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Understanding formulations with advanced chemical imaging

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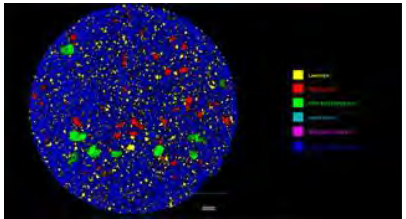

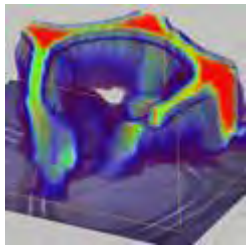

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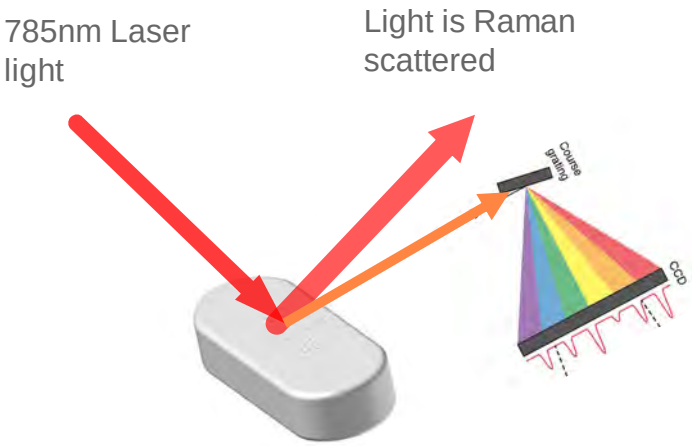
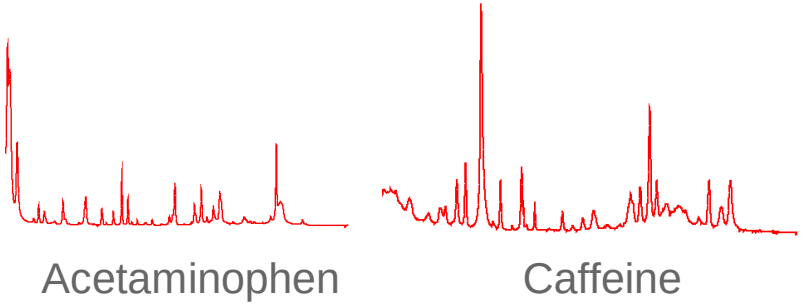
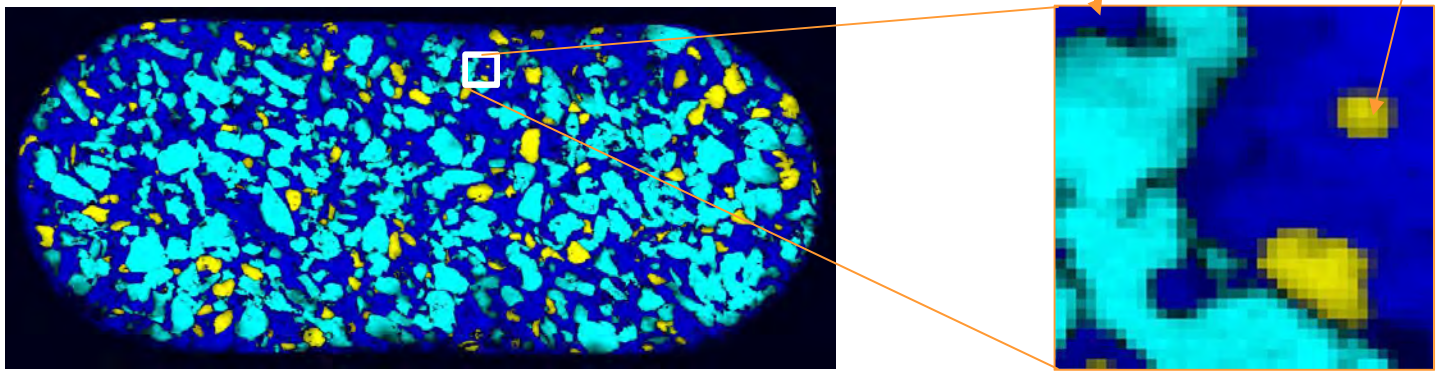
What is Raman imaging?

