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Beyond particle size: Introducing the Morphologi 4-ID and MDRS

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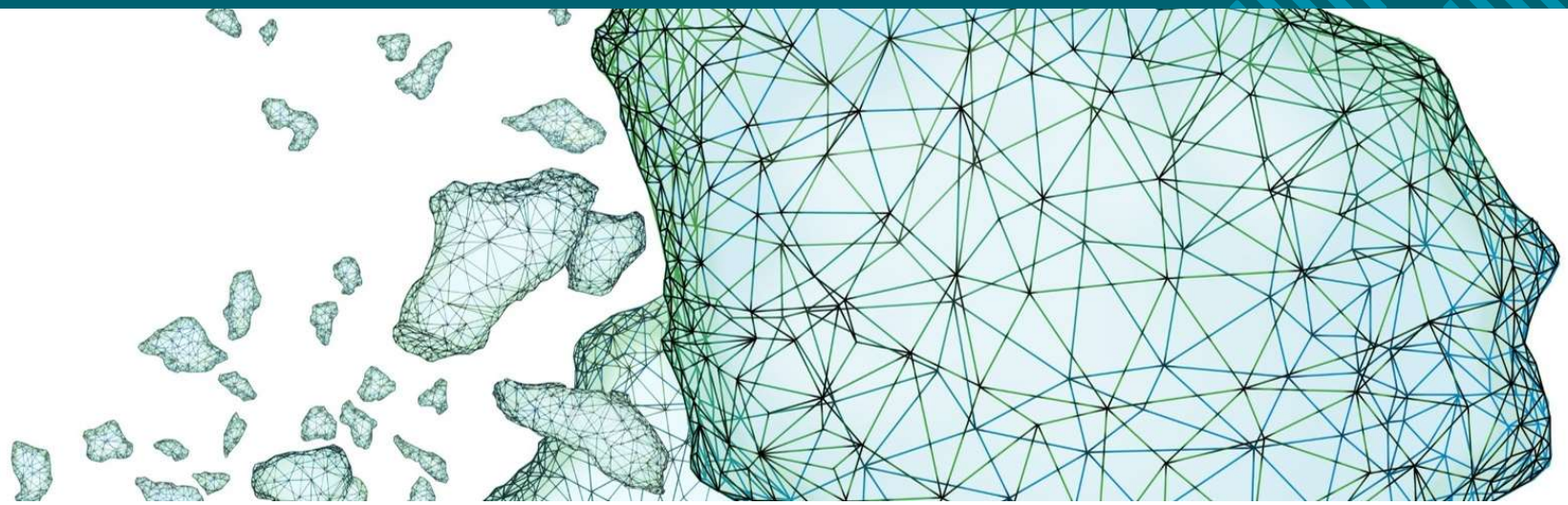
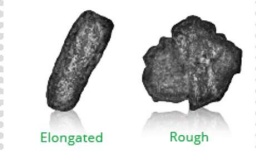


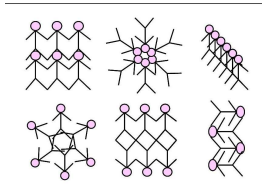
Overview



Introduction to Imaging and MDRS

Introduction to Morphologi 4 and 4-ID

Pharma – Nasal Sprays



Pharma – Polymorphism

Food - Flour

Metallurgy – Additive manufacture

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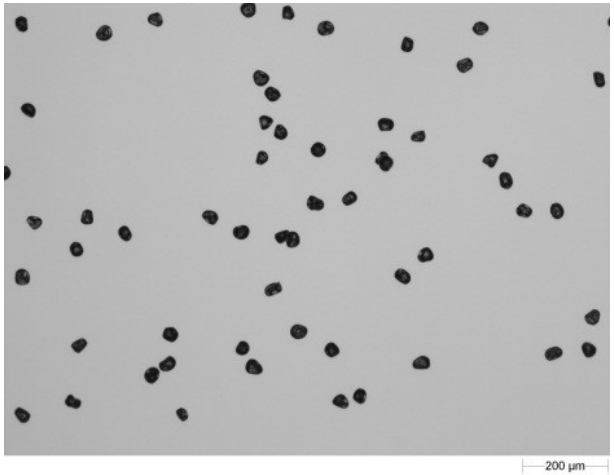
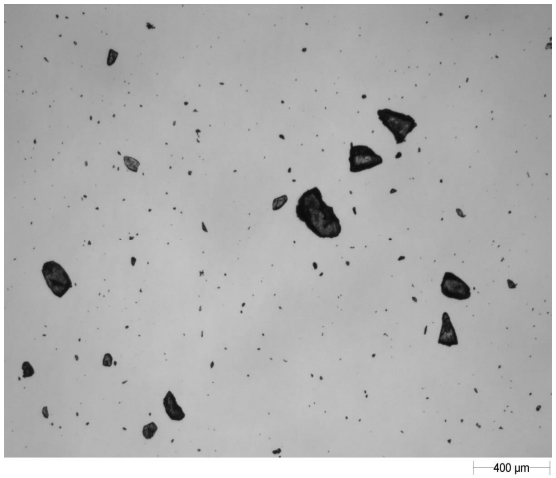
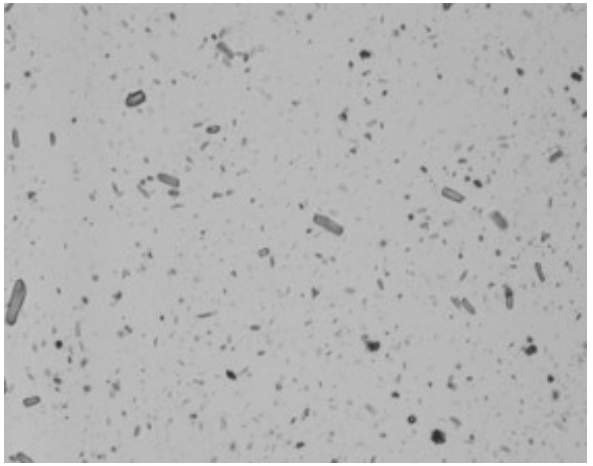
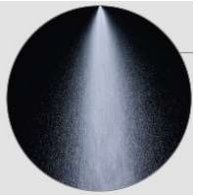
Why characterize particles?









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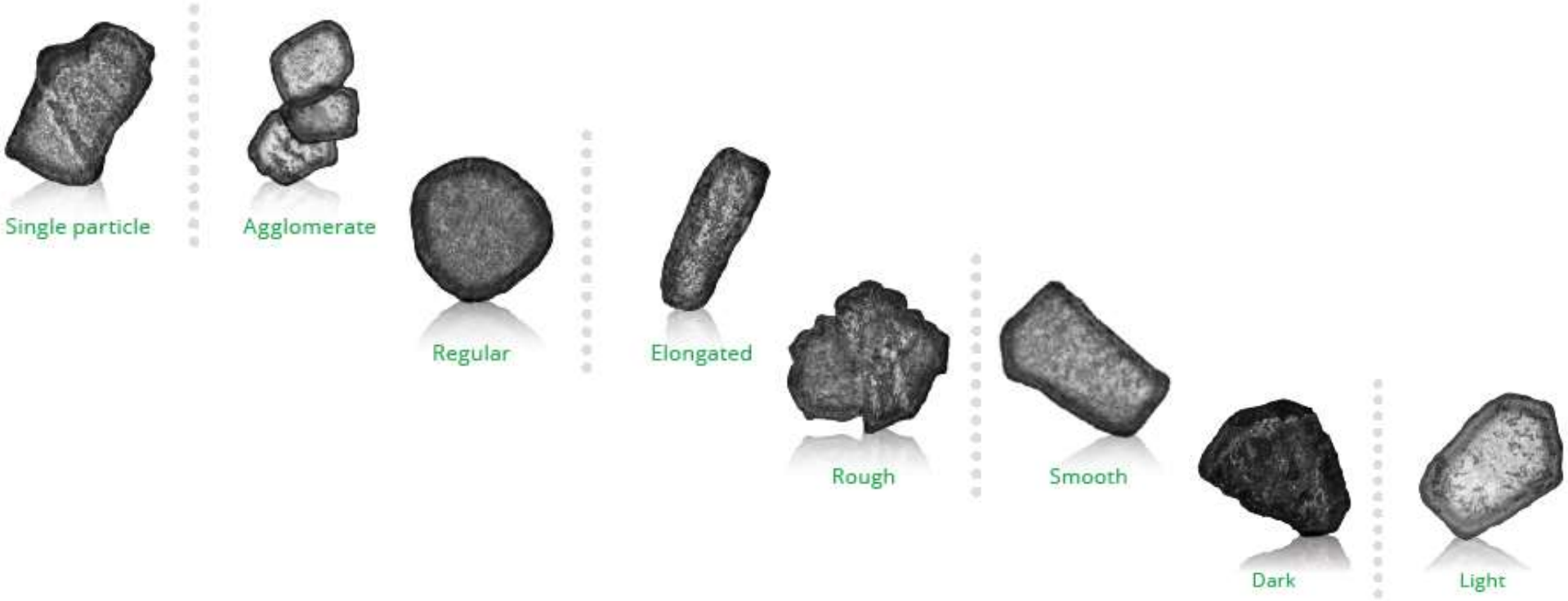
Beyond particle size

Why measure particle shape



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How can particle shape be measured?

Traditional methods

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Why Automated Image Analysis ?

- Fast measurement compared with manual microscopy
- Statistically significant sampling: typically 10,000 – 500,000 particles in one measurement
  - Measures size and shape (from 2D images)   (size range: ~0.5 – 1300um)
- SOP driven measurements – from dispersion through to results analysis
  - Eliminates operator bias and fatigue
  - Transferability of measurements from site to site

SPEED

Higher throughput
Faster measurements

- Up to 25% reduction

CONTROL

Intuitive method development
Fully-enclosed system

DEFINITION

Enhanced shape differentiation (sharp edge)
Increased sensitivity to low contrast samples

RANGE

Extended particle sizing range

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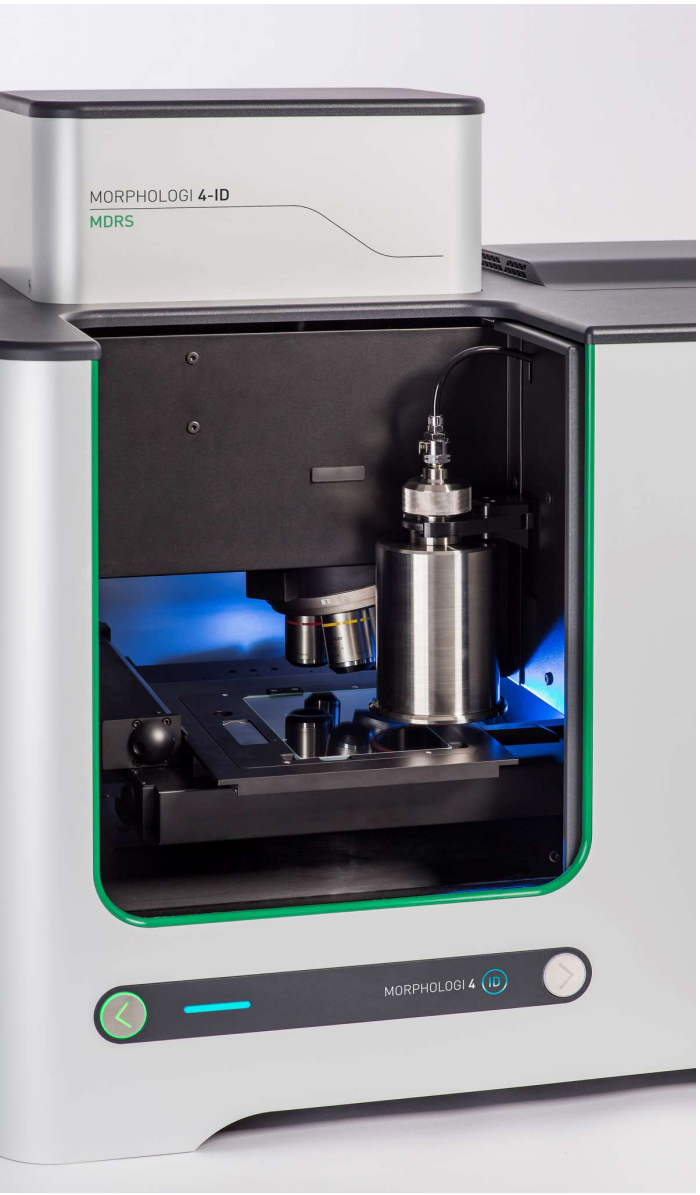

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Automated Image Analysis

- 2 LED light sources
  - reflected (episcopic)
  - and transmitted (diascopic) illumination

- 18 Mega pixel digital camera
- Motorized objective revolver for automatic magnification changeover
- Precision XY stage for scanning sample & motorized Z axis actuator
- Sample dispersion unit (SDU)
- Integrated spectrometer (4-ID variant only)

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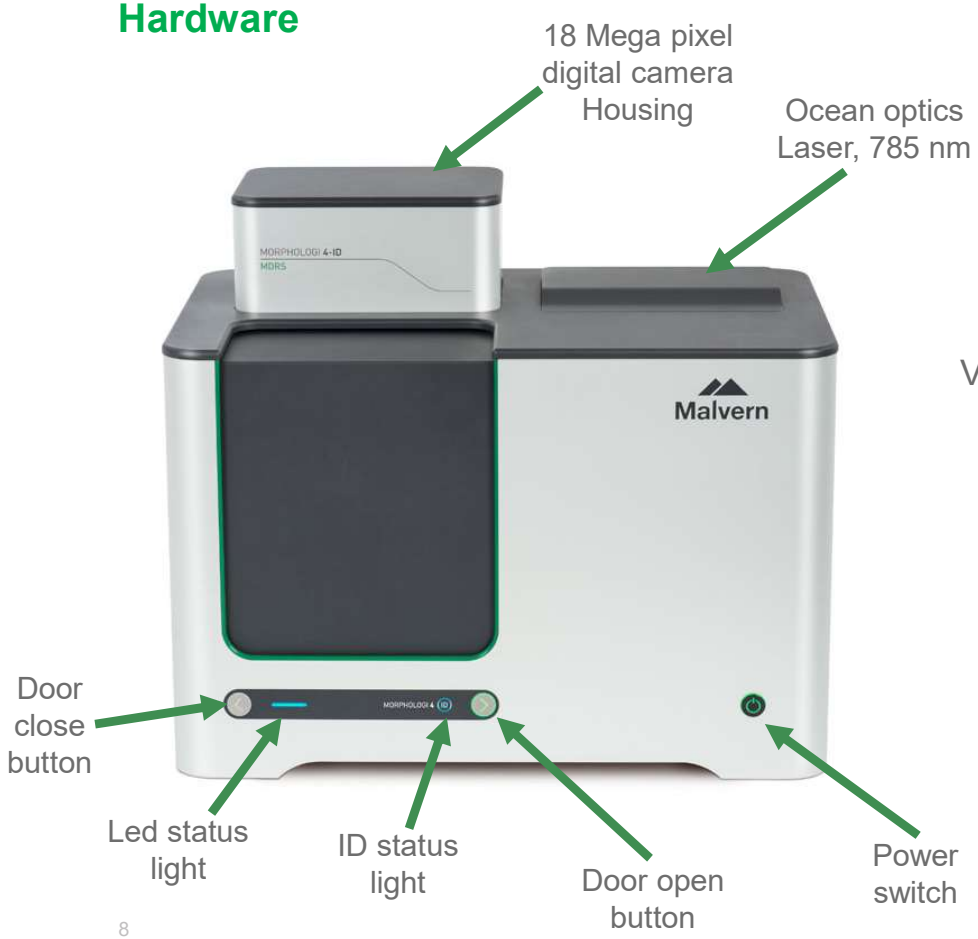
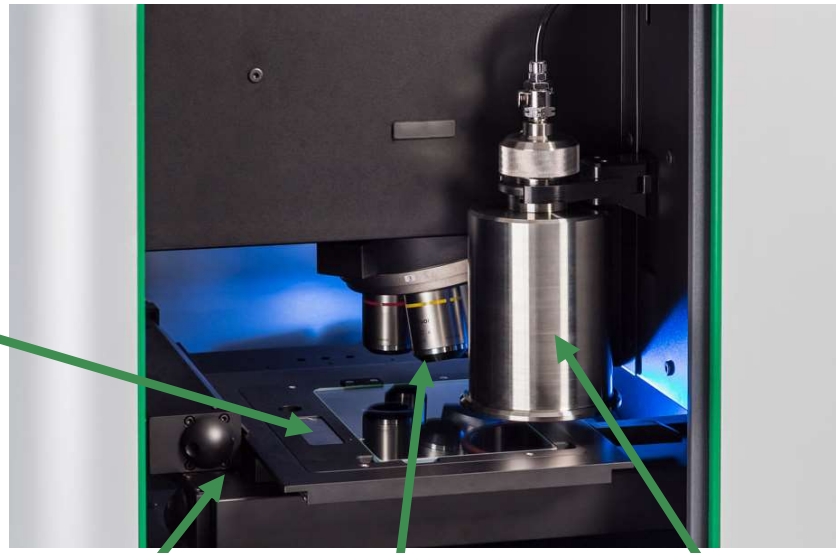
Morphologi 4 & 4ID Hardware

