

In Vitro Comparison of Particle Size Distribution/Respirable Dose for LiteAire™ Spacer Versus Misty Max 10™ Nebulizer Using Albuterol

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INTRODUCTION

There is tremendous variability in the number of MDI actuations (2-12) used in studies comparing beta agonist delivery via MDI/spacer to a single unit dose ampule with a nebulizer (1-4). As delivery systems influence the inhaled dose, it would be prudent to determine the *in vitro* fine particle dose using the two delivery systems prior to conducting a clinical efficacy comparison between MDI/Spacer and a standard jet nebulizer. Since some clinical trials have suggested the use of 6 MDI actuations (1-4), we chose to determine the emitted dose, particle size distribution and fine particle dose between 6 actuations of albuterol MDI with LiteAire™ Spacer versus one unit dose ampule with a jet nebulizer.

MATERIALS AND METHODS

To determine the fine particle dose, a test device was attached to a USP throat feeding into a filter connected to a Michigan Instrument (Grand Rapids, MI) Dual Test Lung System. The lung was driven by a Puritan Bennet (Pleasanton, CA) 7200 Ventilator set at 14 breaths/minute, tidal volume (TV) of 600 ml and inspiratory to expiratory (I:E) ratio of 1:4. With LiteAire, a CFC Albuterol (generic) MDI (Warrick Pharmaceuticals Inc., Reno, NV) was actuated at the beginning of inhalation for 6 respiratory cycles (n=6 actuations) and with the jet nebulizer Misty Max 10™ (Cardinal Health, Dublin, OH), one 3-ml vial (0.833mg/ml) of Albuterol Sulfate Inhalation (generic) solution (Hi -Tech Pharmaceuticals, Amityville, NY) was delivered over five minutes.

The flow to the nebulizer was supplied by a medical grade oxygen tank that supplied gas through a Western Medica (Westlake, OH) two stage regulator to a Western Medica oxygen flowmeter (Westlake, OH) set to deliver 8L/min. Each filter was washed with 0.05mM KCl with 1 % acetic acid buffer to collect the deposited drug. Dosage was determined quantitatively using a UV spectrophotometer, at a wavelength of 276 nm. Both devices were tested 3 times each.

Particle size was determined using an Andersen 8-Stage Cascade Impactor (ACI) with USP throat. A filter for collection of particle was placed after the last plate of the ACI instead of a terminal filter inside the impactor. Flow rate of 28.3 L/min was confirmed with a TSI 4040 flow meter (TSI Incorporated, Shoreview, MN) at the air entry to the USP throat model when the ACI was operated at 28.3 L/min. The TSI flow meter placed downstream of the ACI was calibrated to provide accurate flow measurement under negative pressure conditions to ensure that there was no drift in the flow during the experiment. For the spacer unit (Figure 1), the vacuum pump was turned on for at least 60 seconds. Six doses of medication were dispensed at the rate of one actuation of albuterol MDI every 10 seconds.

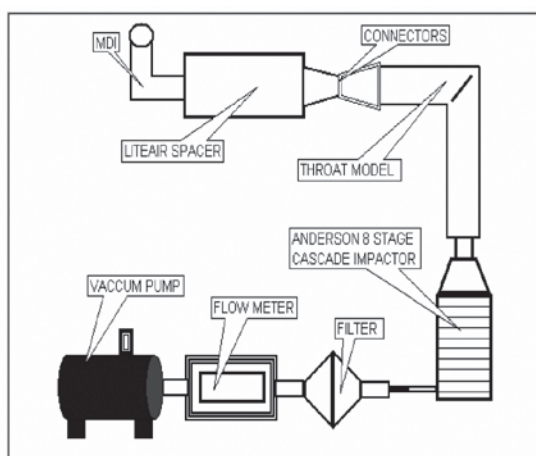


Figure 1. ACI set up for LiteAir Spacer with MDI.

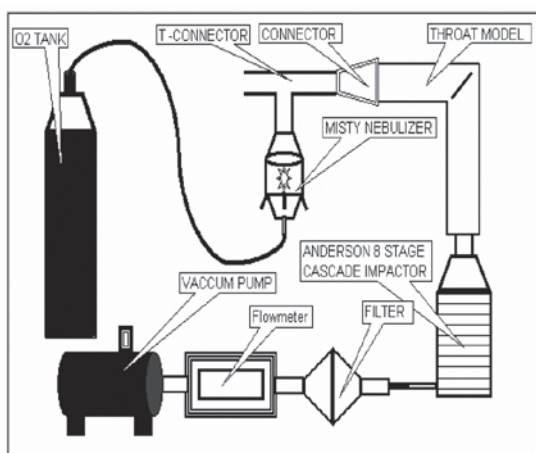


Figure 2. ACI set up for Misty Max 10 nebulizer.

For the T-nebulizer, setup using the Misty Max 10 (Figure 2), the vacuum pump was turned on for at least 60 seconds and one 3-ml vial (0.833mg/ml) albuterol solution was delivered over five minute period using O₂ at 8 L/min to the nebulizer. Each plate and the filter were washed separately with 10ml of 0.05 mM KCl with 1% acetic acid solution to obtain 9 samples. The 9 samples underwent analysis to quantify the dose of albuterol using a Unico 2100 UV (Unico Ltd., Dayton, NJ) Spectrophotometer ($\lambda=276$ nm). The above experiment was repeated three times ($n=3$), for both devices.

