Powder Blending in the PAT Era

Current Research and Resources

DUQUESNE UNIVERSITY
CENTER FOR PHARMACEUTICAL TECHNOLOGY

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Heidelberg PAT Conference

Outline of Presentation

- Basics of Powder Blending
- Critical Parameters Affecting Performance
- Effect of Blending on Product Quality
- (Optical) PAT Sensors for Monitoring & Analysis
  - Case Study: Blend Analysis via NIR Imaging Spectroscopy
  - Case Study: Efficient Calibration
  - Case Study: Advanced Endpoint Criteria
- Future Directions in Pharma Blending

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Basics of Powder Blending

- Objective: Mechanical agitation of powder mixtures to achieve uniformity
- Mixture Classifications:
  - Ordered
    - Interaction between major and minor component
    - Size mis-match between components
    - Uniformity is independent of sample scale
    - Cohesive particles
  - Partially-ordered
  - Random
    - Equal size/weight particles
    - Little or no surface interaction (>100 μm)
    - Level of uniformity is dependent on sample scale

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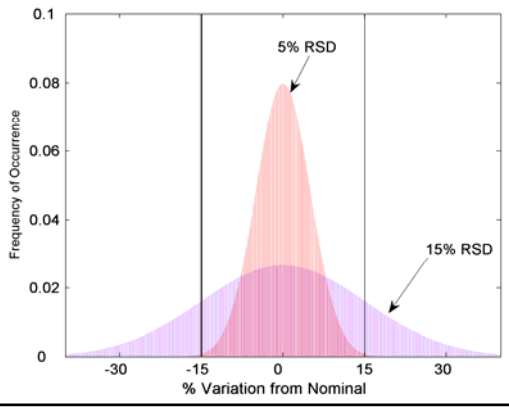
Basics of Powder Blending

- Measurement of Blend Uniformity:
  - Between-Sample Variance (σ^2)
  - Maximizing Uniformity ≈ Minimizing Variance (at a given scale)



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Basics of Powder Blending

- Mixing Mechanisms:
  - Diffusion
    - Random particle movement throughout powder bed
    - Dominant mechanism for tumbling powder blenders (e.g. bin-, V-blenders)
  - Convection
    - *En masse* movement of large volumes within powder bed
    - Dominant mechanism for stationary mixers with moving parts (e.g. Hobart mixer, ribbon blender, etc.)
  - Shear
    - Mixing occurs along slip planes between regions of particles
    - Often considered a combination of diffusion & convection
    - Level of shear is controlled by rate of kinetic energy transfer to particles (e.g. intensifier bar)

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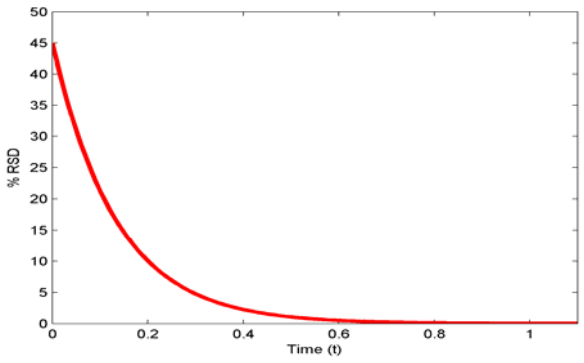
5

Basics of Powder Blending

- Mixing Rate: $\sigma_t^2 = Ae^{-(k_{diff}+k_{conv}+k_{shear})wt}$
  - w = rate of rotation, agitation
  - t = time
  - k = rate constant for mixing
  - A = arbitrary constant



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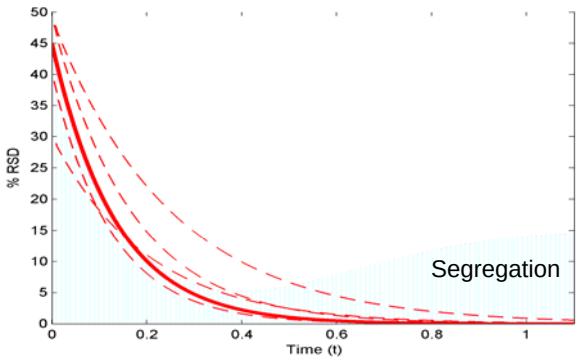
Basics of Powder Blending

- Mixing Rate: $\sigma_t^2 = Ae^{-\sum k_{unk_{t,c,h}} wt} + P_{seg_{t,w,c}}$
  - Most pharmaceutical powder blends are seperable, with stochastic rate
  - Finite probability of spontaneous segregation ("de-mixing")
  - True (observed) rate is a function of many uncontrolled variables



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Critical Parameters Affecting Performance

- Particle Morphology Distribution
  - Size
    - Often cited as most critical variable
    - Smaller particles "sift" while larger particles "float"
    - Size mismatch can be detrimental or beneficial, depending on mechanism and classification of mixing
  - Shape
    - Impacts rate of particle interaction, cohesiveness
  - Density
    - Larger, more dense particles will have greater momentum
- Cohesiveness
  - More cohesive powders have limited ability to flow
  - Tendency to aggregate with other cohesive particles, induces size segregation
  - Cohesive powder beds are more likely to create motionless "voids"
- Friability