Hardware





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The Morphologi 4 and 4ID

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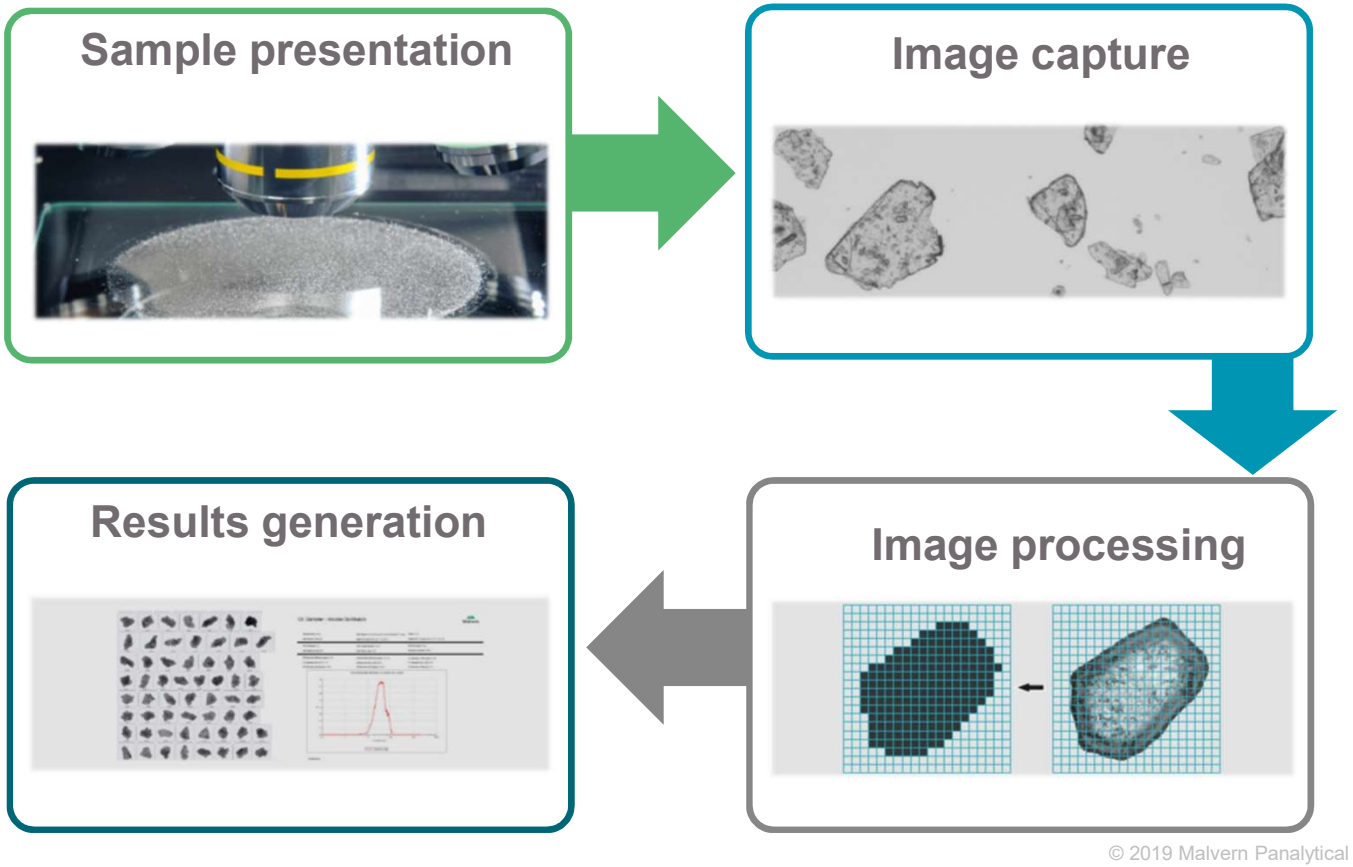
Morphological imaging workflow



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Sample Presentation

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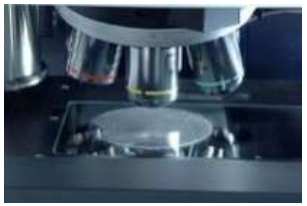
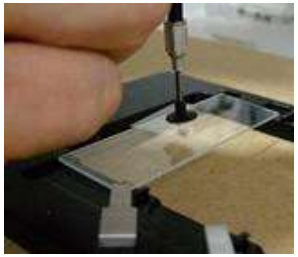


Manual dry dispersion

Dry sample dispersion unit

Evaporative dispersion

Wet cell



Thin path wet cell

Wet (slide and coverslip)

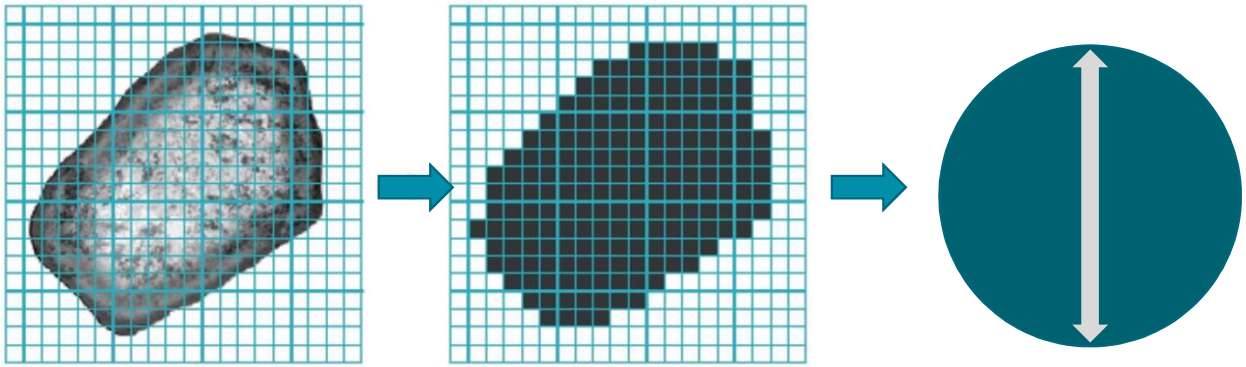
100nm 1µm 10µm 100µm 1mm 10mm

Particle size

Morphological results

Particle size

- Capture 2D digital image of particle
- Binarise 2D image using foreground segmentation
- Calculate size and shape parameter



3D particle image

2D particle image

Circle with the same area

Circular equivalent diameter
CED

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Morphological shape descriptors

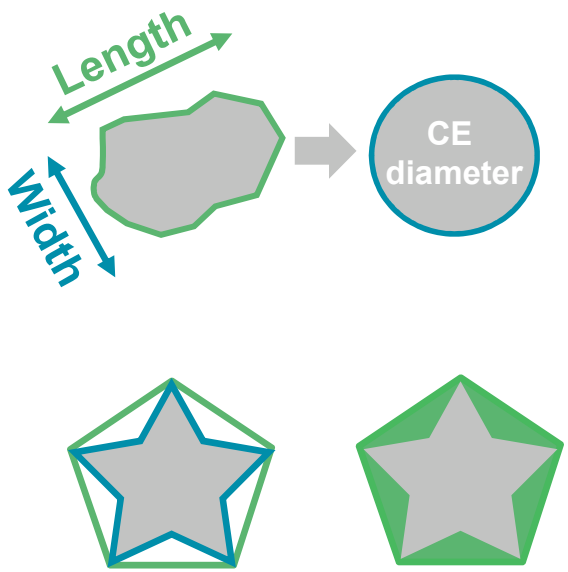
Summary

- Particle size
  - Circular equivalent (CE) diameter
  - Length
  - Width
- Particle form

$$Aspect\ ratio = \frac{width}{length}$$

$$Elongation = 1 - \frac{width}{length}$$

- Particle outline
  - Convexity (perimeter)
  - Solidity (area)
- Combination of form and outline
  - Circularity/HS circularity
- Light transmission
  - Intensity mean
  - Intensity SD



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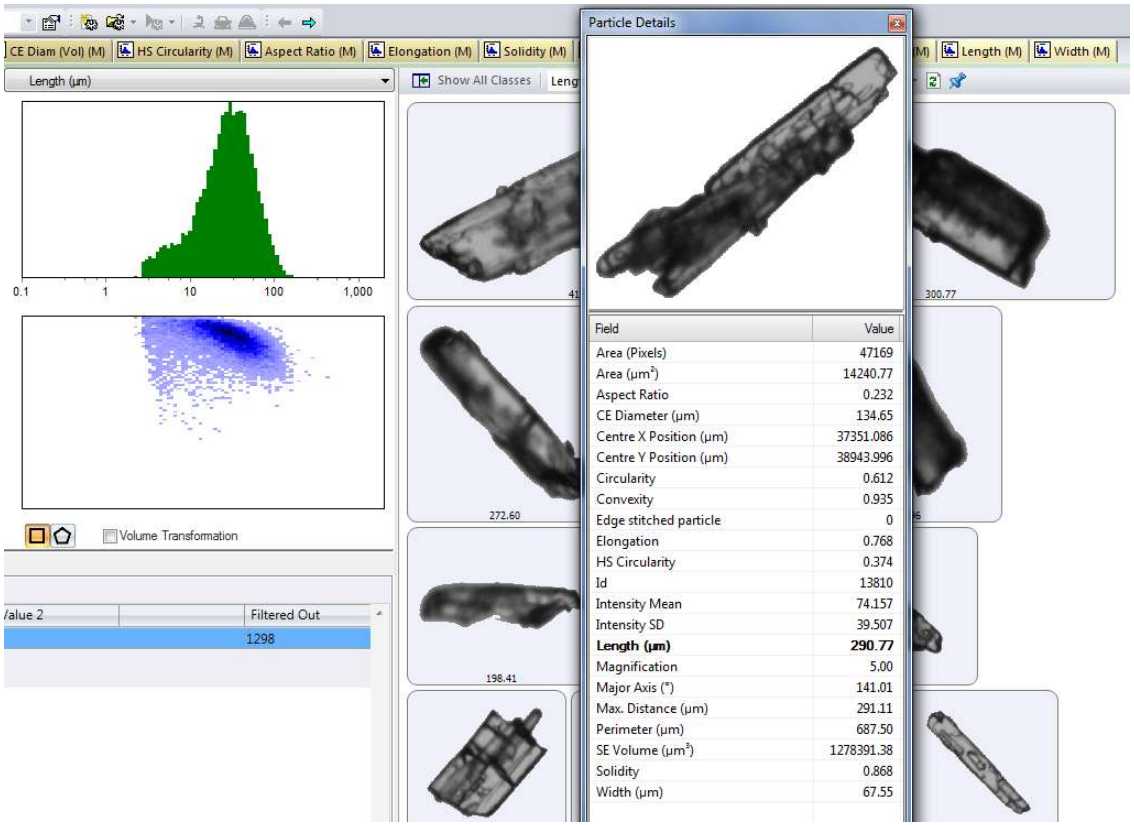
Result interpretation

Individual particle detail



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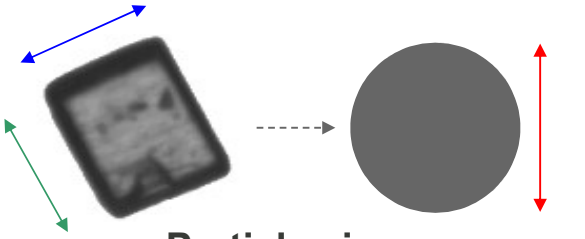
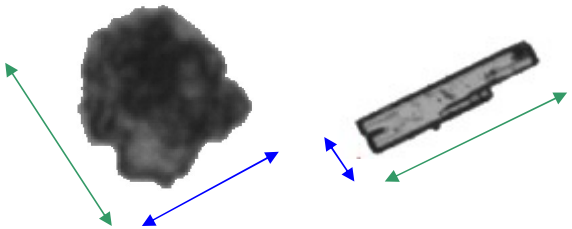
How can particle shape be measured?

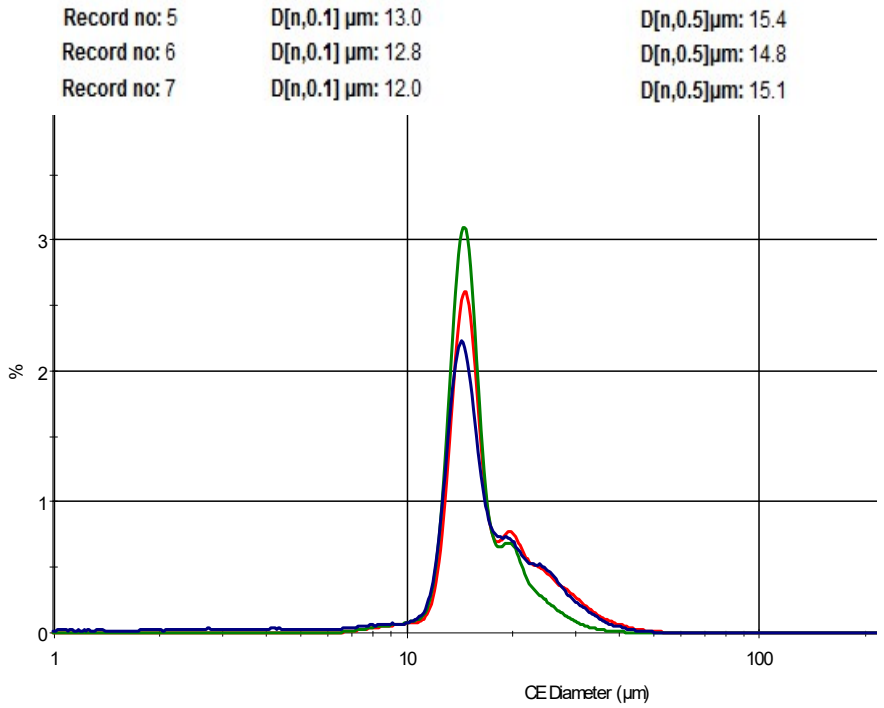
Morphological imaging

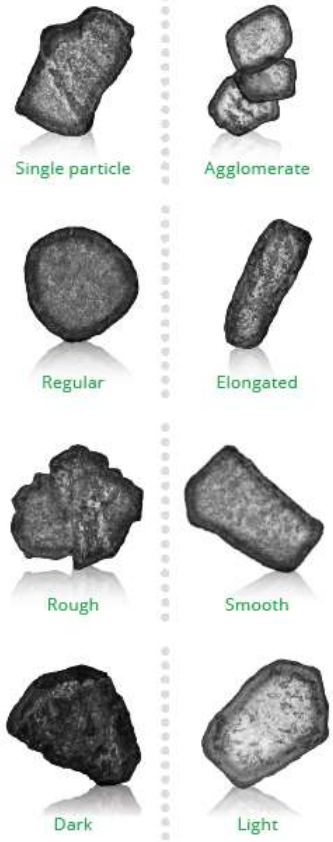


Particle size



Particle shape





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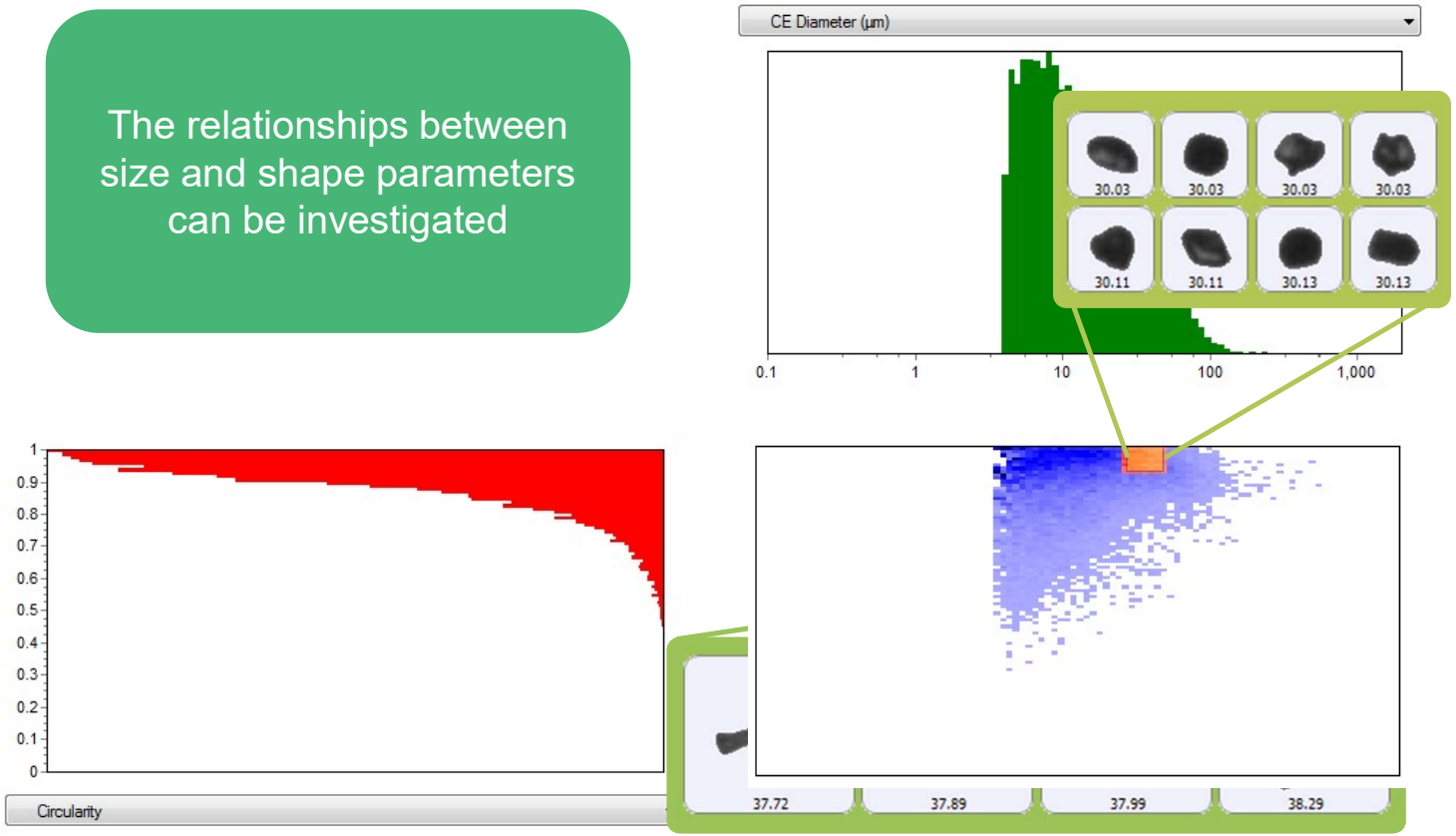
Result interpretation

Scattergram

The relationships between size and shape parameters can be investigated



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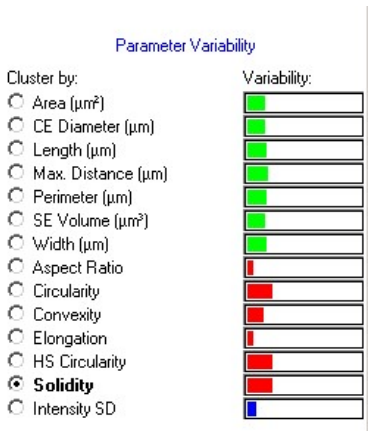
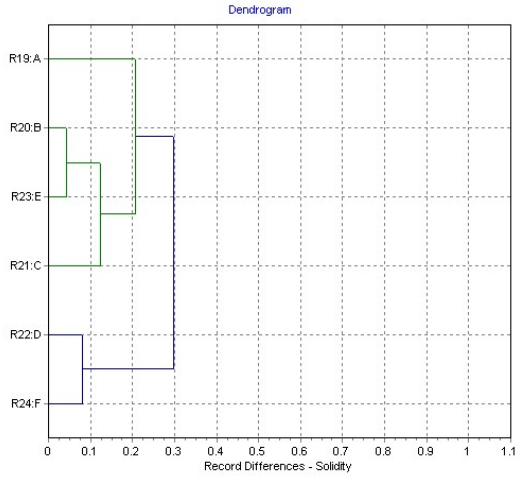
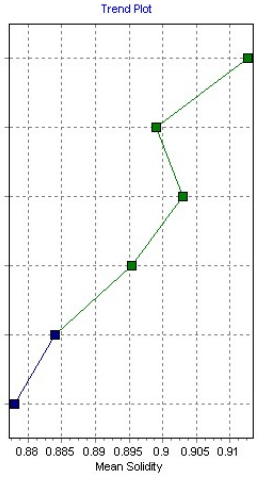
Result interpretation

