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

Shawn Yin, George Crull, Martha Davidovich, Denette Murphy, Anisha Patel, Beth Sarsfield, Ray Scaringe, Boris Shekunov and John Grosso

Solid-State Chemistry Group
Analytical Research and Development
Research and Development
Bristol-Myers Squibb Co.
New Brunswick, New Jersey, USA

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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

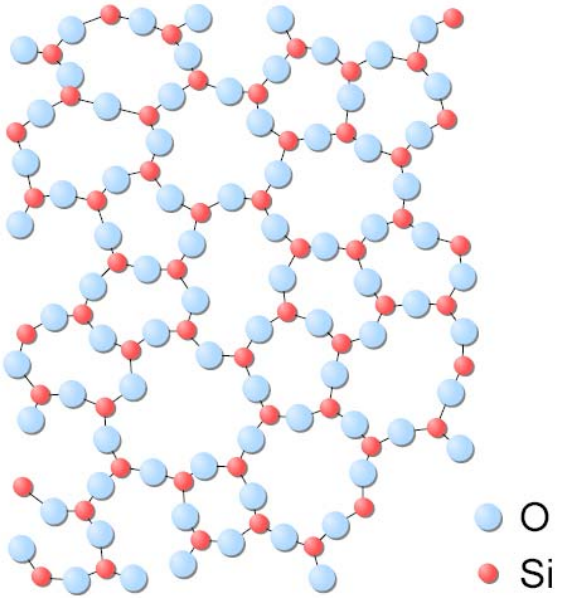
- **Pharmaceutical solid substances:**
  - **API, API Intermediates, excipients, mixtures (granules, tablets), etc.**
- **Physical states:**
  - **crystalline, amorphous, their mixtures (semi-crystalline) and liquid crystal**
- **Properties:**
  - **stability, solubility, crystallinity, hygroscopicity, dissolution rate, bioavailability, powder properties, etc.**

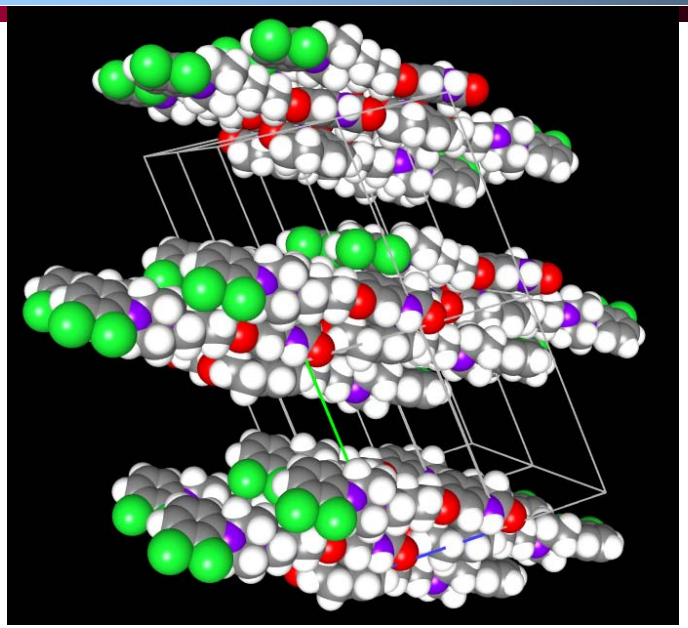
Crystalline and Amorphous Solids

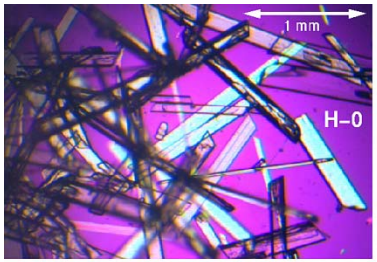
- **Crystalline solid:**
  - **Solid having a regularly repeating arrangement of the positions of atoms or chemical entity (atoms and molecules).**

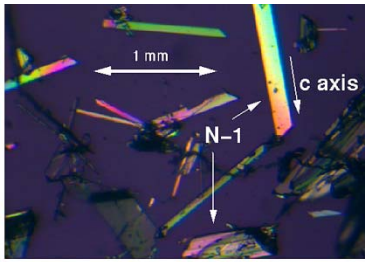
- **Amorphous solid:**
  - **An amorphous solid is a solid in which there is no long-range order of the positions of the atoms. Usually, amorphous materials have some short-range order at the atomic length scale due to the nature of chemical bonding.**

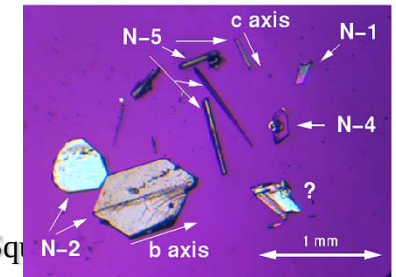
Amorphous and Crystalline Solids

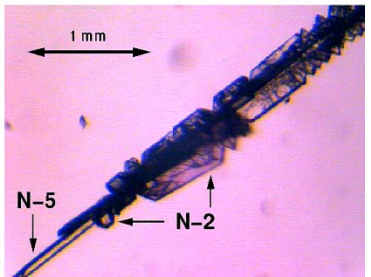












Amorphous Pharmaceutical Solids

- **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*

Properties	Crystalline API	Amorphous API
Energy State	Low	High
Physical Stability	High	Low
Chemical Stability	High	Low
Hygroscopicity	Low	High
Purity	High	Low
Characterizability	High	low
Process Scalability	High	Low
Process Reproducibility	High	Low
Solubility	Low	High
Dissolution Rate	Slow	Fast
Bioavailability	Low	High
Process and Formulation Process-ability	Good	Poor
Development and Manufacturing Risks	Low	High

