

## Flow Rate Ramp Profile Effects on the Emitted Dose from Dry Powder Inhalers

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### Summary

Emitted dose and aerodynamic particle size distribution testing of dry powder inhalers are often performed using pharmacopeial apparatuses. Due to the differences in internal volumes between these apparatuses, the flow increase rate profile to steady state conditions at the inhaler varies, with the emitted dose apparatus exhibiting a flow increase rate that is two to three times the rate observed in commonly used impactors. In this study, the emitted dose from two dry powder inhaler products was evaluated at several flow increase rates including rates similar to those observed for the Dose Uniformity Sampling Apparatus, Andersen Cascade Impactor and Next Generation Impactor. Differences were observed in emitted dose results in data sets obtained where flow increase rates were below values typically observed for compendial apparatuses.

### Introduction

Air flow characteristics through a passive dry powder inhaler (DPI) affect the amount of drug delivered from the device, which is an important consideration in patients where inhalation profiles are highly variable (1). Identifying, understanding and controlling parameters affecting air flow through an inhaler is necessary in an inhaler product testing laboratory where control of variability is important in making decisions regarding batch acceptability. Methods for characterizing the emitted aerosol from an inhaler are generally based on compendial approaches which outline testing to be performed at an air flow rate,  $Q$ , which generates a fixed pressure gradient across the specific device and for a duration of time such that 4 liters of air is drawn through the device. To achieve these specifications, a fast-response, timer-controlled solenoid valve is incorporated into the flow system to generate a square-wave flow profile of vacuum flow through the system upon test initiation.

Once the solenoid valve opens, though, the time for vacuum flow acceleration to propagate back through the system from the valve to the inhaler will vary depending on the volume existing between these points. Consideration of the apparatuses described in the compendias for emitted dose uniformity and aerodynamic particle size distribution (APSD) testing of inhalers shows a wide range of internal volumes exist. For example, the apparatus described for emitted dose testing has an internal volume of approximately 100 mL while the Next Generation Pharmaceutical Impactor (NGI), used for the aerodynamic particle size distribution test, has an internal volume of over two liters when equipped with a preseparator, as is generally required for DPI testing. As a result, the flow rate ramp profiles to steady state flow at the inhaler will be different between these two systems and a square-wave flow profile may not actually be achieved.

Parameters such as flow rate, rise time and total air volume through an inhaler have been evaluated for observed effect on measured delivered dose and emitted particle size distribution (PSD) for some inhalers. De Boer showed that the acceleration in flow rate (rise time) affected the emitted fine particle dose obtained from Pulmicort Turbuhaler (2). Chavan and Dalby reported that trends in both device emptying and particle deaggregation were observed over a range of flow rate ramp rates for several DPI devices (3, 4). While these studies provide additional evidence to support the current compendial approach, a direct evaluation of inhaler dosing performance with the flow rate profiles present between emitted dose and APSD apparatuses under compendial conditions has not been reported.

In this study, we report on the flow rate ramp profiles observed for emitted dose and APSD apparatuses under conditions outlined in the *US Pharmacopeia* (5). The emitted dose for two passive dry powder inhaler products was then evaluated over these flow profile ranges. This comparison may be relevant as any differences in observed emitted dose have implications for mass balance comparisons during APSD testing.

### Experimental

All flow rate measurements and ramp profiles for this study were obtained using a TSI Model 4043 Thermal Mass Flowmeter (TSI, Inc., Shoreview, MN, USA) set to display volumetric flow and calibrated for exit flow from the meter. For ramp profiles, the flow meter was connected to a computer via the internal RS232 serial port and the output was collected using Microsoft Hyperterminal, version 5.1, and exported to Microsoft Excel 2002 in ASCII format. Data output from the flow meter was triggered at a flow rate threshold of 0.05 L/min and sampled at a rate of 100 points per second. All reported flow rates for this study were made at the apparatus inlet.

To allow for evaluation of dose delivered from the inhaler at flow increase rates representative of cascade impactors, without introduction of additional variability due to assay of multiple impactor components, chambers with various internal volumes were inserted into the emitted dose setup between Apparatus B and the flow controller. These chambers were constructed from polyvinyl chloride (PVC) tubing with the tube ends sealed with PVC caps. A hole was drilled and tapped in both end caps to accommodate nozzle fittings for vacuum tubing.