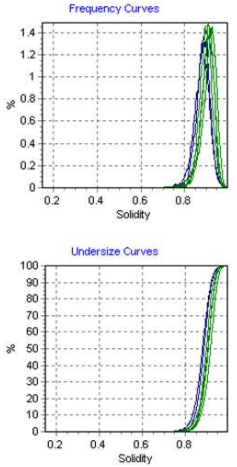
Statistical analysis tools

Group	Record #	Sample Name	Date	Edited	# Particles	CE Diameter Mean (µm)	HS Circularity Mean	Aspect Ratio Mean	Elongation Mean	Solidity Mean	Convexity Mean
	19	A	20 September 2006 11:30:33	True	5701	204.56	0.667	0.777	0.223	0.913	0.901
	20	B	20 September 2006 12:58:58	True	5963	188.44	0.639	0.775	0.225	0.899	0.891
	21	C	20 September 2006 15:55:37	True	4535	201.47	0.624	0.786	0.214	0.895	0.881
	22	D	20 September 2006 17:22:35	True	4091	219.06	0.603	0.776	0.224	0.884	0.877
	23	E	20 September 2006 18:33:52	True	7013	183.93	0.640	0.784	0.216	0.903	0.888
	24	F	21 September 2006 10:03:19	True	4220	208.10	0.585	0.750	0.250	0.878	0.876









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MDRS workflow

Morphologically-Directed Raman Spectroscopy

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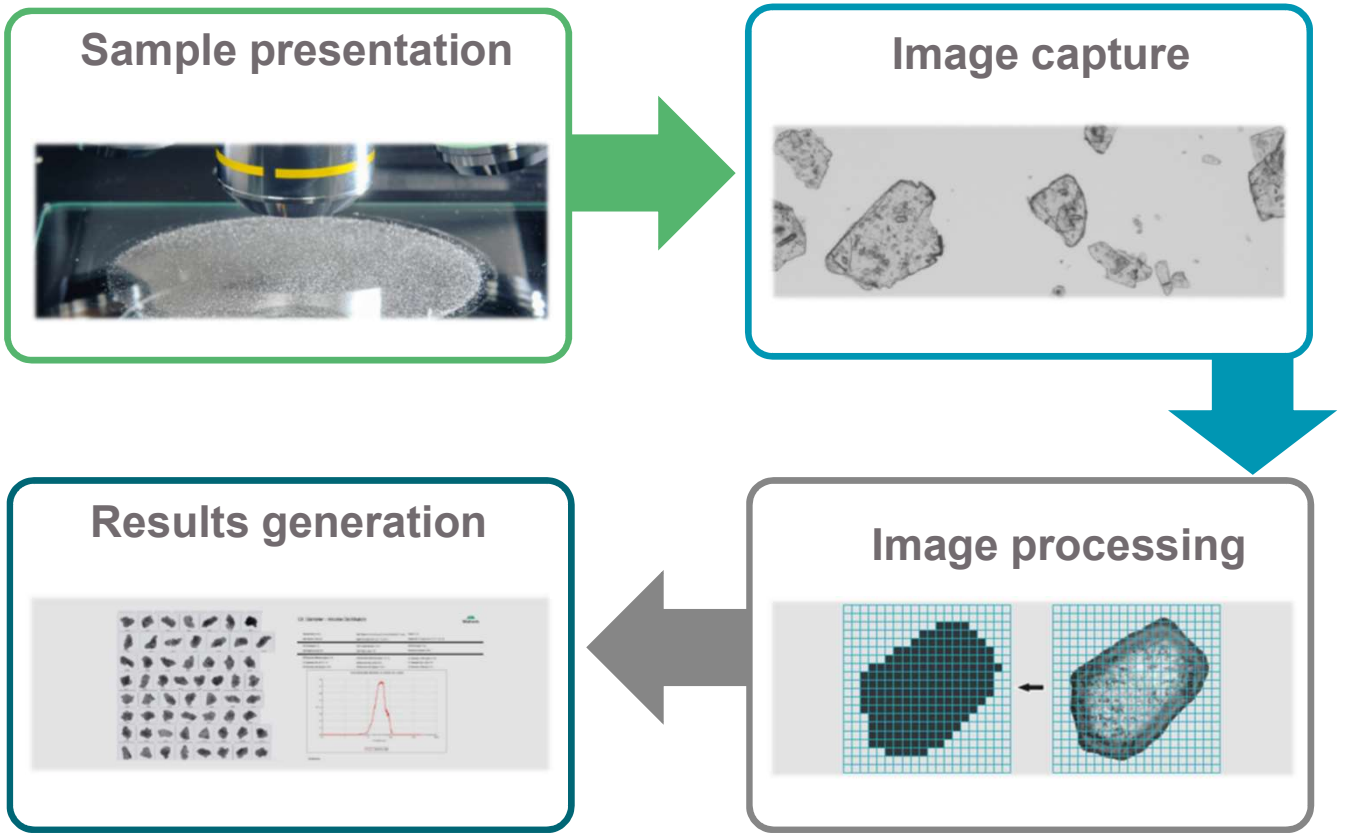

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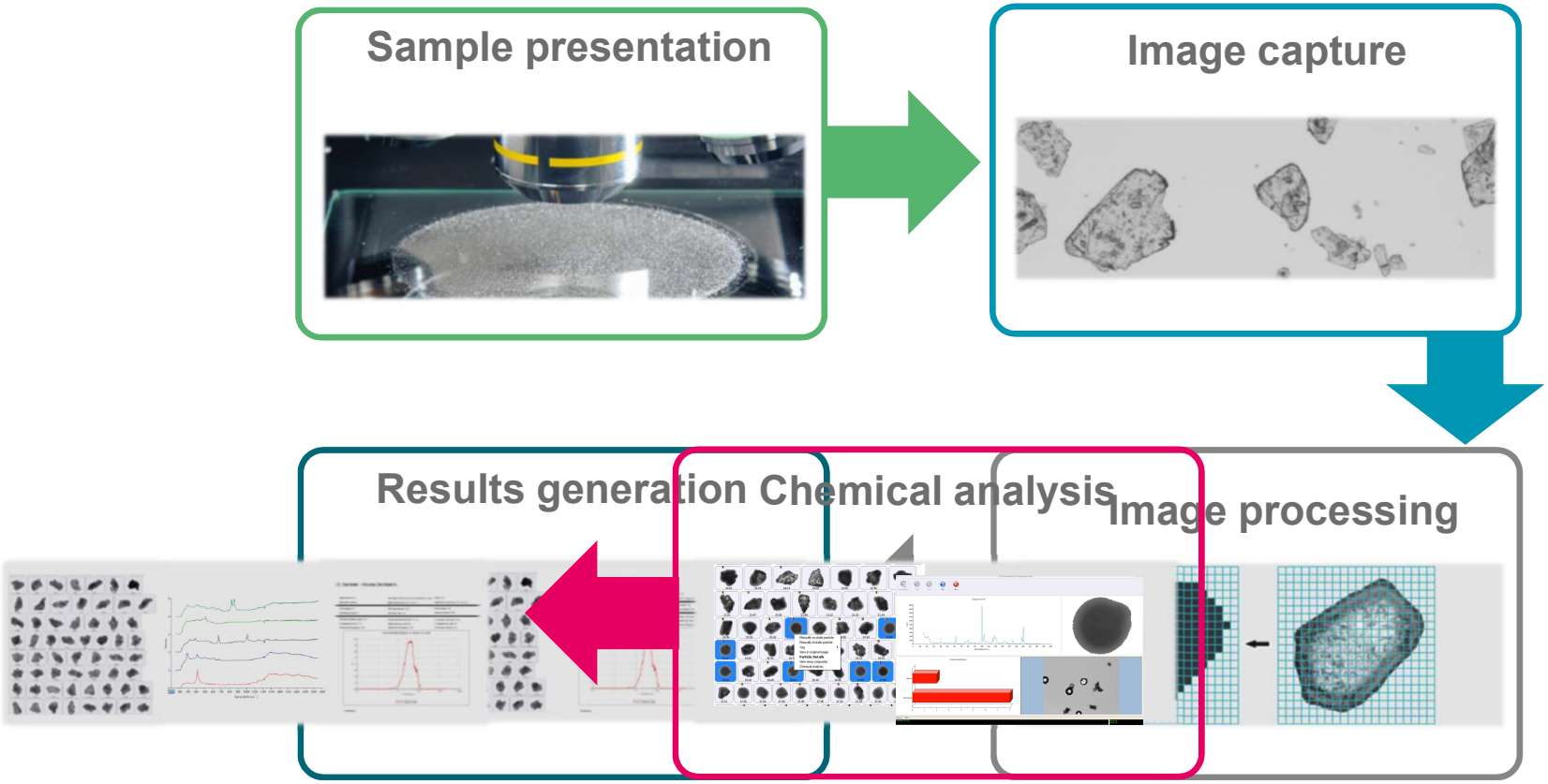
MDRS workflow

Morphologically-Directed Raman Spectroscopy



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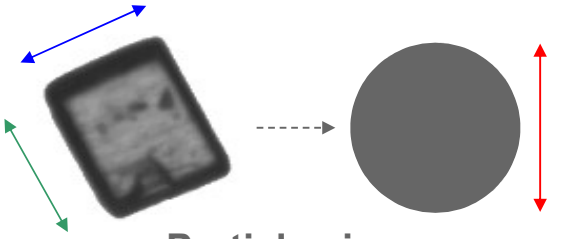
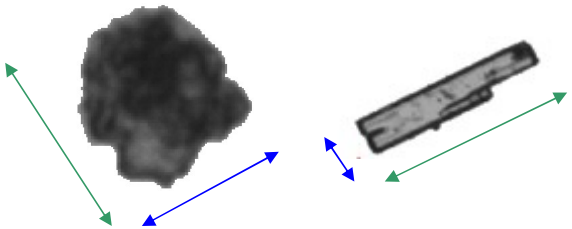
Morphologically-Directed Raman Spectroscopy

Combines automated imaging and Raman spectroscopy in one integrated platform

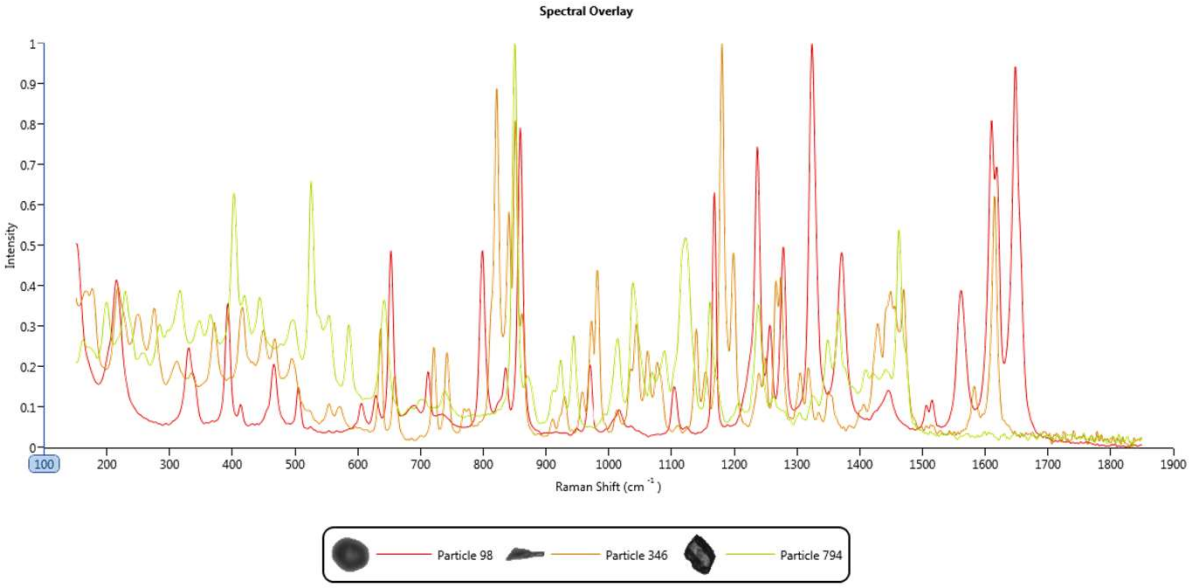


Particle size



Particle shape

Chemical identity



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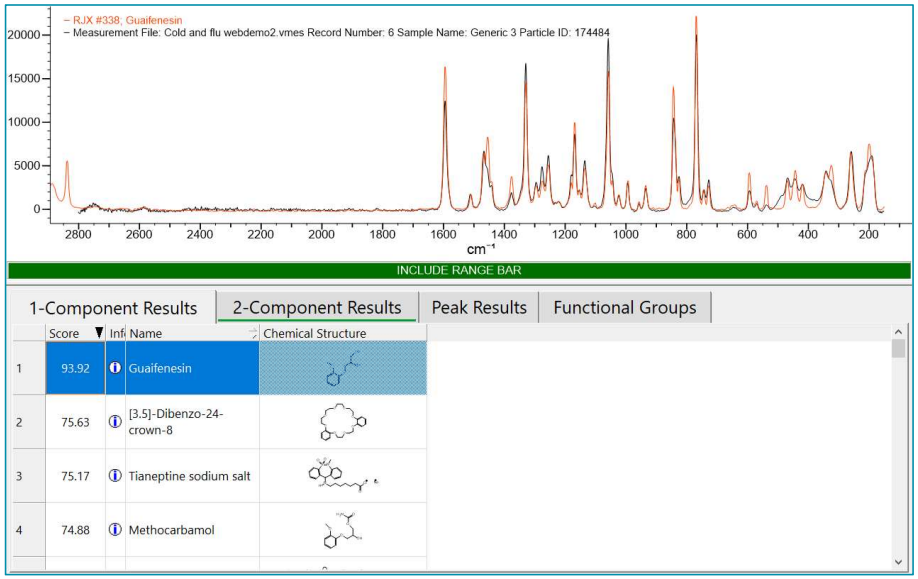
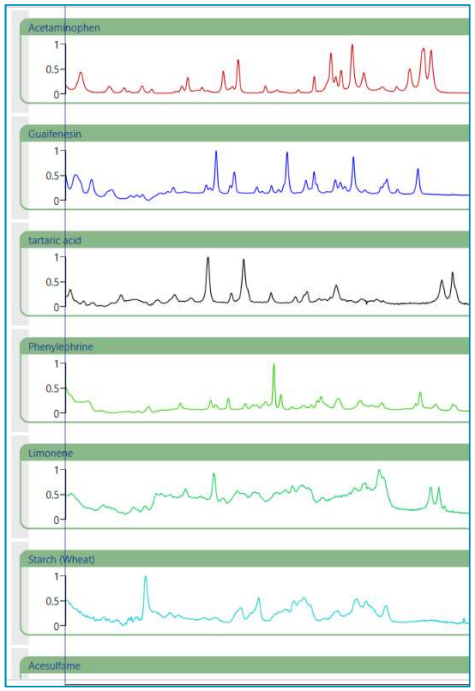
Using libraries

1. Export particle spectrum from Morphologi to KnowItAll

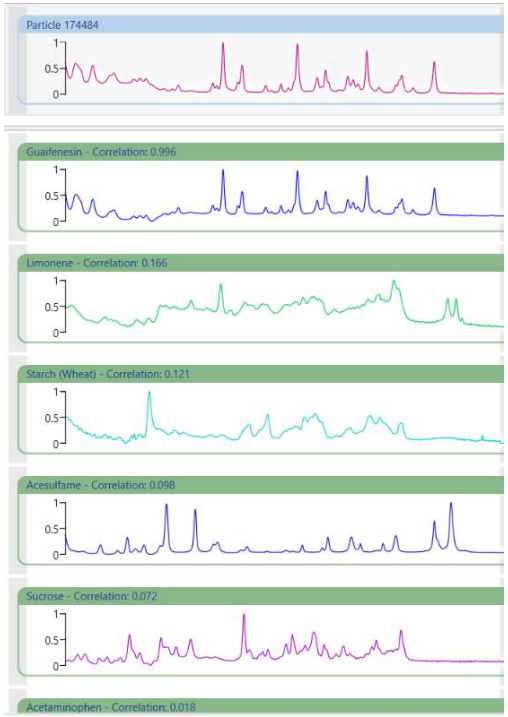
2. KnowItAll identifies the particle



3. Add Spectrum to internal library



4. Compare other particle spectra to internal library



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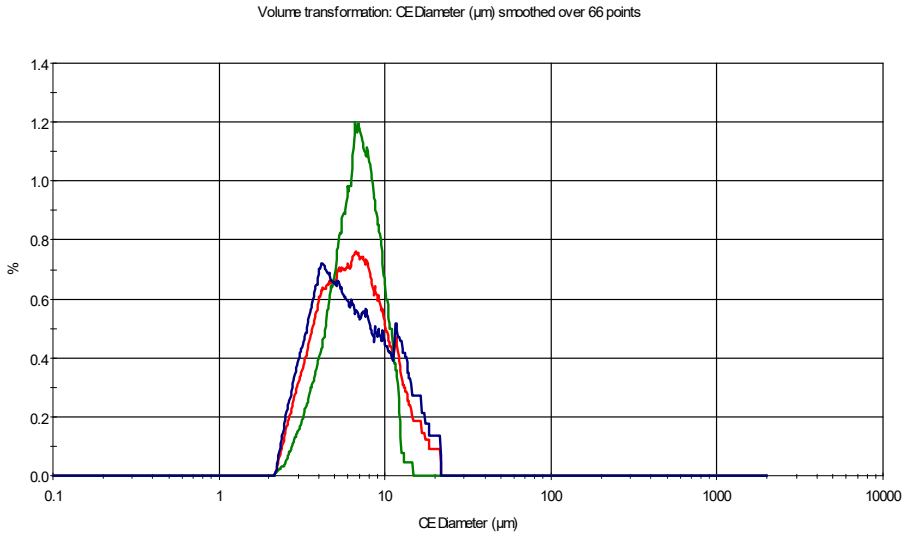
Chemical analysis

Results

- Create component specific classifications
- Compare size distributions of components within a mixture
  - CE Diam. (vol) for Mixture, API(32.15%) and Excipient (67.85%)

Sample Name:			
Nasal Spray FP	D[v,0.1] µm: 3.5	D[v,0.5]µm: 6.3	D[v,0.9]µm: 11.9
API	D[v,0.1] µm: 4.1	D[v,0.5]µm: 6.9	D[v,0.9]µm: 8.9
Excipient	D[v,0.1] µm: 3.4	D[v,0.5]µm: 5.9	D[v,0.9]µm: 13.3



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DPIs

Nasal Sprays

MDIs

Nebulizers

Orally Inhaled and Nasal Drug Products (OINDPs)

