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Developing the Control Strategy for Pharmaceutical Manufacturing Across Scales of Manufacturing

CERSI Meeting 2013

Control Strategies for Pharmaceutical Manufacturing: Real Time Release Testing and Design

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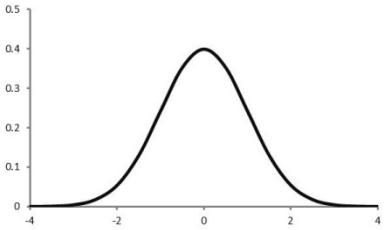
Outline

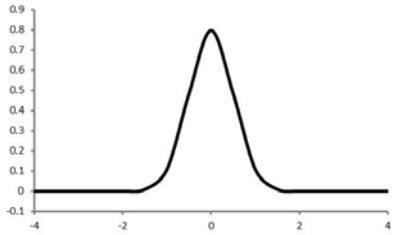
- Introduction
- Case study: Fluid bed coating of multiparticulate beads
  - Process efficiency
  - Extent of curing
  - Loss on drying
  - Dissolution & data fusion

Note, in the interest of time, only selective steps will be shown for each model

- Summary

Dosage Form Variability





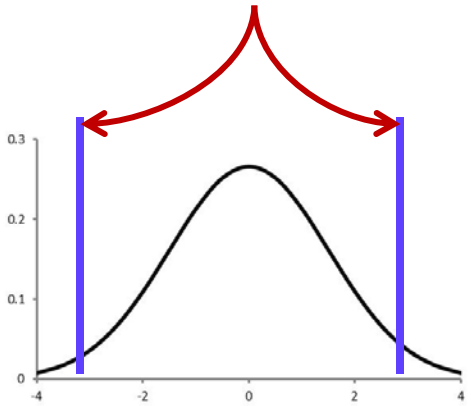
Excipients

API

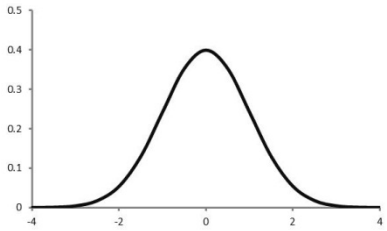
Unit Operation

Dosage Form

Spec. range



Processing Conditions



$$\sigma_{Tot} = \sigma_{Exc} + \sigma_{API} + \sigma_{PC} + \sigma_{Int} + \sigma_{Mes}$$

Implementing a Control Strategy

- Definitions - ICH Q10
- "Control Strategy is a planned set of controls, derived from current product and process understanding that assures process performance and product quality"
- Includes parameters and attributes of:
  - Drug substance
    Drug product materials and components
  - Facilities
  - Equipment operating conditions
  - In-process controls
    - Measurement types and frequency of monitoring
  - Finished product specifications and testing

Source: Guidance for Industry Q10 Pharmaceutical Quality System, April 209, ICH

Developing a Control Strategy

- **Essence of developing a control strategy**
  - **1) Process understanding: ID all likely sources of variability that affects product quality**
  - **3) Using QTPP & design space to determine acceptance ranges**
  - **2) Develop a plan to monitor these variables**
    - **Sensor Selection – soft sensors**
    - **Chemometric model development**
  - **4) Data usage**
    - **Oh "gosh" we have a problem**
    - **Ideally use monitoring data to feed-forward and or feedback into process**
      - **Area that needs more development**
- **If done well → Real Time Release Testing RTRT**

Prediction & Identification of Patterns

- In data rich environment key question:
  - Which variables & samples do you use to a build model
- Minimalist strategy
  - Use a narrow range of variables and samples
    - Use only variables → highly correlated to attribute
    - Use only samples → in sweet spot of design space
      - i.e., only variation in model is directly correlated with parameter of interest
    - Very good for accurate and precise prediction
- Maximalist strategy
  - Use all/most variables
  - Samples spanning the knowledge space with good & bad batches
  - i.e., lots of variation for many different sources
  - Very rugged, but not as accurate or precise
    - For some events predictions can be difficult
    - eg., it may be hard to predict release parameter like dissolution

Variable Selection - Example

Key Message

- To fully implement RTRT system, you need to a comprehensive approach
  - For example the validity of a model may depend:
    - Upon the nature of the starting materials
    - Processing conditions
    - Thus need to ensure these conditions are met
- Can use a combination of different model types
  - RTRT model may use minimalist approach
  - MV process control chart use maximalist approach
- Core GMP concept is to have a comprehensive plan to control all likely critical process inputs
    - When have a sufficient process control models should be predictive and rugged
- Note: may begin implementation 1 step at a time

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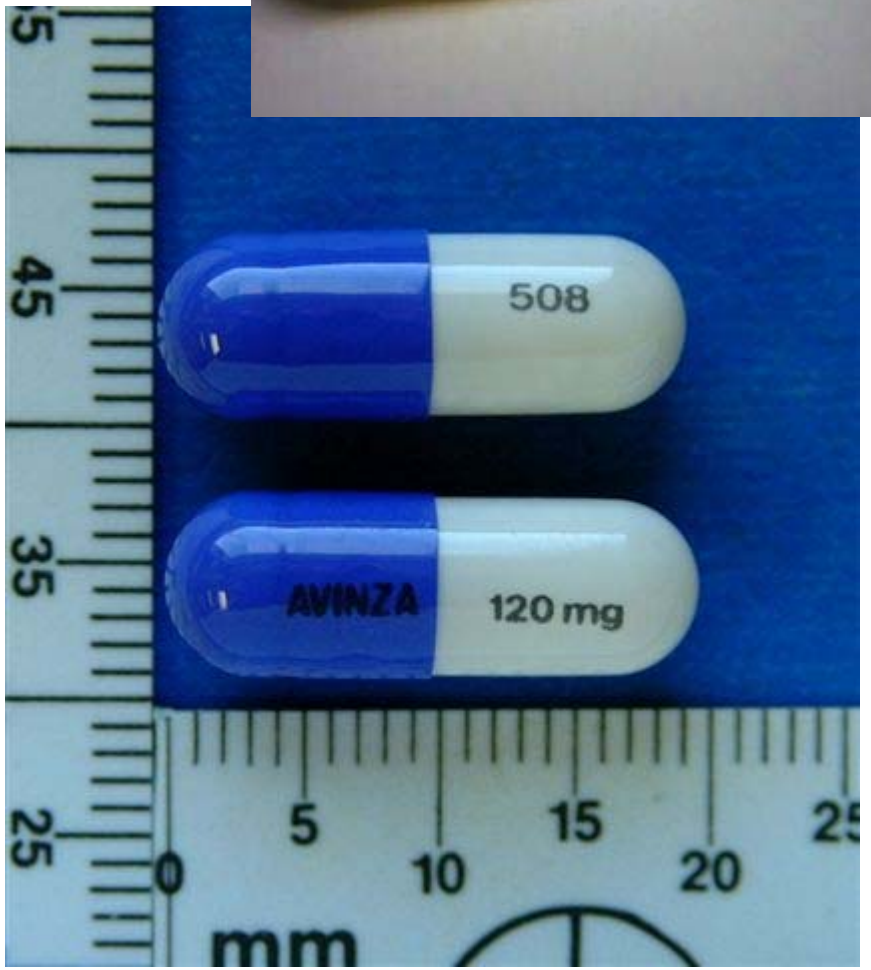
- Summary

Multiparticulate Dosage Form

- **<u>e.g., Avinza</u>**
- Morphine sulfate pentahydrate
- Successful multiparticulate dosage form
- Combines IR with CR for once day dosing



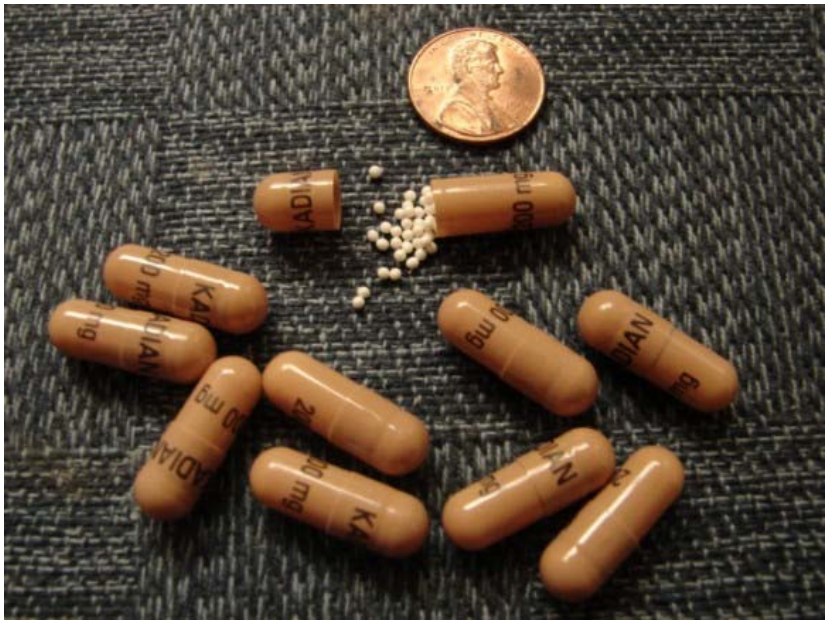
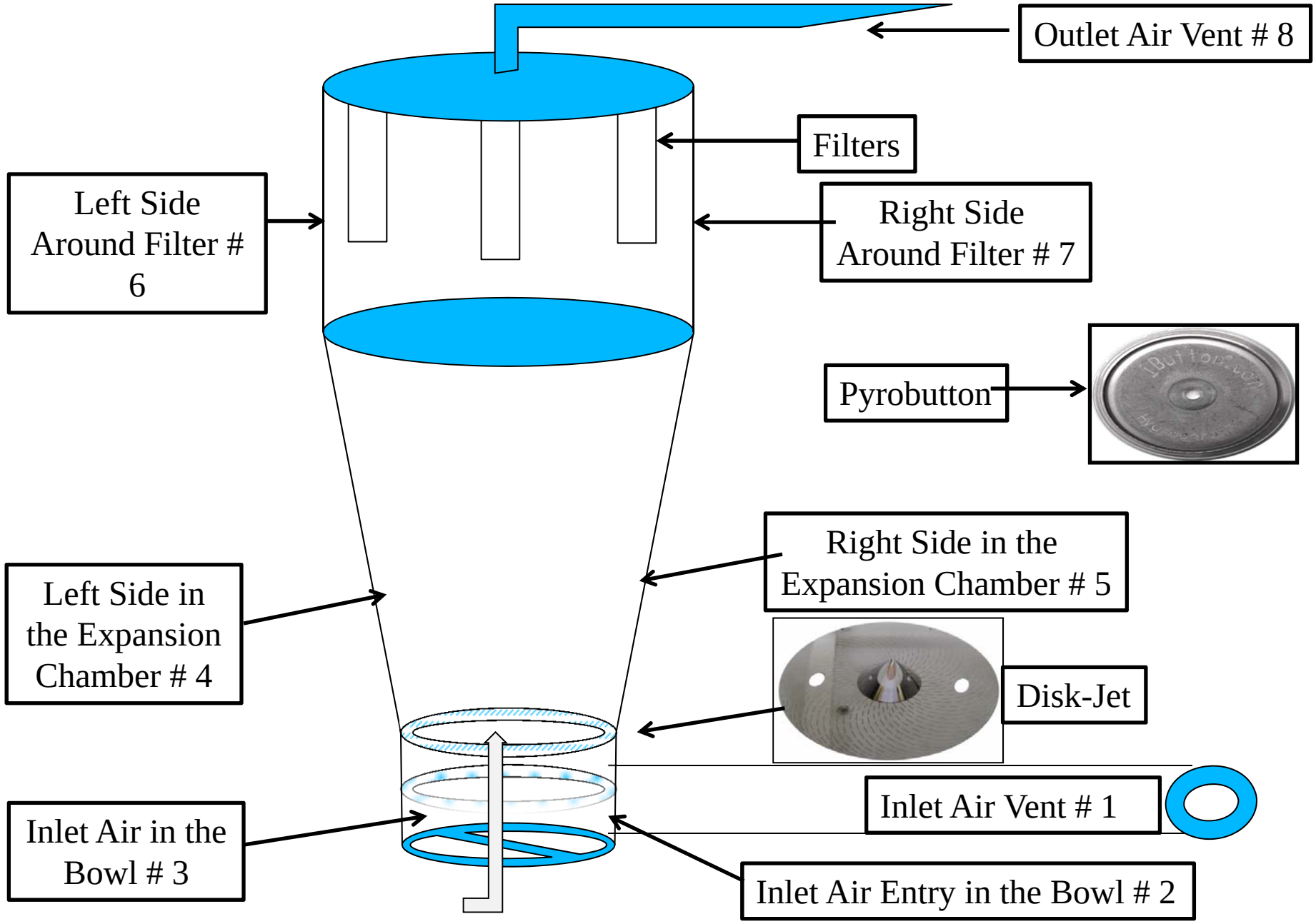
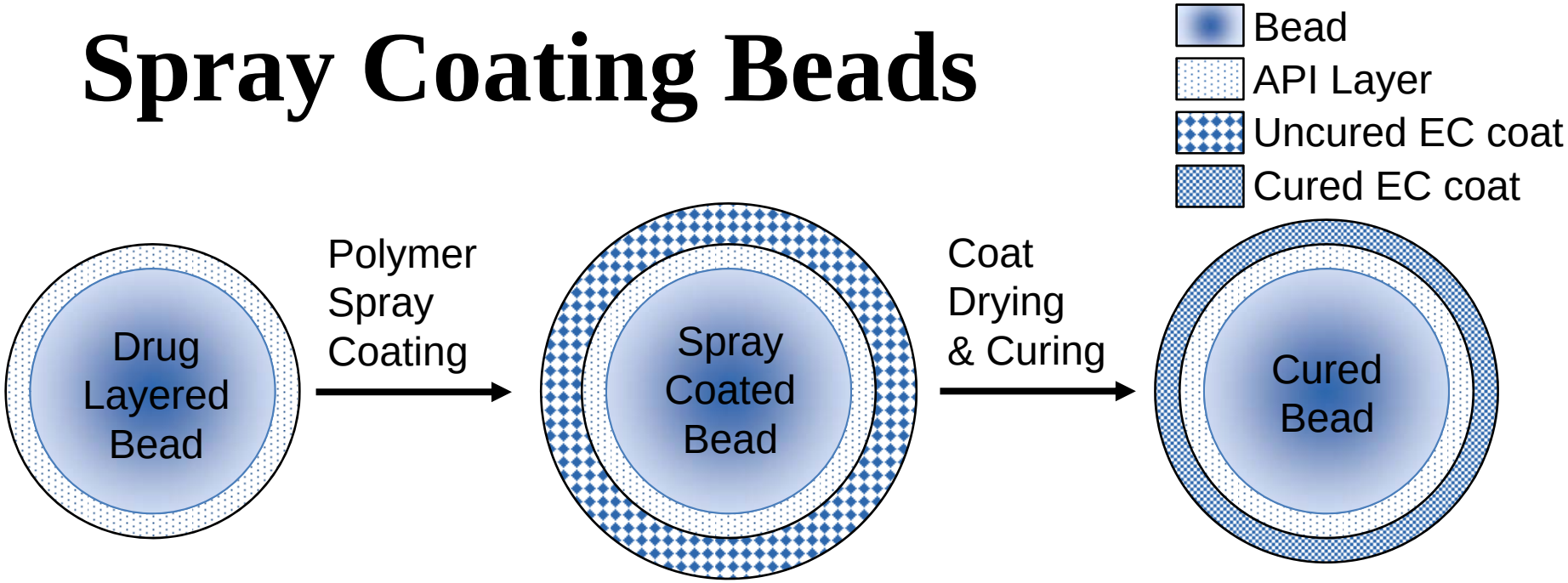


