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Research paper

Selected parameters affecting characterization of nebulized aqueous solutions by inertial impaction and comparison with phase-Doppler analysis

Craig A. Dunbar[1,*], Anthony J. Hickey

Dispersed Systems Laboratory, School of Pharmacy, Chapel Hill, NC, USA

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Abstract

The objective of this study was to evaluate selected parameters affecting the characterization of air-jet nebulized aqueous solutions by inertial impaction. Parameters affecting characterization of the droplet size distribution by inertial impaction were considered to be nebulizer T-piece connecting tube length, solute concentration, droplet charge accumulation, sample time and marker concentration. Parametric effects on nebulizer output characteristics were evaluated using a fractional factorial design. Response factors were defined as mass median aerodynamic diameter (MMAD), relative span factor (Δ), fine particle mass and delivery rate of solute. Connecting tube length, grounding the impaction stages and marker concentration did not significantly affect the response factors ($p > 0.05$). Mass median aerodynamic diameter (MMAD) and delivery rate of solute were significantly affected by solute concentration ($p < 0.05$). Fine particle mass was significantly affected by the interaction between solute concentration and sampling time. Droplets attained an equilibrium size with an MMAD = 1.0 μm, $\Delta = 2.12$ (0.9% solute) and MMAD = 1.7 μm, $\Delta = 2.00$ (9.0% solute) before the exit of the nebulizer T-piece. The droplet size distributions obtained by inertial impaction were compared with data obtained by phase-Doppler analysis.

Keywords: Nebulized aqueous solutions; Inertial impaction; Factorial design; Phase-Doppler analysis

1. Introduction

Air-jet nebulizers are used in the treatment of chronic pulmonary diseases, generating droplets of aqueous solutions and suspensions that are suitable for inhalation and deposition in the pulmonary regions of the lung ($D_{ae} < 5$ μm [1,2]). These devices usually consist of a series of components including a solution or suspension formulation, reservoir, compressed gas source, air-jets, baffles, T-piece, one-way valves, filters, flexible tubing and mouth-piece/face mask. The need for standardized methods of analysis of these devices has been recognized [3].

Inertial impaction is the US pharmacopoeial standard method of aerosol droplet size distribution measurement [4]. The principal advantage of inertial impaction methods is the acquisition of data on the chemical identity of the droplets. Other advantages include analysis of the whole aerosol and characterization of the aerodynamic droplet diameter, appropriate for inhalation aerosols. Disadvantages include the time consuming and laborious nature of the assay. Alternative methods to inertial impaction have been used to characterize the output from air-jet nebulizers and include laser diffraction [5–9], phase-Doppler analysis [10–13], centrifugation [14] and differential mobility analysis [15].

Phase-Doppler analysis (PDA) is a single-particle light scattering technique, providing the simultaneous measurement of droplet size and velocity. Droplet size data obtained by PDA relates the equivalent volume diameter to the Doppler burst interference fringe pattern generated by a single droplet traversing the intersection of two spatially separated laser beams. The Doppler burst is related to droplet size by geometrical optics theory that can be applied for specific optical configurations of the instrument. Advantages of PDA include rapid, in-situ droplet size and velocity characterization. Disadvantages include sampling that may not represent the whole aerosol due to the small measure-

* Corresponding author. Advanced Inhalation Research, Inc., 840 Memorial Drive, Cambridge, MA 02139, USA. Tel.: +1-617-250-1532; fax: +1-617-495-0075.

E-mail address: cdunbar@airpharm.com (C.A. Dunbar)

[1] Present address: Advanced Inhalation Research, Inc., 840 Memorial Drive, Cambridge, MA 02139, USA.

