater than approximately 1 μm in diameter will all have the same concentration if they are in equilibrium with their environment. This follows from the fact that an aerosol droplet is in equilibrium with its environment when the following equilibrium condition is satisfied (Morrow, 1986)

$$\mathrm{RH} = C_K C_R, \tag{7}$$

where RH is the relative humidity of the surrounding air, C_K is the Kelvin correction for surface curvature, and C_R is the vapour pressure reduction due to dissolved solids (Raoult's Law). For droplets greater than approximately 1 μm in size, the Kelvin correction causes

changes in the droplet size of less than 0.1% and can be neglected (Morrow, 1986). The equilibrium condition then becomes

$$\mathrm{RH} = C_{\mathrm{R}} = \frac{n_{\mathrm{w}}}{n_{\mathrm{w}} + i n_{\mathrm{s}}}, \tag{8}$$

where n_{w} is the number of water molecules in the droplet, n_{s} is the number of solute molecules in the droplet, and i is the van't Hoff factor of the solute. There is no dependence on droplet diameter in equation (8), so if the aerosol is in equilibrium with the environment, the solution concentration in all droplets larger than approximately 1 μm in diameter will be the same.

Whether the aerosol droplets are in equilibrium can be checked by adding lengths of tubes to the nebulizer and measuring the aerosol size distribution at several distances from the outlet, thus allowing the aerosol different amounts of time to come to equilibrium before the size distributions are measured. If the size distribution does not change after different times from the nebulizer exit, then the aerosol droplets are in equilibrium, or their rate of change is too slow to be measured. The distributions are compared using an augmented Student's-t test (Shen and Ring, 1986).

EXPERIMENTAL PROCEDURE

We have applied this methodology to the DeVilbiss Pulmo-Neb® disposable nebulizer, driven by a DeVilbiss Pulmo-Aide® compressor (model 5610C, DeVilbiss Health Care (Canada) Inc., Barrie, ON, Canada) delivering two unit dose nebules (5 ml of solution). Each Ventolin® nebule (DIN 00897345, Glaxo Canada Inc., Mississauga, ON, Canada) contains 2.5 mg of salbutamol sulphate dissolved in 2.5 ml of normal saline (0.9% NaCl). Ambient laboratory conditions during data collection were 23.0 $\pm$ 0.2°C and 25.0 $\pm$ 2.5% relative humidity. The flow rate through the nebulizer was measured as 6.6 $\pm$ 0.1 l min^{-1}. Alvine *et al.* (1992) showed that disposable nebulizers can have significant performance variations from one unit to the next, so a random sample of nebulizers was used to give a statistical sample of performance at each data point. All nebulizers used in this study are from the same lot number.

To determine if the droplets are in equilibrium with the air exiting the nebulizer, the output distributions of eight nebulizers were measured using a phase Doppler anemometer (Dantec Electronics Inc., Mahwah, NJ, U.S.A.) with four different lengths of plastic tubes (5, 10, 15, and 20 cm in length, inside diameter 1.87 cm) attached vertically to the opening of the nebulizer (Fig. 1). The 20 cm extension gives the aerosol approximately 2 s of time beyond the nebulizer exit for the aerosol to reach equilibrium. Each nebulizer was measured without an extension, then with each extension added. The distributions measured with the extensions were then compared to the distribution from the same nebulizer with no extension. The results were then averaged over the eight nebulizers, and are presented in

Table 1. Average P-values for nebulizer output distributions

Tube length (cm)	Average P-value (vs no tube)
5	0.88 $\pm$ 0.02
10	0.91 $\pm$ 0.03
15	0.89 $\pm$ 0.03
20	0.89 $\pm$ 0.03

Note: Average values from the augmented Student's-t test comparing the output distributions with attached tubes with the output distributions with no tubes. All values are mean $\pm$ standard error.

