



Real Time Release Testing of Ciprofloxacin HCl Modified Release Capsules. Case Study

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Real Time Release

- The definition of *real-time release testing* in Q8(R2) is “the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data, which typically includes a valid combination of measured material attributes and process controls.”



Objective

- Develop Ciprofloxacin HCl modified release Multiparticulate drug delivery system - Used drug layered beads coated with hydrophobic polymer system utilizing novel disk-jet fluid bed technique
- Develop new strategies for implementing the design space.
- Develop a control strategy for real time release testing.



Outlines

- Our Philosophy
- Formulation development
- Screening studies and risk modeling
- DOE for CPP
- Process understanding
- Process optimization
- Design space
- Process signature
- Studying the curing behavior



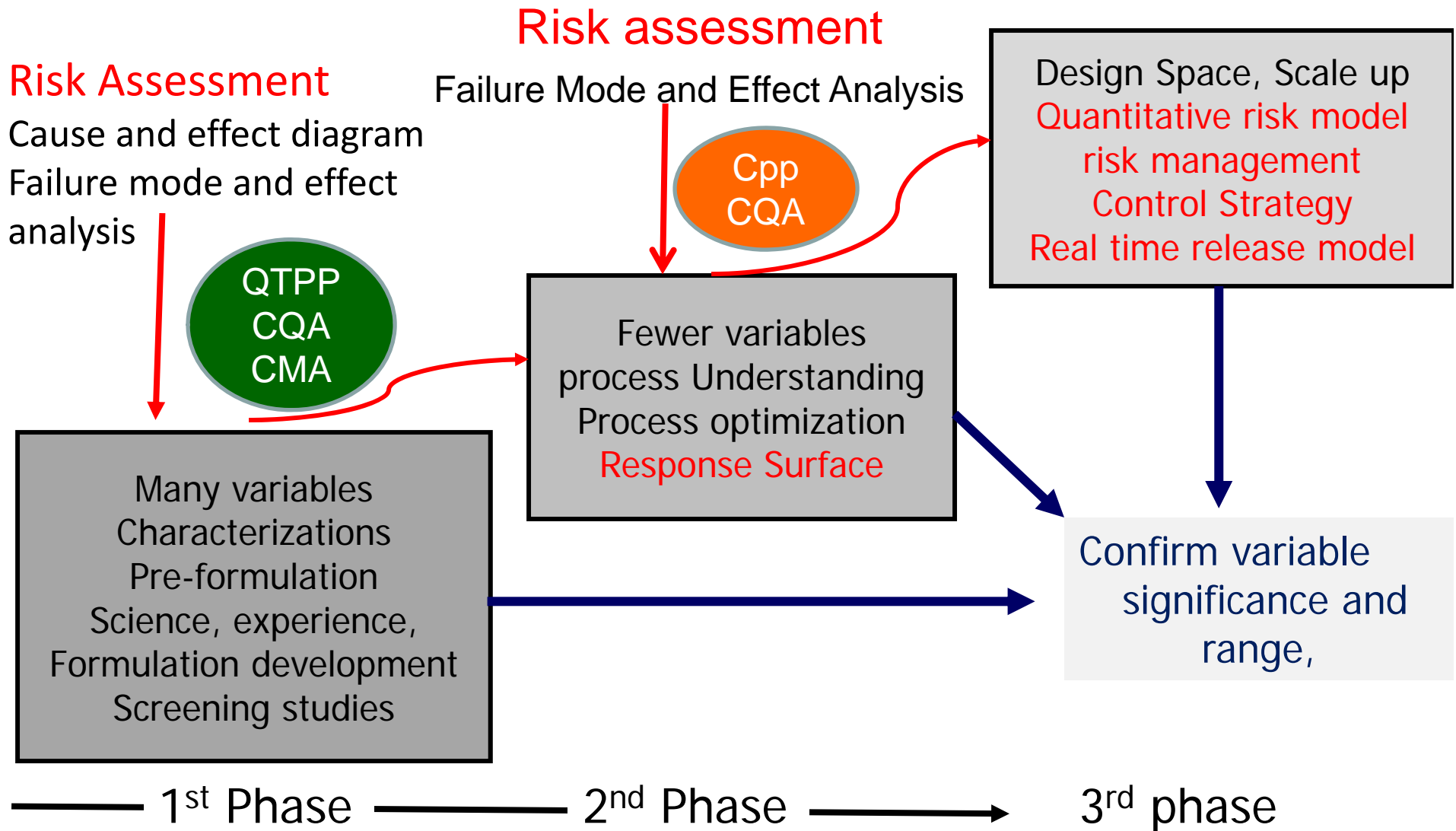
Hypothesis

- Using both qualitative risk assessment models and design of experiments can be used to rationally determine the number of experiments needed for formulation and process development and defining the design space.
 - i.e., using risk methods allows us to find a reasonably robust formulation and define the design space without going broke



Strategy for developing the product

Goal: Find the significant factors from a list of many potential ones.





Systematic Approach

- Define Target product profile, critical quality attributes,
- Use risk and statistical models during the development to define the critical process and material parameters, establish a robust control strategy.
- Define all dependent and independent variables
- Update risk models as we go through the development.
- Keep the design of experiment dynamic (screening, interaction, and confirmatory studies, design space, and scale up studies) and use the right analysis (response surface, ANOVA, contouring plot..)
- Establish process signature for the manufacturing process.
- Establish a corrective and preventive action (CAPA).
- Continual monitoring (e.g., via continuous process verification) to assure process consistency and provide the basis for continual improvement of the product.
- Establish the design space
- continuous process verification as we go with the development and scaling up.



Quality Target Product Profile and Critical Quality Attributes

- QTPP: 100 mg ciprofloxacin capsule modified release multiparticulate beads.
- CQAs: assay and dissolution.



Formulation

- Preformulation and preliminary studies was performed to identify the formulations and characterize the polymer and plasticizer.
- Hydrophobic system was chosen based on the nature of the drug substance, the unit operation coating system, and the requirement of Quality Target Product Profile “QTPP”. Weight gain is 3%.



