A European Pharmaceutical Aerosol Group (EPAG)-Led Cross-Industry Assessment of Inlet Flow Rate Profiles of Compendial DPI Test Systems: Part 1 – Experimental Data

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Summary

We report outcomes from an EPAG-led cross-industry study, characterizing flow rate/elapsed-time profiles of equipment used for testing dry powder inhalers (DPIs). A thermal mass flow sensor was used by nine organizations in a round-robin approach to record inlet flow rate-time profiles of individual participant compendial test systems (TS) including either sample collection tubes (SCT) or a cascade impactor (either the Andersen 8-stage non-viable impactor, ACI, or the Next Generation Impactor, NGI) equipped with USP/PhEur induction port and pre-separator. An inlet orifice generated a 4-kPa pressure drop at each of the target flow rates (30, 60 and 90 L/min), simulating a pressure drop typical for high-, medium- and low-resistance DPIs respectively. Rise times to 90% of these target flow rates (t_{90}) were longest with largest internal dead volume and followed the order NGI>ACI >SCT>TS. When the surrogate DPI (4-kPa orifice) was absent, t_{90} values generally lengthened with increasing target flow rate. In contrast, the opposite behaviour was observed when the surrogate DPI was present. A flow acceleration parameter was also calculated, expressed as the slope between the 20% and 80% flow rates of each final steady flow value ($slope_{t20/t80}$). Greater flow acceleration occurred at higher final flow rates, irrespective of apparatus, but the presence of the surrogate DPI was associated with slower flow acceleration. These flow rate-rise time profiles will be useful for those involved in evaluating equipment for characterizing both existing and new DPIs.

Key Message

Flow rate rise times associated with DPI testing are correlated with the magnitude of the internal dead-volume and intrinsic resistance of the measurement apparatus. The resistance associated with a surrogate DPI has a marked influence on profile shape. These data will prove useful for evaluating and using DPI testing equipment.

Introduction

Compendial methods for testing DPIs require the rapid opening of a solenoid valve to start drawing air into and through the inhaler at the start of the test[1]. The flow-rate/rise-time profile has the potential to affect the measured *in vitro* characteristics of the dose that comes from the DPI, as the aerosol formation and subsequent transport of the bolus to the measurement apparatus takes place from the inhaler during this period. Furthemore, the cut-point sizes of the impactor stages are flow rate dependent. The objectives of the present multi-laboratory investigation were therefore as follows:

1. to measure the influence of DPI resistance on flow-elapsed time profiles for a wide range of equipment used in the industry for DPI testing either for content uniformity or emitted aerosol APSD, following compendial procedures:

    a. without any resistance at the entry to the measurement apparatus (baseline condition);

    b. with resistance imposed by placing an orifice at the inlet of the apparatus whose aperture was sized to mimic a high-, medium- or low-resistance DPI by generating a pressure drop of approximately 4-kPa at the chosen target final flow rates of 30, 60 and 90 L/min respectively.

2. to define and report the following measures of the flow-time profile that are believed to be helpful to the user community:

    a. the area under the flow rate-time profile (*AUC*), equivalent to the sampled volume;

    b. the associated time for the flow rate to achieve 90% of the final steady-state flow rate value, t_{90};

    c. a flow acceleration parameter derived from the slope of the rising flow rate profile, calculated by linear interpolation between the times where the flow rate attained 20% and 80% of the final flow rate values ($slope_{t20/t80}$);

    d. the presence of any peak in the flow profile (Q_{peak}) before reaching the steady-state flow rate;

Preliminary outcomes from this investigation were reported previously[2]. Since then, further examination of the data has been undertaken, including the exclusion of measurements made by a participant not evaluating DPI products, and repeating tests that had produced anomalous results. The present evaluation therefore reflects a more accurate assessment of the flow rate-rise time profiles as an ensemble. The interpretation has been extended by comparing the outcomes with internal dead volume (V_{int}) of the apparatuses, which is the apparatus-specific parameter deemed most likely to be correlated with the above metrics.

