

Cascade Impactors

Theory, design, and practical information for optimal testing

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Since aerodynamic particle size correlates directly with regional deposition in the lungs and respiratory tract, effective delivery of API relies on achieving inhalation of drug in a particular particle size range known as the fine particle fraction (FPF). Particles larger than 4-6 μm will deposit in the trachea or upper respiratory tract instead of in the lungs; particles below 1 μm may be exhaled. As a result, accurate characterization of particles for pharmaceutical aerosols is crucial, and the measurement range is generally less than 10 μm .

Cascade impaction is the only particle size measurement technique that can differentiate API from other components in a formulation, so this technique is the key analytical method for both development and quality assurance of inhaled products; all of the major pharmaceutical regulatory agencies specify the use of cascade impactors for these analyses. Accurate testing is critical, and impactor testing requires substantial investments of time and money. A basic understanding of the design and operation of cascade impactors and their operating parameters can help achieve optimum performance in return.

Why cascade impaction?

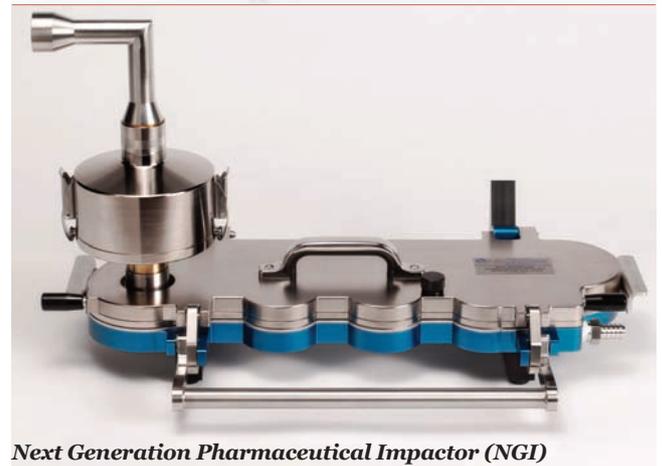
The inertial measurement technique used by the cascade impactor has two major advantages over other analytical methods, including particle time of flight (TOF), laser diffractometry (LD), and Phase-Doppler particle size analysis (PDA), that accurately measure particle sizes under 10 μm . Only the inertial technique used by the cascade impactor permits differentiation between API and other components in a formulation; other methods measure only overall particle size distribution. In addition, the inertial technique measures aerodynamic diameter, a parameter particularly relevant to particle behavior during inhalation, while most of the other methods cal-

culate volume equivalent diameter. One other significant benefit is that a cascade impactor captures the entire dose, allowing complete characterization. Other techniques utilize real-time measurements and take only a quick snap-shot of part of the dose, which may not be representative of the entire dose as it passes through the measurement system.

Both of the widely used types of cascade impactor provide the required degree of resolution in the particle size range of greatest interest for inhalation products: 0 to 5 μm . The Andersen Cascade Impactor (ACI) and the Next Generation Pharmaceutical Impactor (NGI) both include multiple stages with cut-off diameters in the required range across most operating conditions.



Andersen Cascade Impactor (ACI)



Next Generation Pharmaceutical Impactor (NGI)

How does cascade impaction work?

Cascade impactors separate a sample into fractions on the basis of differences in inertia, which is a function of particle density, shape, and velocity. A cascade impactor includes a number of stages, each machined with a specified number of nozzles of known diameter, with nozzle size and total nozzle area decreasing with stage number. A vacuum pump draws sample-laden air sequentially through the stages.

At each stage, particles with sufficient inertia break out of the air stream and impact and collect on a surface located beneath the stage, while the remainder of the particles remain entrained in the air stream, passing onto the next stage (Figure 1). In the ACI, the collection surfaces consist of plates; the NGI uses removable cups. The volumetric air flow remains constant, so velocity through the nozzles increases at each stage, meaning that smaller and smaller particles achieve sufficient inertia to reach the collection surface. Any residual material is captured in a final collector or filter, and the samples on each collection surface are recovered for analysis, usually by high pressure liquid chromatography (HPLC).

Both the ACI and, in particular, the NGI are calibrated to provide a defined particle size fraction retained on the collection surfaces at any flow rate in the range of interest. The particles collected after each stage fall within a narrow size range for which the stage cut-off diameter, D_{50} , represents the midway point in the curve on a graph of aerodynamic diameter vs. collection efficiency (Figure 2).

