Medical Nebulizer Performance: Effects of Cascade Impactor Temperature

Yue Zhou PhD, Amitkumar Ahuja MSc, Clinton M Irvin, Dean A Kracko, Jacob D McDonald PhD, and Yung-Sung Cheng PhD

BACKGROUND: During operation of a jet nebulizer, the temperature of the nebulizer outlet could decrease by more than 10°C, depending on the nebulizer type and operating conditions, such as driving flow rate and fill volume. The droplet size distribution generated from the nebulizer can be measured by a cascade impactor. However, when the cascade impactor is operated at ambient room temperature, the droplets could evaporate because of the temperature difference between the nebulizer outlet and the body of the impactor. METHODS: An 8-stage cascade impactor was used to measure the particle size distribution from 4 different types of jet nebulizer (LC Plus, Side-Stream, VixOne, and Micromist) in 2 temperature conditions: ambient (22°C) and low (10°C). Two different formulations, albuterol (aqueous solution) and budesonide (suspension), were used. RESULTS: There was a significantly larger ($p < 0.05$) mass median aerodynamic diameter and smaller respirable fraction for each nebulizer with the impactor at low temperature than with the impactor at ambient temperature. The mass median aerodynamic diameter of the nebulizers with the impactor operating at low temperature appeared 15–130% larger than with the impactor operating at ambient temperature, for both formulations. The respirable fraction also changed from 10% when the impactor was operated at low temperature to 65% when the impactor was operated at ambient temperature. CONCLUSION: The results provide important information for the use of a cascade impactor to measure the particle-size distribution of nebulizer aerosols. *Key words: nebulizer, aerosol, cascade impactor.* [Respir Care 2005;50(8):1077–1082. © 2005 Daedalus Enterprises]

Introduction

The choice of a proper nebulizer system is very crucial for the efficient delivery of aerosolized respiratory drugs.[1] A nebulizer system includes all the components attached to the nebulizer that can alter its performance. The system may include compressed gas (air, oxygen, or helium-oxygen mixture), connectors, tubing, mouth piece, and/or face mask.[1]

Jet nebulizers are widely used, because of their durability, ease of maintenance, and availability at low cost. In a jet nebulizer, compressed air is forced through a narrow orifice, which leads to a decrease in lateral pressure, thereby drawing up liquid from the feed tube. The primary droplets are produced in the nozzle region and then broken down into smaller droplets. The nonrespirable droplets are removed by baffles.[2] The droplets may increase in diameter because of condensation of water vapor. This condensation occurs because the droplets are at a low temperature (about 10°C) after being released from the nebulizer, if the surrounding air stream was unsaturated.[3] With aqueous solutions the extremely large surface area created by small droplets and a dry power-gas cause considerable evaporation, and the temperature of the solution containing the drug begins to decrease as soon as nebulization begins.[2]

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Dennis et al[4] measured the change in temperature of a reservoir solution with the help of a thermocouple and found that the solution temperature started decreasing from room temperature (20–25°C) as soon as nebulization began, and went down to as low as 10°C. They also found that, because of rapid evaporation of the solvent, the solution concentration also increased as nebulization progressed.[4]

A study by Dolovich also found a typical 12°C temperature decrease with 5 different types of nebulizers tested.[5] She mentioned that the temperature change differs among nebulizer designs and also varies with fill volume. Most of the temperature drop occurs in the first 60–90 seconds. Dahlbäck mentioned that, for the initial 2 minutes of nebulizer operation, the temperature decreases rapidly, and then it stabilizes.[6]

In a temperature comparison study, Finlay and Stapleton evaluated the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the LC Plus nebulizer with an Andersen cascade impactor operating at an ambient temperature of 22°C and a low temperature of 10°C, in a water bath.[7] They found that the average MMAD was significantly lower for the impactor operated at ambient conditions than that for the immersed impactor. The GSD was significantly higher with the ambient-temperature impactor than with the immersed impactor. Kwong et al also compared the MMAD and GSD of an LC Star nebulizer by operating an impactor at room temperature and low temperature,[8] and obtained results identical to those of Finlay and Stapleton. However, in the study by Kwong et al, the MMAD and GSD from an impactor were also compared with that from the Malvern Mastersizer X impactor. Their results showed that the MMAD and GSD measured by an impactor at low temperature were the same as those compared with the Malvern Mastersizer X.

