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RA802 pharmaceutical analyser

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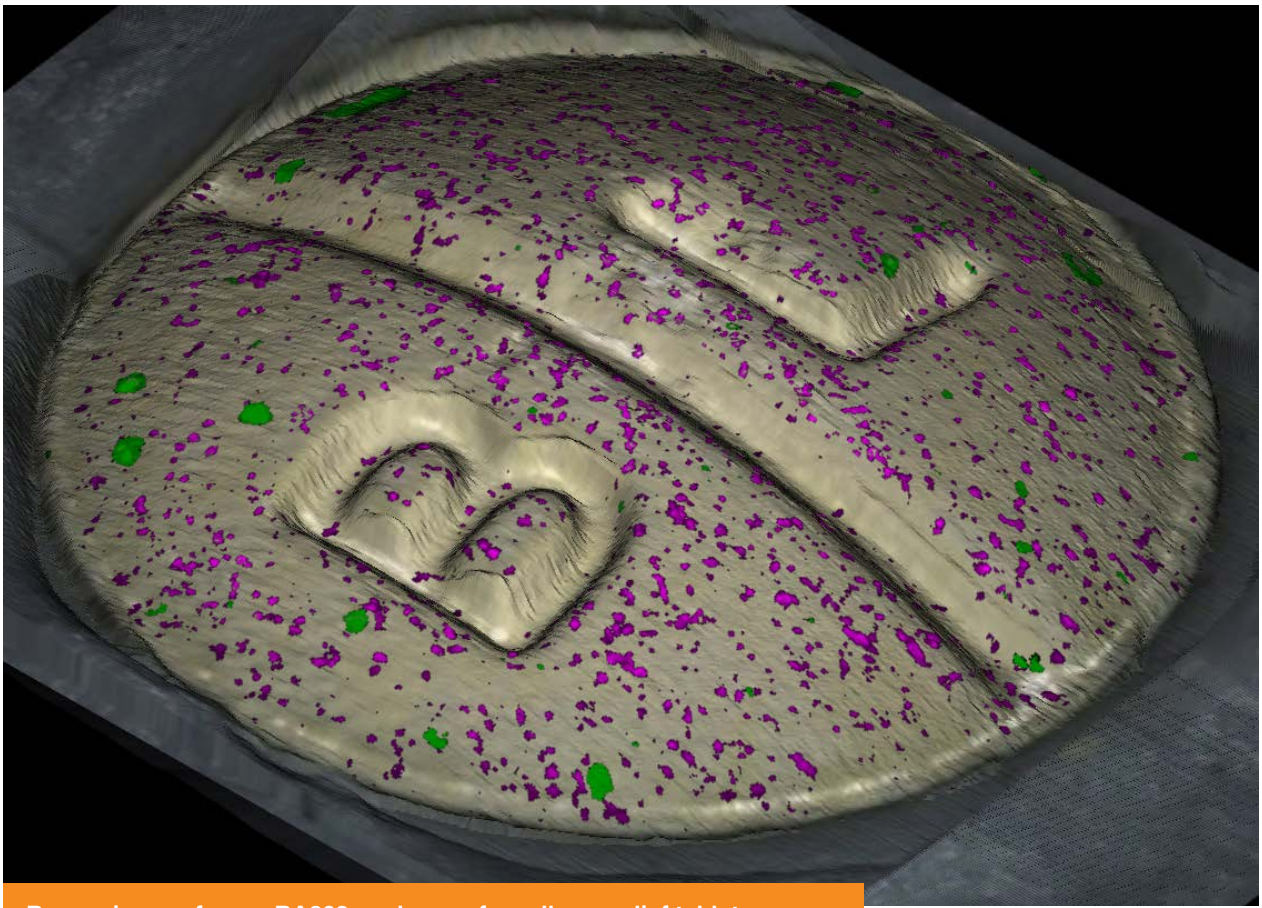
Solving problems in the pharmaceutical industry with Raman imaging

Understanding how a formulation's properties determine its performance continues to be a key challenge for the pharmaceutical industry. There are many examples of drugs which were thought to be the next 'magic bullet' but never made it to market because of the difficulties they posed to formulators.

In the last few decades this problem has become more pronounced with the rise of computational chemistry as a method of drug design. This has resulted in the emergence of drugs with increasingly large, complex combinations of active pharmaceutical ingredients (APIs) which diverge ever further from Lipinski's rules for druglikeness.

