

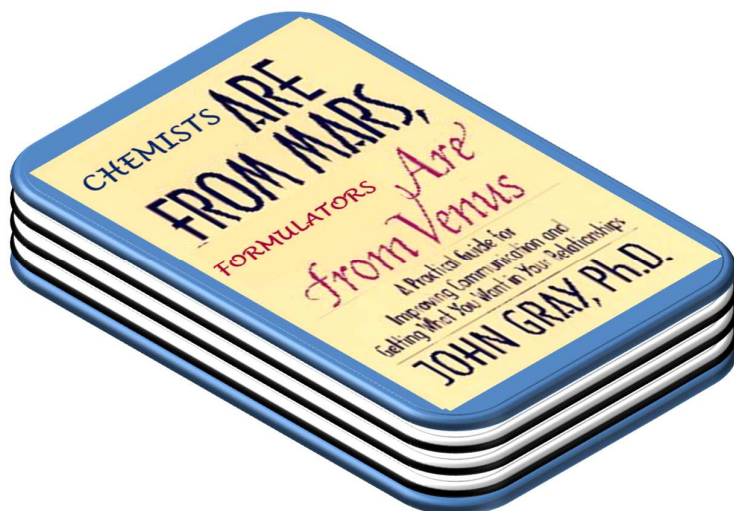
# The Impact of Materials Sciences in Increasing Understanding of Drug Product Performance and Manufacturability

Fiona Clarke



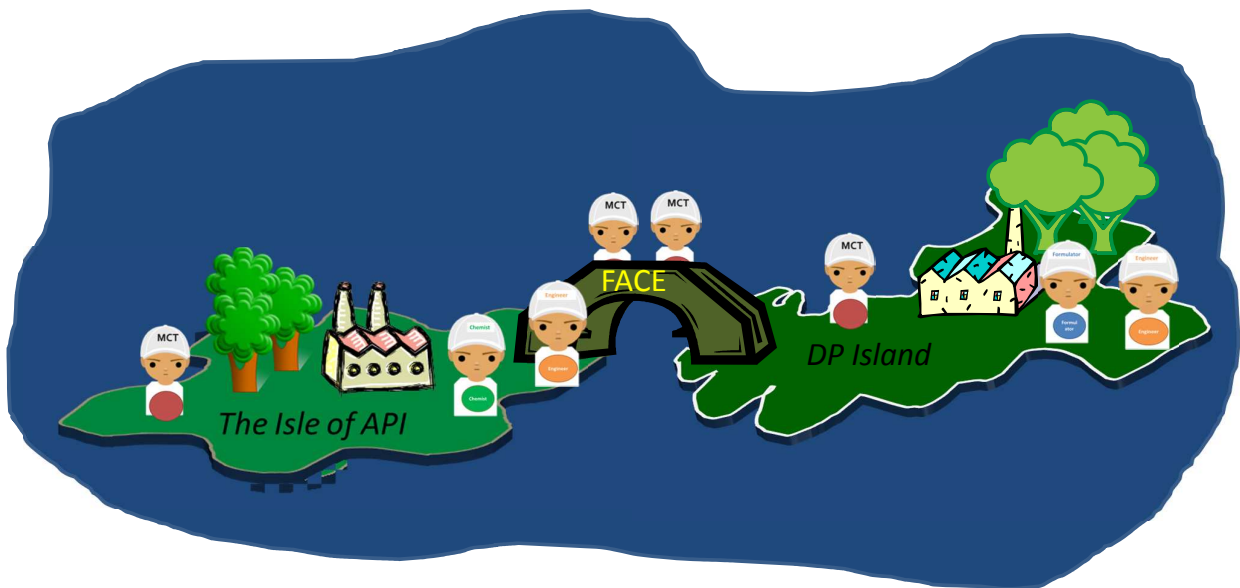
## Its All About Relationships

Materials Science will be the language of “reconciliation”



FACE  
ormulator  
nalyst  
hemist  
ngineer

# Bridging with Characterisation



FACE is the bridge between the world of API and DP, facilitated by material characteristics.

## Equipment

<p><b>Chemical Imaging / Spectroscopy</b></p> <ul style="list-style-type: none"> <li>•Near-infrared, Infrared, Raman and X-Ray Fluorescence Microscopes</li> <li>•Terahertz Imaging</li> <li>•Tablet Press</li> <li>•Microtome and Rapid Trim</li> <li>•X-Ray <math>\mu</math>Tomography</li> <li>•Near-infrared, Raman and infrared spectroscopy</li> </ul>	<p><b>Physical Characterisation/ Surface Properties</b></p> <ul style="list-style-type: none"> <li>•Malvern and Sympatec Laser Diffraction</li> <li>•Light Microscopes</li> <li>•QicPic</li> <li>•G3</li> <li>•Specific Surface Area</li> <li>•Kruss Tensiometer</li> <li>•Surface Energy Analyser (IGC)</li> <li>•Multi-Station Dynamic Vapor Sorption</li> </ul>	<p><b>Physico-Chemical / Crystallisation</b></p> <ul style="list-style-type: none"> <li>•Powder X-Ray Diffraction</li> <li>•Crystal 16</li> <li>•Thermal Gravimetric Analysis coupled with Mass Spectrometer</li> <li>•Hyper and Heat Flux Differential Scanning Calorimetry</li> <li>•Simultaneous Analyser coupled with infrared spectroscopy</li> <li>•Dynamic Mechanical Analyser</li> </ul>	<p><b>Particulate Matter</b></p> <ul style="list-style-type: none"> <li>•Light Microscope</li> <li>•Inverted light microscope</li> <li>•Infrared Microscope</li> <li>•Scanning electron microscopy coupled with energy dispersive X-rays</li> </ul>
<p><b>Material Assessment</b></p> <ul style="list-style-type: none"> <li>•Kinexus Rheometer</li> <li>•Powder Rheometer</li> <li>•Ring Shear Tester</li> <li>•Helium Pycnometer</li> <li>•Air Jet Sieve</li> <li>•Compaction Simulator</li> <li>•Texture Analyser</li> </ul>	<p><b>Non-Solids</b></p> <ul style="list-style-type: none"> <li>•Ultrasonics Spectroscopy</li> <li>•Brightwell Image Analyser</li> <li>•TurbiScan</li> <li>•ZetaSizer</li> <li>•Rheolaser</li> </ul>	<p><b>Chemical Comparability</b></p> <ul style="list-style-type: none"> <li>•Complete Orthogonal Method Evaluation (Liquid Chromatography)</li> <li>•Inductively Coupled Plasma-Optical Emission Spectroscopy</li> <li>•Nuclear Magnetic Resonance</li> <li>•Structural Elucidation (through ARD)</li> </ul>	<p><b>Regularly Outsourced</b></p> <ul style="list-style-type: none"> <li>•Residual Solvents (GC)</li> <li>•Solid State NMR</li> <li>•Gel Permeation Chromatography</li> <li>•Time of Flight –Secondary Ion Mass Spectrometry/X-Ray Photon Spectroscopy</li> </ul>

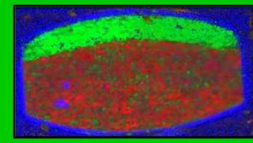
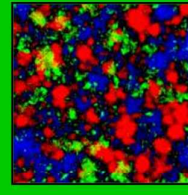
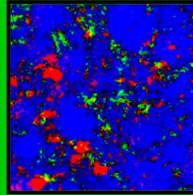
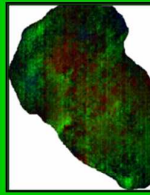
Note: Equipment can be used in different work area, but one shown is where there has been greatest application

# Technologies for Chemical Imaging

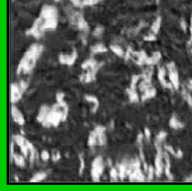
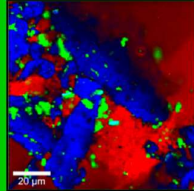
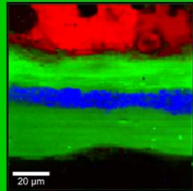
Pfizer GLOBAL SUPPLY

## Matrix Elucidation

Near-Infrared  
Microscopy

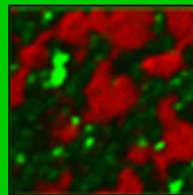
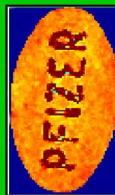
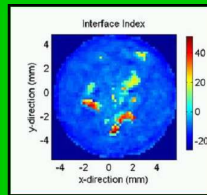


