Studying Amorphous Pharmaceutical Materials by Powder X-Ray Diffraction and other Solid-State Techniques

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Outline

- Pharmaceutical amorphous and crystalline substances
- Understanding pharmaceutical amorphous materials
- Pharmaceutical “Amorphous Challenges”
- Amorphous characterization
  - Powder X-ray diffraction
  - Other Techniques
Pharmaceutical Solids

• Pharmaceutical solid substances:
  - API, API Intermediates, excipients, mixtures (granules, tablets), etc.

• Physical states:
  - crystalline, amorphous, their mixtures (semi-crystalline) and liquid crystal

• Properties:
  - stability, solubility, crystallinity, hygroscopicity, dissolution rate, bioavailability, powder properties, etc.
• **Crystalline solid:**
  - Solid having a regularly repeating arrangement of the positions of atoms or chemical entity (atoms and molecules).

• **Amorphous solid:**
  - An amorphous solid is a solid in which there is no long-range order of the positions of the atoms. Usually, amorphous materials have some short-range order at the atomic length scale due to the nature of chemical bonding.
Amorphous and Crystalline Solids
Amorphous Pharmaceutical Solids

- **API**
  - Most of the pharmaceutical oral dosage products on the market contain crystalline API; only several products contain amorphous API (like Cefuroxime Axetil and BMS’s Coumadin - Warfarin Sodium)
  - ICH guideline defines amorphous as one of the API polymorph forms (ICH Guideline Q6A (2), included solvation products and amorphous forms for API polymorphism)
  - Amorphous API, in general, can not easily been handled, controlled and processed, compared to its crystalline form(s)

- **Excipients**
  - Many commonly used pharmaceutical excipients are in amorphous state (like cellulose, starch, PVA, fumed silica, povidone, etc.)
  - In general, amorphous excipients are well characterized
# Amorphous vs. Crystalline Solids

- **Key Pharmaceutical Relevant Properties**

<table>
<thead>
<tr>
<th>Properties</th>
<th>Crystalline API</th>
<th>Amorphous API</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy State</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Physical Stability</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Chemical Stability</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Hygroscopicity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Purity</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Characterizability</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Process Scalability</td>
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<td>Low</td>
</tr>
<tr>
<td>Process Reproducibility</td>
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<td>Low</td>
</tr>
<tr>
<td>Solubility</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Dissolution Rate</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Process and Formulation Process-ability</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>Development and Manufacturing Risks</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

* Generally true
The Main Pharmaceutical “Amorphous Challenges”

- **Physical stability (as it is thermodynamically unstable)**
  - Keeping desirable amorphous component for better bioavailability
  - Identifying a co-processing agent to stabilize amorphous API to achieve best bioavailability and understanding the mechanism
  - Avoiding unwanted amorphous component in crystalline API synthesis and product formulation processes
  - Identifying the key kinetic stability factors to avoid conversions

- **Physical characterization**
  - Amorphous material, usually, is poorly understood and characterized
  - Detecting the trace level of amorphous API in crystalline matrix or vise versa
  - Identifying characterizable performance/quality indictor(s) for QbD
  - Understanding the interaction between API and co-processing agent(s)

- **Processing and Handling**
  - Extra efforts, comparing to crystalline API

- **No amorphous API until it is necessary!**
Common Amorphous Physical Characterization Techniques

- **(sub)-Molecular (or Micro-) level techniques:**
  - Vibrational spectroscopy: Raman, FT-IR, Near IR
  - ssNMR spectroscopy
  - Electronic microscopy (TEM and STM)

- **Particular (or Meso-) level techniques:**
  - PXRD
  - Thermal analysis (DSC and MDSC, TSC)
  - Optical/Electronic microscopy (SEM, EDOX)

- **Bulk (or Marco-) level techniques:**
  - Moisture and solvent sorption
  - Solubility
  - Powder techniques: particle size distribution, particle morphology, surface area, density, flowability, compressibility, wetability, etc.
Characterizing Amorphous Solids by PXRD