* 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)**

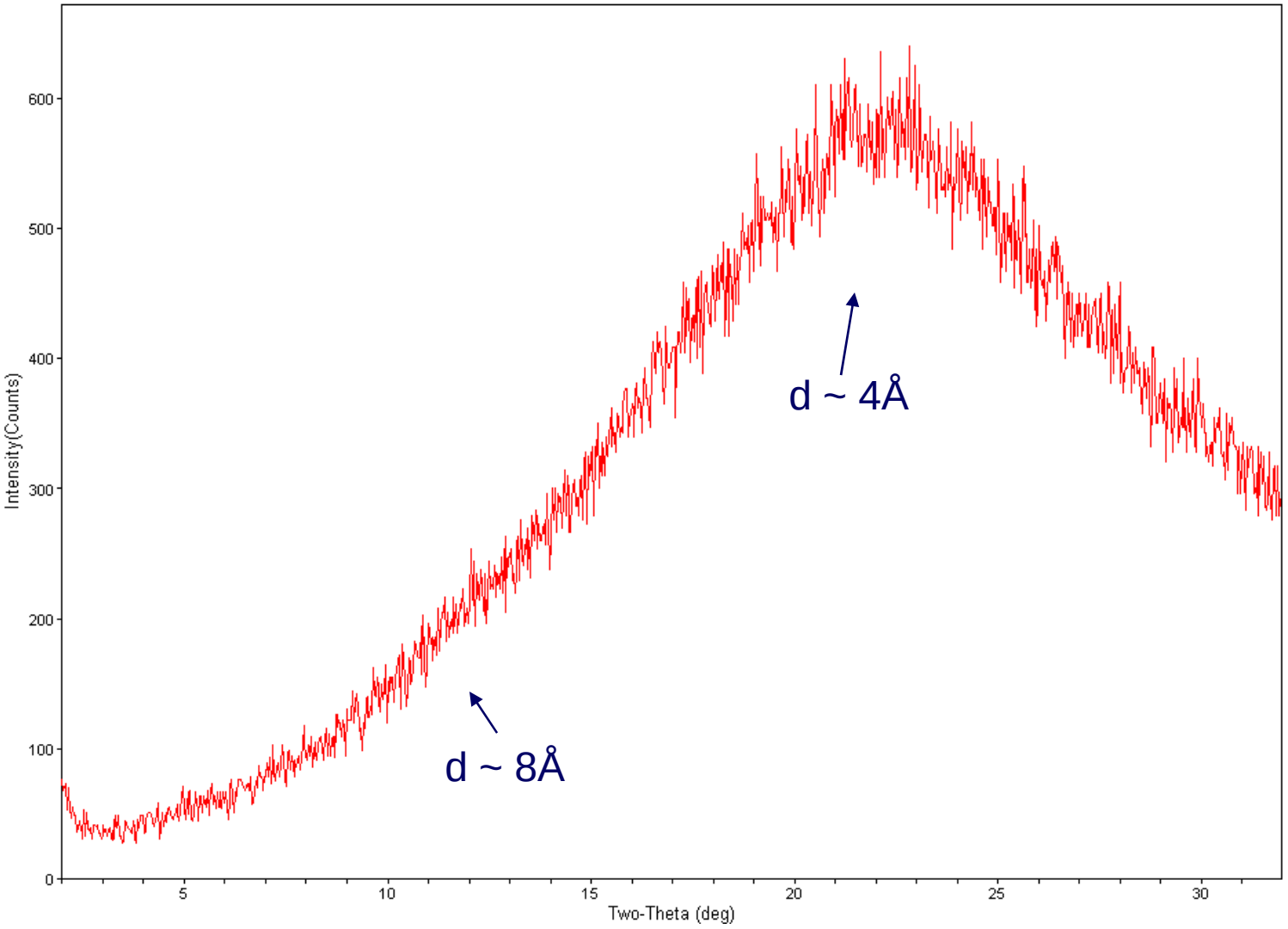
- **Particular (or Meso-) level techniques:**
  - **PXRD**
  - **Thermal analysis (DSC and MDSC, TSC)**
  - **Optical/Electronic microscopy (SEM, EDOX)**

- **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



Indomethacin Grinding Experiments*

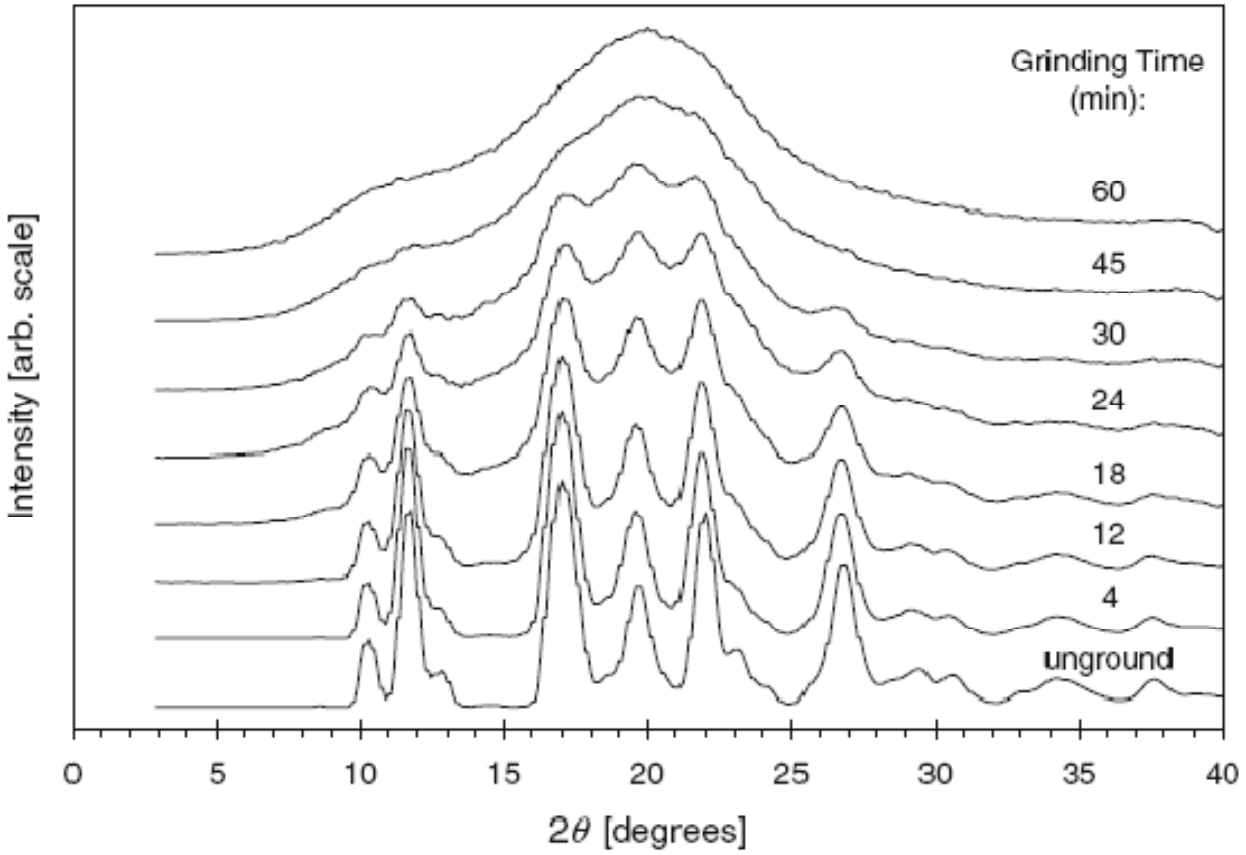
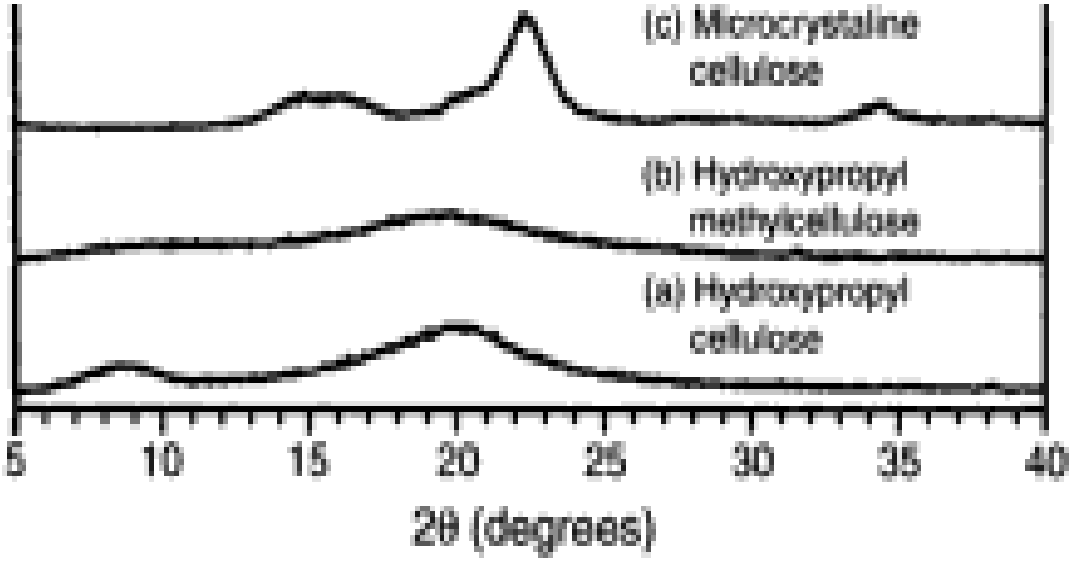


