Advanced Pharmaceutical Manufacturing: An Integrated Approach for Manufacturing Process Monitoring, Control, and Risk Mitigation

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Outline

- Introduction:
  - ✓ Traditional vs. Advanced Pharmaceutical Manufacturing
- Process Analytical Technology (PAT)
  - ✓ Tools and Concept
- Case Studies for Advanced Manufacturing Process Monitoring and Control
  - ✓ Crystallization
  - ✓ Blending
  - ✓ Cell culture
- Manufacturing Innovation Implementation Status
- Conclusions
- Acknowledgements

Traditional Pharmaceutical Manufacturing

- Same or similar practice used for more than one century
- Characteristics
  - ✓ Relatively discrete unit operations
  - ✓ Minimal monitoring and control measures
  - ✓ Limited sampling and off-line testing for QC/QA
  - ✓ Advantage: Flexibility for manufacturing based on demanding
- Areas for continuous improvement
  - ✓ Process monitoring and control barely implemented
  - ✓ Often insufficient process understanding
  - ✓ Testing-into-quality (TIQ), not Quality-by-Design (QbD)
  - ✓ Limited scale of scrutiny to process performance monitoring and product quality: process model has low predictive power
  - ✓ Often low yield and high defect rates

Advanced Manufacturing in General

- The use of ***innovative technology to improve products or processes***
  - ✓ Makes extensive use of computer, high precision, and information technologies integrated with a high performance workforce in a production system
  - ✓ Capable of furnishing a heterogeneous mix of products in small or large volumes with both the efficiency of mass production and the flexibility of custom manufacturing in order to respond quickly to customer demands ((Quoted in PCAST, National Association of Advanced Manufacturing)
- *Ingenuity is transforming manufacturing across the US*
  - Digitalization
  - New hammers: software, sensors, data analytics, and network technologies
  - Competitive advantage

https://www.siemens.com/us/en/home/company/topic-areas/ingenuity-for-life.html

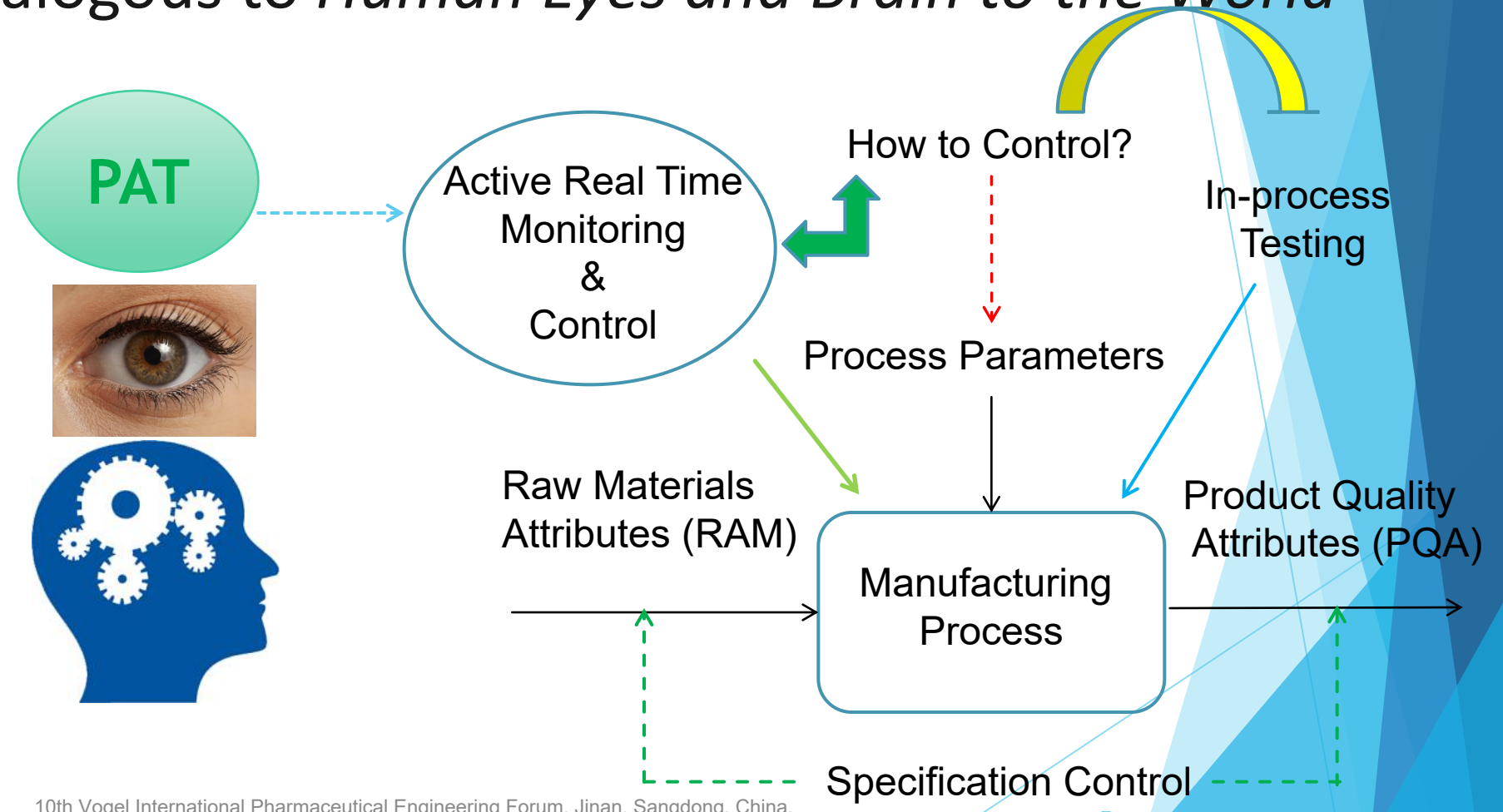
Advanced Pharmaceutical Manufacturing

- Strong industry driving force for innovative drug delivery system development and manufacturing
- Active academic programs on research, including NSF funding support
- Regulatory authorities
  - Actively promoting use of tools and principles in pharmaceutical development and manufacturing
    - Process Analytical Technology (FDA PAT Guidance, 2004)
    - Quality by Design (ICH Q8, Q9, Q10, Q11)
  - Facilitating the practice and implementation of advanced manufacturing
    - 3D printing
    - Continuous Manufacturing (CM, 2008)
    - Emerging Technologies (FDA Emerging Technology Guidance, 2017)

Process Analytical Technology (PAT)

- 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 (FDA PAT Guidance, 2004)
  - ✓ *Defining* critical process parameters (CPP) and critical quality attributes (CQA), and *monitoring* them in a ***timely*** manner
  - ✓ Manufacturing and regulatory science benefits
    - ***More efficient in testing***
    - ***Reducing over-processing***
    - ***Enhancing consistency and minimizing rejects: presents a good case for utilizing continuous manufacturing***
    - ***Transforming from static batch mode to a more dynamic approach***
    - ***Leading to direct or indirect process control***
    - ***Derived control strategy***

Conceptually, PAT to Pharmaceutical Process is Analogous to *Human Eyes and Brain to the World*



Crystallization PAT Case Study

- Understanding process dynamics and nucleation mechanism
- Process design space

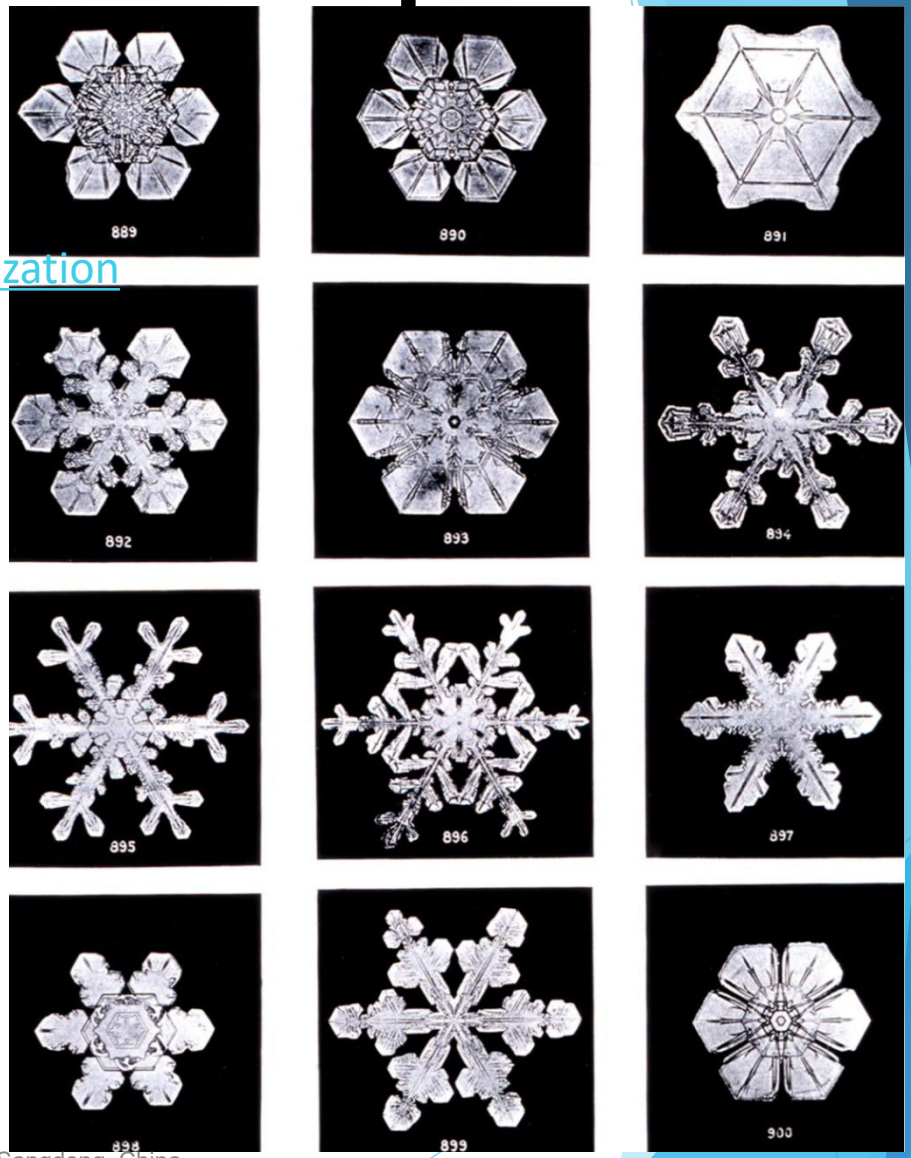
Snowflakes Example

https://en.wikipedia.org/wiki/Crystallization

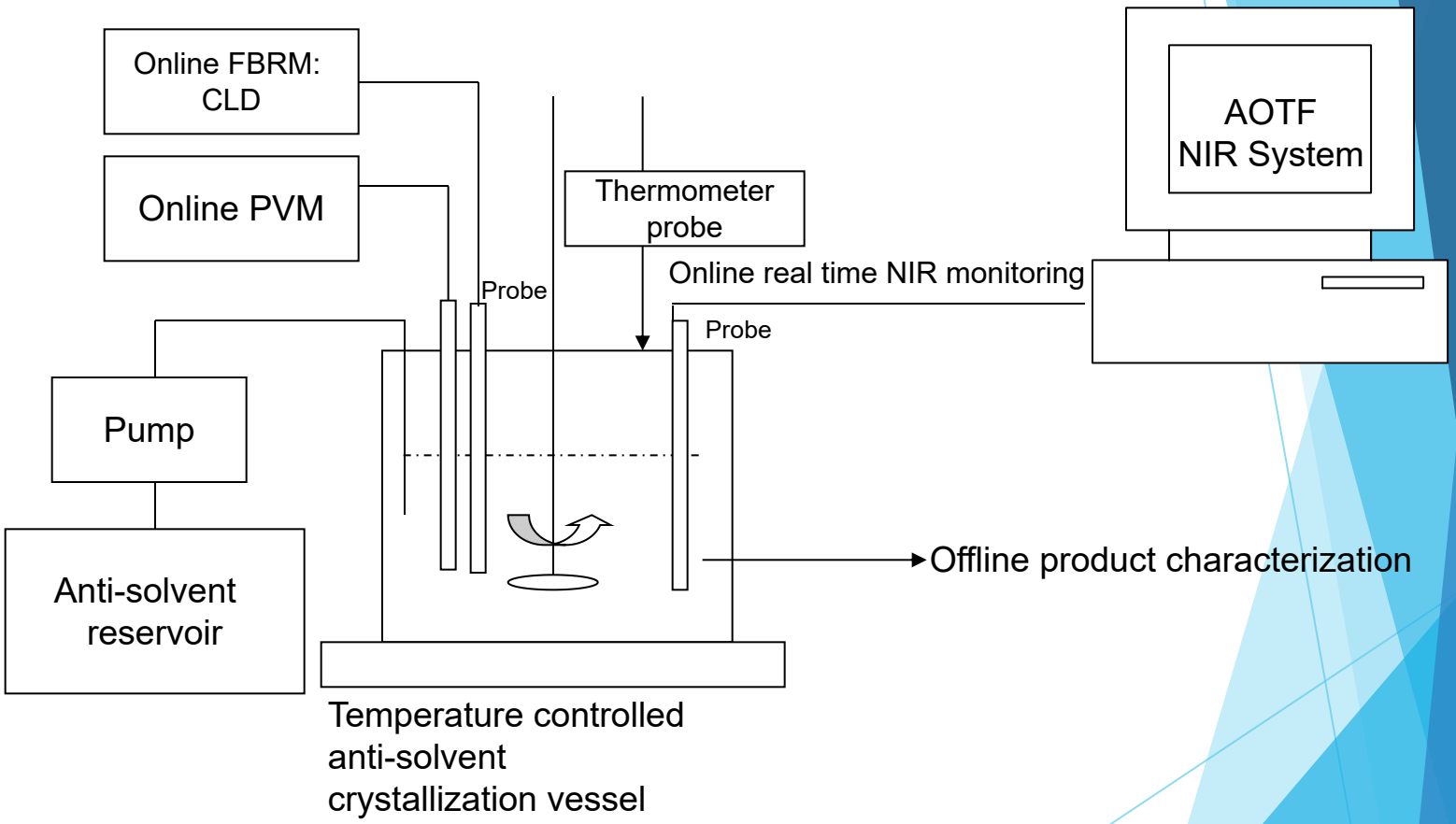
Subtle differences in crystal growth conditions result in

different **geometries**

Necessity for crystallization process control !