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Critical Parameters Affecting Performance

- Mixer design
  - Mechanism of mixing most affected by design
  - Symmetry tends to reduce blending efficiency
- Rotational speed
  - Increases energy intensity and the rate of diffusion and/or convection
  - Large, dense particles can be entrained by centrifugal force
- Fill level
  - Excessive fill level decreases blend efficiency, increases likelihood of voids
- Loading configuration
  - Minor components can become “trapped”
- Energy Intensity (e.g. intensifier speed)
  - Reduces incidence of agglomerates
  - Can cause excessive attrition, change in crystallinity

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Critical Parameters Affecting Performance

- Ambient conditions
  - Variation in humidity will significantly affect the ability of the particles to dissipate charge
- Mixture composition
  - Un-controlled variation in concentration of components (assay) or quality of individual constituents will interact with other factors

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Effect of Blending on Product Quality

- Critical quality attributes (CQAs) form the basis for PAT risk assessment
  - Priority of PAT sensors and controls should be defined by impact on risk to CQAs
- CQAs affected by blending performance:
  - Content Uniformity
  - Assay (loss of material)
  - Physical uniformity
    - Micro-distribution/interaction of powders
    - Crystallinity, compactibility, etc.

11

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Objectives of PAT in Blending

- Blending is often the key critical control point
  - Directly effects multiple CQAs
  - Blend performance is a complex, multivariate function:
    - Most factors have multiple interactions
    - Many factors have limited or no controls
- Objectives of PAT for blending:
  1. Minimize risks to product quality
     - Critical quality attributes (CQAs)
  2. Maximize production efficiency
     - Reduction of cycle time (C/T)
  3. Facilitate process understanding



12

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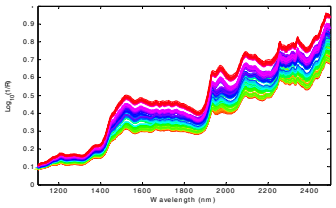
PAT Sensors for Monitoring and Analysis

- NIR Spectroscopy
  - Basics:
    - Measurement of absorbance via diffuse reflectance
    - (Relatively) deep sample penetration
    - Spectra are sensitive to chemical and physical quality of mixture
  - Method development
    - Qualitative (peak monitoring, etc.)
    - Quantitative
      - Current methods can be onerous
  - Commercial Viability/Background
    - In-line NIR research has been public for >10 years
    - Multiple (relatively) low-cost instrumentation choices
    - RF Wireless sensors available OTC
    - Deployment will soon be "algorithmic"

Courtesy of:
Control Developments, Inc.



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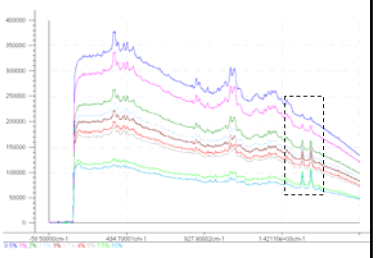
PAT Sensors for Monitoring and Analysis

- Raman Spectroscopy
  - Basics:
    - Measurement of inelastic scatter intensity
    - Shallow sample penetration
    - Spectra are more less sensitive to excipients
    - Mostly robust to physical sample interactions
  - Method development
    - Specificity for API is usually more direct
  - Commercial Viability/Background
    - Raman blend monitoring research is more recent, builds upon NIR experience
    - Choice of in-line instrumentation is much more limited
    - Wireless Raman spectrometers are not yet available

Source: Arwa El Hagrasy
ASQ Fall Tech, 2004



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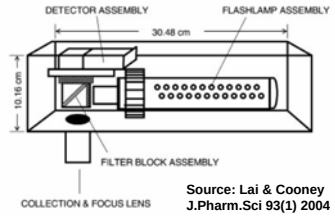
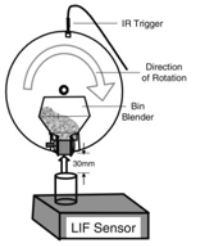
PAT Sensors for Monitoring and Analysis

- Laser-Induced Fluorescence
  - Basics:
    - Measurement of short-lifetime fluorescence induced by high-energy pulse from flashlamp
    - Shallow sample penetration
    - Choice of flashlamp and detector filters determine sensitivity
  - Method development
    - Complete specificity
    - Low sensitivity to excipients (uses background signal)
  - Commercial Viability/Background
    - Continues to be prototypical?



