



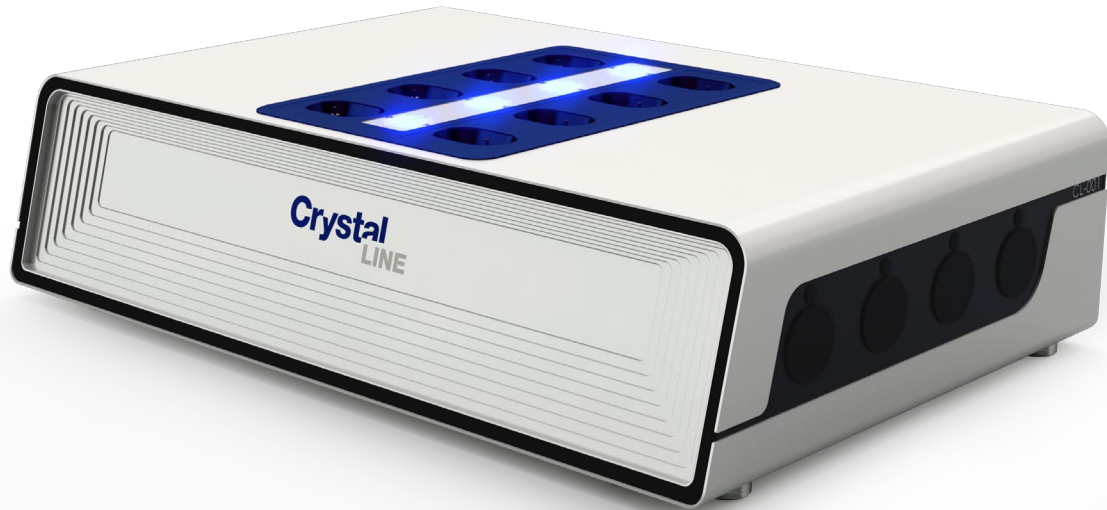
JUNE 2023

Crystalline

Technobis
CRYSTALLIZATION SYSTEMS

Crystalline

Optimization Crystalline PV



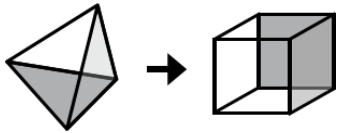
Crystal
LINE

Features:

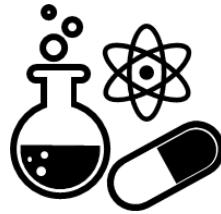
- 8 Independently controlled reactors with 2.5-5 ml scale
- Overhead stirring with a range of impellers
- Temperature range -25 to 145 °C
- Turbidity measurements in all 8 reactors
- Addition 8 in-situ cameras for online & real-time analysis
 - Turbidity measurement
 - Through-the-vial visualization
 - Particle size analysis
- Optional integration of up to 8 reactors with in-situ Raman measurement

Applications

Particle Visualization

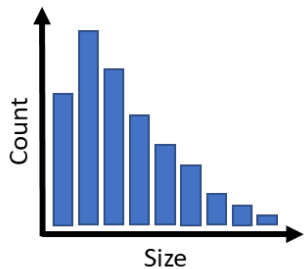


Formulation

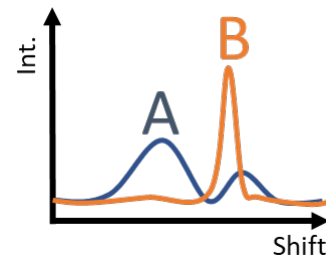


- Real time **particle size and shape** information at the smallest scale
- **Visualization** of the complete crystallization or formulation processes
- **Optimize** and control your **formulation** process

Particle Size Distribution



Polymorph transition



- Monitor **slurry conversions, oiling out, foaming, gelling, aggregation**
- Real time information on **chemical interactions**
- Drive reactions based on **spectroscopic results**
- Measure relative **reaction rates**

Material Considerations

Crystallization Process Development

'Ideal Project'

2 route scouting experiments
4x Process development

20 Vol
30 g total at 100 ml
0.750 g total at 2.5 ml
Saving 29.25g compound

5 Vol
120 g total at 100 ml
3 g total at 2.5 ml
Saving 117g compound

'Reality Project'

8 route scouting experiments
4x Process development

20 Vol
60 g total at 100 ml
1.5 g total at 2.5 ml
Saving 58.5g compound

5 Vol
160 g total at 100 ml
4 g total at 2.5 ml
Saving 156g compound

'Challenging Project'

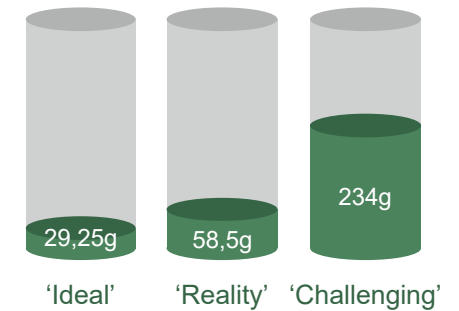
8 route scouting experiments
24x Process development

20 Vol
240 g total at 100 ml
6 g total at 2.5 ml
Saving 234g compound

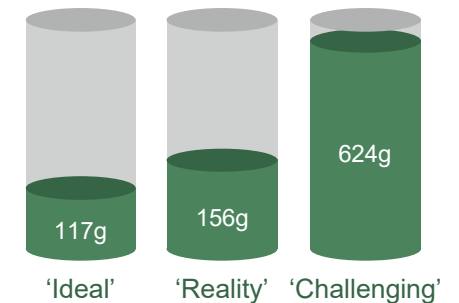
5 Vol
640 g total at 100 ml
16 g total at 2.5 ml
Saving 624g compound

Total compound saved can be up to 600g!

Savings 20 Vol



Savings 5 Vol



Assume an average crystallization is between 5-20 Vol
Smallest vessel in which PVM and Raman is integrated is 100 ml reactor

For a 20 Vol process:

- 5 g/experiment at 100 ml scale
- 0.125 g/experiment at 2.5 ml scale

For a 5 Vol process:

- 20 g/experiment at 100 ml scale
- 0.5 g/experiment at 2.5 ml scale

Crystalline hardware

Instrument and Application

Value Proposition

Background Info

Reactors



Material	Use Case
Glass	Standard use
Silanized Glass (Chemflask)	Prevent adsorption or increase hydrophobicity
Quartz (Technobis)	For use with raman

Caps



Type	Standard Cap	Anti-Solvent / Seeding Cap	Reflux Cap	Evaporation Cap
Material	PEEK	PEEK	ALUMINIUM	PEEK
Inlet Ports	No	Yes	No	Yes
Application	All general applications within a closed vial	Addition experiments - seeds, excipient, solvent etc. is added to the experiment at specific timepoint(s) via inlet port	Reflux experiments - crystallization is initiated by contact with the hot or cold aluminium cap extension	Evaporation experiments where a gas of choice is bubbled directly into the sample vial via inlet port

Crystalline Hardware

Instrument and Application

Value Proposition

Background Info

Stirring



Flexible Stirring options

Options

- Magnetic stir bar or overhead stirring options
- 8 independent stirring zones
- Speed 0 to 1250 rpm
- Chemically compatible: Hastelloy or SS316L