Image source: http://www.summitmalibu.com/tag/detoxification/page/2/; http://www.pharmer.org/images


Outlet Air Vent # 8
Filters
Left Side Around Filter # 6
Right Side Around Filter # 7
Pyrobutton
Right Side in the Expansion Chamber # 5
Left Side in the Expansion Chamber # 4
Disk-Jet
Inlet Air Vent # 1
Inlet Air in the Bowl # 3
Inlet Air Entry in the Bowl # 2

Spray Coating Beads



CMA/CQA

- API Content
- API Homogeneity
- Particle Size
- Thickness
- Uniformity
- Water content
- Extent of curing

CPP

- *Atomization*
- *Spray rate*
- Air flow
- Air temp.
- Air flow
- Air temp
- Curing time
- LOD

Models

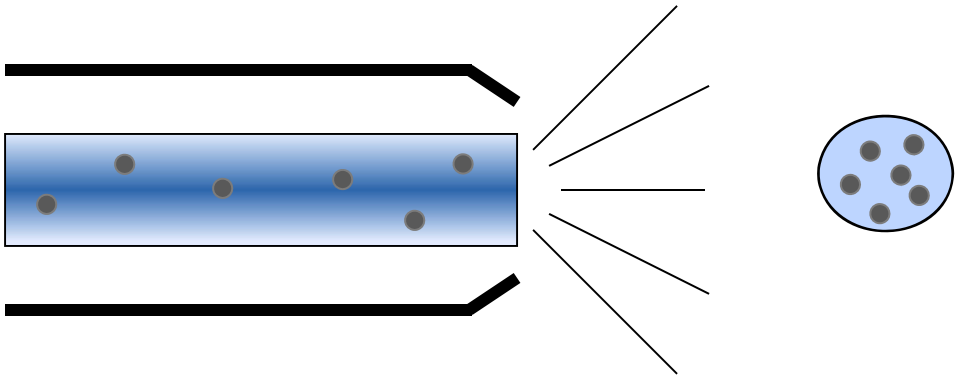
API assay

Process Efficiency

Moisture Content Curing Time

Dissolution Rate

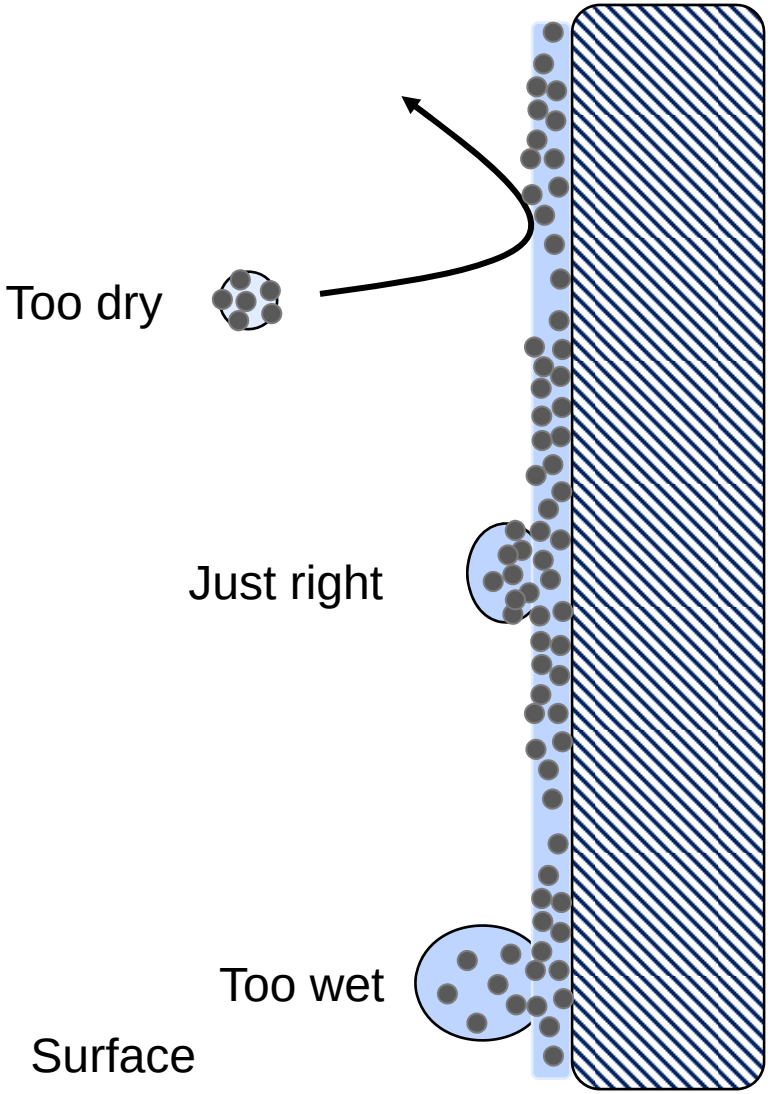
Process Efficiency

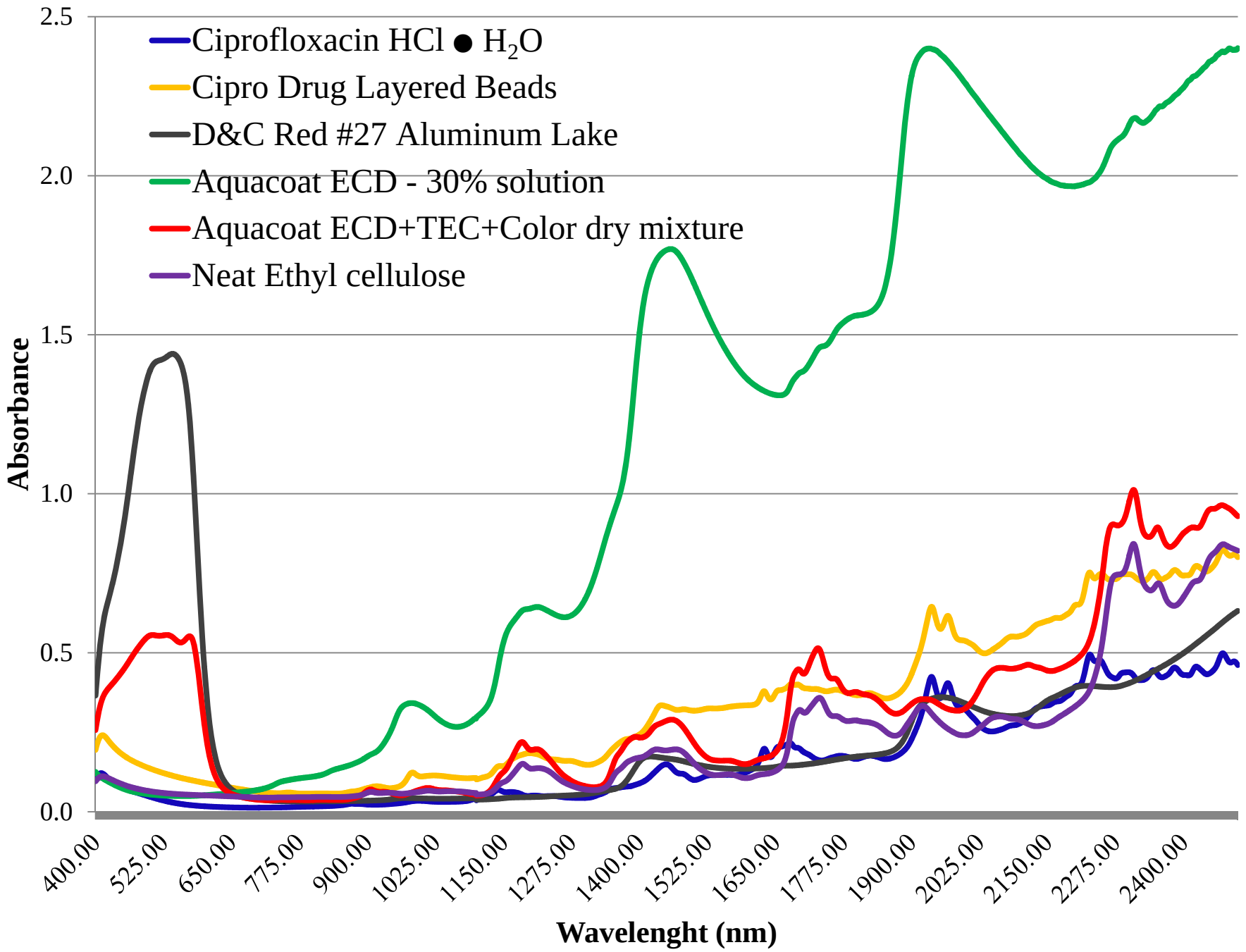


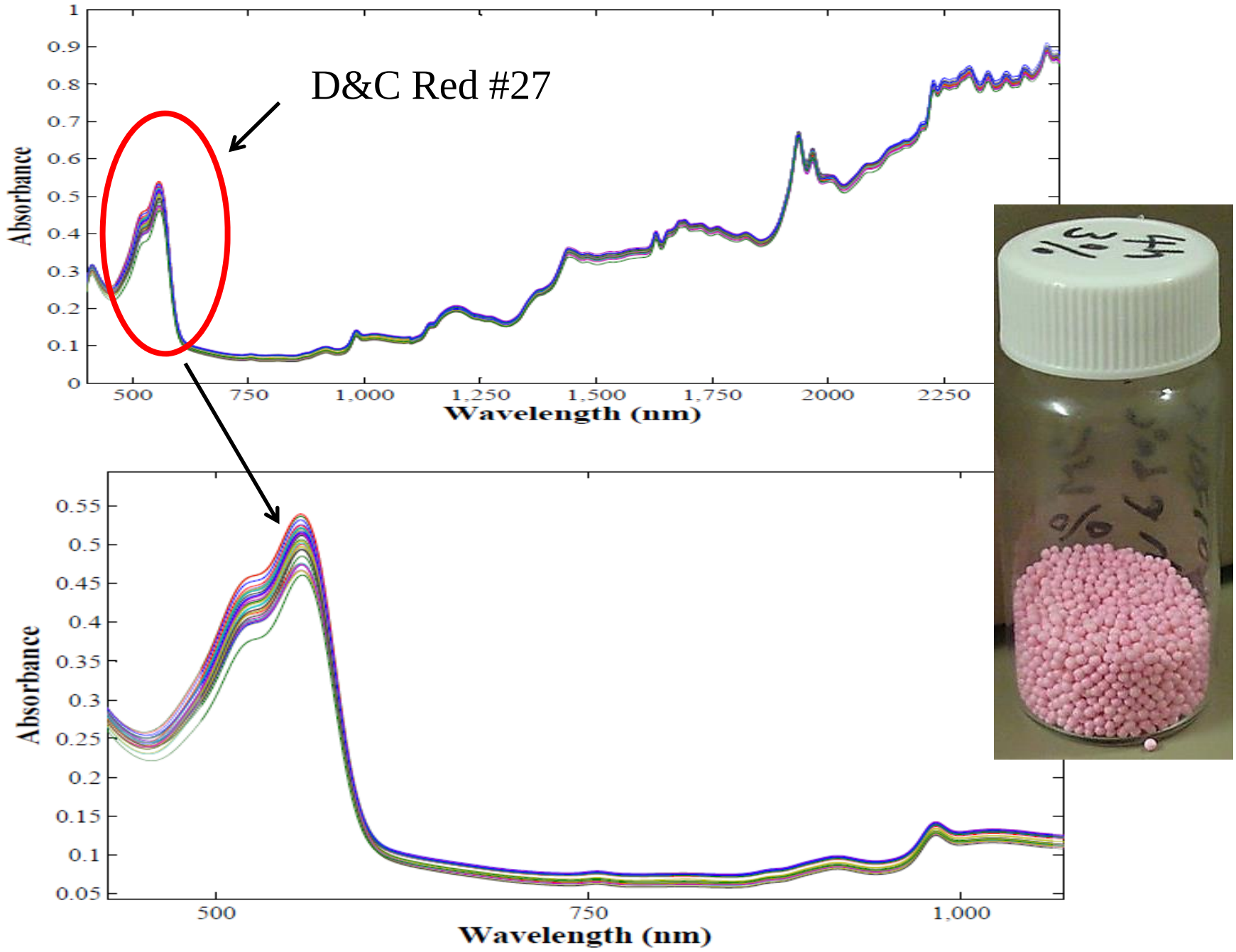
Rate of diffusion Fick's Law

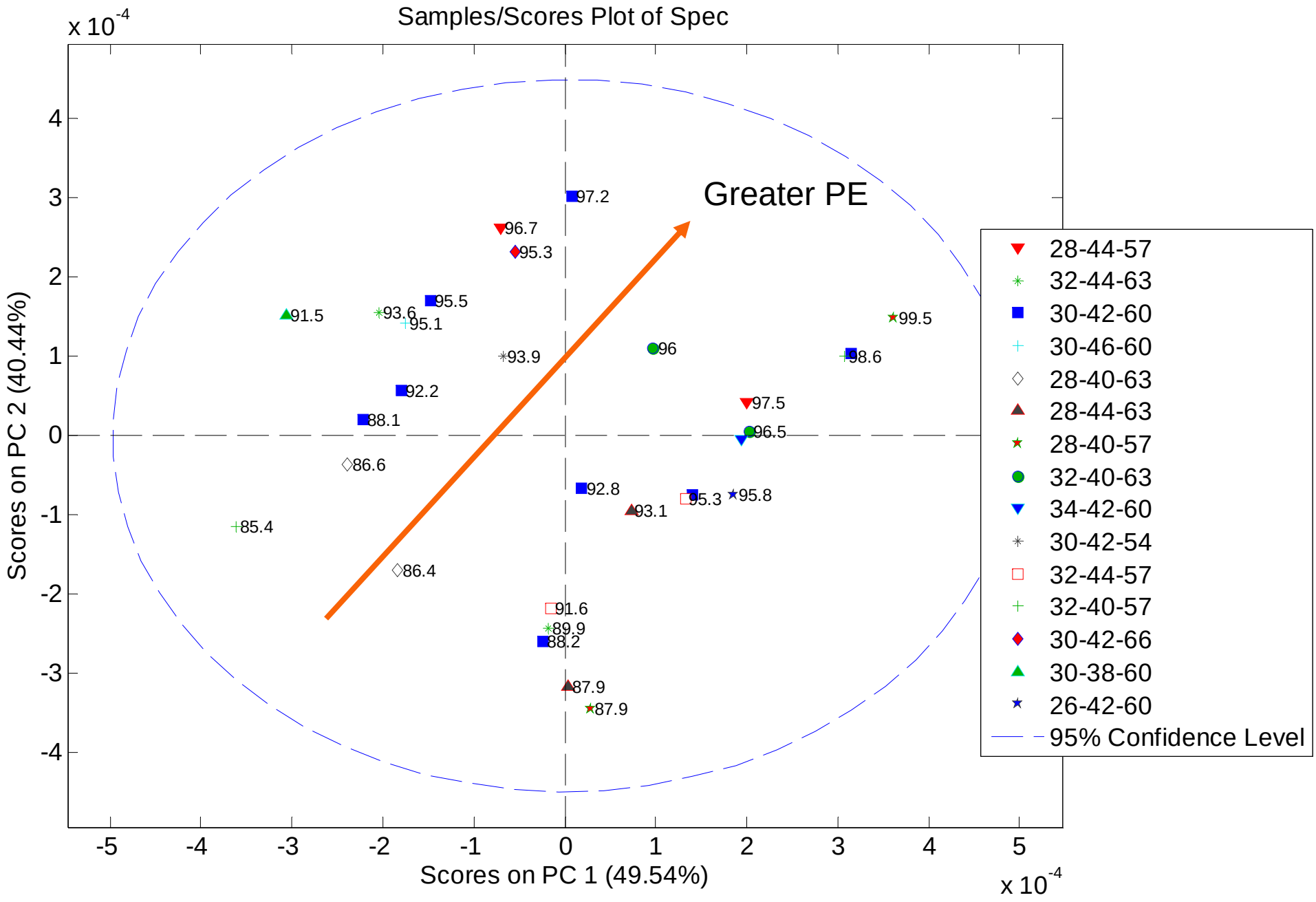
$$\frac{dm}{dt} = \frac{SD}{h}(C_{in} - C_{out})$$

