Ingredient-specific particle sizing

A combination of Raman chemical imaging and optical microscopy allows product developers to obtain particle size distributions of both API and excipient in a suspension

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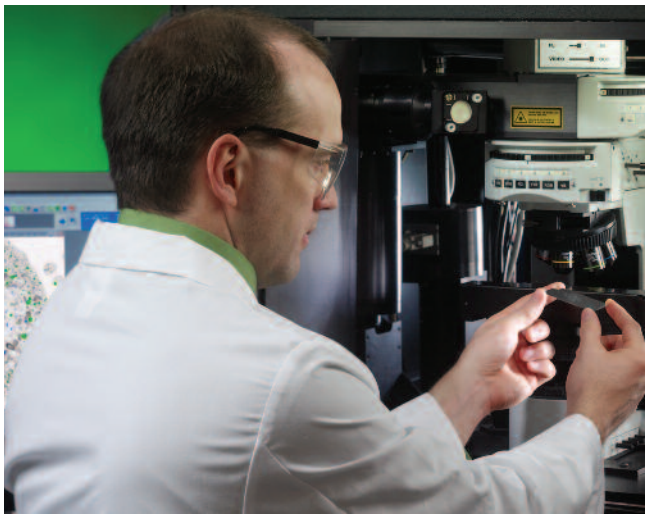


Nasal and MDI suspensions that contain insoluble excipients in addition to the API present a special challenge for product developers who need to determine the particle size distribution of the API. While the pharmaceutical industry has had a number of well-established methods for determining the particle size distribution (PSD) of a drug in orally inhaled and nasal drug products (OINDPs), particularly cascade impaction, those methods cannot differentiate between ingredients. If the PSDs of the API and an excipient overlap, accurately determining the PSD of the API becomes impossible with standard instruments.

Because the particle size of an API in suspension has a direct correlation to the drug's bioavailability, the PSD represents a critical measure of a product's effectiveness and is therefore an important factor in the development of new formulations. Nasal spray suspension formulations typically contain suspended microcrystalline cellulose in addition to dissolved excipients, making accurate determination of the API particle size distribution difficult. Solving that problem could produce substantial cost savings during product development since the FDA has cited particle size equivalence as an opportunity for an *in vitro* bioequivalence test that would allow treatment of a nasal spray suspension in the same manner as a solution, allowing developers of generics to skip *in vivo* studies [1].

Over the past few years, the FDA has participated in studies of a new Raman chemical imaging (RCI) technique that has the ability to distinguish different ingredients within a suspension formulation and to produce separate PSDs for each type of particle. This new technique uses proprietary data analysis software to integrate chemistry data obtained through RCI with particle size data obtained simultaneously by optical microscopy. Using the RCI technique, developers may be able to satisfy the FDA's requirement for reliable particle size equivalence.

The technique also has the potential to provide valuable information for developers of combination products that contain more than one API and in optimizing formulations for delivery with a particular device. In addition to generating PSDs, the technique also identifies contaminants and provides data on the distribution and/or aggregation of the formulation components that might affect aerosolization, deposition, and bioavailability.

How Raman chemical imaging works

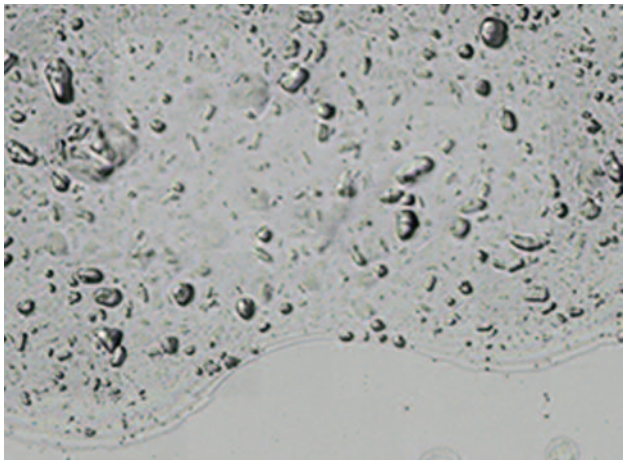
Raman spectroscopy measures energy changes induced in photons in a laser beam as it interacts with a sample as a result of to the vibrational energy of the sample molecule, a phenomenon known as inelastic or Raman scattering. The laser used can consist of light in either the visible, near infrared, or near ultraviolet ranges. Since different molecules produce characteristic profiles of the wavelengths of scattered light, Raman spectroscopy can identify individual chemicals and structures, and the pharmaceutical industry regularly makes use of Raman