The European Pharmacopoeia has published a General Chapter 5.24 specifically addressing chemical imaging, including Raman imaging, and its benefits and applications within the pharmaceutical industry.

Raman imaging is increasingly recognised as a valuable analytical technique for the pharmaceutical industry. It enables scientists to evaluate formulations in both development and quality control environments.



Raman image, from a RA802 analyser, of an allergy relief tablet showing low concentration API (green) and maize starch (magenta).

What is Raman spectroscopy and how can it be applied?

Raman spectroscopy is an information-rich analytical technique.

Each molecule has a unique Raman spectrum that is highly specific; it is sometimes referred to as a 'molecular fingerprint'. So unique is each 'fingerprint', Raman spectroscopy is able to easily differentiate between species which are chemically very similar, including polymorphs, amorphous forms, salt forms and hydrates.

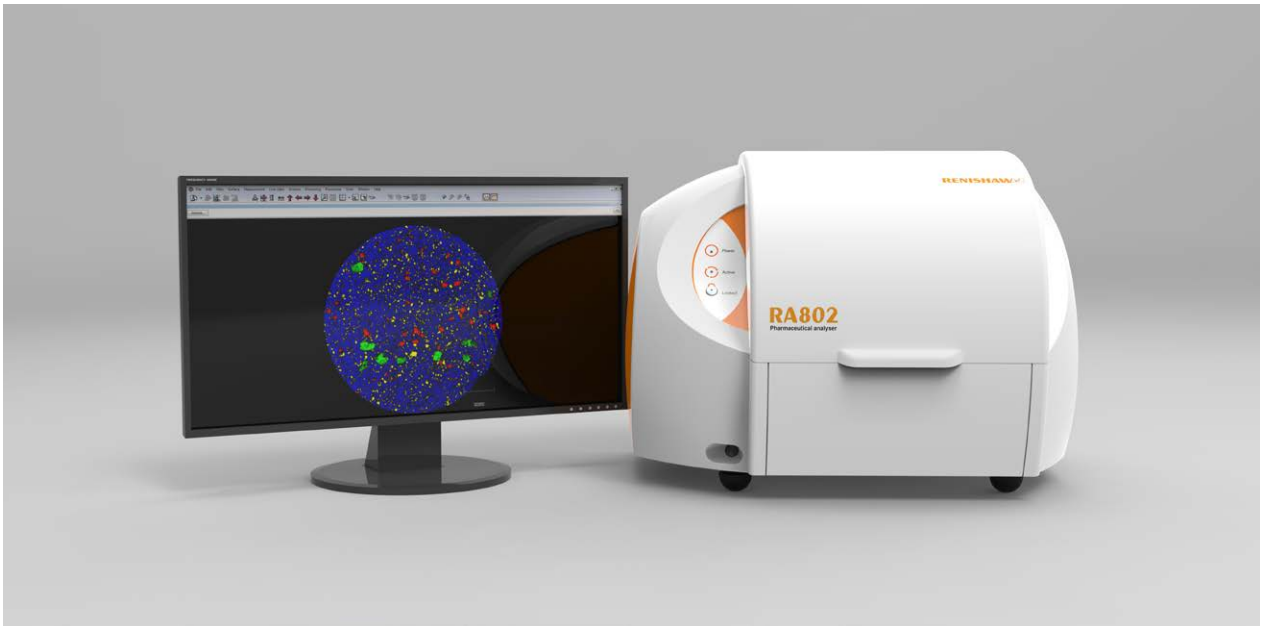
The RA802 pharmaceutical analyser uses Raman imaging to generate high-definition images of pharmaceutical materials. By collecting Raman spectra over a sample surface, it is possible to build up a Raman image of the entire sample, revealing the distribution of its components.

You can identify particles as small as 1 µm within the image which correspond to each formulation component, including:

- API, salts, hydrates, polymorphs and amorphous forms
- Excipients
- Contaminants
- Degradation products

You can also identify information about the characteristics of each component, including:

- Morphology
- Uniformity
- Agglomeration
- Particle size distribution



The RA802 pharmaceutical analyser

The RA802 pharmaceutical analyser is the only dedicated high-speed Raman imaging system designed for pharmaceutical analysis. It can generate a comprehensive Raman image of the sample surface in as little as 5 minutes using Renishaw's unique LiveTrack™ and StreamLine™ technologies.

