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Introduces…

Crystallisation Science and Agrochemical Formulation

Jim Bullock & David Calvert

4th February 2016

Webinar sponsored by

Technobis crystallization systems

www.crystallizationsystems.com

Your Speakers

Jim Bullock

Solubility and Crystallisation: Basic Principles

David Calvert

Practical Importance of these Themes in Agrochemical Formulation

- This webinar is being recorded and will be made available
- The audience is muted and may ask questions using chat or question functions in GoToWebinar
- This webinar will last 45 minutes

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A Little About iFormulate

A company founded in 2012 by two experienced industry professionals…

Combining diverse experiences, knowledge and wide range of contacts:

…polymers, materials science, chemistry, imaging, dyes, pigments, emulsion polymerisation, biocides, anti-counterfeiting, environmental, formulation, consultancy, marketing, business development, strategy, regulatory, training, events, R&D, innovation

Complementary network of Associates

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Our Services

iFormulate Consult

iFormulate Strategic

iFormulate Skills

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TECHNOBIS CRYSTALLIZATION SYSTEMS

- Privately owned company
- 35 employees
- Located in Alkmaar, The Netherlands
- Leader in 3 major markets: Pharma, Agro and Fine Chemicals

Portfolio

- 3 products for: formulation, process optimization and crystallization related research

Products

CrystalBreeder

Discover

- Early stage salt, polymorph screening
- Single crystal preparation

Working volume:
0.05 – 0.2 ml
32 reactors

Crystal16

Screen

- Phase diagrams
- Selecting solvents
- Solubility, MSZW
- Polymorphs, Salt and co-crystals

Working volume:
0.25 – 1.5 ml
16 reactors

Crystalline

Optimize

- Form control
- Habit control
- Particle sizing
- Process optimization
- Formulation

Working volume:
1 –5 ml
8 reactors

Webinar Overview

1. **Basic Principles**
   - What is Solubility and What Factors Can Influence Solubility?
   - How Can Solubility Be Predicted or Measured?
   - Supersaturation and Crystallisation: Thermodynamics and Kinetics
   - Ostwald Ripening, Polymorphism, Mixed Systems
   - In The Real World, Watch Out For…
2. **Practical Importance**
   - Agrochemical Formulation: Brief Overview
   - Some Relevant Agrochemical Formulation Types
   - Instability: Troubleshooting and Diagnosing Problems
   - Use of Additives
3. **Questions and Wrap Up**

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What is Solubility Really?

The Easy Bit…

The amount of a **solute** that will dissolve to form a solution in a given volume of **solvent**

Solute can be a **solid**, liquid or gaseous substance

Solvent is usually a **liquid**, sometimes a solid and rarely a gas.

But What About…

- Equilibrium conditions?
- Measuring solubility?
- Supersaturation?
- Impurities and solid state effects?
- Predicting solubility?
- Temperature?

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One Way of Looking At Solubility

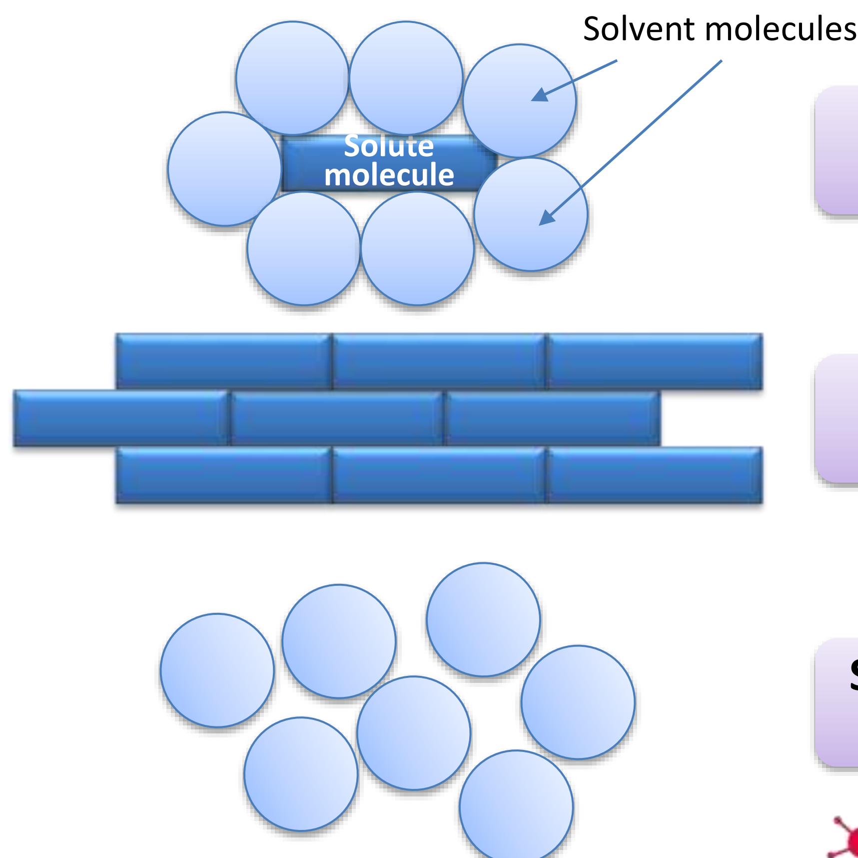
Solubility as an equilibrium: Thermodynamic Free Energy

Pure solute (often solid) $\rightleftharpoons$ Solute dissolved in solvent (i.e. solution)

To <u>increase</u> solubility, make this state more favourable *(reduce free energy of this state)*…

…make this state less favourable *(increase free energy of this state)*…

..and make this state less favourable *(increase free energy of this state)*.



Solute:Solvent interactions

Solute:Solute interactions

Solvent:Solvent interactions

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What Factors Can Influence Solubility? (1)

Choice of Solvent

- Affects molecular interactions between solvent and solute
- Use of solubility parameters, similarity principle

Nature of Solid State of the Solute

- Crystal packing interactions, crystal (or amorphous) form of solute
- Particle size of solute
  - smaller particles → higher free energy → higher solubility
- Melting point as indicator of crystal packing energy
- Complex solid forms possible (co-crystals, hydrates)

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What Factors Can Influence Solubility? (2)

Impurities and Additives

- Impurities usually reduce melting point and increase solubility
- Solubilising additives may be added deliberately
- But e.g. M^{2+} ionic impurities may precipitate salts

Experimental or ambient conditions

- Especially temperature

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How Can Solubility Be Predicted?

