Effect of the Breath-Actuated Mechanism on the Dispersion Performance of the NEXThaler®

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Summary

Background: The innovative breath-actuated mechanism (BAM) within the NEXThaler® controls the dose release in response to pressure drop. The effect of the BAM on the dispersion performance from NEXThaler will be evaluated using in-vivo inhalation profiles. **Methods:** The dispersion performance of a 100µg/dose of Beclometasone Dipropionate (BDP) formulation was assessed, using in-vivo asthmatic inhalation profiles specific to the NEXThaler [1]. The three profiles differed notably from each other with peak inhalation flow rates of 45, 56 and 100 L min^{-1}. **Results:** There was a noticeable reduction in dispersion performance when the BAM was removed from the NEXThaler device; 51% ± 3% compared to 37% ± 6% on average across all three profiles. Dose evacuation profiles demonstrate that without the presence of a BAM the dose is released at the same time, near the start of the inhalation, regardless of the inhalation profile (0.27 ± 0.01s). The NEXThaler Control BAM releases the dose only when a pressure drop of approximately 2kPa has been reached. Removal of the BAM causes the dose to be released into a slower airflow velocity, 9-11 L min^{-1} for the No-BAM device variant and 36-37 L min^{-1} for the NEXThaler Control. This may mean that larger carrier particles are less likely to impact within the device and could reduce the mass of fine active pharmaceutical ingredient (API) detaching from the carrier particles. **Conclusion:** Dispersion performance can be improved by moderating the release point of the dose; this is exemplified by the NEXThaler device which includes a BAM.

Introduction

The Chiesi NEXThaler is a dry powder inhaler (DPI) which utilizes a breath-actuated mechanism (BAM) (Figure 1) and a dose protector in order to restrain dose release until the pressure drop across the device is approximately 2kPa. As airflow passes through the device, the BAM mechanism triggers, the dose protector translocates and the metered dose is aerosolized using the energy provided by the patient's inhalation.

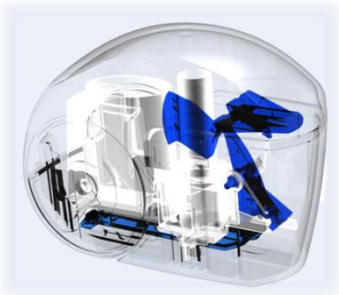


Figure 1- NEXThaler showing the BAM

Dispersion performance from the NEXThaler has been evaluated using in-vivo inhalation profiles[1]. The NEXThaler is able to deliver a consistent aerosol cloud at flow rates representative of an asthmatic population. The aim of this study is to understand the effect of the BAM in the NEXThaler device on aerosol performance using different representative patient inhalation profiles.

Materials and Methods

NEXThaler devices, containing a BDP 100µg/dose formulation, were actuated, with and without BAM (No-BAM) functionality, according to the patient instruction leaflet.

The 10th, 50th, and 90th percentile inhalation profiles (P10, P50 and P90 respectively) from asthmatic patients [1] were generated using a Copley breathing simulator (Copley BRS 3000) coupled with a Fast Screening Impactor (FSI) and mixing inlet (Copley Scientific, Nottingham, UK).

A constant air flow was drawn through the impactor (60 L min^{-1} for the P10 and P50 profiles, 100 L min^{-1} for the P90 profile); an equal flow of compressed air was introduced through the mixing inlet so that the net flow at the induction port was zero (Figure 2).

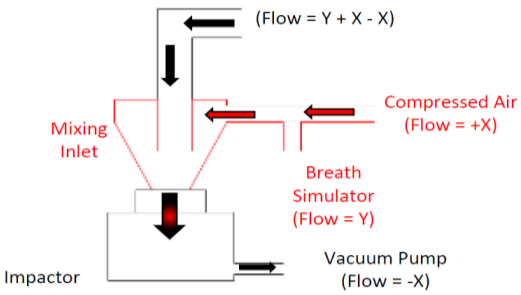


Figure 2- Schematic of impactor and breathing simulator set-up

The LiveShot rig[2] enables recording of device evacuation profiles simultaneously with pressure drop at a sampling flow rate of 1000Hz. It consists of a differential pressure sensor and a laser diode aligned to a photo detector and attaches to the USP induction port. To analyse the LiveShot traces in more detail it was necessary to convert pressure drop into volumetric flow rate. The NEXThaler device resistance was calculated to be 0.110 cm $H_2O^{1/2}$ L^{-1} min^{-1}, based on a flow rate of 58 L min^{-1} required to achieve a 4 kPa pressure drop across the device. After converting pressure drop from kPa to cm H_2O, volumetric flow rate can be calculated by dividing the pressure drop by the device resistance.