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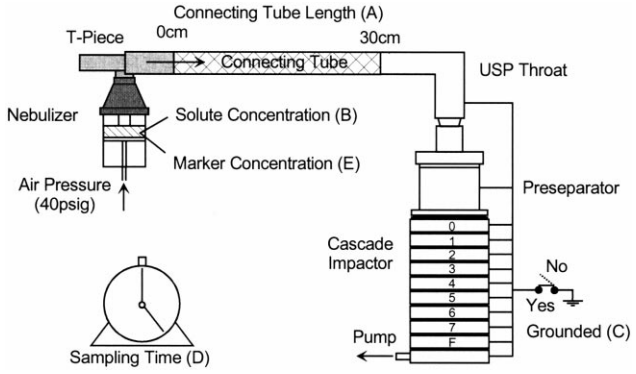

Fig. 1. Parameters investigated for droplet size characterization by inertial impaction.

ment zone diameter (∽ 0.5 mm) and the measurement of spherical droplets only.

Numerous parameters may affect the characterization of nebulized aqueous solutions by inertial impaction. The location at which the measurement is performed, e.g. at the T-piece or mouth-piece exit, may result in increased droplet evaporation. The period over which the aerosol is sampled could lead to particle re-entrainment or build-up of electrostatic charge by deposition of charged droplets. Accumulation of electrostatic charge would also be dependent on whether the impactor stages were grounded and could be affected by the mean ionic strength of the solution. It is common industrial practice to ground the impactor stages during the characterization of inhalation aerosols. However, the effect of grounding the impactor stages on the droplet size distribution characteristics has not been reported. Marker concentration may affect the solution characteristics and influence the accuracy of the sample analysis. Solute concentration could be closely coupled to all of the parameters previously listed, e.g. a high concentration electrolyte solution could significantly change the mass transfer or electrostatic charge of the droplets.

The purpose of this study was to determine the effects selected parameters have on the characterization of nebulized aqueous solutions by inertial impaction. The parameters investigated for air-jet nebulizer characterization were connecting tube length, solute concentration, charge accumulation, sample time and marker concentration. Designed experiments were performed to calculate the main and interactive parametric effects. An evaluation of droplet size distribution characterization by PDA was also performed and compared with data obtained by inertial impaction.

Table 2
2_V^{5-1} experimental design matrix

Standard order	Level of coded variables					Block (AE)
	A	B	C	D	E	
1	−	−	−	−	+	−
2	+	−	−	−	−	−
3	−	+	−	−	−	+
4	+	+	−	−	+	+
5	−	−	+	−	−	+
6	+	−	+	−	+	+
7	−	+	+	−	+	−
8	+	+	+	−	−	−
9	−	−	−	+	−	+
10	+	−	−	+	+	+
11	−	+	−	+	+	−
12	+	+	−	+	−	−
13	−	−	+	+	+	−
14	+	−	+	+	−	−
15	−	+	+	+	−	+
16	+	+	+	+	+	+

2. Materials and methods

The Aerotech II air-jet nebulizer (CIS-US, Inc., Bedford, MA) was selected to complement previous studies [11,12]. A solution volume of 5 ml was used and the operating pressure set at 40 psig. Characterization of the droplet size distribution was performed using: (1) an eight stage, 1 ACFM, non-viable ambient particle sizing sampler Mark II (Graseby-Andersen, Smyrna, GA), including a USP sampling inlet [4] and preseparator; (2) a one-dimensional, three-detector, digital count processor phase-Doppler analyzer (Aerometrics, Sunnyvale, CA). The five parameters investigated for air-jet nebulizer characterization by inertial impaction were connecting tube length (0 cm representing the T-piece exit), solute concentration, grounding the inertial impaction (charge accumulation), sample time and marker concentration. These parameters are shown schematically in Fig. 1 and the values for the two level factorial design summarized in Tables 1 and 2. The low (0.9%) and high (9.0%) solute concentration levels were selected to represent the broad range of drug concentrations found in air-jet nebulized aqueous solutions [16]. Sodium chloride was selected as a model solute, with detailed information being available on the electrolytic properties of this

