Testing dry powder inhalers (DPIs): Pulling back the curtain on the pharmacopeial DPI flow system and thinking critically about it

Improving best practice and being ready when it does not work

Daryl L. Roberts, PhD
Applied Particle Principles, LLC

Control and reproducibility of the testing of dry powder inhalers (DPIs) has been on the minds of serious industry participants for years [1, 2], and new participants enter the field regularly, seeking to learn proper methods [3, 4]. Hasn't *enough* been said already about testing dry powder inhalers? After all, the equipment, setup, and methods are fairly well described in the current industrial handbooks, such as the United States Pharmacopeia (USP) Chapter <601> [5] and European Pharmacopoeia (Pharm. Eur.) Section 2.9.18 [6]. So all testing needs to be done that way, and everything will be okay, won't it?

Yes, true, but… the USP no longer lists some of the example flow system components.

Oh really, why not?

How do I know if the performance of the components changes with time?

Good questions.

Each reader who has gotten this far in this article likely has his or her own question! So another article on dry powder testing? *Yes!* Here, we seek to take the curious user *inside* the flow system to aid in creating understanding, not of "how to" but "why," and not "what went wrong" but "because." We also aim to create enough understanding to take on hard questions such as "What if I have a carrier-free product and do not use a pre-separator; what happens then?"

A better understanding of methods for testing DPIs is important also because regulatory officials, such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), understand that particle size affects the fate of inhaled particles in the lung. So data on the size of particles that contain the active pharmaceutical ingredient (API) are essential to a proper assessment of the safety and efficacy of an inhaled drug product. Cascade impactors make it possible to obtain such data. But this tool does not, and never will, represent a lung. Consequently, there is an ongoing discussion of how realistic cascade test methods should be or even can be; and there is a natural tension between realism and practical equipment that can lead to compromises on both ends of that spectrum. Inhaler testers ideally then will understand their methods well enough to explain the limitations of their well-designed, but necessarily *in vitro*, methods.

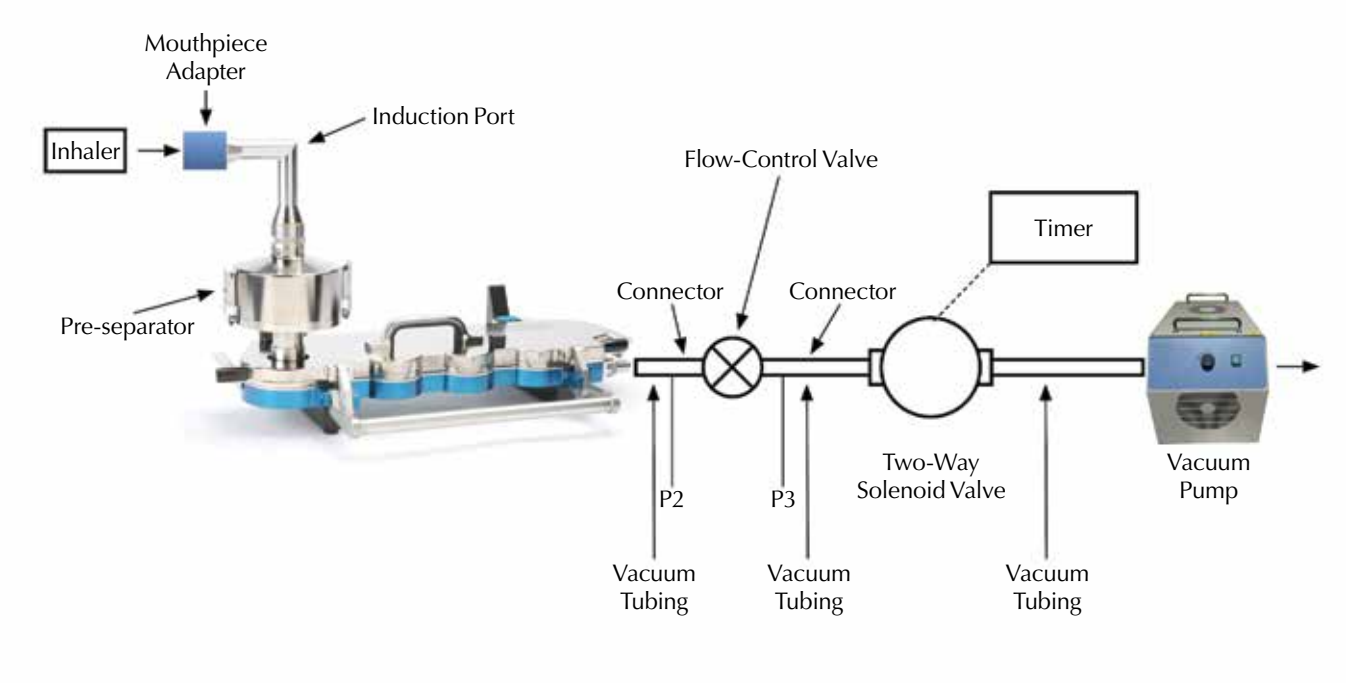
In this article, we will think critically about the motion of air from the moment the solenoid valve gets its signal to open until the solenoid valve closes and the air motion comes to a halt (*Closing does halt the air motion, doesn't it*?). And we will think about the fact that there are *particles* in the system, not just air. After all, the testing is all about the particles, isn't it? Or is it? Our hope is that *each reader* who has a question can better think through any issue after reading this article. Along the way, we describe ongoing investigations of remaining uncertainties in the testing equipment and methods.