Prior to analysis, five waste shots were actuated from each device into a waste Dosage Unit Sampling Apparatus (DUSA) operated at 60 L min^{-1}. Each variant was tested in triplicate. BDP mass was recovered using a suitable solvent mixture (85:15 Methanol:Water) and quantified using a Waters Acquity Ultra-Performance Liquid Chromatography with SQD detector (UPLC-MS).

Results and Discussions

Dispersion performance results are displayed in Figure 3 and Table 1. Delivered dose across all three inhalation profiles increased when the BAM was removed e.g. 67µg for the Control compared to 79µg for the No-BAM variant using the P50 profile. The NEXThaler Control delivered a higher and more consistent Fine Particle Fraction (FPF %) on average across all three profiles compared to the No-BAM variant, 51% ± 3% and 37% ± 6% respectively (Table 1). A possible explanation for these observations may be due to the airflow velocity into which the dose is delivered. Removal of the BAM causes the dose to be released into a slower airflow velocity, meaning that larger carrier particles are less likely to impact within the device, thus increasing the delivered mass. A lower air flow velocity may also reduce the mass of fine active pharmaceutical ingredient (API) detaching from the carrier particles, thus reducing the FPD. Conversely, the dose from the NEXThaler Control is released into a higher velocity airflow, which provides more turbulence for detachment of fine API from carrier particles which is entrained within the airflow for inhalation. Larger API (>5µm) are more likely to impact within the device, reducing the delivered dose of potentially non-respirable particles.

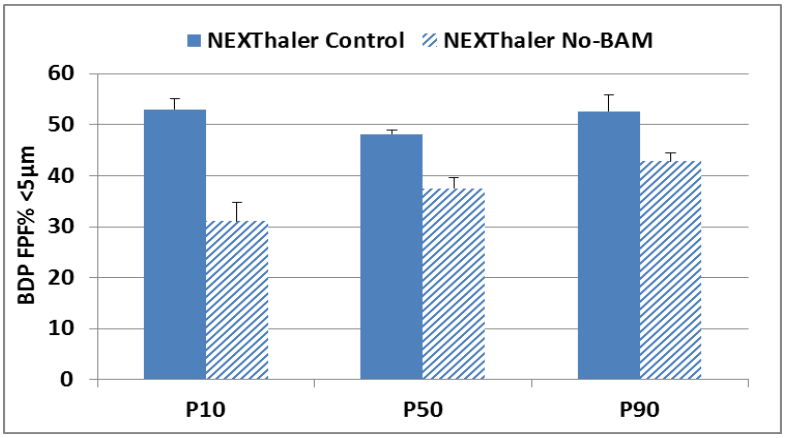


Figure 3 - *FSI performance of NEXThaler using the BRS3000: three inhalation profiles from the Control and the No-BAM device variant (n=3)*

Table 1 - FSI performance of NEXThaler using the BRS3000: three inhalation profiles measured from the Control and the No-BAM device variant (n=3 ± SD)

	P10		P50		P90	
	Control	**No-BAM**	**Control**	**No-BAM**	**Control**	**No-BAM**
Delivered Dose (µg)	79	81	67	79	78	83
	±5	±4	±4	±3	±3	±5
Fine Particle Dose <5µm (µg)	42	25	32	30	41	36
	±4	±2	±2	±2	±3	±3
Fine Particle Fraction <5µm (%)	53	31	48	37	53	43
	±2	±4	±1	±2	±3	±2
Shot Weight (mg)	8.2	8.4	8.1	8.7	8.6	8.7
	±0.1	±0.2	±0.5	±0.4	±0.4	±0.3

Varying the inhalation profile had more of an influence on the FPF % with the No-BAM device, increasing from 31% with the P10 profile to 43% with the P90 profile. This may be due to the differences in the initial acceleration of the sampling flow rates; increasing from zero to 24, 35 and 46 L min^{-1} with the P10, P50 and P90 profile respectively within 0.1s (Figure 4). The greater acceleration rate of the P90 profile produces a higher airflow velocity with more energy to shear fine API from the carrier particle; this energy is reduced at lower initial acceleration rates.

