

Solid State Characterization Technologies for Online Analysis

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Definitions - PAT

- *PAT* is considered to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. It is important to note that the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner. The goal of PAT is to understand and control the manufacturing process, which is consistent with our current drug quality system: *quality cannot be tested into products; it should be built-in or should be by design.*

Definitions – Manufacturing Science

- Manufacturing Science encompasses knowledge about products and processes, technology used to manufacture and control these processes, and the underlying foundation of a robust quality system at the manufacturing site.

Definitions – Quality by Design (QbD)

- A mechanism to ensure product quality and performance by the design of effective and efficient manufacturing processes based on the principles of:
 - engineering,
 - material science,
 - quality assurance
- Quality by design will ensure acceptable and reproducible product quality and performance throughout a product's shelf life
- Quality by design includes formulation design strategies that provide robust processes that are not adversely affected by minor differences in physical attributes of raw materials.

Desired State of Manufacturing Science and the Related Regulatory Processes

- The application of manufacturing science to facilitate the manufacture of pharmaceutical active ingredients and drug products in a reproducible manner, and to mitigate the risk of an event impacting fitness for use.
- The sharing of knowledge between pharmaceutical firms and FDA to define risk in a culture of trust.
- The application of regulatory processes proportional to the level of risk and applied manufacturing science demonstrated by the firm.
- Consistent application and predictability of the regulatory processes .

Solid State Analytical Methods

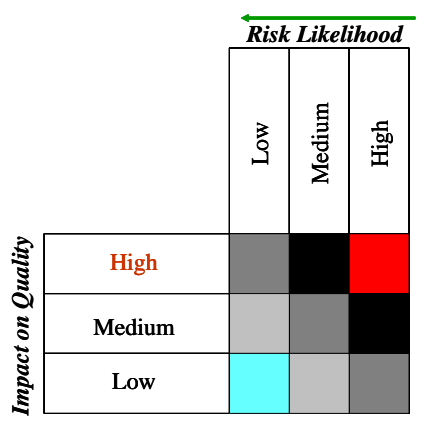
- X-ray Diffraction
- Thermal Methods – DSC, TGA
- Spectroscopy
 - IR
 - NIR
 - Raman
 - DSC
 - TDLS
- Particle Size
- Chemical Imaging – Raman, NIR

PAT Involves Extensive use of Analytical Methods for Solids

- Issues – Sample Withdrawal, Invasive (probes) or Noninvasive (reflectance)
- Issues - Ports or Windows
- Issues - Transmittance or reflectance methods
- Issues - at-line, on-line, or in-line
- Preference - Noninvasive, reflectance, portable, in-line measurements through windows
- Advantages - does not disturb bed, no cleaning, transportable, can be used in development and manufacturing
- Analytical methods are not fully developed

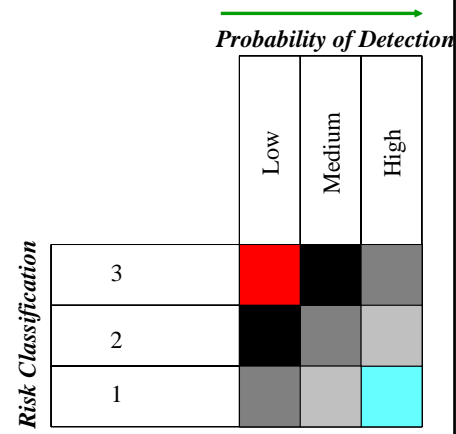
❖ Quality Risk Classification

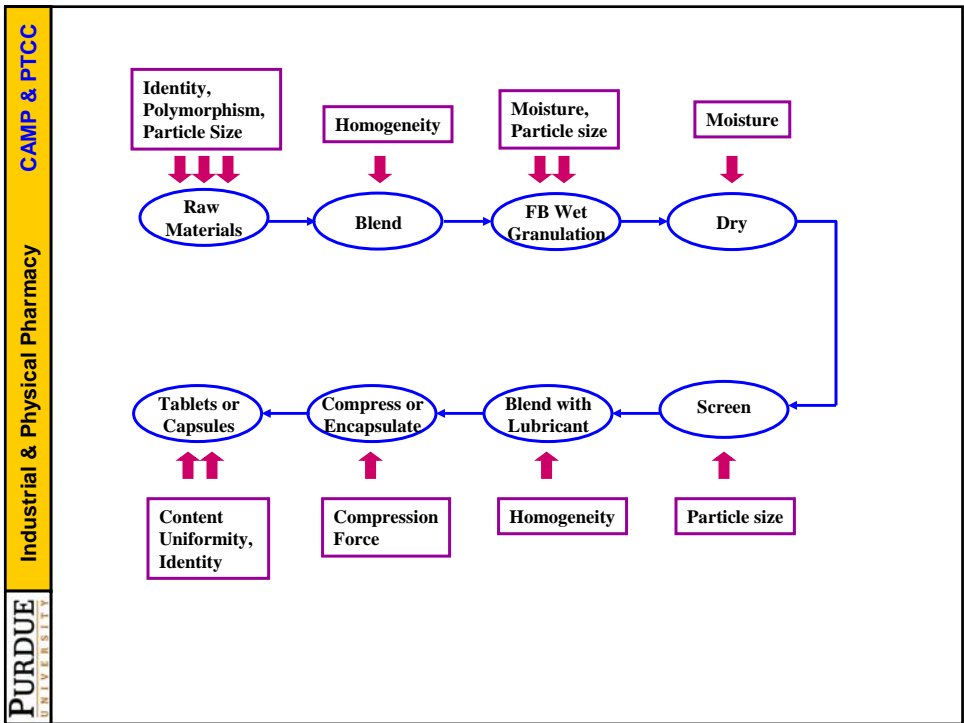
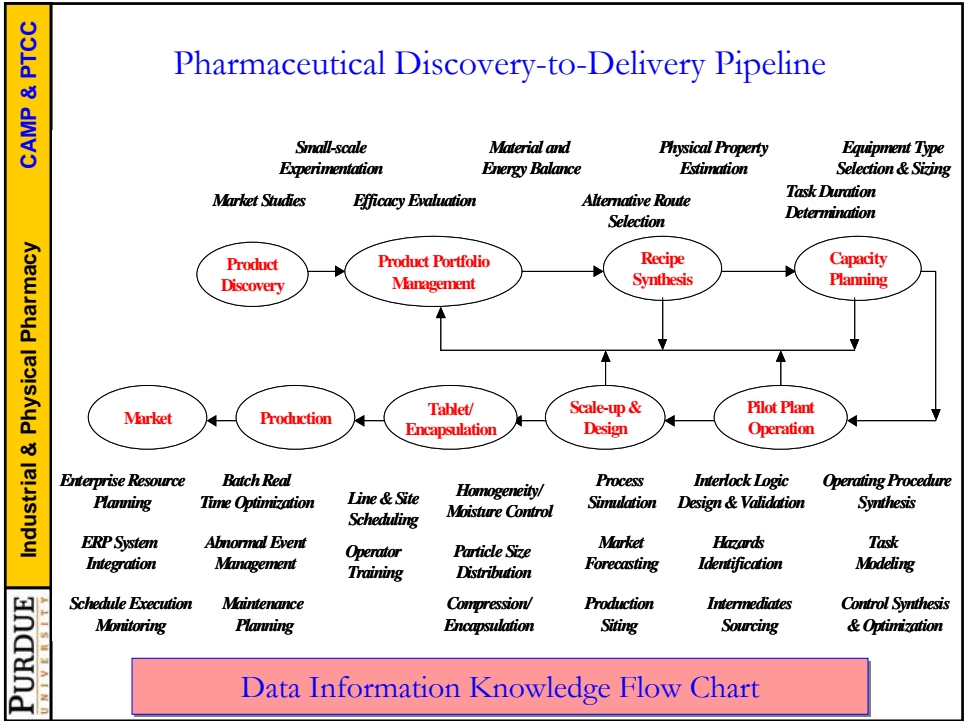
(A. Hussain)
 (based on SUPAC and GAMP-4)



