Understanding cascade impaction and its importance for inhaler testing

Mark Copley, Technical Sales Manager

Inhalation product development is an important area of activity for the pharmaceutical sector. Asthma and chronic obstructive pulmonary disease (COPD) are becoming increasingly common and there is growing recognition of the benefits of the pulmonary route for systemic drug delivery. The industry is responding by investing heavily in both formulation and device research. Inhalation delivery platforms include nebulizers and both dry powder and metered dose inhalers (DPIs and MDIs).

Aerodynamic particle size is a key parameter for all inhaled products, directly influencing regional deposition in the lungs and respiratory tract. Its measurement is therefore critical during the product development cycle and for quality control. Various sizing techniques are available, but cascade impaction is the method specified for regulatory approval, and hence the most widely used. This paper reviews the principles of operation of this technique and its advantages. The design of cascade impactors is also examined, with a particular focus on key features of the Next Generation Pharmaceutical Impactor (NGI), a unit commissioned by a consortium of pharmaceutical manufacturers for use by the industry. To conclude, some practical guidance is offered on achieving and maintaining optimal impactor performance.

Advantages of cascade impaction

The fraction of a dose that, because of its size, will deposit in the lung is often referred to as the fine particle fraction (FPF). The upper limit used to define this fraction varies but tends to lie between four and six microns, the optimal size for central airway deposition. Peak deposition in the peripheral airways of the lung occurs at between two and four microns, so ideally the upper limit should be defined on the basis of drug action and preferred deposition area [1].

In general no lower limit is defined for FPF, although there is an argument for one since very small particles below one micron may be exhaled. The measurement range of interest for inhalation product development therefore tends to be ten microns and below. Suitable techniques for particle sizing in this range include: particle time of flight (TOF); laser diffractometry (LD); Phase–Doppler particle size analysis (PDA); and inertial techniques i.e. multiple stage cascade impaction.

The primary advantage offered by inertial techniques, compared with all alternative methods, is that they allow determination of an assay for the FPF and other size fractions. The other methods provide no differentiation between active pharmaceutical ingredient (API) and any other components in the formulation; they simply measure *overall* particle size distribution. As the information ultimately required from testing is the site of deposition of the API, then the capability to differentiate between different components is extremely valuable.

A second important feature of inertial methods is that they directly measure *aerodynamic* diameter, the parameter most closely correlated with particle behavior during inhalation. TOF analyzers also measure this variable, but with other techniques it must be calculated from volume equivalent diameter. It is clear then why inertial techniques are preferable for inhaler characterization, but what makes cascade impaction particularly appropriate?

The answer is that cascade impactors uniquely provide the required degree of resolution in the particle size range of greatest interest for inhalation products: 0.5 to 5 microns. Both the Andersen cascade impactor (ACI) and the NGI give five stages with cut-off diameters in the required range, over most operating conditions. This combination of factors explains why cascade impaction, despite being a time-consuming method, retains its position as the standard technique recommended by the regulatory bodies for the validation of new inhalation products.

How does it work?

Cascade impactors operate on the principle of inertial impaction i.e. separation is provided on the basis of differences in inertia - a function of particle size and velocity. They consist of a series of stages each made up of a plate, with specific nozzle arrangement, and collection surface. Sample laden air is drawn into the impactor, flowing sequentially through the stages; nozzle size and total nozzle area decrease with stage number.