Source: Lai & Cooney J.Pharm.Sci 93(1) 2004



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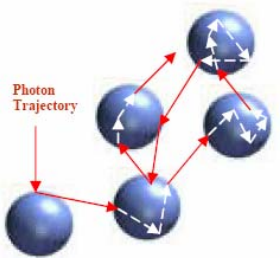
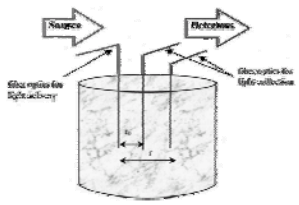
PAT Sensors for Monitoring and Analysis

- Frequency-Domain Photon Migration (FDPM)
  - Basics:
    - Measurement of the change in frequency and phase of radiation during in-sample diffusion
    - Can independently measure particle size and optical absorbance
    - effectively separates scatter and absorption
  - Method development
    - Materials constants must be known for prediction & calibration
      - Refractive index
      - Powder bed solid fraction
  - Commercial Viability/Background
    - Fully prototypical
    - May be an ideal extension of NIR





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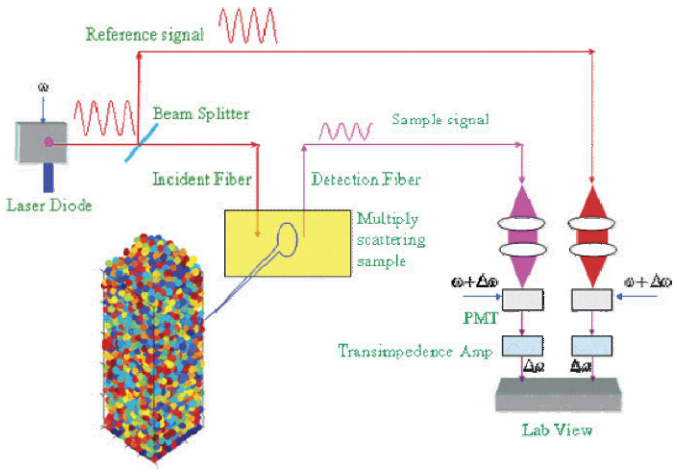
Frequency-Domain Photon Migration (FDPM)



Pan T.S., Sevick-Muraca E.M. J. Pharm. Sci. 2006, 95:530-541

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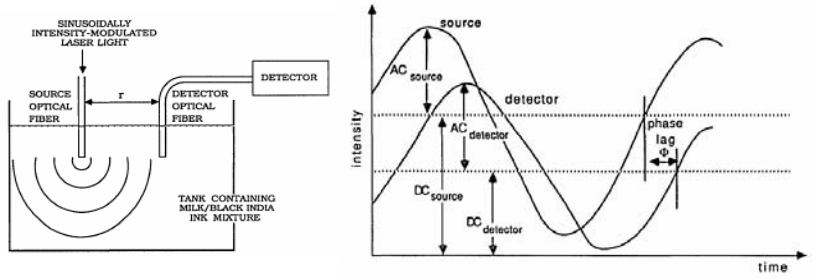
Frequency-Domain Photon Migration (FDPM)



- Light-density wave is measured in term of relative AC, DC and PS:
  - AC: the amplitude of the light intensity oscillation
  - DC: average light intensity
  - PS: phase shift

Fishkin J.B. and Gratton E. J. Opt. Soc. Am. A. 1993,10: 127-140

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PAT Sensors for Monitoring and Analysis

- NIR Imaging Spectroscopy
  - Basics:
    - Measurement of microscopic/ macroscopic distribution of diffuse reflectance
    - Image resolution limited by depth of penetration/ diffusion
  - Method development
    - Requires two levels:
      - calibration+image analysis
    - Single-image calibration is often feasible (using curve resolution, etc.)
    - Currently, blend homogeneity is assessed using histogram description statistics
  - Commercial Viability/Background
    - At-line instruments available OTC
    - In-line instrumentation is in prototypical development

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Case Study: NIR Imaging Spectroscopy

- Dissertation work of Hua Ma at Duquesne
  - For questions/comments: mah@duq.edu
- Objectives:
  - Establish imaging as an effective tool for characterization of blending
    - End Point - correlation between imaging method and traditional monitoring methods
    - Critical Blending Areas – optimal sampling locations
    - Distribution of Components (API & Excipients) – distribution variability during blending

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20

Case Study:
NIR Imaging Spectroscopy

- **Materials:**
  - APAP (powder, 150µm, 5%)
  - MCC (PH 200, 180µm, 31.7%)
  - Lactose (Fast-Flo® monohydrate, 100µm, 63.3%)
- **Imaging and UV Sampling Time Points:**
  - 10 identical three component mixtures (30g/mixture) corresponding to 10 time points:

    0.5, 1, 2, 5,10, 15, 20, 25, 30, 40 minutes (10 time points)
- **Equipment:**
  - Aluminum mini blender
  - MatrixNIR™ imaging system
    - FOV: 17.2×21.5 mm (0.5X objective)
    - Wavelength Range: 1400-1675nm, 5 nm interval
  - HP 8543 UV-Vis spectrometer
- **Bin charging order**: Lactose, MCC, APAP

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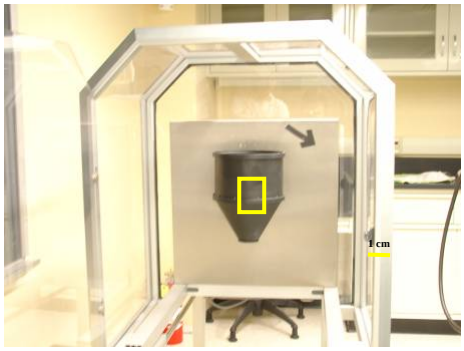

