Thermodynamics and Kinetic Considerations of Solids State Behaviour for the Control of Agrochemical Process and Product Design

Fundamentals of Solid Formulation, 11th March 2014

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Abstract

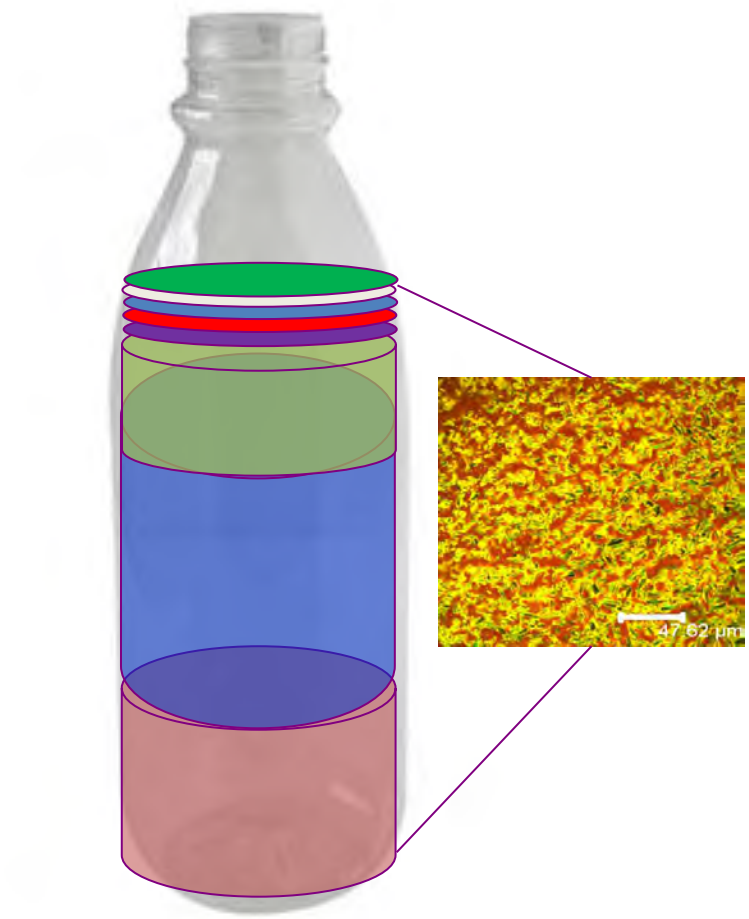
- Crystallisation in formulated products often leads to instability and poor formulation performance.
- In contrast to crystallisation for purification purposes, formulation of active compounds generally aims towards minimising crystallisation phenomena.
- Finding and manufacturing the most thermodynamically stable crystal state is key to delivering stable formulated products.
- In application of the formulation, generation of supersaturation is often inevitable due to temperature, composition changes or solid state transitions.
- Controlling rates of crystallisation is then essential but can often be challenging to measure and control.
- The application of measurement and modelling tools in an industrial context and highlight opportunities for research.

Content

- Formulation Types
- Crystallisation in Formulation – Industrial Context: time and number
- Crystallisation Measurement and Modelling Status and Challenges
- Solid State Control
- Nucleation Control
- Growth Control
- Conclusions and Recommendations

Formulation Types

Suspension Concentrate Formulation



- 25% active ingredient
- bio-enhancing agent
- dispersant
- viscosity modifier 1 (clay)
- viscosity modifier 2 (polymer)
- Biocide & antifreeze
- Bead mill to reduce particle size.

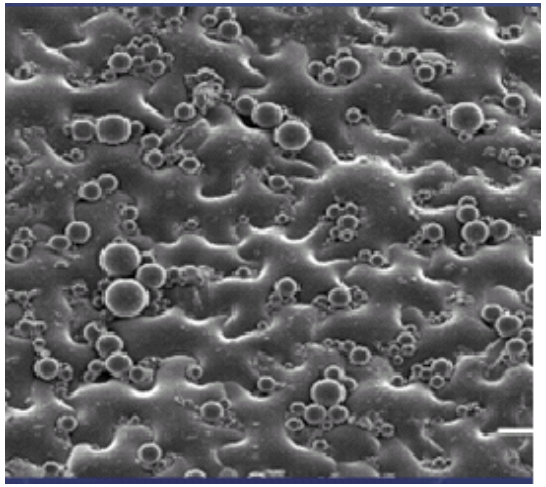
Emulsifiable Concentrate Formulation

- 10% Active ingredient
- Solvents
- Emulsifiers
- **Tank Mixing**

Water Dispersible Granule Formulations

<80% active ingredient
Dispersant
Binder
Extrusion
Spray Agglomeration

Applied to the Field through Foliar Spray & Directly to Soil Through Coated Seeds

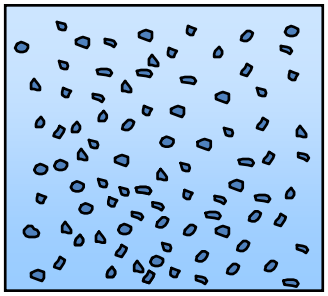


Requirements of Formulation

- Act as a convenient dispersion medium for field a
  application
- Biological activity *e.g.* adjuvancy, co
- Maintain homogeneity “2 yea es of
  temperature and cyclin
- Ease of pouring , fine mesh clear
- Formulat d *e.g.* milling, wetting
- E and regulatory
- Co mixtures, additives
- IP M ket Differentiation

The Solid State and Its Interaction With Formulation Additives Influences All of These !

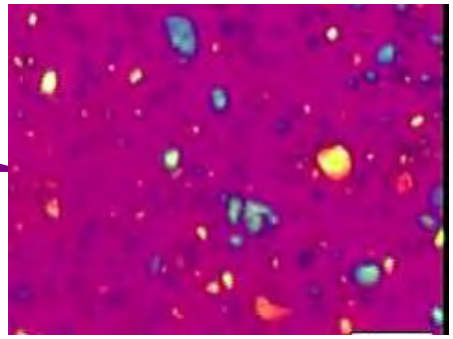
Common Formulation Instability Mechanism Due to Low Energy, Slow Transformations