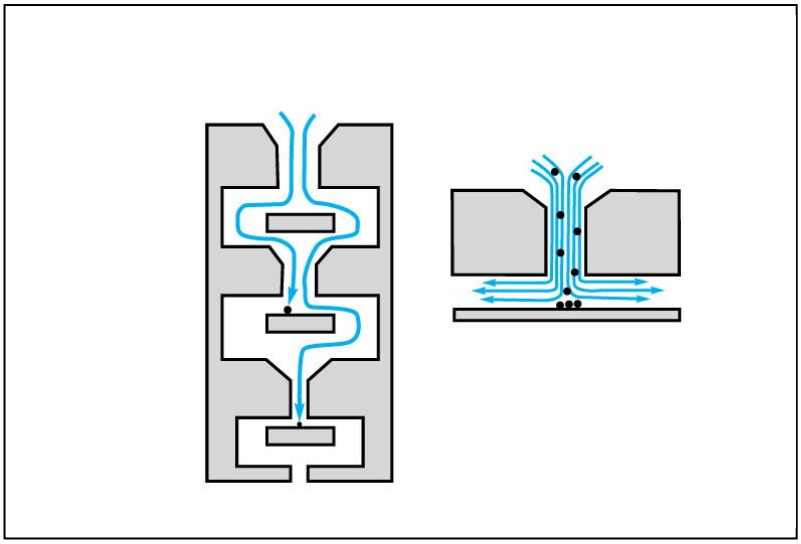

Figure 1: Flow in a cascade impactor

As particles pass through the nozzles (see figure 1) they either remain entrained in the air stream, which is directed through a right angle at the exit of the nozzle, or break through the lines of flow, impacting on the collection surface. Particles with sufficient inertia are collected, the rest pass onto the next stage. Each stage of the impactor is therefore associated with a cut-off diameter, a figure defining the size of particles that are retained on the collection surface of that stage. Ideally collection efficiency would be a step function – all of the particles above a certain size would be captured and those below it would pass through. In reality there is a curve from which D50, the stage cut-off diameter, is determined (see figure 2).

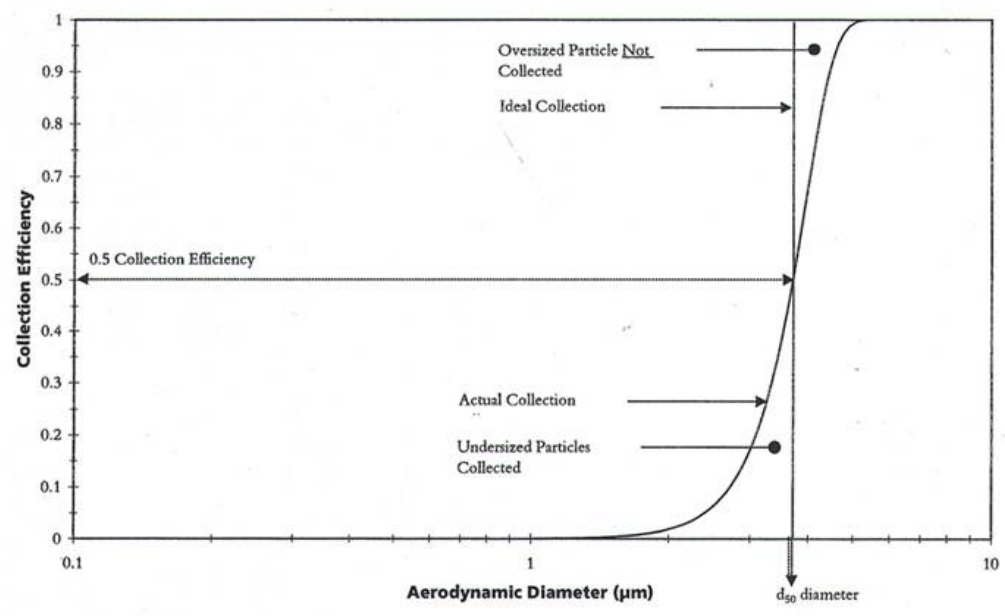

Figure 2: Collection efficiency curve for a cascade impactor stage

As nozzle size decreases, velocity increases, allowing the collection of increasingly small particles, any residual material being captured in a final stage or filter. The sample is thereby separated into a series of size fractions, each of which is individually collected for subsequent analysis, typically by high pressure liquid chromatography (HPLC).

An understanding of how impaction works is important for effective use of the instrument; even a relatively simple analysis highlights the following issues:

- The diameter of the nozzles is critical because it directly impacts particle velocity. This has implications for impactor design, manufacture and ongoing maintenance.
- The size of particle that is collected on each stage will be a function of air flow rate through the impactor, as this determines velocity through a given nozzle. Air flow therefore needs to reflect the conditions under which an inhaler device will operate and must be closely controlled.
- Other dimensions of the impactor will also be important for determining which particles are captured, a key parameter being distance between nozzle exit and collection surface.
- If particles bounce off the collection surface and are re-entrained in the air flow then ultimately they will be collected on the wrong stage and accuracy will be compromised. Effective collection surface coating is therefore an important issue.
- Ideally all material should be captured on one or other of the collection surfaces, rather than in any other part of the impactor, in order to determine an accurate particle size distribution.

