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ENHANCING THE PERFORMANCE OF DRY POWDER INHALERS: BREATH ACTUATED MECHANISMS

The vast majority of dry powder inhalers (DPIs) rely solely on the energy provided by the inhalation action of the patient to achieve successful drug delivery. In many DPIs the only control that is imposed on this process is to increase or lower the internal resistance of the device, but some, more sophisticated systems deploy breath-actuated mechanisms (BAMs). In this article, David Lewis, PhD, Head of Laboratory, and Alan Tweedie, Senior Scientist, both of Chiesi, explain how BAMs work and present experimental data demonstrating their ability to control dose delivery.

Inhaled pharmaceutical therapies are the cornerstone of treatments for obstructive lung disease treatment. They allow for effective administration and high lung deposition of the active pharmaceutical ingredients (APIs), while at the same time minimising systemic bioavailability, and any associated adverse side effects. Along with metered-dose inhalers (MDIs), DPIs are among the most commonly used devices for drug delivery in the treatment of asthma and chronic obstructive pulmonary disease (COPD).

Commercially available since the 1970s, DPIs are often considered simpler to use than MDIs, as they are breath-activated; eliminating the need to co-ordinate inhalation and actuation. In addition, they avoid the use of propellants, add-on spacers and do not produce the "Cold Freon" sensation associated with some MDIs.[1]

DPIs currently on the market are mainly passive devices, which rely on a patient's inspiratory air flow to disperse the powder formulation into single particles or agglomerates small enough for deposition in the lung, typically less than 5 µm.

Ensuring adequate de-aggregation occurs from the inhalation technique of the patient is the primary challenge associated with DPI technology. Patients are typically encouraged to breathe forcefully and deeply when using a DPI though some patients have problems achieving a fast inhalation rate[2] and compliance/inadequate technique remains an issue.[3,4]

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Additionally, the breathing pattern of a patient is influenced by physical size and strength, and health. Geriatric and paediatric patients, or those with severely compromised respiratory capacity, may be unable to produce the same breathing profile as a healthy adult and might, therefore, struggle to disperse an API dose effectively.[3] This can result in a lower dose of API to the lungs and, ultimately, poor disease control, which in the case of chronic conditions may be undetectable to the patient.

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USING A BAM TO CONTROL DOSE DISPERSION

The use of BAMs has been proposed as a way of addressing the issue of inconsistent/poor dose dispersion with certain breathing profiles, and these are now incorporated in some DPI devices. NEXThaler® (Chiesi, Parma, Italy), a multi-dose inhaler, exemplifies a device incorporating a novel BAM and dose protector that restrain dose release until the pressure drop across the device is approximately 1.8 kPa. As air is drawn through the device the BAM mechanism triggers, the dose protector translocates and the metered dose is aerosolised using the energy provided by the patient's inhalation, under highly consistent conditions.

Here we report results from experimental studies designed to investigate the effect of BAM pressure and inhalation flow rate on the controlled dose delivery achieved.

STUDY 1: INVESTIGATING INFLUENCE OF BAM PRESSURE

To investigate the impact of trigger pressure for a BAM, four DPI variants (NEXThaler, Chiesi) were produced, each with a BAM different release pressure. The control variant had a pressure drop of ~1.8 kPa which is representative of the marketed device; two further variants were constructed to release at ~0.6 kPa and ~4.0 kPa, respectively. A final device was manually pre-triggered before firing, so that the dose was unprotected and free to evacuate into the airflow immediately, so effectively mimicked the action of a DPI with no BAM.

All device variants were assessed using the 90th percentile inhalation profiles of asthmatic patients,[5] generated using a BRS 3000 breath simulator (Copley Scientific, Nottingham, UK). Dispersion performance was assessed using a Fast Screening Impactor (FSI) (Copley Scientific) containing a 5 µm cut-off plate, and operating at a constant flow rate of 100 L min^{-1}. The FSI was attached to a BRS 3000 breath simulator using a mixing flow inlet to allow the application of different flow profiles over the device while keeping a constant flow through the impactor.

A flow rate of 100 L min^{-1} was selected to prevent backflow of powder-laden air into the breathing simulator and to match the P90 inhalation profile. A modified USP induction port containing the LiveShot rig[6] was used to record dose evacuation kinetics from each device.

