COMPLEMENTARY TECHNIQUES FOR NASAL SPRAY ANALYSIS

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The FDA draft guidance document 'Bioequivalence (BE) and bioavailability (BA) studies for nasal sprays and nasal aerosols for local action,'[1] describes the testing requirements for new drug applications and abbreviated new drug applications. It highlights the benefits of in vitro testing for this important class of product, prescribing an approach based on comparative studies. To demonstrate BA/BE, the parameters that control performance are measured and compared with data sets for products with established clinical behaviour. Such an approach is quite different from that required for other pharmaceuticals.

With the continuing high interest in nasal drug delivery, analytical methods that accelerate the characterization of drug/device systems are in great demand. Here we examine two separate but complementary technologies that provide relevant analytical solutions. The first, image analysis, enables characterization of the API (active pharmaceutical ingredient) suspended in a nasal spray formulation. The second, laser diffraction, is ideal for the measurement of droplet size and the detailed study of spray dynamics. Fully automated systems, such as the ones cited here (Morphologi G3 and Spraytec, Malvern Instruments), deliver the high quality data required to fulfil regulatory requirements, while minimizing operator involvement.

Nasal Spray Performance

In nasal spray formulations the API is either suspended or dissolved in an aqueous medium. Excipients and additives are also incorporated, for example to enhance absorption and/or tailor viscosity to deliver improved performance. The formulation is supplied with a metered pump that is actuated by the patient during use. Consistent delivery is critical.

The FDA draft guidance recognizes that the way in which a nasal spray product interacts with the body depends on key variables, such as particle size of both the delivered droplets and any suspended API. For suspensions, the regulations state that 'drug particle size may be important for rate of dissolution and availability to sites of action within the nose.' It recommends that API particle size distribution is characterized both before and after actuation. The intent is to confirm that this parameter is the same for the test and reference material, prior to delivery, and that it is similarly affected by the dispersion process, in both cases. The guidance also addresses the complicating factor of insoluble suspending agents/excipients and the need to take this into account when developing a suitable analytical method. Light microscopy, or other appropriate means, is recommended for this aspect of testing.

With respect to droplet size distribution, the guidance states that this 'is an important property influencing the nasal deposition of aerosols and sprays.' Droplet size is controlled to ensure nasal rather than pulmonary deposition — droplets smaller than 9 microns in diameter tend to be drawn into the lung. Relatively large droplets are quickly cleared from the nose, so droplet size directly influences retention time in the nasal passages. Laser diffraction is highlighted as being suitable for droplet size measurement.

Drug Particle Size Distribution

For the reasons outlined above, suspension nasal spray formulations tend to have a specification that defines the allowable proportion of drug particles above an upper size limit and/or below a lower one. QC procedures ensure that this specification is met. Often manual microscopy is used for verification, but this technique requires a skilled analyst and is time-consuming. As with all manual techniques there is also scope for human bias. Automated image analysis,

Morphologi G3

Spraytec

which is fast and easy to use, is a better option. In the following example, image analysis was used to automate an existing manual microscopy procedure.

Case Study

The established microscopy technique for a specific nasal spray formulation required analysts to identify 500 API particles, each one distinct from the insoluble excipient present in the suspension. The QC specification states that no more than 10% of the measured particles can have a CE (circular equivalent) diameter greater than 10 microns, and that 55–70% of the particles must lie in the size range of 1–7 microns. For each batch of product, two samples were taken, representing a total analysis time of 2 hours — even for experienced personnel.

When the Morphologi G3 was used to accelerate testing and reduce manual input, complete analysis times were reduced to just 20 minutes and, additionally, data were recorded for 3800, rather than 500 particles. This automated particle characterization system is based on light microscopy and uses image analysis technology, capturing statistically relevant size and shape data for thousands of particles, in minutes. Samples were prepared in the same way as for microscopy: to measure the size of particles in the formulation before use, drops were placed on a slide under a cover slip; measurements of the particle size following pump actuation were done by spraying onto a slide using the pump supplied with the formulation. In each case the instrument measures the sample using SOPs (standard operating procedures) in which all hardware and software parameters are defined.

Classification methods applied to the raw data identify active particles in the size range of interest. Any images where active excipients are touching are excluded from the final analysis. This ensures the procedure is consistent with the established manual method.

Sophisticated classification software ensures that image analysis is focused on the particle population of interest. In this case, a combination of the particle intensity and the particle aspect ratio was used to determine which particles were excipient and should be excluded from the calculation of the API size distributions. As the classification strategy is fully defined in the SOP, the analysis automatically concentrates on the particle population of interest, every time.

Figure 1 shows results obtained using automated image analysis. These show that there is a shift in particle size distribution towards finer particle sizes after spraying. This suggests that some shear-induced deagglomeration occurs within the nozzle of the nasal spray device during the actuation of the pump. However, the product meets the specification for the API particle size both before and after spraying (Figure 2), so this change was deemed to have an insignificant impact on the product bioavailability.

