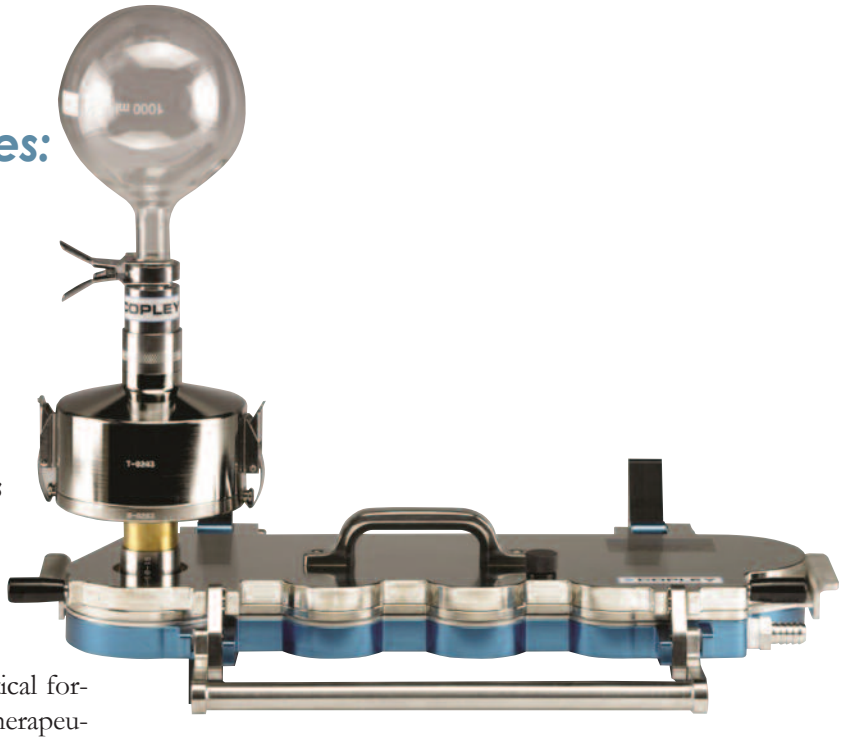
From actuation to deposition: Particle sizing techniques for characterizing nasal drug delivery systems

An examination of two complementary techniques: Laser diffraction and cascade impaction



Mark Copley and Paul Kippax
Copley Scientific and Malvern Instruments

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 act systemically.[1] The opportunity for rapid and targeted drug absorption provided by the turbinates 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.[2] 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.[3]

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.[4-6]

In its draft guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" (April 2003),[4] the FDA highlights the use of laser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 article 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.

Nasal drug delivery technology

FDA guidance[4,5] 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.[5]

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.

Developing 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.[4] 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.

Introducing 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 3,000 microns, 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 1.

Figure 1

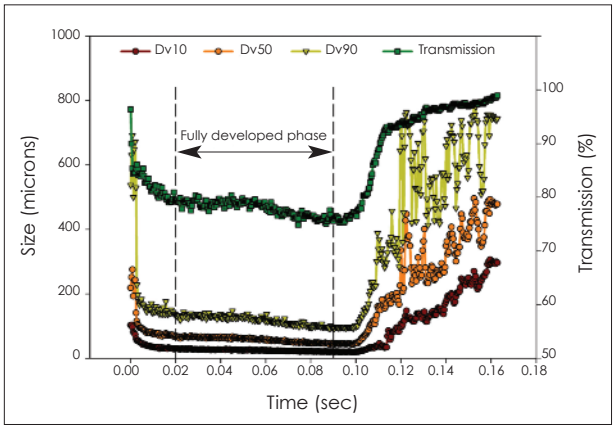
Laser diffraction system (Spraytec, Malvern) set up for nasal spray analysis. The nasal spray is actuated directly into the measurement zone to trigger the start of analysis.

Figure 2 shows 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.

Figure 2

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



The bulk of drug delivery occurs during the next stage of the event, the fully developed or stable phase, which is clearly evident on the graph in Figure 2. 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 the fully developed phase. Such data support the efficient optimization of the device and the formulation to meet drug delivery and product stability targets.