Prediction from molecular structure

Hansen Solubility Parameters (HSP) - "like dissolves like"

- Describe solute and solvent with parameters which relate to dispersion, polar and hydrogen-bonding interactions
- Very useful for solvent selection, solvent mixtures
- Not an absolute method: Does not account for solute crystal packing

Molecular Modelling Methods

- In principle accounts for all interactions, free energy calculations
- Complex and computationally intensive, expertise requirements

For a **gentle** introduction to some equations on solubility see Paul Mahon's article on our website: http://iformulate.biz/news-and-views/dissolution-solution-solubility-stable-formulations/

How Can Solubility Be Measured?

Experimental Measurement

Saturated solution has to be in contact with undissolved solute, **at equilibrium**

Practical Issues:

- Time taken to reach equilibrium, has equilibrium been reached?
- Control of temperature
- Multiple data points – temperature, concentration, stepwise addition of solvent
- How to measure the concentration in solution? E.g. gravimetric, HPLC?
- May require large reactor with attached analytics
- Multiple heating and cooling cycles needed
- Manual intervention – detection of solute by eye

Automated Solubility Measurement

Example: Technobis Crystal16

- Automated, small volumes (~ ml)
- Programmable temperature
- Multiple solvents/concentrations
- Integrated turbidity measurement to detect solid

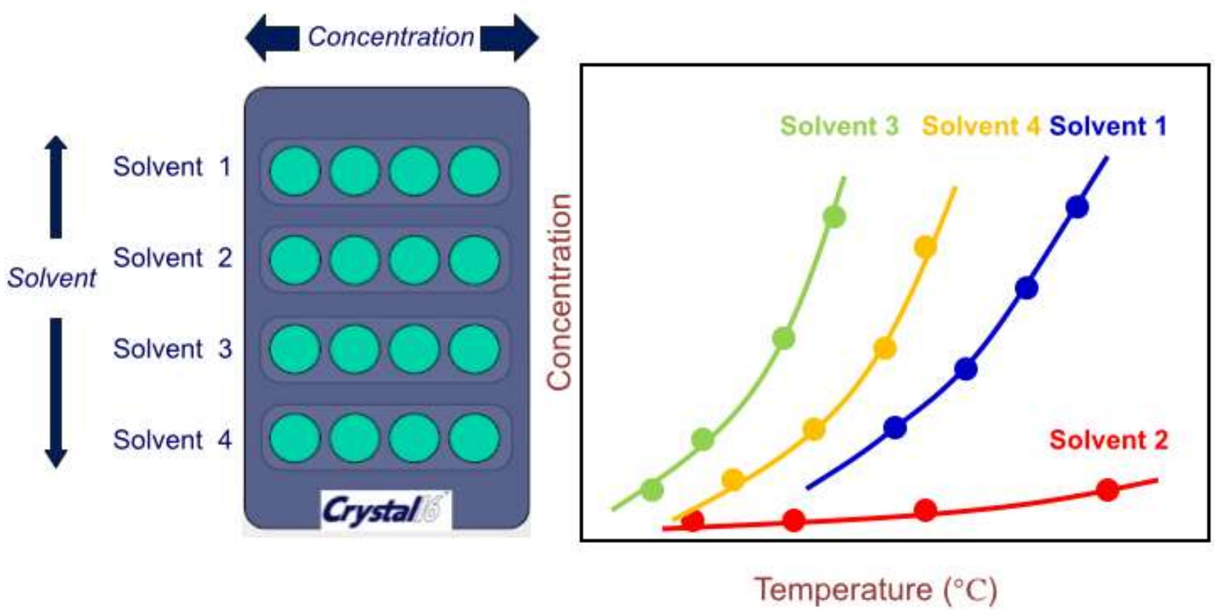

Figure courtesy of Technobis

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Supersaturation and the Metastable Zone

- Supersaturated: Solute concentration **higher than the equilibrium solubility**
- A supersaturated solution is **thermodynamically unstable** but kinetics prevent crystallisation if the concentration remains within the **metastable zone**
- **Controlled crystallisation** can take place within the metastable zone (seeding, control cooling, evaporation or addition of antisolvent)

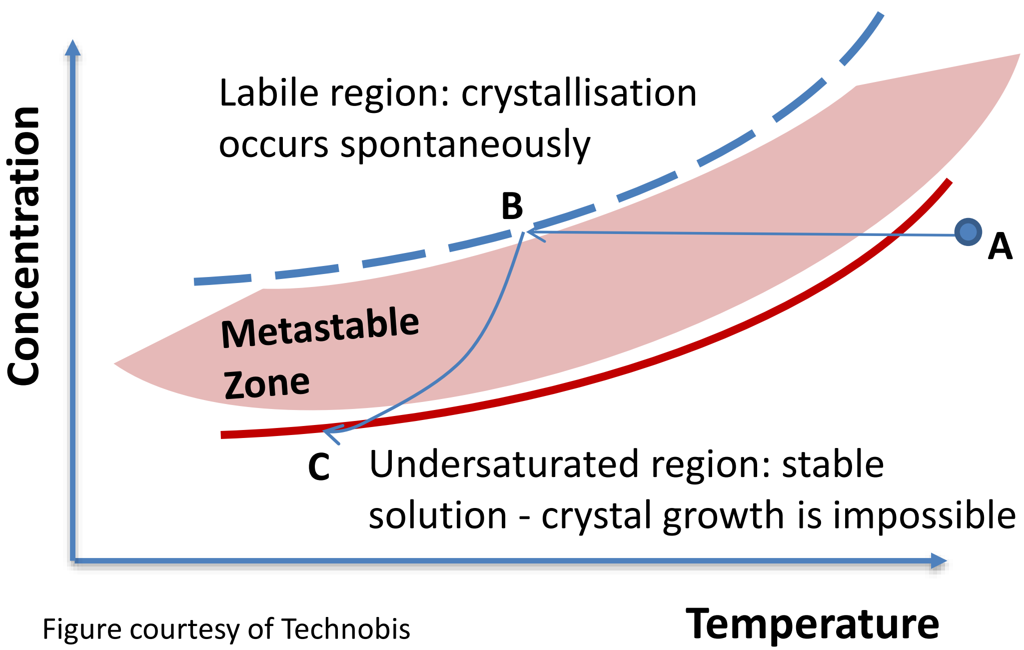

Figure courtesy of Technobis

Example:

