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Errors in regional lung deposition predictions of nebulized salbutamol sulphate due to neglect or partial inclusion of hygroscopic effects

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Abstract

Regional lung deposition predictions from a stable particle model and a conventional, one-way hygroscopic model (Stapleton, K.W., Finlay, W.H. and Zuberbuhler, P., An in vitro method for determining regional dosages delivered by jet nebulizers. *J. Aerosol Med.*, 7 (1994) 325–344) are compared with results from a more general, fully two-way coupled hygroscopic model (Finlay, W.H. and Stapleton, K.W., The effect on deposition of coupled heat and mass transfer between hygroscopic droplets and their surrounding phase. *J. Aerosol Sci.* 26, (1995) 137–145) for actual nebulized aerosols characterized experimentally. Data is obtained for Ventolin® (2.5 ml nebule, 1 mg/ml salbutamol sulphate in normal saline) with ambient conditions of 50% RH and six nebulizer brands, and for 15% RH and 90% RH for three nebulizer brands, all at room temperature. This data is entered into a deposition model with the three hygroscopic models for an inhalation flow rate of 300 ml/s and tidal volume of 750 ml. The results indicate that errors in regional dosages of less than 14% of the two-way coupled value occur when using either a stable particle model or a one-way coupled hygrosopic model at 90% RH. Similarly small errors occur at all humidities tested with the stable particle model for the nebulizer brands having high number density; however, for the other nebulizer brands, errors up to 19% in extrathoracic deposition and 35% in alveolar deposition occur at 15% RH and 50% RH. The one-way coupled model gives significant errors (up to 48%) in alveolar and extrathoracic deposition at these two lower humidities for most nebulizer brands tested. © 1997 Elsevier Science B.V.

Keywords: Hygroscopic; Nebulizer; Model; Regional deposition

1. Introduction

Nebulizers are commonly used to deliver pharmaceutical aerosols to the lung for the treatment

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of respiratory illness. The regional deposition of aerosol in the lung, normally measured in vivo with gamma scintigraphy, is a frequently used method of assessing nebulizer performance. Such assessment is useful because of the widely varying performance of different nebulizer models with different solutions, and the lack of any *a priori* theoretical method for predicting the aerosol emitted by a given nebulizer design.

As an alternative to in vivo gamma scintigraphy, lung deposition models have been used to provide in vitro estimates of regional lung deposition with nebulizers (Stapleton et al., 1994; Waldrep et al., 1994; Clark, 1995; Finlay and Stapleton, 1995). These authors make quite different assumptions regarding the hygroscopic behavior of the inhaled aerosols. The purpose of the present article is to examine the validity of these different models of hygrosopicity when applied to a number of actual nebulizers at different ambient humidities when nebulizing a commonly used pharmaceutical solution (Ventolin®).

Many nebulized pharmaceutical solutions have a relatively small amount of active ingredient dissolved in isotonic saline (e.g. Ventolin®, Atrovent®, Pulmozyme®). Once nebulized, the hygroscopic behavior of these formulations is very similar to isotonic saline, since at the usual concentrations of these formulations the vapor pressure reduction at the droplet surface is almost entirely due to the dissolved NaCl. Nebulized isotonic saline aerosols undergo rapid evaporation when exposed to typical ambient room conditions, so that earlier hygroscopic deposition models (Martonen et al., 1982; Persons et al., 1987; Ferron et al., 1988) would predict significant size changes in these aerosols due to dilution with ambient air in a T-mouthpiece or mask. However, these earlier models assume the continuous phase (or 'carrier' phase) is 'uncoupled' from the droplets, meaning that heat and mass transferred to or from the inhaled droplets does not affect the properties of the continuous phase (strictly speaking these models should be referred to as 'one-way coupled', since the droplets are affected by the properties of the continuous phase, but not vice versa; however, any model which is called 'hygroscopic' would be expected to include such one-way coupling, so that the term 'uncoupled hygroscopic model' has also been used to refer to these models). Recent hygroscopic deposition models that include two-way coupling of heat and mass transfer (Finlay and Stapleton, 1995), and which have been referred to as coupled hygroscopic models, suggest that nebulized isotonic saline aerosols have quite different regional deposition patterns for high aerosol number densities (i.e. high number of droplets/cc) vs. low number densities when diluted with 50% ambient room air in a T-mouthpiece. This effect is not predicted by one-way coupled hygroscopic models. In particular, at high number densities the droplets can come into equilibrium with the continuous phase by supplying mass and heat to the continuous phase without significant size changes of the droplets because of the large number of droplets present. As a result, it may be possible to model lung deposition of high number density nebulized aerosols using a stable particle deposition model. Indeed, Clark (1995) uses the stable particle deposition model of Rudolf et al. (1990) to estimate relative deposition of nebulized aerosols between the lung and extrathoracic region, and finds reasonable agreement with in vivo scintigraphic data.