In addition to producing statistical data for the sample, image analysis also allows further investigation of the nature of different particle populations through visual inspection of the captured images. Figure 3 shows oversized particles present in the formulation, those with a circular equivalent diameter greater than 10 microns.

Droplet Size Distribution

Although image analysis is ideal for characterizing API particles within a formulation, studying how a suspension or solution will aerosolize during use is very different. Capturing droplet size evolution in detail

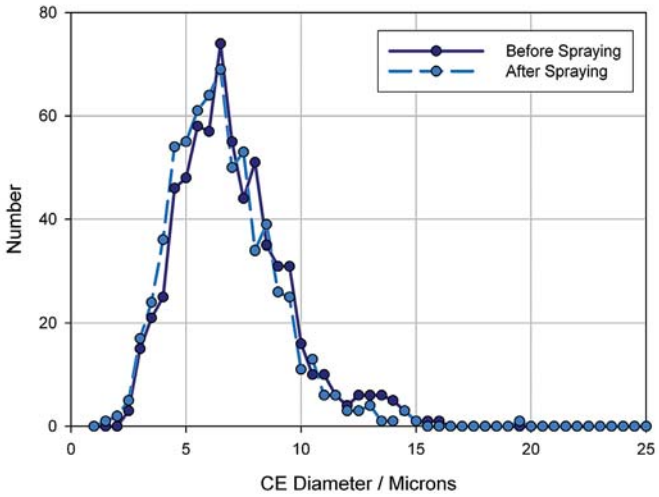

Figure 1: QC data for a nasal spray formulation collected by image analysis.

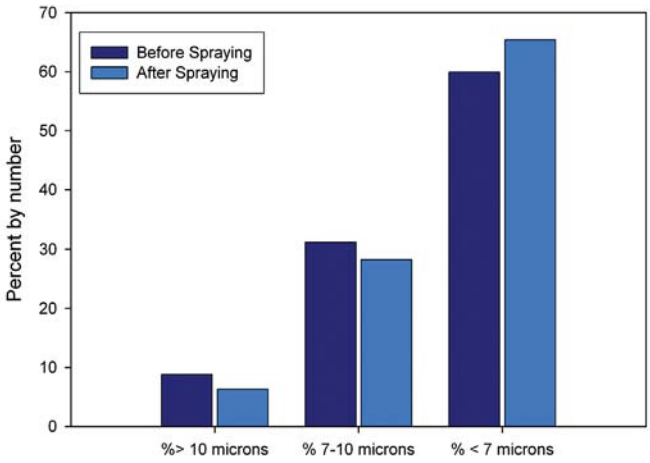

Figure 2: QC data generated derived from size distributions reported using image analysis.

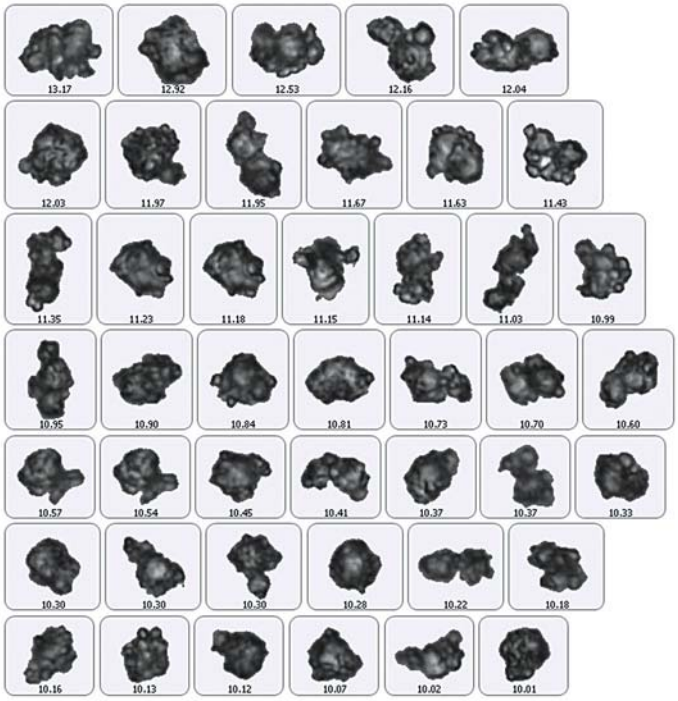

Figure 3: Images of particles with a CE diameter in excess of 10 microns.

