



## PARTICLE SIZE DETERMINATION OF NASAL DRUG DELIVERY SYSTEM: A REVIEW

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### ABSTRACT

Until quite recently nasal delivery of pharmaceutical formulations was confined largely to locally acting therapeutics such as decongestants and antihistamines. Today though, the nasal route is receiving considerable attention for administering drugs that net systemically. The opportunity for rapid and targeted drug absorption provided by the turbinate's and lymphoid tissues at the back of the nasal cavity is being exploited in areas such as pain and migraine relief, vaccine delivery and the treatment of osteoporosis. The olfactory region at the top of the nasal cavity provides direct access to the central nervous system and potentially has advantages for delivering drugs to treat conditions such as Alzheimer's disease. Conventional nasal sprays are the most widely used of the available technologies. To ensure successful deposition within the nasal cavities, their typical median particle size is between 30 and 120 microns. Droplets larger than this tend to deposit at the front of the nose, while finer particles may penetrate further into the body. Characterization of the sub-ten micron fraction is advised to specifically assess the risk of drug delivery via the lungs. In its draft guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" (April 2003), the FDA highlights the use of laser diffraction for measurement of the particle size distribution of both nasal sprays and nasal aerosols. Cascade impaction is recommended for scrutiny of the finer end of the distribution. This project examines these two complementary techniques, explains in some detail how they work and shows how they can be applied in tandem to deliver valuable information for nasal product characterization.

**Keywords:** Andersen Cascade Impactor, Next Generation Pharmaceutical Impactor, Laser Diffraction, Inertial technique.

### INTRODUCTION

Cascade impactor<sup>1</sup> analysis is the standard technique for *in vitro* characterization of aerosol clouds generated by medical aerosol generators. One important reason for using this inertial separation principle is that drug fractions are classified into aerodynamic size ranges that are relevant to the deposition in the respiratory tract. Measurement of these fractions with chemical detection methods enables establishment of the particle size distribution of the drug in the presence of excipients. However, the technique is laborious and time consuming and most of the devices used for inhaler evaluation lack sufficient possibilities for automation. In addition to that, impactors often have to be operated under conditions for which they were not designed and calibrated. Particularly, flow rates through impactors are increased to values at which the flow through the nozzles is highly turbulent. This has an uncontrolled influence on the collection efficiencies and cut-off curves of these nozzles. Moreover, the cut-off value varies with the flow rate through an impactor nozzle.

On the other hand, the high air flow resistances of most impactors are rather restricting to the attainable (fixed) inspiratory flow curves through these devices. Especially for breath actuated dry powder inhalers, higher flow rates and flow increase rates may be desirable than can be achieved in combination with a particular type of impactor. In this paper, the applicability of laser diffraction technology is evaluated as a very fast and highly reliable alternative for cascade impactor analysis. With this technique, aerodynamic diameters cannot be

measured, but for comparative evaluation and development, comprising most *in vitro* applications, this is not necessary.

Laser diffraction has excellent possibilities for automated recording of data and testing conditions, and the size classes are independent of the flow rate. Practical limitations can be overcome by using a special inhaler adapter which enables control of the inspiratory flow curve through the inhaler, analysis of the emitted fine particle mass fraction and pre-separation of large particles during testing of dry powder inhalers containing adhesive mixtures.

### Particle size analysis of general pharmaceutical products

- Why measure particle size of pharmaceuticals???
- Particle size can affect:
  - Final formulation: performance, appearance, stability.
  - "Process ability" of powder (API or excipient).

### METHODS FOR DETERMINING PARTICLE SIZE<sup>2</sup>

- Microscopy
- Sieving
- Sedimentation techniques
- Optical and electrical sensing zone method
- Laser light scattering techniques
- Surface area measurement techniques



**Choosing a method for particle sizing**

- Nature of the material to be sized, e.g.
- Estimated particle size and particle size range
- Solubility
- Ease of handling
- Toxicity
- Flowability
- Intended use
- Cost
- Capital
- Running
- Specification requirements
- Time restrictions

**Microscopy**

Optical microscopy used for particle size between 1-150 $\mu\text{m}$  and Electron microscopy used for particle size 0.001 $\mu\text{m}$  onwards.

