

Recent In Vitro & In Vivo Studies

**IMPROVED AEROSOL DELIVERY CHARACTERISTICS
OF A BREATH ENHANCED NEBULIZER
OVER A BREATH-ACTUATED NEBULIZER**

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Improved Aerosol Delivery Characteristics of a High Density Breath-Enhanced Nebulizer (NebuTech® HDN®) Over a Breath Actuated Nebulizer

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Abstract

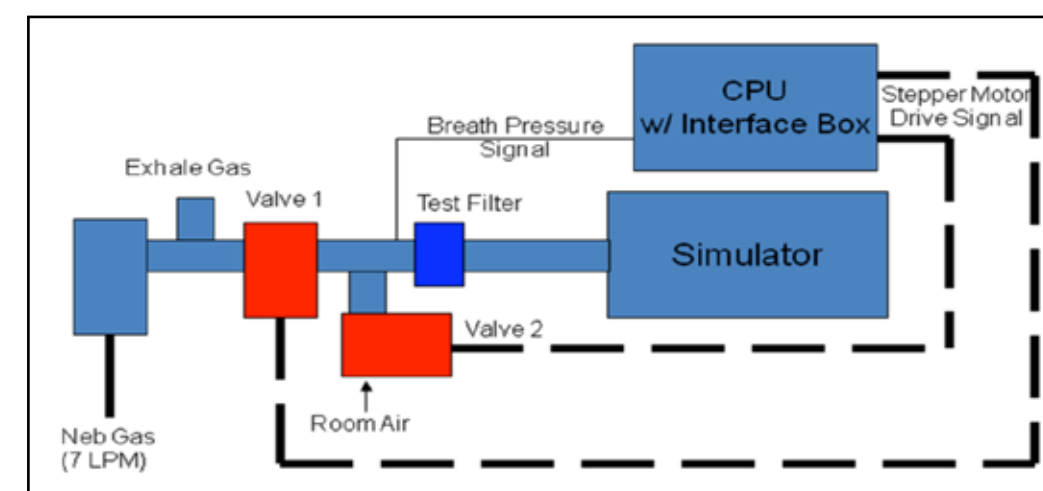
The high density breath-enhanced nebulizers provide a high density aerosol during the initial phase of the inhalation cycle. This results in a bolus of higher dose of medication being delivered to the lungs during the onset of the inhalation cycle, which is critical in improving treatment efficacy (especially in emergency room treatments) and can also reduce the treatment time and patient care costs significantly. This study compares the delivery of albuterol sulfate (in saline solution) by a breath-enhanced jet nebulizer (NebuTech® HDN®, Salter Labs, Arvin, CA) against a breath actuated nebulizer (AeroEclipse® II BAN, Monaghan Medical Corp, Plattsburgh, NY). NebuTech® HDN® (n=6) was charged with 3 mL of albuterol sulfate solution (5mg/mL) and operated at 7 L/min with compressed clean air at 50 psig. Similarly, AeroEclipse® II BAN (n=6) was charged with 3 mL of albuterol sulfate (5 mg/mL) and operated at manufacturers recommended settings. The nebulizers were connected to a lung simulator and aerosol was collected on a filter during the first 250 mL of the inhalation cycle and also for the full inhalation cycle. Analysis of albuterol sulfate collected on the filters was performed using a UV Spectrophotometer. In a parallel experiment, optical density measurements of the aerosol output were taken for both nebulizers during a complete inhalation cycle. Additionally, a 10-stage quartz crystal microbalance (QCM) impactor was used to determine the particle size distribution. Results indicate that NebuTech® HDN® produced a higher aerosol dose (249 ± 40 µg/min) during the first 250 mL of inhalation cycle versus AeroEclipse® II BAN (73 ± 20 µg/min). The total dose delivered during a complete inhalation cycle by NebuTech® HDN® (469 ± 64 µg/min) was also higher than that for AeroEclipse® II BAN (304 ± 33 µg/min). Both the NebuTech® HDN® (1.5 µm ± 0.08) and AeroEclipse® II BAN (1.33 µm ± 0.09) had comparable mass median aerodynamic diameter (MMAD). The fine particle fraction (FPF), defined as particles less than 4.7µm in diameter, were also comparable for NebuTech® HDN® (60.2%) and AeroEclipse® II BAN (61.2%). The treatment time with NebuTech® HDN® was close to 3 min while AeroEclipse® II BAN took more than 9 min for nebulizing the entire dose. These results clearly show that NebuTech® HDN® is not only capable of delivering higher concentration of respirable dose in the critical initial phase of the inhalation cycle to maximize drug deposition in the lungs, but it also produces an overall higher dose for the entire inhalation cycle in shorter periods. Additionally, *in vivo* scintigraphy tests were performed for NebuTech® HDN® (n=2) and AeroEclipse® II BAN (n=2) on healthy male subjects (n=2) to graphically demonstrate the deposition of radio-labeled technetium diethylene triamine penta-acetic acid (99m TcD TPA) using ventilation lung scanning. The results of lung scans reveal that the NebuTech® HDN® delivered higher drug concentration to the lungs with minimal loss in oropharyngeal region. The results of this study illustrate that NebuTech® HDN® offers higher drug delivery efficiency in shorter time periods than that provided by AeroEclipse® II BAN.

