Crystalline Solids

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Outline

- Introduction – Importance of Polymorphism
- Thermodynamics of Polymorphs
- Kinetics of Polymorphs
- Physical Characterization Methods
- Phase Transformation Considerations During Process Development and Manufacturing
- Future Opportunities and Challenges
Solid-States

Organic Molecular Solid

- Amorphous
- Crystalline

Polymorphs

- Monotropic
- Enantiotropic

Solvates/Hydrates

- Reversible
- Non-reversible
Background - Definitions

- **Form** – a term encompassing all solids – polymorphs, solvates, amorphous forms
- **Polymorph** – the different crystal structures (of unsolvated forms) in which a compound can crystallize
- **Solvate** – a crystal form with either stoichiometric or non-stoichiometric amount of solvent
- **Hydrate** – solvate with water as the solvent
- **Morphology** – a term referring to the shape of solids. Crystals or solids with different shapes are said to have different morphologies.
- **Habit** – Same unit cell, different external shape
- **Unit Cell** – The crystal axes a, b, c form three adjacent edges of a parallelepiped. The smallest parallelepiped built upon the three translations is known as the unit cell.
Importance of Polymorphism

- Physical properties
- Reactivity – chemical properties
- Regulatory issues
- Patents
Impact on Pharmaceutical Properties

• Bioavailability (solubility/dissolution rate)
• Stability (physical and chemical)
• Processing Factors
  – Hygroscopicity
  – Bulk, mechanical, and rheological properties
  – Ease of isolation, filtration, and drying
  – Degree of purification
Impact on Solubility and Dissolution Rate

- Different lattice energies of polymorphs or solvates give rise to different solubility and dissolution rates.
- The biggest difference in solubility is between amorphous and crystalline materials.
- Solubility ratios of polymorphs are typically independent of the solvents.
- Hydrates are typically less soluble in aqueous media than anhydrous forms and solvates.
Impact on Chemical Stability

• Higher melting point typically results in better stability
• Hygroscopicity also plays an important role
• Example:
  ● NCEX: 2 forms (160°C and 140°C)
  ● % degradation observed after 4 weeks at 40°C/75%RH
    – Form 1: 0.3%
    – Form 2: 6%
    – Amorphous: 20%
• > 500 crystal form patents

• Advantage Claims:
  
  • Stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hygroscopicity, recovery, or prevention of precipitation.

Regulatory Considerations

• Due diligence should be exercised to isolate and identify crystalline forms:
  - likely to arise during the normal course of drug development
  - reasonably stable in the range of conditions encountered during the drug's lifetime

• FDA drug substance guideline:
  “By the time of an NDA submission, the applicant should have established whether (or not) the drug substance exists in multiple solid-state forms, whether these affect the dissolution and bioavailability of the drug product, and whether particle size is important for dissolution and bioavailability of the drug product. It is not necessary to ‘create’ additional solid-state forms by techniques or conditions irrelevant to the synthetic process.”

• Polymorph Question 1
  ● Can different polymorphs be formed?
  ● If yes, characterize the forms and go to Question 2

• Polymorph Question 2
  ● Do the forms have different properties?
  ● If yes, is product safety, performance, or efficacy affected?
  ● If yes, set acceptance criteria for polymorph content in drug substance and go to Question 3

• Polymorph Question 3:
  ● Does drug product performance testing provide adequate control if polymorph ratio changes (e.g. dissolution)?
  ● If not, monitor polymorph form during stability of drug product
  ● Does a change occur which could affect safety or efficacy?
  ● If yes, establish acceptance criteria consistent with safety and/or efficacy
Thermodynamics of Polymorphism
\[ \Delta G = -RT/\text{(less soluble form/more soluble form)} \]
Monotropy and Enantiotropy

- **Monotropic system**
  - Only one polymorph is stable at all reasonable temperatures
  - e.g. metalazone

- **Enantiotropic system**
  - One polymorph is stable over one temperature range, another polymorph is stable over a different temperature range
  - e.g. carbamazepine and acetazolamine
The van’t Hoff plot of Carbamazepine Forms I and II in 2-propanol
Establishing Thermodynamic Relationships

- **Only one form is stable in a given system (i.e. temperature, pressure)**
  - **Solubility**
    - The most stable form has the lowest solubility.
    - Hydrates always have lower solubility in aqueous media.
  - **Intrinsic Dissolution Rate**
    - The most stable form has the lowest IDR.
  - **Slurry (Suspension) Equilibration**
    - A slurried mixture of crystal forms will equilibrate to most stable form, given sufficient time.
    - Slurring in aqueous and/or non-aqueous media
    - Effect of temperature
Only one form is stable in a given system (i.e. temperature, pressure)

- **Heat of Fusion Rule**
  - If the higher melting form has the lower heat of fusion, then the forms are enantiotropic.