Fully dispersed particles

Sedimentation

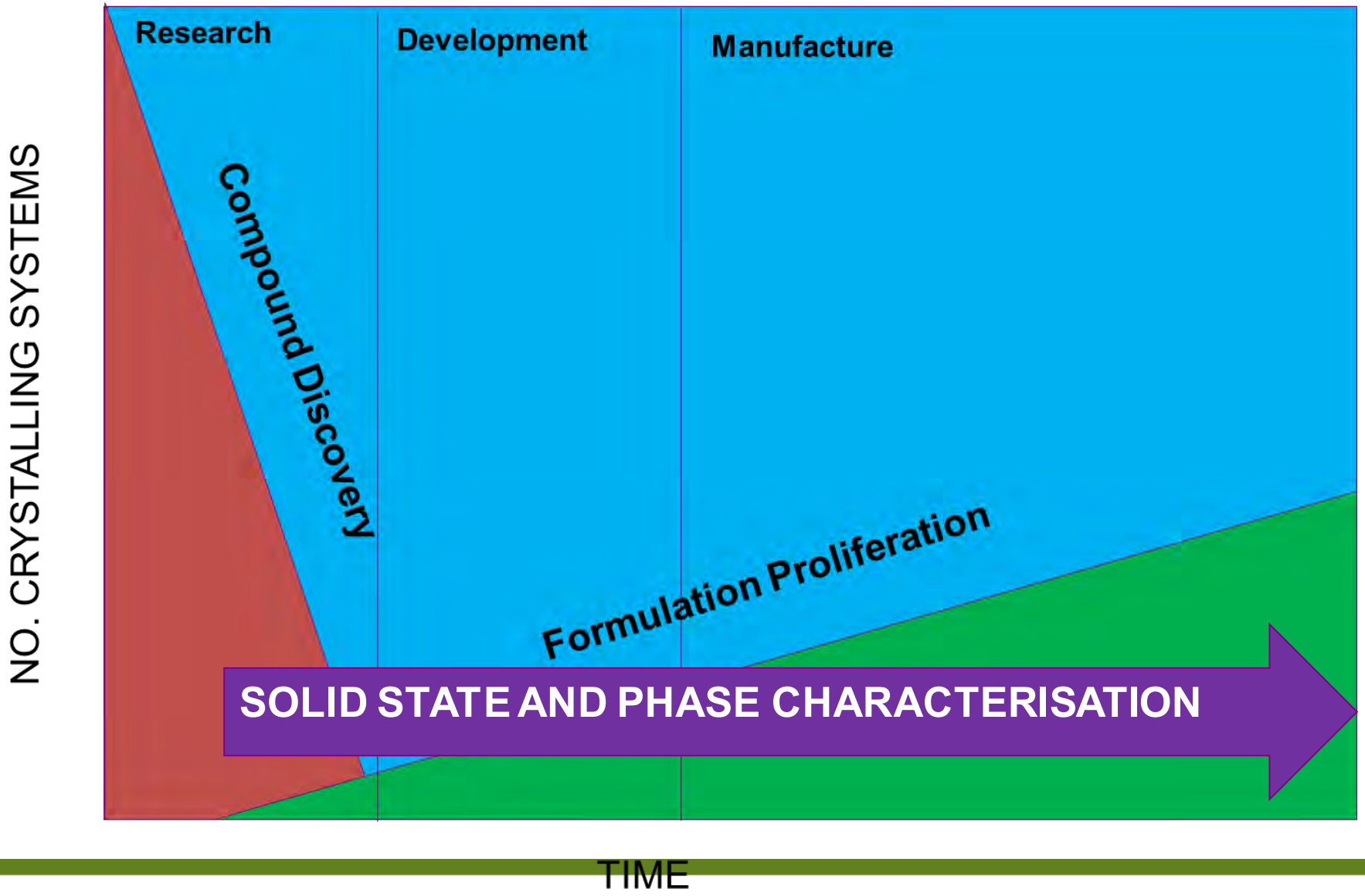
Gross Flocculation



Crystal Growth

Industrial Context

Solid State Characterisation Challenge

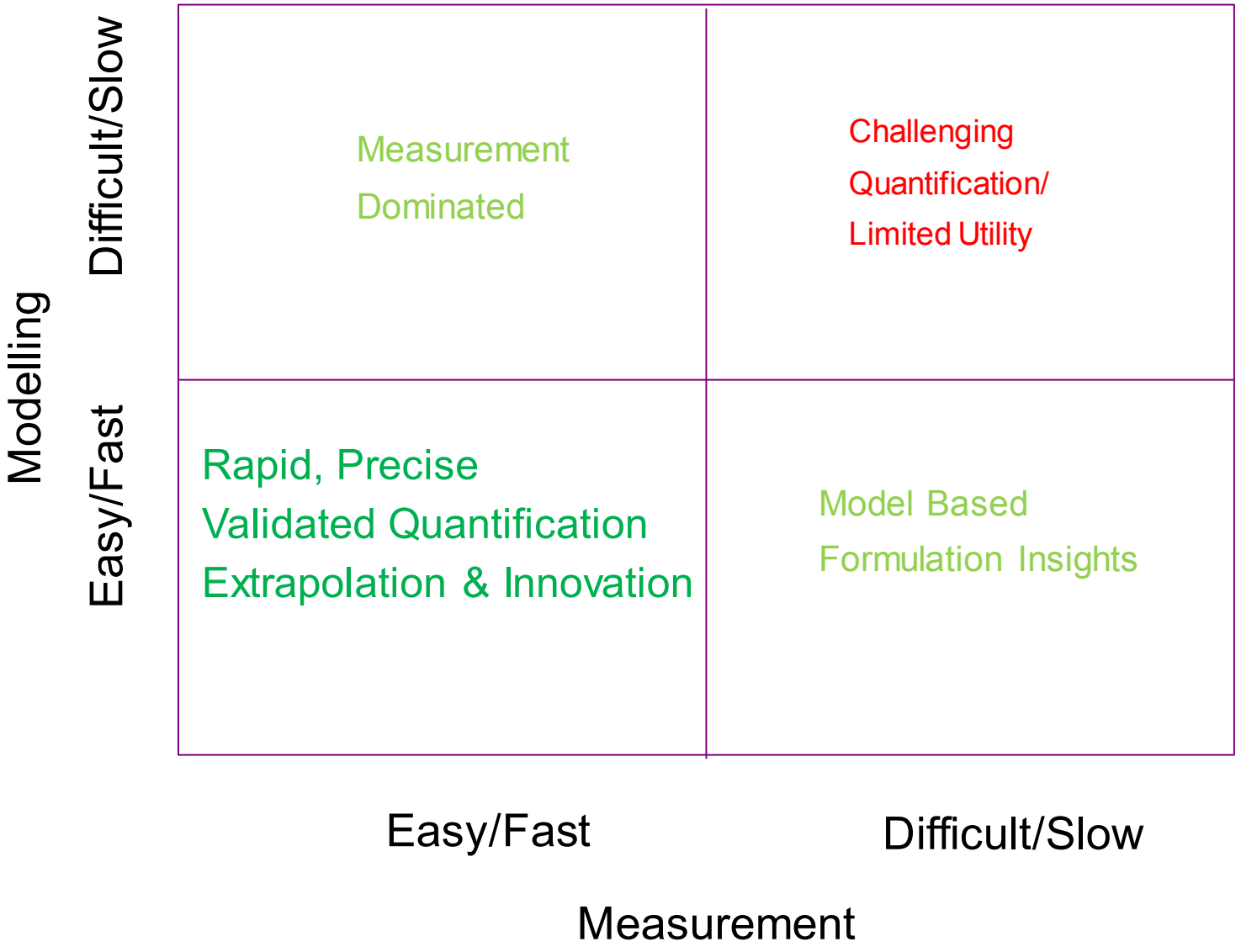


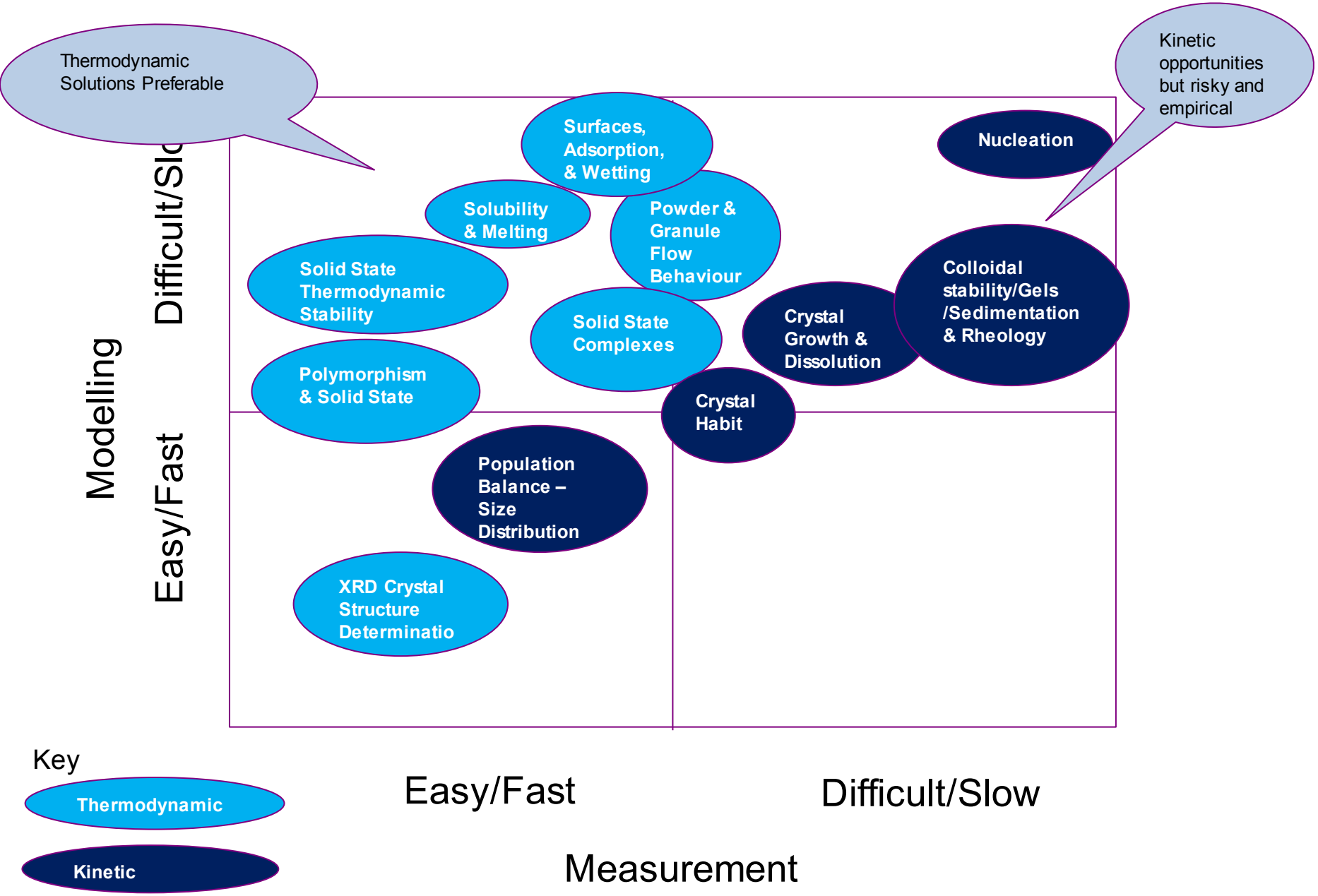
Crystallisation Isolation & Purification Versus Formulation

- **Isolation& Purification**
- Yield, productivity, purity
- High driving forces, steep solubility, high supersaturation, fast and complete crystallisation. Easy to measure
- Generally want large crystal size (high growth, low nucleation)
- Thermodynamics Controlled temperature and composition
- Rate - Timescale - hours
- One optimised process, well characterised and developed over several years
- Robustness to impurities

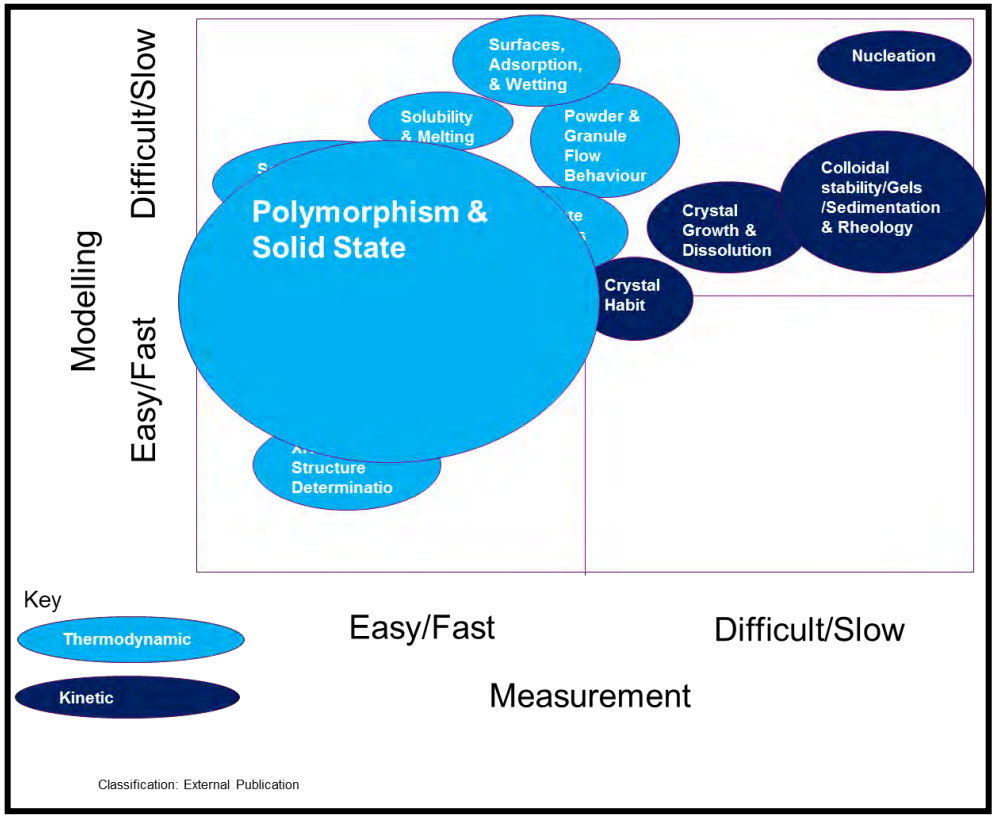
- **Formulation**
- Stability, Compatibility, Activity
- Low driving forces. Slow. Hard to Measure and predict
- Generally want little or no crystallisation
- Themodynamics Uncontrolled - variable temperature and composition in application
- Timescale days to years
- Multiple formulation compositions, region, crop and time specific
- Robustness to impurities and physical quality

The Role of Modelling& Measurement in Solid State Discovery & Characterisation





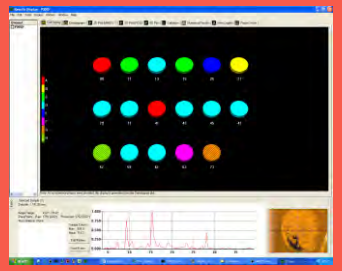
Defining and Controlling The Solid State

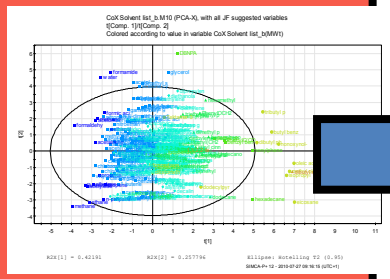


Rapid automated polymorphism discovery aided with modelling and targeting screen

Form Identification -Experimental

- ❑ High-throughput screening
- ❑Diverse Solvent Screening
- ❑Emerging Propensity Statistical Modeling
- ❑ Polymorphism Prediction ?





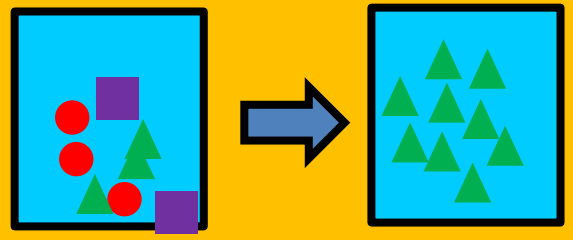
- ❑ Solid state analysis:
  HTPXRD
  DSC
  Raman
  TGA / GVS

- ❑ Screen individual isomers and phase behaviour can add greatly to work load

Identify stable forms -Experimental

- ❑DSC and Van't Hoff
- ❑Relative Polymorphism Stability
- ❑Slurrying
- ❑Temperature Sensitivity

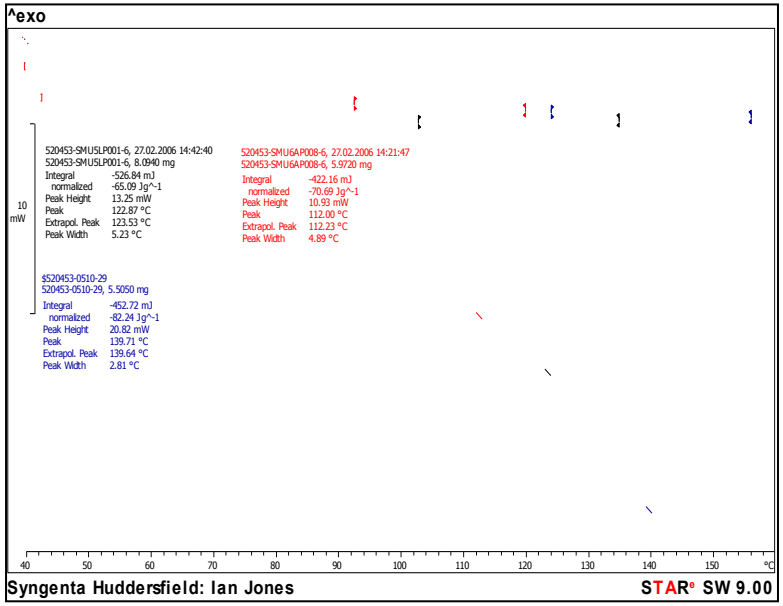
$$\ln x = \frac{\Delta H_{fus}}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right)$$

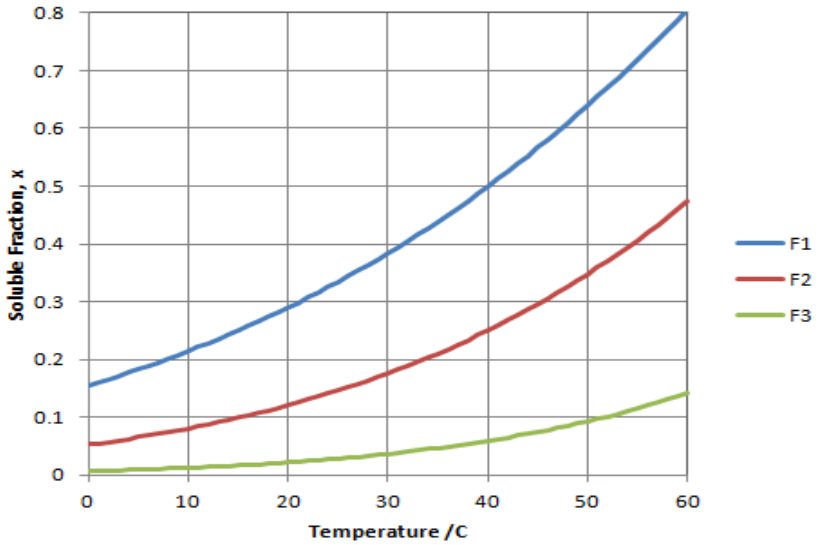


Slurry known forms

Conversion to stable form

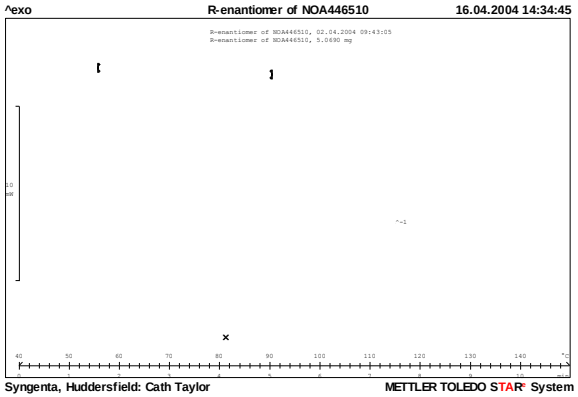
Solid State Stability – Minimising Formulation Supersaturation

