Drying Processes in the PAT Era

Current Research and Resources

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CENTER FOR PHARMACEUTICAL TECHNOLOGY

Robert P. Cogdill

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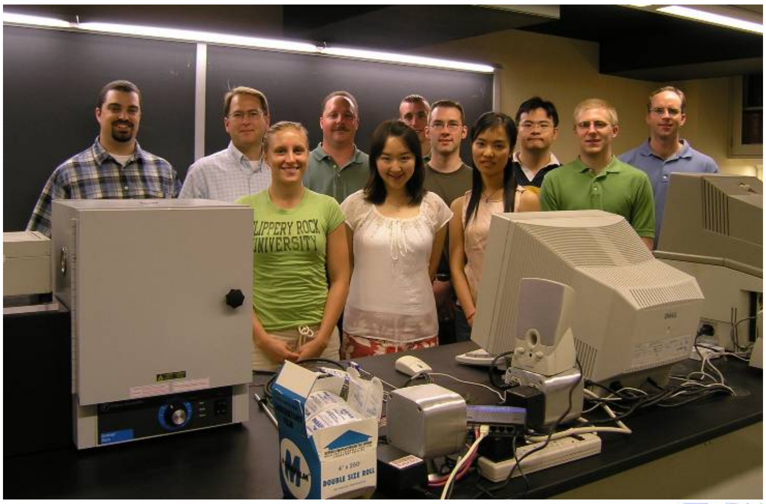
Heidelberg PAT Conference

Who We Are…

2

Who We Are…



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3

Who We Are…And What We Do

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- Pharmaceutical science & technology research
- Lab/pilot-scale production experiments
- Technology development
- Chemometrics/data analysis research
- www.dcpt.duq.edu

SPC Technologies, LLC

- Applied pharmaceutical science & manufacturing consulting
- Multivariate Calibration
- PAT method development
- Compliance/validation
- Industrial training

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4

…And What We Do

…And What We Do

- Lab/Pilot production facilities
  - Fluid bed processing
  - High shear/roller compaction
  - Pan/Wurster coating
  - Capsule filling
  - Tablet compaction
- Instrumentation
  - NIR Imaging Spectroscopy
  - NIR/FT-NIR
  - Raman
  - Terahertz (THz)
  - PXRD
  - Calorimetry
  - …

Outline of Presentation

- Basics of Drying
- PAT Applied to Drying
  - Implementation Philosophy
  - Critical Parameters Affecting Performance
  - Effect of Drying on Product Quality
  - PAT Sensors for Monitoring & Control
    - Case Study: Lab-scale tray drying
- Future Directions in Pharmaceutical Drying
  - Fundamental design space modeling & optimization

7

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Basics of Drying

- Pharma benefits from fundamental understanding of drying processes developed over centuries across many fields
- Drying process dynamics can be described by transfer equations:
  - Heat transfer
  - Mass transfer
  - Momentum transfer (fluid bed operations)

8

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Mechanisms of Heat Transfer

- Conduction - transfer of heat by direct physical contact - Fourier's Law (*k=thermal conductivity*):

$$q = -kA\frac{\partial T}{\partial x}$$

- Convection - transfer of heat by contact with a hot moving fluid (air). ***Major mech. for dryers*** - Newton's Law of cooling (*h=heat transfer coef*):

$$\mathbf{q=hA\Delta T}$$

- Radiation - transfer of heat by electromagnetic radiation between unconnected bodies - Stefan-Boltzman Law of Thermal radiation (black body):

$$\mathbf{e_b = \sigma T^4}$$

Adapted with permission from K. Morris

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Mechanisms of Mass Transfer

- **Diffusion** - transfer of mass by molecular movement in response to gradients - Ficks Law

$$J_i^* = -D\ ^{dCi}/dx$$

  - solved for different boundary conditions and specific to medium

- **Convection** - transfer of mass by contact with moving "bulk" phase. ***This is the major mechanism for most of our dryers*** in the constant rate phase:

$$J_i^* = [^{(Di+\varepsilon)} / (Z_2 - Z_1)] * (C_1 - C_2) = K\ (C_1 - C_2)$$

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Two-Stage Drying Model

- Stage I: (constant-rate period)
  - Heat transfer limited
  - Heat lost by air equals heat used to vaporize water
  - Evaporation of surface, or loosely-associated water (Q)

$$Q = Q_o - Kt$$

- Stage II: (falling-rate period)
  - Diffusion (mass-transfer) limited
  - Water must diffuse to the surface of the particle

$$Q = Q_\infty + Q_o^{'} k * e^{(-k^{'}t)}$$

[Kunii and Levenspiel, *Fluidization Engineering*, Pub. Krieger, pg. 424-428,1977]