Introduction

- Penetration of aerosol to the lungs is important for enhanced drug deposition and treatment. The initial phase of the inspiration cycle is critical in achieving that enhanced drug delivery to the lungs.
- Dose assurance and quick response to medication is crucial in emergency room treatments. The aerosol device must deliver drug in a short time to be effective.
- This study establishes that the breath-enhanced nebulizer, NebuTech® HDN®, delivers a bolus of higher dose to lungs in relatively short duration and can cut treatment time (and costs) significantly.
- Patient compliance is important when using an aerosol device. NebuTech® HDN® allows full patient compliance and does not require inspiratory effort from the patient to nebulize aerosol.
- This study also indicates that AeroEclipse®II BAN delivers minimal to no dose during the initial phase of inhalation cycle. Additionally, majority of the dose is delivered at the end of the inhalation cycle. This in turn can lead to: (i) ineffective treatment of the patient's symptoms, (ii) prolonged treatment time (raising treatment costs)



NebuTech® HDN® Nebulizer

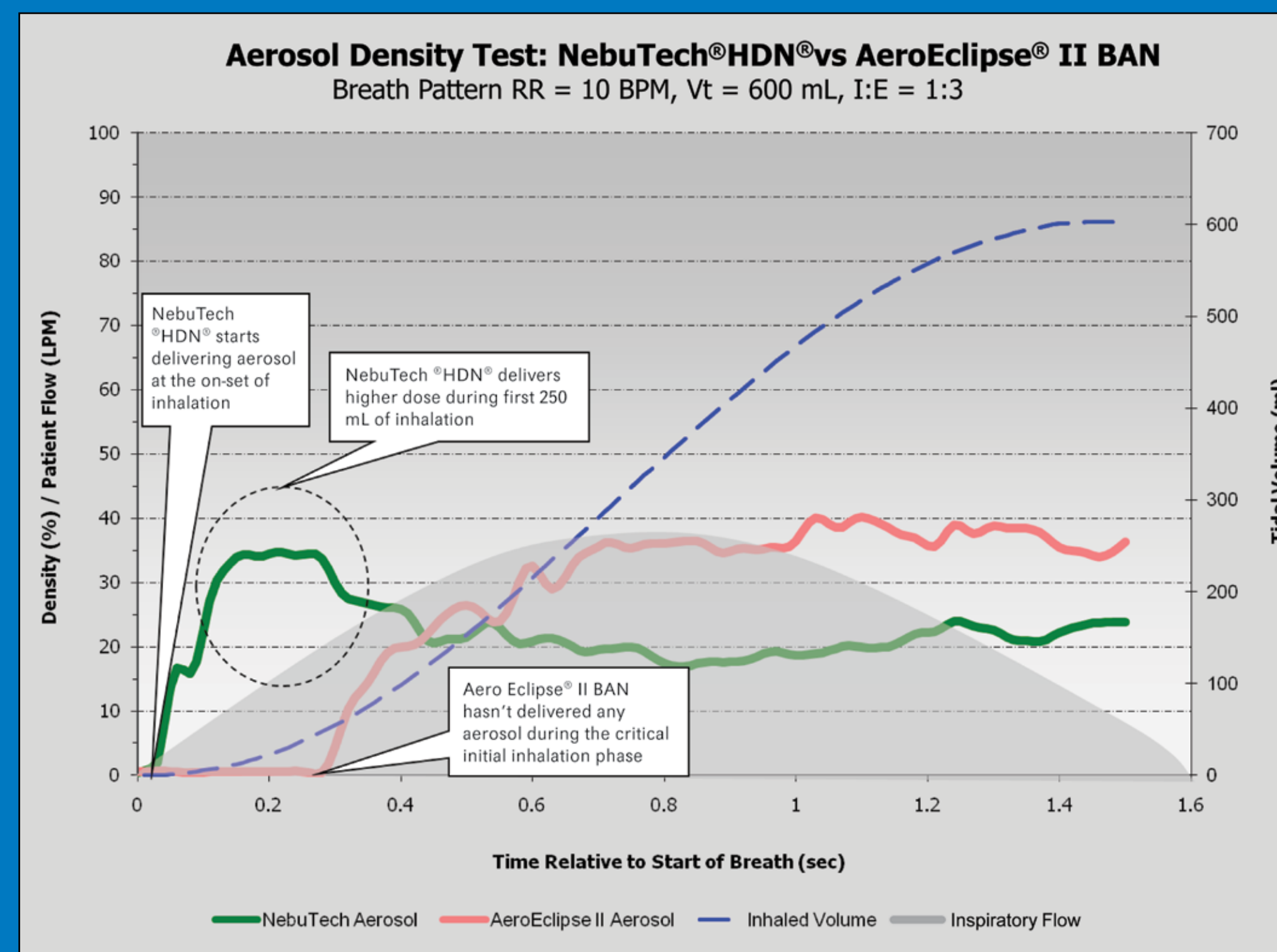


Setup for filter based measurements



AeroEclipse® II BAN

In-Vitro Testing



Summary of Results: In-Vitro Testing

Parameter	NebuTech® HDN®	AeroEclipse®II BAN
Albuterol dose (initial 250 mL inhalation cycle)	249 ± 40 µg/min	73 ± 20 µg/min
