PPXRD - 17 Workshop

Pharmaceutical Applications of Powder X-Ray Diffraction (Part I)

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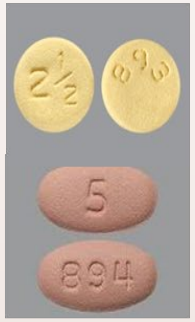
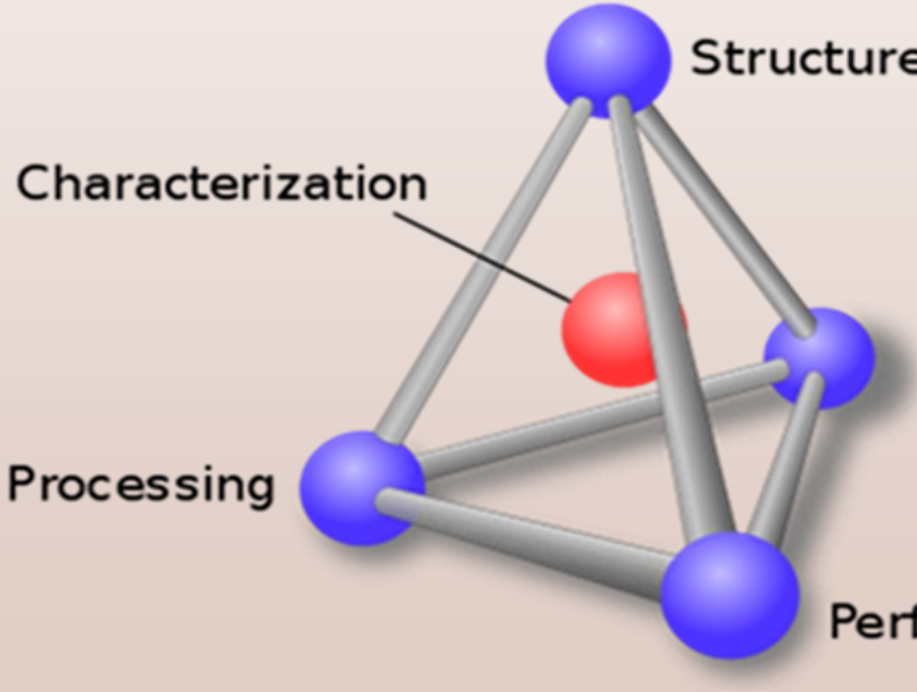
Agenda

- Pharmaceutical solid-state characterization and PXRD applications
- Simulating PXRD patterns and the case studies
- Using PXRD for API crystallite size estimation (if time allows)
- Anisha will cover everything else

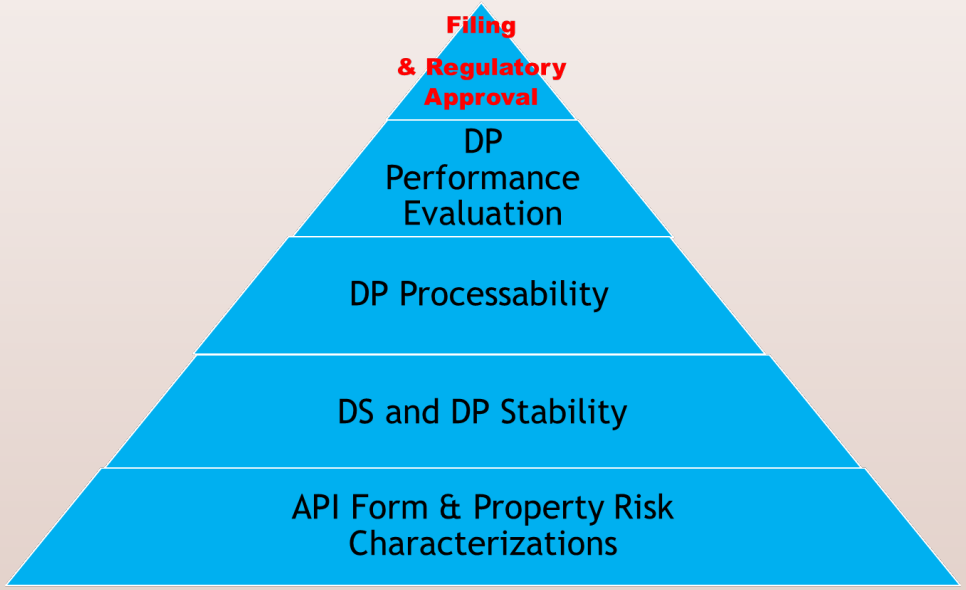
Solid State Characterization - What and Why





Solid State Characterization - When and What

- Up to First in Human (FIH), supporting
  - Drug discovery (crystalline vs. amorphous; compound ID etc.)
  - Preliminary crystal form screening and selection
  - “Fit for purpose” early-stage material strategy (including IND filing)
- Between FIH and New Drug Application (NDA), supporting
  - Commercial material/form selection
  - DS and DP risk assessments (i.e. stability and other risks)
  - Identifying DS/DP critical quality attributes
  - Qualitative and quantitative method development
  - Sample testing per GxP standards, non GxP tests
  - Commercial drug substance and product material strategies (including spec., methods, product regulatory and IP strategies)
  - NDA filing
- Post Approval, supporting
  - Product manufacturing trouble shooting (both DS and DP)
  - Product life cycle management (LCM)
  - Product/Brand protection



Critical Quality Attributes (CQA)

- A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. Ref. FDA Guidance for Industry Q8(R2) Pharmaceutical Development
- Examples of some relevant DS/DP CQAs
  - Purity, assay, potency
  - Dissolution rate
  - Water content
    - The hygroscopicity and hydration state of API (DS) are two different factors
    - Up to the mobility of water in crystal lattice/surface
  - Form (or the ratio if mixture), crystallinity, particle size distribution PSD (or surface area)
- We need to understand, prior to proposing form/crystallinity as CQAs or vice verse
  - The probability of API form/crystallinity change during DS/DP processes, stability studies and storage
  - The detectability of change
  - The impacts of change

Common Techniques for Pharmaceutical Solid-State Characterizations

- Diffractions (single crystal/powder)
  - X-ray, electron, etc.
- Thermal analysis
  - DSC (mDSC), TGA, TAM, DMA, etc.
- Spectroscopic
  - IR, NIR, Raman, ssNMR, Terahertz, etc.
- Micromeritics
  - Surface Area, Particle Size, iGC, Vapor Sorption (DVS), etc.
- Microscopy
  - Optical, SEM, cryo-EM, AFM, etc.
- Combinations
  - Hot-stage microscopy, VT/PXRD, DSC/PXRD, TG-IR/MS, Raman/VTI, etc.

- **Multi-disciplinary approaches**


In 1975 and 2001, before the Bell moved to its new homes, technicians x-rayed it for hidden flaws.
Left: Photograph, "X-ray of the Liberty Bell," by Eastman Kodak Company, 30 October 1975.
Right: Photograph, "X-ray of the Liberty Bell," by Conam Inspection, 27 April 2001.

Common Pharmaceutical Applications of PXRD

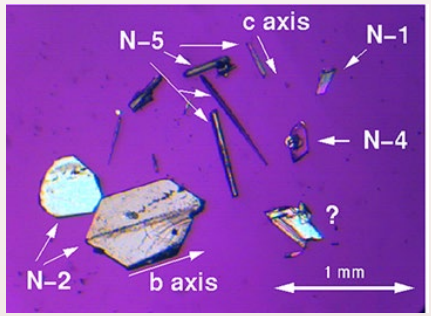
- PXRD is a primary, the golden standard, crystal form/structure/phase/polymorph identification technique, for API, excipient and drug product:
  - Qualitative (most of the time)
  - Quantitative form composition determination
  - Pure form or mixture of forms
  - Large or small sample quantity
  - Simple or no sample preparation
  - Non-destructive

- Plus
  - Crystallinity of solid materials (crystalline vs. amorphous)
  - Average crystallite size analysis (for crystallite size in the sub-micron to nanometer ranges)
  - Solving crystal structures from powder diffraction data
  - Powder pattern indexing for form/phase purity
  - Connecting observed patterns of unknow materials to the forms/structures predicated by CSP
  - Confirming reference standards for secondary techniques (FT-IR/NIR/Raman, ssNMR, DSC, etc.)
  - More……