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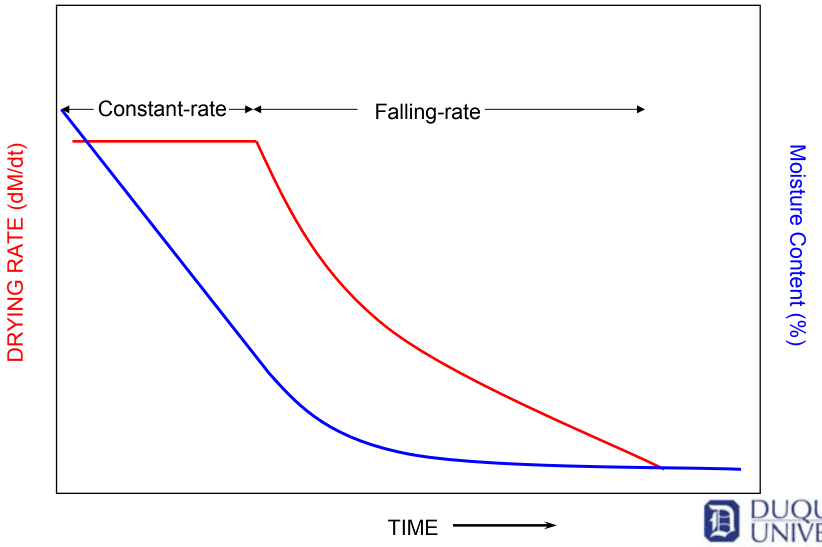
Two-Stage Drying Model

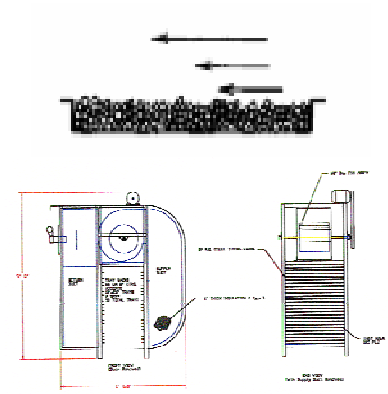


12

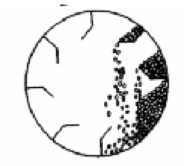
Common Drying Equipment

Fluid Bed

Tray



Rotary "Pan"



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PAT Applied to Drying

- Philosophy and roadmap of PAT Implementation:

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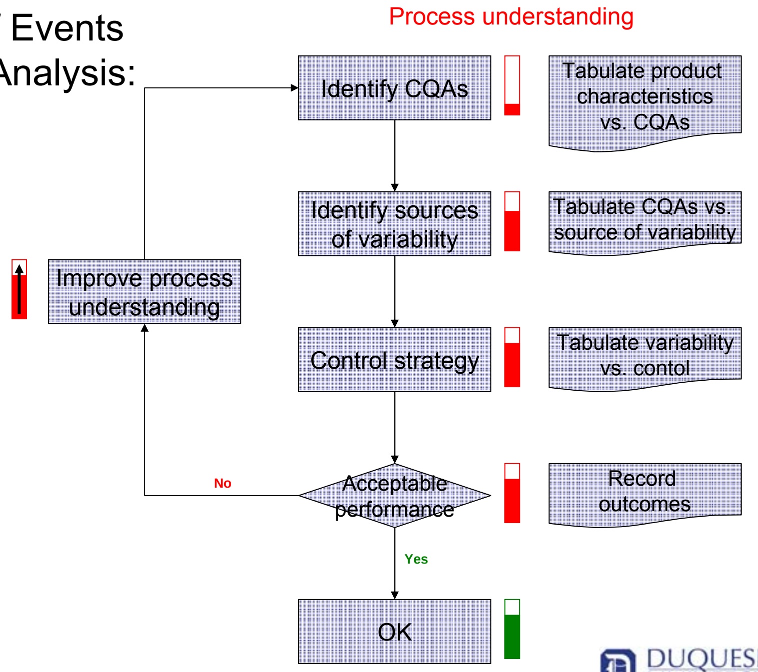
Order of Events In Risk Analysis:



15

Critical Parameters Affecting Performance

- Material Characteristics
  - Particle Morphology Distribution
    - Size
      - Significant particle size dispersity can cause wide variability in output quality
      - Impacts the duration of stage II drying
      - Determines allowable airflow regime (FBD)
      - Smaller particles achieve thermal equilibrium with the mobile phase more quickly
    - Shape
      - Affects effective heat transfer rate
      - Reduces allowable airflow regime (increases the variability in Reynolds number)
    - Density, porosity, tortuosity
      - Impacts the maximum rate of moisture diffusion
  - Friability
    - Overly-friable granules will easily break apart
  - Starting moisture level of particles
  - Heat transfer coefficient & heat capacity
  - Thermal stability
    - Threshold temperature before risk of phase transition (polymorphic form change, amorphization, melting)

