CRYSTALLIZATION SCREENINGS

CRYSTALLIZATION WORKSHOP

Institut Català d’Investigació Química
Tarragona
Content

1. Importance of solid state

2. Crystallization screenings
   a. Polymorphism screening
   b. Salt / Co-crystal screening
   c. Optimization

3. Practical examples
Active molecule

One component solid form:

More than one component solid form:

Salt: - counter ion  Ionic interaction

Solvate: - solvent  Weak interaction

Hydrate: - water  Weak interaction

Co-crystal: - former  Weak interaction
Solid state of an API

Polymorph: Each crystalline phase of a chemical compound that crystallizes at least in two different crystalline structures

One component solid form:

More than one component solid form:

Salt / solvate / hydrate / co-crystal

Different crystalline phases

Polymorphism screenings of 250 APIs

13% Monomorphism

87% Polymorphism

Importance of solid state

Different solid forms can have different solid state properties

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Kinetic</th>
<th>Mechanical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical reactivity/stability</td>
<td>Rate of dissolution</td>
<td>Compactability</td>
</tr>
<tr>
<td>Photochemical reactivity</td>
<td>Solid-state reaction kinetics</td>
<td>Hardness</td>
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<tr>
<td></td>
<td>Stability</td>
<td>Powder flow</td>
</tr>
<tr>
<td></td>
<td>Rate of crystal growth</td>
<td>Tableting</td>
</tr>
</tbody>
</table>

- Packing/physical
  - Conductivity
  - Density (or molar volume)
  - Hygroscopicity
  - Refractive index
  - Color
  - Particle morphology

- Surface
  - Interfacial tensions
  - Surface area
  - Surface free energy

- Thermodynamic
  - Chemical potential, free energy, and solubility
  - Enthalpy and entropy
  - Heat capacity
  - Melting and sublimation temperature
  - Vapor pressure

- Pharmacological implications
  - Bioavailability
  - Stability
  - Manufacturability


Effect on Drug Safety, Efficacy and Quality
Patent protection

Solid forms can be protected by patent

✓ **Originators**: protection of solid forms to avoid the introduction of generics
✓ **Generic companies**: seek and protect alternative solid forms

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(54) **Title**: POLYMORPHIC FORMS OF Icotinib AND USES THEREOF

(57) **Abstract**: Provided are polymorphic forms of the compound of Formula I, preparation thereof and pharmaceutical compositions, and use of a polymorph above in the treatment of a disease, a disorder or a condition, or in the manufacturing of a medicament for the treatment of a disease, a disorder or a condition.
Opportunity for the pharmaceutical industry

- Optimization of solid state properties of an API
- Improvement of existing drugs
- Opportunity for patent protection (IP)
- Increase of the lifecycle of a drug
- Requirement by the Regulatory Agencies

Discover the different solid forms of the API
Aims in crystallization screening of an API

- Identify and select the solid form/phase of the API with optimal solid state properties for the desired pharmacological application
  - Solubility
  - Dissolution rate
  - Melting temperature
  - Non hygroscopic API
  - Physical and chemical stability
  - Particle shape and size

- Avoid risks during the production and commercialization of the API or the pharmaceutical formulation
  - Appearance of new polymorphs
  - Polymorphic transformations

- IP strategy optimization

- Optimize the process to obtain a solid form
  - Yield
  - Purity (chemical, ee)
  - Particle size
  - Solid form
  - Crystallinity
  - Morphology
Crystallization screenings

- Comprehensive screening to discover different polymorphs / solvates of an API
- Relative stability between different polymorphic forms
- Scale-up of procedures to obtain the polymorphs

- Crystallization screening to discover crystalline salts or co-crystals of an API
- Development and scale-up of crystallization processes to obtain salts / co-crystals
- Resolution of chiral APIs by selective crystallization of diastereomeric salts / co-crystals

- Crystallization of amorphous solids or products difficult to crystallize
- Development and scale-up of crystallization procedures (optimization)
- Crystallizations aimed to generate single crystals
Stages in the solid state development of an API

- Selection of the form to be investigated: neutral molecule, salt, co-crystal
- Identification of the optimal salt or co-crystal
- Identification of the most relevant solid phases (polymorphs, solvates, amorphous phase) of the selected form
- IP protection of the active forms and the solid phases
- Selection of the optimal polymorph for pharmaceutical development
- Development of a scalable crystallization process
- Development of an analytical method to determine API polymorphic purity
- Development of an analytical method to determine the polymorphic purity of the API in the final pharmaceutical specialty

