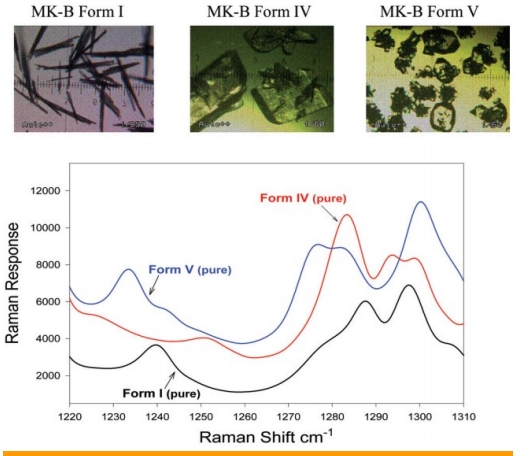
Technologies for the characterisation of crystals and crystallisation.

Particular Sciences

Winter 2016/2017 **"We do more for you…"**

Raman Spectroscopy **Kaiser Optical**

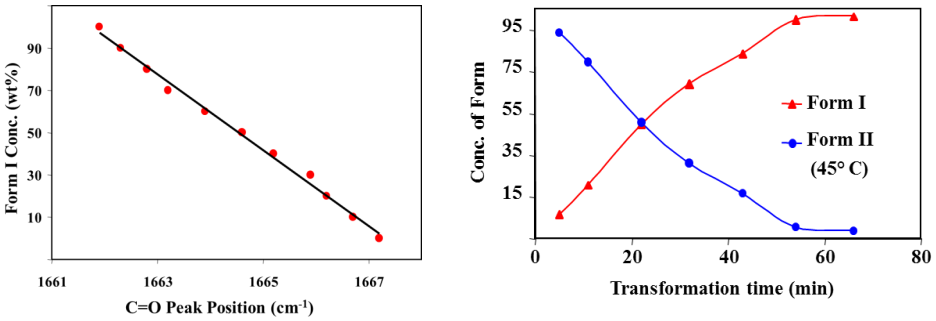


Microscope images of three crystal forms of pharmaceutical compound MK-B (top), and their Raman spectra in toluene (bottom) (Kaiser)

Raman spectroscopy is a particularly effective tool for the characterisation of different types of crystalline forms of the same material (polymorphic forms), and has become an established tool in monitoring crystallisation phenomena as it can be used in development to understand a process and then transition with the chemistry through scale-up and into manufacturing. In manufacturing, Raman can be used to: monitor the progress of the crystallisation process; assess the endpoint; assure that the correct polymorph has been formed.

From left-to-right: Kaiser Raman RXN3 for process; RXN2 Analyser with 4 fiber optic immersion probes; Rxn2 Hybrid with PhAT (macro) non-contact probe. Traditional (micro) non-contact probes are also available

The ability to characterise, optimise, and control the crystallisation process, polymorphic forms and co-crystals are thus industrially critical. Raman spectroscopy enables in situ, non-destructive and fast quantitative measurements to meet these needs as well as offering the ability to analyse forms non-destructively in a manner that is scalable from Discovery to Manufacturing. Kaiser's RAMANRXN Systems™ family represents the state of the art in Raman analysers and is the choice for Raman spectroscopy, both in the laboratory and on the process line.



Calibration plot of form I concentration (top) and in-situ monitoring of polymorphic transformation of progesterone form I to form II in solution (bottom) (Kaiser)

Study:

- Crystals of small//medium sized molecules
- Protein/large molecule crystals
- Crystallisation
- Nucleation and Ostwald ripening
- Polymorphic transformations

Quantify:

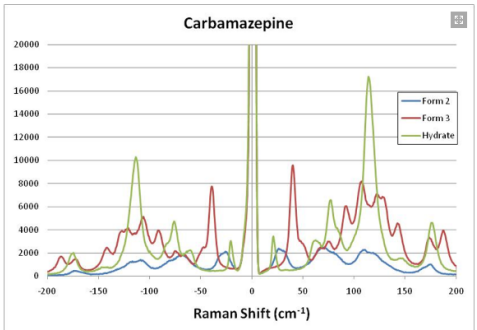
- Particle Size
- Particle Shape
- Particle Concentration
- Flow rate
- Chemical identity
- Polymorphic forms
- Powder flowability

PAT & Process:

- Offline / batch analysis
- On-line (flow-through cells)
- In-line probes

ONDAX

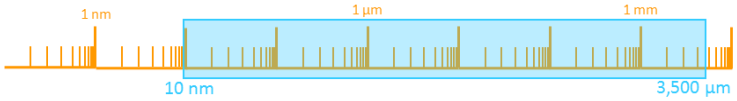
THz Raman for Morphology information



Crystal Sizing

Laser Diffraction

Dry Wet



< 5 minutes / sample

Malvern's **Mastersizer 3000** is the world's leading laser diffraction particle sizing instrument. It packs exceptional performance into the smallest of footprints with the minimum of effort. Size distributions (volume-based) of crystals can be measured as dry powders, or be suspended in a suitable liquid (dispersant) for wet measurement.

