Employing Design of Experiments (DoE) to Evaluate the Robustness of an Automated Content Uniformity Method for Triple Fixed Dose Combination Tablets

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Background

- A fixed dose combination tablet with three active components is under development.
- The content uniformity determination of three actives was automated using a Tablet Processing Workstation (TPW) bench-top robotic system. To our knowledge, this is the first TPW method developed for a triple fixed dose combination product.
- The method was implemented to support in-process Content Uniformity (CU) testing for over 180 drug product process justification (PJ) samples, which represents a significant number of samples requiring fast data turnaround.
- DoE was employed to investigate method robustness.

The Benefits of Automated Sample Preparation

- Completely automated & unattended operation
- Reduced analytical labor
- Higher productivity

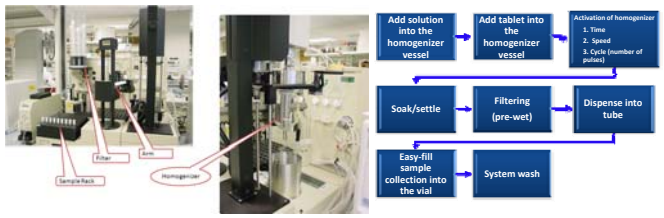
Prior Knowledge and Method Design

API characteristics
- ✓API1 is a basic drug
- ✓API2 is a zwitterionic drug
- ✓API3 is an acidic drug
- ✓Insoluble in neutral water
- ✓All 3 APIs have good solubility in MeOH

Manual sample preparation procedure:
- ✓Sonicate 15 min with water to disintegrate the tablet
- ✓Add MeOH and shake 50 min
- ✓QS with diluent

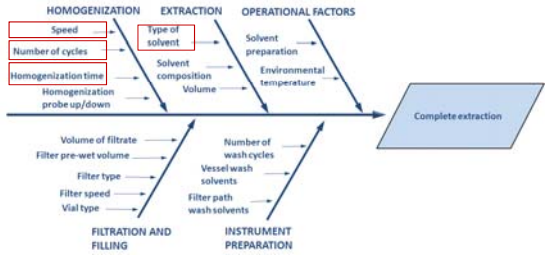
Solution / Objectives
- Develop an automated TPW tablet preparation method
- Develop a design space to understand TPW parameter settings' impact on extraction
  - ✓Identify critical extraction factors
  - ✓Determine how assay values are affected by the factors' levels
  - ✓Ascertain how the factors interact with each other
  - ✓Establish the optimum combination of factors that yields robust and complete extraction

Diagram and Flow Chart of TPW



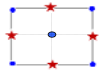
TPW Risk Assessment

- Risks were assessed qualitatively, based on product and instrument knowledge. Factors considered highest risk for systematic optimization are highlighted in red boxes.



DoE Study

- Face-Centered Central Composite Design with 4 factors & 6 center point replicates
- The axial points are at the center of each face of the factorial space
- JMP Design 30 experiments run in random order



Factorial & center points	Homogenization Time (s)	Speed (krpm)	Cycle (number of pulses)	Diluent composition (MeOH/Water)
-	10	6	3	65/35
0	20	12	6	80/20
+	30	18	9	95/5

Elimination of Outliers

	Pattern	Speed	Time	Cycle	Diluent composition
Exp 4	----	6	10	3	65
Exp 12	--+-	6	10	9	65

- ✓Exp design with all low parameters showed large variation in response for 8 replicate experiments performed across 3 days
- ✓It appears that the under these parameters tablet will not reliably be disintegrated completely
- ✓Hampel test performed to remove outliers to obtain suitable data for modeling

With all 8 replicates for API1

	API1 (Exp 4)	API1 (Exp 12)
Mean	68.8	86.4
Min	11.5	14.1
Max	95.4	97.5
SD	33.6	29.2

API1 (Exp 4)	API1 (Exp 12)
11.5	14.1
35.9	96.6
95.4	97.5
93.5	97.0
82.6	96.5
42.6	96.8
95.0	96.4
94.4	96.2

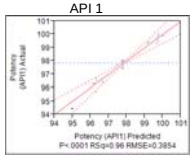
Without outlier for API1

	API1 (Exp 4)	API1 (Exp 12)
Mean	94.6	96.7
Min	93.5	96.2
Max	95.4	97.5
SD	0.8	0.4

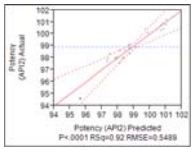
Model Fitting Plots: Actual vs. Predicted

- The data were fit using JMP software to a full quadratic least squares regression model that included linear, quadratic, and cross product terms for the studied factors

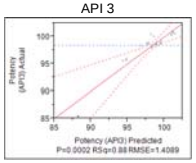
API 1



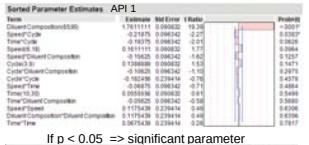
API 2



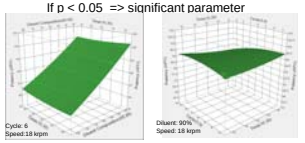
API 3

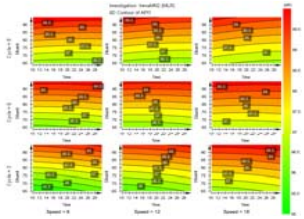


Results for API 1



If p < 0.05 => significant parameter

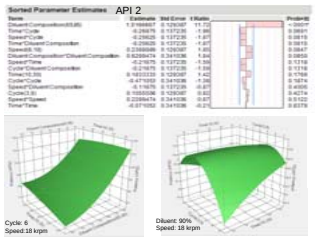


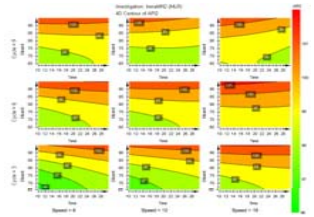


The response surface was modeled by performing a least squares fit to a quadratic function

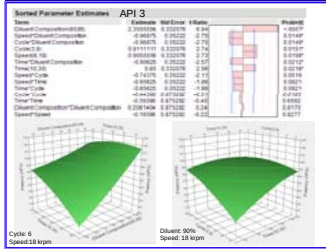
Potency = a + bX + cY + dZ + eP+ fX² + gY² + hZ² + iP²+jXY + kXZ + lYZ + mXY, etc

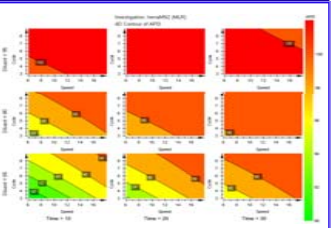
Results for API 2





Results for API 3





Conclusions & Future Work

- Diluent composition was determined to have largest impact on extraction of all 3 API's and is the key to accurate results.
- Other factors' interactions can also have an impact:
  - API1: Speed & Cycle
  - API2: No significant interactions
  - API3: Time & Cycle
  - API3: Diluent composition and all other studied factors
- Potency has an upward trend with higher methanol content in the diluent.
- 65% MeOH and low number of cycles as this is the edge of the failure (outliers).
- The modeling results made us decide to further study the region with 100% MeOH.

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