- Chemical images are produced from the analysis of Raman spectra







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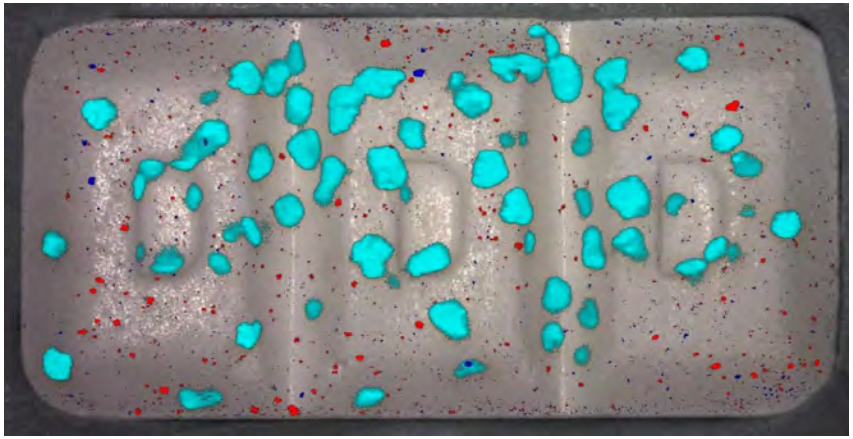
Why Raman analysis

- Information rich
  - Presence/absence of materials
  - Highly specific – chemically and structure
  - Chemical composition/identification
    - Unknowns/contaminants
  - Distribution/domain size/thickness
  - Morphology
  - Coating integrity
  - Quantitative (relative amounts of material)

- Versatile
  - Wide range of sample sizes and states
  - Configurable spatial resolution options
  - Non destructive



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How it can help

- Chemical Imaging provides a unique “fingerprint” of the drug with spatial, structural and chemical information.
  - Speed up development by better understanding of formulations and active/excipient interaction
  - Provide more robust formulations for easier manufacture/ more uniform
  - Aid with patent protection (eg polymorphic form)
  - Understand the production process better
    - Faster scale up – know when product is chemically and spatially identical.
    - Identify variables that effect form
    - Identify process changes and contamination
    - Understand the effects of storage

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Renishaw - experts in Raman imaging

Over 20 years experience in designing, building and selling Raman equipment

inVia Raman Microscope

- World's best selling Raman Microscope
- Many installations into pharma
- Flexible, high performance,
  - multiple lasers/transmission Raman

Combined Systems

Raman & SEM

Raman & AFM

RA802 - dedicated to Pharmaceutical imaging

- Using our Raman expertise and application knowledge we have developed a system dedicated to pharmaceutical imaging applications

Fast convenient, easy to use

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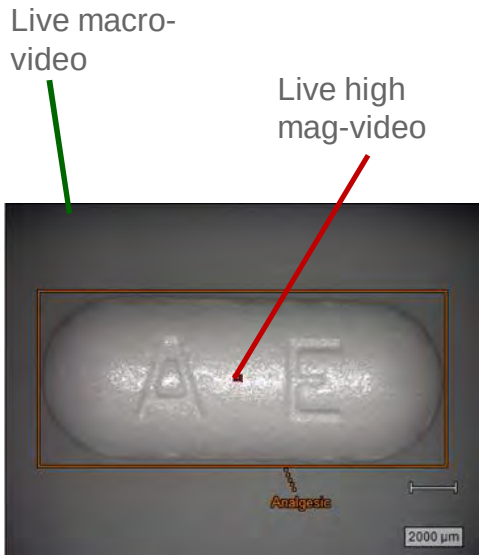
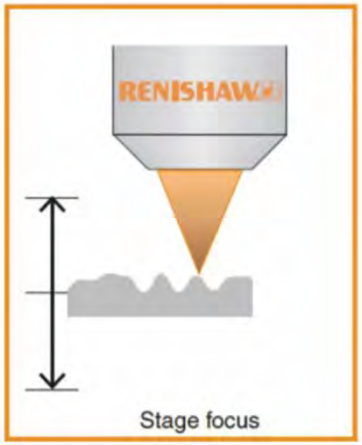
What makes RA802 different?

1. Live Macro view of sample



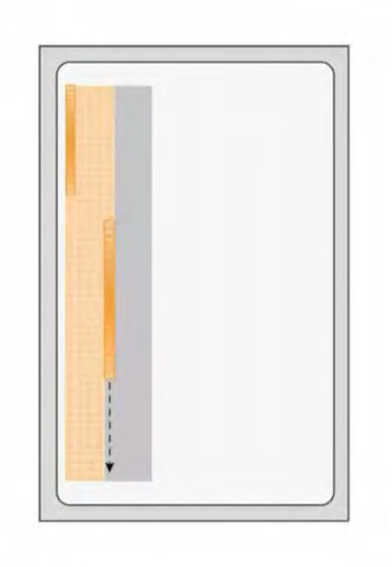
Fast, convenient visualisation and context of analysis
Intermediate digital zooming options
Very large depth of field (1 mm)