RESULTS

The emitted dose was 176 ± 27 μg for 6 actuations of albuterol delivered to a LiteAir Spacer via MDI versus 220 ± 14 μg for a Misty Max 10 with T-piece. The percent respirable fraction (defined as the total mass on plates # 3-7 indicating a size range of 4.7-0.4 μm) was $91 \pm 2\%$ for LiteAir and $82 \pm 1\%$ for the Misty Max 10 ($p < 0.001$). The particle size distributions are shown in Figure 3. Table 1 summarizes the ACI results. The MMAD was 2.05 ± 0.0 μm for the LiteAir versus 1.49 ± 0.05 μm for the

Misty Max 10 ($p < 0.0001$) and the GSD was 1.64 ± 0.03 for the LiteAire versus 2.25 ± 0.06 for the Misty Max 10 ($p < 0.001$). The fine particle dose was $159 \pm 24 \mu\text{g}$ with the LiteAire vs. $180 \pm 11 \mu\text{g}$ for the Misty Max 10 ($p = 0.27$). P values were calculated by the two tailed T- test with unequal variances.

Table 1.

Characterization of particle size distribution.

	LITEAIRE / MDI	MISTY MAX 10
MMAD (μm) \pm SD	2.05 ± 0.03	1.49 ± 0.05
GSD \pm SD	1.64 ± 0.03	2.25 ± 0.06
Fine Particle Dose (μg) \pm SD	159 ± 24	180 ± 11

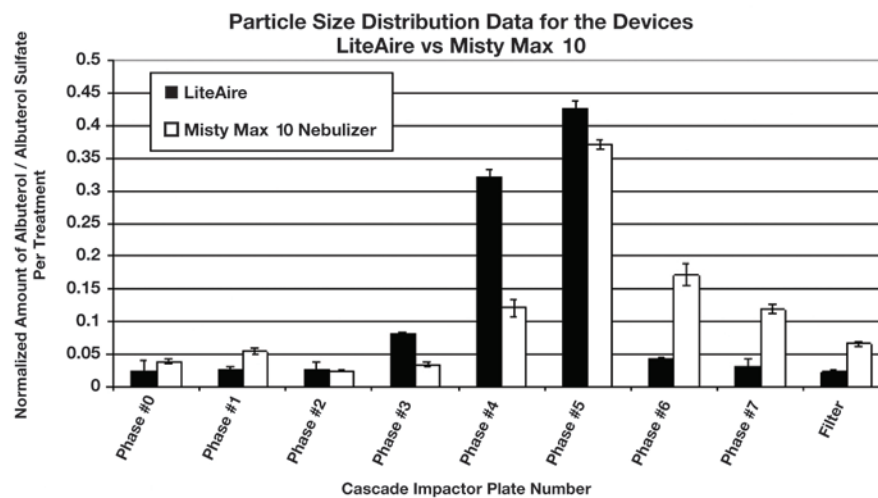


Figure 3. Graph of particle size distribution.

DISCUSSION

With the hardware and drug products we evaluated, this study demonstrates that there is no significant difference in the fine particle dose using 6 actuations of albuterol MDI with spacer versus one unit dose of nebulized albuterol. Even though the difference in the respirable fraction between the two modes of delivery using the ACI was significant, there was no difference in the fine particle dose calculated using the dose emitted with the breath simulation technique multiplied by the respirable fraction using the ACI.

We used oxygen at a flow rate of 8 L/min for nebulizing albuterol, a standard practice for acute asthma in the emergency department. We determined that the impact of using oxygen instead of room air on the cut off diameter in the ACI is negligible as the cut off diameters for the ACI are dependant on the viscosities of gas used with the impactor (5). Moreover, since the TSI flow meter was calibrated for air and oxygen during albuterol delivery with MDI/spacer versus nebulization respectively, the flow measured would not influence the cutoff diameters for the ACI. The viscosity of air is 0.018centiPoise while that of 100% oxygen is 0.020centiPoise. The concentration of oxygen and the respective viscosity when delivered at 8 L/min, with ACI operating at 28.3L/min flow was 43% and 0.019centiPoise, respectively. Hence, the difference in viscosities of

the two gases used for the two modes of delivery (MDI / Spacer vs. Nebulizer) would be 0.001 centiPoise. The impact of this difference on the cutoff diameters of ACI and therefore the respiratory particle size would be negligible.

In a study by Malone *et al.*, it was determined that aerosolization via a standard jet nebulizer past the sputtering point did not increase albuterol delivery (6). The study observed an abrupt decline in aerosol output that always corresponded to the nebulizer sputtering with no change in the albuterol output between 30 to 60 seconds after the sputtering time for three different volumes (1.5 ml, 2.5 ml, and 3.5 ml albuterol solutions). Since the 5 minutes nebulization time in our study was approximately 60 seconds more than the sputtering time, we think the nebulization time was optimal.

CONCLUSION

When conducting a clinical efficacy study comparing albuterol delivered by MDI/LiteAire Spacer versus a single unit dose of 3 ml albuterol solution delivered via jet nebulization at 8 L/min oxygen, we recommend using 6 albuterol MDI actuations with spacer if the intent is to achieve an equivalent *in vitro* fine particle dose with the two modes of administration. These results may not be applicable for other spacer devices and MDI combinations.

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