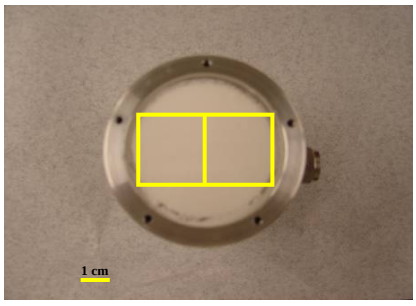

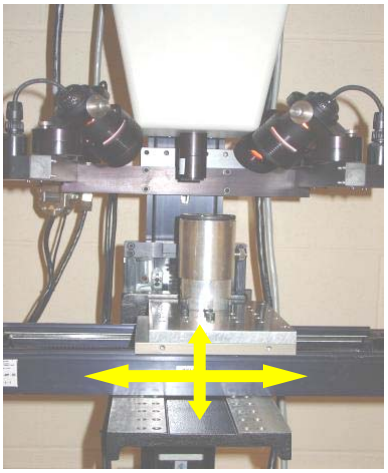

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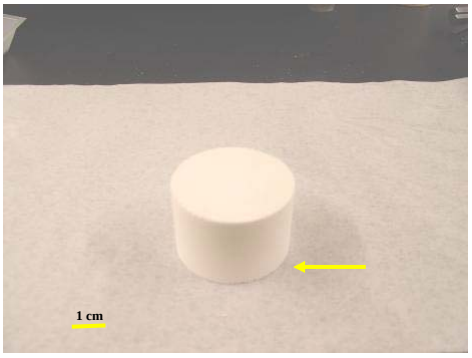
22

Case Study:
NIR Imaging Spectroscopy



Compression Force: 1200 Pounds

Dwell Time: 30 Seconds.

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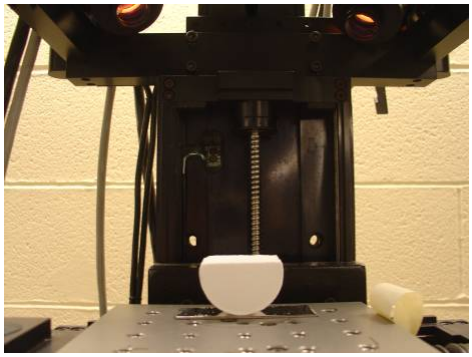
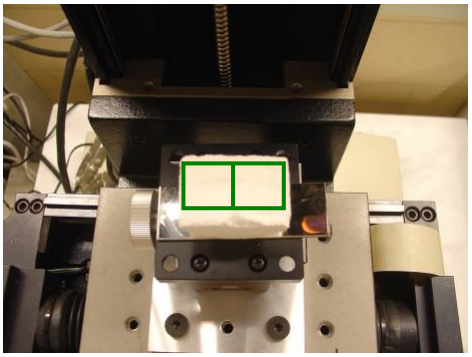
Case Study:
NIR Imaging Spectroscopy





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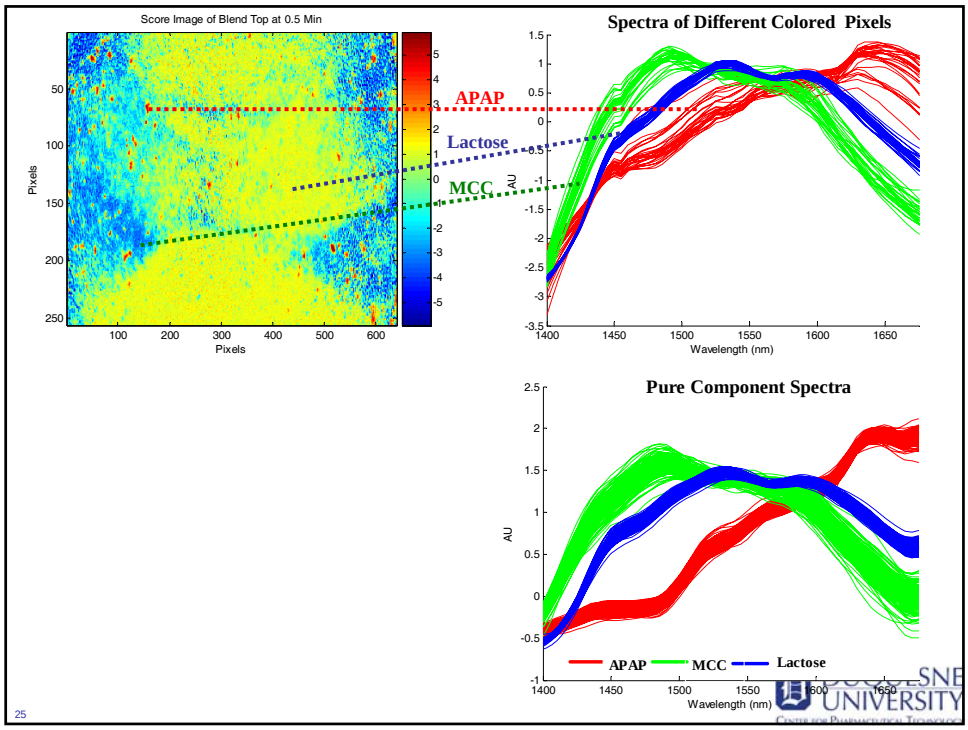
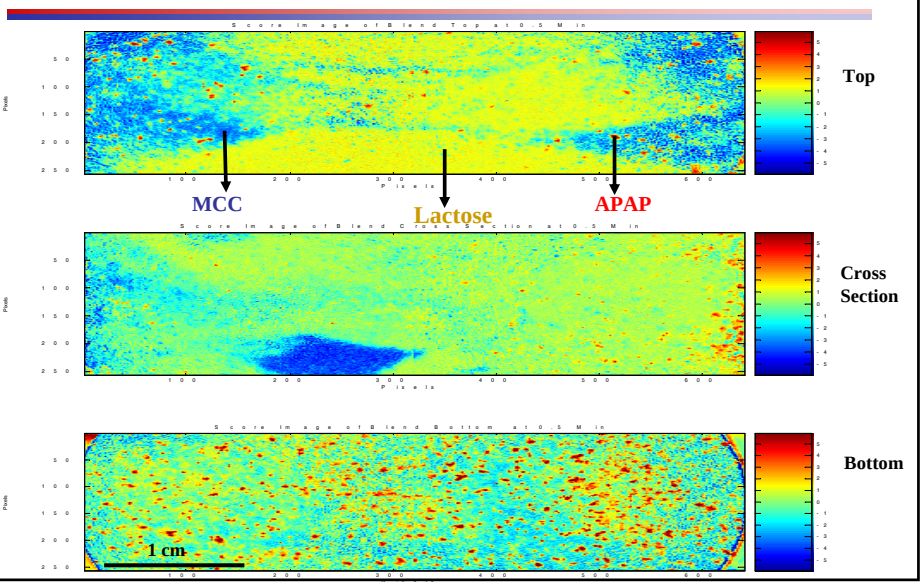
24