2. LiveTrack™ focus tracking technology



Focussing is completely automated for both white light and data collection

3. StreamLine™ Rapide



StreamLine Rapide reduces risk of damage and can collect data at ~1000 spectra/s

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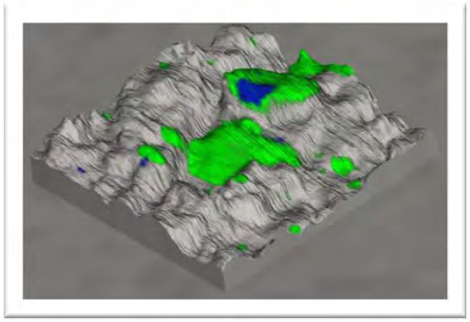
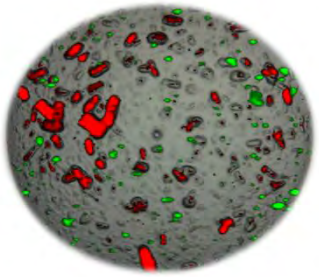
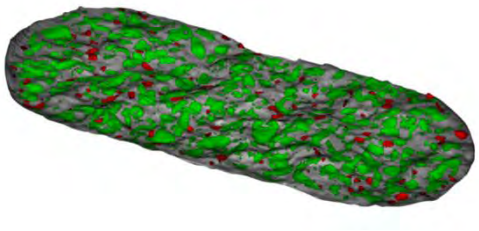
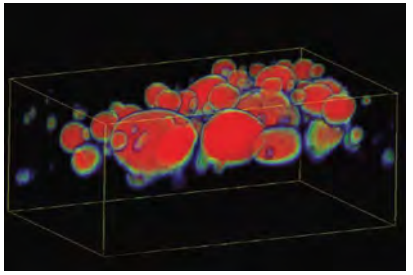
Variety of formulations can be measured

Can be used for many formulations – powders, droplets, tablets, creams, liquids





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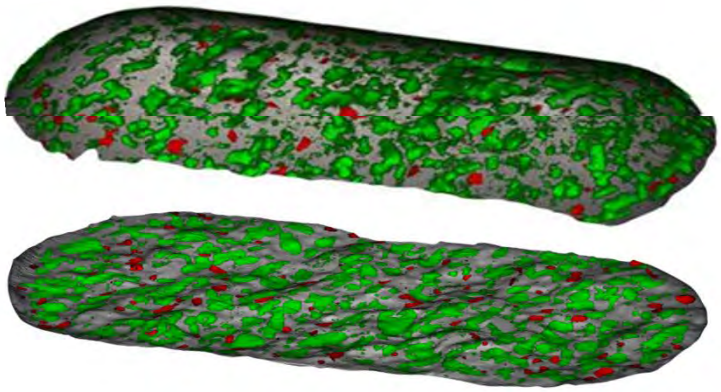
Multi-API tablets – compression effect

- Tablet containing acetaminophen, caffeine (red) and aspirin (green)
- Outer surface was found to have a different particle distribution than the internal core due to compression effects



Outer surface measured through film coating

Split inner surface

Caffeine domain statistics summary for same tablet			
	Outer surface	Inner surface Split 1	Inner surface Split 2
Number of domains	238	387	430
Average domain area	7,300 μm^2	20600 μm^2	22100 μm^2
Equivalent circle diameter	60 µm	102 µm	98 µm

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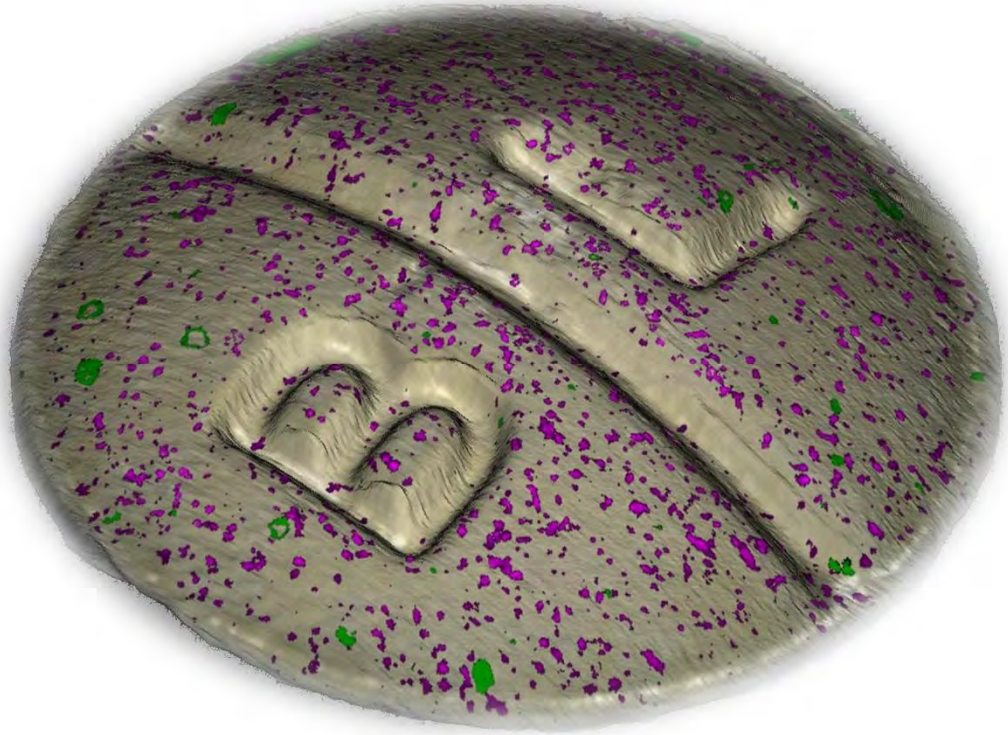
Allergy relief tablet – Raman chemical map