16

Critical Parameters Affecting Performance

- Operating Conditions
  - Inlet air temperature (driving force)
  - Air flow rate/ pressure
  - Inlet humidity (dew point)
  - Amount of product dried (mass of charge/ bed depth)
  - Drying time

Effects of Drying on Product Quality

- Moisture content (mean & variability)
- Crystallinity/ form
  - Solvent/temperature-mediated phase change
- Content uniformity/ assay
  - Example: drug volatilization and migration or loss
- Particle size distribution
  - Attrition
  - Agglomeration
- Physical quality of particles/granules
  - Compressibility
  - Cohesiveness
  - Flowability
- Yield loss
  - Elutriation due to air entrainment (interacts with attrition/ friability)

PAT Sensors for Monitoring & Control

- Input space (PCCPs, material characteristics) and output space (quality, rate, yield) is highly multivariate, with nonlinear interactions
  - Suitable drying control can be achieved effectively in many cases using "traditional" sensors and controls
    - Temperature (inlet, product, outlet), humidity, airflow
- What, then, is the role of advanced analytics, such as NIR?
  - **New sensors aren't always required to do PAT…**
  - (incremental) Improvement in control
  - Identification of key material transitions
    - Changes in crystallinity
    - Identification of "skinning"
    - Determination of drying stage transition
  - Mitigation of latent risks from upstream processes
  - Real-time adjustment of controls to reflect incoming material characteristics
  - Feed-forward of data to downstream operations

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PAT Sensors for Monitoring & Control

- Sensor integration issues
  - Sampling:
    - Location of probes
    - Sampling frequency
    - Volume of sample interrogation
    - Probe fouling
  - Method development
    - Chemometrics (calibration development)
    - Integration with "traditional" data
    - Correspondence between data, samples (in-line), and reference measurements (in-lab)

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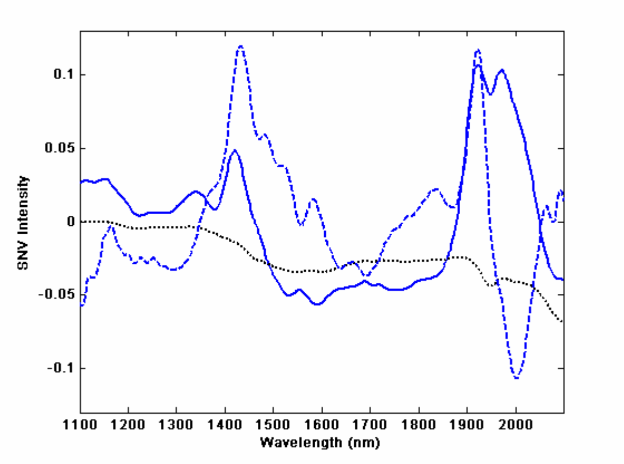
PAT Sensors for Monitoring & Control



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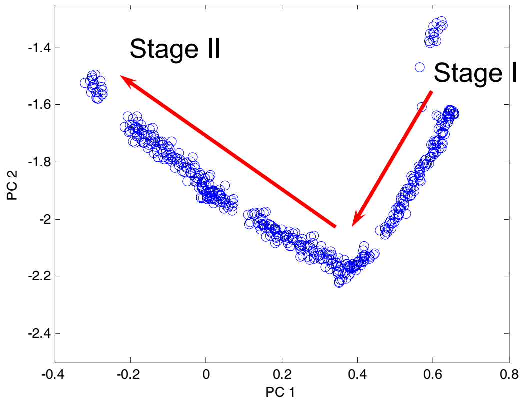
PAT Sensors for Monitoring & Control



- NIR identifies "high-risk" transition between stages, no calibration is required (PCA analysis)

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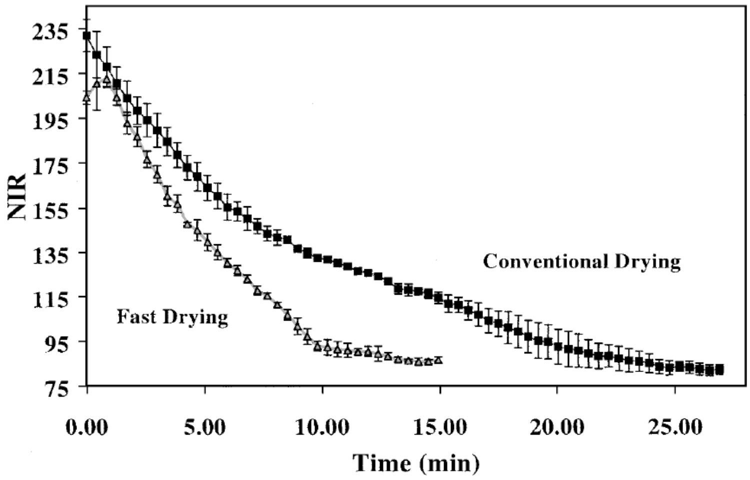
PAT Sensors for Monitoring & Control