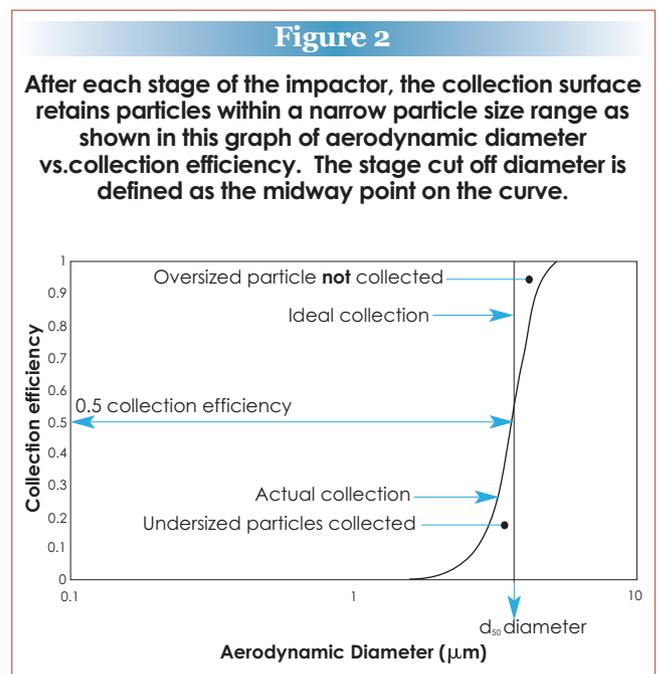
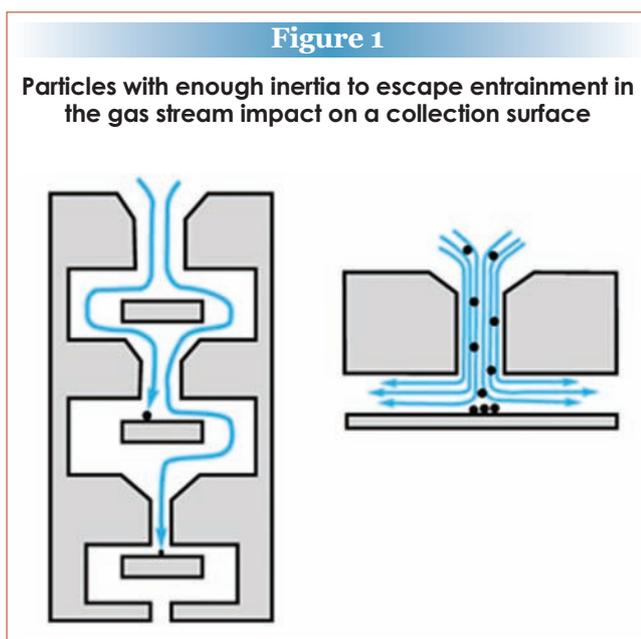
The following factors affect impactor performance:

- Nozzle diameter—the separation characteristics of an impactor are defined by this variable, which must be effectively specified, controlled, and maintained.
- Air flow rate—must be constant, reflect the conditions under which an inhaler device will operate, and be tightly controlled.
- Other dimensions (such as the distance between nozzle exit and collection surface)—effective specification and control of these dimensions is vital.
- Re-entrainment—ultimately results in collection on the wrong stage, compromising accuracy; effective collection surface coating to retain impacted particles is often required.
- Interstage losses—sample deposited on internal surfaces other than the collection surfaces will affect the results.
- Leakage—air entering into an impactor through points other than the inlet can affect its aerodynamic performance.

Types of cascade impactor

Two models, the Andersen cascade impactor (ACI) and the Next Generation impactor (NGI) are used for the vast majority of pharmaceutical applications, although many labs still use the Multi-Stage Liquid Impinger (MSLI), particularly in Europe, despite its limited number of stages.

The ACI, designed originally for air sampling and analysis, has eight stages with cut-off diameters less than 10 μm stacked vertically. Available in aluminium as well as titanium and stainless steel, the



ACI is particularly suitable for corrosive duties. The stacked design simplifies handling and allows damaged stages to be removed and replaced if necessary; however, the design does not lend itself to full automation because the entire instrument must be disassembled piece by piece during sample recovery.

The original specifications for the ACI called for operation at a fixed air flow rate of 28.3 L/min (1 scfm) for air sampling; but for dry powder inhaler (DPI) testing, the pressure drop across the device determines the flow rate, which can be as high as 100 L/min. Conversion kits allow operation of the ACI at 60 and 90 L/min, but only limited pharmaceutical quality archival calibration data for the instrument has been published. Manufacturing quality has also been an issue, although since the late 1990's ACIs have been manufactured to much tighter specifications and much higher standards [1], improving reproducibility. Manufacturing standards now are comparable to those of the NGI.

