

**The Art of Crystallization Development –
From Form Screening to a Stable Crystallization Process**

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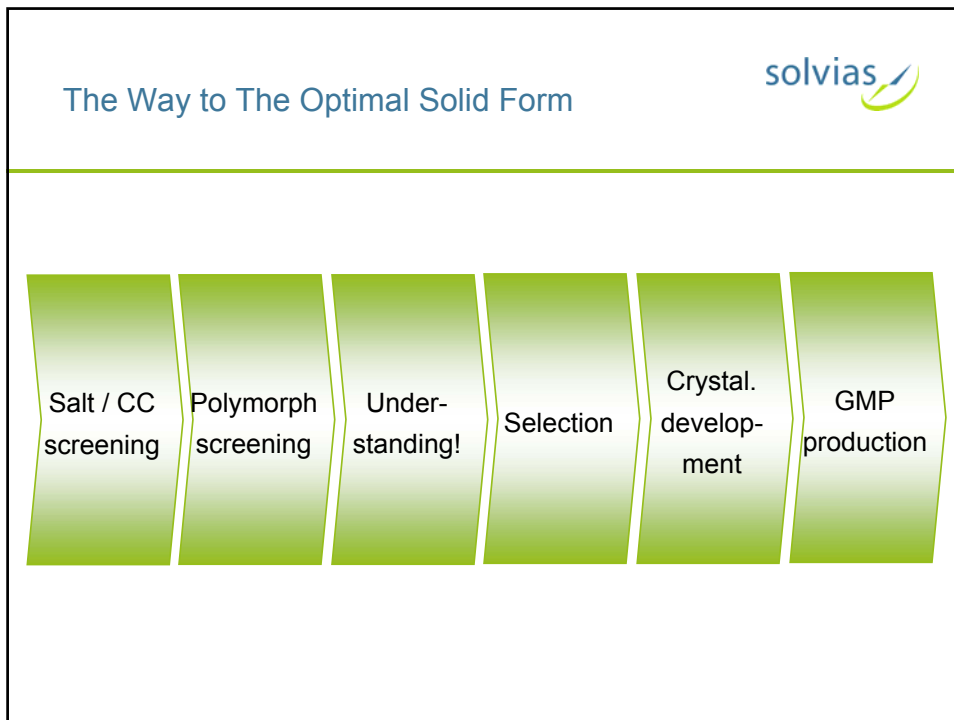
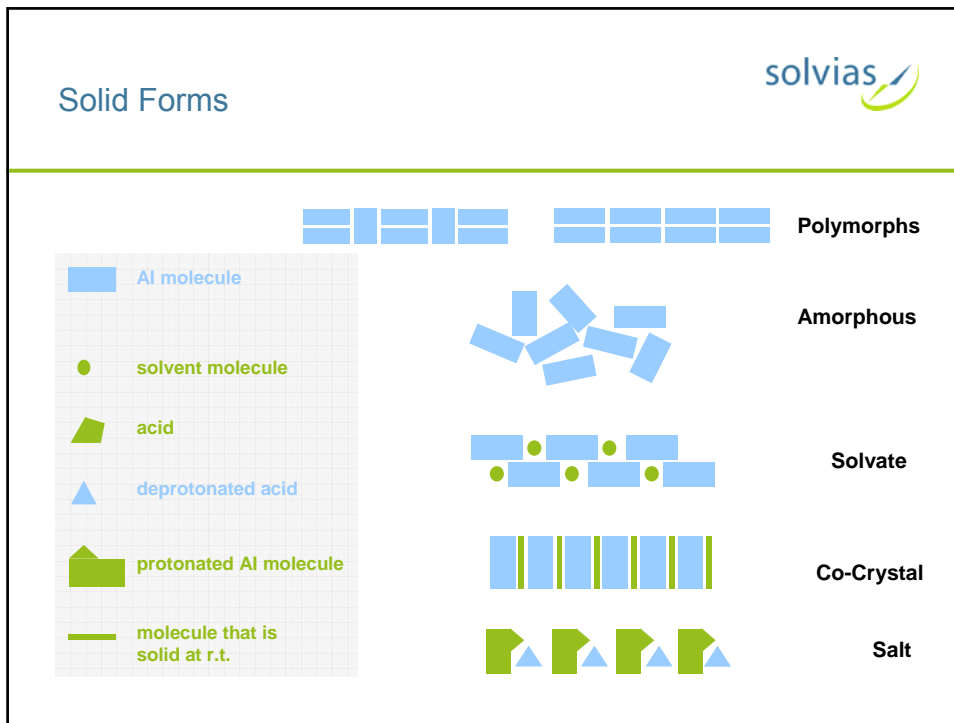
Amazing where you can go

