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Combined chemical and particle distribution analysis of pharmaceutical powders

Chemical sciences

Particle chemistry and morphology

When formulating pharmaceuticals, it is important to understand the chemical composition and morphologies of the ingredients, as these can lead to changes in product performance. For example, active ingredient co-localisation and particle adhesion can affect the efficacy of formulation.

Raman microscopy is an ideal tool as it provides chemical information, supplementing optical microscopy images with information-rich chemical images.

Renishaw's Raman systems support two methods suitable for this analysis: optical image directed Raman spectroscopy, and Raman chemical imaging. Which method you use depends on the data needed and the type of sample. Analysis can be on completed tablets or on dispersed powder mixtures, which are better for studying individual particles.

These Raman analyses can speed up tasks such as demonstrating bio-equivalence. The US Food and Drug Administration has recently approved a generic drug product using Q3 equivalence, based on a combination of Raman chemical information and particle shape metrics. This significantly reduced the need for extensive clinical trials.

1. Optical image directed Raman spectroscopy

For basic morphology/composition studies

- Optical images — using white light, dark field or Rayleigh contrast methods — are used to quantify particle metrics, and to direct subsequent automated Raman single point analyses
- Fast point analysis of individual particles

2. Raman chemical imaging

For more information-rich studies of particles and agglomerates

- High specificity chemical images are produced from Raman data, from which morphology is quantified
- Morphology statistics can be more accurate as they are only calculated from high resolution Raman images
- You can determine particle co-localisation and agglomeration by combining chemical images
- Ultra-fast Raman data collection; over 1000 spectra/s

Common benefits of both methods

- Chemical/morphological information and quantitative statistics
- Thousands of particles can be analysed
- Raman analysis provides definitive chemical identification
- Both methods are highly specific and can distinguish similar materials (e.g. polymorphs and hydrates)
- They are compatible with LiveTrack™ focus-tracking technology, which maintains optimum Raman signals over non-flat surfaces
- It is quick and easy to identify particles using Raman spectral libraries

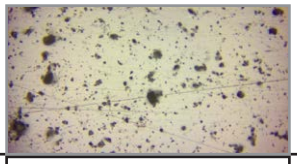
Workflows of the methods

Renishaw Raman system

(Figure. 1)

Nebula particle dispenser

(Figure. 2)



White light image of dispersed particles/ agglomerates

(Figure. 3)

Method 1: Optical image directed Raman

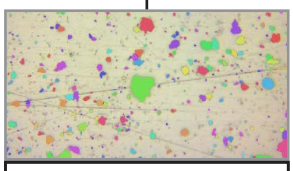
(Typically, 1 spectrum/s)

Spectra taken of individual particles

Method 2: Raman chemical imaging

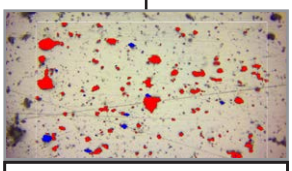
(over 1000 spectra/s)

Raman image generated by mapping area



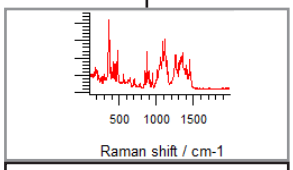
Particle metrics quantified from white light image

(Figure. 4)



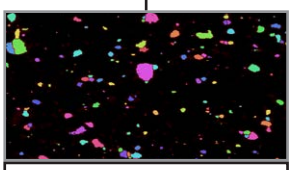
Particles identified from Raman data, and chemical images created for each chemical present

(Figure. 5)



Particles identified from Raman data collected at the centre of each particle

(Figure. 6)



Particle metrics quantified from each specific chemical image

(Figure. 7)

Raman chemical imaging - for analysis of powder mixture

In this example, Renishaw's RA802 Pharmaceutical Analyser (a compact benchtop Raman imaging system) was used in conjunction with a Nebula vacuum particle dispenser to provide fast, easy and detailed information about a powder mixture, using the Raman chemical imaging method.

Figure 8. Nebula vacuum particle dispenser

A lactose/magnesium carbonate powder mixture was dispersed onto a mirror-polished stainless steel microscope slide using a Nebula. The Nebula system chamber was pumped down to a low vacuum, separating any agglomerates into individual particles.

