Exploring the robustness of the pharmacopeial methods for testing dry powder inhalers (DPIs); Part 1: Delivered dose uniformity (DDU)

Uncovering the potential for systematic bias in the pharmacopeial test protocol

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Introduction

Much improvement has taken place during the past 20 years on the subject of evaluating sources of variability in the resulting measures of delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD). The methods described in the United States Pharmacopeia (USP) [1] and European Pharmacopoeia (Pharm. Eur.) [2] now include dimensions and diagrams for all components that are critical to their robustness. The question of bias has not, however, been carefully addressed in the same way. Bias is, in its simplest form, a systematic error, conveying information about the accuracy of the measurement being made. Bias is demonstrated by a shift in the mean value from the true value of the sought metric if more than one replicate measurement is made. In contrast, variability is the random error that is always associated with replicate measurements made with real-world instruments that themselves have random uncertainty. Variability is often expressed by the standard deviation about the mean measurement value from a series of replicate measurements.

Control of the volumetric flow rate into sampling apparatuses for the performance testing of all types of passive dry powder inhalers (DPIs) is critical, as this measure influences the kinetics associated with mass transfer of the active pharmaceutical ingredient(s) (API(s)) from the inhaler to the measurement apparatus [3]. For example, a lower actual flow rate than the expected value from the measurement will affect the imparted energy-time profile to the powder, thereby resulting in slower aerosol generation, powder dispersion and transfer [4]. However, and perhaps surprisingly, volumetric flow rate is a *dependent variable* in the standard pharmacopeial protocols. Given this situation, it is incumbent for stakeholders to be aware of sources of potential bias to have complete confidence in this important inhaler performance measure. In this article, we show that there are sources of bias in the standard methods for DDU, and in a future article in *Inhalation*, our aim will be to extend the analysis to the measurement of APSD.

Defining the problem

The test for delivered dose uniformity (DDU) of a passive DPI has three discrete stages:

a. drawing air through the device at a rate sufficient to impart a pressure drop of nominally 4 kPa across the device,

b. removing the device and measuring the flow rate to enable the calculation of the test run time required to draw two liters of air through the device, and

c. reattaching the device and dispensing the dose by drawing air through the device for the specified run time.

We have depicted these steps in Figures 1a, b and c to enable a nomenclature for the relevant parameters that we will need for analyzing the system in detail.

Derivation of independent equations

Perhaps surprisingly there are ten independent equations and ten unknowns describing these three steps. We begin by deriving these ten equations, according to the three major steps of the testing procedure for total dose (TD) content from a DPI, in the context of determining DDU. When reading this detailed section, it is important to understand that our purpose is to enable the practicing user to evaluate when bias might be important and how to address it, if desired and needed.

Step 1: Set-up at a device pressure drop of 4 kPa

The pharmacopeial procedure [1, 2] aims to draw a specified volume of air (two liters) through the inhaler-on-test at a target flow rate that is chosen to impart a pressure drop of 4 kPa across the device (Figure 1a). The vacuum equipment for fixing the flow rate at this target value must be sufficient to achieve sonic air flow velocity across the flow control valve, a condition indicated by a ratio P_3/P_2 that is smaller than 0.5 (an approximation of the sonic flow condition predicted by adiabatic ideal gas behavior; e.g., equations 2.18 and 2.19 of Baker [5]). This flow condition is often called "critical" flow.

When the sonic flow condition is obtained, the mass flow rate of air throughout the system (inhaler, Dose Uniformity Sampling Apparatus (DUSA), vacuum source) is proportional to the gas density at the flow control valve (equation 1):

$$\dot{M}_s = K_s \frac{MW * P_{2,s}}{RT} \qquad (1)$$

Here, $\dot{M}$ is the mass flow rate, R is the universal gas constant, T is the absolute temperature just upstream of the control valve, and MW is the molecular weight of air (29 g/mole). The subscript "S" on the mass flow rate, on the proportionality constant K, and on the pressure P_2 indicates that the values are those derived when "setting" the conditions along the flow path before dispensing a dose from the inhaler.