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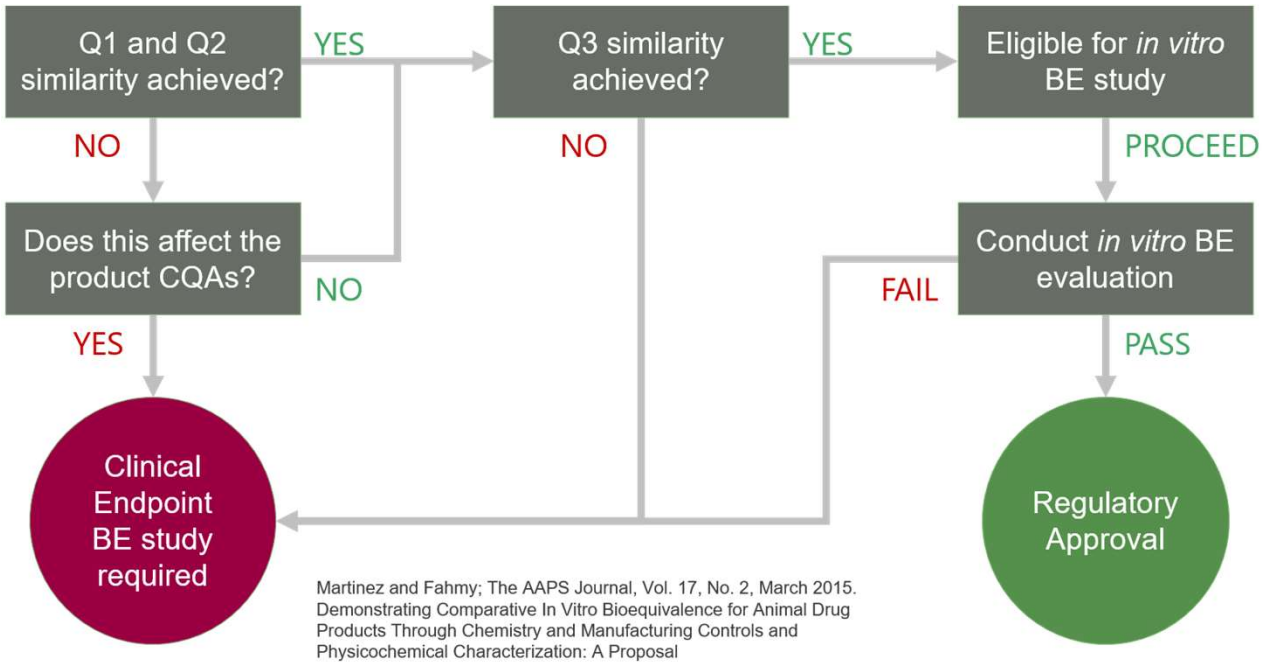
Inhaled (locally-acting) generic formulation

Benefit of Q3 equivalence testing



Martinez and Fahmy; The AAPS Journal, Vol. 17, No. 2, March 2015. Demonstrating Comparative In Vitro Bioequivalence for Animal Drug Products Through Chemistry and Manufacturing Controls and Physicochemical Characterization: A Proposal

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Generics bioequivalence requirements

	Requirement	Definition
Q1	Qualitatively the same	Test and RLD products contain the same active (API) and inactive (excipient) ingredients.
Q2	Quantitatively the same	Test and reference products contain the same concentration of API and excipient ingredients.
Q3	**Physicochemical attributes are the same**	**Test and reference products have the same arrangement of matter (microstructure)**

Q3 physicochemical properties may include:

- Globule Size Distribution
- **Particle Size Distribution**
- Rheological behaviour
- Particle charge
- **Polymorphic Form**
- Phase Behaviour
- **Morphology**
- Molecular structure

Robert Lionberger, Office of Generic Drugs, CDER, FDA.
Pharmaceutical Science of Generic Drugs: The Science of Equivalence. NIPTE Research Conference, April 30, 2015.

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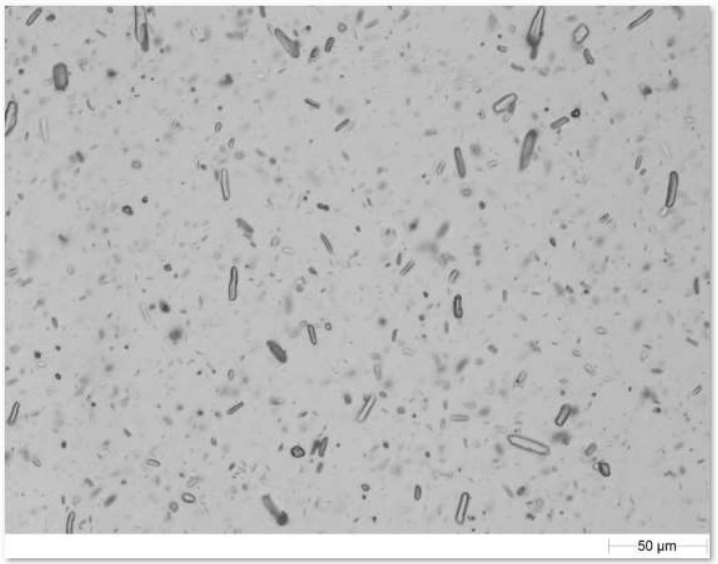
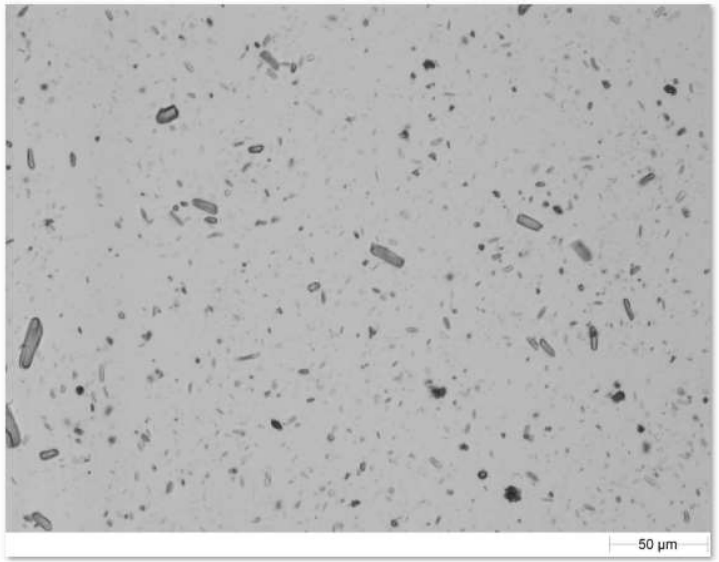
Case study 1: Nasal spray

Morphological analysis

Sharp Edge can help to improve the image quality of the particles



Generic Nasal Spray



RLD

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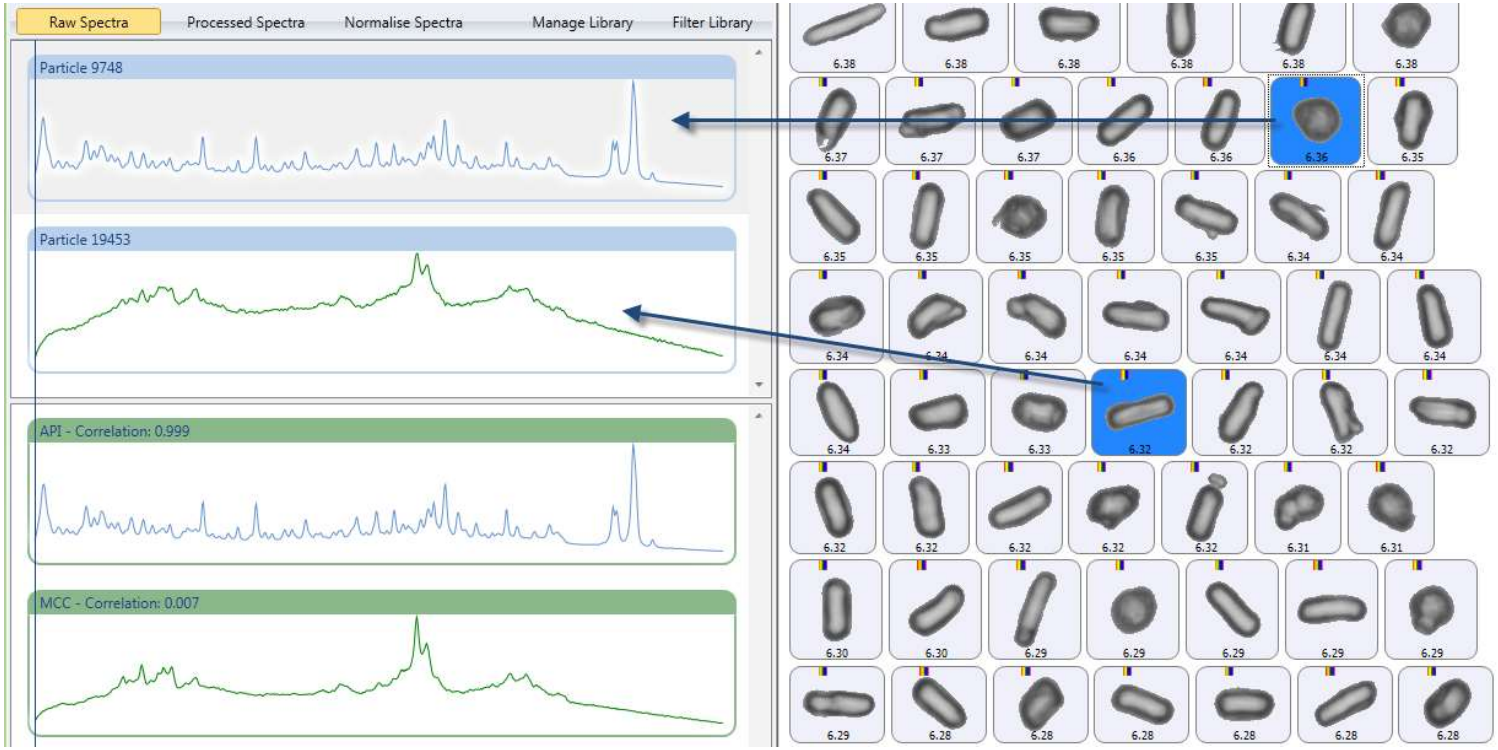
Case Study 1: bioequivalence of Nasal sprays

MDRS



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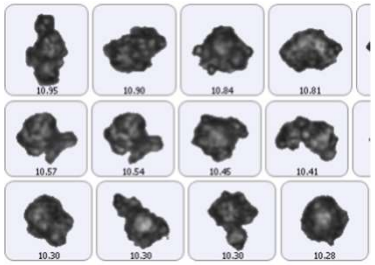
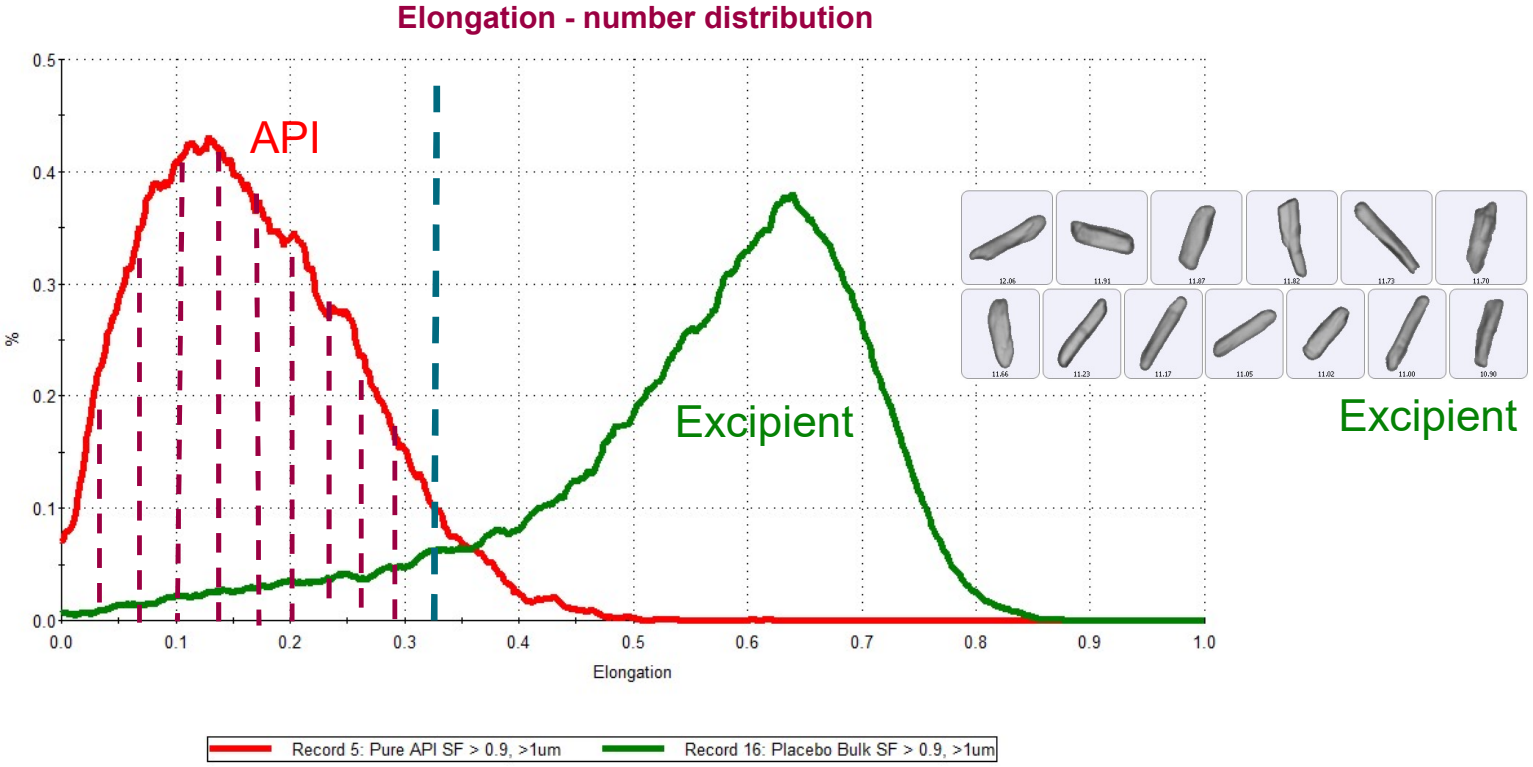
Case study 1: bioequivalence of Nasal sprays

Filter selection with the MDRS



API



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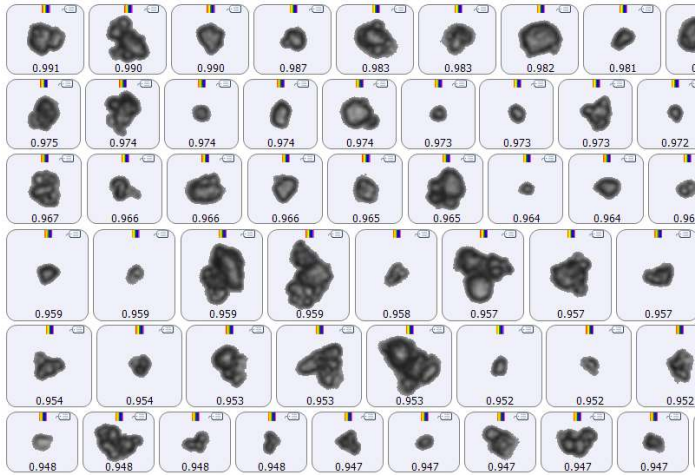
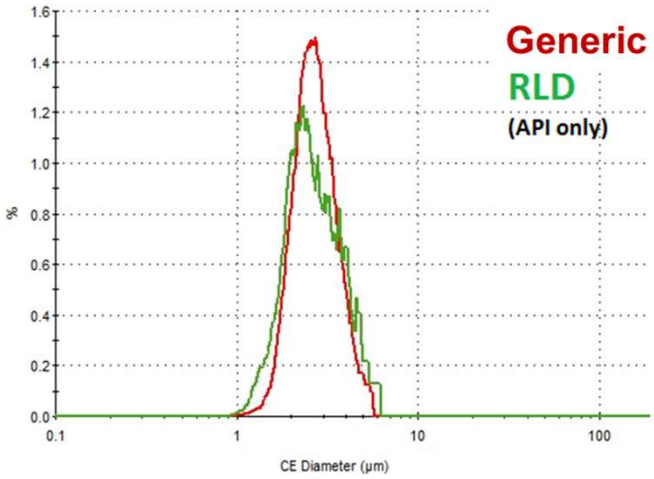
Case study 1: Nasal spray

MDRS comparison of the shape of the API and excipient



Particle Size Distribution of one chemical entity



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Case study 1: bioequivalence of Nasal sprays

FDA recognises the use of MDRS in establishing in vitro bioequivalence

"Apotex used data from an *in vitro* approach utilizing innovative technology… called Morphologically-Directed Raman Spectroscopy (MDRS)."

"Successful use of this technology sets a precedent to accept an *in vitro* approach in lieu of a clinical endpoint BE study."

FDA/CDER SBIA CHRONICLES

FDA Embraces Emerging Technology for Bioequivalence Evaluation of Locally Acting Nasal Sprays

Dr. Bing Li
Acting Director
Office of Generic Drugs

"FDA is very happy to have approved an application that included this innovative technology just four years after it became available. This shows our inclination to embrace emerging technology…"

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM502012.pdf

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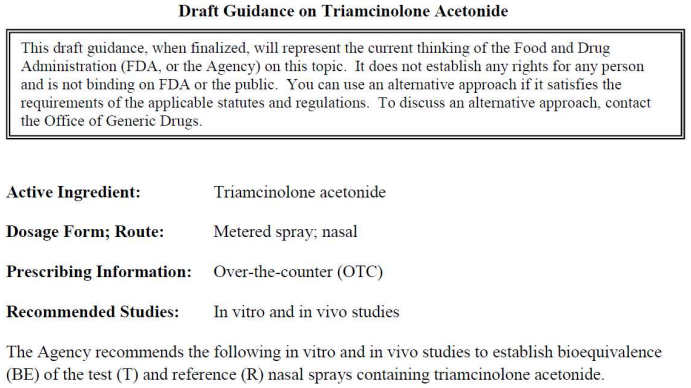
Nasal sprays

Recent Guidance from Oct 2016



Draft Guidance on Triamcinolone Acetonide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Triamcinolone acetonide

Dosage Form; Route: Metered spray; nasal

Prescribing Information: Over-the-counter (OTC)

Recommended Studies: In vitro and in vivo studies

The Agency recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) nasal sprays containing triamcinolone acetonide.

- **…….Alternate approach to the comparative clinical endpoint study:**

- A clinical endpoint BE study is recommended … because of an inability to adequately characterize drug particle size distribution (PSD) ……..using commonly used analytical methods. ….. **If drug PSD in the T and R products can be accurately measured using a validated analytical method such as morphologically directed Raman spectroscopy or any other advanced methodology**, sponsors may submit comparative particle size distribution data as part of their drug characterization within their ANDA application.

