Continuous Quality Verification and Its Role in the Application of Design Space

Carl A. Anderson, Ph.D.

6 October 2011

Heidelberg PAT Conference

Outline

- Definitions
- “Enhanced Approach” to Product Development and Manufacturing
- Examples
  - Formal design of experiments and multivariate modeling
  - Raw materials variability

Definitions (1)

- Continuous process verification
  - An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.
- Process analytical design
  - 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.

Definitions (2)

- Design space
  - An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.*
- Quality
  - The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity**
- Quality by design
  - A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management

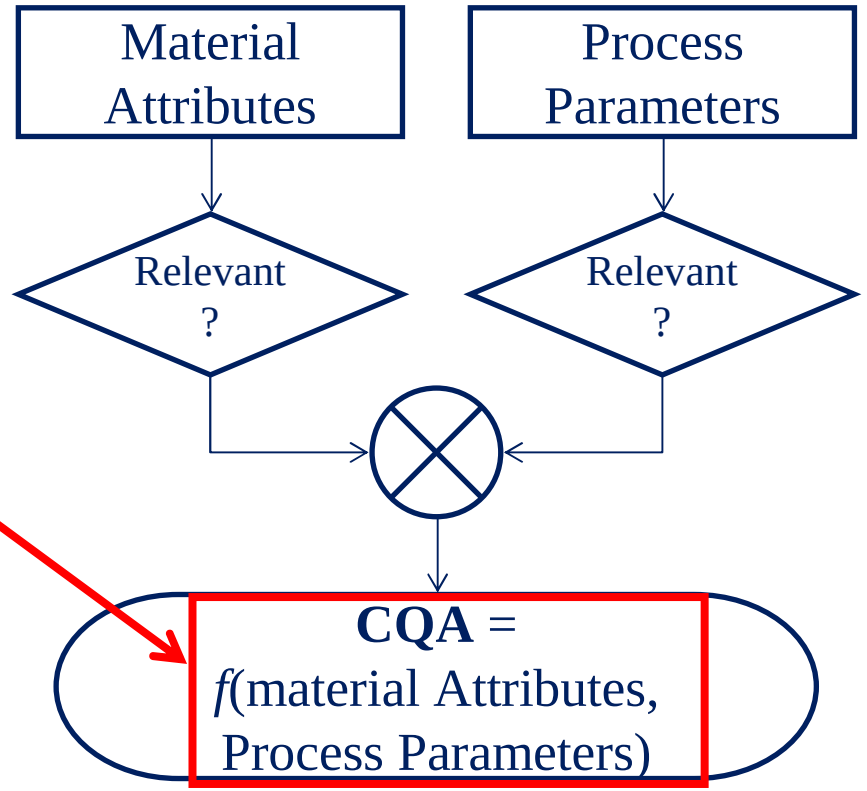
* ICH *Q8(R2), Pharmaceutical Development*
**ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*

Design Space

- Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.
- **Is this really a step forward?**

Enhance Approach to Product Development

- Requires
  - Process understanding
    - Systemic evaluation, understanding, and refining of the manufacturing process
    - Determine the functional relationship between material attributes/process parameters and CQAs
- Allows
  - Design space
  - Real-time release



Raw materials variability

Experiment

- Scan a calibration set on day 1
- During the next 12 weeks, scan a validation set (at center point) where one of the components has been altered
- Through ANOVA, look for trends and significant impacts of raw mat variability on API prediction

Calibration design

Row 29 is the center point

Two environmental conditions:
- Ambient (average 50% RH)
- Chamber 35% RH

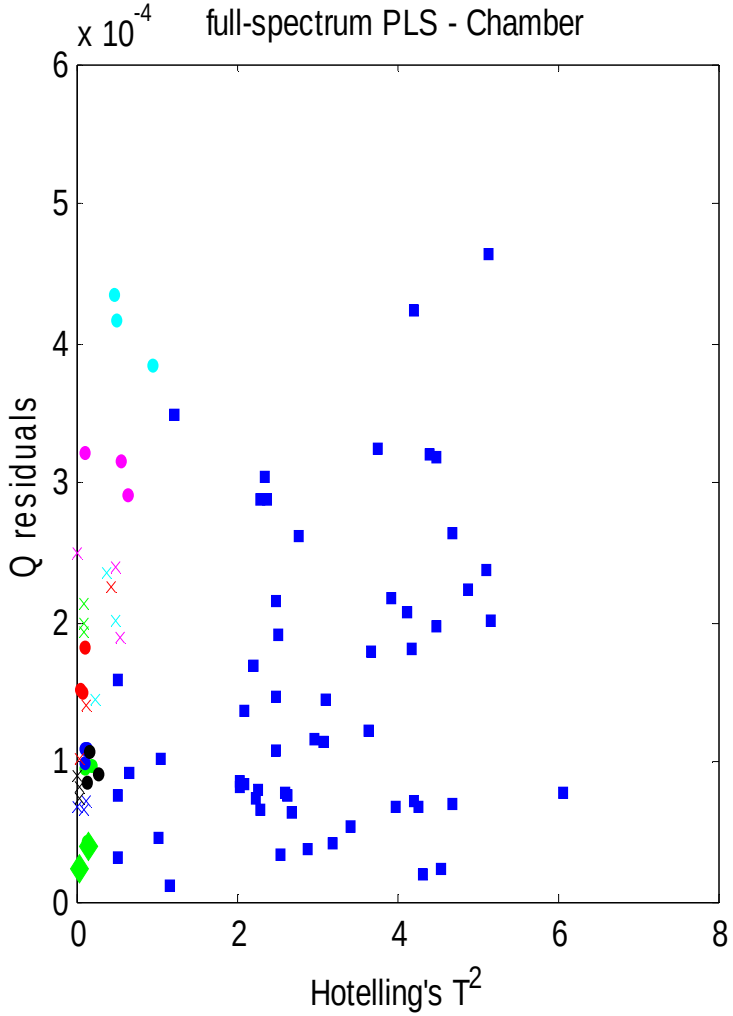
Design points	Anhydrous theophylline	Lactose monohydrate	Microcrystalline cellulose	Soluble starch	Compression force (MPa)
1	0.600	0.200	0.200	0.000	117.3/217.8
2	0.400	0.400	0.201	0.000	67.0/268.1
3	0.201	0.599	0.200	0.000	268.1/268.1
4	0.400	0.201	0.399	0.000	217.8/217.8
5	0.200	0.400	0.399	0.000	67.0/117.3
6	0.200	0.200	0.600	0.000	67.0/167.6
7	0.600	0.200	0.000	0.199	67.0217.8
8	0.398	0.401	0.000	0.201	67.0/167.6
9	0.201	0.599	0.000	0.200	117.3/217.8
10	0.600	0.000	0.199	0.200	67.0/67.0
11	0.400	0.201	0.200	0.199	167.6/268.1
12	0.200	0.400	0.200	0.199	67.0/117.3
13	0.000	0.599	0.200	0.200	67.0/268.1
14	0.399	0.000	0.401	0.200	217.8/268.1
15	0.200	0.200	0.400	0.200	117.3/268.1
16	0.000	0.400	0.399	0.200	117.3/117.3
17	0.201	0.000	0.599	0.201	117.3/217.8
18	0.000	0.200	0.599	0.200	67.0/167.6
19	0.400	0.200	0.000	0.400	67.0/268.1
20	0.201	0.400	0.000	0.400	67.0/167.6
21	0.400	0.000	0.200	0.400	268.1/268.1
22	0.201	0.200	0.200	0.399	167.6/217.8
23	0.000	0.400	0.200	0.400	117.3/268.1
24	0.201	0.000	0.399	0.400	67.0/217.8
25	0.000	0.200	0.400	0.400	117.3/117.3
26	0.199	0.200	0.000	0.600	167.6/217.8
27	0.201	0.000	0.199	0.600	117.3/217.8
28	0.000	0.200	0.200	0.600	67.0/268.1
29	0.250	0.250	0.250	0.249	167.3/217.8

