Cascade impactor flow control

The importance of controlling air flow for accurate cascade impaction inhaler product testing

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The US and European pharmacopoeias both specify cascade impaction for aerodynamic particle size measurement among the *in vitro* tests required for all inhaled products to confirm consistency of drug delivery and to characterize deposition behavior. Because the air flow rate used for measurement in cascade impaction affects the precision of the test equipment, and potentially affects the formulation being assessed as well as the discharge characteristics of the device, the accuracy of these tests relies on precise air flow control.

For many inhaled products, air flow drives aerosolization of the formulation and can therefore have a marked impact on how the dose disperses and on the resulting aerodynamic particle size determination. In addition, for some devices, especially dry powder inhalers (DPIs), the air flow through the device provides the motive force for dose delivery, and some breath-operated devices trigger only when the flow rate through them exceeds a certain value.

Understanding how volumetric air flow affects the results of cascade impactor tests, and more importantly, how to measure and control flow rate accurately, requires some knowledge of flow meter technology, including calibration and the appropriate application of correction factors, as well as an understanding of the issues involved in the set-up of test equipment.

Principles of cascade impaction air flow

Cascade impaction divides a sample into fractions on the basis of particle inertia, which is a function of aerodynamic particle size and velocity (Fig. 1). A vacuum pump draws sample-laden air through a series of stages, each with a set number of nozzles of defined diameter (Fig. 2). Total nozzle area decreases with increasing stage number, so providing that the volumetric flow rate remains constant, the air velocity increases at each stage. As a result, at each successive stage, the inertia becomes sufficient for smaller and smaller particles to break free of the air stream and to impact onto a collection plate.

As long as the nozzle diameters, and to a lesser extent, the jet-to-plate distances, remain within defined tolerances, cascade impactors give well-defined stage cut-off diameters (the aerodynamic diameter of particles that accumulate on any given collection surface) at given inlet air flow rates. Significant variation in these parameters or in the air flow rate leads to incorrect particle size measurement.

Figure 1

Cascade impactor principles of operation

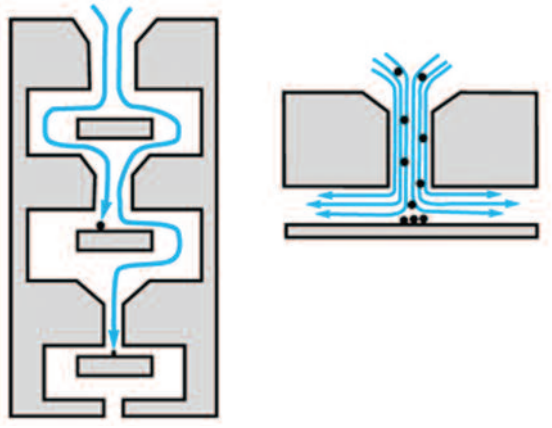
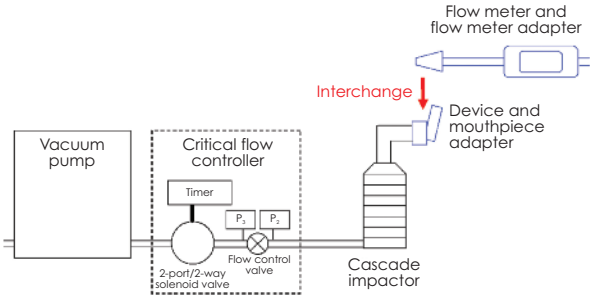


Figure 2

Schematic of cascade impactor system for DPIs



Note: This diagram is a general guide to the test set-up for DPIs. Please refer to the individual test monographs (e.g. USP or Ph.Eur.) for detailed instructions. *Not drawn to scale.*

Both of the pharmacopoeias specify that the test flow rate should lie within +/-5% of the target flow. That variance includes not only the accuracy of the flow meter, but also errors associated with determining, setting, and controlling flow. A simplified version of Stokes' law, which describes the relationship between the stage cut-off diameter, air flow rate, and nozzle diameter, demonstrates that a 5% deviation in flow rate changes the stage cut-off diameter by approximately 2.5%:

$$D_{50,2}/D_{50,1} = (Q_1/Q_2)^{1/2}$$

Where D_{50} is stage cut-off diameter and Q is volumetric air flow rate at the inlet to the impactor. In other words, if a flow rate set at 57 L/min is actually 60 L/min, or high by approximately 5%, the stage cut-off diameter would be only 0.975 as large as it would be at 60 L/min.

Ensuring accuracy requires active attention to the flow rate, with both rigorous routine practice and regular external calibration of the flow meter. On the most commonly used cascade impactors, jet-to-plate distance is generally fixed and therefore remains unchanged throughout the life of the instrument. Nozzle diameter maintenance relies on routine visual inspection and on regular stage mensuration, typically on an annual basis, to verify the critical mechanical dimensions of the instrument. Depending on use the frequency of stage mensuration may vary.