Each device was filled with 1.5g ± 5% of lactose carrier based formulation containing approximately 4.7% w/w beclomethasone dipropionate (BDP) and then stored at 20°C 40% RH for at least 24 hours. Prior to measuring dispersion performance analysis, five waste shots, around 10 mg each, were actuated from each device into a waste dose uniformity sampling apparatus tube operated at 60 L min^{-1}. All measurements were conducted in triplicate. BDP was recovered from the apparatus using an appropriate diluent and analysed using ultra-performance liquid chromatography (UPLC) with Single Quad (SQ) Detector (Waters Acquity).

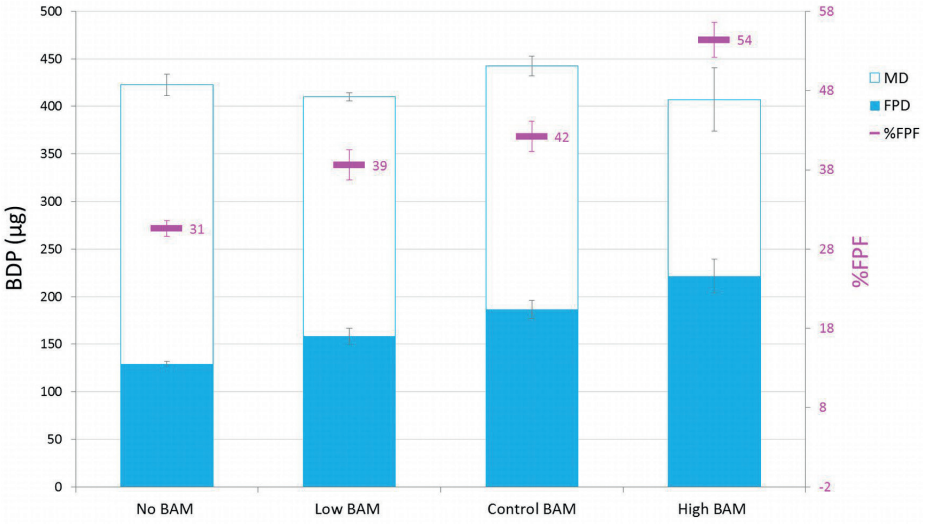

Figure 1: Impaction data shows that dose dispersion performance improves with increasing BAM set pressure; mean values (n=3); error bars ±SD.

	No BAM	Low BAM	Control BAM	High BAM
Shot weight (mg)	9.7 ± 1.0	9.2 ± 0.1	10.0 ± 0.6	9.1 ± 0.3
Metered dose (µg)	423 ± 11	410 ± 4	443 ± 10	407 ± 33
Fine particle dose <5µm (µg)	129 ± 2	158 ± 9	187 ± 9	222 ± 18
Fine particle fraction <5µm (%)	31 ± 1	39 ± 2	42 ± 2	54 ± 2

Table 1: FSI dispersion performance from the four DPI variants; mean values (n=3).

Results and Discussion

With increasing BAM pressure, the dispersion performance, as quantified by the fine particle dose (FPD <5 µm) improves, with the no BAM variant producing the lowest FPD in comparison with a much higher FPD from the high BAM variant (see Figure 1 and Table 1).

However, with the high BAM variant, data variability is also higher – the dose evacuation kinetics data from the LiveShot rig reveal a possible explanation (Figure 2 and Table 2).

The LiveShot data shows that altering the BAM trigger point impacts dose evacuation kinetics, in particular, the time taken to reach peak powder discharge (Obs_{peak}) and the flow rate at which Obs_{peak} occurs. Discrepancies between the BAM opening pressure and the pressure drop at Obs_{peak} arise because of the formulation residence time as it passes through the device.

In comparison with the control variant, the low BAM device reduces the time taken to reach peak flow and, as a result, the powder is released into a slightly lower airflow rate. Removal of the BAM causes a similar effect, but of much greater magnitude. Conversely, increasing the BAM trigger pressure delays the time taken to reach peak powder discharge ensuring release of the powder into a higher airflow

rate. The correlation between enhanced dispersion and BAM set pressure suggests that releasing the powder into an increased airflow velocity may be advantageous in terms of DPI performance.