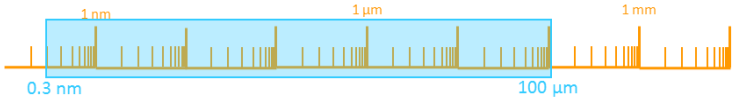
See your Crystal Dispersion!

Hydro Sight™ is a relatively new and revolutionary image accessory that provides rapid visualization and assessment of your liquid particle dispersion while its being recirculated in the MS3000. It is quickly connected in-line with any wet dispersion accessory, and measures the dispersion quality for method development, and qualitative size and shape to aid interpretation of the main Mastersizer data.

MS3000 with Hydro EV accessory for wet dispersion (left) and Hydro Sight accessory (right) (Malvern)

DLS and NTA

Wet



10—30 minutes / sample

The class leading **Zetasizer Nano** (for Dynamic Light Scattering, DLS) and the leading **NanoSight NS300** (for Nanoparticle Tracking Analysis, NTA) can be used to detect, size and monitor submicron crystals and even molecular clusters in solution.

Zetasizer Nano ZSP (Malvern)

NanoSight NS300 (Malvern)

The singular benefit of either of these systems is their sub-micron sensitivity...down to the nanometer ranges. The Nano ZSP especially can sense sub 1 nm material.

Process Sizing

In-line, On-line, At-line

Laser Diffraction

Insitec (Malvern)

Malvern's **Insitec** range can be regarded as the in-line version of the Mastersizer 3000 and be installed directly into a dry or wet flow of crystalline material to measure 0.1 to 2,500 um powders. Insitec is available with all the IP classifications and ATEX ratings you may require, and can be integrated with process control.

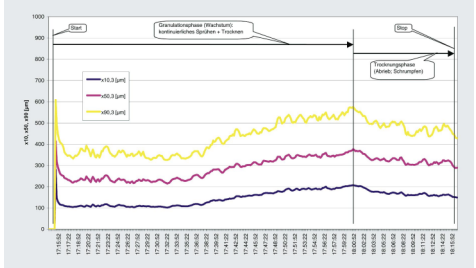
Spatial Filter Velocimetry

Parsum from Malvern

This special probe product range adds velocity to size measurement and is installed directly into a dry or wet flow of crystalline material to measure 50—6,000 um crystals.

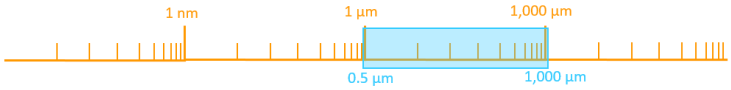
Parsum (Malvern)

One very useful application area for **Parsum** is with granulation, pilot scale or plant scale. The plot below is of particle sizes with time in a fluidized bed granulator:



Crystal size & shape analysis

Static Image Analysis



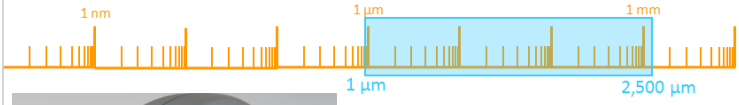
1-3 hours / sample

Malvern's **Morphologi G3** is an advanced yet easy-to-use static automated imaging microscope, providing the ultimate crystal-by-crystal sizing and shaping tool—the G3-iD even adds Raman spectroscopy to identify the chemical species and polymorphic form of individual crystals. Crystals can be analysed dry & wet.

Batch / Offline

Raman

Dynamic Image Analysis



10—30 minutes / sample

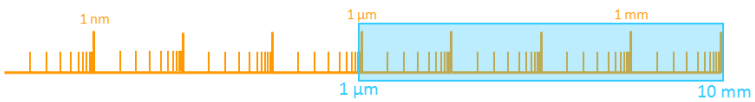
Micromeritics' **Particle Insight** is a state-of-the art dynamic image analyser which is ideal for applications where the shape of crystals, not just the diameter, is critical. The Particle Insight offers up to 28 different shape parameters analysed in real-time in either aqueous or organic solvent suspensions (wet only) and can be used in batch mode (re-circulation) or continuous (flow-through, PAT-suitable).

Batch / Offline

PAT: **On**-line

Concentration

In-line Image Analysis **SOPAT**



Real-time

SOPAT, made by a German company of the same name, is an inline microscope containing a smart image analysis software to deliver robust and accurate real-time particle detection and characterisation.

This approach allows full automation and process control in crystallisation processes. A range of probes are available to suit different process conditions.

PAT: **In**-line

Concentration

Seeing is believing...

Laser diffraction (Mastersizer 3000) measure volume-based distributions which are influenced by larger particles, while image analysis (Particle Insight & Morphologi G3) will yield number-based size distributions, which are great with the fines, smaller particles and individual coarse particles.

Additionally, image analysis gives images of every crystal measured, and numerous shape parameters (e.g. circularity, aspect ratio, smoothness, polygon order).