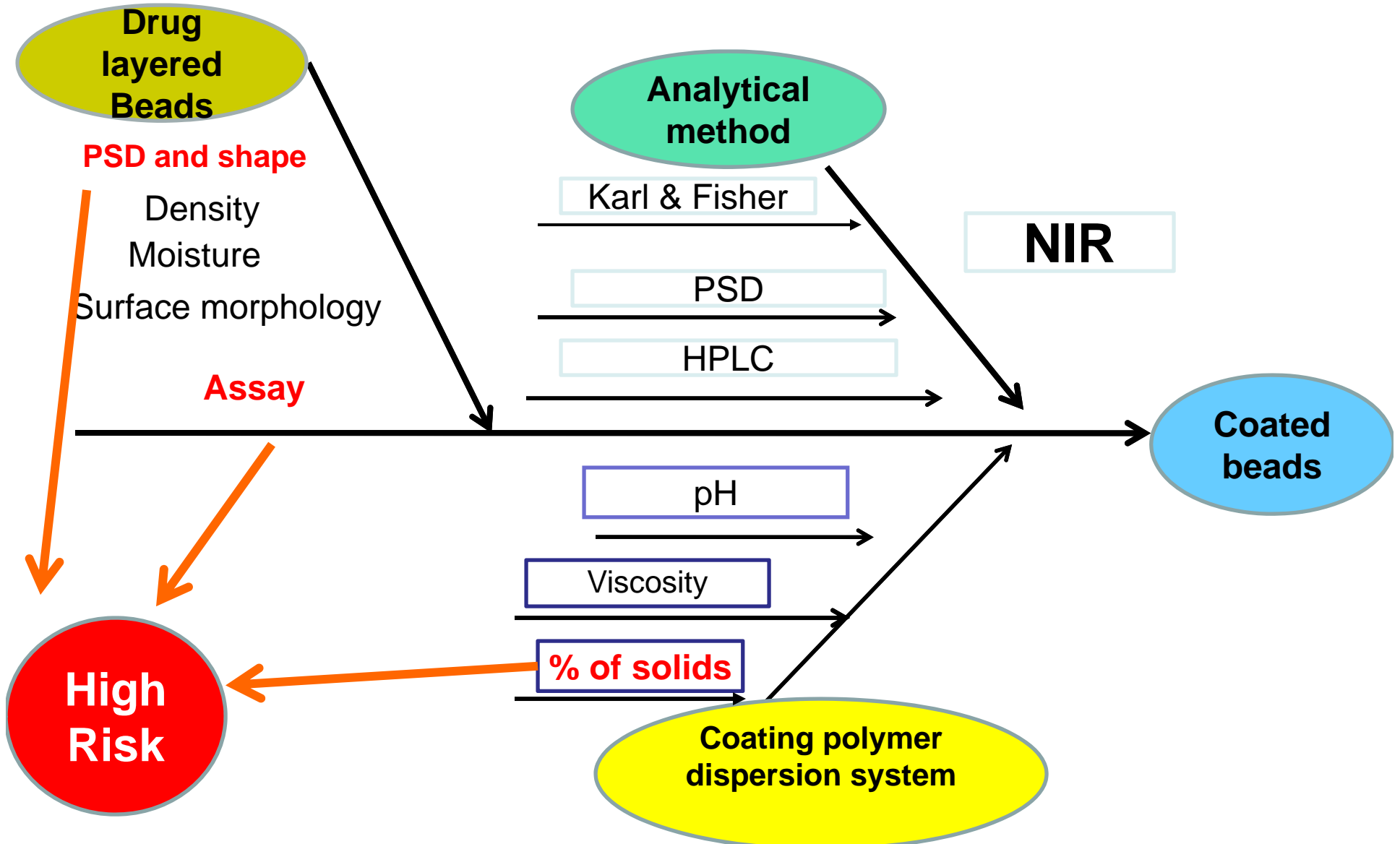
Formulations

- Ciprofloxacin HCl Drug Layered Bead
- Dispersion system:
 - Ethyl cellulose Aqueous dispersion (15% solid)
 - Triethyl citrate (25% w/w of polymer weight)
 - Deionized water
 - D&C Red # 27 pigment

Critical Material Attributes: PSD, Aspect ratio how spherical the beads are, surface morphology and assay. Based on OCAT



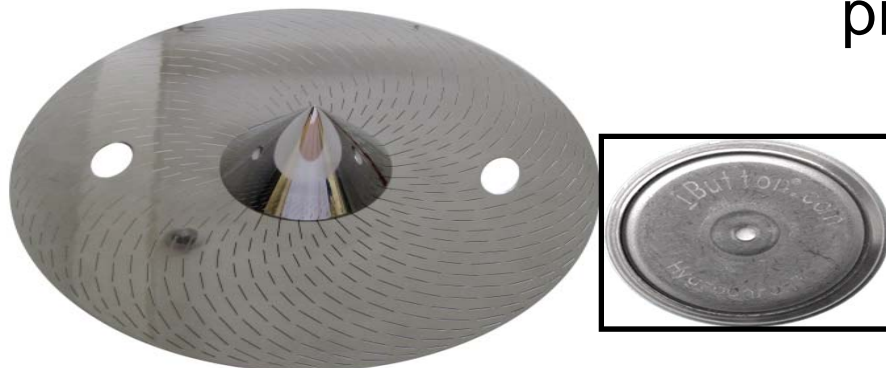
Cause and Effect Diagram For drug layered beads and excipients