The internal volume of the spacer was determined experimentally by measuring the volume of water required to fill the chamber to capacity.

Two commercially-available, multi-dose passive dry powder inhaler products were selected for use in this study to represent low to medium resistance inhalers. Handling and actuation of each inhalation device was conducted as described by the enclosed patient insert. Devices were primed once each day, and dose collection consisted of actuation of a single dosage unit from the inhaler device.

Emitted dose testing of the inhalers was performed using Apparatus B for dry powder inhalers as detailed in the *US Pharmacopoeia* <601> (5). Air flow rate and duration through the apparatus and device was controlled using a TPK Flow Controller (Copley Scientific, Nottingham, UK). Sufficient vacuum capacity was verified each day by confirming sonic flow through the control valve with a P3/P2 ratio of  $\leq 0.5$ . The air flow rate used for testing the medium resistance inhaler generated a 4 kPa pressure drop across the inhaler. An air flow rate of 100 L/min was used for testing the low resistance inhaler since a flow rate generating 4 kPa differential pressure drop across the inhaler was greater than this limit. Following dose collection, the contents of the collection tube (Apparatus B) were dissolved in 50 mL of diluent and the resulting solution assayed by HPLC.

JMP statistical software, version 5.1, (SAS Institute, Cary, NC, USA) was used for randomization of experiments to allow for variance analysis of day and flow increase rate factors. Testing of both products was performed over four days, and each day testing was performed in triplicate for each set of experimental conditions. Statistical analysis of generated results was also performed using JMP software.

## Results and Discussion

Flow rate profiles obtained for Apparatus B, modified Andersen Cascade Impactor (ACI) equipped with preseparator and induction port, and Next Generation Pharmaceutical Impactor (NGI) equipped with preseparator and induction port at both 60 L/min and 100 L/min air flow rates are shown in Figure 1. From these profiles, it is clear that the time to achieve steady state flow at the apparatus inlet is shortest for Apparatus B and longest for the NGI.

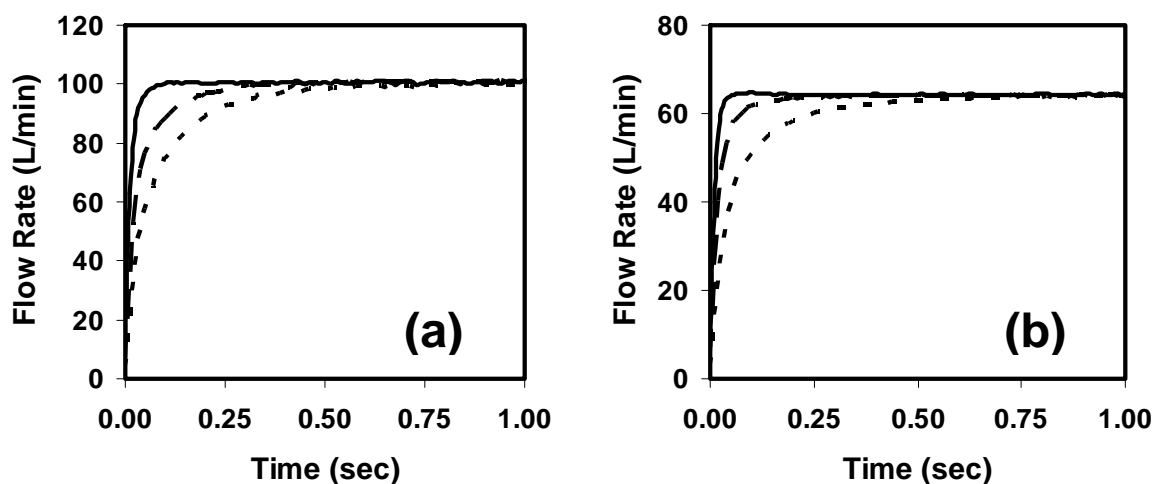


Figure 1: Flow rate profiles to 100 L/min (a) and 60 L/min (b) for Apparatus B (solid line), modified ACI (— —) and NGI (- - -).

