

CASCADE I M P A C T I O N

Optimizing Cascade Impactor Testing for Characterizing Orally Inhaled & Nasal Drug Products

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INTRODUCTION

Cascade impaction is a core analytical technique for characterizing orally inhaled and nasal drug products (OINDPs), yielding the aerodynamic particle size distribution (APSD) data used to assess product consistency and provide a broad indication of deposition behavior. The challenge to individual laboratories is to ensure the technique is used to optimum effect to achieve maximum accuracy and productivity.

The unique value of cascade impaction lies in its ability to deliver APSD data for the active ingredient in an OINDP formulation. Particle size is of interest because it influences in vivo deposition behavior. To achieve clinical efficacy, OINDP developers tend to target a certain aerodynamic particle size profile, even though it is difficult to obtain robust in vitro/in vivo correlations. Cascade impaction data are used to increase the probability of achieving efficient delivery and to confirm dosing consistency, rather than to predict exactly how and where an active will deposit in the respiratory system.

High-quality, reliable data provide a firm foundation for decision-making throughout development and manufacture. Cascade impaction makes such an important contribution to this that it has to be used effectively. It is a lengthy and predominantly manual analytical method, and there is no doubt that understanding the factors affecting its performance ensures its better use.

HOW CASCADE IMPACTORS WORK

Although the information set out here focuses (because of their market leading positions) on the Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI), all multistage cascade impactors operate on the same principle: size fractionation on the basis of inertial impaction. Instruments such as the ACI and NGI consist of a series of stages each made up of a nozzle plate, with a specific nozzle arrangement and a collection surface. Sample-laden air is drawn into the impactor and passes sequentially through the stages; nozzle

size and total nozzle area decrease with stage number.

Volumetric air flow rate through the system is constant; so as nozzle area decreases, air and particle velocities increase. As a result, smaller and smaller particles acquire sufficient inertia to impact on the collection surface rather than remaining entrained in the air stream (Figure 1). Therefore, for a given flow rate, each stage of the impactor is associated with a cut-off diameter, a figure that defines the size of the particles retained on that collection surface; any residual material is captured by a Micro-Orifice Collector (MOC) or glass fiber filter. Analyzing these size fractions,

typically by high pressure liquid chromatography (HPLC), produces APSD data for the active.

This simple outline raises some of the key issues relating to cascade impactor use:

- Nozzle diameter and air flow rate through the impactor together dictate particle velocity, particle inertia, and ultimately, the size of the particles that collect on any given stage.
- The accuracy of particle size measurement depends on retaining the impacting particles on the collection surface.

- Ideally, the entire dose drawn into the impactor should be captured on the collection surfaces rather than, for example, on the walls of the impactor (inter-stage losses).

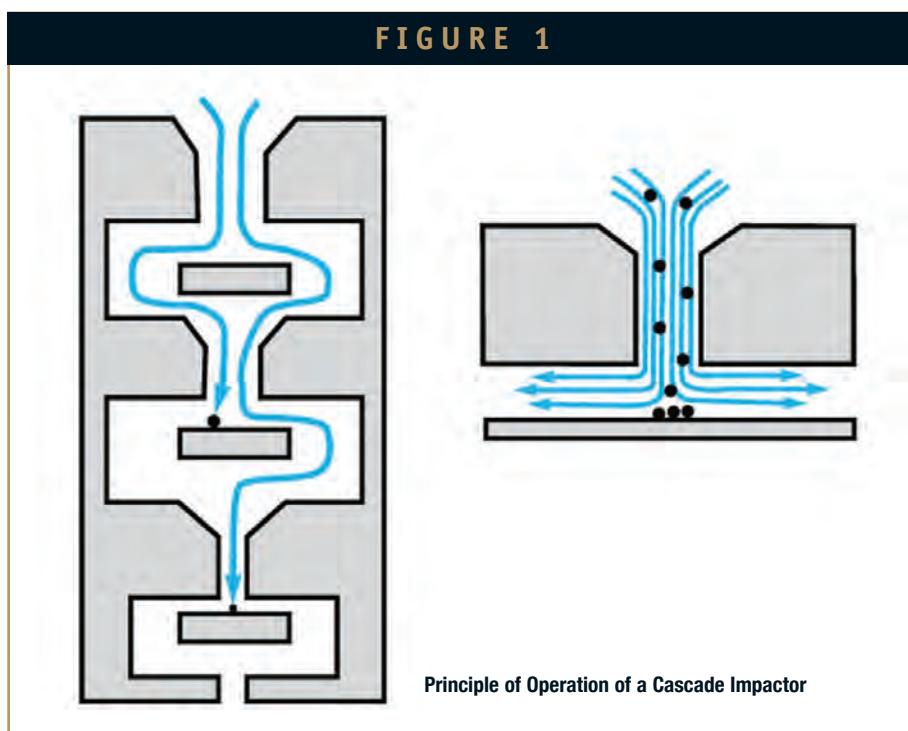
This final point is reflected in data analysis procedures. These include completion of a mass balance (MB) for each experiment, ie, comparison of the mass entering the instrument with the total mass recovered from all rinsed surfaces. Checking that the MB lies within the acceptability criteria specified by the regulators verifies to some degree the integrity of analysis. However, a good MB result does not mean that APSD measurements are correct, as material may have simply collected on the wrong surface. Developing a robust method and establishing good routine practice is the way to making certain that both MB and APSD are within specification.