Nomenclature

K_s – setting of the flow control valve

$\dot{M}_s$ – mass flow rate into the total dose tube during the set-up step (Figure 1a)

$\dot{M}_m$ – mass flow rate into the total dose tube during the measurement step (Figure 1b)

$\dot{M}_a$ – mass flow rate into the total dose tube during the dose dispensing step (Figure 1c)

MW - molecular weight of air (29 g/mole)

P_1 – pressure inside the total dose tube

P_2 – pressure upstream of the flow control valve

P_3 – pressure downstream of the flow control valve

ΔP – pressure difference between the atmosphere and the inside of the total dose tube

$\Delta P_{fm,m}$ – pressure drop across the flow meter at the time of the flow measurement

$\Delta P_{f,s}$ – pressure drop across the filter at the time of the set-up

$\Delta P_{f,m}$ – pressure drop across the filter at the time of the measurement

$\Delta P_{f,a}$ – pressure drop across the filter at the time of the actual test

$\Delta P_{dev,a}$ – device pressure drop at the time of the actual test

Q_s – volumetric flow rate entering the total dose tube during the set-up

Q_m – measured volumetric flow rate

Q_a – volumetric flow rate entering the total dose tube during the actual test

T_{TD} – run time of the total dose test

$V_{TD,a}$ – actual volume of air that flows out of the device during a test

Y – dimensionless form of the measured volumetric flow rate; equal to Q_m/Q_s

Z – dimensionless form of the volumetric flow rate during the actual test; equal to Q_a/Q_s

Since the flow control valve has been adjusted so that the pressure inside the total dose tube is 4 kPa below atmospheric pressure, we can write:

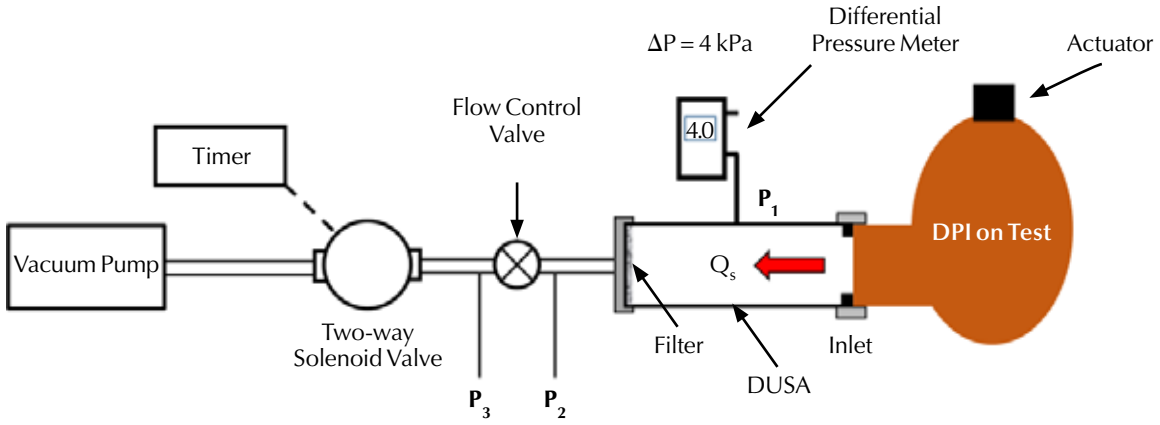
$$\dot{M}_s = Q_s \frac{MW}{RT}(P_{0,s} - 4kPa) = K_s \frac{MW}{RT}(P_{0,s} - 4kPa - \Delta P_{f,s}) \quad (2)$$

Here, Q_s is the volumetric flow rate exiting the device into the DUSA at the time of setting up the flow conditions to achieve the 4-kPa pressure drop across the device. This volumetric flow rate is a result of the detailed design of the device. To appreciate this point, we note that it is possible to design hardware to mimic low-, medium- and high-resistance DPIs with simply one orifice in a plate inserted in the flow path to give a fixed flow rate between 30 L/min and