However, the buffering effect of two-way coupled heat and mass transfer on hygroscopic size changes is dependent on several factors, including ambient RH, aerosol number density, aerosol size distribution, nebulizer design, and patient breathing pattern, so that it is unlikely that either a stable particle or one-way coupled deposition model is universally valid for all nebulized isotonic saline aerosols. Because of the complexity and computational expense of two-way coupled hygroscopic models, it is of interest to determine the error that occurs in using either stable particle or one-way coupled hygroscopic models when predicting regional lung deposition. Finlay and Stapleton (1995) examine the difference between one-way and two-way coupled hygroscopic models for two specified aerosols at 50% ambient RH and room temperature. However, because hygroscopic effects are likely strongly dependent on ambient humidity, here we explore the differences between these models as well as with a stable

particle model, at ambient humidities ranging from 15% to 90%. Additionally, we examine these differences in terms of regional dosages delivered for a number of actual nebulizers.

2. Methods

The methods used consist essentially of characterizing the properties of the aerosol emitted by each nebulizer, and combining this data with each of three different lung deposition models (stable particle, one-way and two-way coupled hygroscopic models).

2.1. Experimental procedures

For conventional T-mouthpiece (nonvented) jet nebulizers, an experimental procedure similar to that described by Stapleton et al. (1994) was used to characterize the aerosol properties. Briefly, the size distribution of the aerosol exiting the nebulizer before exposure to ambient air was determined using a phase Doppler anemometer (Dantec Electronics Inc., Mahwah, NJ, USA). Flow rate through the nebulizer was measured using volume displacement. Solution concentration in the nebulizer was measured before and after nebulization using freezing point osmometry (Precision Systems Inc., Natick, MA, USA). The temperature of the continuous phase exiting the nebulizer was measured using a shielded thermocouple. Combining this data with measurements of the nebulized mass, and assuming the droplets exiting the nebulizer are in equilibrium with the continuous phase before they are exposed to ambient air in the mouthpiece (justified by Stapleton and Finlay (1995)), the properties of the aerosol that are needed in order to perform a calculation of regional deposition are known. Note that although the phase Doppler anemometer measures droplet number densities, these values can be unreliable (Bachalo, 1994) and instead we infer the number of droplets/cm^3 from the measured size distribution, solution concentration and solute output.

One of the nebulizers tested, the Pari LC Jet +, cannot be considered a conventional T-mouthpiece nebulizer since all ambient air travels through the nebulizer bowl before reaching the patient. This in contrast to conventional T-mouthpiece nebulizers where only the compressor air travels through the nebulizer bowl and any dilution air needed to make up the patient's inhalation flow rate is entrained directly through the T-mouthpiece. We will refer to the Pari LC Jet + as a 'vented' nebulizer, since there is a vent in the nebulizer where air is entrained that subsequently convects through the droplet production region of the nebulizer. Conventional T-mouthpiece nebulizers have an opening in them at the open end of the T-mouthpiece, but the air entrained here does not flow through the droplet production region of the nebulizer, which makes them behave differently than what we will call 'vented' nebulizers. In particular, the aerosol emitted by conventional nebulizers prior to the mouthpiece is independent of patient breathing, while that of vented nebulizers may not be. For this reason, the above described procedure for conventional (i.e. nonvented) nebulizers cannot be used for vented nebulizers.

