Dissolution Method Development Combination Product

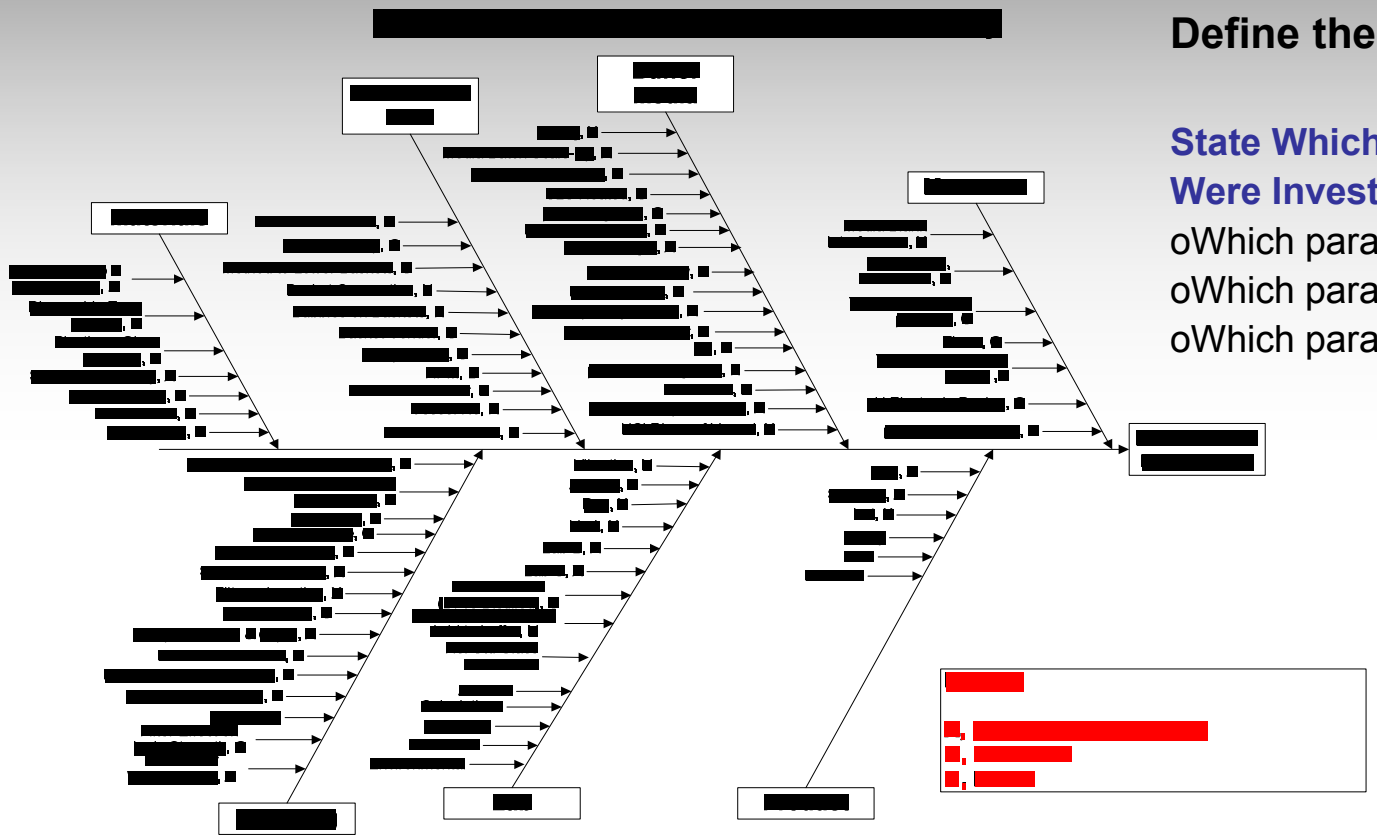
Case 1 Study

Justification of an Alternative Drug Release Method Using Taguchi Method for API-FDC Tablets

General Flow for Analytical Method Development

A. Identify potential method variables
B. Perform preliminary risk assessment for method
C. Classification of method variables (X, C, N)
D. Identify preliminary controls for experiment(s) including factors which will be set as constants
   - Note: need to understand how & why
E. Conduct screening experiment(s) to identify important parameters
   - Note: need to understand how & why
   - One Factor at a Time Experiments (OFAT) or screening depending on variable
F. Full-scale optimization of method through DOE
G. Develop control strategy for method

Identifying Potential Method Variables Example (Ishikawa Diagram)



Define the Design Space

State Which Parameters Were Investigated & Why

oWhich parameters held constant

oWhich parameters were varied

oWhich parameters are critical

Failure Mode Effects Analysis (FMEA)