- **Heat of Transition Rule**
  - If an endothermic transition is observed between two polymorphs, then the forms are enantiotropic.

- **Density**
  - The crystal form with the greatest density is often the most stable.
Relationship between Polymorphs and Solvates

- Thermodynamically most stable anhydrous form may no longer be most stable: will convert to solvate in the present of the right amount of the solvent.

- The thermodynamically most stable solvate is not necessarily associated with the lowest degree of solvate.

- A particular solvate may have polymorphs.
  - e.g. Nedocromil Zinc
    - solubility: Anhydrous > Octahydrate > heptahydrate > pentahydrate (Form B) > Pentahydrate (Form A)
Kinetics of Polymorphism
In all processes, it is not the most stable state with the lowest amount of free energy that is initially formed, but the least stable state lying nearest to the original state in free energy.

During crystallization, unstable forms are frequently obtained first, and then they transform into a stable form.

Nucleation Processes

Nucleation

Homogeneous
(Spontaneous)

Surface Catalyzed

Heterogeneous
(Induced by foreign particles or surfaces)

Secondary
(Induced by crystals)
Crystallization Methods

- **Crystallization from Solution**
  - Single solvent crystallization
  - Binary solvent mixtures

- **Solvent Selection Criteria**
  - Distribution of solvent properties
  - Potential solvents of synthesis, purification, and processing
  - Potential solvents for formulations (e.g. PEG400, PEG4000, Vitamin E TPGS)

- **From Neat Substance**
  - Sublimation
  - Thermal treatment
  - Crystallization from the melt
  - Grinding
  - Heat/pressure stressing of crystalline solvates (thermal desolvation)
# Common solvents used in crystal form screening

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Boiling point (°C)</th>
<th>Dielectric Constant (ε)</th>
<th>Proton Donor/Acceptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>N,N-Dimethylformamide</td>
<td>153</td>
<td>37</td>
<td>A</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>118</td>
<td>6.2</td>
<td>D&gt;A</td>
</tr>
<tr>
<td>Water</td>
<td>100</td>
<td>78.4</td>
<td>D-A</td>
</tr>
<tr>
<td>1-Propanol</td>
<td>97</td>
<td>20.3</td>
<td>A&gt;D</td>
</tr>
<tr>
<td>2-Propanol</td>
<td>83</td>
<td>19.9</td>
<td>A&gt;D</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>82</td>
<td>37.5</td>
<td>A</td>
</tr>
<tr>
<td>2-Butanone</td>
<td>80</td>
<td>18.5</td>
<td>A</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>77</td>
<td>6.0</td>
<td>A&gt;D</td>
</tr>
<tr>
<td>Ethanol</td>
<td>78</td>
<td>24.6</td>
<td>A&gt;D</td>
</tr>
<tr>
<td>n-Hexane</td>
<td>69</td>
<td>1.9</td>
<td>N</td>
</tr>
<tr>
<td>Isopropyl ether</td>
<td>68</td>
<td>3.9</td>
<td>A</td>
</tr>
<tr>
<td>Methanol</td>
<td>65</td>
<td>32.2</td>
<td>A&gt;D</td>
</tr>
<tr>
<td>Acetone</td>
<td>57</td>
<td>20.7</td>
<td>A</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>40</td>
<td>8.9</td>
<td>N</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>35</td>
<td>4.3</td>
<td>A</td>
</tr>
</tbody>
</table>
Recrystallization from neat drug substance

- Desolvation process of a non-reversible solvate
  1. molecular loosening  
     (separation of the lattice)
  2. breaking of the host-solvent hydrogen bonds  
     (or other associations)
  3. solution or solid solution formation
  4. crystallization of the new phase
Heat / Pressure Stressing of Crystalline Solvates

Bottom: initial thermogram. Top: stored at 80 °C /75% RH for 20 days
Effect of Excipients on Crystallization

Growing crystals of acetaminophen on different polymer surfaces yields different crystal structures: One polymer gives rise to tiny prisms (left); another, miniature monoliths (right).
Analytical Techniques for Solid State Characterization
Analytical Techniques for Solid State Characterization