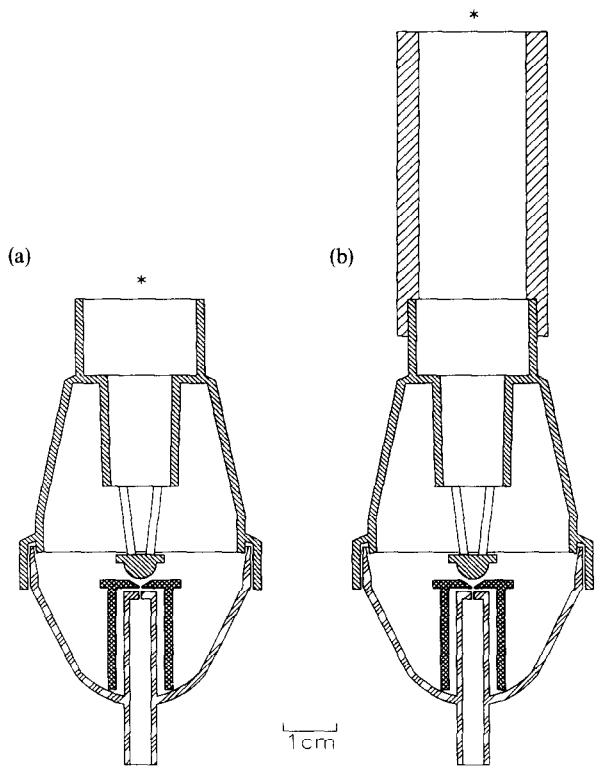

Fig. 1. A schematic representation of the DeVilbiss Pulmoneb® nebulizer with no extension (a), and with attached 5 cm extension (b) for testing. The asterisk (*) indicates the location of the measuring point.

Table 1. With no tube attached, the average mass median diameter of the measurements was 9.2 ± 0.2 μm, and the geometric standard deviation was 1.64 ± 0.01.

At a 5% level of significance, two distributions are said to be different if $P < 0.05$, which is much lower than the P-values obtained here. Figure 2 compares two droplet size distributions with $P = 0.88$. The consistency of the results indicates that the droplet size distributions do not change with increased tube length. Ferron and Soderholm (1990) estimate that the time required for a single pure water droplet with a size equal to the MMD of the distribution measured here to reach equilibrium with 99.5% air is approximately 20 s. Approximately the same time is required for a single solid salt particle to absorb water and become isotonic. However in the present case, the equilibrium relative humidity of the droplets being produced is so close to the relative humidity output by the nebulizer, that the droplets need to change size only a little to reach equilibrium with the surrounding air. Thus, their stabilization times are much shorter than that for the evaporation of a pure water droplet, or the stabilization of a solid salt particle. Eisner *et al.* (1990) predict stabilization times of a few tenths of seconds for aerosols with similar properties to those here.

To calculate the concentration of the droplet solution, a nebulizer was weighed after the addition of the Ventolin® nebules, then run for 1 min, during which all droplets exiting the nebulizer were collected on a filter (Watman EPM2000) that collects 99.997% of particles > 0.3 μm (Fig. 3). At the end of the minute, the nebulizer was reweighed, then a 50 μl sample of the remaining nebulizer solution was removed to measure the solute concentration by freezing point osmometry (model 5004, Precision Systems Inc., Natick, MA, U.S.A.).

For the second minute, the nebulizer was first weighed, run for a minute during which the droplets are again collected on a filter, weighed again, and another sample removed for concentration measurement. This procedure was repeated until the nebulizer began to operate intermittently. The results of these measurements are shown in Table 2. Data were not collected while the nebulizer operated intermittently. When the nebulizer is not running

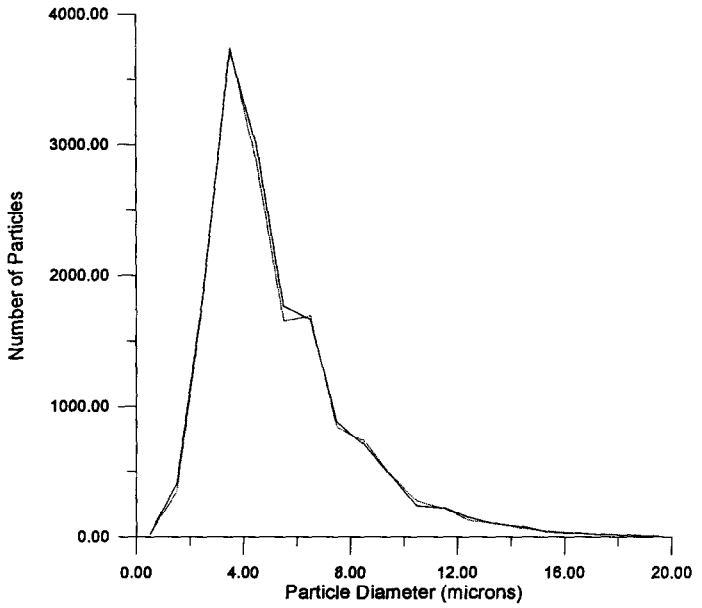

Fig. 2. Two aerosol distributions measured in the study with $P=0.88$ when compared with an augmented Student's-t test. The MMDs of the distributions are 9.6 ± 0.2 and 9.8 ± 0.2 μm.