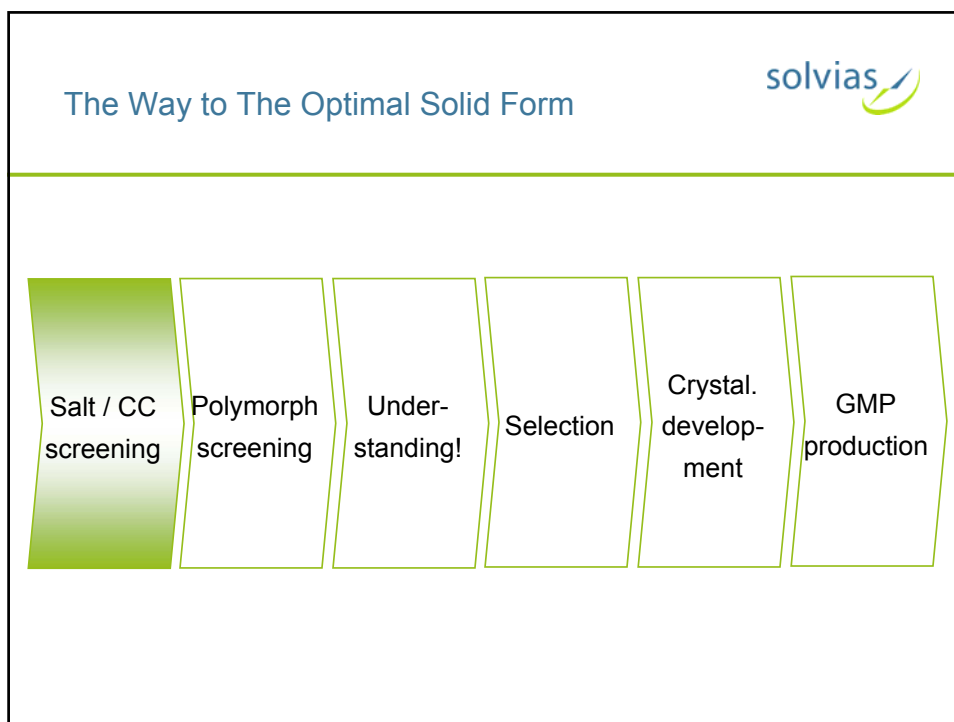



Solvias AG- A Technology Company

- Founded in 1999
- Independent contract research company
- Solid-state, synthesis/catalysis, analytics
- 300 employees, near Basel, Switzerland
- www.solvias.com







Salt Screening and Salt Selection 

- Reasons to develop salt:
 - neutral molecule is poorly soluble
 - neutral molecule is not crystalline
 - neutral molecule has low MP, etc.
- Optimization of solid-state properties, selection criteria:
 - crystallinity
 - solubility/bioavailability
 - hygroscopicity
 - chemical and physical stability
 - processability
 - no "problem solid forms"