Raman  
Microscopy



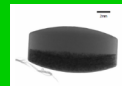
Mid-Infrared  
Microscopy

Terahertz  
Imaging



X-Ray Fluorescence  
Microscopy

X-Ray  $\mu$ Tomography



# Toolbox for Liquid and Suspension Formulations

Pfizer GLOBAL SUPPLY

### Optical Microscopy



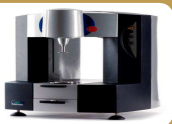
- Used to determine particle morphology
- Structural information by phase contrast microscopy

### Scanning Electron Microscopy



- Particulate matter or particle morphology
- Surface characteristics

### Rheology



- Rheology for structural information
- Stability of a liquid product

### Rheolaser



- For sedimentation and structural properties
- Stability of a suspension

### Tensiometer



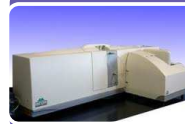
- Wettability of powder beds for wet granulation and dissolution issues

### Sympatec Laser Diffraction



- Particle size for liquid dispersions with focused measurement range

### Malvern Laser Diffraction



- Particle size for liquid dispersions with wide measurement range

### Image Analysis



- Optical particle sizing technique

### Turbiscan



- De-stabilisation of a network structure i.e. Sedimentation or creaming

### Zeta-Sizer



- Zeta potential
- Sizing

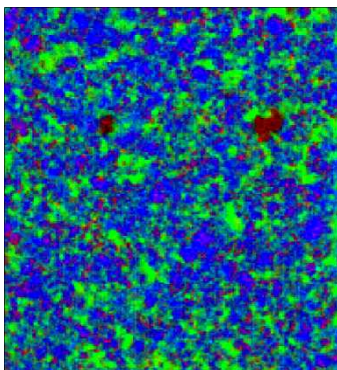
# Roots in Drug Product Characterisation

Using Chemical Images to Understand Product Performance

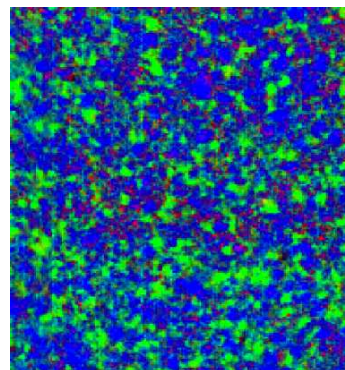


## Matrix Elucidation Providing Insights into Slow Dissolution

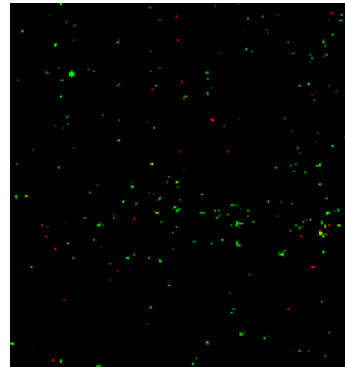
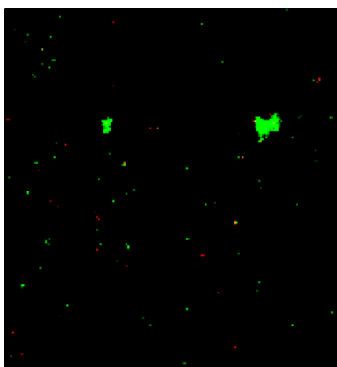
Typical



Slow Disso



No differences in distribution of major components

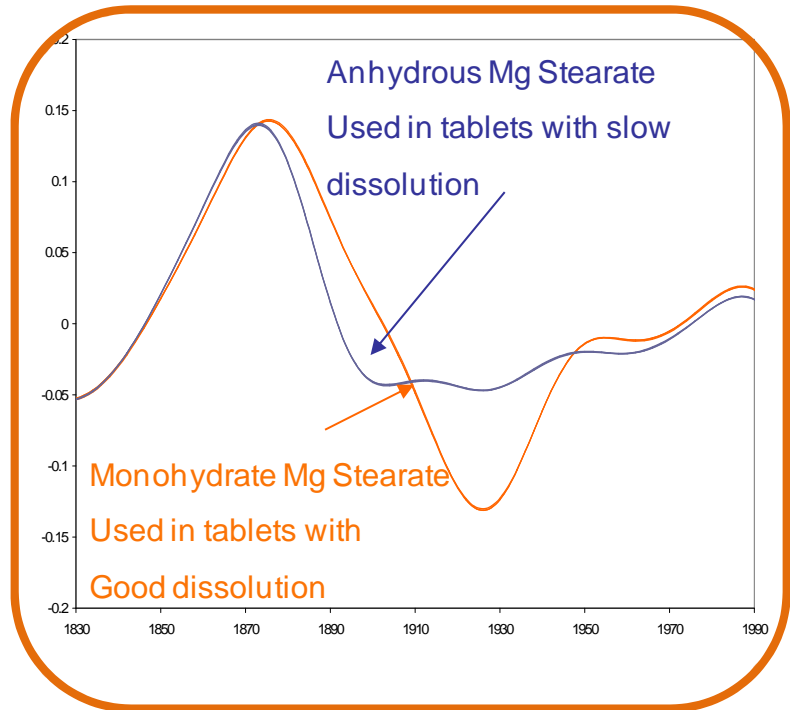
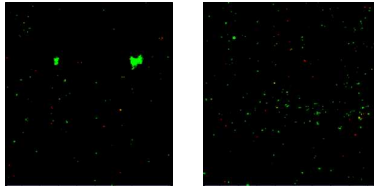


Focuses Investigation Team of Raw Material Variation or Blending Operation



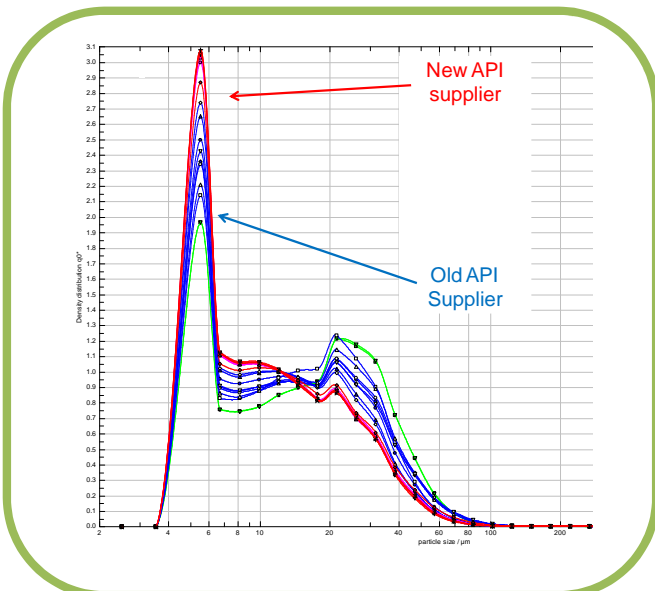
# Excipient Variability

- CoA comparison of Raw Materials Identified no variations
- Characterisation Identified difference in hydration state of magnesium stearate
- Now known as a critical attribute for this product

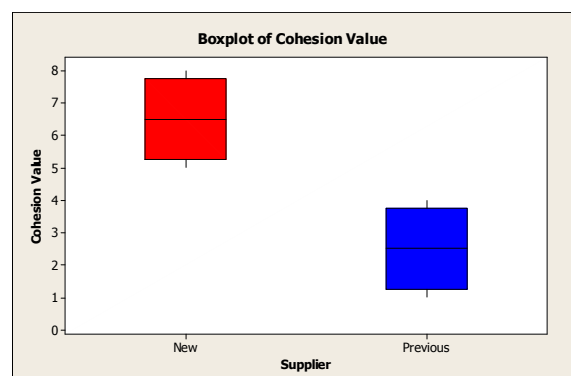


# Drug Product Issue – Blend Uniformity

- Flow issues during DP manufacture resulted in blend uniformity issues following an API source change.
  - API from new supplier had passed all specifications

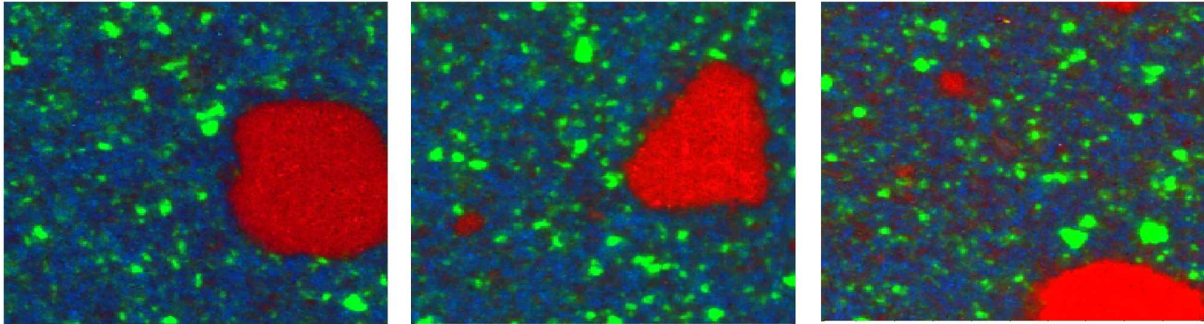


Characterisation Studies identify new API has a greater proportion of fines (<10 µm) which results in different cohesion properties.