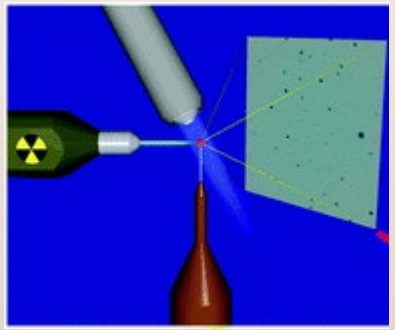
Connecting Common PXRD Applications to Pharma R & D

PXRD Applications	Amorphous/ Crystalline	Crystal Form ID (qualitative)	Composition and Structural Determination	DS, DP Development Support & Critical Quality Attributes	GxP Sample Analysis	Method Development (qualitative/quantitative), for Spec.	Regulatory Strategies and Filings	Data Package to Support IP Strategies
Drug Discovery	✓	✓	✓					
GLP Tox and FIH		✓	✓	✓	✓		✓	
Between FIH and NDA		✓	✓	✓	✓	✓	✓	✓
Post Approval		✓	✓	✓	✓	✓	✓	✓

Single Crystal X-ray Diffraction & Crystal Structures



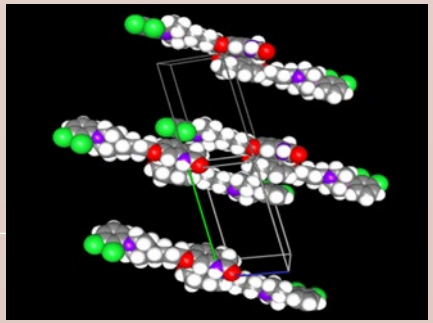
- Measure observed intensity
  - $I(hkl) \approx K F^2(hkl)$
    where K = scale factor and other set-up coefficients



- Extract structure factor
  - $F(hkl)_{obs} = \Sigma f_N \exp[2\pi i(hx_N + ky_N + lz_N)]$

- Perform reverse Fourier transformation
  - $\rho(xyz) = (1/V_c) \Sigma F(hkl) \exp[-2\pi i(hx_N + ky_N + lz_N)]$

- Extract atomic coordinates x,y,z

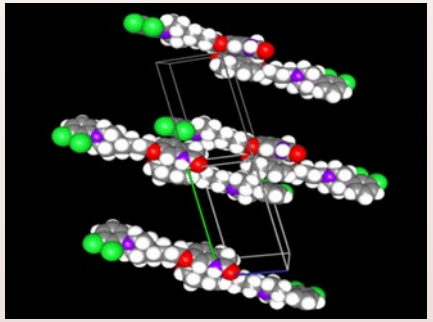


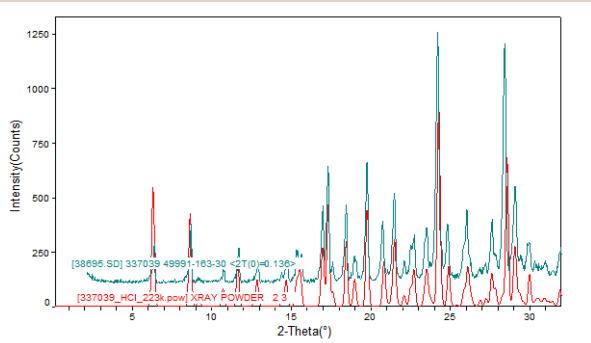
- 3D reciprocal space (hkl) to 3D direct space (xyz) for single crystal work

Simulating Powder XRD Patterns from Single Crystal Structures

- Solve (or model) crystal structure:
  - Derive atomic coordinates (xyz) (or from Cambridge Database)
- Structure factor:
  - $F(hkl)_{cal} = \Sigma f_N \exp[2\pi i(hx_N + ky_N + lz_N)]$ or $F(hkl)_{obs}$
- 3D calculated intensities (hkl):
  - $I(hkl) \approx K F^2(hkl)$
- 1D calculated intensities (2θ):
  - $I(2\theta) = K L(\theta) I(hkl) A(\theta)$
  - Bragg's Law: $2 d \sin\theta = n \lambda$

    where $I(\theta)$ is associated to I(hkl) by the relationships of (hkl), d and then Bragg's Law
- 3D direct space to 1D reciprocal space for PXRD
- Squeezing 3D into 1D (single crystal vs. powder diffraction data)





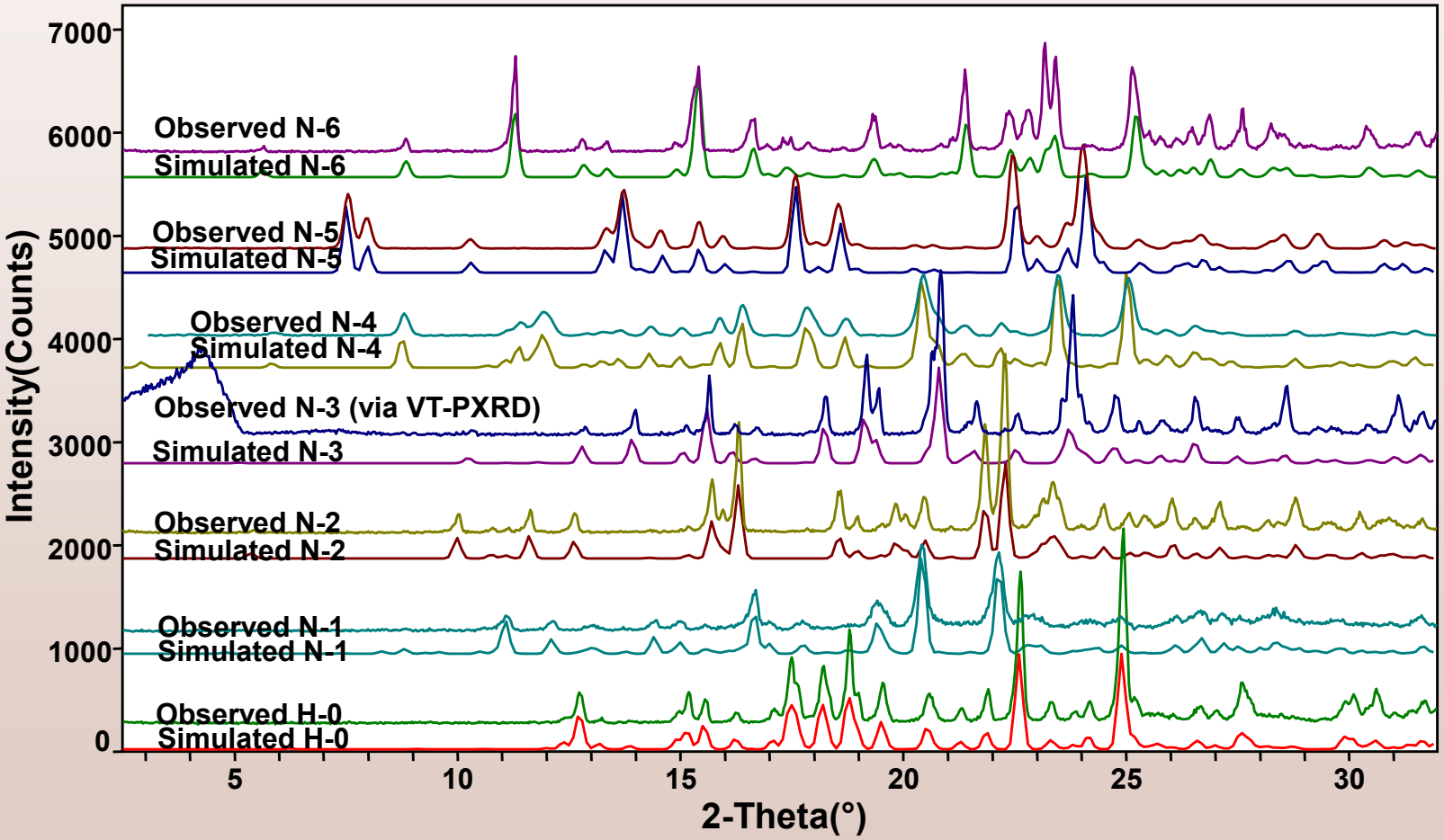
How to Simulate PXRD Patterns from Single Crystal Structures

- Can be done by most SCXRD and PXRD software
  - You need the unite cell parameters, space group, xyz, etc. from the cif file (SCXRD work)

- You also can use the $F(hkl)_{obs}$, if the single crystal structure can not be completely resolved