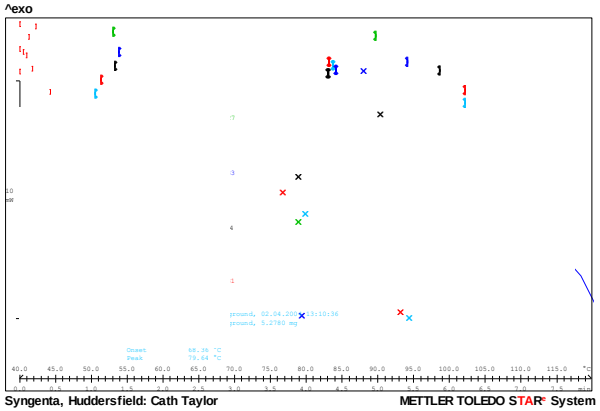


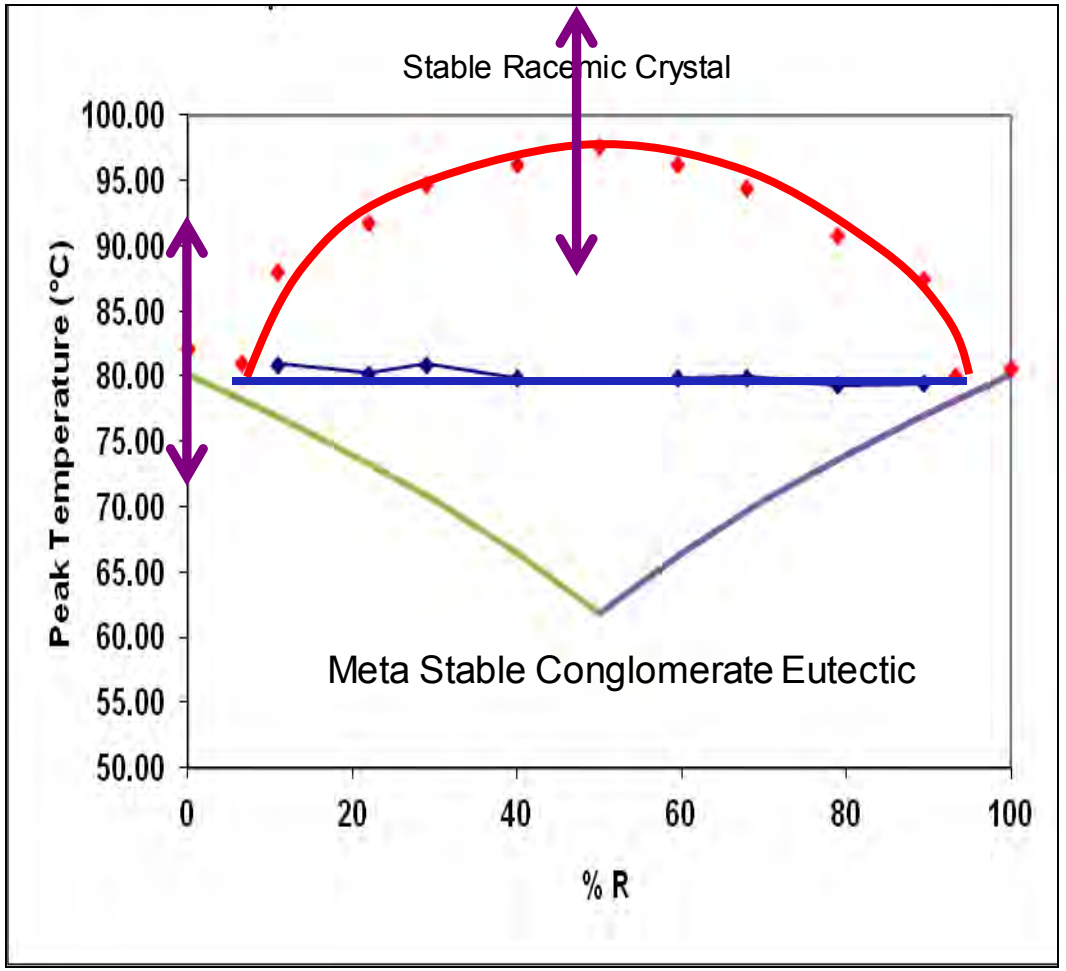


Stereo Isomers: Mapping Complex Phase Behaviour

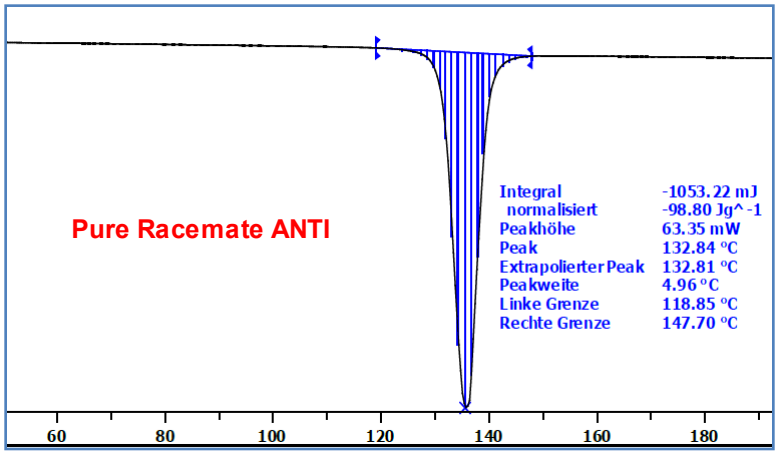
Defining the Stable States of the Pure Components and of Complex (can be the rate limiting step)

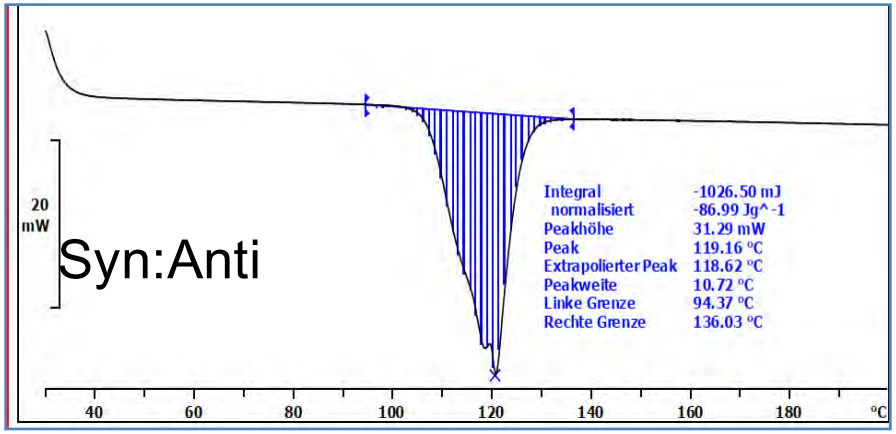


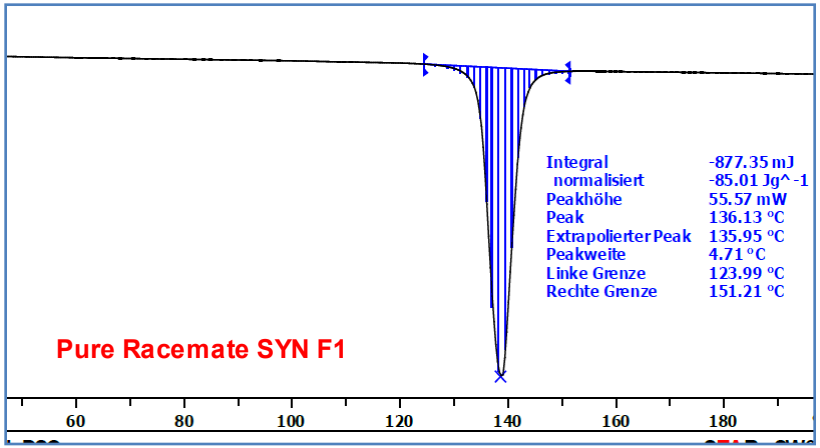


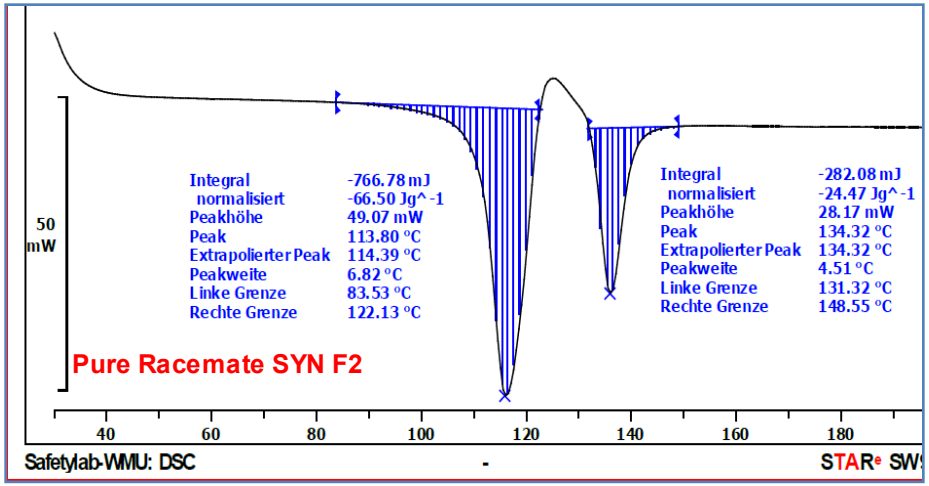


Diastereoisomer Polymorphism Detection Challenges





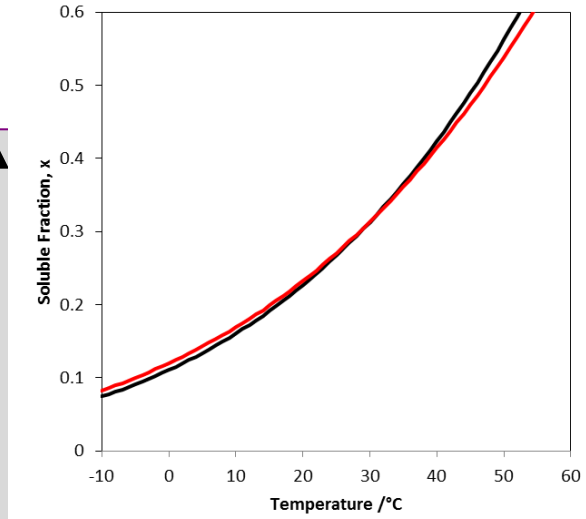




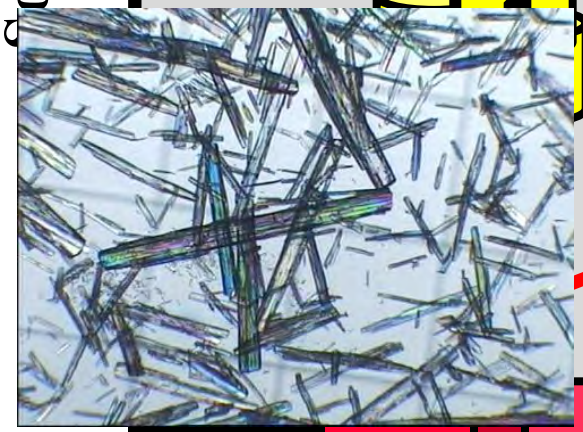
Generation of Supersaturation within Formulations is Inevitable !

- Solid State Transitions Within the Formulation Storage Temperature Range (Solid-Solid, Solvate-Non Solvate, Liquid –Solid)
- Temperature Changes
- Composition Changes

Low Temperature Solid State Phase Transitions



Solubility



0°C

Temperature

50°C

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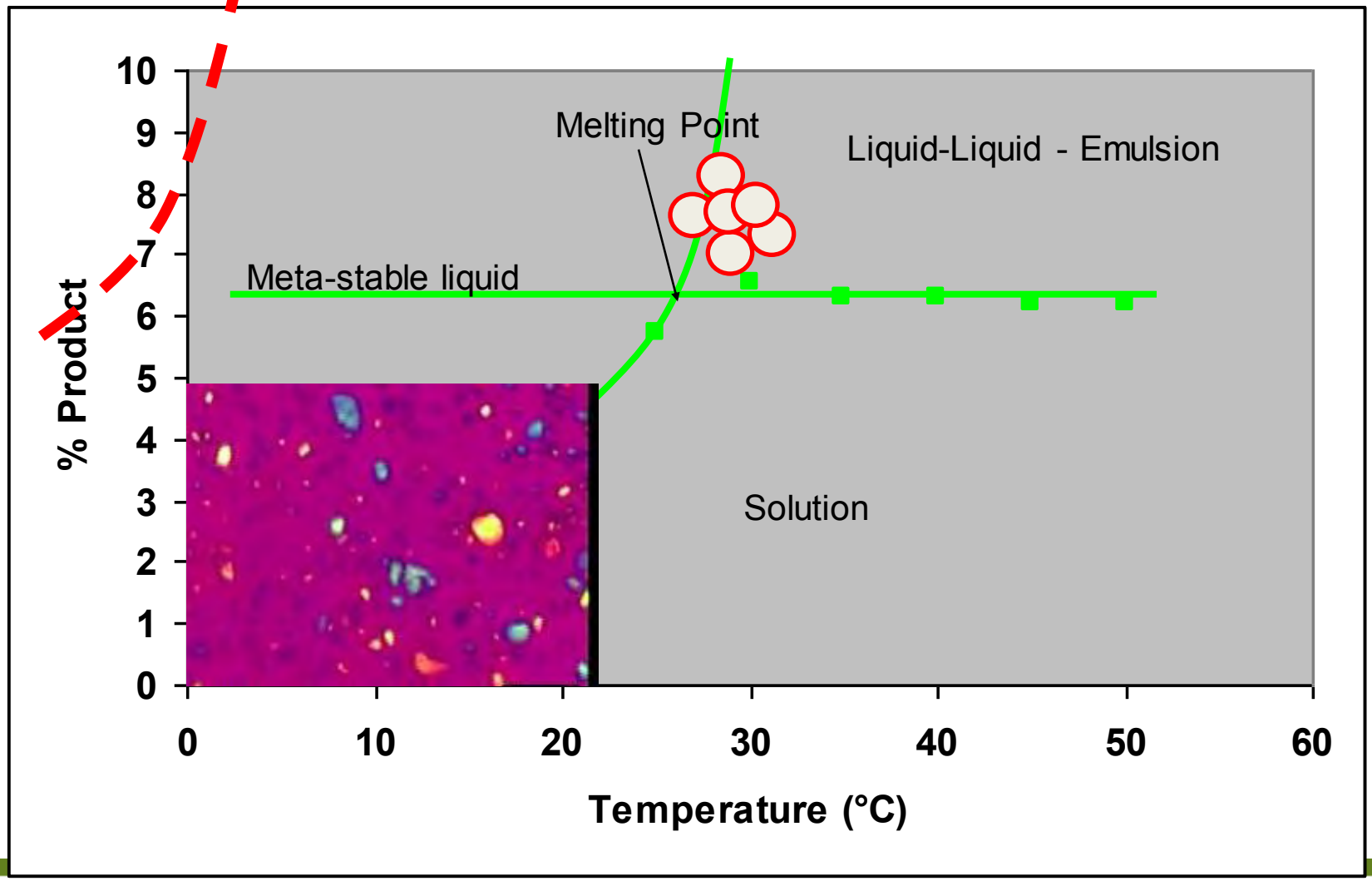
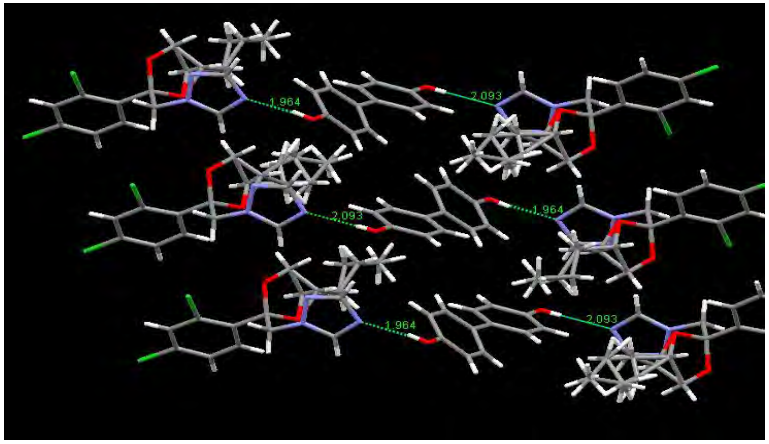
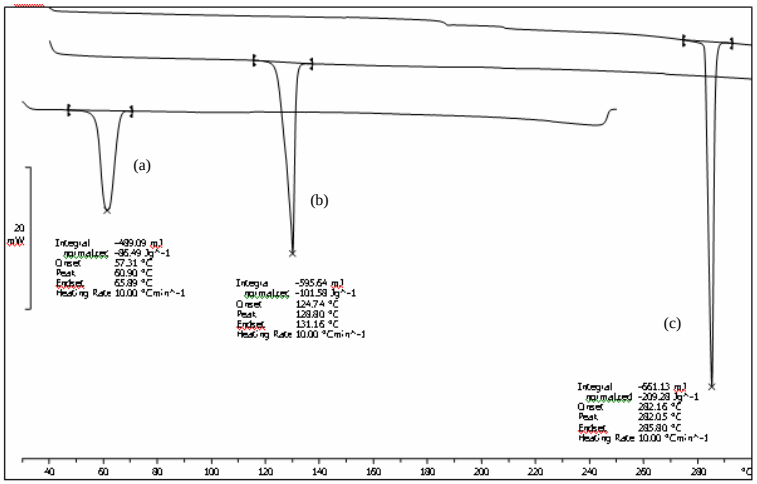
Emulsion Phase Stability – Low Melting Active



