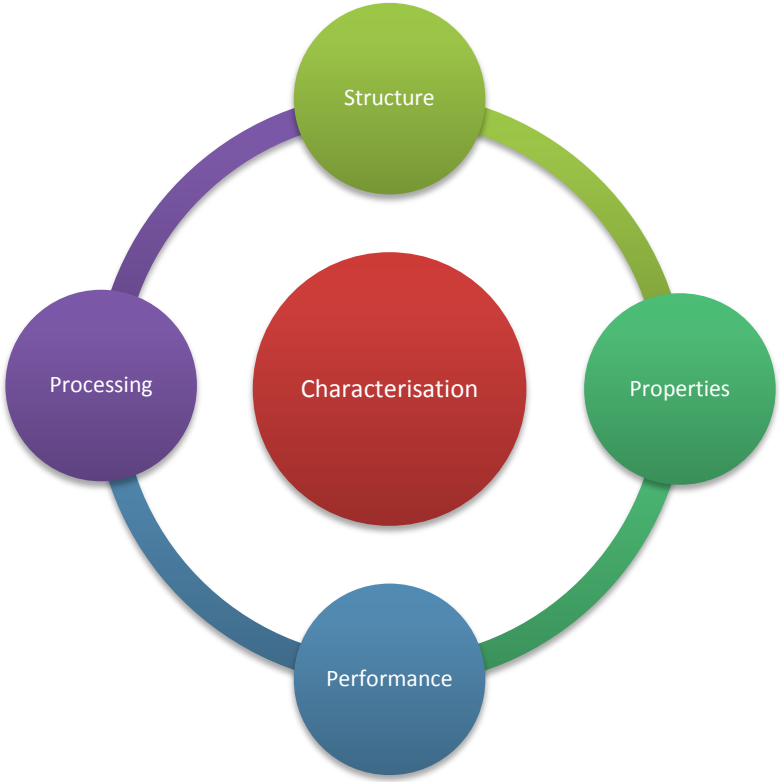
# Materials Sciences

- The basis of materials science involves studying the **structure** of materials, and relating them to their **properties**.



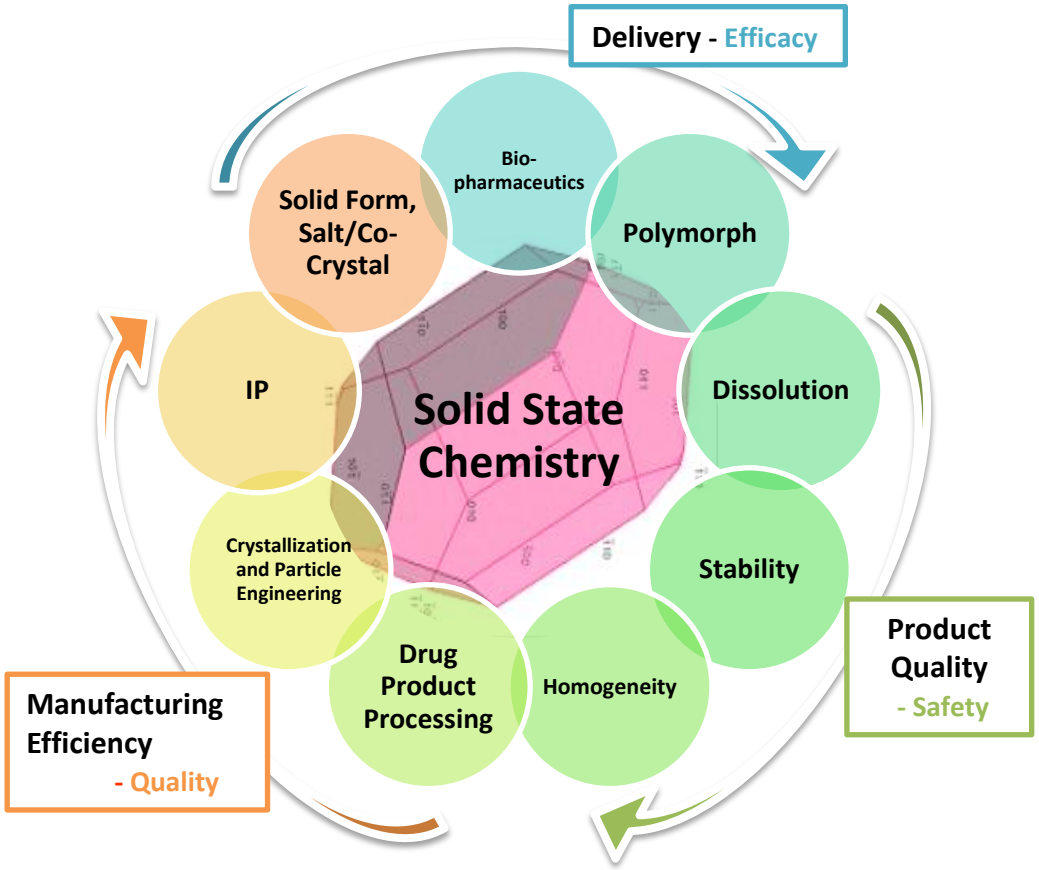

- If the structure-property correlation is known then the relative performance of a material in a certain application can be evaluated.

# Pharmaceutical Materials Sciences

Pfizer GLOBAL SUPPLY

- In the context of pharmaceuticals, materials science is applied to challenges such as drug delivery, control of drug form, **manufacture** and **processing** of particle systems, and the **structure** and **properties** of bulk powders and their assemblies (e.g.tablets) for use in pharmaceutical applications.

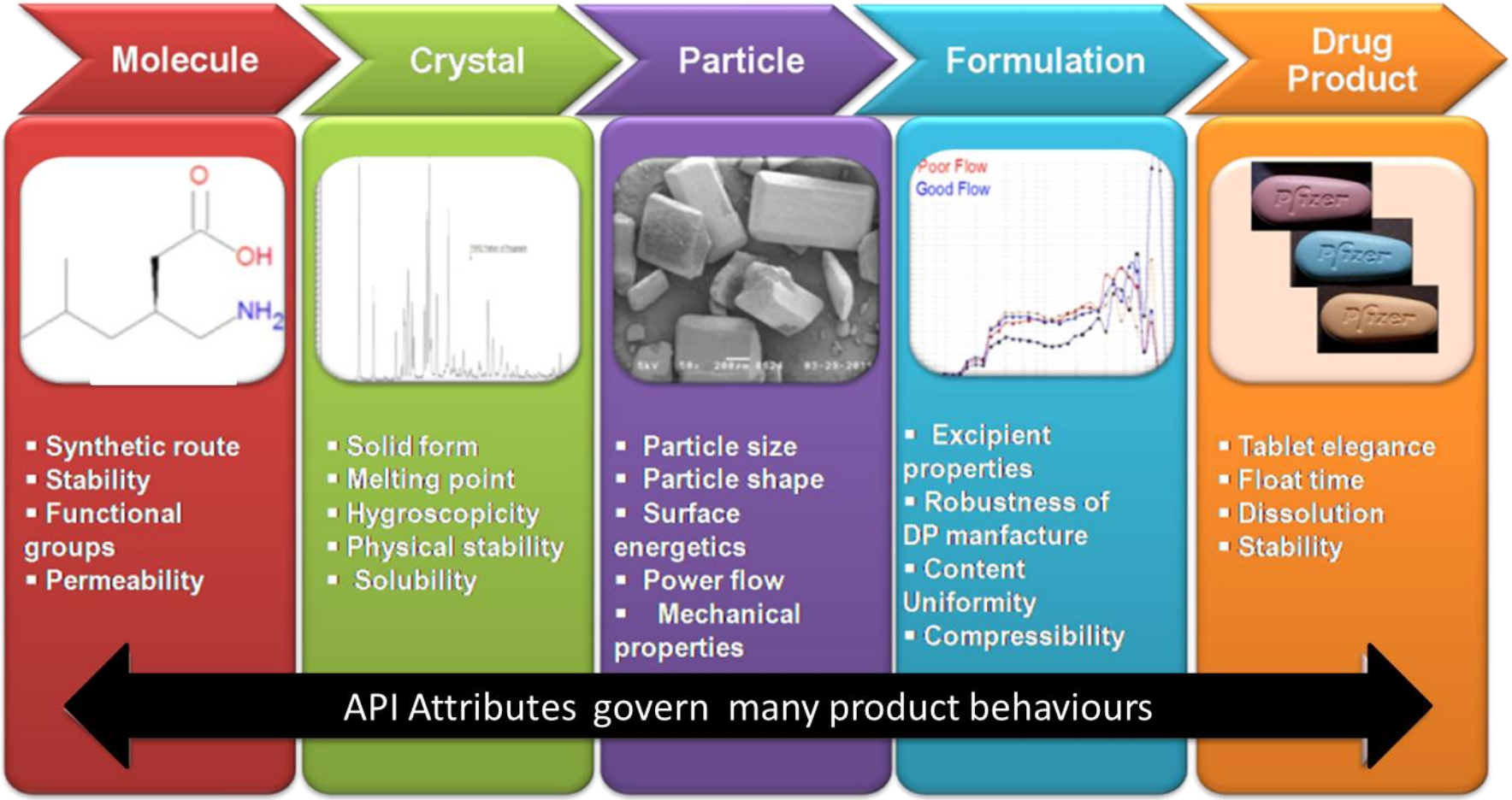

*Pharmaceutical Materials Science: An Active New Frontier in Materials Research (MRS Bulletin / Volume 31 / Issue 11 / Nov2006, pp 869-873)*



# Materials Science through Product Development

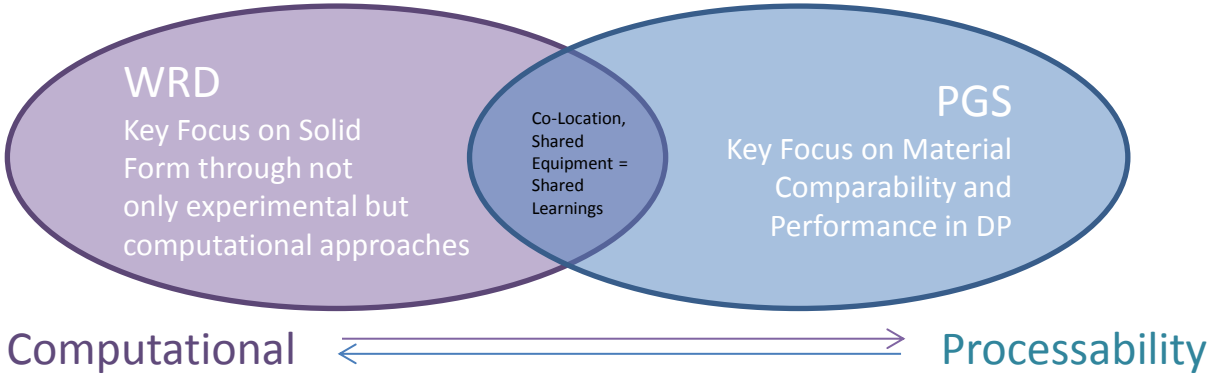
Pfizer GLOBAL SUPPLY

- Understanding API attributes are critical to product performance

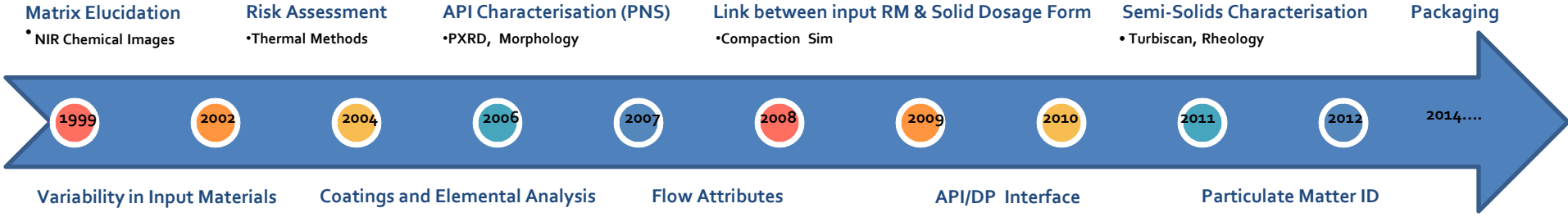


# Materials Science at Pfizer

- Strong, closely aligned groups in both R&D and Supply Organisations




- PGS Growth and Focus Areas:



