

# Solid State Studies

Center of Excellence for Crystallization and Solid State Chemistry

CML-Europe

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# Why Solid State Studies?

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- 1) Crystallization is the effective way to purify a product.
- 2) The crystallization conditions determine the properties of a product.
- 3) Selection of the optimal form to avoid batch to batch variability, polymorphic transformation, product degradation and stability issues.
- 4) Selective scale-up of the preferred form requires in depth understanding of the crystallization process.
- 5) The “most” stable form is determined by conditions like temperature and humidity.

# Solid State Studies at CML

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- 1) Material Characterization
- 2) Solubility Determination
- 3) Salt Selection
- 4) Polymorph Study
- 5) Crystallization Process Development
- 6) Crystal Habit Optimization

# Material Characterization

- XRPD (Bruker D2 Phaser)
- DSC, melting point, hot-stage
- TGA, KF, head-space GC
- FT-IR,  $^1\text{H-NMR}$
- HPLC, LC-MS
- Ion chromatography
- Optical microscopy, SEM
- DVS, stability (RH, T / t)
- ...



on starting material, intermediates, impurities, final API

# Solubility Determination

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## 1) Solubility range

- shake flask method, using 10 solvents
- XRPD of the solids after complete evaporation of solvent

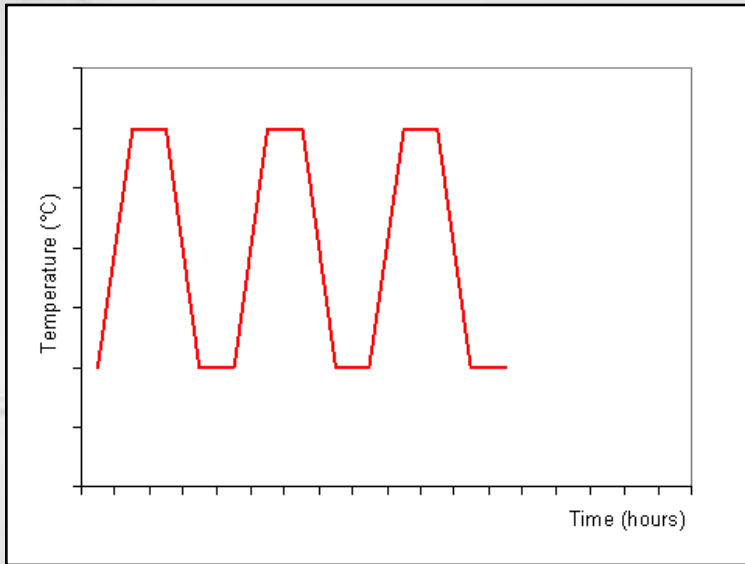
## 2) Solubility determination

- HPLC method, slurry in 28 solvents, 2 times, 2 temperatures
- XRPD of the (wet) remaining solids

## 3) Temperature dependent solubility (MSZW)

- Crystal 16 method, 4-8 concentrations, 2-4 solvents
- XRPD of the crystallized solids