Solid State Thermodynamic Solutions to Phase Transitions

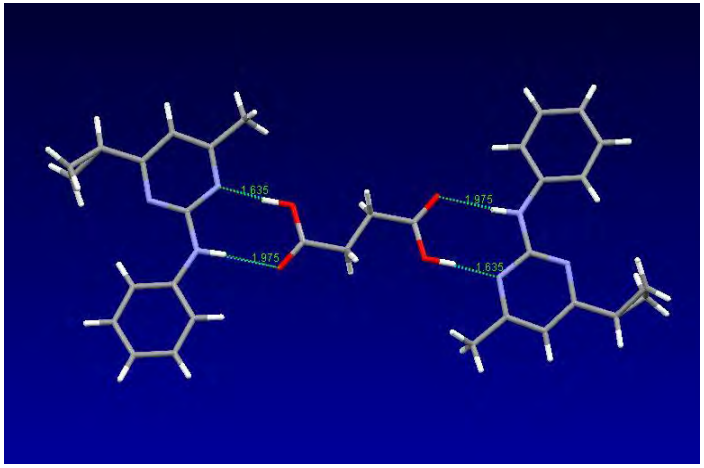
Propiconazole Dihydroxybiphenol Co-crystal

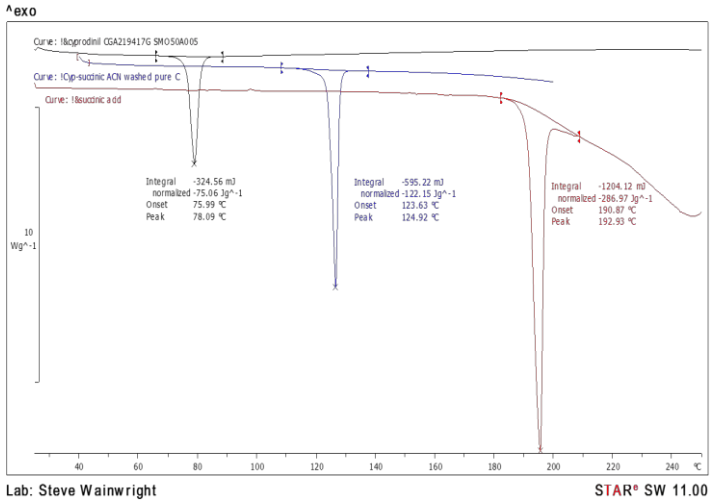




Patent: PCT2008/117037 ***N.George****, J. Forrest, P.Bonnett, P Gavin*

Cyprodinil–Succininc Acid Co-crystal





Patent PCT 2008/107060 ***N.George****, J.Forrest, P. Gavin, R. Burton, L. Gregory*

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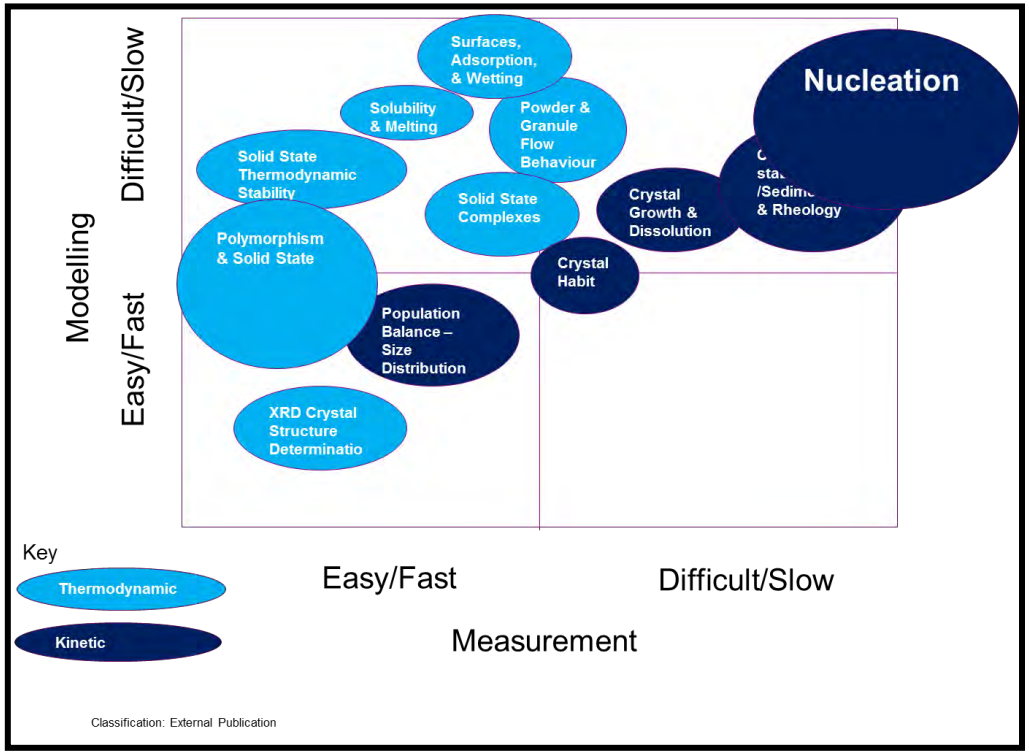
Formulation Thermodynamic Challenges

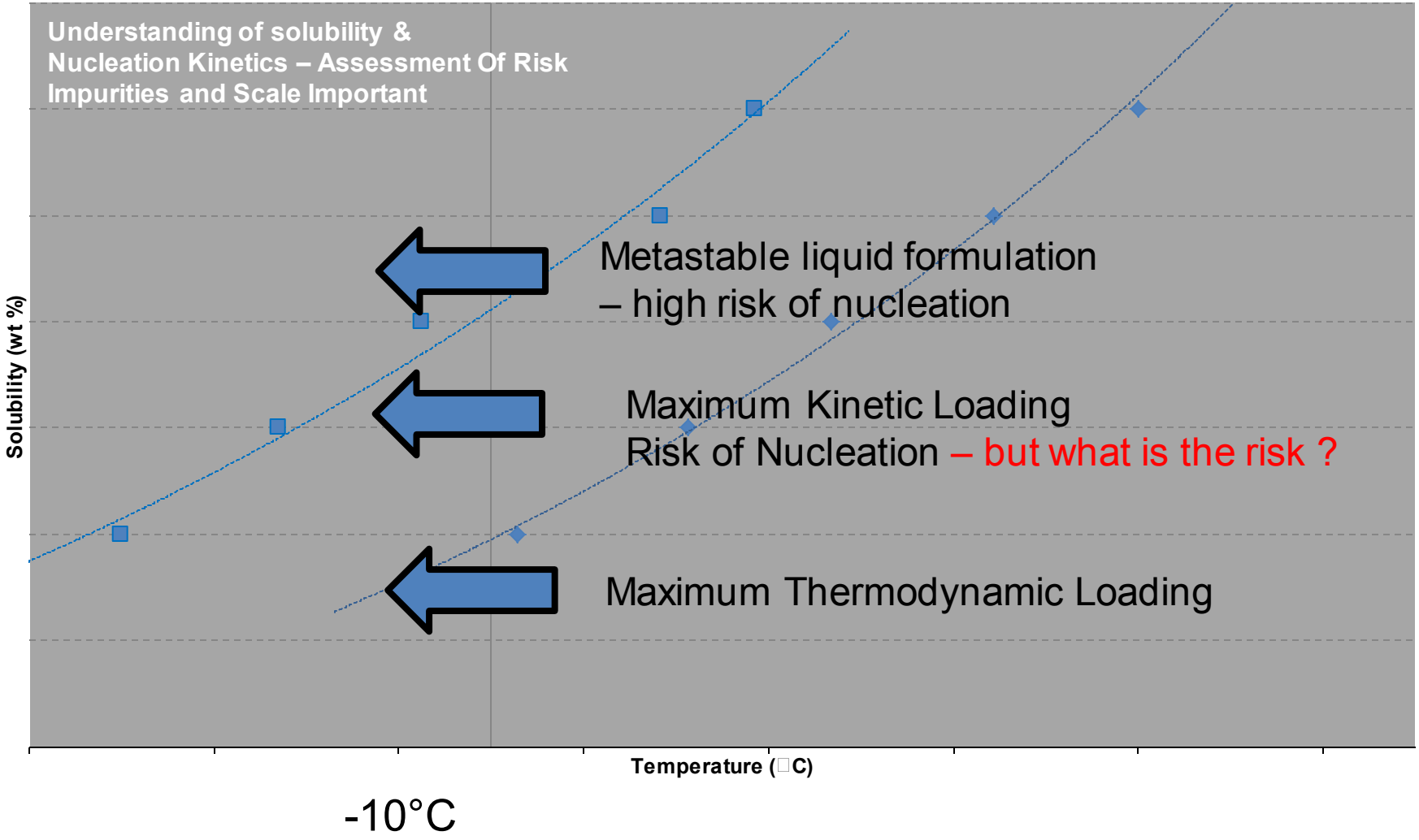
- **Temperature**
- In Manufacture
- Storage and Application -20’C to 50’C

- **Composition**
- In Application
- Dilution – spray tank
- Drying – leaf deposit drying
- Mixing - formulation mixtures and additives

Minimising Nucleation



Nucleation Temperature: Formulation Loading Below Minimum Solubility for Storage



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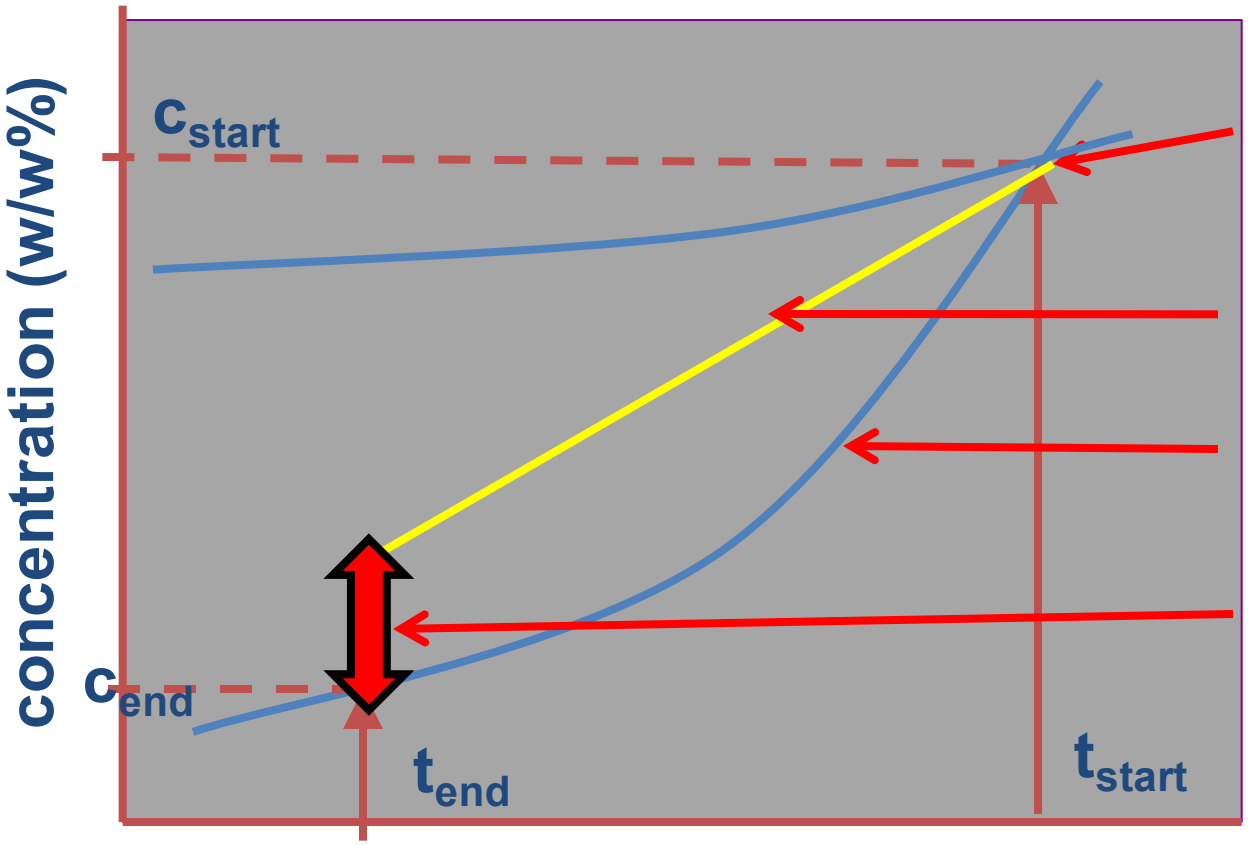
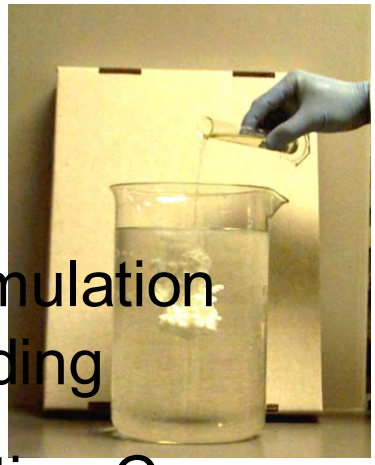
Nucleation Composition : Solubility for Spray Tank Dilution