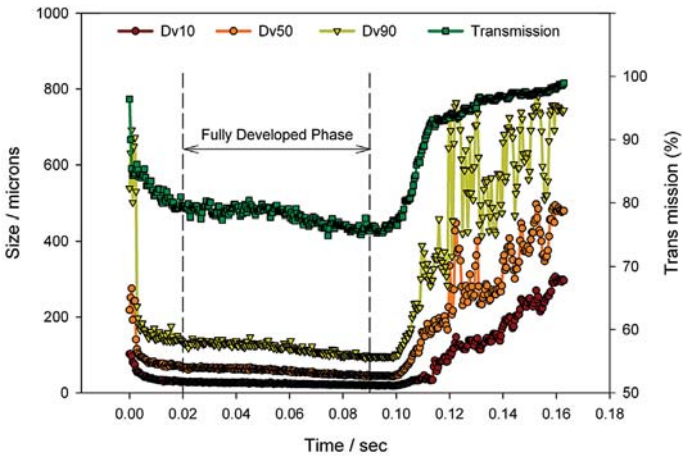

Figure 4: Typical particle size profile for a nasal spray actuation.

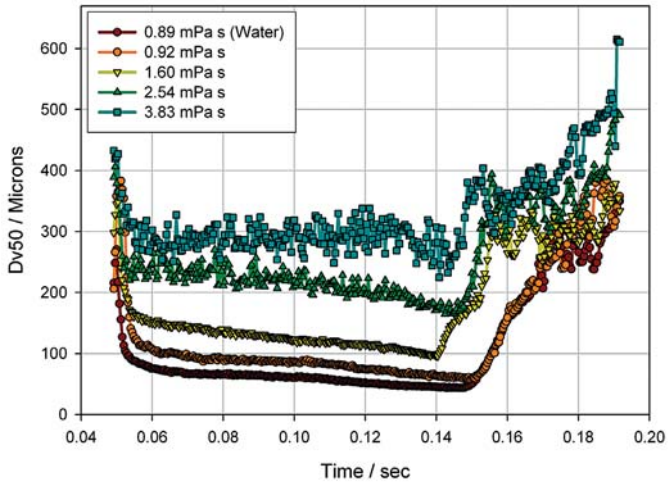

Figure 5: The impact of viscosity on the droplet size for a nasal spray formulation.

during a spray event demands in situ analytical techniques that can measure particle size extremely rapidly. The best laser diffraction systems have data acquisition rates as high as 10 kHz, making it possible to measure droplet size in real time during nasal pump spray actuation. Furthermore, the measurement range for laser diffraction — 0.1–2000 microns — is also highly suited for nasal spray applications.

Figure 4 shows a typical particle size profile for a nasal spray actuation, measured using a Spraytec system from Malvern Instruments. The timescale shows the spray event is complete at approximately 160 ms, confirming the need for rapid data acquisition. Spraytec measures every 100 microseconds — providing detailed information about the dynamics of the spray event — and three distinct phases are clearly visible from the recorded profile.

Initially, at the start of actuation, droplet size is quite large because initial flow through the spray pump nozzle is low. This phase is referred to by the FDA as the formation phase, as the output of the pump is not yet stable and the spray concentration is low. Transmission, the upper green line, is a measure of how much of the source laser light is not scattered by the droplets in the spray, and gives an indication of spray density. This measurement confirms that the droplet concentration increases rapidly during the formation phase, as the liquid flow rate increases. After decreasing quite sharply, droplet size stabilizes and remains constant throughout the fully developed phase. During this period, the formulation flows through the nozzle at an optimal rate. However, towards the end of the spray event, the metering chamber within the device empties and flow rate decreases once more — and droplet size rises. This final stage is referred to as the dissipation phase.

It is clear from Figure 4 that droplet size varies considerably during the course of a spray event, so the issue arises of how to determine a representative droplet size for comparative studies. The FDA guidance recommends the use of data from the fully developed phase to ensure statistically valid comparisons between different products. From profiles of the type shown here, the fully developed phase is easily identified, and can be defined in the data handling software, on the basis of a time window in which all three size parameters (Dv10, Dv50 and Dv90) are stable. This makes it easy to produce representative averaged particle size data, thus simplifying comparison.

Confirmation of the value of analysing the particle size delivered during the stable phase in determining the performance of the product is provided in Figure 5. Here, the profiles obtained for different viscosity solutions delivered through the same pump type are presented. Data from the fully developed phase alone are sufficient to show how viscosity affects droplet size — and confirm that as the viscosity increases, the droplet size becomes much larger and less stable. This relates to the greater resistance to liquid break-up at high viscosities.

Because viscosity influences a formulation's performance, it is one of the parameters optimized in the development stage. High viscosity can be an advantage for product stability and retention in the nasal cavity but, as these data show, can make dispersion to a fine droplet size more difficult. Shear thinning formulations (fluids with a viscosity that decreases with increasing shear rate) are often the most suitable. These exhibit high viscosity under conditions of low shear (when stored or held in the nasal passages) but have low viscosity when pumped or sprayed.

Conclusion

The FDA guidance for BA/BE studies for locally acting nasal sprays recommends that critical parameters such as active drug particle size and droplet size are measured to assess product performance. Image analysis and laser diffraction are excellent and complementary techniques, rapidly providing high quality data that meet the regulatory requirements. Fully automated systems reduce the analytical burden, enhance reproducibility and reduce measurement times. **Pharma**

References

1. www.fda.gov/cder/guidance/5383DFT.pdf

More information

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