Mycrolab – Fluid Bed in Lab Scale



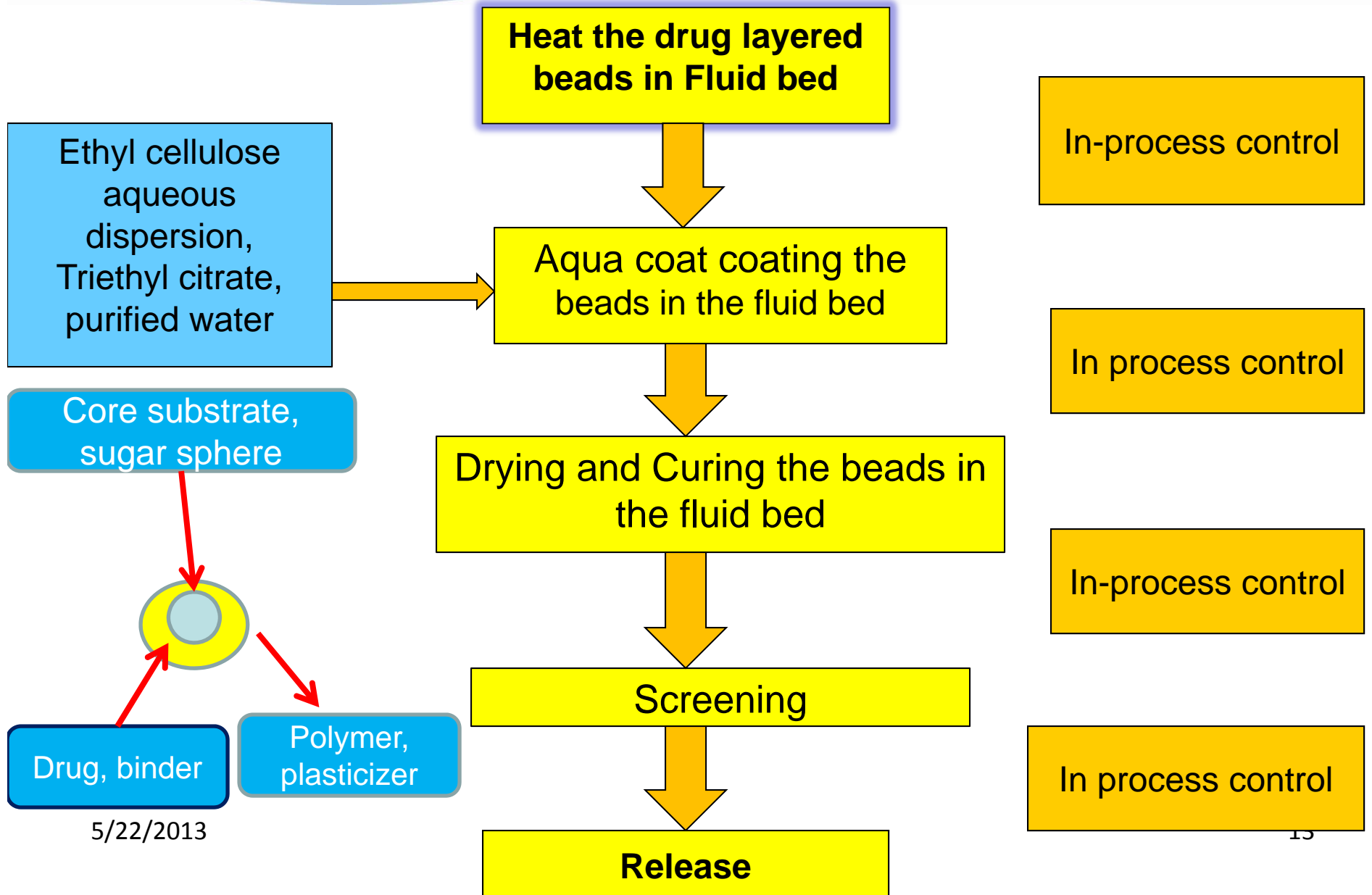
- The disk-jet is a patented technology of OYSTAR Hüttlin fluid bed system and consists of unique stainless steel perforated air distributor plate to provide homogeneous airflow.
- The opening from the bottom stainless steel air distribution plate creates a vortex in the expansion chamber ensuring fast and uniform product mixing with no dead zones.