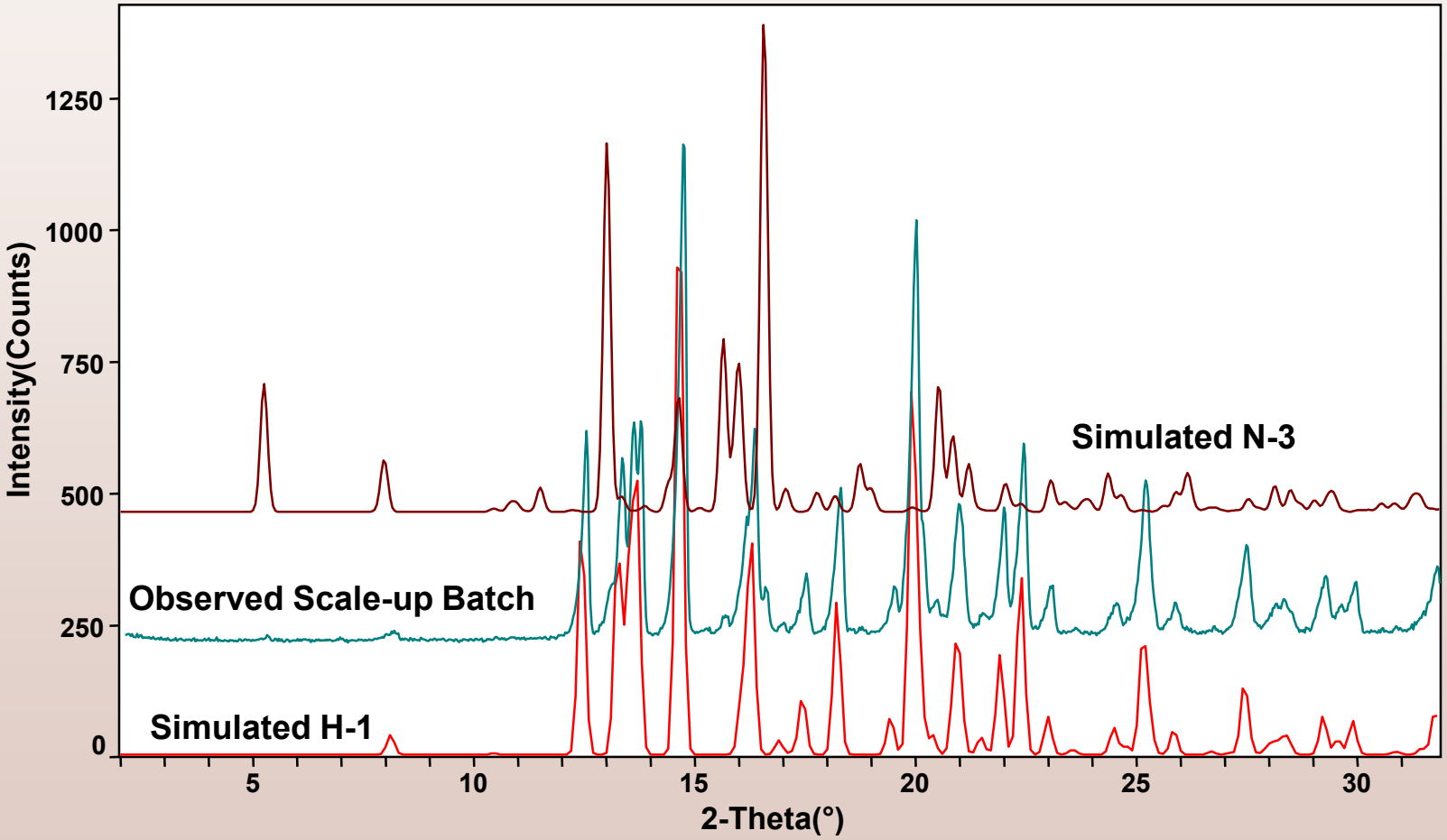
- The differences between simulated (of single crystal) and observed (of powder) may come from the differences of the samples, used for SCXRD and PXRD
  - There is a reason(s) of two patterns matched or not
  - Be curious, if not
  - Most of the issues: hydration state; tempateure; mixtures, preferred orientations (using Miller index file to help you), wrong sample.

Examples: Polymorphism & Pseudo Polymorphism



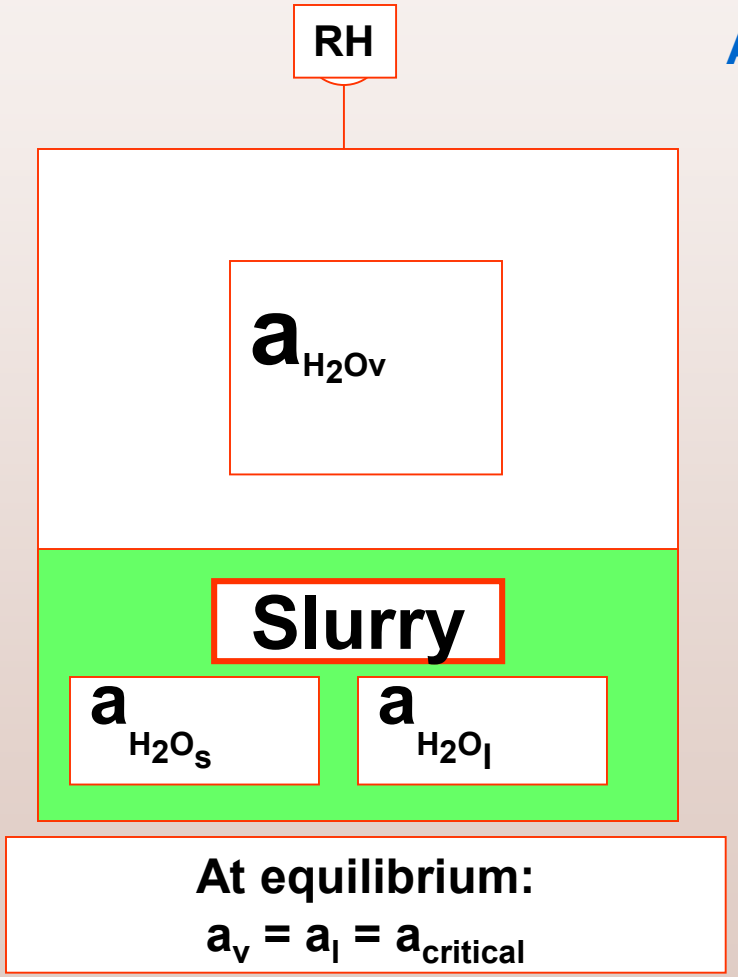
S. Yin, *9th Annual Polymorphism & Crystallization Scientific Forum*, Phila, PA, 2010