# Equipment

Pfizer GLOBAL SUPPLY

## Chemical Imaging / Spectroscopy

- Near-infrared, Infrared, Raman and X-Ray Fluorescence Microscopes
- Terahertz Imaging
- Tablet Press
- Microtome and Rapid Trim
- X-Ray µTomography
- Near-infrared, Raman and infrared spectroscopy

## Physical Characterisation/ Surface Properties

- Malvern and Sympatec Laser Diffraction
- Light Microscopes
- QicPic
- G3
- Specific Surface Area
- Kruss Tensiometer
- Surface Energy Analyser (IGC)
- Multi-Station Dynamic Vapor Sorption

## Physico-Chemical / Crystallisation

- Powder X-Ray Diffraction
- Crystal 16
- Thermal Gravimetric Analysis coupled with Mass Spectrometer
- Hyper and Heat Flux Differential Scanning Calorimetry
- Simultaneous Analyser coupled with infrared spectroscopy
- Dynamic Mechanical Analyser

## Particulate Matter

- Light Microscope
- Inverted light microscope
- Infrared Microscope
- Scanning electron microscopy coupled with energy dispersive X-rays

## Material Assessment

- Kinexus Rheometer
- Powder Rheometer
- Ring Shear Tester
- Helium Pycnometer
- Air Jet Sieve
- Compaction Simulator
- Texture Analyser

## Non-Solids

- Ultrasonics Spectroscopy
- Brightwell Image Analyser
- TurbiScan
- ZetaSizer
- Rheolaser

## Chemical Comparability

- Complete Orthagonal Method Evaluation (Liquid Chromatography)
- Inductively Coupled Plasma-Optical Emission Spectroscopy
- Nuclear Magnetic Resonance
- Structural Elucidation (through ARD)

## Regularly Outsourced

- Residual Solvents (GC)
- Solid State NMR
- Gel Permation Chromatography
- Time of Flight –Secondary Ion Mass Spectrometry/X-Ray Photon Spectroscopy

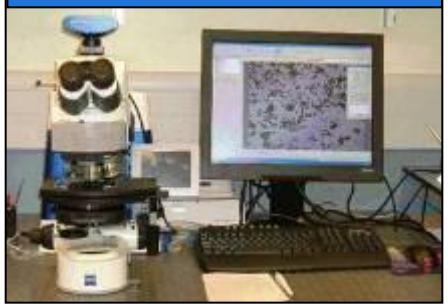
**Note: Equipment can be used in different work area, but one shown is where there has been greatest application**

# Particle Size and Shape Characterisation

Pfizer GLOBAL SUPPLY

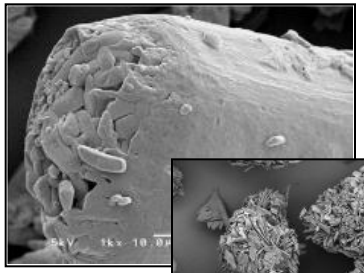
**SCANNING ELECTRON MICROSCOPY**

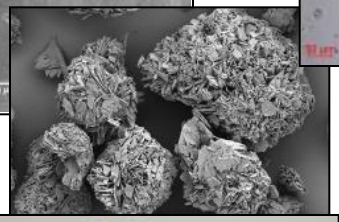
**LIGHT MICROSCOPY**

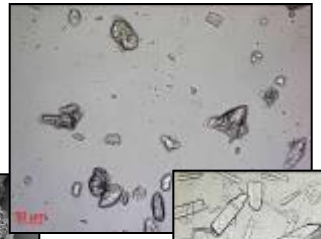


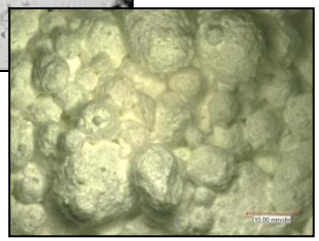
**DIGITAL MICROSCOPY**

**NIR SPECTROSCOPY**

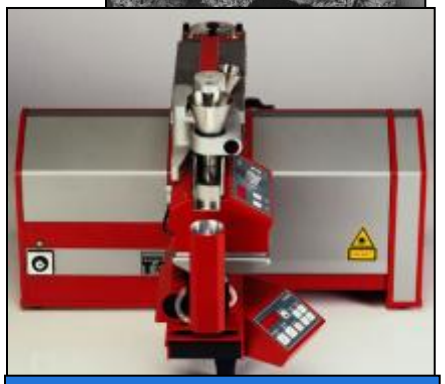








**DYNAMIC VISION PS (Liquids)**



**LASER DIFFRACTION**

**STATIC VISION PS**

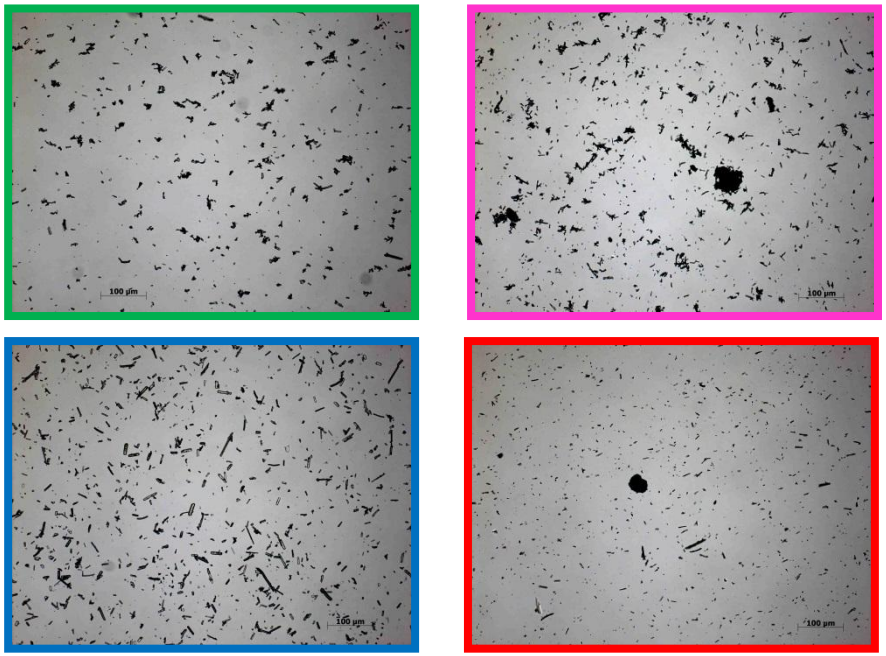
**DYNAMIC VISION PS**

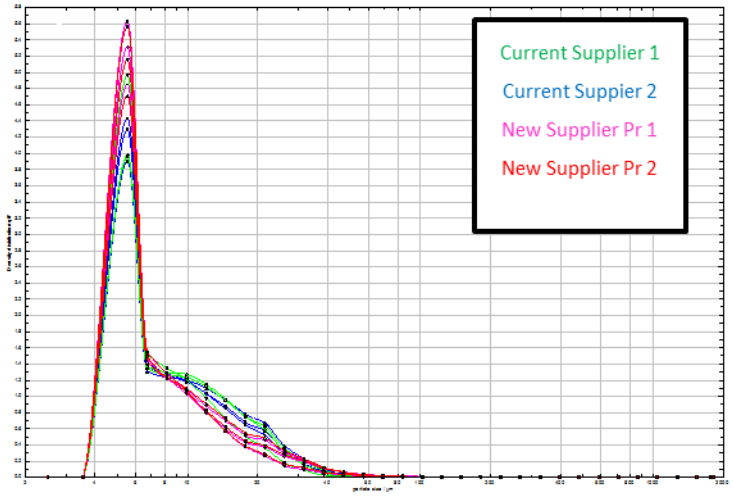
# Case Studies

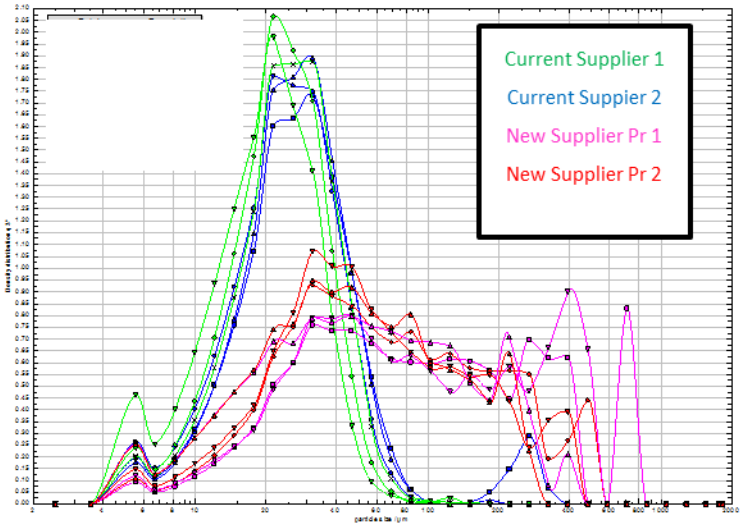
- Looking for Alternative API Supplier for Low Dose Tablet Formulation
- Reactive Look at Site Change after API Fails to Meet KF Spec upon Stability
- Evaluation of Alternative API Supplier from Drug Product Formulation with known sticking issues during tablet compression
- Building Understanding of Criticality of Particle Shape

# API Comparability Using Particle Attributes

Looking for Alternative API Supplier for Low Dose Tablet Formulation

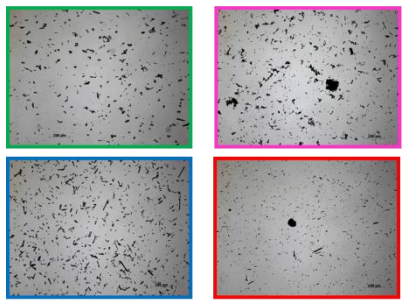


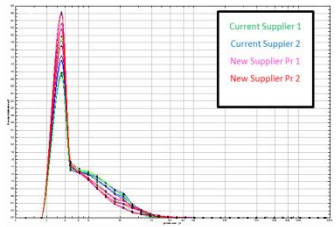


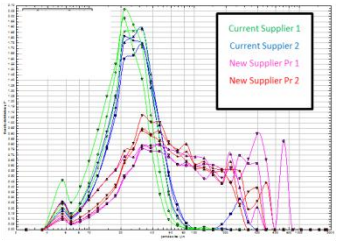



# API Comparability Using Particle Attributes

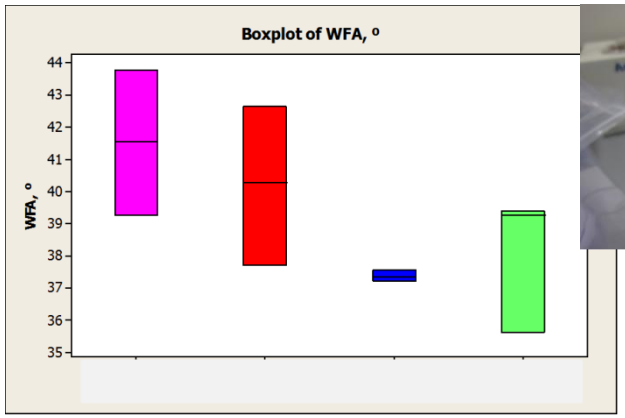
Looking for Alternative API Supplier for Low Dose Tablet Formulation