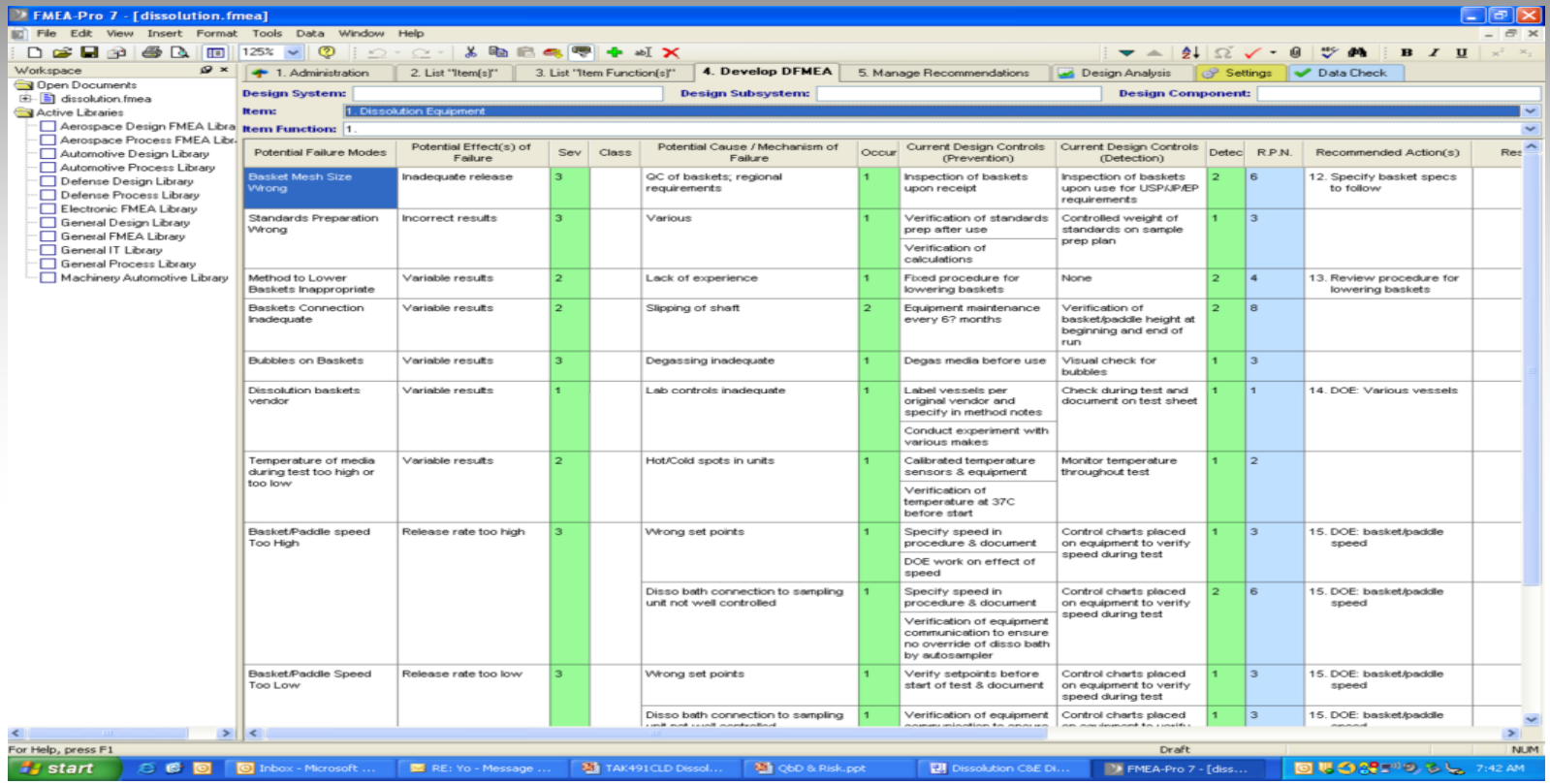
A-priori

FMEA: Break down large complex processes into manageable steps

- Evaluation of potential failure modes for drug release method (holistically but with emphasis in APIFDC Tablets)
- The likely effect on CQAs
- Once failure modes are established, risk reduction can be used to eliminate, reduce or control the potential failures
- FMEA relies on process understanding
- Summarize the important modes of failure, the likely effects of these failures, factors causing these failures, and our ability to detect these failures