Process Efficiency

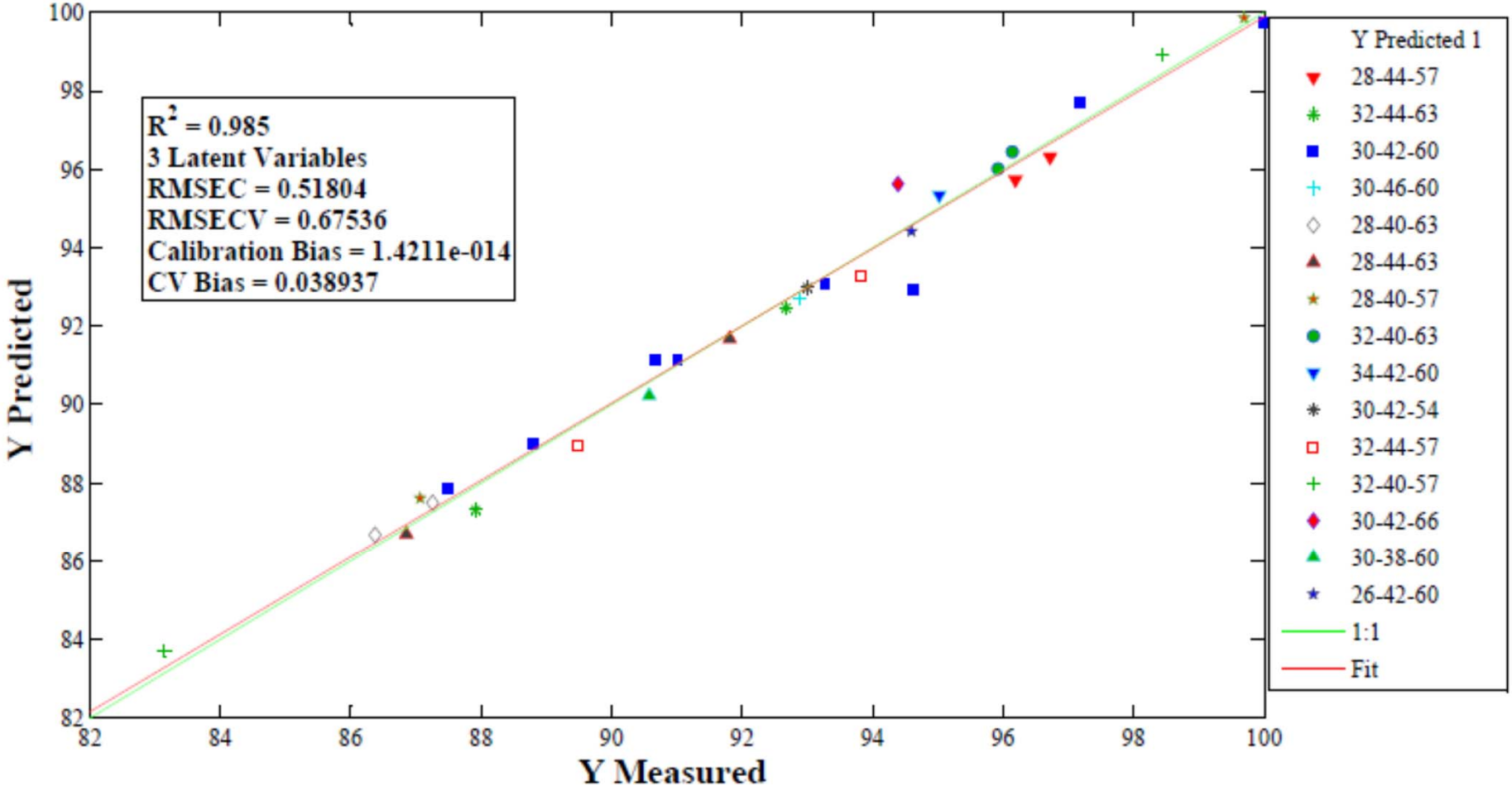



Ciprofloxacin HCl ● H_2O
Cipro Drug Layered Beads
D&C Red #27 Aluminum Lake
Aquacoat ECD - 30% solution
Aquacoat ECD+TEC+Color dry mixture
Neat Ethyl cellulose
Absorbance
2.5
2.0
1.5
1.0
0.5
0.0
400.00
525.00
650.00
775.00
900.00
1025.00
1150.00
1275.00
1400.00
1525.00
1650.00
1775.00
1900.00
2025.00
2150.00
2275.00
2400.00
Wavelenght (nm)

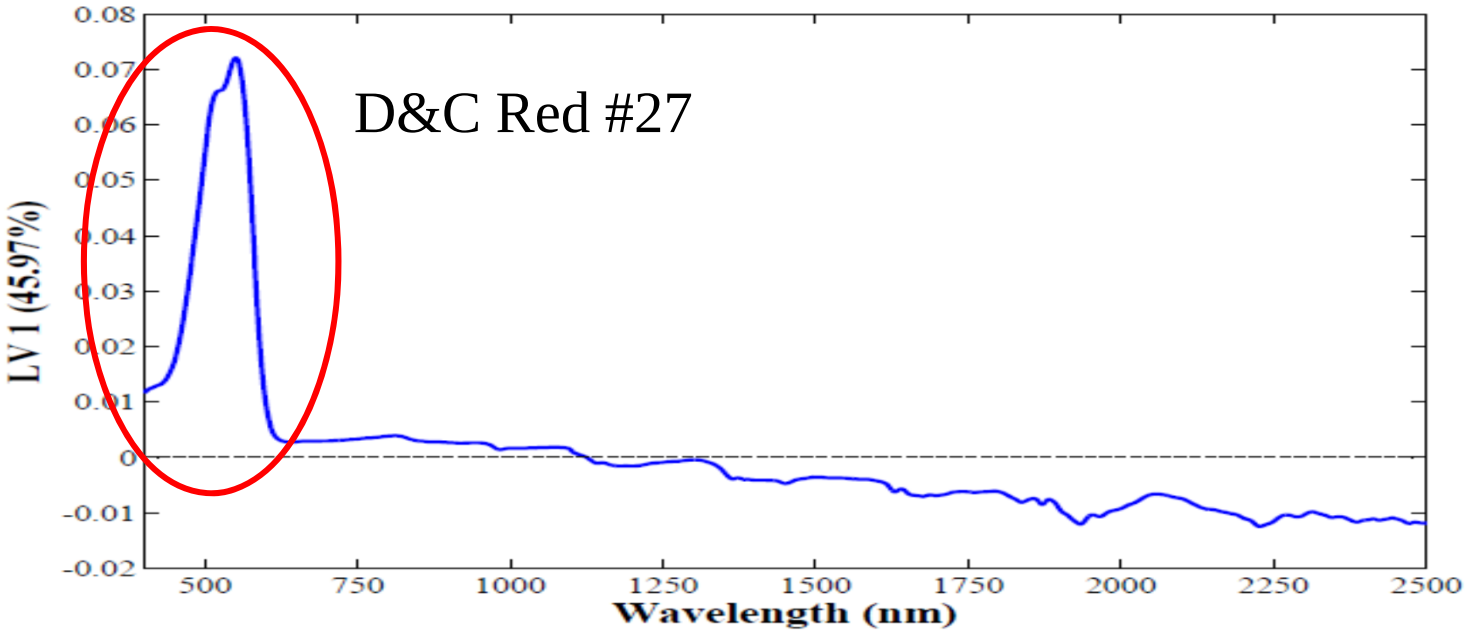

D&C Red #27
Absorbance
Wavelength (nm)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
500
750
1,000
1,250
1,500
1,750
2000
2250
Absorbance
Wavelength (nm)
0.55
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
500
750
1,000

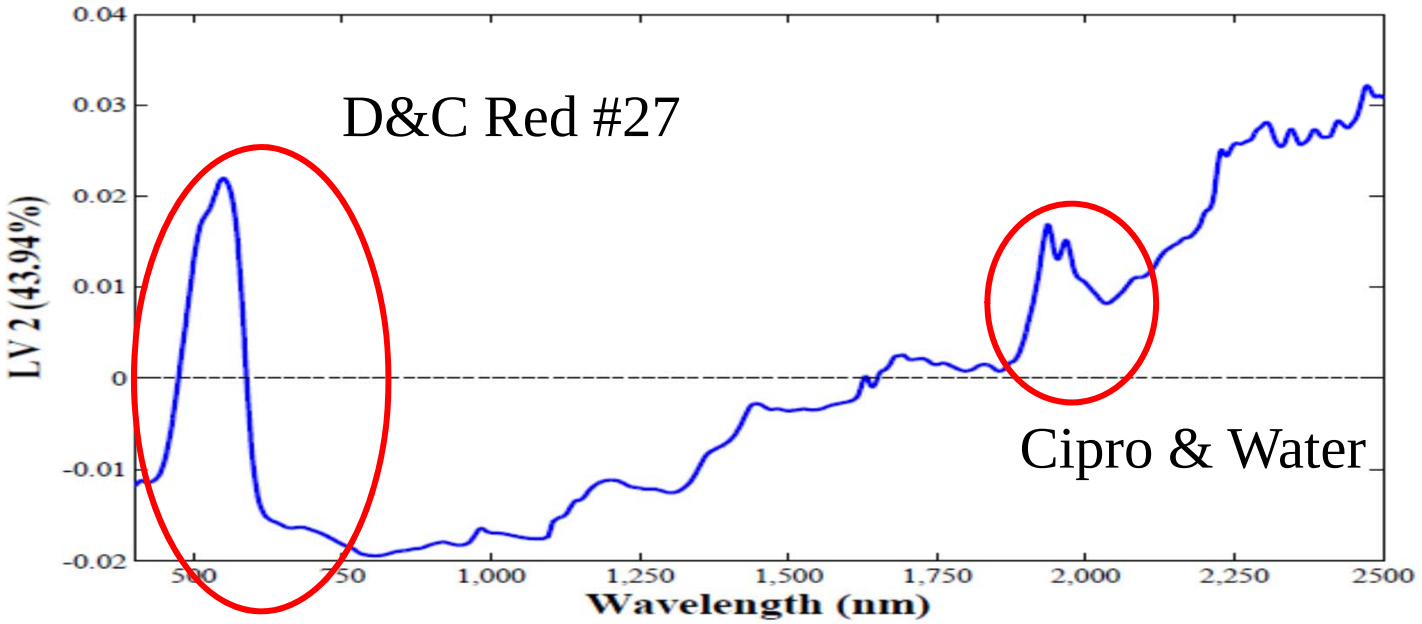

Samples/Scores Plot of Spec
x 10^-4
Greater PE
Scores on PC 2 (40.44%)
Scores on PC 1 (49.54%)
x 10^-4
97.2
96.7
95.3
95.5
91.5
93.6
95.1
99.5
93.9
96
98.6
92.2
97.5
88.1
96.5
86.6
92.8
95.3
95.8
93.1
85.4
86.4
91.6
89.9
88.2
87.9
87.9
28-44-57
32-44-63
30-42-60
30-46-60
28-40-63
28-44-63
28-40-57
32-40-63
34-42-60
30-42-54
32-44-57
32-40-57
30-42-66
30-38-60
26-42-60
95% Confidence Level

Calibration Model using RSM Batches
Legend – (Air volume-Product Temp-Curing Temp)



Loadings of the Latent Variables





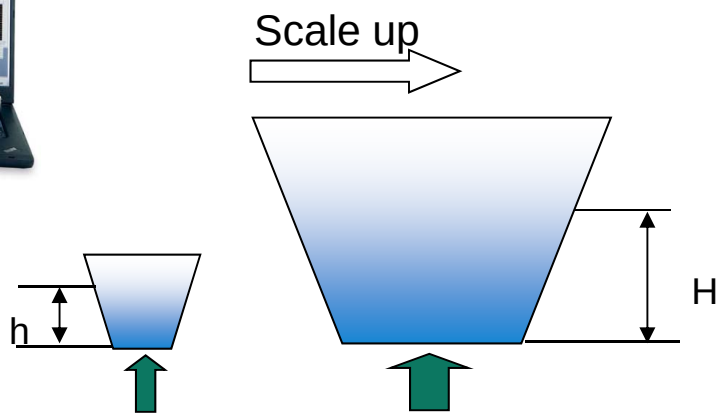
Scale Up Work Using Linear Approach

Non Critical Parameters Kept Constant = Microclimate and Atomization Pressure
Critical Process Parameters Based on Design Space = Product Temp. & Curing Temp.

Spray Rate (amount of solution sprayed/kg of material)
$= S_1 * M_1 * / S_2 * M_2$

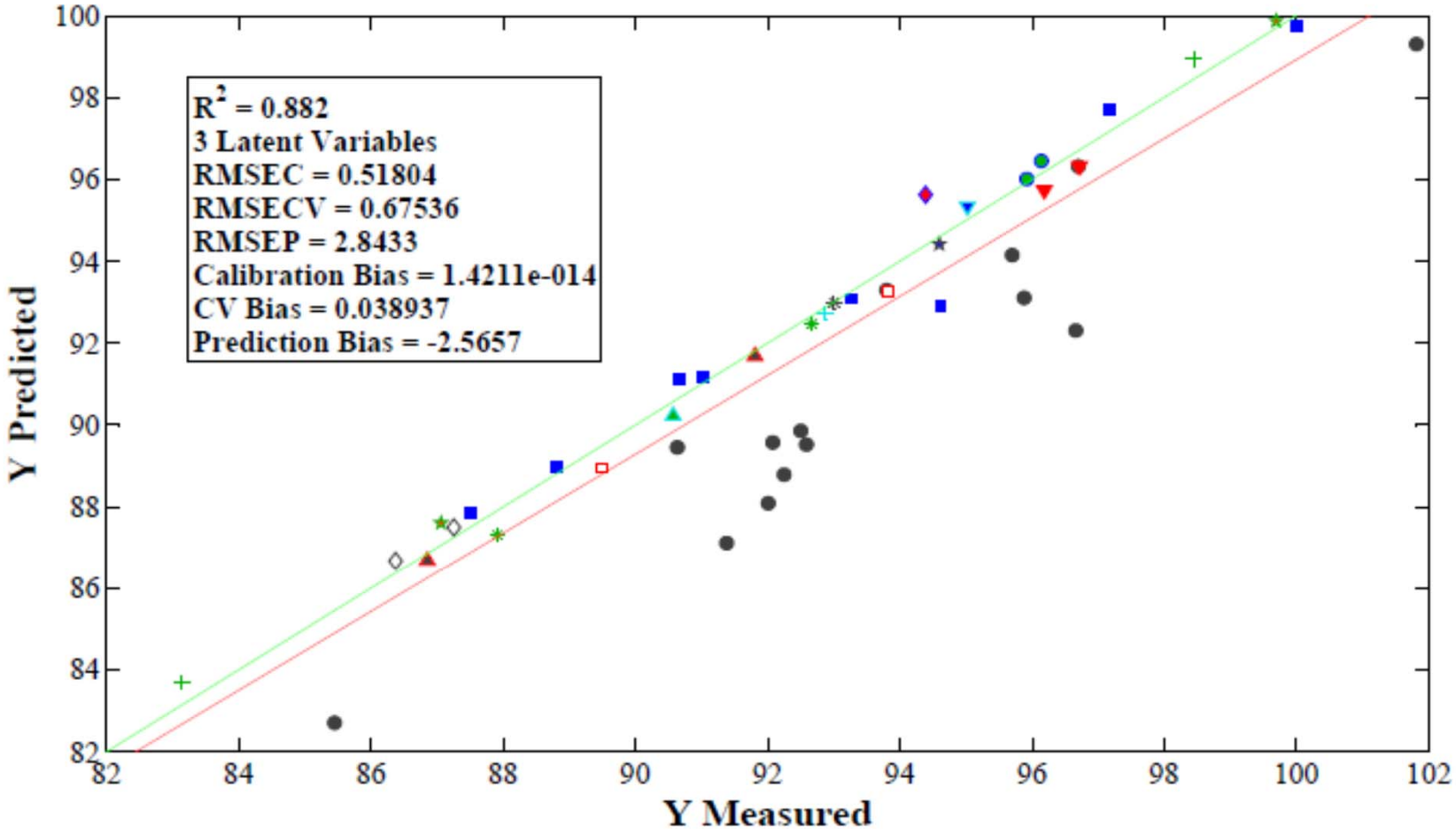
Mycrolab

Air Volume (air volume to bed size ratio)
$= A_1 * M_1 * / A_2 * M_2$



Unilab

External Validation of the Predictive Model using Scale-Up Batches (Unilab Batches)