Wildfong, et al., J.Pharm.Sci. 91(3) 2002

Case Study: NIR Monitoring of Tray Drying

- Tray drying study was developed as part of a student project and as a module in a hands-on industrial training course
  - Sensor integration
  - Calibration development
  - Implementation of real-time controls
- A parallel study was done to use the apparatus to better understand the sources of variability in product quality after tray drying

Summary of System

- Process inputs
  - Starting moisture level of product
  - Physical features of raw material
  - Oven temperature
  - Air flow
  - Time
- Process sensors
  - Temperature (thermocouples)
  - NIR
- Output monitoring (quality)
  - LOD evaluation of moisture level

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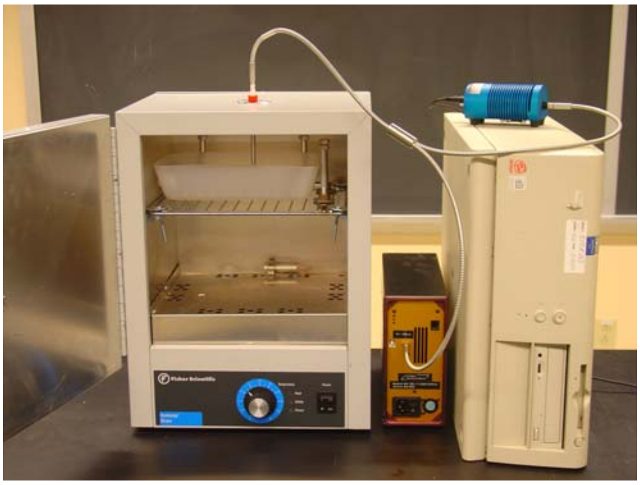
Laboratory-Scale Tray Dryer (Fiber Probe)



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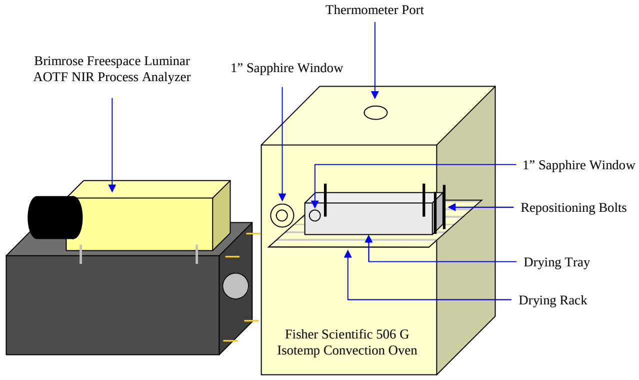
Laboratory-Scale Tray Dryer (side window remote sensing)



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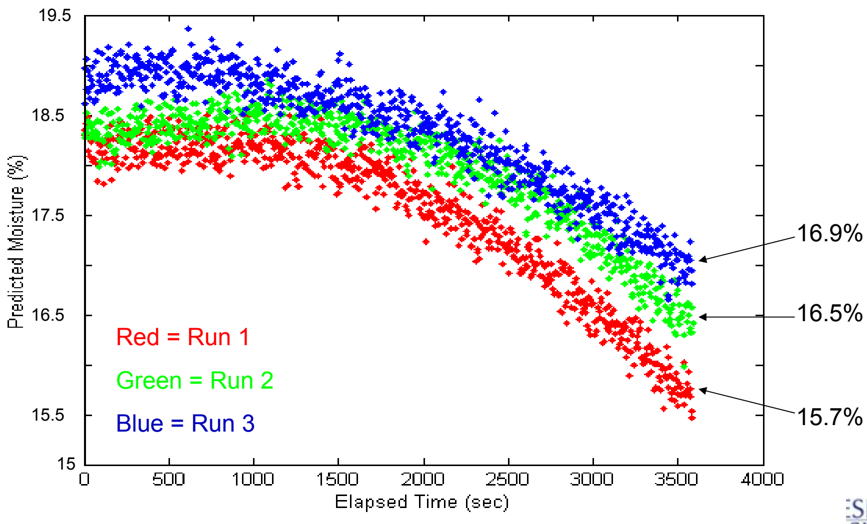
NIR Prediction During Drying