- Tablet containing chlorphenamine maleate (API - green), lactose (transparent) and maize starch (magenta)



Letters are indented ~220 µm

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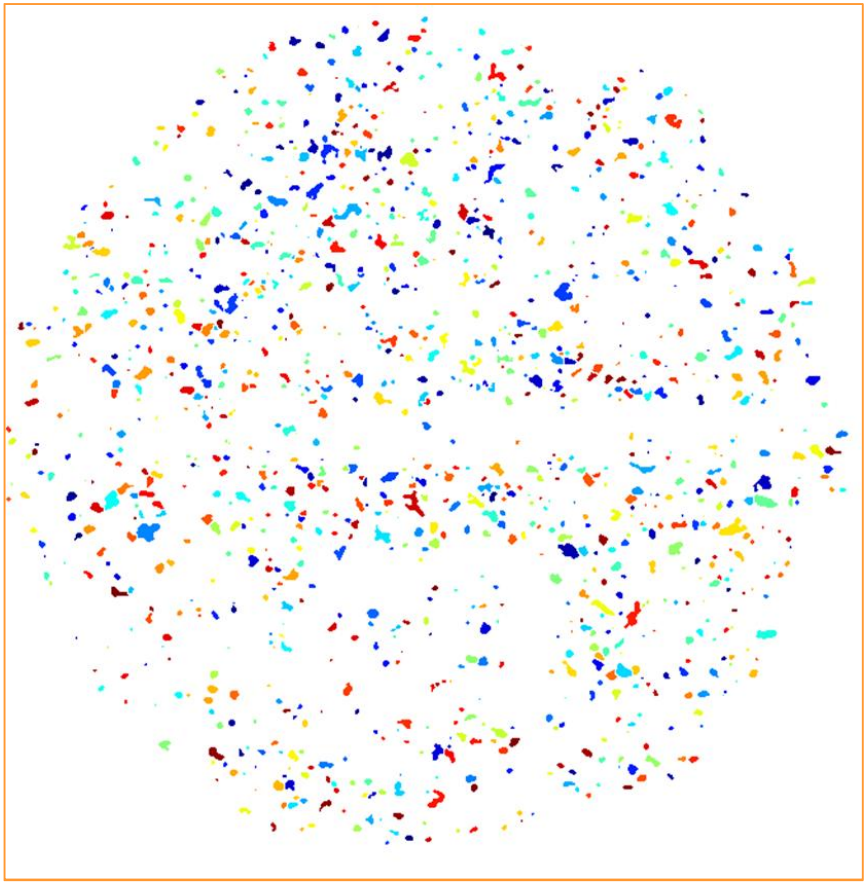
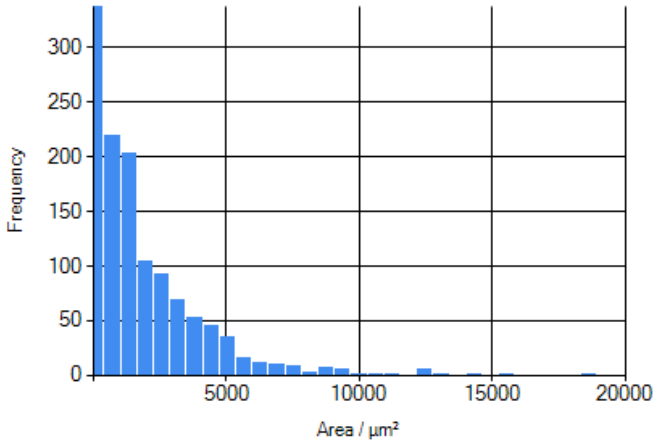
Allergy relief tablet – particle statistics