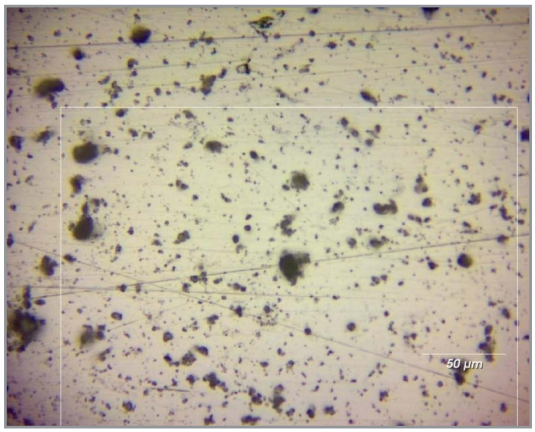
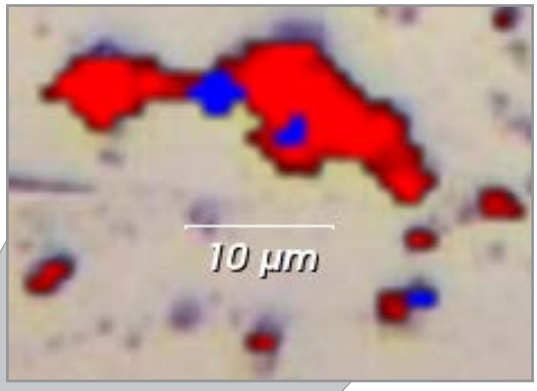


Figure 9. White light image of lactose/magnesium carbonate dispersion

A slide was placed into the RA802 Pharmaceutical Analyser, and automatically generated a white light image to enable the user to select the area to be mapped.



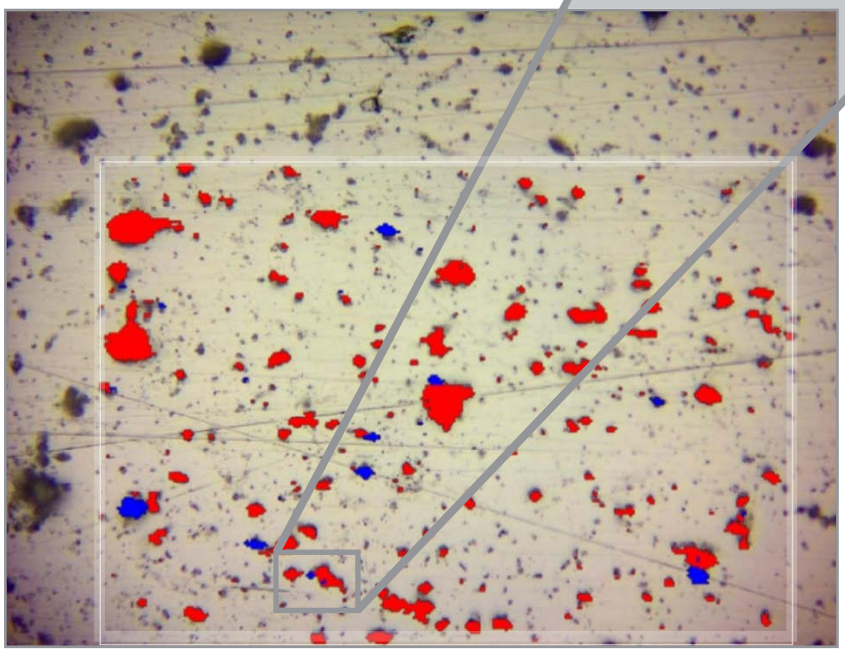


Figure 10. Raman image of lactose (Blue)/magnesium carbonate (Red) dispersion overlaid over the white-light image. A section of the image is magnified to demonstrate co-localised particles

StreamLine™ software was used to obtain chemical specific Raman images of the particles. Chemical images of lactose (blue) and magnesium carbonate (red) were created from the Raman data using component analysis (non-negative least squares correlation method) with pure reference Raman spectra. Regions of particle co-localisation can be seen in the images, and can be quantified. This is only possible using the Raman chemical imaging method, providing additional valuable information about the context of the chemical particle interactions.