Quality Risk Priority

(A. Hussain)

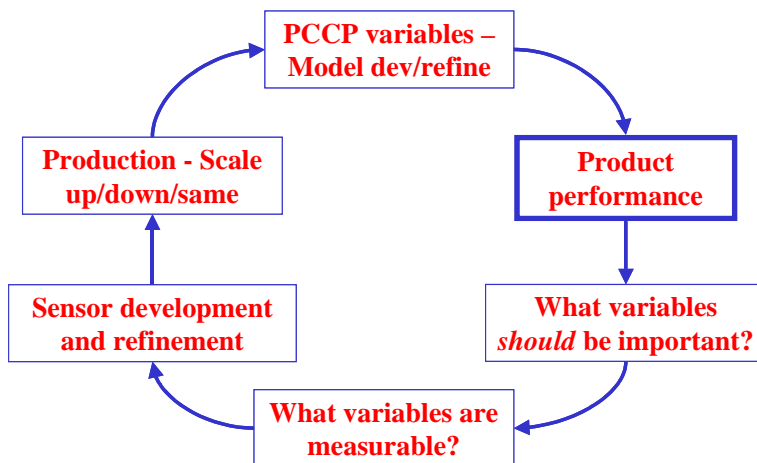




Sensor Evaluation

- Identity – X-ray, Raman, NIR
- Polymorphism – X-ray, Raman, NIR
- Particle Size – Imaging
- Blend Homogeneity – NIR, Raman, LIF
- Moisture – NIR
- Granulation (including dry granulation)– NIR, Raman, FBRM
- Particle Size – Imaging
- Compression Force – Instrumented tablet press
- Content Uniformity – NIR, Raman

Strategy

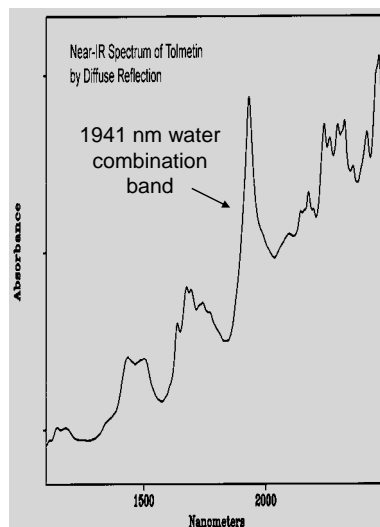


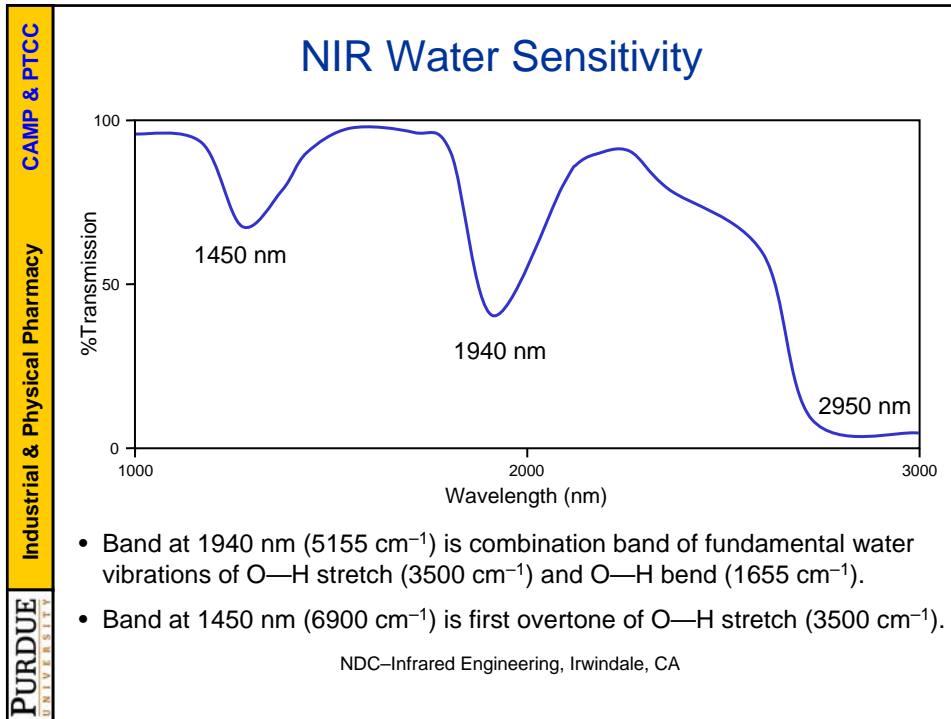
Moving to Quality by Design

- Move away from testing to document quality
- Move to quality by design
- Have the right methods for the right application
- Establish causal links between measurements and
 - Variability
 - Performance
- Avoid artifacts from
 - Sampling errors
 - Transport errors
 - Errors that arise from holding the sample

NIR Spectroscopy in Processing

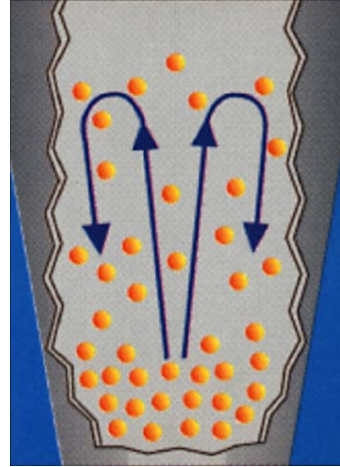
- NIR region is between the visible and MIR, 780–2526 nm (ASTM) (or 12820–3959 cm^{-1} MIR 4000–400 cm^{-1})
- Depends upon overtone and combination of normal vibrations in poly-atomic molecules
- Best for hydrogen on hetero-atoms (e.g., H—O—R)
- Diffuse reflectance is ideal for NIR (weak absorbance)
- Sensitive to particle size





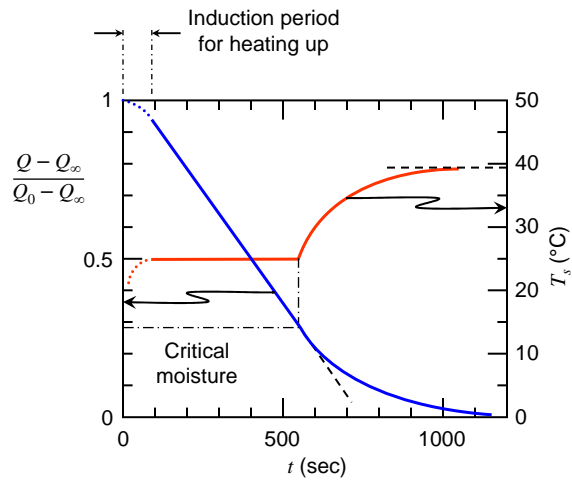
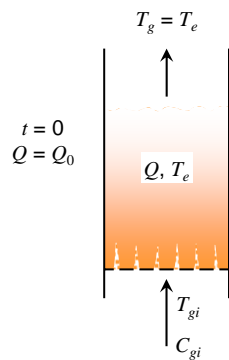
- Water in Pharmaceutical Solids**
- Bulk surface water
 - Intergranular water
 - agglomerates
 - amorphous phase
 - capillaries
 - solutions (e.g., binders)
 - Water in crystalline hydrates