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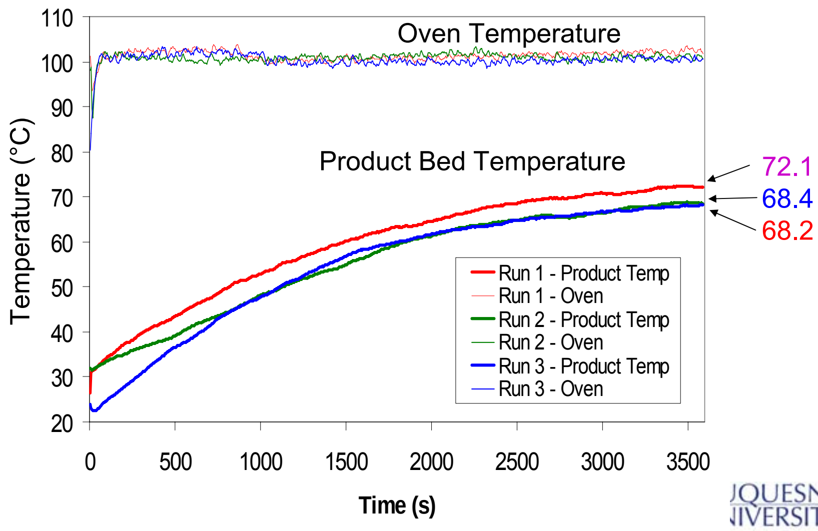
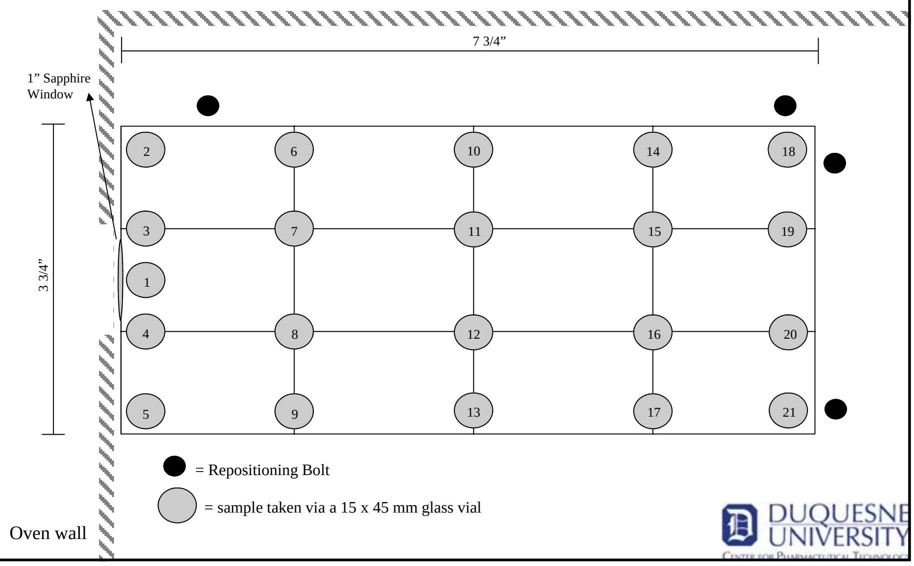
Temperature During Drying



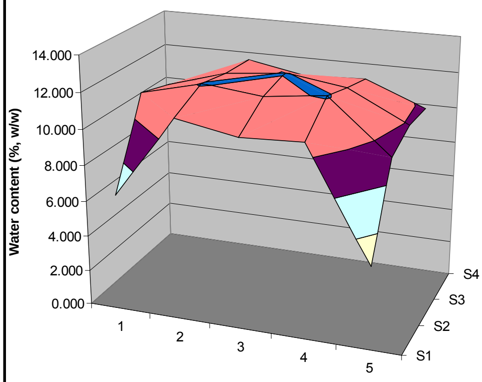
29

Sampling from Drying Tray for Water Content

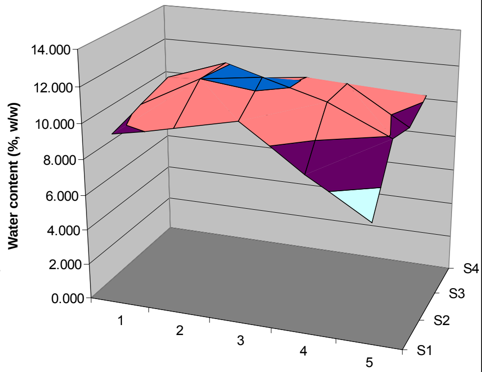


30

Results from Samples Taken at 1 hour for 2 Trials



Run 1



Run 2
(similar to Run 3)