Fig. 5. XRPD patterns of unground and ground γ indomethacin (*bottom to top*); 4, 12, 18, 24, 30, 45, and 60 min of grinding. Note: no significant change in peak width is observed with increased grinding time.

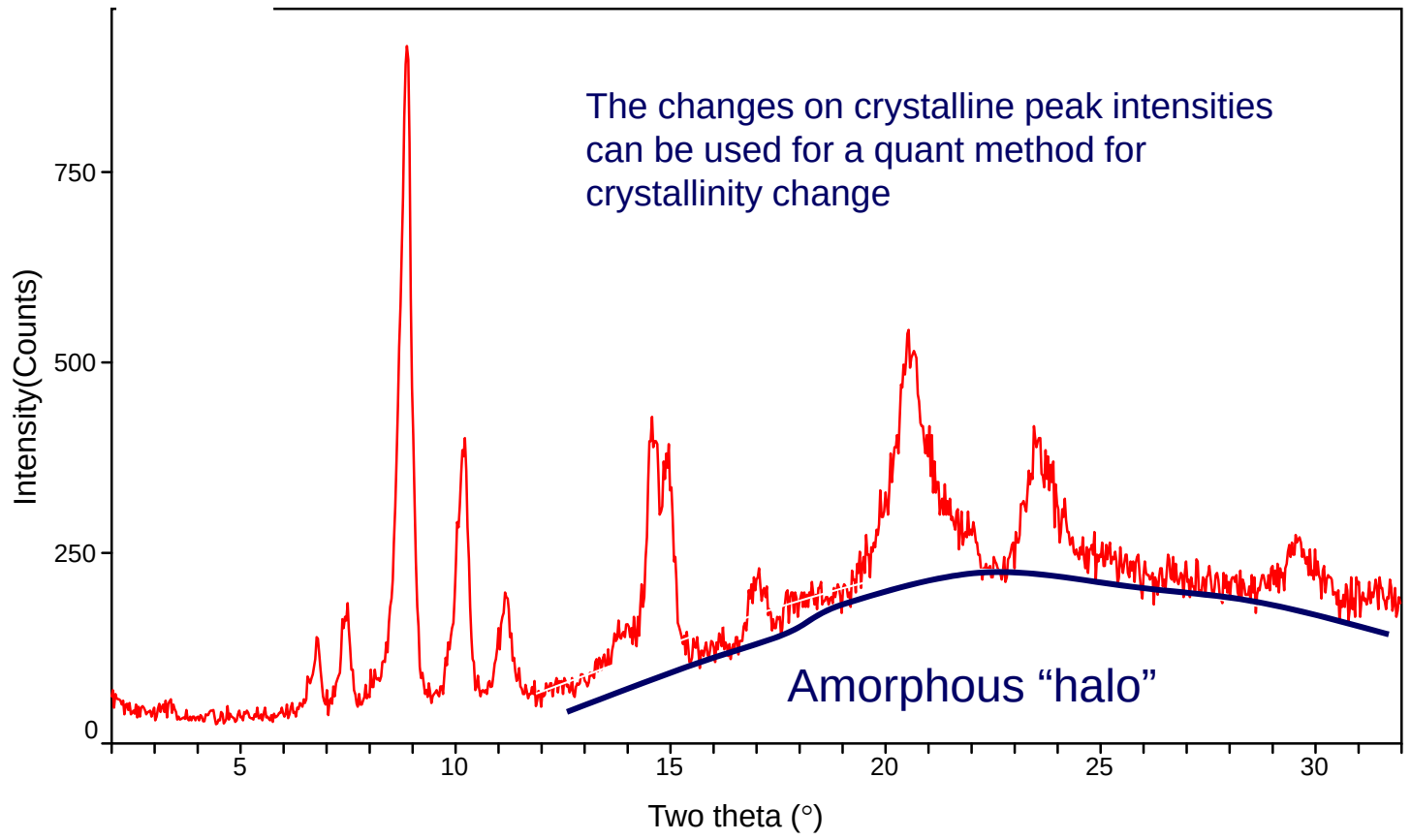
*S. Bates, G. Zografi, D. Engers K. Morris, K. Crownley & A. Newman, Pharm Res., Vol. 23, No. 10, 2333-2349 (2006)