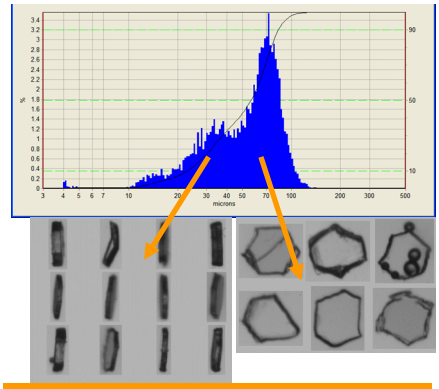
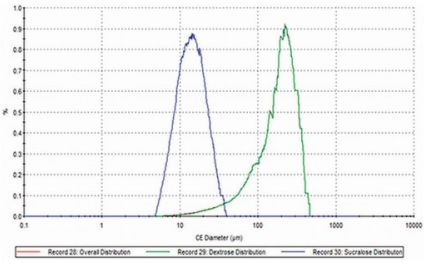


Image analysis (data from Particle Insight) can correlate different modes in a size distribution with crystal shape

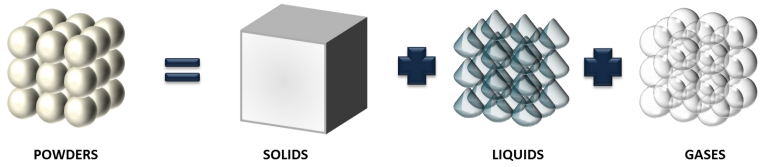
Then if you have a Raman facility in your imaging instrument (as the Morphologi G3 ID has) you can drill further into your sample and check the chemical identity of the crystals in the sample.



Morphologi G3-iD can resolve the different chemical species in a size distribution by capturing Raman for individual crystals

Powder flow investigations Freeman FT4

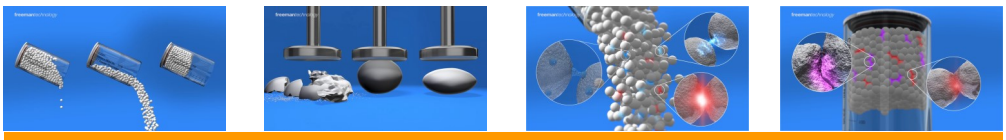
Powders are integral to a huge range of industrial processes, contributing to up to 80% of all manufactured goods. However, despite their ubiquity they continue to present challenges during product development, manufacturing, and in quality assurance. Comprehensive powder characterisation is usually required.



Powder flow properties are complex and cannot be quantified by a single number. Flowability must be considered in relation to the conditions imposed by the process and application. Effects of consolidation, aeration, flow rate, moisture, electrostatic charge, storage time, etc. have to be investigated in any tests done.

Manufactured by Freeman Technology - specialist in measuring the flow properties of powders with over 15 years of experience in powder flow and powder characterisation - **FT4 Powder Rheometer®** is known as the world's most versatile instrument for measuring and understanding powder behaviour. It's not just a shear tester or compaction tester. It's a complete **Universal Powder Tester** to investigate dynamic flow properties, shear properties, bulk properties and other processability aspects of your powders.

The Freeman FT4 Powder Rheometer



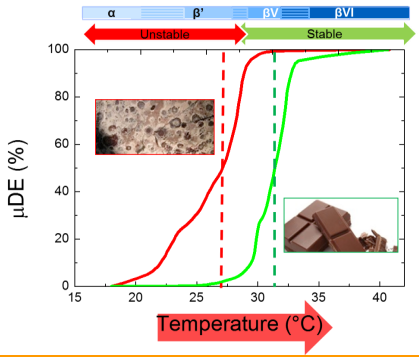
The FT4 Powder Rheometer is a truly universal powder tester, with four categories of methodologies, defined as Bulk, Dynamic Flow, Shear, and Process

Bulk phase transitions Rheolaser Crystal

Where the crystallisation behavior including polymorphic transformation of bulk samples is of concern, the **Rheolaser Crystal** enables monitoring the microstructure evolution depending on temperature in heterogeneous products with an innovative optical method (using Multispeckle Diffuse Wave Spectroscopy), combining a non-invasive measurement with accurate temperature control and sufficiently large sample volume (0.1—5g) to overcome problems of heterogeneities.

For example, the polymorphic form of cocoa butter crystals in finished chocolate needs to be analysed in bulk as representatively sampling smaller amounts is very difficult. With the Rheolaser Crystal critical polymorphic information is obtained from a complete chocolate piece in a one hour test without sample preparation.

The Rheolaser Crystal can measure temperature dependent phase transitions of bulk samples with sample preparation



Rheolaser Crystal distinguishes between chocolate with long-term stability (green) and chocolate known to lead to "blooming" after months of storage (red)

Particular Sciences

Contact us

Phone:
(+353) 01 8205395

Emails:
manuel@particular.ie
aoife@particular.ie

info@particular.ie

Web:
www.particular.ie

Delivery Address:
Particular Sciences Ltd.,
2 Birch House,
Rosemount Business Park,
Ballycoolin Road,
Dublin D11 T327, Ireland.

Sales, support, services

For material sciences in Academia, Life Sciences and Industry.

"We do more for you…"

Contact our crystallisation specialists for applications advice, demonstrations, prices or support.