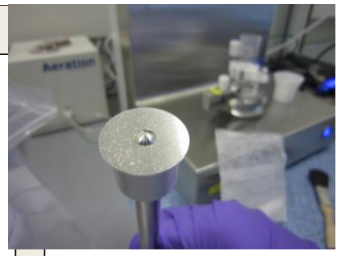


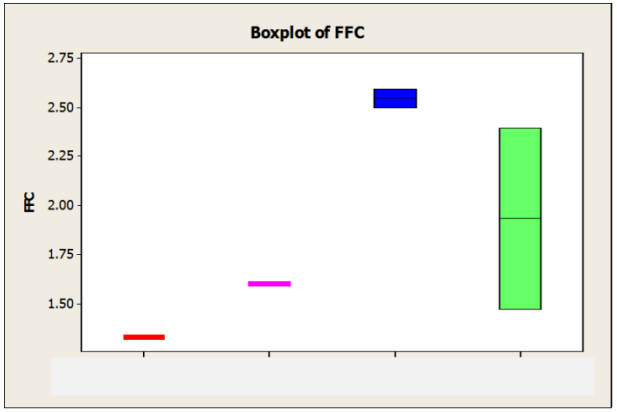


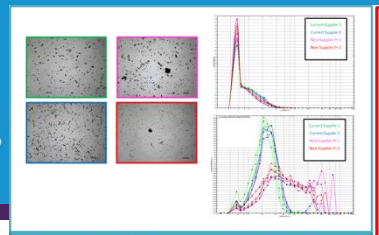

Secondary Agglomerates in New Source pose potential risk to DP



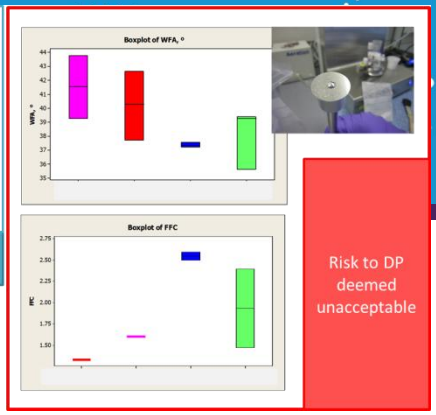





# Alternative API Supplier for Low Dose Tablet

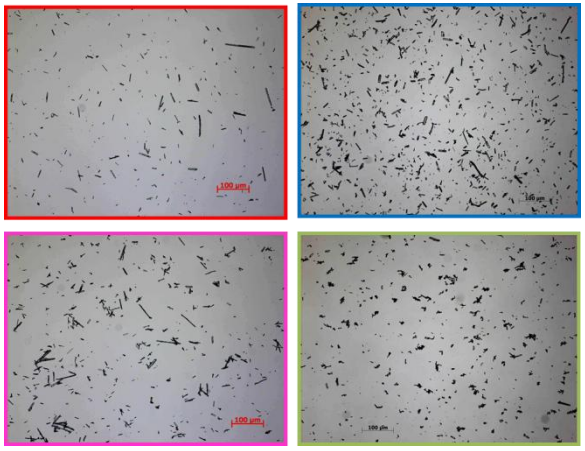


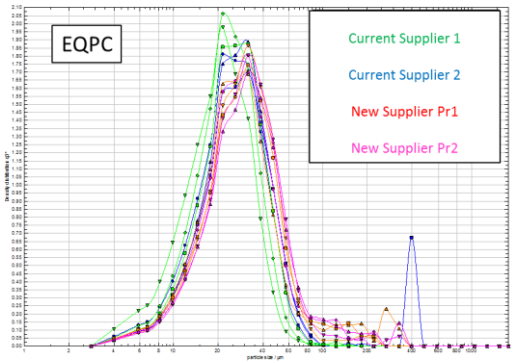
Secondary Agglomerates in New Source pose potential risk to DP

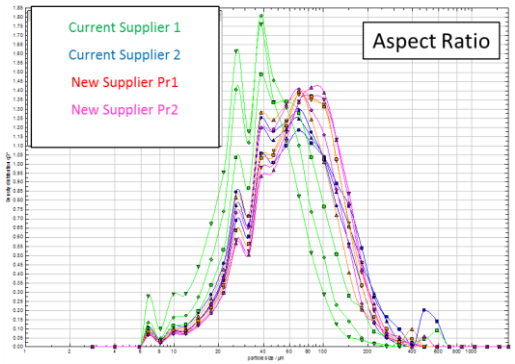


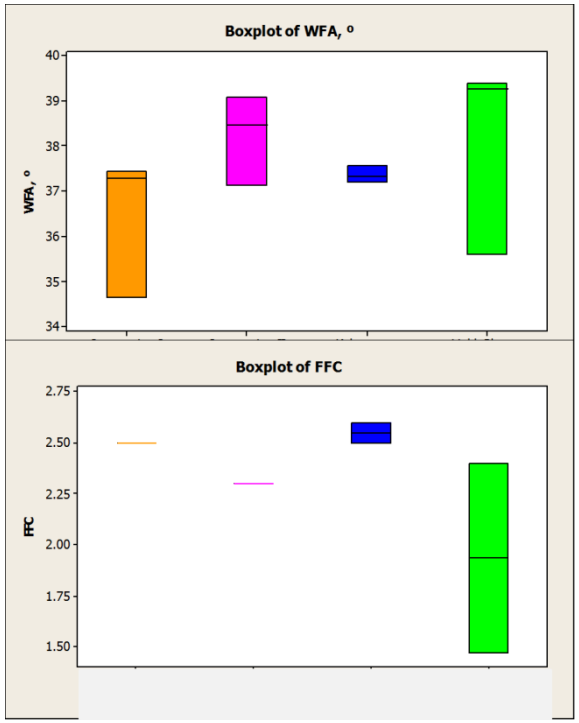

Risk to DP deemed unacceptable

Through process modification API attributes are optimised





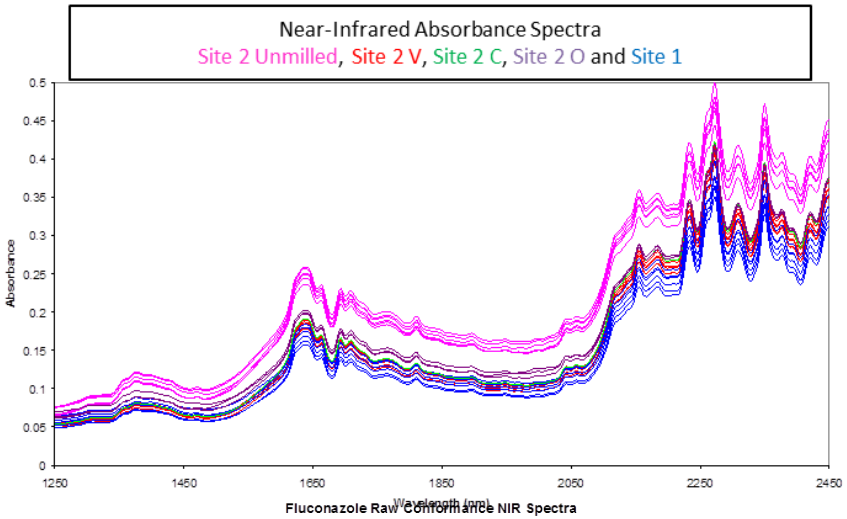



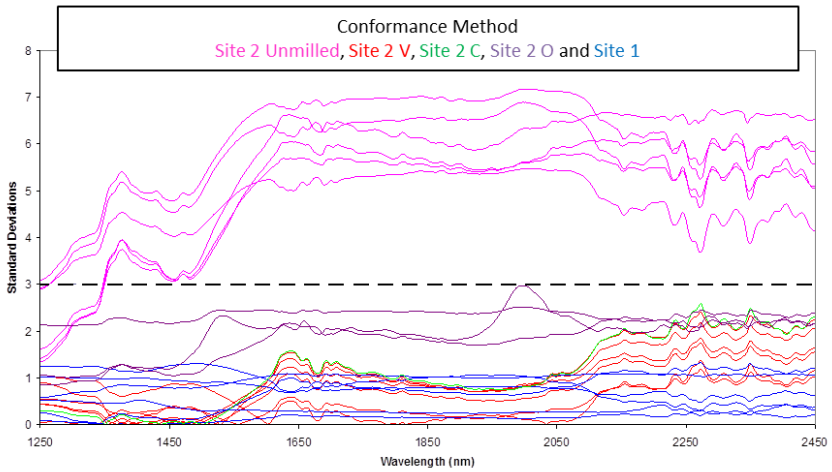

Through full characterisation of physical attributes beyond primary particles the risk of any impact of API supplier change was mitigated.

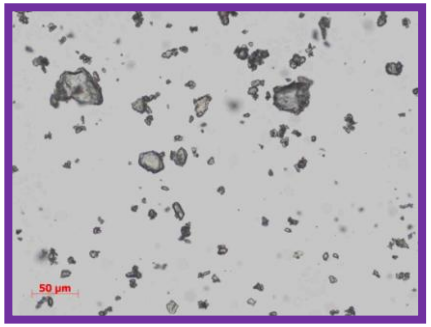
# Understanding API Physical Stability

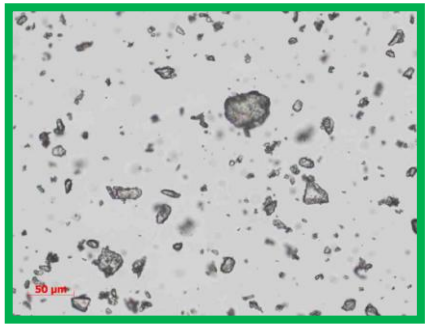
Pfizer GLOBAL SUPPLY

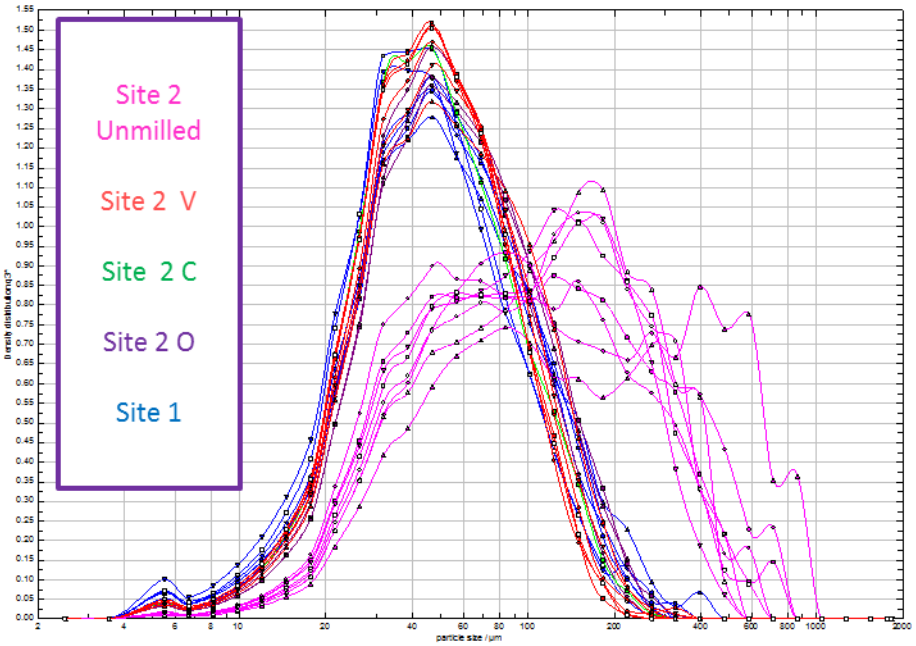
## Reactive Look at Site Change after API Fails to Meet KF Spec upon Stability