Amorphous Excipient PXRD Patterns

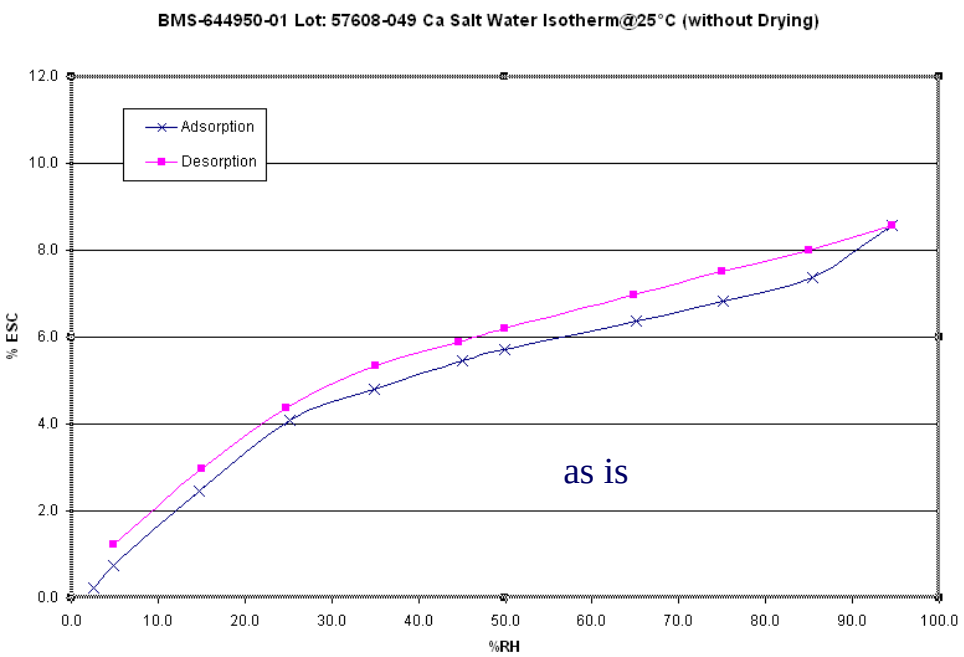


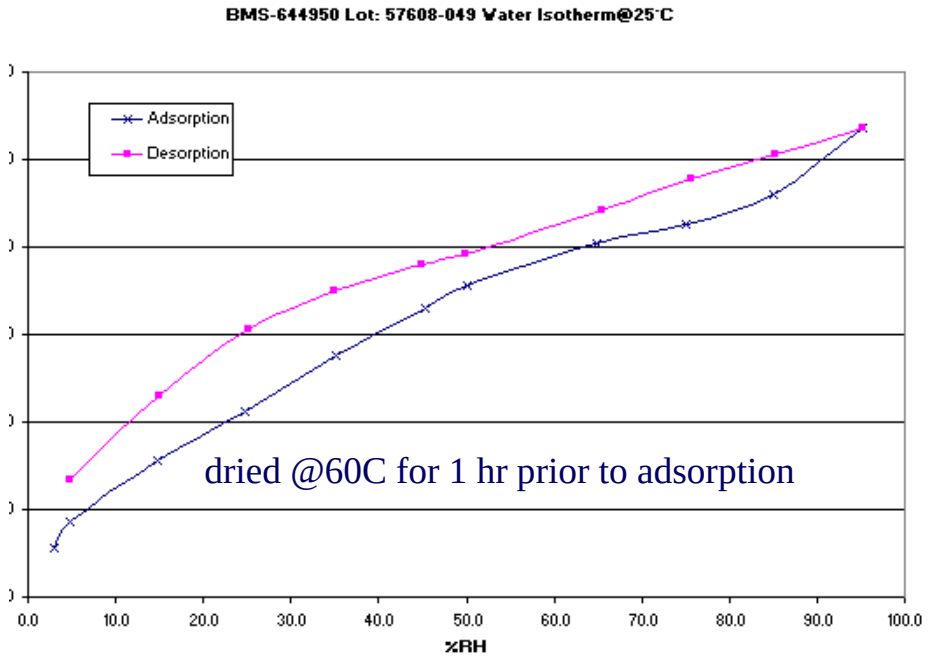
Encyclopedia of Pharmaceutical Technology, J. Swarbrick (ED), 3rd edition, pp4106

