Analytical techniques are chosen for their ability to meet specific informational requirements. Therefore, a good starting point for a discussion of cascade impact is the consideration of how particle size data are used in the development and manufacture of orally inhaled products (OIPs).

The size of the particles or droplets delivered by an OIP, such as an inhaler or nebulizer, directly influences the success, or otherwise, of drug delivery. This is because size has an impact on in vivo behavior, most specifically on the regional deposition of the drug active within the respiratory system. When developing inhaled products, particle size is therefore manipulated or modified to target specific areas of the respiratory tract and to ensure efficacy. In pharmaceutical production, particle size is also carefully controlled to ensure consistent end-product performance. Developers and manufacturers must confirm that the particle size being delivered is constant from dose to dose and device to device, and this extends the need for particle size data right through quality control.

The upper size limit for delivery to the lungs is generally agreed to be around five microns, with particles larger than 10 microns tending not to penetrate beyond the mouth and throat; particles less than one micron are mostly exhaled. The sub-10 micron range is therefore of most interest to anyone investigating pulmonary deposition, either to ensure successful delivery to the lungs or, in the case of nasal drug delivery, to prevent it. Various methods can meet this sizing requirement, but multi-stage cascade impaction has risen to prominence because of a unique combination of advantages. These include the ability to:

- Fractionate and collect the entire dose, enabling measurement of a particle size distribution specifically for the active ingredient (by chemical assay), rather than for the formulation as a whole;
- Measure aerodynamic particle size distribution, the metric most closely associated with in vivo deposition behavior. Aerodynamic particle size is a function of geometric particle size, density, and shape and defines how a particle behaves in a moving air stream;
- Provide the required degree of resolution in the particle size range of greatest interest for inhalation products—from zero to five microns.

**How Does It Work?**

Multi-stage cascade impactors separate a sample on the basis of differences in the inertia of particles, a function of the aerodynamic particle size and velocity. The impactors consist of a series of stages, each made up of a plate with a specific nozzle...
arrangement and a collection surface. Various designs are available, but the ones used most widely are the Andersen Cascade Impactor and the Next Generation Impactor.

Sample-laden air is drawn into the impactor sequentially through the stages at a defined, constant volumetric flow rate (Figure 1). Nozzle size and total nozzle area decrease with stage number, but flow rate is constant, so the particles acquire progressively higher velocity. At each stage, particles with sufficient inertia break through the lines of flow and impact on the collection surface, while the rest pass on through the instrument. The net result of this process is a series of sized samples that can then be chemically analyzed, typically using high performance liquid chromatography, to produce an APSD specifically for the active ingredient.

As a result of these operating principles, the separation characteristics of a cascade impactor depend on both the dimensions of the instrument and the flow rate through it. The diameter of the nozzles and other critical dimensions must be specified, manufactured, and maintained to appropriate tolerances to ensure correct performance. The flow rate used must be carefully selected and controlled to ensure representative and accurate testing.

**Testing Inhaled Products**

Metered dose inhalers, dry powder inhalers, and nebulizers all deliver active ingredients to the lungs. Nasal sprays also fall into the area of inhaled drug delivery, although here the aim is to target the nasal cavity and avoid unwanted deposition in the lung. Each device has advantages and limitations, and each works in a different way. The test set-up for APSD measurement for all OIPs is broadly similar, but different test conditions and, especially, different test flow rates are required to ensure representative testing for each type of device. Detailed monographs for the testing of inhaled products can be found in the United States and European Pharmacopoeias.

**Metered Dose Inhalers (MDIs)**

The vast majority of MDIs are pressurized, with dose delivery driven by a propellant. This makes dose dispersion independent of the flow rate applied during testing. A test flow rate of 28.3 L/min (1 SCFM) is recommended for all MDIs, because this is the flow rate at which the Andersen Cascade Impactor, the multi-stage cascade impactor first used to a significant degree in OIP testing, has well-defined, calibrated performance. The flow rate varies when using the Next Generation Impactor, which is calibrated at 30 L/min for convenience.

**Dry Powder Inhalers**

In contrast to MDIs, the majority of DPIs are described as passive, which means that the motive force for drug delivery is provided by the forced inhalation of the patient. Here it is crucial to apply a test flow rate that reflects in-use conditions, in order to ensure comparable aerosolization of the dose. Pharmacopoeial methods are based on the assumption that a 4 kPa pressure drop across the device is representative of the inhalation profile applied by a typical patient.

To establish the appropriate flow rate for DPI testing, measurements are carried out to determine the flow rate associated with a 4 kPa pressure drop across the device. This means that low-resistance products are tested at higher flow rates than those with high resistance, with an upper limit of 100 L/min imposed. Because delivery is associated with a single inhalation, this flow rate is applied for the time necessary to draw a total volume of 4L (2L is recommended by FDA guidance), which is considered broadly equivalent to the inspiratory volume of an adult. For example, if test flow rate is determined to be 60 L/min, that flow rate is applied as a square wave function for a duration of four seconds to measure APSD.

**Nebulizers**

Dose delivery test methods for nebulizers have recently been revised and now specify testing via the application of sinusoidal flow profiles simulating tidal breathing conditions. Profile specifications are defined according to the target user group: adult, child, infant, and neonate. However, because cascade impactors must be operated with a constant flow rate, a test flow rate of 15 L/min is specified for APSD measurement, based on the mid-inhalation flow rate of a typical adult user. The Next Generation Impactor has calibrated performance at this relatively low flow rate and is therefore especially useful for this important class of OIPs. Cooling of the impactor may also be necessary in some cases to mitigate heat transfer-related droplet evaporation.

**Nasal Sprays**

In sharp contrast to OIP testing, multi-stage cascade impaction is used for nasal spray characterization, where the goals are to assess and limit the extent of pulmonary drug deposition. Like MDIs, the test flow rate applied has no direct impact on dose dispersion and is set at a standard 28.3 L/min.

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However, testing is carried out using an appropriately sized expansion chamber of one, two, or five liters to ensure that the dose is adequately dispersed and effectively drawn into the impactor. Used in this way, multi-stage cascade impaction supports the reduction—or, in the case of generics, matching—of the fines tail of nasal spray products. Multi-stage cascade impaction is a pivotal analytical instrument for characterizing inhaled products, with associated test methods designed to provide an acceptable in vitro representation of in vivo behavior for each device type and a rugged, reproducible quality control tool. The centrality of the technique makes it a focus for ongoing development, and, today, both equipment and methodologies are under intense scrutiny as leading researchers consider how best to fashion cascade impaction to meet modern requirements for more detailed information and greater productivity. These developmental efforts, in combination with the intrinsic advantages of cascade impaction, will ensure that this technology retains its value and relevance for inhaled product testing long into the future.

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**Editor’s Choice**