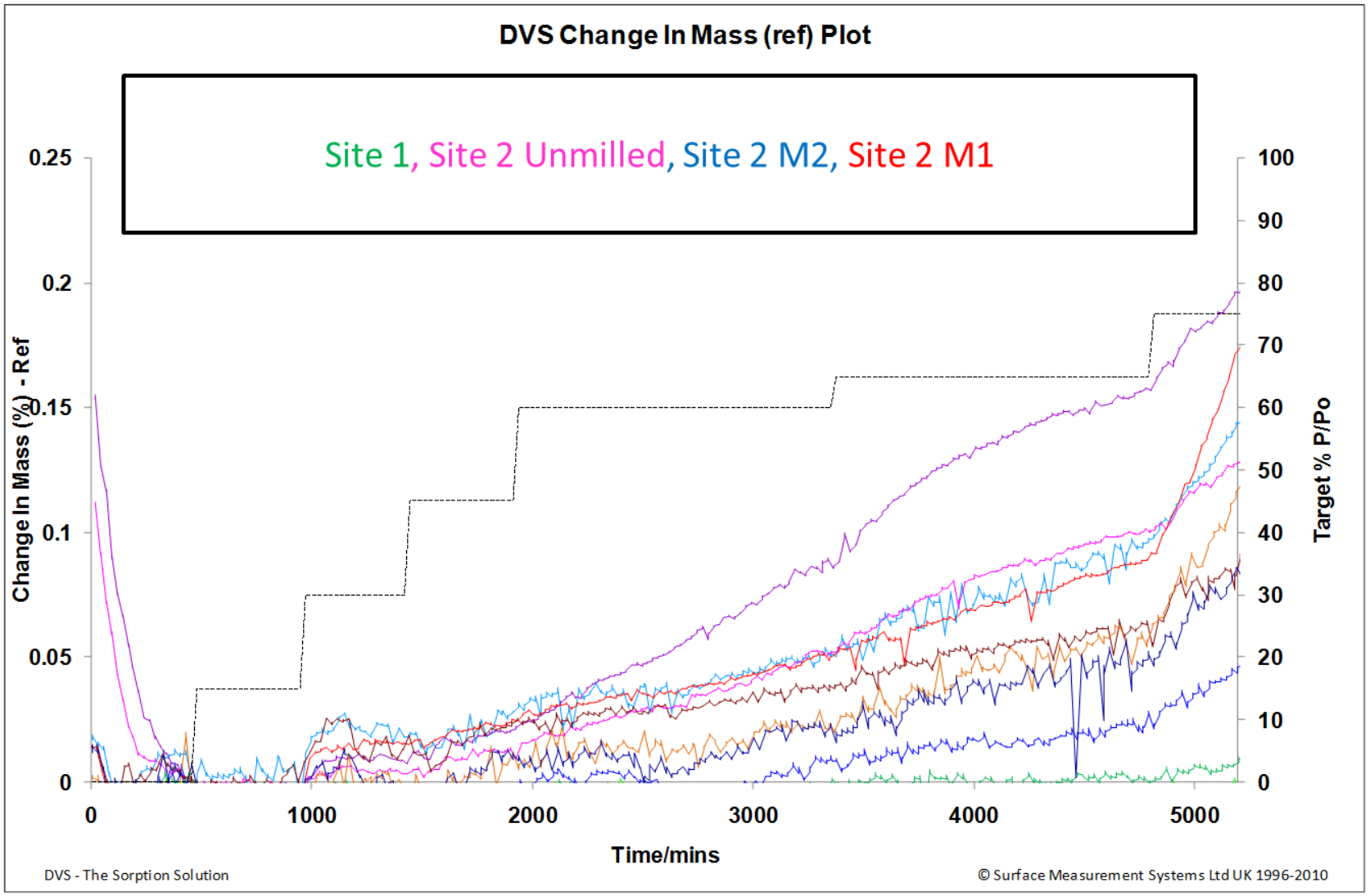



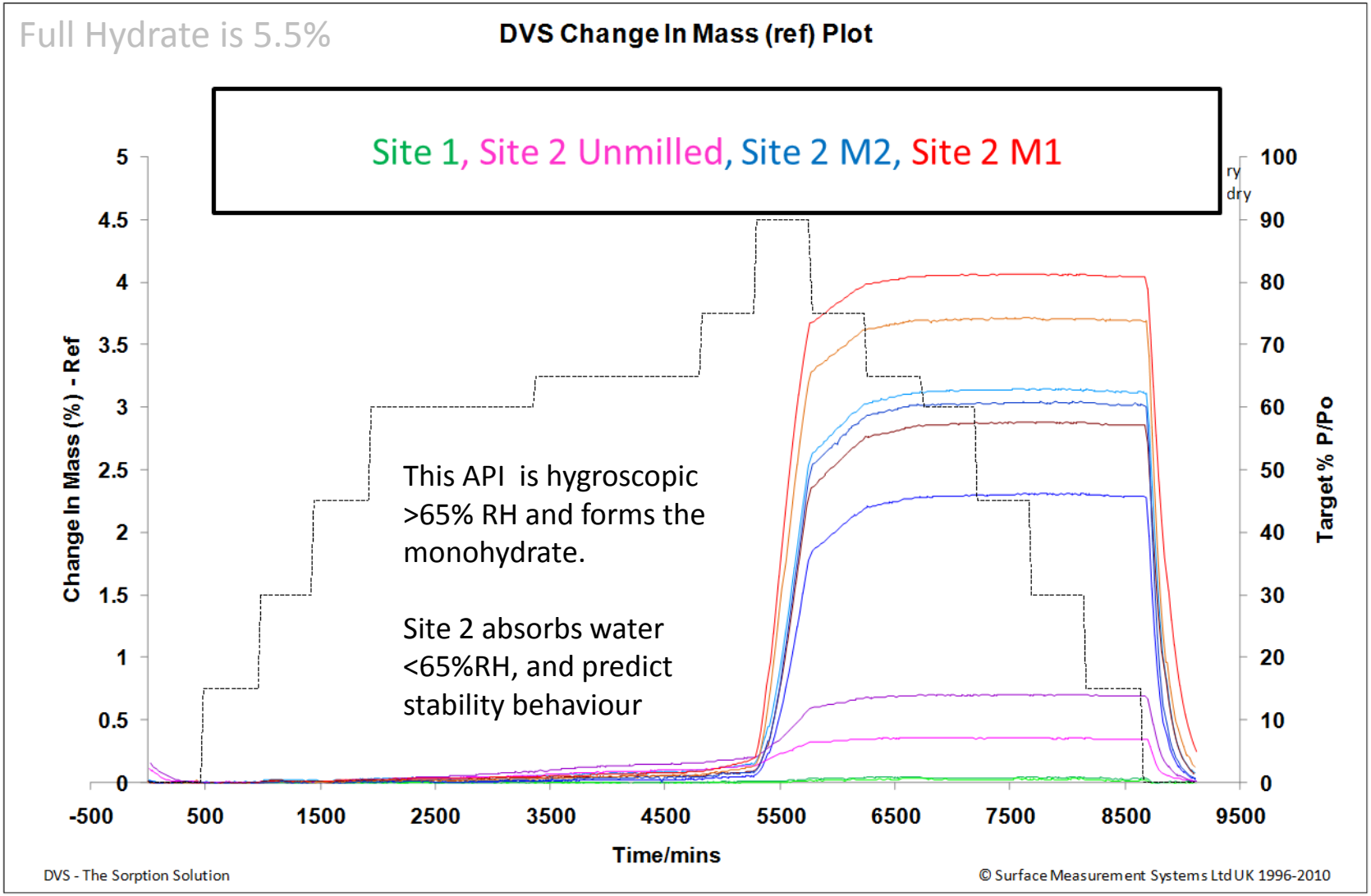



# Dynamic Vapour Sorption (Up to 75% RH)

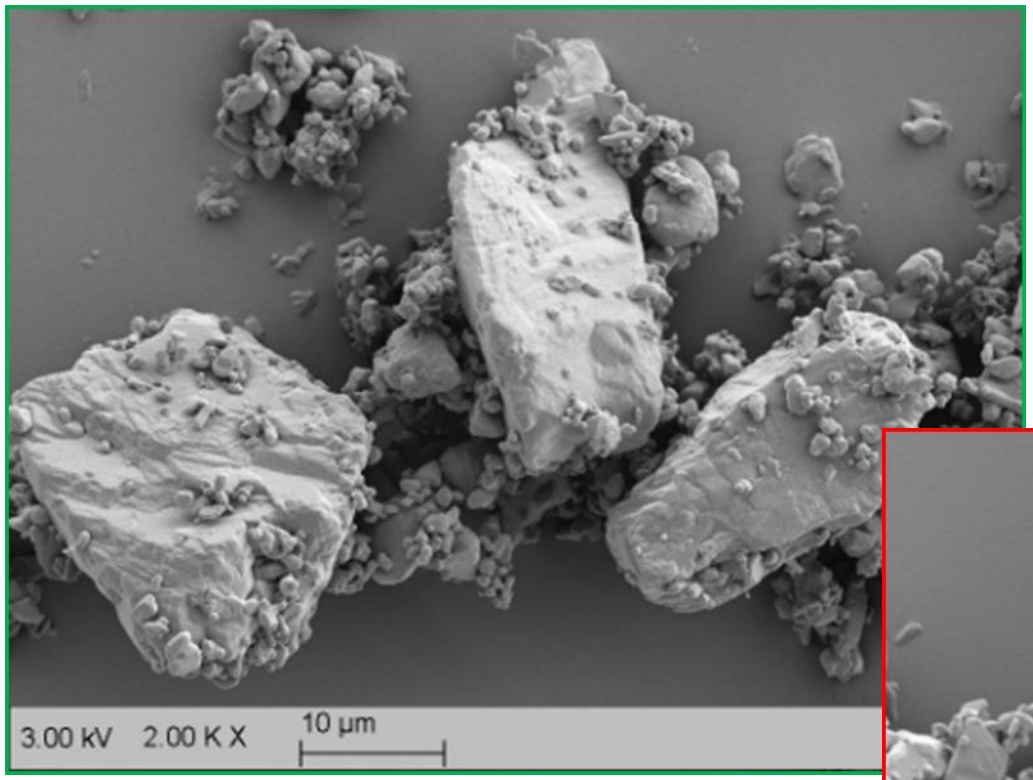


# Dynamic Vapour Sorption

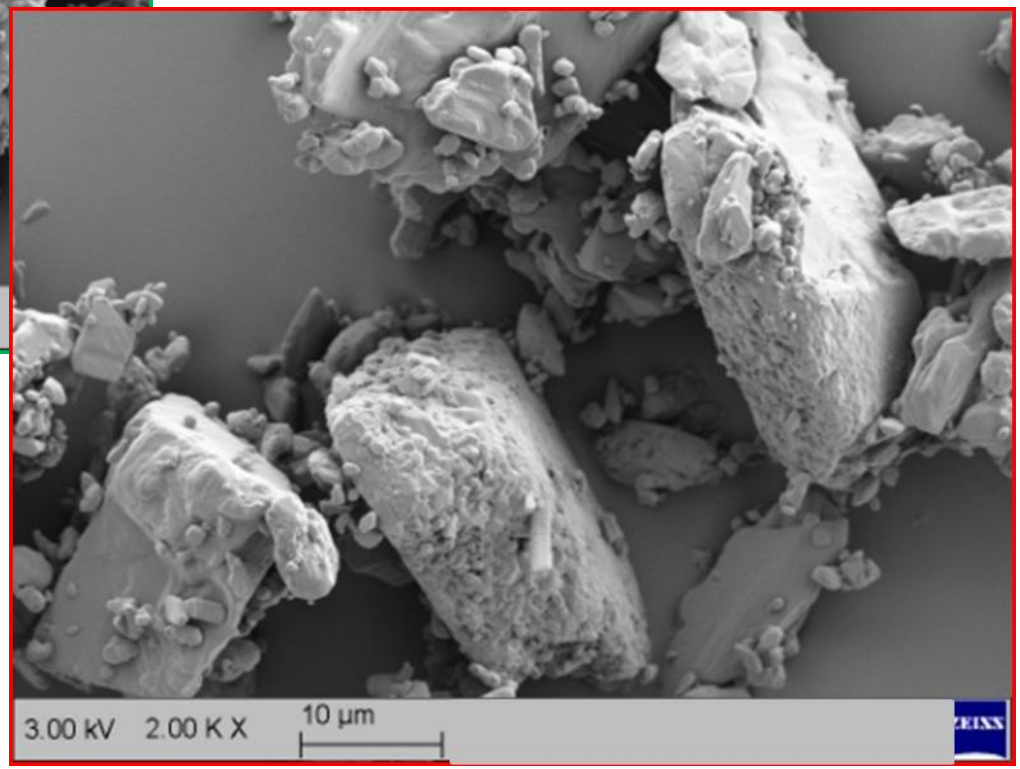
Full Hydrate is 5.5%



# Further Morphology Evaluation



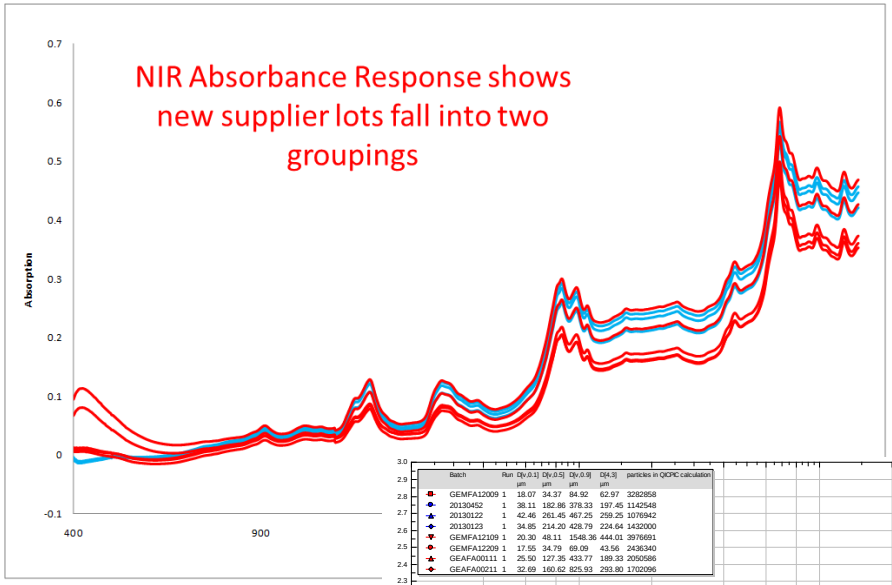

- Porous Structure of Material from Site 2 explains Moisture Uptake Differences.
- Crystallisation and Drying Focus for investigation

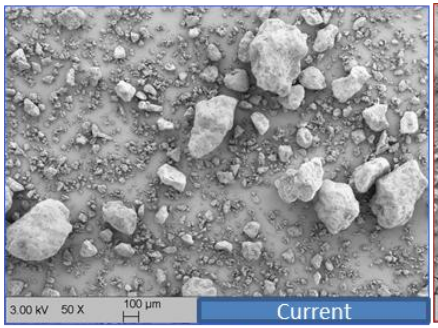


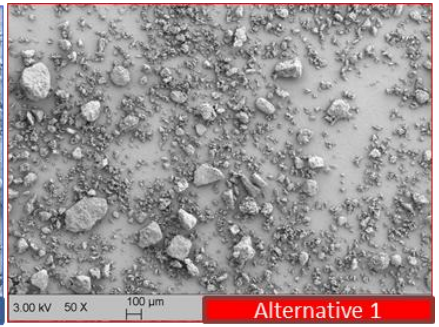
# Physical Attributes Assessment for Alternate API Supplier

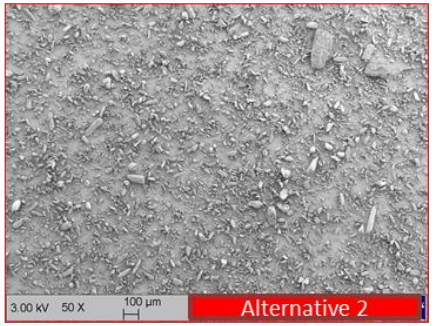
Pfizer GLOBAL SUPPLY

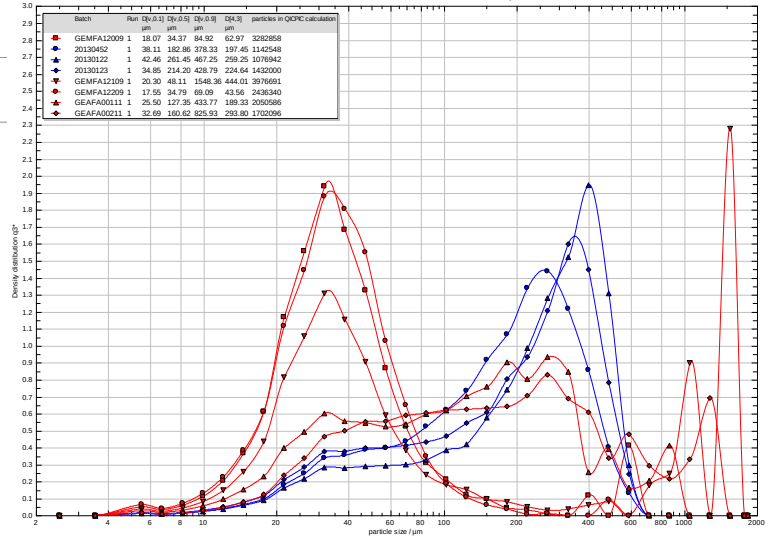
Evaluation of Alternative API Supplier from Drug Product Formulation with known sticking issues during tablet compression



