A European Pharmaceutical Aerosol Group (EPAG)-Led Cross-Industry Assessment of Inlet Flow Rate Profiles of Compendial DPI Test Systems: Part 2 – First-Order Impactor Model

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Summary

A simple two-compartment, first-order flow resistance model of a cascade impactor reveals the reasons for the major trends observed in the companion, cross-industry study of the transient behavior of the inlet flow rate in compendial DPI test systems. This model is physically reasonable because most of the internal volume of compendial impactors is comprised of stages with rather small resistance to flow, and when no DPI is attached to the induction port, the major flow resistance is contributed by the final one or two stages of the impactor. The typical DPI, then, with approximately 4-kPa pressure drop at the sampling flow rate, changes this situation by placing a significant flow resistance upstream of the otherwise insignificant resistance of the bulk of the impactor volume. Results with the two-compartment model reasonably agree with the experimental data in three important aspects: (a) the substantial increase in rise time when a surrogate DPI is present, (b) the decrease in rise time as the steady-state flow rate increases but only if the surrogate DPI is present (and opposite to the observed trend when the surrogate DPI is absent), and (c) the increase in rise time with larger total internal volume of the test equipment.

Compared with three-dimensional, unsteady-state numerical solutions of flow rate behaviour at start-up, the simple model intuitively conveys important physics that will assist users in understanding compendial DPI quality control test results, which could be very helpful when a user experiences unexpected trends or outliers in a data set.

Key Message

The role of the DPI and of the impactor volume in compendial testing for particle size can be physically understood by considering the impactor to consist of a low-resistance major volume and a high-resistance minor volume. This two-compartment model agrees qualitatively with nearly all of the EPAG cross-industry experimental data.

Introduction

Compendial methods for testing dry-powder inhalers **DRAW** air through the inhaler device and the cascade impactor by quickly opening a solenoid valve placed downstream of the test apparatus. The air flow begins by passing through the solenoid valve, and the point of forward air flow propagates upstream to the inlet of the DPI. Consequently, the air flow drawn into and through the inhaler device itself is delayed relative to the flow drawn through the solenoid valve. This inlet air flow increases with time at the outset of the test and reaches steady state in tens or hundreds of milliseconds after the solenoid valve opens, depending on the details of the test system and of the DPI. A major experimental study of these flow start-up kinetics is described in a companion publication [1].

We report here on a simple first-order computational model designed to explain the major trends seen in these experimental data, specifically those with the Andersen impactor or the NGI, with and without a surrogate DPI with 4 kPa of flow resistance attached to the impactor's induction port. We summarize in Table 1 the key experimental observations to which this model applies; we strongly advise the reader to take the time to understand the experimental set ups described in reference 1 before proceeding further.

Table 1 – Selected Experimental Values of t90 for Flow Start-Up in DPI Testing (milliseconds)

Configuration	Target Flow Rate (L/min)		
	30	60	90
Test system only	12	13	13
ACI	32	46	65
NGI	49	91	106
Test system + 4kPa orifice*	31	20	17
ACI + 4kPa orifice	281	158	131
NGI + 4kPa orifice	431	266	197

*one of three fixed orifices described in reference 1 imparting 4 kPa of pressure drop at the target flow rate and therefore acting as a surrogate DPI

Several issues are apparent from these data. First, the rise time increased by a multiple of two to eight when the surrogate DPI was present, seemingly disproportionately to its 4-kPa flow resistance. Second, with this 4-kPa pressure drop, the rise time decreased when the flow rate increased, a behavior opposite to that observed when the surrogate DPI was absent. Third, the system with the largest internal volume exhibited the largest rise time. This third observation is likely the only one of the three that would fit the intuition of most inhaler testers. For this reason, we believe that a model that outlines the fundamental physics of these trends would go a long way toward educating the user community about the factors that control rise time in compendial DPI test systems.

Physical Model

The internals of a cascade impactor, along with the typical ancilliary tubing, valves, and fittings of a compendial DPI test system contain substantial details that may or may not be significant to the observed behavior. Surprisingly, no complete three-dimensional model of a compendial system has appeared in the literature. However, 3-D and one-dimensional computational models of the impactor itself have been described [2,3]. Even so, in these models, no attempt has been made to study the effect of the DPI itself. To remedy this situation at the same time as conveying the important physics, we consider flow start up in a cascade impactor to consist simply of two volumes separated from the ambient air and each other by two arbitrary nozzle plates that provide a "low resistance" to flow, denoted by R_1, and a "high resistance" to flow, denoted by R_2 (Figure 1).