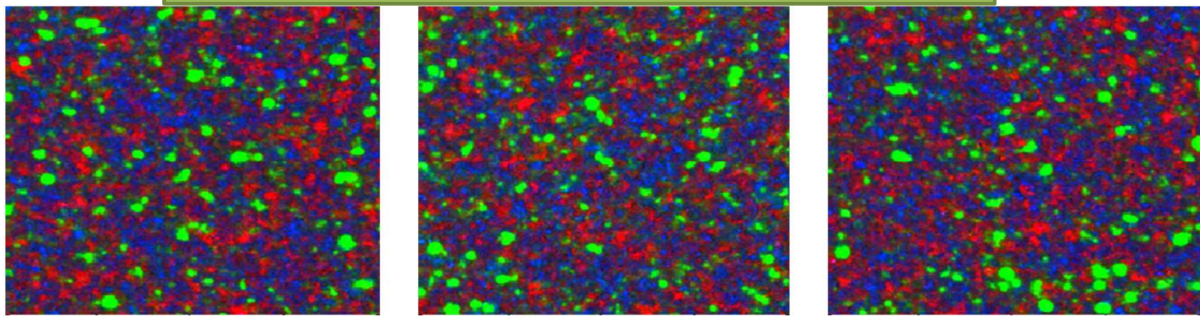


# Supporting DP Trials

## Trial Batch with New API Source



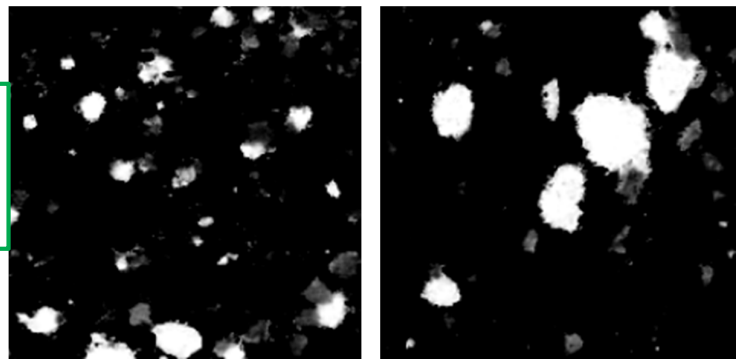
## Commercial Batch with New API Source



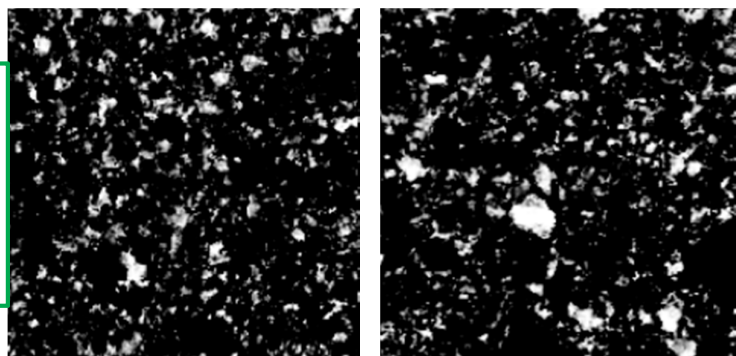
# Inhomogeneity in Drug Product

- Following a site change inhomogeneity observed in drug product results.
- Processing equipment and parameters had been comparable.
- Raw materials all meet CoA.

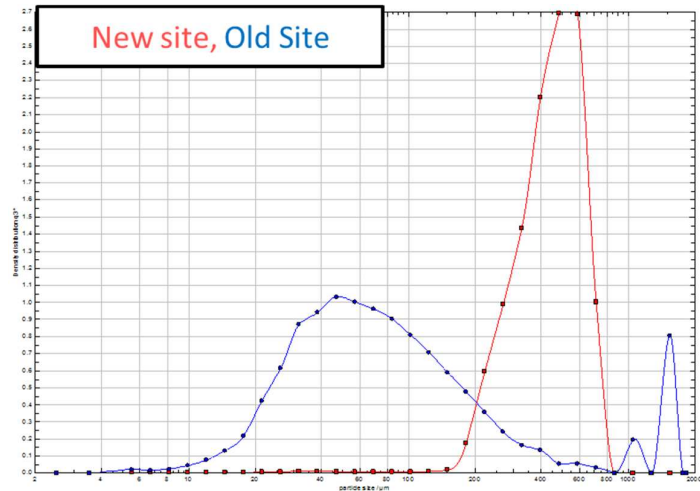
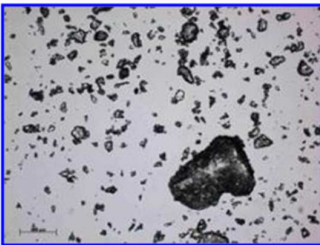
New Site



Previous Site



- Full characterisation of 15+ components identified differences in particle size and chemical content of some raw materials
  - Issues linked to particle size differences
- Utilisation of raw materials from initial DP site gave rise to good homogeneity



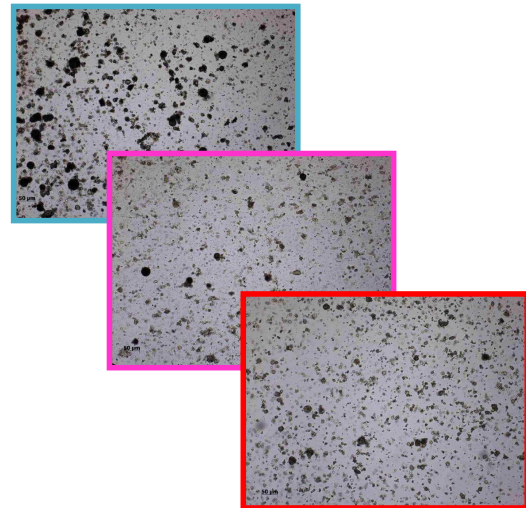
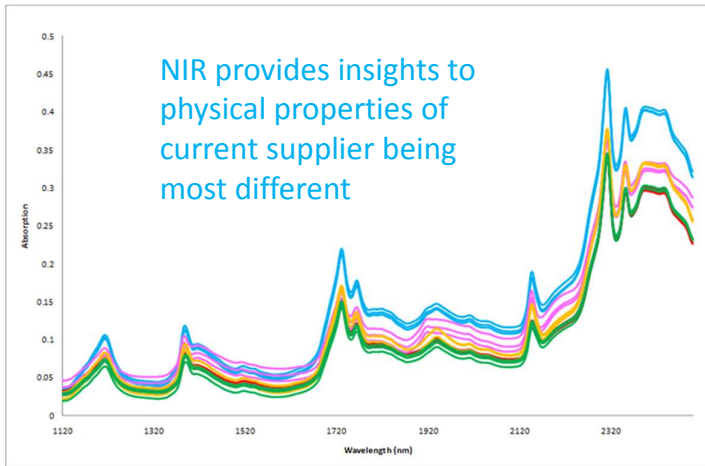
## Selecting Excipient for Ophthalmic Suspension