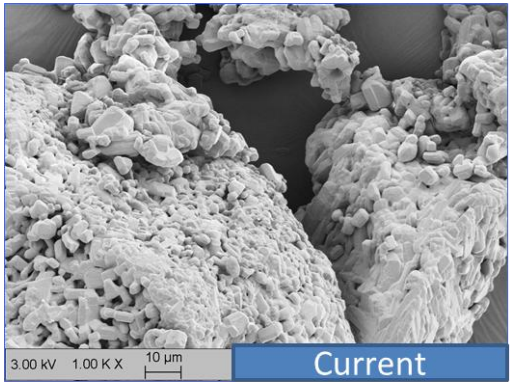



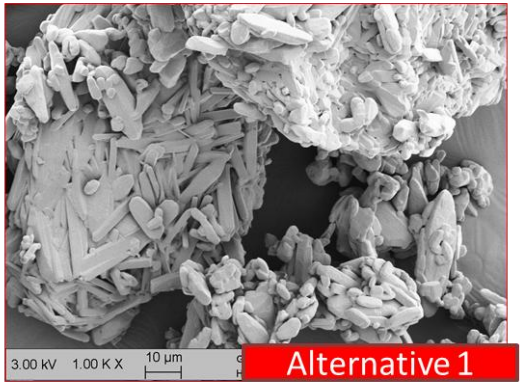



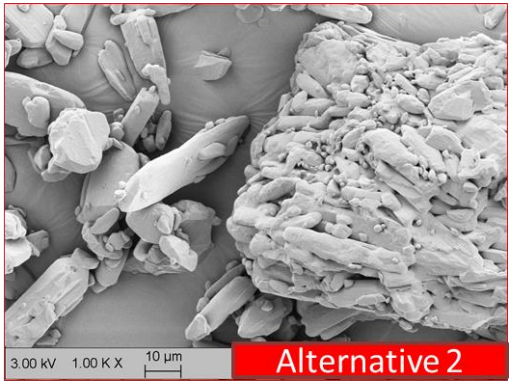
# Looking beyond only particle morphology

Pfizer GLOBAL SUPPLY

Evaluation of Alternative API Supplier from Drug Product Formulation with known sticking issues during tablet compression



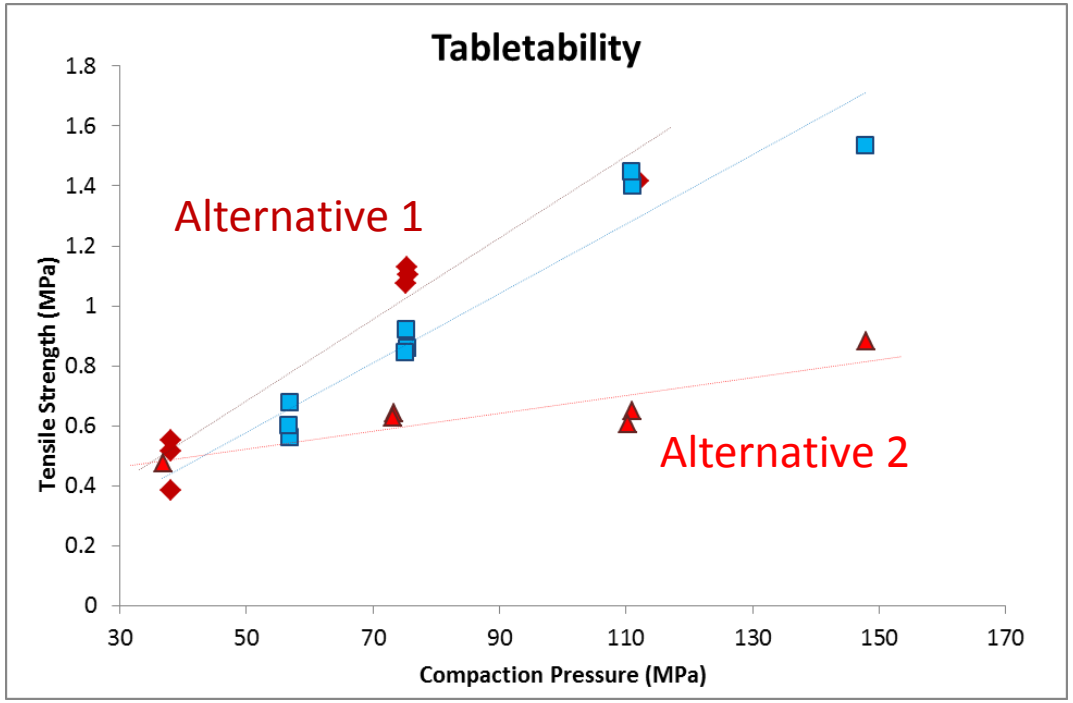



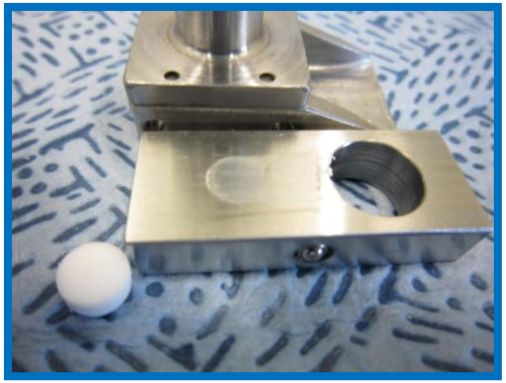

- Further interrogation of SEM's show that the agglomerates in the current material are made up of much smaller particles. Alternative supplier particles are more lath shaped. Infers porosity differences and something which may impact density of agglomerates.

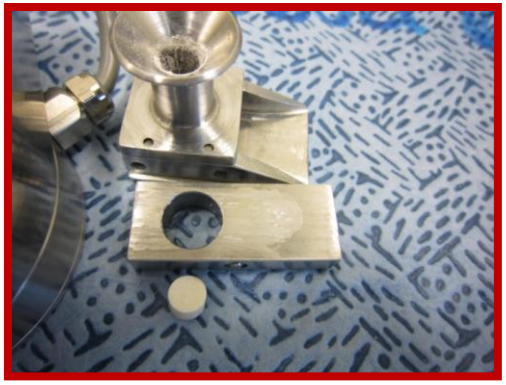
# Tabletting Performance

- Compression of Alternative 1 is most similar to Current Supplier.

