iFormulate

Introduces...

Crystallisation Science and Agrochemical Formulation

Jim Bullock & David Calvert
4th February 2016

Webinar sponsored by 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.
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
Our Services

iFormulate Consult

iFormulate Strategic

iFormulate Skills
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

**Discover**
- Early stage salt, polymorph screening
- Single crystal preparation

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

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

*Note: The images show different crystallization equipment with their respective working volumes and reactor capacities.*
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
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?
One Way of Looking At Solubility

Solubility as an equilibrium: Thermodynamic Free Energy

Pure solute (often solid) ⇌ Solute dissolved in solvent (i.e. solution)

To increase 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:Solute interactions

Solute:Solvent interactions

Solvent:Solvent interactions

Solvent molecules

Solute molecule

Solute molecule
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 $\rightarrow$ higher free energy $\rightarrow$ higher solubility
• Melting point as indicator of crystal packing energy
• Complex solid forms possible (co-crystals, hydrates)
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
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

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
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)

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**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**
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
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
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
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

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![Graph showing percentage of surface atoms vs. cluster size](image)

After: Nützenadel et al The European Physical Journal D 2000, Volume 8 pp 245-250
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 polymorphs of the same substance have different thermodynamic stability - so their **solubility** and **other physical properties** will differ.

Many solids also have an amorphous form which is in general **less thermodynamically stable** than the crystalline forms.
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 a new substance can be automated
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
Mixed Systems

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

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
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
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!
Agrochemical Formulation: Brief Overview

• Active Ingredients
  – Herbicide
  – Insecticide
  – Fungicide

• Formulants
  – Improve/Maintain Stability
  – Disperse active
  – Increase performance of active
Formulation Types Where Solubility and Crystallisation Are Important

- Soluble Liquids (SL)
- Suspension Concentrates (SC)
- Emulsifiable Concentrates (EC)
- Oil Dispersions (OD)
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, pH 4.3)
- Potassium 918.7 g/l (pH 7, 20°C)
- Sequisodium 335 +/- 31.5 g glyphosate-sodium/l of solution

# Solubility of Glyphosate*

<table>
<thead>
<tr>
<th>Salt Cation</th>
<th>% ae w/w solubility at 20°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isopropylamine</td>
<td>47% at pH 4.6</td>
</tr>
<tr>
<td>Sodium</td>
<td>30% at pH 3.6</td>
</tr>
<tr>
<td>Potassium</td>
<td>44% at pH 4.2</td>
</tr>
<tr>
<td>Ammonium</td>
<td>35% at pH 4.3</td>
</tr>
<tr>
<td>Trimethylsulfonium (TMS)</td>
<td>34% at pH 4.2</td>
</tr>
</tbody>
</table>

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

“What the h*** is going on?”
Instability

- Crystal Growth
- Flocculation
- Settling
- Clear layer
  Compacted AI particles
Brownian motion
Agitation of medium

Collision events

Attraction
Dispersive (Van der Waals)
Entropic (solvation)

Flocculation
Loosely aggregated particle
Open structures
Reversible

Repulsion
Electrostatic (electrical double layer)
Steric (non-ionic surfactant)

Coagulation
Closely aggregated particles
Permanent

Dispersed particles
Stable colloid
Isolated particles
Dispersed in medium

Effect of colloidal interactions
Dispersion
Aggregation, coalescence
Molecular Dynamics Simulation of Ostwald Ripening

Consequences of Lack of Control or Knowledge

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

- 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
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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W: www.iformulate.biz
An Introduction to Agrochemical Formulation Strategies
1st-2nd March 2016, London UK
From and delivered by iFormulate

Spray Drying and Atomisation of Formulations
12th – 14th April 2016, University of Leeds, UK
From 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:
W: www.iformulate.biz/training-and-events
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