- Being able to examine each particle individually has led to microscopy being considered as an absolute measurement of particle size.
- Can distinguish aggregates from single particles.
- When coupled to image analysis computers each field can be examined, and a distribution obtained.
- Number distribution.
- Most severe limitation of optical microscopy is the depth of focus being about 10 $\mu\text{m}$  at x100 and only 0.5 $\mu\text{m}$  at x1000.
- With small particles, diffraction effects increase causing blurring at the edges - determination of particles < 3 $\mu\text{m}$  is less and less certain.

For submicron particles it is necessary to use either

- TEM (Transmission Electron Microscopy) or
- SEM (Scanning Electron Microscopy).
- TEM and SEM (0.001-5 $\mu\text{m}$ ).

**Types of Diameters***Martin's diameter (M)*

The length of the line which bisects the particle image. The lines may be drawn in any direction which must be maintained constant for all image measurements.

*Ferret's diameter (F)*

It is the distance between two tangents on opposite sides of the particle, parallel to some fixed direction.

*Projected area diameter ( $d_a$  or  $d_p$ )*

It is the diameter of a circle having the same area as the particle viewed normally to the plane surface on which the particle is at rest in a stable position.

**Manual Optical Microscopy**

Advantages:

- Relatively inexpensive.
- Each particle individually examined - detect aggregates, 2D shape, colour, melting point etc.
- Permanent record – photograph.
- Small sample sizes required.

Disadvantages:

- Time consuming - high operator fatigue - few particles examined.
- Very low throughput.
- No information on 3D shape.
- Certain amount of subjectivity associated with sizing - operator bias.

**Transmission and Scanning Electron Microscopy**

Advantages:

- Particles are individually examined.
- Visual means to see sub-micron specimens.
- Particle shape can be measured.

Disadvantages:

- Very expensive.
- Time consuming sample preparation.
- Materials such as emulsions difficult/impossible to prepare.
- Low throughput - Not for routine use.

**Automatic and Image Analysis Microscopes**

Advantages:

- Faster and less operator fatigue than manual
- No operator bias

Disadvantages:

- Can be very expensive
- No human judgement retained e.g. to separate out aggregates, select or reject particles etc. (unlike semi-automatic)

**Sieving**

- Sieve analysis is performed using a nest or stack of sieves where each lower sieve has a smaller aperture size than that of the sieve above it.
- Sieves can be referred to either by their aperture size or by their mesh size (or sieve number).
- The mesh size is the number of wires per linear inch.
- Approx. size range : 5 $\mu\text{m}$  - ~3mm
  - Standard woven wire sieves



- Electroformed micromesh sieves at the lower end or range (< 20 $\mu$ m)
- Punch plate sieves at the upper range.
- Sieving may be performed wet or dry; by machine or by hand, for a fixed time or until powder passes through the sieve at a constant low rate
- Wet sieving
- Air-jet sieving
- Weight distribution

#### Advantages:

- Easy to perform.
- Wide size range.
- Inexpensive.

#### Disadvantages:

- Known problems of reproducibility.
- Wear/damage in use or cleaning.
- Irregular/agglomerated particles.
- Rod-like particles : overestimate of under-size.
- Labour intensive.



Figure 1: Sieve shaker

### Particle size classification of powders<sup>3</sup>

The degree of fineness of a powder may be expressed by reference to sieves that comply with the specifications for non-analytical sieves.

Where the degree of fineness of powders is determined by sieving, it is defined in relation to the sieve number(s) used either by means of the following terms or, where such terms cannot be used, by expressing the fineness of the powder as a percentage m/m passing the sieve(s) used.

The following terms are used in the description of powders:

**Coarse powder:** Not less than 95% by mass passes through a number 1400 sieve and not more than 40 % by mass passes through a number 355 sieve.

**Moderately fine powder:** Not less than 95% by mass passes through a number 355 sieve and not more than 40% by mass passes through a number 180 sieve.

**Fine powder:** Not less than 95% by mass passes through a number 180 sieve and not more than 40% by mass passes through a number 125 sieve.

Size distribution is determined by allowing a homogeneous suspension to settle in a cylinder and taking samples from the settling suspension at a fixed horizontal level at intervals of time.

Each sample will contain a representative sample of the suspension, with the exception of particles greater than a critical size, all of which will have settled below the level of the sampling point.

The concentration of solid in a sample taken at time t is determined by centrifugation of the sample followed by drying and weighing or simply by drying and weighing.

