Combining Inhalation By A Breath-Actuated Nebulizer (BAN) With Exhalation Through An Oscillating Positive Pressure Device (OPEP) Offers The Potential For Combined Therapy

Jolyon Mitchell [1], Jason Suggett [2], Mark Nagel [2], Valentina Avvakoumova [2], Rubina Ali [2], and Heather Schneider [2]

[1] Jolyon Mitchell Inhaler Consulting Services Inc., 1154 St. Anthony Road London, Ontario N6H 2R1
[2] Trudell Medical International, 725 Third Street, London, Ontario, Canada N5V 5G4

Summary

A novel hand-held oscillating positive expiratory pressure (OPEP) therapy device (Aerobika*, Trudell Medical International (TMI), London, Canada) has been developed that can be used in conjuction with the AeroEclipse®-II breath actuated nebulizer (BAN, TMI). The Aerobika* OPEP device by itself has shown promising signs from lung imaging studies for the opening of secretion-obstructed airways. A follow-on study is reported here, evaluating how the OPEP-BAN configuration performs for the delivery of three different inhaled medications deliverable by nebulizer that might be used clinically in support of improving airway patency or reducing underlying inflammation. Combining the AeroEclipse-II® BAN with the Aerobika* OPEP therapy device reduced only slightly the overall aerosol delivery in terms of either total emitted mass (TEM) with all three formulations. The resulting aerodynamic particle size distribution (APSD) data were also slightly displaced to finer sizes by the presence of the OPEP device. These size shifts represent marginally increased retention of the coarser, less therapeutically beneficial particles in transit through the OPEP device, most likely due to inertial effects at the valve support as otherwise the flow path contains no obstructions or bends that might increase turbulent deposition. Hence, in terms of fine particle mass (FPM), the presence of the Aerobika* device resulted in no difference for two of the three formulations (paired t-test, $p \geq 0.38$), and only a statistically marginal reduction for the third.

Introduction

The burden of therapy for secretion mobilization for patients with cystic fibrosis (CF) to mitigate inflammation of the airways as the result of bacterial and fungal infection (1) has a major impact on their quality of life, mainly because of treatment duration and frequency (2). In bronchiectasis, failure to clear secretions allows bacteria and fungal spores to collect in them, which leads to the generation of more secretions accompanied by inflammation that further damages the airways, thereby causing more dilation in a vicious cycle (3). Similar considerations apply with the management of secretions in pulmonary rehabilitation for patients with chronic obstructive pulmonary disease (COPD) (4). Oscillating positive expiratory pressure (OPEP) therapy is an established component in secretion management therapy (5). To date, OPEP has been routinely given at separate time to inhaled medical aerosol therapy, because the former is associated with exhalation whereas the latter can only be done effectively during inhalation.

A novel OPEP therapy system (*Aerobika**, Trudell Medical International, London, Canada) has recently been developed to provide patients undergoing secretion management the opportunity to receive therapy using a hand-held device (6). If the *Aerobika** device is considered by itself, when the patient exhales, the one-way valve closes, diverting the flow through the body of the device, mechanically operating the vane that generates oscillatory pressure pulsations which are transmitted back to the patient (Figure 1a).

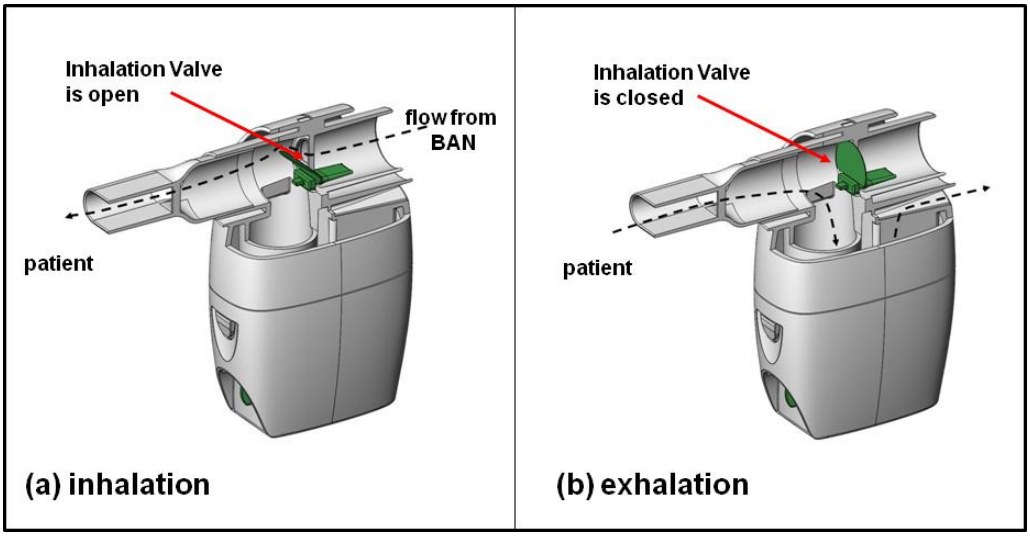


Figure 1. Aerobika* OPEP Device Air Flow Pathways During Complete Tidal Breathing Cycle

Importantly, however, when the patient inhales through the device, the one-way valve opens allowing inhalation air-flow to pass directly through the device with the minimum of internal obstruction (Figure 1b).