- Maize starch domain statistics



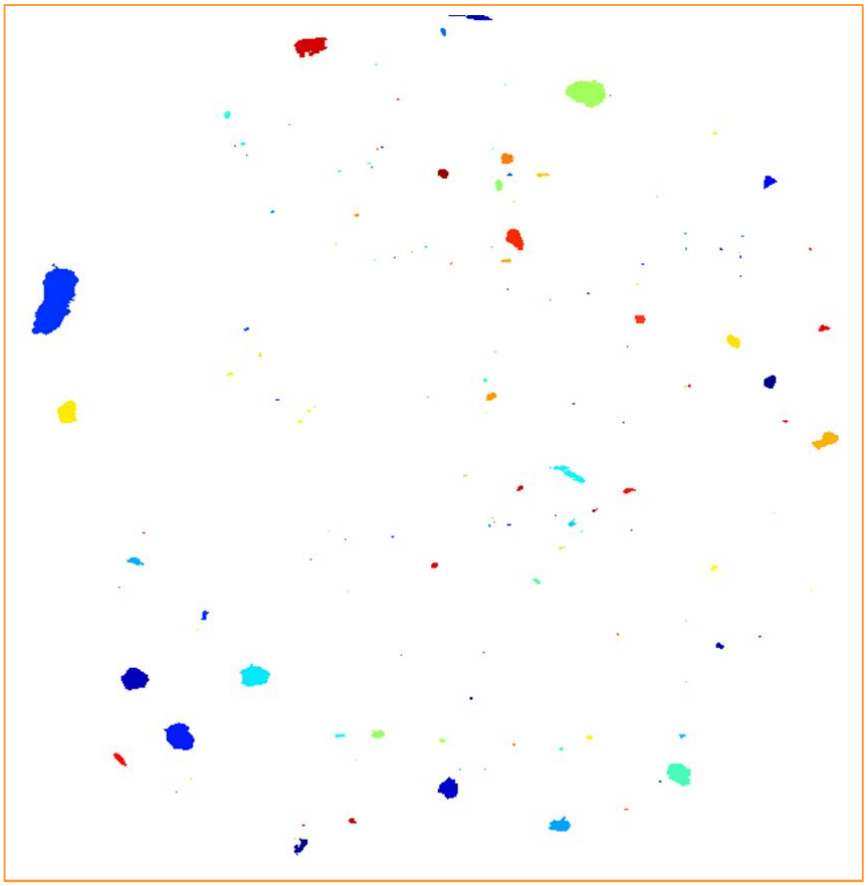
2 mm

Domain statistics summary (maize starch)	
	Surface
Number of domains	1,232
Average domain area	2,100 µm²
Equivalent circle diameter	47 µm
Nearest neighbour distance	97 µm



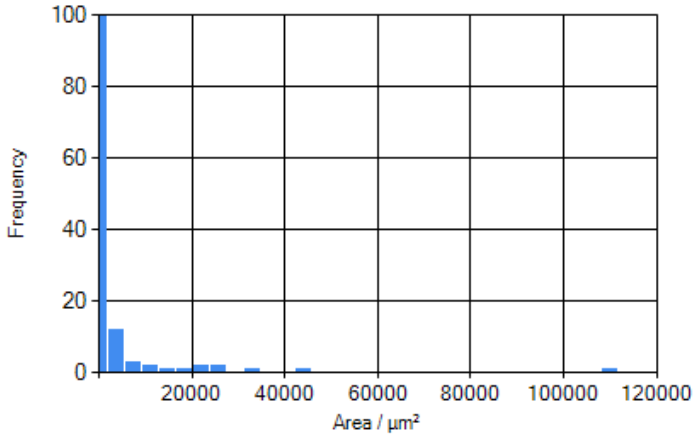
2 – Allergy relief tablet

- API particle statistics



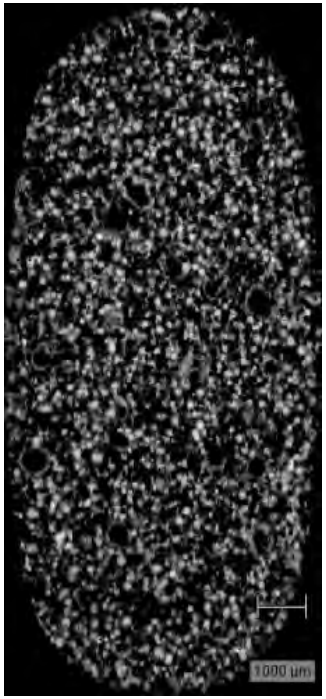
2 mm

Domain statistics summary (API)	
	Surface
Number of domains	141
Average domain area	3,910 µm^2
Equivalent circle diameter	44 µm
Nearest neighbour distance	259 µm

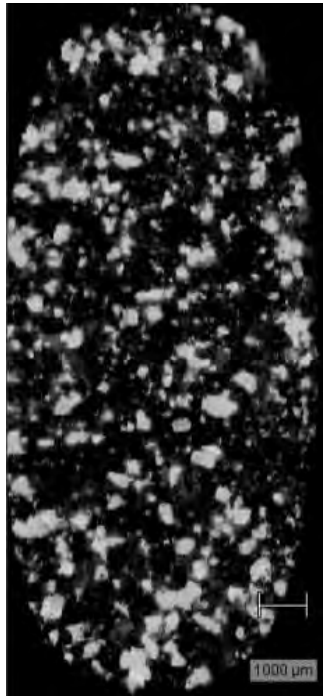


Multi-API tablets – particle size differences

- Two tablets with same constituents but different production processes
- Whole tablet chemically identical
- Effect of API milling effects dissolution profile and drug distribution