Table 1
2_V^{5-1} experimental design matrix

Parameter	Connecting tube length (cm)		Solute concentration (% w/v)		Grounded		Sampling time (s)		Marker concentration (% w/v)	
Code	A		B		C		D		E	
Level	−	+	−	+	−	+	−	+	−	+
Value	0	30	0.9	9.0	No	Yes	30	120	0.01	0.05

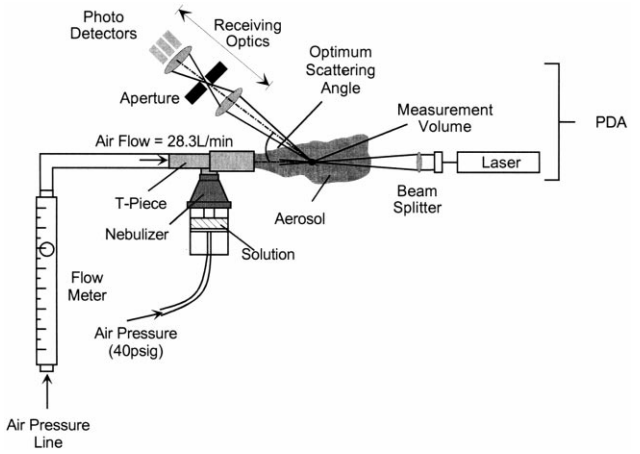

Fig. 2. PDA optical configuration.

compound. Sodium chloride solution did not represent a therapeutic formulation. Disodium flourescein was used as the marker probe.

The response factors were mass median aerodynamic diameter (MMAD), relative span factor (Δ), fine particle mass (FPM) and delivery rate of solute ($\dot{m}_s$). Relative span factor provides a dimensionless measure of the width of the droplet size distribution and is defined as:

$$\Delta = \frac{D_{0.9} - D_{0.1}}{D_{0.5}} \quad (1)$$

where $D_{0.1}$ and $D_{0.9}$ are the droplet diameters at the 10th and 90th percentiles of the cumulative frequency distribution, respectively. Fine particle mass was defined as the mass of droplets with an aerodynamic diameter $D_{ae} < 5.8$ μm relative to the total mass of droplets. Evaluation and comparison of droplet size distributions obtained by PDA were performed with two parameters: connecting tube length and solute concentration, the values being the same as those used in the inertial impaction study (Tables 1 and 2). Charge accumulation, sampling time and marker concentration do not contribute to the droplet size analysis by PDA and were not investigated. Environmental conditions were monitored using a digital thermometer/hygrometer (Control Company, Friendswood, TX).

The impactor flow rate was calibrated at 1 ACFM (28.3 l/min) before each experiment using a D6067 flowmeter (Gilmont Instruments, Inc., Great Neck, NY). The impaction plates and filter were thoroughly rinsed with 5 ml phosphate buffer (pH 7.4) after collection of the nebulized aerosol. The sample was subsequently collected for analysis of the disodium fluorescein marker by UV spectrophotometry, $\lambda = 480$ nm (UV160U, Shimadzu Scientific Instuments, Inc., Columbia, MA). Each stage of the inertial impactor was connected with copper braid to ground the individual stages which are insulated by rubber o-rings. MMAD and Δ were calculated by fitting a straight line to the relationship between cumulative mass frequency distribution on a probability scale and the log of droplet size [17,18].

An experimental design was developed for the inertial impaction experiments. Experiments were conducted on separate days in two randomized blocks of eight ($n = 1$). Blocking was defined such that environmental conditions were confounded with the interaction between connecting tube length and marker concentration. Effects were calculated using Yates' algorithm [19]. The experimental design matrix is shown in Tables 1 and 2. (A brief introduction to experimental design is presented in Appendix A with more detailed descriptions available in the literature [19–21].) Effects of changing different design parameters were analyzed using linear regression (ANOVA) and statistical significance was declared for $P < 0.05$ (Design-Expert v5.05, Stat-Ease Corp., Minneapolis, MN).