- However Alternative 1 shows higher sticking
  - Linked to particle shape

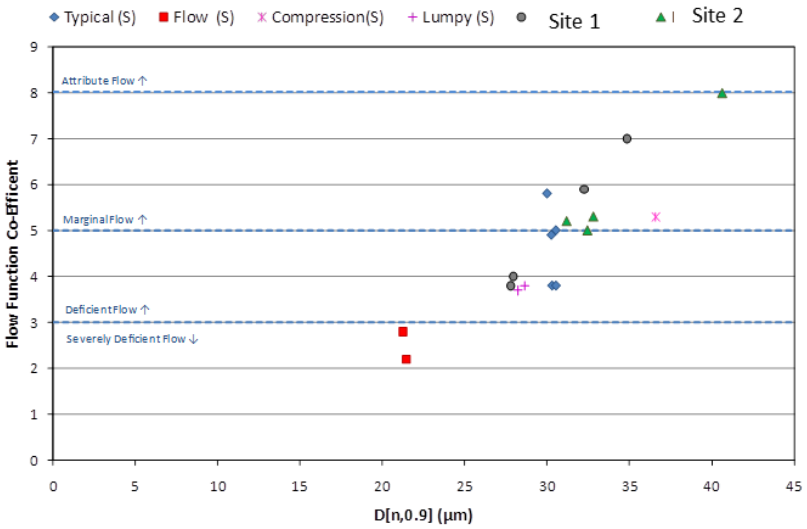


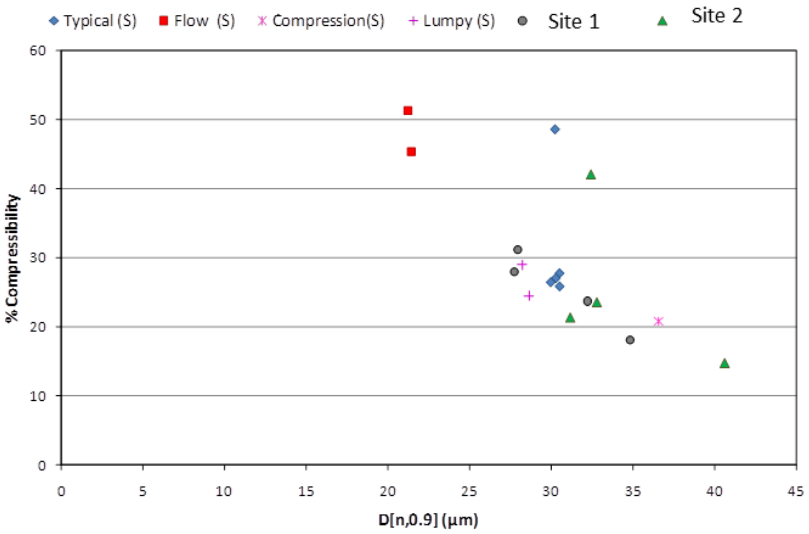





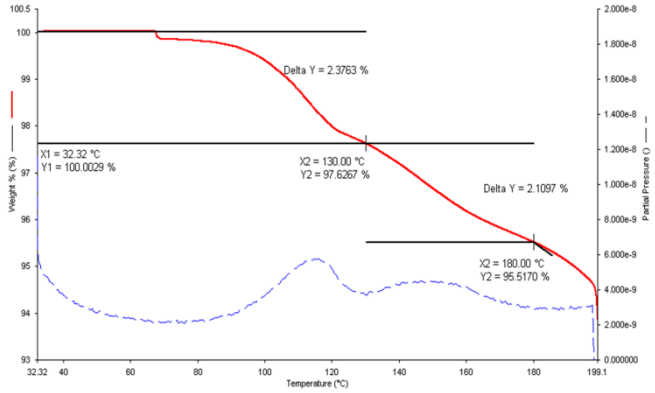
# Building Understanding of Criticality of Particle Shape

- Product has both a movement to API and DP site of manufacture.
  - API known to show variability in PSD
  - DP known to suffer from flow and compression issues



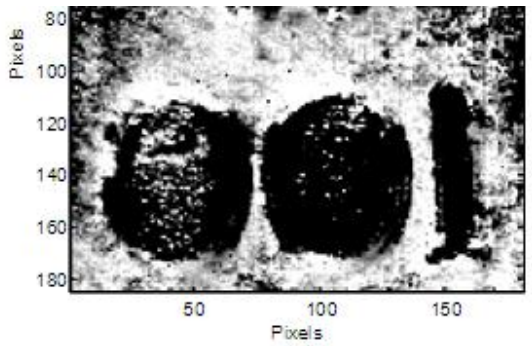




- Project identifies that thermal profile is not ‘typical’ of monhydrate species

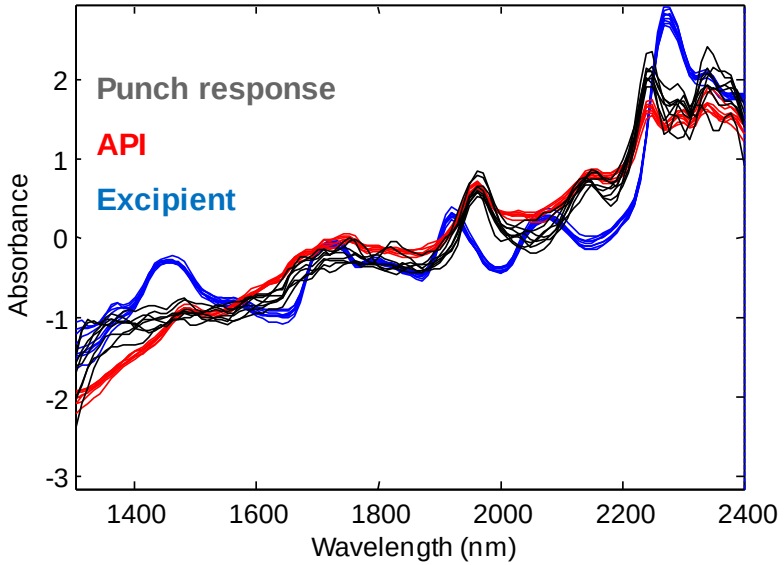


# Understanding Role of API in Compression Issues

- Evaluation of ‘sticking’ material to punch shows primarily API




Material adhered to punch tip using NIR Camera

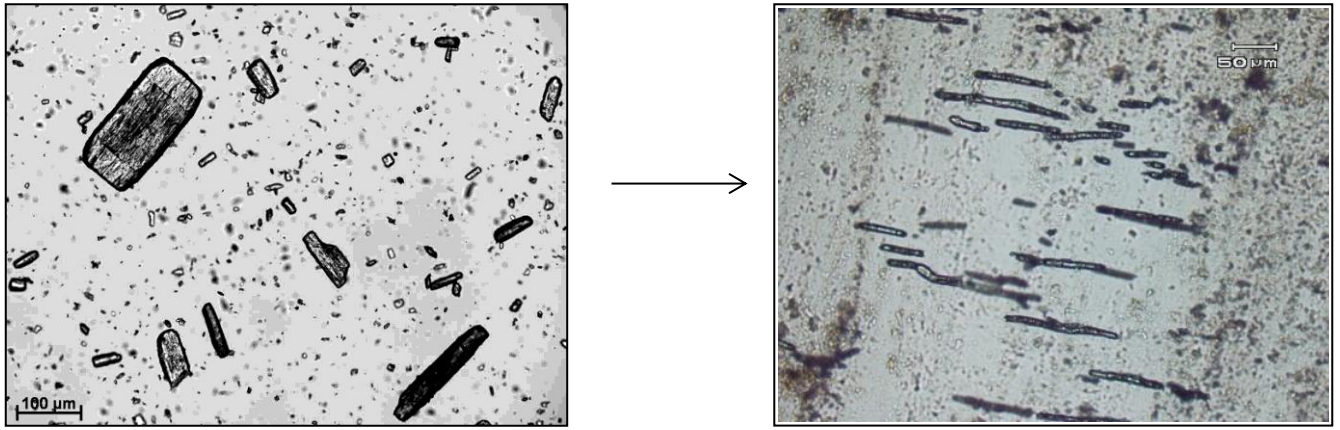



- Question posed by project team:

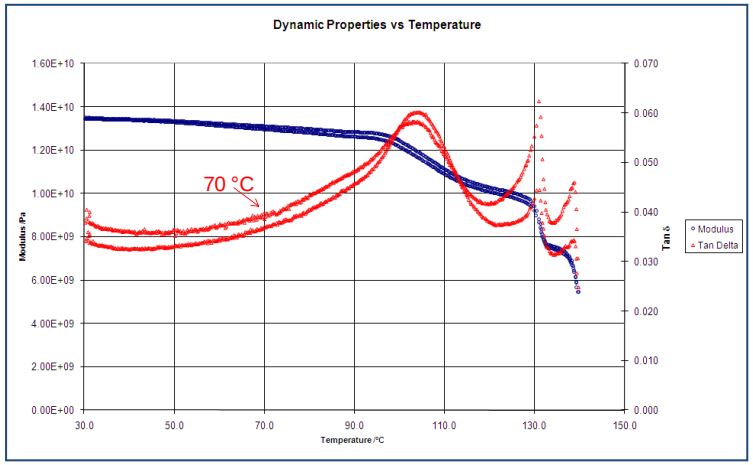
API site change includes change to crystallisation parameters and therefore scope to manufacture API with critical attributes for manufacturability but what are they?