Lung imaging studies in adults with COPD have shown significant improvements in lung ventilation and dyspnoea when the *Aerobika** OPEP device was used on its own (7). However, this device is designed so that the *AeroEclipse-II*® breath actuated nebulizer (BAN) can be coupled directly in tandem to its inlet (Figure 2), so that nebulized inhaled medications can be delivered upon inhalation. This combination of devices therefore offers the potential to combine secretion mobilization therapy with the administration of inhaled bronchodilators or corticosteroids to improve airway patency or inflammation respectively in one treatment.

The object of this study was to evaluate the performance of this combination with three different nebulizer-delivered medications that might be used in the clinic in support of bronchodilatation and reduction of inflammation in the airways of the lungs.

Figure 2: Aerobika* OPEP-AeroEclipse-II® BAN for Secretion Mobilization and Nebulized Aerosol Therapy

Materials and Methods

Measurements were made (9 replicates/condition) in accordance with the procedure for aerodynamic particle size analysis in <1601> of the US Pharmacopeia (8), using a Next Generation Impactor (NGI) equipped with a Ph.Eur./USP induction port and operated at 15.0 L/min ± 5%. The BAN on test was operated by a compressed air supply at 345 kPa (50 psig). Fill volumes and concentration of active pharmaceutical ingredient(s) (APIs) are given in Table 1. Measurements were made during the entire run time of the nebulizer from start of nebulization until one minute past the onset of sputter. API recovery and subsequent assay for each solution were each undertaken by validated procedures involving HPLC-spectrophotometry for API assay. Total emitted mass (TEM) and fine particle fraction < 5.4 µm aerodynamic diameter ($FPF_{<5.4\mu m}$) of recovered active pharmaceutical ingredient(s) were determined from the collected particles in the CI system, and subsequently used to calculate emitted fine particle mass ($FPM_{<5.4\mu m}$). Benchmark measurements were made with the same nebulizers without the OPEP device present.

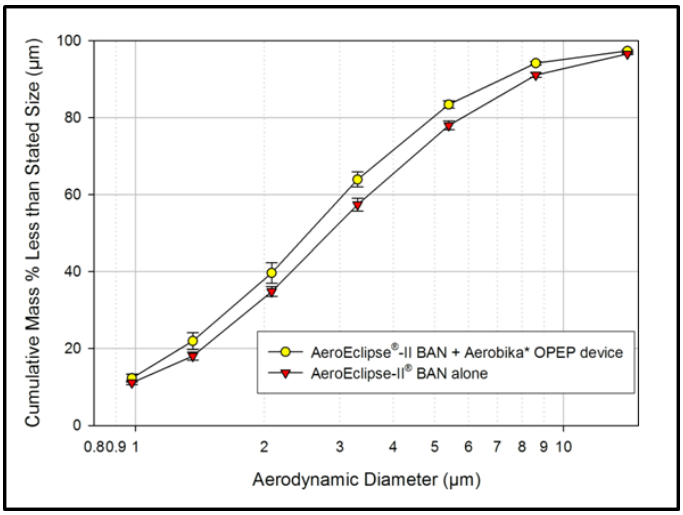
Table 1. API Fill Volumes and Solution Concentrations Evaluated

Formulation/Manufacturer	API mass concentration (%w/v)	Fill Volume (mL)
Ventolin® nebules/GSK (Canada)	833 µg/mL albuterol sulfate	1 x 3.0 mL
Ipratroprium/PharmaScience Canada	250 µg/mL ipratropium bromide	2 x 2.0 mL
Pulmocort® Nebuamp®/ AstraZeneca Canada	250 µg/mL budesonide	2 x 2.0 mL

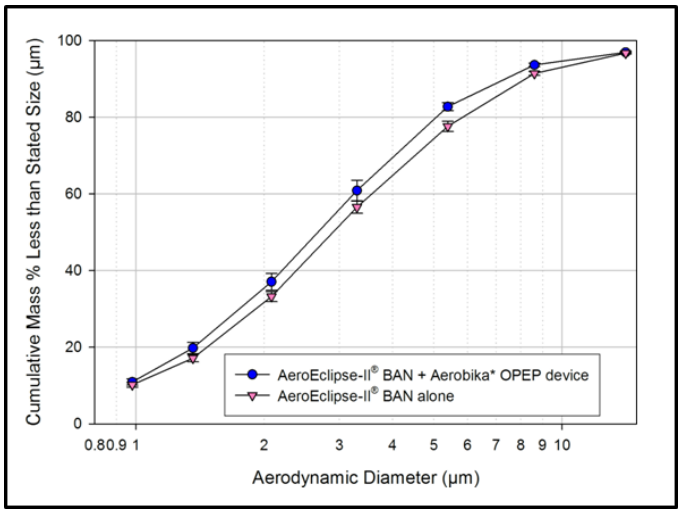
Results

The results of the CI measurements are summarized in Table 2. Comparative APSDs obtained with and without the Aerobika® OPEP device are illustrated in Figures 3a, 3b and 3c.