This concentration expressed as a percentage of the initial concentration gives the percentage (w/w) of particles whose falling velocities are equal to or less than  $x/t$ . Substitution in the equation above gives the corresponding Stokes' diameter.

#### Stokes's Law

- Stokes's diameter ( $d_{st}$ ) is defined as the diameter of the sphere that would settle at the same rate as the particle
- The particle size distribution of fine powder can be determined by examining a sedimenting suspension of the powder.

#### Two categories

(1) Incremental: Changes with time in the concentration or density of the suspension at known depths are determined. Can be either fixed time or fixed depth techniques.

(2) Cumulative: The rate at which the powder is settling out of suspension is determined. I.e. the accumulated particles are measured at a fixed level after all particles between it and the fluid's surface have settled.

#### Advantages:

- Equipment required can be relatively simple and inexpensive.
- Can measure a wide range of sizes with considerable accuracy and reproducibility.

#### Disadvantages:

- Sedimentation analyses must be carried out at concentrations which are sufficiently low for interactive effects between particles to be negligible so that their terminal falling velocities can be taken as equal to those of isolated particles.
- Large particles create turbulence, are slowed and are recorded undersize.

- Careful temperature control is necessary to suppress convection currents.
- The lower limit of particle size is set by the increasing importance of Brownian motion for progressively smaller particles.
- Particle re-aggregation during extended measurements.
- Particles have to be completely insoluble in the suspending liquid.

### Electrical sensing zone method – Coulter Counter

Instrument measures particle volume which can be expressed as  $dv$ : the diameter of a sphere that has the same volume as the particle.

The number and size of particles suspended in an electrolyte is determined by causing them to pass through an orifice on either side of which is immersed an electrode.

The changes in electric impedance (resistance) as particles pass through the orifice generate voltage pulses whose amplitude is proportional to the volumes of the particles.

### Optical sensing zone method

- Obscuration of light source relates to particle size (area)
- Advantage of not requiring medium to be an electrolyte

### Laser light scattering techniques

- Laser Diffraction Particle Size Analysis

Particle size range 0.02-2000 $\mu$ m

- Photon Correlation Spectroscopy

Particle size range :1nm to 5 $\mu$ m

### Laser diffraction

Particles pass through a laser beam and the light scattered by them is collected over a range of angles in the forward direction.

The angles of diffraction are, in the simplest case inversely related to the particle size.

The particles pass through an expanded and collimated laser beam in front of a lens in whose focal plane is positioned a photosensitive detector consisting of a series of concentric rings.

Distribution of scattered intensity is analysed by computer to yield the particle size distribution.

Advantages:

- Non-intrusive : uses a low power laser beam
- Fast: typically <3minutes to take a measurement and analyse.

- Precise and wide range - up to 64 size bands can be displayed covering a range of up to 1000000:1 in size.
- Absolute measurement, no calibration is required. The instrument is based on fundamental physical properties.
- Simple to use.
- Highly versatile.

Disadvantages:

- Expensive.
- Volume measurement all other outputs are numerical transformations of this basic output form, assuming spherical particles.
- Must be a difference in refractive indices between particles and suspending medium.

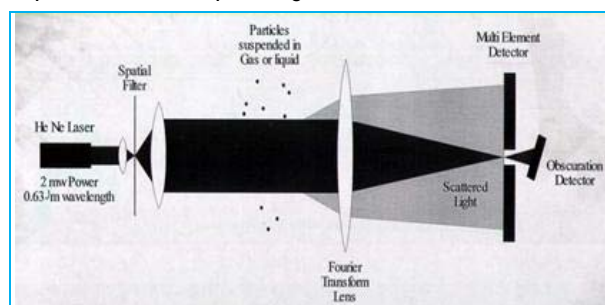


Figure 2: Laser diffraction

### Photon Correlation Spectroscopy (PCS)

Large particles move more slowly than small particles, so that the rate of fluctuation of the light scattered from them is also slower. PCS uses the rate of change of these light fluctuations to determine the size distribution of the particles scattering light. Comparison of a "snap-shot" of each speckle pattern with another taken at a very short time later (microseconds).