Focusing on cascade impaction

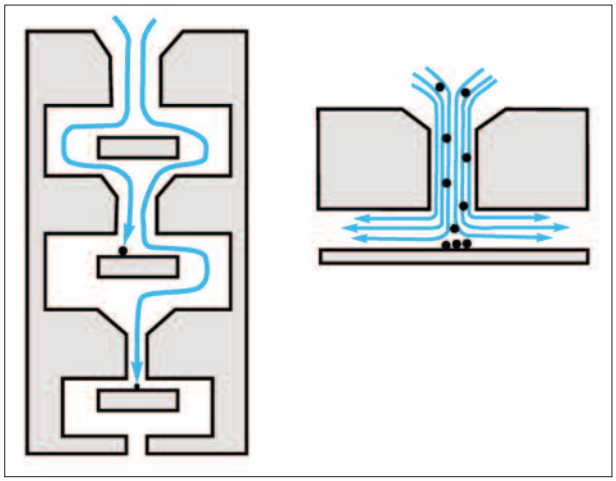
Cascade impaction is a well-established technique used for analyzing all orally inhaled and nasal drug products (OINDPs). Specifically developed for the analysis of fine particles, principally the sub-ten micron size fraction, it generates an aerodynamic particle size distribution (APSD) for the active, rather than the formulation as a whole.[7]

In nasal drug delivery, cascade impaction complements laser diffraction by enabling closer scrutiny of any fines, fulfilling the requirement to assess whether there is active in this size fraction that could penetrate beyond the nasal cavities into the lung. Engineering the product to minimize such delivery may be important or even essential to match bioequivalence. However, producing a spray or aerosol with a tightly controlled particle size cut-off above ten microns can be challenging.

The technique of cascade impaction involves separating the dose on the basis of inertial impaction (Figure 3). 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.

Figure 3

In a cascade impactor, particles with sufficient inertia break free of the prevailing air stream and impact on a collection surface. In this way, the instrument size fractionates the dose, enabling generation of an APSD for the API.



A glass expansion chamber (Figure 4) 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.[8] 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

Figure 4

A reduced Andersen Cascade Impactor (Copley Scientific) set up for nasal spray testing with a two liter glass expansion chamber, as recommended by the US FDA.

amount of active collected beneath the first stage because nasal sprays tend to produce so little very fine material. A two liter or larger (typically five liter) 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.[9] 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 aerosols. 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 liter 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.[10] Research has shown that reducing expansion chamber size down below one liter, decreases the measured fine particle dose so the one liter 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.[10]

In conclusion

For nasal sprays and aerosols, particle size is a critical performance parameter because of its influence on deposition behavior 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 fines 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.[11]

Such products are a complex challenge for developers, because of the difficulty of controlling the dispersion behavior 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.

References

1. "Valois launches new generation nasal spray" item from in-pharmatechnologist.com. This can be downloaded from http://www.in-pharmatechnologist.com/Packaging/Valois-launches-new-generation-nasal-spray

2. Kippax, P, Suman, J and Williams, G "Understanding the requirements for effective nasal drug delivery" Pharmaceutical Technology Europe Vol 22, Issue 9, 2010

3. "Insulin nasal spray shows promise for Alzheimer's disease" item from US National Institutes of Health website. This can be downloaded from http://www.nih.gov/researchmatters/october2011/10032011alzheimers.htm

4. US FDA draft bioequivalence guidance for nasal sprays (2003). This can be downloaded from the FDA web site at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070111.pdf

5. US FDA CMC Guidance for nasal sprays (2002). This can be downloaded from the FDA web site at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070575.pdf

6. EMEA Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (2005). This can be downloaded from the EMEA web site at: http://www.ema.europa.eu/pdfs/human/qwp/4931305en.pdf

7. Copley, M "Cascade impactors – Theory, design and practical information for optimal testing" Inhalation, February 2008, Vol 2, No 1, pp 19 - 23

8. Doub, W et al "Measurement of drug in small particles/droplets from aqueous nasal spray by cascade impactor" Poster presented at AAPS 2002

9. Garmise, R and Hickey, A "Characterization of the Andersen Cascade Impactor for the charcaterization of nasal sprays" Journal of Pharmaceutical Sciences Vol 97, Issue 8, pp 3462-66

10. Nixon, GC "Current analytical methodologies for ex-actuator characterization of nasal pMDIs" Presented at DDL2006.

11. Kippax, P and Suman, J "Characterizing the Performance of Nasal Dry Powder Devices." Presentation at RDD 2011

Mark Copley is Sales Director, Copley Scientific, Colwick Quays Business Park, Private Road No. 2, Colwick, Nottingham UK NG4 2JY, Tel: +44 1159 616229, m.copley@copleyscientific.co.uk. Website: www.copleyscientific.com. Paul Kippax is Product Group Manager, Malvern Instruments Ltd., Enigma Business Park, Grovewood Road, Malvern, Worcestershire, WR14 1XZ, UK, Tel: +44 1684 892456, www.malvern.com.