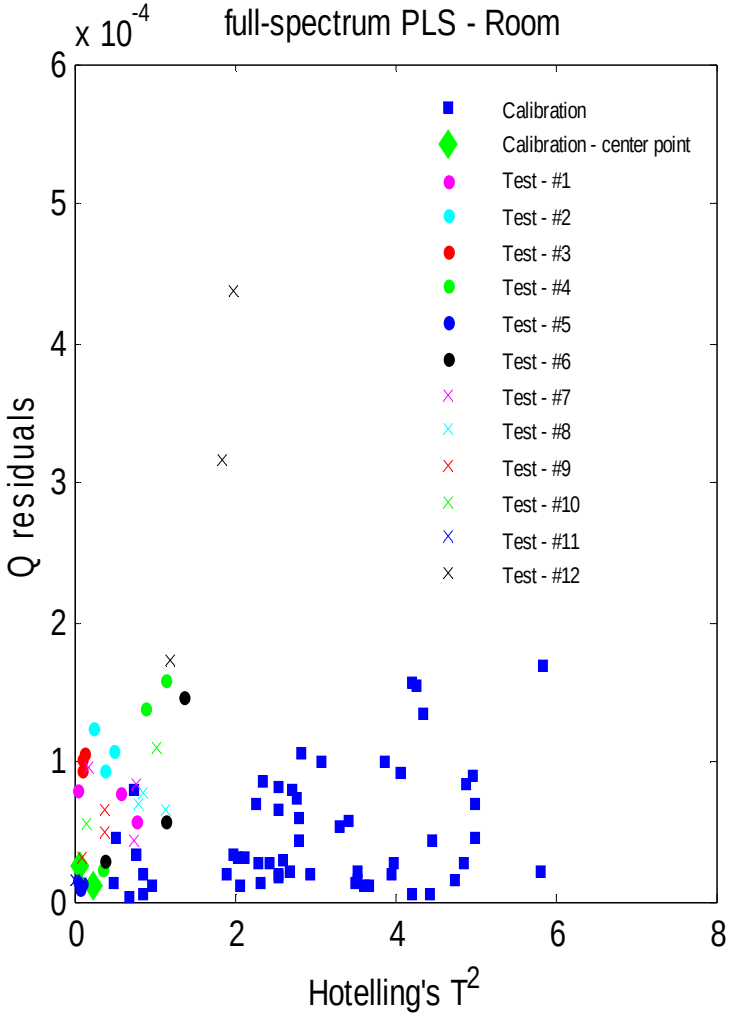
Test design

Run order	Design	Theophylline	LAC part size (µm)	Starch vendors
8	1	anhydrous*	50	EMD Chemicals*
9	2	monohydrate	50	EMD Chemicals*
12	3	anhydrous*	100*	EMD Chemicals*
2	4	monohydrate	100*	EMD Chemicals*
10	5	anhydrous*	125	EMD Chemicals*
3	6	monohydrate	125	EMD Chemicals*
7	7	anhydrous*	50	Acros Organics
4	8	monohydrate	50	Acros Organics
1	9	anhydrous*	100*	Acros Organics
11	10	monohydrate	100*	Acros Organics
5	11	anhydrous*	125	Acros Organics
6	12	monohydrate	125	Acros Organics

All these were prepared for design point 29

Results

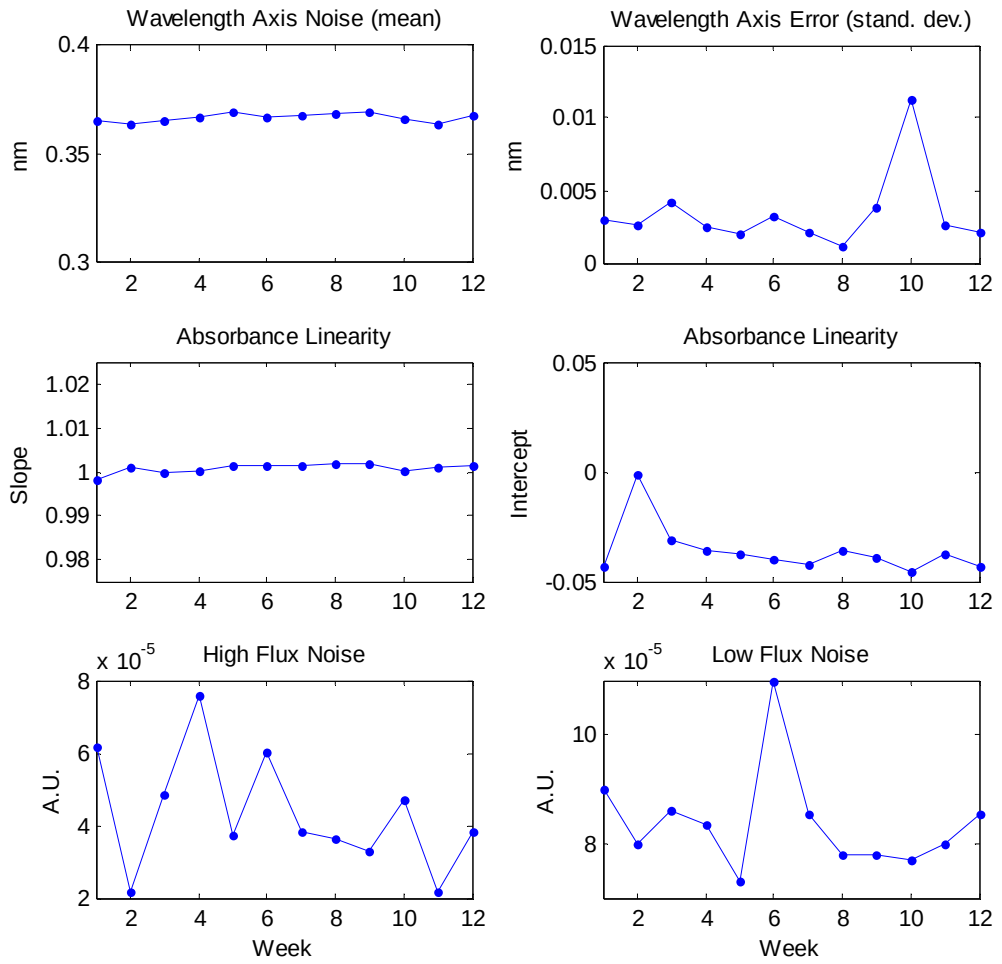

full-spectrum PLS - Chamber
x 10^-4
Q residuals
Hotelling's T^2
0
1
2
3
4
5
6
0
2
4
6
8


full-spectrum PLS - Room
x 10^-4
Q residuals
Hotelling's T^2
Calibration
Calibration - center point
Test - #1
Test - #2
Test - #3
Test - #4
Test - #5
Test - #6
Test - #7
Test - #8
Test - #9
Test - #10
Test - #11
Test - #12
0
1
2
3
4
5
6
0
2
4
6
8

Results

- No significant effect of changes in physical forms
- No significant difference between starch manufacturers but significant differences in trends due to changes in environmental conditions
- Significant effect of particle size differences
- No effect of time!