Albuterol dose (full inhalation cycle)	469 ± 64 µg/min	304 ± 33 µg/min
Mass Median Aerodynamic Diameter (MMAD)	1.52 µm ± 0.08	1.33 µm ± 0.09
Fine Particle Fraction (FPF)	60.2 %	61.1 %
Treatment time	3 min	> 9 min

Materials

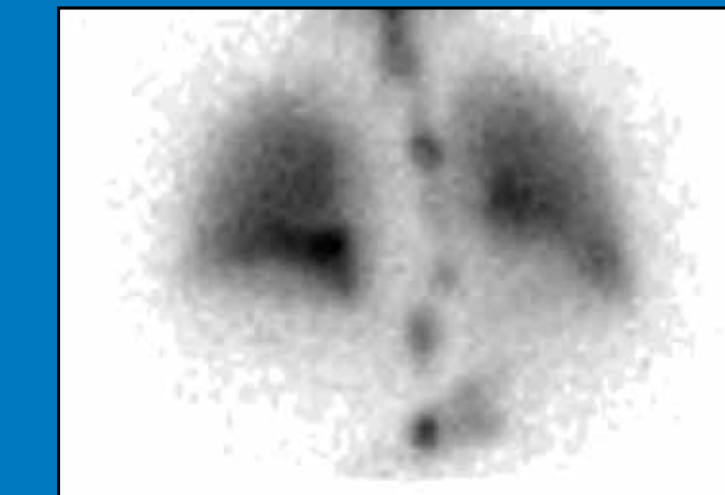
- Breath-enhanced nebulizer (NebuTech® HDN®, Salter Labs, Arvin, CA)
- Breath actuated nebulizer (AeroEclipse®II BAN, Monaghan Medical Corp, Plattsburgh, NY)
- Albuterol sulfate in saline (5 mg/mL)
- Lung Simulator (ASL 5000, Ingmar Medical Corp, Pittsburgh, PA)
 - Tidal volume: 600 mL; Duty cycle: 1:3 ratio; Rate: 10 bpm
- Pari filter
- UV Spectrophotometer (DR 4000U, Hach, Loveland, CO)
- Quartz crystal microbalance (QCM, PC-2, California Measurements, Sierra Madre, CA)

Methods: In-Vitro Testing

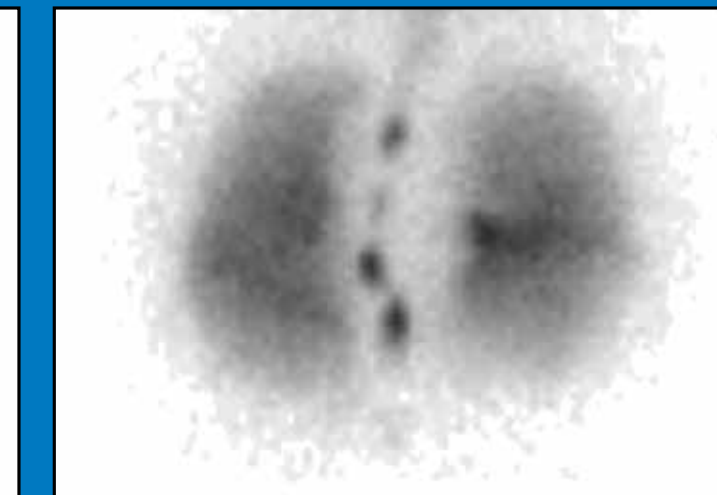
- A total of 12 nebulizers (6 NebuTech® HDN® and 6 AeroEclipse®II BAN) were randomly selected.
- Aerosol was collected during the onset of the inspiration and also for the complete inhalation cycle. Albuterol sulfate was extracted using normal saline and analyzed using UV Spectrophotometer. Calibration curve was plotted using standard solutions of albuterol sulfate in saline.
- Particle size distribution was determined using the QCM which was operated based on manufacturers recommended settings. The data was plotted on log-normal scale and the MMAD was determined.