You can collect high specificity chemical information from micro-regions and generate large chemical images of the sample surface

When generating Raman images, chemical components can be segregated using false colours and characterised using particle statistics. This gives users a tool to understand how each component is distributed throughout the sample and rationalise real-world performance between different batches and formulations.

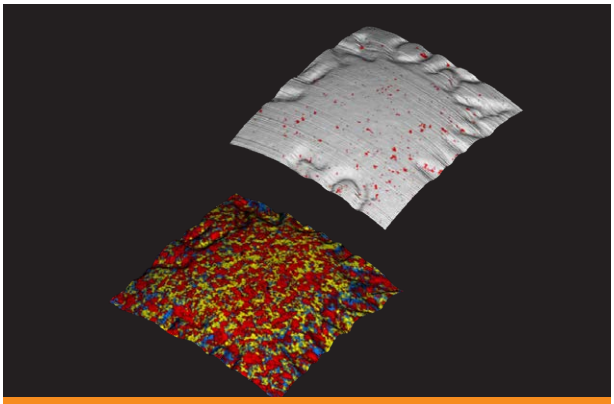
Why use the RA802 pharmaceutical analyser?

Renishaw's RA802 pharmaceutical analyser is a Raman imaging system designed to help scientists tackle formulation challenges and expedite drug development by enabling users to:

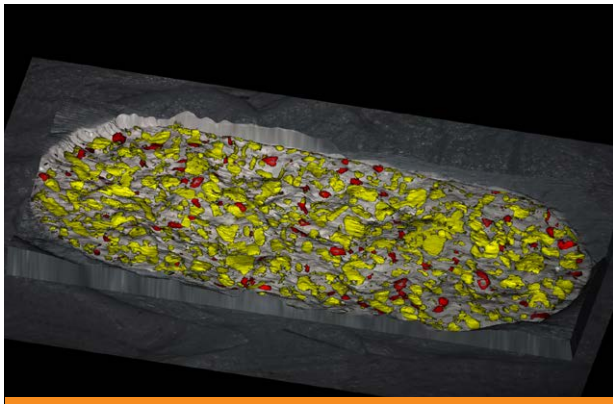
- Understand distribution of formulation components.
- Relate formulation properties to real-world outcomes.
- Quantify content uniformity/homogeneity.
- Compare batch-to-batch variation.
- Identify CPPs, CQAs and CMAs.
- Diagnose issues quickly.
- Identify the nature and presence of anomalous material.

The advantages of the RA802 pharmaceutical analyser include:

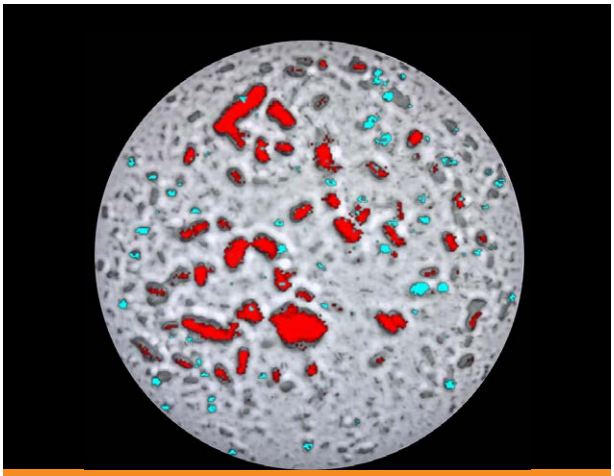
- Ease of use – no need for expert users.
- Small footprint.
- No need for sample preparation.
- Simple method development.
- Internal reference standards.
- No risk of contamination.
- Relate formulation properties to real-world outcomes.



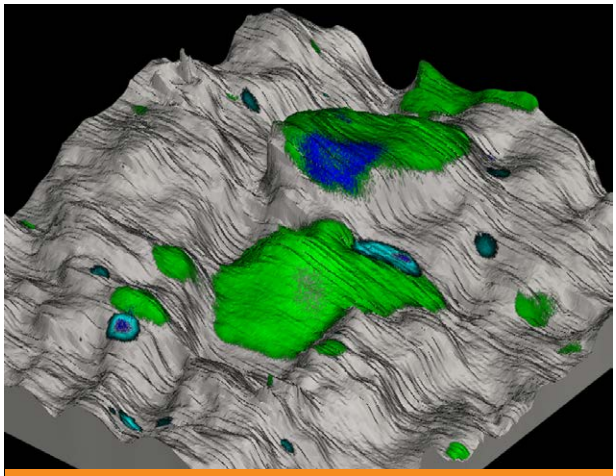
Raman image of the outer surface of counterfeit and authentic tablets revealing differences in constituents.