STUDY 2: INFLUENCE OF BAM AT DIFFERING FLOW RATES

To investigate the impact of inhalation flow rate on dose delivery, two devices containing a BDP 100 µg/dose formulation were actuated according to the patient instruction leaflet. One device had BAM functionality, the other did not. The 10th, 50th and 90th percentile inhalation profiles (P10, P50 and P90, respectively) from asthmatic patients were applied using a breathing simulator coupled with a FSI and flow-mixing inlet exactly as described in the first study. This flow rate through the FSI was set at 60 L min^{-1} for the P10 and P50 profiles and 100 L min^{-1} for the P90 profile.

The LiveShot rig enables the recording of device evacuation profiles as a function of pressure drop at a sampling flow rate of 1000 Hz. For the purposes of this study, the requirement was to analyse the LiveShot evacuation traces in detail, as a function of flow rate, and so pressure drop was converted into volumetric flow rate. The device resistance of the DPI was calculated to be 0.110 cm $H_2O^{1/2}$ L^{-1} min^{-1} at 58 L min^{-1}, the test flow rate required to achieve a 4 kPa pressure drop across the device.

The volumetric flow rate corresponding to a certain pressure drop was therefore calculated by dividing the overall pressure drop (converted into comparable units) 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}. All other aspects of testing were carried out as in the first experimental study.

Results and Discussion

Dispersion performance results are displayed in Figure 3 and Table 3. Without a BAM the delivered dose is higher with all three inhalation profiles. However, the inclusion of a BAM results in a higher and more consistent FPF on average across all three profiles: 51% ± 3% and 37% ± 6%, respectively.

A possible explanation for this is that the removal of the BAM, as discussed above, causes the dose to be released into a slower airflow velocity, meaning that larger carrier particles are less likely to impact

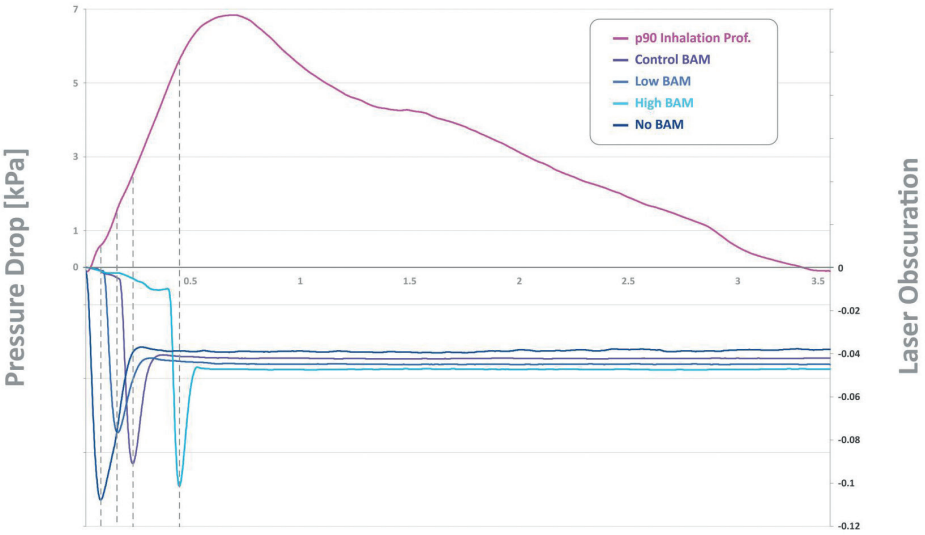

Figure 2: LiveShot dose evacuation kinetics, showing both laser obscuration and differential pressure, provide insight into the enhanced dose dispersion delivered by higher BAM set pressures (n=3).

Device variant	BAM opening pressure (kPa)	Time to Obs_{peak} (s)	Pressure drop at Obs_{peak} (kPa)	Flow rate at Obs_{peak} (L min^{-1})	Peak duration (s)
No BAM	N/A	0.068 ± 0.003	0.6 ± 0.0	22.0 ± 1.0	0.215 ± 0.010
Low BAM	0.6	0.196 ± 0.021	2.2 ± 0.2	42.6 ± 2.1	0.250 ± 0.010
Control BAM	1.8	0.223 ± 0.005	2.5 ± 0.1	46.3 ± 0.6	0.177 ± 0.005
High BAM	4	0.466 ± 0.005	6.7 ± 0.1	75.0 ± 0.0	0.170 ± 0.006

Table 2: Key characteristics identified from the LiveShot dose evacuation kinetics; mean values (n=3).