Using a cascade impactor to measure the droplet size distribution from a nebulizer is still very common.[7] In a United States Food and Drug Administration guideline, no temperature suggestions are mentioned for a nebulizer evaluation with cascade impactor.[9] However, according to the operation principle of a jet nebulizer, most nebulizer aerosols are below ambient temperature.[10] Unless the mixed air is saturated, droplet evaporation is likely in most practical situations. It was found that cascade-impactor measurement of nebulizer aerosol could be biased as a result of heat transfer.[7] However, the study by Finlay and Stapleton[7] was carried out only with saline. No publication was found that indicated that bias with a drug formulation.

In the present study, 4 jet nebulizers were tested with the Andersen impactor and both aqueous solution and suspension formulations. The aim of the study was to investigate the effect of temperature on nebulizer particle-size distribution with 2 typical drug formulations (aqueous solution and suspension).

Methods

Nebulizer

Four nebulizers were tested: LC Plus (Pari Respiratory Equipment, Midlothian, Virginia), SideStream (Profile Therapeutics, United Kingdom), VixOne (Westmed, Tucson, Arizona), and Micromist (Hudson Respiratory Care, Temecula, California).

By mixing inhaled air inside the nebulizer, the droplets produced with the LC Plus evaporated quickly. However, air inside the nebulizer also increases the rate at which droplets are produced, so saturation is reached sooner, and further droplet evaporation is inhibited. This design proved to be more efficient than traditional jet nebulizers.[11] Hence, the LC Plus was chosen for the study.

The SideStream nebulizer was selected because it is widely used in Europe and has been shown to be a highly efficient device in vivo.[12] Large droplets produced by the SideStream could be removed from the side tube. It is also the only nebulizer with an external mixing nozzle design.[13] With the internal mixing nozzle and traditional design, VixOne and Micromist, which were evaluated by several sources,[14–16] were also included. These nebulizers were used to generate the aerosol at a flow rate of 7 L/min, measured with a DryCal flow calibrator (BIOS International, Pompton Plains, New Jersey) that has a precision of within 2%.

The compressed air was from a wall air supply, at pressures of 13, 14, 14, and 34 psi for the VixOne, Micromist, SideStream, and LC Plus, respectively. Because the performance of these 4 nebulizers was compared in this study, the nebulizer flow rate was the same. The relative humidity of the surrounding air stream was maintained at 50% with a humidifier.

Experiment Setup

The experimental setup used in the study is shown in Figure 1. The nebulizer on the test was connected to a T-piece and collar. The collar was designed to connect one end of the T-piece to the entrance of the USP throat. A bubble humidifier or a silica gel dryer was placed in the system as needed to maintain the relative humidity at 50 ± 5%. Thermocouples were placed at the inlet and outlet of the impactor to record the temperature changes during the test, and a vacuum source was connected to the impactor. For room-temperature (ambient) tests, the nebulizer and impactor were placed in the laboratory, with the temperature maintained at 22 ± 1°C. For the low-temperature tests the nebulizer was placed in the laboratory and main-

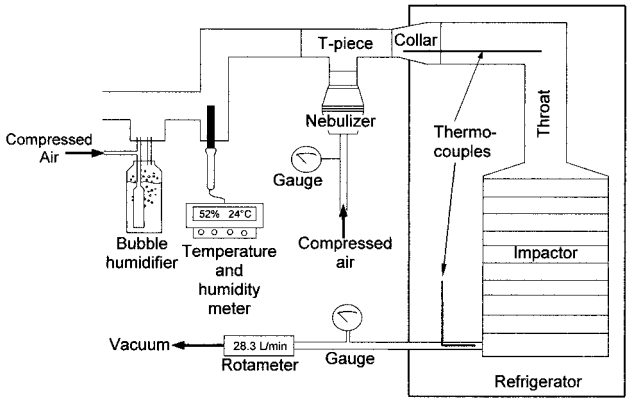

Fig. 1. Experiment setup.

tained at ambient conditions, but the impactor was kept in a refrigerator, with a temperature of 10 ± 1°C. When initial sputtering was observed, the nebulizer was run for an additional 1 min, with periodic tapping of the side of the nebulizer. The impactor was disassembled after the test. All collection surfaces in the impactor were washed with ultrapure water (Milli-Q, Millipore Corporation, Billerica, Massachusetts) for the albuterol, and a 50:50 mixture of Milli-Q water and methanol for the budesonide. The nebulizer also was washed after each test, to determine the residual mass, in order to check the mass balance.