For vented nebulizers, the following experimental procedure was used to characterize the inhaled aerosol. Tidal breathing through the nebulizer was simulated using a square wave breathing pattern generated by a computer controlled stepper motor driving a piston connected by hosing to the nebulizer mouthpiece. A tidal volume of 750 ml, inhalation flow rate of 300 ml/s with equal inspiratory and expiratory times, and no inhalation pause were used. A cellulose filter (Evenflow, Brantford, ON) was used to collect the mass of drug inhaled by the breath simulator. Because the filter was not placed directly at the exit of the nebulizer mouthpiece, a small amount of aerosol that would have been inhaled was not collected. This was corrected for by scaling the collected mass of drug by the ratio of inhaled volume to the volume of air passing through the filter. The filter was treated with 5 ml of water, sonicated for 30 min, and the aqueous solution pipetted out. The amount of collected solute was then determined using freezing point osmometry, and the solution concentration of the inhaled droplets calculated by combining this with filter weight measure-

Table 1
Nebulizers with their measured mass median diameter (MMD), geometric standard deviation (GSD) (measured before exposure to ambient air for the conventional T-mouthpiece nebulizers) and flow rate

Nebulizer name	Part/model no.	Supplier/manufacturer	MMD	GSD	Flow rate (l/min)	Droplets/cc $\times 10^{-5}$
Cirrus	Pulmo-Neb 5650D	DeVilbiss, Somerset, PA	5.34	1.71	6.2	1.07
LC Jet+		Pari, Richmond, VA	6.91	1.72	4.8	6.24
Mefar	Pulmo-Neb 7427C	DeVilbiss, Somerset, PA	8.75	1.97	6.8	0.63
Raindrop	001144	Puritan Bennett, Lenexa, Kansas	5.68	1.59	6.2	1.47
T-Updraft	Neb-U-Mist1720	Hudson RCI, Temecula, CA	5.76	1.90	6.1	0.27
T-Updraft II	1732	Hudson RCI, Temecula, CA	5.89	1.78	5.7	2.39

Also shown is the number of droplets/cc in the inhaled stream for an inhalation flow rate of 300 ml/s. Ambient conditions were 50% RH and 20–25°C. All nebulizers were driven by a single Pulmo-Aide compressor nebulizing 2.5 ml of Ventolin® (1 mg/ml). The numbers given are for one nebulizer only. Intra-nebulizer variations in these numbers can be significant.

ments. The RH of the air exiting the nebulizer was determined by assuming the droplets exiting the nebulizer are in equilibrium (this assumption is reasonable, since a calculation using the two-way coupled hygroscopic model of Finlay and Stapleton (1995) to track the droplets from the droplet production region in the Pari nebulizer to the mouthpiece exit shows that $>99\%$ of the mass of droplets are in equilibrium). Measurement of the inhaled particle size distribution was done simultaneously with tidal breathing and filter collection using an inline, optically clear measuring volume, as described by Prokop et al. (1995b), placed between the filter and the nebulizer mouthpiece. The remainder of the procedure is the same as for the conventional T-mouthpiece nebulizers.

Ambient humidity and temperature were controlled using a humidity chamber, described in Prokop et al. (1995a), in which dried air was mixed with saturated air to obtain a continuous supply of air of the desired humidity, as measured with a hygrometer (Fisher Scientific, Ottawa, ON) placed in the chamber. All nebulizers were driven by a single Pulmo-Aide compressor (model 5610C, DeVilbiss, Somerset, PA) placed in the humidity chamber. A single nebulizer of each of the six models shown in Table 1 was used. One 2.5-ml nebule of Ventolin® (Glaxo-Wellcome, Mississagua, ON), consisting of 1 mg/ml salbutamol sulphate with 9 mg/ml NaCl, was used with each nebulizer.