API Drying Process Control



S. Yin et. al., *Opinion in Drug Discovery & Development*, 11(6), 771-777 (2008)

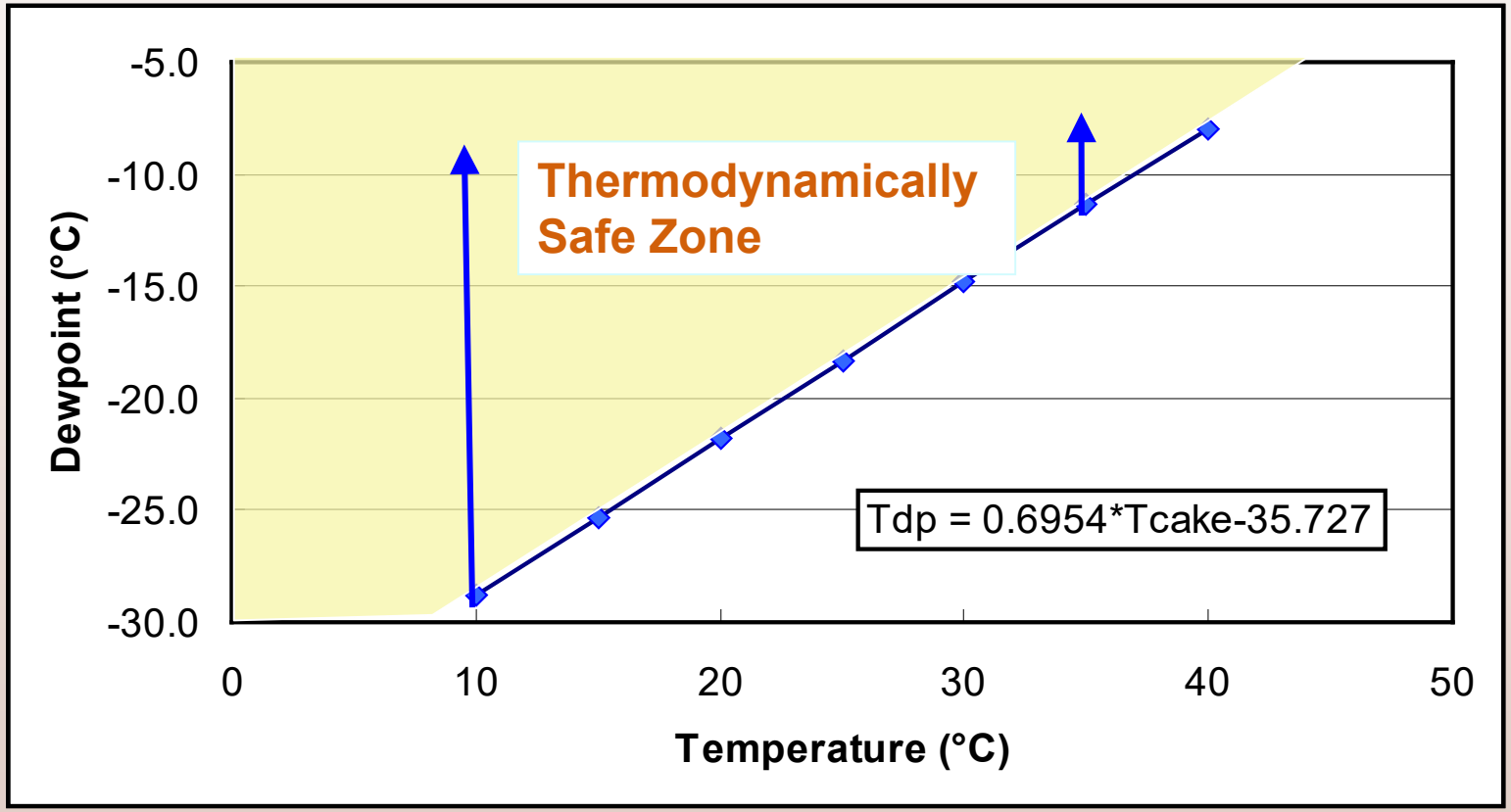
Drying A Hydrate
- The Thermodynamics



$A \cdot H_2O \leftrightarrow A + H_2O$

- Vary H_2O in slurry while observing form conversion
- Slurry approach minimizes mass transfer concerns
- Checked form by slurry PXRD:
  - H-1 -> N-3 favored for RH < 2%;
  - N-3 -> H-1 favored for RH > 9%
- On scale process drying studies suggested the same RH range for conversions between H-1/N-3
- Preliminary results indicate ~4.5%RH is thermodynamic limit (estimated with slurry exp., KF data and VLE calculator)

API Drying Process Control



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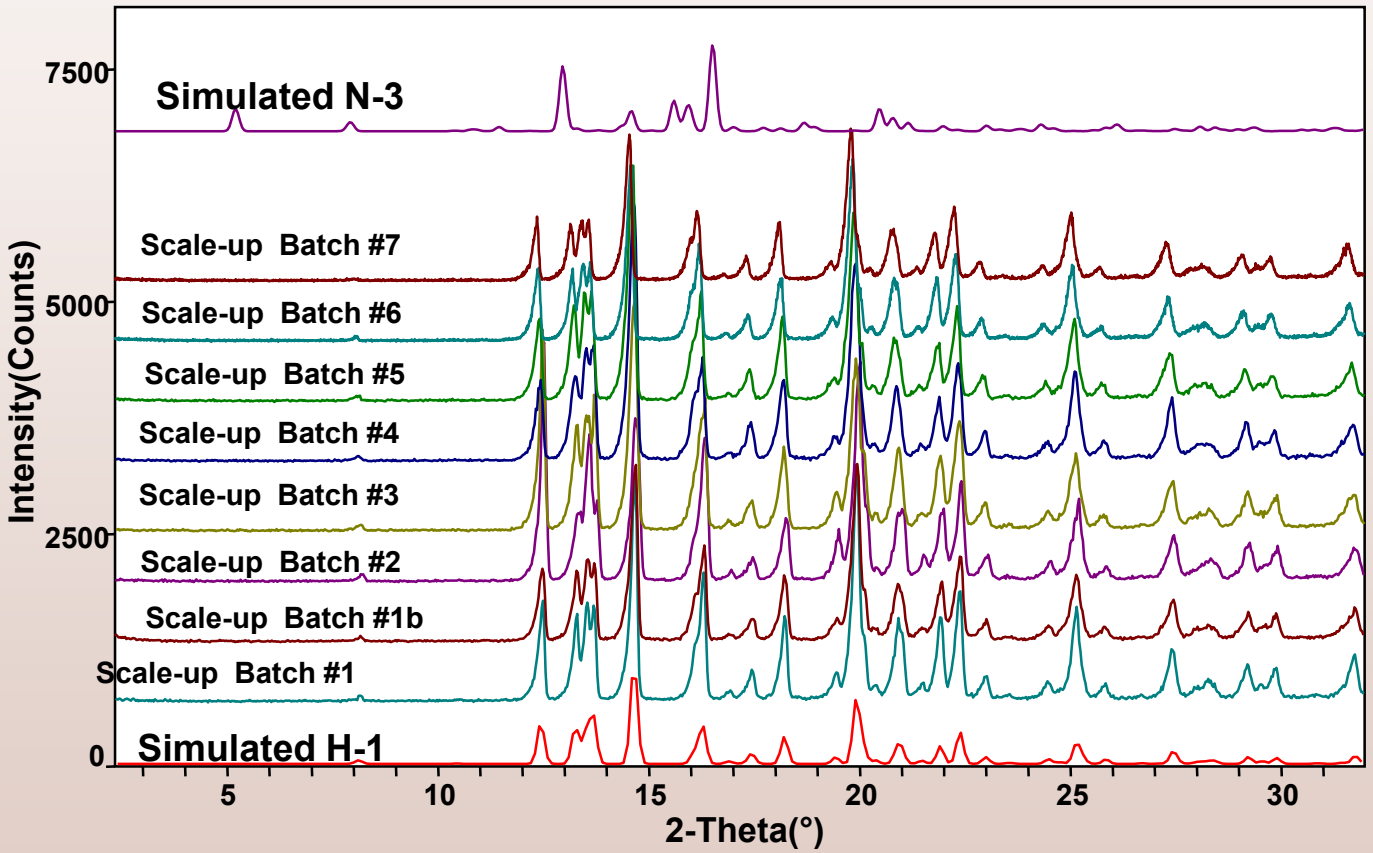


This case demonstrated that quality should be built into a product with an understanding of the CQAs of product and process