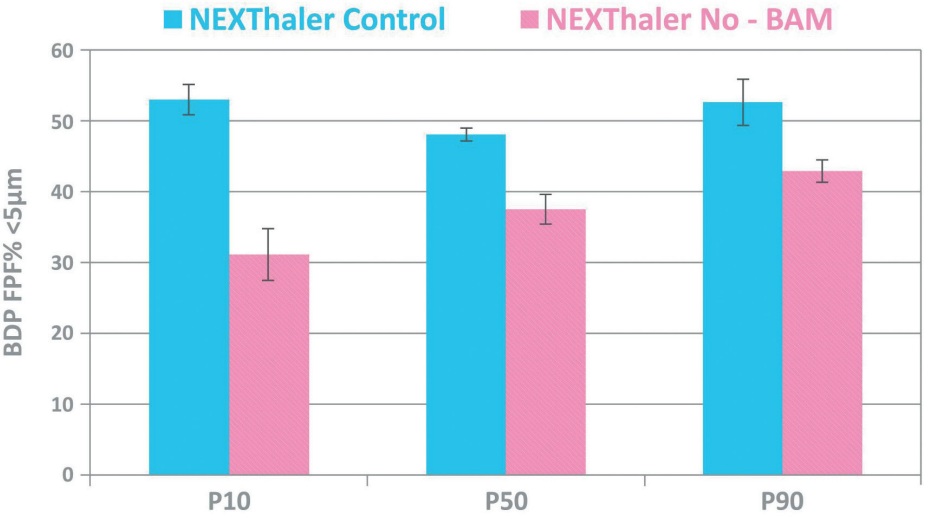

Figure 3: Incorporating a BAM in the DPI device improves the magnitude and consistency of the FPF% across a range of flow rates (n=3).

	P10		P50		P90	
	Control	No-BAM	Control	No-BAM	Control	No-BAM
Delivered dose (µg)	79	81	67	79	78	83
Fine particle dose <5µm (µg)	42	25	32	30	41	36
Fine particle fraction <5µm (%)	53	31	48	37	53	43
Shot weight (mg)	8.2	8.4	8.1	8.7	8.6	8.7

Table 3: Incorporating a BAM in the DPI device improves the magnitude and consistency of the FPF% across a range of flow rates (n=3).

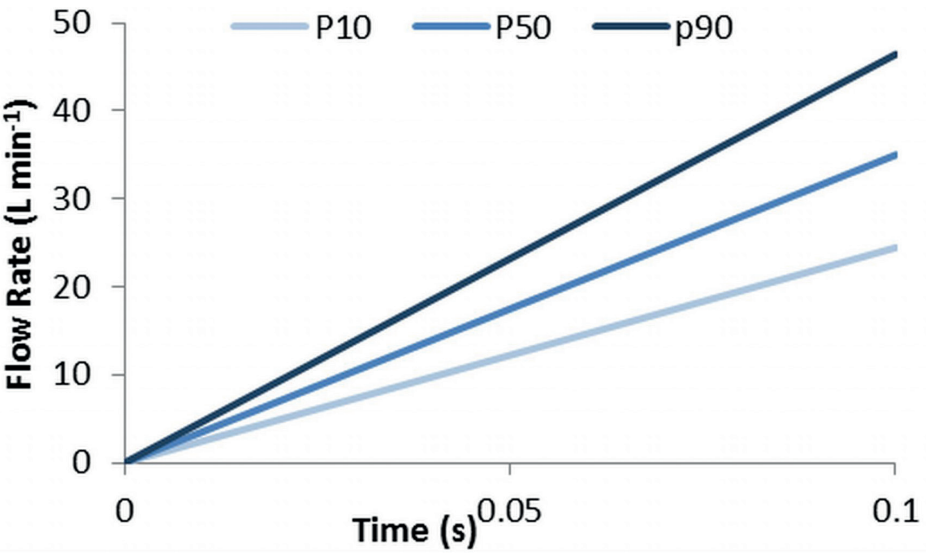

Figure 4: Increase in flow rate between 0 and 0.1 secs for the P10, P50 and P90 inhalation profiles; P90 is associated with the fastest acceleration rate.