Tubing



Material / Ø

Use Case

Silicon 4mm

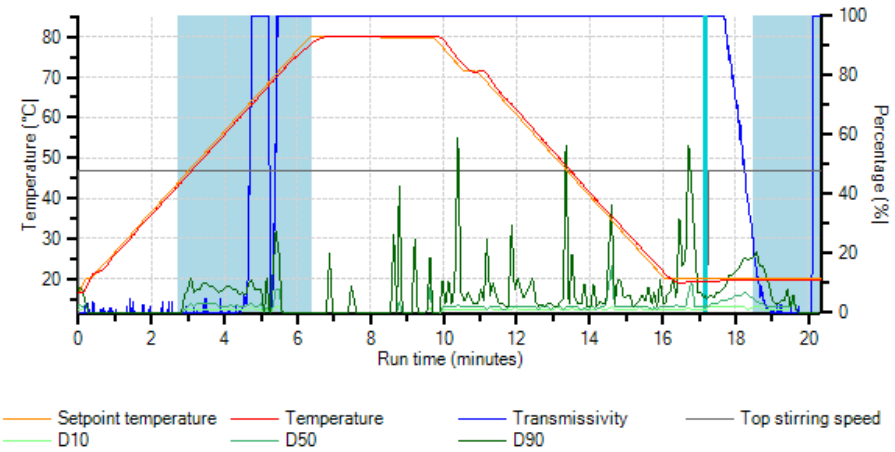
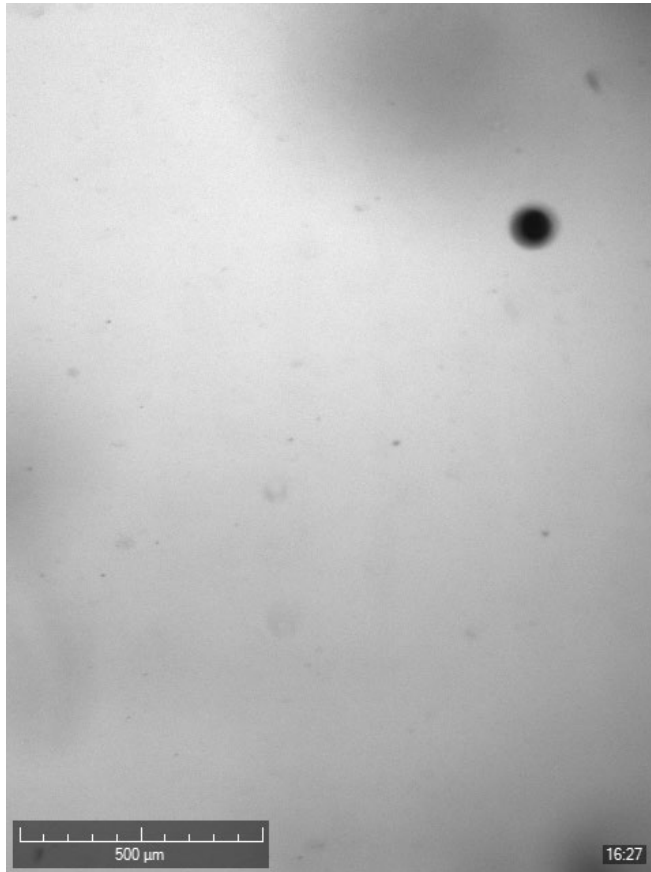
- add evaporation gas and to create a plug for an inlet/outlet port that needs to be blocked.
- Also used as a guide for the Teflon tubing to enter the inlet ports

Teflon 1/16"

Used to add seeds, solvents, excipients etc. into the vial during experiment progression.

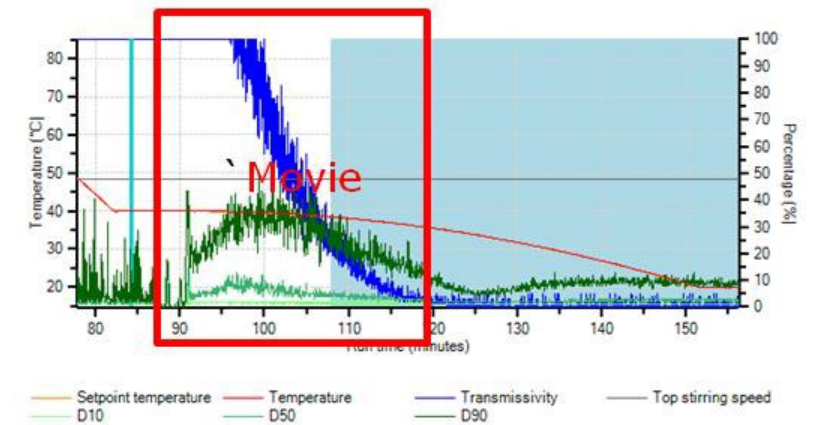
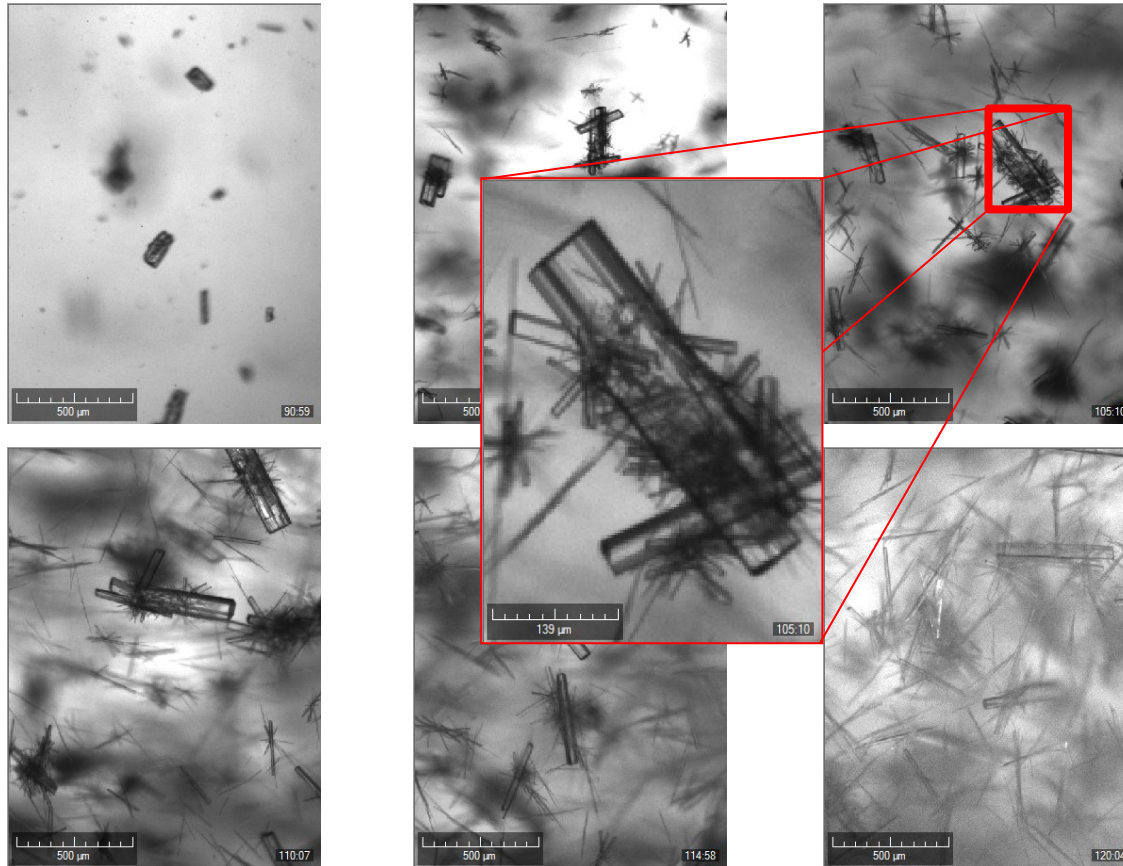
Seeding Crystallisation