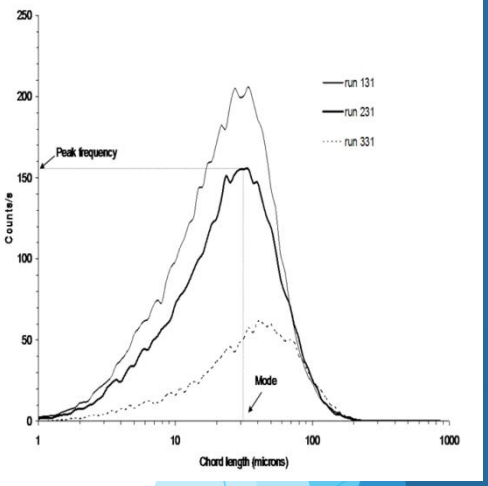


Schematic of Experimental Setup



Discontinuous Anti-solvent Crystallization: Multivariate Approach

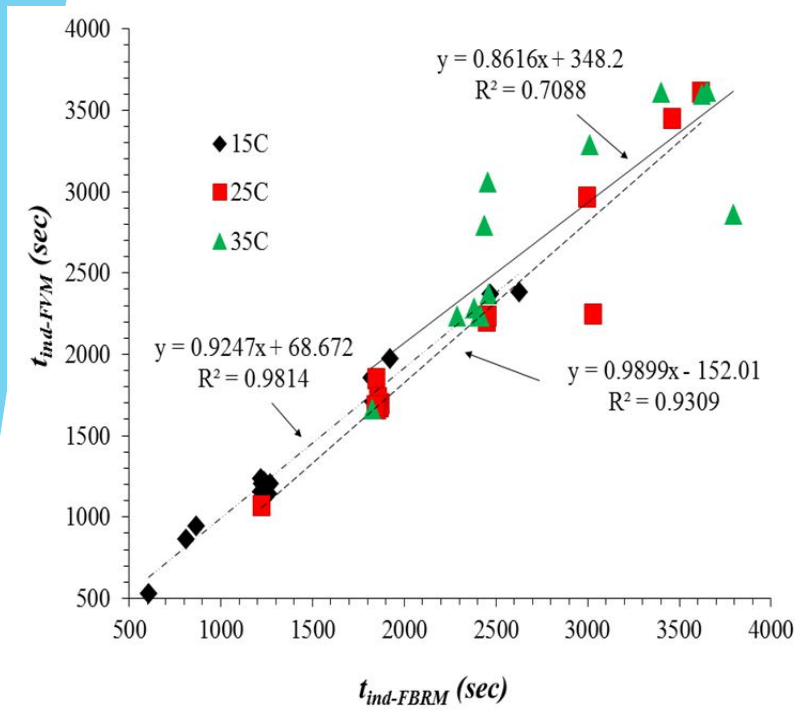
- Multivariate statistical design experiments
  - Independ variables
    - Slurry temperature (^{0}C)
    - Stirring speed (RPM)
    - Anti-solvent addition rate (ml/sec)
    - All other conditions the same
      - ✓ Main formulation components and usages (except anti-solvent)
      - ✓ Crystallization vessel and associated control
      - ✓ Online monitoring instrument settings: NIR, FBRM, PVM
  - Response variables measured/derived
    - Nucleation induction time (t_{ind}) based on time series of NIR spectra, FBRM CLD cluster, and PVM images
    - Derived process rate based on FBRM CLD: ($\partial CLD/\partial t$)
    - Mode and peak frequency at the end of steady state

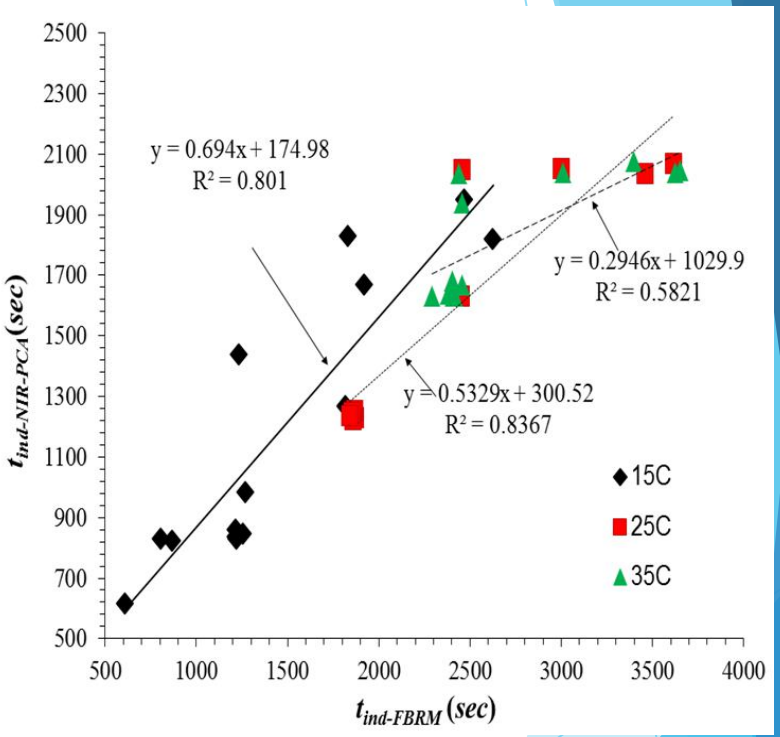


DOE: 3^3 Full Factorial Design

- Factors & levels
  - Temperature (15, 25, 35 ^{0}C)
  - Stirring rate (50, 200, 400 rpm)
  - Anti-solvent addition rate (0.83, 3.66, 6.66 ml/sec)
- Real-time PAT process monitoring
  - Near-infrared spectroscopy
  - Focused Beam Reflectance Measurement (FBRM)
  - Particle Vision Microscopy
- Off-line characterization
  - NIR and chemical imaging
  - Raman spectroscopy
  - Powder X-Ray Diffraction (PXRD)
- Process Design Space Establishment

Discontinuous: t_{ind} Measurement Verification





- **Better correlations between $t_{ind\text{-}PVM}$ & $t_{ind\text{-}FBRM}$ than between $t_{ind\text{-}NIR\text{-}PCA}$ & $t_{ind\text{-}FBRM}$**
- **Better correlations at 15^{0}C and 25^{0}C than at 35^{0}C**

Classical Nucleation Theory (CNT) and Modified CNT (MCNT)

- Solubility calculated by Jouyban-Soltanpour-Acree Equation (2010)
- Super-saturation calculated by mass balance
- For homogeneous nucleation mechanism

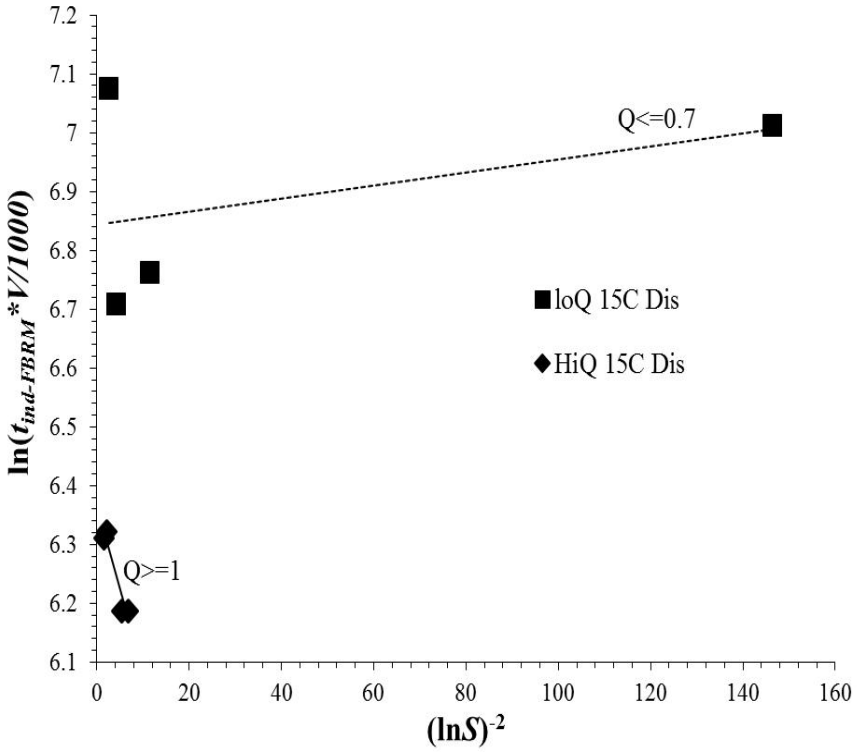
$$\ln(t_{ind}\mathrm{V}) \approx ln\left(\frac{N_c}{A_{hom,J}}\right) + \frac{16\pi\gamma^3 v^2}{3(kT)^3}\frac{1}{(lnS)^2}$$

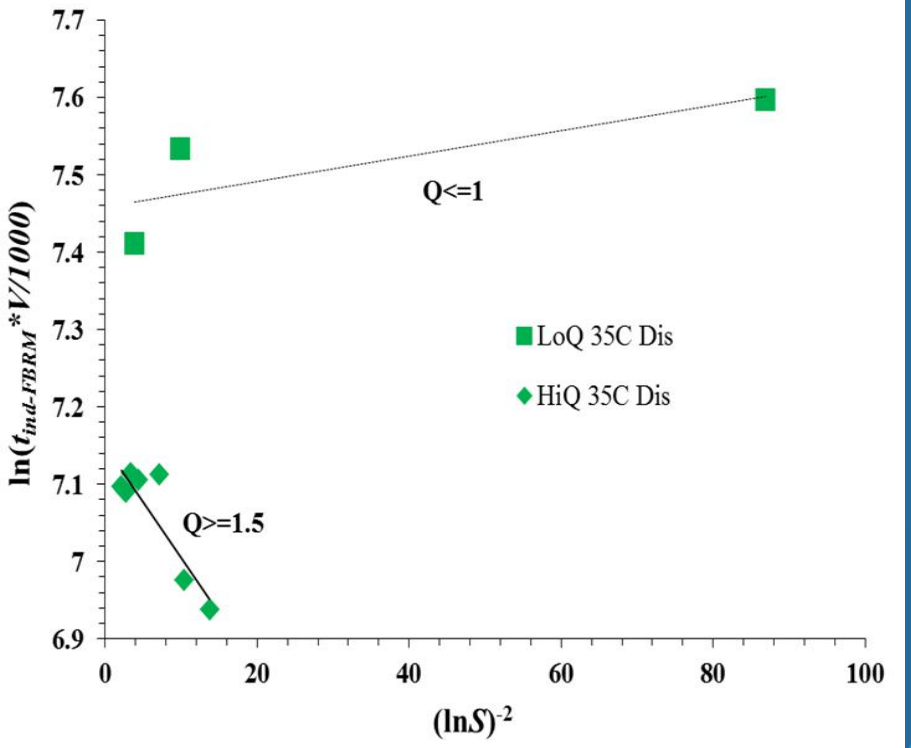
- For heterogeneous nucleation mechanism

$$\ln(t_{ind}\mathrm{V}) \approx ln\left(\frac{N_c}{A_{het,J}}\right) + \frac{16\pi\gamma^3 v^2}{3(kT)^3} f(\theta)\frac{1}{(lnS)^2}$$