**Table 1: Apparatus volumes and measured flow increase rates from flow profiles shown in Figure 1.**

| Apparatus   | Internal Volume (mL) | Flow Increase Rate over 20-80% range of 60 L/min (L/s <sup>2</sup> ) | Flow Increase Rate over 20-80% range of 100 L/min (L/s <sup>2</sup> ) |
|-------------|----------------------|--|---|
| Apparatus B | 122                  | 30.0   | 41.5  |
| ACI         | 1155                 | 17.3   | 18.7  |
| NGI         | 2025                 | 6.5  | 8.1   |

These observations trend with the internal volumes for each apparatus as shown in Table 1. The internal volumes for the ACI and NGI were obtained from reference 6 and the internal volume of Apparatus B used in this study was determined experimentally. Also noted from the profiles in Figure 1 is that flow acceleration to achieve steady state conditions is not constant. For comparative purposes in this report, flow increase rates for each apparatus, presented in Table 1, were calculated over the region representing 20% to 80% of the steady state flow, which is the steepest region of the curve. From the flow increase rates in Table 1, air acceleration through the emitted dose apparatus is at least two times that observed for the impactors.

Chambers were initially constructed for this study to match the internal volumes for the ACI and NGI. However, due to the low resistance of the chambers, the flow rate profiles observed between the ACI or NGI and the corresponding chamber were not comparable. Therefore, two additional chambers were prepared in an effort to better match the impactors' flow profiles. A summary of the measured internal volume and flow increase rate from 20% to 80% of the steady state flow for each chamber are shown in Table 2. For the product evaluation, chambers 1 and 3 were selected for use, along with the control condition (Apparatus B without a chamber) to generate a flow increase rate range comparable to compendial apparatuses. Chamber 4 was included in the study as well to represent an extreme condition for comparison.

**Table 2: Chamber volumes and measured flow increase rates.**

| Chamber | Internal Volume (mL) | Flow Increase Rate over 20-80% range of 60 L/min (L/s <sup>2</sup> ) | Flow Increase Rate over 20-80% range of 100 L/min (L/s <sup>2</sup> ) |
|---------|----------------------|--|---|
| 1       | 456                  | 11.8   | 12.9  |
| 2       | 1146                 | 5.8  | 6.3   |
| 3       | 1436                 | 4.6  | 5.2   |
| 4       | 2012                 | 3.6  | 3.9   |

Mean emitted drug mass obtained with the chambers are presented graphically in Figures 2 (low resistance inhaler) and 3 (medium resistance inhaler) as a percentage of the mean emitted dose obtained with the control (Apparatus B). From Figure 2, the low resistance inhaler exhibited a decrease in emitted dose when chamber 4 (2000 mL) was introduced. Although the internal volume of chamber 4 was similar to that for the NGI, the actual flow rate profile (not shown) for this chamber had a much lower flow increase rate (Table 2) than the NGI, which would not be encountered under compendial conditions. The dose result for the medium resistance inhaler (Figure 3) shows an apparent step change above 1000 mL chamber volume (chambers 3 and 4). The flow rate profile comparison for chamber 3 and the NGI at 60 L/min is shown in Figure 4, where it is observed that the chamber shows a slightly lower flow increase rate than the NGI. It is not clear whether this difference in flow increase rate is significant enough to explain the large change in emitted dose for this inhaler, suggesting some dependency of device performance on flow increase rate. Statistical evaluation of the results using a standard t-test for comparison of means showed a statistically significant difference ( $p < 0.05$ ) between control and chamber 4 for the low resistance inhaler and between the control and chambers 3 and 4 for the medium resistance inhaler.

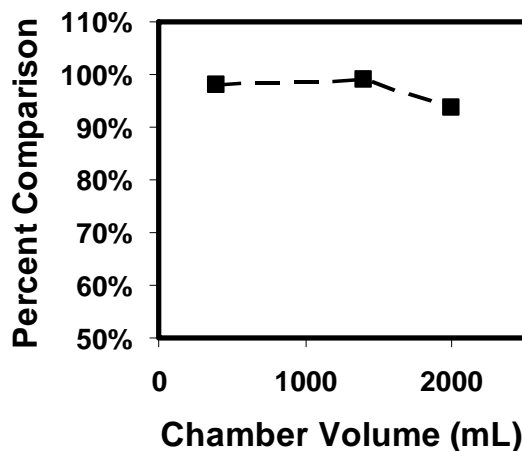


Figure 2: Emitted dose results for the low resistance device obtained for chambers 1, 3 and 4 as a percentage comparison to results from Apparatus B.