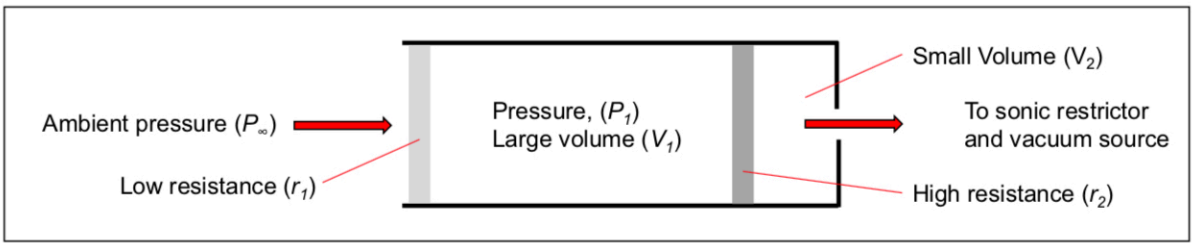

Figure 1: Two-compartment conceptual model of present analytical study

These flow resistances can be contributed physically by anything in the flow path. For the purposes of this model, resistance r_1 can include an inhaler device or not. This resistance can also be the aggregate resistance of several nozzle plates, with or without an inhaler device. Resistance r_2 can be the resistance of a particular nozzle plate or can be the aggregate resistance of several nozzle plates. For the ACI and the NGI, the first five or six stages have typically less than 10% of the overall flow resistance [4,5]. We postulate therefore that these impactors can be represented by two regions, one of which constitutes the majority of the internal volume (V_1) with little flow resistance and one with a small portion of the total volume (V_2) but with the bulk of the flow resistance.

Mathematical Model

Using the ideal gas law, the time rate of change of pressure in volume V_1 and in volume V_2 can be expressed in terms of the mass flow rate of air into and out of each chamber as follows:

$$\frac{dP_1}{dt} = \left(\frac{RT}{V_1}\right).(\dot{m}_1 - \dot{m}_2) \quad \text{and} \quad \frac{dP_2}{dt} = \left(\frac{RT}{V_2}\right).(\dot{m}_2 - \dot{m}_{SS}) \qquad (1a,b)$$

Here, $\dot{m}_1$ and $\dot{m}_2$ are the mass flow rates of air entering V_1 and into V_2, T is the absolute temperature of the air (assumed to be isothermal throughout), and R is the universal gas constant. The term $\dot{m}_{SS}$ is the mass flow rate of air leaving the impactor at steady-state flow conditions. We assume that this mass flow rate of air begins to leave volume V_2 immediately at time zero, an assumption that is reasonably accurate because the velocity of air leaving the control valve just downstream of the solenoid valve reaches sonic speed nearly instantaneously under the compendial protocol conditions. A more accurate boundary condition would include an expression for the mass flow rate through a sonic control valve [3]. However, such an approach would thwart development of an analytical solution to the relevant equations.

Equations 1a and 1b can be rearranged into two "pressure difference" equations – that is, the pressure drop across each of the two resistances -- as follows:

$$-\frac{d(P_\infty - P_1)}{dt} = \left(\frac{RT_\infty}{V_1}\right).(\dot{m}_1 - \dot{m}_2) \quad \text{and} \quad \frac{d(P_1 - P_2)}{dt} = \left(\frac{RT_\infty}{V_1}\right).(\dot{m}_1 - \dot{m}_2) - \left(\frac{RT_\infty}{V_2}\right).(\dot{m}_2 - \dot{m}_{SS}) \qquad (2a,b)$$

Here P_∞ is the (constant) ambient pressure; its time derivative is equal to zero. In general, $\dot{m}_2$ exceeds $\dot{m}_1$, accounting for the negative sign on the left-hand side of equation 2a.

The functional relationship of the mass flow rate to the resistances r_1 and r_2 and the pressure drop across a DPI is typically regarded as a square root relationship [6]: ($\dot{m} = K * \sqrt{\Delta P}$). Cascade impactor stages also follow this "Bernoulli-type" relationship [7]. The ratio of the resistances in any portion of the flow path is therefore independent of the flow rate (true for any power-law relationship of $\dot{m}$ to ΔP, provided that the relationship is the same in each component of the flow path). Therefore, assuming a linear relationship is very likely to exhibit the proper trends, and, IMPORTANTLY, the linear assumption affords us an analytical solution that reveals much of the relevant physics. [Proper parameter selection is described below].

With the linear relationship of the pressure drop to the mass flow rate, equations 2a and 2b can be written in a non-dimensional format as follows:

$$\frac{d\mu_1}{d\tau} = -\frac{1}{R_V R_r}\mu_1 + \frac{1}{R_V R_r}\mu_2 \quad \text{and} \quad \frac{d\mu_2}{d\tau} = \frac{1}{R_V(1-R_r)}\mu_1 - \frac{1}{R_V(1-R_V)(1-R_r)}\mu_2 + \frac{1}{(1-R_V)(1-R_r)} \tag{3a,b}$$

Here, the dimensionless mass flow rates are a fraction of the steady-state mass flow rate ($\mu_1 = \dot{m}_1/\dot{m}_{SS}$ and $\mu_2 = \dot{m}_2/\dot{m}_{SS}$). The dimensionless (characteristic) time is given by $\tau = t/\tilde{t}$ with $\tilde{t} = \frac{(V_1+V_2)(r_1+r_2)}{RT_\infty}$. Finally, the dimensionless parameters R_v: ($R_V = \frac{V_1}{V_1+V_2}$) and R_r: ($R_r = \frac{r_1}{r_1+r_2}$) show that the qualitative behavior of the system will be governed by the ratio of the two volumes and the ratio of the two resistances, *not the individual values*, an intuitively reasonable outcome.