2.2. Mathematical deposition models

The above obtained properties of the aerosol exiting the nebulizer were input into a mathematical lung deposition model that allowed either stable particles, one-way hygroscopic coupling or two-way hygroscopic coupling. This deposition model is described in more detail elsewhere (Finlay and Stapleton, 1995) and has been found to be in good agreement with in vivo SPECT measurements of relative regional lung deposition patterns for nebulized hygroscopic aerosols (Finlay et al., 1996).

Briefly, the deposition model estimates the deposition in a Weibel A lung scaled to FRC (we use a value of 3050 ml for FRC here). Within each generation, sedimentation and diffusion deposition probabilities are obtained from theoretical equations for deposition in laminar flow through inclined tubes (Gormley and Kennedy, 1949; Wang, 1975; Taulbee et al., 1978), while inertial impaction approximates the experimental data of Johnston et al. (1977). Extrathoracic deposition was determined using the equations of Rudolf et al. (1990) applied to droplet sizes in the pharynx. One-way coupling is modeled by tracking the droplet size distribution of a bolus as it

Table 2
Three of the nebulizers listed in Table 1 with their measured MMD, GSD and number of droplets/cc in the inhaled stream (for an inhalation flow rate of 300 ml/s) at the given ambient relative humidity (RH) and ambient temperature (T)

Nebulizer	RH (%)	T (°C)	MMD (μm)	GSD	Droplets/cc $\times 10^{-5}$
Mefar	15	26	8.05	2.02	0.95
Mefar	90	25	8.78	1.85	0.70
T-Updraft II	15	22	4.87	1.71	1.88
T-Updraft II	90	22	6.17	1.70	0.59
LC Jet+	15	20	6.58	1.74	5.59
LC Jet+	90	20	7.26	1.70	7.57

All nebulizers were driven by a single Pulmo-Aide compressor.
The numbers given are for one nebulizer only.
Intra-nebulizer variations in these numbers can be significant.

progresses through the generations of the respiratory tract with RH and temperature specified using the equations of Daviskas et al. (1990). Two-way coupling is modeled by treating the RH and temperature of the continuous phase in the bolus as additional unknowns. With either one-way or two-way coupling, heat and mass transfer rates to and from the continuous phase and the droplets are affected by latent heat, and conduction effects (Ferron and Soderholm, 1990), as well as vapor pressure reductions due to dissolved NaCl (Cinkotai, 1971) and salbutamol sulphate (Stapleton et al., 1994). For two-way coupling, heat and mass transfer at the airway walls is accounted for using heat and mass transfer coefficients, as described in Finlay and Stapleton (1995). The effect of depositing droplets on the properties of the airway walls is not accounted for, but is expected to be negligible for the nearly isotonic aerosols considered here (see Finlay et al., 1996; Finlay and Stapleton, 1995 for further discussion of this issue). The breathing pattern used in the model was the same as that described in the experimental procedure above. Mouth breathing through the nebulizer's supplied mouthpiece and a lung volume of 3050 ml at 50% TLC were assumed.

3. Results and discussion

The measured MMD, GSD, flow rate and number density (number of droplets/cc) of the aerosols from the nebulizers tested are listed for reference in Table 1 at 50% RH, and at 15% and 90% RH in Table 2. The nebulizers in Table 1 were intentionally chosen to cover a wide range of MMD and number density. These results and all those that follow were obtained using the nearly isotonic solution of Ventolin® mentioned previously, and can be expected to be different for other solutions.

Regional deposition predictions for the three models of hygroscopic behavior are shown in Table 3 at 50% RH. For the jet nebulizers tested at this humidity, the stable particle model predictions are close to the two-way coupled values except for a few cases. In particular, the stable particle model overpredicts tracheo-bronchial dosages by an average of only 1.6% of the two-way coupled value, ranging among the different nebulizers tested from an underprediction of 1.6% to an overprediction of 5.1% of the two-way coupled value. The stable particle model overestimates extrathoracic dosages by an average 8.4% of the two-way coupled value, ranging from an underprediction of 1.4% to an overprediction of 18.9% (for the Cirrus) of the two-way coupled value. Alveolar deposition is underestimated with the stable particle model by an average of 8.3% of the two-way coupled value, but ranges from an underprediction of 24.0% (for the Pulmo-Neb) to an overprediction of 2.1% of the two-way coupled value. Lung deposition (tracheo-bronchial + alveolar deposition) is underestimated with the stable particle model by an average of 3.7% of the