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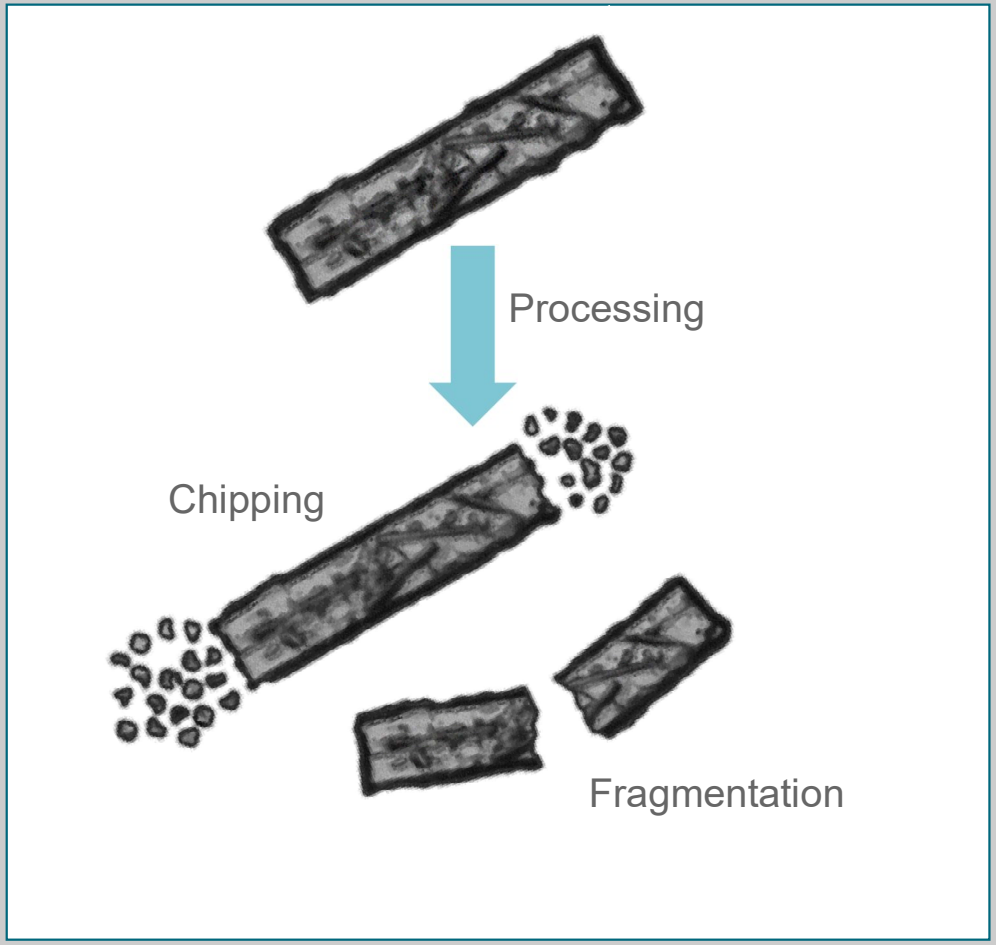

Process induced attrition

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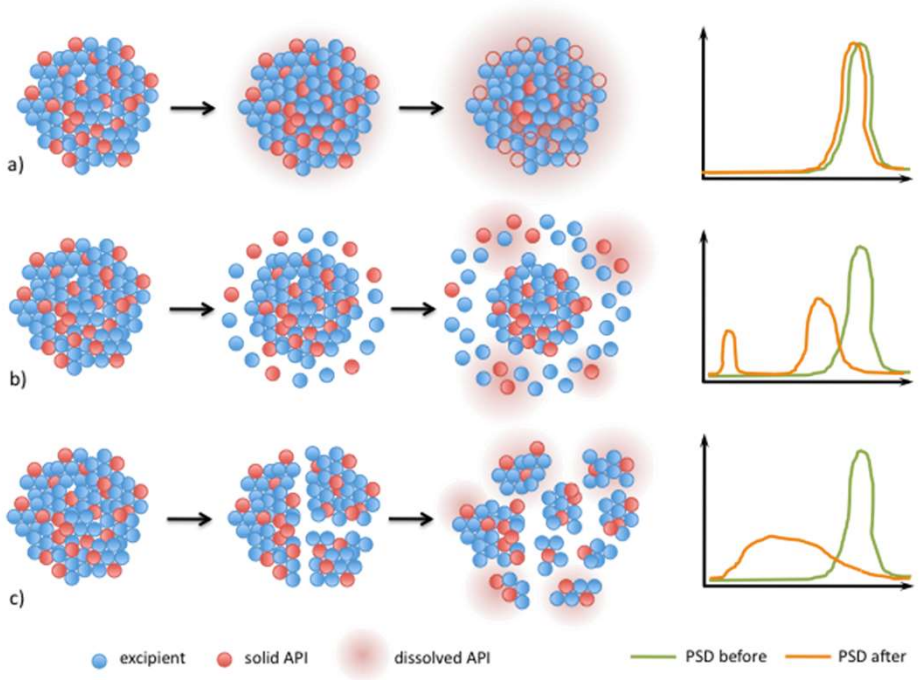
Process induced attrition

Some powders are more prone to attrition than others and this can affect quality

- Surface abrasion, chipping
- Generate fines
  - Bimodal dissolution profile
    - Fast then slow
    - Alter the intended release profile
  - Increase adhesion to tooling
  - Create particles with satellites
    - Change flow characteristics
      - **Product out of specification**

- Fragmentation
- Significant reduction in size
  - Alter the PSD of the API
  - **Product out of specification**



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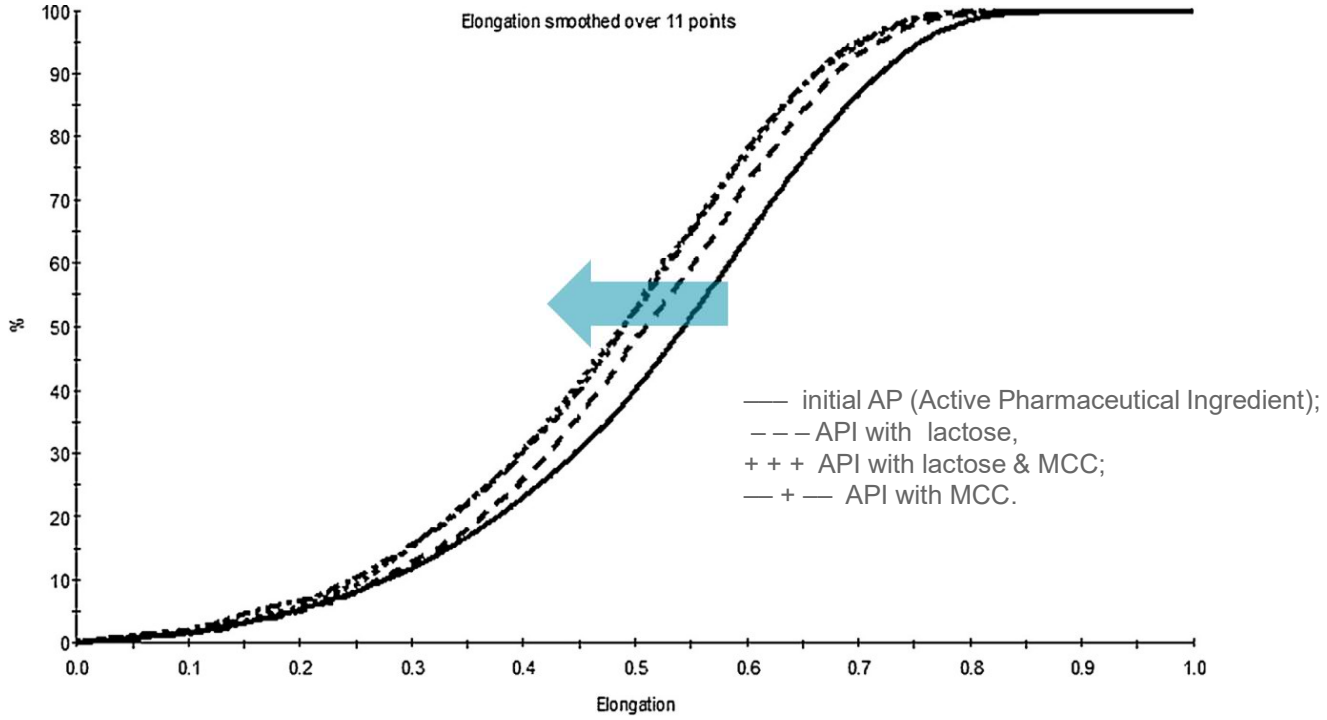
Pharmaceutical formulation processing

Pinpointing process problems using MDRS

Morphological characteristics of API measured in the presence of excipient using **MDRS** data

Tumble blended



John Gamble *et. al.* International Journal of Pharmaceutics 470 (2014) 77–87

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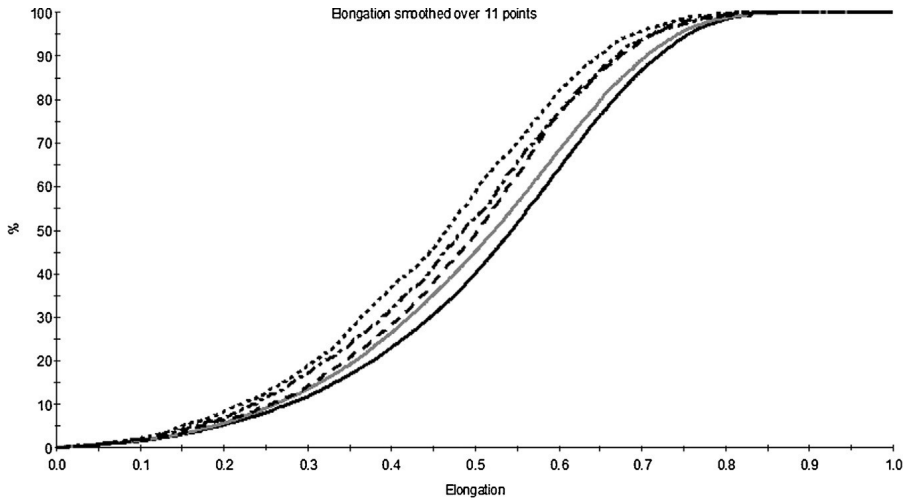
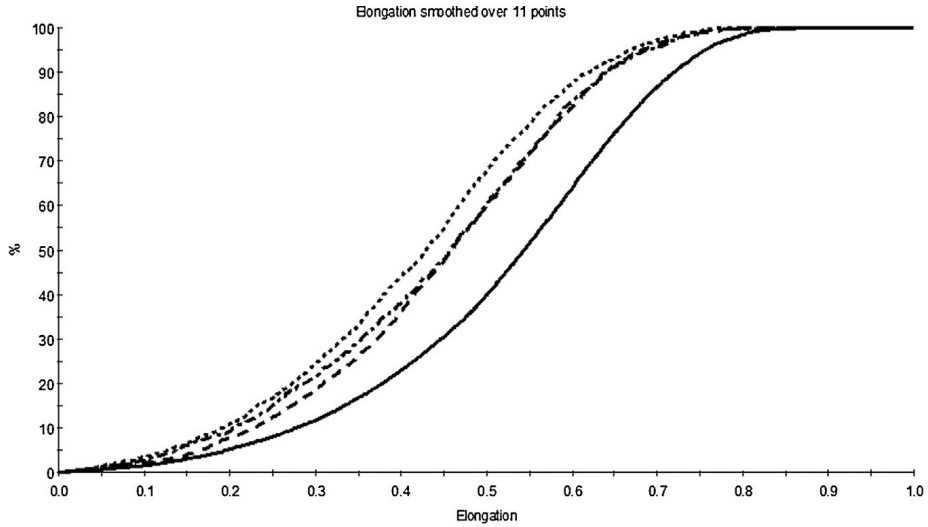
Pharmaceutical formulation processing

Cone milled
- Similar behaviour to tumble blending



Roller compaction
- More pronounced shift in elongation



—— = initial API; – – – – = API in lactose formulation; + + + = API in lactose and MCC formulation; — + — = API in MCC formulation.

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conclusions

- Similar **low** level attrition seen with **tumble blended** and **cone milled** processes
- More pronounced, **high** level attrition from the **roller compaction** process

- Both excipients caused more attrition than API alone
- MCC caused higher level of attrition than lactose

If particle size and shape is **critical to quality** then the formulation, blending and milling processes should be optimised to **control process induced attrition**

Use MDRS to test the effect of processes

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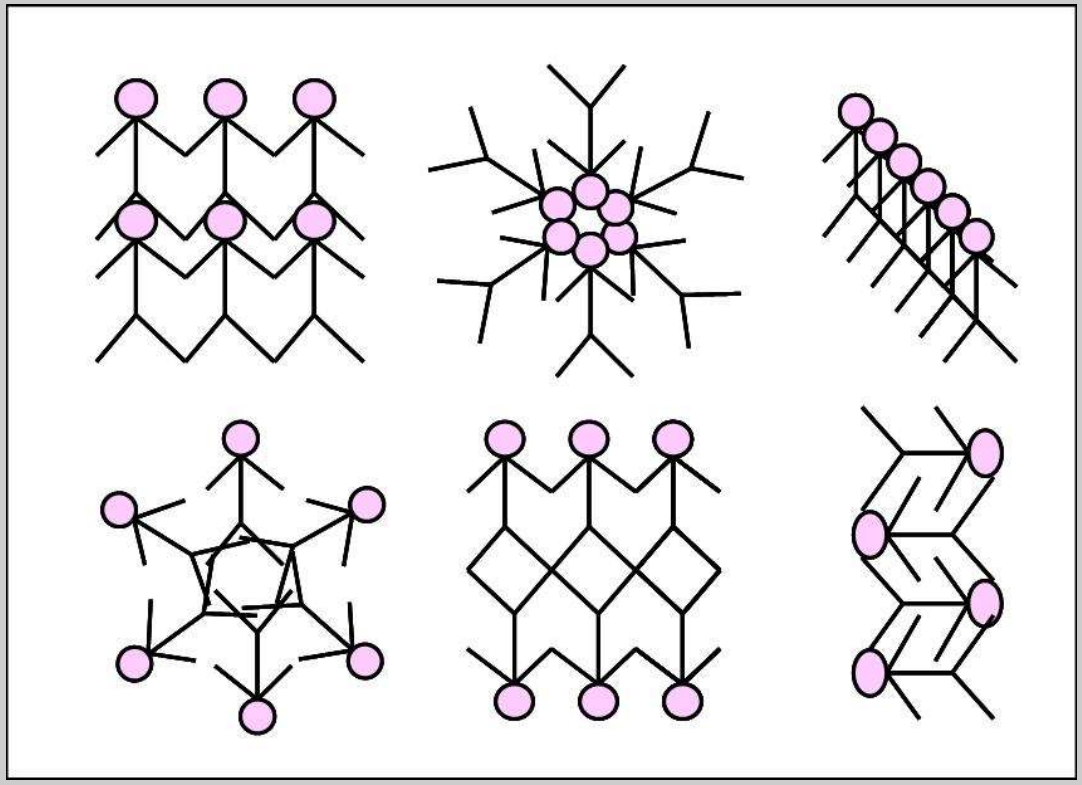

polymorphism

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Polymorphism

"A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state." – McCrone, 1965

- Drug performance – bioavailability and manufacturing

- Solubility: different polymorphs can have significantly different aqueous **solubility.**
- Crystal habit: differing density and shape may influence the **flowability** and **packing density** of the powder, but also the **rate of dissolution.**
- Stability: less stable polymorph can **convert** to more stable polymorph.
- Batch composition: all batches have the same polymorphs to the same ratio – GLP.

- Intellectual Property

- Fully characterised: all polymorphs identified and protected.

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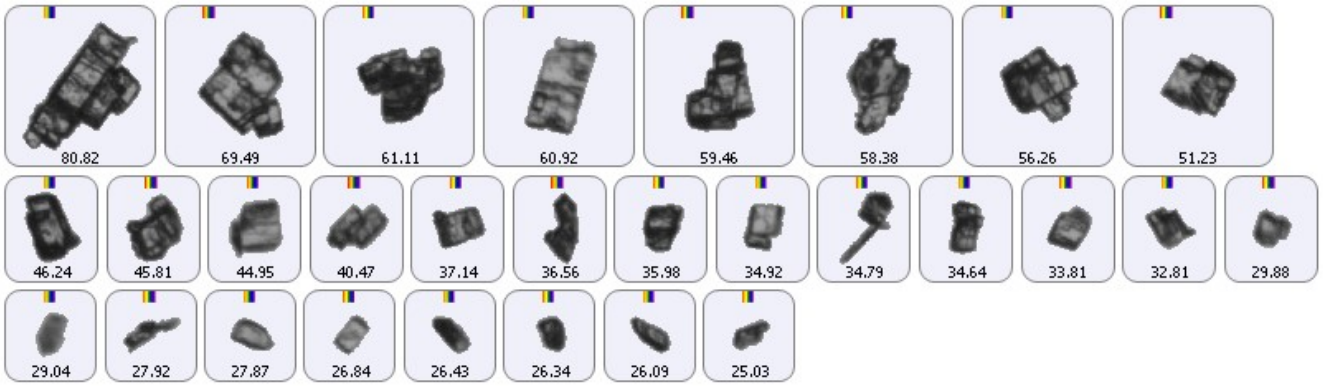
CASE STUDY 1: POLYMORPHS B AND C

Particle class - Polymorph B



Particle class - Polymorph C

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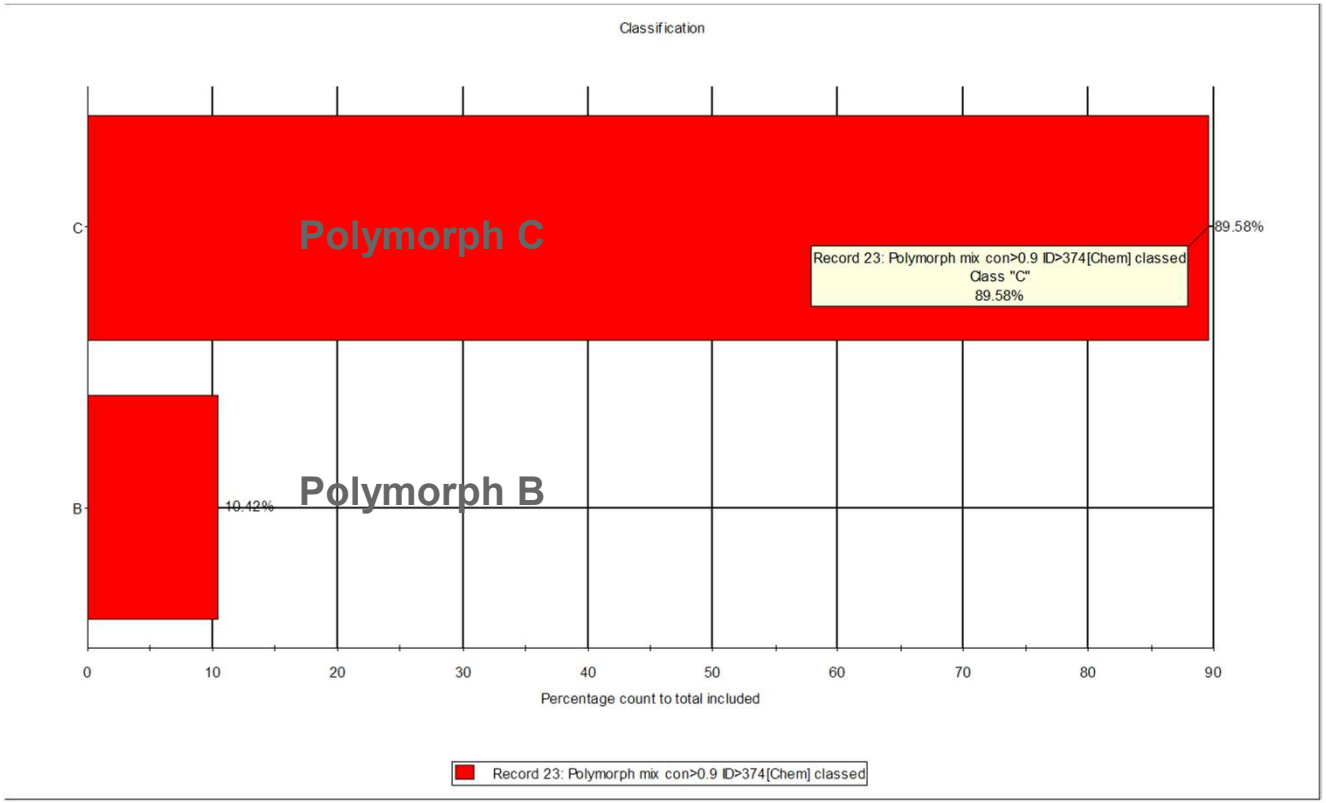
Case study 1: Composition by number of particles