A. Ventolin®



B. Ipratropium Bromide



C. Pulmicort®

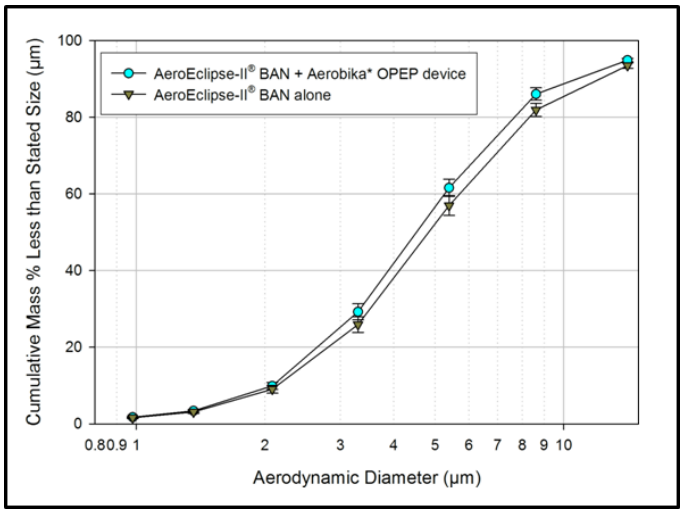


Figure 3. Cumulative Mass-Weighted APSDs for Each of the Formulations Evaluated with and without the Aerobika* OPEP Therapy Device in Tandem with the AeroEclipse®-II BAN

Table 2: Summary of NGI-Based Measurements (mean ± SD) of API Delivery from the AeroEclipse®-II BAN with and without Aerobika® OPEP Therapy Device

Formulation	API	Aerobika* OPEP present	TEM (µg API)	$FPF_{<5.4\mu m}$ (%)	$FPM_{<5.4\mu m}$ (µg API)
Ventolin® Nebule®	salbutamol sulphate	NO	1288 ± 79	78.0 ± 1.2	1004 ± 70
		YES	1258 ± 60	82.8 ± 1.2	1042 ± 43
Ipratropium (generic)	ipratropium bromide	NO	582 ± 30	77.6 ± 1.3	452 ± 28
		YES	515 ± 23	82.8 ± 1.0	426 ± 27
Pulmicort® Nebuamp®	budesonide	NO	488 ± 20	57.0 ± 2.6	278 ± 8
		YES	406 ± 26	61.6 ± 2.2	250 ± 21

Discussion

Combining the AeroEclipse-II® BAN with the Aerobika OPEP device had minimal effect on the overall aerosol delivery in terms of TEM with all three formulations. The resulting APSD data were also slightly displaced to finer sizes by the presence of the OPEP device. These size shifts represent marginally increased retention of the coarser, less therapeutically beneficial particles in transit through the OPEP device, most likely due to inertial effects at the valve support, since the flow path otherwise contains no obstructions or bends that might increase turbulent deposition. Hence the delivery of budesonide fine particles (FPM) was only marginally reduced by ca. 5% when the Aerobika* device was present (paired t-test, $p = 0.043$), and the effect was statistically insignificant with either of the other formulations ($p \geq 0.38$).

The ability to carry out inhalation therapy at the same time as receiving OPEP secretion mobilization treatment has obvious advantages for the patient and caregiver, however, the precise timing when to introduce BAN-based therapy will be established by individual clinical experience. In this context, it is important to note that the Aerobika* device is sufficiently versatile that it can be used on its own to begin with until secretion movement has become significant, indicating that airway patency is improving to the point at which bronchodilatation or anti-inflammatory inhaled aerosol therapy would be beneficial.

Since this work has demonstrated that the new OPEP therapy device can be used with the AeroEclipse®-II BAN with negligible impact on the performance of the latter, it may be tempting to combine the BAN with an alternative OPEP device. However, *in vitro* studies have shown that such combinations are unlikely to be effective (6), unless the inhalation air flow pathway through the secretion mobilization device is optimized. .

Conclusions

This investigation of a novel OPEP therapy device used in conjunction with the AeroEclipse®-II BAN has the potential to offer the ability to give simultaneous combined secretion mobilization treatment with the delivery of inhaled medications for the treatment of the underlying broncho-constriction and inflammation.

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