Seeding crystallisation



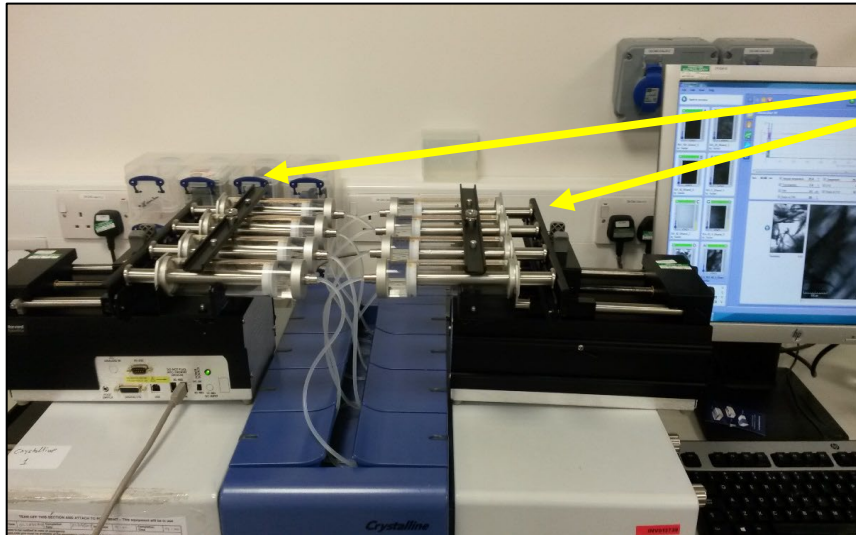
Antisolvent Crystallisation

Anti-solvent crystallisation



Antisolvent Crystallisation

Anti-solvent crystallisation



2x4 Syringe Pumps:

- Each syringe can hold a different solvent composition.
- Different flow rates can be tested in one go.

End-User Benefits of the New Crystalline v2

✓ AI-BASED IMAGE ANALYSIS

✓ IMPROVED HARD- & SOFTWARE

✓ READY FOR ROBOTICS INTEGRATION



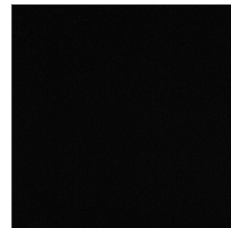
Crystalline v1



New Crystalline v2

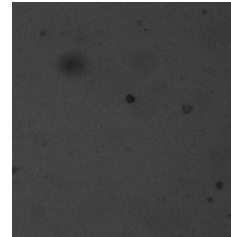
Improved Optics & Front Light

Crystalline experiment with a **dark sample (oil)**

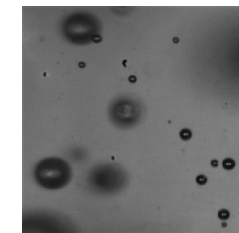


dark sample (oil)

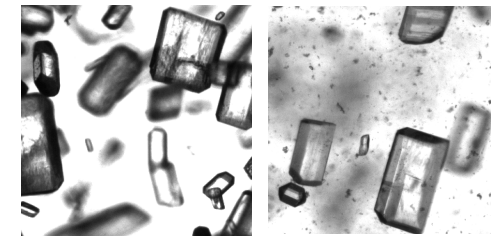
Crystalline experiment with **honey**



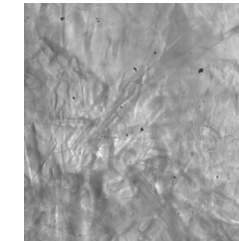
honey



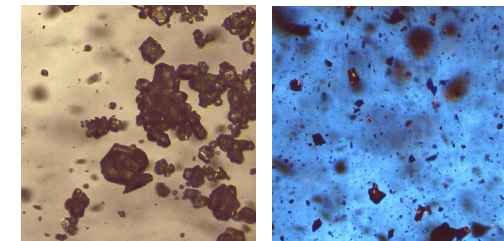
dark sample (oil)



Other samples



honey

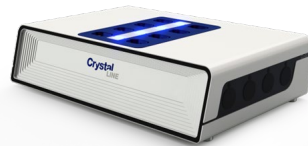


Colored samples

Comparison Material Used

Experimental
scales
& systems

Crystalline
5mL



Optimax
1L

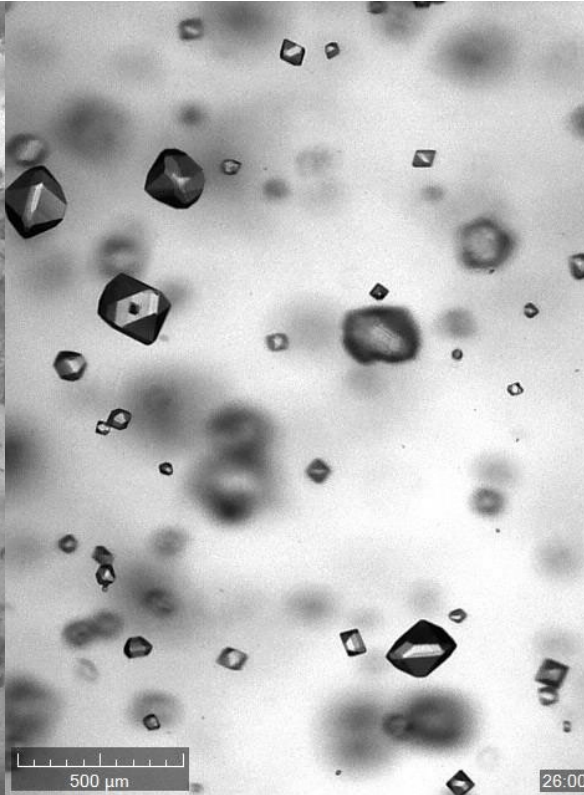
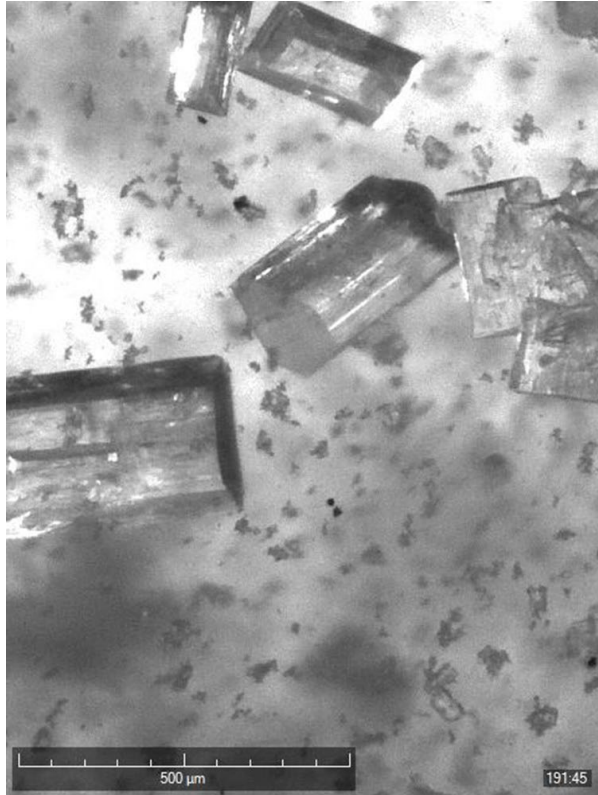


Combination

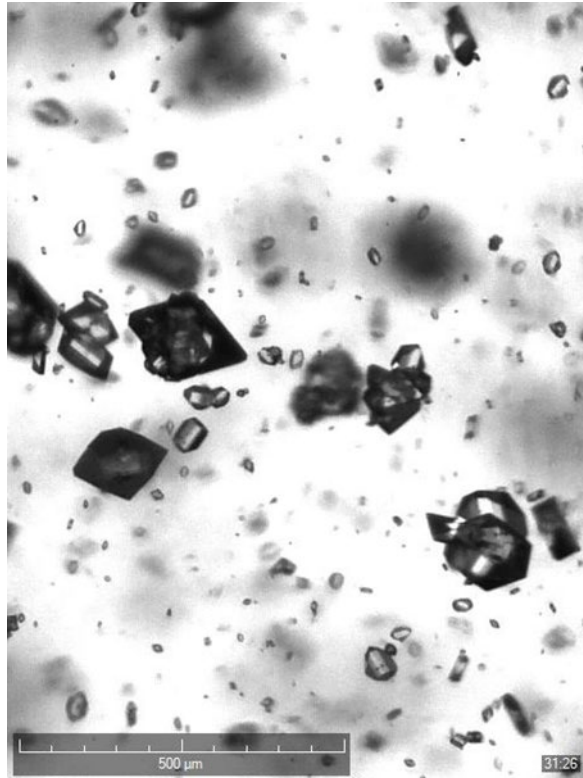


	Estimation at microscale	Estimation at 1 L scale	Estimation at microscale with <u>refinement at 1 L scale</u>
Microscale experiments (5 mL each)	8 (as part of solubility measurement)	-	8 (as part of solubility measurement)
1 L scale experiments	-	7	3
Total API usage	4 g	1200 g	520 g