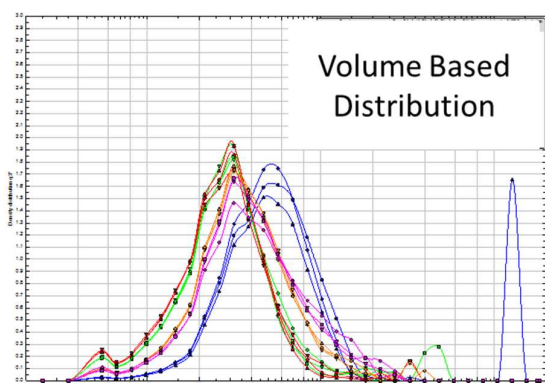
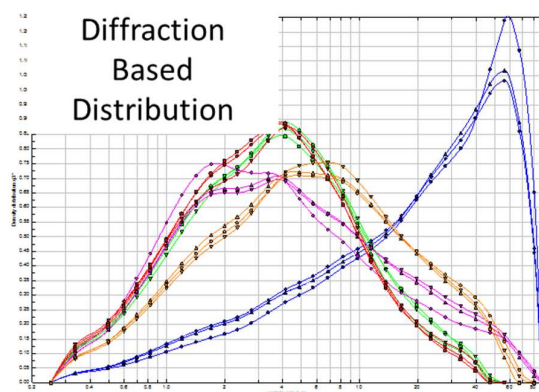
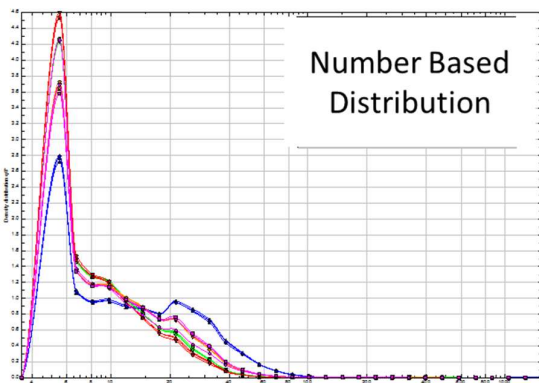


# Excipient Identification

- Notified that current raw material supplier will be ceasing manufacture.
- Understanding of this material and its attributes in DP deemed a necessary for low risk change.
  - Material from 4 alternate suppliers sourced for comparison.



# Assessing PSD

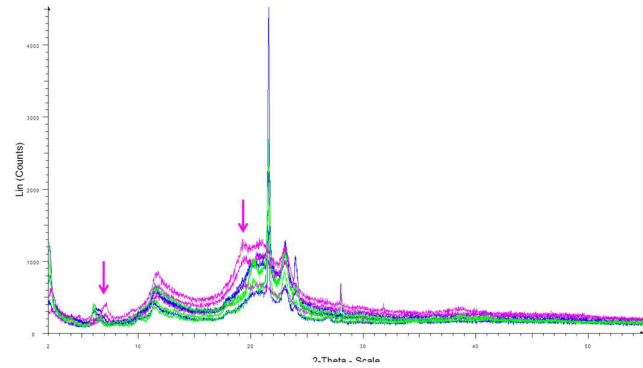
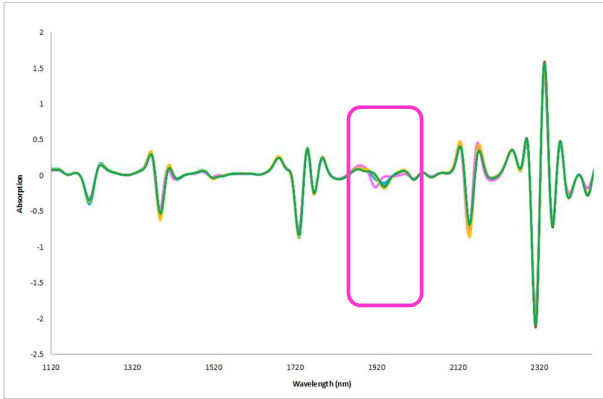


Alternate sources offer very different PSD from current source

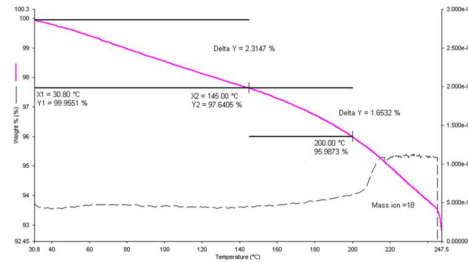


# Evaluation of Physico-Chemical Properties

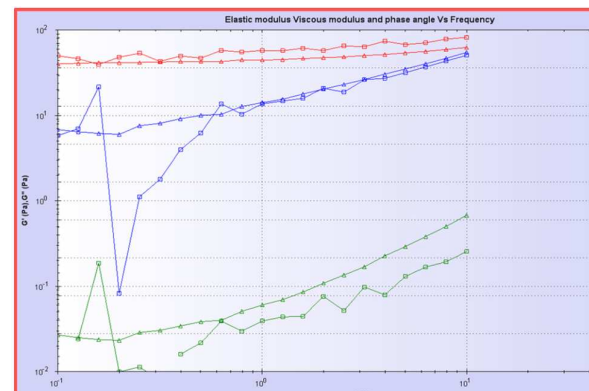
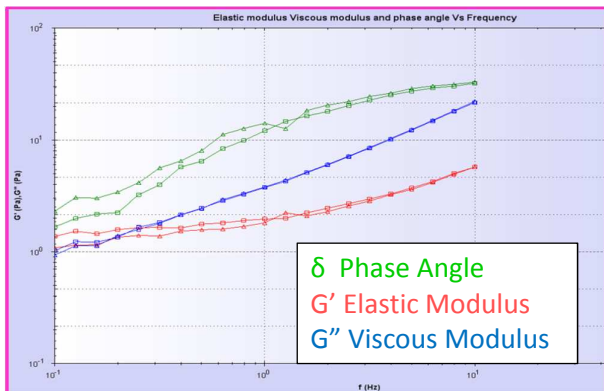
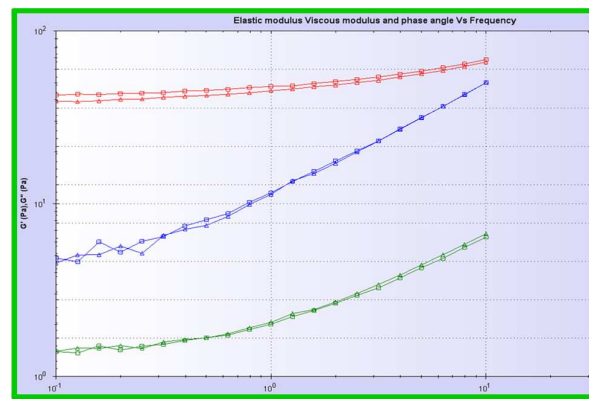
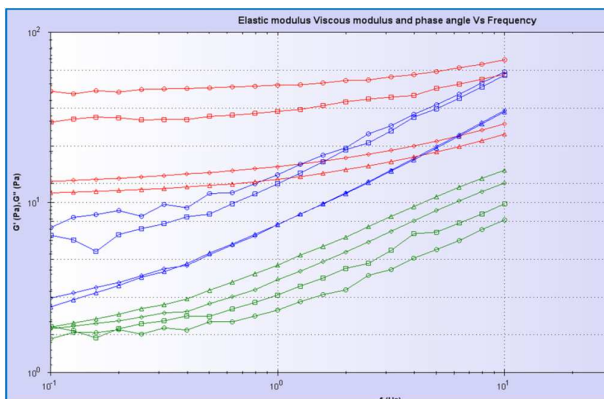
- NIR and PXRD identify chemical variations in one alternative source, which by EGA is shown to be an anhydrous form.