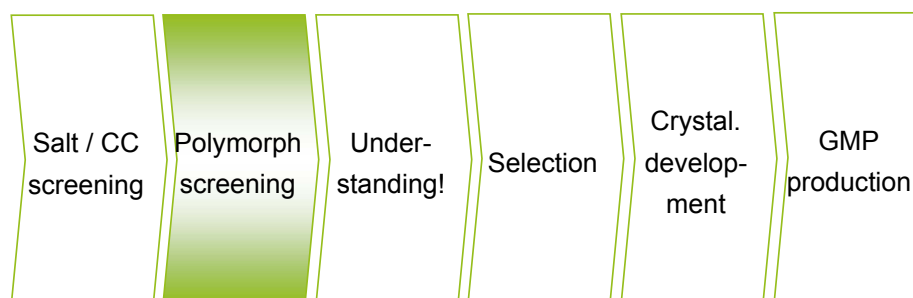
Reasons to Consider Co-Crystals



- salt formation is not an option
- API (salts) not soluble enough or too soluble
- API (salts) have other undesirable properties (morphology, stability, hygroscopicity, "problem polymorphs", etc.)
- API cannot be crystallized
→ co-crystal for purification, resolution, structure elucidation, or as DS
- IP reasons

Solubility is not the only reason!

The Way to The Optimal Solid Form



Important Tool for Salt / CC / Polymorph Screen: HTS



HTS platform

- Zinsser "Crissy" robotic system
 - Panalytical "X'Pert Pro MPD-HTS"
 - Raman microscope
- time reduction for analytics
 - Raman and XRPD on same plate
 - cooling crystallizations
 - slurries
 - precipitation
 - filtration of hot slurries

The Way to The Optimal Solid Form

Salt / CC
screening

Polymorph
screening

Under-
standing!

Selection

Crystal.
develop-
ment

GMP
production

Characterization



Salts/Co-Crystals:

- Solubility, stability, hygroscopicity, habit,

Polymorphs:

- Stability as a function of temperature, solubility, ...

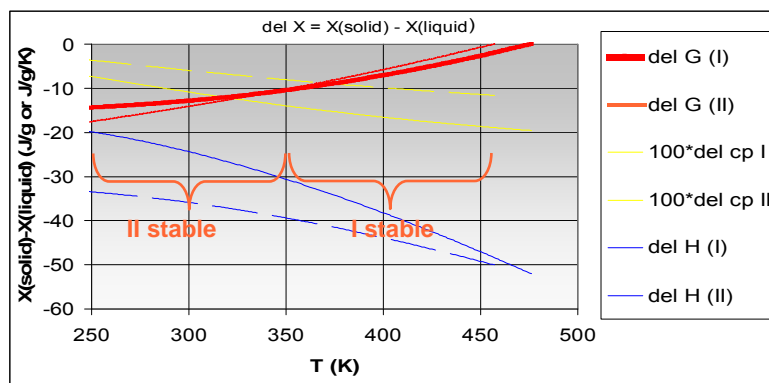
Hydrates:

- Critical water activity as a function of temperature
- Channel hydrates?
- Conversion rate

Solvates:

- Which solvent can / cannot be used in crystallization process
- Impact on formulation

Determining Stability (T): Quantitative ET-Diagram...e.g. from MP, ΔH_{melt} , c_p

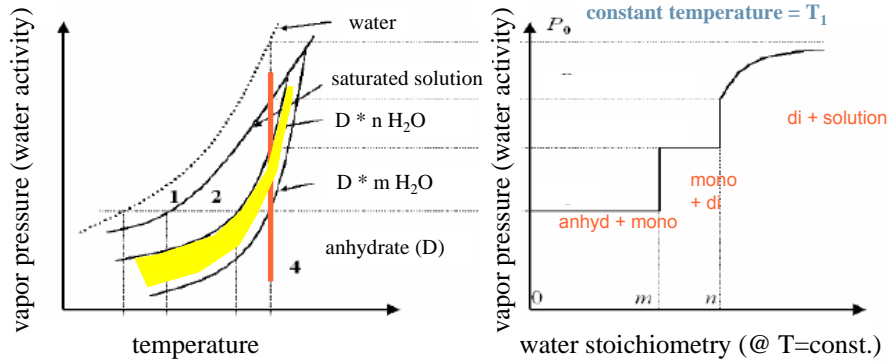


Quantitative energy difference at every temperature!