$\boldsymbol{\theta}$ contact angle, $\mathbf{0} \leq \mathbf{f(\theta)} \leq \mathbf{1}$; **V** Slurry volume, **V=f(t)**

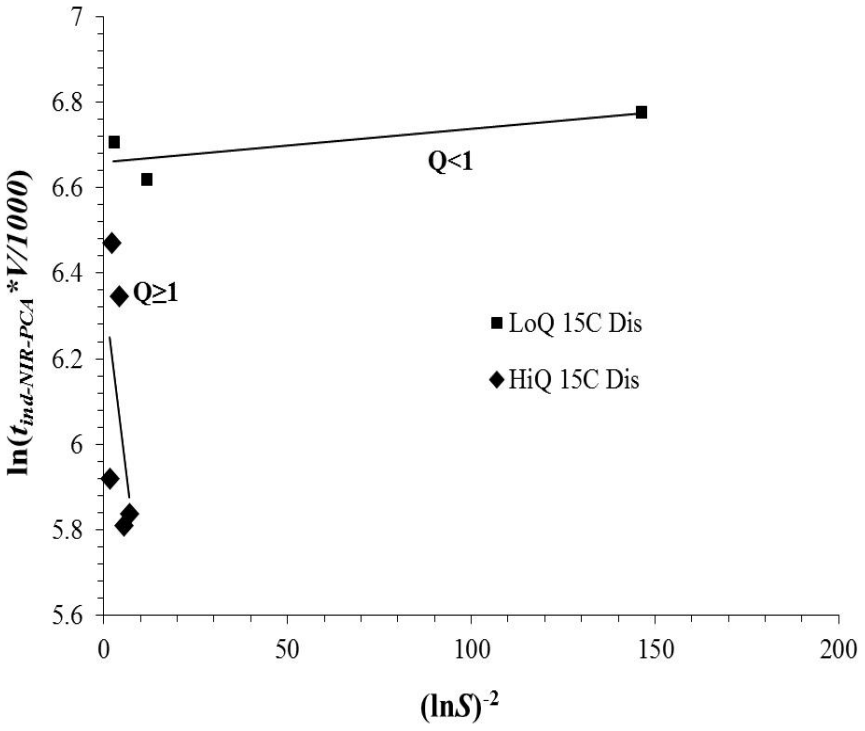
Discontinuous: $\ln(t_{ind\text{-}FBRM}V)$ vs. $(\ln S)^{-2}$

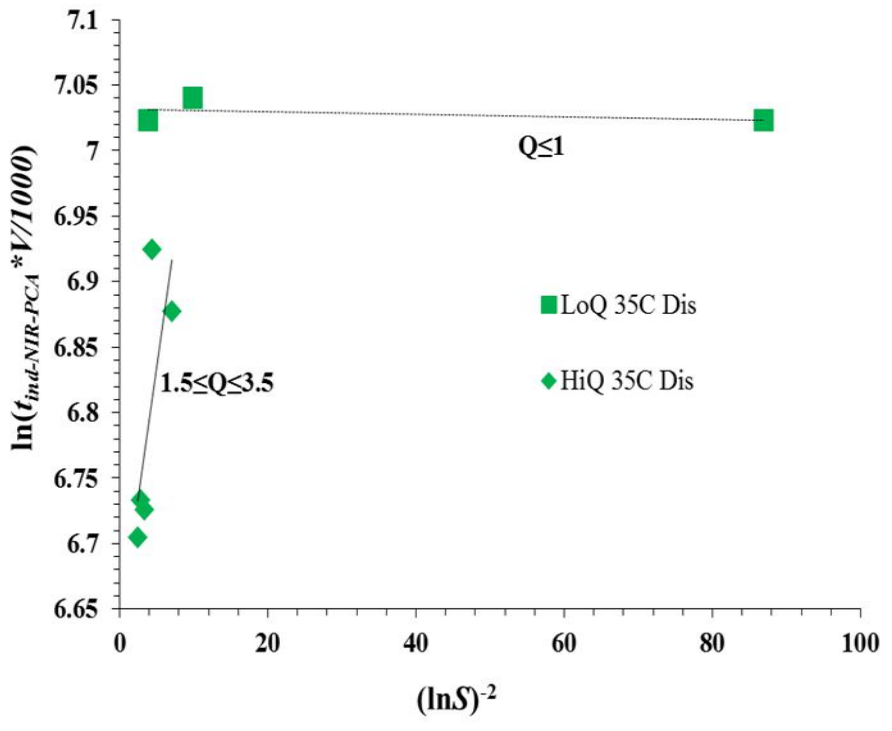




- **Small slope with low Q regime, heterogeneous nucleation mechanism**
- **Large slope with high Q regime, homogeneous nucleation mechanism**

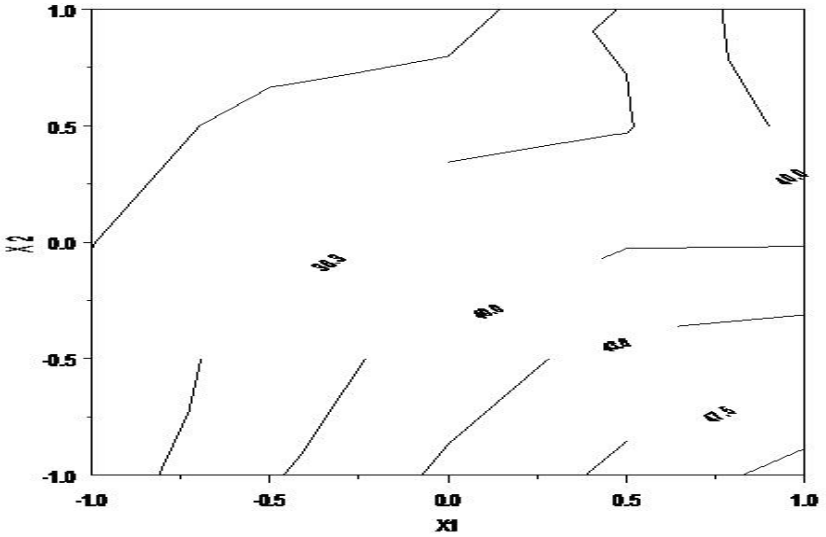
Discontinuous: $\ln(t_{ind\text{-}NIR\text{-}PCA}V)$ vs. $(\ln S)^{-2}$



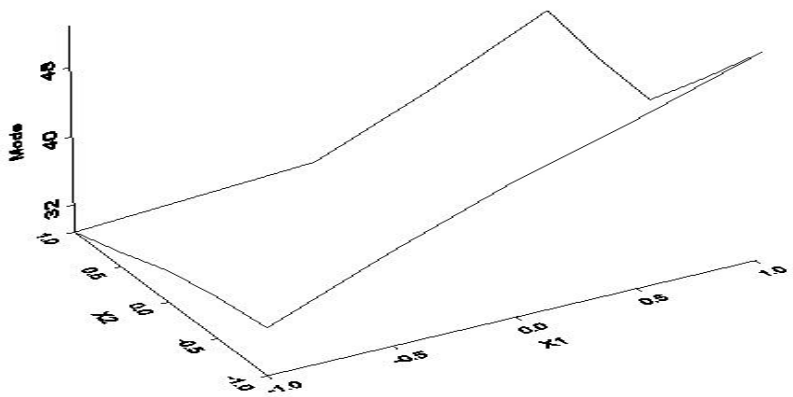


- **Small slope with low Q regime, heterogeneous nucleation mechanism**
- **Large slope with high Q regime, homogeneous nucleation mechanism**

Design Space for Discontinuous Anti-solvent Crystallization



(a)



(b)

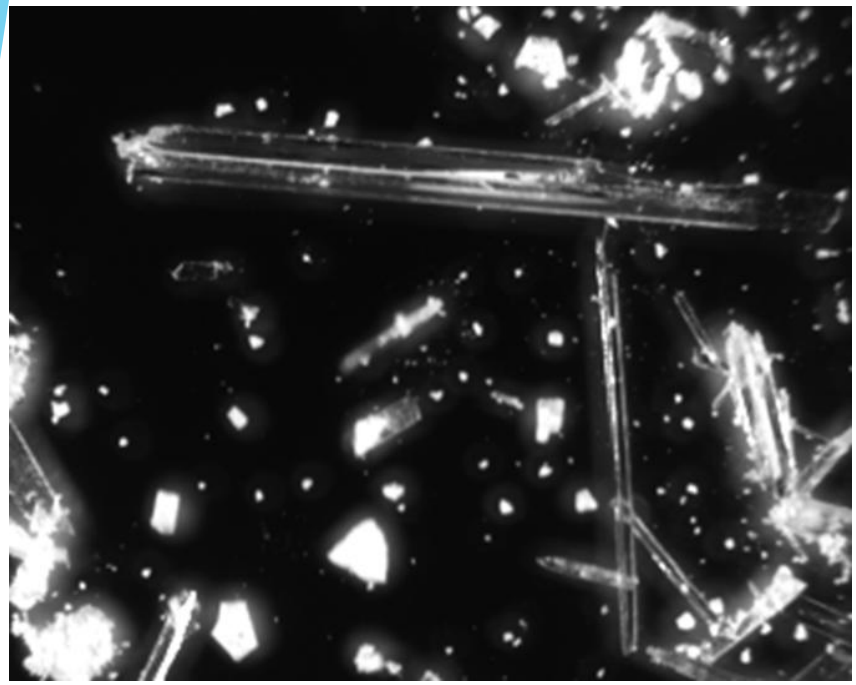
X1: Temperature; X2: Stirring speed; Mode: Final Medium Particle Size

- **Quick estimation of the response variable with a set of process conditions**
- **Defining final particle size range with biopharmaceutical or clinical inputs**

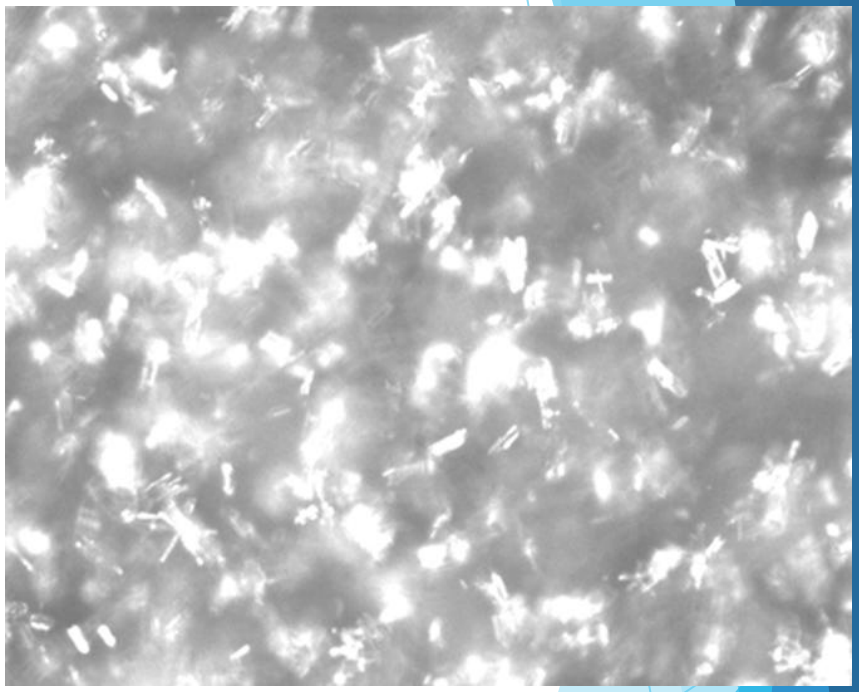
Discontinuous Anti-solvent Crystallization: Technology Verification

- Use of three online techniques (NIR, FBRM, and PVM) for simultaneously real-time process monitoring & measuring t_{ind} and other process stream's properties, respectively
  - Off-line materials characterization (Raman, XRD, NIR Imaging, etc.) to verify crystallinity, final crystal size and crystal morphology
  - Model construction
    - Linear regression model for correlations among t_{ind} data from various methods
    - First principle model for mechanistic understanding
      - ✓ Classical Nucleation Theory (CNT), etc.
  - Model verifications
    - Correlations
      - ✓ Data-driven and empirical, extrapolating discouraged
      - ✓ Additional data points for verification and scale up
    - First principle model
      - ✓ May need to verify validity of model assumptions (if any)
      - ✓ Extrapolating possible
      - ✓ Scale independent