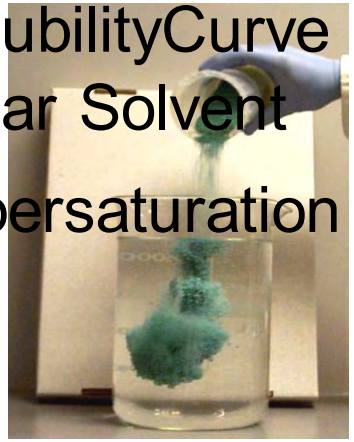


Formulation Loading

Dilution Curve

SolubilityCurve Polar Solvent

Supersaturation



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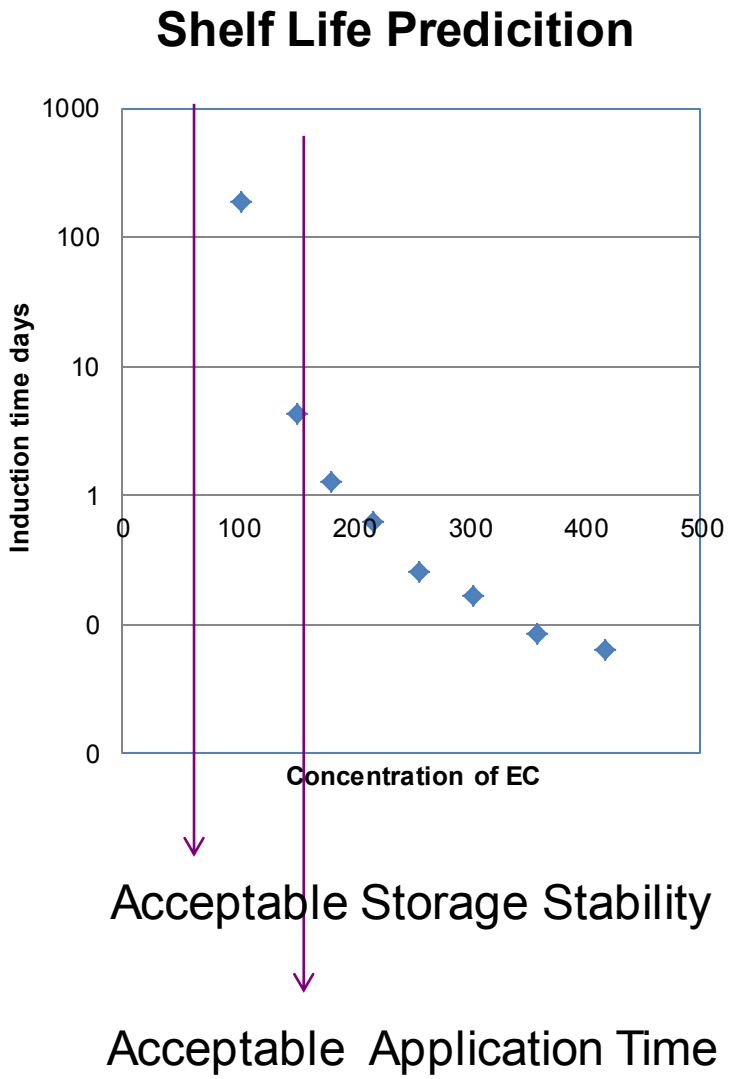
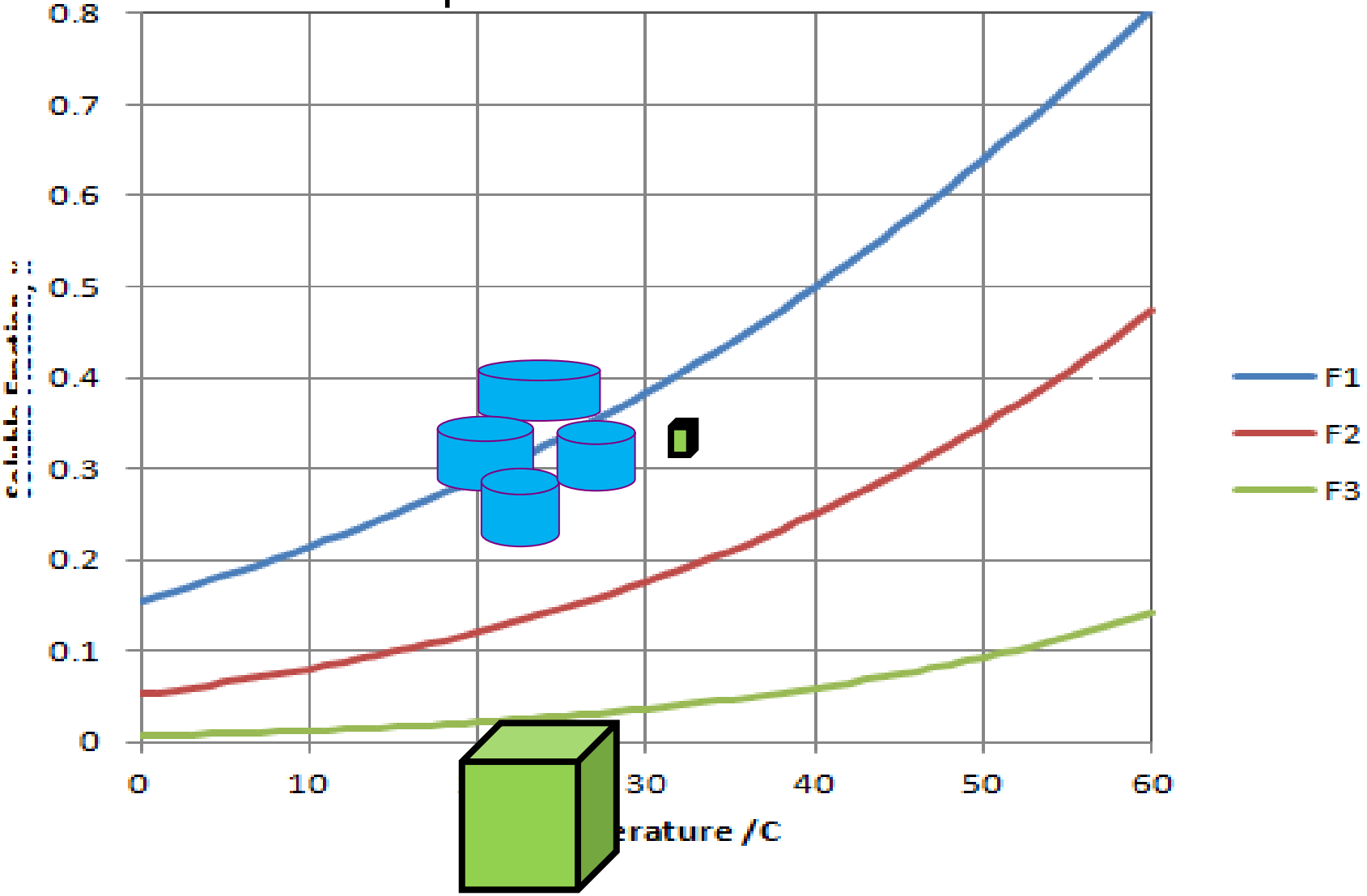
Nucleation Time

- Induction time experiments are a feasible estimation of acceptable stability
- Extrapolation over long time scales questionable
- But sensitive to impurities, scale, variation in temperature conditions

$$t_N = \frac{N_N}{J} = \frac{N_N}{A} \exp\left(-\frac{16\pi\sigma^3 V_m^2}{3(kT_K)^3 (\ln S_R)^2} \right)$$



Monotropic Polymorph Transformation on Storage – Nucleation at Low Supersaturation



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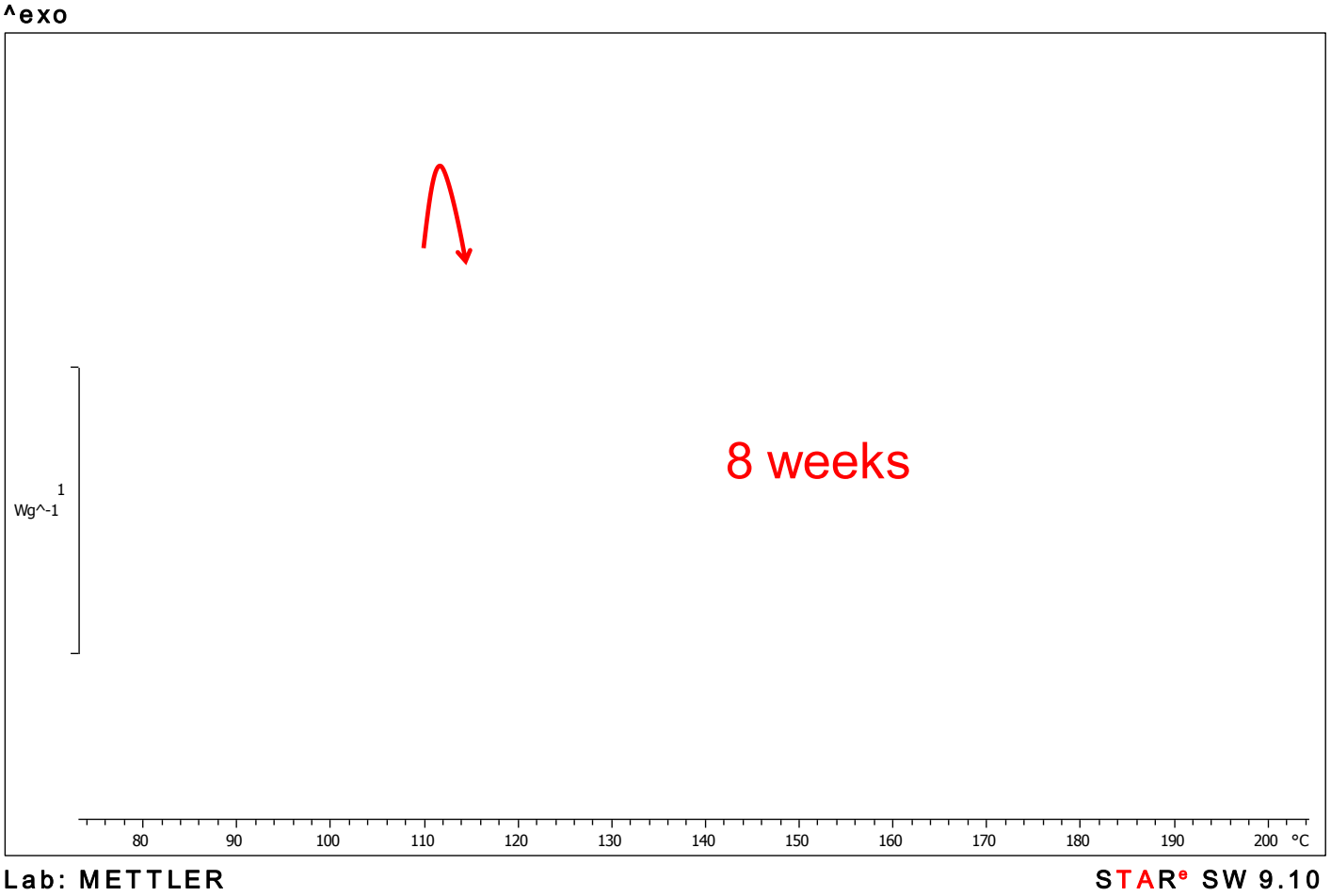
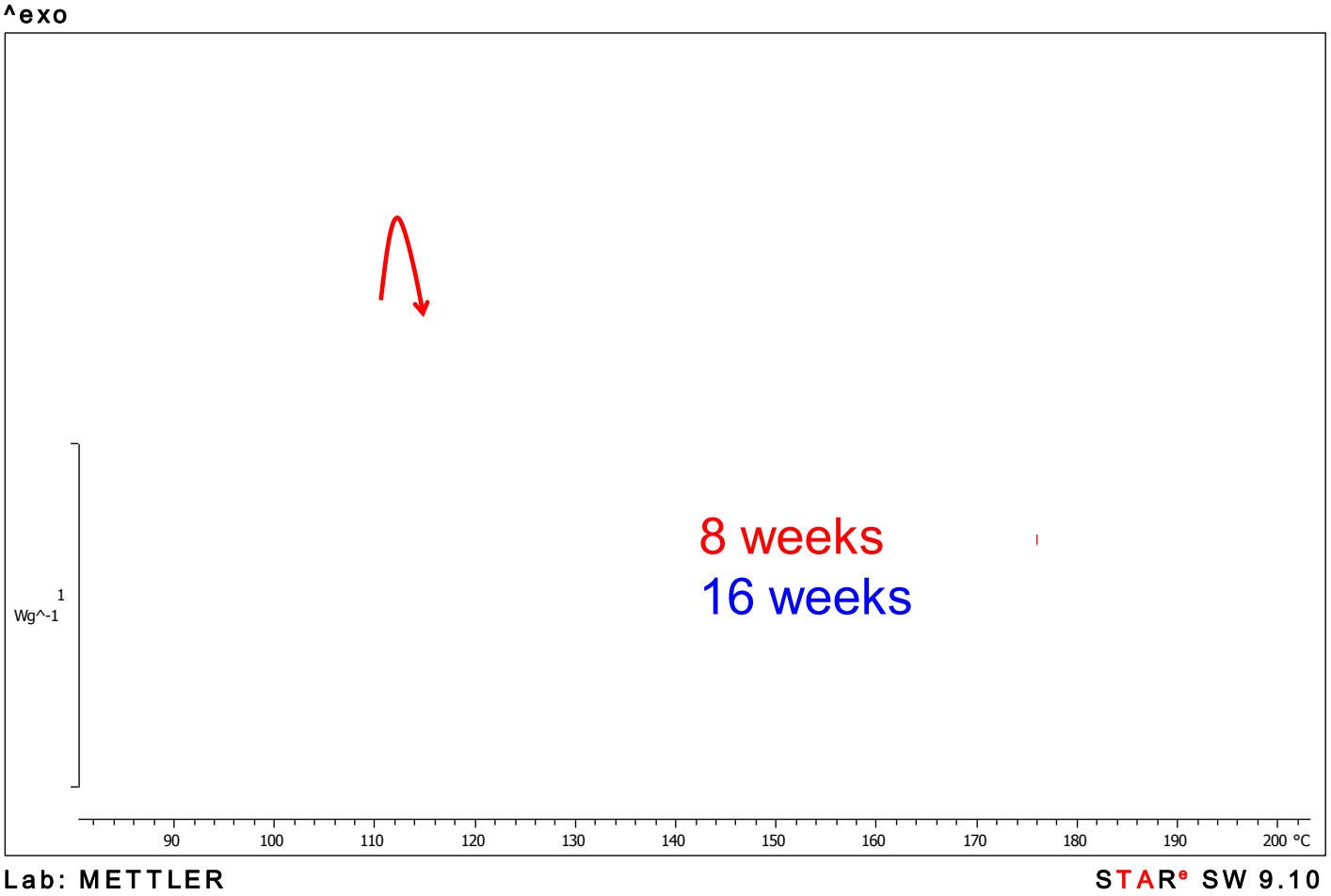
Polymorph Transition Within a Suspension concentrate