Raman image of an analgesic tablet split in half showing caffeine (red) and aspirin (yellow).



Raman image of an allergy relief spray showing the distribution of API (cyan) and micro crystalline cellulose (red).

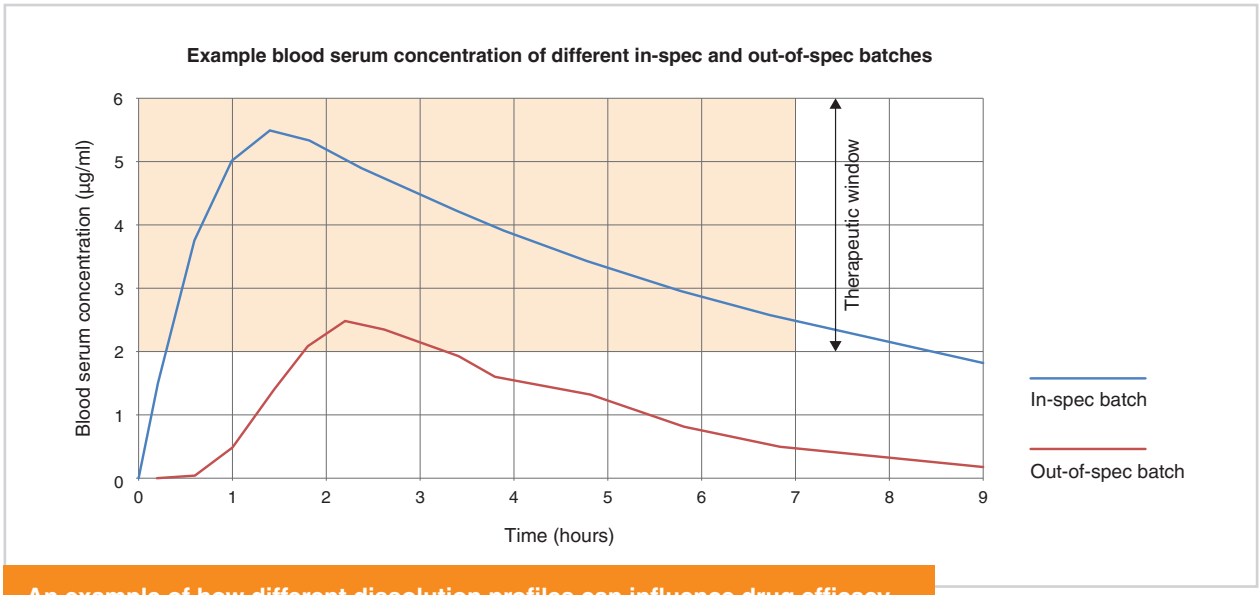


Raman image of powder mixture showing form III (blue) and form V (green) API.

Raman image of a tablet showing the distribution of API (cyan).