Real Time PVM Images: Discontinuous vs. Continuous



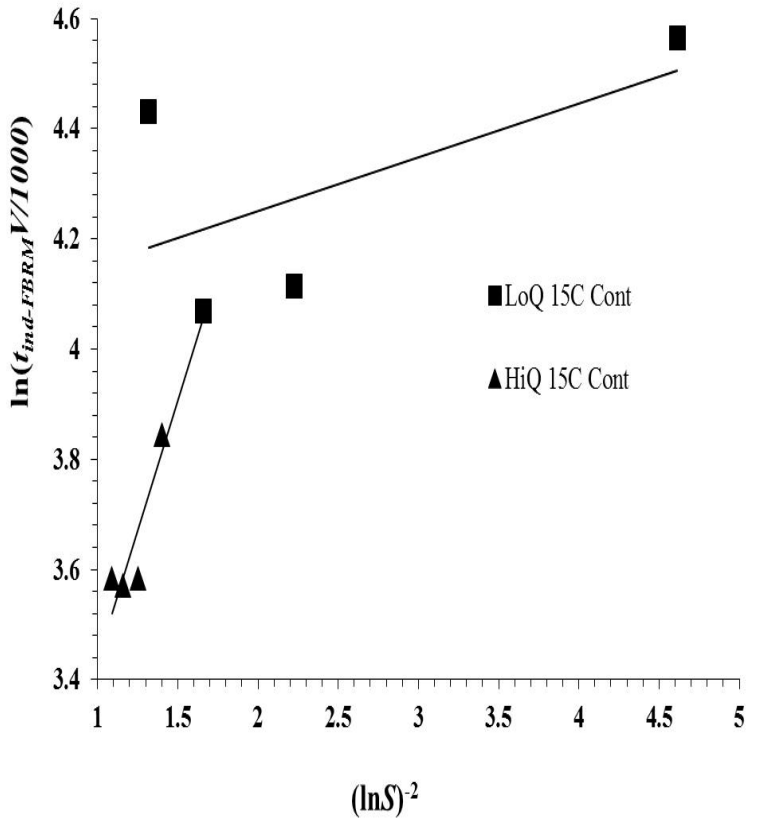
After discontinuous addition of 150 ml anti-solvent at 150C and 50 rpm

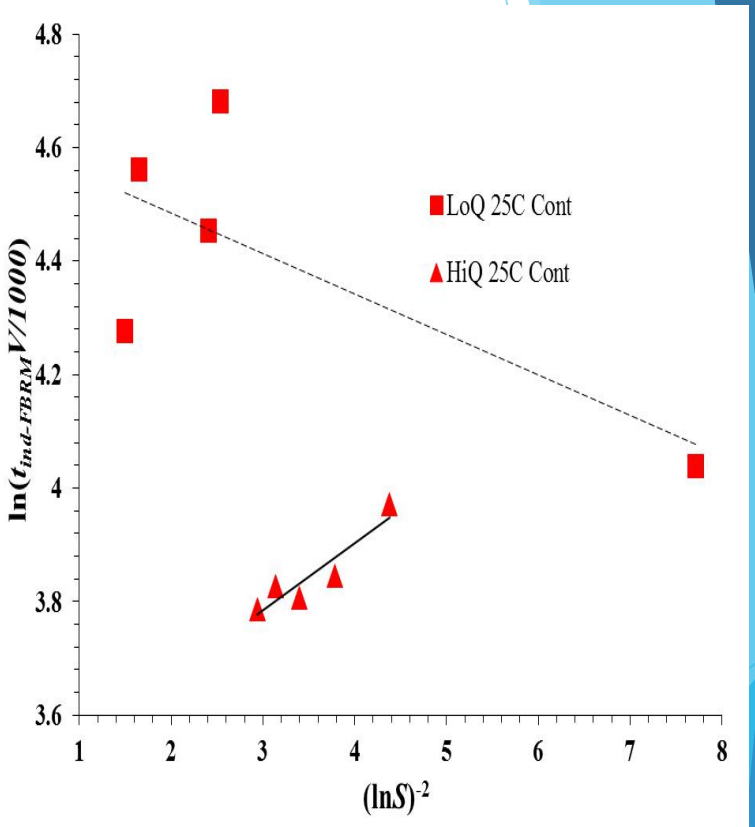


After continuous addition of 150 ml anti-solvent at 150C and 50 rpm

- **Continuous addition mode can generate more uniform CSD**
- **Continuous addition mode has advantage of better CSD control and hence better physicochemical properties control**

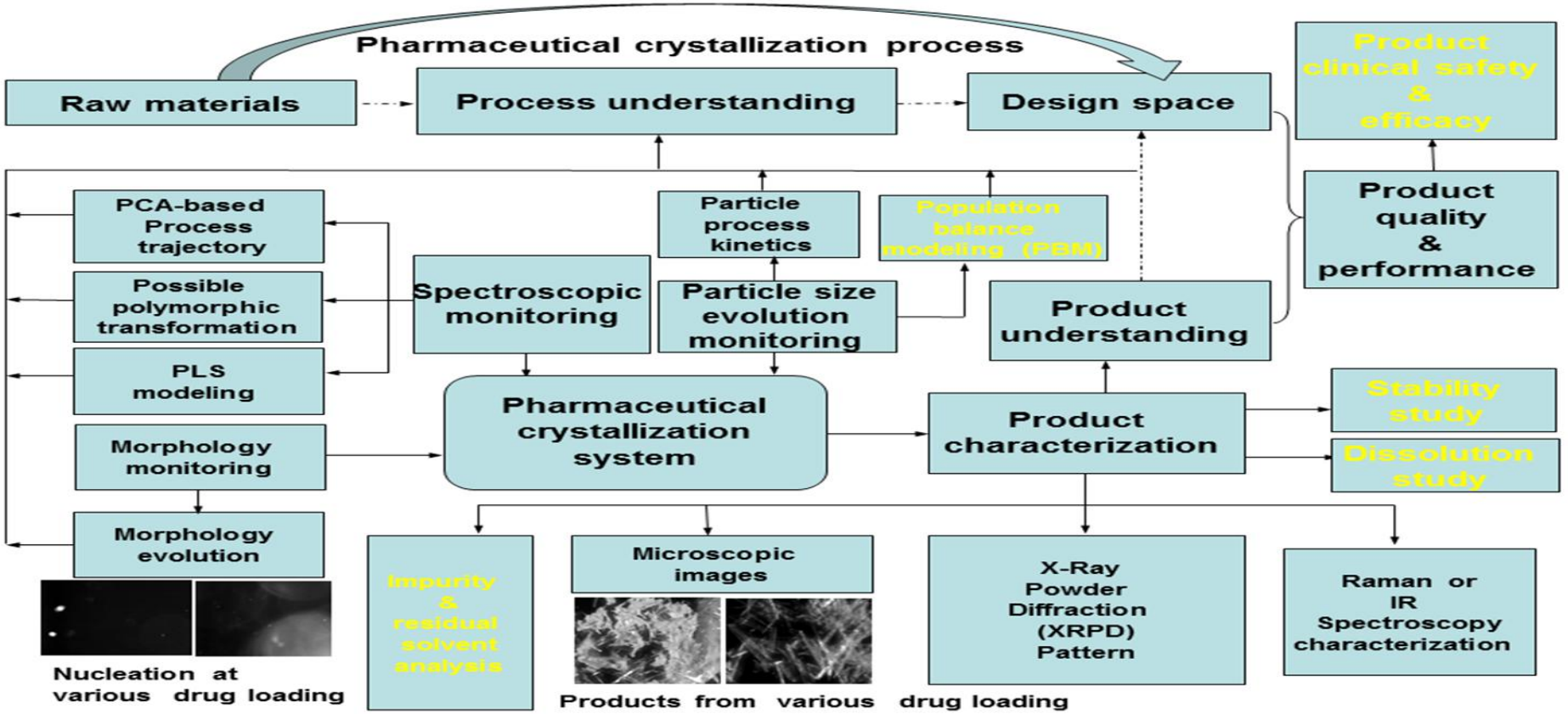
Continuous: MCNT Applicable?





- **At 15^{0}C, MCNT fits data well ; the angle b/w two regression lines $> 90^0$**
- **At 25^{0}C, MCNT fits data well; the angle b/w two regression lines $\approx 90^0$**

Integrated Approach for Pharmaceutical Crystallization PAT Study



Conclusions on crystallization

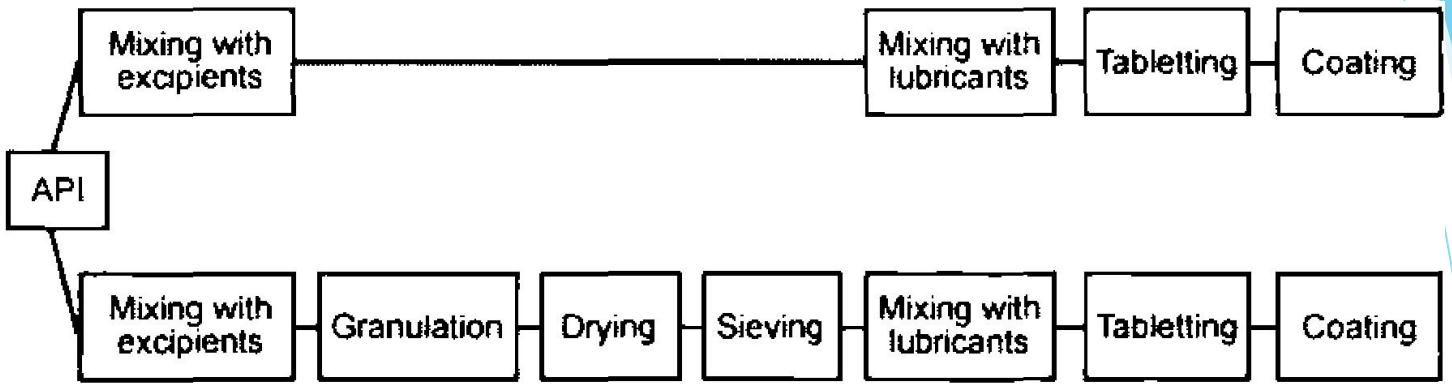
- It is a key process to pharmaceutical product quality. Innovative/emerging technologies brings new promises for pharmaceutical crystallization process development, scale up, and manufacturing
  - ✓ Multivariate approach help to identify CPP and construct design space between CCP and CQA
  - ✓ Real time monitoring provides unprecedented opportunities and plenty of data for
    - ✓ process understanding including process transition and steady state, process kinetics, etc.
    - ✓ Probing the nucleation and crystal growth mechanisms
- The application of novel/emerging technologies (including PAT and CM) in pharmaceutical sector is encouraged.

Powder Blending PAT Case Study

- Process end-point determination
- Design space

Why Powder Blending Important? A Process Engineering Perspective

- Two major manufacturing routes for tablets



- Wet granulation could mitigate Blending Uniformity (BU) risk
- Direct compression has potential BU issue, which could be translated to content uniformity (CU) issue and final drug product quality issues(e.g., sub-potency or over-potency)
  - Content and CU linked to safety, efficacy, and quality

Mixing & Segregation: Twin Sisters

- Powder mixing: governed by one or several mechanisms, i.e., Diffusive mixing/Shear/Convective
- Powder segregation: caused by differences in Size/Density/Shape/Other properties of particles
- Challenges and strategies to achieve a balance to ensure adequacy of mixing
  - ✓ Formulation strategy: product design and development
  - ✓ Process development: process design and development
  - ✓ Manufacturing: mixer design & selection, mixing process parameters, and scale up (i.e., kinetic, dynamic, and geometric similarity, etc.)
  - ✓ Regulatory science and assessment: science- and risk-based approaches
    - Risk mitigated via various process engineering methods
    - Risk mitigated via science-based scrutiny and release strategy

BU High Risk Category Products

- BU high risk category products
  - Highly potent drugs
  - Low dose drugs
  - Narrow therapeutic indices (NTI) drugs
  - Drugs of strong segregation or cohesion tendencies
- Unique challenges for BU assessment towards high risk category products
  - e.g., sensitivity, accuracy, precision of the analytical method, especially for low dose drugs
  - e.g., representativeness and accuracy of the sampling strategy

Applying PAT for Powder Blending Process: A System and Holistic Approach

- Materials
  - Inherent heterogeneity of pure components (raw materials) and mixture
  - Material properties
- Sampling
  - Sampling strategy (sampling device, sampling location, sample size, etc.)
  - Scale of scrutiny
- Measurement
  - Experimental errors associated with sampling practices
  - Dynamic process environment and measurement environment
- Analytical
  - Appropriate reference method establishment