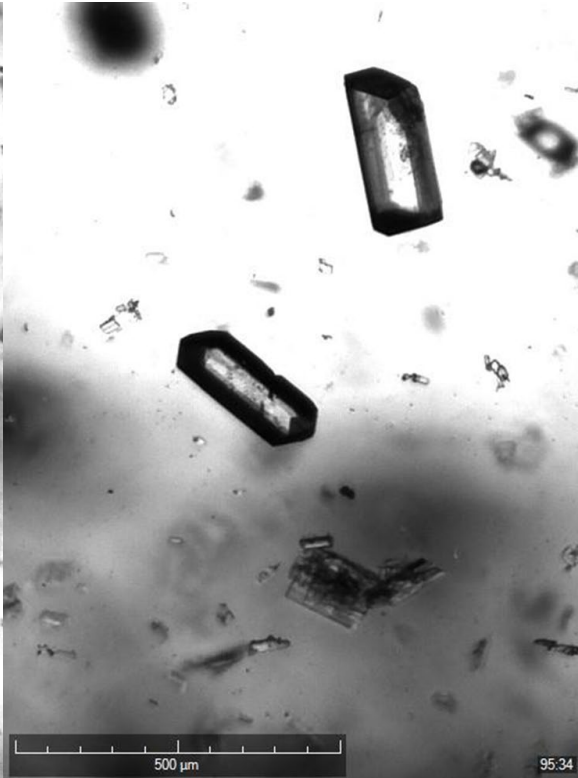
Particle Shape



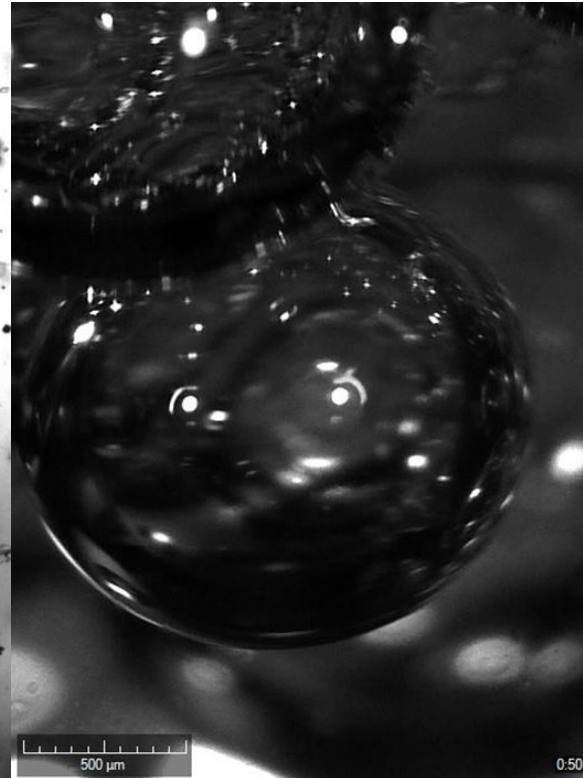
Capture Events



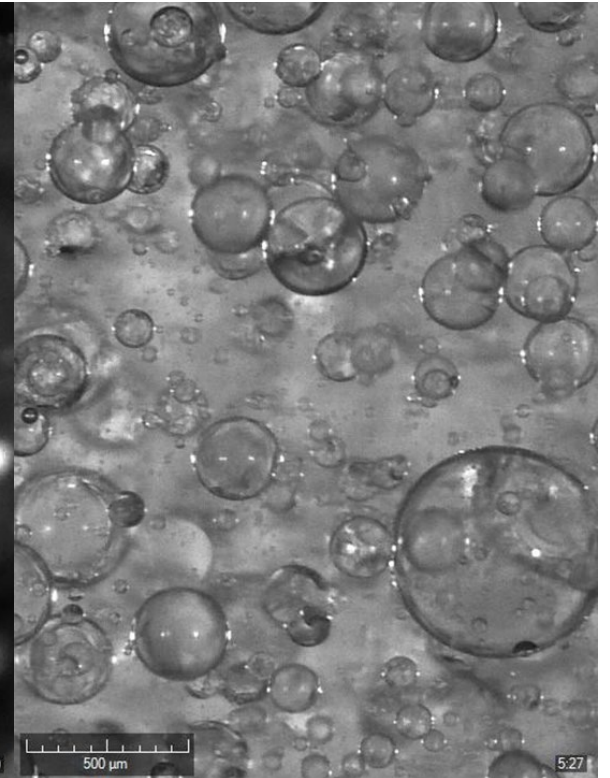
Agglomeration



Crystallization

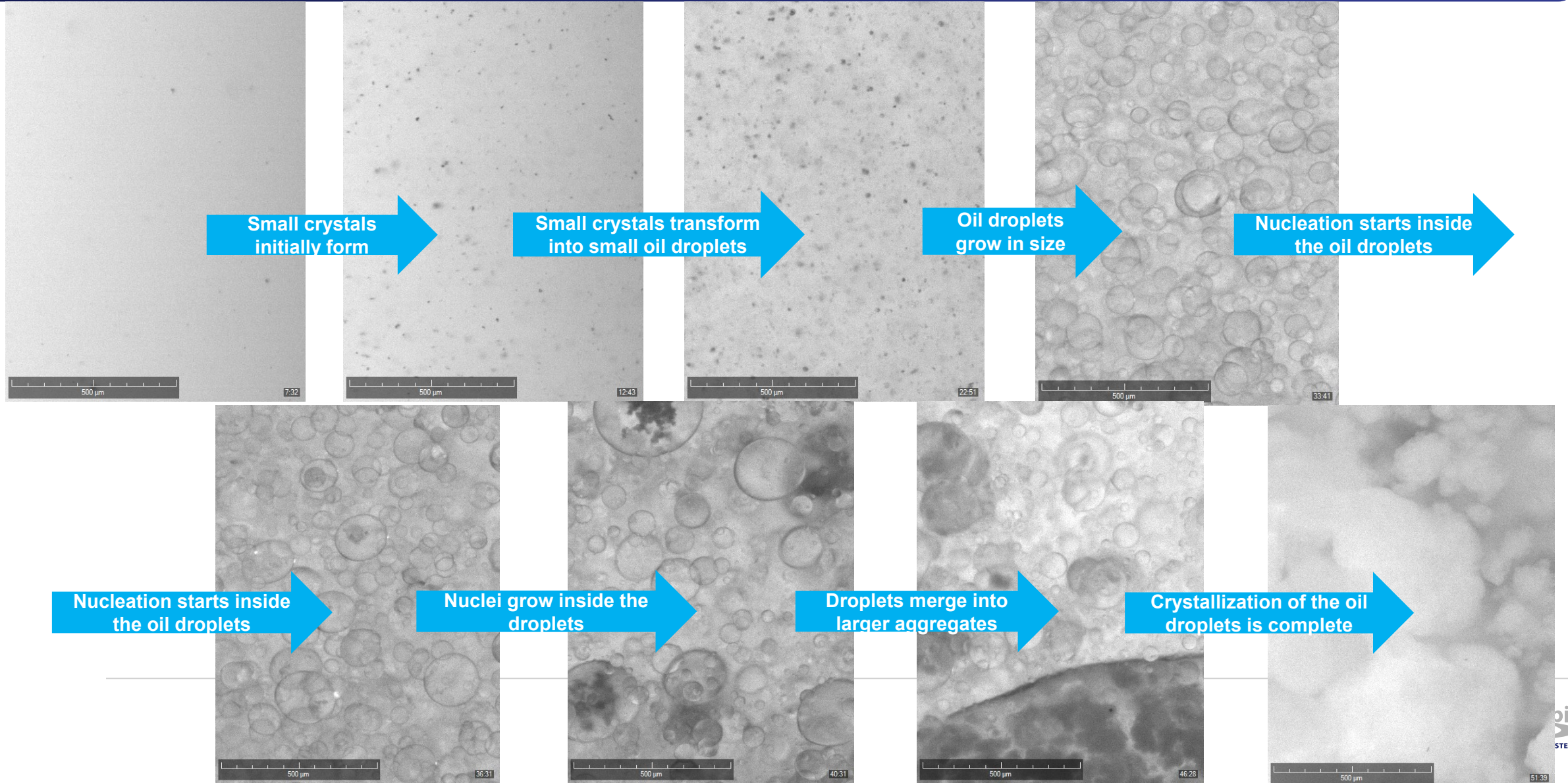


Foaming



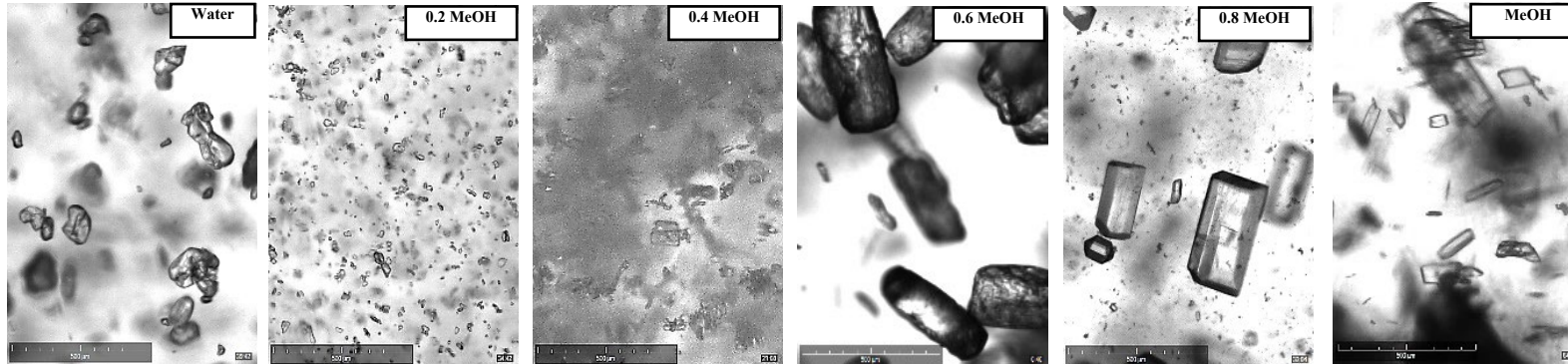
Oiling

Capture Complexity

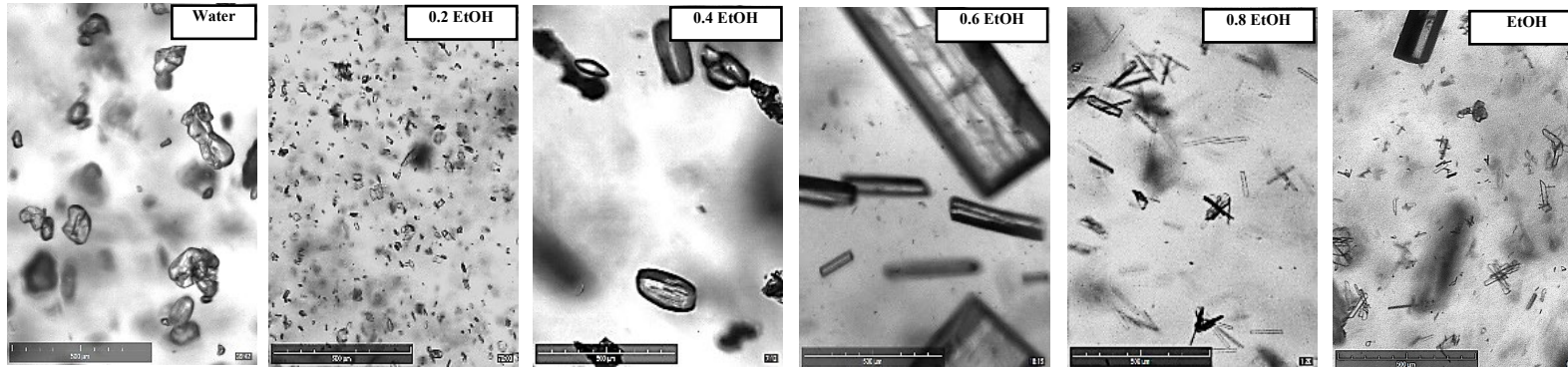