PE Summary

- Process efficiency is key quality attribute that needs to be monitored
  - It depends upon:
    - Prod. Temp, Air volume, RH
  - 95 – 100% Design space sweet spot
  - 90 – 100% mostly good, but if low RH & combination of other parameters can get failures
- Some model adjustments are needed when changing scale
  - Lower scale data is very useful

Model Details for PE

- Major change (variance) in Spectra Modeled
- D&C Red #27 Color Wavelength (557 nm) for determining polymer deposition i.e. Surrogate marker for process efficiency
- Wavelength range used for Modeling
  - 400-2500 nm with resolution of 0.5 nm
- Preprocessing of the X-block
  - Normalize (1-Norm, Area = 1), Smoothing (order: 0, window: 15 pt, incl only), Mean Center
- Preprocessing of the Y-block
  - Mean Center
- Latent Variables - 3
- Cross validation: venetian blinds with 5 splits
- No of Samples Utilized for Calibration Model – 30 uncured samples with varying process efficiency - RSM study

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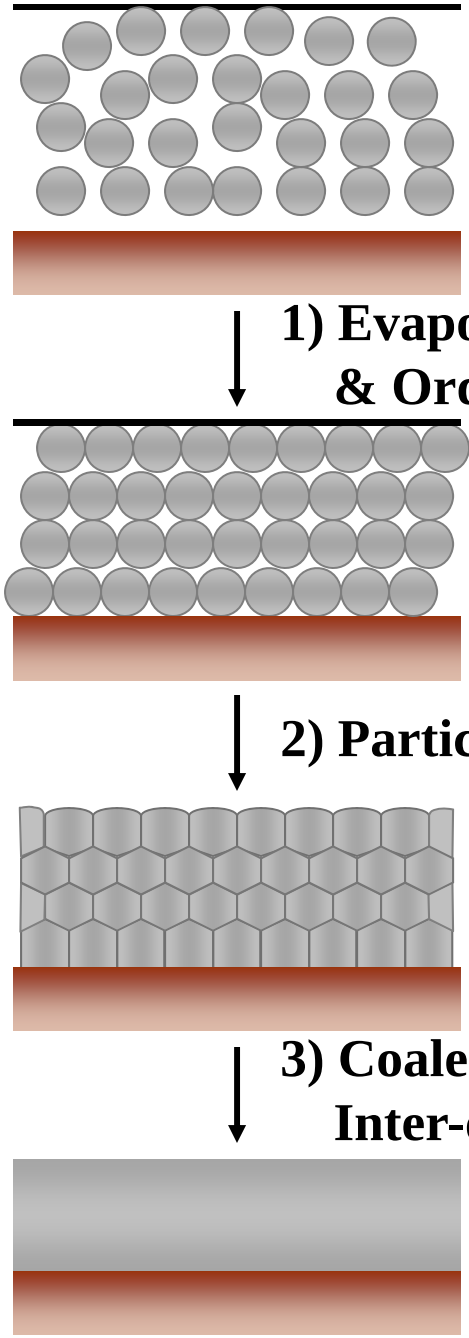
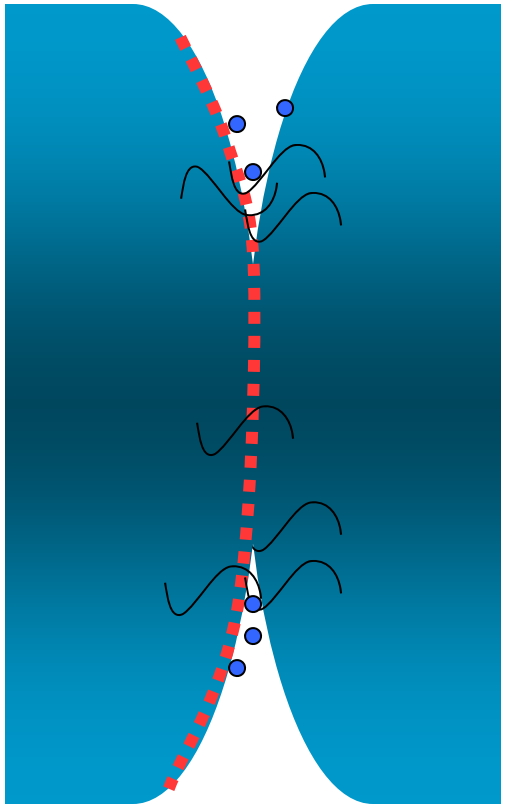
Note, in the interest of time, only selective steps will be shown for each model



Latex Particle Interface



Rate is very Temp.
Dependent
Coat @ T ~ Tg

Not to scale

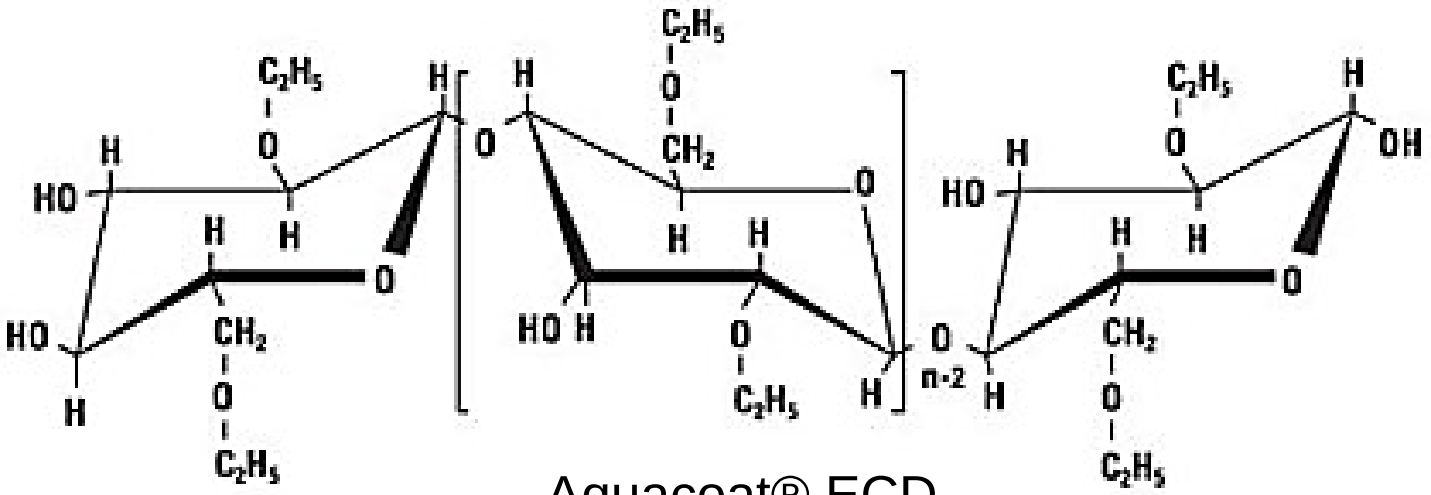
Ethylcellulose Aqueous Dispersion

USP DEFINITION

"Ethylcellulose Aqueous Dispersion is a colloidal dispersion of Ethylcellulose in water. It contains NLT 90.0% and NMT 110.0% of the labeled amount of ethylcellulose. It contains suitable amounts of **Cetyl Alcohol** and **Na Lauryl Sulfate**, which assist in the formation and stabilization of the dispersion. It may contain suitable antifoaming and antimicrobial agents."

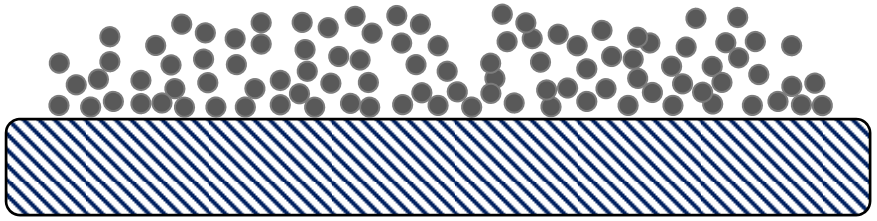
Ethylcellulose Tg 131-150ºC
Aquacoat 30% dispersion (Tg = 91ºC)
Aquacoat 30% dispersion + 25% w/w/ TEC = Tg 36-38ºC
Aquacoat 30% dispersion particle size 85% < 500 nm