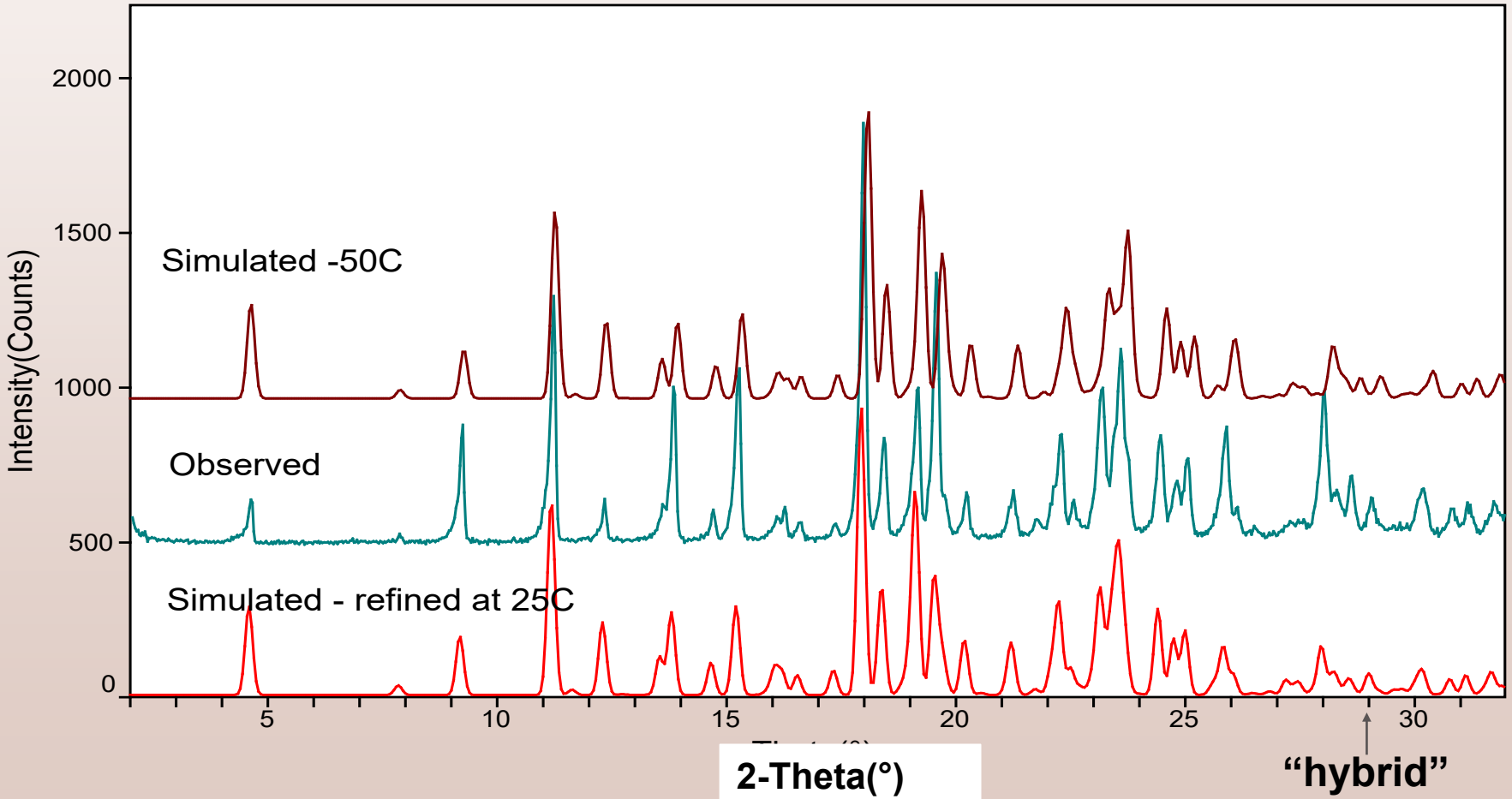
S. Yin et. al., *Opinion in Drug Discovery & Development*, 11(6), 771-777 (2008)

Thermal Study - Variable Temperature PXRD
- Problems

- PXRD pattern change can be
  - Sample displacement shift due to sample movement
  - Cell expansion (contraction) due to temperature change
  - Possible phase transition(s)
  - Possible degradation at elevated temperatures

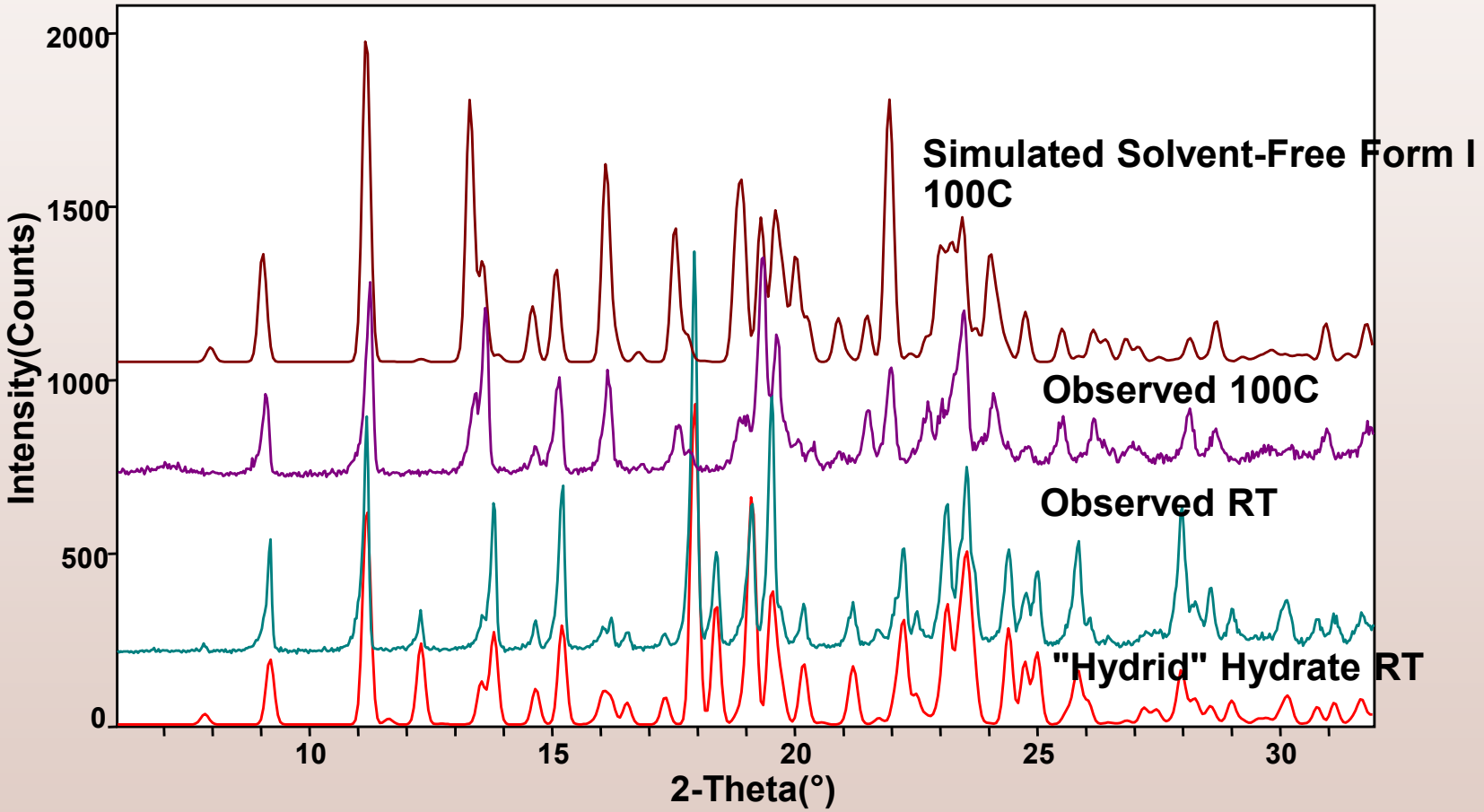
Simulated vs. Observed PXRD Patterns

- Refine the simulated pattern



S. Yin et. al., *American Pharmaceutical Review*, Vol.8, Issue 2, p56-62, (2005)

Thermal Study - Variable Temperature PXRD



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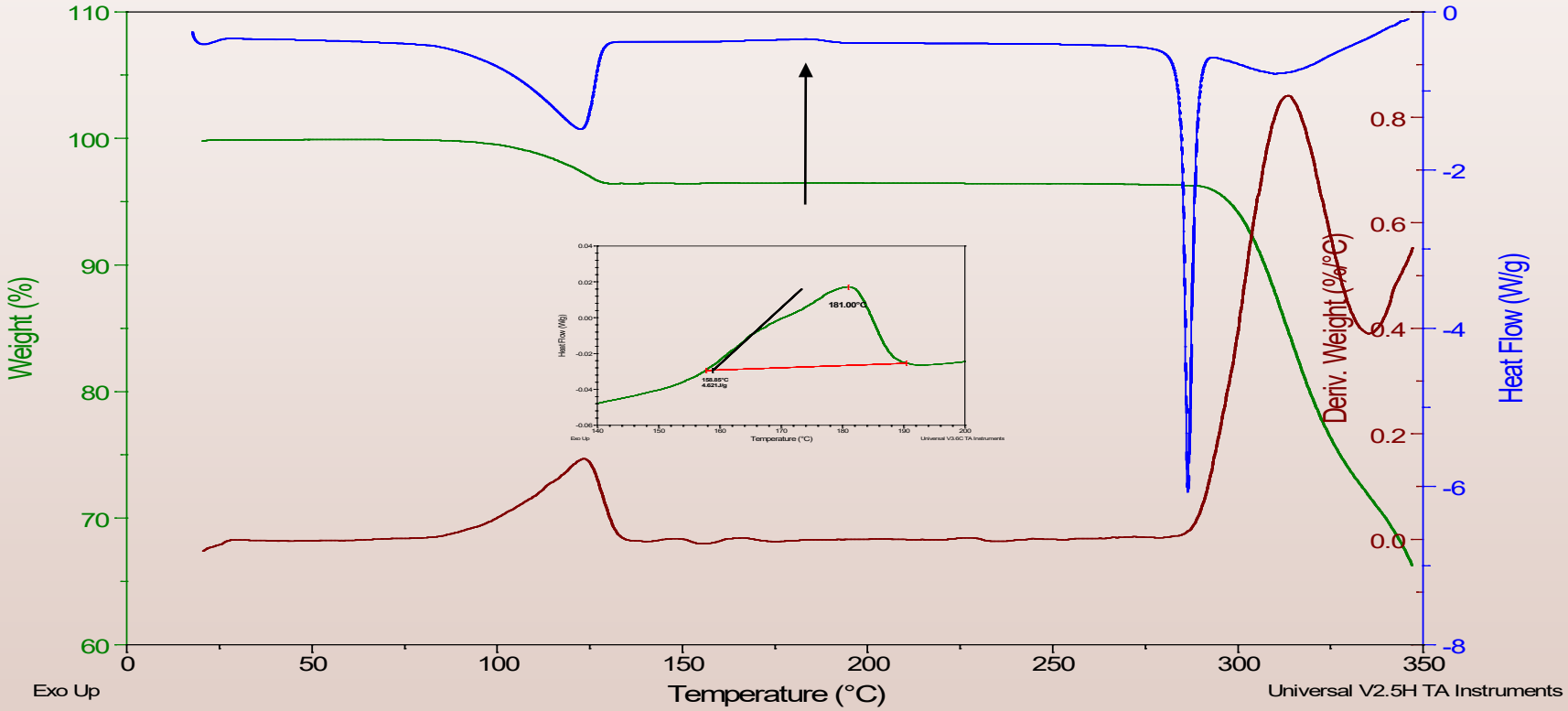
Thermal Study - Variable Temperature PXRD