Cascade impactor design

The most commonly used cascade impactors are the ACI and NGI; both are recommended in the US and European pharmacopoeia (USP and Ph.Eur) monographs detailing test procedures for inhaled products. The multi-stage liquid impinger (MSLI) is

also quite widely used, predominantly in Europe. However, it provides reduced resolution in the size range of interest and therefore has somewhat limited value when submitting data to support a new drug application, especially in the USA. Here then the focus will be design features of the ACI and NGI.

The ACI is a well-established impactor originally designed for air sampling and analysis. It has eight stages with cut-off diameters less than 10 microns, and is available in aluminium, as well as titanium and stainless steel for especially corrosive applications. The stacked design makes for easy handling; damaged stages can simply be removed and replaced should this be necessary. This impactor does, however, have some limitations for pharmaceutical applications.

The ACI was designed to operate at air flow rates of 28.3 L/min (1 scfm), and at this flow rate there is no published 'pharmaceutical quality' archival calibration data. For DPI testing, flow rate is set on the basis of pressure drop across the device and can be as high as 100 l/min. Conversion kits are therefore necessary for operation of the ACI at 60 and 90 l/min. In the past, manufacturing quality has also been poor and has directly influenced accuracy, although since the 1990's ACIs have been manufactured by Copley Scientific Ltd to much tighter specifications and to much higher standards [2].

The NGI is the result of a collaborative project between a consortium of leading pharmaceutical companies and MSP Corporation (Shoreview MN, USA). The consortium was formed in the late 1990's with the aim of commissioning a new impactor specifically for the pharmaceutical industry. Bearing in mind the limitations of the ACI, and the widespread impactor use within the sector, the consortium specified the following:

- A fast manual cycle time (<30 minutes) with a configuration suitable for automation
- Calibrated operation across a wide flow range: 30-100 L/min
- Steep stage efficiency curves (GSD <1.2) and minimal stage overlap
- Accurate characterization of the '<10 micron' particle cloud size range, with a minimum of five stages with cut-off diameters in the range 0.5–5.0 microns, ideally over the full flow rate range
- Interstage losses of <5% on any stage and 5% overall, in line with USP system suitability requirements, to ensure mass-balance

An optimized design was developed on the basis of operational experience and sound aerodynamic theory (see ref 3 for further details) and the result - the NGI – is now in widespread use. It has a horizontal seven stage planar layout with removable collection cups and trays; multiple cup sets can be used with a single impactor. These features facilitate semi- and full automation and improve productivity – an important issue for the industry.

The NGI was originally designed to operate between 30 and 100 L/min, but has now been rigorously calibrated for flow rates between 15 and 100 L/min using an archival NGI. This costly calibration is part of the process put in place to ensure consistency. The mechanical dimensions of the NGI are precisely defined and therefore any NGI that conforms to this design is considered, by definition, to have the same calibration characteristics as the archival NGI. Since all routinely manufactured NGIs are

engineered to the same specification, confidence in the fundamental reproducibility of the instrument can therefore be high.