Water is critical to Tg



Aquacoat® ECD

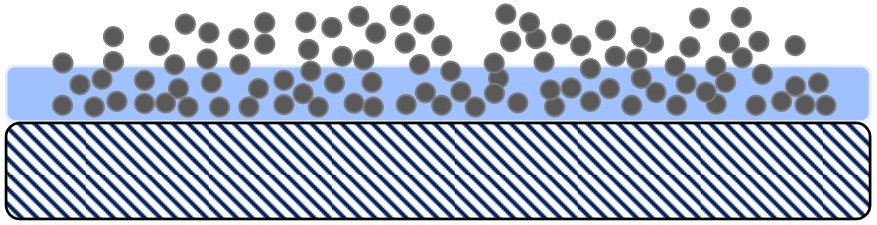
Film Formation and Water



Dry Sintering

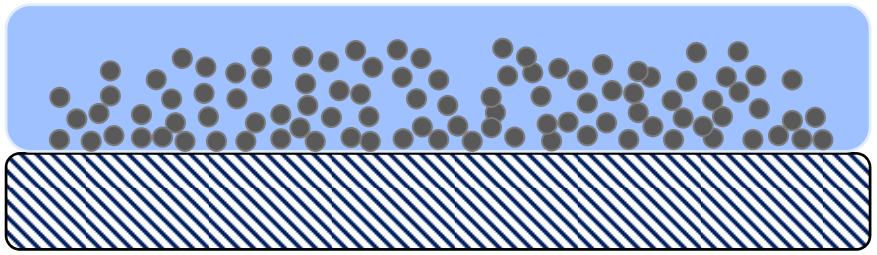
Interfacial Tension

Particle / air



Capillary Deformation

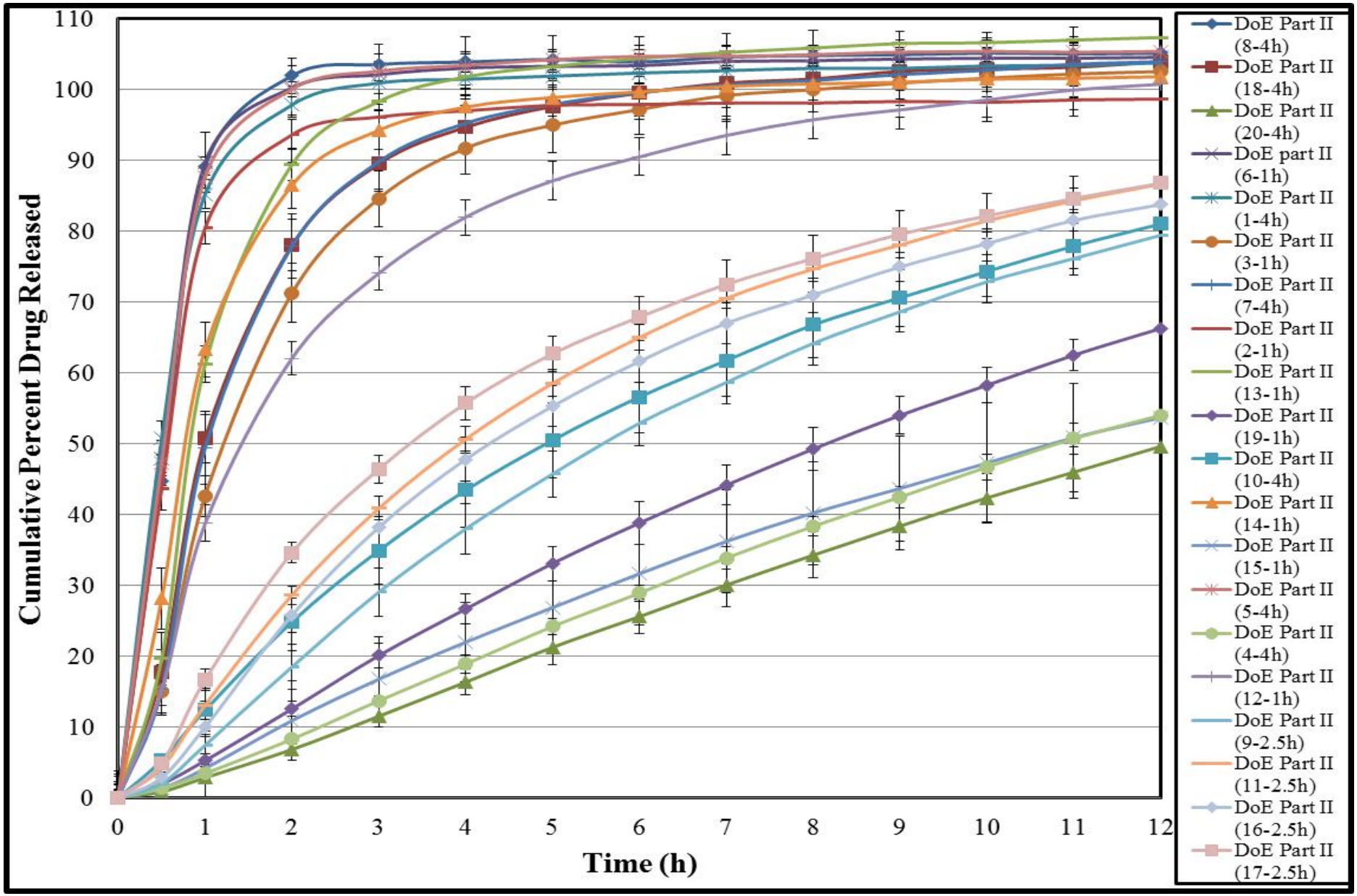
Water / air
Particle / air

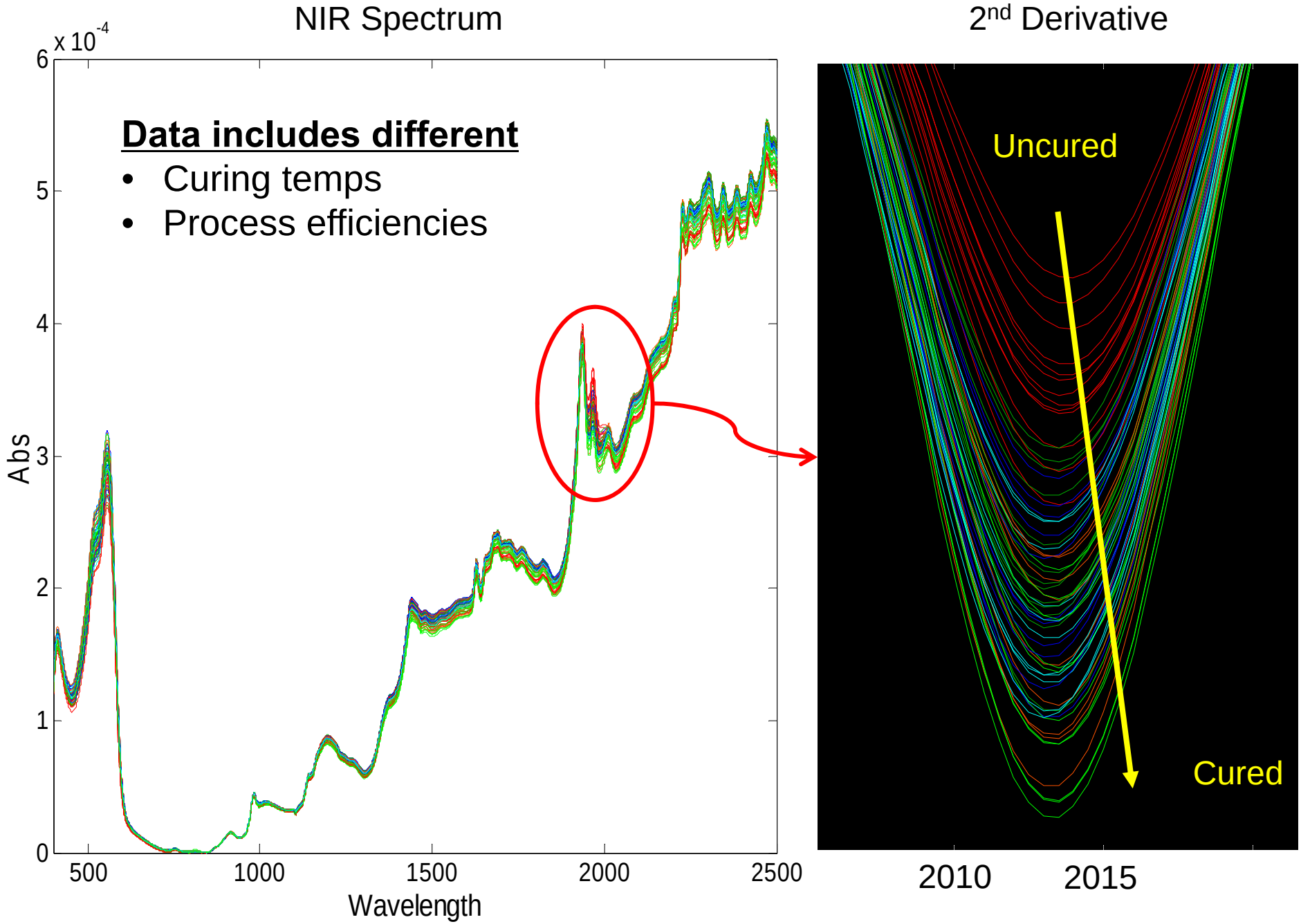


Wet Sintering

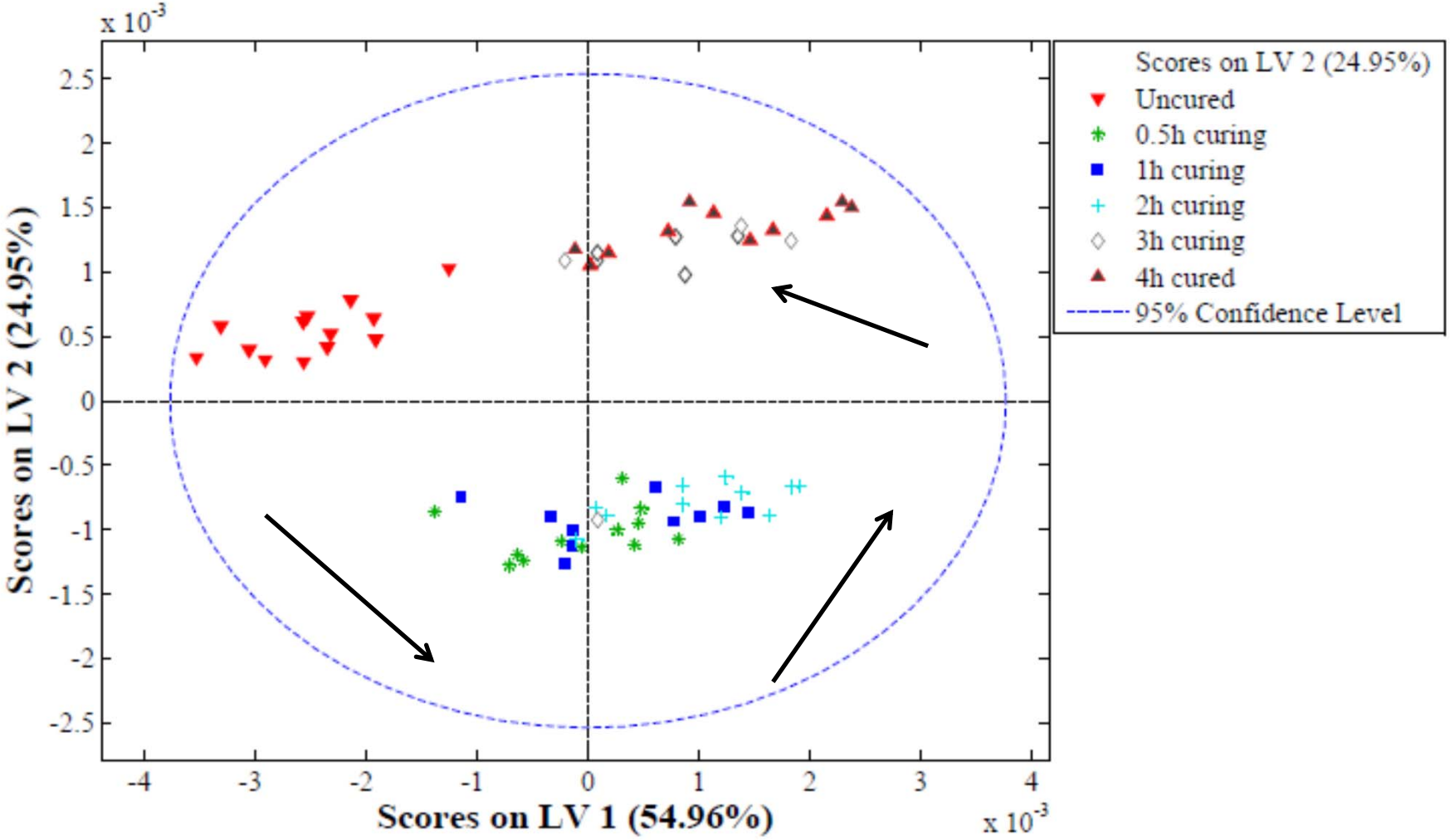
Particle / water

Dissolution Profiles of Ciprofloxacin HCl Bead Batches, 252 mg/g DoE – Part II (with center points)

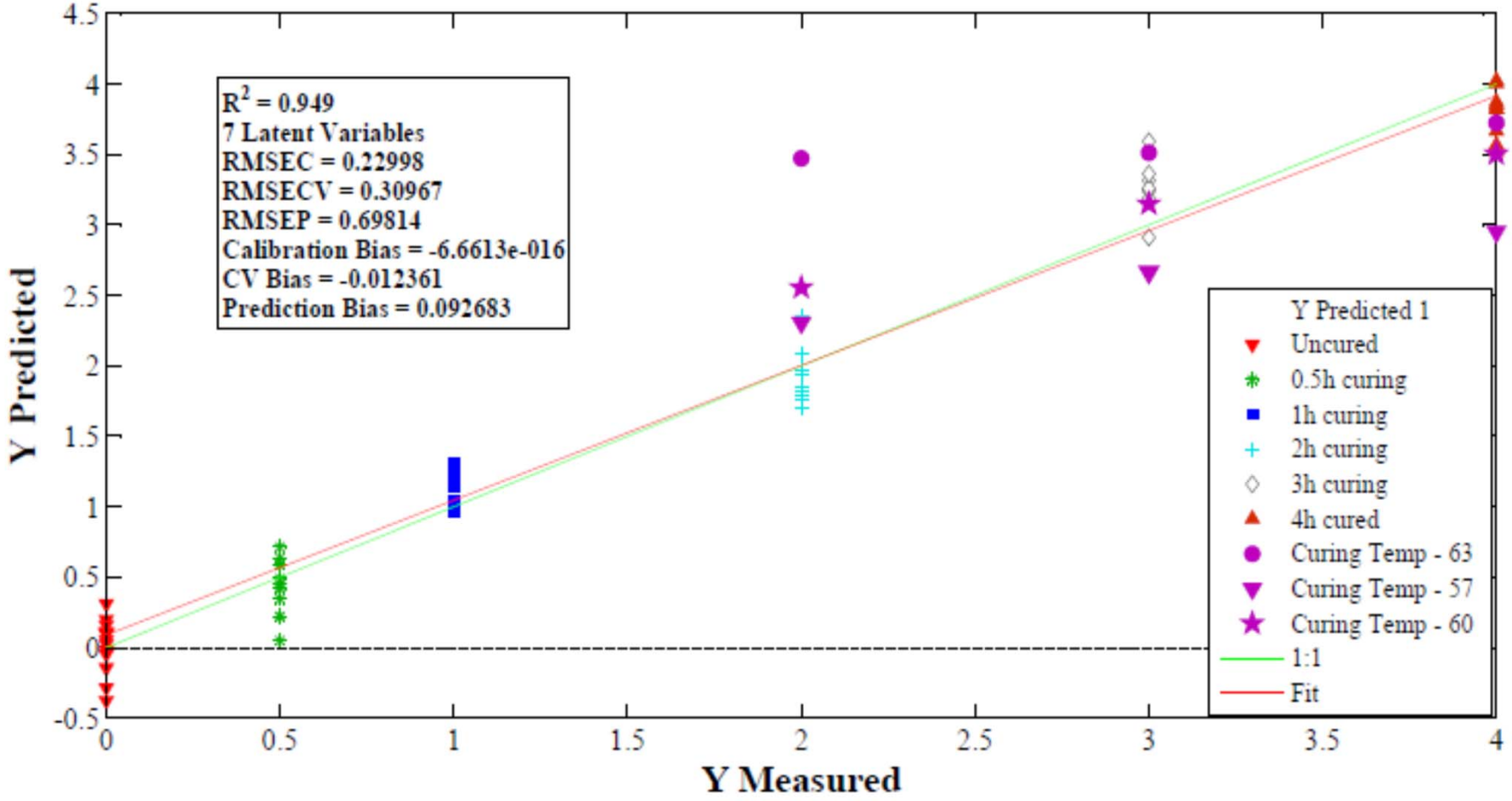



NIR Spectrum
2nd Derivative
x 10-4
6
5
4
3
2
1
0
Abs
500
1000
1500
2000
2500
Wavelength
Data includes different
• Curing temps
• Process efficiencies
Uncured
Cured
2010
2015

Scores Plot and Curing Process Trajectory



External Validation of the Predictive Model
Scale-Up Batches (Unilab) @ Different Curing Temperature



Low Curing Temperature batch will take longer time to reach optimum curing
Optimal Curing Temperature batch will take target time to reach optimum curing
Higher Curing Temperature will take less time to reach optimum curing

Model Details for Extent of Curing

Major change (variance) in Spectra Modeled

- Water Band and Ethylcellulose Band (~1950 nm) for change in surface moisture/residual moisture from the core of the beads

Wavelength range used for Modeling

- 400-2500 nm

Preprocessing of the X-block

- 2nd Derivative (order: 2, window: 15 pt, incl only), Smoothing (order: 0, window: 15 pt, incl only),Normalize, Mean Center