Slow Polymorph Transitions in Suspension Concentrates
Early Crystal Nucleation & Growth



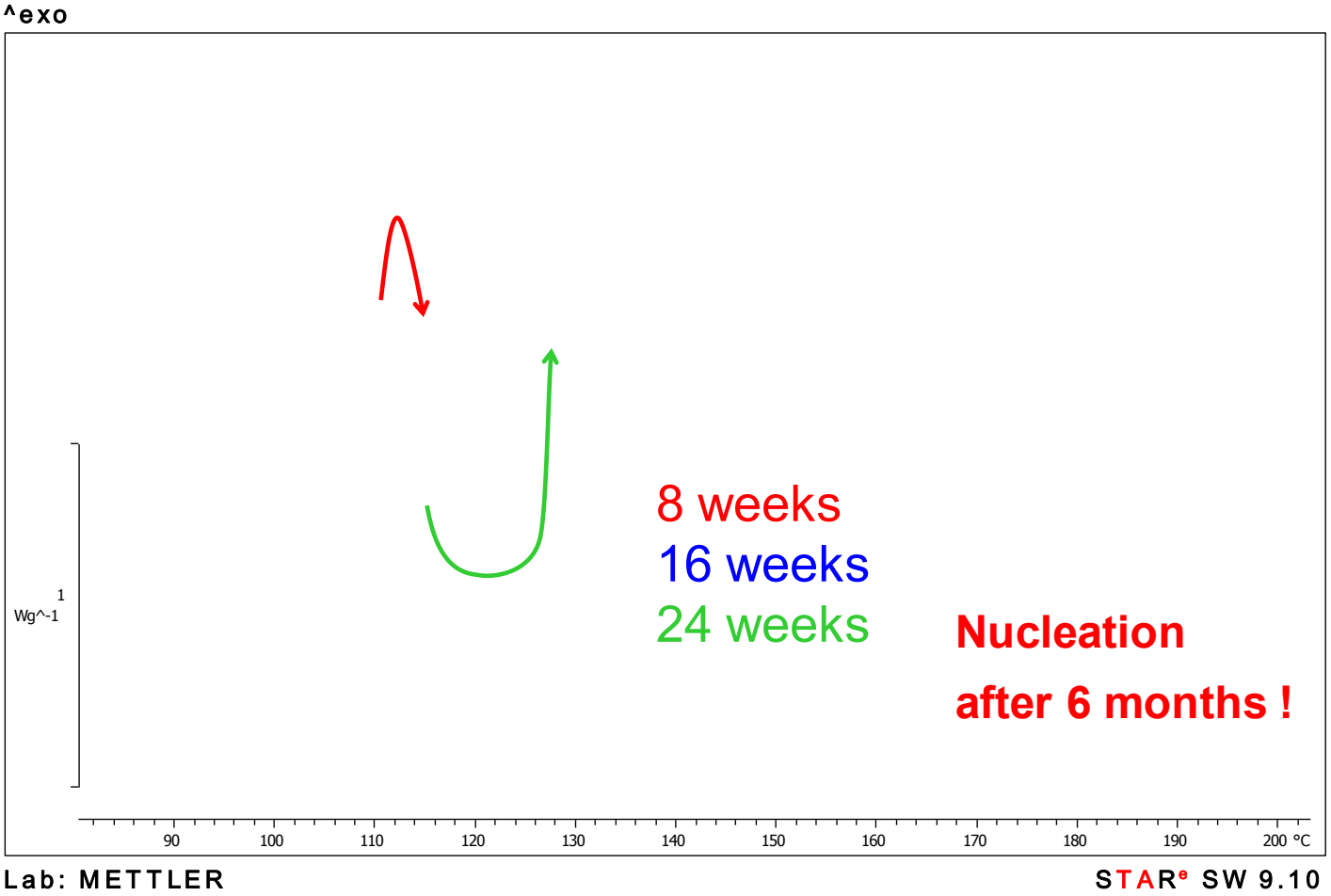
Crystal Growth Through Polymorph

Slow Growth

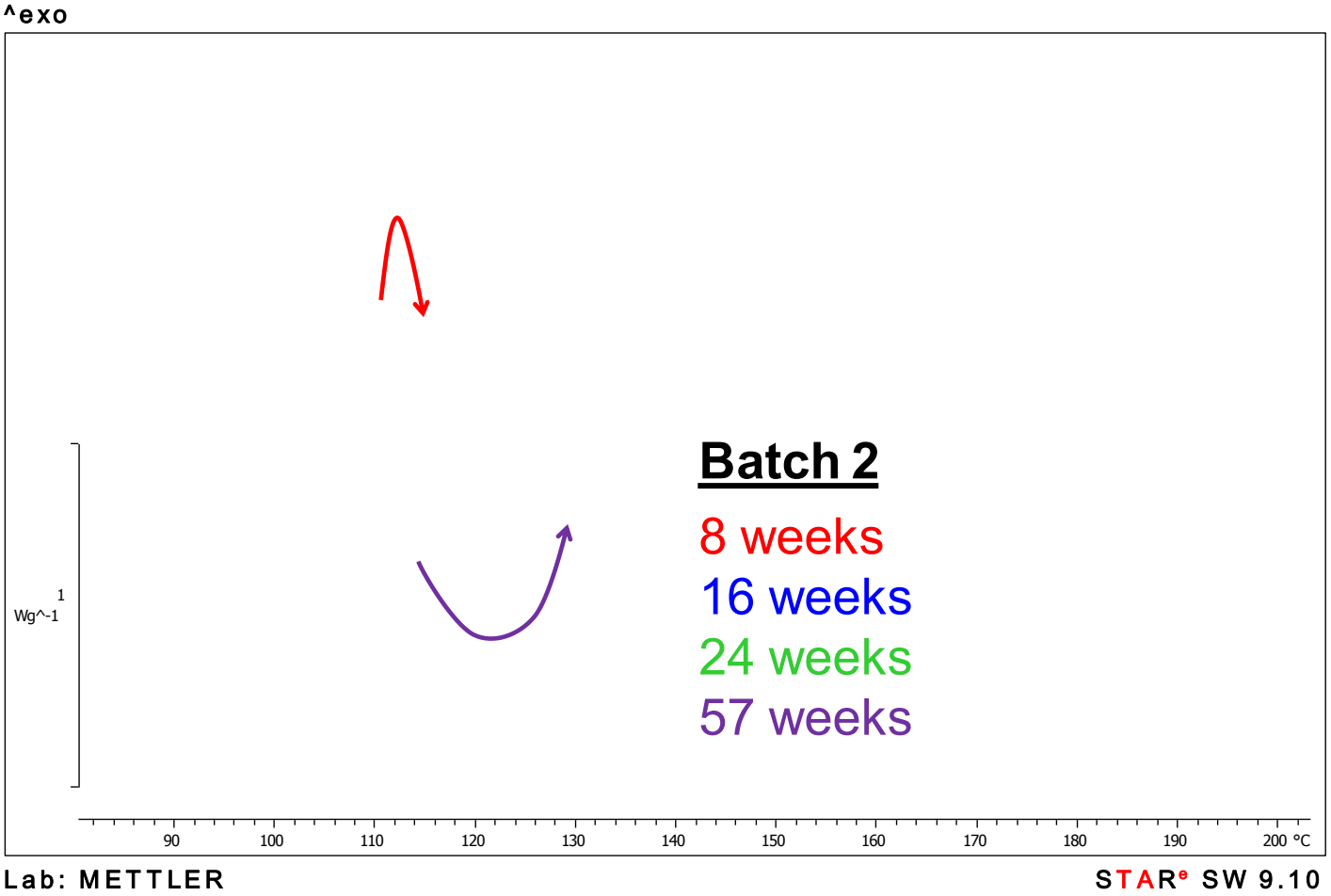


Nucleation

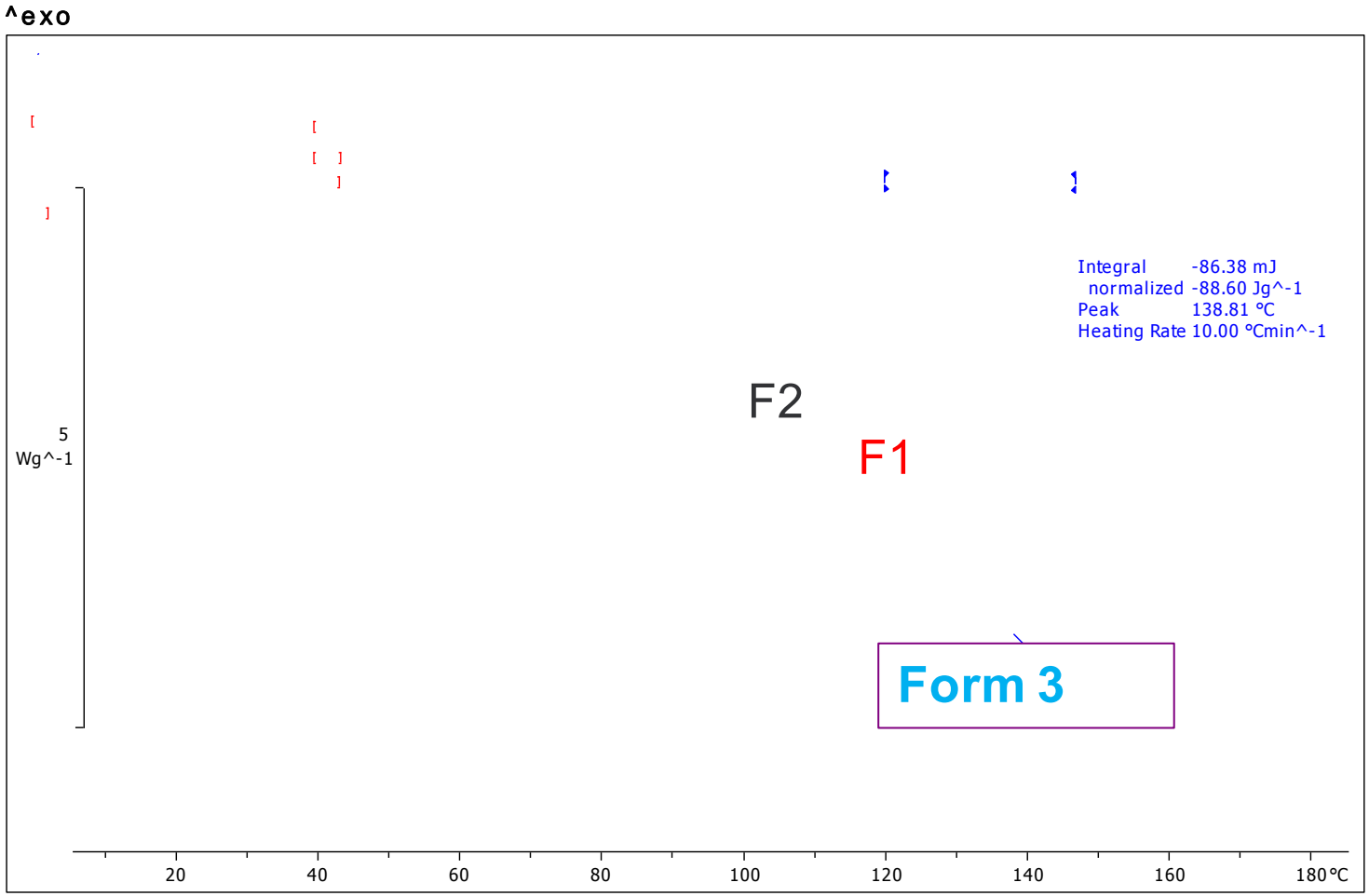
Slow Nucleation



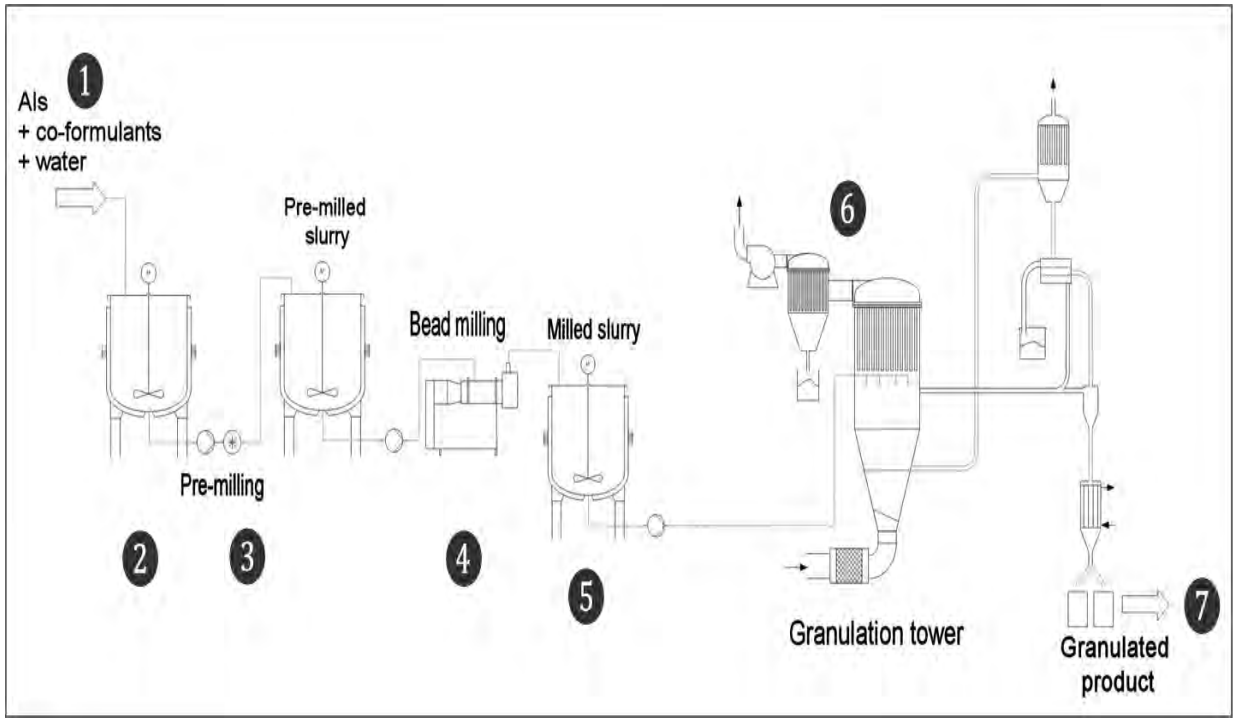
Product Instability – Sedimentation of Field Nozzle Blockage