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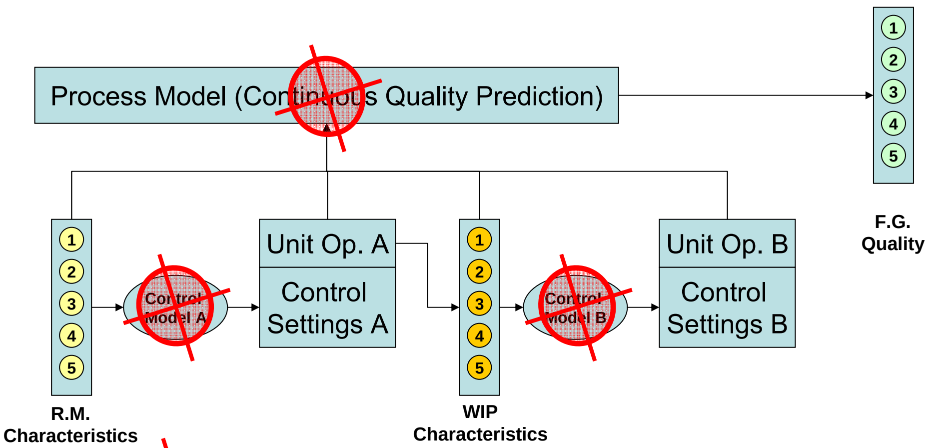
31

PAT, Design Space, and Controls



Fundamental Design Space…

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32

Fundamental Design Space Simulation

- Objectives:
  - Develop a fundamental design space *in silicio* for fluidized bed drying based on first principles, mechanistic, and semi-empirical (and dimensionless) relationships from the literature
  - Utilize the design space model to investigate the expected interaction of process parameters
  - Pre-identify critical parameters for efficiency optimization, risk mitigation, and control installations
- Fluidized bed model was developed using literature models for drying and fluidization dynamics at the particle and bulk scales

Intra-particle Moisture Distribution

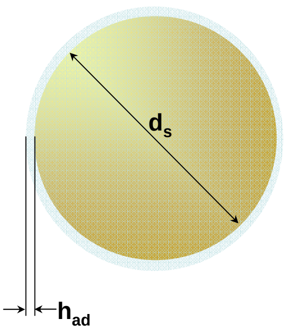
- Assumptions:
  - Liquid H_2O: $\rho_l = 1.0$ g/cm^3
  - Adsorbed water is preferred
  - Three reservoirs of water storage:

1. Adsorbed Volume: V_{ad}
2. Absorbed Volume: V_{ab}

- $V_{total} = V_{ad} + V_{ab}$, $V_{ab} = V_{total} - V_{ad}$
- $V_{ad} = (4\pi/3)[((d_s/2)+h_{ad})^3 - (d_s/2)^3]$
- $V_{total} = [M_s / (1-W)]\rho_l^{-1}$
- M_s = Dry mass
- W = Moisture content, wet basis

3. Crystalline Hydrates

(will not be considered here)

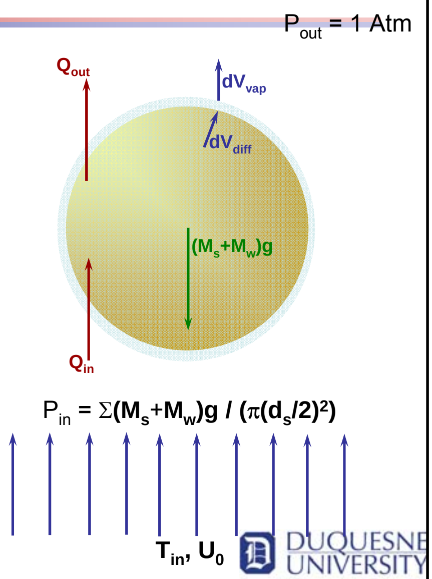


Heat-Transfer Limited Drying

- Assumptions:
  - Intraparticle diffusion (and drying rate) is limited by vapor removal
  - Particle and air temperature will rise quickly to near wet-bulb temperature of inlet air
  - Hydrodynamics of FBD modeled by empirical H_20 flux relationship from literature:

Flux = $[(T_g-T_s)h_{gp}]/\Delta_{vap}H$, $g/(m^2 \cdot s)$

  - Other (more complex) models are available which directly consider FBD hydrodynamics
  - Semi-empirical relationships have been shown to be very effective within uniform material classifications



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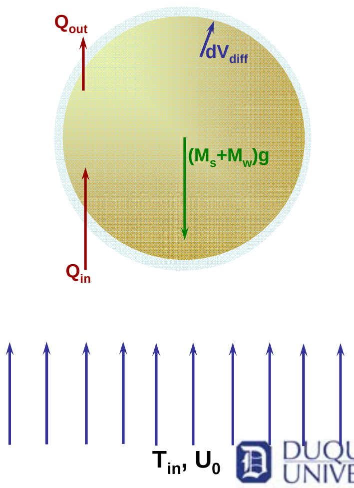
Mass-Transfer Limited Drying