We have developed an explicit analytical solution to these two simultaneous first-order differential equations (equations 3a and 3b), via Laplace transformations, leading to the following expression for the inlet flow rate *Q(t)*:

$$Q(t) = Q_{SS}.\left[1 + \frac{B.\exp\left(-\frac{t}{\tilde{t}/s_1}\right) + C.\exp\left(-\frac{t}{\tilde{t}/s_2}\right)}{R_V R_r(1-R_V)(1-R_r)}\right] \quad \text{or} \quad Q(t)/Q_{SS} - 1 = \frac{B.\exp\left(-\frac{t}{\tilde{t}/s_1}\right) + C.\exp\left(-\frac{t}{\tilde{t}/s_2}\right)}{R_V R_r(1-R_V)(1-R_r)} \tag{4a,b}$$

Here, Q_{ss} is the steady-state flow rate, and the coefficients *B* and *C* are non-linear expressions involving R_v, R_r and the time-scaling coefficients S_1 and S_2. The rearrangement, equation 4b, reveals that the deviation of the inlet flow rate from the steady-state value decays to zero exponentially at a rate that is a complex combination of the several relevant physical parameters (proper values of the coefficients *B* and *C* ensure that *Q(t)* is less than Q_{ss}).

Parameters for the Mathematical Model

Two aspects of the parameter estimation derive from available data and are independent of assumptions intrinsic to the approximate model. First, values of V_1 and V_2 must be consistent with the internal volumes of the induction port, pre-separator, and impactor [8]. Second, the dimensionless ratio R_r must be consistent with the reported pressure drop data for the impactors [4,5,7]. The question becomes "what reasonable fraction" of the total volume should be considered in the "low resistance" compartment as opposed to the "high resistance" compartment.

If we take stages -1 to 5 of the ACI (60-L/min configuration) and stages 1 to 6 of the NGI to constitute the low-resistance, larger volume (including the induction port and pre-separator), we find that the fraction of the total flow resistance found in volume V_2 is indeed less than 10%. Additionally, V_1 is more than 75% of the system volume. Both of these results are intuitively sensible for the two-compartment model. Now, we calculate the linear resistance coefficient r_1 by dividing the actual, known pressure drop in V_1 at the steady-state flow rate by the steady-state mass flow rate, and we calculate the dimensionless ratio R_r from the actual, known values for V_1 and for the total impactor (Table 2). For 30 L/min and 90 L/min steady-state flow rates, the value of r_1 is 0.5 and 1.5 times the value at 60 L/min, respectively, but the ratio R_r is the same regardless of the steady-state flow rate.

Table 2 –Volume and 60-L/min Resistance Parameters for the ACI and the NGI

Impactor	V_1 (cm^3)	V_2 (cm^3)	$R_V = \frac{V_1}{V_1+V_2}$	r_1 (Pa-s/kg)	r_2 (Pa-s/kg)	$R_r = \frac{r_1}{r_1+r_2}$
ACI[a]	885	270	0.77	2.251x10^5	1.556x10^7	0.014
NGI	1540	485	0.76	8.176x10^5	9.026x10^6	0.083

[a]60-L/min configuration of the ACI

Results and Discussion

The results in Table 3 reveal the combined effect of surrogate device resistance, impactor volume, and steady-state flow rate on the behavior of t_{90}:

- addition of the surrogate device is responsible for a significant increase of the rise time.
- the rise time for cases without surrogate device increases with target flow rate; for cases with the 4 kPa surrogate device, the rise time decreases with flow rate (although not smoothly for the ACI system).
- the rise time increases with impactor system volume.

Table 3 – Predicted Values of t_{90} for Flow Start-Up in DPI Testing

	Target Flow Rate (L/min)		
Configuration	30	60	90
ACI	56	112	168
NGI	67	131	212
ACI + 4kPa orifice	228	164	192
NGI + 4kPa orifice	407	272	261

Because linearization of the flow resistance means that the calculated flow resistance always exceeds the actual, the model should and does predict larger values of t_{90} than those observed experimentally. Also, the trends are very much the same, and the effects are of a magnitude that is in the same range as the experimental data.

Conclusions

A simple two-compartment, first-order flow resistance model of a cascade impactor anticipates the major trends in the experimental data described in the EPAG Cross-Industry study [1] and in a manner that conveys an intuitive understanding of the physics controlling the kinetics of the inlet flow to the inhaler in compendial DPI testing.

The model reasonably agrees with the experimental data in three important aspects:

(1) the substantial increase in rise time when a surrogate DPI is present;

(2) the decrease in rise time as the steady-state flow rate increases but only if the surrogate DPI is present (and opposite to the observed trend when the surrogate DPI is absent);

(3) the increased rise time for impactors with larger total internal volume.

Compared with three-dimensional, unsteady-state numerical solutions of cascade impactor behavior, the current model conveys important physics that will assist users in understanding compendial DPI quality control test results, which can be very helpful when a user experiences unexpected trends or outliers in a data set.

References

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