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Featured Application

Ingredient-Specific Particle Sizing of Aerosolized Nasal Spray Using Wide-Field Raman Chemical Imaging

Introduction

Intranasal drug delivery is an attractive delivery method for a broad range of pharmaceuticals that treat a variety of diseases. This patient-friendly delivery method can provide multiple benefits like the reduction in potential side effects and increased compliance of the drug treatment.

Creating the correct nasal formulation is challenging, yet critical. Nasal sprays formulated as suspensions typically contain micronized active pharmaceutical ingredient (API) in the presence of multiple excipient materials.

Drug particle size directly correlates to bioavailability and drug effectiveness, and is a key measurement in evaluating bioequivalence of generic nasal spray suspensions. Although particle size distribution (PSD) of the drug substance can be easily determined prior to the formulation, it has been a challenge to determine drug PSD in the formulation.

Particle sizing techniques based on laser scattering, cascade impaction or optical image analysis cannot discriminate between particles of API and those of an excipient or a surfactant. Optical microscopy is the current recommended method for particle sizing, but the selection of particles is manual and relies on human subjectivity. In vitro testing methods are frequently preferred over in vivo methods, which are often costly, time consuming and inconclusive. Consequently, the development of an efficient ingredient-specific particle sizing approach is essential for ensuring that all ingredients fall into the proper size range, particularly during the early stage of product development.

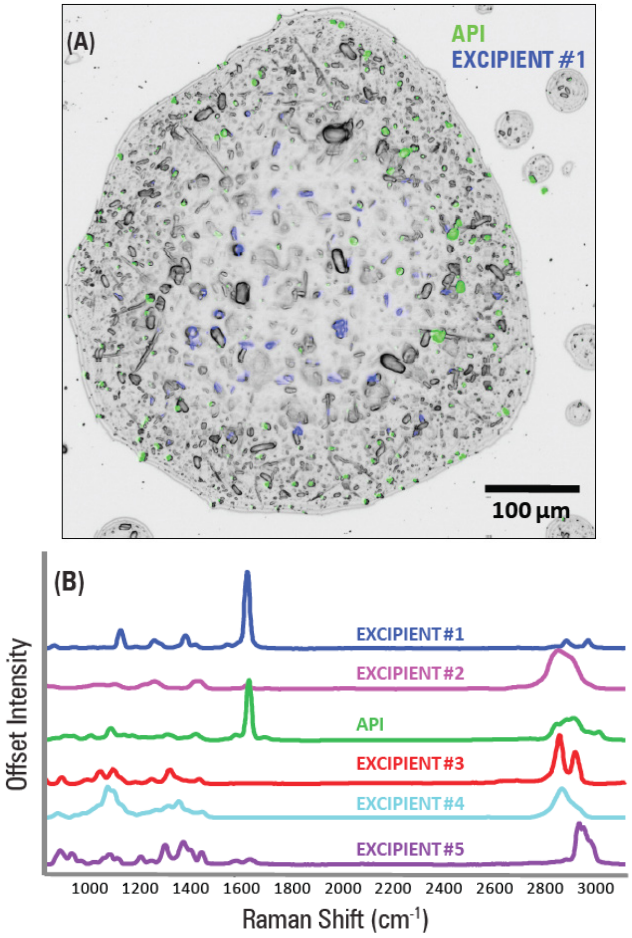

FIGURE 1: (A) Raman/Brightfield image fusion of API and Excipient #1. (B) Raman dispersive spectra of API and the excipients.

Bioequivalence Testing: cGMP Compliant Method for Measuring Drug PSD

Gateway Analytical has developed a cGMP-compliant, automated method of ingredient-specific PSD measurements utilizing wide-field Raman Chemical Imaging (RCI). Optical microscopy alone is incapable of discerning differences between drug and excipient at the chemical level. Scientists at Gateway Analytical can determine the drug PSD in aqueous nasal spray suspension formulations, providing information is especially important when developing generic nasal spray formulations. The FDA's Critical Path Initiative has identified a specific need to determine ***in vitro*** drug PSD in generic nasal spray formulations, indicating if such information were obtained in an accurate and precise manner, ***in vivo*** biostudies would be waived. This would result in significant cost savings and increase speed to market. To this end, significant validation work has been performed at Gateway Analytical using RCI to determine suitability, accuracy, precision, detection limits and linearity of the method as well as suitability, accuracy, precision and specificity of the procedure. Using these validated methodologies, a comparison of the PSD based on equivalent circle diameter of the generic and innovator product can be achieved.