Case Study - Effect of solvent composition on crystal habit

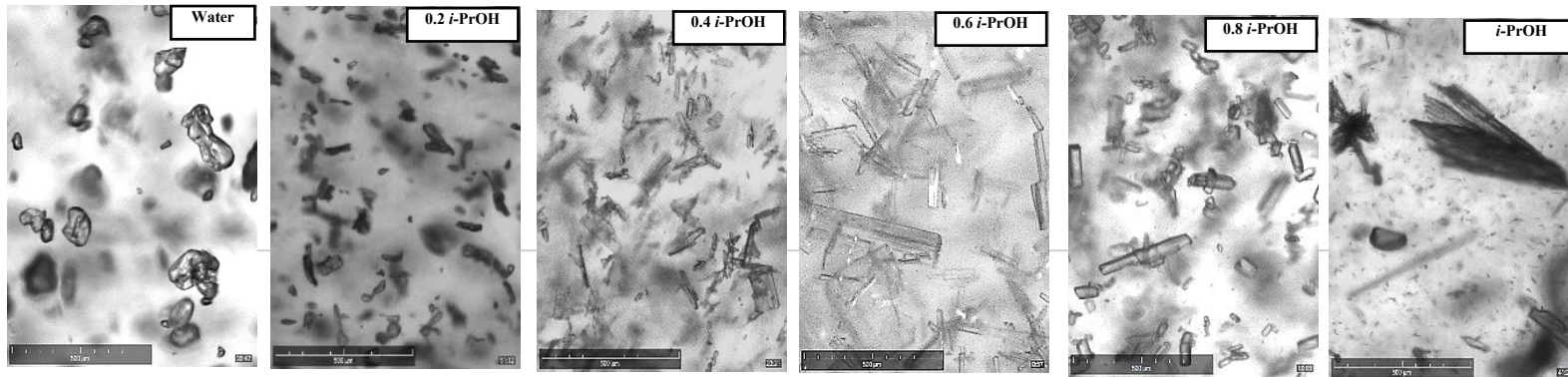
Water-Methanol



Water-Ethanol



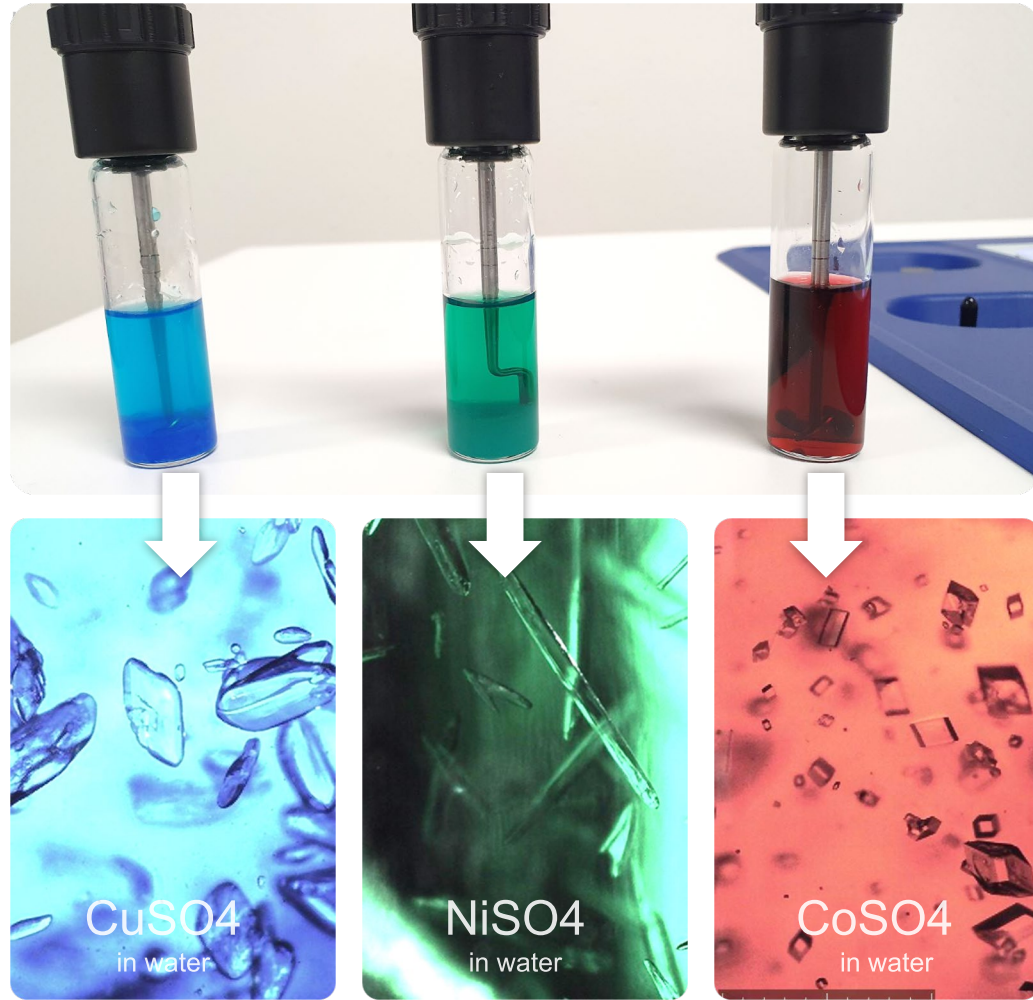
Water-Isopropanol



- More **cubical or prism shaped** crystal were witnessed in **water**.
- With the increase in alcohol concentration more and more **lengthened crystals** were formed resulting in **rod shaped crystals** in **pure ethanol** and **cluster of needle crystal** in pure isopropanol.



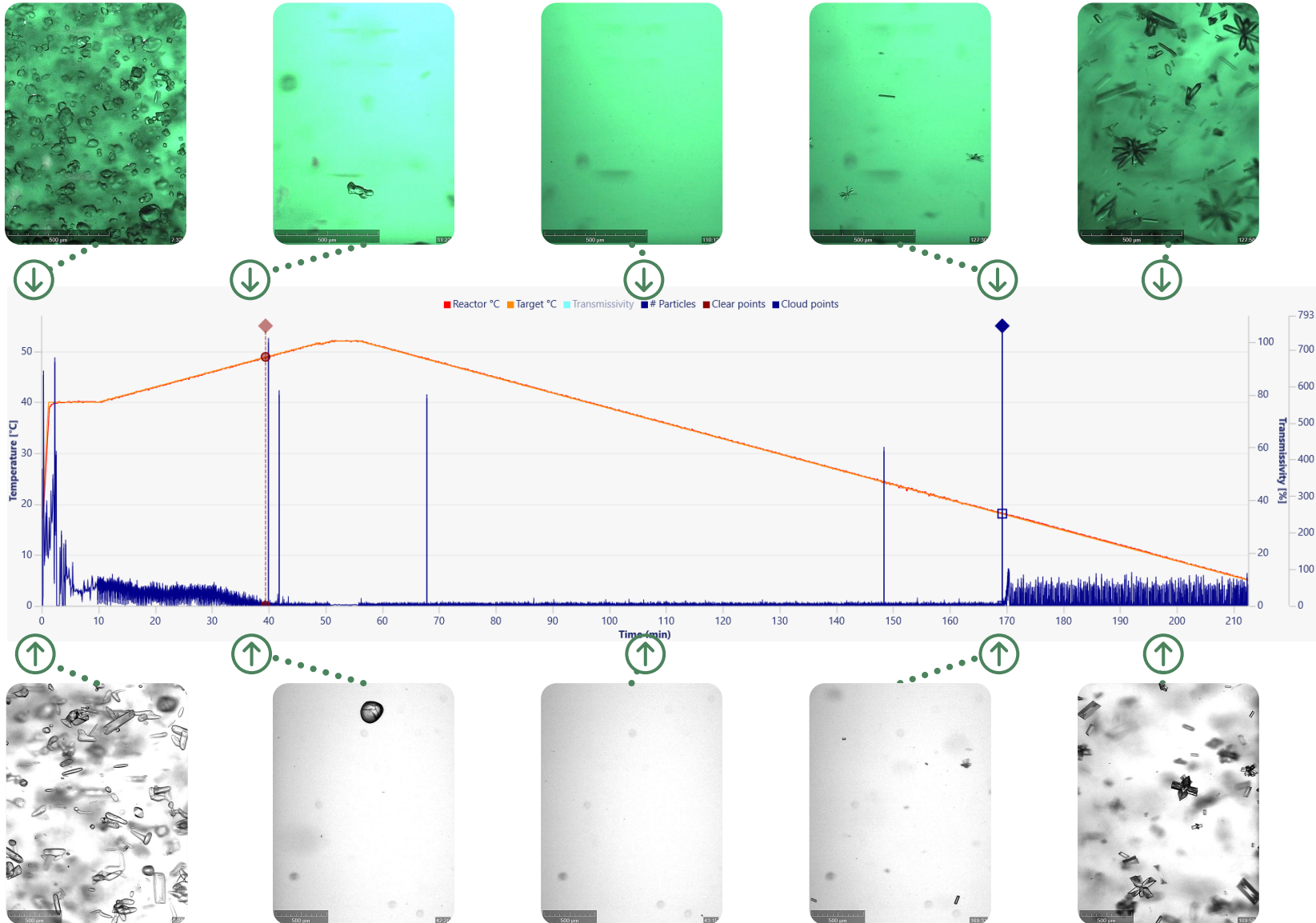
Capture Colour



- Capturing images of dark and coloured samples is easier than ever
- By introducing a colour option in our camera offering we help addressing this
- An optic slot in a crystalline reactor can either be configured with either a mono or colour camera