The time dependent change in position of the speckles relates to the change of position of the particles and hence particle size. The dynamic light signal is sampled and correlated with itself at different time intervals using a digital correlator and associated computer software. The relationship of the auto-correlation function obtained to time intervals is processed to provide estimates of the particle size distribution.

Advantages:

- Non-intrusive.
- Fast.
- Nanometre size range.

Disadvantages:

- Sample preparation is critical.
- Vibration, temperature fluctuations can interfere with analysis.
- Restricted to solid in liquid or liquid in liquid samples.
- Expensive.
- Need to know R.I. values and viscosity.

## TECHNIQUE OF NASAL DRUG DELIVERY SYSTEM

FDA guidance<sup>4,5</sup> focuses on the two most well-established nasal drug delivery technologies: nasal sprays and nasal aerosols. Mechanical metered dose nasal sprays currently dominate the nasal drug delivery market, having largely replaced droppers and squeeze bottles which were prone to inaccurate and inconsistent delivery. With a metered dose nasal spray, the active pharmaceutical ingredient (API or "active") is dissolved or suspended, usually in an aqueous medium, and a spray pump atomizes and delivers the dose. These products are self-administered by the patient, with the efficiency of drug delivery influenced by a number of factors: patient technique and physiology; the physical properties of the suspension/solution; and the design of the pump

Multi-dose metered sprays are widely available but increasingly attention is turning to unit dose devices that deliver just one or two shots per nostril. Especially suitable for the delivery of pain relief and vaccines, unit dose systems avoid the microbiological contamination problems that necessitate the inclusion of preservatives in multi-dose products.

Propellant-based products, pressurized metered dose inhalers (pMDI) analogous to those used for pulmonary delivery, can also be formulated to deliver drugs via the nasal mucosa. These products deliver a "dry" nasal aerosol because the propellant evaporates rapidly during use, reducing drug losses attributable to dripping. Following the prohibition of chlorofluorocarbons, they are generally formulated with hydrofluoroalkane propellants. One criticism levelled at nasal aerosols is the force generated by the spray during use, so the trend here is towards using reduced actuation forces that give "softer" delivery<sup>6</sup>.

### Development of nasal drug delivery products

In the development of nasal drug delivery products, performance targets are met by manipulating the design of the device or the properties of the formulation or both. Focusing on nasal sprays, for example, device parameters that can be varied include: the action of the pump and its pre-compression ratio; and the length, geometry and orifice size of the actuator. In terms of the formulation, its response to the shear applied by the pump during actuation can be tuned by varying physical properties such as viscosity, manipulated through the inclusion of modifiers and additives.

Analytical data support systematic progression towards target bioavailability/ bioequivalence, and later, during manufacture, are also essential for quality control (QC). Laser diffraction and cascade impaction are both used to measure particle size, which is a critical parameter because of its influence on *in vivo* deposition, retention and uptake. Laser diffraction enables real-time measurement of the entire delivered dose while cascade impaction, in contrast, is a technique designed specifically

for analysis of the particles in the sub-ten micron region, for which it provides API-specific data.

For completeness, it is worth noting that when dealing with suspension formulations, the need for API-specific data extends to the entire dose<sup>4</sup>. This is because of the influence of API particle size on dissolution and bioavailability. Pre- and post-actuation measurements characterize particle size in order to confirm that it is unaltered by the drug delivery process. This regulatory requirement is usually met using microscopy, or increasingly and more efficiently with automated imaging, which comfortably spans the particle size range of interest.

## METHODS OF PARTICLE SIZING FOR NASAL PRODUCTS

### 1. Laser Diffraction

Fast and efficient, laser diffraction is a non-destructive analytical technique for the real-time measurement of both sprays and aerosols. Working within a dynamic range of 0.1 to 3000 µm, it measures all size fractions of the delivered dose. Laser diffraction is used in development to ensure that delivered droplet size is optimized for clinical efficacy and/or bioequivalence. It is also a valuable QC tool with which to confirm the consistency of delivery from dose-to-dose and batch-to-batch.

A laser diffraction analyzer detects the diffraction pattern produced as a collimated light beam passes through a particulate sample. Large particles in the sample scatter the light strongly at relative small angles to the incident beam, while finer particles scatter weakly at wider angles. The particle size distribution of the sample can therefore be generated from the detected scattered light pattern, a calculation realized through application of the Mie theory of light. A typical set-up is shown in Figure 3.