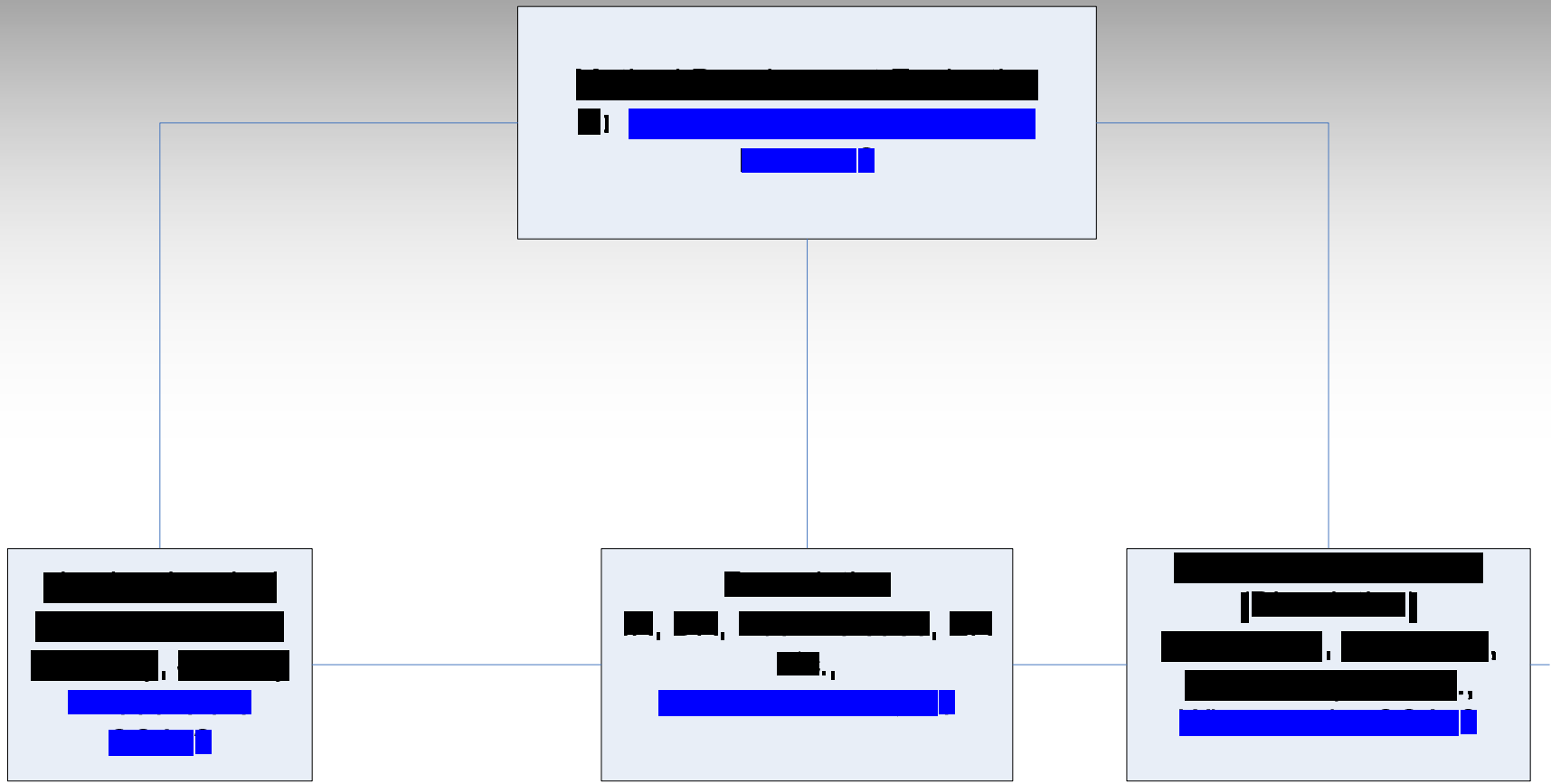
ICH Q9

Preliminary Risk Assessment



- Drug release method for API-FDC tablets to identify high-risk steps or critical parameters
- Define, assess and prioritize risks
- Monitor the effectiveness of risk control activities

Method Development Considerations



What we know? CQAs?

Know/CQAs	Proposals/Solutions/Investigations
API- more stable in solution at pH 3 – 5; pKa (calculated) = 4.2;	A pH of 6.8 is a good option based on pKa value (~2 pH units above its pKa)
Active is sensitive to moisture	Package with desiccants
IR formulation	Film coated to protect from light
Monitoring Product quality and performance after changes such as manufacturing process, scale-up	Multiple lots of product available? What are the differences in raw materials, processes, etc.? This could facilitate decisions on discriminatory capability?
Guidance for Industry: Dissolution testing of IR Solid Oral Dosage Form Dissolution	Appendix A: Sink conditions are desirable but not mandatory A pH 6.8 should be employed; a higher pH should be justified on a case-by-case basis Apparatus 1 (50-100 rpm) or Apparatus 2 (50- 75 rpm) – simple, robust Addition of surfactant acceptable for water insoluble or sparingly water soluble. The need and amount should be justified.
Physiological pH range of 1.2 – 6.8, solubility low	Use surfactant: Use minimally 100% Saturated solubility
Specifications	TBD

Establishment Of The Alternative Condition For API-FDC Tablets

According to the FDA guidance, we investigated the alternative condition in order to characterize the quality of the product

<Investigated Conditions>

- pH of media: 6.0 and 6.8
- Surfactant: SDS, Tween80, CTAB
- Apparatus: 1 and 2

<Points for selecting condition>

- Lower dissolution rate @ early time points (slower release)
- 85% dissolution rate @ 45 min
- Observation (artifacts such as coning, undissolved materials, large particles floating, etc.)