#1: Transition temperature at 75 °C: verify with slurries.

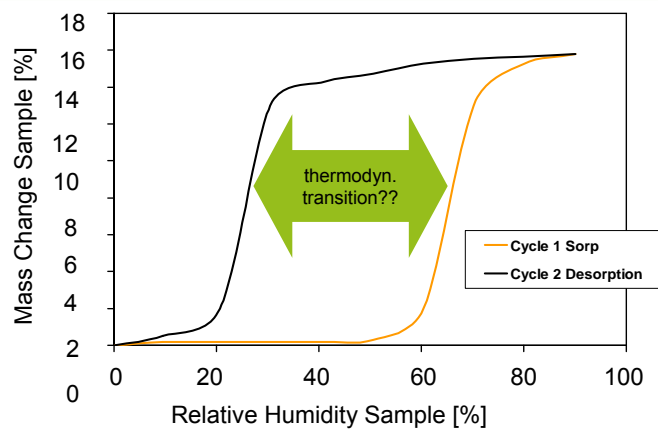
#2: Crystallization: Better to seed below 75 °C.

Selection Hydrate/Anhydrate: Understanding Phase Diagram of Hydrate)



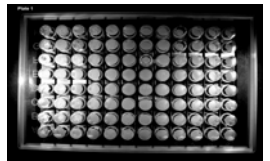
Solvias Hydrate Screen and Characterization
 ⇒ Stay in yellow region if you want to produce the m-hydrate!

Hydrate Formation with Water Vapor



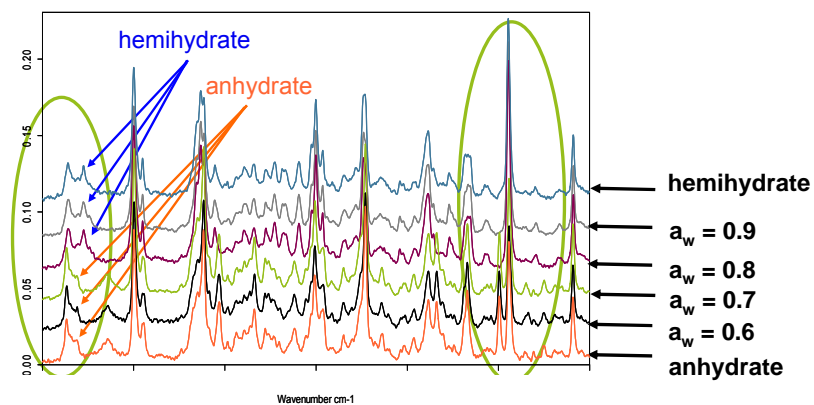
Kinetic effect: Hysteresis, can be even broader

The Solvias Hydrate Stability Screen



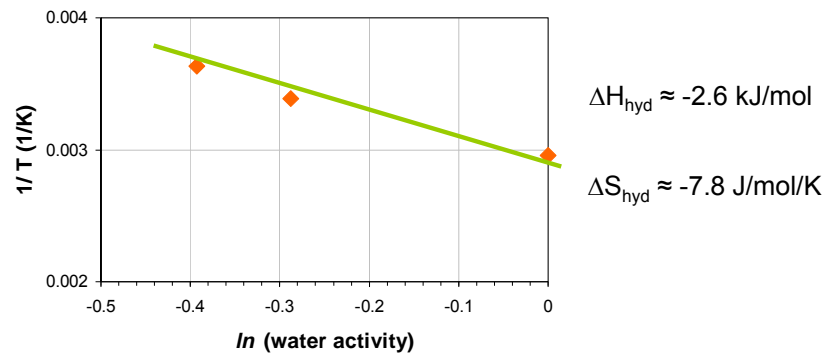
- 96-well quartz microtiter plates with PTFE seals
- 5 to 10 mg of drug substance per microplate well
- solvent water mixtures with water activity increments of 0.05 or 0.1
- Determination of solid form by Raman spectroscopy through the well plate glass