Materials and Methods

The procedures associated with this investigation were previously described[2], so only a brief outline is given here. A series of flow rate profiles (n = 3 replicates at each condition per apparatus configuration) was therefore determined in a round-robin approach by each participating laboratory, using the same calibrated, high-resolution (±2% of actual reading) thermal mass flow sensor (model 4040, TSI Corp, Shoreview, MN, USA) located at the inlet of each of the following sampling apparatuses, including induction port and pre-separator:

a. individual participant flow rate test systems (TS) - average V_{int} = 87 mL;

b. sample collection tubes (SCT) - average V_{int} = 115 mL;

c. an Andersen 8-stage non-viable impactor (ACI) - V_{int} = 1155 mL[3];

d. a Next Generation Impactor (NGI) - V_{int} = 2025 mL[3].

The target sample volumes corresponding to the three final flow rates of 30 L/min, 60 L/min and 90 L/min were 2.0 L, 4.0 L and 6.0 L respectively, assuming an ideal rectangular flow-time profile for the 4.0-s time period of each measurement sequence. Flow rate-elapsed time profiles (n=3 replicates) were initially determined at each target flow rate, with the inlet to each apparatus fully unrestricted (*i.e.* open). The measurement sequence was subsequently repeated with an orifice-based flow restriction (surrogate DPI). This restriction, when fitted to the inlet of each apparatus, applied a fixed 4-kPa pressure drop to simulate either a high-, medium- or low-resistance DPI at the final flow rates of 30, 60 and 90 L/min respectively, by adjusting the size of the orifice aperture. The signal from the flow sensor was processed for flow-time data recording by a purpose-developed proprietary recording software (FlowMonitor version 1.2, Sofotec GmbH, Germany), that is based on the LabVIEW™ platform (National Instruments Corp., Austin, TX, USA). Each participant recorded the instantaneous flow rate once every five milliseconds. The recording software stored the flow-time raw data in csv-text file format and performed the following calculations:

a. integration of the resulting flow rate-elapsed time profile to enable the total volume sampled to be calculated as the area-under-the-curve (*AUC*);

b. determination of the maximum peak flow rate (Q_{peak}) from the entire flow rate-time profile for that particular measurement sequence.

The following calculations were undertaken subsequently using the collected data for each measurement:

a. determination of characteristic rise time indicators in milliseconds, t_{20}, t_{80} and t_{90}, corresponding to times to attain 20%, 80%, and 90% of the final steady-state reference flow level respectively.

b. determination of the slope of the rising flow rate (L/min/ms) by linear interpolation between t_{20} and t_{80}, to evaluate a flow acceleration metric in the middle of the flow rate-time profile ($slope_{t20/t80}$).

Results

Sampled air volumes (*AUC*) with or without the surrogate DPI were all close to the nominal values of 2.0 L, 4.0 L and 6.0 L, with most data within the ±5% interval for all apparatus configurations. The overall associated measures of variability (RSD) were low at 1.7%, 1.3% and 2.0% for target flow rates of 30 L/min, 60 L/min, and 90 L/min, respectively, confirming that a high degree of measurement accuracy and precision existed overall.

A few values of Q_{peak} greater than 110% of the targeted flow rate (overshoot) were observed at all target flow rates. However, these incidences were confined almost exclusively to the measurements with TS alone (with no SCT nor impactor). The phenomenon was most apparent at the highest flow rate (Figure 1).

At each target rate, values of t_{90} lengthened as the internal volume of the test setup increased when the surrogate DPI was present (Table 1). The NGI, having the largest V_{int}, in combination with the surrogate DPI having the highest intrinsic resistance (lowest target flow rate), was associated with the longest t_{90} values at each target flow rate. This cascade impactor was also associated with the greatest change in t_{90} when the target flow rate was increased from either 30 to 60 L/min or from 60 to 90 L/min. Significantly, when the surrogate inhaler was present, the opposite behaviour was evident for the t_{90} values associated with all sampling configurations; that is, $t_{90\%}$ decreased as the final flow rate was increased. The presence of the surrogate DPI at the inlet also significantly increased the t_{90} values associated with each apparatus compared with corresponding values when that flow restriction was absent.