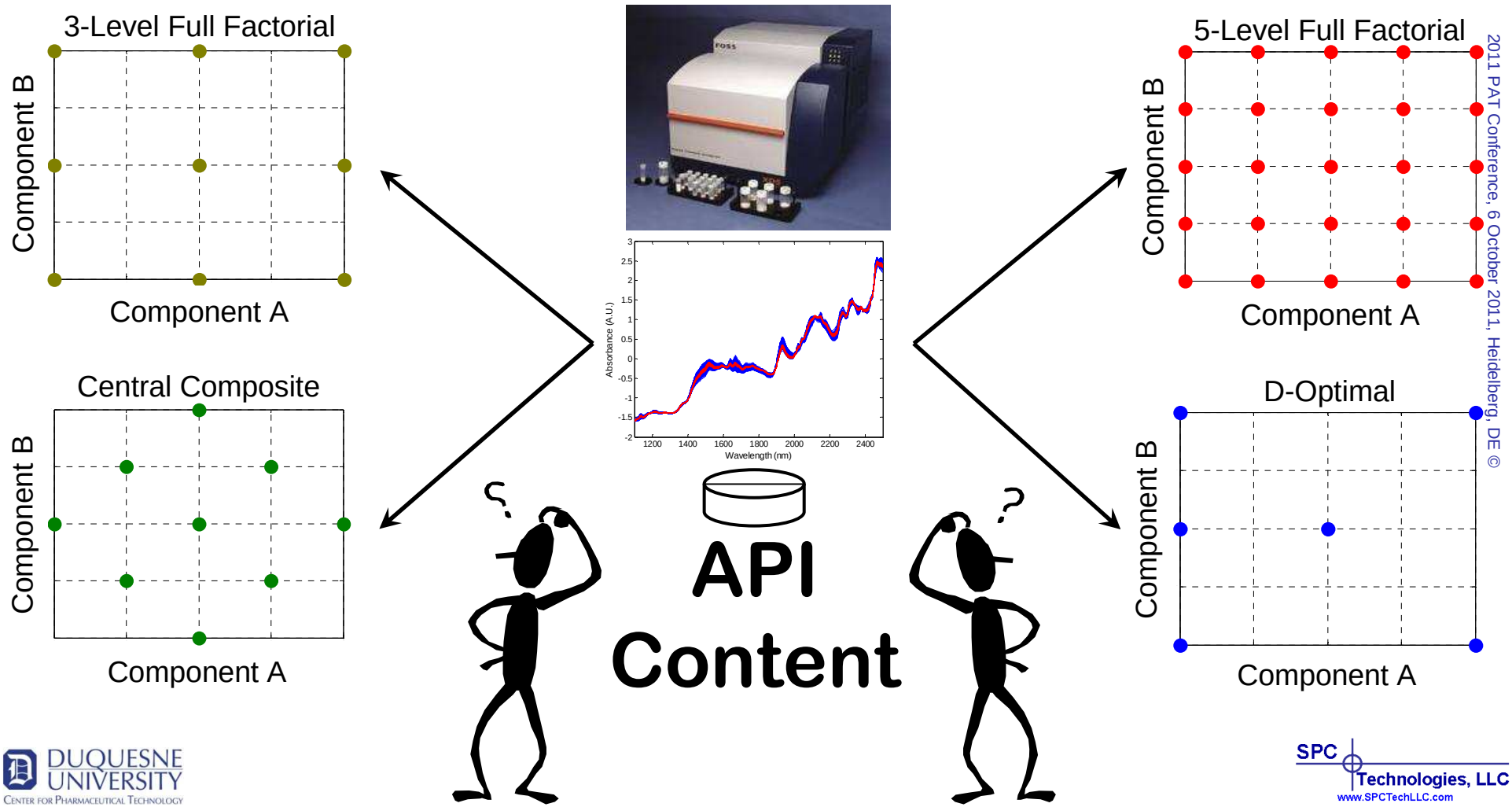
Instrument stability



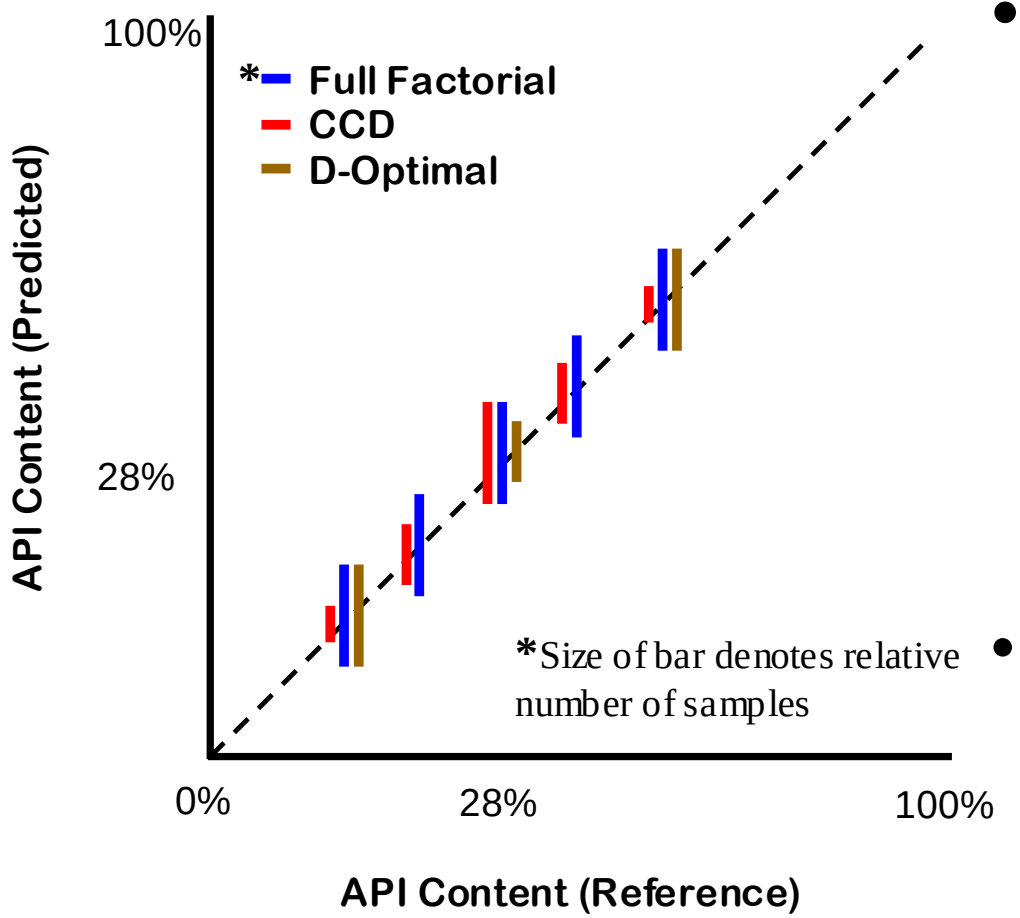
Formal Design of Experiments and Multivariate Modeling