<Approaches>

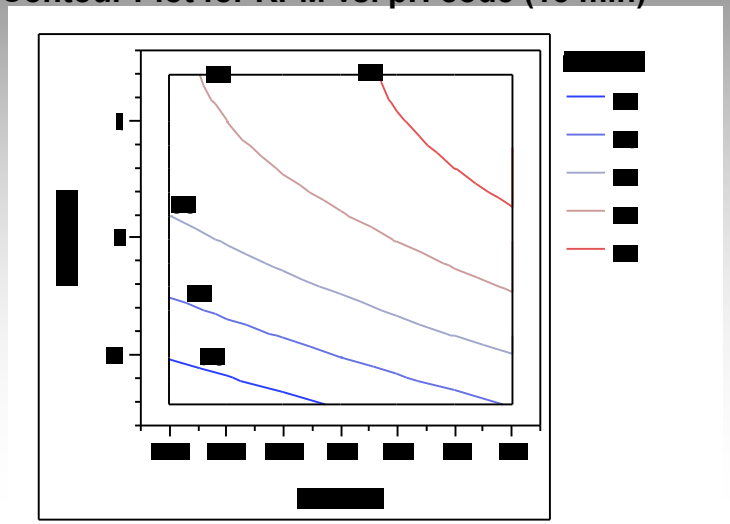
- OFAT or screening depending on variable
- Statistical methods such as Taguchi

A Modified 4-Factor Central Composite Design Was Used

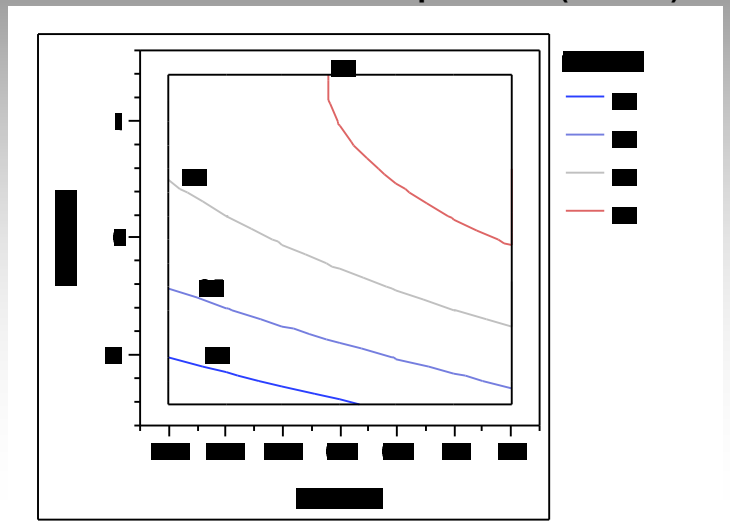
	Coded Unit				Actual Conditions				X4 = Vendor
Pattern	X1	X2	X3	X4	X1 (pH)	X2 (Conc.)	X3 (RPM)	X4	
–––	-1	-1	-1	L1	6.7	0.9	50	L1	
––+	-1	-1	1	L2	6.7	0.9	75	L2	
–+–	-1	1	-1	L2	6.7	1.2	50	L2	
–++	-1	1	1	L1	6.7	1.2	75	L1	
+––	1	-1	-1	L2	6.9	0.9	50	L2	
+–+	1	-1	1	L1	6.9	0.9	75	L1	
++–	1	1	-1	L1	6.9	1.2	50	L1	
+++	1	1	1	L2	6.9	1.2	75	L2	
a00	-1.2	0	0	L2	6.65	1	62.5	L2	
A00	1.2	0	0	L2	6.95	1	62.5	L2	
0a0	0	-1.2	0	L2	6.8	0.85	62.5	L2	
0A0	0	1.2	0	L2	6.8	1.25	62.5	L2	
00a	0	0	-1.2	L2	6.8	1	45	L2	
00A	0	0	1.2	L2	6.8	1	80	L2	
000	0	0	0	L1	6.8	1	62.5	L1	
000	0	0	0	L2	6.8	1	62.5	L2	