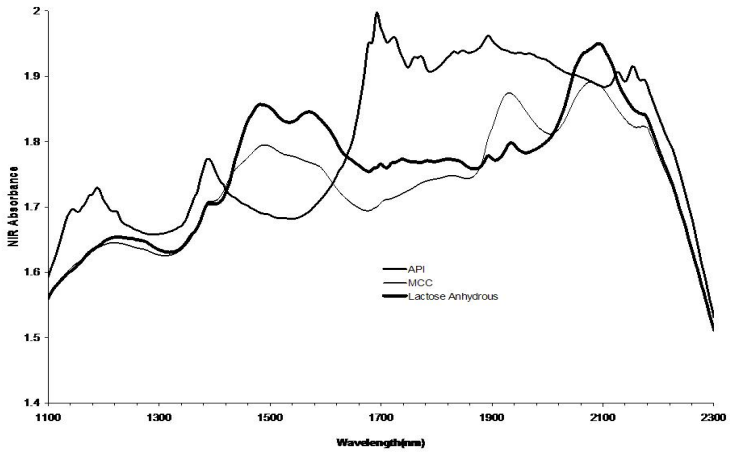
Innovative Approaches for Evaluating BU

- Spectroscopic method
- Imaging method to detect heterogeneity and potential segregation
  - Online or near real time
- Other method sensitive to compositions and properties of powder blend
- Emerging pharmaceutical manufacturing technology: continuous mixing
  - Residence time distribution (RTD)

Evaluation of Blending Progress via Near-infrared Spectroscopy Monitoring

NIR measurement

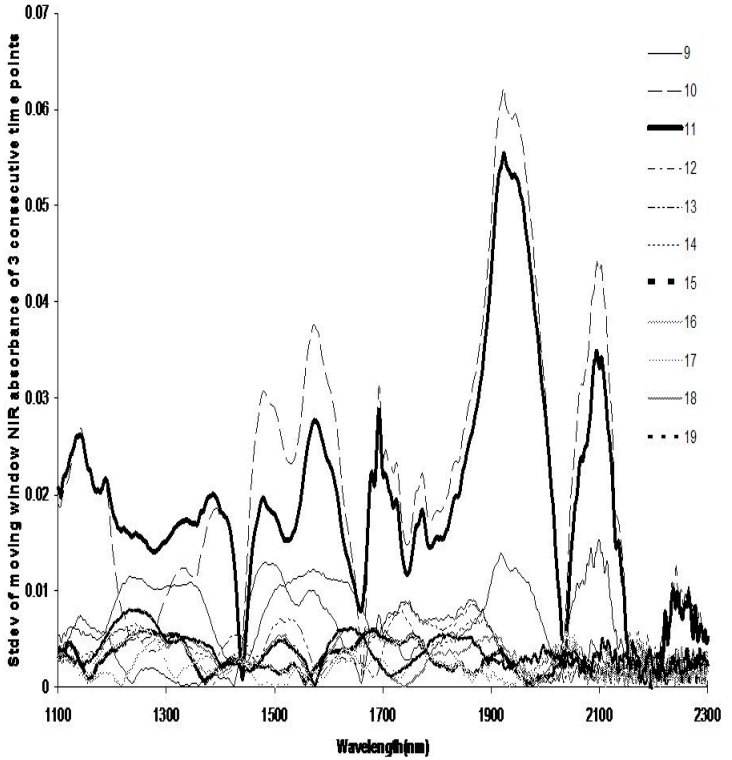
Pure components' spectra



Powder blending NIR monitoring

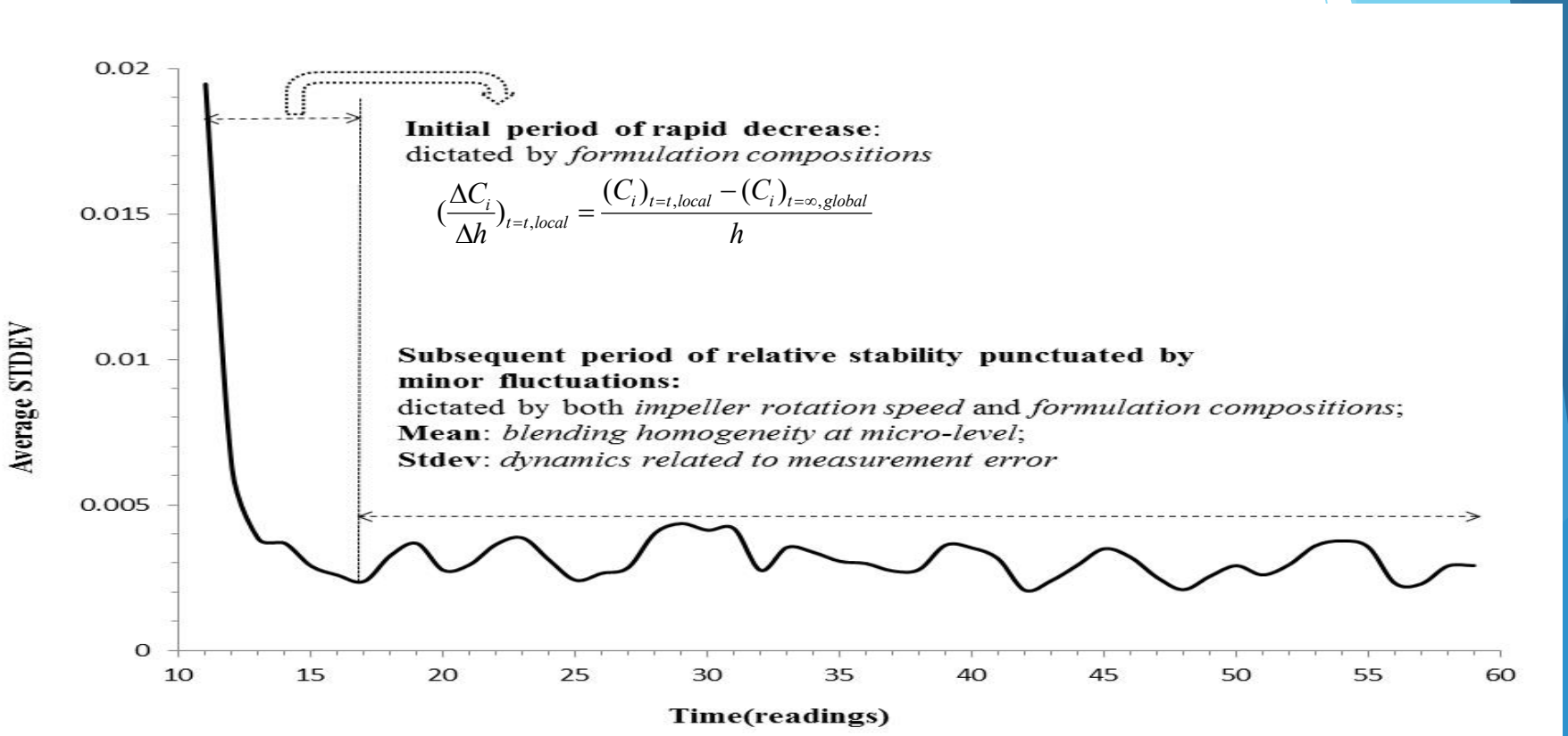
Time series of process spectra

Stdev of three consecutive NIR spectra



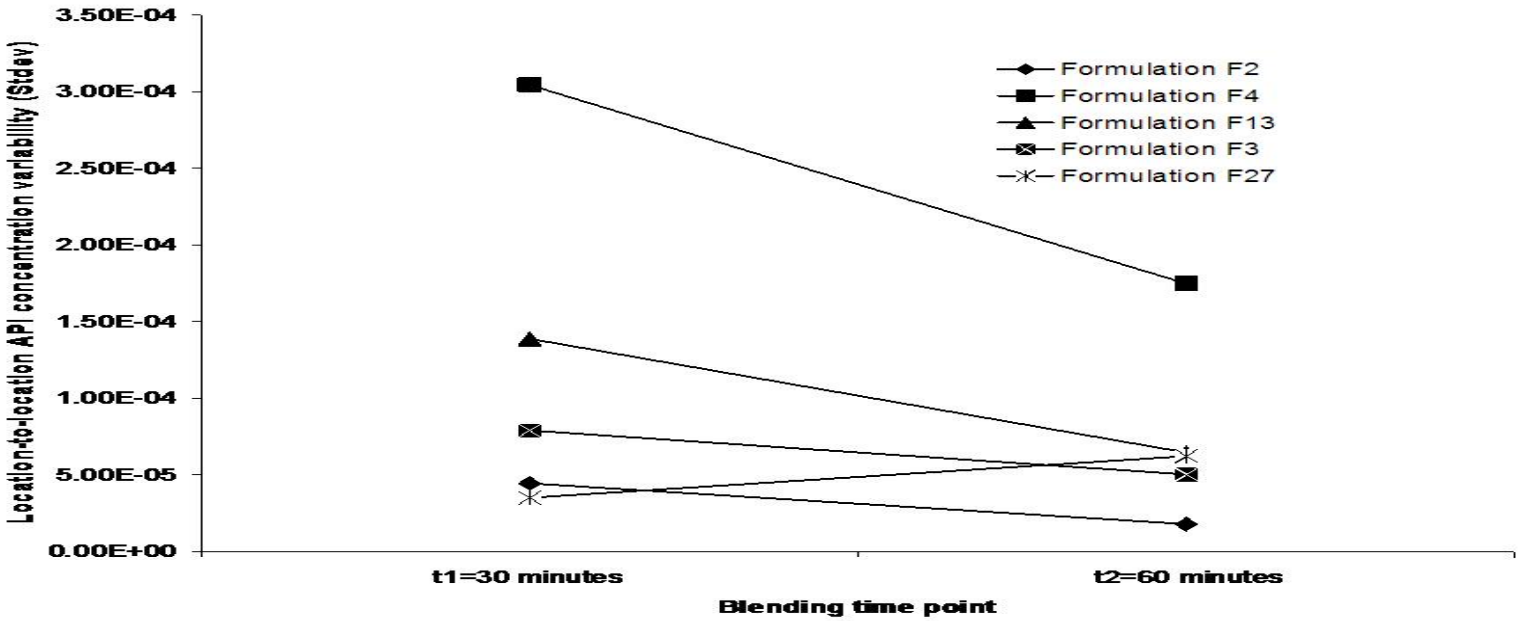
Process end-point

Blending Process Thermodynamics and Dynamics Interplay



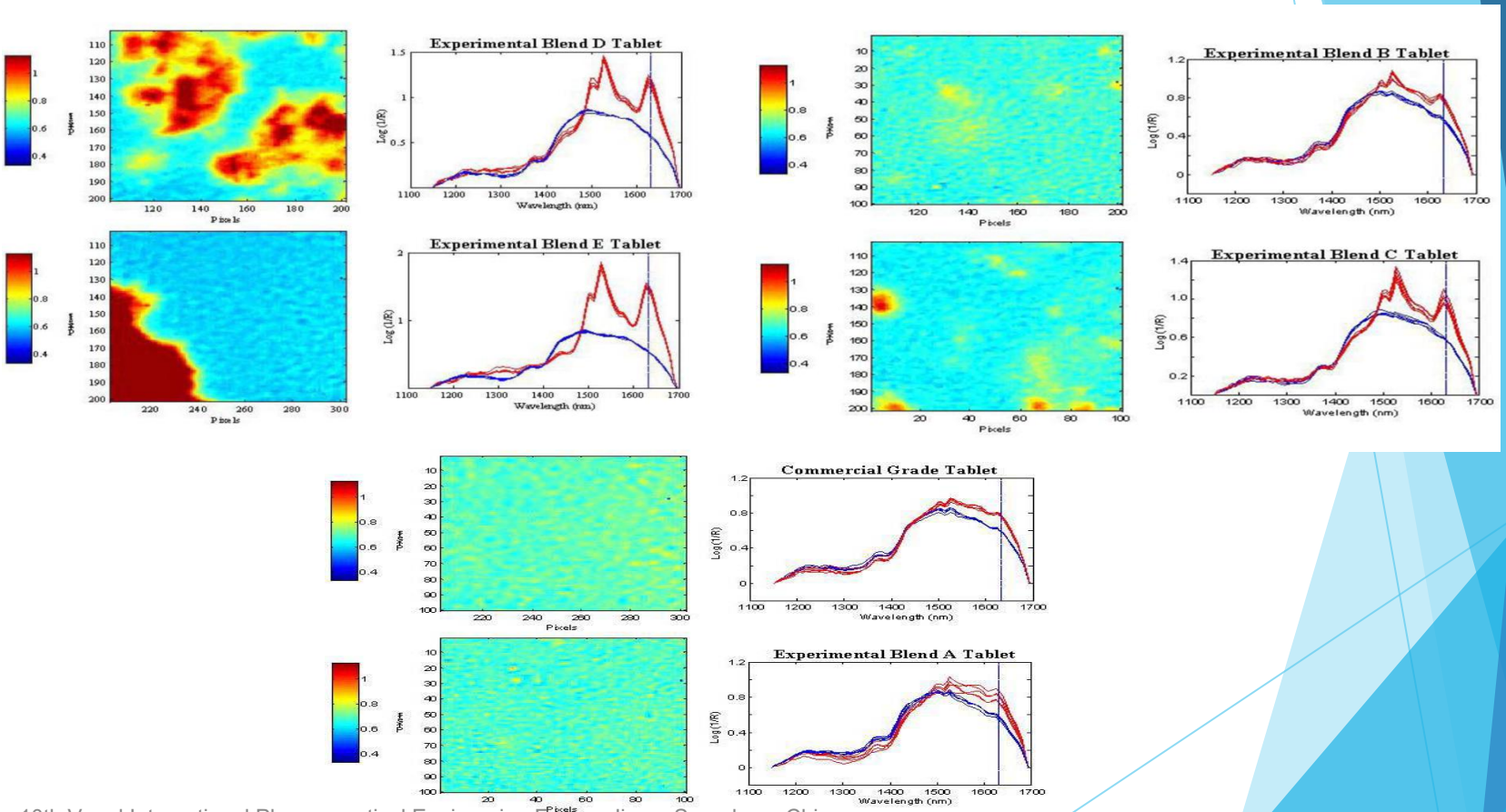
h: characteristic length that powder molecule should travel within the powder bed

Evolution of Location-to-Location Variability vs. Blending Time



- 4 out of 5 blending batches, the location-to-location variability decreases over time;
- Batch F27: an opposite behavior, probably due to it representing a worst case scenario,i.e., the lowest API concentration and the lowest impeller speed.