Anhydrate to Hemihydrate Conversion followed by Raman Spectroscopy



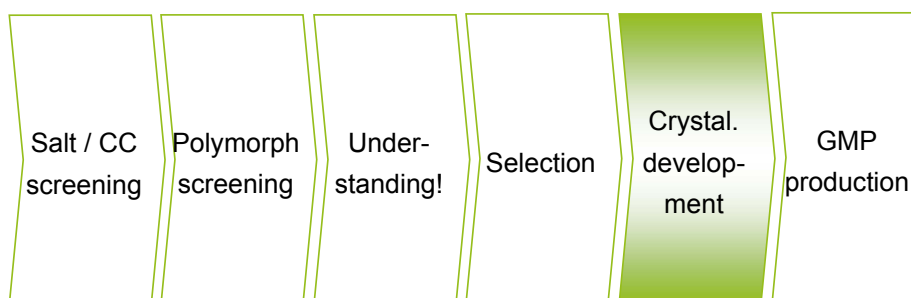
Equilibrium is between $a_w = 0.7$ and 0.8

Temperature Dependence of Critical a_w

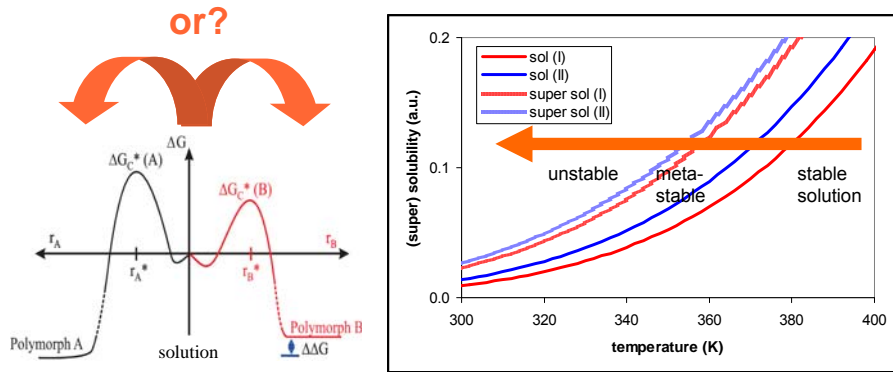


For process optimization, knowledge of T-dependence important!

The Way to The Optimal Solid Form



Why develop a seeded process?



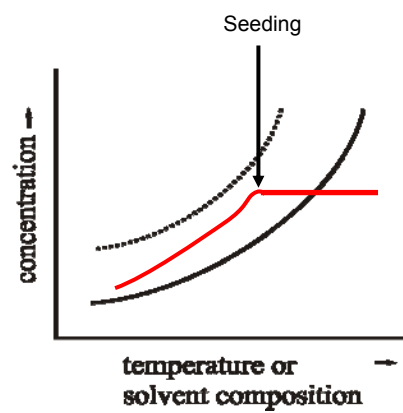
Without seeding: No control over process!

Why develop a seeded process?