Contour Plots: API-FDC Tablets, Drug Release

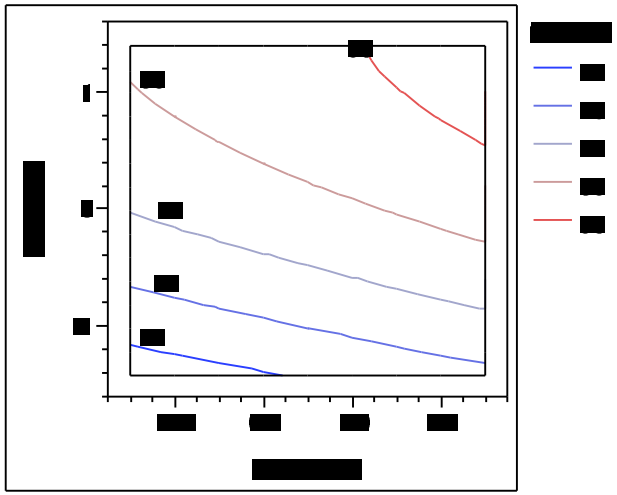
Contour Plot for RPM vs. pH code (15 min)



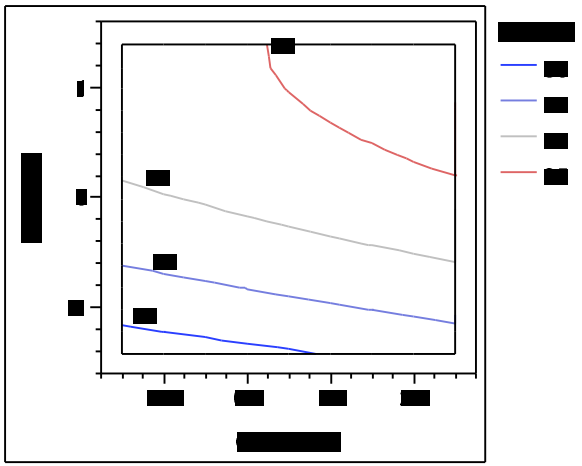
Contour Plot for RPM vs. pH Code (20 min)



Contour Plot for RPM vs. concentration code (15 min)

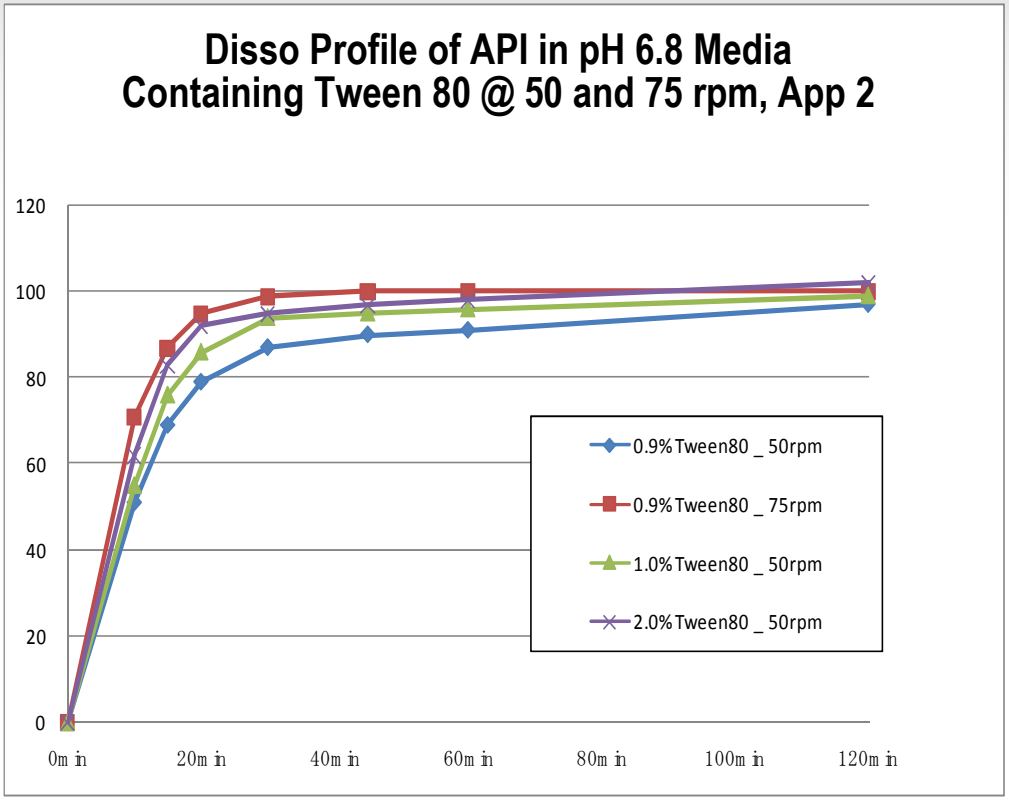


Contour Plot for RPM vs. concentration code (20 min)



Alternative Condition for API-FDC

Mild test conditions such as Apparatus 2 @ 50 rpm and lower conc., Tween such as 1.0% could be selected as an alternative method