25

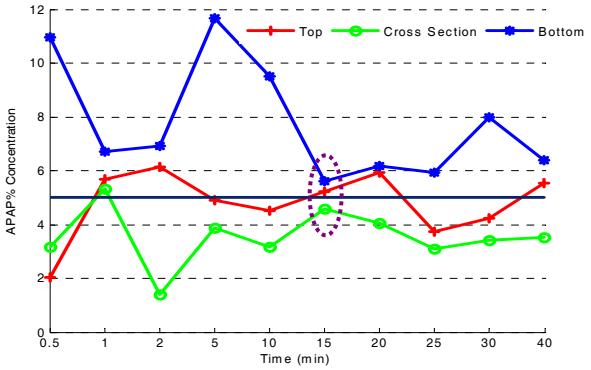
Score Images On PC1 of the Three Locations of the Blend At the First Time Point (0.5 min)



26

Case Study:
NIR Imaging Spectroscopy

Overall Predicted APAP Concentration at Three Locations



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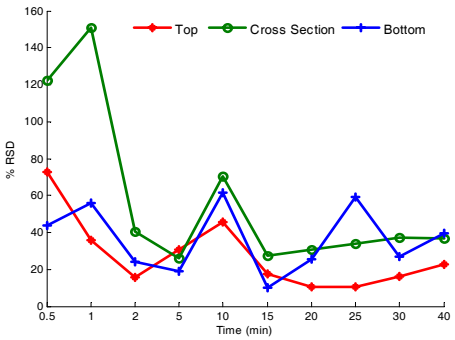
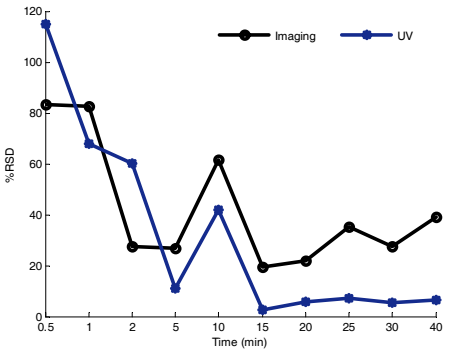
Case Study:
NIR Imaging Spectroscopy

%RSD Change in Three Locations of the Blend



Correlation %RSD Profiles Between UV and Imaging Analysis



28

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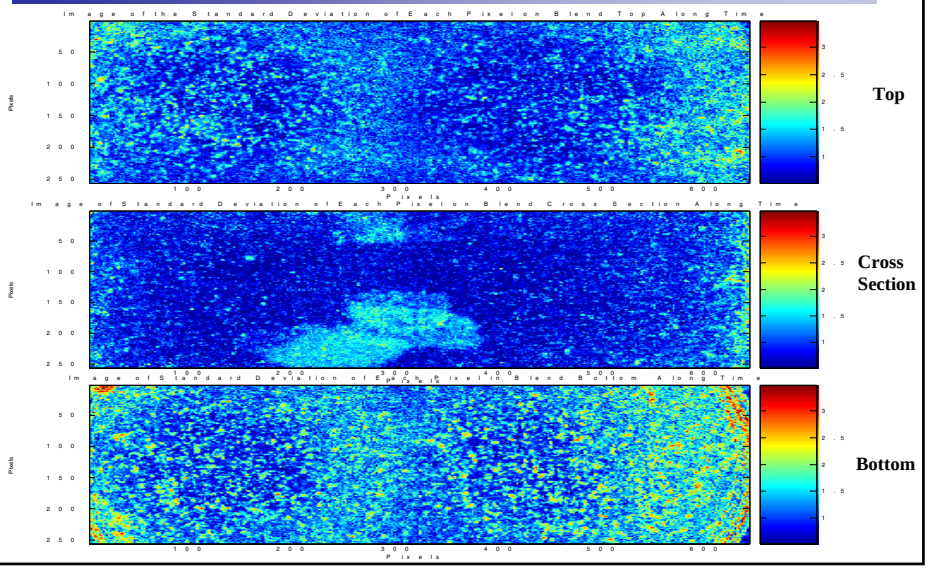
Temporal Spectral Variation Map