Sample	% Mass lost (30-145°C)
M Alternative	2.31
Current	0.83
P Alternative	0.77
F Alternative	0.60



# Viscosity of Lab Scale Formulations

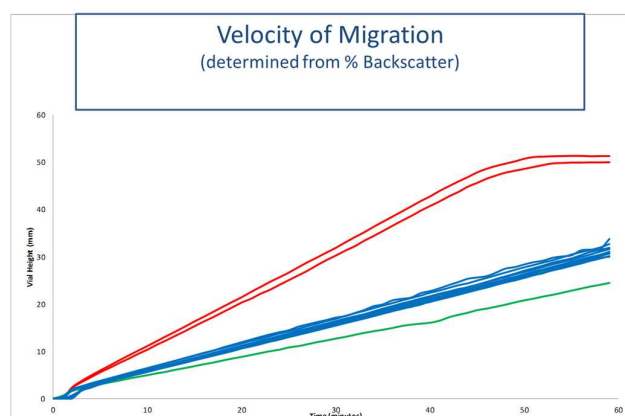
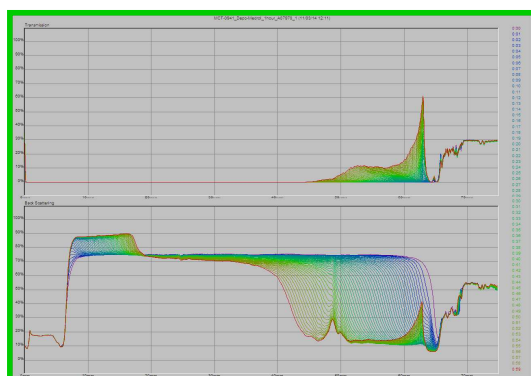
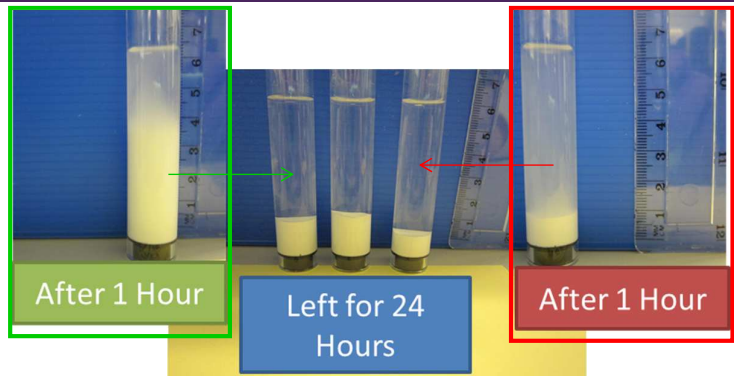
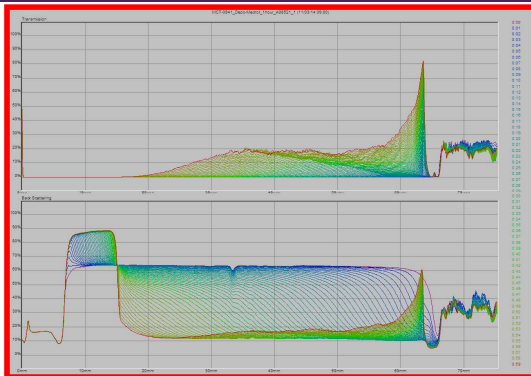