A: System is undersaturated

Cool until point **B -** crystals are formed

Crystal growth (controlled cooling) until point **C**

At C system is in **equilibrium** and thermodynamically **stable**

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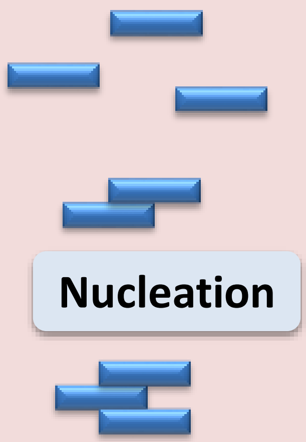
What Happens in Crystallisation?

Crystallisation proceeds via **nucleation** and **growth**

Nucleation:

- Solute molecules (ions, atoms) move within the solution (Brownian motion) colliding with each other, **attaching and detaching**
- Within the **metastable zone** nucleus must be of a **critical size** before it can grow spontaneously
  - **Seed crystals** may be added to initiate crystallisation within the metastable zone
- In the **labile zone** nuclei form **spontaneously** because the solute concentration is high, ensuring many collisions and formation of nuclei above the critical size



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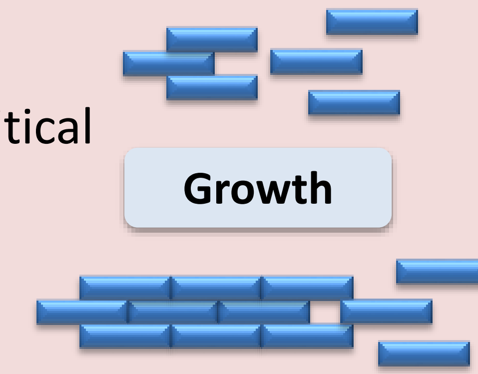
What Happens in Crystallisation?

Crystallisation proceeds via **nucleation** and **growth**

Growth:

- **In the metastable zone** the crystals will grow (once critical nuclei are present)
- Molecules attach to the various faces of the crystal



Primary Nucleation:

- Occurs in systems **not already containing crystals** of solute
- **Homogeneous** (spontaneous) – e.g. precipitation
- **Heterogeneous** (induced by foreign particles)

Secondary Nucleation:

- Secondary nucleation is **induced by parent (seed) crystals**
- e.g. controlled crystallisation

Thermodynamics and Kinetics: But No Mathematics!

Undersaturated Region: Solution state is **thermodynamically stable**

- Any crystals added will dissolve and critical nuclei cannot form

Metastable Zone: Solution state is **thermodynamically unstable**

- But **kinetic barrier** prevents spontaneous formation
- **Growth is thermodynamically favoured:** added seed crystals will grow

Labile Zone: Supersaturation is very high

- No kinetic barrier to nucleation – **nuclei form spontaneously**
- High nucleation rate, so **many small crystals** are formed

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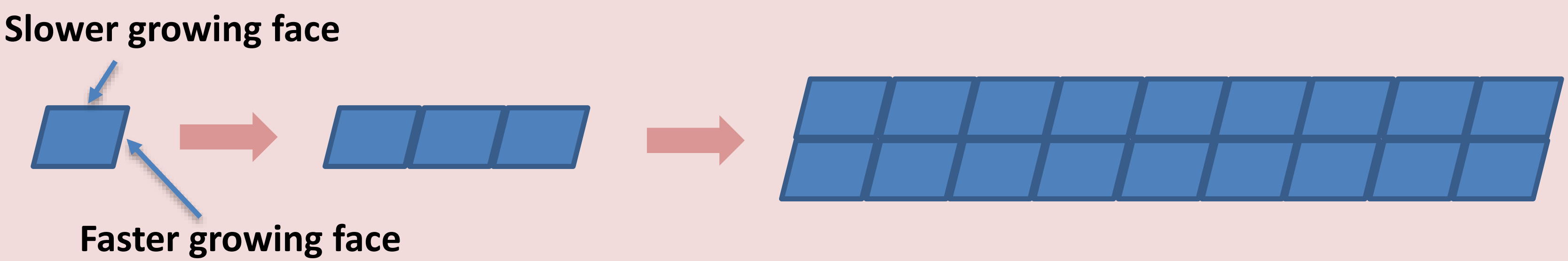
The Bad Habits of Crystals: Morphology and Habit Modification

- The shape ("habit") of a crystal depends on the internal crystal structure and the **rate of growth of its geometrical faces**
- Some faces will grow faster than others (attachment energy and kinetics)
- The **slower growing faces will more prominent** in the visual morphology



- Growth rates of faces (and **habit**) **can be modified** by:
  - Solvent
  - Degree of supersaturation
  - Impurities
  - Deliberate use of additives

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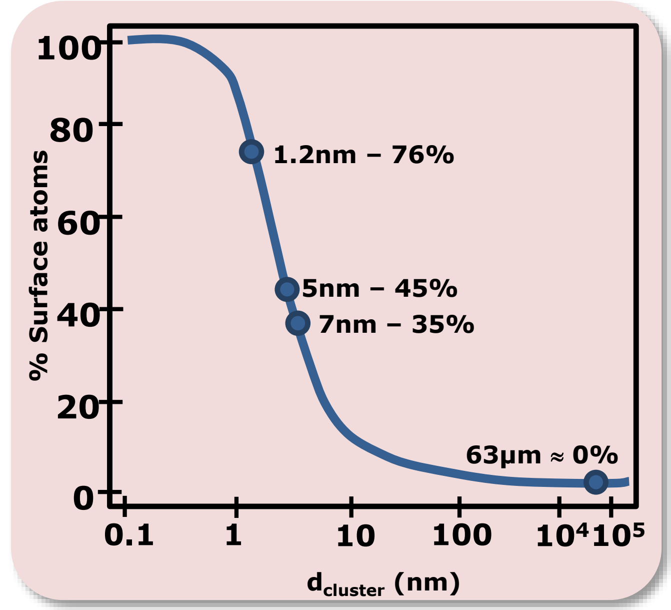
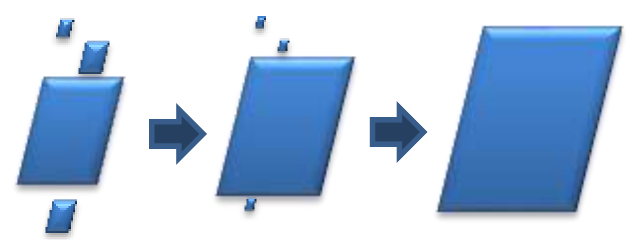
A Favourite Topic: Ostwald Ripening