Tablet A



Tablet B

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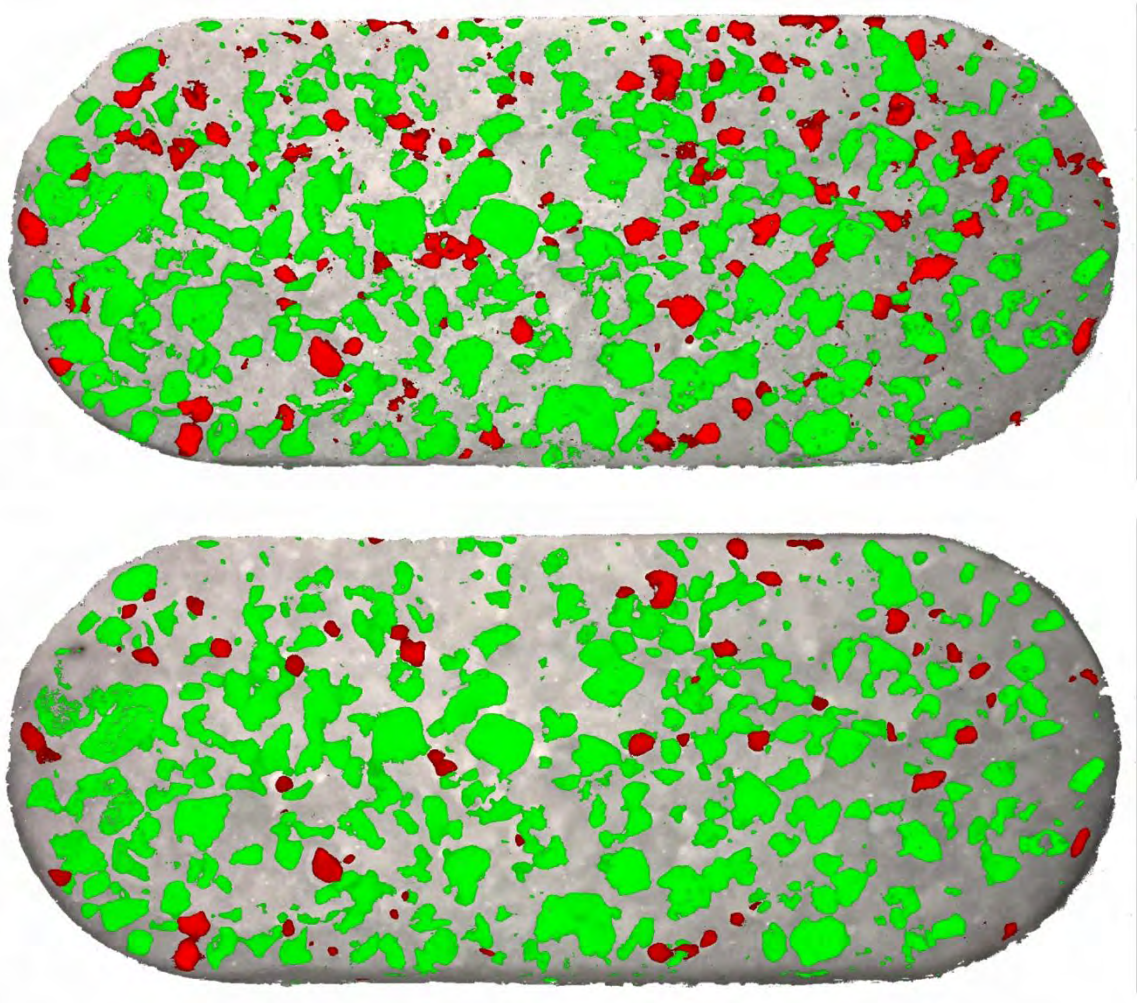
Partial dissolution study

The dissolving effects different particles.