Types of flow meters

Although the many different types of flow meters available commercially operate on different principles, they all have the potential to produce valid measurements and comparable results if calibrated and operated correctly. However, companies usually stick to one particular type throughout the product lifecycle in order to reduce the potential for variability. Comparative studies [1,2] have shown that the accuracy of flow meters used in different pharmaceutical laboratories typically ranges between 2 and 4 %.

Laminar flow/differential pressure element

The pressure drop across any element in a flowing system, a venturi for example, relates to the volumetric flow rate through it, with laminar flow exhibiting a linear correlation. Both laminar flow and differential pressure elements exploit this relationship, determining flow rate by measuring pressure drop across a defined path. Laminar flow elements split the stream and feeds into many parallel tubes to achieve laminar flow, simplifying the calculation.

Mass flow meter

Some mass flow meters use a combination of heated elements and temperature sensors to record the influence of air flow on heat transfer within the device. Others detect the change in electrical resistance of a hot wire as it cools during contact with the flowing air. Because these flowmeters measure mass flow and not volumetric flow, inhaler testing data requires conversion to volumetric units.

Rotameter

Rotameters are simple mechanical devices in which a float rises higher in a tube as flow rate through the tube increases. Having no electronics, they have little risk of long term drift; however, stability and parallax error issues can compromise reading accuracy. As a result, rotameter users must know which part of the float to use for the reading and whether the float should rotate during measurement.

Determining the proper test flow rate

Although patient inspiration subjects inhalers to varying flow rates, cascade impaction requires a constant volumetric air flow; within this constraint, the flow rate must, as far possible reflect the conditions of use. For propellant or pump-driven delivery, particle aerosolization is generally insensitive to, and therefore considered independent of, test flow rate. Pharmacopeial guidance for metered dose inhalers and for the majority of nasal sprays recommends a flow rate of 28.3 L/min because, historically, the industry calibrated impactors at 1 SCFM. The NGI, however, was calibrated at an inlet air flow rate of 30 L/min, and is, therefore, operated at that rate for those types of devices.

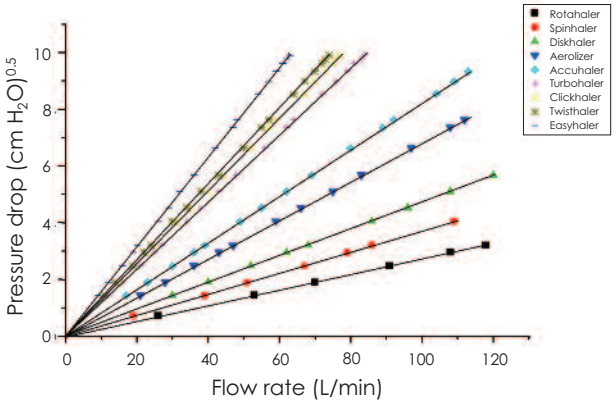
Inspiration-dependent devices, where aerosolization is sensitive to air flow rate, present more complicated cases. For nebulizers, which rely on tidal breathing instead of a single forced inspiration, the pharmacopoeias recommend an air flow of 15 L/min, the typical adult mid-inhalation flow rate. For DPIs, specifications call for a flow rate that induces a 4 kPa pressure drop across the device, typical for adult patient inspiration, or 100 L/min, whichever is lower. Because flow resistance differs from device to device (Fig. 3) [3], the easiest way to determine the correct flow rate for a particular DPI is to use a modified delivered dose sampling apparatus in conjunction with a flow controller that has the capacity to measure and record the required parameters.

Proper set up

To generate the required flow rate at the inlet of the impactor and device, the analyst installs a flow meter in place of the device and adjusts a flow control valve to the correct rate. DPI testing requires an additional step since the pharmacopoeias recommend that the

Figure 3

The resistance to flow presented by different DPI devices [3].



pressure downstream of the valve measure less than 50% of the upstream pressure, i.e. P3/P2 ≤ 0.5, so that the set point for the control valve delivers critical (sonic) flow to ensure flow stability [4].

Because the air velocity cannot exceed the speed of sound at the prevailing conditions, any fluctuations in pressure downstream of the control valve therefore will not impact the rate of flow through it. After setting the flow rate, the analyst returns the delivery device to the impactor inlet. Although the pressure drop across the flow meter may differ from the pressure drop across a DPI, potentially creating a discrepancy between the measured flow and the test flow [5], a systematic investigation [4] has shown that upstream changes in pressure drop of up to 12 kPa result in a flow rate change of less than 1% provided that the critical flow condition is met.