Table 3
Regional dosages as % of 2.5 mg nominal dose[a]

Nebulizer	Region	Two-way coupled	One-way coupled	Stable particle
Cirrus	Extrathoracic	5.65	4.09	6.72
	Tracheo-bronchial	6.02	5.68	6.33
	Alveolar	9.21	10.72	8.22
	Lung	15.23	16.4	14.55
LC Jet+	Extrathoracic	9.39	7.20	9.26
	Tracheo-bronchial	7.66	7.34	7.57
	Alveolar	7.01	9.05	7.16
	Lung	14.67	16.39	14.73
Mefar	Extrathoracic	10.20	9.55	10.80
	Tracheo-bronchial	2.54	2.61	2.50
	Alveolar	2.00	2.55	1.52
	Lung	4.54	5.16	4.02
Raindrop	Extrathoracic	7.55	5.70	8.23
	Tracheo-bronchial	5.80	5.36	5.93
	Alveolar	7.41	9.22	6.81
	Lung	13.21	14.58	12.74
T-Updraft	Extrathoracic	3.15	2.36	3.64
	Tracheo-bronchial	3.08	2.94	3.21
	Alveolar	4.24	5.02	3.81
	Lung	7.32	7.96	7.02
T-Updraft II	Extrathoracic	7.82	4.89	8.64
	Tracheo-bronchial	8.06	7.50	8.26
	Alveolar	10.46	13.28	9.73
	Lung	18.52	20.78	17.99

[a] Predicted for the nebulizers and conditions given in Table 1 by each of the indicated three treatments of hygroscopic behaviour.

two-way coupled value, but ranges from an underprediction of 11.5% (for the Pulmo-Neb) to an overprediction of 0.4% of the two-way coupled value.

The one-way coupled hygroscopic model results shown in Table 3 differ considerably from the two-way coupled values, particularly in extrathoracic and alveolar dosages. For example, extrathoracic deposition is underestimated with the one-way model by an average of 20.6% of the two-way coupled value, ranging from underpredictions of 37.5% (for the T-Updraft II) to 6.4% of the two-way value. Alveolar dosages are overpredicted with the one-way model by an average of 20.4%, ranging from overpredictions of 16.4–29.1% of the two-way values. Tracheo-bronchial and lung dosages using the one-way model are closer to the two-way values, with tracheo-bronchial dosages being underestimated by an average of 3.7% (ranging from an underprediction of 7.6% to an overprediction by 2.8%) and lung dosages overestimated by an average of 9.2% (ranging from overpredictions of 7.7–13.7%) of the two-way coupled values.

The error in using the one-way hygroscopic model is larger than that incurred using a stable particle model for most of the nebulizers tested here because these nebulizers have number densities in the range that Finlay and Stapleton (1995) predict a significant reduction in hygroscopic size changes due to two-way coupling. Although Finlay and Stapleton (1995) do not compare their regional deposition estimates to a stable particle model, we calculate that for their 6.0 μm MMD, 1.7 GSD aerosol there is less than a 1% difference between a two-way coupled model and a stable

particle model when 10^6 droplets/cc are present in the inhaled stream. None of the nebulizers tested here reach this high a number density for the present inhalation flow rate, but this does indicate that if number densities are high enough, stable particle models can provide adequate estimates of regional deposition. Here, the stable particle model is closest to the two-way coupled model for the LC Jet+, where the stable particle model differs from the two-way coupled regional dosages by less than 2.1% of the two-way coupled values. This difference is small because of the high number density ($>600\,000$ droplets/cc), and the vented design of this nebulizer. These factors allow two-way coupled effects to almost completely buffer hygroscopic size changes in the respiratory tract for this nebulizer at this ambient humidity and inhalation flow rate.