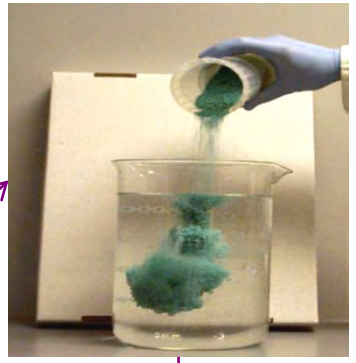
Early Thermodynamic Resolution of Solid State Stability Isolation Crystallisation Optimised to Deliver this Form

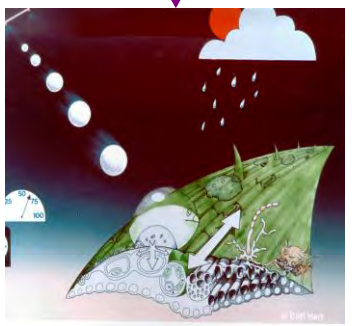


Nucleation Composition: Water Activity and Anhydrous to Hydrate Transformation



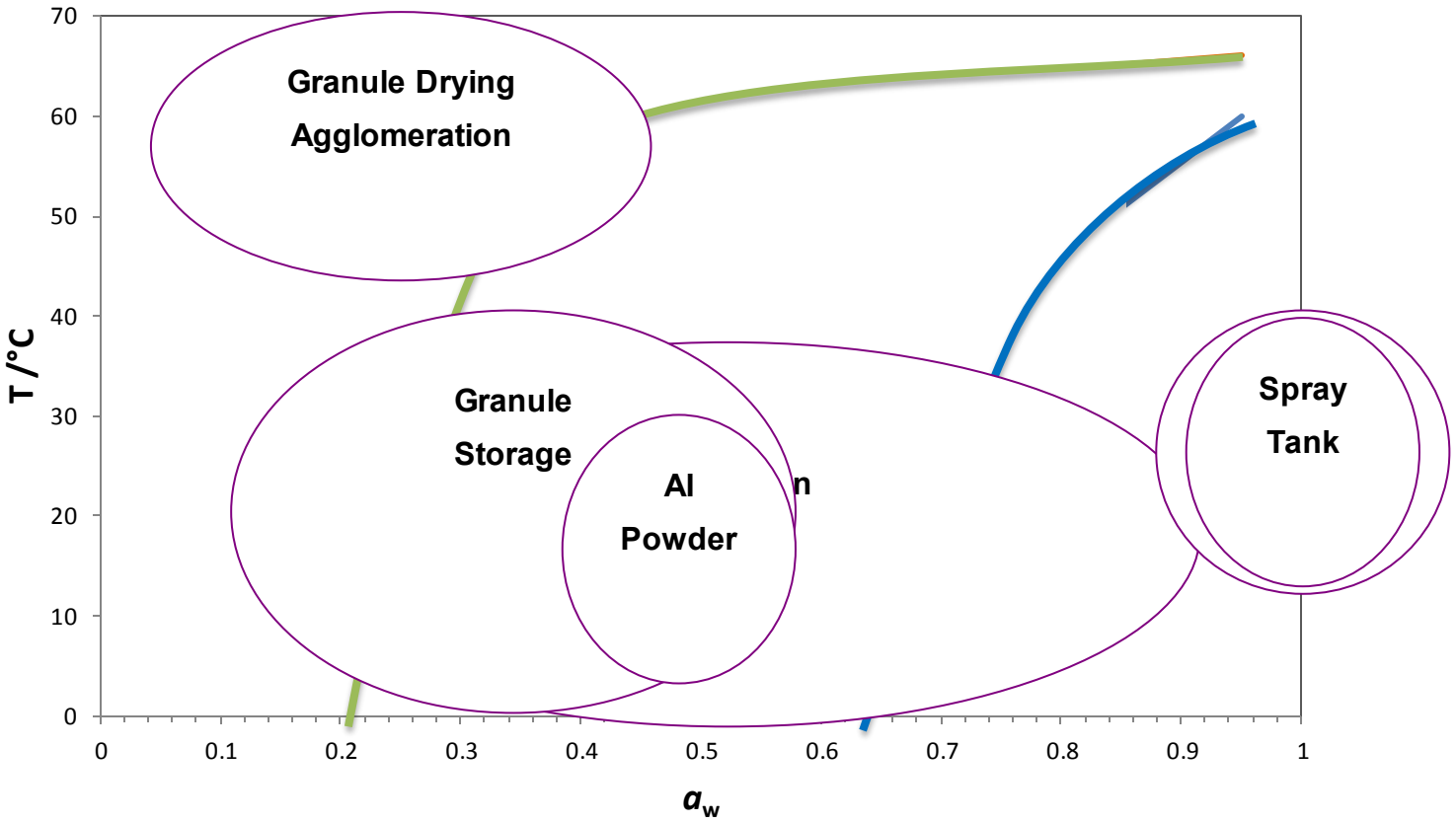
Spray Tank



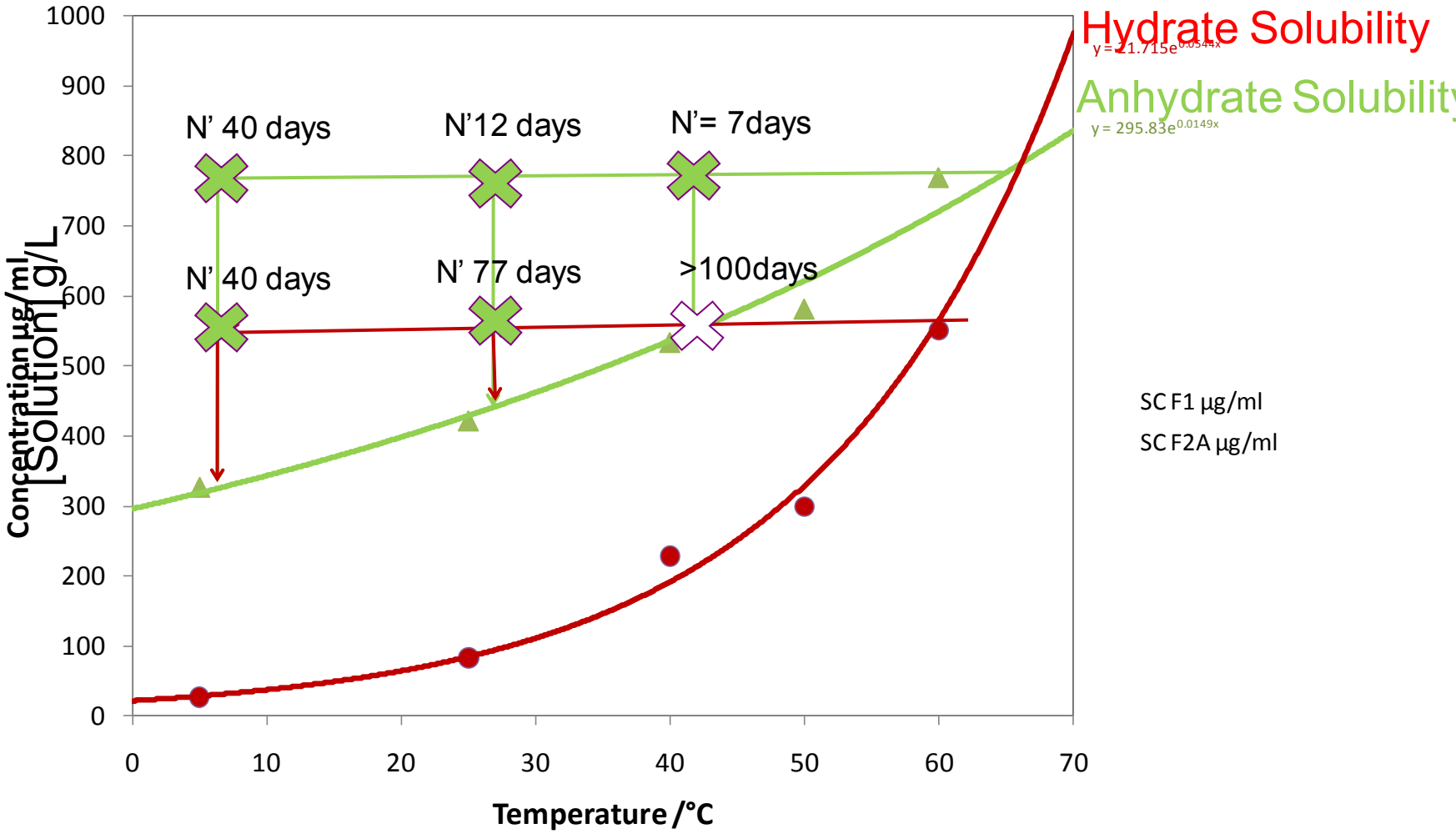


Field

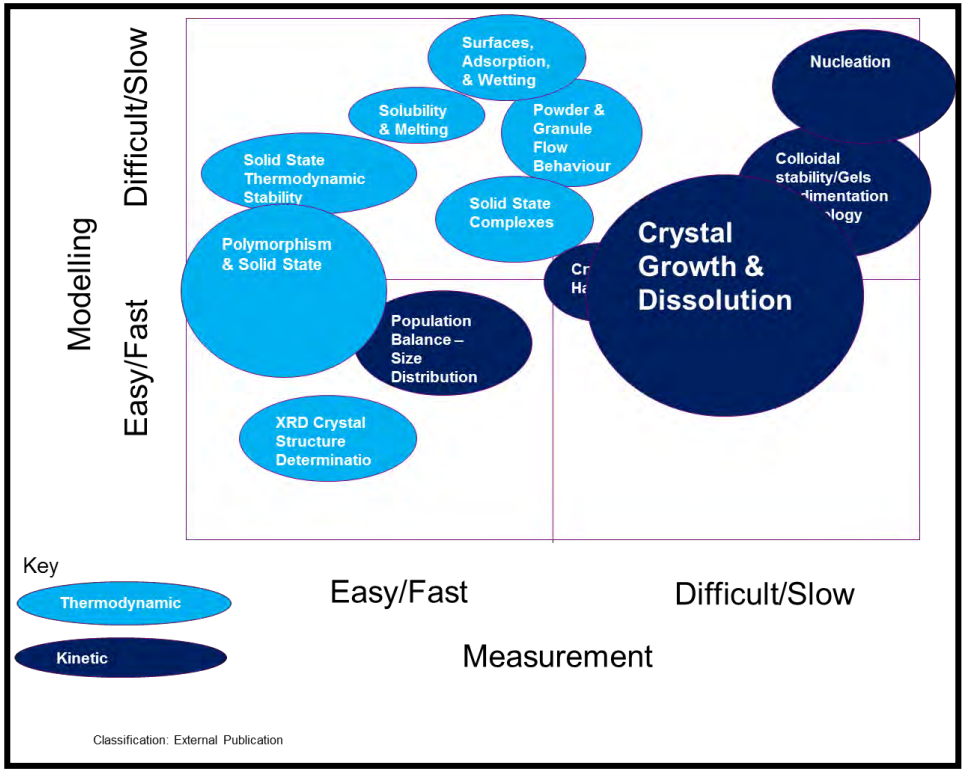
Hydrate Stability In Processing and Application Traversing The Phase Diagram – Nucleation at Low Supersaturation



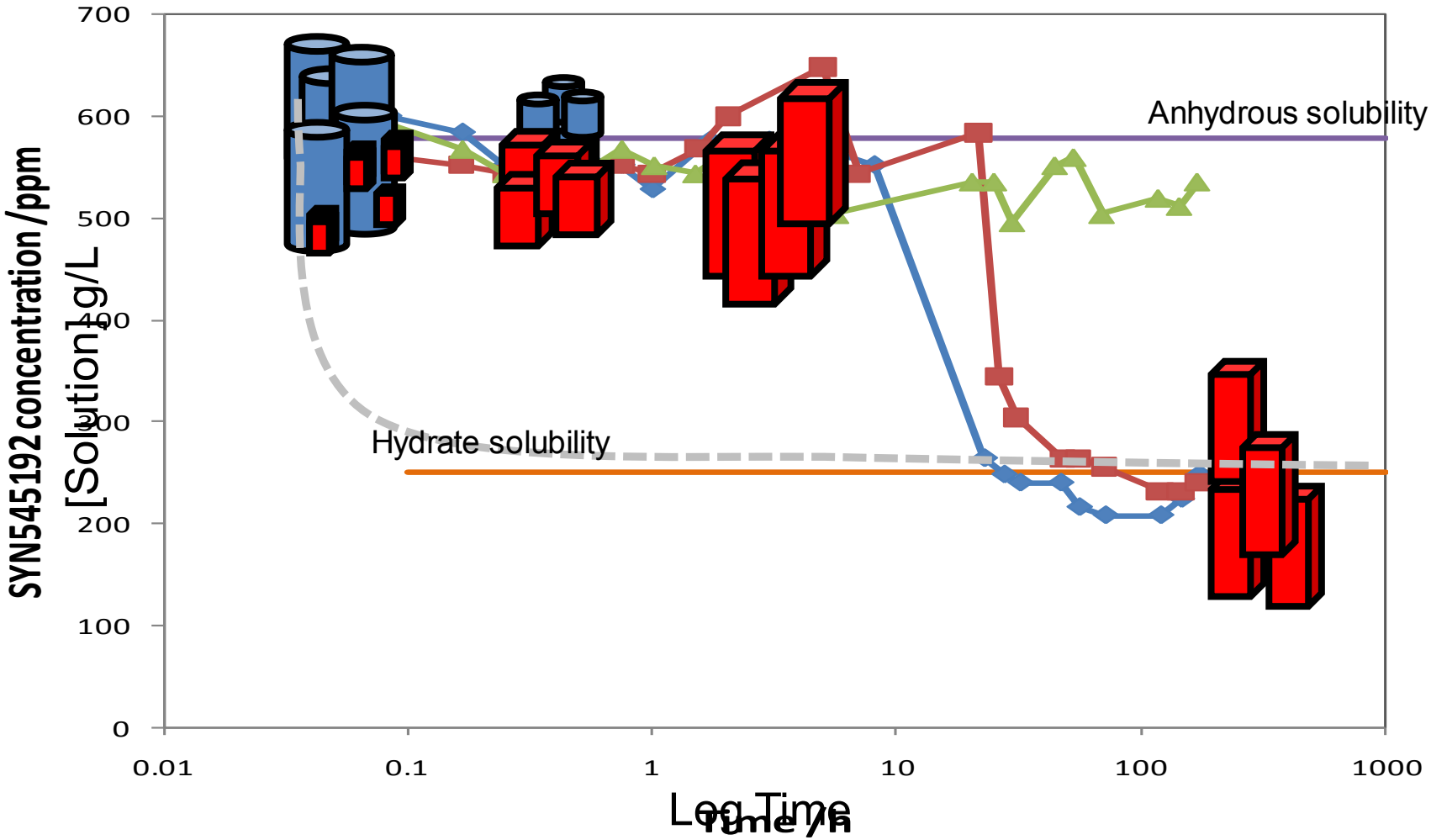
Nucleation Times: Anhydrate Nucleates More Rapidly