Preprocessing of the Y-block

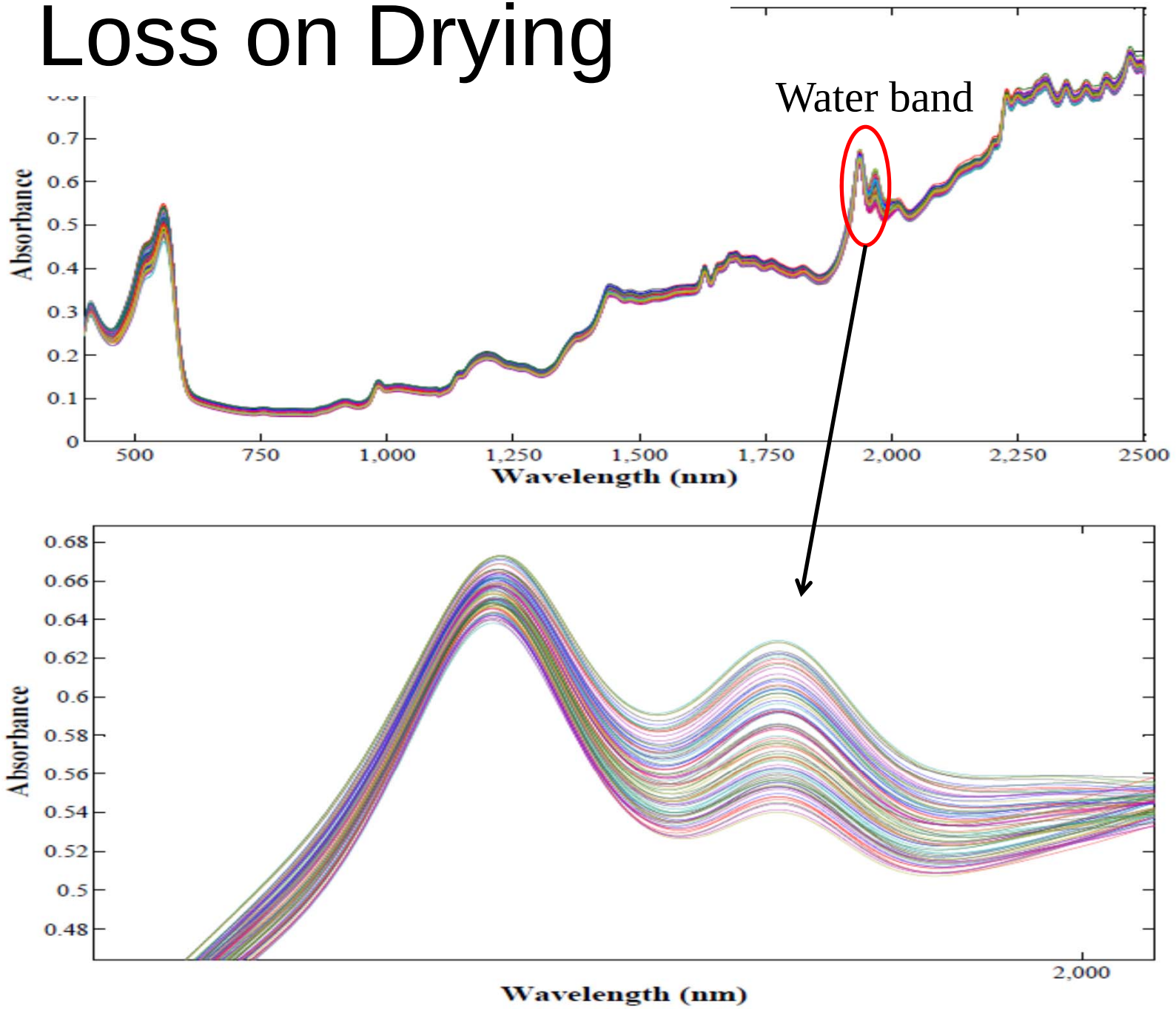
- Auto-scale

Latent Variables - 7

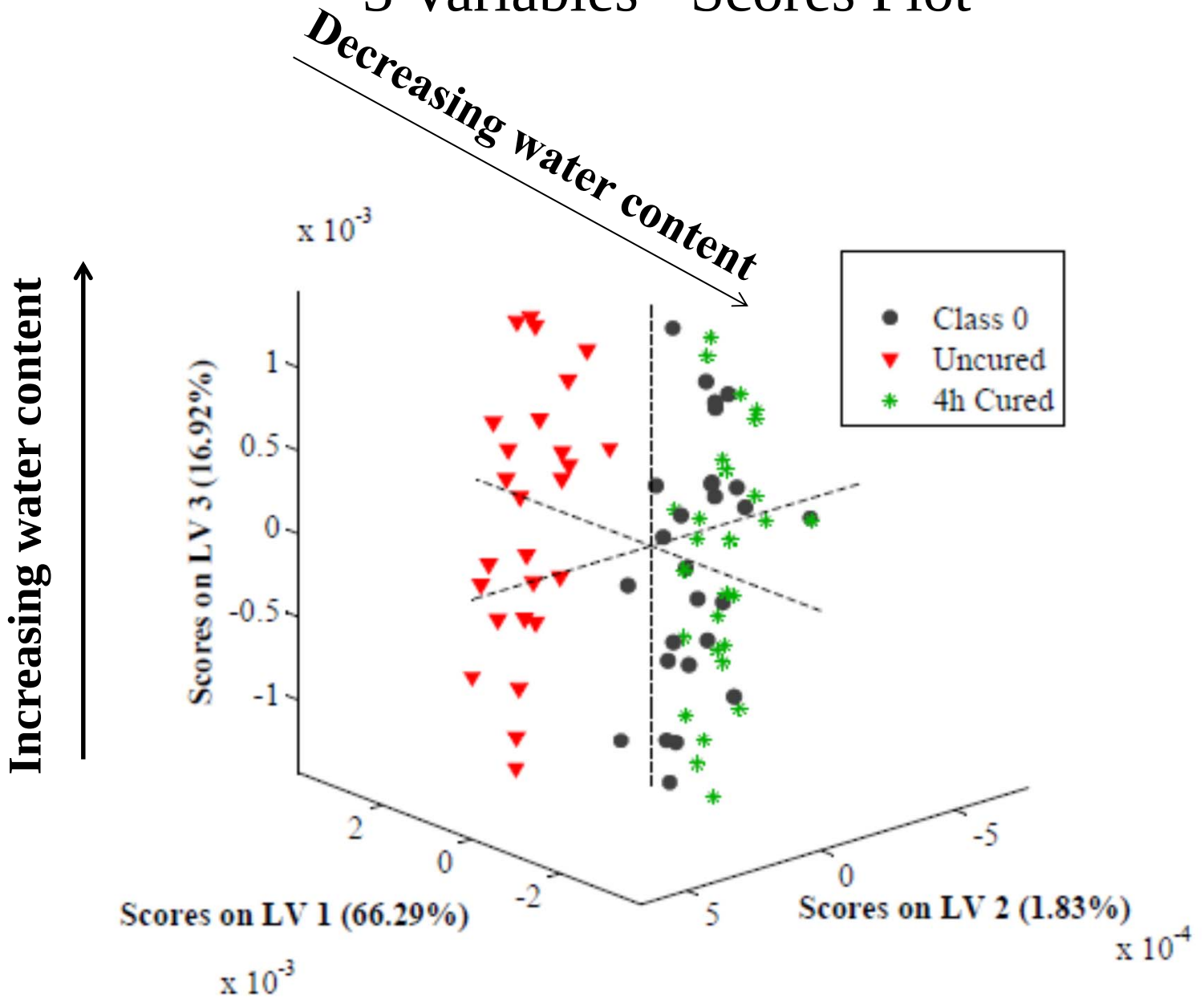
Cross validation: venetian blinds with 8 splits

No of samples used for calibration model – 66 samples (uncured, 0.5h, 1h, 2h, 3h and 4h cured beads)

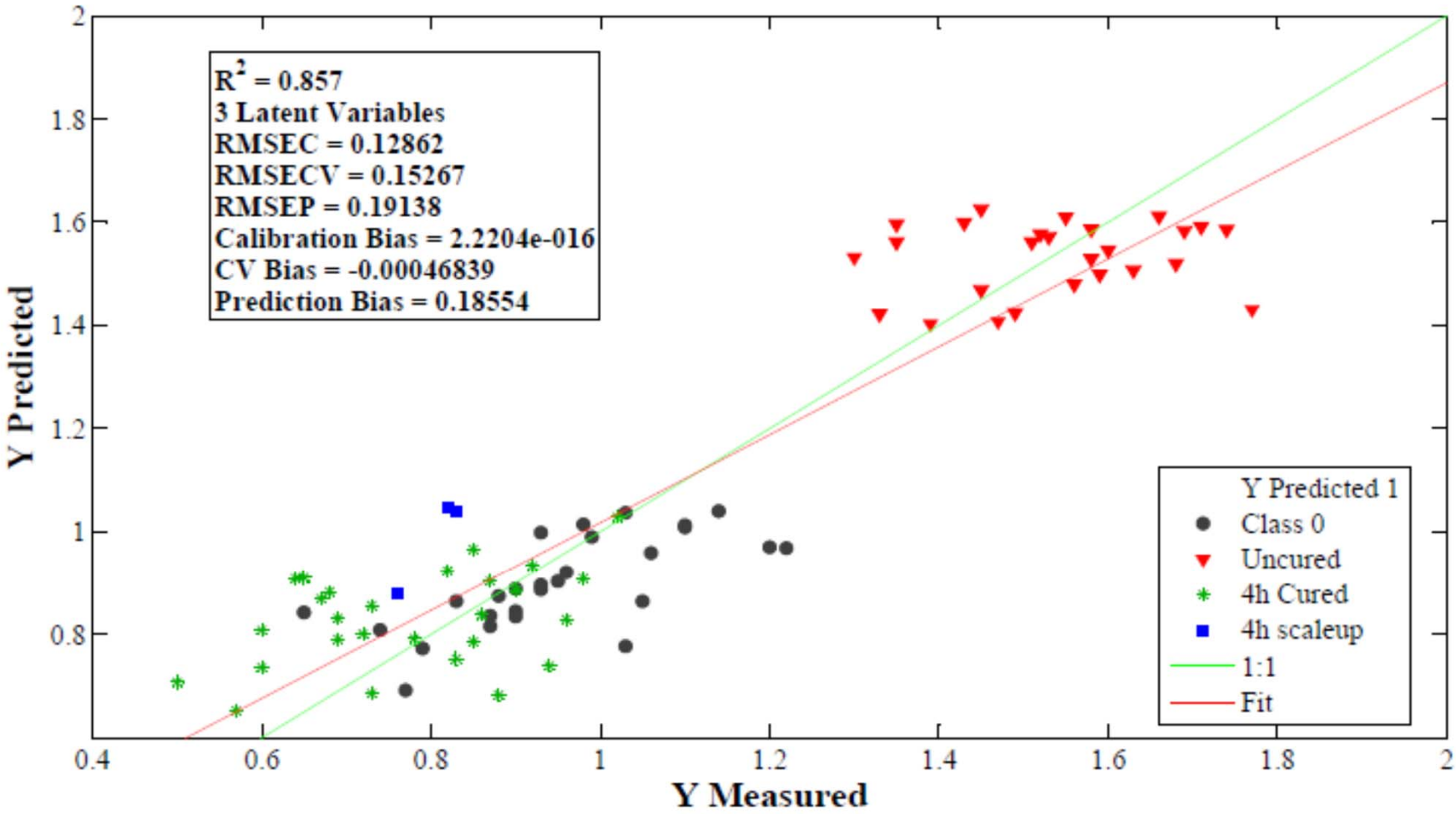
Loss on Drying



3 Variables - Scores Plot



External Validation of the Predictive Model
Scale-Up Batches (Unilab Batches)



Model Details for Loss on Drying

Major change (variance) in Spectra Modeled

Water Band (~1940 nm)

Wavelength range used for Modeling

400-2500 nm

Preprocessing of the X-block

1st Derivative (order: 2, window: 15 pt, incl only), Normalize (1- Norm, Area =1), Mean Center

Preprocessing of the Y-block

Auto-scale

Latent Variables - 3

Cross validation: venetian blinds w/ 9 splits

No of samples used for calibration model – 80 samples (RSM batches: Uncured, Design Point and 4h Cured)

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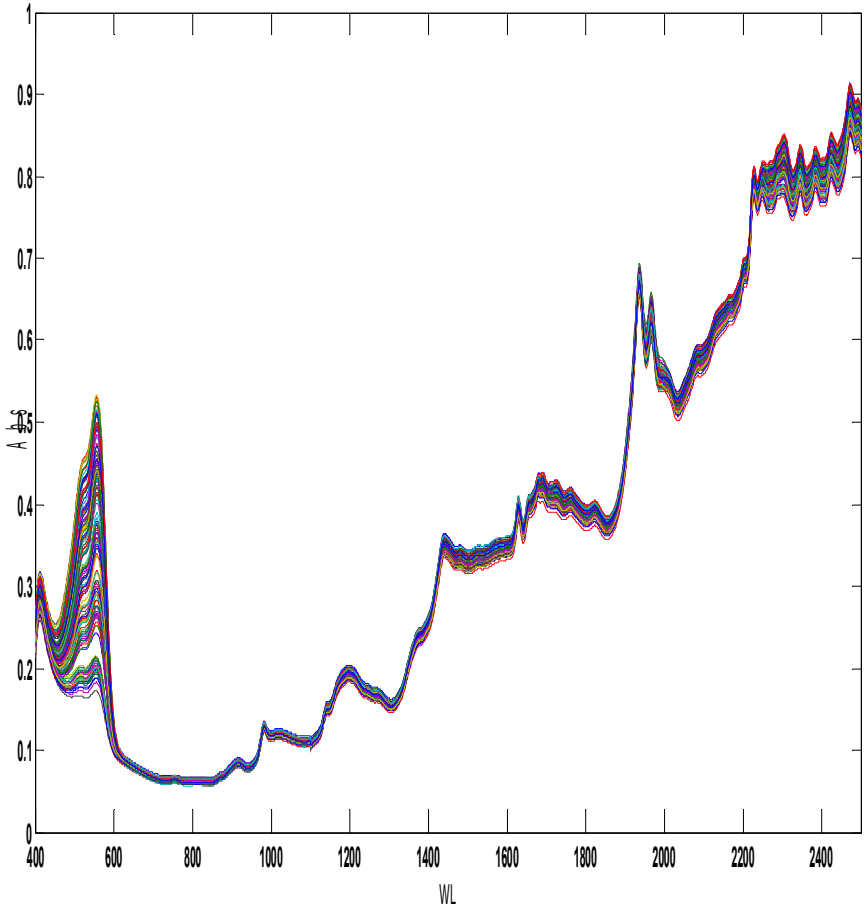
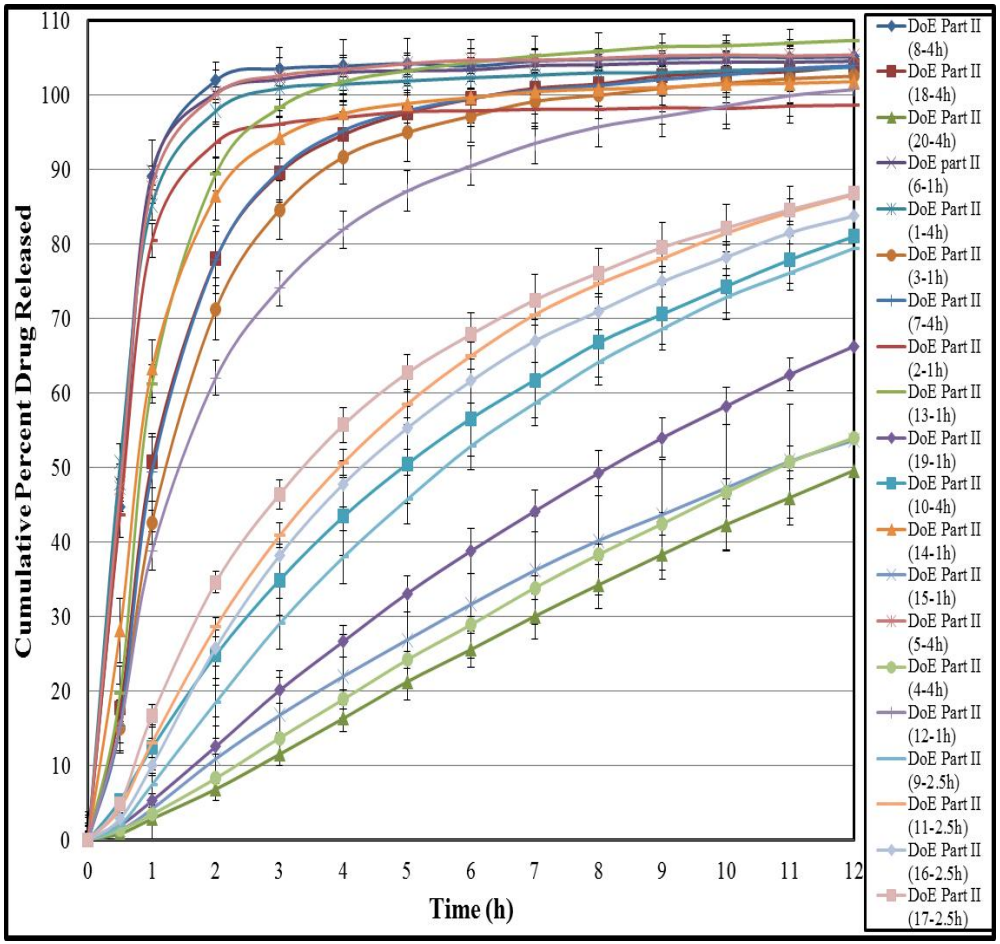
Dissolution Prediction: The Problem

- Coating of Multiparticulate beads involves:
  - Spraying with a coating solution
  - Curing at higher temperature.
- Complex process involving optimization of many parameters :
  - **Process Parameters**: Product temperature, atomization air volume, curing temperature, curing time
  - **Environmental measurements:** Humidity
- Changes in any of these parameters can have an impact on the final product quality.