The PDA optical configuration is shown in Fig. 2 and summarized in Table 3. Measurements were obtained in the center and approximately 1 cm downstream from the exit of the measurement location ($n = 3$). A droplet count of 10^4 was considered sufficient to obtain a representative sample (smooth droplet size number distribution). The droplet size distribution obtained by PDA was corrected for the droplet size bias of the measurement volume [22]. Auxiliary air was supplied to the air-jet nebulizer T-piece at a flow rate of 28.3 l/min, using a D6067 flowmeter (Gilmont Instruments, Inc., Great Neck, NY), to simulate the conditions produced by the inertial impaction. Multi-variant analysis of the droplet size frequency distributions measured by PDA and inertial impaction was performed using a general linear models procedure and statistical significance was declared for $P < 0.05$ (SAS v6.12, SAS Institute, Cary, NC).

3. Results

The normal plot of effects for the respective response factors (MMAD, Δ, FPM and $\dot{m}_s$) is shown in Fig. 3. Those points lying on a straight line are normally distributed (associated with random error) and do not affect the

Table 3
PDA optical configuration

PDA parameters	Values
Droplet size range (μm)	0.5–17.5
Droplet velocity range (m/s)	0.6–4.5 (0.0–3.0)[a]
Velocity offset (m/s)	1.0
Optimum scattering angle (deg)	30
Collimating lens (mm)	300
Transmit lens (mm)	200
Receiver aperture (μm)	100
High voltage (V)	350
Refractive index [26]	1.334, 1.349[b]

[a] Sampling distance 30 cm.
[b] 9.0% w/v solute.

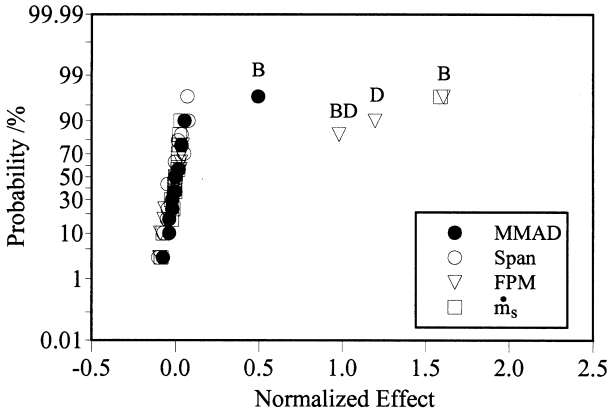

Fig. 3. Normal plot of effects for the designed experiments (*B* solute concentration, *D* sampling time).

response (see Appendix A). Those points located away from the normal distribution are considered prominent effects. Fig. 3 shows that solute concentration (B) significantly affected the MMAD and $\dot{m}_s$ ($P < 0.05$). MMAD and increased with increased solute concentration. Solute and marker concentrations interacted to produce a small but significant affect on MMAD and $\dot{m}_s$ ($P < 0.05$). Fine particle mass was significantly affected by the interaction between solute concentration and sampling time ($P < 0.05$). FPM increased with increased solute concentration and sampling time. The main effects of solute concentration on MMAD are shown in Fig. 4a, and the interactive effect of sampling time and solute concentration on FPM is shown in Fig. 4b. Connecting tube length, grounding the inertial impaction, marker concentration and blocking the experiments did not significantly affect the response factors ($P > 0.05$). The environmental conditions of the blocked experiments (conducted on separate days) were $T_1 = 21.7$ (1.2)°C, $RH_1 = 31$ (1.7)% and $T_2 = 21.9$ (2.4)°C, $RH_2 = 31$ (2.5)%, the percentage relative standard deviations shown in parentheses.