Poorly, Moderately, and Well-blended Tablets: NIR Chemical Imaging



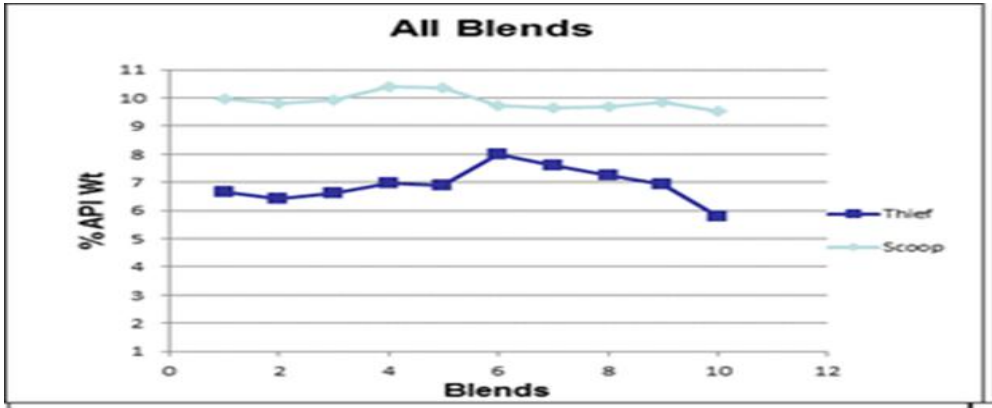
Measurement variance analysis

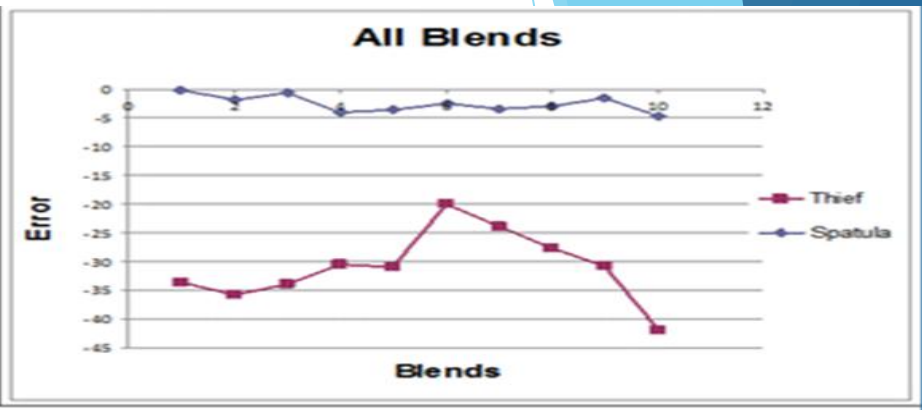
- Variance partition

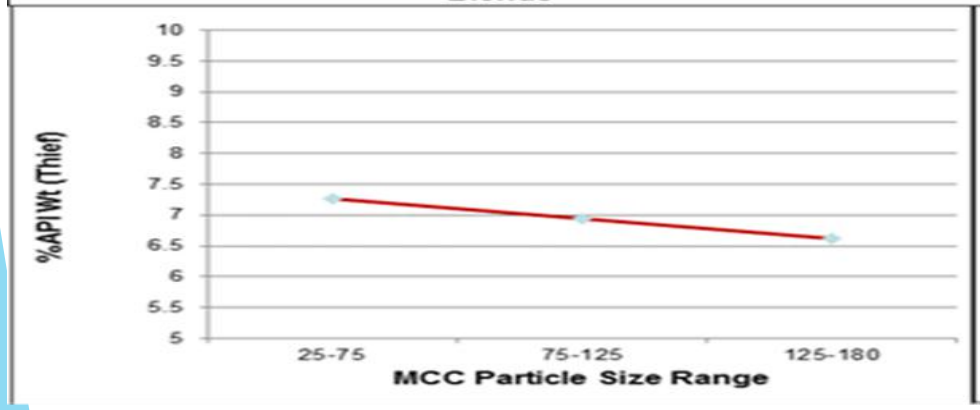
$$\sigma_e^2 = \sigma_m^2 + \sigma_{s,online}^2 + \sigma_{s,offline}^2 + \sigma_a^2$$

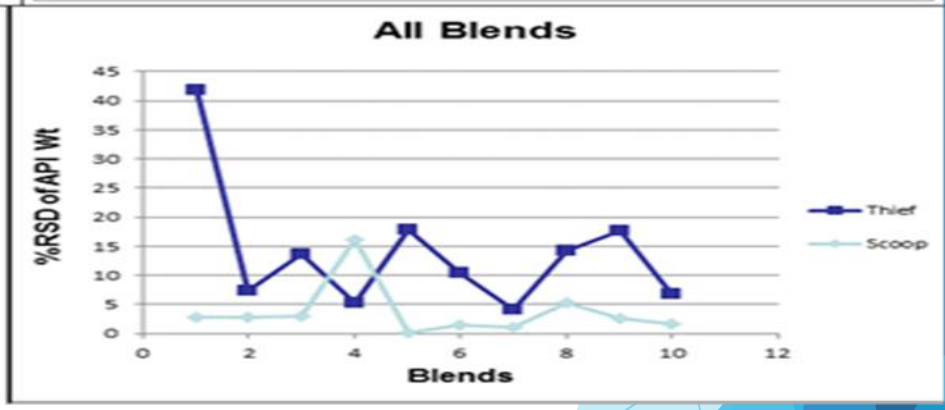
- Variance by virtual sampling error of the NIR probe:
  - Dynamic error due to powder bed microstructure fluctuations during blending; possible voids or cavities in powder bed; moment of no powder present in the optical path length.
  - Static sampling error due to inherent electronic noise of the NIR instrument.
- Variance by sampling error of taking real time sample from powder bed via actual sampling device

Sampling Bias of Thief Device







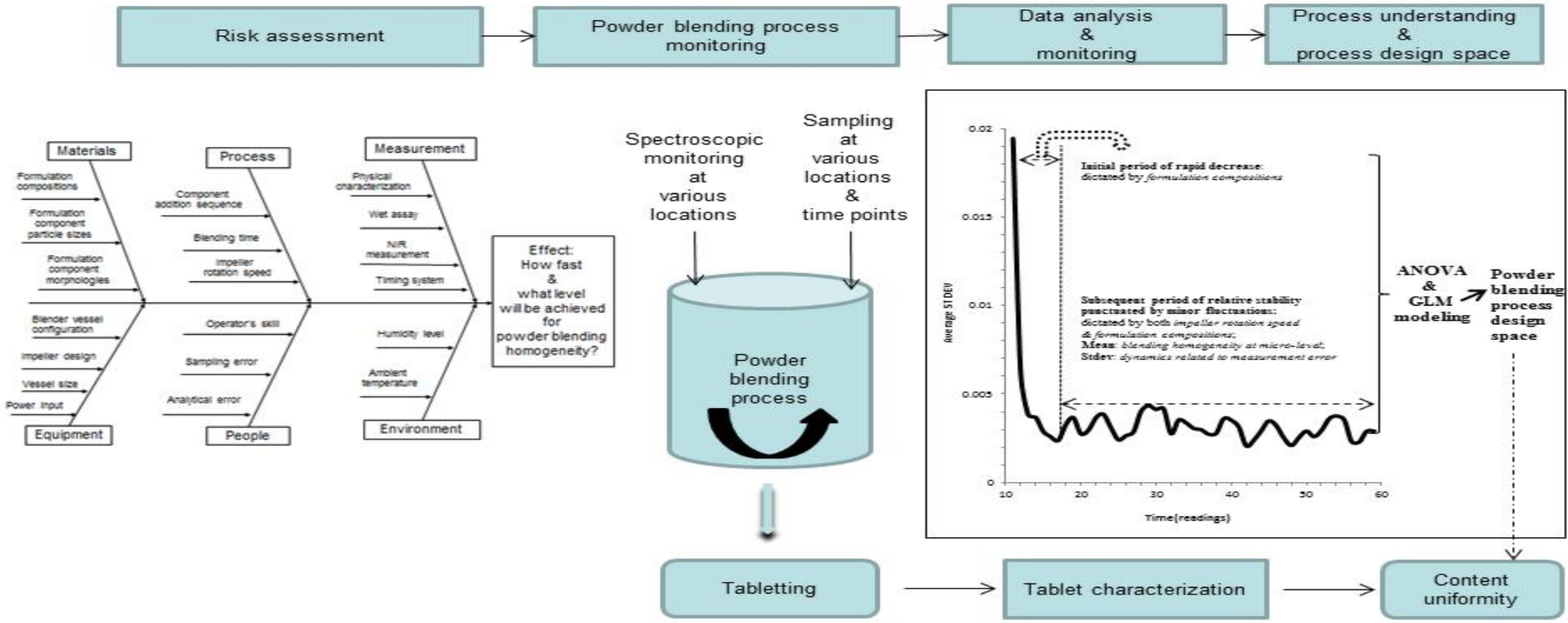


1. Thief sampler provides significantly lower accuracy of phenytoin sodium content assessment than spatula sampling.
2. the thief sampler has a sampling bias towards larger excipient particles, hence neglecting the smaller phenytoin sodium particles.

Scale-up Considerations

- Combination of DOE multivariate models, process monitoring, and mechanistic studies
- Blending vessel size may be significant
- First principle models and computation tools (CFD, DEM, etc.) insightful
- Scale-independent parameters and dimensionless numbers for process scale-up
- Challenges
  - ✓ Resolution, sensitivity, reliability, and mature level of novel and emerging technologies for assessing BU either in real time or near real time
  - ✓ Validation of the measurement
  - ✓ How to assess the true uniformity of powder blends given the possible sampling error, measurement error and uncertainty, and analytical error involved?