Unwanted Amorphous Component in Crystalline API



Undesired Amorphous Component in Crystalline API

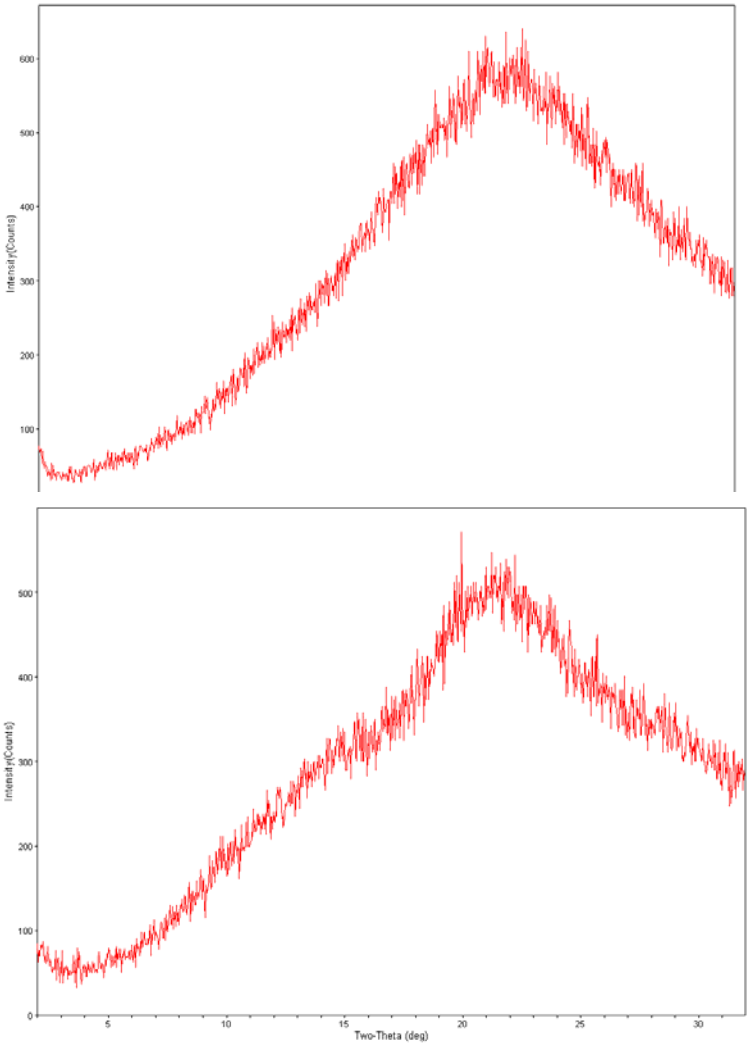


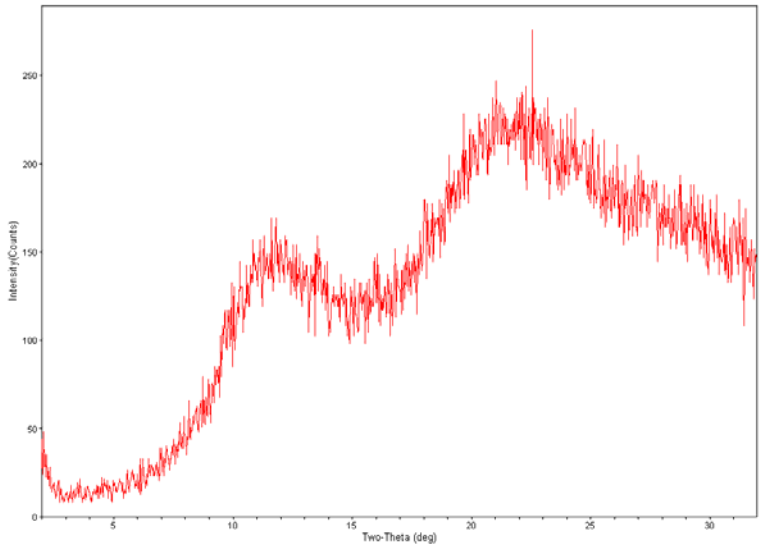


- Moisture is a powerful tool to detect the amorphous component, even at trace levels
- Materials which have amorphous are usually hygroscopic
- In this case:
  - Particles swell slightly during water adsorption
  - Samples dried @ elevated T take up more H_2O than those dried @ ambient
  - Structural changes caused by higher T drying are not reversible (by PXRD)