Ostwald ripening can happen in solid/solid, solid/liquid and liquid/liquid systems:

- **Larger particles grow,** smaller particles dissolve
- Due to **thermodynamics:** larger particles more energetically stable than smaller ones
  - Smaller particles have more surface molecules which are **energetically less stable** than ones packed in the interior
- **Slow it down:** Get kinetics on your side!
  - Slow ripening by starting with a more monosize particle distribution
  - Additives may block faces and slow ripening rate



After: Nützenadel et al The European Physical Journal D 2000, Volume 8 pp 245-250



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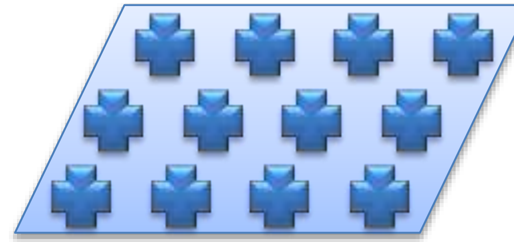
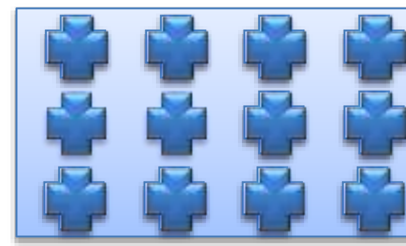
Crystal Polymorphism and Amorphous Solids

The same substance may appear in more than one **crystal form (polymorph)** depending on the arrangement of atoms, ions or molecules in the solid state



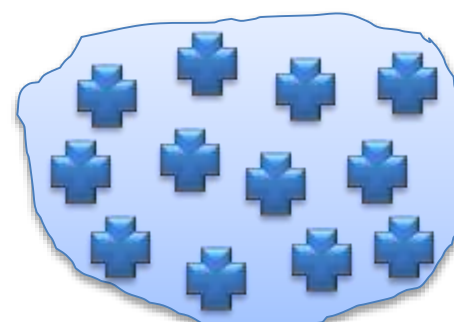
Crystal Polymorph 1

Crystal polymorphs of the same substance have different thermodynamic stability - so their **solubility** and **other physical properties** will differ



Crystal Polymorph 2

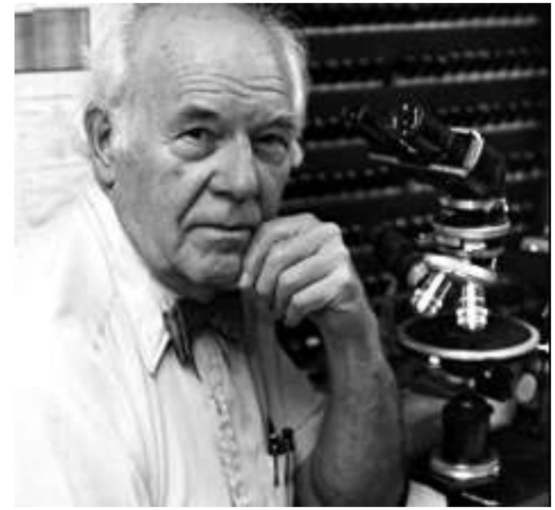
Many solids also have an amorphous form which is in general **less thermodynamically stable** than the crystalline forms



Amorphous solid form

Crystal Polymorphism and Amorphous Solids

"Every compound has different polymorphic forms, and…the number of forms known for a given compound is ***proportional to the time and money spent in research*** *on that compound."*
W.C.McCrone 1965



- Distinguish crystal polymorphs and amorphous forms by (e.g.):
  - X-ray powder diffraction
  - Differential scanning calorimetry
  - IR and Raman spectroscopy
- Screening for polymorphs of an new substance **can be automated**

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Mixed Systems of Crystalline Solids

Solid solution:

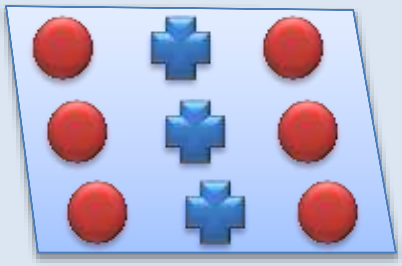
Molecules of solute B replace molecules of A at random in crystal structure of A

Stoichiometric co-crystal:

Molecules of B and A form a new ordered crystal structure

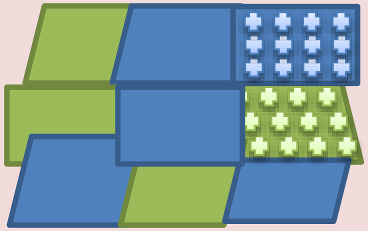
Solvate (e.g. hydrate):

Molecules of solvent (e.g. water) co-crystallise with molecules of A to form new ordered crystal structure



Eutectic mixtures:

Separate crystalline domains of A and B which are intimately mixed in the solid state



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In The Real World…Watch Out For:

Supersaturation

- A supersaturated solution is unstable to crystallisation (e.g. seeding - impurities)
- A stable solution may become supersaturated when cooled

Ostwald Ripening

- Suspensions may become unstable to settling due to particle growth
- May be accelerated by temperature cycling

Polymorphism

- Less stable polymorphs will be **more soluble and more bioavailable**
- Suspensions of a less stable polymorph may re-crystallise out as the stable form

Crystal Habit

- Can affect filtration rate of press-cake → depend on crystallisation conditions
- Can affect powder flow properties of dried crystalline solid product

Mixed Systems

- May have very different properties from single components
- May be unstable with respect to their single components

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What Could (Should) You Know About Your System?