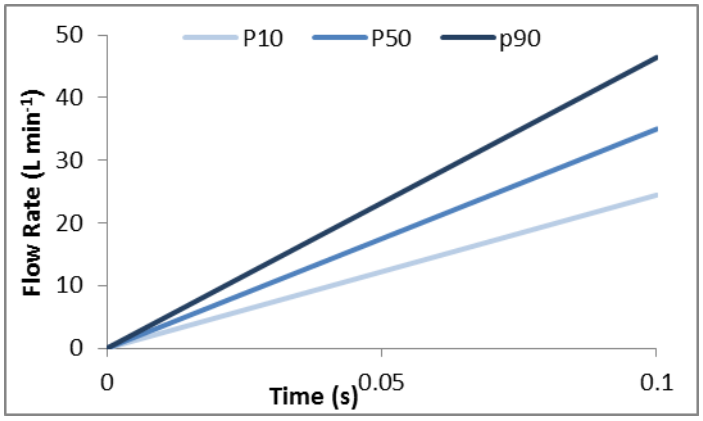
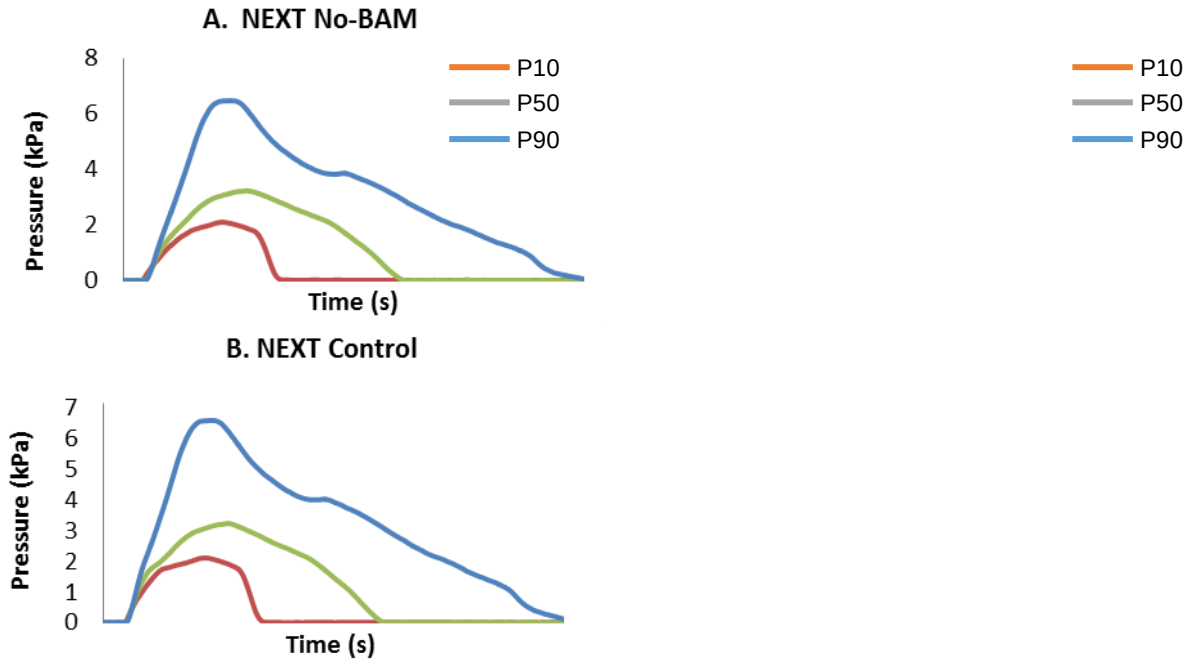


Figure 4 - *Increase in flow rate between 0 and 0.1 secs for the P10, P50 and P90 inhalation profiles*

In order to understand these effects further, the LiveShot rig was utilised to capture dose characteristics. The obscuration of the laser within the USP throat was plotted against time (s) and used as an indication of dose evacuation. The pressure generated during inhalation was also obtained (Figure 4).

Figure 5a demonstrates that with the No-BAM variant, the dose is released at the same point regardless of the inhalation profile. The peak laser obscuration (Obs_{peak}), detailed in Table 2 for the No-BAM device is consistent (0.26s, 0.27s and 0.27s for the P10, P50 and P90 profiles respectively). The NEXThaler Control BAM triggers and releases the dose only when a pressure drop of approximately 2kPa is been reached (Figure 4b).



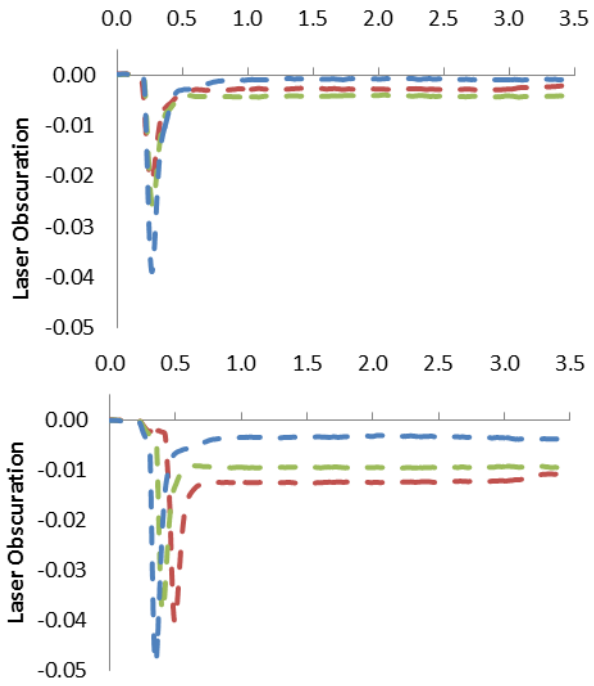


Figure 5 - *LiveShot evacuation profiles (pressure and laser obscuration) of (A) The NEXThaler device No-BAM variant and (B) The Control NEXThaler device, using the P10, P50 and P90 inhalation profiles (n=3)*