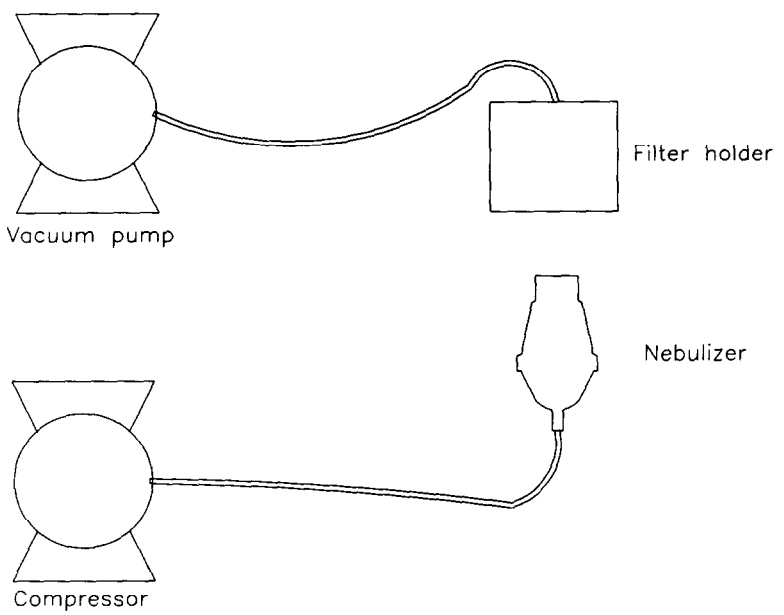

Fig. 3. A schematic of the experimental setup. The nebulizer is driven by the compressor using ambient laboratory air. Output of the nebulizer is collected on a filter for analysis.

continuously, there is no droplet production and no evaporation from the droplets, so the output water vapour content is no longer a simple function of time (cf. equation (10)).

The temperature of the air leaving the nebulizer was measured with a thermocouple in the jet exiting the airflow and protected from droplet impaction by a small plastic shield, and was found to have an exponential character. Figure 4 shows the data and the function

$$T_a = 18.5 + 5.5\exp(-1.29 \cdot t), \tag{9}$$

Table 2. Nebulizer output characteristics

Data minute	Δm_{neb} (g)	m_s (mg)	Concentration (mg ml^{-1})
1	0.302 ± 0.004	2.15 ± 0.08	10.21 ± 0.04
2	0.282 ± 0.007	2.10 ± 0.06	10.26 ± 0.03
3	0.267 ± 0.006	2.03 ± 0.07	10.41 ± 0.04
4	0.278 ± 0.004	2.18 ± 0.03	10.61 ± 0.05
5	0.276 ± 0.002	2.18 ± 0.01	10.79 ± 0.07
6	0.259 ± 0.005	2.05 ± 0.06	11.01 ± 0.04
7	0.265 ± 0.002	2.20 ± 0.02	11.28 ± 0.04

Note: The table gives the total mass Δm_{neb} leaving the nebulizer during each minute, the mass of solids m_s collected on the filter during each minute, and the measured concentration of solute in the nebulizer solution at the end of each minute, for an initial volume of 5.0 ml in the nebulizer. All values are mean ± standard error.