Choosing a DOE

NIRS Calibration



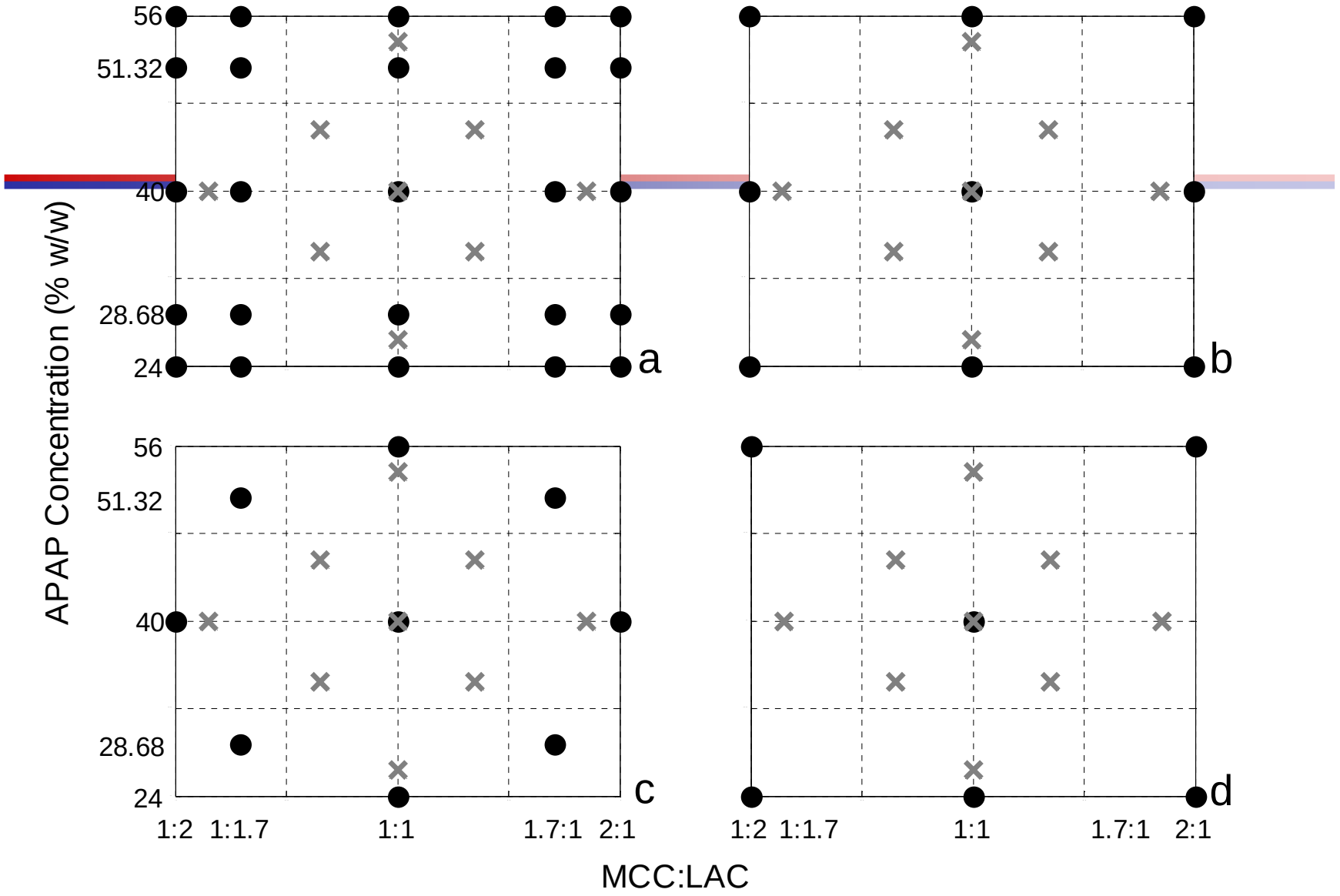
Model Differences



- Objective: Determine if the predictive performance of multivariate models based on near-infrared (NIR) spectroscopy is affected by the choice of designed experiment for a model pharmaceutical composite system
- What is the loss in performance for using a reduced design?

Methods (brief)

- 5 level full factorial
  - APAP and MCC:lactose ratio
  - Croscarmellose-Na and magnesium stearate remained constant
- Produced 25 independent blends from which 5 compacts were generated
- Scanned both faces using reflectance NIR
- Experimental designs investiaged:
  - 5 level FF, 3 level FF, inscribed CCD, and D-Optimal
- Models were compared based on prediction of an independent validation set (see next slide for validation set with respect to experimental designs)
- Models were optimized independently based on minimization of CV error



a) 5 Level Full Factorial, b) 3 Level Full Factorial, c) Central Composite, d) D-Optimal

• represents calibration and x represents validation

Model Comparison

- Prediction performance (RMSEP) for each model was compared using a method published by Fearn[1]
  - t values were adjusted using Tukey-Kramer method[2]

$$RMSEP = \sqrt{\frac{\sum_{i=1}^{n} e_i^2}{n}} = \sqrt{\frac{(n-1)SD^2 + n \times bias^2}{n}}$$

Standard Deviation (SD)

bias

$$SD = \sqrt{\frac{\sum_{i=1}^{n} (e_i - m)^2}{n-1}}$$

$$bias = 1/n \sum_{i=1}^{n} e_i$$

$$\frac{SD_1}{SD_2} \times \frac{1}{L} \text{ and } \frac{SD_1}{SD_2} \times L$$

$$(bias_1 - bias_2) \pm t_{1,0.025} \times s_d$$

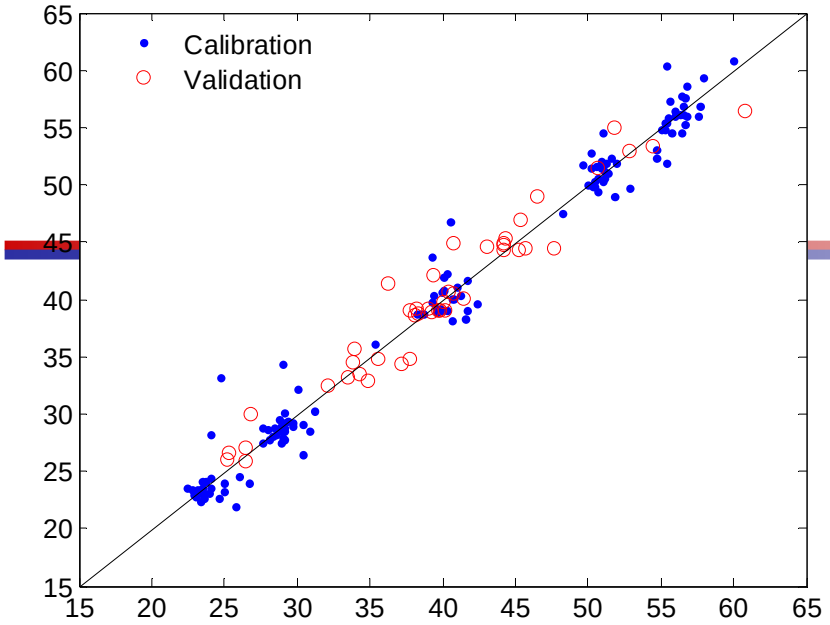
NOTE: Models were deemed statistically similar only if bias ***and*** standard deviation were statistically similar

1. Fearn, T. *NIR News*. Vol. 7 No. 5 (1996), pp. 5
2. Kleinbaum, et al. Applied Regression Analysis and Other Multivariate Methods. Thomson Brooks/Cole. 2008.

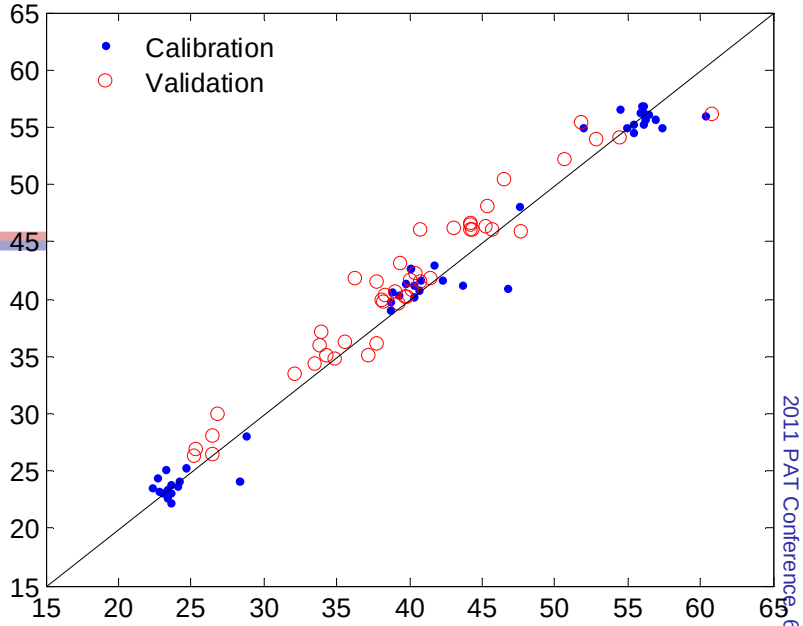
Test for Nonlinearity

- Nonlinearity in calibration and validation predictions was tested according to a method proposed by Mark. Briefly, NIR predictions were fit to reference values using a quadratic function. Reference values represented the X variable, and squared reference values represented the X^2 variable. It should be noted that the X^2 variable was transformed to be independent of the X variable. The model fit was assessed at the 95% confidence level using MATLAB. If the quadratic term was significant ($p<0.05$), the model was deemed nonlinear.