- Assumptions:
  - Surface layer of adsorbed moisture is rapidly depleted
  - Heat loss by vaporization is less than heat gained by conduction, temperature rises
  - Moisture diffusion is limited by kinetics:

$W_{t+1}=(6/\pi^2)K(W_t-W_{EMC})+W_{EMC}$
$K=\Sigma(1/n^2)\exp(-2n\pi^2 D_m t/d_s)\ 1\rightarrow\infty$
$\Delta V_{diff}=M_{dry}[(1-W_{t+1})^{-1}-(1-W_t)^{-1}]$

  - Temperature (and velocity, via increased thermal conductivity) impacts diffusion by changing vapor diffusivity:

$D_m=D_k+D_f$
$D_k=(d_s/3)(8RT/\pi M_g)^{1/2}$
$D_f=1.735E^{-9}(T_g/P_g)^{1.685} \rightarrow 0$ (consider to be insignificant)



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Anticipated Results

- Smaller particles will dry faster due to increased specific surface area
- Without considering risk factors, the optimal drying conditions will maximize air velocity and temperature
- Significant risk factors anticipated:
  - Quality reduction due to increased temperature (e.g. phase transition)
  - Entrainment and elutriation of solids at high velocity
  - Quality reduction due to increased variability in product moisture content, temperature, and physical factors (e.g. case hardening, skinning)

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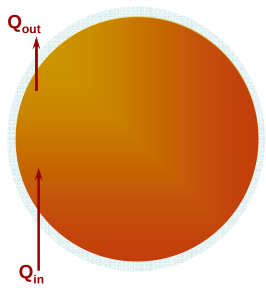
Risk Factors- Phase Transition

- Assumptions:
  - Heat capacity is assumed to be weighted average of granule and water specific heat capacities at the current granule temperature
  - Heat not lost to vaporization is applied to heating of granule (and V_{ab}, V_{ad})
  - Phase change occurs immediately upon reaching T_{crit}
  - Future models may consider kinetics of phase transformation, or other types of thermal quality degradation



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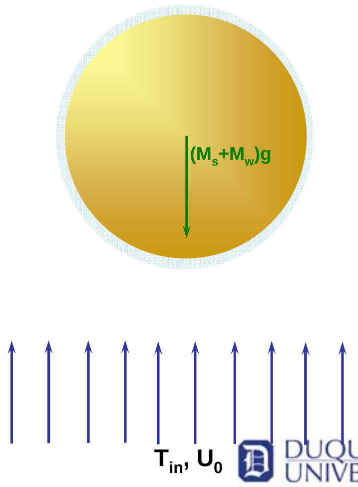
Risk Factors- Elutriation

- Assumptions:
  - Smaller particles have lower U_{max}, leading to vertical stratification of PSD
  - PSD shifts to larger diameters as $U_0 \rightarrow U_{max}$ and fines are entrained
  - As mass decreases through drying, U_{max} will decrease
  - U_{max} determined by empirical relationship from literature:

$$U_{max}=[(4Gd_s Re^{.5}(\rho_s-\rho_g))/30\rho_g]^{.5}$$



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Anticipated Results

- The boundaries of T_{in} will be limited by phase conversion
- The time to reach T_{crit} will be shorter for smaller particles, leading to dispersity in particle moisture, temperature, and quality at the mid-point of drying
- The boundaries of U_0 will be limited only by elutriation (settling is not a risk factor)
- T_{in} and U_0 are expected to interact with the affect on phase change and elutriation since, for example, Reynolds number and thermal conductivity both change with temperature and velocity
- The addition of cost and value variables to time and product may alter the definition of optimal yield conditions (e.g.- the point of maximum efficiency may include some loss of material)
- A functional description of the kinetics, as well as the risk premium, of phase transformation may further alter the optimal yield conditions.

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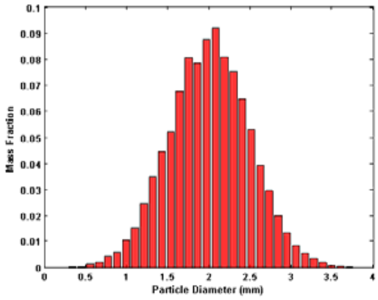
Simulation I

- Experimental Parameters:
  - Solid Density, ρ_s: 0.36 g/cm^3
  - PSD: μ_d=2.0mm, σ_d = 0.5mm
  - Temperature: 70-110 °C
  - Velocity: 550-1100 cm/s
  - Moisture, wet basis:
    - Initial = 0.40
    - Critical = 0.10
    - Equilibrium = 0.03