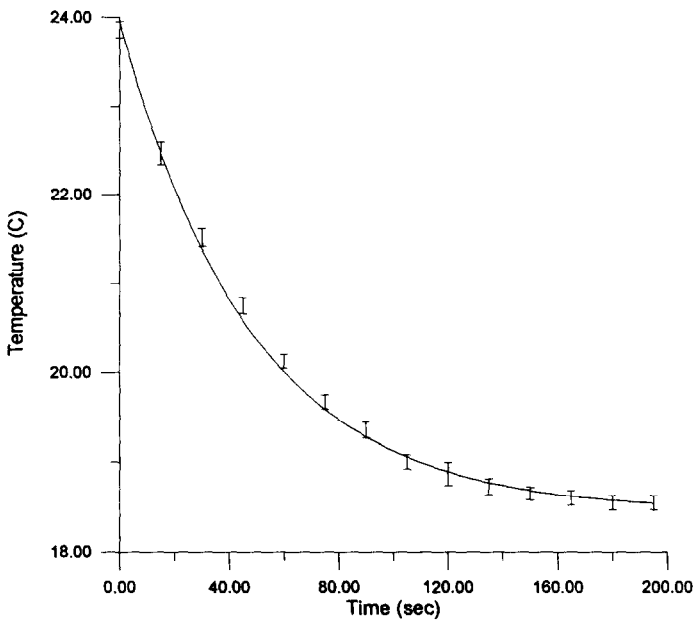

Fig. 4. Temperature of the air exiting the nebulizer, and the exponential approximation given by equation (9).

where t is the time in minutes. This equation is substituted into the Antoine equation (4) to give an equation for the output concentration of water vapour $c_{w,out}$ as a function of time. The output relative humidity of medical nebulizers delivering isotonic solutions has been estimated as greater than 99% (Ferron and Gebhart, 1988b). Since we have found that the droplets are in equilibrium upon exiting the nebulizer, we can use equation (8) to give us the relative humidity of the air exiting the nebulizer. The initial concentration of the nebule solution gives an equilibrium relative humidity of 99.48%, and a value of 99.41% is obtained for a solution concentration 10% greater than the initial concentration. Thus, the change in solution concentration during nebulization has little effect on the output relative humidity, and a relative humidity of 99.4% is used. Substituting equation (9) into equation (4) with a relative humidity of 99.4% gives

$$c_{w,out} = 361.6\exp\left(\frac{-4943}{291.65 + 5.5\exp(-1.29\cdot t)}\right). \quad (10)$$

Equation (10) is then multiplied by the flow rate of air out of the nebulizer to convert the

Table 3. Comparison of droplet solution concentration and nebulizer solution concentration

Minute	Calculate average droplet concentration ($mg\,ml^{-1}$)	Measured nebulizer solution concentration ($mg\,ml^{-1}$)
1	10.2 ± 0.4	10.21 ± 0.04
2	10.2 ± 0.5	10.26 ± 0.03
3	10.4 ± 0.5	10.41 ± 0.04
4	10.5 ± 0.4	10.61 ± 0.05
5	10.6 ± 0.2	10.79 ± 0.07
6	10.9 ± 0.4	11.01 ± 0.04
7	11.3 ± 0.3	11.28 ± 0.04

Note: The calculated average concentration of the solution in the droplets over 1 min of nebulizer operation compared to the concentration of the nebulizer solution measured at the end of the minute for an initial concentration of the nebulizer solution of 10.0 $mg\,ml^{-1}$ salbutamol sulphate, and 9.0 $mg\,ml^{-1}$ NaCl).

units to $g\,s^{-1}$, and integrated numerically to give the total amount of water vapour leaving the nebulizer in a given time period.

Integrating equation (10), the amount of water leaving the nebulizer as vapour during the first minute of operation is 0.124 ± 0.002 g, so that from Table 2 and equations (1) and (2) we find the amount of solution leaving the nebulizer is $m_l + m_s = 0.212 \pm 0.005$ g. The average concentration of the solution in the droplets is then calculated by equation (5)

$$c_{sp} = \frac{0.00215 \pm 0.00008}{\left(\frac{(0.212 \pm 0.005)}{1.004}\right)} = 0.0102 \pm 0.0004 \frac{g}{ml}.$$

Values for the other minutes of nebulizer operation are given in Table 3. In each minute, the average solution concentration within the droplets is within 2% of the concentration measured in the nebulizer solution at the end of the minute.