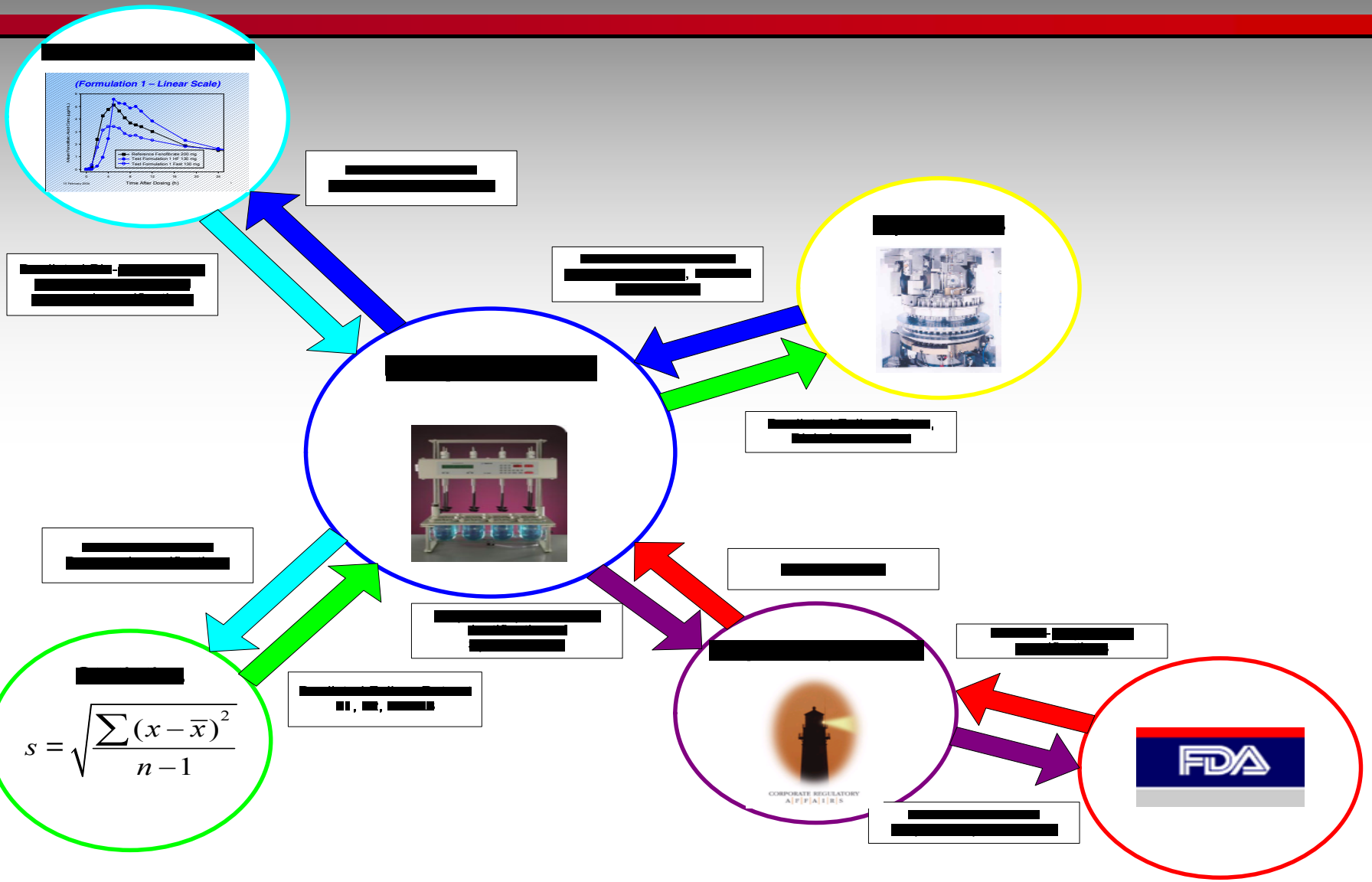
Solubility of API in the various conc. of Tween80 solutions (37°C)

Solution	Solubility (mg/mL)
Phosphate buffer (pH 6.8)	-
+Tween80 0%	0.021
+Tween80 0.5%	0.063
+Tween80 0.6%	0.072
+Tween80 0.7%	0.076
+Tween80 0.8%	0.087
+Tween80 1.0%	0.104
+Tween80 1.2%	0.123
+Tween80 2.0%	0.197