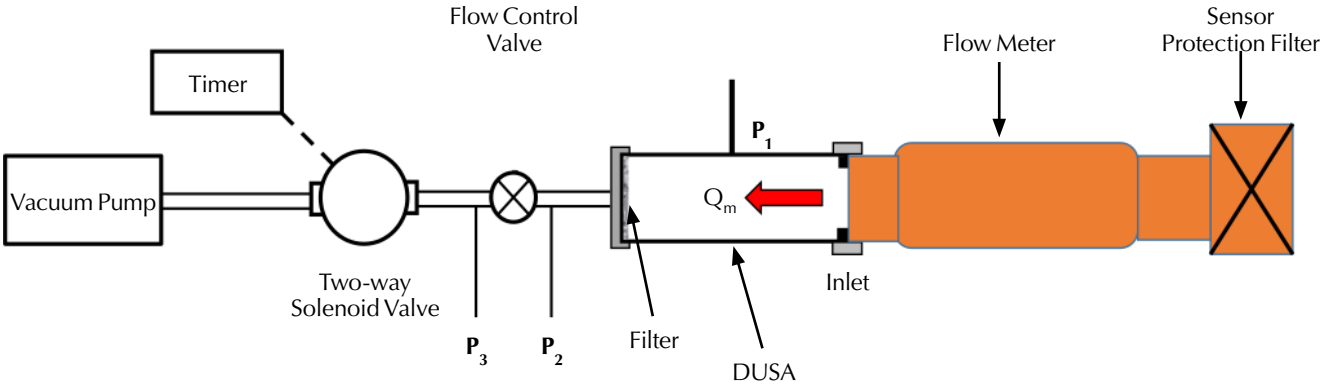
Figure 1

Setting up the air flow conditions for total dose collection for DDU testing of a passive DPI

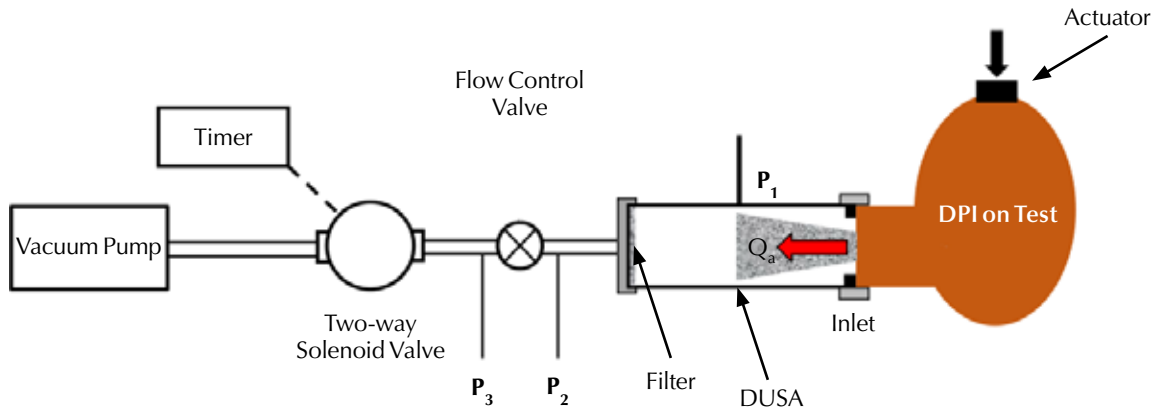
(a) Set flow control valve to reduce P_1 value to 4 kPa below atmospheric pressure; maintain critical flow ($P_3/P_2 < 0.5$)



(b) Measure volumetric flow rate at same flow control valve setting; Calculate run time



(c) Reattach DPI; Actuate and sample for run time calculated in step b



100 L/min and maintain a pressure drop of 4 kPa (see Figure 2 of Greguletz, et al., [6]). That is why we regard Q_s as an *independent variable* in the analysis.