At the opposite extreme, i.e. very low number densities, a one-way coupled model should be a valid approximation, although none of the nebulizers tested here at 50% RH have few enough particles for this to be the case. The number densities of the nebulizers tested here lie either in the high number density range closer to where a stable particle model becomes a reasonable approximation, or in the intermediate range, where neither stable particle nor one-way coupled models perform well (e.g. for the Mefar, alveolar deposition is underestimated by 24.0% by the stable particle model, but overestimated by 27.5% with the one-way model; for the Cirrus, extrathoracic deposition is overestimated by 18.9% by the stable particle model and underestimated by 27.6% with the one-way coupled model).

It might be suggested that the data given by Finlay and Stapleton (1995) can be used to estimate whether number densities are high enough or low enough that stable particle or one-way coupled models are reasonable. However, such estimation is confounded by the number of parameters affecting the magnitude of two-way coupled effects, which in addition to number densities include the aerosol MMD, GSD, and vapor pressure reduction at droplet surfaces, as well as the continuous phase RH and temperature (which are affected by the ambient RH and temperature, but also by the nebulizer and mouthpiece design and compressor flow rate). For example, Finlay and Stapleton (1995) find that a one-way coupled model is within 10% of a two-way coupled model in regional dosage predictions for an isotonic aerosol with number densities $<25\,000$/cc (for an MMD of 6.0 μm, GSD of 1.7, supplied at a rate of 6 l/min. through a T-mouthpiece of diameter 1.87 cm and length 4.0 cm, and inhaled at the same tidal volume and flow rate but slightly lower frequency). In contrast, here we find the one-way coupled model underpredicts extrathoracic dosages by 25.4% and overpredicts alveolar dosages by 18.4% of the two-way coupled values for a T-Updraft nebulizer that had nearly this same aerosol number density and size distribution (approximately 27 000 particles/cc, with MMD 5.76 mm, GSD 1.90). Thus, it would appear that a combination of differences in MMD, GSD, mouthpiece dimensions, breathing frequency, compressor flow rate, and droplet solution concentration (the droplets here deviate from isotonicity by up to roughly 50% in initial concentration) can prevent accurate estimation of the range of validity of one-way coupled models from the data of Finlay and Stapleton (1995).

3.1. Ambient humidity effects

The validity of stable particle or one-way coupled models is affected significantly by the ambient humidity, as shown in Table 4 where the regional dosages for the three nebulizers listed in Table 2 are given at 15% and 90% RH. These three nebulizers represent the low, middle and high number density ranges of the seven nebulizers listed in Table 1. Note that intranebulizer variations can be significant, so that these regional dosages do not reflect average values for these nebulizer models. For example, Prokop et al. (1995a) find the average regional dosage for five Mefar nebulizers increases significantly with increasing ambient RH, whereas for the one Mefar nebulizer tested here once at 15% RH and once at 50% RH the results show a lower alveolar dose at the higher RH. This difference is likely caused by the large variations in nebulized dose that occurs from run to run with this nebulizer, so that multiple runs are necessary to determine average values of nebulizer performance.

Table 4
Regional dosages as % of 2.5 mg nominal dose[a]

Nebulizer	Region	15% RH			90% RH		
		Two-way coupled	One-way coupled	Stable particle	Two-way coupled	One-way coupled	Stable particle
LC Jet+	Extrathoracic	8.22	5.02	8.08	9.84	9.45	9.72
	Tracheo-bronchial	7.26	7.04	7.15	7.69	7.54	7.63
	Alveolar	7.07	9.96	7.23	6.45	6.86	6.58
	Lung	14.33	17.00	14.38	14.14	14.40	14.21
Mefar	Extrathoracic	7.80	4.05	8.08	11.30	10.63	11.47
	Tracheo-bronchial	5.41	5.11	4.80	6.37	6.27	6.40
	Alveolar	5.71	7.13	3.73	4.59	5.23	4.43
	Lung	11.12	12.24	8.53	10.96	11.50	10.83
T-Updraft II	Extrathoracic	4.99	2.87	5.41	10.97	10.19	11.07
	Tracheo-bronchial	4.98	4.74	5.07	9.90	9.54	9.91
	Alveolar	8.61	9.49	7.25	11.06	11.88	10.98
	Lung	13.59	14.23	12.32	20.96	21.72	20.89

[a] Predicted for the nebulizers and conditions given in Table 2 by each of the indicated three treatments of hygroscopic behaviour.