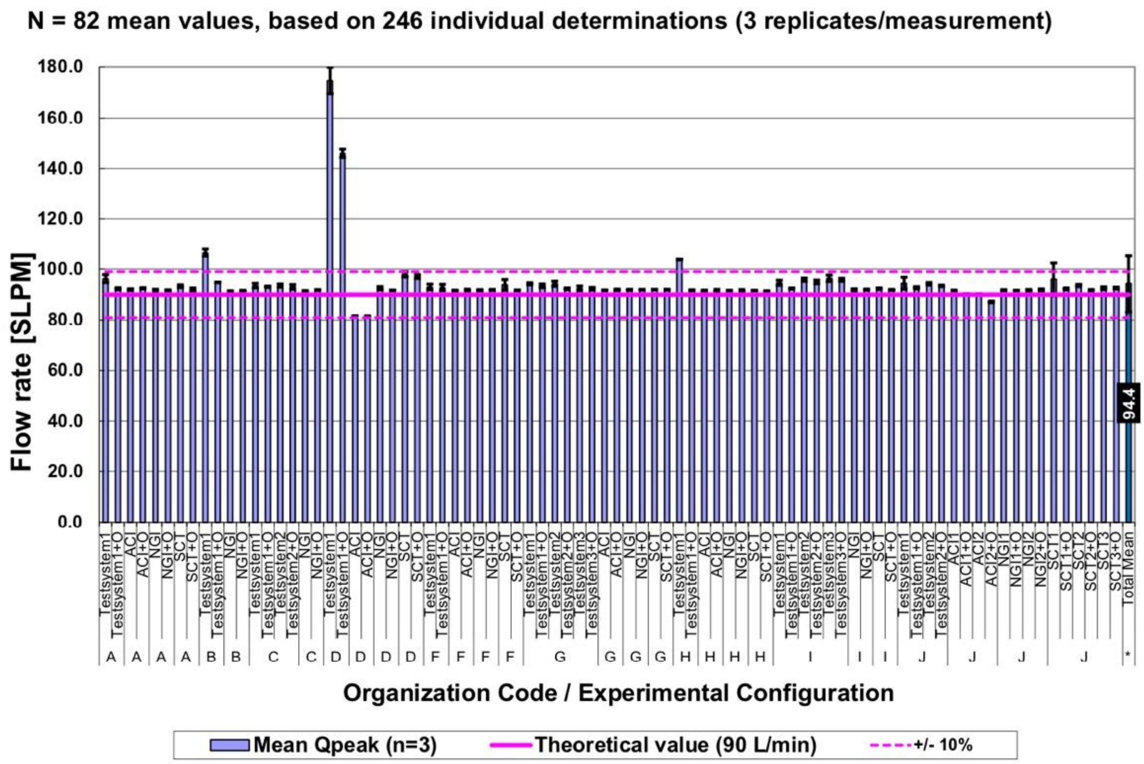

Figure 1 - Participant-by-Participant Measures of Q_{peak} for target flow rate of 90 L/min, Organized by Identity Letter Code A to J; TS= Organization-Specific Test System; SCT = Sample Collection Tube; ACI = Andersen 8-Stage Cascade Impactor; NGI = Next Generation Impactor

Longer rise times, in combination with decreased values of the flow acceleration parameter (Table 2), were associated with apparatus configurations having larger internal volumes. This behaviour is best illustrated by the data for the NGI, whose internal volume with pre-separator is almost twice that of the ACI with pre-separator.