Solubility curves (vs. temperature) and preferably **supersolubility curves**

How are these influenced by impurities, additives?

Characterisation of any **mixed solid phases**

Composition, properties of mixed phases

Tendency of suspensions to undergo **Ostwald ripening**

Influence of additives, impurities on ripening behaviour

What **polymorphs** could you get? Which one is more stable?

Characterisation (analysis, fingerprinting) of polymorphs

When might polymorphic **transitions** occur in your system?

What in your system might influence **crystal habit**?

Influence of additives, impurities, supersaturation

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Industry Context: Where is this Important?

Formulations where there are

- At least two phases
- Solid/Solid
- Liquid/Liquid
- Solid/Liquid
- Gas/Solid

- In essence every formulation of practical value!

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Agrochemical Formulation: Brief Overview

- Active Ingredients
  - Herbicide
  - Insecticide
  - Fungicide
- Formulants
  - Improve/Maintain Stability
  - Disperse active
  - Increase performance of active

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Formulation Types Where Solubility and Crystallisation Are Important

- Soluble Liquids (SL)
- Suspension Concentrates (SC)
- Emulsifiable Concentrates (EC)
- Oil Dispersions (OD)

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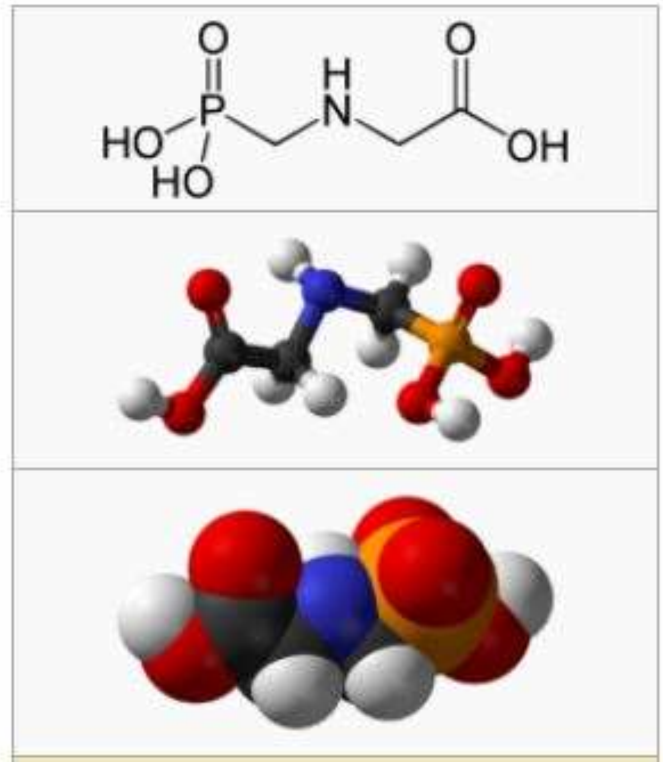
Soluble Liquids (SL)

- Simplest, most traditional formulations
- 127 pesticides in latest Pesticide Manual
- Most commercially successful Herbicide Glyphosate is an SL formulation
- Number of salts
  - Ammonium, diammonium, dimethylammonium, isopropylammonium, potassium, sequisodium

Solubility of Glyphosate*

- Glyphosate in water 10.5g/l (pH 1.9, 20°C)
- Ammonium in water 144 +/- 19 g/l (pH 3.2)
- Isopropylammonium 1050g/l (25°C, pH4.3)
- Potassium 918.7 g/l (pH 7,20°C)
- Sequisodium 335 +/- 31.5 g glyphosate-sodium/l of solution

Glyphosate



Source : Wikipedia

* Pesticides Manual on-line version Jan 2016

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Solubility of Glyphosate*

Salt Cation	%ae w/w solubility at 20°C
Isopropylamine	47% at pH 4.6
Sodium	30% at pH 3.6
Potassium	44% at pH 4.2
Ammonium	35% at pH 4.3
Trimethylsulfonium (TMS)	34% at pH 4.2

*9th International Symposium on Adjuvants for Agrochemicals, ISAA August 2010

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Commercial Glyphosate

- Often mixtures
  - Salts
  - Adjuvants
    - (Tallowamine ethoxylate)
  - Surfactants
  - Other pesticides
- Commonly 120, 240, 360, 480 and 680g/l of active ingredient
- Solubility clearly important

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Suspension Concentrates (SC)

- Normally solid suspended in a liquid medium (often water)
- Up to 60% active ingredient
- Dispersants, wetting agents, defoamer. Stabiliser/rheology modifier, anti-microbial, anti-freeze, Buffers, other adjuvants
- 322 pesticides in latest Pesticide Manual

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Emulsifiable Concentrate (EC)

- A solution of active ingredient with emulsifying agents in a water insoluble organic solvent which forms an emulsion when added to water
- Typically up to 40% active ingredient
- Solvents, co-solvents, emulsifiers, antifoam, other adjuvants (stickers, spreaders etc)
- 444 pesticides listed in Pesticide Manual

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Oil Dispersions (OD)

- A non-aqueous suspension concentrate, active ingredient suspended in organic solvent
- Up to 20% active ingredient
- Emulsifiers, dispersants, rheology modifiers, stabilisers
- 16 pesticides listed in pesticide manual

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Donald Trump and Agrochemicals

"What the h*** is going on?"