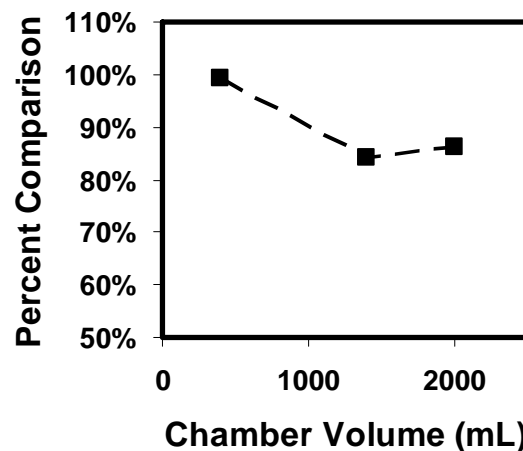


Figure 3: Emitted dose results for the medium resistance device obtained for chambers 1, 3 and 4 as a percentage comparison to results from Apparatus B.

Results obtained in this study are also presented graphically in Figure 5 as a function of flow increase rate for each inhaler. From Figure 5, it is observed that the observed emitted dose of both inhalers decreases below a flow increase rate of  $5 \text{ L/s}^2$ , which should not be encountered under compendial conditions. Thus, flow increase rate may be the parameter to control for comparison of dose results between apparatuses. From results obtained in this study, a flow increase rate of  $5 \text{ L/s}^2$  was the lower limit below which inhaler dosing was affected.

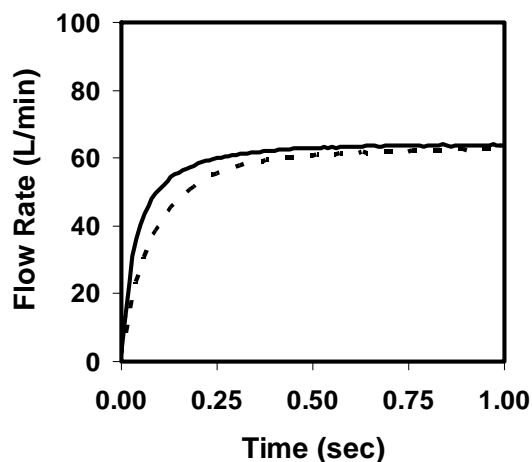


Figure 4: Flow rate profile comparison between NGI (continuous) and Chamber 3 (discontinuous) to 60 L/min flow rate.

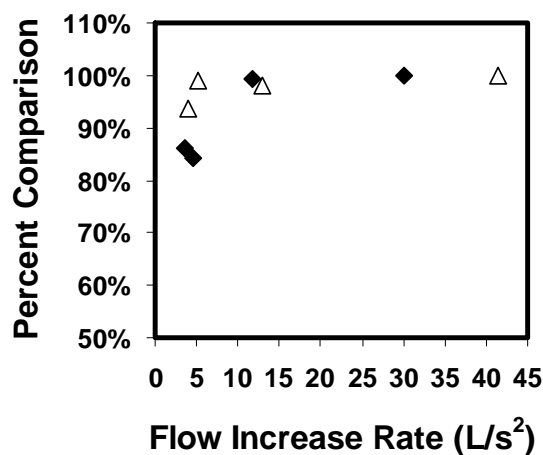


Figure 5: Emitted dose results for the low resistance device ( $\Delta$ ) and medium resistance device ( $\blacklozenge$ ) versus flow increase rate. Results are shown as a percentage comparison to results from Apparatus B (highest acceleration).

## Conclusion

Different flow rate ramp profiles are observed between the emitted dose apparatus, ACI and NGI as a result of the internal volume for each apparatus. For both products evaluated, statistically significant differences were observed in emitted dose results. However, these differences occurred in data sets where flow increase rates were below  $5 \text{ L/s}^2$ , which is less than the flow increase rates determined for compendial apparatuses.

## References

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