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We used Renishaw's Particle Statistics software to analyse the chemical images to determine the distributions of particle domain metrics (e.g. length, width, area, equivalent circle diameter, aspect ratio, nearest neighbour distance, area percentage).

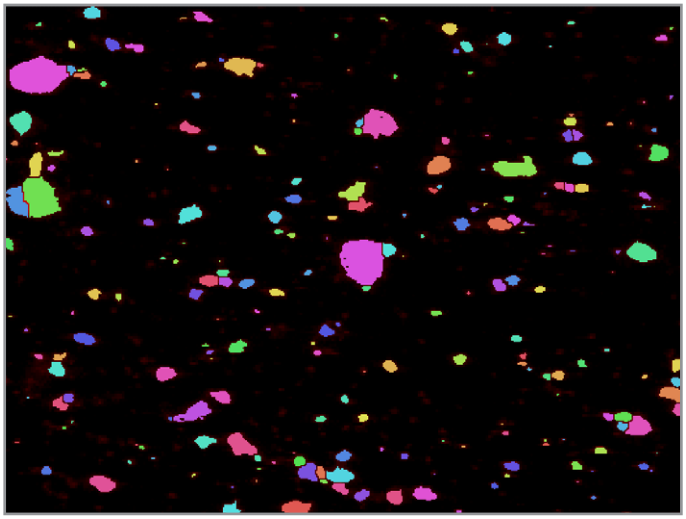

Figure 11. Particle statistics image of magnesium carbonate dispersion

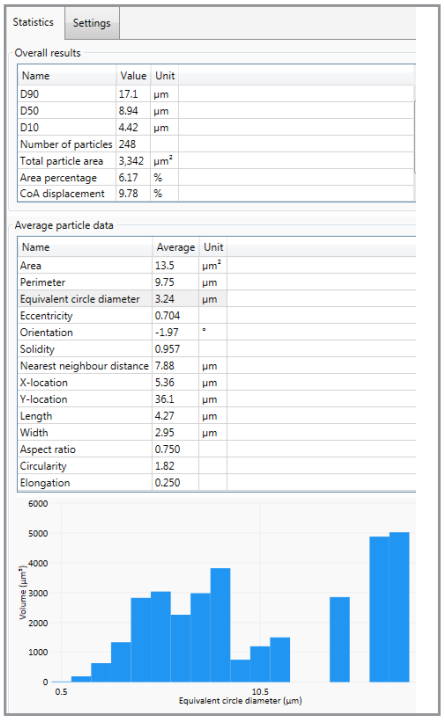

Figure 12. Particle statistics data as produced by WiRE™, Renishaw's Raman analysis software

Conclusion

Determining accurate particle size information from powders requires appropriate sample preparation, such as the use of a particle dispenser. Once the sample is prepared, Renishaw's Raman systems can produce both particle morphology information and chemical identification with high specificity.

With Renishaw Raman systems, two different methods can be used depending on sample type and analysis required. Full Raman chemical images can be produced, or individual point spectra initiated from an optical image.

Using the Raman chemical imaging method, statistical output information provides the context of chemical information with particle location. This enables co-localisation to be quantified, where dry powder efficacy can be affected by the adhesion of particles of differing chemistry.

Renishaw. The Raman innovators

Renishaw manufactures a wide range of high performance optical spectroscopy products, including confocal Raman microscopes with high speed chemical imaging technology, dedicated Raman analysers, interfaces for scanning electron and atomic force microscopes, solid state lasers for spectroscopy and state-of-the-art cooled CCD detectors.

Offering the highest levels of performance, sensitivity and reliability across a diverse range of fields and applications, the instruments are designed to meet your needs, so you can tackle even the most challenging analytical problems with confidence.

A worldwide network of subsidiary companies and distributors provides exceptional service and support for its customers.

Please visit www.renishaw.com/raman for more information.

A range of related Renishaw literature is available. Please ask your local Renishaw representative for more information.