Droplet size characteristics obtained by PDA for the two solute concentrations (0.9 and 9.0% w/v) and two connecting tube lengths (0 and 30 cm from the T-piece exit) are shown in Table 4 in terms of volume median diameter ($D_{V,0.5}$) and relative span factor (Δ), time-averaged axial droplet velocity ($\bar{U}_d$), turbulence intensity (I_d) and droplet count ratio (corrected:validated droplet count). The temperature and relative humidity during the PDA experiments (conducted over a 2 h period) were 18°C and 34% (0% rsd), respectively. Table 4 shows that $D_{V,0.5}$, $\bar{U}_d$ and I_d decreased with increased connecting tube length. Relative span factor and droplet count ratio increased with increased connecting tube length. The droplet size frequency distributions obtained by inertial impaction and PDA for the two solute concentrations and connecting tube lengths are shown in Fig. 5. Data for the droplet size distributions obtained by inertial impaction were calculated by taking the mean value of the relevant connecting tube length and solute concentration experiments ($n = 4$), noting that the charge accumulation, sampling time and marker concentration parameters did not affect the droplet size distribution, i.e. hidden replicates. There was no significant difference between the inertial impaction droplet size frequency distributions obtained at the T-piece exit (0 cm) and the connecting tube exit for the two solute concentrations ($P > 0.05$). There were significant differences between the distributions obtained by PDA and inertial impaction ($P < 0.05$), with the exception of the distribution obtained for the 9% solute concentration and 30 cm connecting tube ($P > 0.05$).

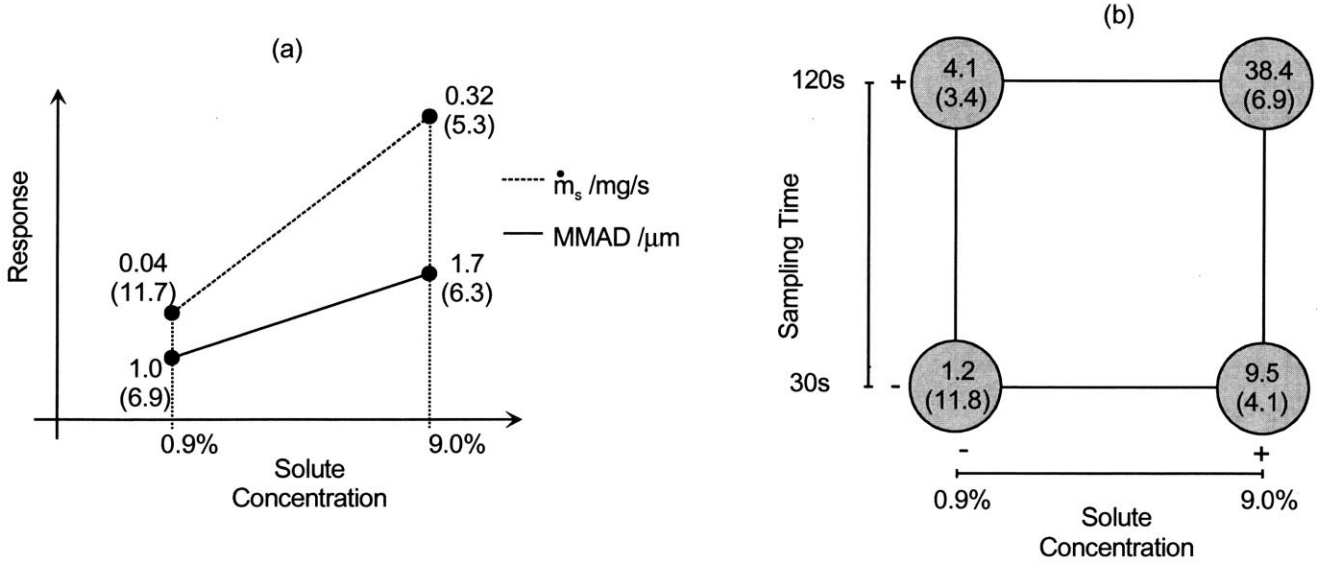

Fig. 4. (a) Effect of solute concentration on MMAD and (b) interactive effect of solute concentration and sampling time on FPM (μg) (%rsd in parentheses).