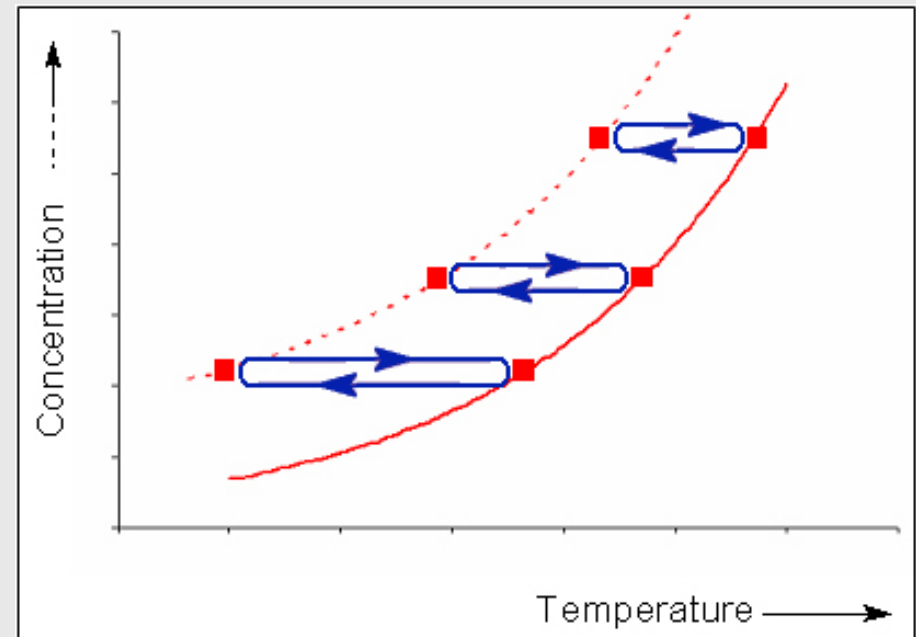
# MSZW determination



The meta-stable zone width can be determined by measuring the dissolution and nucleation temperatures at different concentrations.



The Crystal16 uses turbidity measurements to determine the “clear” and “cloud” points.



# Salt Selection

## 1) Salt study

- 4-24 pharmaceutically acceptable counter ions (ICH & FDA generally approved)
- 2-48 (process) solvents and solvent mixtures (ICH class 2 and 3)
- selection based on pKa, stability, dosage form, preferred use, aimed property to improve

## 2) Salt ranking by aqueous solubility

- < 1 gram API available
- 8 counter ions; water
- use common ion effect, calculate solubility



# Polymorph Study

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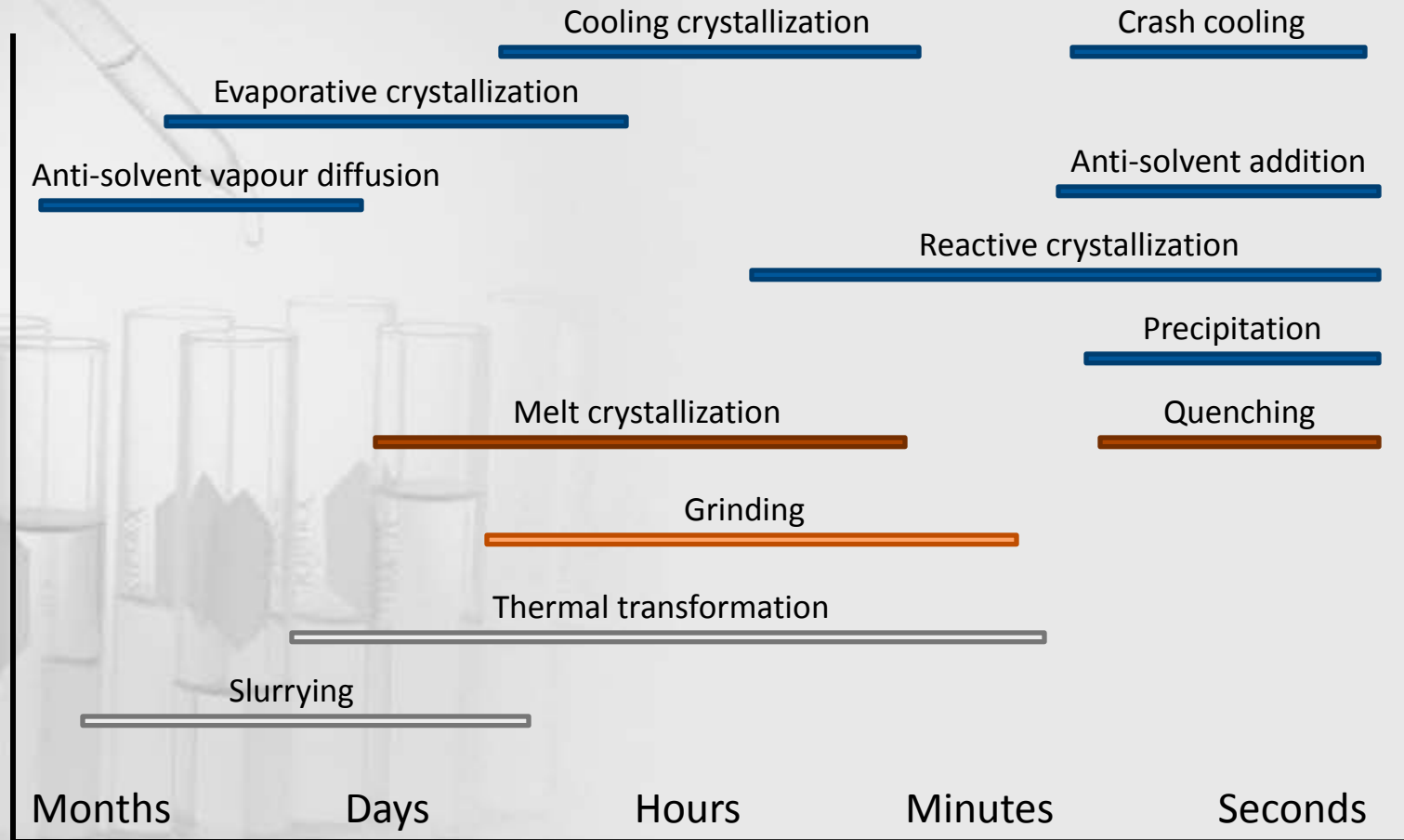
1) Polymorph Study: find a suitable form for further development

