Characterizing a nasal spray formulation from droplet to API particle size.

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Introduction

Interaction of a nasal spray product with the patients body depends on key variables such as the particle size of the delivered droplets and the suspended active pharmaceutical ingredient (API) [1].

Droplet size is controlled to ensure nasal rather than pulmonary deposition since relatively large droplets are quickly cleared from the nose whilst droplets smaller than 9 microns in diameter tend to be drawn into the lung. The particle size of the drug can be an important parameter for the rate of dissolution and availability to sites of action within the nose.

This paper describes fully automated, complimentary techniques for measuring droplet size and carrying out a detailed study of spray dynamics (the Spraytec, Malvern Instruments), and identifying and measuring the API particle size distribution (the Morphologi G3-ID, Malvern Instruments). These have been applied in understanding the output of a commercially available device.

Investigating the robustness of the nasal spray delivery system

Detailed droplet size evolution during a spray event requires an in situ analytical technique where particle size can be measured extremely rapidly. Laser diffraction data can be acquired at rates up to 10kHz allowing for dynamic droplet size information to be obtained for very short events and the atomisation process to be investigated. For a nasal spray this allows the formation, fully developed and dissipation phases to be clearly defined.

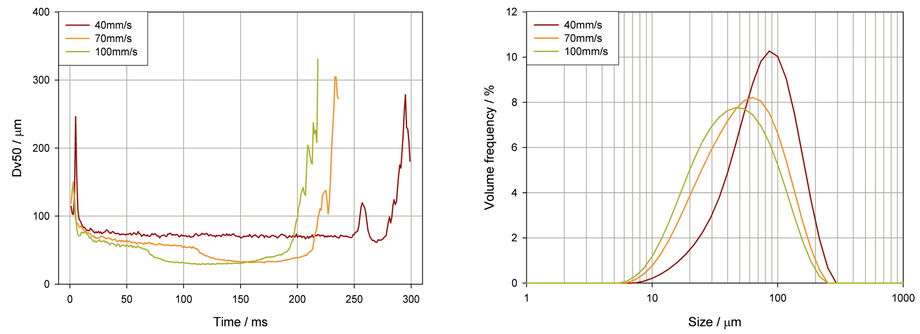

Figure 1: Particle size profiles and averaged particle size distributions (from the stable phase), for a commercial nasal spray product actuated at 40, 70 and 100 mm/s

As a nasal spray has to be operated by a patient, it is important to investigate the effect of actuation conditions on the droplet size produced by the nasal spray. Figure 1 shows the average droplet size profiles measured using three actuation velocity profiles. This shows a reduction in the duration of the fully developed phase as the velocity is increased, indicating a faster delivery of the dose. The change in the shape of the profiles shows that structure within the liquid and liquid flow rate at the nozzle orifice affect the mode of atomisation. The actuations at 70mm/s and 100mm/s show similar shaped profiles, and reach a similar size within the fully developed phase (35.4µm and 32.2µm respectively). Where as a significantly larger Dv50 (72.1 µm) is observed over a longer fully developed phase when the device is actuated using 40mm/s. The averaged particle size distributions from the fully developed phase at each actuation velocity are also shown in Figure 1, this confirms that the droplet size is significantly larger when the device is actuated at 40mm/s, and that there is only a slight decrease in droplet size between the 70mm/s and 100mm/s actuations.

Assessing the particle size distribution of the active pharmaceutical ingredient using morphologically directed raman spectroscopy

In order to measure the particle size distribution of the API, the API particles must be distinctly identified from the insoluble excipient also present in the formulation. The implementation of automated microscopy coupled with image analysis and Raman Spectroscopy allows rapid measurement of all particles within a selected scan area. Many thousands of particles can be analysed avoiding the bias or subjectivity that is often associated with manual microscopy. For every particle detected, an image is recorded and a Raman spectrum can be collected. Classification can be applied to the raw result to distinguish between and the API particles and the excipient particles.

Assessing Particle size distribution of API workflow

1) Perform Morphologi Measurement **2)** Collect Raman Spectra of individual Particles **3)** Classification of API based on morphology and Raman correlation score **4)** Produce particle size distribution of API particles.

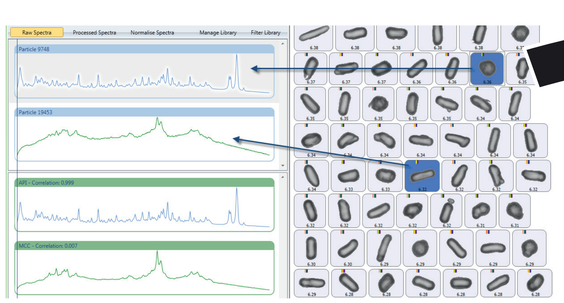

Figure 2: The Raman spectra of two individual particles, showing the ability of Raman to differentiate API and excipient particles. Reference spectra for the API and excipient are shown in the green boxes.

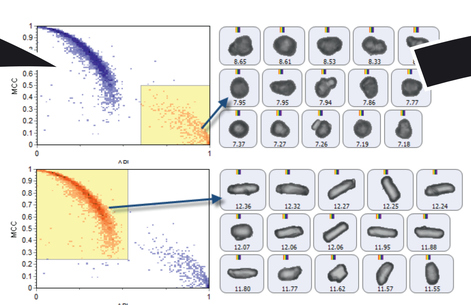

Figure 3: Scatterplots for Raman correlation scores of API and excipient particles and examples of associated particle images for the two chemical classes defined by the yellow regions.

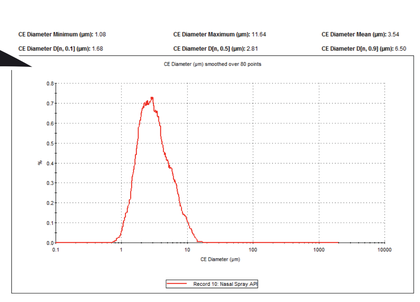

Figure 4: Particle size distribution of API in a nasal spray based upon Raman chemical classification.

Conclusion

- Automated Image analysis combined with Raman Spectroscopy and laser diffraction are excellent complimentary techniques for characterising nasal spray formulations.
- Nasal Spray deposition relates to droplet size and the bioavailability at the deposition site relates to, amongst other factors, the API size distribution.
- Laser Diffraction allows changes in droplet size to be monitored. It can therefore be used to investigate the robustness of the delivery system.
- Morphologically directed Raman spectroscopy allows definitive measurement of the API particle size distribution. Subtle effects such as the effect of spraying on agglomerates may be studied.
- Using such automated systems substantially reduces analysis time and subjectivity therefore enhancing the reproducibility of results.
- The same measurement techniques can be applied to other ONIDPs such as DPIs and MDIs.

References

[1] FDA draft guidance document ‘Bioequivalance (BE) and bioavailability (BA) studies for nasal sprays and nasal aerosols for local action’. This can be downloaded from the FDA web site at http://www.fda.gov/cder/guidance/5383DFT.pdf .

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