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Case study 2: Acetaminophen

- Type 1 and Type 2 polymorphs

- A sample containing a mixture of type 1 and type 2 was created by
  - Recrystallizing a saturated solution of type 1 by cooling slowly
  - Recovered material dried at 75C
  - Half of the sample removed and heated to 170C to convert to Type 2
  - A mixture of 9 parts Type 1 and Type 2 milled in a hand mill

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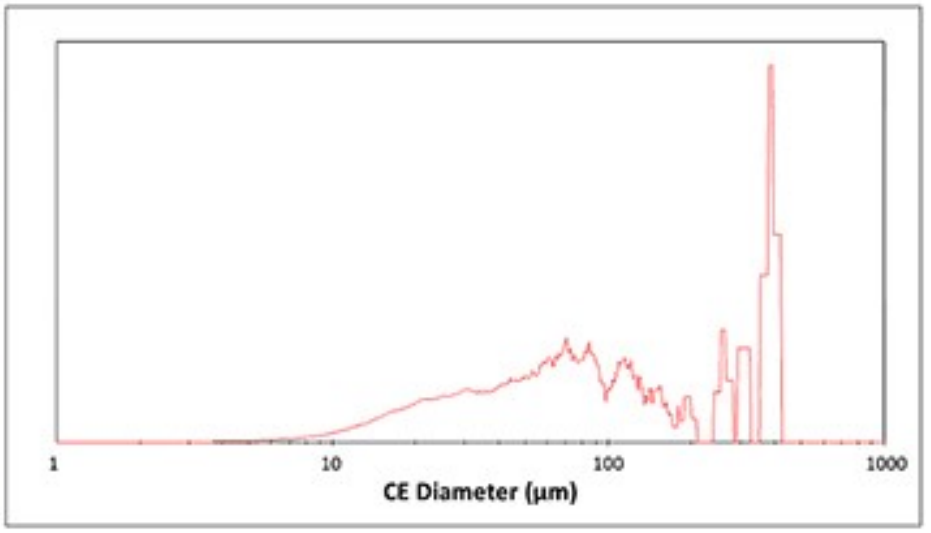
Case study 2: Morphological results

- 70,000 particles measured by automated image analysis
- 1375 particles targeted for chemical analysis
- Use the morphological result to classify particles for chemical analysis
  - >50µm
  - 25µm to 50µm
  - 10µm to 25µm

Example particles



Volume based particle size distribution

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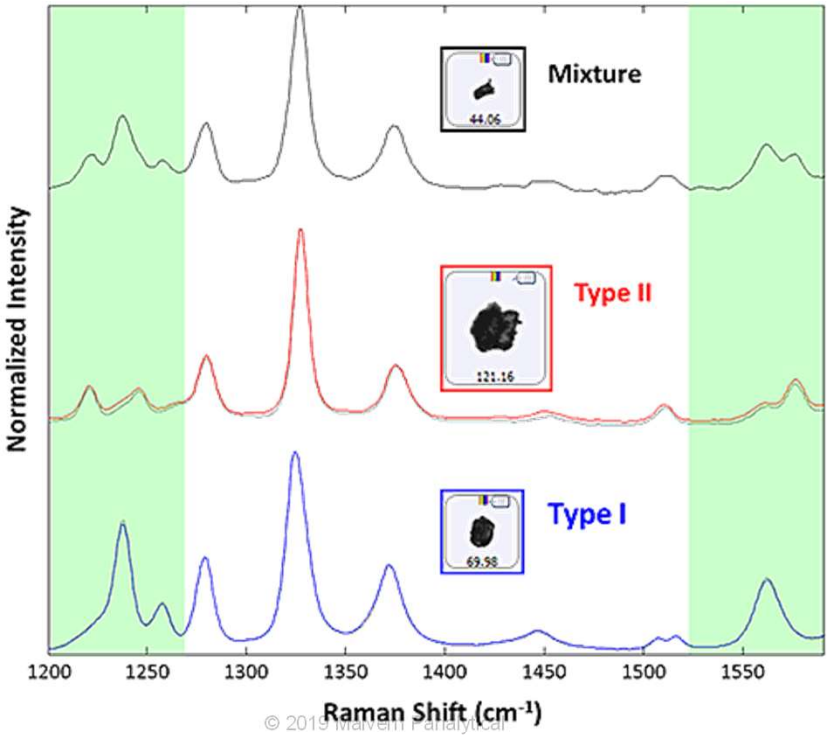
Case study 2: Chemical results

- Particles identified by correlation to library spectra
- Spectral range masking applied
  - 1200cm-1 to 1260cm-1
  - 1540cm-1 to 1590cm-1
- 1220 particles identified as Type 1
- 144 particles identified as Type 2
  - 10.5% of the total
- 11 particles show features from both type 1 and type 2
  - Aggregates formed during milling or dispersion



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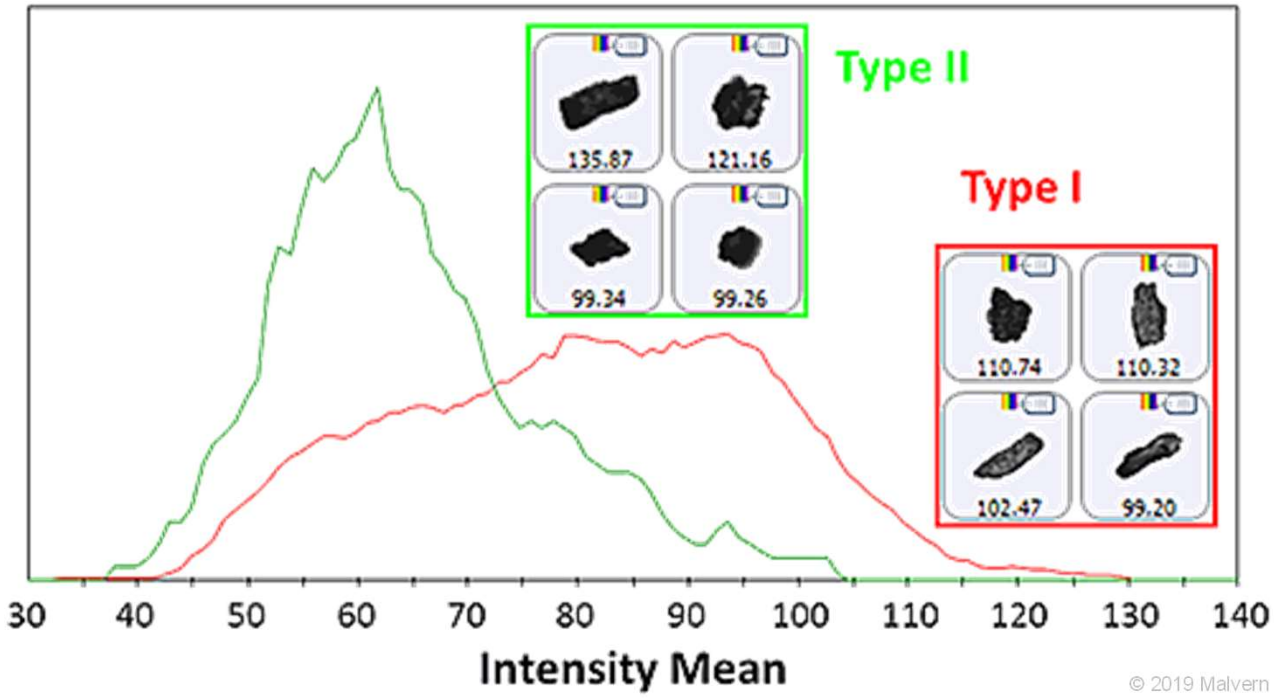
Case study 2: Linking ID to morphology

- Biggest difference is in the Intensity Mean
  - Type 1 particles are more transparent
  - However, there is an overlap so chemical identification is still required



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conclusions

- Characterise the polymorph composition using MDRS
- Perform morphological analysis on each polymorph
  - Correlate to powder performance
    - Flowability
    - Packing density
    - Dissolution rate

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Wheat Flour

Gluten free

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Context for flours

- Three different flour products
  - Leading brand wheat flour
  - Supermarket brand wheat flour
  - Gluten free flour
- Composition of flour
  - Starch
    - Wheat
    - Rice, potato, maize, tapioca, buckwheat (gluten free)
  - Protein
  - Trace constituents
- Starch has two particle types:
  - A-type: >10 µm
  - B-type: <10 µm

- A-type particle function
  - Higher gelatinization enthalpy
  - Higher peak viscosity of paste
  - Higher final viscosity of paste
- B-type particle function
  - Higher farinograph water absorption
  - Higher glycemic index

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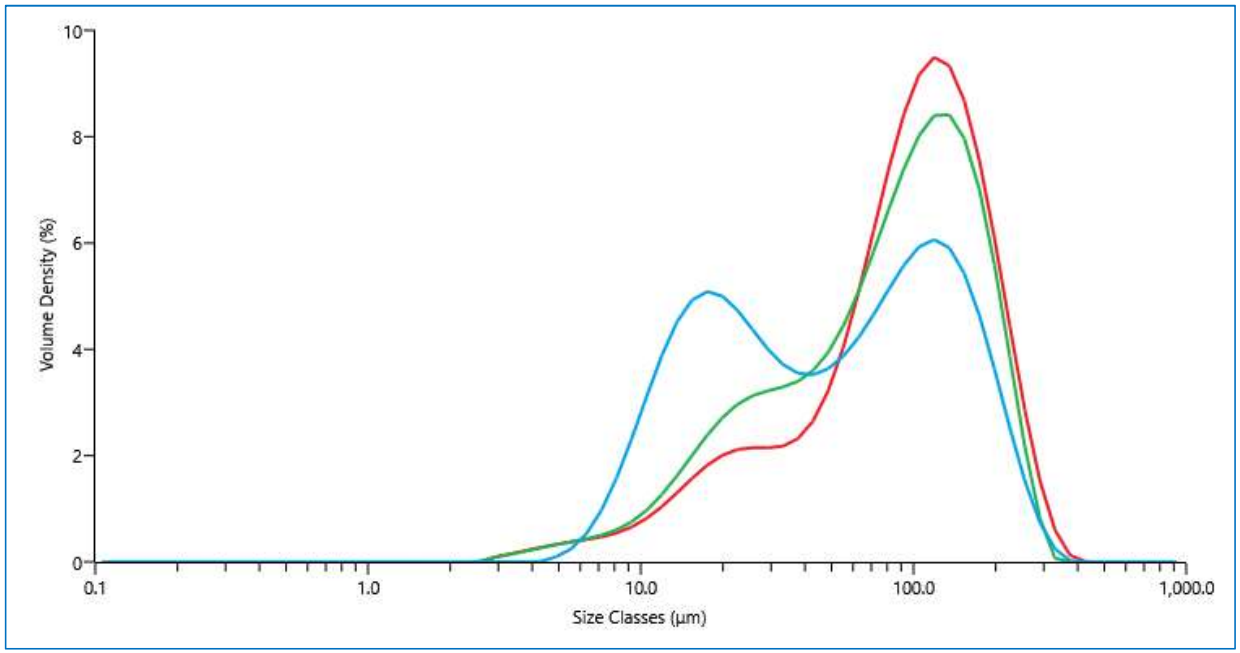
Particle size distribution by volume

Mastersizer 3000

- Comparable distributions for leading brand and supermarket brand of wheat flour
- Gluten free flour very different
- What causes this difference?



- Lead brand - Supermarket brand - Gluten free

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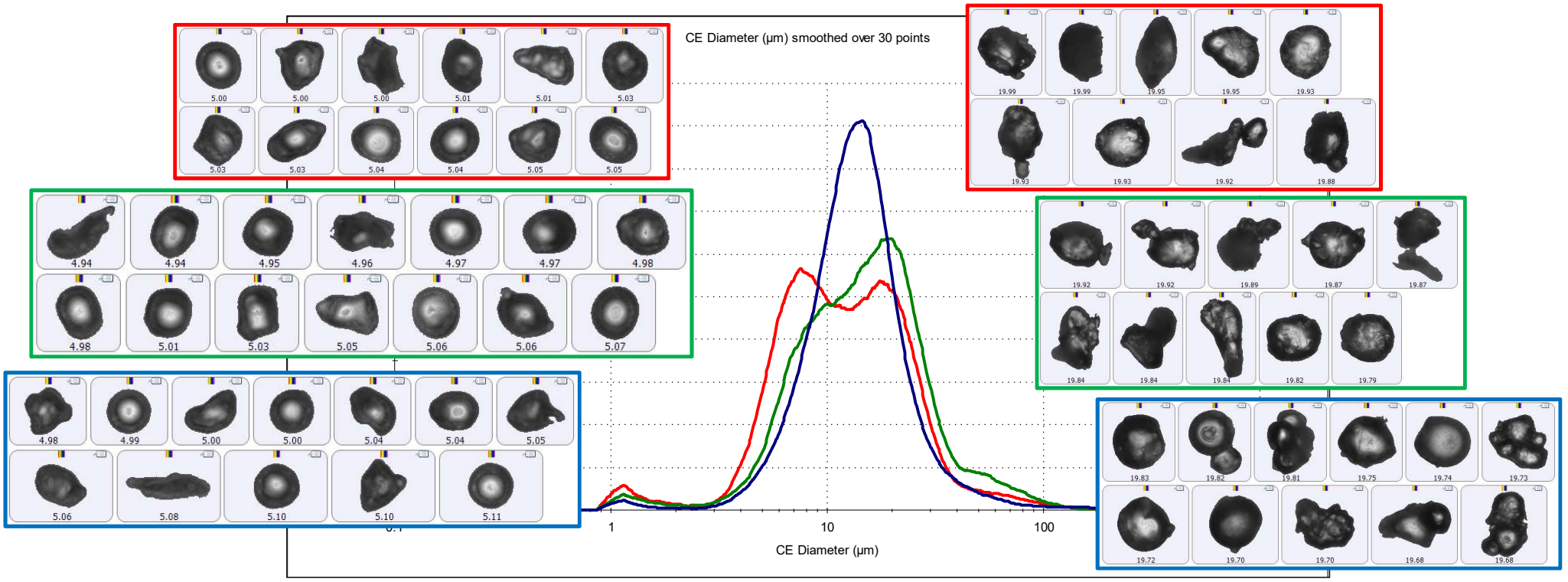
Particle size distribution by number

Morphologi 4-ID



- Lead brand
- Supermarket brand
- Gluten free

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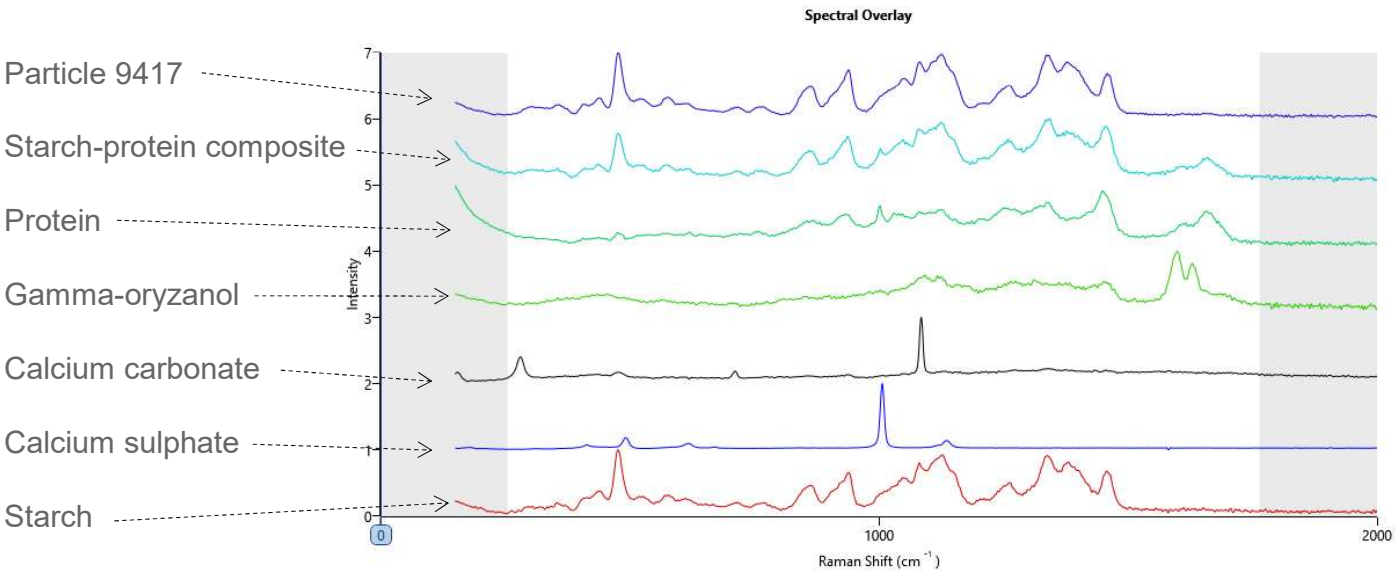
Raman spectral library

A particle spectrum and the library spectra



Correlate particle spectrum to library spectra

Correlations	Particle ID 9417
Starch	0.994
Calcium sulphate	0.105
Calcium carbonate	0.172
Gamma-oryzanol	0.088
Protein	0.593
Starch-protein c...	0.959