Stabilizing the Amorphous API

- Two Component Amorphous System





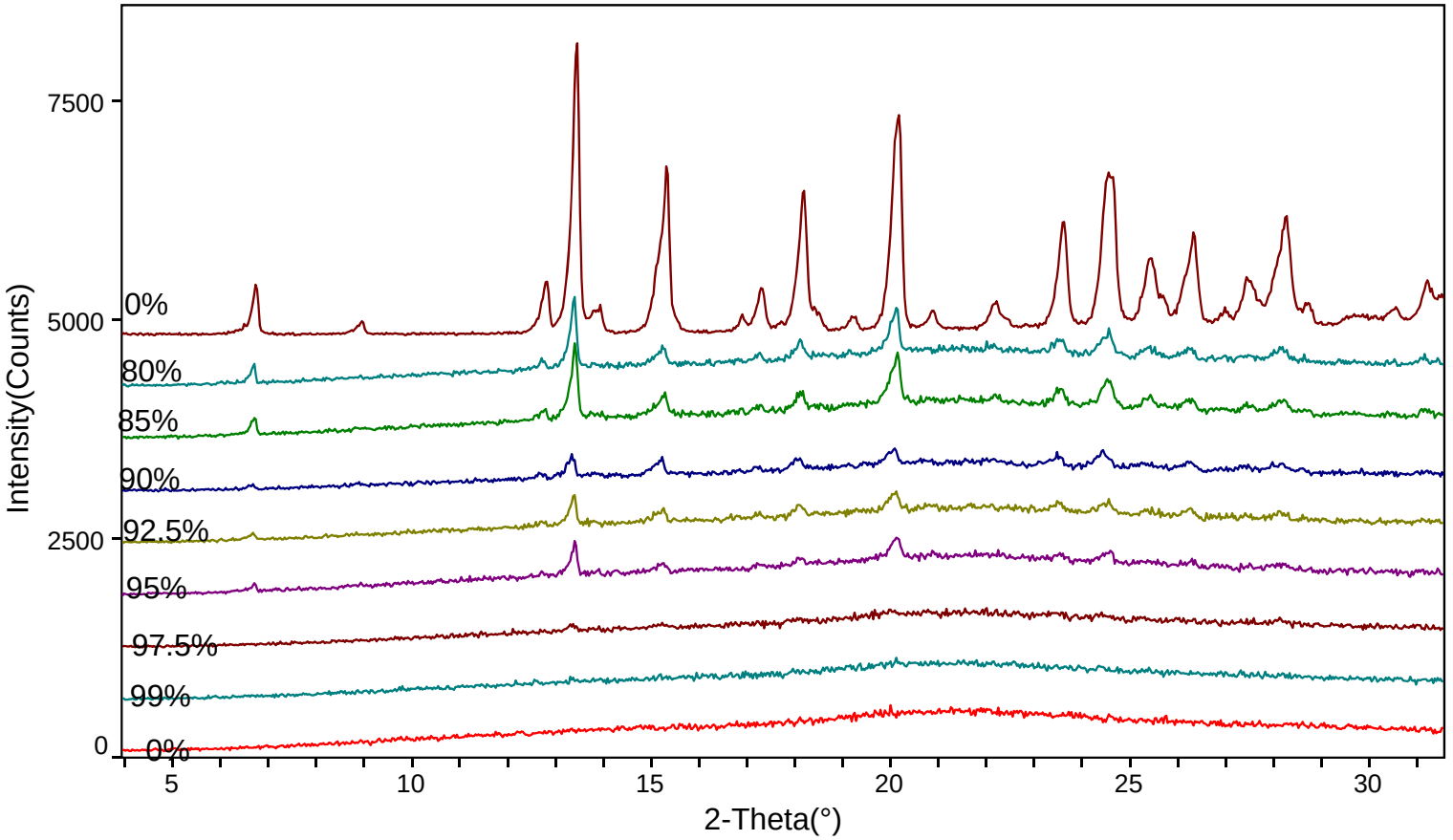
PVP

API

API + PVP

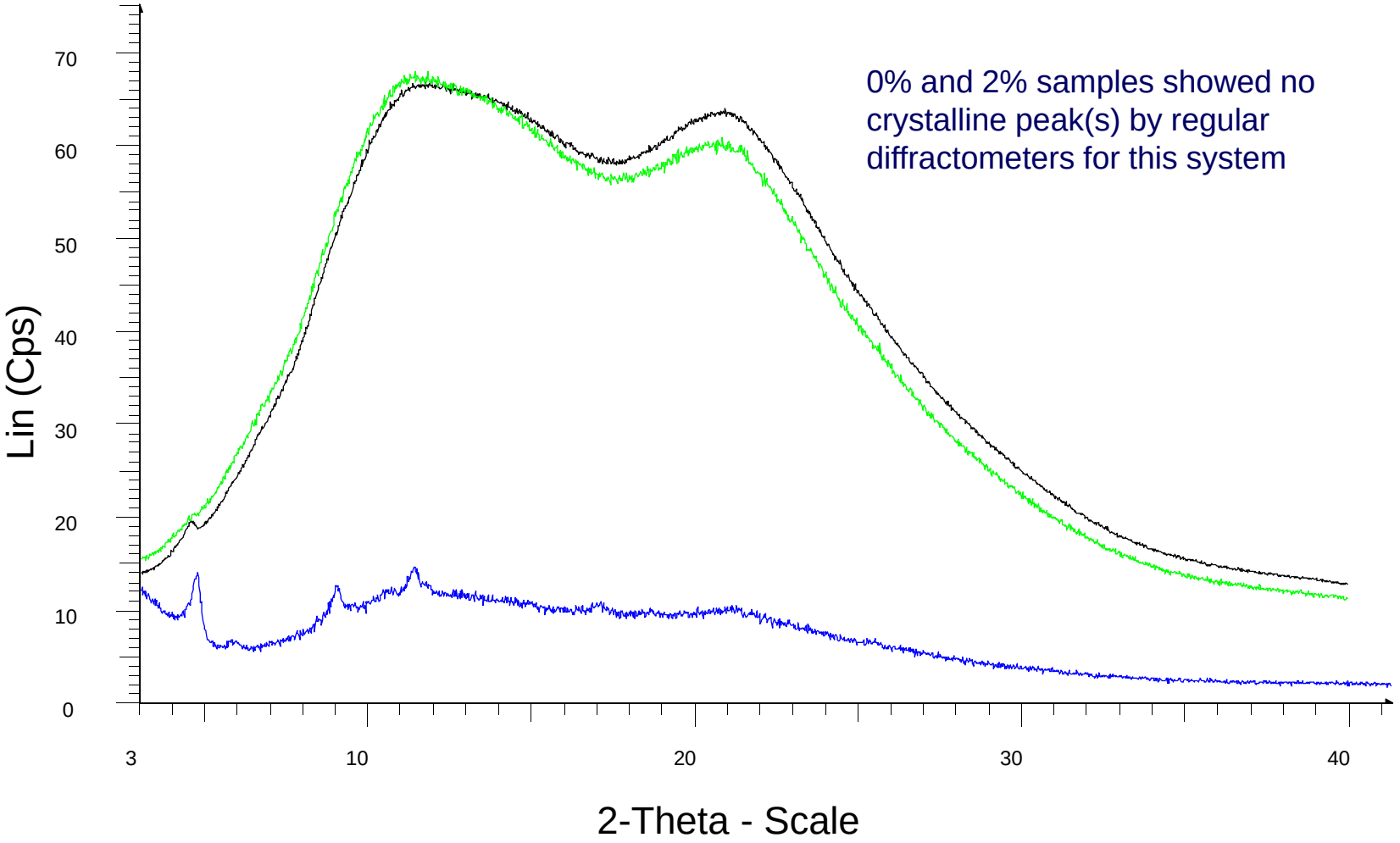
Trace Crystalline API in Amorphous Matrix