DISCUSSION

During the operation of a jet nebulizer, the number of droplets per cm^3 inside the nebulizer is high, and it has been estimated that more than 99% of the droplets are returned to the reservoir (Mercer *et al.*, 1968; Smye *et al.*, 1991). Due to the high droplet number concentration, the amount of water that must evaporate from or condense onto each droplet is small, and thus the length of time needed for the droplets to come into equilibrium with the air in the nebulizer is short. In addition, due to the relatively small change in particle size, the concentration of the solution in the particle increases only slightly as the particle moves from the point at which it is formed in the venturi at a concentration equal to the concentration of the nebulizer solution, to the point at which it is in equilibrium with the surrounding air. Therefore, at a given point in time, the reservoir solution concentration will be slightly different than the concentration of the droplet solution, but the concentration within the droplets will remain close to the concentration in the nebulizer reservoir, and both concentrations will increase at approximately the same rate. This is seen in our results above in which the droplet solution concentration *averaged* over each minute is equal to the measured nebulizer solution concentration at the *end* of each minute. These results are for initially isotonic solutions; hypertonic and hypotonic solutions may behave differently.

Because the concentration is increasing over the nebulization period, the average solution concentration calculated with equation (5) will depend on the time interval over which the averaging occurs. This dependence can be investigated with the data in Table 2 by determining the average concentration over intervals varying from 1 to 7 min. The results are given in Table 4. It can be seen from Table 4 that measuring the concentration of the nebulizer solution over 1 min intervals gives the best estimate of the average solution concentration in the particles compared with less frequent measurement intervals.

Table 4. Effect of measurement period duration on the average particle solution concentration

Start time (min)	End time (min)	Measurement interval (min)	Average particle concentration ($mg\,ml^{-1}$)
0	7	7	10.6 ± 0.1
1	7	6	10.7 ± 0.1
2	7	5	10.8 ± 0.1
3	7	4	10.9 ± 0.1
4	7	3	11.0 ± 0.17
5	7	2	11.1 ± 0.2
6	7	1	11.3 ± 0.3

Note: The average concentration of the droplets produced by the nebulizer over different time intervals calculated by equation (5) and the data from Table 2. The measured concentration of the nebulizer solution at the end of the 7th minute of operation was $11.28 \pm 0.04\ mg\,ml^{-1}$.

The vapour output by the nebulizer is only easily calculated when the nebulizer is operating without sputtering. During sputtering, the operation of the nebulizer is characterized by short periods where the nebulizer is running "continuously", and periods when the nebulizer is not producing droplets. It has been reported by Mercer *et al.* (1968), O'Callaghan *et al.* (1989) and Langford and Allen (1993) that during the final period of the nebulization session, there was minimal drug output, but continued water output by the nebulizers these authors tested. This is consistent with the loss of water from the nebulizer solution through evaporation during the periods when the nebulizer is not producing droplets. During sputtering, m_v in equation (2) must include water losses due to evaporation or equation (5) will underestimate the calculated average concentration in the droplets.

More important is the effect that any evaporative losses during sputtering would have on the ability of the measurement of the nebulizer solution concentration at the end of a minute to predict the average concentration of the particles during that minute. It is reasonable to expect that any increase in concentration of the nebulizer solution when the nebulizer is not producing droplets will be at a rate equal to or lower than when the nebulizer is producing droplets, as the surface area of liquid in the nebulizer available for evaporation is lower when the nebulizer is not producing droplets. Precise rates of the evaporative water loss when nebulizers are not producing droplets are difficult to calculate from data recorded in the literature without knowing exactly how much sputtering occurred.

The evaporation of liquid from the nebulizer solution when the nebulizer is not producing droplets during the sputtering period will cause the concentration of the nebulizer solution at the end of the minute to overestimate the average concentration of the droplet solution during the minute. In general, the concentration of the nebulizer solution measured at the end of the minute will be a reasonable estimate of the average concentration of the droplets produced during that minute if the amount of sputtering is minimal. Techniques such as "tapping" the nebulizer, which encourages the droplets on the walls of the nebulizer to return to the reservoir, will enhance the accuracy.

The results of this analysis show that the aerosol droplets leaving the Pulmo-Neb® nebulizer are in equilibrium with the surrounding air, indicating that all droplets larger than approximately 1 μm in diameter have the same concentration. In addition, the average solution concentration in the droplets output in 1 min can be approximated by the concentration of the solution remaining in the nebulizer at the end of the minute.