Table 4
Droplet size characteristics obtained by PDA (%rsd in parentheses, $n = 3$)

Solute concentration (% w/v)	Connecting tube length (cm)	$D_{V,0.5}$ (μm)	Δ	U_d (m/s)	I_d (%)	Droplet count ratio
0.9	0	4.1 (3.3)	1.36 (2.6)	2.4 (1.7)	18 (1.6)	1.12 (3.4)
	30	2.4 (10.6)	2.38 (11.2)	1.7 (0.8)	6 (2.9)	1.48 (5.8)
9.0	0	4.5 (8.0)	1.38 (2.3)	2.6 (0.3)	17 (0.5)	1.56 (59.1)
	30	1.8 (11.1)	1.87 (7.5)	1.7 (0.5)	5 (3.1)	1.81 (66.1)

4. Discussion

The effects observed in the inertial impaction experiments were that MMAD and $\dot{m}_s$ increased with increased solute concentration. Fine particle mass increased with increased solute concentration and sampling time. Connecting tube length, grounding the impactor (droplet charge accumulation) and marker concentration did not affect the response factors.

The 0.9% and 9.0% solutions attained equilibrium MMADs of 1.0 μm (6.9%rsd) and 1.7 μm (6.3%rsd), respectively. Droplets of solutions with concentrations >0.1% w/v attain an equilibrium droplet size within a very short time scale (90% of the diameter change occurs within 10^{-3} to 10^{-1} s) [23,24]. The equilibrium droplet size is dependent on the saturation ratio and solute concentration, as follows:

$$\frac{p}{p_s} = \left(1 + i\frac{n_s}{n_w}\right)^{-1} \exp\left(\frac{4\sigma M_w}{\rho_w RTD_d}\right) \quad (2)$$

The first term in parentheses represents the contribution from the dissolved solute and the second term represents the Kelvin effect (mass transfer due to the droplet radius of curvature). The relationship between saturation ratio and droplet size is presented in Fig. 6. Droplets having an initial size to the left of the saturation line increased in size by hygroscopic growth until equilibrium was reached, those to the right attained equilibrium by evaporation. Fig. 6 shows that the partial pressure at the surface of the droplets for both solutions was approximately $0.98p_s$, which is the lower limit produced by jet nebulizers [24]. Thus, Eq. (1) could be used to estimate the equilibrium droplet sized attained by nebulized solutions. The saturation ratio for pure water droplets shows that supersaturation can be reached at the surface due to the Kelvin effect, occurring for droplet sizes <0.1 μm.

The final droplet size distributions produced by the different solute concentrations were dependent on the equilibrium condition rather than primary atomization. The process of generating droplets in the Aerotech II nebulizer is plain-jet airblast atomization. Correlations for the initial droplet size produced by plain-jet atomizers are governed by the liquid/air ratio, Weber number and liquid viscosity [25,26]. Values of the liquid thermo-physical properties that influence the primary atomization process are shown in Table 5, revealing little change in these properties over the solute concentrations used.

Charged droplets are generated during the primary atomization of aqueous solutions [29]. This can affect the transport properties of the droplets [30]. It has been shown that sampling becomes size selective during spray drying of disodium fluorescein solutions due to diffusion charging, increasing the mobility of droplets in the size range $1 < D_{ae} < 2$ μm [31]. The results of the present study showed that characterization of air-jet nebulized solutions