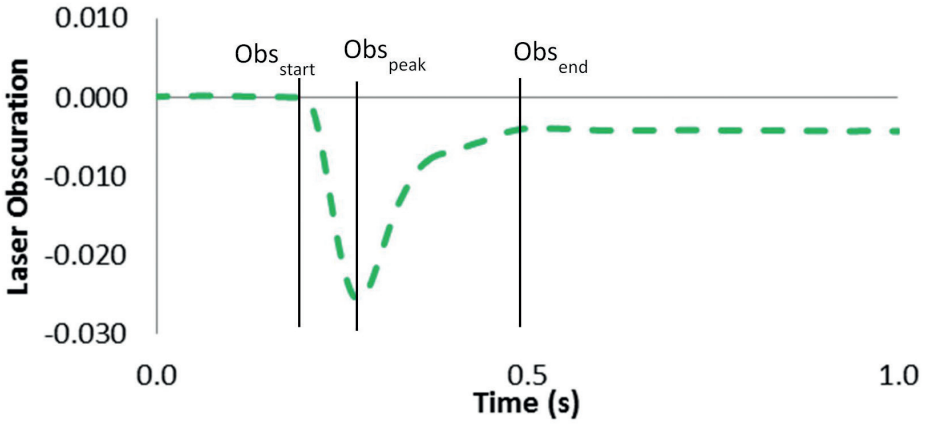

Figure 5: Dose evacuation data using the No-BAM device with the P50 inhalation profile demonstrating the start (Obs_{start}), peak (Obs_{peak}) and end (Obs_{end}) of the laser obscuration, which characterise the dose dispersion event.

within the device, increasing delivered mass. However, a lower airflow velocity may also reduce the mass of fine API detaching from the carrier particles, thus reducing the FPF% and FPD. Releasing the dose into a higher velocity, more turbulent airflow promotes more effective detachment of the fine API from carrier particles, facilitating drug delivery.

An additional observation is that varying the inhalation profile has a greater influence on the FPF % measured with the No-BAM device; this may be attributable to the differences in the initial acceleration rates associated with the different profiles (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 substantially reduced at lower initial acceleration rates and without the BAM to promote dispersion it becomes a less energetic and effective process.

The LiveShot data provides further insight into these effects. With the No-BAM variant, the dose releases at the same point regardless of the inhalation profile, and the Obs_{peak} is consistent). However, with a BAM in place the dose only releases when a pressure drop of approximately 1.8 kPa is reached. This difference means that the dose is released into a different airflow rate regime, depending on the device used (Figure 5 and Table 4).

This effect means that the device with a BAM begins to release the dose at a flow rate of 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} at all inhalation profiles. Flow rates at the Obs_{peak} and Obs_{end} are also lower with the No-BAM variant; indicating that the dose leaves the device at a slower rate. Average dose duration (Obs_{end} minus Obs_{peak}) of the three inhalation profiles increased from 51ms ± 2ms for the device with a BAM to 72ms ± 6ms for the No-BAM variant, confirming that in the absence of a BAM dose dispersion is a slower, less energetic process.

CONCLUSION

For effective treatment of chronic obstructive lung disease, the delivery of APIs to the lung must be controlled. DPIs are relatively easy to use, as they do not require co-ordination of inhalation and actuation, but can be less effective than MDIs because de-aggregation of the dose to a respirable size is driven

Device	Inhalation profile	Obspeak		Obspeak		Obspeak		Dose duration (s)
		Time (s)	Flow rate (L min^{-1})	Time (s)	Flow rate (L min^{-1})	Time (s)	Flow rate (L min^{-1})	
NEXThaler control	P10	0.44	36	0.49	37	0.49	37	0.52
	P50	0.35	36	0.40	38	0.40	38	0.51
	P90	0.30	37	0.35	43	0.35	43	0.49
NEXThaler No-BAM	P10	0.18	9	0.26	23	0.26	22	0.79
	P50	0.20	11	0.27	27	0.27	27	0.68
	P90	0.20	10	0.27	30	0.27	30	0.68

Table 4: LiveShot data measured at P10, P50 and P90 inhalation profiles (n=3 ± RSD) shows that in the absence of a BAM the dose is released more slowly into a lower air flow.

only by the inhalation profile applied by the patient. This can be compromised either as a result of poor lung function or inadequate training.

The use of a BAM improves the drug delivery efficiency of DPIs and has the potential to ensure more consistent performance, for a wider range of patients. The results presented here confirm the ability of BAMs to enhance FPF and FPD by controlling release of the formulation, and entraining the dose into higher velocity airflow. They illustrate how BAMs can be used to ensure that patients receive the maximum dose of APIs, and receive better treatment.

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