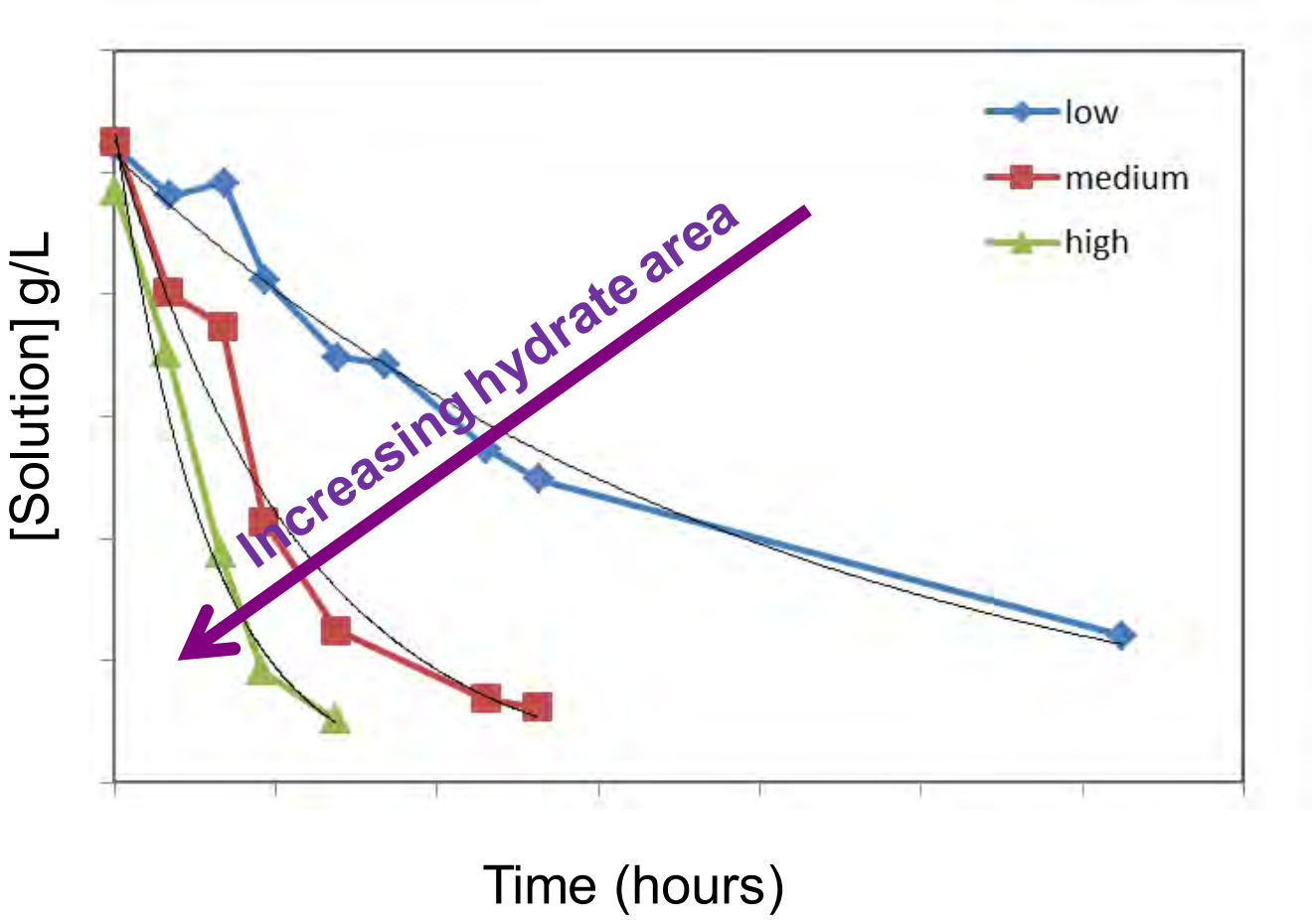
Minimising Crystal Growth



Crystal Growth: Isothermal Anhydrate to Hydrate Transformation Rate – Hydrate Crystallisation Rate Limited



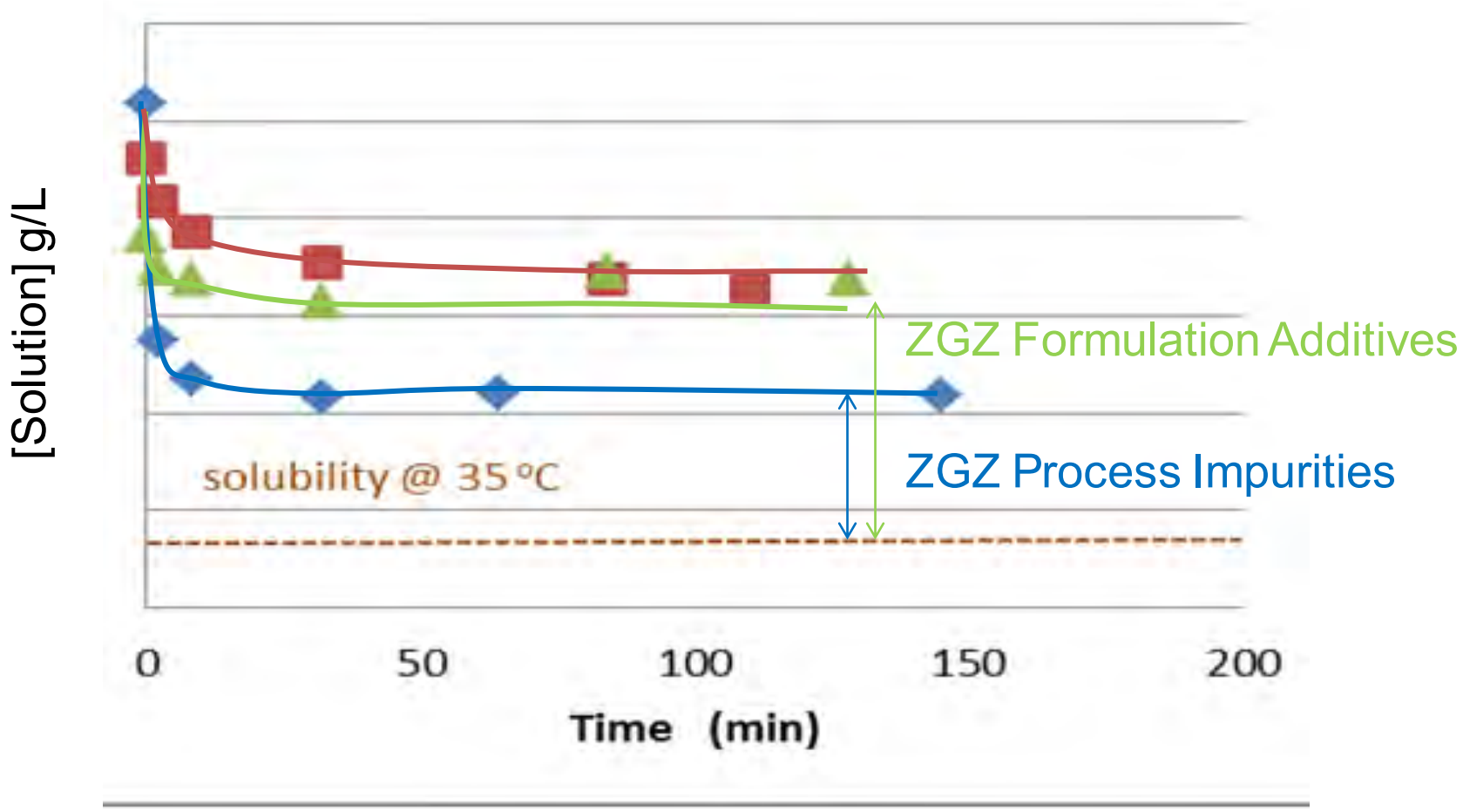
Rate of Transformation in Anhydrous SC With Hydrate Contamination – Robust Processing Dry Granule Formulation



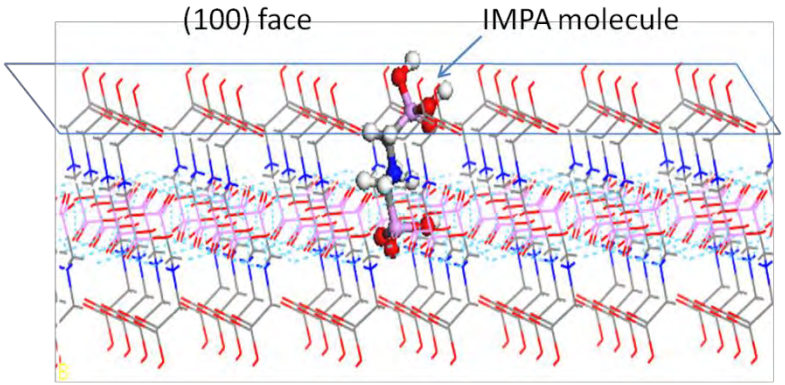
Low Supersaturation Growth Inhibition: Zero Growth Zone

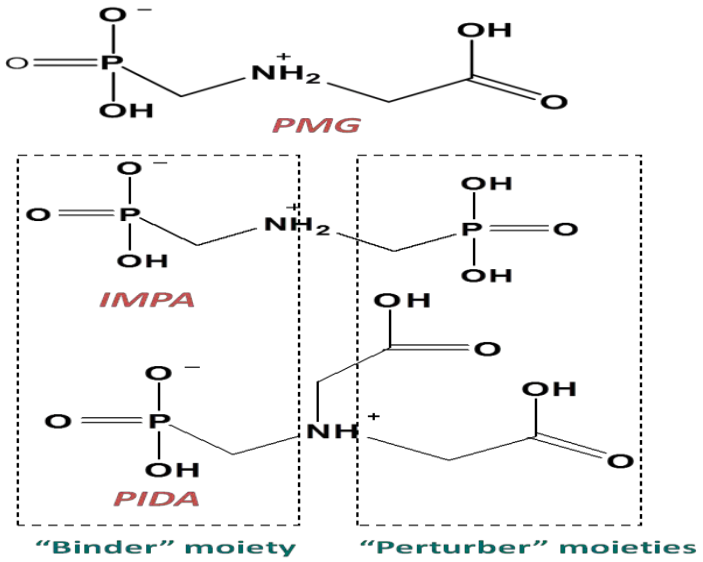
If overall ZGZ > (C-C*) gives stability

Face Specific ZGZ = anisotropic growth

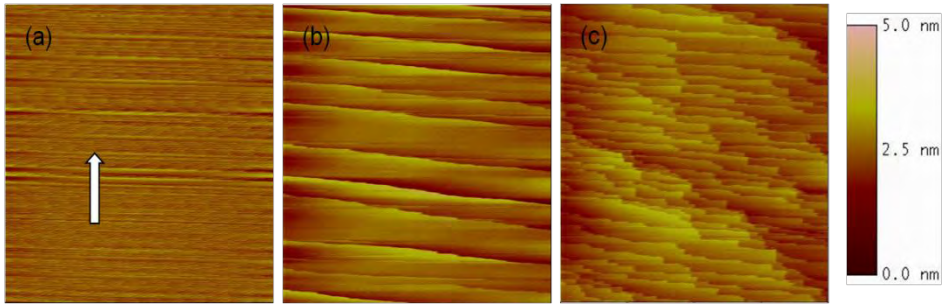


Solid Solutions – Molecular analogues





Face (hkl)	E_b	ΔE_b	
	PMG (host)	IMPA	PIDA
(100)	−42.4	−22.8	+189.0
(011)	−18.0	+24.4	+2.9
(001)	−19.6	−21.8	+89.3



Poornachary, S. K.; Lau, G.; Chow, P. S.; Tan, R. B. H.; George, N. The Effect and Counter-Effect of Impurities on Crystallization of an Agrochemical Active Ingredient: Stereochemical Rationalization and Nanoscale Crystal Growth Visualization. Cryst. Growth Des., **2011, 11, 492-500.**

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Summary – solid state information for maximum impact

- Generally we aim to minimise crystallisation in formulations
- Defining solid state stability is central to stable formulations – minimises supersaturation
- Automation of solid state screening for rapid and early discovery of solid state has become established over the last decade able to cope with the rising complexity of active ingredients and formulations. Emerging solid state modelling will help streamline experimentation.
- Supersaturation generation in formulation is inevitable due to phase transitions, composition and temperature variation.
- Rapid and precise determination of crystallisation kinetics in formulations is challenging but can be very helpful in minimising formulation risk
- Measurement and prediction of crystal nucleation particularly at low supersaturations is challenging. There are great opportunities here for improved formulations and enhanced formulation performance – including metastable phases
- Measurement of crystal growth is most cases is achievable and a means of modelling modification of crystal growth is emerging. The link between surface properties and crystal growth requires more study.

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