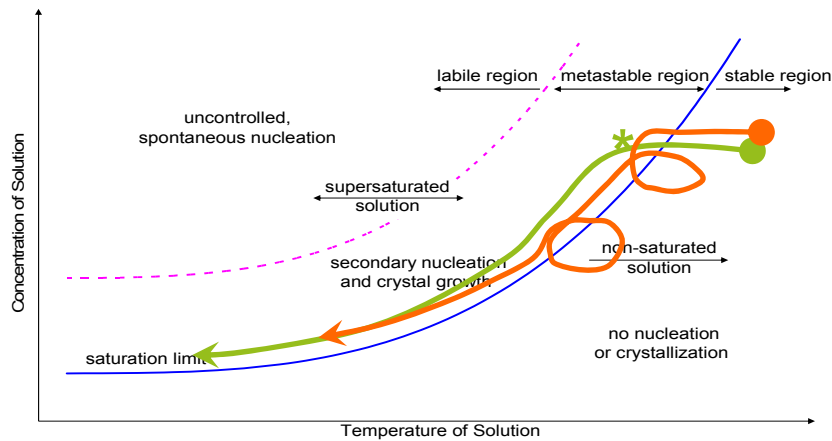


Control of

- supersaturation level
- nucleation
- polymorphism
- crystal size

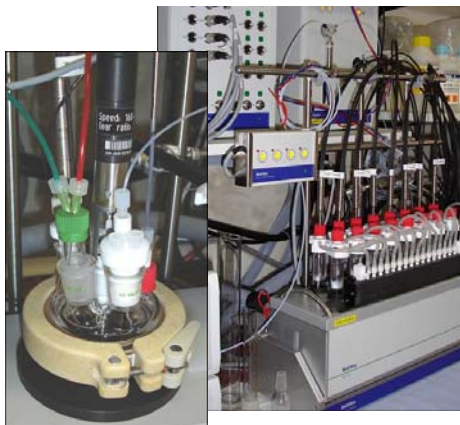


Crystallization Development General Temperature / Concentration Scheme



Classical approach: continuous cooling
Variant: cool-heat cycles to make particle size distribution narrower

Crystallization Development



- scale up from 100 mg to 10 g
- parallel experiments
 - 16 x 10 ml
 - or 2 x 250 ml
- dosing facility
- precise temperature control
- inert atmosphere
- excellent reproducibility
- turbidity measurement
- pH control
- Lasentec probe

The Way to The Optimal Solid Form



Salt / CC
screening

Polymorph
screening

Under-
standing!

Selection

Crystal.
develop-
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GMP
production


GMP Production




- 160 liter vessels
- Smooth transfer



...to be used for clinical trials or seeds for large-scale production.



Case Studies



Case Study #1 Seeded Cooling Crystallization

Situation:

- Polymorph screen \Rightarrow 3 non-solvated monotropic forms (A, B, C) and mono-hydrate
- A most stable, but B **very close in free energy**

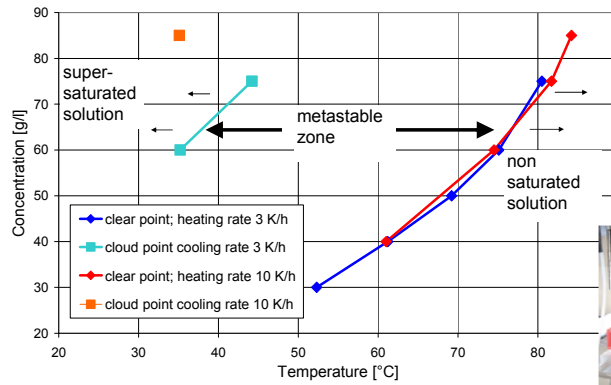
Goals:

- Develop seeded crystallization process for the production of pure form A

Requirements:

- High volume efficiency (< 15 mL/g)
- Robust process: pure form A, no mixtures
- Starting material: anhydrous form or hydrate

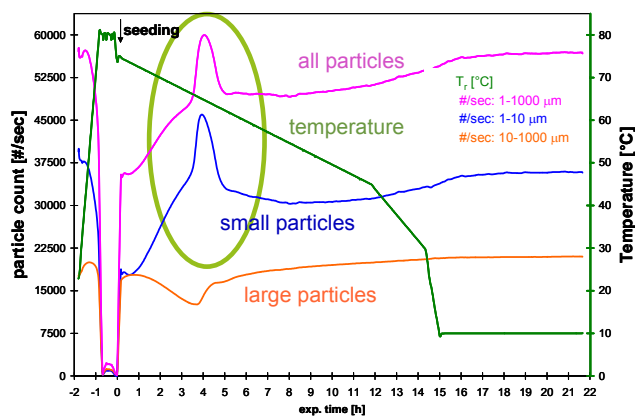
Crystallization Development for Form A: Metastable Zone Width