METHOD DEVELOPMENT

Developing a robust method for a specific OINDP demands consideration of the following issues:^{1,2}

- Use of a pre-separator
- Solvent choice
- Number of actuations required during testing
- Collection surface coating
- Environmental and electrostatic effects
- Drug recovery and sample work-up technique
- Selection of back-up filter
- Cleaning regime

For dry powder inhalers (DPIs), a



Principle of Operation of a Cascade Impactor

pre-separator is often installed immediately before the impactor inlet. This acts in the same way as an impactor stage, separating out any powder boluses and non-inhalable particles larger than approximately 10 microns, depending on test flow rate, prior to entry into the impactor. Failure to remove any particles in this size range has a significant impact on APSD results but little if any effect on MB, as the amount of material trapped in the pre-separator is analyzed in the same way as for any other stage.

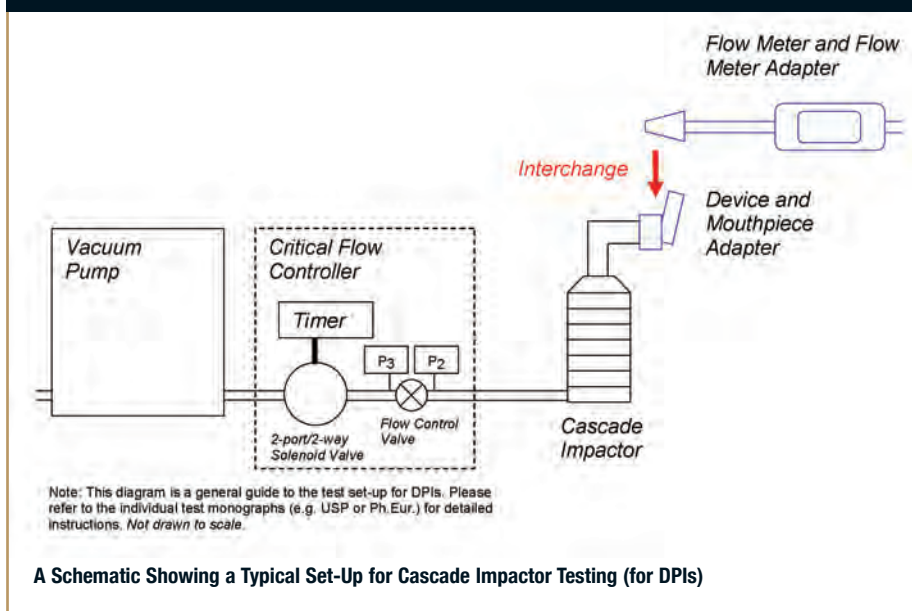
Solvent choice is driven largely by the solubility of the active. The number of actuations for each test then derives directly from this as it is a function of the quantitation lower limit (the lowest detectable concentration of active in the solvent) and APSD. Best practice is to minimize the number of actuations, within the constraint of ensuring that each stage collects sufficient active for reliable analysis. This reduces the risk of overloading the collection surfaces, lessening the chances of particle re-entrainment into the air stream, and reduces dose averaging effects.

Coating the collection surface, a

process that potentially eliminates “particle bounce,” also reduces the probability of particles collecting on the wrong stage. Applying a thin layer of glycerol or silicone oil, for example, makes the collection surface more adhesive. This practice is widespread with DPIs, due to the propensity for dry particles to bounce and, to a lesser extent, pressurized metered dose inhalers (pMDIs). For OINDPs producing liquid droplets (which are less prone to re-entrainment), the need for coating is often considered and discounted as part of method development. Application of a coating raises a number of additional questions, including which coating agent? how much? which application technique? impact on drug recovery and HPLC analysis?