Testing basics

The standard for testing the aerodynamic particle size distribution (APSD) of powders emitted by DPIs involves drawing air through the DPI for a specified

Figure 1

Flow configuration for routine APSD testing of DPIs.



number of seconds at a target flow rate when it is attached to a good-quality cascade impactor (Figure 1). This figure calls out common test components described in USP Chapter <601> [5] and in Pharm. Eur. Section 2.9.18 [6].

Before running a test of a DPI with the components shown in Figure 1, the user has the additional challenge of setting the flow rate so that the pressure drop across the inhaler is 4 kPa. *Why that pressure drop? And further, why not simply measure the flow rate in real time at the exit of the impactor?* Good questions.

But hasn't the USP and Pharm. Eur. description changed over the years?

Yes. This question is not news to many practitioners of the art. It is even considered a "normal" event, to be expected. After all, one might say the description should improve in a cautious and orderly way. In fact, the USP and equivalent organizations in other regions of the world convene expert panels to consider and adjust the published protocols. Further, the USP publishes proposed revisions to its protocols [7, 8] and invites public comment. It is instructive, then, to see a few aspects of the "evolution" of the USP depictions because it highlights some of the background thinking of the leaders in the field (Table 1).

There are some components of Figure 1 that have not changed at all in 20 years—rightly or wrongly—namely the flow control valve (Parker Hannifin 8FV12LNSS; still available today), the location of the pressure tap on the dry powder total dose tube (integral to the determination of the test flow rate), and the concept that the solenoid valve should open in less than 100 milliseconds.

Other curiosities come up in reviewing the USP and Pharm. Eur. descriptions of DPI testing. The USP until recently named the ASCO 8030G13 solenoid valve as an adequate valve for the testing (https://www.emerson.com/en-us/catalog/asco-sku-8030g013ac11060d) whereas the Pharm. Eur. Section 2.9.18 names the type 256-A08 valve by Bürkert GmbH (https://www.burkert-usa.com/en/products/solenoid-valves/general-purpose-2-2-solenoids/145766).

Additionally, the Pharm. Eur. description declares the inside diameter (ID) of the passageway through the seat of the solenoid valve to be ≥ 8 mm, saying "A 2-way, 2-port solenoid valve having a minimum airflow resistance orifice with ID ≥ 8 mm and an opening time ≤ 100 ms (e.g., type 256-A08, Burkert GmbH, D-74653 Ingelfingen), or equivalent."