Fluid Bed Drying



www.glattair.com

Batch Drying of Solids



D. Kunii and O. Levenspiel *Fluidization Engineering*, John Wiley & Sons, 1968.

Fixed-Wavelength (Filter) NIR Gauge

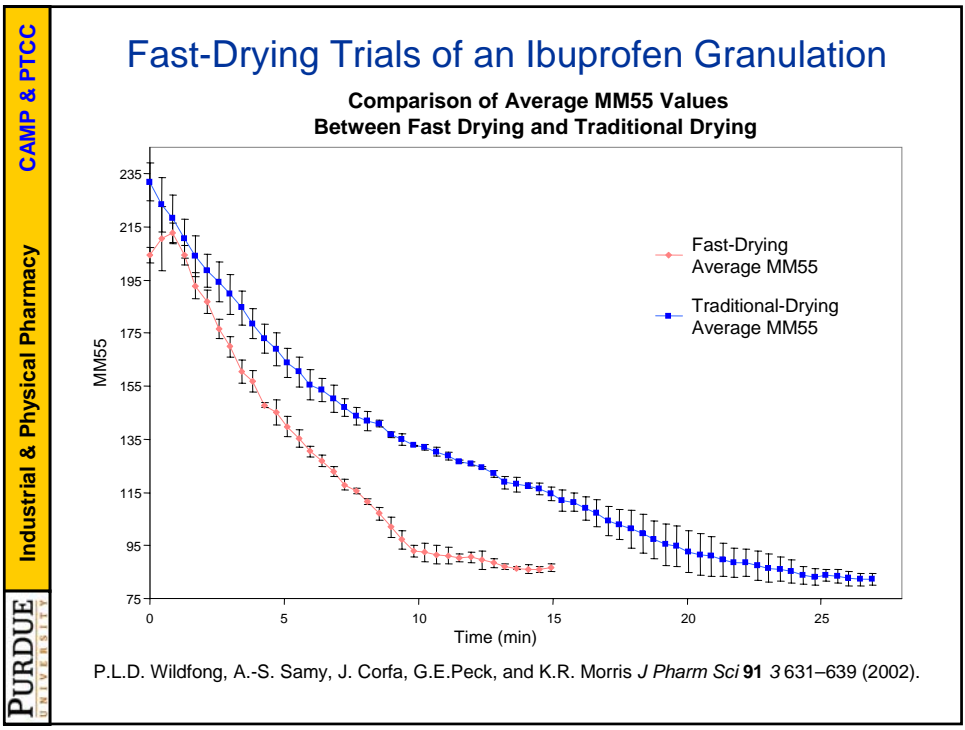
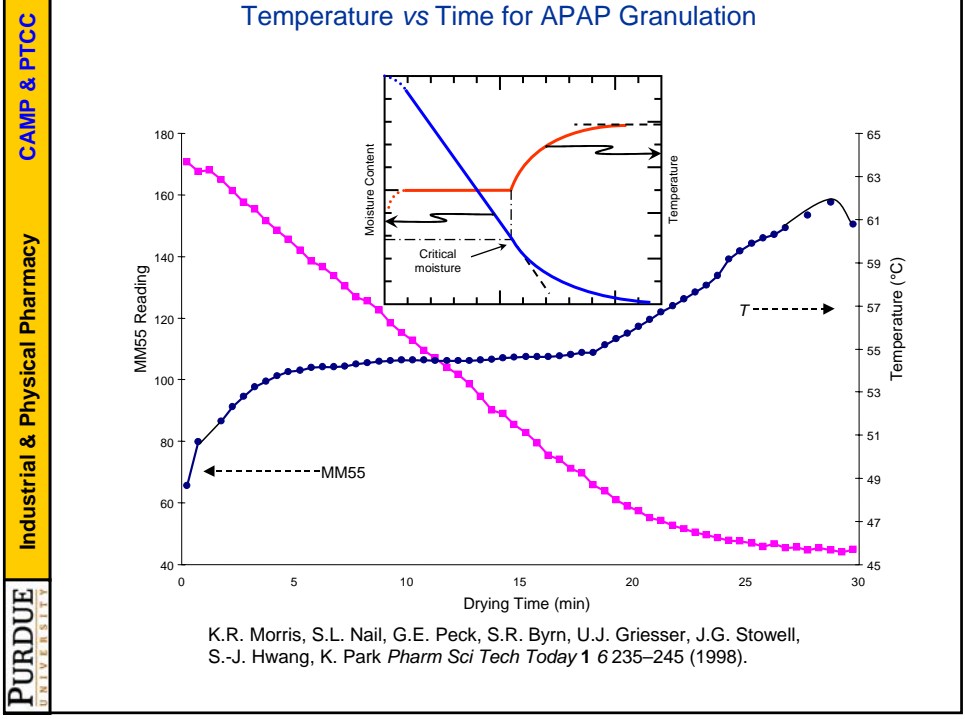
NDC-Infrared Engineering
Irwindale, CA

Two-Stage Drying In a UniGlatt
APAP Granulation at 60 °C

$Q = Q_0 - Kt$

$Q = Q_\infty + Q_0' \cdot k \cdot \exp(-k't)$

P.L.D. Wildfong, A.-S. Samy, J. Corfa, G.E. Peck, and K.R. Morris *J Pharm Sci* **91** 3 631–639 (2002).