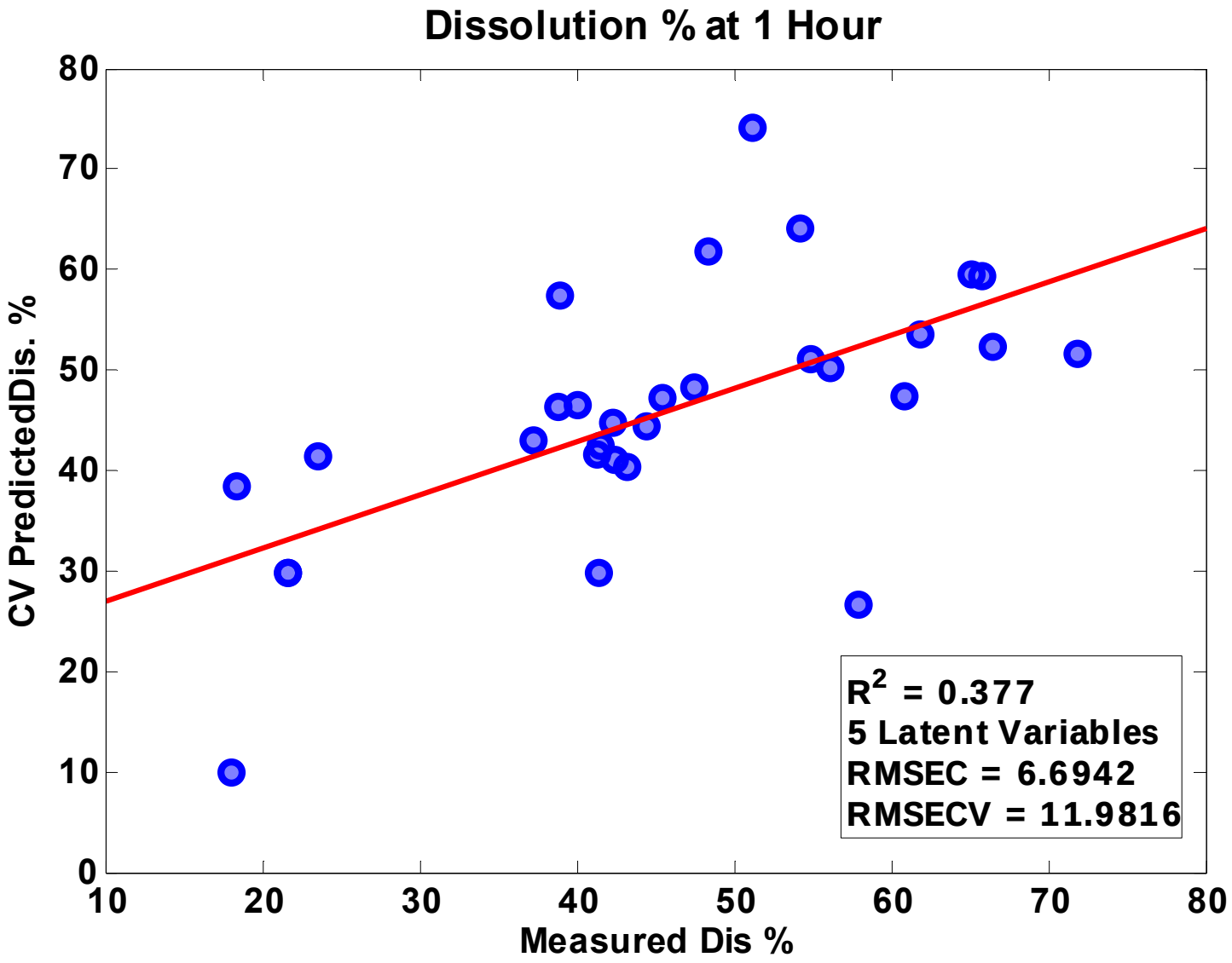
Dissolution Profiles



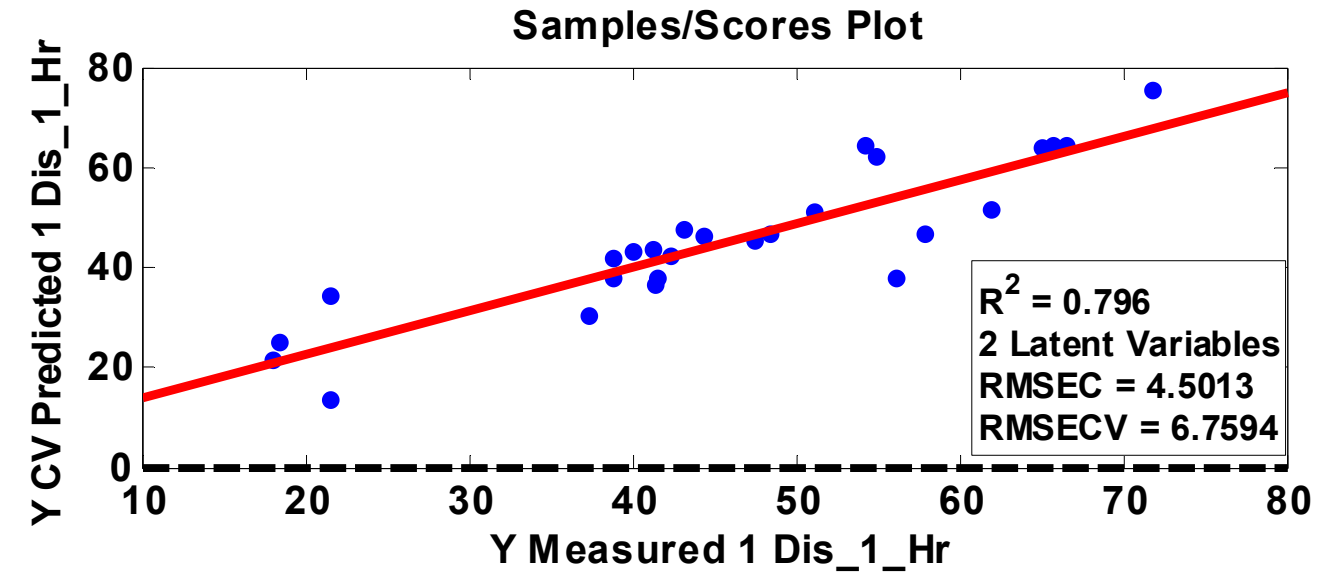


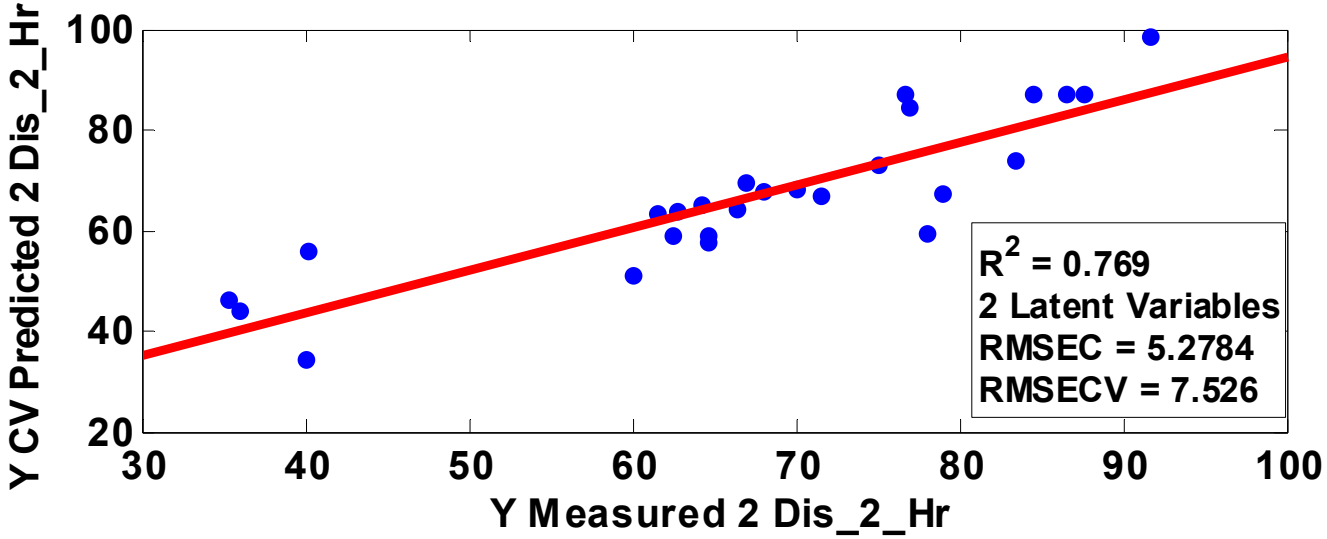
- **Dissolution data is difficult to predict:**
  - **Physical property – typically weaker NIR signal**
  - **Depends upon many parameters**

Prediction Using NIR Spectra Only



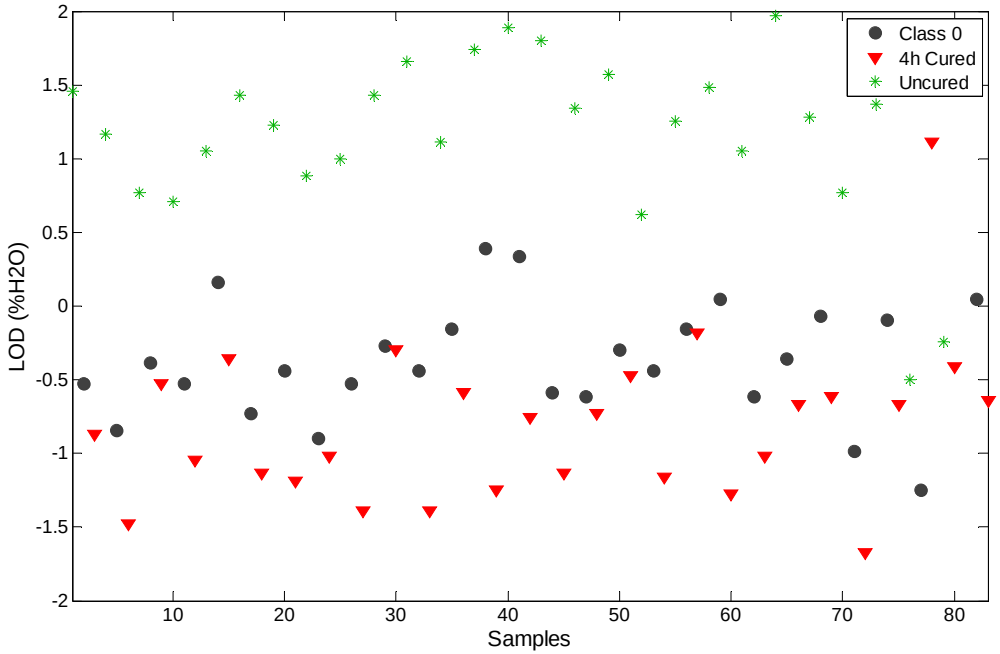
Prediction Using Process Data Only





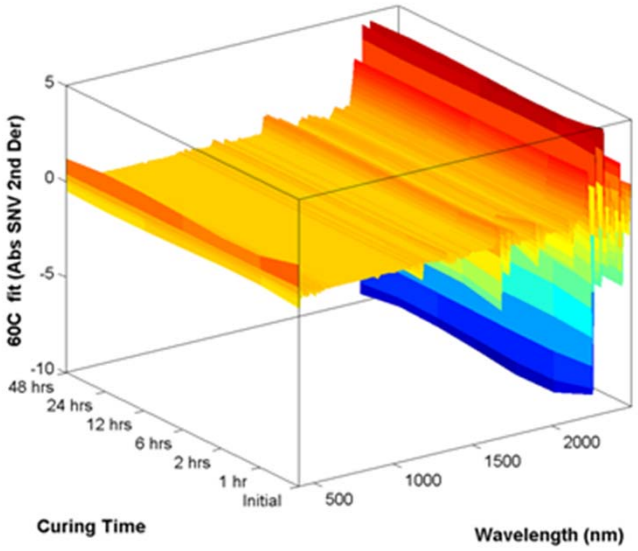
Data Fusion

- Environmental and spectral datasets very different structure
  - Spectral data will overwhelm environmental data
  - To fuse data need to reduce dimensions of spectral



1 Temp + RH every 15 sec
4 hr run = 1,920 data pts.

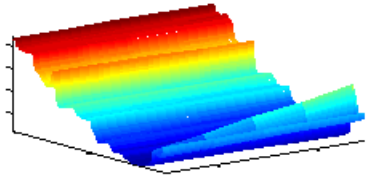
Environmental Data



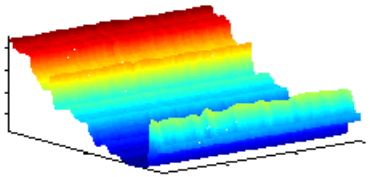
1 spectra every 2 min
4 hr run = 482,400 data pts.

Spectral Data

NIR of Spraying Process



NIR of Curing Process



Parafa PCA

Parafc PAC

Process Param.

Spraying Scores

Curing Scores

Spraying Process

Air Volume

Product Temp.

Curing Process

Curing Temp.

Curing Time

Relative Humidity

Data Fusion

Spraying Scores

Spraying Scores

Air Volume

Curing Temp.