But the USP has dropped the 8-mm orifice dimension from its description (Table 1). Therefore, a serious and reasonable user is certainly within his or her rights to ask "Why the differences and changes? Do these matter?"

The pump is on and the solenoid valve starts to open—now what?

A typical carbon vane vacuum pump suitable for this testing (e.g., Becker Seco SV 1025) rotates 30 times per second, with five or six carbon vanes, thereby moving small packets of air every five to six milliseconds. Pressure waves travel at approximately 340

Table 1

Portions of USP descriptions of equipment for testing dry powder inhalers

USP Edition	Vacuum Tubing	Solenoid Valve	Vacuum Pump
Vol. 28, 2002	8 ± 0.5 mm ID and 50 ± 10 cm long	2-way solenoid valve; internal diameter orifice of 9.5 mm and a flow coefficeint (Cv) equal to 1.8, minimal resistance to air flow and a response time < 100 ms	Pump must be capable of drawing the required flow rate through the assembled apparatus with the dry powder inhaler in the mouthpiece adapter. Connect the pump to the solenoid valve using short and wide (≥ 10 mm ID) vacuum tubing and connectors to minimize pump capacity requirements.
Vol. 29, 2005	A length of suitable tubing ≥ 8 mm ID with an internal volume of 25 ± 5 mL	2-way, 2-port, having an ID ≥ 8 mm and an opening response time of ≤ 100 ms	Pump must be capable of drawing the required flow rate through the assembled apparatus with the dry powder inhaler in the mouthpiece adapter. Connect the pump to the solenoid valve using short and wide (≥ 10 mm ID) vacuum tubing and connectors to minimize pump capacity requirements.
Official as of May 1, 2021*	A short length of suitable vacuum tubing, e.g., silicone tubing with an inside diameter of 16 mm. The internal volume of the tubing between the impactor and the flow control valve should be 25 ± 5 mL.	2-way, 2-port, with an opening response time of ≤ 100 ms	Pump must be capable of drawing the required flow rate through the assembled apparatus with the test product seated in the mouthpiece/ nosepiece adapter. Connect the pump to the solenoid valve using a short length of suitable vacuum tubing and connectors to minimize pump capacity requirements.

*See reference 9 for now-closed public comment invitation before this update to USP <601>.

m/s; and given that a basic test station is no longer than about one meter, from the inhaler to the solenoid valve, air with absolutely no obstructions to flow would begin to move *at the inhaler* in 3 milliseconds or less, after the solenoid valve starts to open. However, observed flow rate rise times for testing DPIs with an NGI that includes its pre-separator are on the order of hundreds of milliseconds (Figure 2).

Therefore, with a first glance at the vacuum pump and natural pressure-wave speed, we can conclude that the vacuum pump is not important in the start-up rate of air flow (provided it is strong enough to enable sonic velocity at the control valve) and that "something" between the sealing orifice inside the solenoid valve and the inhaler is indeed providing significant resistance to the air flow. *Why go through this logic?* So that the reader can better understand how to think about the system. And at the same time, it helps elucidate the conclusion that it is still possible that solenoid opening *rate* could be making a difference. Do we know the rate at which the orifice of a solenoid valve comes open, say, for example, the fraction of "openness" versus time? No; we are not aware of any published data on this subject.

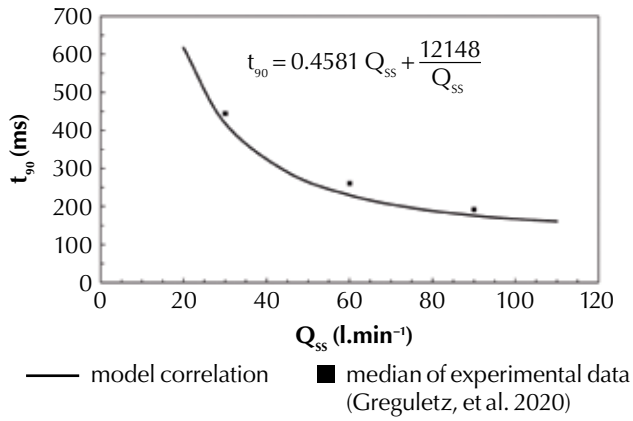
The air flow has started—it has to get through the pre-separator