$\delta$  Phase Angle  
 $G'$  Elastic Modulus  
 $G''$  Viscous Modulus

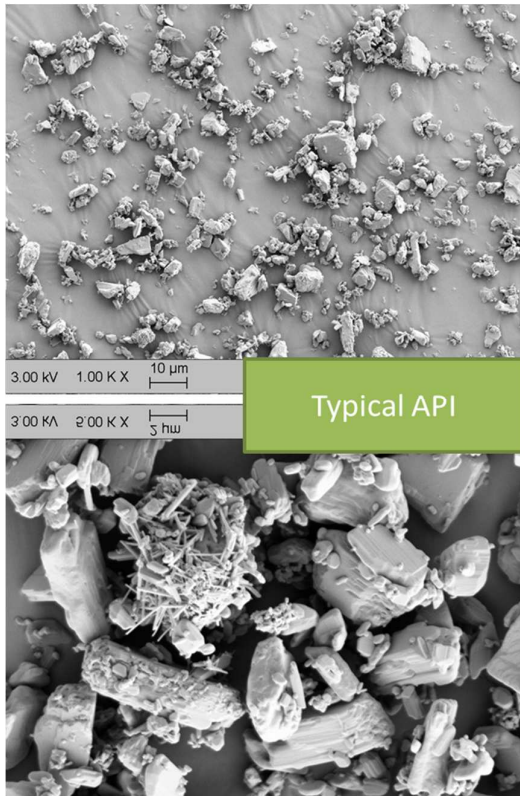
# Suspension Properties



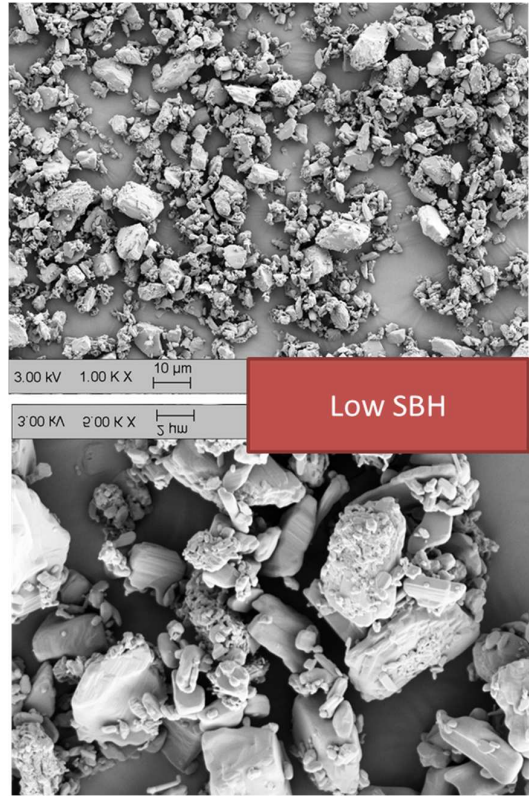
## Variation in Settled Bed Height



# API Morphology

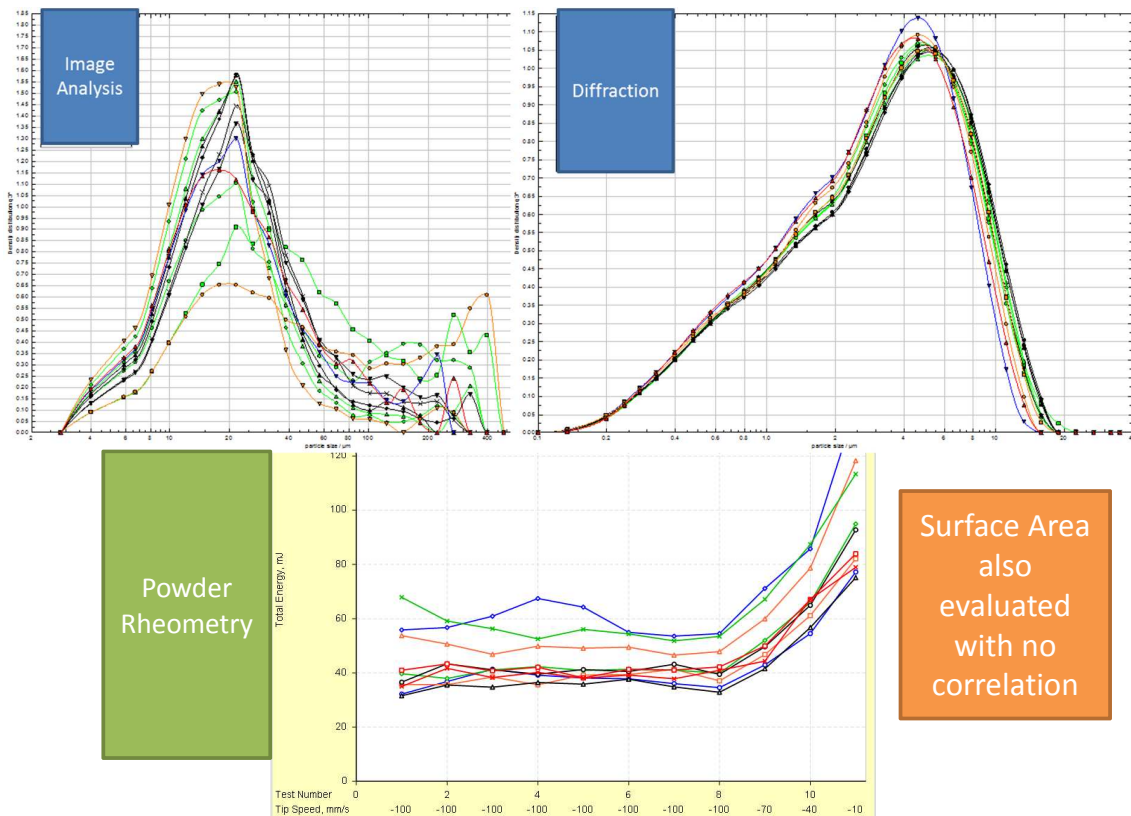


Typical API



Low SBH

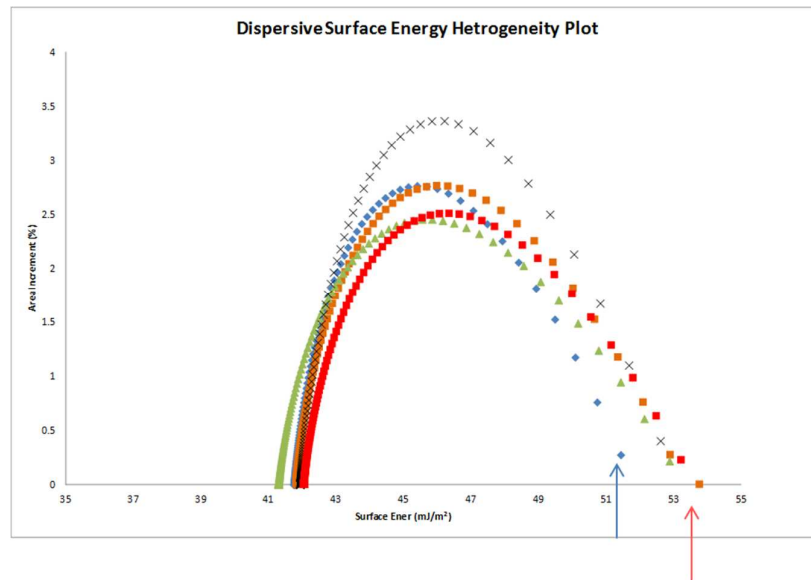
# Size and Flow Attributes





# Surface Properties Drive Sedimentation

- Issues lots have higher surface heterogeneity, which could be driving the stability of the suspension of the final drug product.



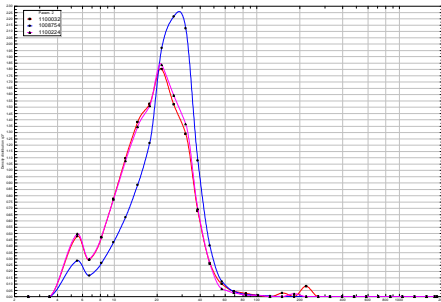
# Variable Dissolution

A physical attribute

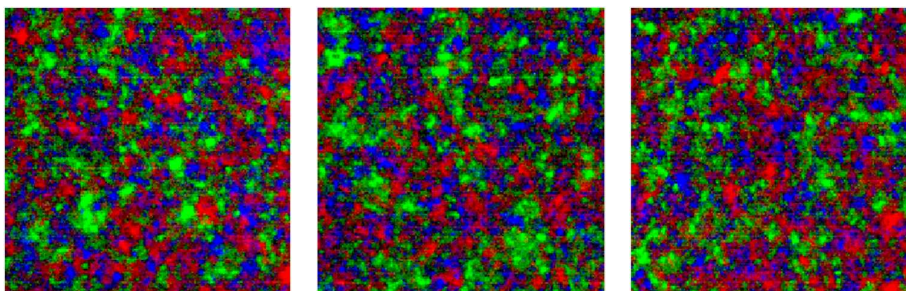


# Understand Root Cause of Dissolution Performance Variability using Imaging Methods

- Five capsule lots with variable dissolution performance



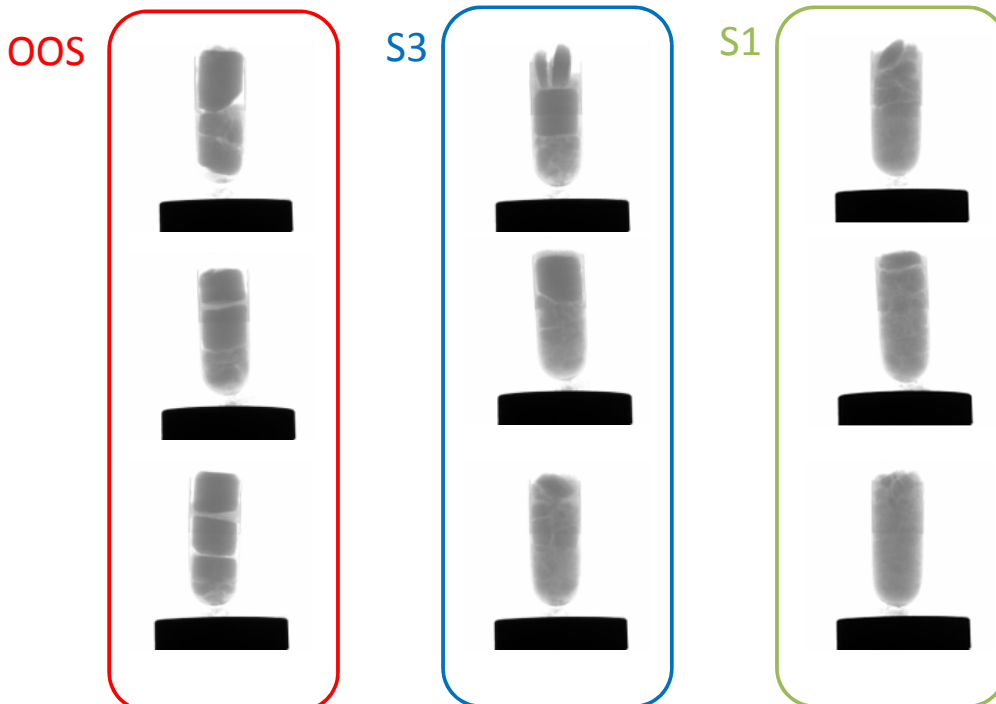
Only excipient with variation through characterisation testing was magnesium stearate



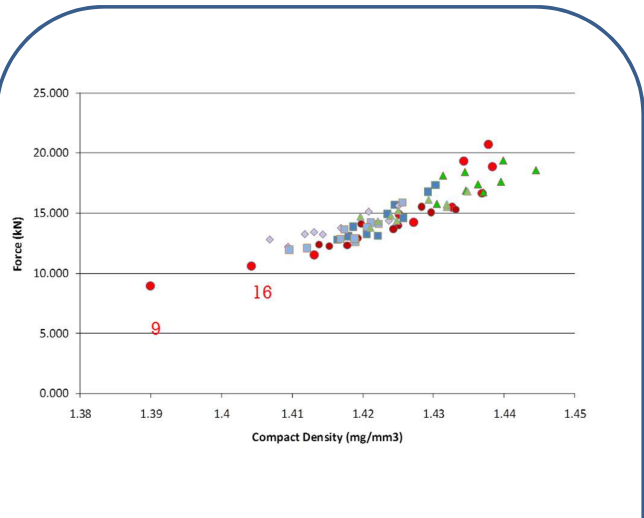
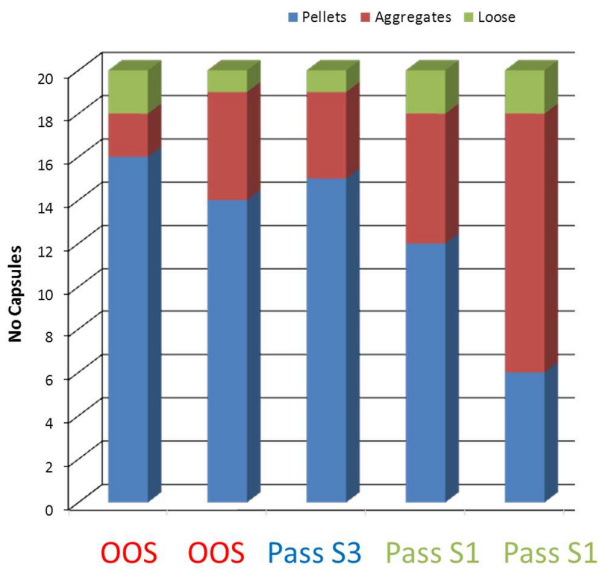
NIR Chemical Images Identify No significant Variation

# Looking at the Capsule Contents

- X-ray images reveal variation in powder packing



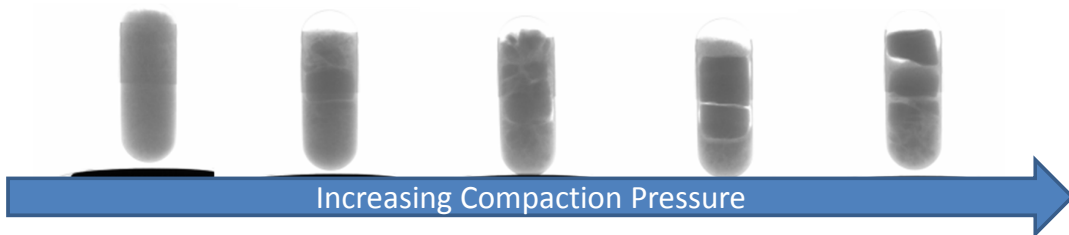
# Crude Classification of Powder State in Capsules (Compaction)