Salt / co-crystal screening
Polymorph screening
Optimization screening
Single crystal screening
Stages in the selection of the solid form of an API

Late stage discovery
- Solid form selection:
  - Free API
  - Salts
  - Co-crystals

Pre-clinical
- Polymorph screening to select development phase (Polymorph, amorphous, hydrate)

Phase 1
- Crystallization scale-up
- Analytical method development for polymorph purity
- Early formulation

Phase 2
- Polymorph screening for IP protection
- Final formulation

Phase 3
- Alternative salts, co-crystals for life cycle management
Stages in the selection of the solid form of an API

1. Obtaining the thermodynamically most stable phase of the API
2. Polymorphism screening
   - Suitable solid state properties?
     - YES
     - Development of the selected salt of the active molecule (stable phase)
     - NO
     - Salt screening
       - Suitable solid state properties?
         - YES
         - Development of the selected salt of the active molecule (stable phase)
         - NO
         - Co-crystal screening
           - Suitable solid state properties?
             - YES
             - Development of the selected co-crystal of the active molecule (stable phase)
             - NO
             - Polymorphism screening
               - NO
               - Development of a metastable phase of the active molecule, salt or co-crystal
4. Polymorphism screening
   - Ionisable active molecule?
     - YES
     - Development of the active molecule (stable phase)
     - NO
     - Suitable solid state properties?
Polymorphism screening
Polymorphism screening:

Massive crystallization program to determine whether a compound exists in various polymorphic forms, solvates (hydrates) and amorphous phases

Polymorph selection:

Investigation of the properties of the most relevant polymorphs obtained in the screening to select the optimum form for a given application
Polymorphism Screening

General remarks:

✓ No screening guarantees the discovery of all polymorphs.
✓ Use the highest purity available API.
✓ Analysis to assess the chemical integrity of the samples (NMR / chromatography).
✓ Specific to each API according to its properties: solubility, thermal stability, chemical stability.
✓ Supersaturation level where the nucleation and growth occurs
✓ Depends on the starting form: metastable, stable, amorphous, solvate
✓ Not possible to know, *a priori*, the supersaturation conditions that generates each polymorph

![Diagram showing supersaturation and solubility curves with metastable zone limiting experimental conditions as varied as possible in which nucleation may occur](image-url)
Selection of crystallization solvents

✓ Solubility
✓ Diversity (functional groups, polarity, hydrogen bonding,…)
✓ Not limited to solvents of industrial use

Crystallization / precipitation techniques

✓ Diversity (kinetic control / thermodynamic control)
✓ With solvent / without solvent
✓ Drying of solvates

Starting material

✓ Crystalline anhydrous solid
✓ Amorphous solid
✓ Hydrates / solvates
Experiments with solvent:

• Evaporation at different temperatures
• Evaporation at different rates
• Crystallization from hot saturated solutions
• Crystallization by addition of antisolvent
• Crystallization by vapour diffusion
• Crystallization by liquid - liquid diffusion
• Slurry experiments
• Crystallization induced by additives (polymers)
• Experiments aimed at obtaining hydrates
• Crystallization varying the pH
• Crystallization induced by ultrasounds

Solid State Experiments:

• Melting experiments
• Grinding experiments
• Sublimation
• Pressure experiments
• Solvent vapour exposure
• Exposure to different relative humidity
Polymorphism Screening and selection of the phase

Characterization of initial API
PXRD / NMR / DSC / TGA / Hot-stage / IR / Raman / Microscopy

Generation of solid samples
Extensive crystallization

Characterization of solid samples
PXRD / Raman

Classification of solid samples by phases

Selection of solid phases of interest

Characterization of discovered phases
PXRD/ NMR / DSC / TGA / Hot-stage / IR / Raman / Microscopy

Scale-up of solid phases of interest
Optimization of the crystallization methodology

Determination of the crystalline structure
SCXRD

Study of relative stability among the different phases (polymorphs / hydrates)
Slurry experiments / DSC

Compare the solid state properties of different phases

Select the optimum solid phase
Salt / Co-Crystal Screening
Salt / Co-crystal Screening:

Crystallization screening of the API with different counter ions (salt screening) or co-crystal formers (co-crystal screening) to discover new salts / co-crystals of the API with more suitable properties for development.