Acknowledgements—This work was made possible through the financial support of the Natural Sciences and Engineering Research Council (NSERC), the Alberta Lung Association, Glaxo Canada Inc., and DeVilbiss Health Care (Canada) Inc.

REFERENCES

Alvine, G. F., Rodgers, P., Fitzsimmons, K. M. and Agrens, R. C. (1992) Disposable nebulizers: how reliable are they? *Chest* **101,** 316.

Clay, M. M., Pavia, D., Newman, S. P., Lennard-Jones, T. and Clarke, S. W. (1983) Factors influencing the size distribution of aerosols from jet nebulizers. *Thorax* **38,** 755.

Eisner, A. D., Graham, R. C. and Martonen, T. B. (1990) Coupled mass and energy transport phenomena in aerosol/vapor-laden gases: I. Theory of the hygroscopic aerosol effects on temperature and relative humidity patterns of inspired air. *J. Aerosol Sci.* **21,** 833.

Ferron, G. A. (1977) The size of soluble aerosol particles as a function of the humidity of the air: application to the human respiratory tract. *J. Aerosol Sci.* **8,** 251.

Ferron, G. A., Kreyling, W. G. and Haider, B. (1988a) Inhalation of salt aerosol particles—II. Growth and deposition in the human respiratory tract. *J. Aerosol Sci.* **19,** 611.

Ferron, G. A. and Gebhart, J. (1988b) Estimation of the lung deposition of aerosol particles produced with medical nebulizers. *J. Aerosol Sci.* **19,** 1083.

Ferron, G. A. and Soderholm, S. C. (1990) Estimation of the times for evaporation of pure water droplets and for stabilisation of salt solution particles. *J. Aerosol Sci.* **21,** 415.

Langford, S. A. and Allen, M. B. (1993) Salbutamol output from two jet nebulizers. *Resp. Med.* **87,** 99.

Martonen, T. B., Bell, K. A., Phalen, R. F., Wilson, A. F. and Ho, A. (1982) Growth rate measurements and deposition modelling of hygroscopic aerosols in human tracheobronchial models. *Ann. Occup. Hyg.* **26,** 93.

Mercer, T. T. (1981) Production of therapeutic aerosols. *Chest* **80,** 813.

Mercer, T. T., Tillery, M. I. and Chow, H. Y. (1968) Operating characteristics of some compressed-air nebulizers. *Am. Ind. Hyg. Assoc. J.* **29,** 66–78.

Morrow, P. E. (1986) Factors determining hygroscopic aerosol deposition in airways. *Physiol. Rev.* **66,** 330.

Orr, C. Jr., Hurd, F. K. and Corbett, W. J. (1958) Aerosol size and relative humidity. *J. Coll. Sci.* **13,** 472.

Persons, D. D., Hess, G. D., Muller, W. J. and Scherer, P. W. (1987) Airway deposition of hygroscopic hetrodispersed aerosols: results of a computer calculation. *J. appl. Physiol.* **63,** 1195.

Phipps, P. R. and Gonda, I. (1990) Droplets produced by medical nebulizers. *Chest* **97,** 1327.

Reid, R. C., Prausnitz, J. M. and Sherwood, T. K. (1977) *The Properties of Gases and Liquids.* McGraw-Hill, New York.

Shen, A.-T. and Ring, T. A. (1986) Distinguishing between two aerosol size distributions. *Aerosol Sci. Tech.* **5,** 477.

Smye, S. W., Jollie, M. I. and Littlewood, J. M. (1991) A mathematical model of some aspects of jet nebulizer performance. *Clin. Phys. Physiol. Meas.* **12,** 289.

Smye, S. W., Jollie, M. I., Cunliffe, H. and Littlewood, J. M. (1992) Measurement and prediction of drug solvent losses by evaporation from a jet nebulizer. *Clin. Phys. Physiol. Meas.* **13,** 129.

Stapleton, K. W., Finlay, W. H. and Zuberbuhler, P. (1994) An *in vitro* method for determining regional dosages delivered by jet nebulizers. *J. Aerosol Med.* **6**(4).

Sterk, P. J., Plomp, A., van de Vate J. F. and Quanjer, P. H. (1984) Physical properties of aerosols produced by several jet and ultrasonic nebulizers. *Bull. Eur. Physiopathol. Respir.* **20,** 65.