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Case Study

A nasal spray formulation was prepared on aluminum-coated glass microscope slide. Raman dispersive spectra, brightfield images, polarized light and Raman chemical images were obtained. Raman chemical images were collected over 15x15 (or 225) fields of view, yielding a sampling area of 565x565 mm2 in size. The time required for imaging a single field of view varies based on the total number of spectral frames and the integration time per frame. Images were analyzed using automated software, yielding both the Raman/brightfield image fusion as well as the ingredient-specific PSD statistics.

Results

The PSD of the API and excipient were measured. The Raman/brightfield image fusion in Figure 1A is comprised of approximately 59,000,000 individual spectra collected at a rate of >3500 spectra/second, providing very specific chemical identification in a fast, automated manner. Figure 1B illustrates the ability to identify ingredient-specific particles based on unique Raman spectra. The histograms in Figure 2 show the full distribution of 313 API and 96 Excipient #1 particles in 225 fields of view. The median maximum chord is 3.5 ± 3.1 µm for the API particles and 6.1 ± 5.8 µm for the Excipient #1.

Conclusion

Ingredient-Specific Particle Sizing Service Provides:

- Accurate, reliable method to determine the drug PSD in nasal spray suspensions
- Cost effective alternative to *in vivo* biostudies to demonstrate bioequivalence
- Capability to distinguish one or more API particles in formulated products
- Count and measurement of only API particles
- Confirmation of particle identity with Raman spectra
- Quick and automated method

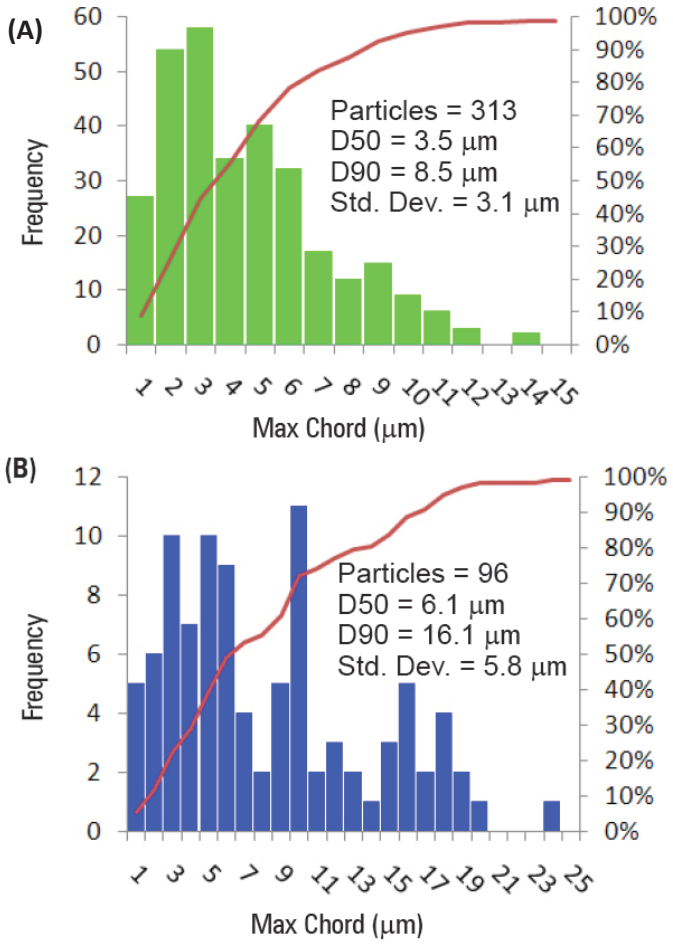

FIGURE 2: (A) API and (B) Excipient #1 PSD histogram based on 15x15 chemical image montage from a nasal spray suspension.

Wide-field RCI enables differentiation between and identification of the chemical makeup of multiple components in complex mixtures. API particles are clearly distinguishable from those of excipients where RCI displays both solitary and aggregated API particles.

This method provides much more accurate, objective information than optical microscopy. The substantial time and labor savings are ultimately transformed into cost savings and a reduced time to market.

For more details, please refer to: Doub, W.H. et al. (2007), *"Raman Chemical Imaging for Ingredient-Specific Particle Size Characterization of Aqueous Suspension Nasal Spray Formulations,"* Pharm. Research, Vol 24, No 5, pp 934-945.