Table 4 shows that at 90% RH and room temperature, hygroscopic effects have a relatively small effect on regional deposition for the nearly isotonic solution tested here. For example, the stable particle model is within 3.5% of the two-way coupled model in its predictions of dosages for all regions, while the one-way coupled model gives values of extrathoracic, tracheo-bronchial, alveolar and lung deposition that differ from the two-way coupled values by an average of −5.7%, −2.4%, +9.2%, and +3.5% of the two-way coupled value, respectively (ranging from −7.1% to −4.1%, −3.6% to +1.6%, 6.4% to 14%, and +1.8% to +4.9%, respectively).

Table 4 also shows that at 15% RH, the error incurred in regional dosage estimates by using a stable particle model is on average +3.4%, −3.6%, −15.1% and −11.8% (ranging from −1.7% to +8.4%, −11.3% to +1.8%, −34.5% to +2.3%, and −23.3% to 0.3%) of the two-way coupled value for the extrathoracic, tracheo-bronchial, alveolar and lung regions, respectively. Not surprisingly, at this humidity the largest magnitude errors for the stable particle model occur for the nebulizer with the lowest number density of the three nebulizers tested at this humidity (the Mefar), while the smallest magnitude errors occur with the nebulizer with the largest number density (the LC Jet+).

Table 4 also shows that at 15% RH, regional dosages from the one-way coupled model differ from the two-way coupled values by an average of −43.2%, −4.5%, +25.3% and +11.1% (ranging from −48% to −39%, −5.5% to −3.3%, +10.2% to +40.9%, +4.7% to +18.6%) of the two-way coupled value for the extrathoracic, tracheo-bronchial, alveolar and lung regions, respectively.

These results indicate that at low humidity both stable particle and one-way coupled models can differ considerably from the two-way coupled model in alveolar dosages for nebulizers having number densities outside the asymptotic regions of validity of these models. Extrathoracic and tracheo-bronchial deposition are surprisingly well modeled by the stable particle model at low humidity, while extrathoracic deposition is underpredicted considerably by the one-way coupled model, suggesting that even at low humidity two-way coupled effects are able to buffer of the hygroscopic size changes in the respiratory tract.

4. Concluding remarks

The ability of stable particle and one-way coupled hygroscopic lung deposition models to predict regional deposition of inhaled nebulized Ventolin® (1 mg/ml salbutamol sulphate in normal saline) has been examined by comparing to results from a fully two-way coupled hygroscopic model for six different nebulizers operating at ambient humidities ranging from 15%–90% RH and room temperature. Results for other nearly isotonic pharmaceutical formulations with similar static and dynamic surface tensions and viscosity are expected to be similar to those presented here.

Although stable particle models and one-way coupled models are valid approximations to full two-way hygroscopic coupling in the limit of small and large number particle number densities, respectively, nebulizers in current use do not all fall into the asymptotic regions of validity of either of these two simplified models. The present results indicate that a stable particle model performs well ($< 2.3\%$ error in regional dosages in comparison with a two-way coupled model) for a high number density vented nebulizer (Pari LC Jet +) at all humidities tested, while either one-way coupled or stable particle models are reasonable at 90% RH for the three nebulizers tested ($< 14\%$ error in regional dosages in comparison with two-way coupled model). However, because of the number of factors affecting the magnitude of two-way coupled effects, which include ambient RH and temperature, aerosol MMD and GSD, the magnitude of vapor pressure reduction, nebulizer design, and inhalation flow rate, in addition to aerosol number density, general *a priori* estimation of the validity of stable particle or one-way coupled models is difficult, with significant errors in regional deposition estimates occurring when these models are applied outside their range of validity, which can occur with nebulizers under typical ambient conditions.

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