# API Deformation Properties

- API is found to undergo plastic deformation

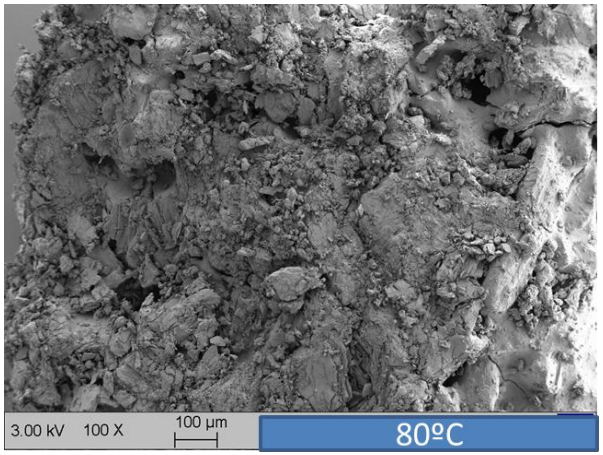


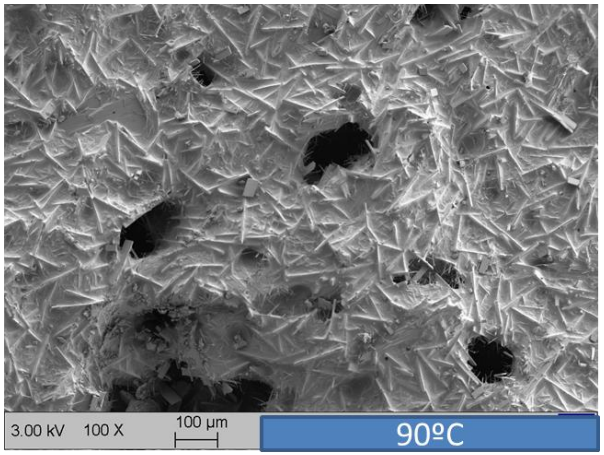

- Dynamic Mechanical analysis shows softening point is around 70ºC



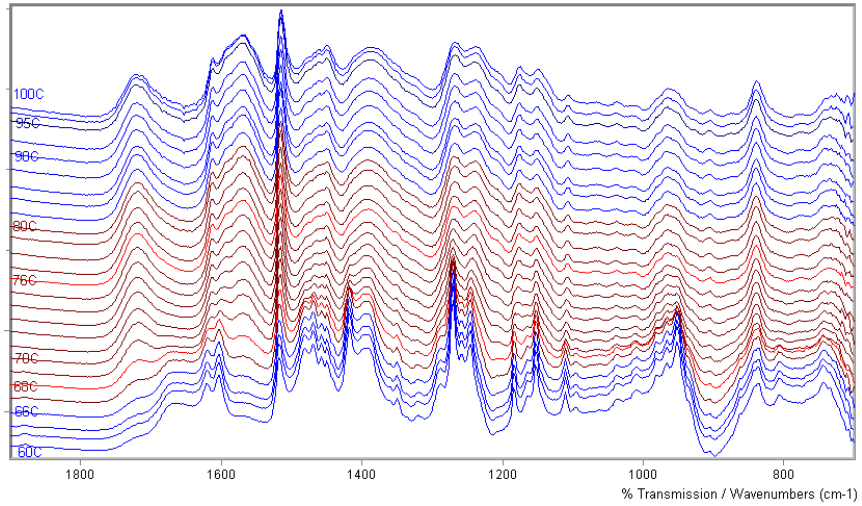
# Evaluation of Form vs Temperature

- Material shows an apparent re-crystallisation event around ~90ºC



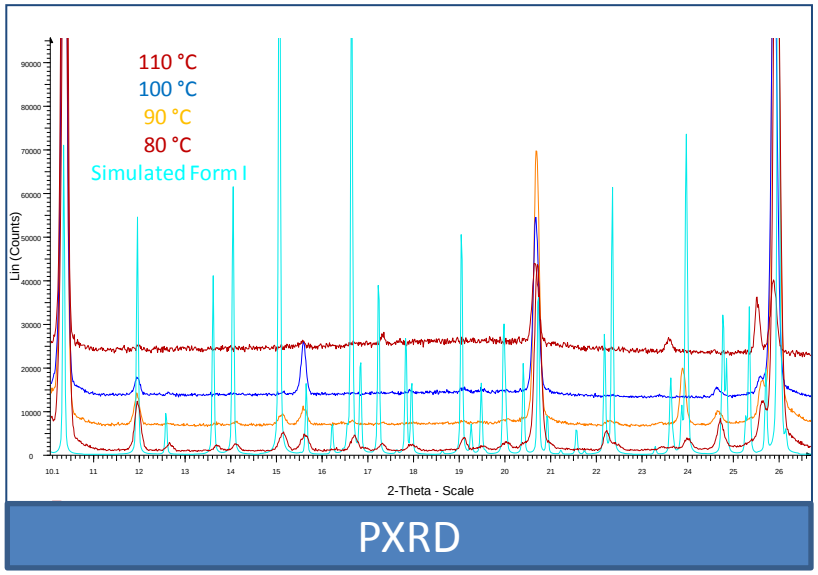



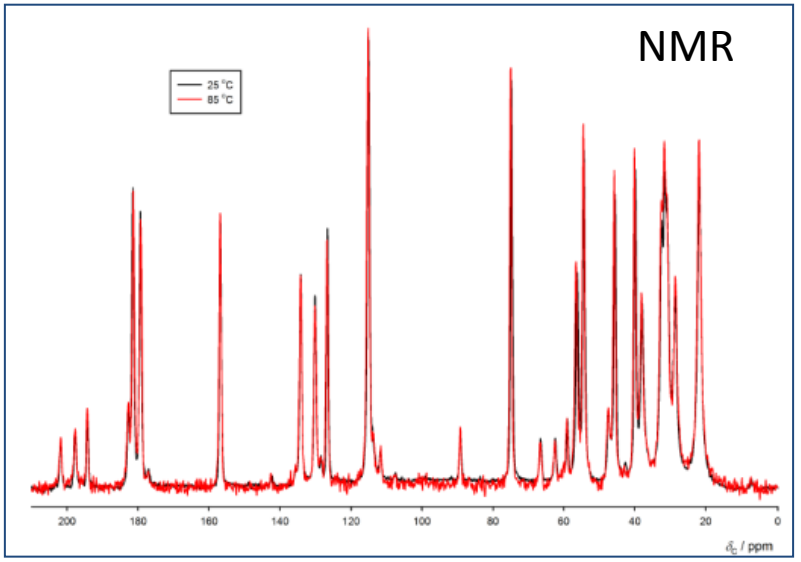

- Infrared microspectroscopy suggests a conversion (most likely on surface) from a hydrated to an anhydrous phase through the temperature ramp, and between 68 and 74 C the sample is a mixture of forms.



# Thermal Properties of Bulk

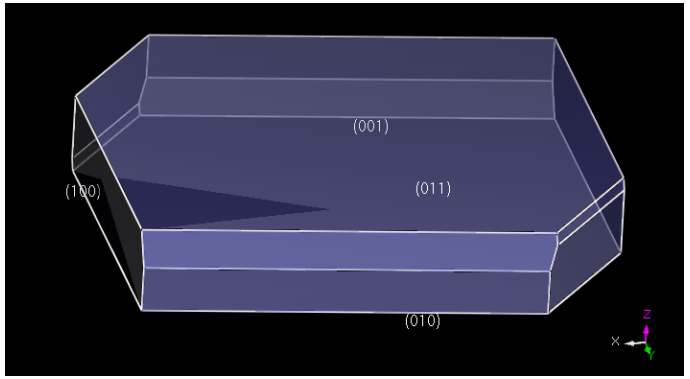
- Hot Stage PXRD and solid state NMR show no major differences in response at temperature, implying only the surface of the material is being affected

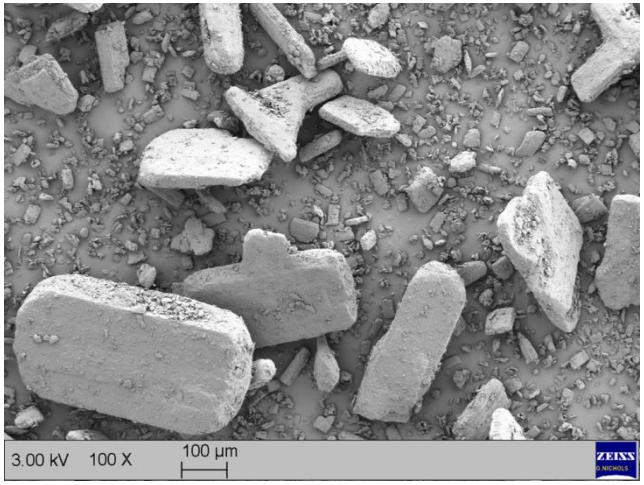


# Crystal Structure

- Using Single Crystal Data the molecular arrangement and particle morphology can be simulated.
  - In vacuum conditions where solvent or impurities are not taken into account



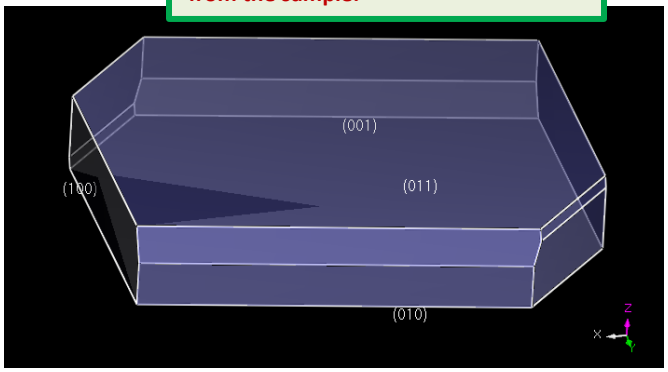

Crystal structure shows that water is tightly bound within crystal lattice.

# Particle Shape is a Critical Attribute

The second side long face 011 shows that water could be easily evolved from the surface of the crystal as well as the succinate salt.

**If the dominant face is reduced and any of the side faces are more exaggerated (for example with a more lath shaped particle rather than plate like particle) then it would be expected that the water would be more easily evolved from the sample.**

The surface chemistry of the dominant (70%) crystal face 001 has the water within the crystal. Therefore it is very well protected and fully engaged in the hydrogen bonding network at this face

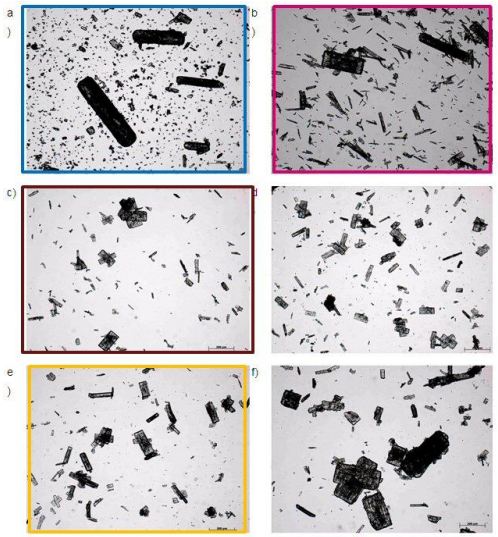


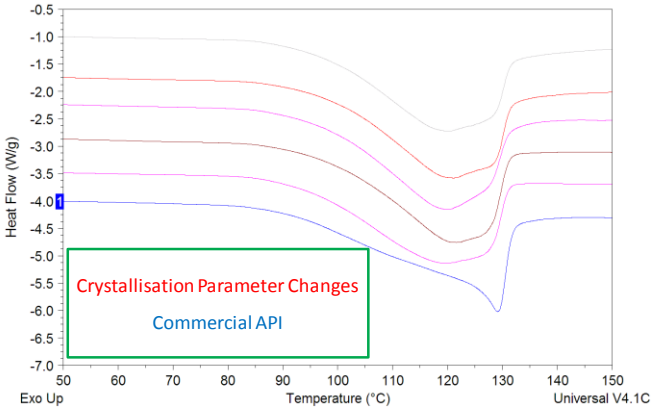

The first side long face 010 has the water readily exposed on the surface and participates with only two of the three possible hydrogen bonds being utilised. Therefore if this crystal face was heated it would be expected that the surface water could easily evolve from the surface of the crystal.

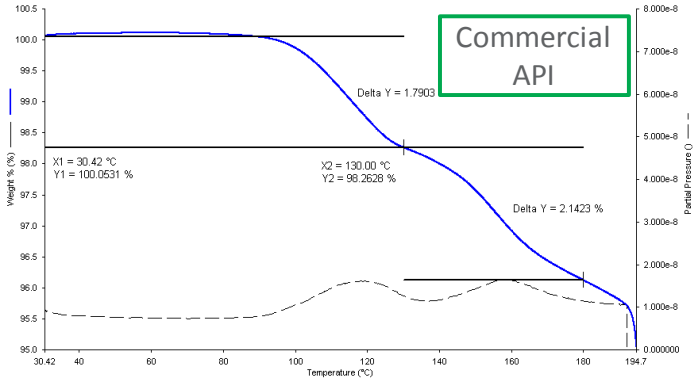
The third side face shows that water could be easily evolved from the surface of the crystal

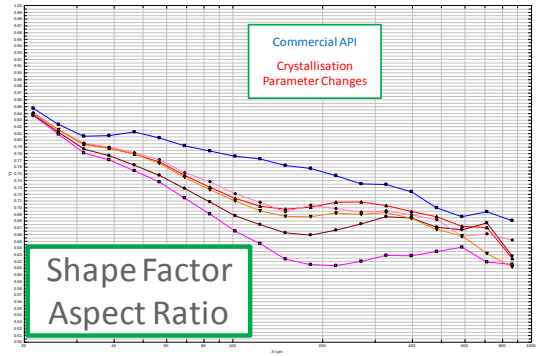
# Particle Size and Shape Drive Manufacturability

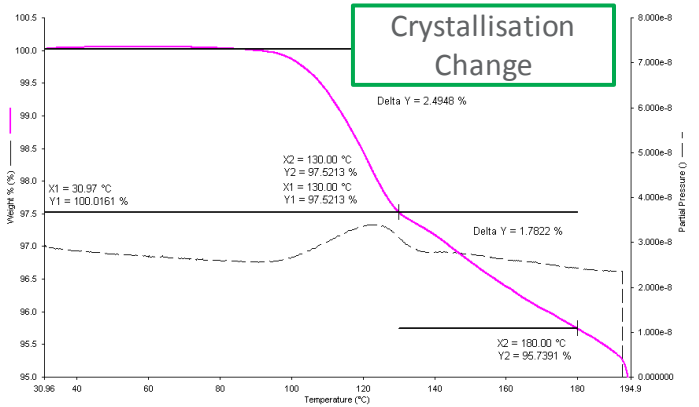
- Crystallisation trials confirm the impact of particle shape on materials water loss and deformation.
- Critical attributes for API site change are both **particle size** and **shape**.



