Polymorphie – Grundlagen und Bedeutung für die Galenk
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Solvias AG- A Technology Company

- Founded in 1999
- Solid-state, synthesis/catalysis, analytics
- 300 employees, based in Basel, Switzerland
- From QC to contract research
- www.solvias.com
Polymorphism

Definition

“Polymorphism is the ability of a compound to crystallize in more than one distinct crystal structure”

More than 50% of all organic solids are polymorphic.
Polymorphs

Solvate

Salt

Co-Crystal

In the ICH guidelines, the term "polymorph" is also used for solvates, hydrates and the amorphous form!

In the ICH definition almost 100% of all organic solids are polymorphic!
Solid Forms of Pharmaceutical Solids

808 solid organic drug compounds in Ph Eur 4.02

- only one form described: 43%
- polymorphs: 36%
- hydrates: 29%
- solvates: 10%

180 polymorph screens at a CRO

- only one form: 13%
- polymorphs: 52%
- hydrates: 38%
- solvates: 32%

Multiple solid forms are very common!

The Influences of Polymorphism: $\Delta G_f^0$

Different $\Delta G_f^0$ means different physical properties:
- Different melting point, solubility, hygroscopicity, etc.

Whole life cycle is affected:
- Application: bioavailability (class 2 & 4)
- Storage: polymorph must be stable
- Formulation: e.g., knowledge about solvates important
- Production: robust method required
- IP situation: solid forms can be patented

Polymorphic form affects just about anything!
Step 1: Guideline ICH Q6A

Drug Substance

Conduct polymorphism screen

Can different polymorphs be formed?

NO

No further action

YES

Characterize the forms

“What physicochemical measurements and techniques are commonly used to determine whether multiple forms exist. ... melting point, IR, XRD, DSC, TG, Raman,...”

What are Regulators’ Concerns about Polymorphism?

- Polymorphs may act as though they were different compounds
- Pseudo polymorphs may have unwanted effects due to the solvent
- May require different formulation
- May have different bioavailability
- May result in unexpected analytical observations
- There may be interconversion during formulation
- Appropriate steps may be required in manufacture
**Biopharmaceutics Classification System**

**Class 1**
good solubility
good permeability
(paracetamol, captopril)

**Class 2**
bad solubility
good permeability
(carbamazepine)

**Class 3**
good solubility
bad permeability
(cimetidin, ranitidine)

**Class 4**
bad solubility
bad permeability
(cyclosporine, terfenadine)

Solubility is bottleneck for Class 2 and 4.

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**What is "Insoluble"?**

Freely soluble: therapeutic dose soluble in 250 ml at pH 1.0 to 7.5

Minimal acceptable solubility = f(dose, permeability)
Maximum Absorbable Dose (MAD)

\[
\text{MAD} = (\text{solubility}) \times (\text{absorption rate}) \times (\text{small intestinal water volume}) \times (\text{small intestinal transit time})
\]

Typical values:
- Absorption rate: 0.001 to 0.05 min\(^{-1}\)
- Therapeutic dose: 70 mg (1 mg/kg)

Frequent values of minimal acceptable solubility: 20 \(\mu\)g/ml to 1 mg/ml

Dissolution-Rate or Solubility Limit?

Absorption number = residence time / absorption time = 10
Solubility: Polymorphs

Solubility Differences of Polymorphs

Figure 1. (a) Solubility ratios for polymorphs ($n=84$). (b) Solubility ratios for polymorphs on an expanded scale (not including pefloxacin).


Ratio often between 1 and 2.
Definition of Solubility

\[ \mu_{\text{solid}} = \mu_{\text{solution}} = \mu^0_{\text{solid}} = \mu^0_{\text{solution}} + RT \ln (f \cdot \text{solubility}) \]

Impact For Formulation

- In the rare case where a metastable form is chosen for development, the kinetic stability of that form has to be tested in the presence of the excipients!
Solubility: Salts

Solubility of a Salt as a Function of pH

Unbuffered, no common ion effect

Dramatic increase possible.
Solubility of Salts

Differentiation of salts at pH >> pKa


Solubility: Co-Crystals

Amazing where you can go
Reasons to Consider Co-Crystals

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

**Solubility is not the only reason!**

Co-Crystal Engineering Strategies

**Electrostatic interactions**
- Hydrogen bonds
- Van der Waals interactions
  - dipole – dipole
  - dipole – induced-dipole
  - induced-dipole – induced-dipole

**π-Stacking**

"Crystal engineering is the target-oriented and property-directed synthesis of molecular crystals."

Itraconazole: Molecular Co-Crystals

PCT Publication WO 01/97853 (2001)
Remenar et al, JACS 125 (2003) 8456-8457

Impact For Formulation

- Be sure that none of the excipients forms a co-crystal with the API!
Hydrate or Anhydrate?

Propensity for Solvate/Hydrate Formation

Frequency of polymorphs (P), hydrates (H) and solvates (S) with organic solvents among the substances of the Pharmacopoeia Europaea divided into salts and neutral compounds.