- **Powder X-ray Diffractometry (PXRD)**
  - “gold” standard for phase ID
  - preferred orientation; interference from crystalline excipients

- **Single Crystal XRD**
  - ultimate phase ID with in depth understanding of the structure
  - may be difficult to prepare single crystals

- **DSC/MDSC**
  - information in phase transition and interaction with excipients
  - “black box”: no information on the nature of the transition
  - interference from both crystalline and amorphous excipients

- **TGA**
  - quantitative information on the stoichiometry of solvates/hydrates
  - interference from water-containing excipients
Analytical Techniques for Solid State Characterization

- **IR**
  - complementary phase ID method
  - ability to show the different states of water
  - interference from moisture and excipients
  - difference may be small

- **NIR**
  - ability to penetrate through containers
  - low intensity, significant baseline slope

- **Raman**
  - complementary phase ID method
  - ability to penetrate through containers
  - minimum interference from water but interference from excipients

- **Solid State NMR, HSM, Sorption (e.g. VTI)**
FT-IR spectra of the two polymorphs of nabumetone
Raman spectra of selected region of two polymorphs of acetaminophen
PXRD of four polymorphs of carbamazepine
DSC overlay of the four polymorphs of carbamazepine
Phase Transformation Considerations
During Process Development and Manufacturing
Three Classes of Phase Transitions

- **Polymorphic transition**
  - interconversion among polymorphic forms

- **Hydration and dehydration**
  - interconversion between crystalline anhydrates and hydrates
  - mechanical treatments, such as milling, tend to accelerate the kinetics of dehydration by generating surface defects and by local heating

- **Vitrification and amorphous crystallization**
  - interconversion between the amorphous phase and crystalline polymorphs or hydrates
Phase Transition Mechanisms

- **Solid State**
  - without passing through transient liquid or vapor phases
  - kinetics is influenced by the environment (temp, RH, etc.), the presence of crystalline defects and impurities

- **Melt**
  - upon melting and cooling, the original solid phase may change
  - determining factors: relative rates of nucleation, crystal growth and cooling, impurity or excipients

- **Solution**
  - upon dissolving, the original solid phase may change
  - determining factors: similar to melt

- **Solution-mediated**
  - when the metastable phase is in contact with saturated solution
**Size reduction**

- Impact milling typically impacts mechanical stress and often generate heat.
- The rate and extent of phase transformations depend on characteristics of the original solid phase, the type of mill and the milling conditions.
- E.g. Digoxin, spironolactone and estradiol.
Granulation
- wet granulation and drying
- dry granulation
- melt granulation
Spray drying and freeze-drying
- typically leading to metastable phase or amorphous
Effect of Pharmaceutical Processes on Polymorphs/Solvates

- Compression
  - Temperature
  - Pressure
  - Excipients
To have a rational salt and crystal screening and selection strategy
Balancing Various Factors:

- Physical stability: the thermodynamically most stable form is always the preferred choice
- Bioavailability: clinically relevant doses vs. tox coverage
- Process consideration
- Other physicochemical properties such as hygroscopicity, morphology and chemical stability

Salt Selection vs. Form Selection

- An integrated process
The Fundamental Question:

What will be the consequence should a new thermodynamically more stable form appear?

- **High risk** if this could lead to significant delay in the overall project timeline or product failure
- **Low risk** if impact on timeline and resources are minimum
High Risk Compounds

- Poorly soluble compounds as defined by the FDA biopharmaceutical classification system:
  
  Solubility in pH 1-8 solutions x 250 mL < Dose

- Compounds that would require one of the non-equilibrium methods or semi-solid/liquid formulations to enhance dissolution rate/bioavailability
  - amorphous
  - meta-stable polymorphs
  - solid dispersion
  - lipid based formulations

- Compounds with parenteral formulations formulated close to equilibrium solubilities at given temperature
Potential Risks Due to Salt or Form Changes

- Additional Studies Required Due to Salt and/or Form Changes
  - PK bridging studies
  - Repeated tox (1 month or 3 months)
  - Additional considerations due to potential impurity changes
  - Bio-equivalent studies
Anticipating and Preventing Phase Transformation in Process Development

- To have a thorough understanding of crystal forms and the amorphous phase of the API and excipients, as well as the interconversion mechanisms and factors affecting these conversions.