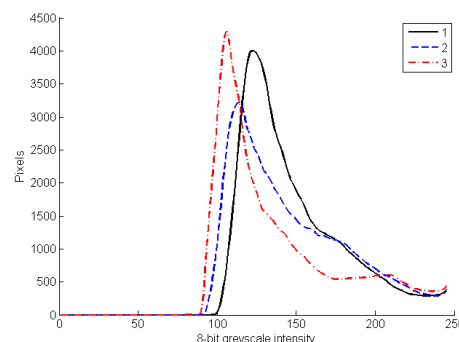
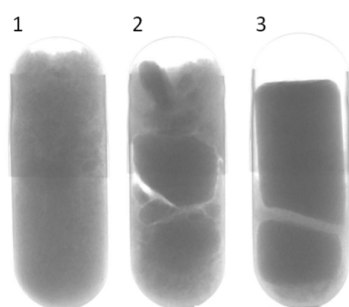
Using a compaction simulator, compaction behaviour of capsule contents were evaluated

# Understanding Dissolution Performance of Capsule Product

- To build understanding of prediction ability of X-ray images, a 'calibration set' was generated using different tamping pin settings.



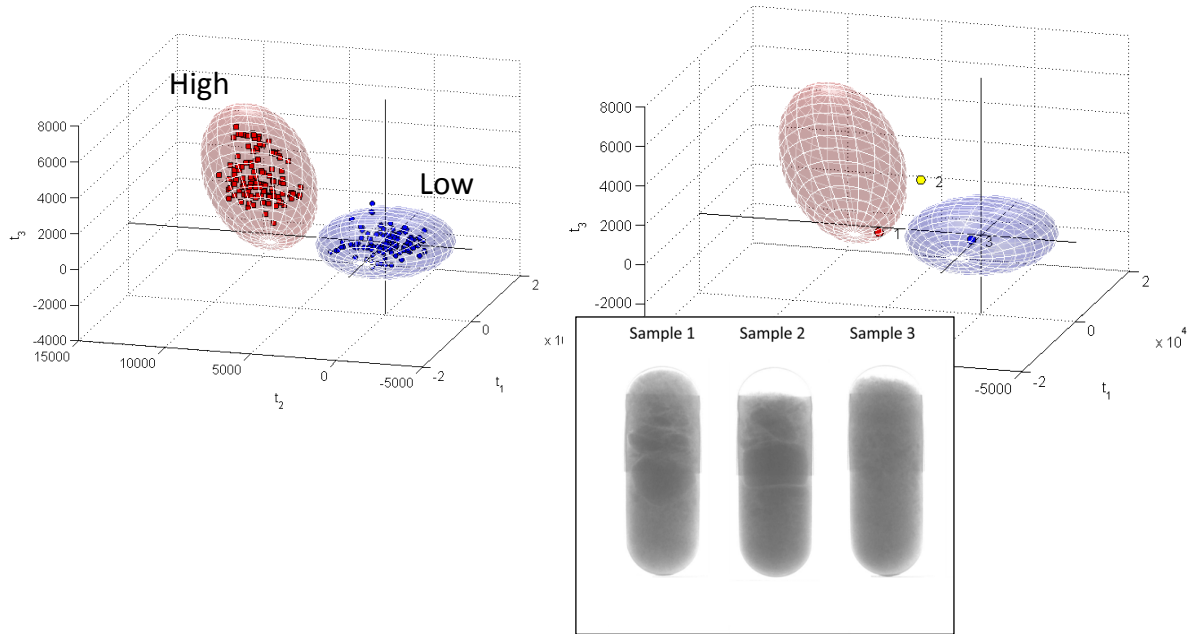
- Greyscale Histograms were generated from X-ray Images



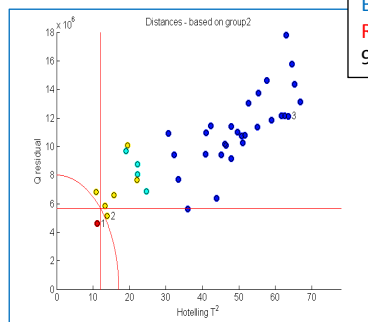
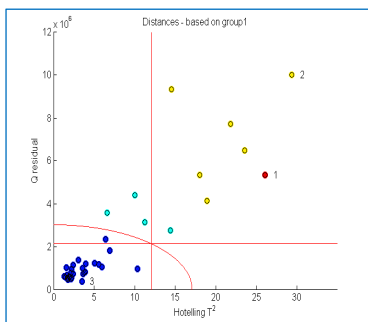


# Understanding Dissolution Performance of Capsule Product

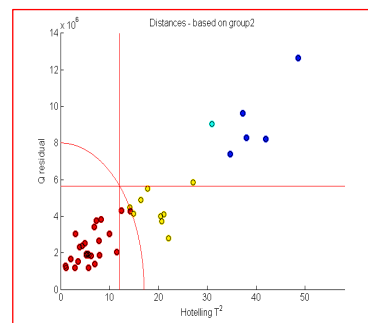
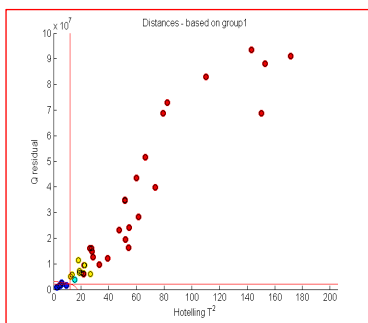
- A 2-class SIMCA model was created using low-pressure and high-pressure capsules.



# Chemometrics and Classification Success



Blue and Cyan = Acceptable  
 Red and Yellow = Unacceptable  
 99% Confidence Limit Shown in Red



Low Pressure Plot

High Pressure Plot

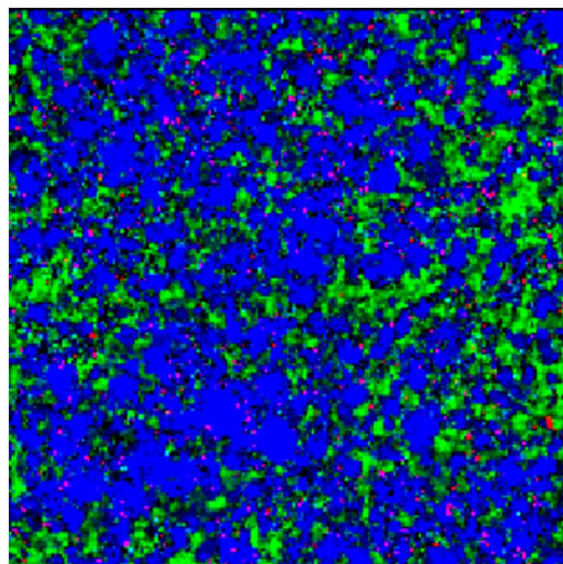
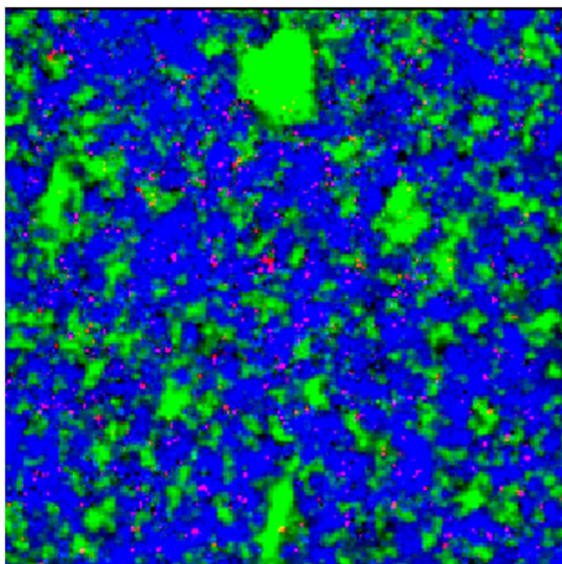
- 6 Rotational Angles used to represent a capsule.
- Classification Success rates of 97.5% and 95% for unagglomerated and agglomerated validation sets.
- X-ray images coupled with greyscale histograms and chemometrics can be used to classify the performance of this product.