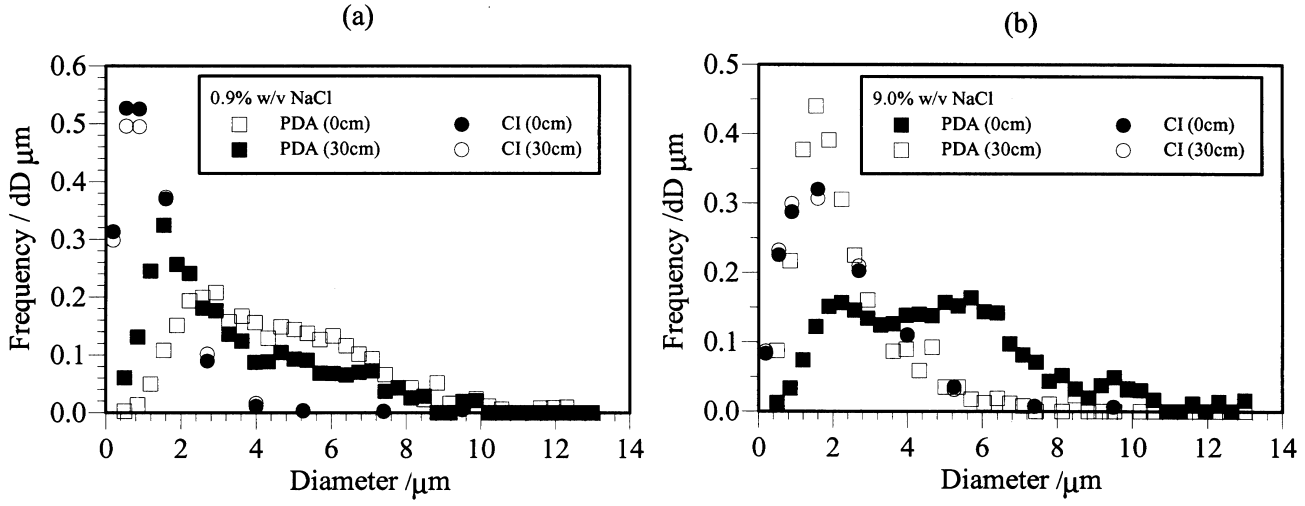

Fig. 5. Droplet size frequency distributions obtained by inertial impaction (mass) and PDA (volume) for (a) 0.9% NaCl and (b) 9.0% NaCl solutions.

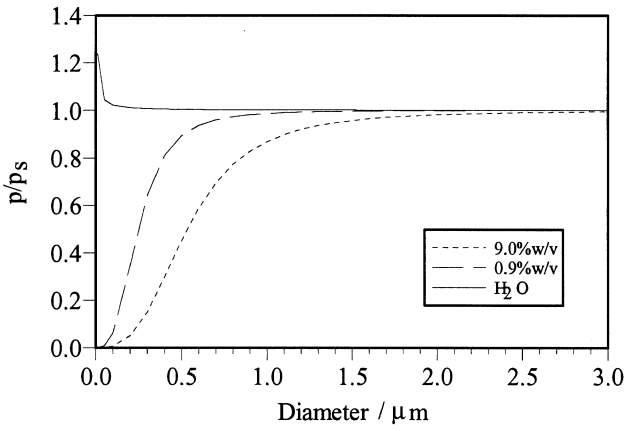

Fig. 6. Saturation ratio as a function of droplet size for 0.9% and 9.0% NaCl solutions.

by inertial impaction was not affected by the accumulation of droplet charge. This may have been due to the small residence time and low velocity of the nebulized droplets, reducing the effects of diffusion charging.

The droplet size frequency distributions obtained by PDA (volume) and inertial impaction (mass) are shown in Fig. 5a,b for the 0.9% and 9.0% solute concentrations, respectively. There was no significant difference between the droplet size distributions obtained by inertial impaction at a given connecting tube length, confirming the equilibrium condition attained by the droplets ($P > 0.05$). The PDA distributions for the 0.9% solute concentration at 0 and 30 cm (Fig. 5a) and 9% solute concentration at 0 cm (Fig. 5b) were significantly different due to truncation of the distributions ($P < 0.05$). However, there was no significant difference between the PDA and inertial impaction distributions for the 9% solution at 30 cm ($P > 0.05$). Truncation of the droplet size distribution by PDA was a consequence of two effects. The optical resolution of the PDA has a lower limit of 0.5 μm. Thus, a large proportion of the droplets (approximately 50% by number) for the 0.9% solution were not detected. The 9% solution produced larger droplet sizes (MMAD = 1.7 μm (6.3) relative to the 0.9% solution (MMAD = 1.0 μm (6.9) and was not affected by the lower size limit.