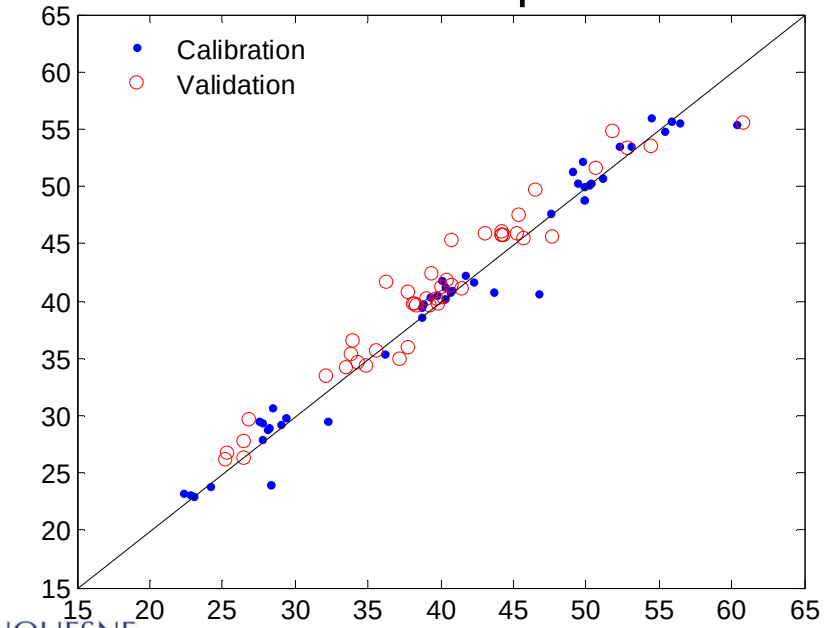
5 Level Full Factorial



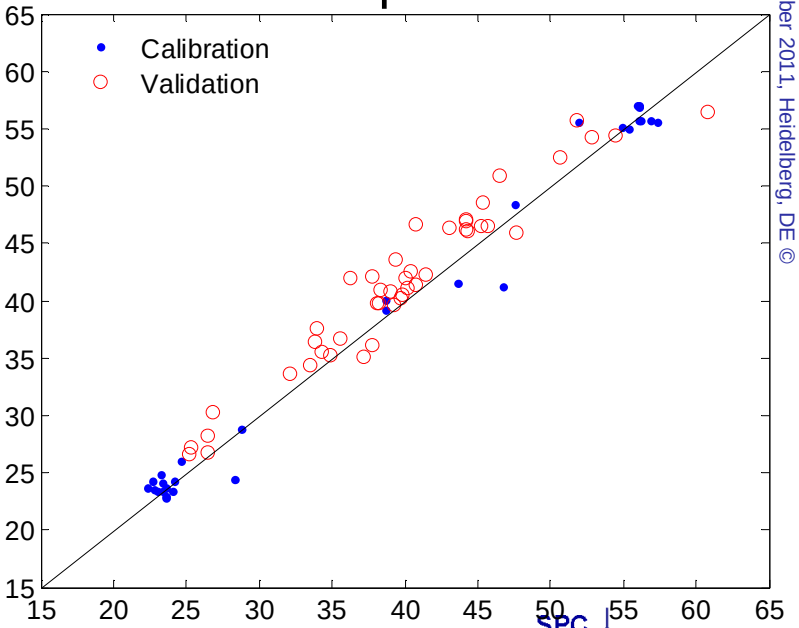
3 Level Full Factorial



Central Composite



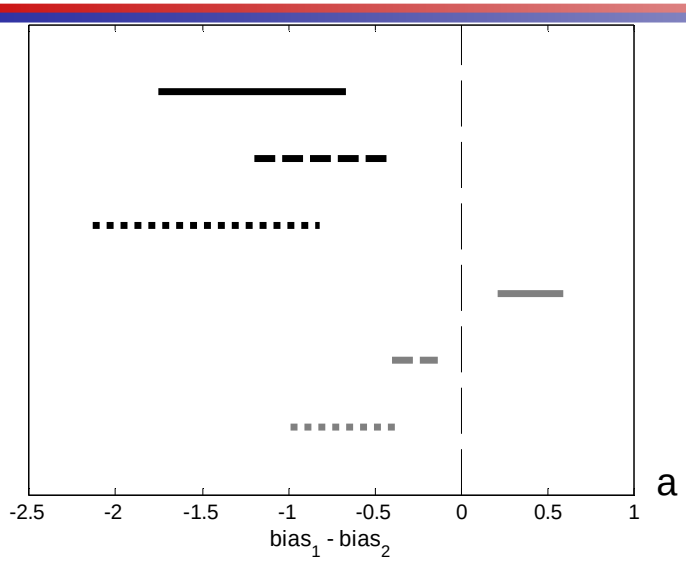
D-Optimal



APAP Predicted (%w/w)

APAP Reference (%w/w)

Model Comparison



Confidence intervals for bias (a) and standard deviation (SEP, b) comparisons for all possible comparisons. Comparisons made: — 5-L FFD vs. 3-L FFD, – – 5-L FFD vs. CCD, ····· 5-L FFD vs. D-Optimal, — 3-L FFD vs. CCD, – – 3-L FFD vs. D-Optimal, ····· CCD vs. D-Optimal. If confidence interval crosses the broken line, bias and/or SEP are statistically similar.

Results

Model Summary				
Experimental Design	5-L FF	3-L FF	CCD	D-Optimal
No. Samples	125	45	45	30
No. Levels[a]	5	3	5	3
Preprocessing	SNV	2nd Deriv. (31,3)[b]	2nd Deriv. (31,3)	2nd Deriv. (31,3)
No. Latent Variables	2	2	2	2
Calibration and CV Statistics				
R^2	0.978	0.983	0.973	0.987
RMSEC (%w/w[c])	1.817	1.699	1.749	1.668
RMSECV (%w/w)	1.874	1.795	1.884	1.811
Validation Statistics				
RMSEP (%w/w)	1.839	2.325	2.060	2.538
bias (%w/w)	0.239	1.449	1.043	1.715
SD (%w/w)	1.845	1.865	1.810	1.927

[a]Number of levels of APAP in experimental design

[b]Savitsky-Golay 2nd derivative (window size, polynomial order)

[c]percentage by weight

Because the structure of the validation set resembled the CCD, the model based on the CCD outperformed all others except the 5-L FF

Nonlinearity Test

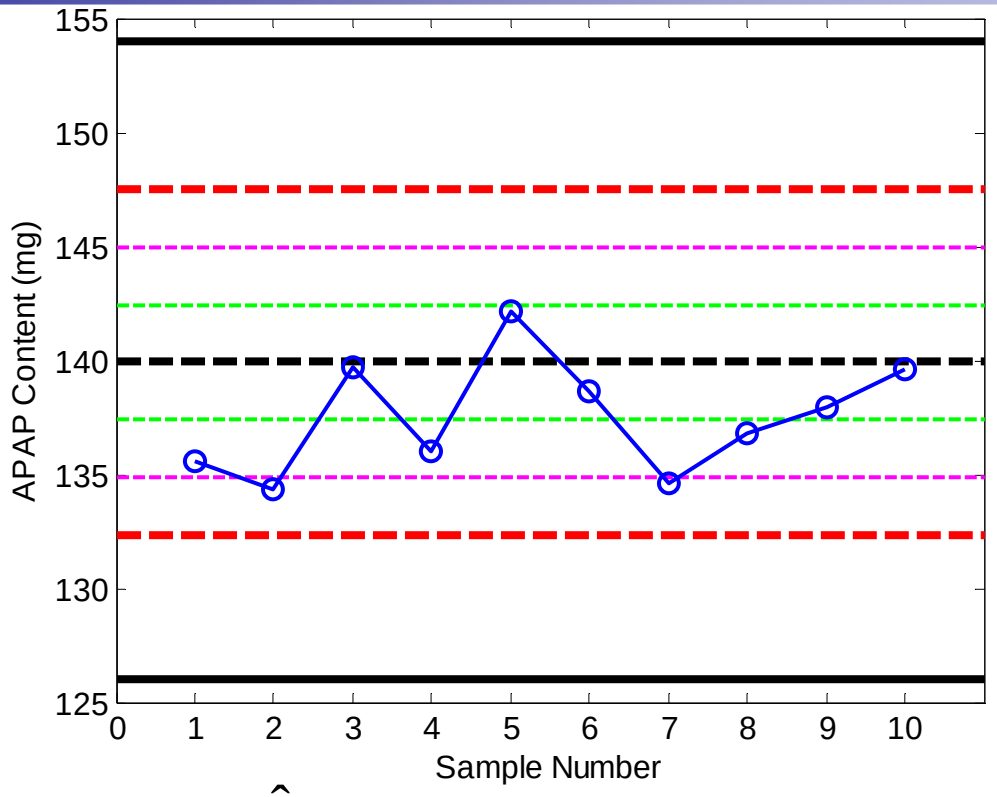
	Experimental Design	*p*, X^a	*p*, X^{2b}
Calibration	5-L FF	~0	0.669
	3-L FF	~0	0.205
	CCD	~0	0.342
	D-Optimal	~0	0.280
Cross-Validation	5-L FF	~0	0.619
	3-L FF	~0	0.226
	CCD	~0	0.353
	D-Optimal	~0	0.350
Validation	5-L FF	~0	0.396
	3-L FF	~0	0.024
	CCD	~0	0.022
	D-Optimal	~0	0.029

[a] *p* value of linear term

[b] *p* value of quadratic term

Nonlinearity was present in validation predictions for 3-L FF, CCD, and D-Optimal. Models were generated again with SNV and nonlinearity was not present; therefore, preprocessing (2nd derivative) induced nonlinearity. However, note that RMSEP still followed the same order.