29

Case Study: NIR Imaging Spectroscopy

- Conclusions
  - Imaging spectroscopy was successful in providing a rapid estimate of the distribution of chemical components
  - Imaging spectroscopy identified key understanding of the (model) process:
    - A dead zone exists in the current configuration; may be related to cohesiveness of materials or fill level
    - Substantial differences in the rate of mixing was observed for different portions of the mixer
    - Correlation with (traditional) UV-VIS sampling was observed

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Case Study: Efficient Method Development

- Quantitative analysis is more powerful
  - Directionality is important for root cause analysis
  - Easier to determine limits
  - Results can be scaled according to risk
- Empirical calibration is expensive
  - Development of high-leverage training samples
  - Reference chemistry/lab time
- Calibration should be (relatively) simple
  - Number of components known
  - Interference effects are expected (hardness, particle size, density, etc.)
  - Pure-component spectra are generally available
  - Concentrations vary over a very narrow range
    - Linearly additive

With everything we know, why must (calibration) be so costly?

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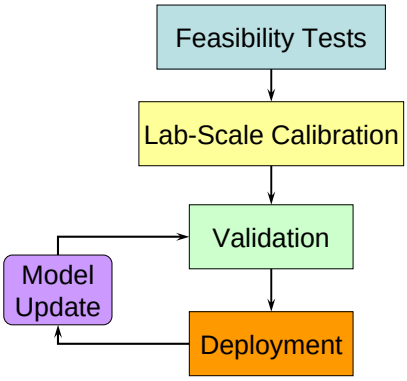
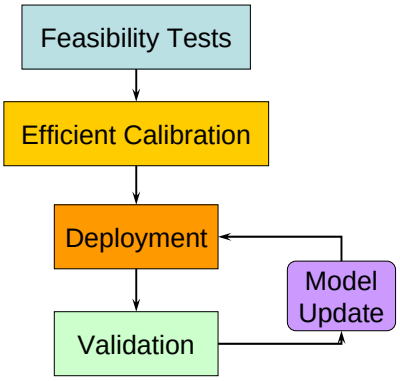
31

Case Study: Efficient Method Development

Current Method Development Path:



Efficient Calibration Development Path:



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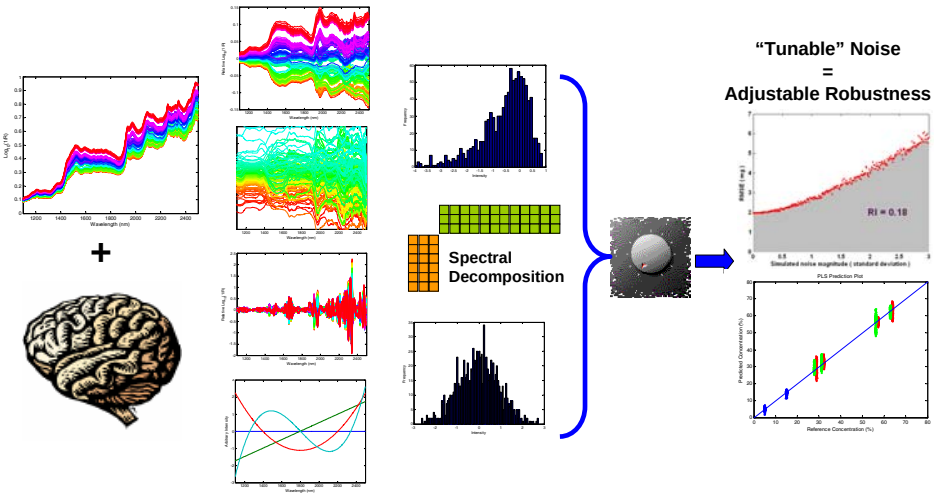
Case Study:
Efficient Method Development



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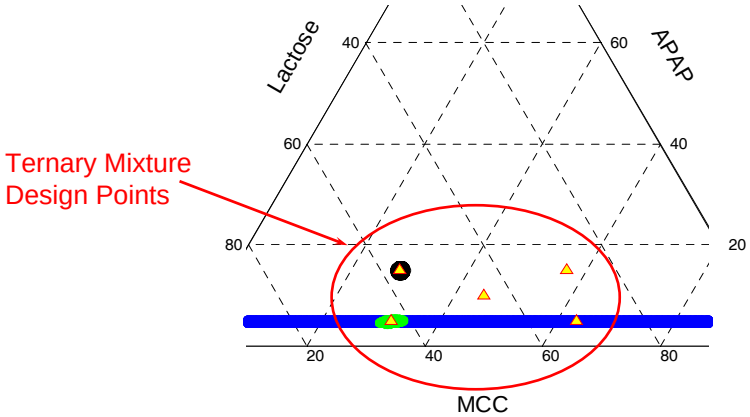
Case Study:
Efficient Method Development