The pre-separator of the NGI is an obvious first place to look into the question, "What is responsible for the start-up times of several hundred milliseconds?" *Why?* Because it is something the air flow must past through immediately after leaving the inhaler, and its volume is approximately 730 mL (see Table 1 of reference 11). At a typical flow rate of 60 L/min coming out of the inhaler, the average residence time in the pre-separator is on the order of 700 ms. This figure is a factor of approximately two to four larger than the typical flow start-up times observed experimentally (Figure 2). *So wait a minute; the flow starts up faster than the residence time in the pre-separator. Hmmm… there must be some way for the air flow to pass through the pre-separator faster than one might first think.* Hold onto that thought for a moment.

Even without fluid mechanics details, we immediately realize qualitatively that one of the most important aspects of the testing system is simply whether a pre-separator is included. Most testing of DPIs requires the pre-separator, but there are dry powder formulations that do not require a pre-separator because the

Figure 2

Start-up time (t_{90}) for the NGI with pre-separator for typical test flow rates (Q_{ss}). (From reference 10, used with permission.)

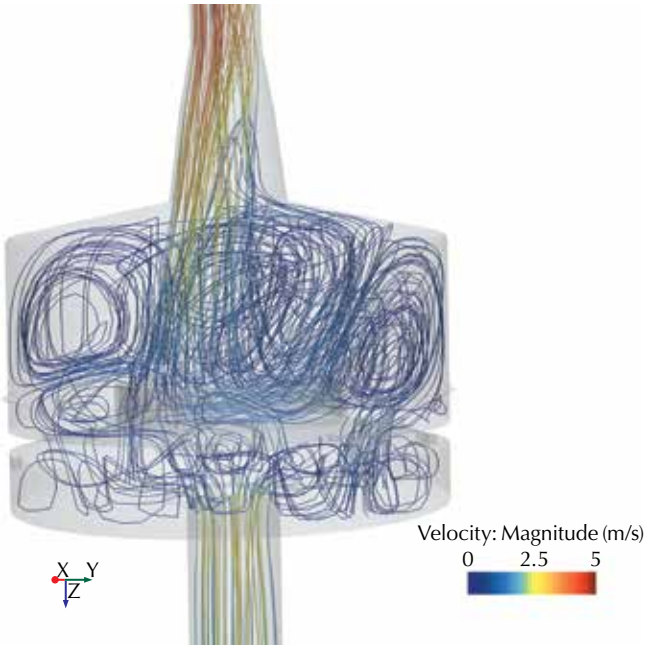


formulation has no (large) carrier particles. In these cases, it is common practice to leave out the pre-separator. But, now, if we start thinking about the start-up of the flow rate, we can see that it might be a possible improvement for carrier-free formulations if the test protocol purposely includes the pre-separator. *Why*? Because the flow start-up time is reduced approximately 40% by eliminating the pre-separator *(It is?),* and now the start-up time begins to be on the order of the 100 ms opening time of the pre-separator. Therefore, the testing results could possibly be affected by variability among a batch of solenoid valves. This issue is yet to be investigated theoretically and experimentally, to our knowledge. *But why do we say that the start-up time is reduced by about 40%? Where are those data?* Here we are simply noting the reduction of total NGI system volume from about 1,904 mL with the pre-separator to 1,172 mL when the pre-separator is absent (Table 1 of reference 11).