- Thermal Analysis Confirmation



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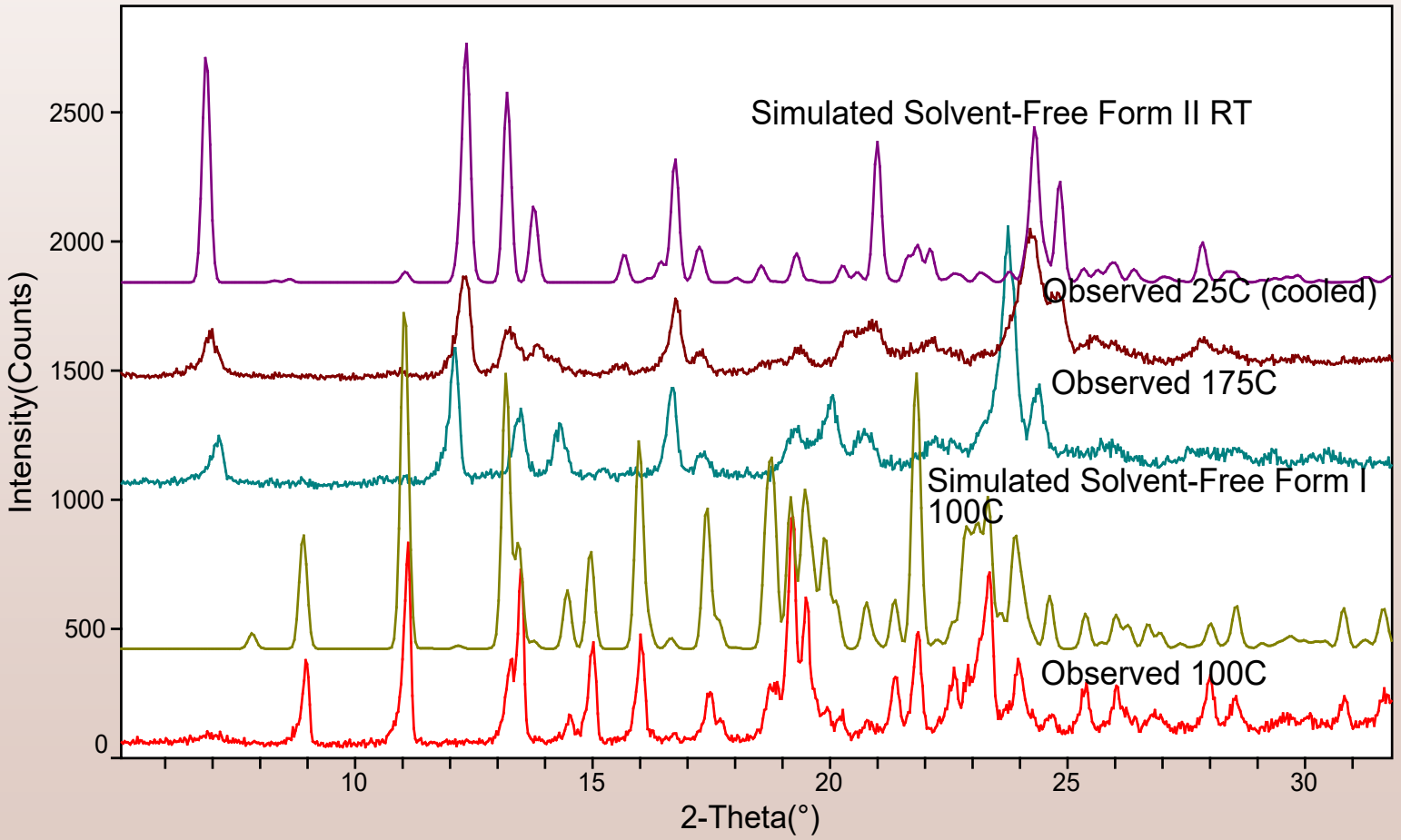

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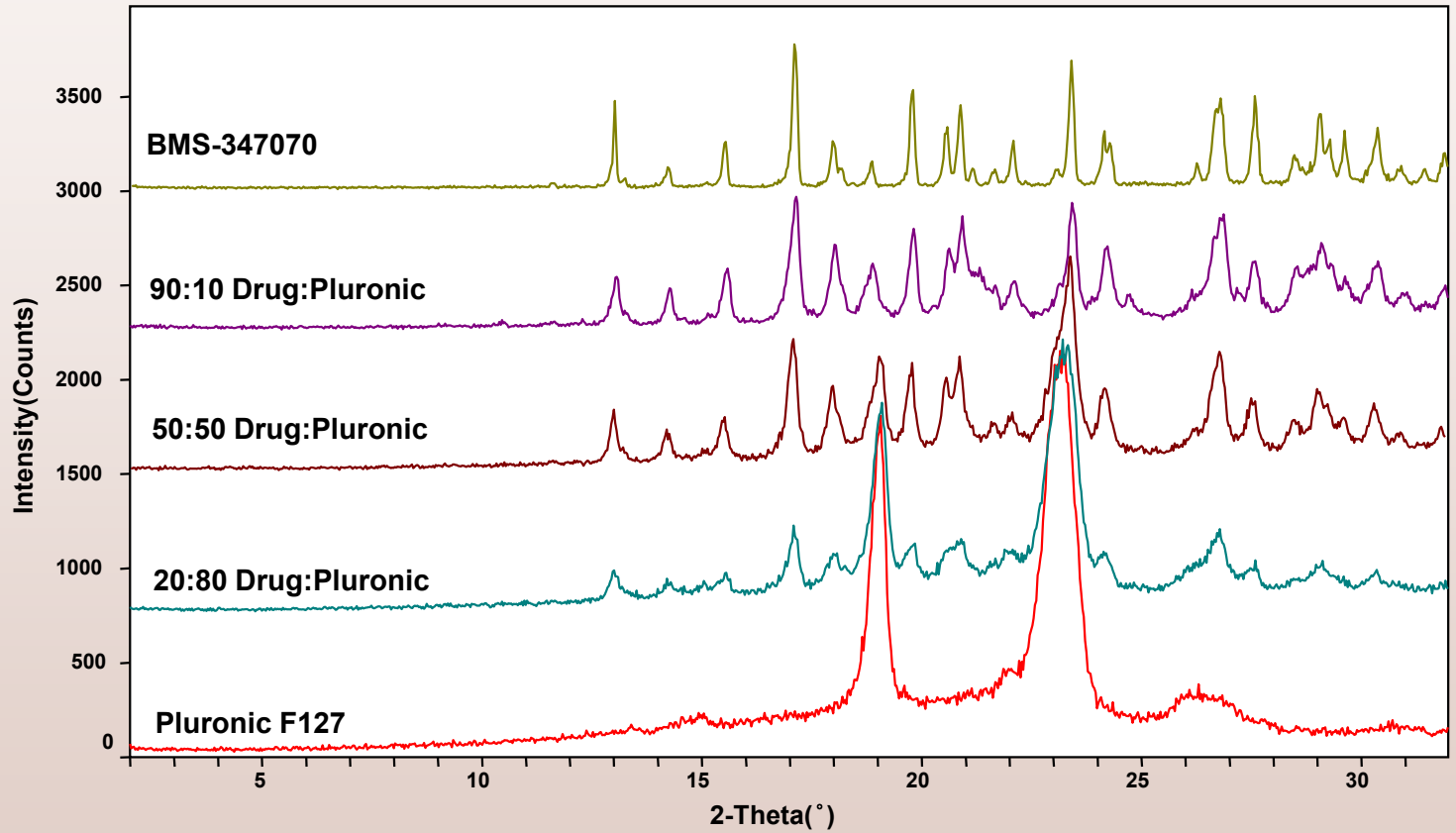
Backup Slides