Before

After

Green = Aspirin
Red = Caffeine

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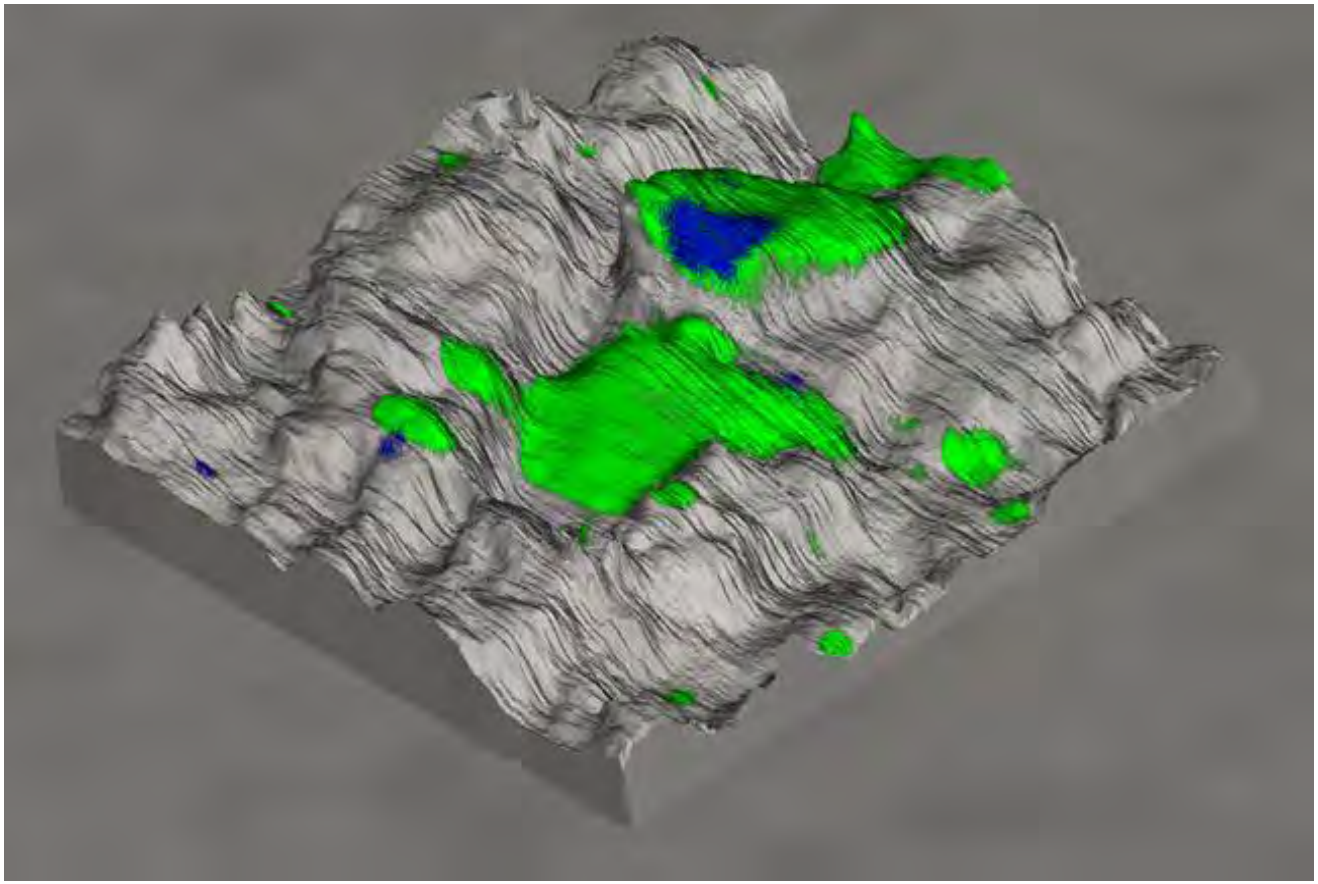
Powder mixture

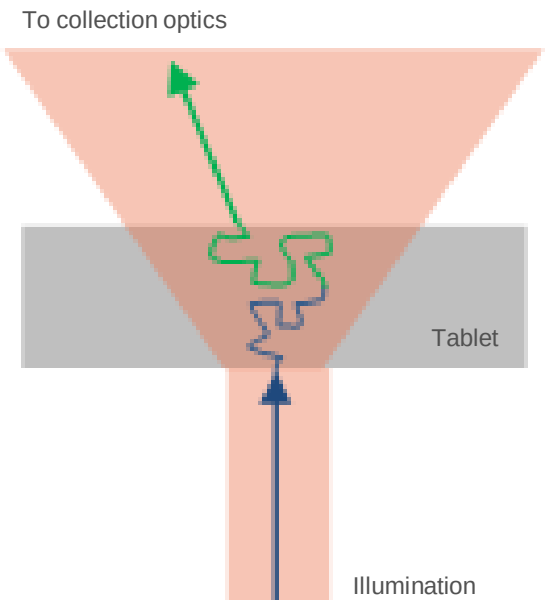
- Powder mixture high spatial resolution view in 3D
  API form V (green) to API form III (blue)



224 µm height variation

Transmission Raman in inVia

- Transmission Raman a non surface technique
- Interrogates a greater volume than surface Raman
- Large volumes analysis for quantification of mixtures
- Used to generate a model and monitor content uniformity
- Can be used to investigate on a macro scale mixtures.