Impactor

An Andersen 8-stage cascade impactor (Thermo Electron Corporation, Franklin, Massachusetts) was used in this study and operated at an airflow of 28.3 ± 0.2 L/min, set with the flow calibrator. The Andersen cascade impactor size-classifies aerosol particles between 9 μm and 0.4 μm aerodynamic diameter on the deposition plate, when operated at 28.3 L/min. A final filter collects all particles smaller than 0.4 μm. The Andersen cascade impactor is specifically cited in the United States Pharmacopoeia (USP) for size-classifying aerosols from nebulizers and other inhalers.[17]

In this study the impactor was operated at ambient temperature (22°C) and at low temperature, in a refrigerator maintained at 10 ± 2°C (see Fig. 1). The temperature in the impactor was recorded every 1 second after the impactor was put into the refrigerator. For most tests the temperature reached 10°C about 10 min after the impactor was put into the refrigerator.

Formulation

The nebulizer performance can differ for different solutions and suspensions.[6] We tested albuterol (solution, 0.083%) and budesonide (suspension, 0.025%), which are widely used for treating asthma and other respiratory ailments. Albuterol was tested with all the nebulizers. Budesonide was tested only with the VixOne and LC Plus, for comparison with the albuterol. Table 1 shows the formulations used in each nebulizer.

Table 1. Formulations Used in the Nebulizers

	Ambient Temperature (22°C)	Low Temperature (10°C)
VixOne	Albuterol and Budesonide	Albuterol and Budesonide
SideStream	Albuterol only	Albuterol only
MicroMist	Albuterol only	Albuterol only
LC Plus	Albuterol and Budesonide	Albuterol and Budesonide

Albuterol samples were analyzed with a validated ultraviolet spectrophotometer at 224 nm. A high-performance liquid chromatography system (model 1050LC, Hewlett Packard, Palo Alto, California) was used to analyze the budesonide samples, in accordance with good laboratory practices.

Particle-Size Distribution

Some nebulizer aerosol particle-size distributions are not normal (eg, some are bi-modal), as discovered previously (internal report), in which case no meaningful MMAD or GSD can be obtained. However, non-normal distribution was not apparent in this study. The MMAD and GSD were calculated using technical graphing software (SigmaPlot 8.0, SPSS, Chicago, Illinois), with a lognormal, 3-parameter, nonlinear regression. The distribution was considered log normal if the correlation coefficient of the regression was larger than 90%.

Respirable Fraction

The respirable fraction is generally considered the fraction of an aerosol contained in particles that are < 4.7 μm aerodynamic diameter, which are likely to be deposited below the oropharynx and in the lung.[18]

Statistical Analysis

An unpaired *t* test was used to determine whether the MMAD and GSD differences were significant (3 replicates, using spreadsheet software [Excel, Microsoft, Redmond, Washington]). A p value of < 0.05 was considered significant.

Results

The temperature profile of nebulizer-outlet flow stream for the 4 tested nebulizers at the flow rate of 7 L/min is

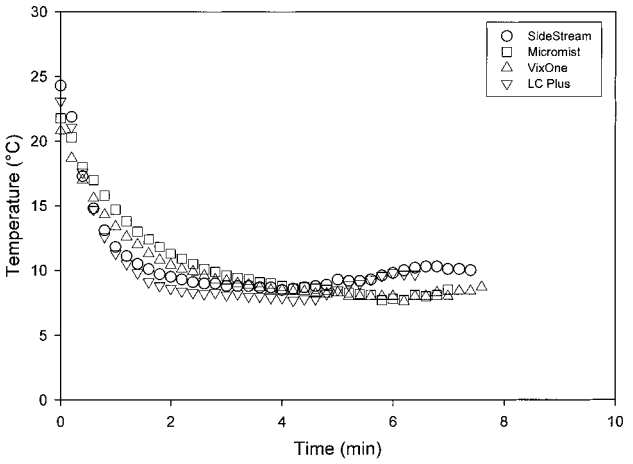

Fig. 2. Temperature profile at the outlet of the 4 tested nebulizers, operating with albuterol.

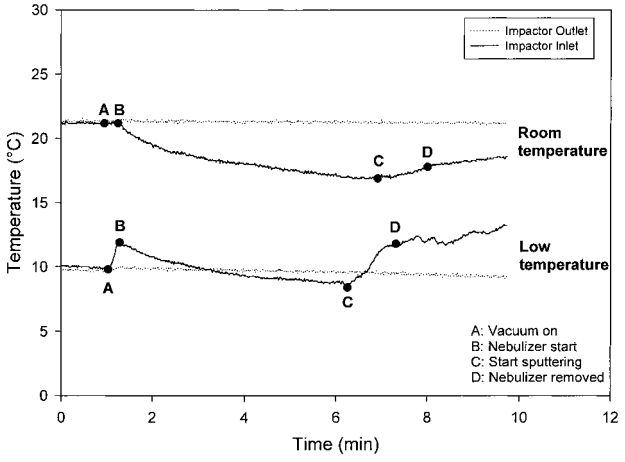

Fig. 3. Inlet and outlet temperature profile of the impactor operating at the ambient and low temperature.

shown in Figure 2. The temperature was observed to fall more than 10°C, depending on the evaporation rate. The temperature dropped very fast in the first 60 s and stabilized within 2 min.