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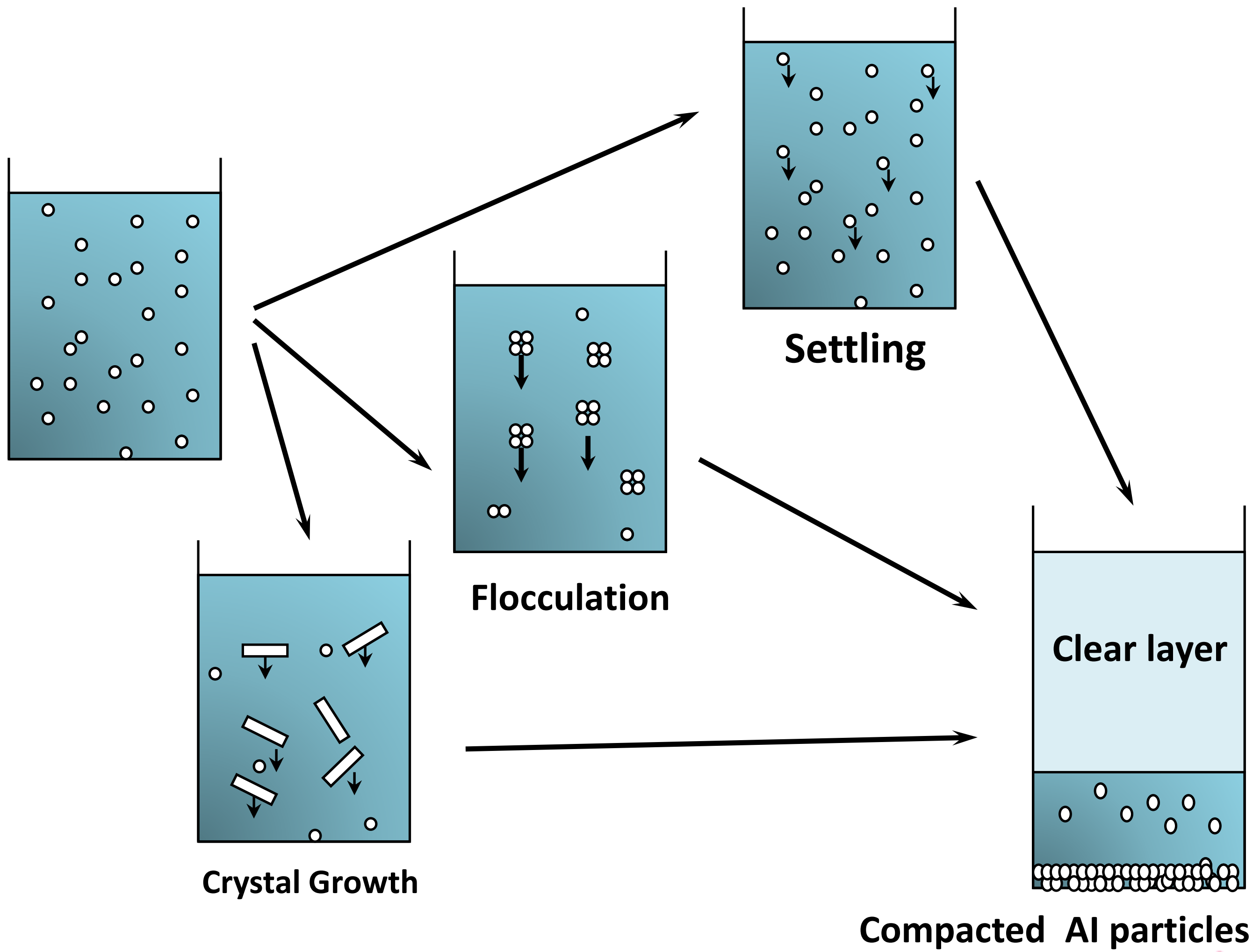
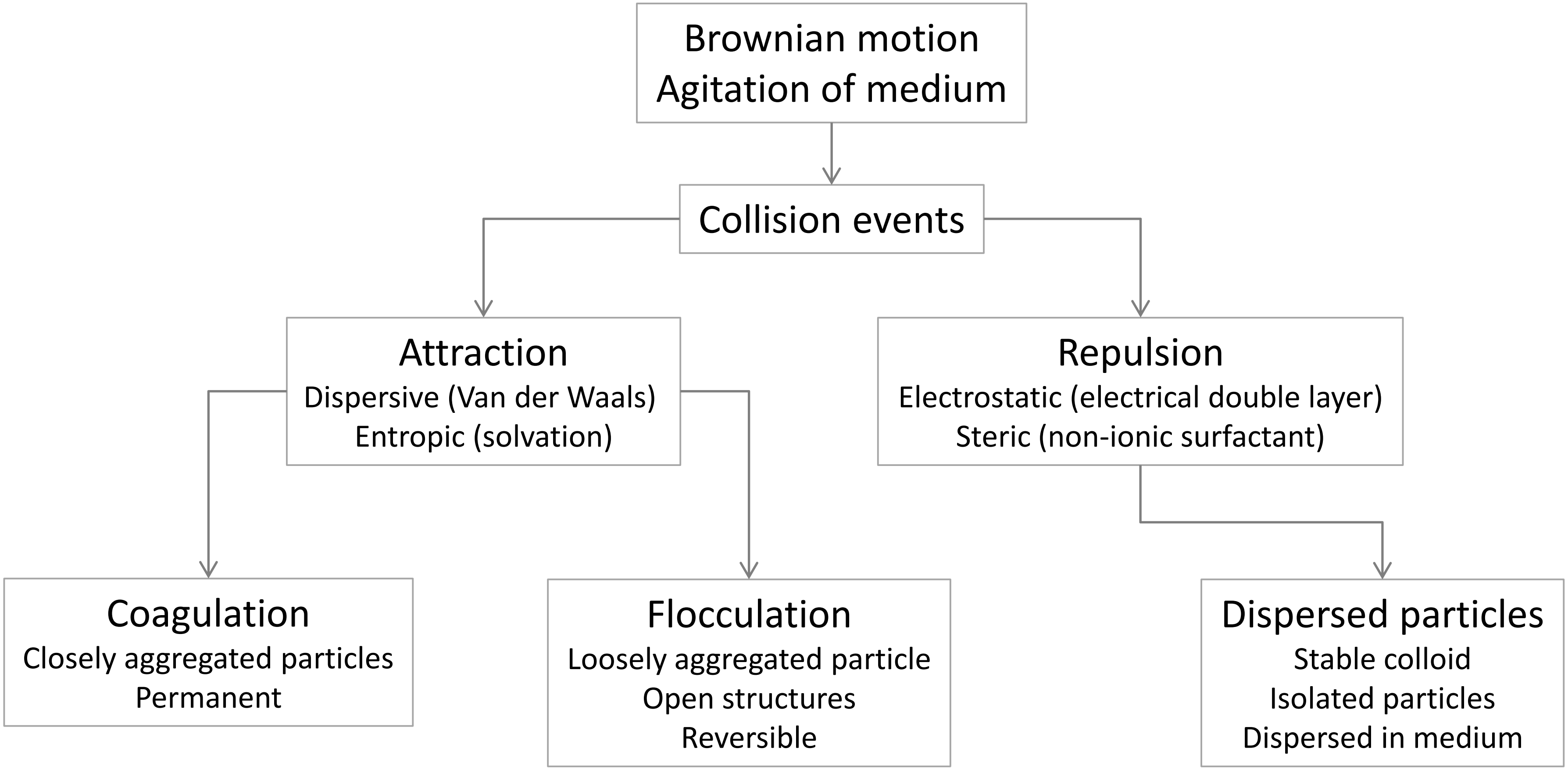
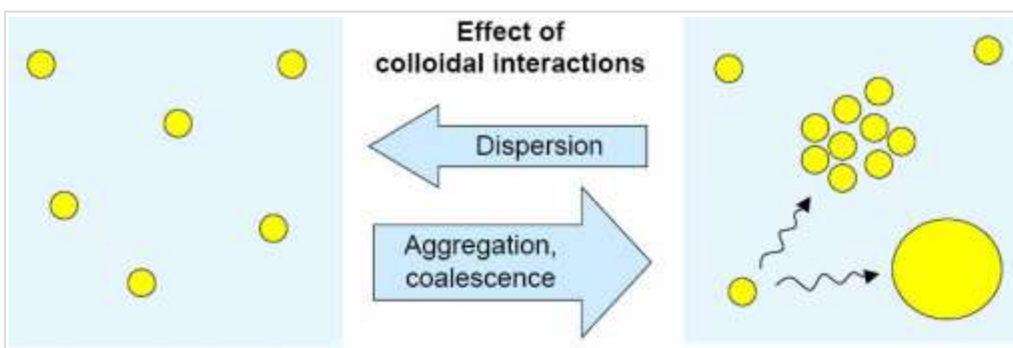
Instability