Table 1 - Mean Values of t_{90} for Each Apparatus

Surrogate DPI	Apparatus Configuration	Average V_{int} (mL)	Final Flow Rate = 30 L/min	Final Flow Rate = 60 L/min	Final Flow Rate = 90 L/min
			t_{90} (ms)		
Absent	TS	87	12 (n=45)	13 (n=45)	13 (n=44)
	SCT	115	33 (n=27)	34 (n=27)	34 (n=27)
	ACI 60 L/min* + preseparator	1155	32 (n=9)	46 (n=12)	65 (n=9)
	NGI + preseparator	2025	49 (n=27)	91 (n=27)	106 (n=27)
Present	TS	87	31 (n=45)	20 (n=45)	17 (n=45)
	SCT	115	62 (n=27)	46 (n=27)	41 (n=27)
	ACI 60 L/min* + preseparator	1155	281 (n=9)	158 (n=12)	131 (n=9)
	NGI + preseparator	2025	431 (n=27)	266 (n=27)	197 (n=27)

* ACI 60 L/min stage configuration: stages -1, -0, 1 to 6, and back-up filter

Table 2: Mean Values of Flow Acceleration Parameter (*$slope_{t20/t80}$*) for Each Apparatus

Surrogate DPI	Apparatus Configuration	Average V_{int} (mL)	Final Flow Rate = 30 L/min	Final Flow Rate = 60 L/min	Final Flow Rate = 90 L/min
			$Slope_{t20/t80}$ (L/min/ms)		
Absent	TS	87	3.72 (n=45)	7.15 (n=45)	10.30 (n=44)
	SCT	115	2.37 (n=27)	4.59 (n=27)	6.84 (n=27)
	ACI 60 L/min*+ preseparator	1155	1.83 (n=9)	2.18 (n=12)	2.00 (n=9)
	NGI + preseparator	2025	1.74 (n=27)	0.98 (n=27)	1.14 (n=27)
Present	TS	87	1.67 (n=45)	4.42 (n=45)	8.46 (n=45)
	SCT	115	0.85 (n=27)	2.96 (n=27)	4.87 (n=27)
	ACI 60 L/min*+ preseparator	1155	0.14 (n=9)	0.49 (n=12)	0.88 (n=9)
	NGI + preseparator	2025	0.08 (n=27)	0.27 (n=27)	0.54 (n=27)

* ACI 60 L/min stage configuration: stages -1, -0, 1 to 6, and back-up filter

Discussion and Conclusion:

Rise time performance, both with and without the surrogate DPI present, was relatively undamped for either the TS or SCT apparatuses (where both V_{int} and intrinsic apparatus resistance were small), reflected in short t_{90} and large $slope_{t20/t80}$ values. This behaviour was largely independent of whether the surrogate DPI was present or absent. The increased resistance imposed by the surrogate DPI resulted in slower rise times and reduced $slope_{t20/t80}$ values. This behaviour was evident with all apparatus configurations, but was most apparent with both the CIs, that had substantially larger values of V_{int}.

The greatly dampened flow rate rise time behaviour with these apparatuses requires further explanation, as does the reversal in the behaviour of the relationships between both rise time and slope and target flow rate for a given apparatus configuration, comparing the situations when the surrogate DPI was absent or present. The first few stages of either CI comprise at least half, if not more, of the total internal dead volume, and contribute only a small flow resistance compared to that imposed by the presence of the 4-kPa pressure drop associated with the surrogate device. When the surrogate DPI was absent, the CI volume encompassing these low-resistance stages filled up relatively rapidly, so that the magnitude of t_{90} was dictated almost exclusively by the resistance of the last one or two stages having the highest intrinsic resistance. When the 4-kPa surrogate device was present, however, the air flowing into the CI took much longer to fill up the half or more of the impactor internal volume that in the previous case had been almost instantaneously filled. This delay decreased as the target flow rate was increased. Regardless of the presence or absence of the surrogate device, the smallest values of the acceleration parameter were associated with configurations having the largest internal dead volumes and highest intrinsic apparatus resistance, an intuitive outcome. A simple two-compartment first-order model aiming to qualitatively interpret these and other observed effects, has been presented at this conference [4].

References:

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