Leak testing

Any leaks in the cascade impactor could cause variance from the set flow rate, making leak testing before measurement vitally important. The usual method involves applying a vacuum to the impactor and monitoring pressure rise, although other techniques exist. No group to date has generated harmonized standards for leak testing of all impactor types; however, the European Pharmaceutical Aerosol Group (EPAG) has recommended an approach for determining an appropriate test method [6].

If the vacuum applied during leak testing is too high, worn seals that may not perform adequately under correct test conditions might not leak during the test. On the other hand, very low vacuum levels may compromise measurement sensitivity. The user guide for the Next Generation Impactor (NGI) recommends applying a vacuum of 2.5kPa and checking that pressure rises by no more than 100 Pa/s. This figure, based on a mathematical model of acceptable flow deviation, should ensure that the leak rate does not exceed 0.5% of the total flow at the inlet to the impactor, even at the lowest calibrated flow rate.

Operating practices

Routine good practices that recognize the importance of pressure differences throughout the test system and the effect of atmospheric temperature and pressure on volumetric measurements can improve measurement quality with all flow meters.

Tubing size. For practical reasons, labs will want to use a single diameter of tubing for all connections. The size of the tubing should, within the constraints of the system, provide a maximum diameter for the tube that connects the outlet of the flow meter to the impactor in order to avoid excessive pressure drop. The inlet to the flow meter remains open to the atmosphere.

Correction factors. Operating at a different temperature and/or pressure from the calibration conditions introduces a discrepancy between the recorded and actual flow rate that can be offset through the application of correction factors. Mass flow meters may also require a correction for use with air if the calibration took place with another gas. Although pressure drop across the flow meter will vary depending on the design, analysts may need to know its value at all operating flow rates in order to apply correction factors properly, if necessary.

Atmospheric pressure fluctuates by about +/- 4%, which can lead to significant variations in recorded flow rate; changes in altitude can exacerbate this effect. Temperature swings usually vary less in absolute terms but may differ significantly enough to necessitate a correction for the laboratory temperature. Some flow meters have operating modes in which they use internal temperature and pressure sensors to correct automatically for ambient conditions. If not, analysts should always follow the manufacturer's formulas to calculate correction factors since meter design affects the correction, and reference conditions for different instruments may vary (Table 1).

Calibration and maintenance

Most pharmaceutical companies send their flow meters to organizations with suitable flow meter calibration facilities for an annual calibration. Such organizations provide certification traceable to national or international standards (e.g. UKAS, NIST). The organization should provide details of the calibration conditions, including atmospheric temperature and pressure, as well as whether they cali-

Table 1

The impact of pressure and temperature on measured flow rate for a typical mass flow and differential pressure flow meter. (All flows are in L/Min)

	Actual flow rate (differential flow meter) Ref. conditions: 20.0 deg C, 101.3 kPa	Actual flow rate (mass flow meter) Ref. conditions: 21.1 deg C, 101.3 kPa
Flow rate displayed	**Laboratory pressure = 101.3 kPa, Temperature = 25 deg C**	
40	41.3	40.5
60	62.0	60.8
80	82.6	81.0
	Laboratory pressure = 95 kPa, Temperature = 20 deg C	
40	40.3	42.5
60	60.5	63.7
80	80.7	84.9

brated for inlet or outlet flow, since these conditions set the baseline for applying correction factors.

Although the pharmacopoeias state that the flow meter should be calibrated for the volumetric air flow leaving the meter, which is the flow that enters the impactor, organizations commonly calibrate on inlet air flow. In that case, US Pharmacopoeia section 601/European Pharmacopoeia section 2.9.18 provides an equation for conversion:

$$Q_{out} = Q_{in} P_{amb}*/(P_{amb}-\Delta P)$$

Where Q_{out} is volumetric flowrate exiting the meter (L/min), Q_{in} is volumetric flowrate entering the flow meter (L/min), P_{amb} is ambient pressure (kPa), and ΔP is the pressure drop over the meter (kPa). Some flow meter manufacturers that calibrate for inlet flow provide details of the relationship between flow rate and pressure drop over the flow meter to allow for more ready calculations.

In the best case scenario, the calibration reveals that the flow meter produces readings equal to the calibration reference standard, requiring no further action. If not, the calibration organization may be able to adjust the flow meter scale to reflect the calibration reference standard, or the analyst can modify the set point for each instrument prior to use. For example, if the calibration shows that the instrument reads 0.3 L/min too low, the analyst can set the meter for 75.3 L/min in order to achieve a target flow rate of 75 L/min.

Companies can carry out other good practices in house, including verifying the flow meter calibration against a "master" flow meter to confirm accuracy and to check for drift. Also allowing a period of stabilization after switching on produces more reliable results for many flow meters. Other aspects of routine practice depend on the type of flow meter used and the manufacturer's recommendations. For example, some instruments may require inlet filters, especially mass flow meters sensitive to particle contamination.

References

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