The droplet size distribution obtained by PDA was corrected for droplet size bias by approximating the size of the measurement volume to the average Doppler burst length for a given droplet size class [22]. The accuracy of this approximation is dependent on the droplet motion being parallel to the plane of the intersecting laser beams, low levels of turbulence and large sample numbers for each droplet size class. The turbulent motion of the droplets at the T-piece exit ($I_d = 18\%$) breached the criteria for the correction of the measurement volume droplet size bias, diminishing the contribution from the smaller sized droplets. The effect of droplet size bias can be related to the droplet count ratio (DCR), defined as the ratio of corrected to validated signals. The validated droplet count is the number of droplet Doppler signals that have passed the processor validation criteria, i.e. sphericity, signal-to-noise ratio and cross-correlation. Corrected droplet count is the number of droplets after correction of the droplet size bias of the measurement volume. It was found that a droplet count ratio greater than 1.7 was required to satisfy the criteria for the correction of the droplet size bias (Table 4). Droplet count ratio can be increased by damping the turbulent motion of the droplets (relaminarization), achieved by passing the aerosol through a smooth connecting tube. The turbulence intensity of the droplets at the exit of the 30 cm connecting tube was 5%.

Table 5
Thermo-physical properties of NaCl solutions; values at 20°C taken from [27]

NaCl concentration (%w/v)	ρ_l (kg/m^3)	μ_l (cP)[a]	σ (N/m)	η
0.9	1.0064	1.010	0.073	1.334
9.0	1.0652	1.013	0.076	1.349

[a] From [28].

5. Conclusions

Selected factors affecting characterization of air-jet nebulizer output by cascade impaction were evaluated. MMAD and solute delivery rate increased with increasing solute concentration. Fine particle mass increased with increasing solute concentration and sampling time. Connecting tube length had no significant effect on the nebulizer output as the droplets attained equilibrium before being emitted through the T-piece ($p > 0.05$). Grounding the impaction plates and marker concentration had no significant effect on the characterization of the nebulizer output ($p > 0.05$). This information will be useful when standardizing methods of analysis for nebulizers. Cascade impaction is the method of choice for characterizing nebulizer output, revealing information on the fine particle mass of the active ingredient and aerodynamic droplet size distribution. PDA provides rapid, in-situ droplet size distribution and velocity characterization. It was shown that the droplet size distributions produced by the Aerotech II air-jet nebulizer with low solute concentration (0.9%) were below the lower resolution limit of PDA ($D < 0.5$ μm). Thus, caution must be applied when characterizing nebulizer output by PDA.

Acknowledgements

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Appendix A.

A two-level fractional factorial design was used to investigate the main and interactive effects of selected inertial impaction parameters on the output from an air-jet nebulizer. Effects in a two-level factorial design are defined as the average change in the response obtained from a low (−) and a high (+) level parametric value. A change in response due to a single parameter is known as a main effect and a change in response due to two or more parameters is known as an interactive effect. Effects due to experimental error or noise are normally distributed. Parametric interactions that have a prominent effect on the response factor and effects that are due to random error are estimated by plotting the normal probability of effects. Parameters that do not produce an effect greater than experimental noise are considered to be hidden replicates.

Fractions of a full factorial design can be performed by confounding low order effects with high order effects. Confounding of effects is based on the assumption that high order effects (effects due to the interaction of multiple parameters) can be assumed to be negligible. Interactions of three or more parameters are usually assumed negligible [19]. Confounding can also be used to block parameters that are difficult to control. Environmental conditions can be confounded with high order interaction when experiments are being conducted over a number of days. It is common practice to block effects that are difficult to control with interactions that are initially considered to have little effect on the response. When effects are observed due to blocking, more experiments are required to determine the confounding relationship.

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