# Solid State Characterisation for Understanding Impurity Levels

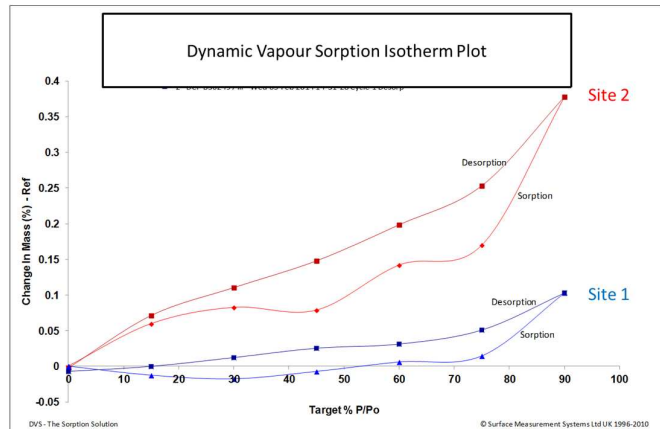
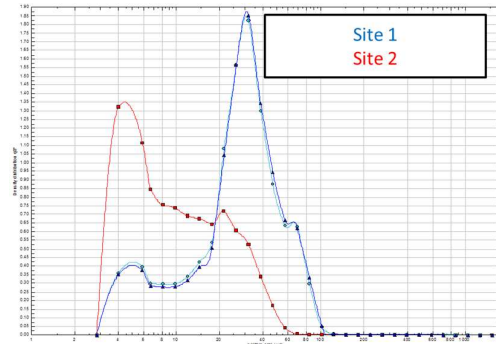
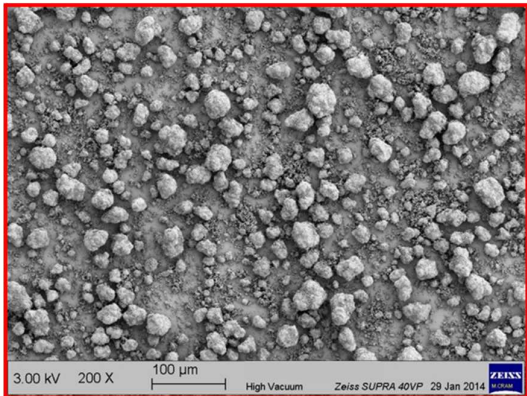
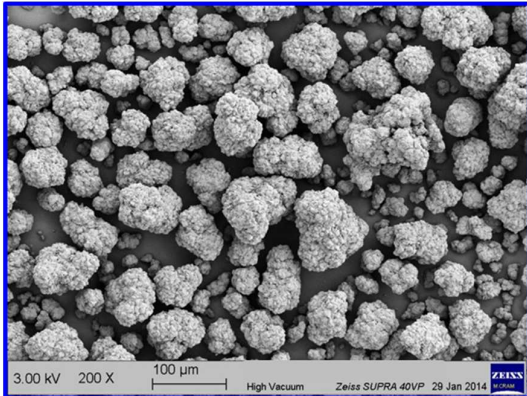


Question: Why are levels of 1 imp higher at one DP site?

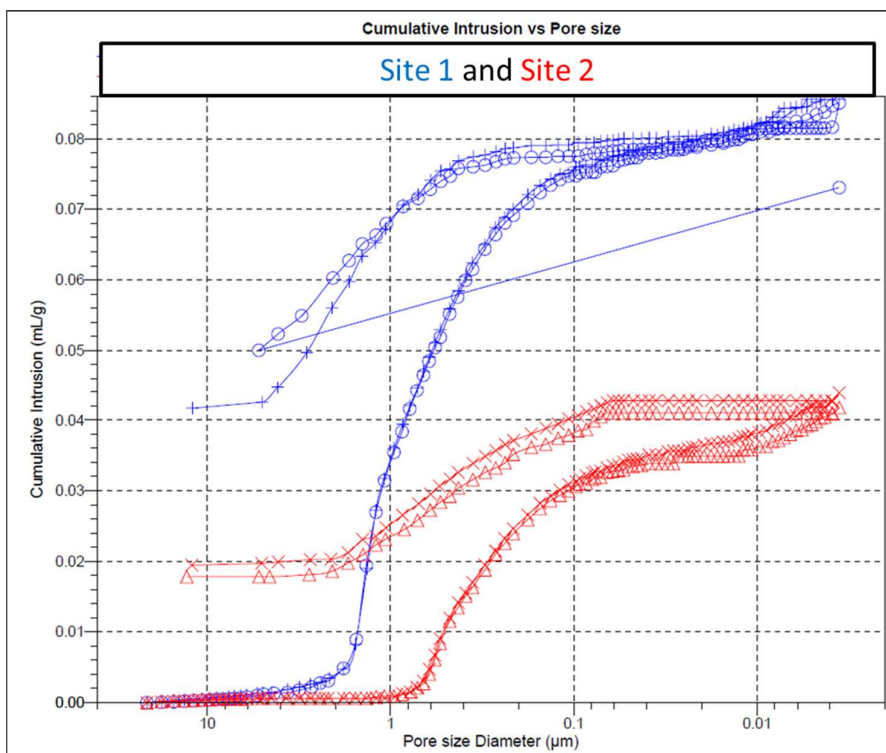
- Both sites use same API source
- Chemical Images reveal difference in one excipient.



# Comparison of Excipient Properties



# How does this impact Tablet Stability Performance?

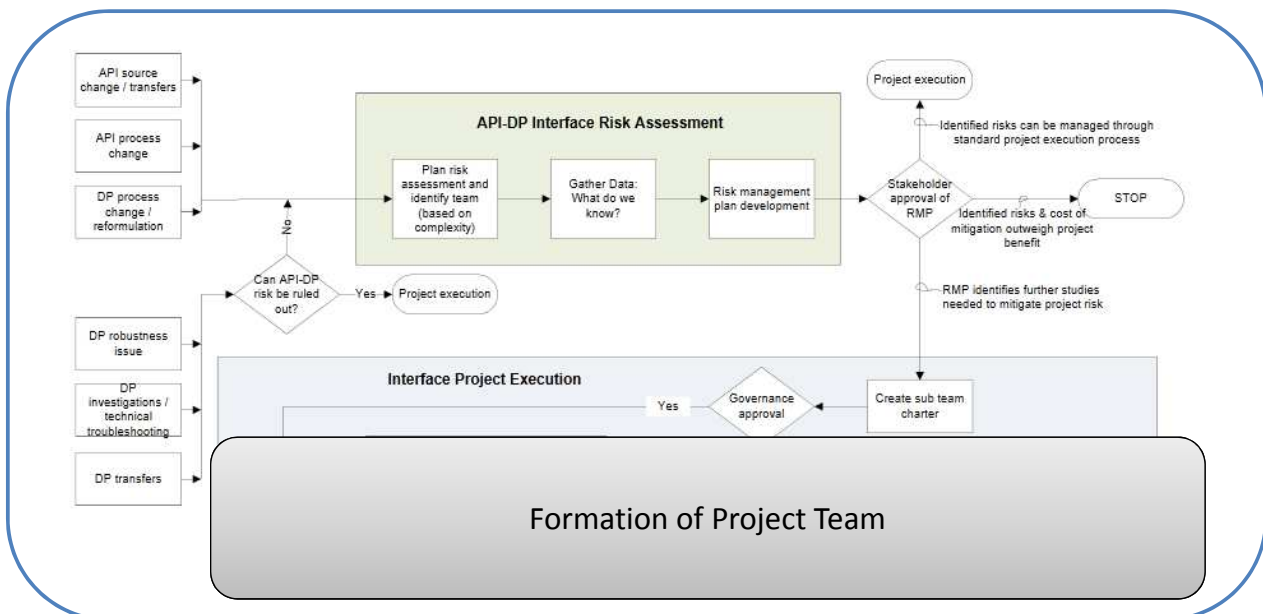




# Implemented Learnings



## Building Learnings into Workflow for API-DP



# Leveraging API-DP Interface

- By building understanding of material characteristics (be that API, excipients or drug product) understanding of product attributes are increased.
- Leveraging this knowledge in combination with that of API and Drug Product enables more robust drug products.
- It also enables low risk transfers and sourcing decisions.