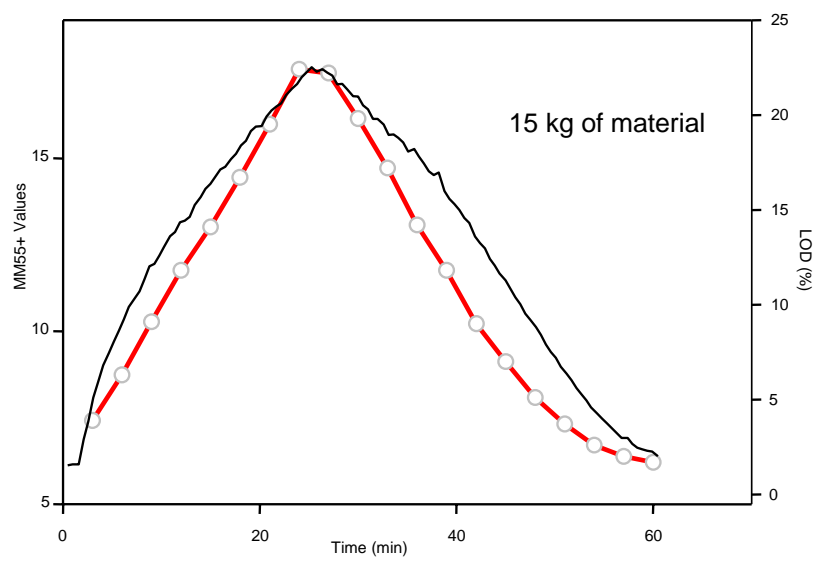


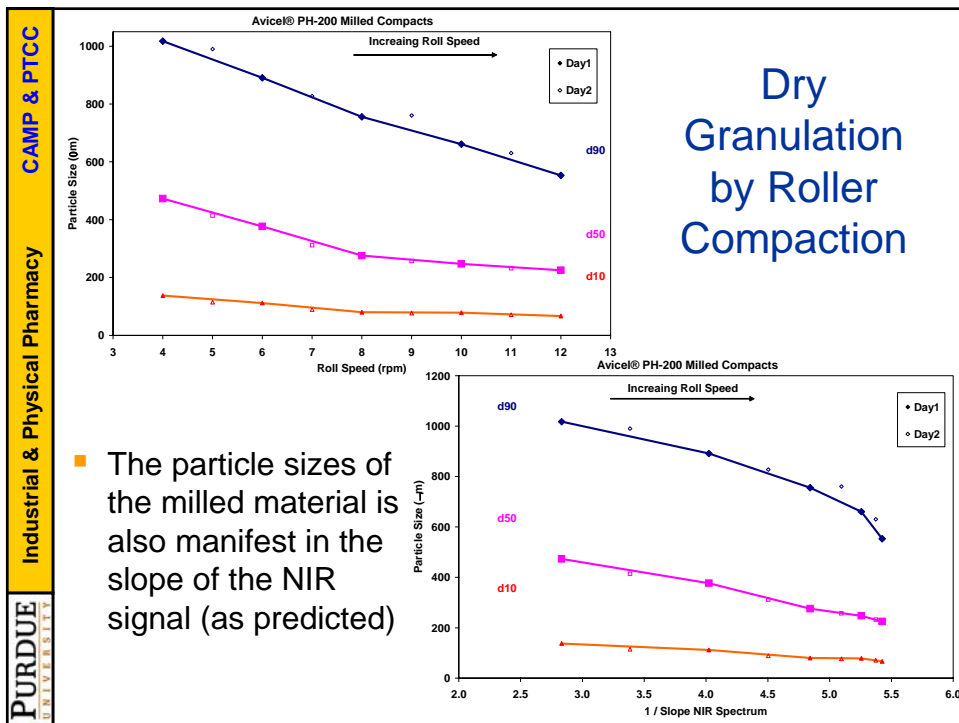
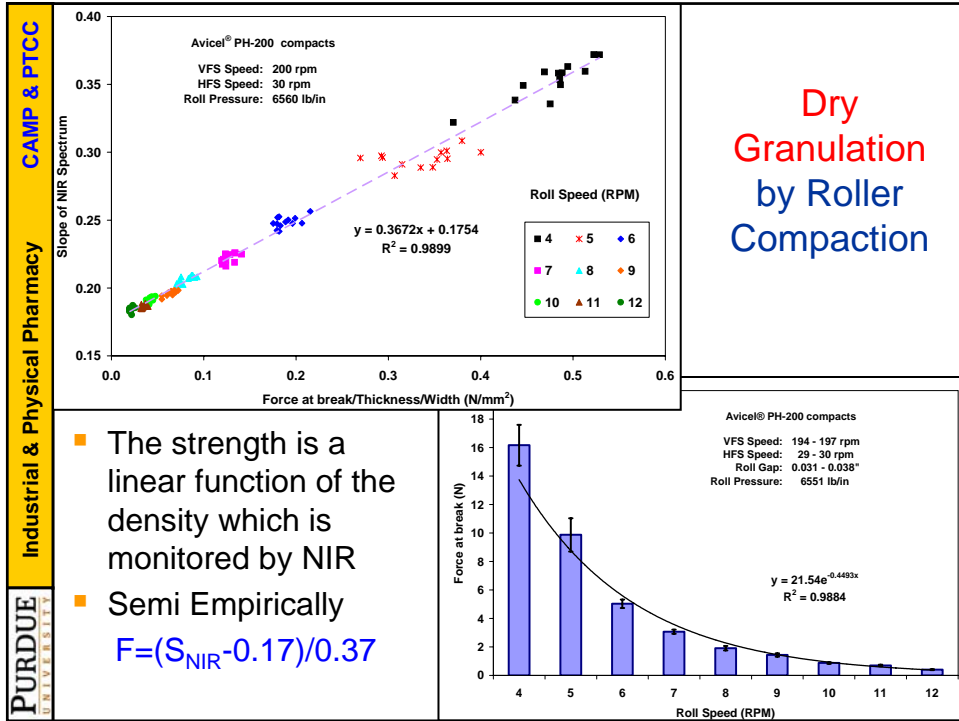
Granulation/Drying Endpoint Monitoring



GPCG-15 Glatt Fluid-Bed Dryer

Fluid-Bed Granulation/Drying

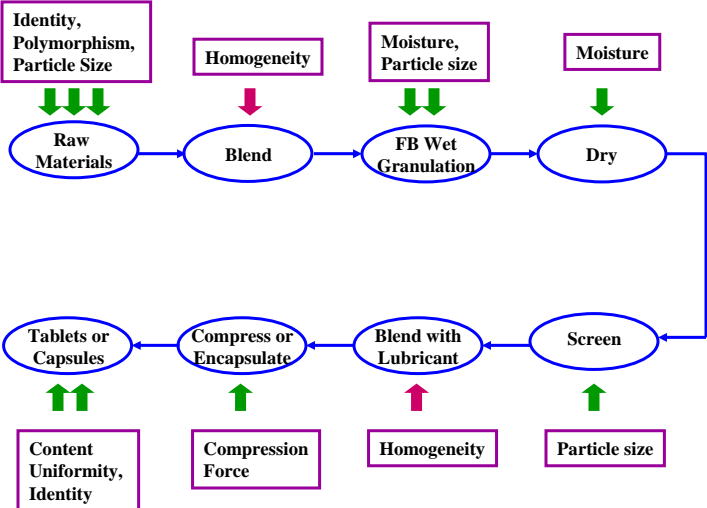




Places to Measure Blend Homogeneity

- In Blender
- Hopper Flow
- On Conveyor
- At the Fill Site

Blend Homogeneity



NIR Mounted for Continuous Monitoring



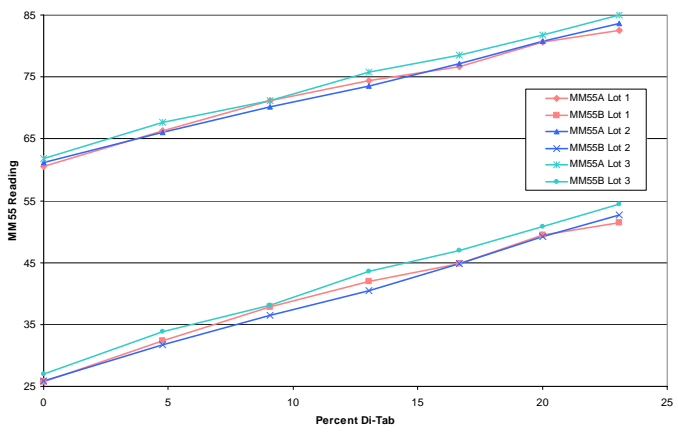
Calibration Curves

One Example Shown Here

Four Additional Examples Not Shown

Final Readings for Three Trials at Different Concentrations of DiTab in Anhydrous Lactose