Selection of Salt / Co-crystal:

Investigate the properties of the salts / co-crystals obtained in the screening to select the ones which have more adequate properties for a determinate application (physical properties, manufactures, pharmacological properties,...)
General remarks:

✓ The objective is to find different crystalline salts / co-crystals and not to find different crystalline forms of a salt / co-crystal.

  • Elevated number of counter ions / co-crystal formers
  • Less variety in crystallization conditions (less solvents, less crystallization methods)

✓ Use of API with the maximum purity accessible.

✓ Stability of the API in acidic / alkaline media should be taken into account. Analysis to evaluate the chemical integrity of the samples (NMR/Chromat.).

✓ The solubility differences between API and co-crystal formers may play an important role: solubility assessment recomendable.
Salt Screening / Co-crystal Screening

Counterions selection:

- $\Delta \text{pKa}$
  - Minimum Difference of $\sim$3 units of pKa between API and the counterion
- Acids and bases pharmaceutically acceptable

Co-crystal formers selection:

- Selection of supramolecular syntones according to the API
- Pharmaceutically acceptable acids ($\Delta \text{pKa} < 0$)
- Pharmaceutical excipients
- *Generally recognized as safe (GRAS) list*
- *Everything added to food in the US (EAFUS) list*

**Computational methods**
Salt / Co-crystal Screening: general procedure

Step 1: Crystallization Salt / Co-crystal Screening
- Scale 10-30 mg

Step 2: Reproduction and characterization
- Scale 0.1 g

Step 3: Scale-up of selected salts/co-crystals
- Scale 0.5 – 1.5 g

Step 4: Salt co-crystal selection

Optimal solid state properties
Salt / Co-Crystal Screening: procedure

Preparation of mixtures of API with selected counter ions (generally equimolar) or coformers (different ratios)

Evaporation of initial solvent

Crystallization in selected solvents using different crystallization methodologies
Crystallization methods

- Cooling crystallization from a saturated solution
- Solvent evaporation
- Reaction crystallization
- Slurry
- Grinding
- Melting or heat induced crystallizations

Parameters in methods in solution: solvent, concentrations, temperature, cooling / evaporation rate,…

Solubility of A and B are important
Salt / Co-Crystal Screening: procedure

- **Grinding**
  - 5 solvents
- **Ball mill**
- **Melting experiments**
- **Kofler table**
- **Hot-stage microscopy**

**Counterions / Co-crystal formers**
- (5-10; different ratios)

**Reaction Crystallization**

**Crystallization from saturated hot solutions**

**Evaporation at different temperatures**

**Slurry experiments**
- Salts Co-crystals
- Salts Co-crystals
- Salts Co-crystals

**4 - 6 solvents**
Characterization techniques of crystalline salts

- Powder X-ray diffraction
- $^1$H-NMR
- Differential scanning calorimetry
- Thermogravimetry
- Karl Fisher
- Elemental analysis
- Single crystal X-ray diffraction
- Infrared (FTIR)
- Microscopy
Optimization of a crystallization process

Optimization screening

- Identify the property that you need to optimize
- Identify the parameters of the process that can affect the property/ies
  - Crystallization temperature
  - Solvent System
  - Cooling rate
  - Antisolvent addition
    - Temperature
    - Addition rate
  - Seeding
    - Amount
    - Temperature
  - Stirring
  - Final temperature
  - Concentration

Mya 4 Reaction Station (Radleys)
EasyMax Workstation (Mettler)
Crystal16 (Technobis)
EXAMPLE

Comprehensive Polymorphism screening study of an API
Initial sample

- New active material in development
- Only the **amorphous phase** was known
- Amino group

Objectives

- Find a crystalline form
- Discover possible polymorphs
- Determine the most stable polymorph
Preparation of Solid Samples

- Evaporation of solvent at different temperatures
- Crystallization from a hot saturated solution
- Evaporation of solvent at different rates at room temperature
- Crystallization by the addition of an antisolvent
- Crystallization in mixtures of organic solvent with water
- Slurry experiments
- Grinding experiments
Polymorphism Screening final result