- Trial Blending DOE Study



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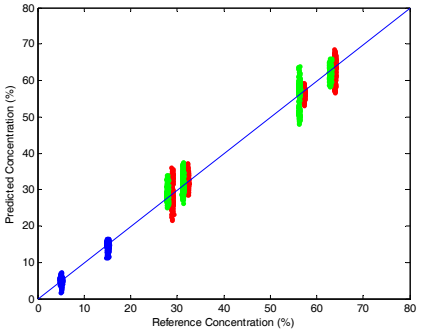
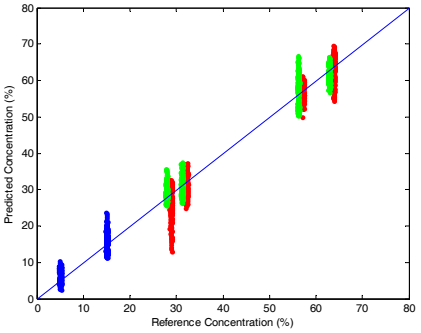
Case Study:
Efficient Method Development

PLS Calibration
(in-sample estimation)



R^2 = 0.991
SEC = 2.0

Synthetic Calibration
(out-of-sample prediction)



R^2 = 0.976
SEP = 3.2

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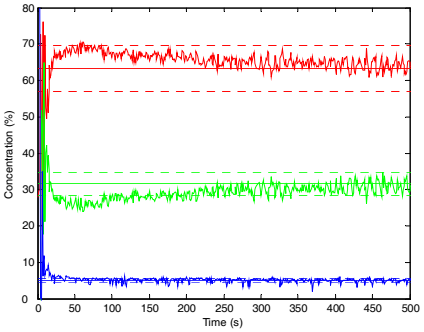
35

Case Study:
Efficient Method Development

PLS Calibration
(in-sample prediction)



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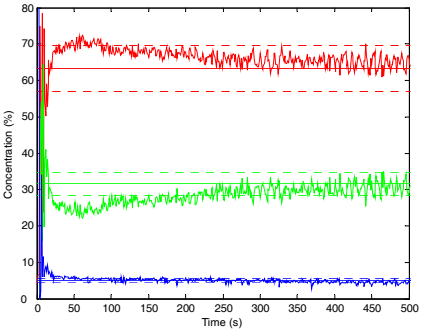

R^2 = 0.976
SEP = 3.2

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36

Case Study: Efficient Method Development

- Synthetic calibration should be considered as an extension of current efforts in efficient calibration
  - PCP, maximum-likelihood weighting, direct orthogonalization
- Conclusions:
  - Synthetic calibration was observed to yield a calibration model having sufficiently-suitable performance using zero high-leverage samples or reference chemistry

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Case Study: Advanced Endpoint Criteria

- Current endpoint criteria for PAT monitoring of blending are mainly an adaptation of traditional criteria
  - RSD of API must be less than 5%
  - Does not consider absolute concentration of API, concentration of excipients, or distribution of excipients
  - Individual components of mixture will often have unique mixing rate constants
- In a PAT-enabled environment, additional information should be leveraged to improve control
  - Balance of constituents (e.g. lactose/MCC) is important to minimizing variation in tablet quality
    - Physical characteristics
    - Dosage form performance (disintegration, release)
  - Better control of blending will mitigate the risk of poor quality through tabletting, and will reduce the need for feedback control of tablet press
  - Acceptance limits (μ, σ) should be reflective of relative risk to CTQs posed by variance in the individual component

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Case Study: Advanced Endpoint Criteria

- Endpoint criteria examined during comparative research studies at DCPT:
  - API variance: moving-window student's t-test of RSD
  - API concentration: moving-window t-test of API concentration
  - Equal-weighted mass-balance: equal-weighted moving-window t-test of RMS deviation from nominal (planned) concentration
  - Risk-weighted mass-balance: weighting on importance of individual components in determining endpoint is adjusted according to risk to CTQs
    - Will often be more "lenient" than equal weighting
    - Risk weighting can be determined by observed variance patterns (e.g. mahalanobis distance) or based on design space
    - Risk weighting can be "fine-tuned" as the level of process understanding increases