- A feasibility study

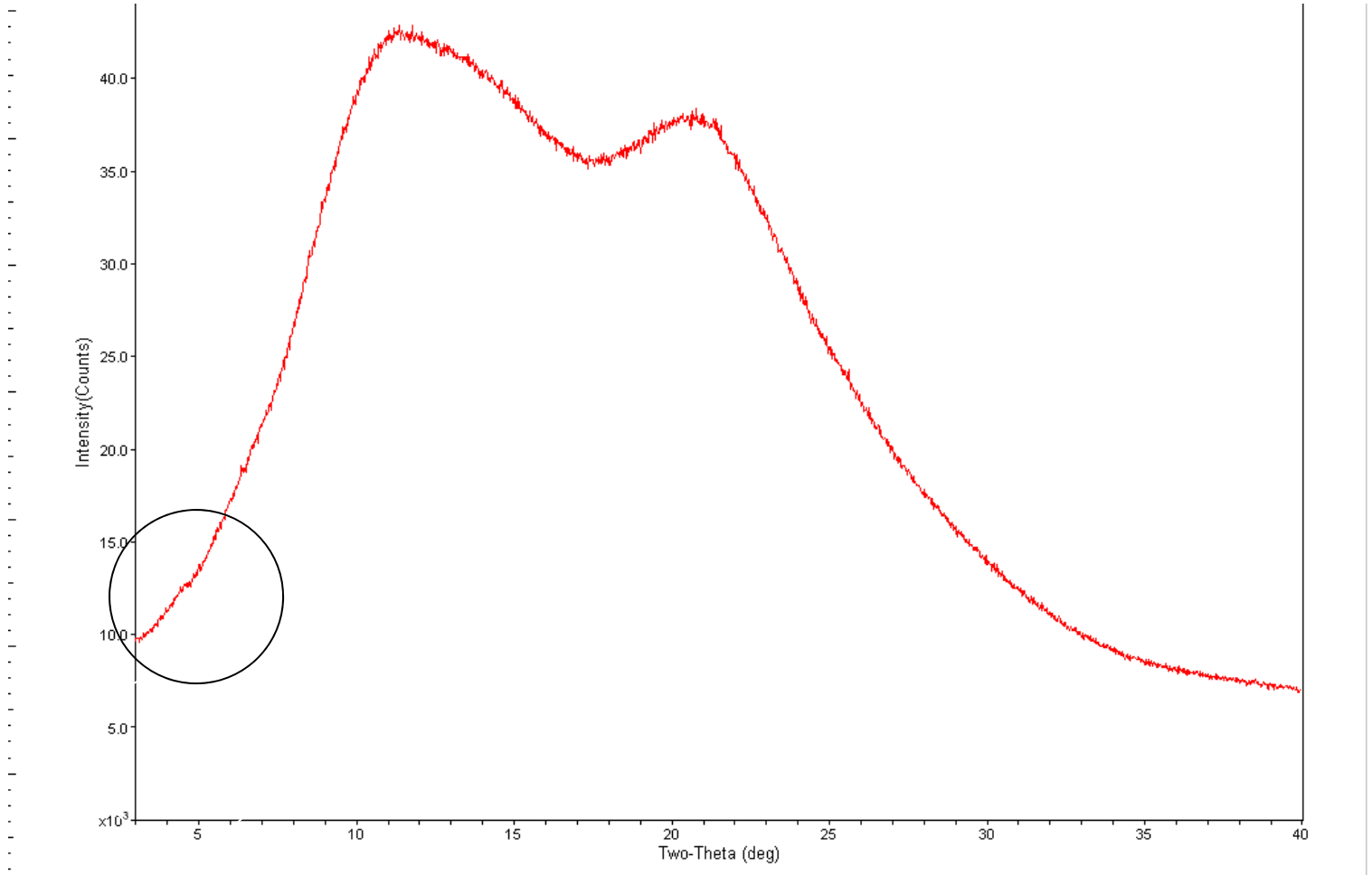


The linearity and detection limit can be determined for a quant method

Even Better with High Power Instrument (TXS)



Sign of Crystalline Component?