In the second half of equation 2, note that we have simply observed that the pressure at the control valve, $P_{2,s}$, is the ambient atmospheric pressure, $P_{0,s}$, minus the 4-kPa target device pressure drop and minus the pressure drop across the filter that is near the exit of the total dose tube, $\Delta P_{f,s}$. In principle, there are small pressure losses caused by other system components, but we can consider these losses to be negligible. We have included the subscript "*S*" on the values of the atmospheric pressure and of the filter pressure drop because these values could possibly change after the 4-kPa device pressure drop value is set.

Step 2: Measure the flow rate and calculate the run time

The DPI-on-test is removed to measure the flow rate and replaced by a flow meter at the entrance of the DUSA (Figure 1b). The flow rate, Q_m, is now measured. The pressure inside the collection tube has now likely changed (most likely increased) because the pressure drop across the flow meter, $\Delta P_{fm,m}$, is likely smaller than the 4-kPa pressure drop across the device when setting the flow control valve. Consequently, the mass flow rate at the time of the measurement is likely different than it is at the time of setting the 4-kPa condition. This mass flow rate is related to other system parameters by equation 3:

$$\dot{M}_m = Q_m \frac{MW}{RT}(P_{0,m} - \Delta P_{fm,m}) = K_s \frac{MW}{RT}(P_{0,m} - \Delta P_{fm,m} - \Delta P_{f,m}) \quad (3)$$

Here, the subscript "*m*" denotes at the time of the measurement of the flow rate. Note that the coefficient K_s is unchanged when the flow rate measurement is made because the flow control valve is not adjusted after the flow conditions are set in step 1.

For the value of the pressure drop across the flow meter, we use equation 1 of Roberts [7]. This relationship includes the pressure drop across the flow meter as well as the pressure drop across the filter that is upstream of the flow meter, which serves to protect the flow meter from particulate matter:

$$\Delta P_{fm,m} = 26.2 \frac{Pa}{L/min} * Q_m - 148Pa \quad (4)$$

This pressure drop is less than approximately 2.5 kPa even when the flow rate is 100 L/min, a figure that is less than the device pressure drop in step 1 and also in step 3.

Step 3: Dispense the dose by drawing air for the specified run time

Finally, when the actual test takes place, the mass flow rate may be different than at the time of setting the 4-kPa condition or measuring the flow rate because the ambient atmospheric pressure may have changed. The mass flow rate during the actual test, in any case, is related to other system parameters by equation 5:

$$\dot{M}_a = Q_a \frac{MW}{RT}(P_{0,a} - \Delta P_{dev,a}) = K_s \frac{MW}{RT}(P_{0,a} - \Delta P_{dev,a} - \Delta P_{f,a}) \quad (5)$$

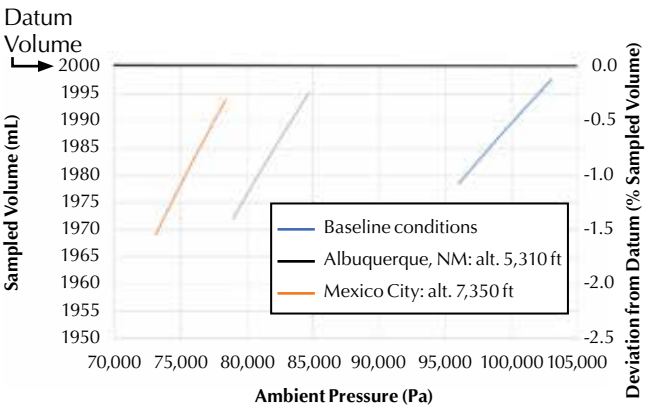
The possibility of a change in atmospheric pressure may seem remote. Best practice, of course, is to check the flow rate entering the DUSA before *every* measurement. However, frequently the flow control valve is set early in a testing program and may not be changed for the duration of the program, and such a series of measurements may possibly last weeks. In addition, it is common practice, after an initial set-up, to test any given batch of DPIs with total dose tubes that do not have a P1 port (e.g., product 8608A, Copley Scientific, Nottingham, UK [8]). So, in practice, it is likely that the atmospheric pressure could change appreciably throughout the duration of a test program. To investigate the sensitivity to ambient pressure changes, therefore, we must allow for the possibility that $P_{0,s}$ and $P_{0,m}$ and $P_{0,a}$ all differ from each other.