Capturing Clear/ Cloud point at coloured material

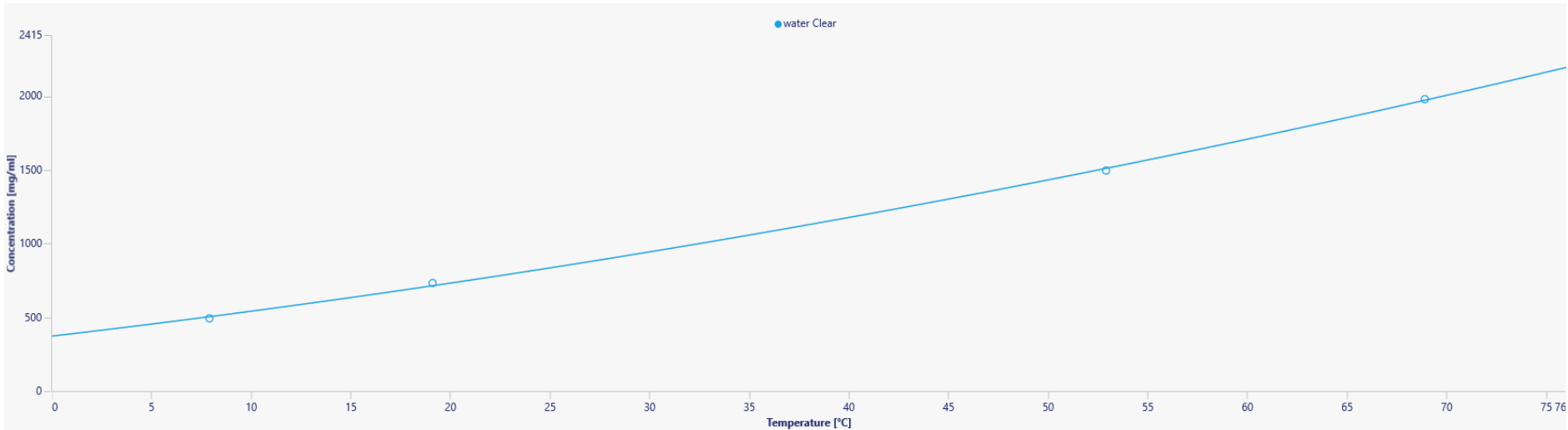


← Clear/ Cloud point detection for coloured and dark materials is now available thanks to:

- Coloured Camera (example shown here)
- Improved front light technology
- Assisted by Image Particle Detection

← Even without coloured camera's it's possible to process dark samples easier.

CoSO₄·7H₂O – solubility determined with the Crystalline v2

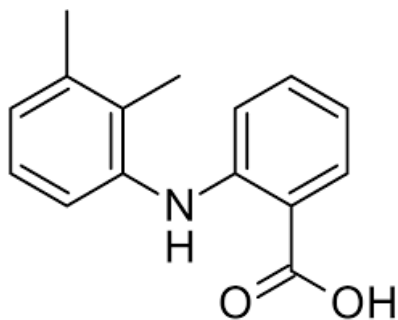
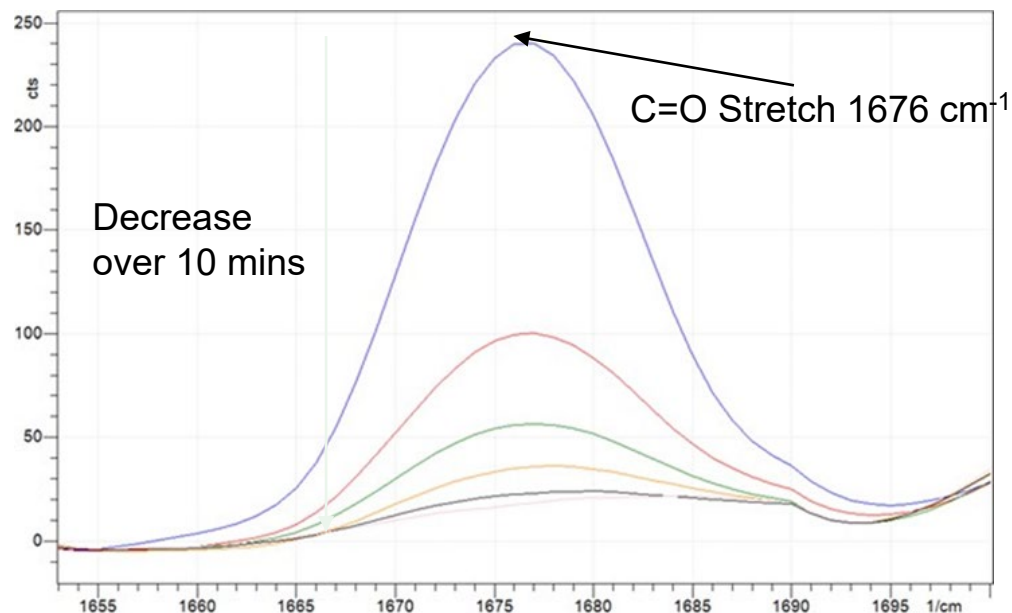


Concentrations (mg/ml)
493
733
1496
1980

Solvent	Point type	Function	Color	R2	AdjR2	Fitted function
water	Clear	Quadratic		0.9995	0.9984	$372.6279 + 15.8422T + 0.1071T^2$

- Metastable curve was not possible due to no vials crystallizing during cooling.
- This would indicate the solution is very stable even at very high supersaturation

Mefenamic Acid

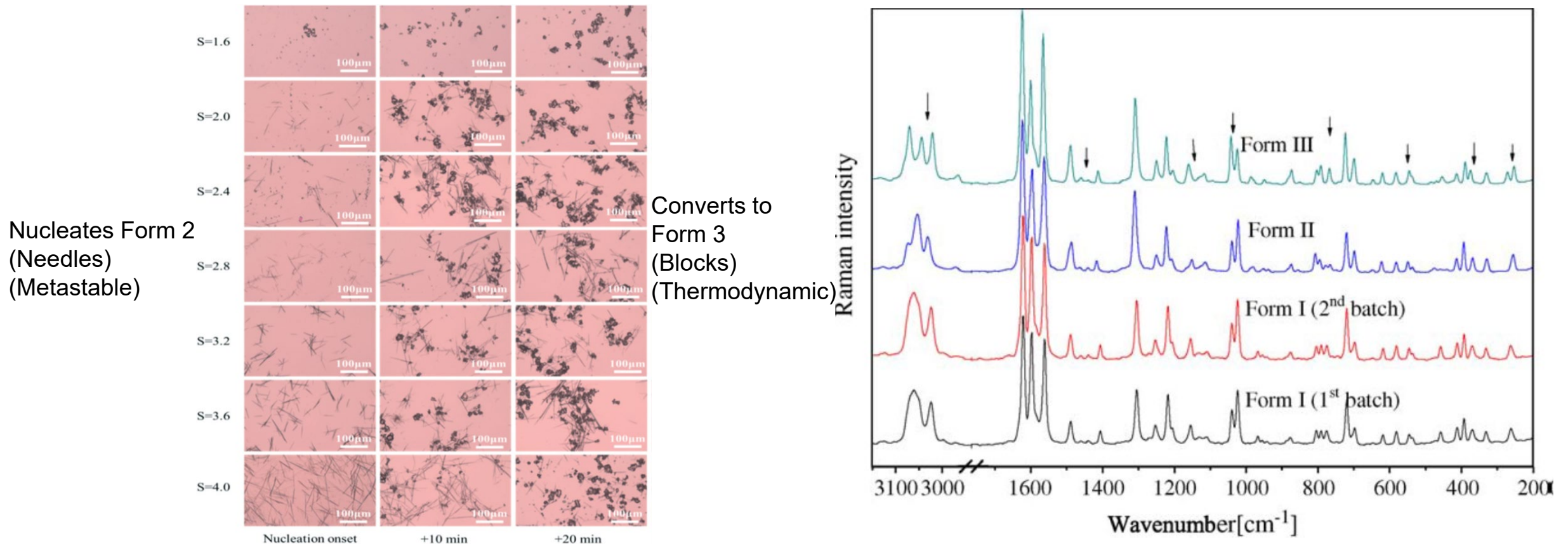


- Mefenamic acid is a nonsteroidal anti-inflammatory used in the treatment of mild pain. It has three polymorphs with Form I being the thermodynamically most stable form.
- Mefenamic acid Form II was suspended in ethanol and stirred (700 rpm) using an overhead hook impeller at 25 °C in the Crystalline instrument. (785 nm, total collection time of 4.8 seconds per spectrum).
- Using Raman spectroscopy it is possible to track the rapid conversion of mefenamic acid Form II to Form I by monitoring the spectral region 1660- 1690 cm^{-1} .