Brownian motion
Agitation of medium
Collision events
Attraction
Dispersive (Van der Waals)
Entropic (solvation)
Repulsion
Electrostatic (electrical double layer)
Steric (non-ionic surfactant)
Coagulation
Closely aggregated particles
Permanent
Flocculation
Loosely aggregated particle
Open structures
Reversible
Dispersed particles
Stable colloid
Isolated particles
Dispersed in medium


Effect of
colloidal interactions
Dispersion
Aggregation,
coalescence

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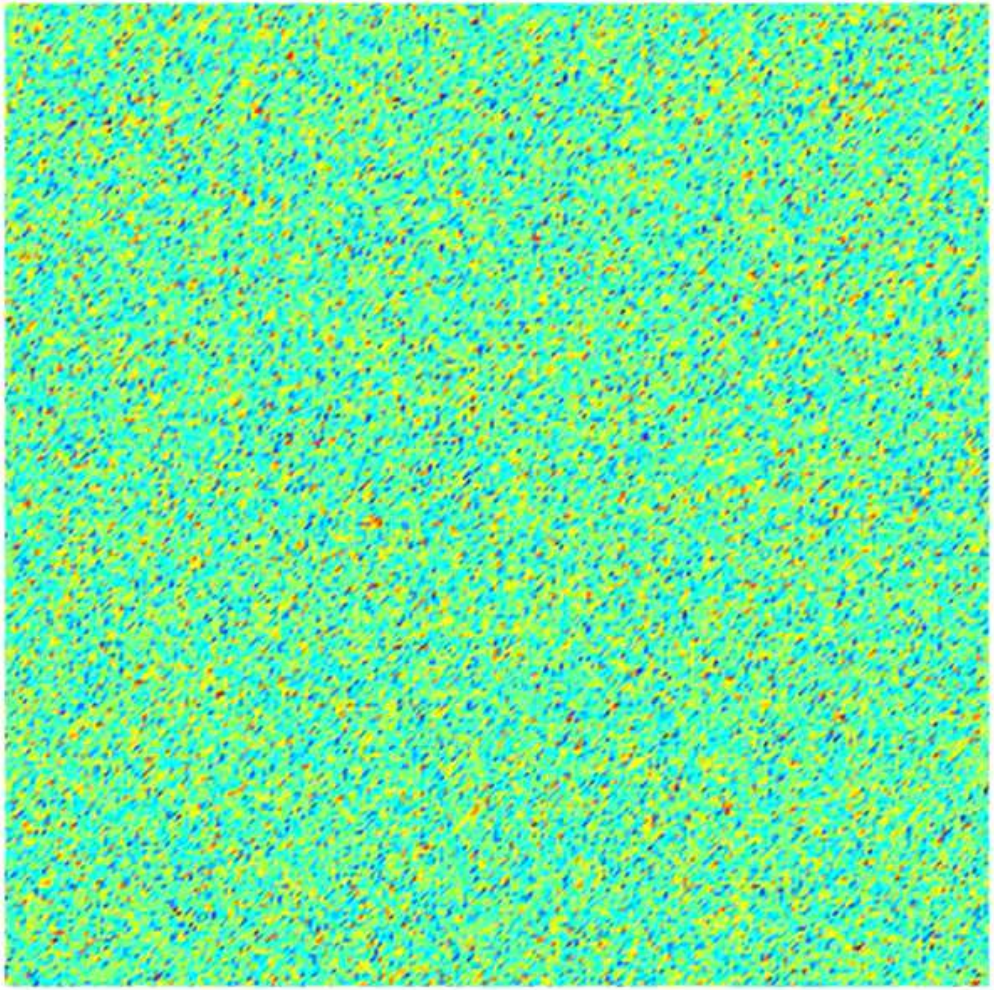
Molecular Dynamics Simulation of Ostwald Ripening



D.Fan, S. P. Chen, L. -Q. Chen, and P. W. Voorhees, "Phase-field simulation of 2-D Ostwald ripening in the high volume fraction regime " Acta Mater. 50, 1895 (2002)

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Consequences of Lack of Control or Knowledge

- Lack of efficacy
- Increased dosage/non-optimum concentration
- Decreased Shelf-life
- Blockage of filters/nozzles

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How to Diagnose and Make Progress

- Stability tests
  - Visual Observations
    - Human eye
    - Microscope
  - Particle Size Measurements (PSD)
  - Zeta Potential
  - Differential Scanning Calorimetry (DSC)
  - X-Ray Diffraction (XRD)

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Troubleshooting Agglomeration

Possible Tools:

- Optical microscopy
- Laser diffraction PSD
- Zeta potential

Questions to Ask:

- Has particle size increased on storage?
  - If so, emulsion coalescence is the likely problem → emulsifier type, amount, emulsification conditions.
- Are particles forming flocs or agglomerates?
  - If so, the particles are inadequately dispersed → choice and quantity of dispersing agent to give electrostatic and steric stabilisation.