spectroscopy's ability to detect small differences in crystal structure to identify drug polymorphs.

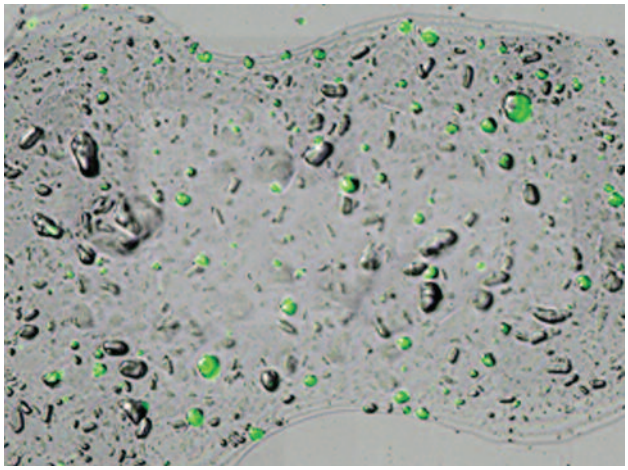
RCI combines wide-field Raman spectroscopy with advanced digital imaging, enabling users to detail material morphology and composition with a high degree of specificity. The wide-field Raman chemical imaging microscope simultaneously provides diffraction-limited spatial resolution approaching 250 nm for high signal-to-noise images and high Raman spectral resolution comparable to other types of Raman spectroscopy. In wide-field Raman spectroscopy, the laser illuminates the entire field of view (FOV) defined by the microscope objective. Unlike point or line scanning Raman spectroscopy, wide-field Raman imaging acquires a series of digital images without any movement of the sample or instrument, allowing for perfect fusion of the Raman image data with optical imaging data (Fig. 1).

Figure 1

RCI image of nasal spray suspension



(a) Optical image alone



(b) Optical image merged with Raman imaging

The RCI microscope samples a series of individual FOVs that the software can assemble into a composite image, or montage, to show a much larger view: an entire drop of a nasal spray formulation, for example (see cover). With RCI, each pixel in the optical image of the nasal spray drop is associated with a Raman spectrum so that interrogation of individual pixels reveals whether or not the Raman spectral features characteristic of the drug or an excipient are present. The combined chemical and spatial data allow the identification and measurement of API and excipient particles and the differentiation of aggregates from individual particles.

Testing requirements

RCI is a non-contact, non-destructive analytical technique that requires relatively small amounts of a formulation, typically about 100 mg. Formulation samples should consist of the commercially available product format for marketed products or in an appropriate actuation device for products in development. First-time analyses of a particular product also necessitate the submission of pure component samples as reference material and positive controls.

The time required for individual RCI analyses depends on the number of FOVs acquired for a particular sample and the integration time for each image frame. At a typical integration time of 40 seconds per image frame, collecting a set of 50 FOVs would take 3 hours, 20 minutes. Full scale studies include three phases: feasibility testing, method development, and the final ingredient-specific particle sizing information. In most cases, companies can obtain final results within a two-week turnaround after receipt of samples for testing.

References

1. US FDA. Office of Generic Drugs. Office of Pharmaceutical Science. Center for Drug Evaluation and Research. Critical path opportunities for generic drugs. May 1, 2007. www.fda.gov/oc/initiatives/criticalpath/reports/generic.html#sprays

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