The pressure drop at the beginning (Obs_{start}), peak (Obs_{peak}) and end (Obs_{end}) of the laser obscuration for each inhalation was determined (Figure 6) and the corresponding flow rates calculated (Table 2). The NEXThaler Control begins to release the dose between 36-37 L min^{-1} whereas the No-BAM variant releases the dose into a significantly lower flow rate, 9-11 L min^{-1}, regardless of the inhalation profile. The flow rates at the Obs_{peak} and Obs_{end} are also lower with the No-BAM variant; the dose therefore leaves the device at a slower rate. The average dose duration (Obs_{end} minus Obs_{peak}) of the three inhalation profiles increases from 51ms ± 2ms for the NEXThaler Control to 72ms ± 6ms for the No-BAM variant.

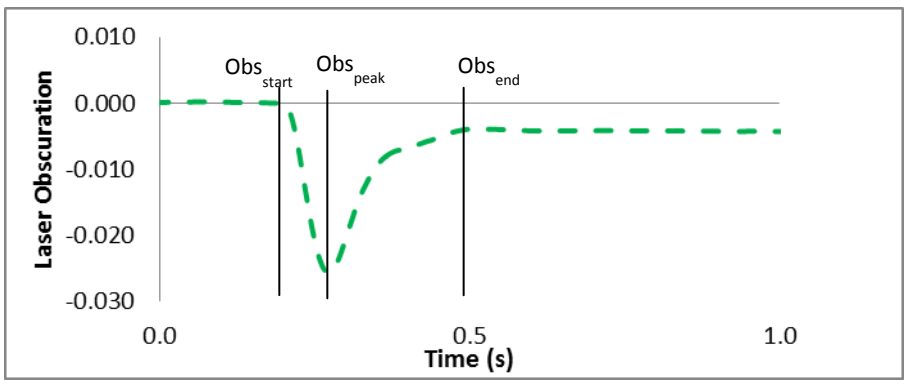


Figure 6 - *Dose Evacuation Profile using the No-Bam NEXThaler device with the P50 inhalation profile demonstrating the start (Obs_{start}), peak (Obs_{peak}) and end (Obs_{end}) of the Laser Obscuration*

Table 2 - *Beginning, peak and end of the laser obscuration of the LiveShot Rig when using the P10, P50 and P90 inhalation profiles (n=3 ±RSD)*

Device	Inhalation Profile	Obs_{Start}		Obs_{peak}		Obs_{end}		Dose Duration (s)
		Time (s)	Flow Rate ($Lmin^{-1}$)	Time (s)	Flow Rate ($Lmin^{-1}$)	Time (s)	Flow Rate ($Lmin^{-1}$)	
NEXThaler	P10	0.44	36	0.49	37	0.49	37	0.52
Control		±5%	±3%	±4%	±2%	±4%	±2%	±3%
	P50	0.35	36	0.40	38	0.40	38	0.51
		±1%	±1%	±2%	±1%	±1%	±1%	±2%
	P90	0.30	37	0.35	43	0.35	43	0.49
		±1%	±1%	±1%	±1%	±1%	±1%	±3%
NEXThaler No-BAM	P10	0.18	9	0.26	23	0.26	22	0.79
		±1%	±5%	±1%	±0.4%	±0.4%	±0.4%	±3%
	P50	0.20	11	0.27	27	0.27	27	0.68
		±0.3%	±5%	±1%	±1%	±1%	±0.8%	±3%
	P90	0.20	10	0.27	30	0.27	30	0.68
		±1%	±9%	±0.4%	±1%	±0.4%	±0.2%	±2%

Conclusion

The coordination between airflow velocity and the release of a DPI formulation has an influence on the dispersion performance. The BAM included within the NEXThaler enables delivery of a consistent and high %FPF across all inhalation profiles.

References

1. Casaro, D., G. Bramilla, I. Pasquali, and V. Sisti: *In vitro aerosol performances of NEXThaler® using representative inhalation profiles from asthmatic patients.* In Proceedings of Respiratory Drug Delivery Conference, pp. 375-380. 2014.
2. Tweedie, A., Keegan, G., M., Lewis, D. A. (2013) 'DPIs – "A LiveShot Experience"', Proc Drug Delivery Australia 23 - 24 October 2013, Sydney.