550 Crystallization attempts

151 Obtained solids

10 Identified phases

Solvent evaporation
Crystallization from a saturated solution
Solvent evaporation at different rates at 25°C
Crystallization by addition of an antisolvent
Slurry experiments
Grinding experiments
Crystallization in mixtures with water

Analysis by PXRD

2 polymorphs (α and β)
7 solvates
1 amorphous phase

Characterization
PXRD
SCXRD
FTIR
FTRaman
TG
DSC

45 solvents

Obtained solids

550

151

10

Solvent evaporation
Crystallization from a saturated solution
Solvent evaporation at different rates at 25°C
Crystallization by addition of an antisolvent
Slurry experiments
Grinding experiments
Crystallization in mixtures with water

Analysis by PXRD

2 polymorphs (α and β)
7 solvates
1 amorphous phase

Characterization
PXRD
SCXRD
FTIR
FTRaman
TG
DSC

45 solvents
Screening development

**Until date X:**

Screening:
- Mainly Polymorph α was obtained
- In a few experiments Polymorph β was obtained

Reproduction/scale-up:
- Polymorph α was scaled-up up to 10 g (amorphous/diisopropyl ether)

**After date X:**

Screening:
- Mainly Polymorph β was obtained
- Polymorph α could not be reproduced

Reproduction/scale-up:
- Polymorph β was obtained in all the scale-up attempts instead of Polymorph α

*Where is α???!?!?*
Screening development

Experiments to determine the thermodynamically most stable polymorph

<table>
<thead>
<tr>
<th>Slurries at RT and 60° C</th>
<th>phase $\alpha$</th>
<th>phase $\beta$</th>
<th>phase $\alpha+\beta$</th>
<th>amorphous</th>
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<tbody>
<tr>
<td>Water</td>
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<td>$\beta$</td>
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<td>$\beta$</td>
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<td>$\beta$</td>
</tr>
</tbody>
</table>

Polymorph $\beta$ is thermodynamically more stable than Polymorph $\alpha$
Experiments aimed to obtain a metastable polymorph: kinetic conditions

Polymorph $\alpha$ appears more frequently in:

- Solvents where the API is very insoluble
- Fast precipitation (kinetic control)
- Room temperature

**Inverse addition of antisolvent:**
Fast crystallization by addition of a toluene solution of API into $n$-heptane
EXAMPLE
Salt screening study of an API
**Initial sample**

- New active material in development
- A crystalline form of the API known
- Low solubility
- Melting point below 70°C
- Amino group ($\text{pK}_a \sim 8$)

**Objectives**

- Discover crystalline salts
- Improve the solubility
- Increase the melting point
Salt Screening: procedure

Preparation of mixtures of API with selected counter ions (1:1 and 1:2) in methanol

Evaporation of methanol

Crystallization in 15 solvents using slurries and cooling crystallization
## Salt screening result

<table>
<thead>
<tr>
<th>Acid/solvent</th>
<th>ACE</th>
<th>CLF</th>
<th>MOH</th>
<th>THF</th>
<th>AET</th>
<th>EOH</th>
<th>ACN</th>
<th>DCE</th>
<th>CDM</th>
<th>H2O</th>
<th>DIX</th>
<th>NIM</th>
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<td>2</td>
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<td>B</td>
</tr>
</tbody>
</table>
EXAMPLE

Optimization to obtain a specific polymorph
Two solid forms known (anhydrous and hydrate)
The hydrate form is not suitable for formulation
API is soluble in water (pH dependant)
API is very low soluble in common organic solvents
In a standard cooling crystallization only the hydrate is formed

Objectives
Find a methodology to obtain the anhydrous form
The solvent system must contain water
API solubility

Solubility curves of **anhydrous** and **hydrate** in water.

- **Anhydrous** less soluble at high T
- **Hydrate** less soluble at low T
Crystallization optimization

Crystallization parameters:

- **Concentration** of API in water: 0.07, 0.17 and 0.20 g/mL
- Crystallization **temperature**: room temperature, 40, 50, 60, 70, 80 ºC
- Crystallization **pH**
- **Seeding** of anhydrous form

Best conditions in order to obtain the anhydrous form:

- Crystallization temperature >70ºC
- Concentration <0.2 g/mL
- Slow crystallization rate
- Seeding
THANK YOU FOR YOUR ATTENTION!!!