Statistical Process Monitoring

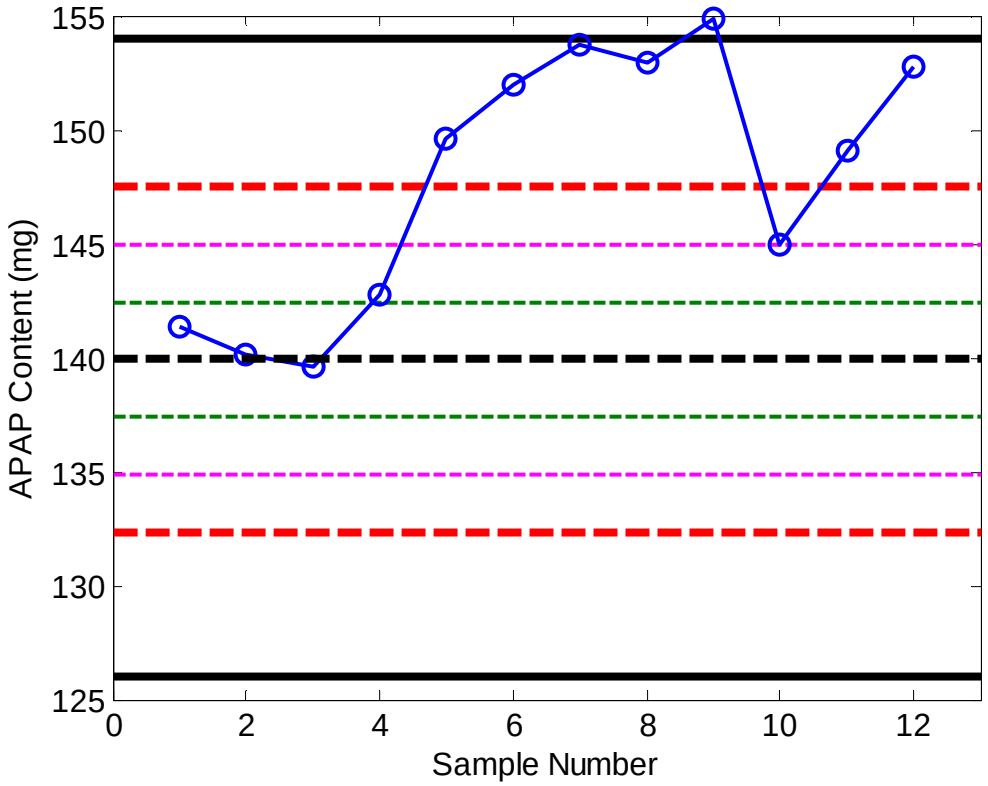


$$\mathrm{UCL} = \bar{x} + \frac{\sigma\,\hat{s}}{\sqrt{n}}$$

$$\mathrm{LCL} = \bar{x} - \frac{\sigma\,\hat{s}}{\sqrt{n}}$$

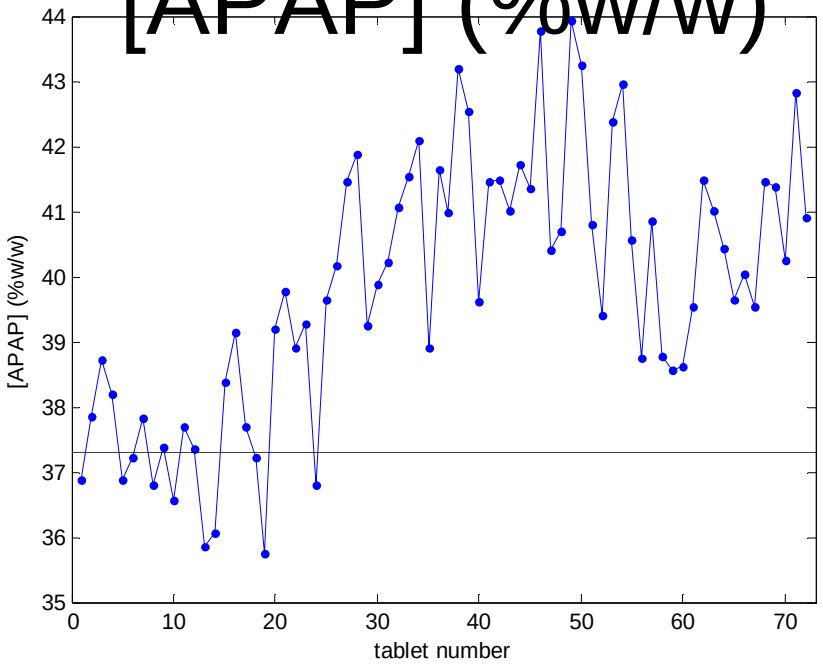
- 3σ control limit
- 2σ control limit
- 1σ control limit
- process mean
- sample mean
- specifications

Out of Control Process

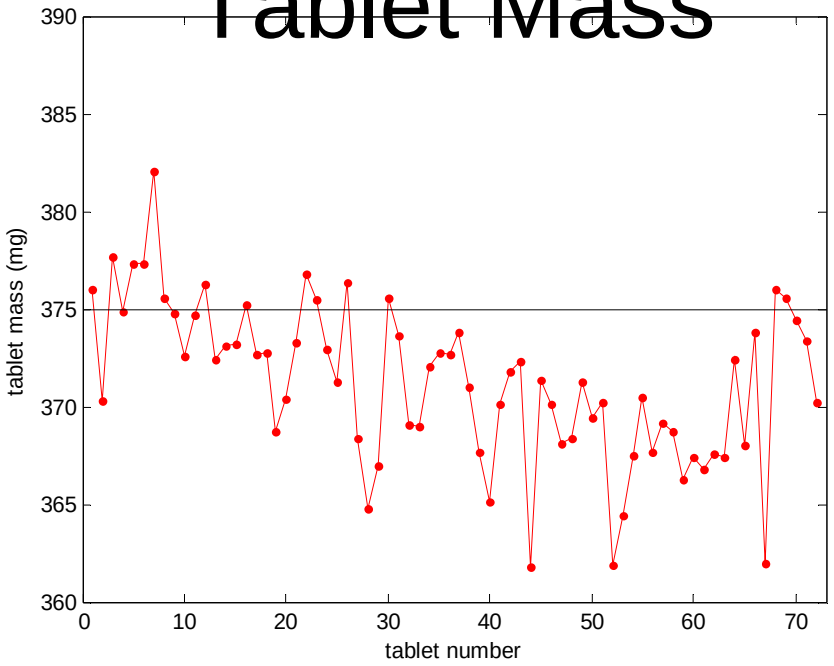


Out of Control Process

[APAP] (%w/w)



Tablet Mass



Adaptation of a Design Space as an Integrated Component of Quality by Design

Benoît Igne, Zhenqi Shi, Sameer Talwar,
Carl A. Anderson, James K. Drennen

Duquesne University Center for Pharmaceutical Technology
Pittsburgh PA, USA

January 2011

Introduction

- Pharmaceutical Quality by Design (QbD) is a "systemic approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control"
- QbD establishes the impact of formulation and manufacturing to product characteristics and identifies all sources of variability to implement a flexible and robust process that can adapt and produce a consistent product over time

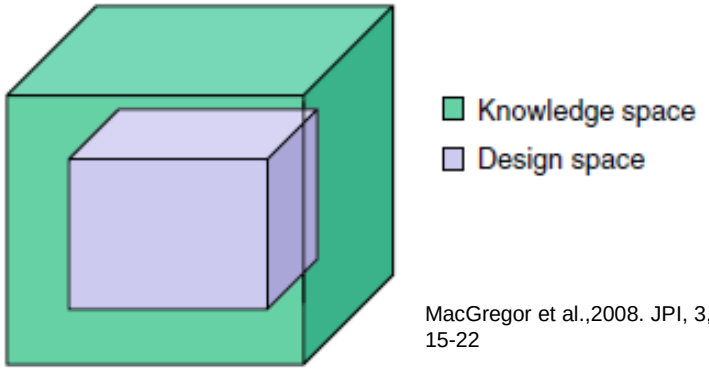
Lionberger et al., 2008. the AAPS journal, 10:2:268-276