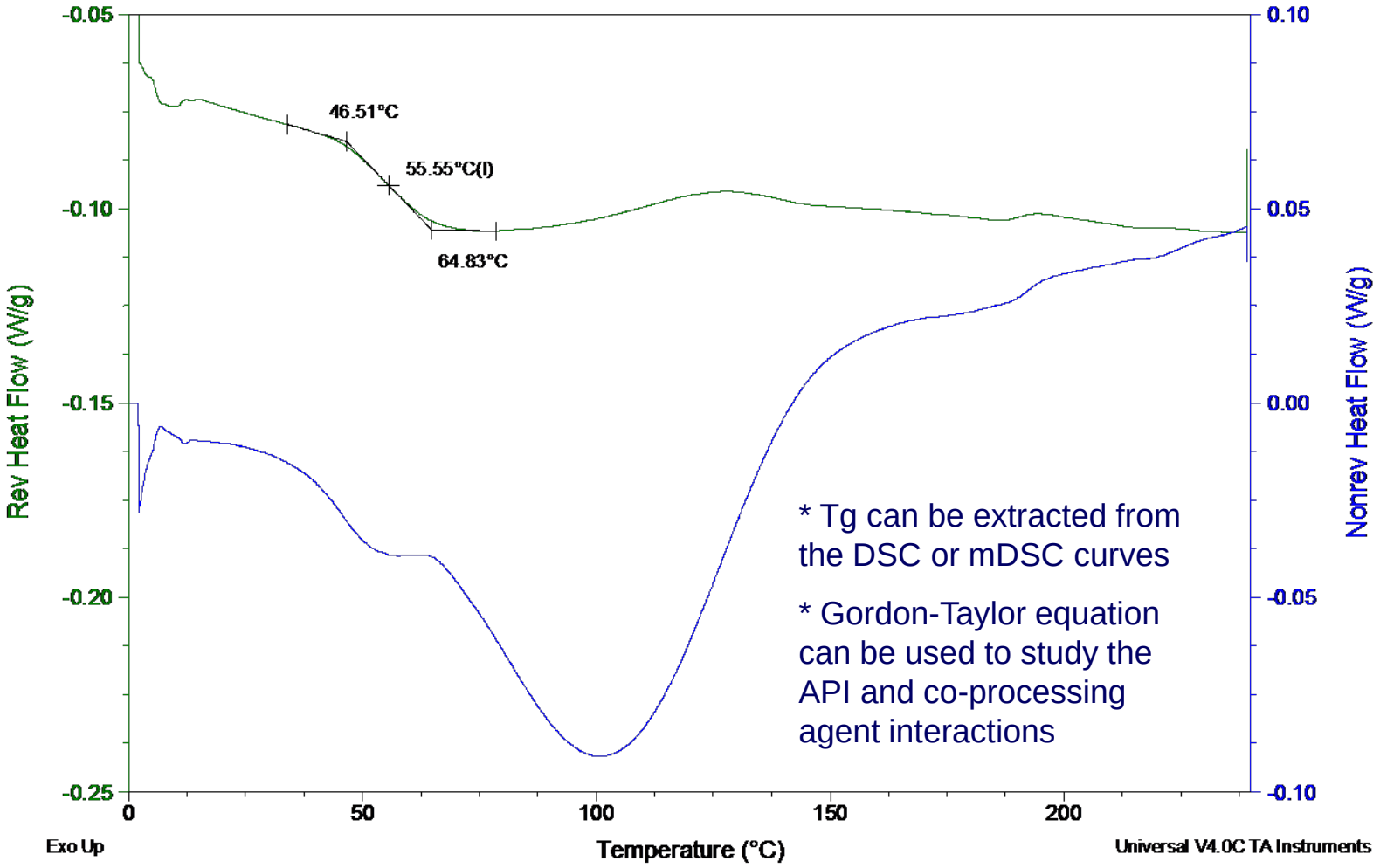


Useful to detect the early sign of crystallization

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



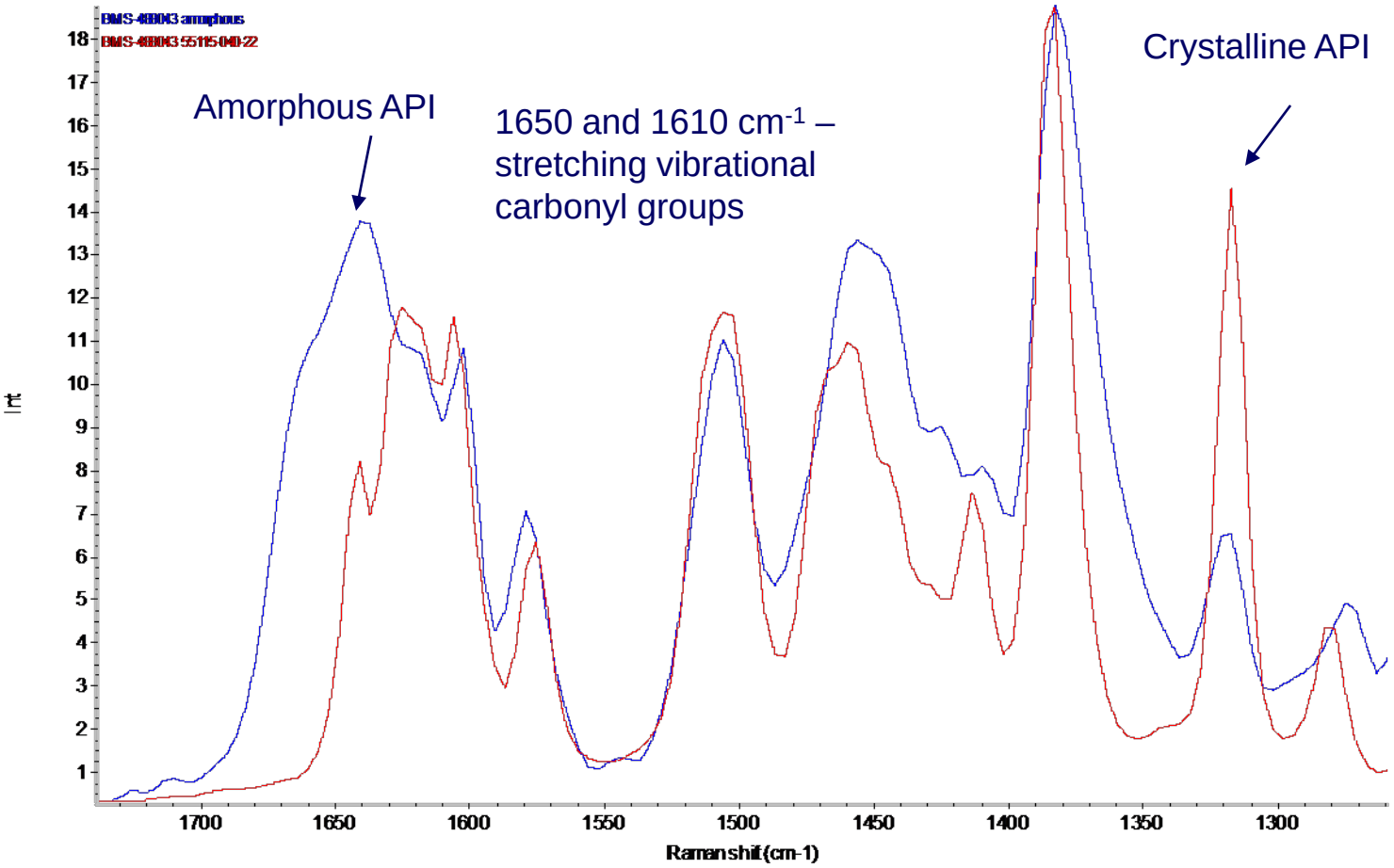
* Tg can be extracted from the DSC or mDSC curves

* 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



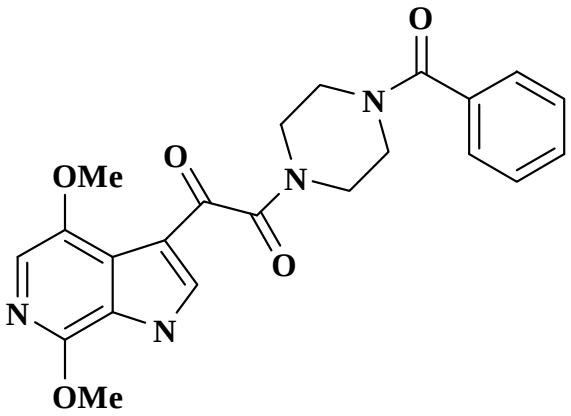
The up-shift above 1640 cm-1 of the amorphous material with respect to the crystalline material indicates that the amorphous material is likely to have a greater energy in the carbonyls and as such may be less hydrogen-bonded.

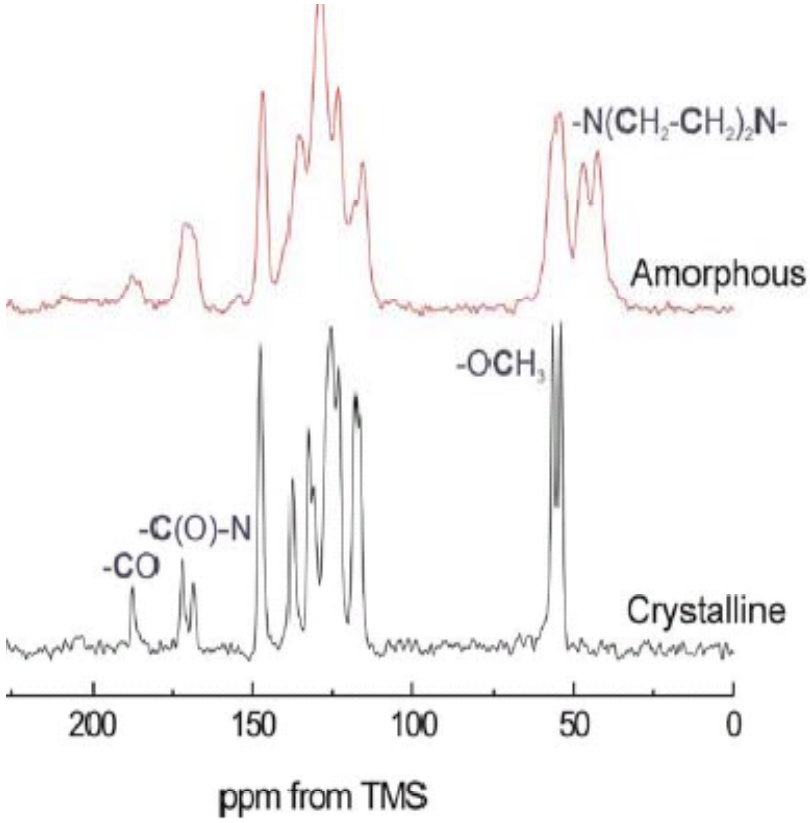
ssNMR

- 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*





* M. Tobyn, J. Brown, M. Fakes, Q. Gao, J. Gamble, Y. Khimyak, G. McGeorge, C. Patel, W. Sinclair, P. Timmins, S. Yin, ***J. Pharm Sci***, in print.

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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