- PXRD is an extremely powerful tool for studying crystalline materials.
- Due to the lack of three dimensional structure, the typical amorphous PXRD patterns are characterized by one or two halos in the range we usually measure; no simulated PXRD pattern for amorphous material (except the PDF or other modeling methods).
- The shape, position, intensity and numbers of “amorphous halo” are unique to each amorphous material and may reflect the degree of material’s “amorphization” (disorder); different amorphous patterns for different amorphous state?
- Unlike commonly used for crystalline materials, it is difficult to use PXRD as a “finger-print” technique, for amorphous materials.
- A material’s amorphous characteristics (like the degree of disordering) are usually confirmed by diffraction techniques (commonly PXRD), prior to the measurements by other techniques.
An Amorphous API PXRD Pattern

The diagram shows a plot of intensity (counts) against two-theta (degrees) for a PXRD pattern. There are two key peaks indicated:

- **d ~ 4Å**
- **d ~ 8Å**

These peaks are critical for understanding the amorphous nature of the API and its crystal structure.
Indomethacin Grinding Experiments*

Amorphous Excipient PXRD Patterns

Unwanted Amorphous Component in Crystalline API

The changes on crystalline peak intensities can be used for a quant method for crystallinity change.

Amorphous “halo”
Undesired Amorphous Component in Crystalline API

- Moisture is a powerful tool to detect the amorphous component, even at trace levels
- Materials which have amorphous are usually hygroscopic
- In this case:
  - Particles swell slightly during water adsorption
  - Samples dried @ elevated T take up more H₂O than those dried @ ambient
  - Structural changes caused by higher T drying are not reversible (by PXRD)
Stabilizing the Amorphous API
- Two Component Amorphous System

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Trace Crystalline API in Amorphous Matrix
- A feasibility study

The linearity and detection limit can be determined for a quant method
Even Better with High Power Instrument (TXS)

0% and 2% samples showed no crystalline peak(s) by regular diffractometers for this system.
Sign of Crystalline Component?

Useful to detect the early sign of crystallization

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Differential Scanning Calorimetry

- Detects the melting temperature and heat of fusion for crystalline component, and glass transition temperature (Tg) for amorphous component

- **Pros**
  - Can be used as a quant method for crystallinity
  - Excellent tool for studying amorphous material’s Tg changes

- **Cons**
  - Sample homogeneity can be an issue
DSC Thermogram of A Two Component Pharmaceutical system

* Tg can be extracted from the DSC or mDSC curves
* Gordon-Taylor equation can be used to study the API and co-processing agent interactions
Vibrational Spectroscopy

- Secondary techniques
- Detects the short range local structural changes (probing the atomic interactions inside/between the molecules)

- Pros
  - Very sensitive tools for studying the interactions between the API molecules and co-processing agent or excipients for physical stability purpose
  - Can be used as a convenient tool for quant method or potentially for PAT applications

- Cons
  - Hardly been used alone
  - Data interpretation can be very challenging
Raman Spectrum
- crystalline vs. amorphous API

Amorphous API
1650 and 1610 cm\(^{-1}\) – stretching vibrational carbonyl groups

Crystalline API

The up-shift above 1640 cm\(^{-1}\) of the amorphous material with respect to the crystalline material indicates that the amorphous material is likely to have a greater energy in the carbonyls and as such may be less hydrogen-bonded.
ssNMR

- The primary tool to probe the material’s structural changes
- It probes the specific nucleus and their inter-/intra-molecular environment; the spectroscopic change reflects the changes occurred in the immediate environment of the nucleus

Pros
- Should be very sensitive to the short range changes, especially by relaxation time measurements
- A excellent tool for basic amorphous material understanding
- Can be used as the quant method

Cons
- High level of expertise
- Data interpretation can be very difficult
- An expensive technique (instrument running time)
ssNMR Spectra
- Crystalline vs. amorphous API*


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Conclusions

- Pharmaceutical amorphous systems are very challenging, but can offer advantages if handled well.
- The PXRD pattern of amorphous material reflects its “structure” features.
- Any changes in amorphous PXRD patterns may represent the changes in the materials.
- PXRD can be used as a primary technique for amorphous material studies.
- Other physical characterization techniques probe the different structural properties of amorphous materials and should be used as the complementary tools.
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