Introduction

- QbD uses Design of Experiments (and other techniques) to establish a knowledge space
- For a fixed formulation, process parameters are varied to identify critical process parameters and their associated critical quality attributes determined based on clinical performance

Introduction

- Acceptable CQA ranges defines the design space: “the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality” (ICHQ8)



MacGregor et al.,2008. JPI, 3, 15-22

Introduction

- Factors not typically studied in initial DoE:
  - Raw material variability
  - Supply chain disruption
  - Manufacturing chain relocation
  - Storage condition variability
  - Equipment wear
- When variability is detected in the underlying factors of the design space, it is necessary to adapt the relevant models (the design space) while maintaining product efficacy and safety

Objectives

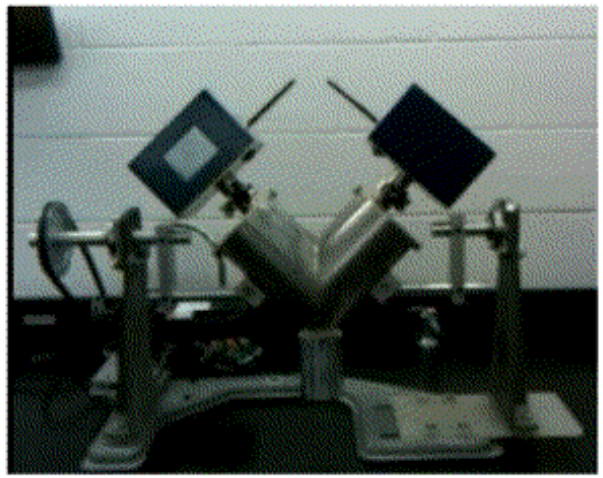
- Evaluate the potential to adapt critical process parameters and consequently establish a dynamic design space based on raw material characteristics while maintaining product quality

Material & Methods

- 2003 Excedrin Tension Headache like formulation
  - 31.25% APAP
  - 4.05% Caffeine
  - Varying ratios of MCC:Lactose – 4 different ratios
  - 1 or 2 % of Croscarmellose Sodium
  - 0.5 % Magnesium Stearate

Material & Methods

- Blending
  - 3.5 quarts V-blender
  - Blend end point monitored by a semi-automated control system based on the RMSNV algorithm
    - Control blend for deviation from the nominal over a period of time
    - Look at all major components
    - SpectralProbes (ThermoFisher)



Material & Methods

- Tableting
  - 38-punch Hata International press
    - Only 2 punches used
  - Force to failure at the press was varied

- Tablets were allowed to equilibrate for 3 weeks before processing

Material & Methods

- Design of experiment
  - Originally: 128 design points
  - Reduced to 16 by D-optimality

Run #	Run Order	Excipient ratio	Croscarmellose Sodium level (%)	Load force (p)	RMSNV weights
1	16	4:1	2	12,000	2 1 0
2	6	4:1	2	6,000	1 1 1
3	14	4:1	1	10,000	2 0 1
4	12	4:1	1	8,000	3 0 0
5	13	3:2	2	10,000	2 1 0
6	1	3:2	2	8,000	1 1 1
7	5	3:2	1	12,000	2 0 1
8	9	3:2	1	6,000	3 0 0
9	15	2:3	2	8,000	2 0 1
10	11	2:3	2	12,000	3 0 0
11	10	2:3	1	10,000	1 1 1
12	3	2:3	1	6,000	2 1 0
13	7	1:4	2	10,000	3 0 0
14	2	1:4	2	6,000	2 0 1
15	8	1:4	1	8,000	2 1 0
16	4	1:4	1	12,000	1 1 1

Material & Methods

- Tablet properties measured and criteria applied (all using USP protocols)
  - Dissolution (> 75 % of label claim after 60 min)
  - Friability (< 0.8% weight loss)
  - Radial Tensile Strength (between 1.25 and 1.60 MPa)
  - Disintegratiaon time (>80s)

Material & Methods

- Raw material variability induced by:
  - Changing the particle size of APAP
    - From 100 um (in the original design) to 600 um
  - Changing the ratio of lactose monohydrate (in the original design) to lactose anhydrous
- Correction for raw material variability at compression
  - Compression force
  - Compression speed

Material & Methods

- Design of experiment for the dynamic design space

Run #	Sub-run #	Acetaminophen particle size	Lactose form[a]	Compression speed (rpm)	Compression force (kp)[b]
1	A	600 µm	100:0	30	9,000
1	B	600 µm	100:0	30	11,000
1	C	600 µm	100:0	30	13,000
1	D	600 µm	100:0	45	9,000
1	E	600 µm	100:0	45	11,000
~~1~~	~~F~~	~~600 µm~~	~~100:0~~	~~45~~	~~13,000~~
2	A	100 µm	50:50	30	9,000
2	B	100 µm	50:50	30	11,000
2	C	100 µm	50:50	30	13,000
2	D	100 µm	50:50	45	9,000
2	E	100 µm	50:50	45	11,000
2	F	100 µm	50:50	45	13,000
3	A	600 µm	50:50	30	9,000
3	B	600 µm	50:50	30	11,000
3	C	600 µm	50:50	30	13,000
3	D	600 µm	50:50	45	9,000
3	E	600 µm	50:50	45	11,000
~~3~~	~~F~~	~~600 µm~~	~~50:50~~	~~45~~	~~13,000~~

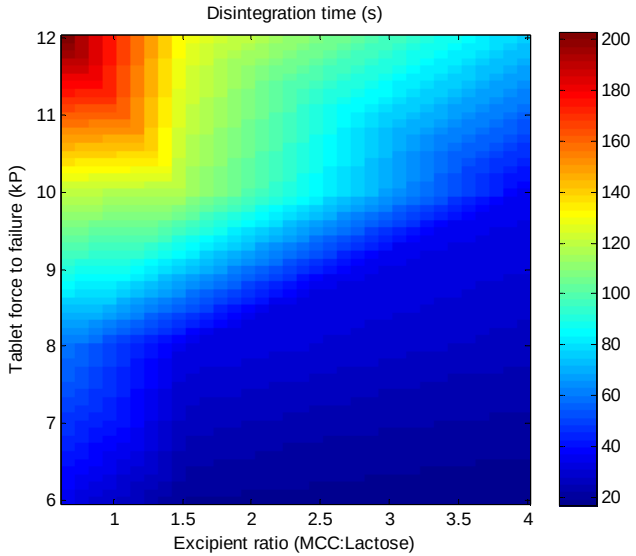
Strategy

1. Create knowledge space
2. Determine CQAs and the design space
3. Test robustness of design space with respect to raw material variability
4. Evaluate the possibilities of a dynamic design space to compensate for variability (from raw material properties)
   - Key goal: maintain product quality

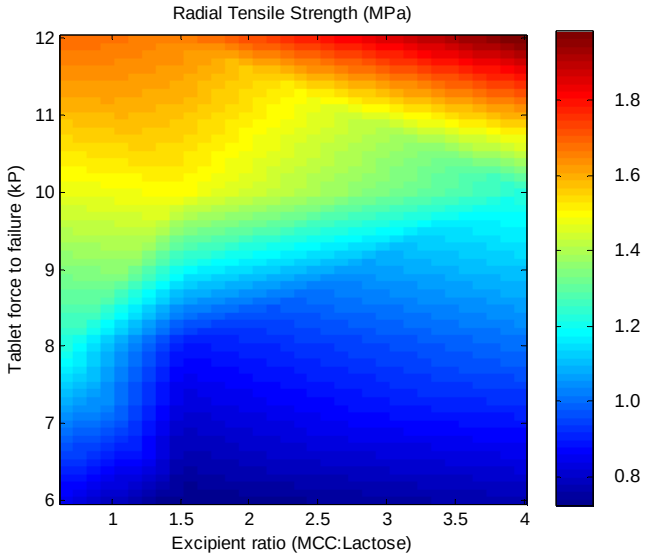
Results

The knowledge and design spaces

- Knowledge space
  - CQAs: RTS and disintegration time
  - CPPs: Excipient ratio and tablet force to failure



