Effect of Recorded Inhalation Waveforms on the *In Vitro* Aerodynamic Performance of a Passive Dry Powder Inhaler

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INTRODUCTION

- The ability of a patient to inhale forcefully for a given period of time is a prerequisite for effective medication delivery from passive Dry Powder Inhalers (DPIs).
- Studies investigating patient compliance have repeatedly observed that maintaining a consistent inhalation technique is difficult for many users.
- The present scoping study was designed to determine the potential impact of variable inhalation technique on both Fine Particle Mass (FPM) and Coarse Particle Mass (CPM) emitted from a widely prescribed Diskus† passive DPI (GSK).

MATERIALS AND METHODS

- A Ventolin† Diskus† DPI was modified to prevent delivery of medication by taping the dose release lever to the body of the inhaler.
- The DPI was attached to a pneumotachometer (SpiroQuant H flow sensor, EnviteC-Wismar GmbH) with a purpose-made fitting and also equipped with a mouthpiece, constructed to the same geometry as the inhaler to avoid any difference in the patient interface, from which the participant inhaled (Figure 1).
- Three DPI naïve adult participants were asked to inhale from an open DPI
- After being told to inhale “quick and deep”, the participant received no further instruction before inhaling from the DPI mouthpiece to obtain the “untrained” inspiratory maneuver.
- The participant was then asked to watch an on-line video describing the correct use of the Diskus† DPI, and the “trained” inspiratory flow profile was recorded
- The recorded “untrained” and “trained” inspiratory flow rate waveforms were recreated by a breathing simulator (ASL 5000, Ingmar Medical) coupled to the mouthpiece of an Advair† Diskus† DPI (250 µg Fluticasone Propionate (FP) + 50 µg Salmeterol Xinafoate (SX)).
- The resulting aerosol particle size distribution (APSD) was size-analyzed by a Next Generation Impactor (NGI) equipped with pre-separator, and operated at 60 L/min.
- A compressed air source and Nephele mixing inlet was used to enable the impactor to operate at constant flow rate throughout the measurement process.
- The inspiratory flow rate-elapsed time profile was recorded at 200 Hz (SmartLab†).

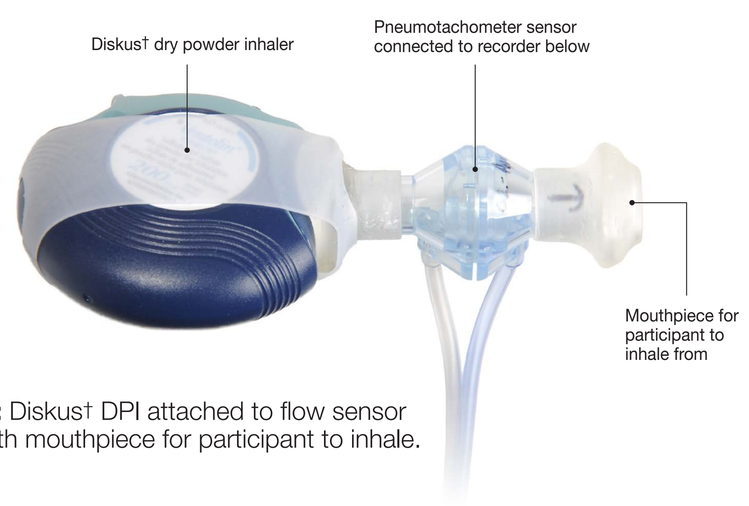

Figure 1: Diskus† DPI attached to flow sensor holder with mouthpiece for participant to inhale.