Flow rate/Pressure drop relationships

An additional relationship that assists in the analysis comes from many studies of practical, passive DPI devices wherein the flow rate has been found to change inversely with the square root of the pressure drop across the device (e.g., equation 1 of Clark and Hollingworth [4]). Consequently, we can be confident that the pressure drop across the device during the actual test is related to the set-up pressure drop

Figure 2

Influence on sampled volume of ambient test pressure



of 4 kPa, the actual test flow rate and the flow rate during the test set-up as follows:

$$\frac{\sqrt{\Delta P_{dev,a}}}{Q_a} = constant = \frac{\sqrt{4kPa}}{Q_s} \quad (6)$$

The constant in equation 6 is sometimes called the DPI "resistance" and its magnitude is a result of detailed device design. In our analysis here, we maintain a generalized approach by not quantifying the DPI "resistance," because we instead consider Q_s to be an independent variable, since the magnitude of its value at 4-kPa pressure drop is fixed by the device design.

Three more of the necessary, independent equations derive from the fact that pressure drop across filters is often regarded as dependent on the face velocity, a quantity equal to the volumetric flow rate approaching the filter divided by the cross-sectional area of the portion of the filter through which the air passes. Consequently, the pressure drop across the filter in equations 2, 3 and 5 can be regarded as a simple function of the volumetric flow rate in the DUSA:

$$\Delta P_{f,s} = F(Q_s) \quad (7a)$$

$$\Delta P_{f,m} = F(Q_m) \quad (7b)$$

$$\Delta P_{f,a} = F(Q_a) \quad (7c)$$

Roberts [7] has reported pressure drop data for typical filter media used in total dose testing and these data provide the necessary input for quantitative evaluations of equations 7a to 7c.

Run time and sampled volume

Two simple equations remain, namely, the relationship between the run time, T_{TD}, and the measured volumetric flow rate, Q_m, and the relationship between the actual sampled volume, $V_{TD,a}$, and the two-liter target volume:

$$T_{TD} = \frac{2L}{Q_m} \quad (8a)$$

$$\frac{V_{TD,a}}{2L} = \frac{Q_a}{Q_m} \quad (8b)$$

In equation 8a, the numerator is the two-liter target sampling volume proscribed by the USP standard protocol for total dose measurement. The subscript "TD" in the run time and in the sampled volume denotes "total dose," a notation that will distinguish these values from the run time and sampled volume in APSD testing in a future article.

Table 1 summarizes the independent variables, the ten unknowns and the ten independent equations that apply to the analysis described above.

Solution method for the independent equations

Equation 8a for the run time, T_{TD}, is very simple and has no influence on the other parameters. Once the value of Q_m is a found, evaluating equation 8a becomes easy. So, no further discussion of the run time is needed; however, we note that two times this run time is the prescribed run time for APSD testing.

Table 1

Parameters Defining Bias Analysis in Total Dose Testing

	Independent Variables	$P_{0,s}$, $P_{0,m}$, $P_{0,a}$, Q_s
	Equation Numbers	**Unknowns**
Physical Principle		
Air Flow at Sonic Control Valve	2, 3, 5	K_s, Q_m, Q_a
Flow Meter Flow Resistance	4	$\Delta P_{fm,m}$
Device Resistance	6	$\Delta P_{dev,a}$
Filter Media Flow Resistance	7a, b, c	$\Delta P_{f,s}$, $\Delta P_{f,m}$, $\Delta P_{f,a}$
Constant Air Flow During Test	8a, b	T_{TD}, $V_{TD,a}$

Equation 8b for $V_{TD,a}$ will be trivial to evaluate once a value can be calculated for the measured volumetric flow rate and the actual volumetric flow rate during a test. So, no further discussion is needed regarding equation 8b.