Drug Release Methods for API/FDC Tablets Summary

Parameters	Method 1 (Current)	Method 2 (Investigated)	Method 3 (Alternative)
Apparatus:	USP Dissolution Apparatus 2 (paddles)	USP Dissolution Apparatus 2 (paddles)	USP Dissolution Apparatus 2 (paddles)
Rotation:	50 RPM ± 4%	50 RPM ± 4%	50 RPM ± 4%
Temperature:	37°C ± 0.5°C	37°C ± 0.5°C	37°C ± 0.5°C
Medium: Drug Release:	900 mL of pH 6.8, potassium phosphate buffer + 2% SDS	900 mL of pH 7.8, potassium phosphate buffer	900 mL of pH 6.8, potassium phosphate buffer + 1% Tween80
Rationale	Drug release too rapid (95% LC in 10 min) May not provide discriminatory power	Visual observations show significant method artifacts such as un-dissolved materials, large particles and film components floating during testing with and/or without surfactant	Slower profiles Visual observations doesn't confirm method artifact Discriminatory power against manufacturing process/changes in vendor excipients
Filter:	35 micron polyethylene	35 micron polyethylene	35 micron polyethylene
Analytical Finish:	UPLC		
Rationale – Analytical Finish	Justified based on API, FDC Stability, Comparison of UV & UPLC, etc.		

Interface


(Formulation 1 – Linear Scale)
Reference Fenofibrate 200 mg
Test Formulation 1 HF 130 mg
Test Formulation 1 Fast 130 mg
Time After Dosing (h)
$s = \sqrt{\frac{\sum (x - \bar{x})^2}{n-1}}$
CORPORATE REGULATORY
A|F|A|I|R|S
FDA

Case 2 Study

Robustness Evaluation for Related Substance Method Using DOE

How Was The Experimental Design Chosen For API-FDC Tablets RS Method?

- Select the number of factors to be explored and the objectives of the experiment
- Collaboration between Analytical Lab & Statisticians
- The Plackett-Burman design was selected based
  - On the number of factors to be evaluated
  - Multifactor-designed (matrix) experiment:
    - more efficient, cost-effective, and informative
  - Very effective screening design when only main effects are of interest-
    - As it was the case for APIFDC Tablets RS method
  - Robustness/Ruggedness evaluation

Plackett-Burman Design

	パターン	Mobilephase pH	Salt Conc of...	Gradient Time	MobilephaseA...	MobilephaseB...	Mobilephase...	Temp.	Wavelength	Flow rate	column	Instrument
1	--+--+-+++-	-1	-1	1	-1	-1	1	-1	1	1	L2	L1
2	--+-+++---+	-1	-1	1	-1	1	1	1	-1	-1	L1	L2
3	+++++++++++	1	1	1	1	1	1	1	1	1	L2	L2
4	---+--+-+++	-1	-1	-1	1	-1	-1	1	-1	1	L2	L2
5	-+++---+--+	-1	1	1	1	-1	-1	-1	1	-1	L1	L2
6	+-+++---+--	1	-1	1	1	1	-1	-1	-1	1	L1	L1
7	-+-+++---+-	-1	1	-1	1	1	1	-1	-1	-1	L2	L1
8	+---+--+-++	1	-1	-1	-1	1	-1	-1	1	-1	L2	L2
9	+++---+--+-	1	1	1	-1	-1	-1	1	-1	-1	L2	L1
10	++---+--+-+	1	1	-1	-1	-1	1	-1	-1	1	L1	L2
11	-+--+-+++--	-1	1	-1	-1	1	-1	1	1	1	L1	L1
12	+--+-+++---	1	-1	-1	1	-1	1	1	1	-1	L1	L1