Figure 3 shows the impactor inlet and outlet temperature profile with the VixOne nebulizer. At ambient temperature the inlet and outlet temperatures did not change before the operation of the nebulizer. However, when nebulization began, the impactor inlet temperature decreased to about 17°C, until the onset of sputtering, when the temperature increased. The outlet temperature was stable for the entire operation. With the impactor operating at low temperature, the inlet temperature had more changes. When the vacuum was turned on, the inlet temperature increased until the nebulizer was operated. After nebulization, the inlet temperature decreased to the minimum of 8.4°C. The temperature was also increased during sputtering (point C to D in Fig. 3). The impactor outlet temperature was only slightly decreased, from 10°C to 9.1°C, with the impactor operating at low temperature.

Tables 2 and 3 list the MMAD, GSD, and respirable fraction of the 4 tested nebulizers sampled by the impactor at ambient and low temperature conditions with albuterol (Table 2) and budesonide (Table 3). The p values from the *t* tests are also listed in the tables. The mass distribution obtained with the impactor was found to be log normal.

Discussion

The nebulizers' output temperature decreased to 7.9 ± 0.4°C from room temperature and then slightly increased when sputtering started. This temperature drop agrees with the study by Dennis et al, who obtained about 10°C at the nebulizer reservoir while operating 3 other types of jet nebulizers, Wright, Micro-Cirrus, and Turbo, with the flows of 8 L/min, 7.5 L/min, and 7.5 L/min, respectively.[4]

As shown in Figure 3, the inlet temperature of the impactor was 17°C during nebulization. The temperature of the nebulizer outlet was about 8°C; thus, there was a 9°C temperature difference between the outlet of the nebulizer and the inlet of the impactor. The aerosol then passed through the impactor and reached the ambient temperature at the impactor outlet. There was a maximum 14°C difference from the outlet of the nebulizer to the outlet of the impactor. This temperature difference caused droplet evaporation during impactor sampling. In comparison, for the impactor operating at low temperature, the minimum inlet temperature (8.4°C) of the impactor was very close to the minimum nebulizer outlet temperature (7.9 ± 0.4°C). No evaporation occurred during the sampling. The impactor temperature profiles also showed an increased inlet temperature during sputtering. This is because less water was being nebulized, causing a decrease in the evaporative cooling effect.

The average MMADs for all the nebulizers with albuterol was significantly lower ($p < 0.05$) with the impactor at ambient than at low temperature. The MMAD of the VixOne, Micromist, and SideStream nebulizers with the impactor at low temperature appeared more than twice as large as that of the impactor operated at ambient temperature. For the LC Plus nebulizer, the MMAD was about 25% larger when operating the impactor at low temperature than at room temperature (3.56 μm vs 2.85 μm).

The MMAD results of the LC Plus agreed with the study by Finlay and Stapleton,[7] who also obtained a larger MMAD for the impactor operating at low temperature than at ambient temperature (3.4 μm vs 2.1 μm). The MMAD results indicate that the nebulized droplet size decreased during the impactor sampling at the ambient temperature. Because the temperature difference between the nebulizer outlet and the inside of the impactor body

Table 2. MMAD, GSD, and Respirable Fraction for Albuterol Aerosol When the Impactor Was Operated at Ambient (22°C) and Low Temperatures (10°C)

	MMAD (mean ± SD μm)			GSD (mean ± SD)			Respirable Fraction (mean ± SD percent)		
	22°C	10°C	p*	22°C	10°C	p*	22°C	10°C	p*
VixOne	1.63 ± 0.07	4.34 ± 0.05	0.0003	1.92 ± 0.09	2.00 ± 0.14	0.068	43.06 ± 2.93	30.00 ± 1.50	0.0174
SideStream	1.36 ± 0.01	2.83 ± 0.07	0.0004	1.80 ± 0.17	1.78 ± 0.09	0.38	34.50 ± 1.67	28.47 ± 1.85	0.0391
MicroMist	1.58 ± 0.02	4.23 ± 0.22	0.0009	1.84 ± 0.06	2.22 ± 0.06	0.0001	35.13 ± 0.84	26.42 ± 1.84	0.0140
LC Plus	2.85 ± 0.03	3.56 ± 0.17	0.0068	2.50 ± 0.04	2.13 ± 0.05	0.0075	36.47 ± 1.76	32.72 ± 1.32	0.0449