Troubleshooting Crystallisation

Possible Tools:

- Optical microscopy (with hot-stage for phase diagram)
- Laser diffraction PSD
- DSC, XRD
- Technobis Crystalline

Questions to Ask:

- Crystals grow from solution (e.g. AI in solvent – organic phase) when:
  - The system is metastable and a seed (nucleus) is present **or**
  - The system is moves into the labile region and crystals grow spontaneously
- How does the temperature regime relate to the phase diagram of the organic phase? Is the system undersaturated, supersaturated or in the labile region? → Solvent choice, AI concentration, solubilisers
- Could the AI have a second (more stable) polymorph which is crystallising

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Additives

- Strong affinity for crystal surface
- Protective colloids
- Comb or graft copolymers
- Number of surfactants
- Some Patent activity
  - EP2164322 B1
    - Azole derivative fungicides
    - Preventing crystallisation in sprayer
  - EP 2375901 A1
    - Suspoemulsion composition
    - Alkyl carboxylic acid amide as a solvent and crystal growth inhibitor

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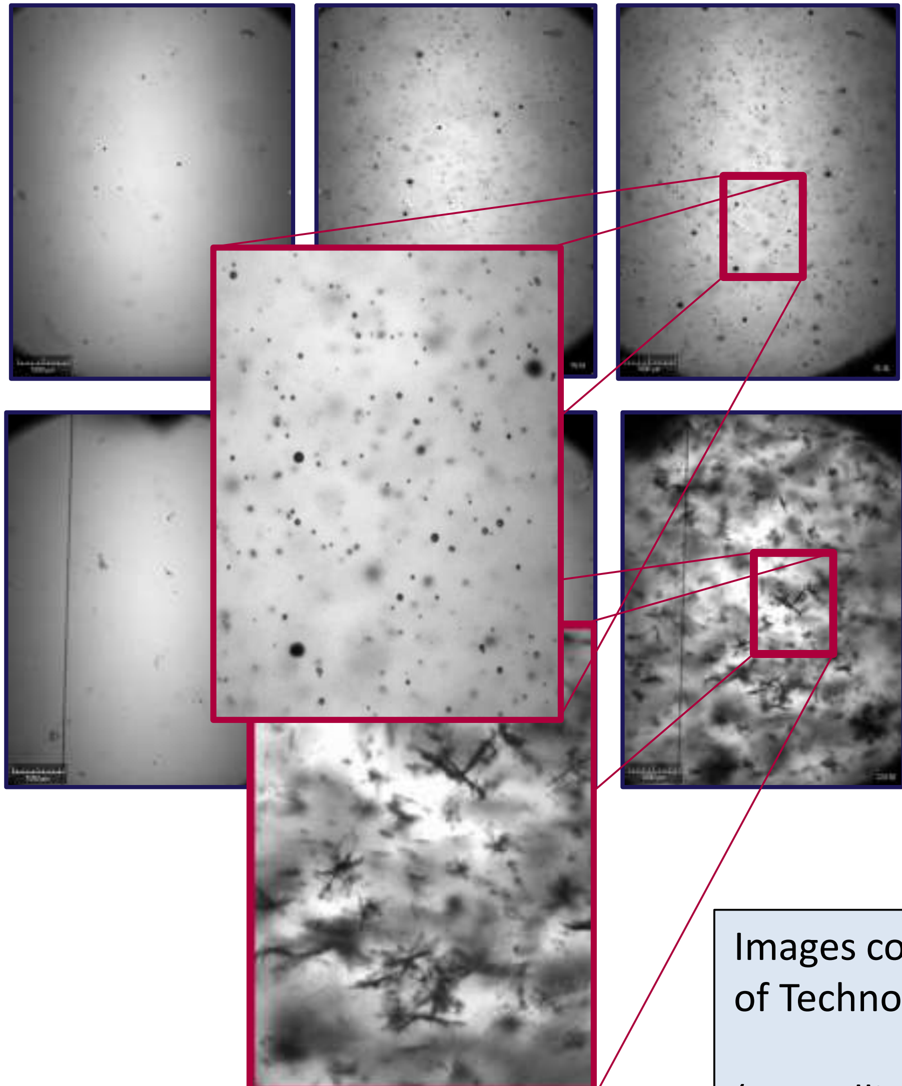
Effect of Additives



Images courtesy of Technobis

(Crystalline)

- AI with amino acid functionality;
- Carboxylic acid functionality additives, *e.g. sodium polyacrylate, sodium octanoate and propanoic acid;*
- Additives acted as a template for directed nucleation;
- Lower particle size distribution - *improved process performance;*
- Modified crystal shape - *avoid caking and filters clogging*;

Additives could:

- effectively control the crystallization process
- affect crystallization/formulation process

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Questions?

- Participants remain muted
- Please use the GoToWebinar question/chat boxes
- Any follow up questions or other enquiries: info@iformulate.biz
- Participants will be sent details of how to access a recording of this webinar

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You Might Also Be Interested In…

An Introduction to Agrochemical Formulation Strategies

1st-2nd March 2016, London UK

From ati and delivered by iFormulate

Spray Drying and Atomisation of Formulations

12th – 14th April 2016, University of Leeds, UK

From UNIVERSITY OF LEEDS and supported by iFormulate

Watch out for our planned "taster" webinar on this topic

Ink Jet Formulation Fundamentals: *9th June 2016, East Midlands, UK*

Adhesion Science for Formulators: *1st December 2016, Sheffield UK*

Information and Registration:
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E: info@iformulate.biz

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