Over Lay of MM55A and MM55B For the Blending of Di-Tab in Lactose

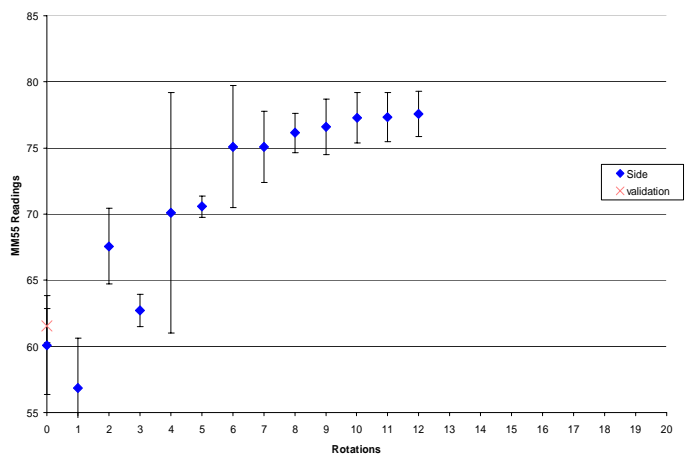


Rather consistent readings are obtained even at the 5% level

Results of Blending Experiments

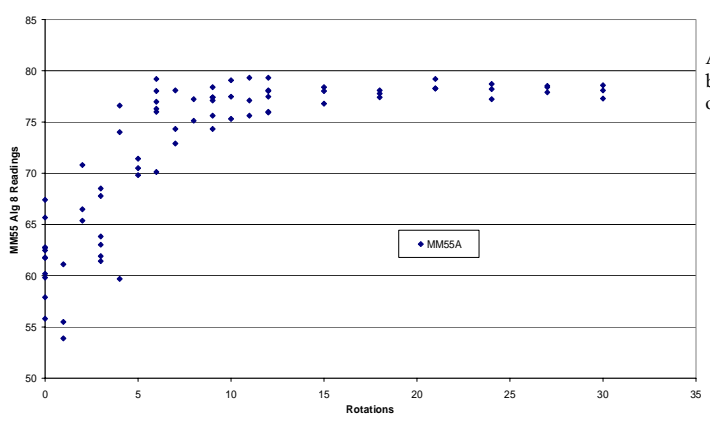
At least 10 NIR blending trials have been performed some multiple times. The results of two representative experiments are shown here

NIR Readings for the Three Runs after only a Few Rotations

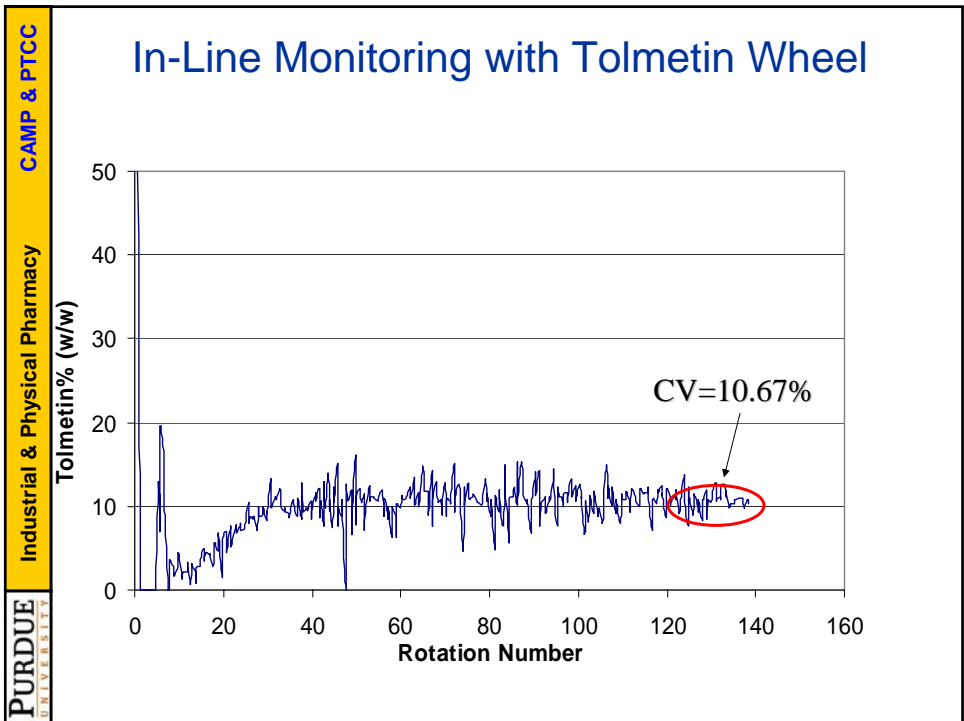
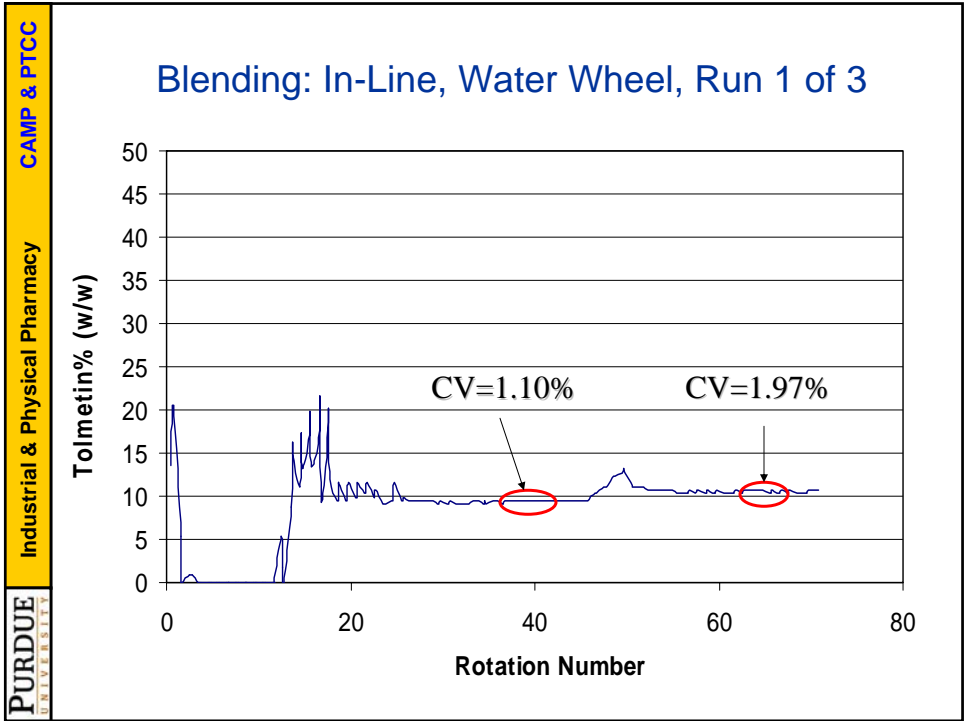