To solve the remaining eight equations, 2 through 7a, b and c, it is beneficial to define the aims of the analysis. The *first aim* is to show whether and to what extent the flow rate coming out of the device and into the total dose tube during the actual test, Q_a, differs from what is measured, Q_m. Any differences in these quantities will mean that the sampled volume during a test will not equal the two-liter sample volume proscribed by the USP and Pharm. Eur. protocols, per equation 8b.

The *second aim* is to show whether and to what extent the pressure drop across the device at the time of the actual test differs from the set-up value of 4 kPa. Any differences in these quantities will introduce device-dependent change in the dynamics of the powder dispersion, potentially affecting the start-up kinetics [9], and therefore potentially affecting both the total dose and the APSD measurements.

In the following solution method, we will consolidate equations 2 through 7a, b and c into two somewhat-complex expressions for the unknown flow rates Q_m and Q_a. Each of these expressions are solved computationally, using the Solver function of Excel.

We first note that the measurement of the volumetric flow rate entering the DUSA at the measurement step allows the calculation of the proportionality constant K_s by rearranging equation 3:

$$K_s = Q_m \frac{(P_{0,m} - \Delta P_{fm,m})}{(P_{0,m} - \Delta P_{fm,m} - F(Q_m))} \tag{9}$$

We substitute this expression for K_s into equation 2 to find:

$$Q_s = Q_m \frac{\left(P_{0,m} - 26.2\frac{Pa}{L/min} * Q_m + 148Pa\right)}{\left(P_{0,m} - 26.2\frac{Pa}{L/min} * Q_m + 148Pa - F(Q_m)\right)} * \frac{(P_{0,s} - 4kPa - F(Q_s))}{(P_{0,s} - 4kPa)} \tag{10}$$

In equation 10, we have inserted equation 4 for $\Delta P_{fm,m}$ to account explicitly for the pressure drop across a typical flow meter with its upstream protective filter. Equation 10 is an implicit equation for Q_m (one that is able to be solved numerically).

We next derive an expression for Q_a. By substituting equation 9 for K_s into equation 5 and then dividing both sides by the gas density in the DUSA during the actual test, we find:

$$Q_a = Q_m \frac{(P_{0,m} - \Delta P_{fm,m})}{(P_{0,m} - \Delta P_{fm,m} - F(Q_m))} \frac{(P_{0,a} - \Delta P_{dev,a} - \Delta P_{f,a})}{(P_{0,a} - \Delta P_{dev,a})} \tag{11}$$

Now with equation 6 for the device pressure drop inserted into equation 11, we find the following relationship for the volumetric flow rate during the actual test:

$$Q_a = Q_s \frac{(P_{0,s} - 4kPa)}{(P_{0,s} - 4kPa - F(Q_s))} \left(1 - \frac{F(Q_a)}{P_{0,a}\left(1 - \frac{4kPa}{P_{0,a}} * \frac{Q_a^2}{Q_s^2}\right)}\right) \tag{12}$$

We solve this equation numerically for Q_a; afterwards, we can calculate the ratio of the actual volumetric flow rate to that measured, Q_a/Q_m, a ratio that is the same as the ratio of the actual sampled volume to the target, two-liter sample volume, per equation 8b. So, solving equation 12 achieves the *first aim* of the analysis.