This particle had the highest correlation to Starch

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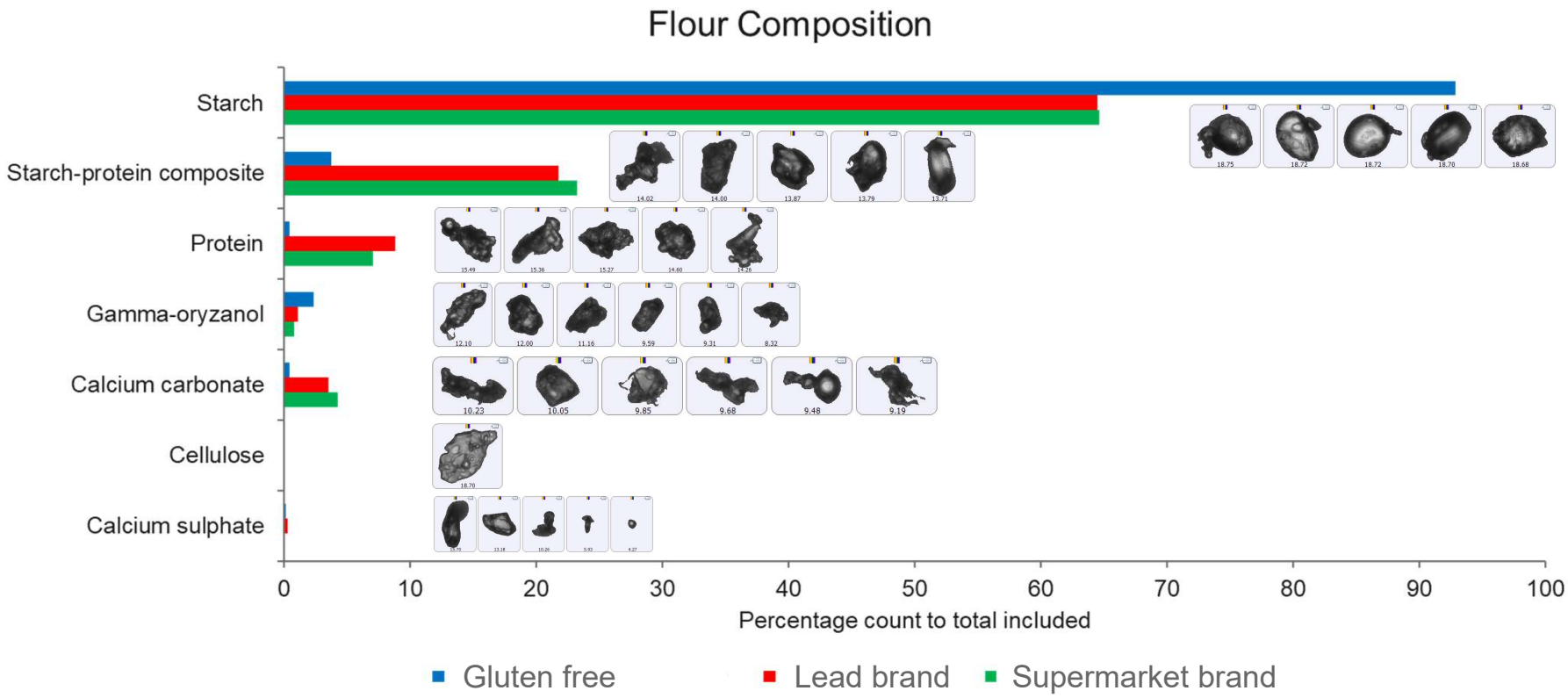
Composition

% number



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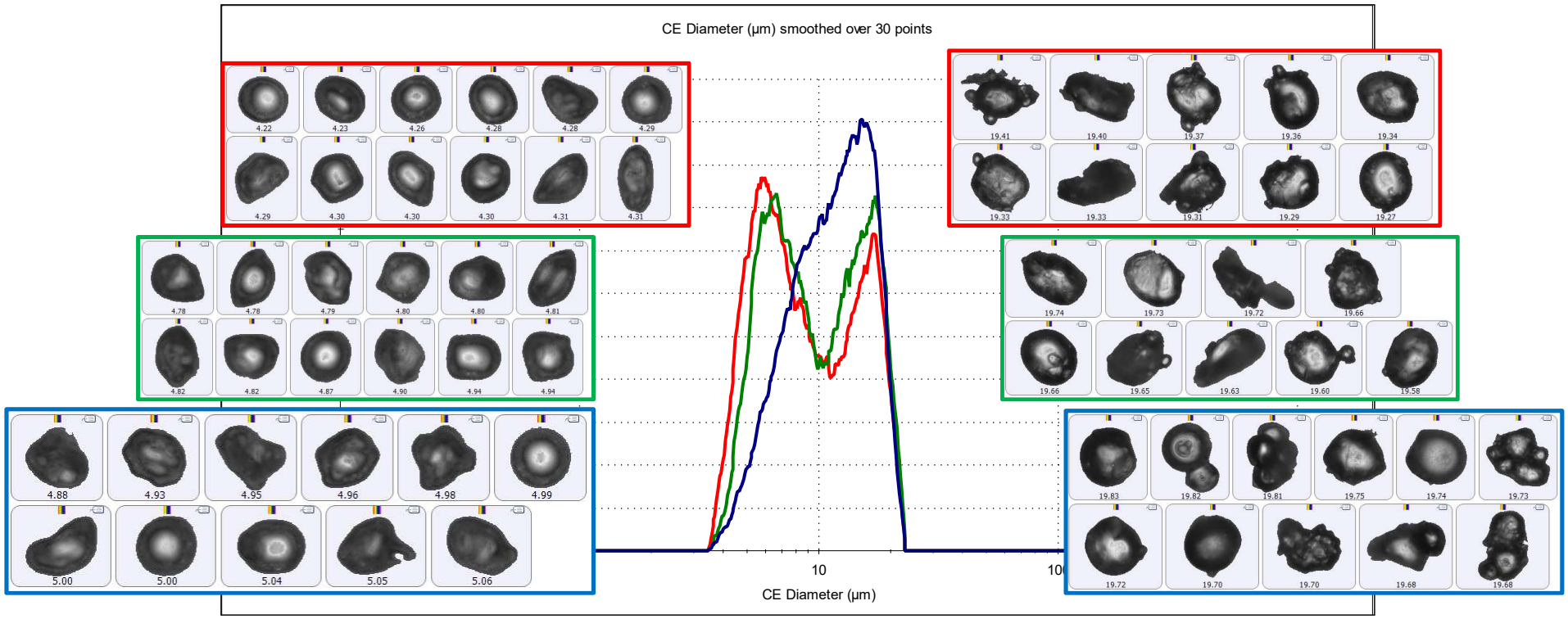
Particle size distribution of starch

Number distribution



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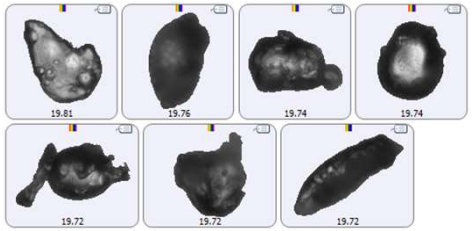
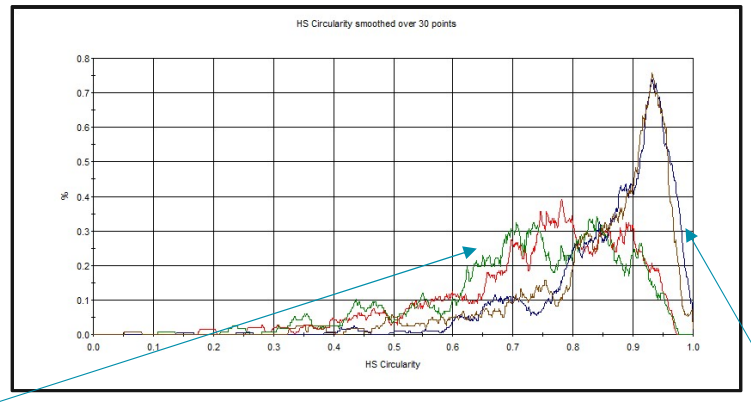
Circularity of A and B-type starch

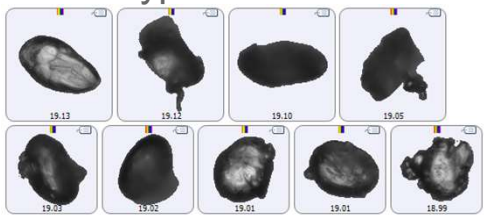
- Lead brand A-type

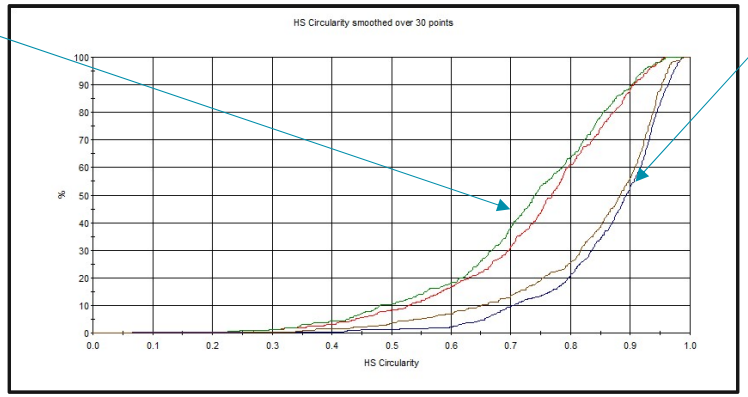




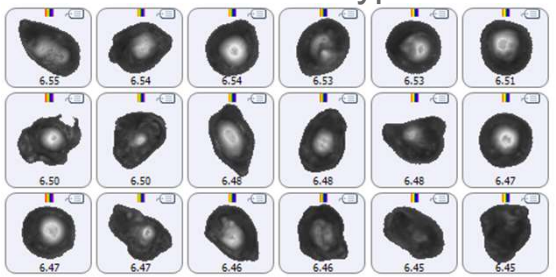
A-type particles

- Supermarket A-type



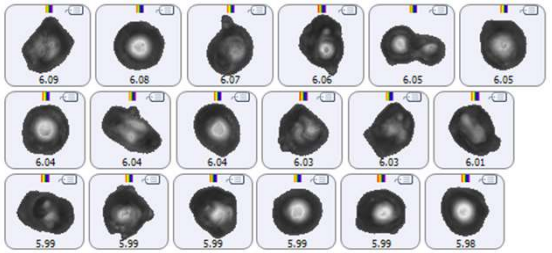


- Lead brand B-type



B-type particles

- Supermarket B-type



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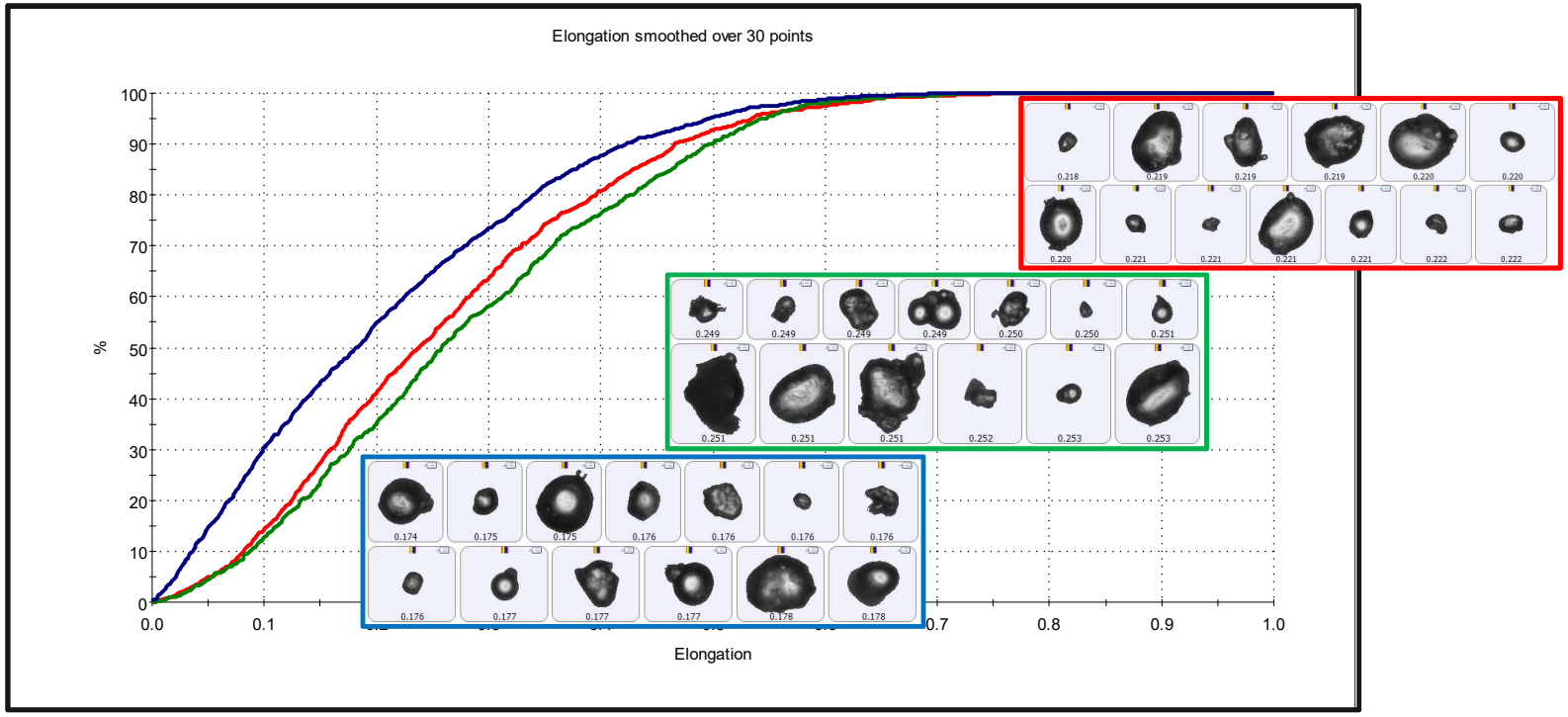
Elongation distribution of starch



- Lead brand
- Supermarket brand
- Gluten free

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Conclusions

Flours

- Three flour brands compared by MDRS
- Starch was the main component with a substantial amount of protein for the standard wheat flours (Lead and supermarket brands).
- Most protein agglomerated with starch to form composite particles
- Notably less protein in gluten free brand
- The starch in the standard wheat flour brands had a bimodal size distribution from the A and B-type particles, whereas the gluten free product was monomodal.
  - B-type particles more spherical than A-type particles
  - Gluten free product was biased towards A-type particles
- Gluten free particles were more spherical than the standard flours
- This will likely affect the manufacturing processes of the flour and structural and nutritional performance of the dough.

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Metallurgy
Additive Manufacture

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May 29, 2019

Applications: Powder metallurgy

Common processes

- Additive Manufacturing: AM
  - Laser Beam Melting: LBM
  - Electron Beam Melting: EBM
  - Direct Energy Deposition: DED/ Laser Metal Deposition: LMD
  - 3D printing
- Metal Injection Moulding: MIM
- Hot Isostatic Pressing: HIP
- Cold Isostatic Pressing: CIP
- Press and Sinter

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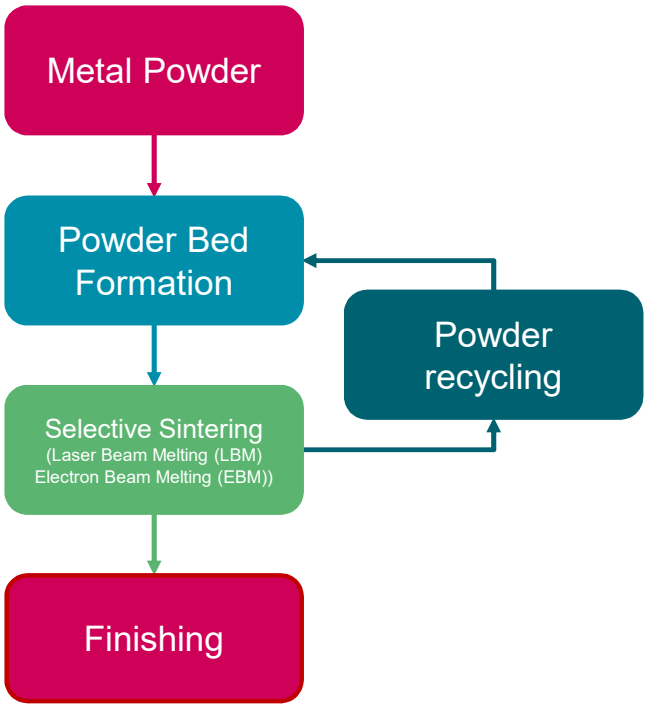
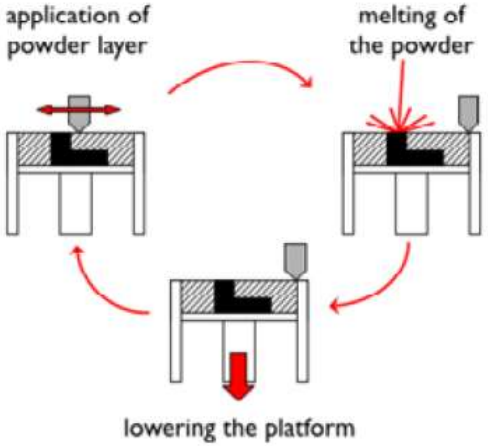
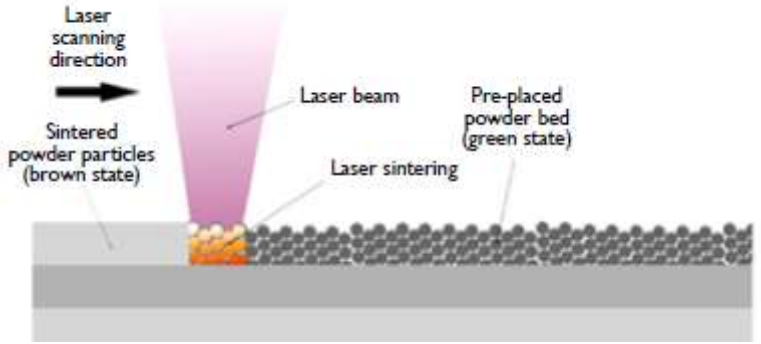
Applications: Additive manufacturing

Processes (Laser Beam/Electron Beam Melting)







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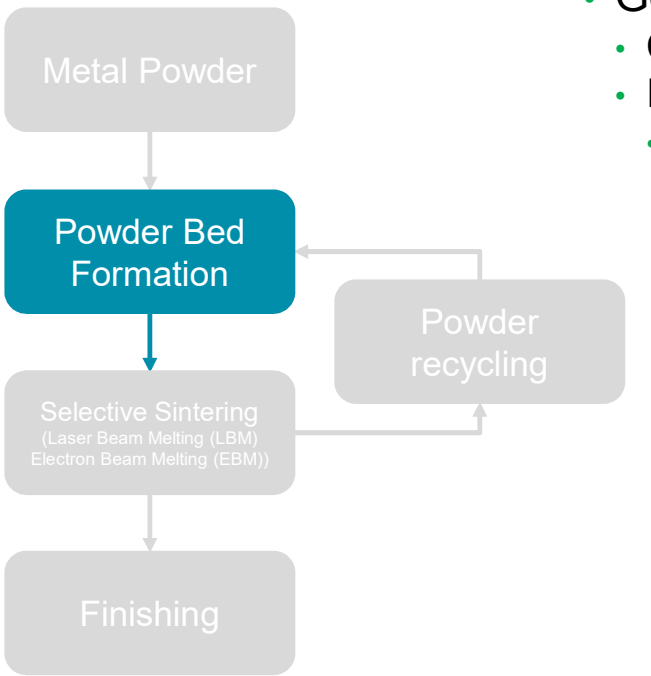
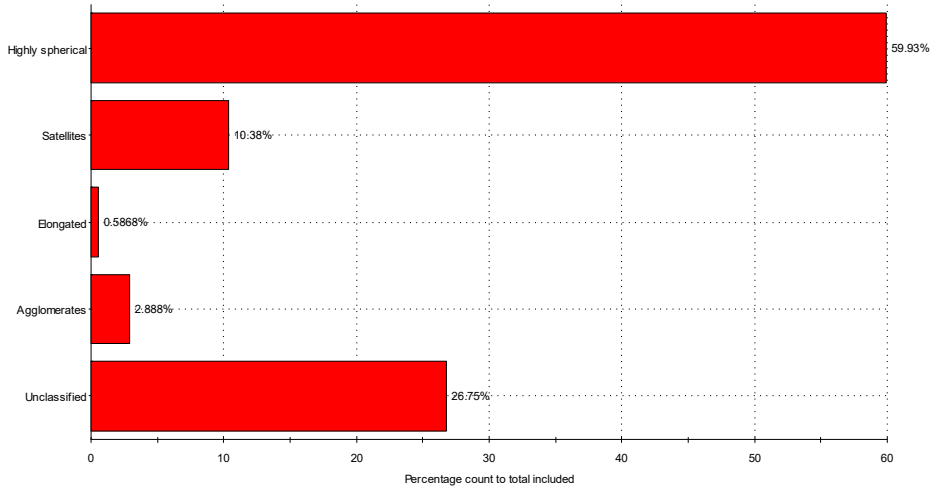
Why is particle morphology important?