Integrated PAT for Powder Blending



Conclusions on Powder Blending

- Ensuring adequacy of mixing
  - critical to product quality and safety, especially for NTI drug
- Innovative approaches promising
  - Innovative formulation strategies
  - Real-time process monitoring and control
- Understanding measurement science
  - Scale of scrutiny
  - Measurement uncertainty
  - Materials heterogeneity across locations and across tablets
- A holistic approach to assess low dose drug manufacturing
  - Material science
  - Sampling strategy
  - Measurement science
  - Analytical

Bioreactor Cell Culture PAT Case Study

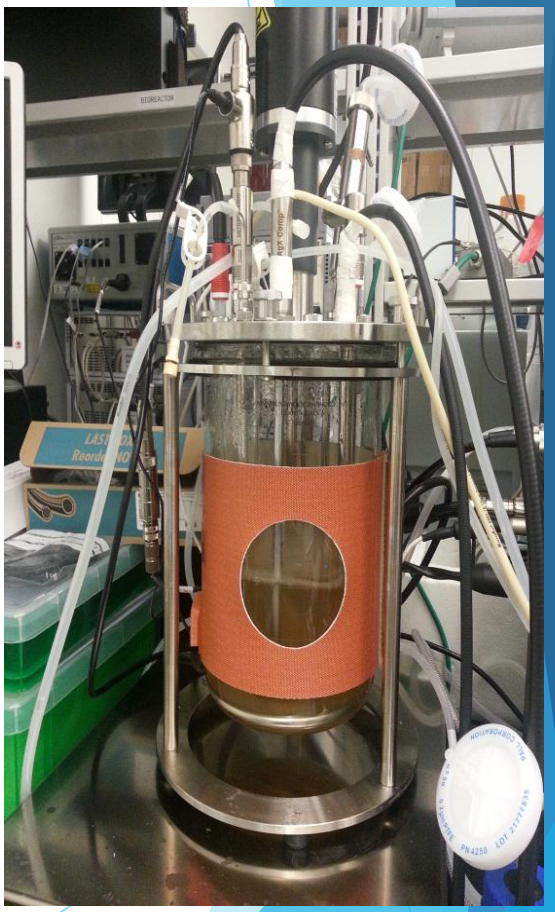
- Predictive modeling
- Rational feeding strategy

Biotech Products Manufacturing Innovation: Current status of process monitoring & control

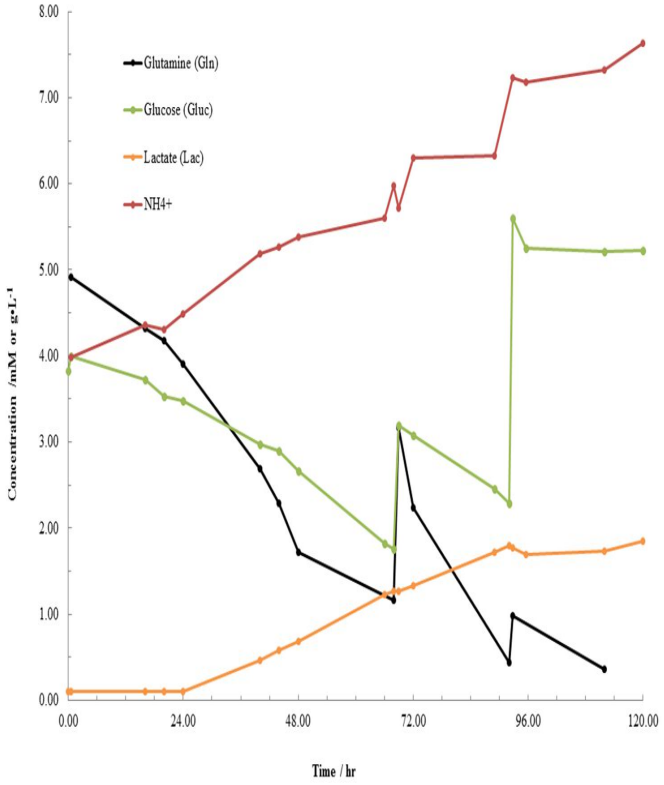
- Promising R&D; Manufacturing experience on unit operations
- Spectroscopic tools (NIR and Raman (N. R. Abu-Absi, *Biotech. & Bioeng.*, Dec. 2010)) for real-time process monitoring
  - Ability to acquire dense process data in real time, and to identify and remedy issues earlier in the process
  - Contact PAT sensors: able to withstand autoclave; function over processing time
    - ✓ Sterilization, stability , and robustness considerations for probe design, fabrication, and qualifications
  - Processing material stream: highly heterogeneous & multi-components system
    - ✓ Specificity, accuracy, and precision considerations for monitoring technologies and validations
    - ✓ FTIR: promising demonstrated through off-line FTIR combined with chemometrics (Sellick C A *et al*, ***Biotechnology & Bioengineering***, 2010, 106(3): 432-442)
- Other online real-time process monitoring tools available
  - Online strategy combined NIR and dielectric spectroscopic technologies for characterization of cellular growth and physiology of CHO cells cultivated in bioreactors. (Franck Courtès, et al., *BMC Proceedings 2015*, 9(Suppl 9):P48)
  - Some tools available for downstream processing

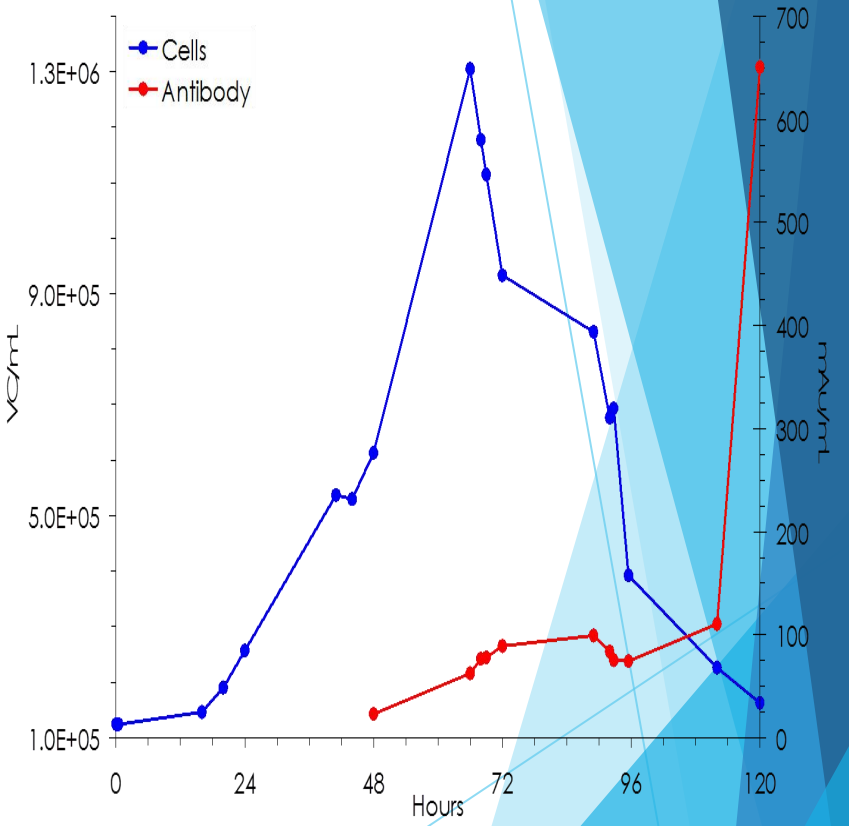
FTIR Monitoring of Bioreactor Cell Culture Process

- Goals
  - Identify fingerprints of key metabolites in the media
  - Develop process chemometric models to correlate FTIR spectra with key metabolites' concentrations and protein yield
  - Develop process monitoring and control strategy

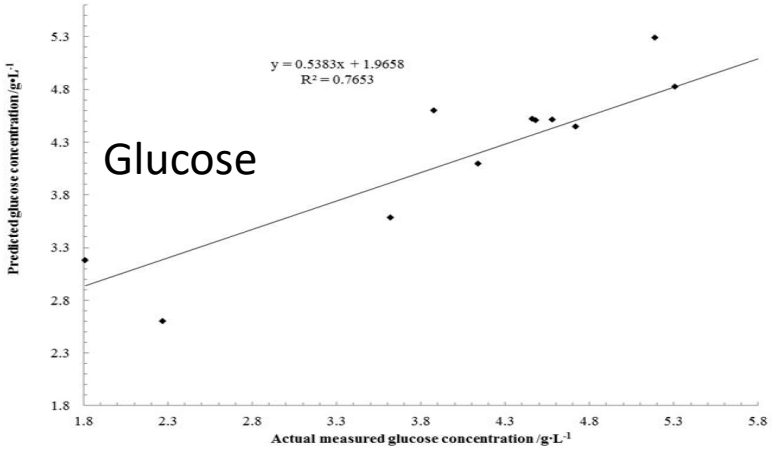


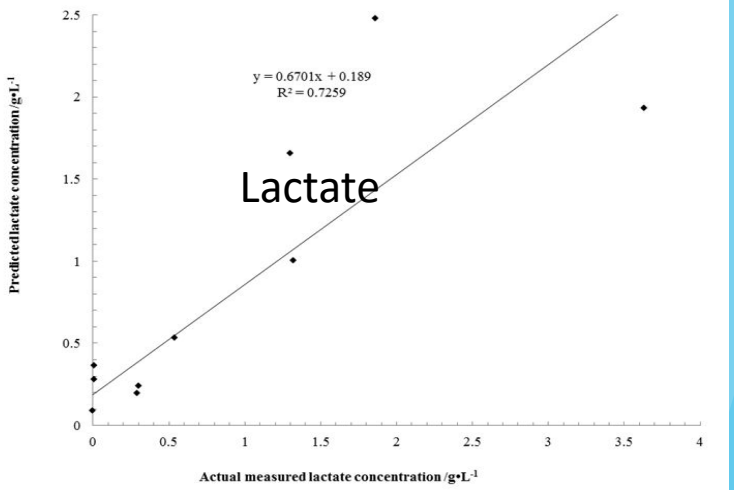
A Bioreactor Cell Culture Process: Key Metabolite Profiles and Process Trajectory

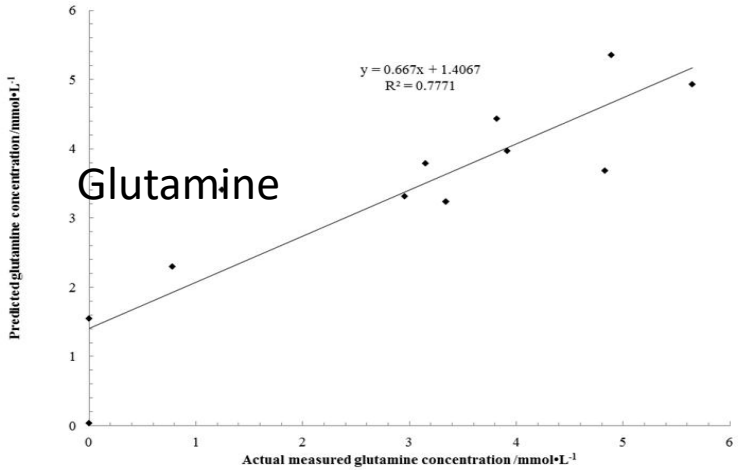


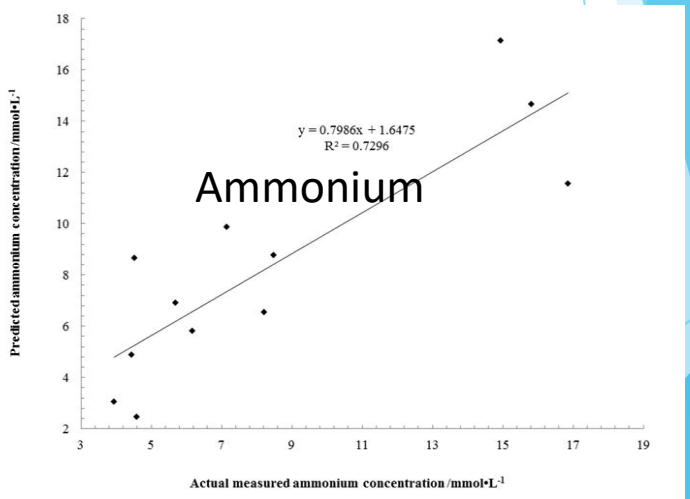


Global PLS Models for Cell Culture Process









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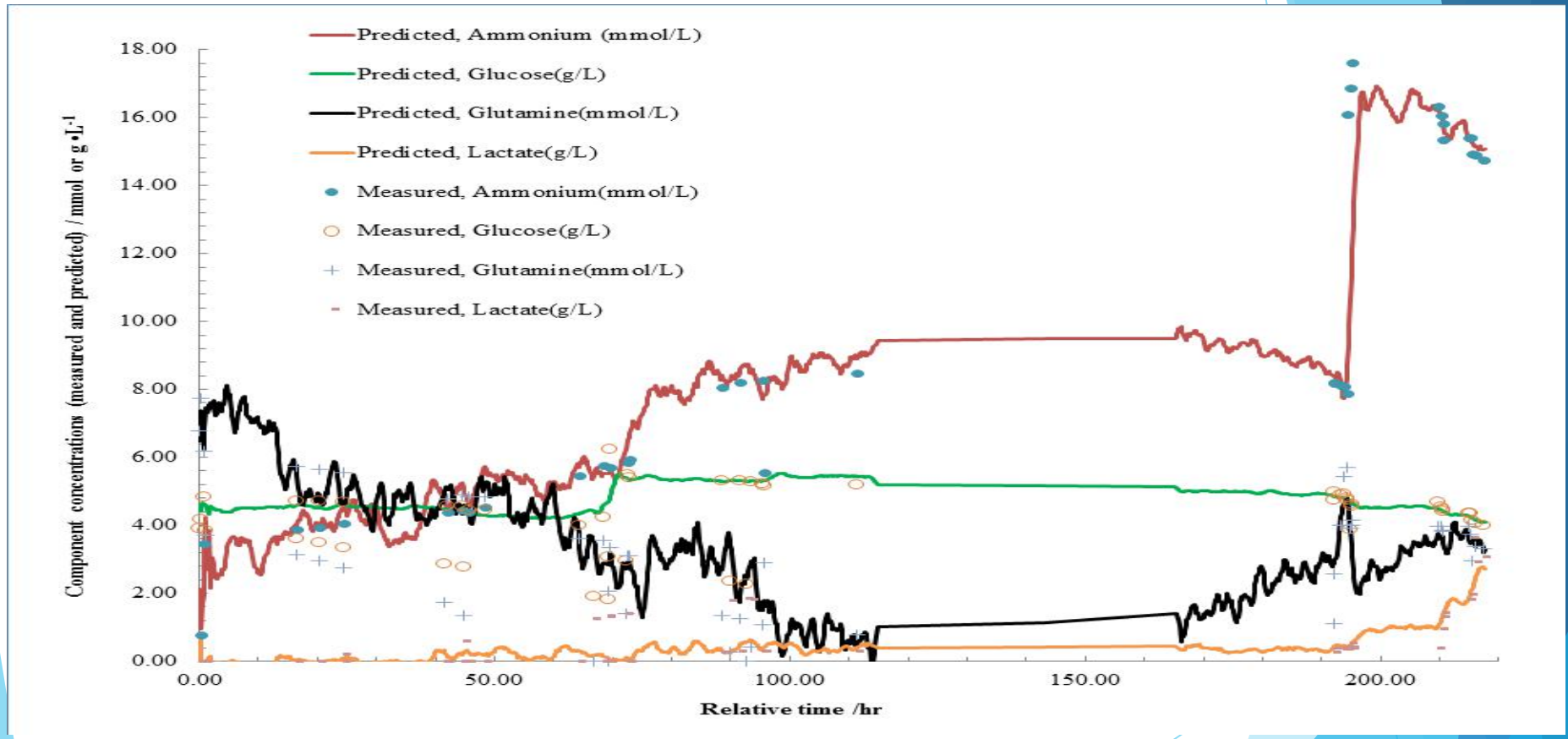
Predictions from Individual PLS Model for Batch A