The Crystalline was interfaced to a Tornado Hyperflux™ PRO Plus Raman spectrometer equipped with a Hudson™ Probe adapted to the Crystalline sampling port

Carbamazepine

Carbamazepine, sold under the trade name Tegretol among others, is an anticonvulsant medication used primarily in the treatment of epilepsy and neuropathic pain. It is used in schizophrenia along with other medications and as a second-line agent in bipolar disorder.

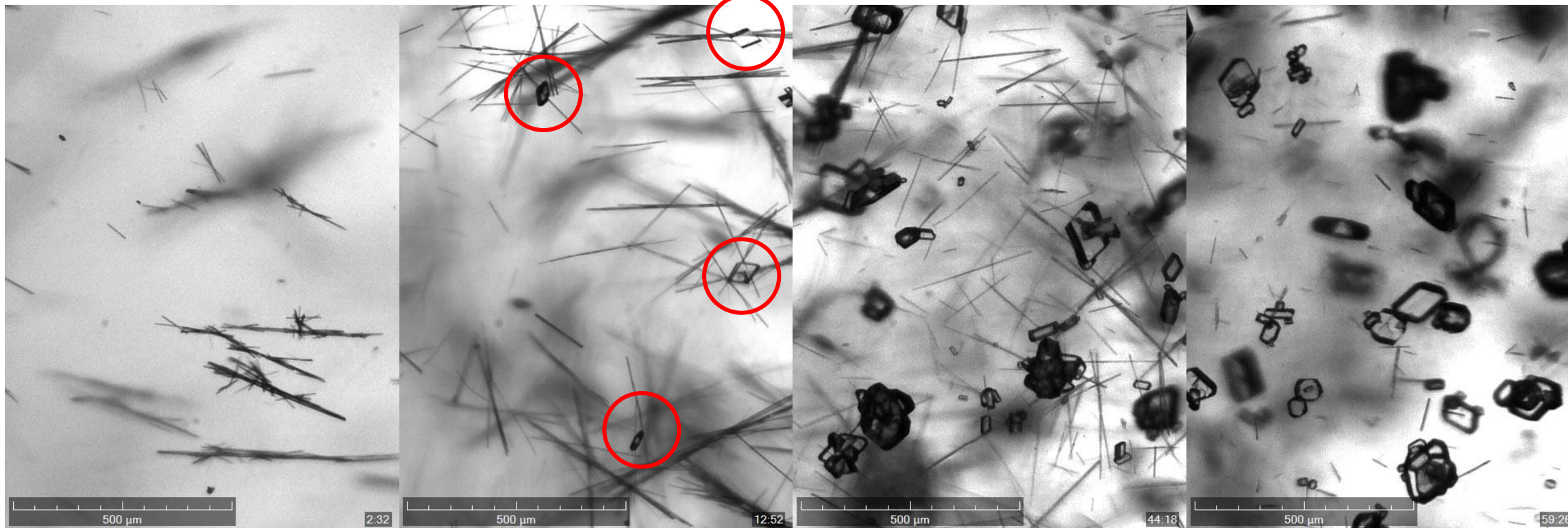


DOI: 10.1039/d0ce01357a. CrystEngComm, 2021,23, 813-823

DOI:10.1016/j.jpba.2005.07.030 Tian F, Zeidler JA, Strachan CJ, Saville DJ, Gordon KC, Rades T. Characterizing the conversion kinetics of carbamazepine polymorphs to the dihydrate in aqueous suspension using Raman spectroscopy. J Pharm Biomed Anal. 2006 Feb 13;40(2):271-80. doi: 10.1016/j.jpba.2005.07.030.

Epub 2005 Sep 16. PMID: 16146681

Carbamazapine: Crystalline Particle Viewer



Nucleating Form 2

Converts to Form 3

Carbamazepine – Raman spectrometry



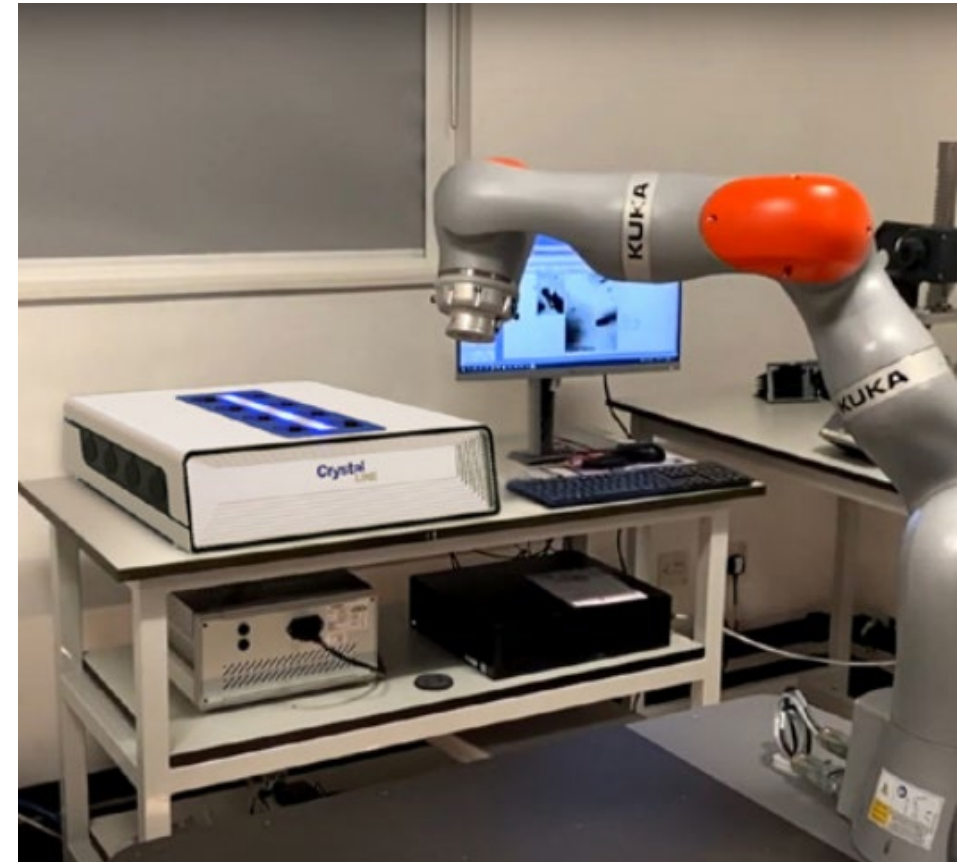
End-User Benefits of the New Crystalline v2

✓ AI-BASED IMAGE ANALYSIS

- Future Research will be more and more automated: e.g. fully automated and AI driven Data Factory
- Easy integration in robotic set-up by access from top
- No lids needed anymore
- Re-designed caps for better robot grip
- Robot pick/ placing samples automatically
- Technobis Crystalline as part of Data Factory

✓ IMPROVED HARD- & SOFTWARE

✓ READY FOR ROBOTICS INTEGRATION



Product Comparison



Aspect	Crystalline v1	The NEW Crystalline v2
Magnification	0.5, 1, 2	1, 2, 4, 6
Pixelsize (µm)	7.5, 3.75, 1.875	3.75, 1.875, 0.94, 0.63
Field of view	(7.2 x 9.6) (3.6 x 4.8) (1.8 x 2.4)	(3.6 x 4.8) (1.8 x 2.4) (0.9 x 1.2) (0.6 x 0.8)
Color/mono	Mono camera	Mono and colour camera option
Focus	Mechanical adjustment at instrument	Software control (remote access)
Raman integration	Tornado, Kaiser, Blaze, Marque Mettix	Tornado, Kaiser, Mettler, Blaze, Marque Mettix, Horiba

Example Configuration



- Default 8 optics
- Either a Raman or a camera
- Camera colour or mono
- Camera magnification either 1.0x, 2.0x, 4.0x or 6.0x