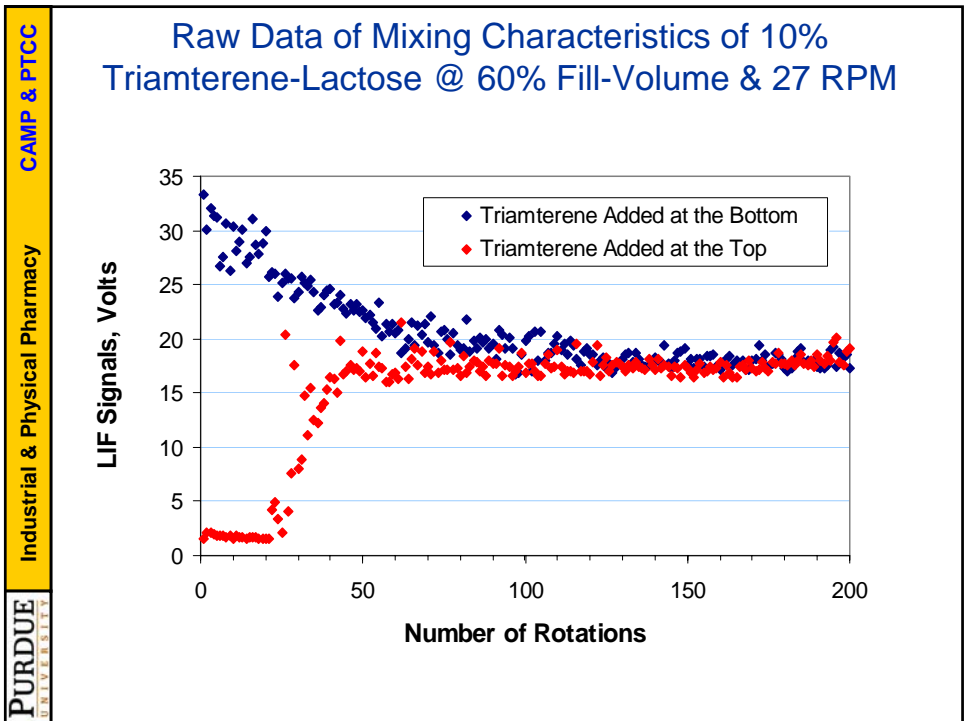
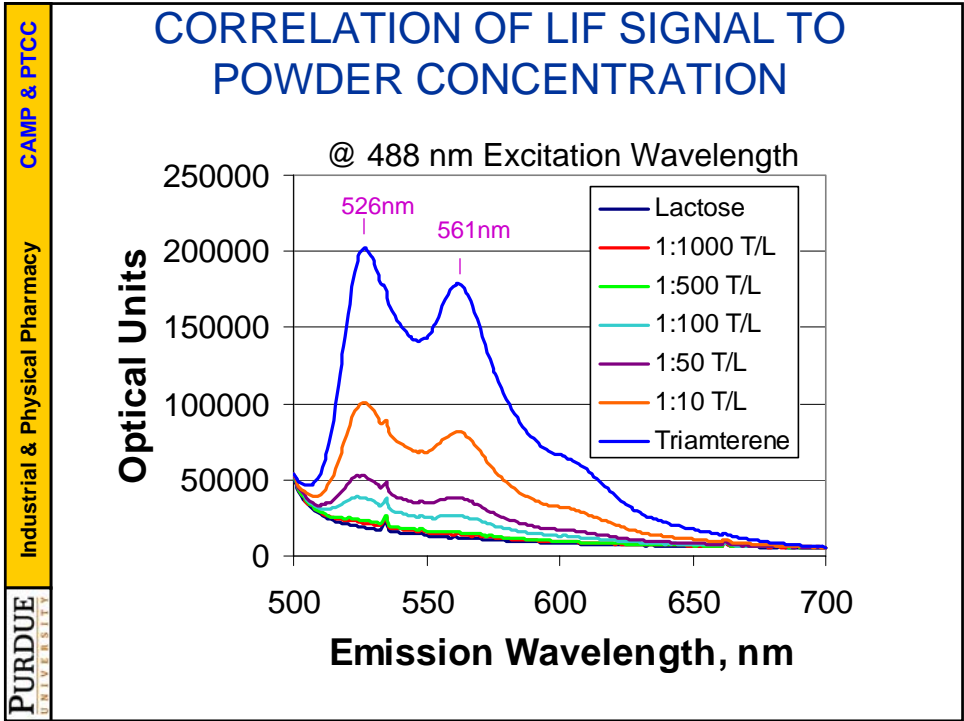
The mixture is blended after only 10 rotations

NIR Readings for all Runs after only a Few Rotations

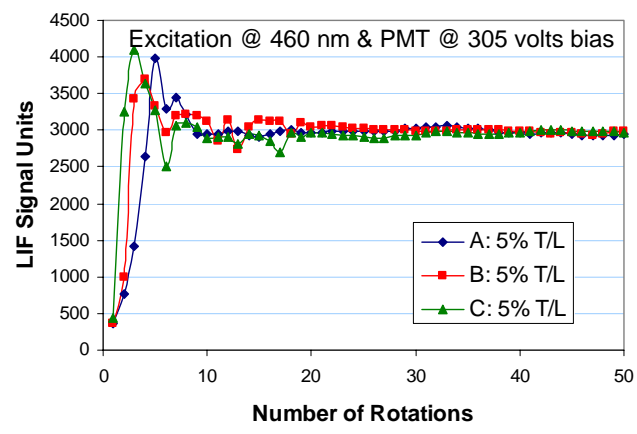


All mixtures are blended after only 15 rotations



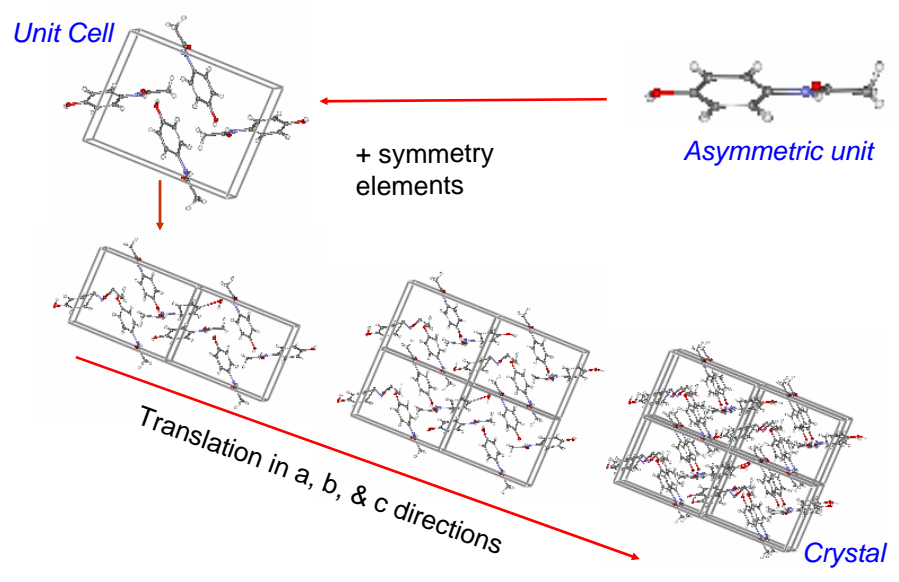


BLEND HOMOGENEITY KINETICS OF 5% TRIAMTERENE-LACTOSE POWDER



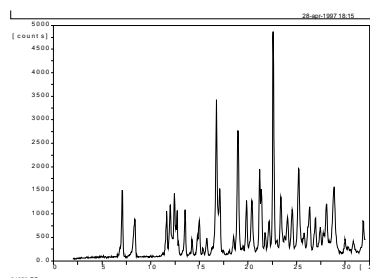
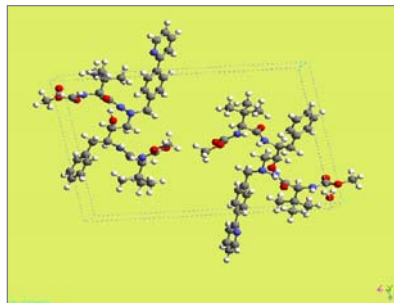
Rot. No.	Run A	Run B	Run C	AVERAGE	STDEV	% RSD
Av.20-30	2990.24	3021.97	2933.02	2981.74	45.08	1.51
Av.30-50	2984.21	2981.90	2975.63	2980.58	4.44	0.15