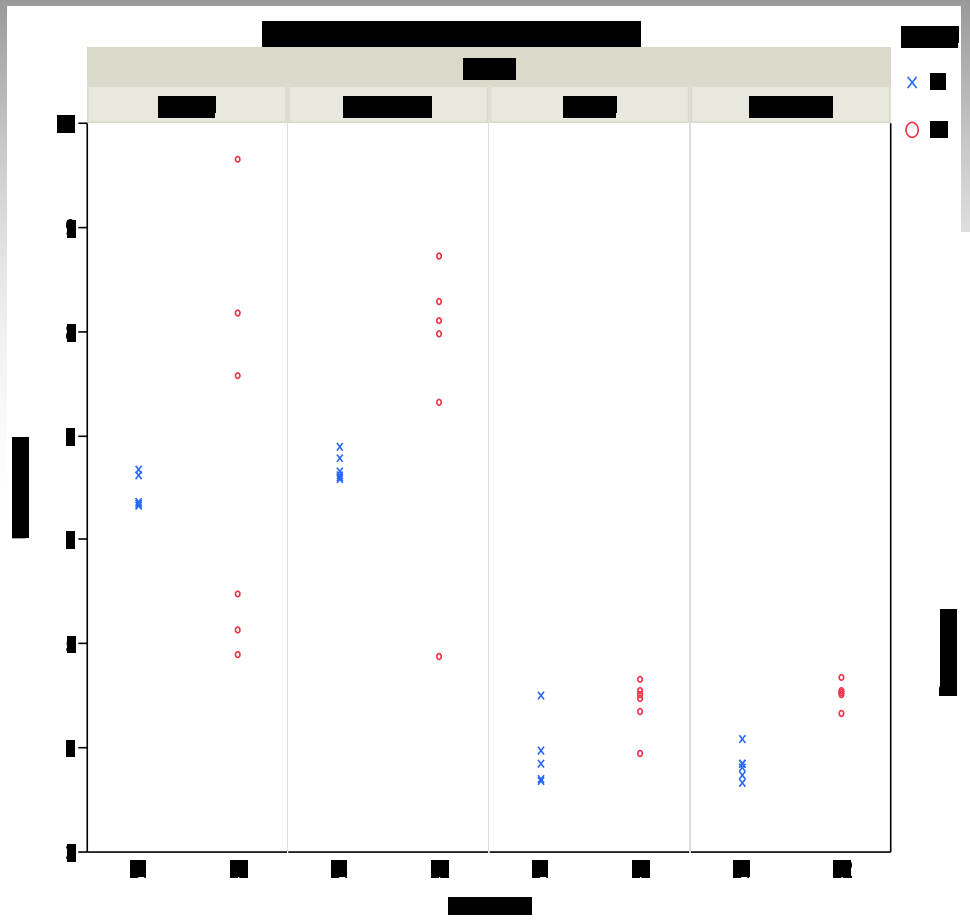
Results and Conclusions RS Method

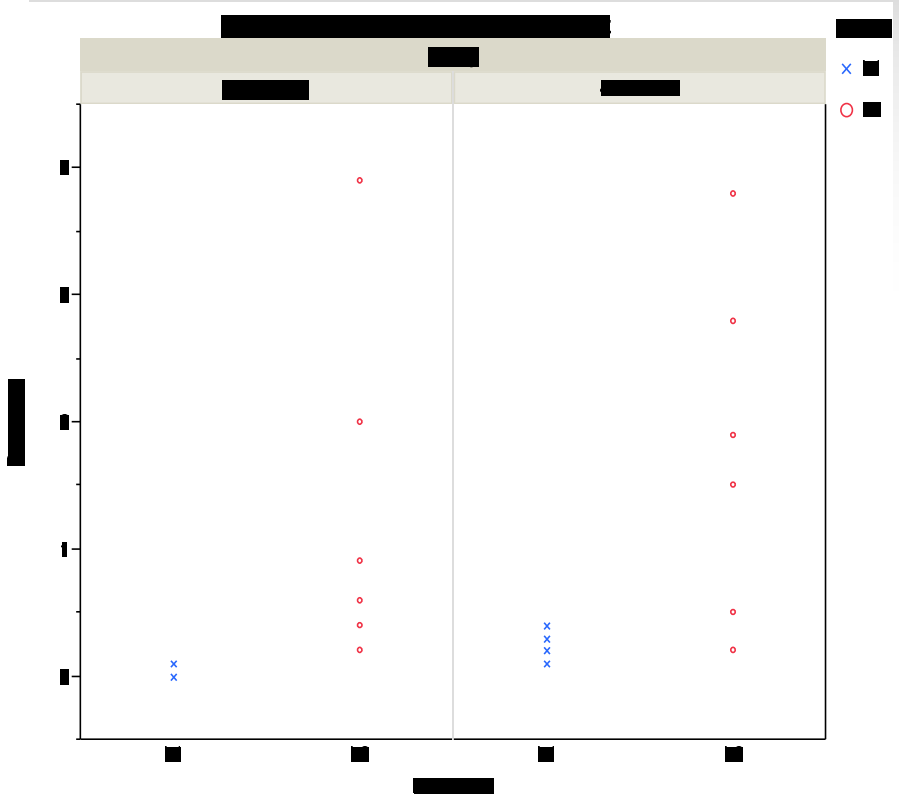
- DOE analysis indicates that for the key resolutions (U-6 vs API and C-1 vs FDC), the only factor that has an effect is instrument.
  1. Generally the L2 instrument (Agilent 1200) gave higher resolution than the L1 (Waters UPLC)
  2. All the resolutions were good (>3).
- For the other minor peaks the key effect was pH and sometimes temperature although pH effect was not consistent
  - All resolutions were very good
- Based on above, instrument was further investigated through a “validation” study
  1. Results confirmed the DOE results
  2. For API the key resolution mean(rsd) was 6.27 (.19) for Waters and 3.83 (1.2) for Agilent.
  3. For FDC the key resolution was 4.20 (.06) for Waters and 6.25 (.94) for Agilent
  4. Waters UPLC seems to have better precision (e.g., for resolution)

Was robustness established for this method?

- Instrument L1 absolutely
- L2 gave higher resolution than L1 but acceptable resolution obtained

Major Peaks – API-FDC Tablets - RS





Minor Peaks – API-FDC Tablets - RS