RESULTS

Figure 2: Recorded Inspiratory Flow Patterns

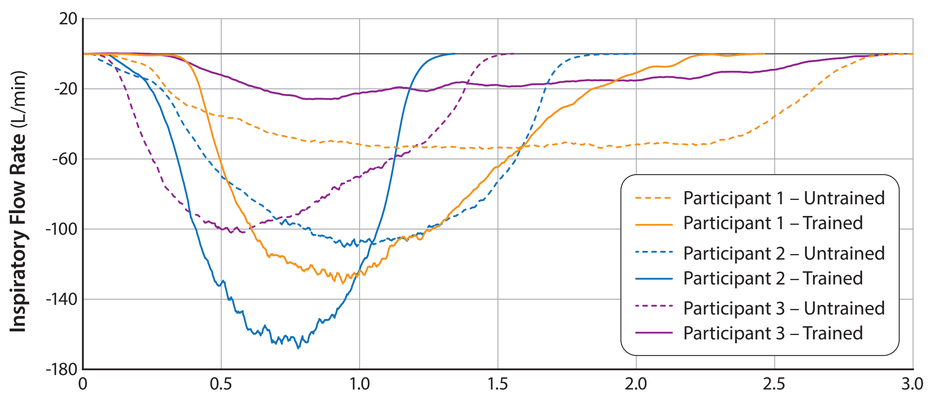

Table 1: Total Inspired Volume, Peak Inspiratory Flow Rate (PIFR) for each recording

Participant	Condition	Inspired Volume (mL)	PIFR (L/min)
1	untrained	1872	52.5
	trained	2099	125.7
2	untrained	1951	107.8
	trained	1876	163.0
3	untrained	1522	100.3
	trained	621	25.7

Table 2: Key parameters derived from APSD measurements by NGI

Participant ($n=5$)	Parameter	Untrained		Trained	
		FP	SX	FP	SX
1	Total Recovered Mass (µg)	177.7 ± 13.5	34.7 ± 3.2	192.5 ± 11.5	36.9 ± 1.7
	FPM$_{<4.5\,\mu m}$ (µg)	42.4 ± 6.6	7.1 ± 1.3	40.3 ± 1.0	6.9 ± 0.1
	CPM$_{>4.5\,\mu m}$ (µg)	135.4 ± 8.0	27.6 ± 2.0	152.2 ± 10.8	30.0 ± 1.6
2	Total Recovered Mass (µg)	236.4 ± 43.1	46.8 ± 9.1	197.3 ± 7.1	39.6 ± 2.6
	FPM$_{<4.5\,\mu m}$ (µg)	47.5 ± 4.3	8.1 ± 0.8	31.8 ± 2.4	5.9 ± 1.2
	CPM$_{>4.5\,\mu m}$ (µg)	188.9 ± 41.0	38.7 ± 8.8	165.5 ± 6.3	33.7 ± 1.6
3	Total Recovered Mass (µg)	203.2 ± 31.7	39.8 ± 6.9	112.8 ± 27.4	21.6 ± 5.2
	FPM$_{<4.5\,\mu m}$ (µg)	41.1 ± 5.0	6.9 ± 0.9	23.6 ± 6.6	4.0 ± 1.2
	CPM$_{>4.5\,\mu m}$ (µg)	162.1 ± 27.2	32.9 ± 6.1	89.2 ± 21.3	17.6 ± 4.1

- A compressed air source and Nephele mixing inlet was used to enable the impactor to operate at constant flow rate throughout the measurement process.
- The inspiratory flow rate-elapsed time profile was recorded at 200 Hz (SmartLab†).
- FPM was defined as the mass of active pharmaceutical ingredient (API) recovered from the cascade impactor less than 4.5 µm aerodynamic diameter.
- Conversely, CPM was defined as the mass of API greater than 4.5 µm plus the mass recovered from the impactor inlet.

DISCUSSION

- It appears that the training was effective for participants 1 and 2 (Table 1), as their PIFR increased substantially after training, although total inhalation volume remained essentially the same.
- **Participant 1:** Training had little impact. The same FPM of FP/SX would have been received irrespective of training had this person inhaled the medication.
- **Participant 2:** Surprisingly, they would have received slightly less FPM of either API after training, but the difference may not be clinically significant.
- **Participant 3:** Did the opposite of anticipated behavior post-training, with a substantially reduced PIFR and associated smaller inhalation volume (Table 1). Before training, this volunteer would have received slightly less of either API compared with the others. After training, this participant would have received significantly less FPM in concordance with the reduced inhalation volume.
- Irrespective of the training, the coarse particle mass emitted from the DPI ranged between 76–82%

CONCLUSIONS

- The widely differing inspiratory flow profiles in response to training is indicative that use of this particular DPI may not be easy to master for all users after video instruction.
- Coarse or ‘non-respirable’ particles may, in real use, result in local or systemic delivery with the potential for adverse effects.
- Further studies are warranted with a larger number of volunteers and with other passive DPIs having different resistances.

ISAM Congress
May 25 – 29, 2019
Montreux, Switzerland

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