In the late 1990's a collaboration between MSP Corporation (Shoreview, MN) and a consortium of leading pharmaceutical companies produced the NGI, designed specifically for inhalation product testing. The consortium considered instrument accuracy, reproducibility, analysis time, and automation at an early stage and then undertook an iterative process, including experimentation with prototype impactors [2] to develop an instrument that met, amongst others, the following design criteria:

- Manual cycle time <30 minutes
- Configuration suitable for automation
- Calibrated operation across a flow range of 30-100 L/min
- Steep stage efficiency curves (GSD <1.2) with minimal stage overlap
- Accurate characterization of the <10 μm particle cloud size range
- Minimum of five stages with cut-off diameters in the range 0.5-5.0 μm , ideally over the full flow rate range
- Interstage losses <5% on any stage and 5% overall

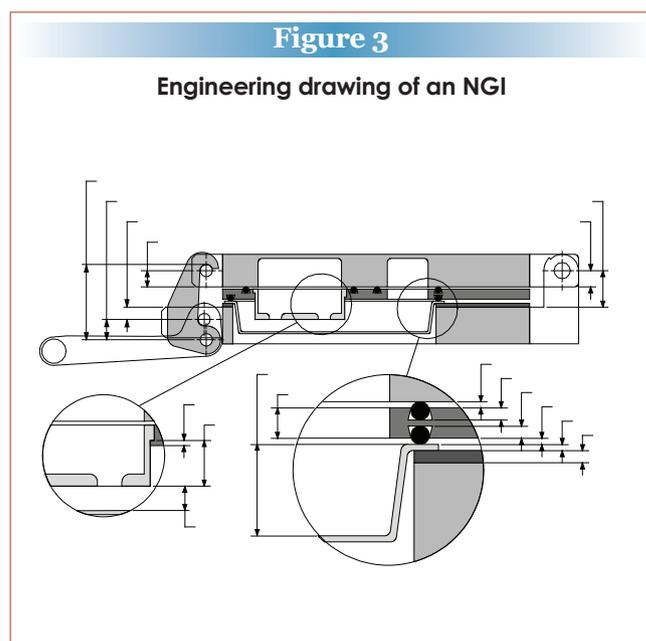
The designers rigorously calibrated an archival instrument within the design flow range of 30 to 100 L/min and then down to a flow rate of 15 L/min. By precisely defining the dimensions of the NGI (Figure 3), and by calibrating its performance, the consortium ensured the fundamental reproducibility and handling properties of the instrument. All commercially available NGIs are engineered to the same specifications and will achieve the same separation characteristics as the calibrated archival impactor if maintained and used correctly.

The NGI features a horizontal seven-stage planar layout with collection cups that sit in a removable tray. Low inter-stage losses, easy tray removal, and multiple cup sets facilitate automation of the sample recovery and processing. Even for manual operation, the NGI is 50% more productive than the ACI because a clean induction port/preseparator and set of cups can be inserted for a new test while samples from a previous test are processed. With semi-automated sample analysis provided by adjunct instruments, the NGI can handle as many as 30 tests per day compared to the typical manual rate for an ACI of 5 per day.

The NGI has some limitations. Experience has shown that the high jet velocities associated with the superior aerodynamics can result in re-entrainment of some particles, particularly with dry powder formulations. Also, the NGI requires careful handling to avoid corrosion in certain applications, especially for nebulizer testing at low temperatures and high humidity levels. To prevent re-entrainment, coating the collection surface may be necessary. One common coating method involves swabbing on glycerol or silicone oil mixed with a volatile solvent; the solvent evaporates rapidly, leaving a uniform coating. Despite these limitations, the industry has widely adopted the NGI, and the designers continue to make improvements.

Achieving optimal performance

Careful operation and maintenance of cascade impactors is essential to achieve the high degree of reproducibility necessary to differentiate between genuine sample differences and analytical inaccuracies. The USP and European Pharmacopeia (Ph. Eur.) monographs define detailed operational proce-



dures for the analysis of inhaled products, and analysts must carry out these tests consistently. Because cascade impaction is a lengthy, largely manual analytical procedure, consistent results require vigilant attention to calibration, cleaning, and inspection. Semi-automation can also help to decrease analyst-to-analyst variability.