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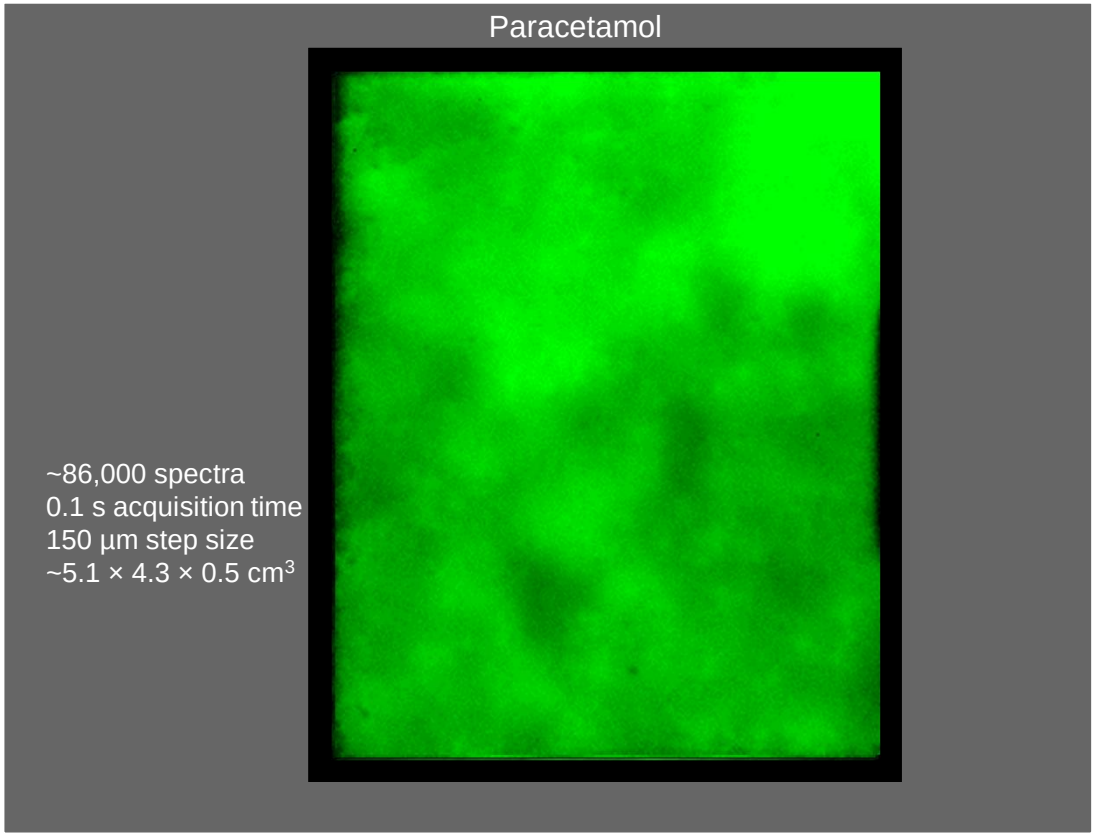
Transmission Raman in InVia

- Scanned image in transmission reveals state of mixing



- Click to play

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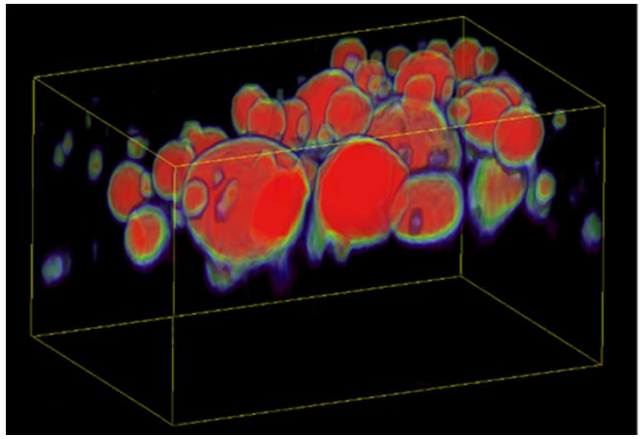
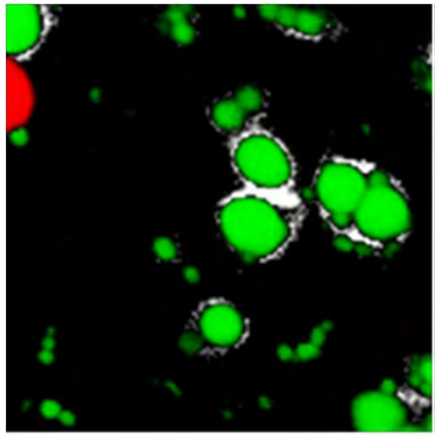
Emulsions

- Can reveal state of mixture, particle size and effects such as coalescence and flocculation in 2D or 3D with an image stack
- Used in creams/cosmetics/food



Moisturising body cream emulsion revealing 3D distribution and particle size of dispersed oil phase



Moisturising hand cream domain size (ranging from 0.5 µm - 4.0 µm);
• Poly(dimethylsiloxane) – silicone oil (red)
• Alkyl benzoate – skin conditioner (green)
• Glyceryl stearate – emulsifier (white) coating skin conditioner
• Aqueous dispersion medium (black)

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Conclusion

- By using both chemical and spatial information a full understanding of a formulation can be obtained.
- This can aid in both development, scale up and as part of QA/QC
- Raman imaging equipment has evolved into easy to use fast systems for routine use.

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Thank you for your attention

RA802 Pharmaceutical Analyser

- Making formulation analysis faster and easier