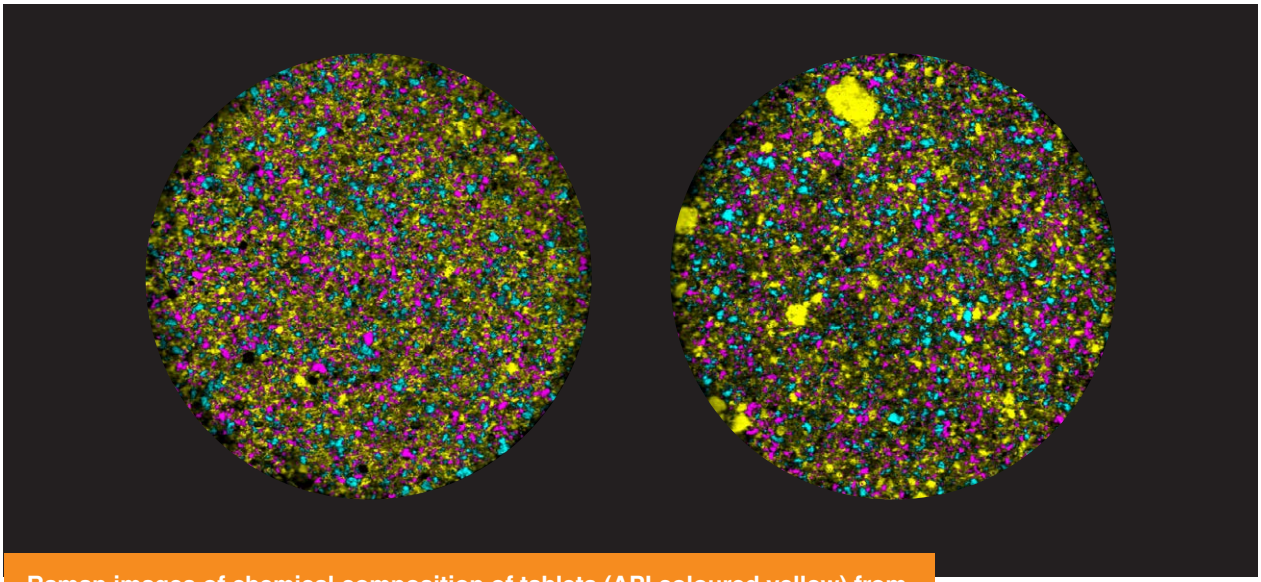
Case study: analysing drug efficacy

It is important that dissolution profiles between batches are equivalent to maintain therapeutic consistency. If the dissolution profiles are different then this can have a marked effect on the bioavailability. Examples of two different blood serum concentration profiles are shown below.



An example of how different dissolution profiles can influence drug efficacy.

One of the factors that can cause differences in bioavailability is the aggregation of granules during the granulation and tableting process. Below are example Raman images of tablets where we would expect to see differences in dissolution and bioavailability.



Raman images of chemical composition of tablets (API coloured yellow) from two different batches: batch A (left) and batch B (right).

Particle statistics for the API granules

Particle statistics (average of 5 tablets)		
	Batch A	**Batch B**
Number of domains	3858 ± 165	2266 ± 155
D90 (number weighted)	189 ± 8 µm	940 ± 110 µm
Centre of Area (lower is more uniform)	2.5 % ± 0.9%	5.8 % ± 1.7%

It is possible to infer the following outcomes in batches with aggregated granules, where the API is less uniformly dispersed throughout the tablet:

1. The aggregation would attenuate the dissolution of API as it passed through the gastrointestinal tract and thus, less drug would be available for absorption into the systemic circulation.
2. This would lead to not only a delayed and lower maximum concentration but also a shorter duration of action and a weaker therapeutic effect.

Conclusion

The RA802 pharmaceutical analyser gives formulators a tool to understand how a formulation's properties (uniformity, component distribution, particle size, morphology) determine its performance (dissolution, bioavailability, stability, robustness). Standard content uniformity measurements cannot do this and are unable to identify this problem prior to batch release.

Raman analysis, as employed in the RA802 pharmaceutical analyser, is one of the only techniques capable of this – conventional techniques such as HPLC and XRD do not give particle data and require the sample to be destroyed to measure its properties.

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Technical highlights: RA802 pharmaceutical analyser

Parameter	Value
Laser wavelength	785 nm Laser power: >150 mW at sample. Innovative StreamLine technology enables higher laser power use without sample damage
Spectral range	100 cm^{-1} to 3250 cm^{-1}
Spectral dispersion	2 cm^{-1} $pixel^{-1}$
Minimum image pixel size	1 µm
Field of view	Macro ~21 mm × 16 mm (with zoom options) Micro ~ 330 µm × 250 µm (with zoom options)
Focusing	Macro – Manual or pre-defined Micro – Automatic (LiveTrack™ technology) or manual
Data collection speed	Over 1500 spectra/s
Maximum sample size	~ (110 mm × 90 mm × 25 mm) – fits 96 well plate
Power, voltage	100 – 240 VAC ± 10%, 50/60Hz, 100 W maximum
Dimensions	720 mm (W) × 502 mm (H) × 535 mm (D)
Mass (not including computer)	54 kg
Laser class	Class 1 laser product complies with IEC60825-1. CE marked
Software	Renishaw WiRE™ software with CFR21 Part 11 functionality database, particle statistics and reporting function
Standards	Inbuilt reference standards and automated performance qualification
Qualification	Full IQ/OQ/PQ

To find out more about the RA802 pharmaceutical analyser, please contact your local representative or visit **www.renishaw.com/ra802**

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