- To use the preformulation studies to anticipate process-induced phase transformations and to design and select the appropriate manufacturing processes to control and circumvent these potential transformations.

- In cases where dissolution or stability of the product is very sensitive to solid phase changes, it is advisable to monitor the crystal form if all incoming raw materials and the physical forms present in the final dosage unit.

- Phase transitions in crystalline excipients and their impact on product performance also cannot be ignored.
Case Studies

- **Case I: Process induced instability due to formation of amorphous material in tablets (ABT-232)**
  - ABT-232 is a small, hydrophilic, highly soluble, low dose compound
  - anhydrous with MP of 189°C
  - a monohydrate, which dehydrated at 90°C and rapidly crystallized to the anhydrous
  - amorphous phase with a Tg of 62°C
  - wet granulation was used to prepare tablets
  - API was chemically stable and compatible with the excipients
  - a gradual loss of potency observed over 6 months at 40°C/75%RH
  - Finding:
    - wet granulation converting to the monohydrate, which converts to amorphous upon drying in the presence of the excipients.
    - although the amorphous API crystallized readily to the anhydrate, the excipients in the formulation inhibited such conversion.
## ABT-232 Stability in Tablets

<table>
<thead>
<tr>
<th>Strength (months)</th>
<th>0.5 mg</th>
<th></th>
<th>1 mg</th>
<th></th>
<th>2 mg</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Potency (%)</td>
<td>R.S.D. (%)</td>
<td>Potency (%)</td>
<td>R.S.D. (%)</td>
<td>Potency (%)</td>
<td>R.S.D. (%)</td>
</tr>
<tr>
<td>0</td>
<td>101.6</td>
<td>0.33</td>
<td>102.4</td>
<td>0.30</td>
<td>102.8</td>
<td>0.29</td>
</tr>
<tr>
<td>0.5</td>
<td>100.8</td>
<td>0.47</td>
<td>98.6</td>
<td>0.48</td>
<td>101.4</td>
<td>0.35</td>
</tr>
<tr>
<td>1</td>
<td>96.6</td>
<td>1.08</td>
<td>97.8</td>
<td>1.02</td>
<td>101.1</td>
<td>0.61</td>
</tr>
<tr>
<td>3</td>
<td>92.5</td>
<td>2.56</td>
<td>94.1</td>
<td>2.56</td>
<td>97.5</td>
<td>1.72</td>
</tr>
<tr>
<td>6</td>
<td>86.3</td>
<td>4.73</td>
<td>91.3</td>
<td>4.57</td>
<td>93.8</td>
<td>3.12</td>
</tr>
</tbody>
</table>
Case II: Acetylsalicylic Acid Stability Induced by roller compaction

- acetylsalicylic acid is known to be prone to hydrolysis.
- when roller compacted material is used in formulation, significant degradation was observed.
- moisture uptake increased
- 10% amorphous detected
Case III: Effect of Wet Granulation on Carbamazepine – Solution mediated phase transformation

- Carbamazepine exists as three anhydrate forms and as a dihydrate
- It is practically insoluble in water
- wet granulation was used to improve the flow and compression properties
- main excipients: lactose monohydrate, cornstarch
- granules prepared using water didn’t contain any dihydrate
- granules prepared using 50% aqueous ethanol contain an appreciable amount of dihydrate
- milled anhydrate converted to the dihydrate at least four times faster than the unmilled material
Case III: Acetaminophen Processability Improvement by phase transformation

- acetaminophen exists as three polymorphic forms
- it is known to have poor tablet properties
- in tablet formulations, Form I (stable, monoclinic) is mixed with binders such as gelatin, PVP, starch, etc. to improve its compressibility
- by desolvating a dioxane solvate, the solid phase rapidly recrystallized to crystals that did not have a well-defined habit:
  - defined as fused and porous crystals
  - still form I by thermal and spectroscopic analyses, but a new habit
  - suitable for direct compression
- milling leads to desolvation of the dioxane solvate
• Case IV: Cox Suspension Stability

A case of effect of crystallinity on stability?
In the Future

- Structure solution from PXRD will be increased applied

- Polymorphic prediction will continue to develop
  - The ability to predict crystal morphology from crystal structure will expand
  - Methods will be developed to predict mechanical and manufacturing properties from the crystal morphology will be developed

- Rapid improvements in analytical selectivity and sensitivity will greatly facilitate control of drug polymorphism

- PAT will be increasingly employed to monitor crystallization (form and particle size) and will expand to drug product