Crystallization Development for Form A: FBRM Lasentec Probe



Slow stirring speed and non-optimized cooling, mixture of A+B

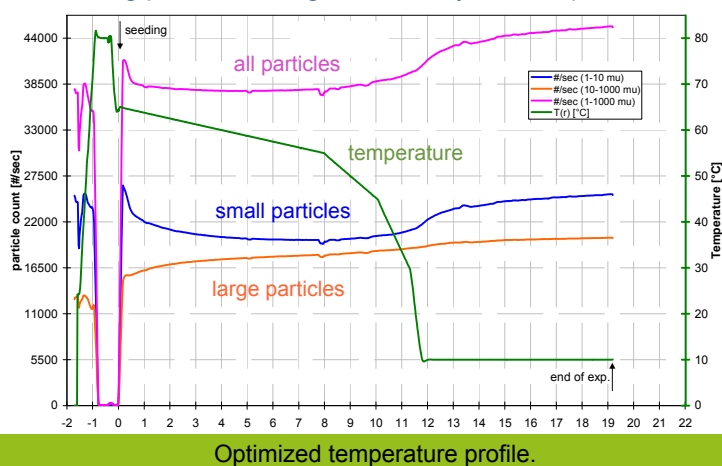


Cooling too fast: Secondary nucleation of B.

Crystallization Development for Form A: FBRM Lasentec Probe



Improved cooling profile, starting with hemihydrate → pure form A



Crystallization Development for Form A Results



Optimized solvent system and volume efficiency:

- 7:3 EtOH/anisole
- ~12 mL solvent / g material

Identified and optimized critical parameters:

- Seeding temperature (70 - 65°C)
- Seed amount (5 - 0.5 wt.-%)
- Cooling profile (non-linear, 0.02-0.8 K/min)
- Stirring speed (600 - 200 rpm)

- Reproducibly produced pure A on 100 mL scale with both starting materials

Case Study #2: Solid-State Development From Co-Crystal Screening to Kilogram Supply



1) Co-Crystal
Screening

2) Characterization

3) Crystallization
Process
Development

4) Multigram to
Kilogram Supply

Objective: Find and develop new solid form of API for IP reasons

Result:

- discovered new co-crystal of API in HTS
- developed robust and scalable crystallization process
- produced kilogram supply

Solid-State Development 1: Co-Crystal Screening

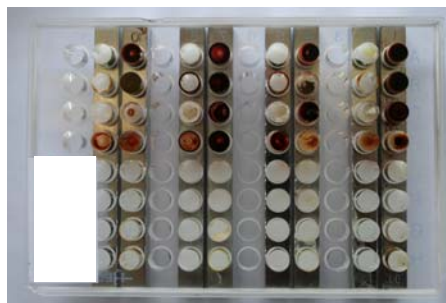


Selection of co-crystal former:

- classical salt list (pharmaceutical accepted salts) & accepted excipients
- Inspiration from "Everything Added to Food in the United States (EAFUS)" and "Generally Recognized As Safe (GRAS)"
- 2x12 diverse co-crystal former

High-throughput co-crystal screening:

- Evaluation of diverse solvents and solvent mixtures
- Raman microscopy
- Lead for a sugar alcohol co-crystal



1) Co-Crystal
Screening

2) Characterization

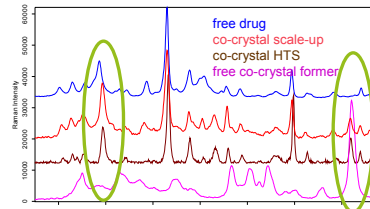
3) Crystallization Process
Development

4) Multigram to
Kilogram Supply

Solid-State Development 2: Characterization

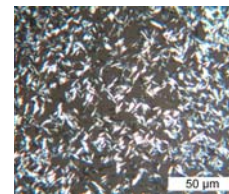


Laboratory scale (~100 mg) crystallization
 ➤ Reproduction of HTS lead (red=black)