**Figure 3:** Laser diffraction system (spraytec, malvern) set up for nasal spray analysis.

Particle size measurements gathered during a typical nasal spray event along with transmission data. Transmission is a parameter related to the amount of source light: penetrating the sample and is therefore indicative of the concentration of droplets in the measurement zone, making it a useful parameter for spray analysis. The system used measures one complete particle size distribution every 0.1 ms and is therefore able to capture the fine detail of a spray event that lasts just 160 ms.

The data show that: immediately post-actuation, transmission falls sharply, indicating a rapidly rising droplet concentration. This stage of the spray event is referred to as the formation phase and occurs when the pump starts to deliver liquid from the metering chamber. Liquid flow increases rapidly to a stable value and droplet size falls as the pump begins to efficiently atomize the dose.

Laser diffraction provides real-time droplet size measurement during the spray event. The fully developed phase is clearly visible at the midpoint of the actuation profile.

The bulk of drug delivery occurs during the next: stage of the event, the fully developed or stable phase. During this phase, flow through the pump is steady, producing relatively constant droplet concentration and size.

As the metering chamber empties, flow through the pump falls once more and droplet size rises. This final, dissipation stage is also marked by an increase in transmission, with droplet concentration falling as flow rate through the pump drops back to zero.

Assessment of the formation and dissipation phases is valuable, a prime aim being to reduce these phases to an absolute minimum to optimize the drug delivery process. However, for comparative testing, the FDA guidance recommends using data from fully developed phase. Such data support the efficient optimization of the device and the formulation to meet drug delivery and product stability targets.

## 2. Cascade Impactor

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  $\mu\text{m}$  will deposit in the trachea or upper respiratory tract instead of in the lungs; particles below 1  $\mu\text{m}$  may be exhaled. As a result, accurate characterization of particles for pharmaceutical aerosols is crucial, and the measurement range is generally less than 10  $\mu\text{m}$ .

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<sup>1</sup>.

### Need of 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 (FDA), that accurately measure particle sizes under 10  $\mu\text{m}$ . 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 behaviour during inhalation, while most of the other methods calculate 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  $\mu\text{m}$ . 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.



Figure 4: Andersen cascade impactor (ACI)

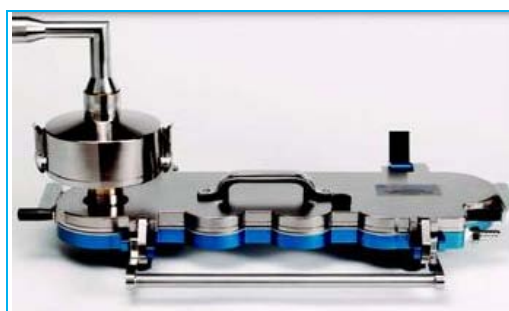
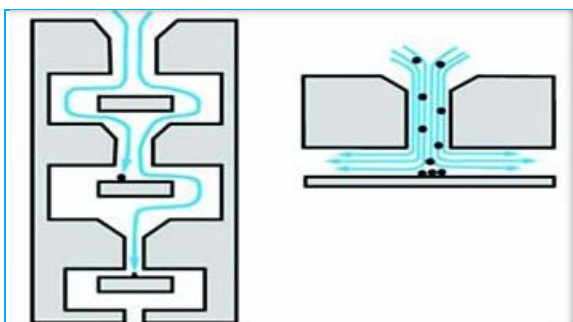


Figure 5: Next generation pharmaceutical impactor (NGI)

### Principle of cascade impaction

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 remains

entrained in the air stream, passing onto the next stage. 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<sup>1</sup>.



**Figure 6:** Particles with enough inertia to escape entrainment in the gas stream impact on a collection surface

#### Factors affecting 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.

#### Technique of cascade impaction

The technique of cascade impaction involves separating the dose on the basis of inertial impaction (Figure 6). A constant volumetric flow rate of sample-laden air is drawn through a series of stages, each of which has a defined number of precision-engineered nozzles. Because

the diameter of these nozzles decreases with stage number, particle velocity increases from one stage to the next. As a result, at each stage, smaller particles acquire sufficient inertia to break free of the prevailing air stream and impact on the collection surface beneath the nozzles. The resulting size fractions are then recovered and analyzed, typically by high performance liquid chromatography (HPLC), to produce an APSD for the active.