Powder bed formation



- Good powder flowability
  - Cohesive fine particles affect flowability
  - Irregular particles increase interlocking and reduce flowability
    - Irregular and satellited particles can be quantified in classifications



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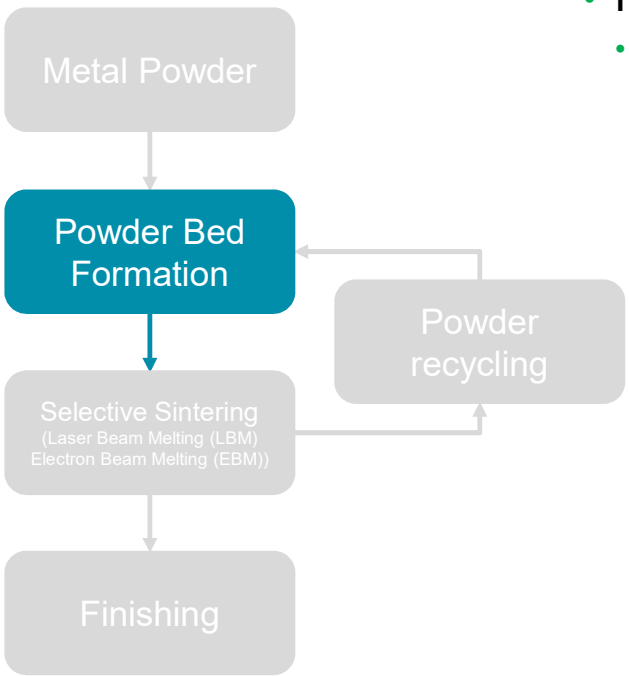
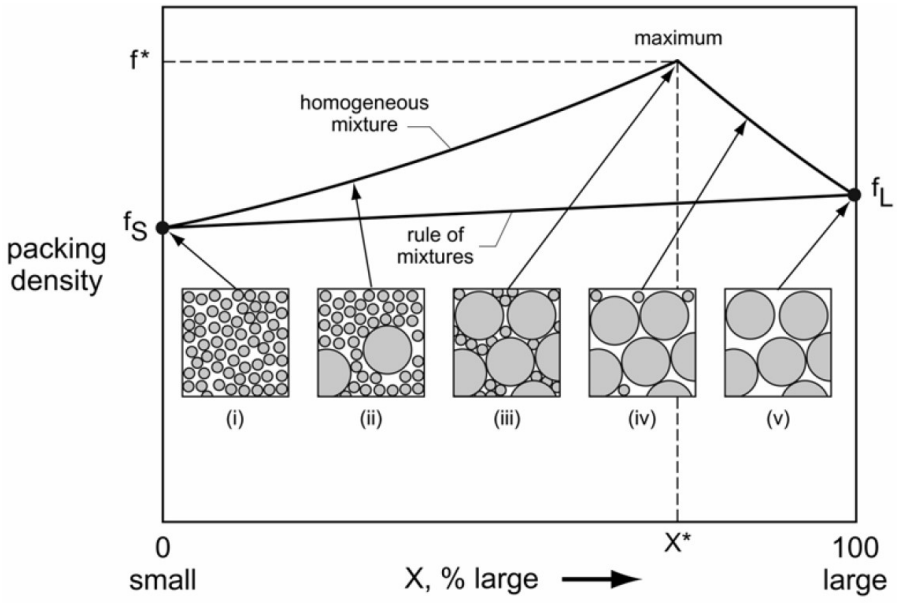
Why is particle morphology important?

Powder bed formation



- High packing fraction
  - Particle size and size distribution affects packing fraction



Fundamentals of Refractory Technology
James P. Bennett & Jeffery D. Smith, Ceramic Transactions, Volume 25, 2001 (American Chemical Society)

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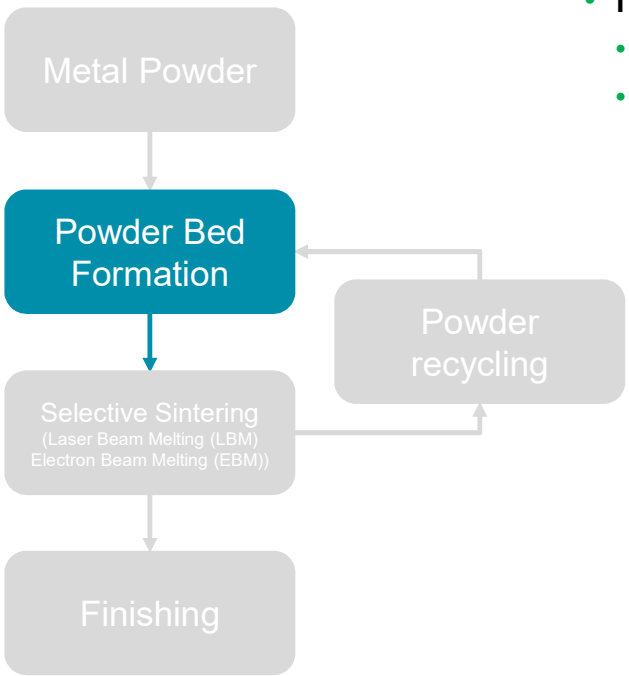
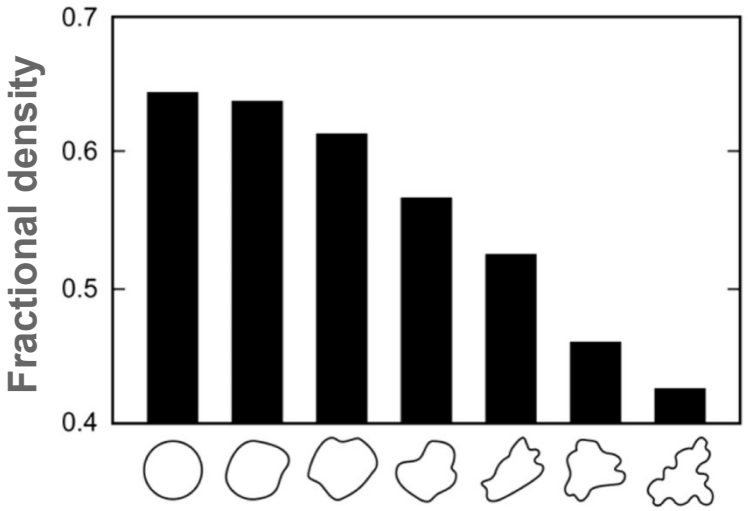
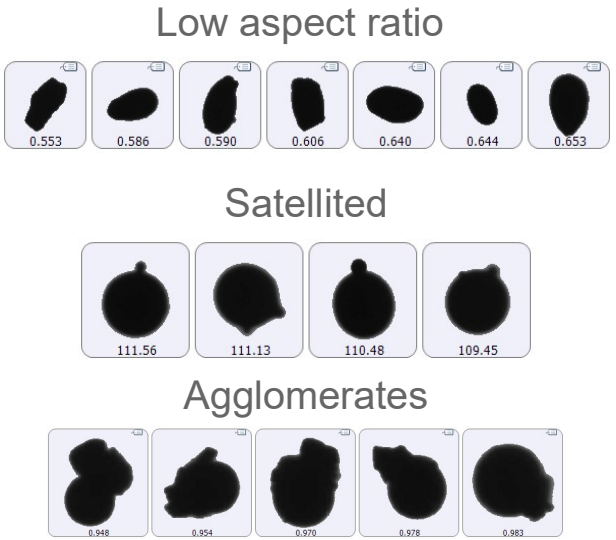
Why is particle morphology important?

Powder bed formation



- High packing fraction
  - Particle size and size distribution affects packing fraction
  - Particle shape affects packing fraction
    - Classify and quantify irregular particles with the Morphologi 4





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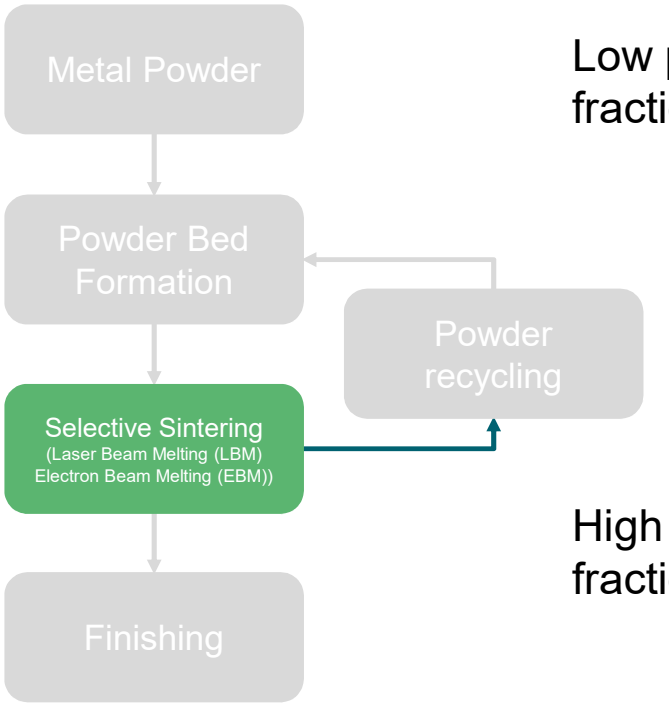
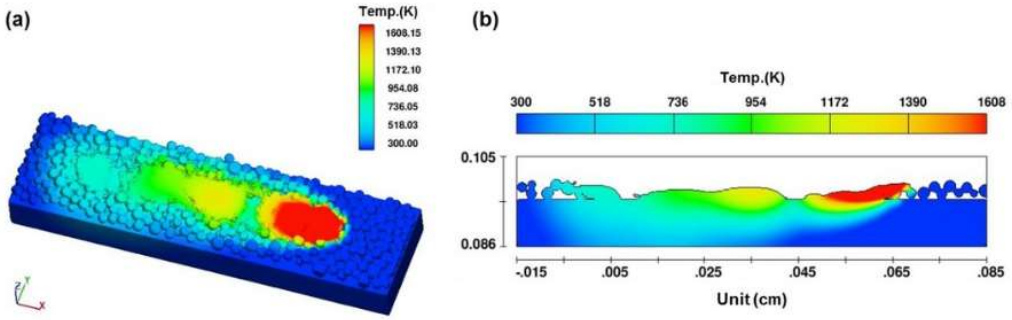
Why is particle morphology important?

Processes (Laser Beam/Electron Beam Melting)

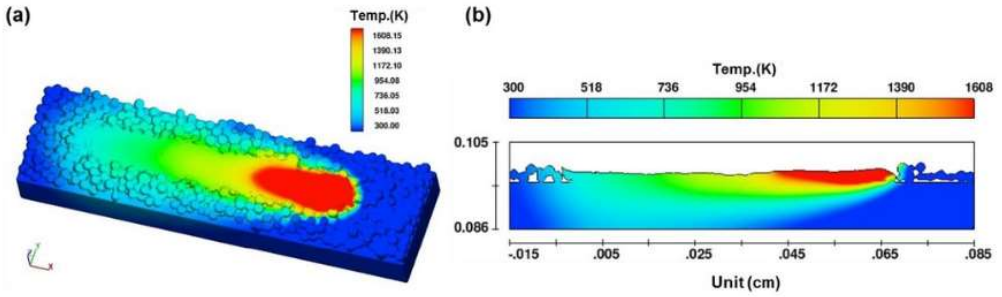


Low packing fraction



melt pool shape of powder bed density =38% [1]

High packing fraction



melt pool shape of powder bed density =45% [1] - (all processing conditions fixed)

[1] Y.S. Lee and W. Zhang, Mesoscopic simulation of heat transfer and fluid flow in laser powder bed additive manufacturing, 2015, http://sffsymposium.engr.utexas.edu/

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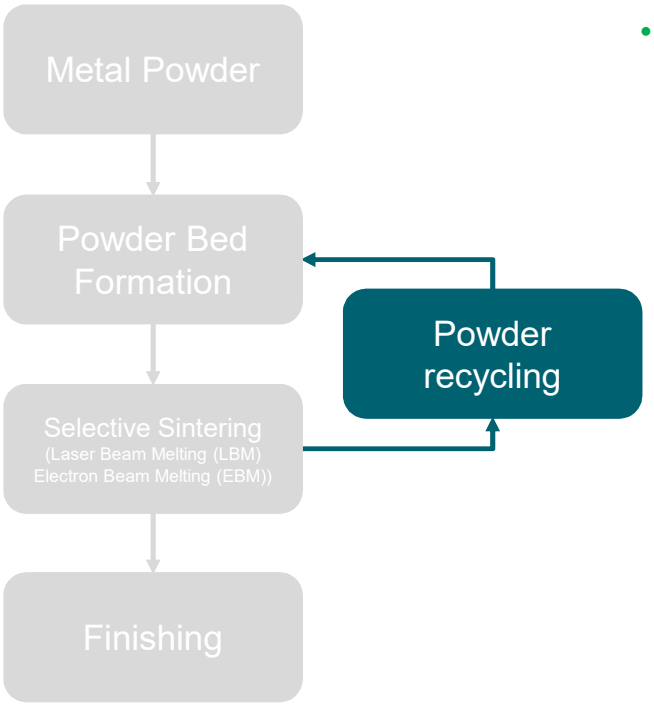
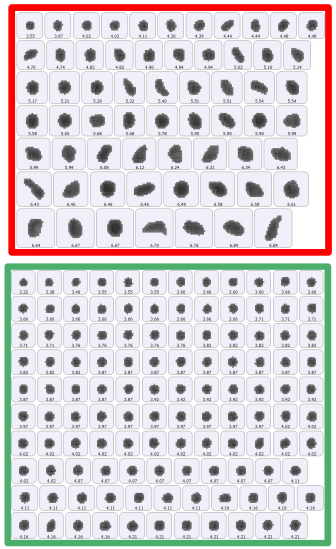
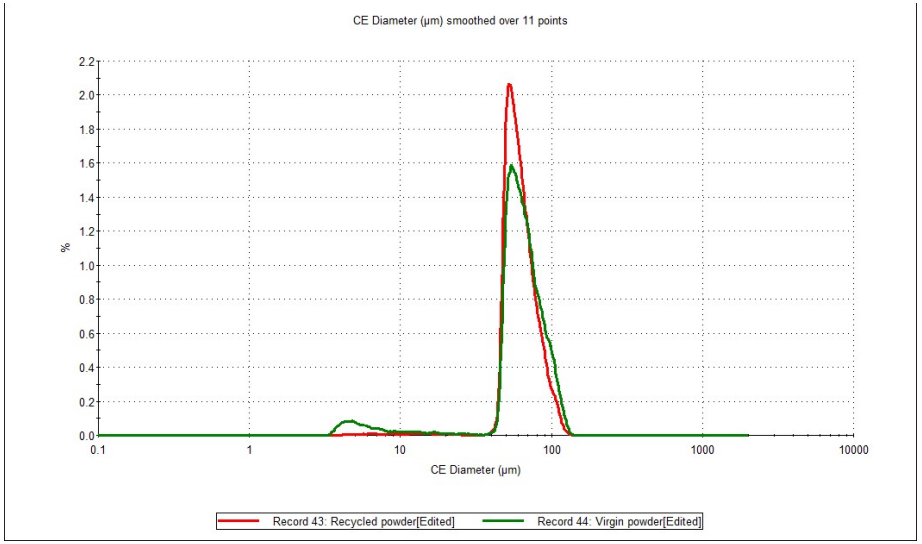
Why is particle morphology important?

Recycling



- Metal powders are expensive, recycling is essential
- Track changes in particle size and shape
  - Blend recycled powders to keep optimum size and shape distributions





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Conclusions

Additive Manufacture

- In LBM/EBM additive manufacture, the integrity of the part is dependent on the quality of the powder bed
  - A homogeneous, high density powder bed is required to form a continuous, defect free layer
- The right balance of coarse and fine particles are required to maximise packing density
- Particle shape will also affect flowability and packing density

- Characterise both particle size and shape of the **virgin powder** using Automated Image Analysis
- Characterise both particle size and shape of the **recycled powder** using Automated Image Analysis

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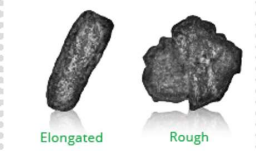
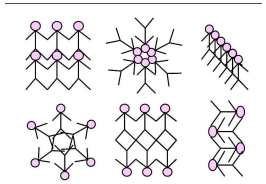
Summary



Introduction to Imaging and MDRS

Introduction to Morphologi 4 and 4-ID

Pharma – Nasal Sprays



Pharma – Polymorphism

Food - Flour

Metallurgy – Additive manufacture

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Thank you for your attention

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