MMAD = mass median aerodynamic diameter
GSD = geometric standard deviation
*p calculated via *t* test

Table 3. MMAD, GSD, and Respirable Fraction for VixOne and LC Plus With Budesonide When the Impactor Was Operated at Ambient (22°C) and Low Temperatures (10°C)

	MMAD (mean ± SD μm)			GSD (mean ± SD)			Respirable Fraction (mean ± SD percent)		
	22°C	10°C	p*	22°C	10°C	p*	22°C	10°C	p*
VixOne	3.04 ± 0.63	5.35 ± 0.07	0.0096	1.88 ± 0.34	1.86 ± 0.04	0.453	19.19 ± 4.54	11.62 ± 0.64	0.0592
LC Plus	5.21 ± 0.02	5.61 ± 0.34	0.081	1.97 ± 0.06	1.91 ± 0.12	0.094	20.81 ± 4.31	14.89 ± 0.37	0.0798

MMAD = mass median aerodynamic diameter
GSD = geometric standard deviation
*p calculated via *t* test

was about 14°C, the droplets traveling through the impactor evaporated. Therefore, the particle distribution measured at ambient temperature was after droplet evaporation and is not representative of the original particle-size distribution produced by the nebulizer.

The GSDs of the tested nebulizers varied with the impactor operating at the ambient and low temperature, but only 2 nebulizers (Micromist and LC Plus) with albuterol had significantly different GSDs when the impactor was operated at ambient and at low temperatures. For the LC Plus ($p = 0.0075$), our results agreed with those obtained by Finlay and Stapleton,[7] who found the higher GSD for the impactor at ambient temperature, versus at low temperature. However, we also obtained the opposite result ($p = 0.0001$) for the Micromist nebulizer and found no significant GSD difference ($p > 0.05$) for the rest of the tests, including all tests with budesonide. Finlay and Stapleton explained 2 phenomena that lead to the spread of the distribution (large GSD) with the ambient impactor: hygroscopic size changes more rapidly with the small droplets than the large droplets, and small droplets experience larger hygroscopic driving forces over a longer time than do large droplets.[7] However, most of our experimental results showed a similar GSD for both temperatures. Other factors can counteract the effect that Finlay and Stapleton mentioned. The nebulizer design and the drug formulation could be the factors that impact the GSD.

Basically, the respirable fraction is based on the MMAD and GSD if the ideal log-normal distribution is applied. In this study the respirable fractions of all the tested nebulizers were significantly higher ($p < 0.05$) with the impactor at ambient temperature than at low temperature. A higher MMAD caused a lower respirable fraction. This low respirable fraction indicates that the actual medicine a patient inhales would be less than expected.

As discussed in the previous section, the particle-size distribution was different when using albuterol and saline. Formulation is one of the important factors that can affect the particle-size distribution.[5] Budesonide as a suspension formulation affects impactor-measured particle-size distribution data, because the budesonide particles have to be enclosed in a water droplet during nebulization. It is possible to have "empty" fine droplets or coarse droplets containing more than one budesonide particle. Therefore, both droplet particle-size distribution and drug product particle-size distribution are important to consider. As shown in Table 3, the trend of the MMAD for the impactor at the 2 temperatures was the same as that with albuterol. However, the level of the change was smaller than that with albuterol. For example, the MMAD of the LC Plus was only 15% larger, but not significantly ($p = 0.081$), for the impactor at low temperature than for the impactor at ambient temperature. The value for the albuterol was 25% (see Table 2, $p = 0.0068$). Because budesonide has a

higher MMAD than albuterol at low temperature, the evaporation rate of large particles is slower than that of small particles at the same temperature.

Conclusions

Cooling the impactor is a way to measure the actual particle-size distribution generated by a nebulizer. However, measurement should be made after the impactor achieves thermal equilibrium with its surroundings. Thermal equilibrium was normally achieved in about 1 hour. Operating the impactor at ambient temperature with saturated surrounding air can speed up the measurement. However, there are no published reports supporting that the droplets inside the nebulizer do not evaporate with the saturated ambient air. Actually, the drive air of the nebulizer is generally dry air; it is very difficult to make a saturated surrounding inside the nebulizer.

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