A glass expansion chamber is used to interface the impactor and device during nasal product testing. Actuation into the chamber, rather than directly into the impactor, ensures that the dose is fully dispersed and atomized, such that it is effectively drawn into the impactor, rather than depositing on the constrained geometry of the impactor inlet. Furthermore, it enables representative atomization of the dose, to produce particle size data more reflective of in-use performance. Chambers of different sizes may be assessed, during method validation, the aim being to maximize the impactor sized mass, to assess the worst case for pulmonary drug delivery<sup>7</sup>. Beyond these general points relating to cascade impaction, it is important to note that the regulatory guidance differentiates between nasal sprays and nasal aerosols in this area of testing, providing more specific guidance for each product type.

#### Nasal spray testing

Turning first to nasal sprays, the recommendation is that it is adequate to simply sum the amount of active collected beneath the first stage because nasal sprays tend to produce so little very fine material. A two litres or larger (typically five litre) expansion chamber is suggested to minimize deposition on the walls and a test flow rate of 28.3 L/min.

The need to measure the total amount of active in the fines, rather than a detailed APSD, enables testing to be simplified by using a reduced impactor stack<sup>8</sup>. For example, combining stages 0, 2 and F of an Andersen Cascade Impactor gives three fractions: >9.0 microns; 4.7 to 9.0 microns; and 0.4 to 4.7 microns respectively, at a flow rate of 28.3 L/min. Such a stack can therefore be considered as indicating the fraction of the dose that may (a) be retained in the intranasal passageways (>9.0 microns), (b) be destined for the gastrointestinal tract [via the upper respiratory system] (4.7 to 9.0 microns), and (c) penetrate to the deep lungs (0.4 to 4.7 microns). This is more than adequate information for nasal spray bioequivalence testing.

#### Nasal aerosol

In nasal aerosol testing, the guidance notes that the amount of drug deposited below the first stage of the impactor is "of the same order of magnitude as from orally inhaled products" leading to the recommendation that a full APSD is measured. Again, testing is carried out at 28.3 L/min but here smaller expansion chambers tend to be used, with a one litre chamber recommended, since

these propellant based devices usually require smaller volumes for the aerosol to become fully developed.

For QC and bioequivalence applications, testing is always comparative and, it can therefore be argued, the consistency of chamber size/test conditions is the crucial issue. More generally though, research into the impact of chamber size continues with the aim of ensuring that testing is more representative of in-use performance<sup>12</sup>. Research has shown that reducing expansion chamber size down below one litre, decreases the measured fine particle close so the one litre should be the worst case scenario for pulmonary deposition. However, there is ongoing debate as to whether smaller chambers produce data that is more representative of activity in the nasal cavities, which have a volume of just 15 ml<sup>9</sup>.

### 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 Pharmacopoeia (Ph.Eur.) monographs define detailed operational procedures 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.

### CONCLUSION

For nasal sprays and aerosols, particle size is a critical performance parameter because of its influence on deposition behaviour and *in vivo* uptake. Laser diffraction and cascade impaction dovetail to provide the particle size information required for various size fractions of the dose, together supporting effective development and QC. Laser diffraction enables the real-time measurement of droplet size across the complete particle size range, while cascade impaction allows active-specific interrogation of any lines present to assess the risk of pulmonary deposition. Understanding the strength and limitations of

each technique supports their efficient application towards the commercialization of effective nasal products, in line with the regulatory guidance.

The focus for this article has been nasal aerosols and sprays, but increasingly new technologies are coming to the fore with dry nasal powders a current area of intense activity. Dry powders, by presenting a less hospitable environment for microbe growth, reduce issues associated with product sterility and are especially suitable for: moisture sensitive actives; the delivery of peptides, hormones and antigens; and instances where high dose concentrations are required. They avoid the unpleasant side effects associated with certain solution/suspension-based products and can deliver longer nasal retention times than liquids<sup>10</sup>.

Such products are a complex challenge for developers, because of the difficulty of controlling the dispersion behaviour of dry, fine particles, and there is an associated need for relevant characterization. Identifying the best analytical techniques to apply is a work in progress. However, given the extensive use of laser diffraction and cascade impaction for existing nasal products, and indeed for dry powder inhalers, it seems likely that both will have a role to play in supporting advancement in this exciting new area.

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