Now, let's get back to the question about the average air residence time being much longer than the observed flow start-up times. The time it takes to reach steady-state flow rate is the time it takes to reach steady-state pressures throughout the system. So the average residence time is likely to be longer; but the particle behavior still depends on the residence time distribution and *when exactly* the particles begin to come out of the device (a device-dependent question). To begin to unravel these issues, Dr. Henk Versteeg and students [12] have recently studied, computationally, the air flow patterns in the pre-separator and found that there are significant recirculation zones, along with preferred passageways, for air to pass through the pre-separator (Figure 3). The implications of these air recirculation zones are yet to be investigated. Continued modeling work is underway, especially focused on the behavior of the particulate matter as it leaves the inhaler device and is carried through the recirculation zones.

Figure 3

Flow streamlines inside the NGI pre-separator. (From reference 12.)



The bottom line is: The pre-separator is an important part of the system and significantly affects the behavior of the particulate matter during the start-up of the system air flow. Many questions remain.

The flow rate is supposed to be constant, constrained by a sonic-velocity restriction. Is that *true*?

We've considered the tail end of the system (the solenoid valve and the pump) and the very front end of the system (the inhaler and the pre-separator). Now, let's look into the system a bit more. The only reason air is coming through the inhaler is because the vacuum pump has drawn it out of the end of the impactor, causing air to move forward through the flow control valve, the NGI exit port, each stage of the NGI from last stage to the first stage, finally starting the flow from the ambient air into and through the inhaler, some tens or hundreds of milliseconds after the solenoid valve starts to open. The flow rate through the inhaler ramps up from zero to a chosen steady-state value.

Are we sure we know that steady-state value? To achieve the desired steady-state flow rate, the standard test protocols [5, 6] say that the pressure downstream of the flow control valve, P3, should be no more than one-half of the pressure upstream of the flow control valve, P2 (P3/P2 < 0.5). They say that this condition ensures that the flow rate at the flow control valve's opening is sonic, also called "critical." That is how the flow rate measured with the total

dose tube and 4 kPa pressure drop can be assured to be the same in impactor testing.

However, we have found that Parker Hannifin, the manufacturer of the flow control valve identified in the USP and Pharm. Eur., (Parker Hannifin, valve model 8FV12LNSS), says that critical flow is reached when P3/P2 ≤ 0.17 (Parker Needle Valve catalog, 4110-NV, June 2019, page 6 of reference 13; found at the following website: https://www.parker.com/Literature/Instrumentation%20Products%20Division/Catalogs/IPD_Needle_Valves_Catalog_4110-NV.pdf.)

We are uncertain exactly why the required ratio of P3/P2 to achieve sonic flow in reality is much smaller than the value of 0.5 stated in the USP and Pharm. Eur. testing guidance. The value of 0.5 is derived from the theory of adiabatic thermodynamics of air passing through an abrupt constricting orifice (e.g., reference 14, equation 8-26) and therefore has to be regarded as an "ideal" condition. However, the realistic value of 0.17, and other such figures for similar valves, needs to be recognized and may result from the somewhat tortutous path that air must follow to get through an ordinary flow control valve.

So we have to face the fact that there is uncertainty about the flow rate when the testing is done according to USP and Pharm. Eur. guidance. Consequently, further work is important to investigate this issue, including aiming to determine whether sonic velocity at the flow control valve matters, how to arrive at an accurately known value of the flow rate, and whether knowing the flow rate is important if it is reproducible from test to test.

On the subject of knowing the flow rate, based on our personal experience and similar anectodal reports from colleagues in the field, there is an "unsteadiness" in the reading on the display of common flow meters, such as those based on hot film or venturi or laminar flow principles, typically used by the inhaler testing community when setting up the system flow rate. In the laboratory of Applied Particle Principles, LLC, we have begun to try to understand this unsteadiness, which tends to be ± 1% to 2% of the time-average flow rate. This unsteadiness matters because it can obscure 20% to 40% of the "± 5% of target flow rate" specification of the pharmacopeial methods [5, 6].