PXRD Patterns of Spray Dried Samples

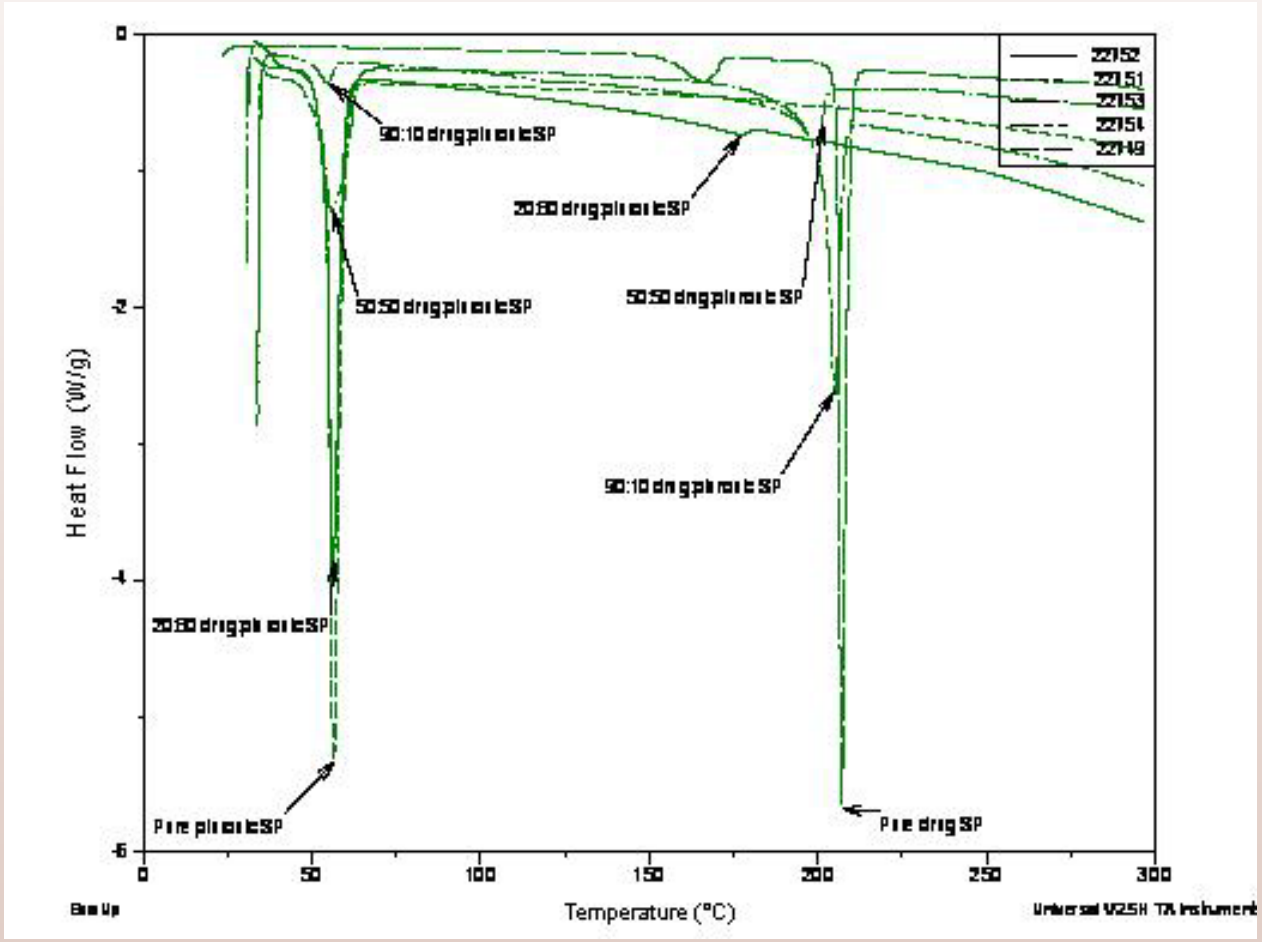


Both crystalline drug and Pluronic are found in the SDD samples by PXRD

The metastable API form was formed in the system

* S. Yin et. al. *J. Pharm. Sci.*, 2005, Vol. 94, No. 7, 1598-1607

DSC Thermograms of Spray Dried Samples



Both crystalline drug and Pluronic are found in the SDD samples by DSC

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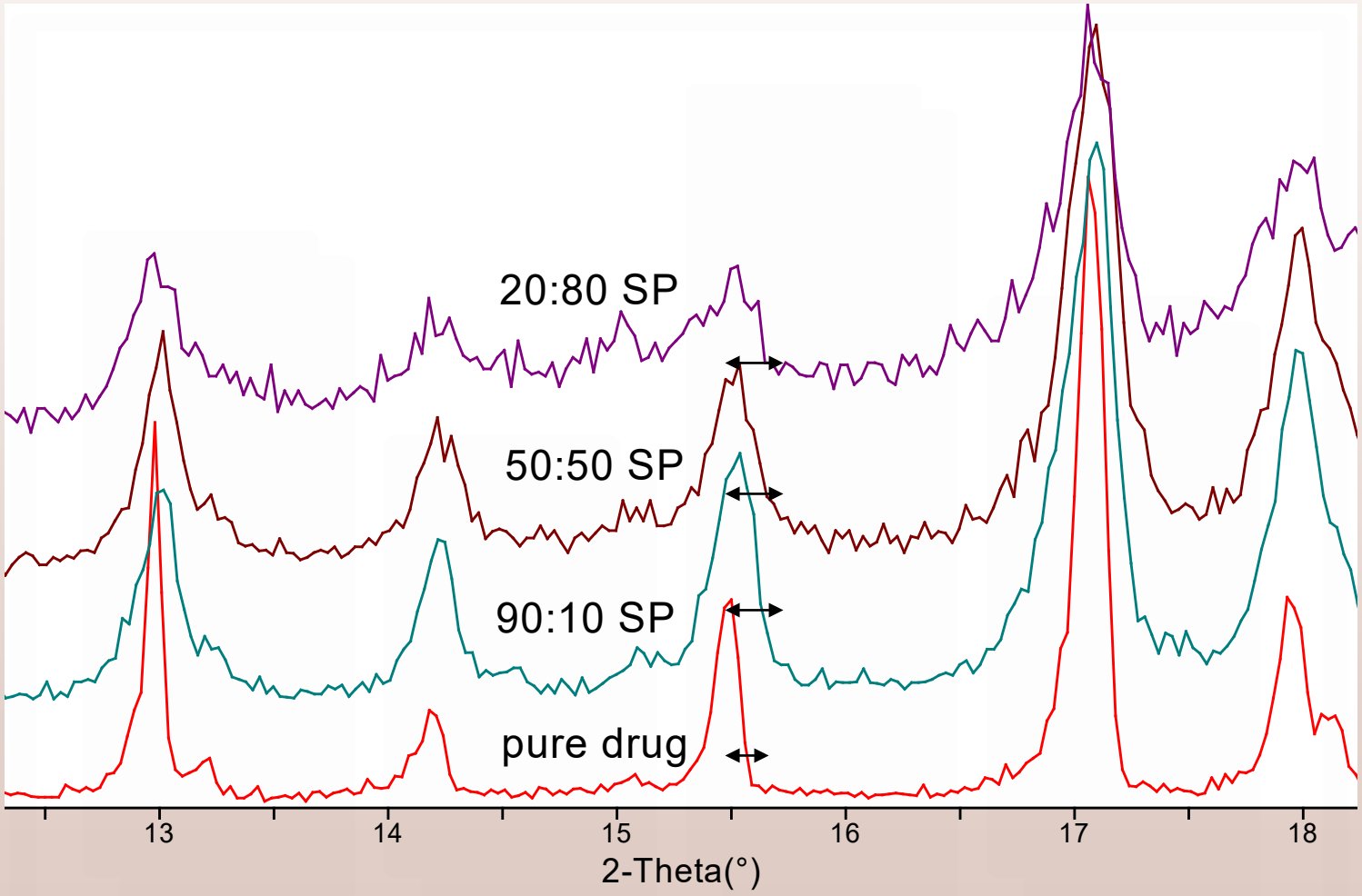
PXRD Patterns of SDD Samples