All of the components used in conjunction with the cascade impactor, especially the critical flow controllers and flow meters, influence measurement accuracy and require regular calibration under defined conditions. As a precision instrument, the impactor itself must be inspected daily, with particular attention paid to the nozzles. Cleaning the impactor, checking for signs of wear, and replacing seals as necessary should be frequent tasks, and any collection surfaces that are scratched, bent, or dented must be replaced in order to assure correct jet-to-plate distance and uniform coating. Leak testing of the impactor at regular intervals also provides a critical check of system integrity.

The importance of stage mensuration

In addition to daily maintenance, impactors require rigorous inspections known as “stage mensuration” at regular intervals (typically annually or after a predetermined number of tests) to verify that the critical dimensions of the instrument remain within the defined tolerances. Stage mensuration accurately measures all of the mechanical dimensions that influence aerodynamic performance, including the diameter of every nozzle at each stage. Nozzles may become larger than specified due to wear or, more commonly, become smaller due to a build-up of corrosion salts. As the nozzle diameter changes, the stage cut-off diameter varies in accordance with Stokes’ law.

A number of companies offer complete stage mensuration services to the many cascade impactor owners lacking the facilities necessary for this procedure in house. Most of these companies use automated vision systems with accuracies as high as $\pm 1 \mu\text{m}$ to calculate an area mean diameter and area median diameter for each stage using edge detection and/or pixel counts. The testing company provides a report of the measurements to the impactor owner.

Many impactor users understand that a link exists between nozzle dimensions and aerodynamic performance but need help interpreting stage mensuration data. For example, if stage mensuration shows that 4 holes on stage 5 of an NGI are completely blocked, has the aerodynamic performance changed enough to require taking the impactor out of service? Is the impactor still operating within the range defined by

the manufacturing tolerances? The answers to these questions depend on the two parameters widely used to analyze and interpret stage mensuration measurements: effective diameter and in-use margin.

Effective diameter values allow quantification of the impact of wear or nozzle occlusion on impactor performance. Although all of the nozzles on a given stage may individually have different measurements after months or years of operation, a theoretical analysis of multi-nozzle impactor stages has shown that a stage performs as if all of the nozzles are the same size. That theoretical dimension is called the effective diameter [3]. For each stage, the effective diameter can be determined by the following formula:

$$\tilde{W} = (W^*)^{2/3} (\bar{W})^{1/3}$$

Where \tilde{W} is effective diameter, W^* is the area mean diameter, and \bar{W} is the area median diameter.

Because the stage performs as if all of the nozzles have the same dimension as the effective diameter, the actual stage cut-offs for the instrument can be calculated by comparing the effective diameter of a worn stage with the nominal diameters and the associated cut-offs quoted in the US and European Pharmacopoeias. Since the nozzle diameter is related to the particle diameter by Stokes’ law, raising the ratio of effective diameters by a power of $3/2$ will convert it to a ratio of cut-off diameters:

$$D_{50,2} / D_{50,1} = (\tilde{W}_2 / \tilde{W}_1)^{3/2}$$

The same method can be used to compare the actual stage cut-off diameter for one impactor with that of another impactor to determine standardization within a laboratory, or it can provide data on change in performance over time by comparing current effective diameter to one calculated in a previous mensuration.

The other parameter, in-use margin, indicates the extent to which the impactor lies within the performance range defined by the manufacturing tolerances of the instrument by comparing present performance to the design specification at each stage. When the variance becomes larger than the specified tolerance, the in-use margin becomes negative, indicating a stage diameter outside the pharmacopoeia tolerance. Analysis of successive mensuration reports allows tracking of wear, prediction of when in-use margin will become unacceptable, and therefore when the impactor will need to be overhauled or taken out of service.

The USP and Ph. Eur. stipulate nominal diameters and tolerances for nozzles at each stage, and the in-

use margin determines whether the current effective diameter meets these specifications. For example, stage 5 of an NGI might have an effective diameter of 0.603 mm, which is 0.005 mm less than the specified nominal diameter of 0.608mm. The specified tolerance for nozzles at stage 5 of an NGI is +/- 0.01 mm. Taking a ratio of the variance from the specification over the tolerance, 0.005mm/0.01mm, times 100, gives an in-use margin of 50%, indicating that the impactor remains within specifications.

Excessive nozzle wear cannot be remedied without the replacement of the stage. However, if the effective diameter is too small, as is more common, pinning—pushing “go” pins through each nozzle to clear away debris—may restore performance, although the procedure risks potential nozzle damage; ultrasonic cleaning provides another alternative for opening blocked nozzles. With proper care, a cascade impactor should perform reliably for years.

References

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