With some formulations, particle collection on the wrong stage may also result from electrostatic effects. These can lead to unpredictable deposition behavior, skew APSD measurements, and affect inter-stage losses, thereby influencing MB. Equipment grounding and the use of static eliminators, amongst other anti-static precautions, can help.

FIGURE 2



Considering the way in which temperature, humidity (especially in the case of hygroscopic formulations), and light affect the active can also help promote the development of a reliable method.

At the drug recovery stage, the aim is to dissolve sample from each collection surface before making accurate measurements of the amount of active present in each of the resulting solutions. This is the most time-consuming, manually intensive part of the technique. Successful recovery relies on the following:

- Using a suitable volume of solvent: too much compromises HPLC accuracy, too little, dissolution efficiency.
- Establishing a dissolution procedure (contact time, degree of agitation, use of ultrasonics) that ensures complete removal of the active from the collection surfaces.
- Selecting equipment and methods that avoid, for example, sample loss to vessel walls, absorption of active from the solution, and solvent evaporation.

Here, semi-automation can significantly improve productivity and reproducibility. Devices range from simple equipment to automate induction port rinsing, for example, to fully integrated solutions such as the Andersen and NGI Sample Recovery Systems (A-SRS and N-SRS) that cover the whole of sample work-up.

Another important element of drug recovery is ensuring the capture of sub-micron particles. Where there is a substantial population of such particles, such as solution MDIs for example, it is necessary to consider matters like porosity, retention efficiency, and compatibility with the selected solvent to ensure adequate particle capture by the back-up filter. In the case of the NGI, in which a Micro-Orifice Collector is routinely used instead of a back-up filter, it may be necessary to consider an additional internal or external filter arrangement.

And finally, there is impactor cleaning. It is common practice to recover drug from the collection surfaces only, in cases where validated inter-stage losses amount to less than 5% of the total drug recovery from the impactor, as this has little material affect on MB. This is

typically the case with the NGI, in which inter-stage losses are low, by design, significantly speeding up analysis times. However, in such cases, it is still necessary to clean the remaining parts of the impactor, such as the inter-stage passageways and nozzle plates after a series of tests, to maintain impactor performance and reduce the risk of drug carryover. Cleaning methods should be tailored to the impactor type, the formulations being tested, and drug recovery methods used to ensure long-term impactor operation remains robust.

SETTING UP THE TEST APPARATUS

Figure 2 shows a typical test set-up for APSD measurement. Most of the ancillaries for the cascade impactor are there in order to ensure a known, constant flow of air during testing. The test apparatus clearly extends well beyond just the impactor, so it is vital to include all items for validation purposes.

The flow rate for testing, for different OINDPs, is set in accordance with regulatory guidance and pharmacopoeial specifications. For example, nebulizers are tested at 15 L/min to reflect the mid-tidal breathing flow of an average adult user. With DPIs, air flow rate is set to generate a 4-kPa pressure drop across the device, mirroring typical patient inhalation. Flow rate for DPIs varies significantly from device to device, up to a maximum of 100 L/min for low-resistance products, for practical reasons.

During testing, any differences between the actual flow rate through the device and impactor inlet, and the indicated flow rate, are a source of error when estimating stage cut-off diameters. For DPIs, this may additionally undermine device performance. Good practice here should include the following:

- Leak testing the cascade impactor to ensure flow is only entering through the inlet as intended and to determine whether acceptance criteria are met.
- Calibrating the flow meter for exiting flow rate (ie, entry flow rate to the impactor) or correctly calculating an exiting flow rate, from the entry flow rate, based on the flow resistance of the meter.
- Applying suitable correction factors to account for differences in temperature and pressure between the calibration and experimental conditions, where applicable.
- Setting the flow control valve to achieve sonic flow; a condition reached if the ratio of downstream-to-upstream absolute pressure across the valve is less-than-or-equal-to 0.5 ($P_3/P_2 \leq 0.5$). In these circumstances, fluctuations in downstream pressure, especially those derived from the vacuum pump, have no impact on flow rate upstream of the valve, through the impactor and device.
- Using the correct ancillaries, a fast-acting leak-free solenoid valve, for example, and tubing of appropriate size.

Poor set-up of the impactor itself is also a source of inaccuracy. Although the NGI has fixed nozzles and only one preseparator type, for the ACI, incorrect ordering of the stages and/or use of the wrong pre-separator configuration are relatively easy mistakes to make, as is mis-counting the number of device actuations. For both the NGI and ACI, misalignment at the interfaces between the device, induction port, and impactor

is a common source of leaks and measurement error. Implementing procedures that ensure routine checking of the impactor stages and that avoid using bent, scratched, or otherwise damaged collection surfaces, on a day-to-day basis, is good practice. However, it is also essential to monitor the long-term performance of the impactor.