The *second aim* of the analysis is to calculate the pressure drop across the device during the actual test and compare it to the 4-kPa value achieved during the test set-up. This computation is now quite simple. We use equation 6 with the known value of Q_s and the value of Q_a calculated from equation 12:

$$\frac{\Delta P_{dev,a}}{4kPa} = \frac{Q_a^2}{Q_s^2} \tag{13}$$

Equations 10 and 12 can be made dimensionless by dividing both sides of both equations by Q_s. If we then define the variable Y to be equal to Q_m/Q_s, and the variable Z to be equal to Q_a/Q_s, we are left with the following two equations needing a numerical solution:

$$Y - \left(1 - \frac{F(Y*Q_s)}{P_{0,m} - 26.2\frac{Pa}{L/min} * Y * Q_s + 148Pa}\right) * \left[1 - \frac{F(Q_s)}{P_{0,s} - 4kPa}\right]^{-1} = 0 \tag{14}$$

$$Z - \frac{(P_{0,s} - 4kPa)}{(P_{0,s} - 4kPa - F(Q_s))}\left(1 - \frac{F(Z*Q_s)}{P_{0,a}\left(1 - \frac{4kPa}{P_{0,a}} * Z^2\right)}\right) = 0 \tag{15}$$

The advantage of introducing the variables Y and Z is that the correct solution to equations 14 and 15 will be with Y and Z rather close to 1.0. We employed the Solver function in Excel [10] to conduct the numerical solution, and a good first guess to the solution

was Y and Z equal to 1.0. Then, the numerical solution method was efficient and accurate (typically, the Solver function found solutions with the left-hand-sides of equations 14 and 15 on the order of 10^{-10}). The aims of the calculations, namely the actual volume sampled and the actual device pressure drop (equations 8b and 13), are given in terms of the variables Y and Z as follows:

$$\frac{V_{TD,a}}{2L} = \frac{Y}{Z} \tag{16}$$

$$\frac{\Delta P_{dev,a}}{4kPa} = Z^2 \tag{17}$$

Results

We assert the following outcomes of the analysis:

1) Deviations can occur from the expected sampled volumes and device pressure drops if the atmospheric pressure changes from the time of the set-up to the time of the actual test; and
2) The actual delivered volume is always smaller than the target of two liters because the flow meter pressure drop is smaller than 4 kPa.

The influence of these outcomes on the actual delivered dose is device-dependent and therefore outside of the scope of the current study. These outcomes are, however, a matter for end-users to investigate, understand and control.

The role of atmospheric pressure

Intuitively, one expects the pressure drop across the device during the actual test will be at the 4-kPa value achieved during the set-up. This intuitive conclusion can be confirmed by inserting $P_{0,a} = P_{0,s}$ in equation 5 (with a variety of algebraic rearrangements of the applicable equations). The thought process here is simply that the flow control valve does not change after being set in step 1. So, when the device is reattached to the system in step 3 after the flow rate measurement during step 2, the flow system is the same as in step 1.

However, what if the atmospheric pressure drifts from the time of the setting of the flow control valve so that $P_{0,a}$ is not equal to $P_{0,s}$? This situation surely takes place in daily practice worldwide; local ambient atmospheric pressure changes can be observed on nearly any smartphone. To address this question in more detail, we have solved the system equations for the following baseline conditions: a flow rate, Q_s, of 60 L/min and an ambient pressure at set-up and at measurement of one standard atmosphere (101,325 Pa). Then, we allow the ambient pressure at the time of testing to range from 96,000 Pa to 103,000 Pa, representing realistic variations in atmospheric pressure at sea level. Furthermore, we postulate the same (fractional) range of ambient pressure variation, but starting at two representative locations that are significantly above sea level, namely Albuquerque, NM, US (5,310 feet) and Mexico City, Mexico (7,350 feet) [11].

The calculation results presented in Figure 2 show that the sampled volume can be up to 1% lower than its expected value if the ambient pressure at the time of measurement drops by a few percentage points. This result derives from the pressure drop of the flow meter in step 2 being smaller than the device pressure drop in steps 1 or 3. In addition, as the atmospheric pressure changes at the time of testing, the flow meter pressure drop offset is a different fraction of the atmospheric air pressure. There is, therefore, an inherent failure to deliver the target sampled volume of two liters even when the atmospheric pressure does not change, simply because the pressure drop of the flow meter is smaller than 4 kPa.