(> 80s)

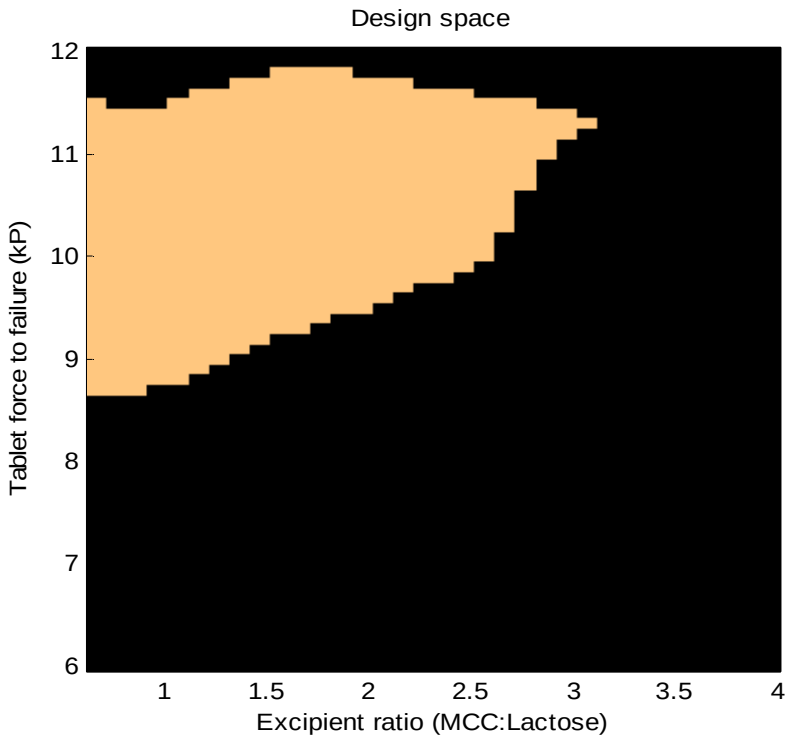


(1.25 - 1.60 MPa)

Results

The knowledge and design spaces

- Design space



The multidimensional combination and interaction of input variables and process parameters

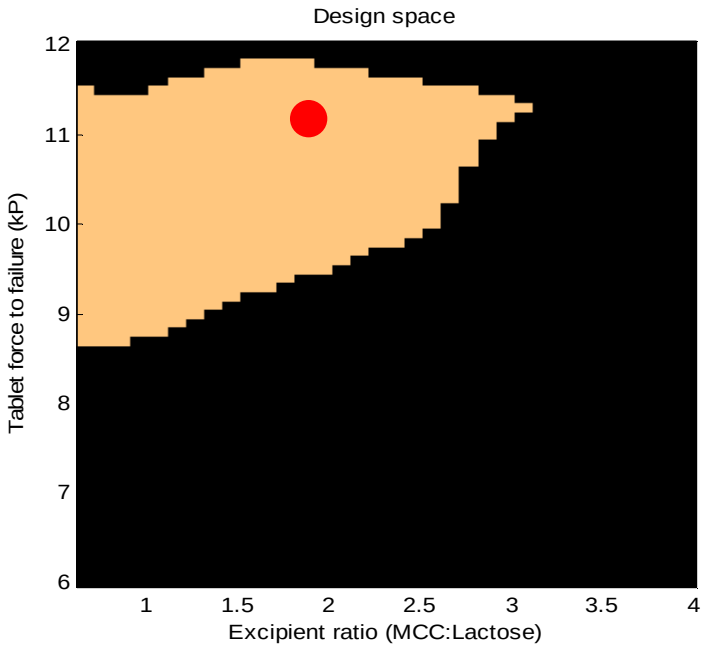
Results

Effect of raw material properties on the robustness of the design space

- An optimal set of critical process parameters was chosen and its robustness tested regarding raw material variability
  - Excipient ratio of 2 (41.3% of MCC and 20.7% of lactose)
  - 2% of Croscarmellose Sodium
  - Target force to failure at the press of 11 kp
  - RMSNV weights were 1-1-1 (for APIs, Excipients and Croscarmellose Sodium respectively)

Results

Effect of raw material properties on the robustness of the design space



- Given these CPPs, the corresponding CQAs were 1.53 MPa and 104 s for RTS and disintegration time respectively.

Results

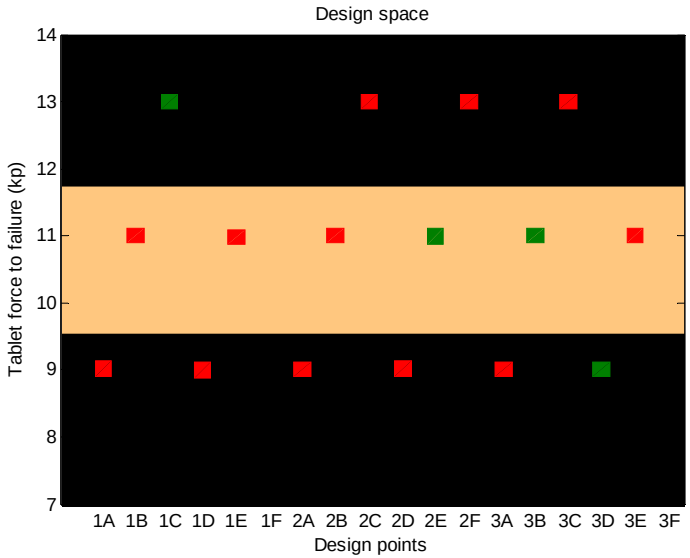
Effect of raw material properties on the robustness of the design space

- When adjusting CPPs, 2 of the 3 runs were outside of the design space when considering the variability in raw materials

Run #	RM Characteristic	Disintegration Time (s)	Radial Tensile Strength (MPa)
1	Larger APAP	63	1452
2	50:50 Lac	68	1396
3	Both	98	1395

Results

Dynamic design space to adjust for raw material characteristics – Tablet force to failure setting



	Run #	Sub-run #	APAP Particle size	Lactose form[a]	Compression speed (rpm)	Compression force (p)
	1	A	600 µm	100:0	30	9,000
	1	B	600 µm	100:0	30	11,000
*	1	C	600 µm	100:0	30	13,000
	1	D	600 µm	100:0	45	9,000
	1	E	600 µm	100:0	45	11,000
	~~1~~	~~F~~	~~600 µm~~	~~100:0~~	~~45~~	~~13,000~~
	2	A	100 µm	50:50	30	9,000
	2	B	100 µm	50:50	30	11,000
	2	C	100 µm	50:50	30	13,000
	2	D	100 µm	50:50	45	9,000
	2	E	100 µm	50:50	45	11,000
	2	F	100 µm	50:50	45	13,000
	3	A	600 µm	50:50	30	9,000
	3	B	600 µm	50:50	30	11,000
	3	C	600 µm	50:50	30	13,000
*	3	D	600 µm	50:50	45	9,000
	3	E	600 µm	50:50	45	11,000
	~~3~~	~~F~~	~~600 µm~~	~~50:50~~	~~45~~	~~13,000~~

*Compression force outside of original design space required to meet specifica

Changing CPPs can allow specifications to be met!

Conclusions

- Adapting CPPs based on raw material characterization allows the creation of drug products with repeatable acceptable characteristics

- An adapted design space is critical to ensure on-going process robustness

Conclusions

- Process analytical technology plays a critical role in monitoring the state of the process and enables control to achieve desired product attributes by adjusting process parameters
  - Improved raw material characterization can mitigate some, but not all of the potential variations
  - Such approach currently exist for granulation and drying control based on Environment Equivalency Factors

Thank you

DUQUESNE UNIVERSITY
CENTER FOR PHARMACEUTICAL TECHNOLOGY

For further information, contact:

Benoît Igne: igneb@duq.edu

Carl A. Anderson: andersonca@duq.edu