X-Ray Powder Diffraction



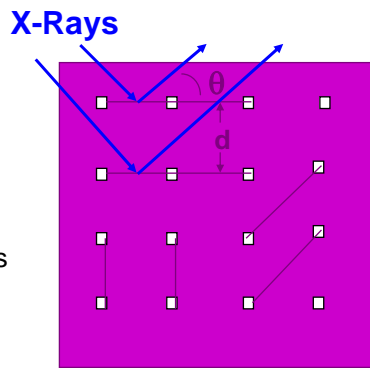
X-Ray Powder Diffraction

- A crystal form is determined by the arrangement of the molecules in the solid state. The specific arrangement of the molecules is defined by the unit cell. This unit cell is the repeating unit which makes up the crystal structure.
- The X-ray powder diffraction (XRPD) pattern can be used to directly compare the crystal structures of materials using powders. It is a “fingerprint” of the material which can be related back to the single crystal structure.



X-Ray Powder Diffraction

- diffraction plane must be oriented correctly in the X-ray beam to satisfy the Bragg condition
- random orientation of powders is necessary to get representative distribution of peak positions and heights
- peak position is directly related to diffraction angle and peak heights are related to the number of planes involved in the diffraction
- the distance between planes, known as the d-spacing, is related to the diffraction angle using Bragg's Law (where n is the order of the reflection and λ is the wavelength of the X-rays used)

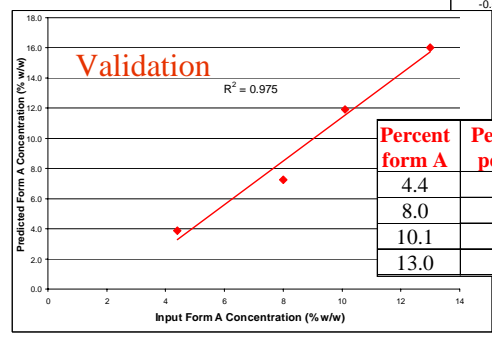
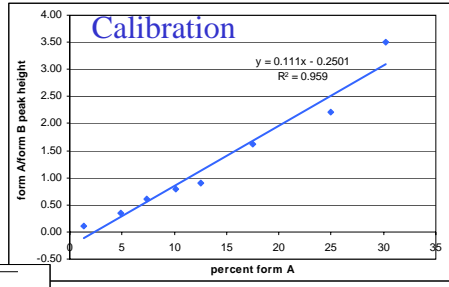


Bragg's Law

$$\sin \theta = n\lambda/2d$$

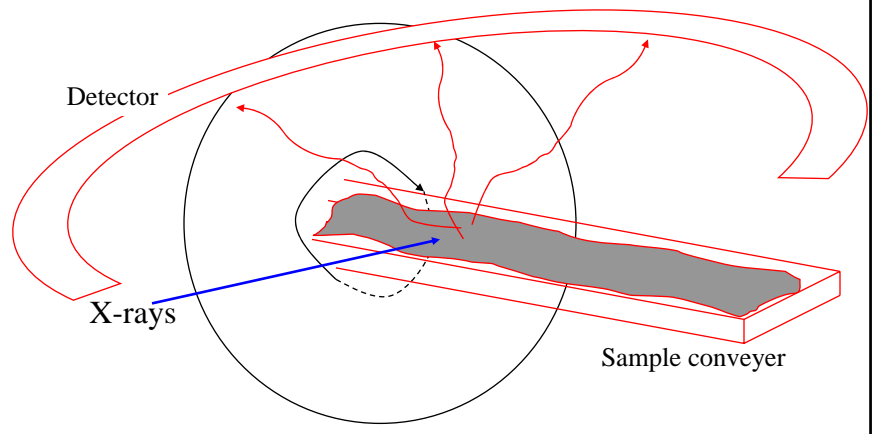
Drug Product Quantitation

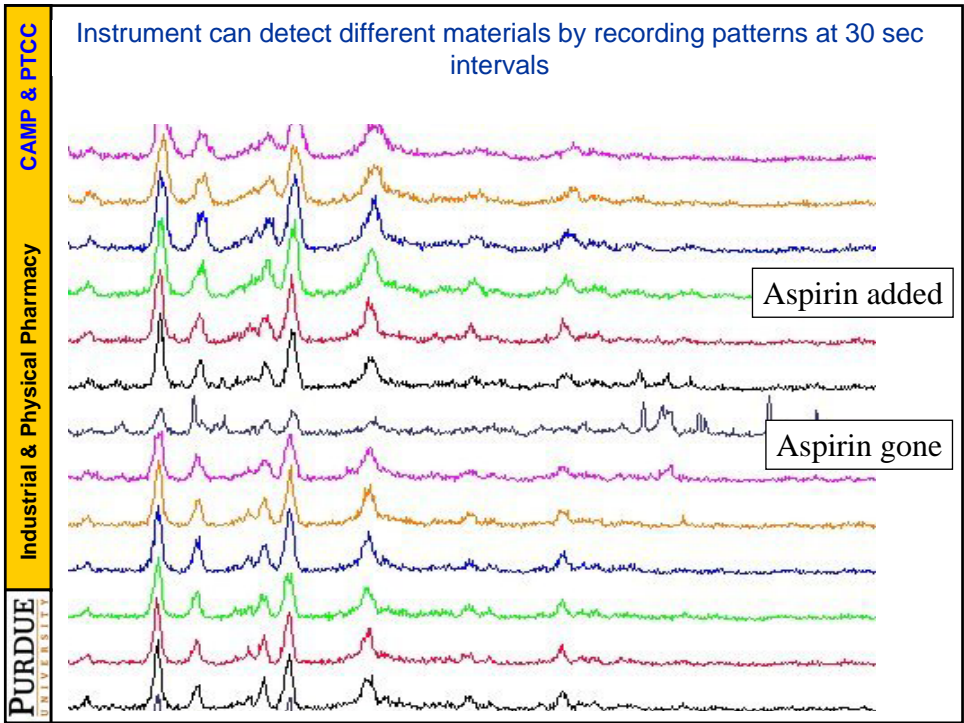
- Range 3-30 % form A
- Method RSD 5%
- Good percent recovery