Curing Time

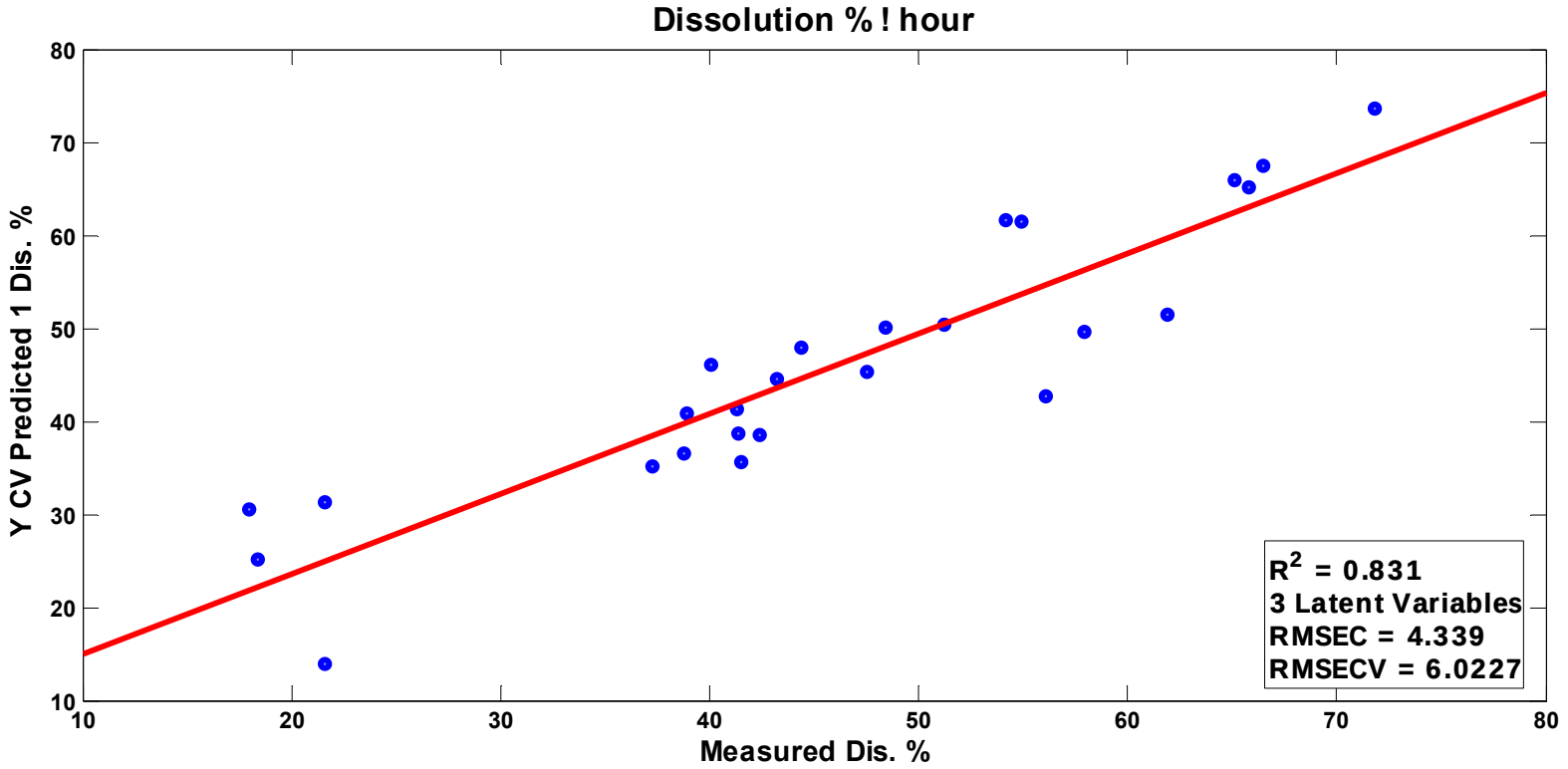
Relative Humidity

Dissolution Results

PLS Model For Dissolution

Parafac = Parallel Factor Analysis

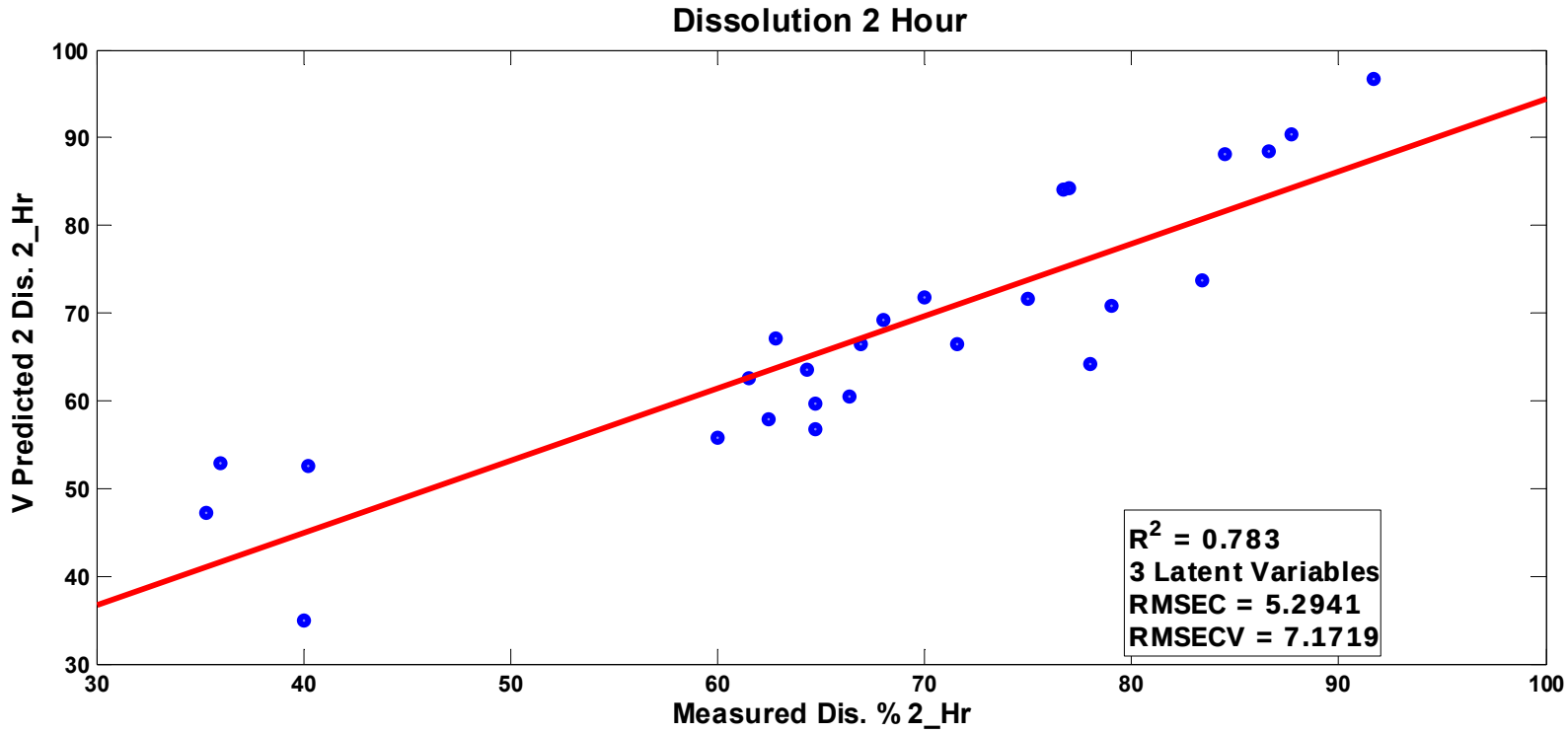
Dissolution 1Hour Parafac Decomposition



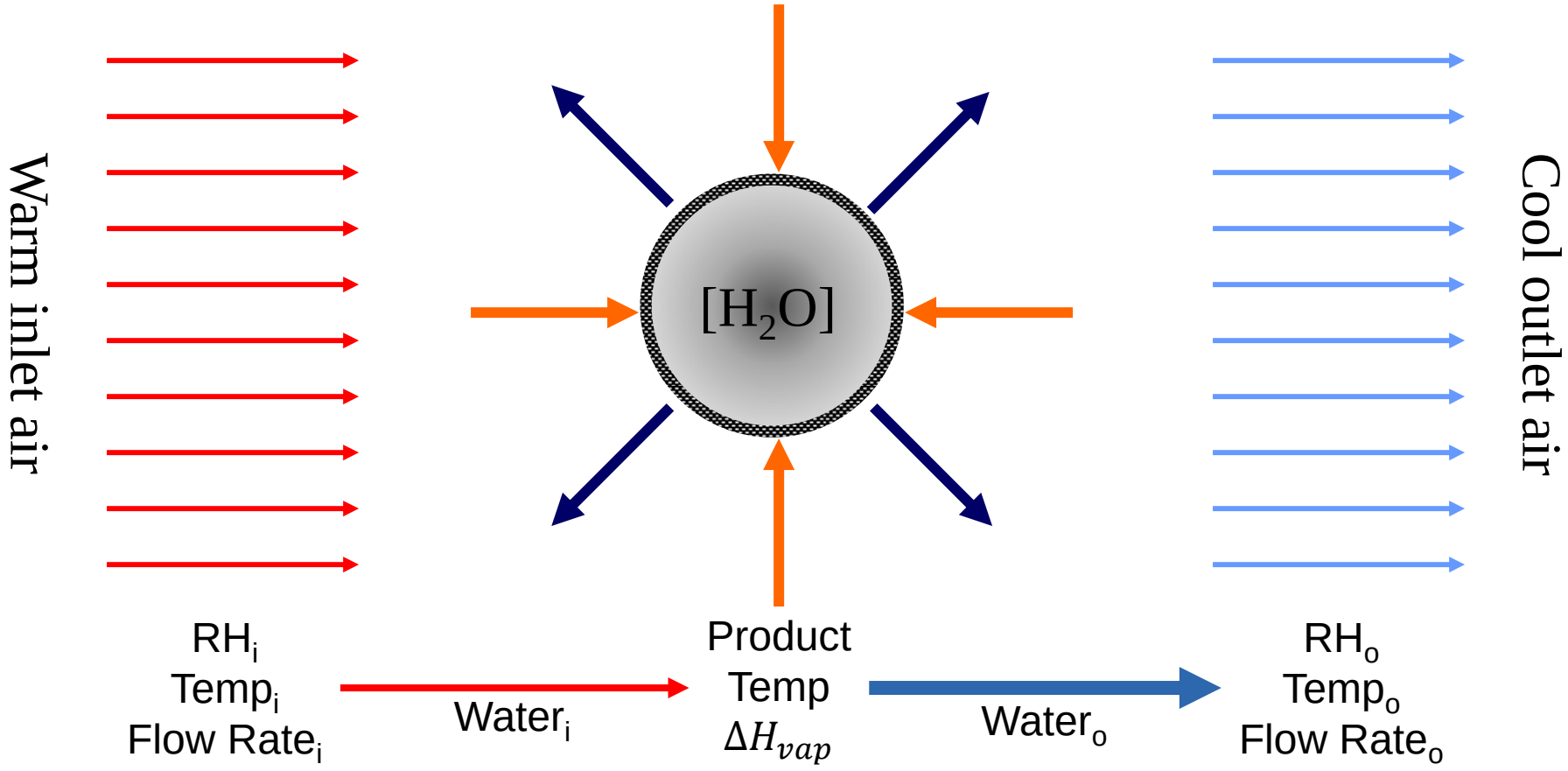
Parafac is similar to 3D multidimensional PCA and process time is the 3rd dimension

-Dimensions are: time, wavelength and batch No.

Dissolution 2 Hour
Parafac scores with Process data



Heat & Mass Transfer



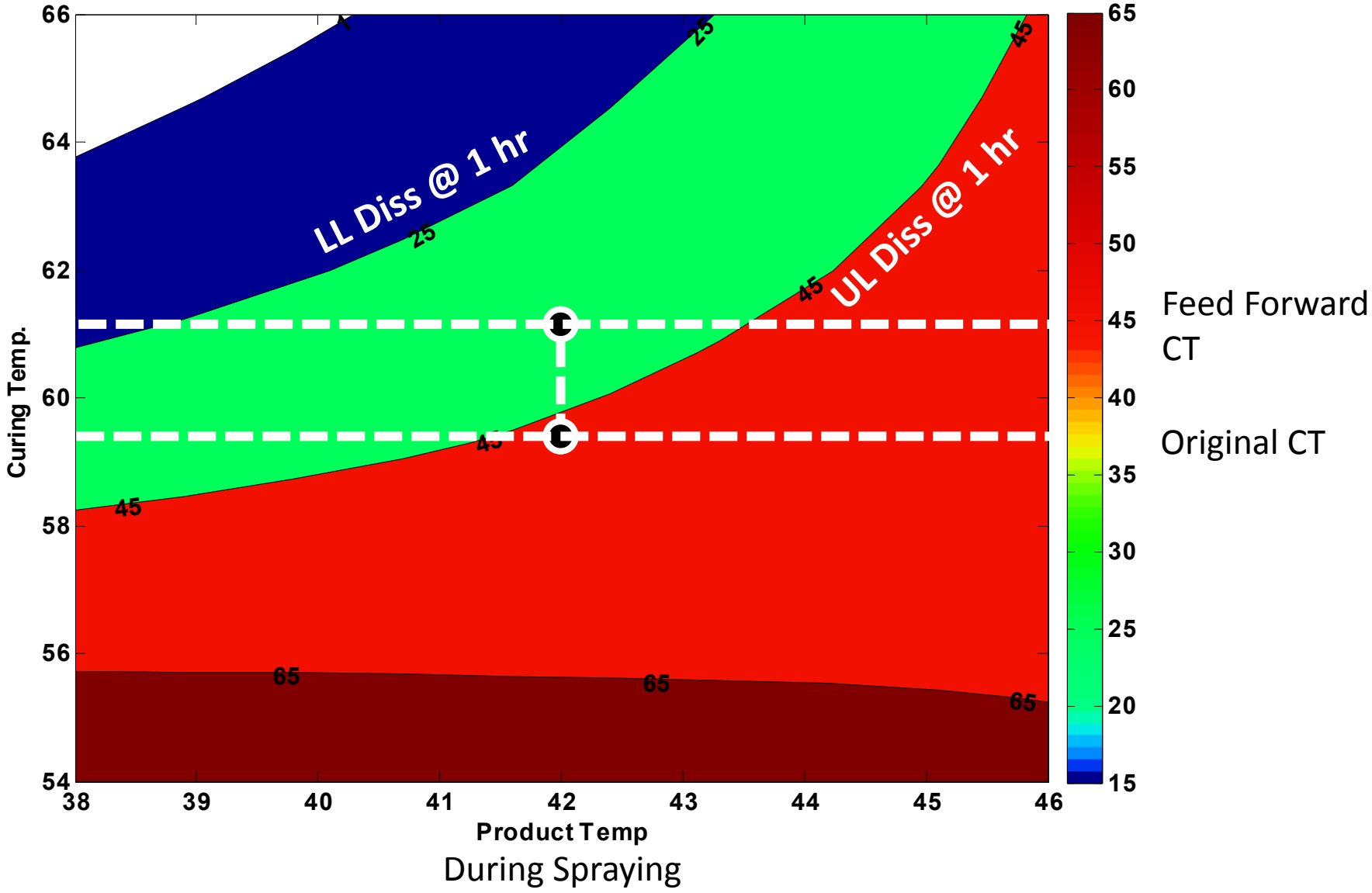
Air liquid interface

Heat transfer (conduction, convection and radiation)

Mass transfer (conduction and convection)

CT Feed-Forward for Diss. 1h

Simulation using PLS model



During Spraying

Control Strategy Summary

Factor	Attribute	Range Studied	Target Range	Validated Range	Purpose of Control	Method of Control
Drug Substance and Excipients - Critical Material Attribute						
Ciprofloxacin HCl	Particle Size	d10 = _____, d50 = _____ d90 = _____	Information unknown as the drug layered beads were procured directly from the vendor.		To ensure batch to batch consistency	NIR –Laser (controlled Upstream)
Mannitol	Particle Size	d10 = _____, d50 = _____ d90 = _____				
Sugar Spheres	Particle Size	Fraction between 18 and 16 mesh				
Povidone K-30	K- value	Tight specs from the vendor	29-32	29-32	To ensure consistent binding property	Vendor Specs
Formulation Variables – Critical Material Attributes						
Core type/Size	Type and PSD	Information unknown as the drug layered beads were procured directly from the vendor			To ensure target assay and desired drug release	Theoretical - Design of Experiments (Full factorial 2^3 = 8 + 2 center points = 10 experiments)
Binder type	Type					
DS/Binder ratio	Concentration					
Drug Layering Process – Critical Process Parameters						
Pan Coating	Product temperature	Information unknown as the drug layered beads were procured directly from the vendor			To ensure target assay and desired drug release achieve consistently	Theoretical - Design of Experiments (Resolution V fractional factorial – two level design i.e. 2^{5-1} = 16 + 4 center points = 20 experiments)
	Atomization Pressure					
	Air volume					
	Flow rate of API/Mannitol					
	Spray rate of Binder					

Drug Layered Beads – Critical Quality Attributes (In-Process Controls)			
Quality Attribute	**Sample Type**	**Specifications**	**Control Strategy**
Assay	Composite Samples	95-105% of label claim	NIR and HPLC
Drug Release	Composite Samples	Q80 % = 30 minutes	Dissolution
PSD	Composite Sample	Retained on 14 and 16 mesh	Laser Diffraction
Moisture	Composite Sample	NMT 2.0%	LOD
Surface Morphology	Composite Sample	Smooth Surface	Optical Microscopy

Control Strategy Summary

Factor	Attribute	Range Studied	Target Range	Validated Range	Purpose of Control	Method of Control
Coating Polymer and Excipients - Critical Material Attribute						
Drug Layered Beads	Assay Dissolution PSD Surface Morphology	Controlled – upstream				
Ethylcellulose dispersion	Ethoxy content Particle Size	Vendor Specifications			To ensure batch to batch consistency	Vendor – tight control
Triethyl citrate	Viscosity	Vendor Specifications				Vendor – tight control
Formulation Variables – Critical Material Attributes						
Polymer lot	Content and PSD	Information not evaluated as the polymer type, plasticizer type its ratio are pre-determined based on project collaboration			To ensure target assay and desired drug release	Ideally, variables can be evaluated using Design of Experiments (Full factorial 2^3 = 8 + 2 center points = 10 experiments)
Plasticizer type	Type					
Polymer/plasticizer ratio	Concentration					
Coating Process – Critical Process Parameters						
Fluid Bed Coating	Microclimate	Information still being collected, experiments conducted in different stages 1. Evaluation of CPP using Neat Polymer System (Resolution V Fractional factorial) 2. Determination of Process range study (including batch size and coating level along with spray rate optimization (OFAT approach as interactions terms not interested) 3. Screening of CPP using information from earlier stages (Resolution IV Fractional factorial in two blocks (with and without center points) 4. Response surface methology using identified CPP to determine optimum operating conditions and design space 5. Confirmation of the design space using full factorial design on next scale equipment				
	Atomization Pressure					
	Product temperature					
	Air volume					
	% Solids					
	Curing Temperature					
	Curing Time					
	Humidity					

Coated Beads – Critical Quality Attributes (In-Process Controls)			
Quality Attribute	**Sample Type**	**Specifications**	**Control Strategy**
Assay	**Composite Samples**	**95-105% of label claim**	**NIR and HPLC**
Drug Release	**Composite Samples**	**1h, 2h, 4h and 7h until 80% drug released**	**NIR and dissolution**
PSD	Composite Sample	Retained on 14 and 16 mesh	Laser Diffraction
Moisture	Composite Sample	NMT 2.0%	LOD
Surface Morphology	Composite Sample	Smooth Surface	Optical Microscopy

Conclusions

- **This study demonstrated the ability of NIR spectroscopy as real-time process monitoring and end point determination tool during the fluid bed spraying and coating**

- **NIR coupled with environmental monitoring could serve as a powerful process analytical technology tools to improve process understanding and establish control**

- **Future research need: to use NIR data to create feed back loop based upon actual product state**
  - **i.e., adaptive manufacturing**
  - **Key barrier getting instruments and models to talk to each other**

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