In-Vivo Testing

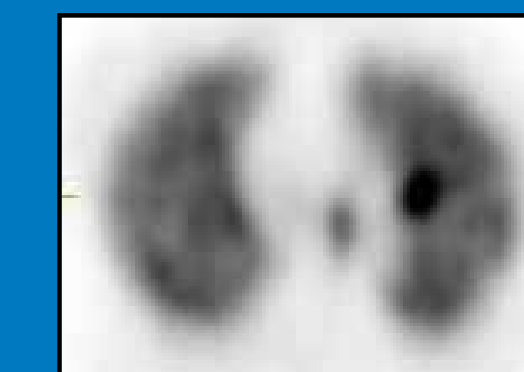
Images show uniform distribution of the tracer in the lungs with minimal activity in the bronchial tree.



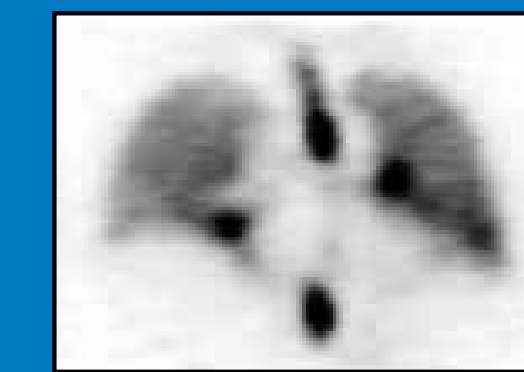
Anterior 323K Duration: 60 sec



Posterior 212K Duration: 60 sec



Axial View



Coronal View

Images and remarks courtesy of: Joseph Mantil, MD, PhD Professor of Medicine Wright State University Dayton, OH

Remarks: Images were acquired using a Dual Heated SPECT Gamma Camera initially in the planar mode. Subsequently, tomographic images were also obtained to determine lung distribution.

Within less than three minutes "NebuTech HDN" device was able to deliver the entire dose to the lung. Tomographic images demonstrated uniform distribution of the activity in the lung with minimal activity in the large bronchial tree.

In Contrast, AeroEclipse device too over 10 minutes to deliver the entire dose to the lung. The lung distribution was similar to NebuTech HDN.

Methods: In-Vivo Testing

- Healthy male subjects (n=2), aged 20-70 years old, were randomly selected.
- Each subject inhaled 3 ml of 99mTcDTPA labeled saline from the NebuTech®HDN® (n=2); and on a separate day (about 3 days later), from AeroEclipse®II (n=2).
- A ventilation lung scan was performed immediately after each inhalation period.

Conclusions

- NebuTech® HDN® delivered 240% higher drug concentration during the onset of the inspiratory cycle than AeroEclipse®II BAN. Additionally, the overall dose delivered by NebuTech® HDN® was 52% higher than that delivered by AeroEclipse®II BAN for a full inhalation cycle. The enhanced drug delivery by NebuTech® HDN® can considerably reduce treatment time and costs.
- The treatment time with NebuTech® HDN® was close to 3 min while AeroEclipse®II BAN took more than 9 min to nebulize the entire dose. This can be of significant benefit in emergency room treatments where quick patient response is vital.
- NebuTech® HDN® delivered significantly higher amount of drug to the lungs than AeroEclipse®II BAN as shown by scintigraphic lung scans. Images show uniform distribution of the tracer in the lungs with some activity in the bronchial tree.
- NebuTech® HDN® does not require patient's inspiratory effort to nebulize aerosol thereby improving patient compliance.
- NebuTech® HDN® can produce high density aerosol for low strength drug solutions. This widens the applicability of NebuTech® HDN® as a variety of medications are sold in low strengths and are less expensive compared to the concentrated drugs. This also cuts the cost of patient care drastically.
- AeroEclipse®II BAN needs significant inspiratory effort from the patient to nebulize aerosol. Additionally, AeroEclipse®II BAN delivers majority of medication at the end of the inhalation cycle. This reduces treatment efficacy and prolongs treatment time.
- This study establishes that while aerosol size and breathing pattern are important parameters that determine the aerosol delivery to the lungs, the **TIMING** of aerosol delivery to the lungs cannot be ruled out when evaluating the treatment efficacy of the device. A thorough evaluation of device characteristics is thus essential when choosing the most optimum device for treatment.