Figure 4 shows the unsteadiness in the pressure just downstream of the NGI when the entry flow rate is 60 L/min, as measured with a pressure transducer accurate to ± 0.02% of reading, reporting data every 20 ms (Mensor Model 6020, Mensor LP, San Marcos, TX, US). The pressure fluctuations are on the order of 20 Pa (the vertical axis has units of kPa). For reference, when measuring ambient pressure, this transducer exhibits fluctuations of only ± 1 Pa. There is a slight drift in the pressure as well, but the most important point is that the pressure fluctuations are real and likely indicate flow rate unsteadiness. This unsteadiness increases along the NGI but is particularly pronounced as the flow exits the micro-orifice collector (MOC) and moves to the outlet fitting. We have made these pressure measurements along the NGI flow path by connecting to the access ports built into the "delta P" lid of the NGI (part number C005019, FIA AB, Lund, Sweden; https://shop.fia.se/all-products/ngi-stage-pressure-drop-lid/ and reference 15). Currently, we are thinking that the pressure fluctuations may be at the source of the flow measurement unsteadiness.

Are we there yet?

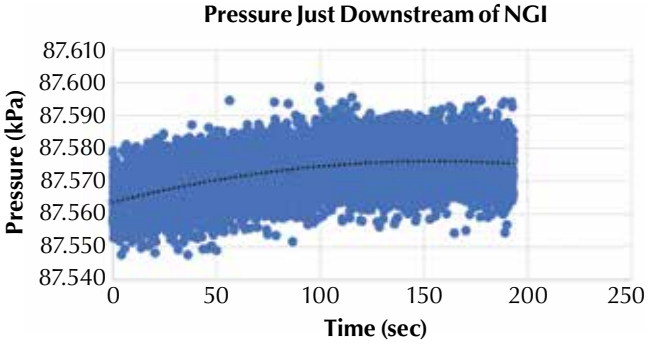
Excellent question. It is fair to say that there is much of value in the "rear view mirror" and "there are good road conditions" ahead. Detailed thinking about the flow conditions in the DPI test system has led us to understand more about why experts have improved the pharmacopeial protocol over time. At the same time, there are aspects of the fundamentals that are not yet clarified but are worth understanding and accommodating in the protocols. Looking in the "rear view mirror," we have seen that one of the trends in the changes shown in Table 1 is the minimization and control of the total volume of tubing downstream of the NGI. Also, the tubing specification includes a greater tubing diameter to reduce pressure drop and to reduce the Reynolds number (promoting a calmer fluid flow). At the same time, the pharmacopeial methods have, in some cases, relaxed detailed control and simply made it the responsibility of the tester to get the necessary flow rate but with the obvious encouragement to focus on larger diameter tubing.

Our detailed thinking about the flow conditions shows that there may be further improvement needed in the following areas:

1) specifications for the solenoid valve, such as the rate of opening of the solenoid valve and possibly the reproducibility from valve to valve;

Figure 4

Pressure fluctuations in tubing connected to the exit port of the NGI. (Inlet flow rate of 60 L/min; ambient air pressure approximately 99.5 kPa.)



2) the effect of the pre-separator, including its flow patterns and residence time distribution, and whether large carrier particles are part of the formulation;
3) control of the flow rate, whether the flow conditions are truly sonic at the flow control valve;
4) measurement of the flow rate, even in the face of pressure fluctuations resulting from turbulence inherent in the air flow

We certainly appreciate each reader who has read this article. Hopefully the detailed thinking we have outlined will lead to better understanding in each individual's laboratory when problems or questions arise.

Ultimately we can hope for a more firm basis in the community at large for testing DPIs as these questions get answered in further research undertakings. The details of the pharmacopeial methods have indeed changed over time. Further improvement will come in a slow and difficult manner, just like changes in the past. We can only hope to do our part; and as is often said "If it were easy, somebody would have already done it!"

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Daryl L. Roberts, PhD, is President of Applied Particle Principles, LLC, 17347 Westham Estates Court, Hamilton, VA, 20158, US, Tel.: +1 612 845-3293, droberts@particleprinciples.com, www.particleprinciples.com.