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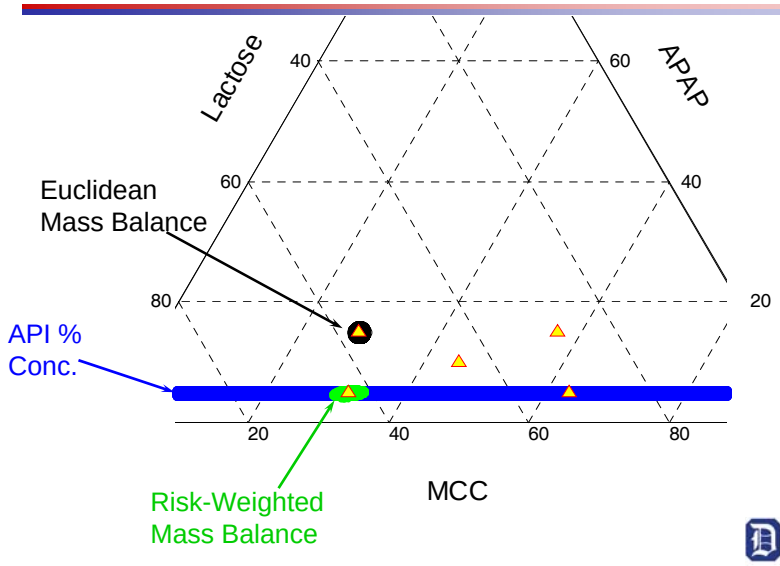
Case Study: Advanced Endpoint Criteria



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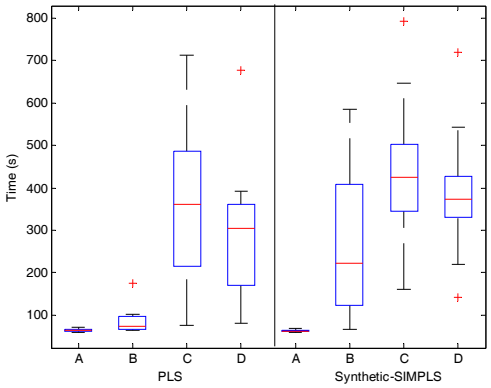
Case Study:
Advanced Endpoint Criteria

- Key:
  - A = API % RSD
  - B = API Conc. t-test
  - C = Equal-Wt. Mass Balance
  - D = Risk-Weighted Mass-Bal
- Y-Axis:
  - Distribution of identified endpoints (n = 24) for each criterion

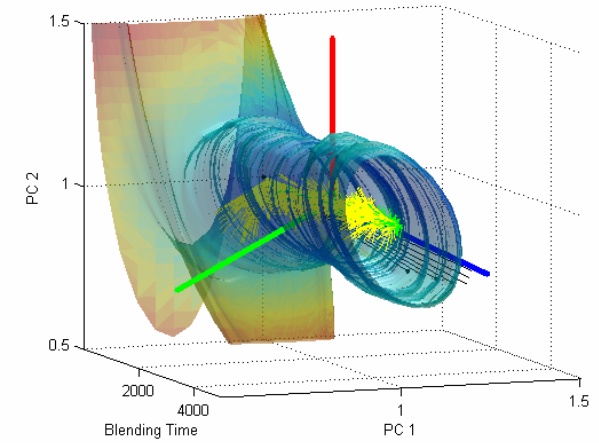


Case Study:
Advanced Endpoint Criteria

- Conclusions
  - Traditional, API variance endpoint criterion consistently underestimated the time required to reach homogeneity in all constituents
    - May be a "lurking effect" since release tests may not directly assess these conditions
  - Risk-weighted (mahalanobis) criterion tended to reach the endpoint sooner, and with less variance in endpoint, than the equal-weighted strategy
  - As level of understanding is increased (e.g. correlation between blend uniformity/composition and F.G. quality), the size of acceptance region can be adjusted to update the new reality for the design space

The Future of Blending

- Higher levels of process understanding:



43

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The Future of Blending

- Feed-forward/ feed-back process control models
  - How will blending data be integrated with control and real-time-release models?
    - Level 1: Binary (yes / no) (current state)
    - Level 2: Descriptive (N = 14 rotations, RSD = 1.4%)
    - Level 3: Component-specific rate constants, statistics
    - Level 4: Whole trajectory modeling? Use in predicting instantaneous CpK thru tabletting? (desired state?)

44

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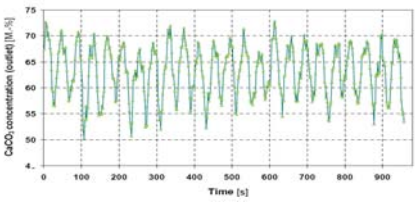
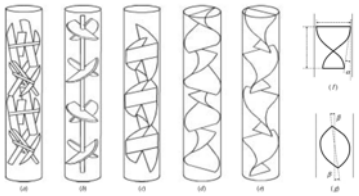
The Future of Blending

- Continuous Processing:
  - Current technologies:
    - Horizontal tumbling (Munson)
    - Continuous fluid-bed
    - "motionless mixers"
  - Much work has already been done…(in other industries)
  - Real-time analytics and controls will be key



Kehlenbeck & Sommer
2002 World Congress on Particle Technology



J. Gyenis, Kona 2002

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45

Parting Shots:

- The evolution of philosophies on pharmaceutical powder blending:
  - Old:

    "(PK says) it takes 30 minutes…call me when its finished…"
  - New:

    "Is it done yet? Why is there so much variability?"
  - Future:

    "Based on up-stream measurements, this blend will be done in ~14 rotations…see you at compression"

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46

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47

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