PRECISION ENGINEERING, CALIBRATED PERFORMANCE

The NGI and ACI are precision-engineered instruments. They are manufactured to defined specifications that detail acceptable tolerances for all the mechanical dimensions influencing aerodynamic performance, most notably nozzle diameter. The NGI is the most recently developed of the commercially available multistage cascade impactors, having been designed specifically for inhaler APSD testing and brought to market in 2001. Calibration of an archival NGI formed part of the development project, so data are available to accurately calculate stage cut-off diameters for any flow in the 15- to 100-L/min range, the range of interest for most OINDPs.³⁻⁵ The ACI has a notable heritage in the air sampling industry, prior to adoption by the pharmaceutical industry, and was originally developed for use at a flow rate of 28.3 L/min (1 cubic foot per minute); conversion kits now allow its operation at 60 and 90 L/min. Despite a lack of rigorous reference calibration data for the ACI, it remains popular due to extensive industry and regulatory experience gained in its use over many years. This can be attributed, in the most part, to its successful implementation as a relative, rather than absolute, measure of product performance and quality.⁶

APSD measurements are generated

by calculating stage cut-off diameters at the test flow rate, using the appropriate equations for the impactor. The underlying assumption is that the nozzle diameters still meet the manufacturing specification. Unfortunately, with repeated use, the nozzle diameters tend to change, most usually occluding due to metallic salt extraction as a result of constant contact with corrosive solvents. The speed of this process varies, and today's use of more corrosion-resistant construction materials, such as 316 stainless steel, reduces the problem in most cases.

Regular stage mensuration, which involves the re-measurement of all critical mechanical dimensions, is an efficient way of monitoring impactor performance.⁷ It also obviates the expensive, time-consuming, and inherently variable method of calibration with particles. Precise measurement of each nozzle results in an "effective diameter" (a theoretically derived parameter that considers a multi-nozzle stage as if it were a single nozzle) that correlates directly with the aerodynamic performance of the impactor. Comparing effective diameters with the nominal diameter for each stage allows the determination of the "in-use margin," a figure that describes the extent to which performance lies within the acceptance tolerances defined by the manufacturing specification.

Stage mensuration therefore indicates the rate of deterioration of an impactor, flagging up the point at which the results are likely to fall out of specification. In some cases, it also highlights an inadequate cleaning regime. When in-use margin falls below an acceptable limit, the instrument must be refurbished to return it to productive use or taken out of service.

OPERATOR-TO-OPERATOR VARIABILITY

Every step of cascade impactor testing requires manual intervention, so there is great scope for operator-induced variability.⁸ Certain parts of the analysis, drug recovery being a prime example, are laborious and time-consuming. Other tasks, such as the calculation of stage cut-off diameters and flow rate setting and control, require appropriate knowledge and understanding. The following help reduce operator variability:⁹

- Good training
- User-friendly ancillary equipment that guides the operator
- Simple tools, such as actuation counters, that reduce the risk of error
- Automating routine tasks to avoid repetitive strain injury, monotony, and stress

SUMMARY

Optimizing cascade impactor use is vital because of the unique value and importance of the resulting data. While optimization relies on developing a robust methodology based on a thorough understanding of the workings of the technique, attention must also be paid to human factors; routine good practice is essential. Investment in training ensures a well-educated team with operators less likely to introduce error, while semi-automation drives down workload and monotony. Both approaches support the goal of optimizing productivity and data quality.

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BIOGRAPHY



Mark Copley graduated from the University of Bath, UK in 2000 with a Masters Degree in Aerospace Engineering. For 8 years he was Technical Sales Manager and product specialist for Copley Scientific's range of inhaler testing equipment and is now Sales Director for the company. Mark is considered a leading authority in testing methods and systems for metered-dose inhalers, dry powder inhalers, nebulisers and nasal sprays; authoring and contributing to more than 20 published articles. He also provides application support and consultancy, runs focused training workshops for the inhaled drug testing sector of the pharmaceutical industry and sits on the editorial advisory panel of Inhalation Magazine. An invited member of the European Pharmaceutical Aerosol Group (EPAG) impactor sub-team, Mark has also made recommendations to the Inhalanda working group, leading to subsequent revisions to Ph. Eur. and USP monographs.