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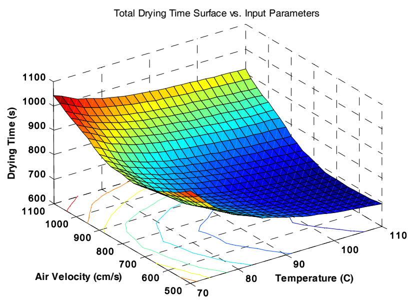
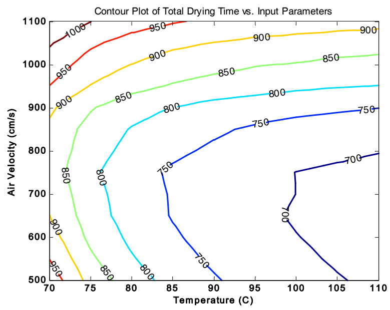
Drying Time Surface





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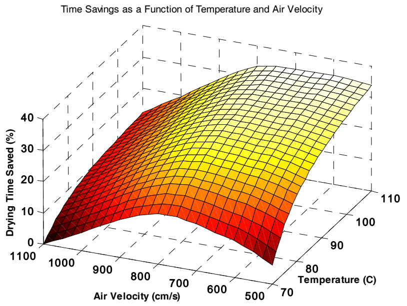
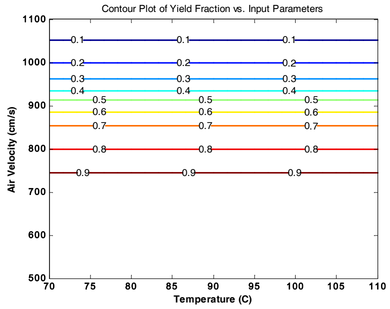
Time and Yield vs. T and U





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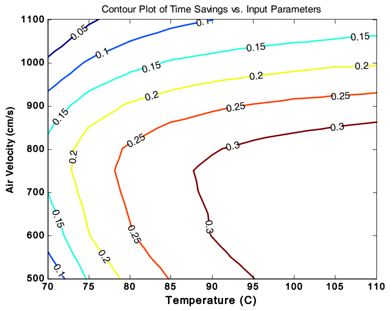
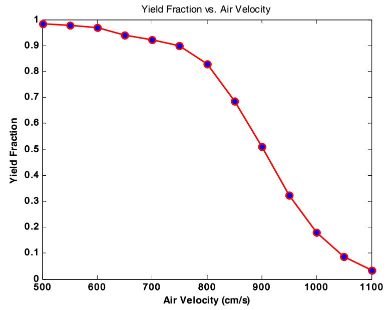
Time Efficiency and Yield





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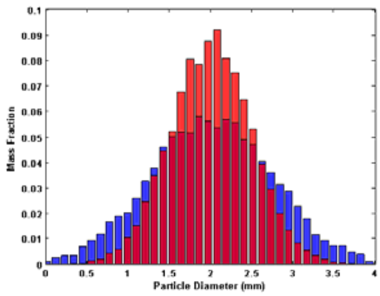
Simulation II

- Experimental Parameters:
  - Solid Density, ρ_s: 0.36 g/cm^3
  - PSD: μ_d=2.0mm, **σ_d = 0.75mm**
  - Temperature: 70-110 °C
  - Velocity: 550-1100 cm/s
  - Moisture, wet basis:
    - Initial = 0.40
    - Critical = 0.10
    - Equilibrium = 0.01



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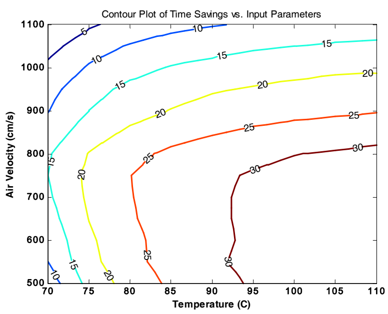
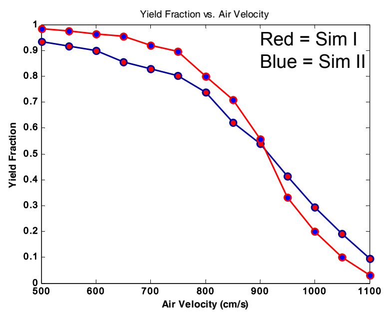
Time Efficiency and Yield





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Conclusions

- Further laboratory research is sorely needed
  - Databases of semi-empirical and dimensionless units (already developed for other industries: coal, steel, etc.) should be created for pharmaceutical materials
  - Surveys of R.M. diversity should be undertaken to understand the variance and covariance of material characteristics and their effect on:
    - fundamental design space models
    - Quality prediction models
    - PAT control models

47

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48