- 16-48 experiments
- scaleable crystallization methods (cooling, anti-solvent)
- determine preferred form
- identification of conditions to produce specific forms

2) Polymorph Screen: find other forms

- 48+ experiments
- diversity in solvents, crystallization methods and conditions
- characterization of forms
- determine best form for further development
- identification of conditions to produce specific forms

# Crystallization Conditions



Mild conditions  
Close to equilibrium

Severe conditions  
Non-equilibrium

# Polymorph Study

- 96 well-plate (uL)
- Symyx crystallization platform (uL – mL)
- Crystal 16 (1 mL)
- Radleys parallel crystallizer (10-250 mL)
- Mettler-Toledo LabMax (1L)



- supersaturation
- concentration
- temperature
- cooling rate
- ageing time
- seeding

# Crystallization Process Development

lab-scale method or ~1 gram material

PD rework method ←

→ SS material characterization

process, purity, yield, solubility, other issues

→ SS solubility determination

process solvents  
polymorphs  
morphology

→ SS salt / polymorph studies

PD solvents, methods ←

intermediates: purity, yield,  
stability, filterability, drying

→ SS improve properties  
intermediates

# Crystallization Process Development

improved process

...

PD final process ←

→ SS final form selection

product isolation, re-crystallization?

→ SS product characterization

PD (kilo)gram production ←

→ SS confirm final form

stability studies  
reference material

PD GMP production ←

# Crystal Habit Optimization

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- ◆ Particle size distribution
  - seeding protocol, cooling / anti-solvent conditions, ageing time, crystallization or ageing temperature
- ◆ Filterability
  - particle shape, solvent selection, filter / washing conditions
- ◆ Drying and handling properties
  - drying conditions, storage conditions, milling / micronize

# Planning

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	
Part 2	Raw material sourcing	█	█	█																												
Part 3	Laboratory reproduction and early process development - EVALUATION				█	█	█	█	█	█	█	█	█	█	█																	
	Quick preparation final material for Part 6,7,8 and 9				█	█	█	█	█																							
Part 4	100 g - 1 kg demo batch production - EVALUATION														█	█	█	█	█	█												
Part 5	5 kg GMP-production - GMP release testing																			█	█	█	█	█	█	█						
Part 6	Physicochemical Characterization of Drug Substance								█	█																						
Part 7	Solubility									█	█																					
Part 8	Polymorph Screen								█	█	█	█	█	█	█																	
Part 9	Chemical stability assessment										█	█	█	█	█																	
Part 10	Analytical development/validation										█	█	█	█	█	█																
Part 11	Accelerated stability study													█	█	█	█	█	█	█	█	█	█									
Part 12	Stability study																													█		
Part 13	Formulation Development										█	█	█	█	█	█	█	█	█	█												
Part 14	Reference Standard Development and Manufacturing report																█	█	█	█	█	█										
Part 15	Development and Manufacturing report																													█	█	
Part 16	IMPD support																														█	

# Report

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- Combined process development and solid state results
- Weekly progress updates by e-mail
- Teleconferences to discuss the results and decide on next steps
- Clear overview of the main results and conclusions
- Relevant measurements as attachment

# Solid State Studies

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Our objectives are to streamline the development process and to provide clear advice with regard to the risk management in matters regarding solid state chemistry.

The connection of process development and solid state chemistry shortens timelines and strengthens the added value of both.