Characterization of obtained co-crystal

- Crystallinity: needle-like morphology
- Thermal behavior: higher melting point
- Hygroscopicity: slightly hygroscopic
- Chemical identity: 1:1 free drug /co-crystal former

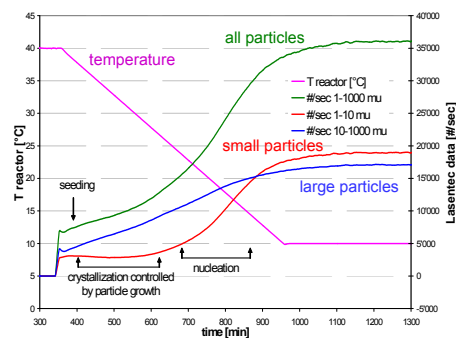


Solid-State Development 3: Crystallization Process Development



Optimization of

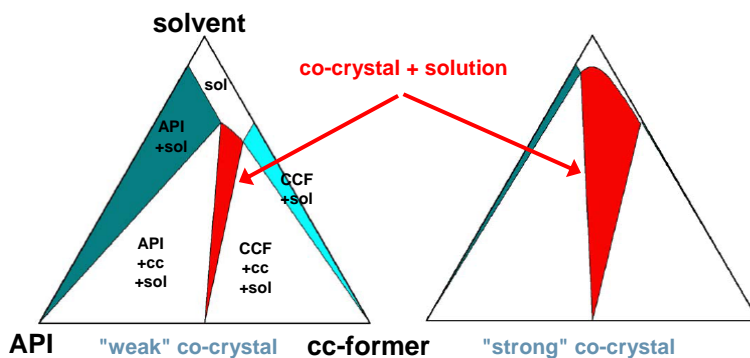
- Solvent system: 3:1 EtOH/DMSO
- Concentration: up to 72 g/L
- Temperature of seeding: 40°C
- Amount of seed: ~1.5 wt.-%
- Cooling speed: 0.1-0.3 K/min
- Yield: >85%



- Developed controlled, seeded cooling crystallization process (10 g scale) of 1:1 co-crystals



Why was it quite straight-forward to develop a co-crystal crystallization process in this case?



Timo Rager and Rolf Hilfiker, *Z. Phys. Chem.* 223 (2009) 793-813.
Timo Rager and Rolf Hilfiker, *Crystal Growth and Design*, 10 (2010) 3237-3241.

Very "strong" co-crystal \Rightarrow large cc-suspension area (red).

Solid-State Development 4: Production of Kilogram Supply



- Transfer of crystallization process to kilo-lab
- Scale-up (one step) from 10 g to 2 kg
- Successful production of 2 kg of co-crystal



1) Co-Crystal Screening 2) Characterization 3) Crystallization Process Development 4) Multigram to Kilogram Supply

Conclusions



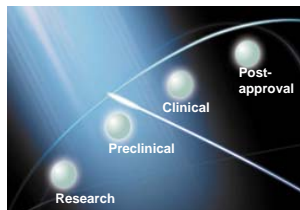
Your Process

- Faster
- More Efficient
- Safer
- More Cost-effective

Your CRO /CMO

- Has to have in-depth knowledge of the whole process from screening to production

Summary



- Outstanding track record
- Comprehensive capabilities for
 - **Chemical** and
 - **Analytical development**
 - **cGMP manufacturing**
- Strong technology base to accelerate your development.
- Dedicated to meet **Your** timelines.

Thank you for your attention!



Questions...

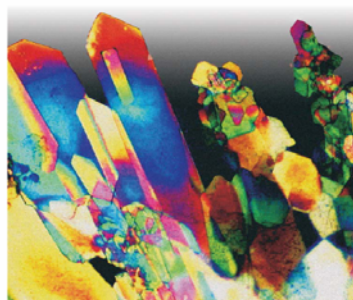
If you would like to know more about
Polymorphism...

Edited by Rolf Hilfiker

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Polymorphism

In the Pharmaceutical Industry



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