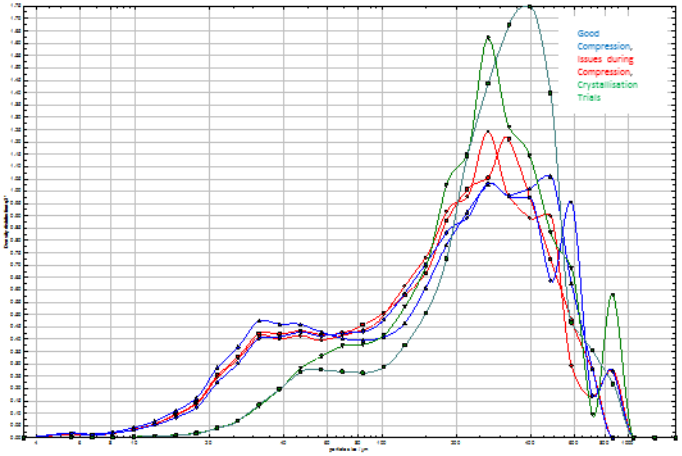



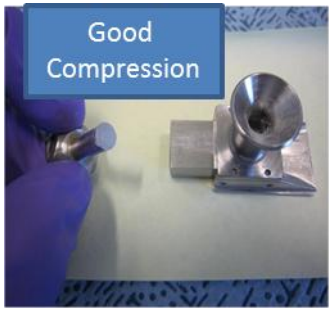



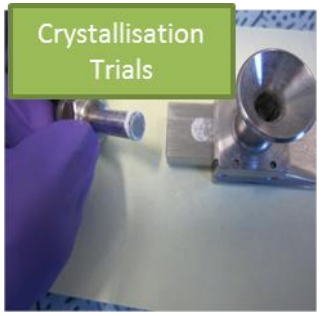



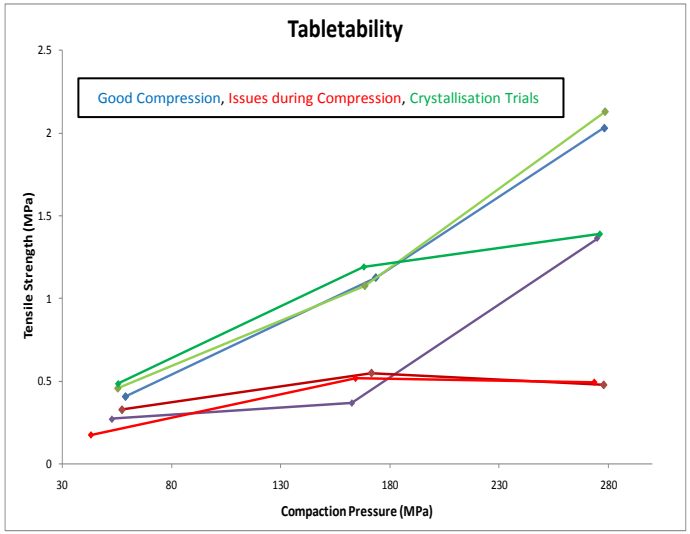
# Particle Shape and Compression Behaviour

- 6 Lots Selected which represented variation in compression performance and crystallisation studies.
- Tablet Compression Profiles Examined.
  - Not linked to particle size/shape
  - However lamination was observed in issue lots overnight.
  - Suggesting could be linked to surface properties.
- Sticking Behaviour Shown to Increase with crystals showing reduction in dominant face.



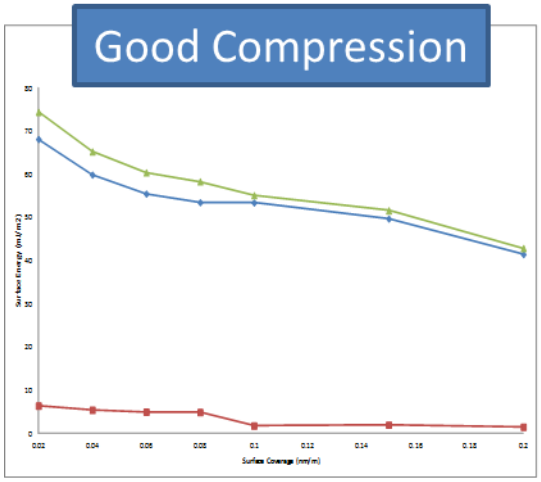



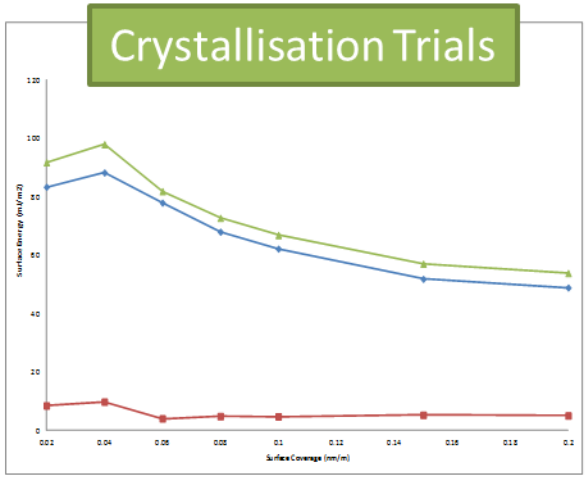



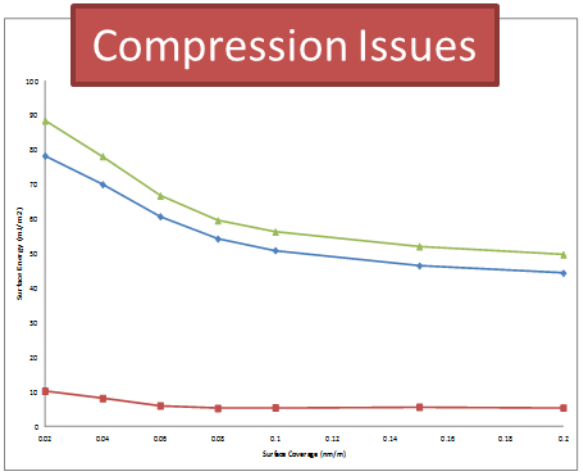



# Surface Properties (1)

- Evaluation by Inverse Gas Chromatography
  - Polar and Non-polar solvents over column of sample
- All samples are energetically heterogeneous as surface energy changes as a function of surface coverage.

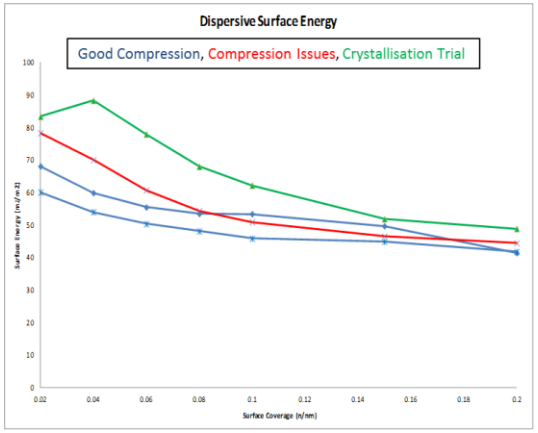


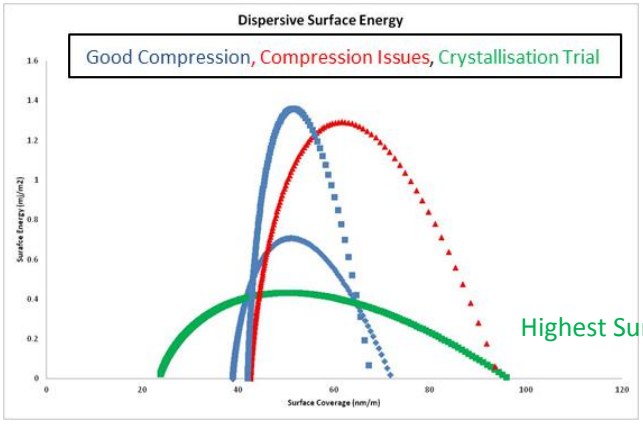



# Surface Properties (2)

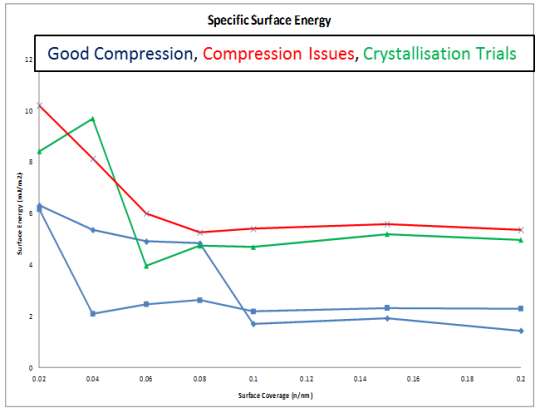
- Crystallisation trial shown to have the highest energy, suggesting it to have a more heterogeneous surface in relation to apolar probes.

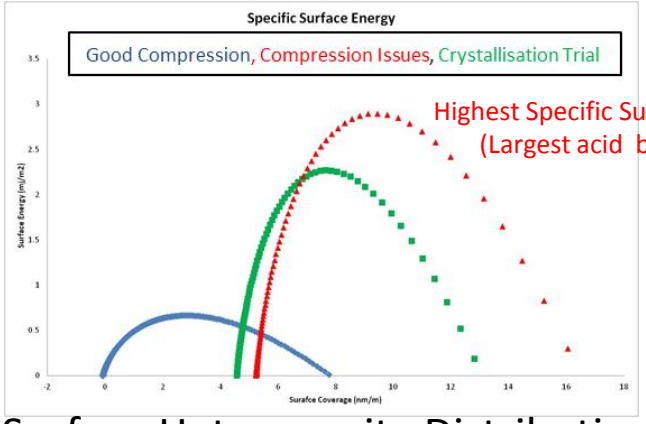



Highest Surface Heterogeneity

- Compression Issue lot shown to have highest specific energy, indicating more heterogenous surface in relation to polar probes.



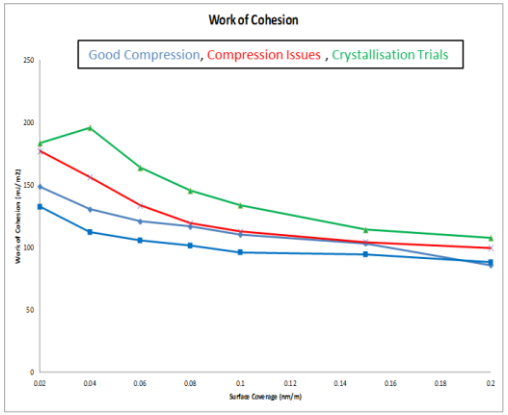




Highest Specific Surface Heterogeneity
(Largest acid bas e interaction)

Surface Heterogenity Distributions

# Surface Properties (3)

- Work of Cohesion can also be determined, which can be a measure of ‘agglomeration tendency’.
- Crystallisation Trials have largest values, which would support highest tensile strength.




- Analysis has shown that surface analysis agrees with the crystal structure modelling.
  - Changing the crystal shape (reducing dominant crystal face) increases the amount of water available at crystal surface.
  - This is shown through this material having higher dispersive surface energy.
  - Crystal shape and surface properties explain the greater sticking propensity of this material.

- Surface analysis shows the compression issue lot to have highest acid-base surface activity, which may explain lamination behaviour and variation from other lots examined.

# Conclusions

- Materials Sciences in the characterisation of Active Pharmaceutical Ingredients has evolved significantly over the past decade.

- With manufacturing materials sciences acts as a pro-active assessment of risk on drug product performance from varying the input material.

- Technology platforms have rapidly evolved to enable these assessments but now also includes the power of computational assessments.