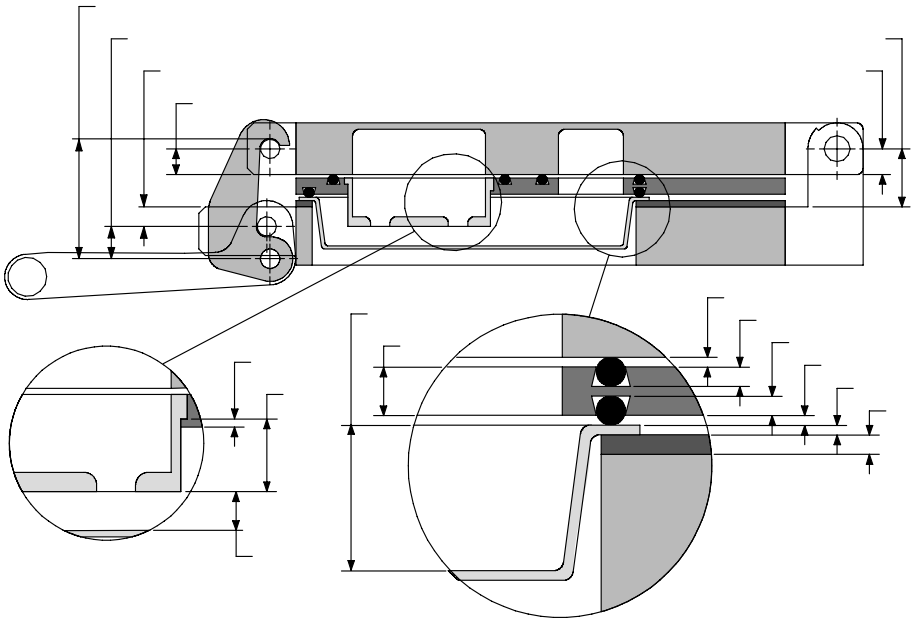

Figure 3: Some of the critical dimensions of the NGI

The NGI also of course has some limitations. Experience has shown that because of the high jet velocities associated with the superior aerodynamics, special attention has to be paid to collection surface coating techniques for some formulations. Also the NGI needs careful handling to avoid corrosion for certain applications, especially when testing nebulizers in conditions of low temperature and high humidity. Extensive use of the NGI within the industry demonstrates however the overall success of the project, and there is ongoing commitment to its further development.

Ensuring optimal impactor performance

While the design and manufacture of cascade impactors are obviously critical, ongoing performance is equally dependent on operational practice and equipment maintenance. Cascade impaction is a lengthy, largely unautomated analytical procedure, but operational consistency is key for good reproducibility. If this is not achieved then it becomes impossible to determine whether differences in results are genuine or a function of analytical inaccuracies. The procedures for inhaled products are as a result defined in detail in the USP and Ph. Eur monographs but it is worth drawing attention to the following issues, which underpin good cascade impaction practice:

Use of the impactor

The impactor is a precision engineered instrument and should always be treated as such. The use of collection cups or plates that have surface roughness 100% inspected will assist with uniform coating and any that are scratched, bent or dented should not be used. Leak testing of the impactor at regular intervals is an important check of system integrity.

Regular stage mensuration - measurement of the exit diameter of each nozzle on each stage - is also recommended in both the USP and Ph.Eur. This process determines the

extent to which any damage to the impactor has influenced its aerodynamic performance, highlighting any corrosion and/or erosion of the nozzles.

Semi-automation

There are various pieces of ancillary equipment available for automating aspects of cascade impactor testing. These include Copley Scientific's sample preparation unit series, NGI induction port and preseparator rinsers, and the NGI Assistant. These tools reduce analyst-to-analyst variability and improve productivity, overcoming many of the historical concerns surrounding cascade impactor testing.

Flow rate control

The equipment used with the cascade impactor, and in particular the critical flow controllers and flow meters that deliver consistent air flow, can have a significant impact on measurement accuracy. Regular calibration of these units under defined conditions is essential to ensure the required aerodynamic performance.

In conclusion

Cascade impaction is a vital analytical tool for the development of inhalation products, uniquely yielding aerodynamic particle size distribution data specifically for an API. As the pharmaceutical industry continues its development of products that exploit the benefits of the pulmonary drug delivery route the use of cascade impaction is expected to increase. The commissioning of the NGI provided recognition of this trend and there is ongoing commitment to the development of tools that will facilitate improved analysis. Greater productivity and automation are important technological goals and development work in this area continues.

References

1. Particle size analysis of aerosols from medicinal inhalers. J.P.Mitchell and M.W. Nagel. KONA Powder and Particle No22 (2004)
2. Variability in Size Distribution Measurements Obtained Using Multiple Andersen Mark II Cascade Impactors. *S.Stein et al., Presented at American Association of Pharmaceutical Scientists, November 2-6, 1997.*
3. Performance Comparison of Copley and Andersen 8-Stage Cascade Impactors. C. Shelton et al., *Aerosol Society: Drug Delivery to the Lungs 13, 2002, p. 176 – 179.*
4. Cascade impactors enter a new decade. M. Copley, *Manufacturing Chemist*, May 2007

www.copleyscientific.com

July 2007