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Scherrer's Equation

$$\tau = (K\lambda)/(\beta_\tau \cos\theta)$$

τ - crystallite dimension

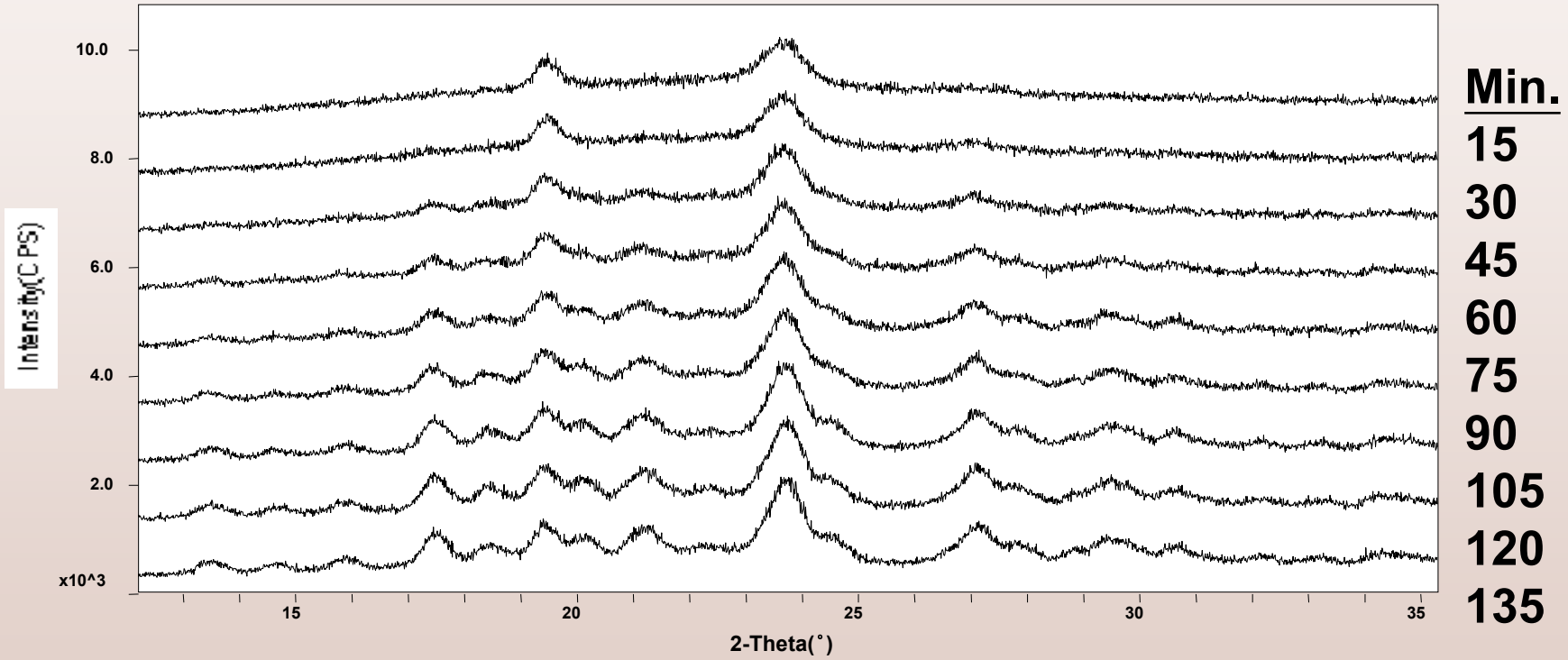
K – shape factor (~0.9) ; λ - the wavelength;

β_τ - line broadening due to the effect of small crystallites

Base on Scherrer's equation, the crystallite size reduction of crystalline drug (assuming that all the peak broadening is caused by crystallite size reduction):

Pure drug (averaged above 5 μm) > Pluronic SP (averaged ~ 60 nm)

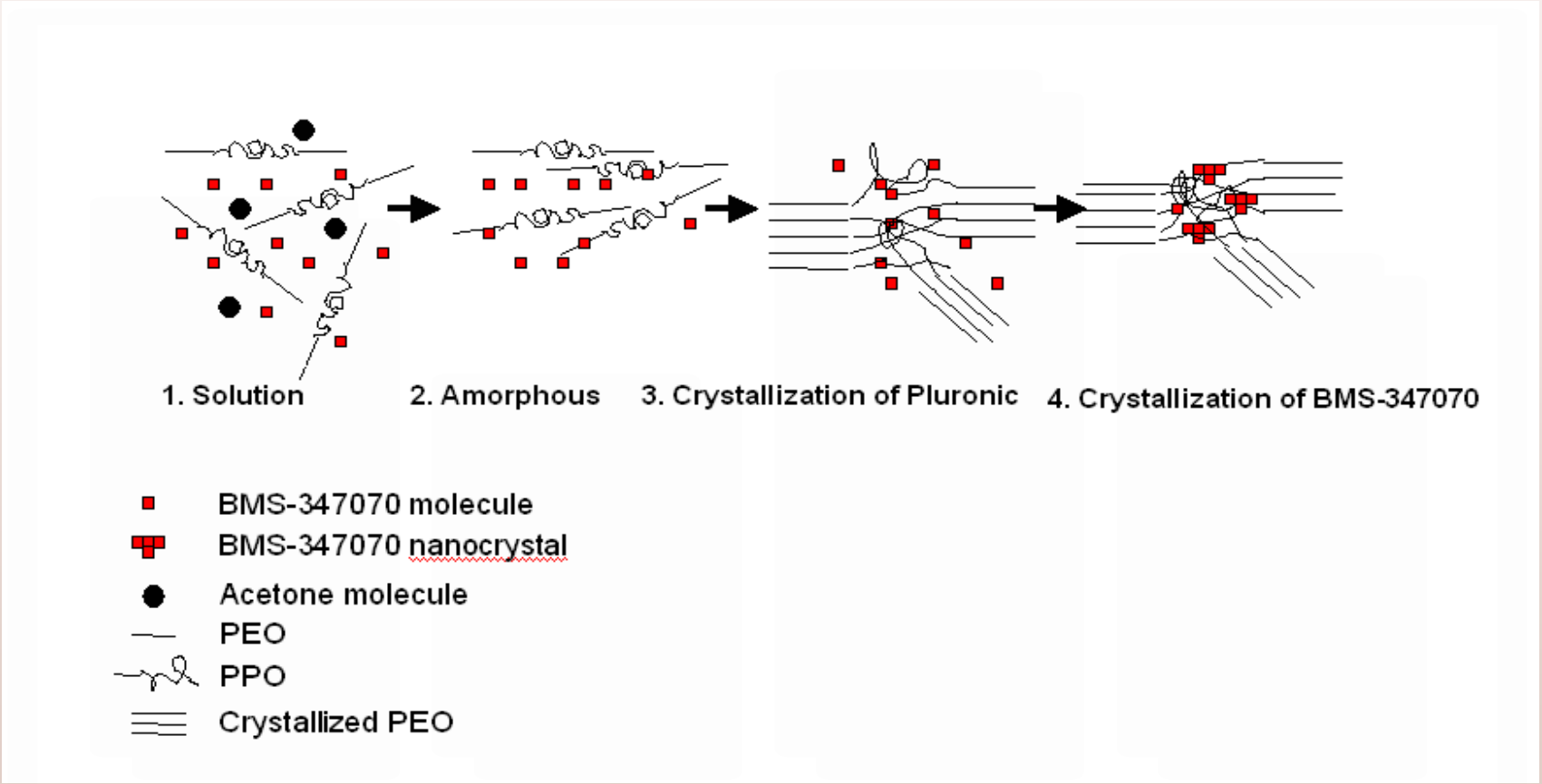
Time Evolution of PXRD



a 50:50 drug:Pluronic F127 film cast from acetone

* S. Yin et. al. *J. Pharm. Sci.*, 2005, Vol. 94, No. 7, 1598-1607

Proposed Model for Nano-sized Crystalline Drug



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Q&A