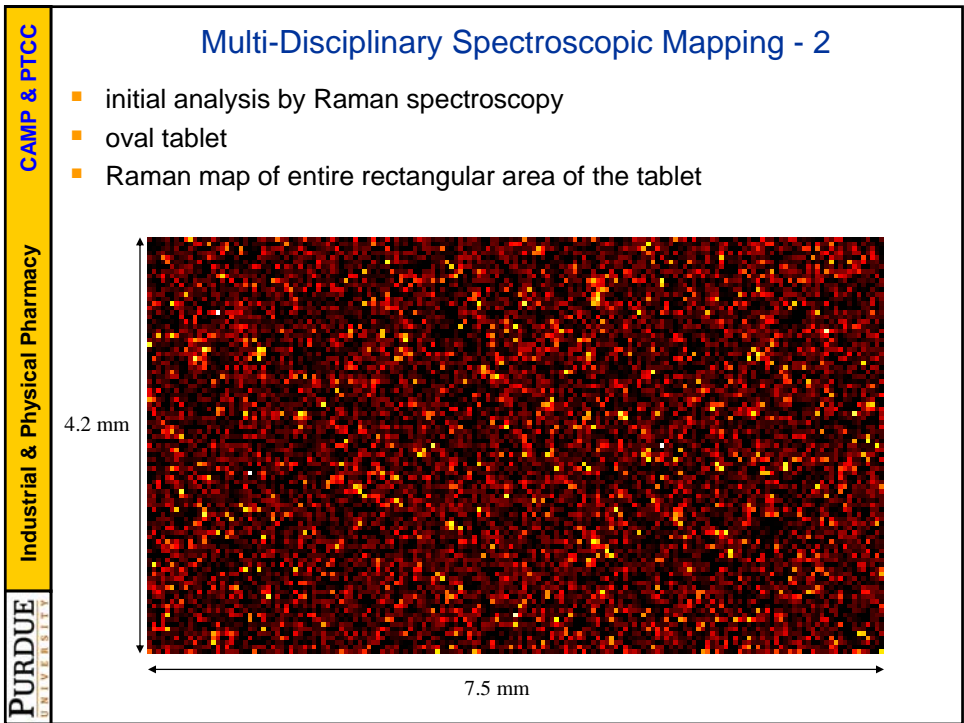
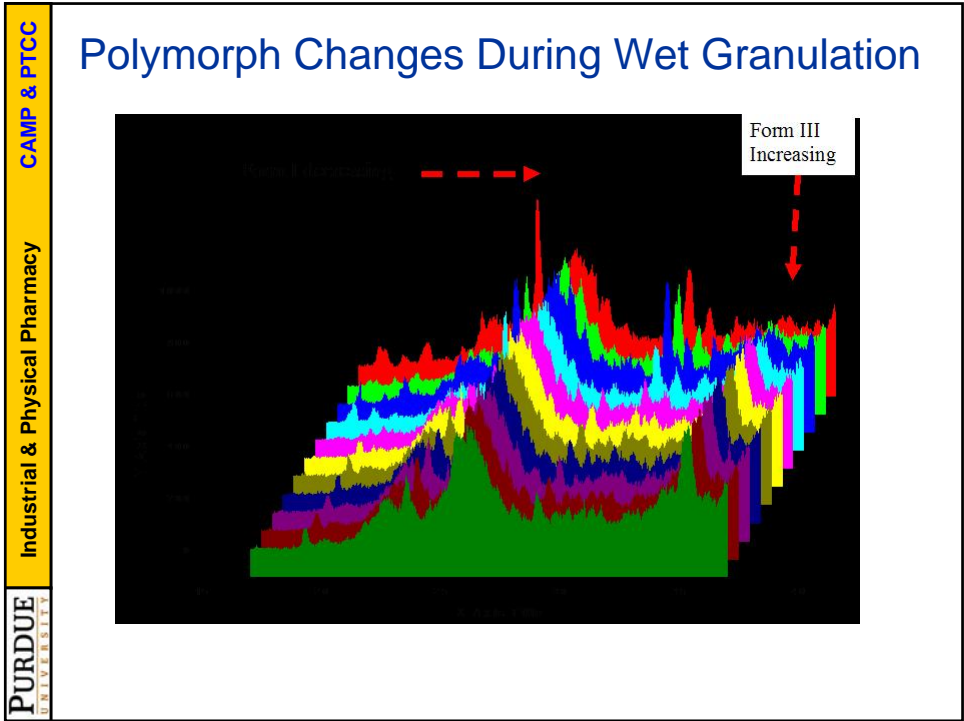


Percent form A	Peak height form A/ peak height formB	Calculated % Form A	Percent Recovery
4.4	0.27	4.6	105
8.0	0.58	7.4	93
10.1	1.00	11.3	112
13.0	1.38	14.7	113

Particle Characterization - INEL XRD Instrument with Purdue Modification







XRPD Mapping

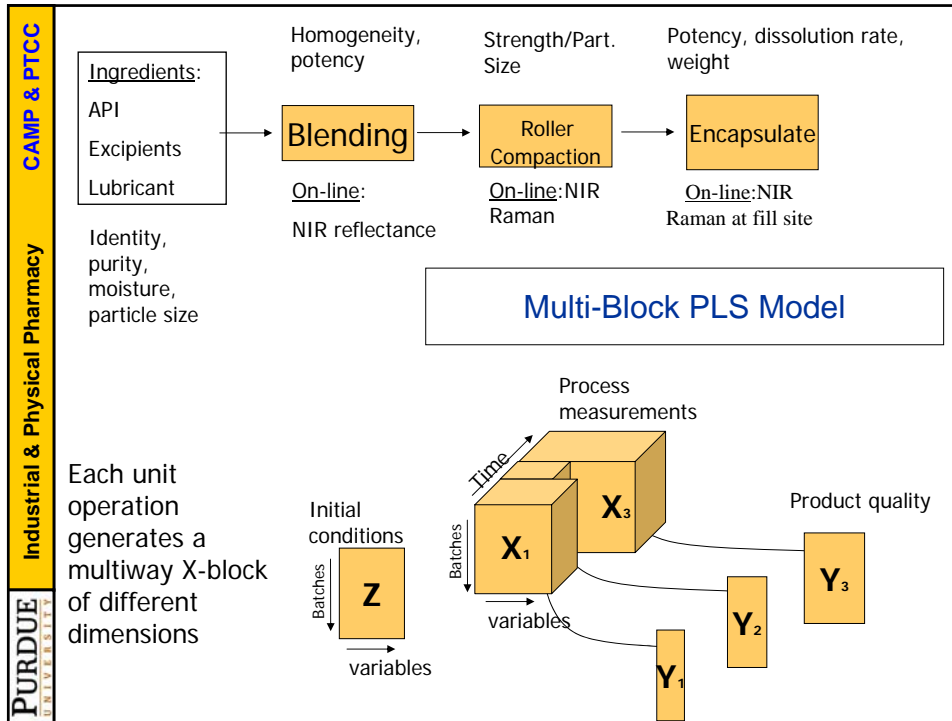
- XRPD analysis of Raman/IR defined area

diffraction angle	length of major axis of ellipsoid, 50 μm spot	length of major axis of ellipsoid, 300 μm spot
5°	574 μm	3442 μm
7°	410 μm	2462 μm
10°	288 μm	1728 μm
15°	193 μm	1159 μm
20°	146 μm	877 μm

$\sin \theta = \frac{\text{snout diameter}}{\text{length of major axis of ellipsoid}}$

XRPD Mapping

- XRPD analysis from Raman defined areas



- PURDUE UNIVERSITY** Industrial & Physical Pharmacy **CAMP & PTCC**
- ## Conclusions
- Noninvasive monitoring is possible
 - There are powerful methods for analysis of most steps
 - Transportable sensors can be used in development and carried through scale-up without inserting probes or disturbing the bed
 - Finding PCCPs are possible
 - QbD is enabled
 - Much more chemometric analysis is needed

The Future – Use PAT to Reduce Time to Market

- Develop tools and strategies to achieve PAT and quality by design as fast as possible
- Identify process critical control points during development
- Identify critical specifications early
- Make decisions quickly
- Explain deviations at small scale in development
- Make drug substance and drug product right first time - Minimize scrap, rework