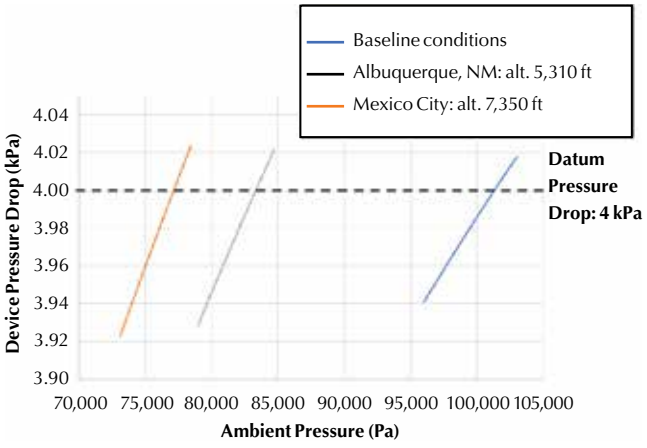
Figure 3 shows that the device pressure drop can also fall by a percentage point or more if or when the ambient pressure at the time of testing decreases by a few percentage points from the atmospheric pressure at the time of set-up. The curves are somewhat steeper as the altitude increases, reflecting the slightly non-linear dependence of the filter flow resistance to the volumetric flow rate approaching the filter face. A change in the device pressure drop can intrinsically affect the powder dispersion [9], and we anticipate that this type of change is more important than an offset in the sampled volume.

Discussion and conclusions

The findings from this exploratory analysis of the underlying physical processes involved with the determination of total dose content from a DPI following methodology advocated in the pharmacopeial compendia [1, 2] support the robustness of these methods, in that bias arising from normal, local, ambient

Figure 3

Influence on device pressure drop of ambient test pressure



pressure fluctuations at sea level in the nominal sampled volume of two liters is predicted to be less than -1% of nominal (Figure 2). Likewise, the equivalent bias at the two higher altitude examples where DPI performance testing likely takes place is predicted to be <1.5%. Similarly, deviations from the nominal 4-kPa pressure drop at the inlet to the DUSA are predicted to be only marginally sensitive to local changes in atmospheric pressure, being in the range -2% to +0.5% at the highest altitude (worst case condition), decreasing slightly to vary from -1.5% to +0.5% at sea level (Figure 3). We conclude that for performance testing at a fixed altitude, corrections of the sampled air volume and inlet pressure drop for ambient pressure variations are unnecessary. Further, there appears to be no need for different set-up procedures at laboratories located significantly above sea level.

However, we take this opportunity to remind users of this method that for the purposes of best practice, filter resistance in the DUSA should be investigated if a change is made to a different filter product, especially if nominal porosity is different. Further, the volumetric flow rate should be set frequently when a series of measurements is being made, ideally before every replicate, but at least daily. Finally, it is important to ensure a protective filter is always present during the flow rate measurement; if it is present at some stations and not others, or changes from test to test, the gas density inside the total dose tube during measurement can be different among the multiple tests and test set-ups in a major manufacturing facility.

We have not considered the effect of a leak at the mouthpiece adapter because our purpose has been to examine the method robustness when followed under ideal conditions. However, such an investigation would be of interest in a future extension of the model, most likely based on well-defined and realistic leak path geometries. Perhaps of more immediate importance, however, would be to continue this modeling in the context of the compendial methods for passive DPI-generated aerosol APSD determinations, given the added potential for changes to the dynamics of powder deagglomeration, subsequent aerosolization and transport into the multi-stage cascade impactor associated with the flow rate-rise time profile following actuation [9]. Achieving this goal will therefore be our next task.

Acknowledgement

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