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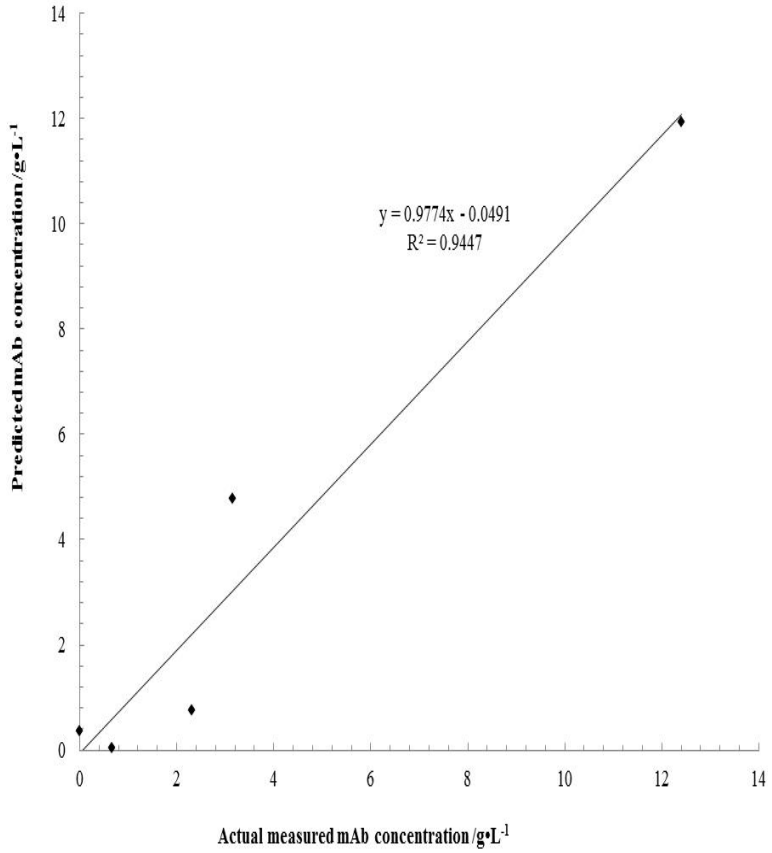
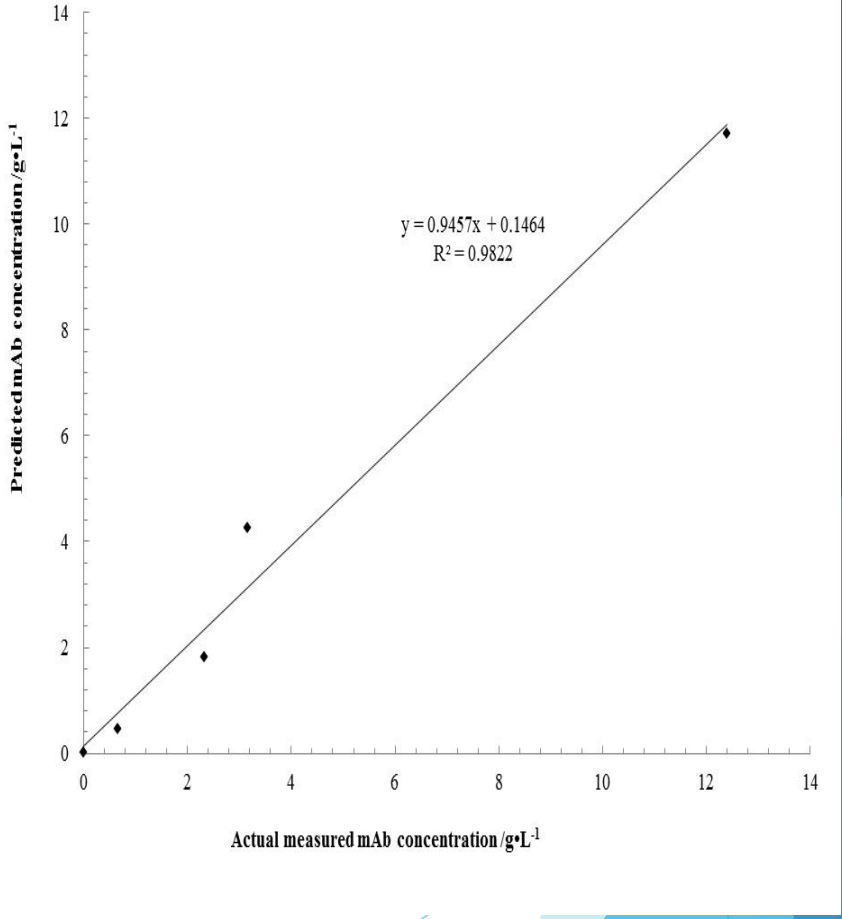
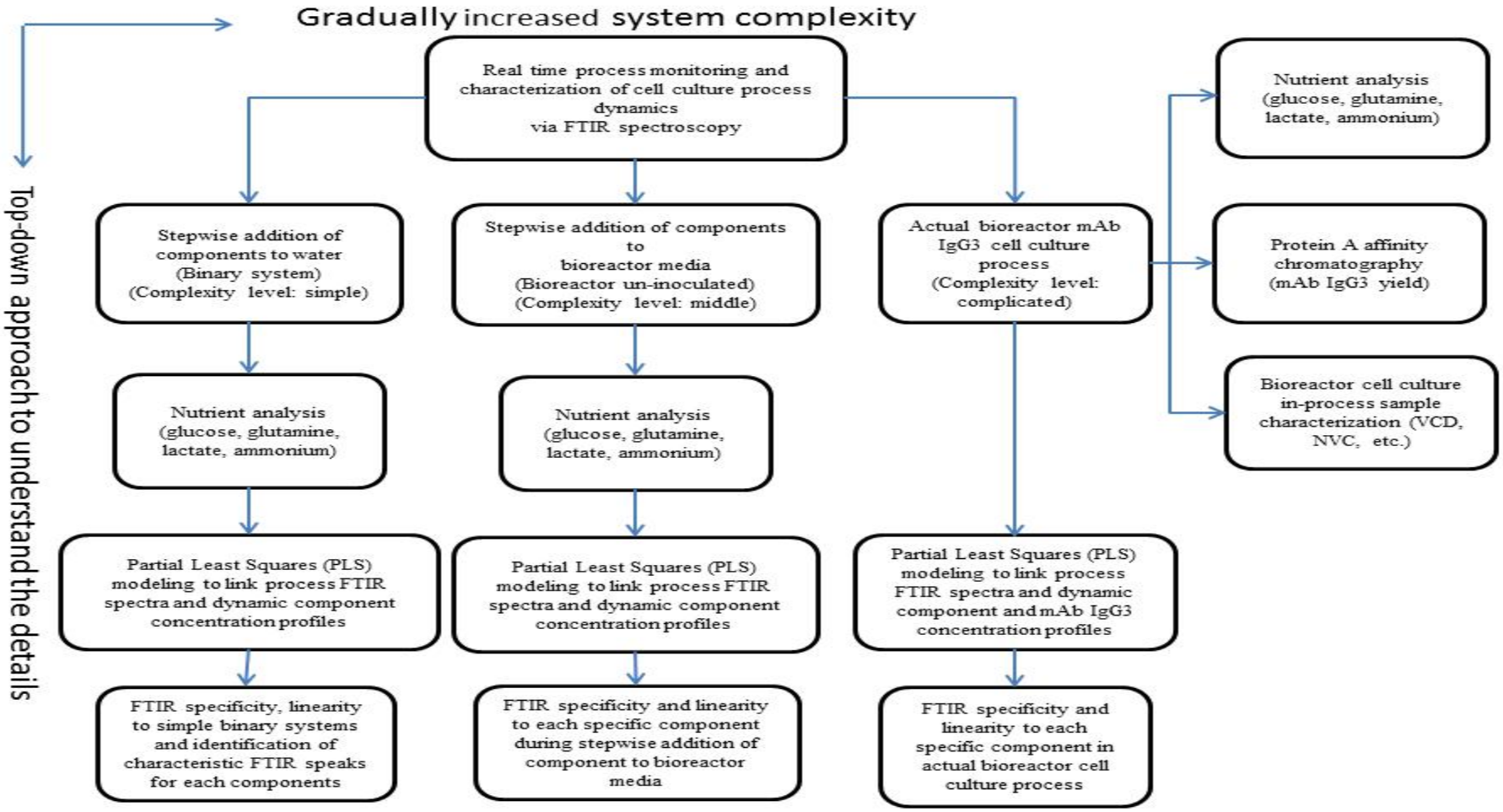
PLS Models for mAb Concentrations





A Top-Down Approach



Wu H., *et al*, ***European Pharmaceutical Review***, Dec 2015 (6), 50-56

Implications and Opportunities

- FTIR for real time process monitoring of bioreactor cell culture dynamics
  - Provide early indicator which enables us to make a go or no go process decision
  - Achieve more rational feed by skipping a guessed feed point and waited until next point to feed, or trigger an automated feed any time before or a guessed point
    - ✓ No need to “break the seal” and draw a sample
    - ✓ No need to keep the nutrient analyzer calibrated or have a technician process samples
- A rationale top-down approach of using novel PAT technologies to gain process understanding of gradually increased system complexity
- Possible to establish process design space for better process control

Industry Implementation Trends of NIR-based Applications

- NIR applications: Real Time Release Testing (RTRT) as part of control strategy
  - RTRT will, in general, comprise a combination of process controls which may utilize PAT tools, e.g., NIR and Raman spectroscopy (usually in combination with multivariate analysis), together with the control of relevant material attributes. Spectral data monitored on-line controlling content of active substance, polymorphism, water content, blending uniformity, particle/powder properties or film thickness could thereby replace end-product testing, e.g., uniformity of content, tablet strength and drug dissolution

-Guideline on Real Time Release Testing (formerly Guideline on Parametric Release). EMA/CHMP/QWP/811210/2009-Rev1

Industry Implementation Trends of Continuous Manufacturing

- Increased interest in continuous manufacturing for both small molecules and biotech processes
- Noticeable interest in continuous manufacturing for drug product, drug substance, and integrated drug substance and drug product
- FDA now have 4 approved continuous manufacturing applications.

Conclusions

- Advanced pharmaceutical manufacturing evolving
  - ✓ Research: systematic progress on real time monitoring and control of batch processing unit operations across both small molecule drugs and large molecule drugs
  - ✓ Industrial implementation: real time release testing (RTRT) as part of control strategy (focused on monitoring and control of CQAs)
  - ✓ Industrial trend: real time and monitoring of continuous processing unit operation and/or entire processing line as essential control strategy
- Unprecedented opportunities for innovations and collaborations for better manufacturing process and product quality
- Early adaption of advanced manufacturing including PAT, continuous manufacturing, and emerging technologies encouraged

Acknowledgements

- FDA CDER OPQ Office of Process and Facilities (OPF)
- FDA CDER OPQ Office of Testing and Research (OTR)
- Funding Support
  - FDA CDER Regulatory Science and Review (RSR) Funding RSR04-16, RSR 12-42, and RSR-13-32
  - FDA CDER OTR PAT-12 Grant
- Former ORISE Fellows: Maury White, Ryan Foringer, Koushik Sowrirajan, Suyang Wu
- Various Technology Vendors
- FDA management team: Drs. R. Shah, R. Madurawe, A. D'Sa, L. Yu, M. Kopcha, J. Woodcock

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