Pharmaceutical Forms on the Market

<table>
<thead>
<tr>
<th>Hydrates in drug product</th>
<th>Anhydrates in DP *, but hydrates exists</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Atorvastatin calcium trihydrate (Lipitor)</td>
<td>• Carbamazepine</td>
</tr>
<tr>
<td>• Amoxicilline trihydrate</td>
<td>• Paroxetine *</td>
</tr>
<tr>
<td>• Rosuvastatin calcium hemihydrate</td>
<td>• Sertraline</td>
</tr>
<tr>
<td>• Pantoprazole sodium sesquihydrate</td>
<td>• Venlafaxine</td>
</tr>
</tbody>
</table>

**Question:** Development of the hydrate or anhydrate?

**Develop Hydrate or Anhydrate?**

- Understand thermodynamics
  - stoichiometry, stability range as a function of temperature, differences in solubility
- Understand kinetics
  - rate of transformation
- Understand application
  - formulation, impact on production

**Thorough understanding of system essential.**
Experimental tools for development

• Water vapor methods (DVS) can be extremely slow and misleading

• Slurry experiments
  if you start with mixture and wait for conversion, you're absolutely sure to have achieved true equilibrium

Compound XZ: Conversion Scheme

6 hydrates! (penta, 3xdi, sesqui, hemi)
Depending on water activity A (penta), C (di) or E (hemi) stable.

Impact For Formulation

- It must be ensured that the water activity in the formulation is within the boundary values of the thermodynamic stability of the hydrate or anhydrate!
- Therefore, solid-state properties of excipients have to be known as well!
Solubility: Solvates

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Results From Suspension Experiments with Solvate Formers

Solubility of hydrates and solvates can be calculated from thermodynamic data.
DP on the Market as Solvates

- Warfarin sodium: (a) amorphous, (b) isopropyl alcohol solvate
- (Prezista) Darunavir ethanolate
- (Crixivan) Indinavir sulfate ethanolate
- ....

Impact For Formulation

- Appropriate vapor pressure of solvent must be maintained!
Solubility: The Amorphous State

Amazing where you can go

Solubility Difference Crystalline/Amorphous

<table>
<thead>
<tr>
<th>Solute</th>
<th>Melting Point (°C)</th>
<th>Solubility Ratio (A/C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>238</td>
<td>5</td>
</tr>
<tr>
<td>Theophylline</td>
<td>272</td>
<td>50</td>
</tr>
<tr>
<td>Morphine</td>
<td>197</td>
<td>270</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>273</td>
<td>1.1</td>
</tr>
<tr>
<td>Sulfamethoxydiazine</td>
<td>215</td>
<td>1.5</td>
</tr>
</tbody>
</table>


Measured ratios between 1.1 and 270.
Some Amorphous DP on the Market

- Itraconazole
- CRESTOR® (rosuvastatin calcium)
- Cerivastatin sodium
- Cefuroxime Axetil
- Warfarin sodium: (a) amorphous, (b) isopropyl alcohol solvate
- Viracept® (nelfinavir mesylate)
- Allopurinol
- Quinapril hydrochloride

Amazing where you can go

Stabilizing the Amorphous Form
How to make sure that AS and PM are miscible: DSC

<table>
<thead>
<tr>
<th>Miscible</th>
<th>Immiscible</th>
</tr>
</thead>
<tbody>
<tr>
<td>polymer + AS</td>
<td>polymer</td>
</tr>
<tr>
<td>AS</td>
<td></td>
</tr>
</tbody>
</table>

One step                                       Two steps

Tg predicted by “plasticiser law”

Stabilization of Amorphous State in PVP:
Successful with AS3
DSC is rapid method to check if polymer is suitable and to optimize conditions (PM, MW, ratio) very fast.

Stabilization of Amorphous State in PVP:
NOT immediately successful with AS1 (partially immiscible)

Increasing the Dissolution Rate

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The Influences of Micronization

Effect of pressure might induce phase changes
- Transformation of a metastable crystalline polymorph to a stable crystalline polymorph
- Formation of amorphous parts

→ Control solid-state characteristics during and after micronization

Be well aware of polymorphic behavior of DS!

Micronization / Amorphous Phase

- Micronization often leads to formation of amorphous fractions
- Crystallization of amorphous fractions can lead to agglomeration
- To understand (avoid) agglomeration upon / after micronization

Characterize the amorphous phase
- Tg
- moisture sorption
- g f((H2O))

If Tg range critical: Protect from moisture or switch solid form.
Solid Form in Drug Product

Amazing where you can go

Polymorphic Purity in Drug Product

ICH Q6A

“It is generally technically very difficult to measure polymorphic changes in drug products. A surrogate test (e.g., dissolution) (see Decision Tree #4(3)) can generally be used to monitor product performance, and polymorph content should only be used as a test and acceptance criterion of last resort”

→ In general: tedious task
**Polymorphic Form in DP: Raman**

Example Raman spectroscopy

→ Essentially Polymorph 1 in 14% formulation

**Polymorphic Form in DP: XRD**

Example XRD spectroscopy (same compound)

→ Essentially Polymorph 1 in 14% formulation
Polymorphic Form in DP: Raman Microscopy

Use of coupled techniques, e.g., Raman microscopy:
Take advantage of spatial resolution

Clear-cut identification in formulation: Form A

Polymorphic Form in DP: Raman Microscopy

Mapping of surfaces:
‘Find the needle in the haystack’ approach

Raman spectra of Forms A and B
Polymorphic Purity in DP: Amorphous Content

**Drug Substance**

DS crystalline
- $T_m = 198.8 \degree C$
- $\Delta H = 89 \text{ J/g}$

DS amorphous
- $T_g = 111.6 \degree C$
- $\Delta c_P = 0.6 \text{ J/g/K}$

**Drug Product**

DP with DS crystalline
- $T_m = 196.9 \degree C$
- $\Delta H = 38 \text{ J/g}$

DP with DS amorphous
- $T_g = 111.5 \degree C$
- $\Delta c_P = 0.3 \text{ J/g/K}$

In favorable cases, even DSC can be an option.
Conclusions

Understanding of solid-state behavior of the drug substance and the excipients is absolutely essential!

→ Allows selection of optimal form for development in order to have the best possible product.

→ It accelerates formulation development, since "errors" will be avoided.

Thank you for your attention!

Questions...