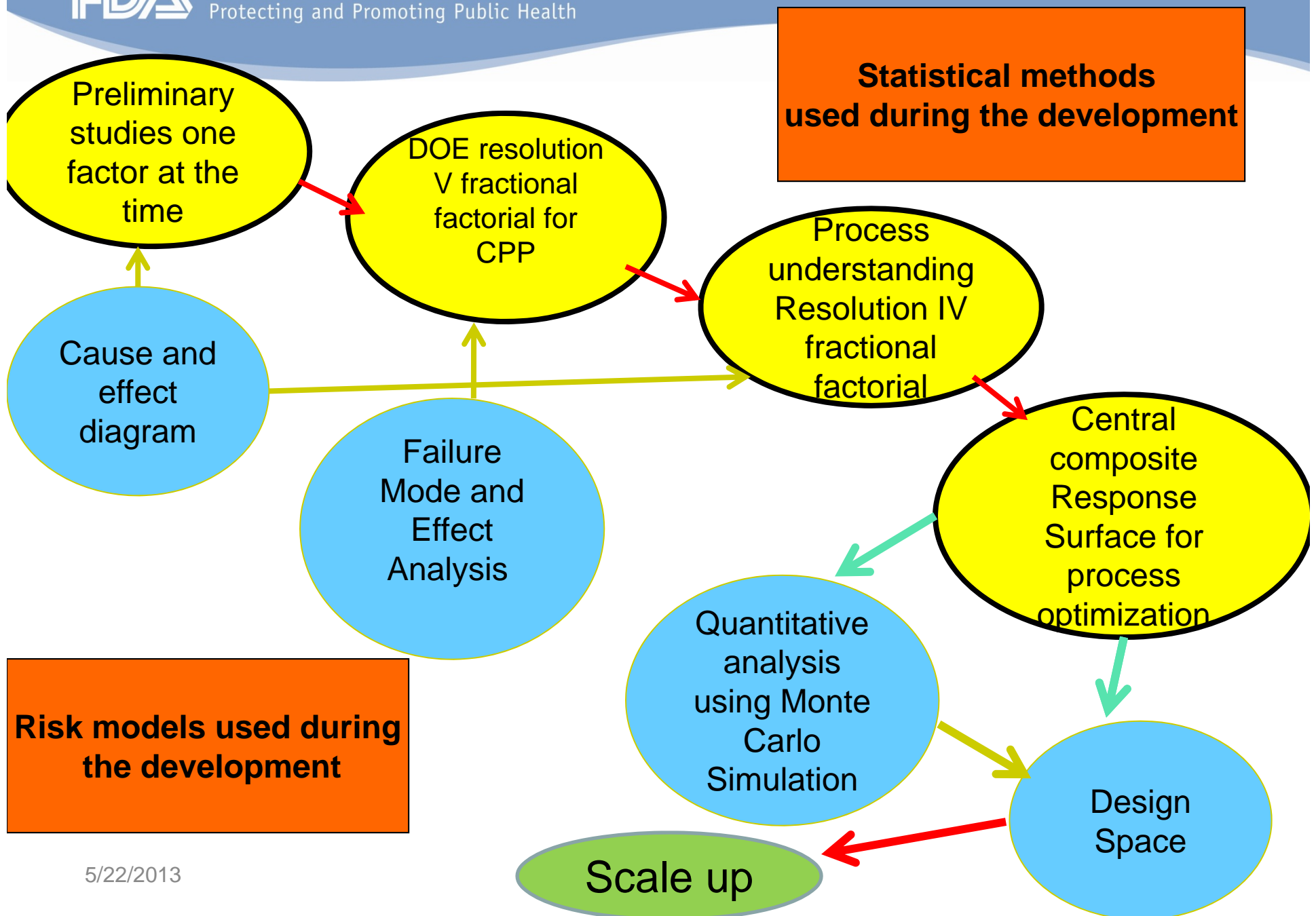


Pyro Button



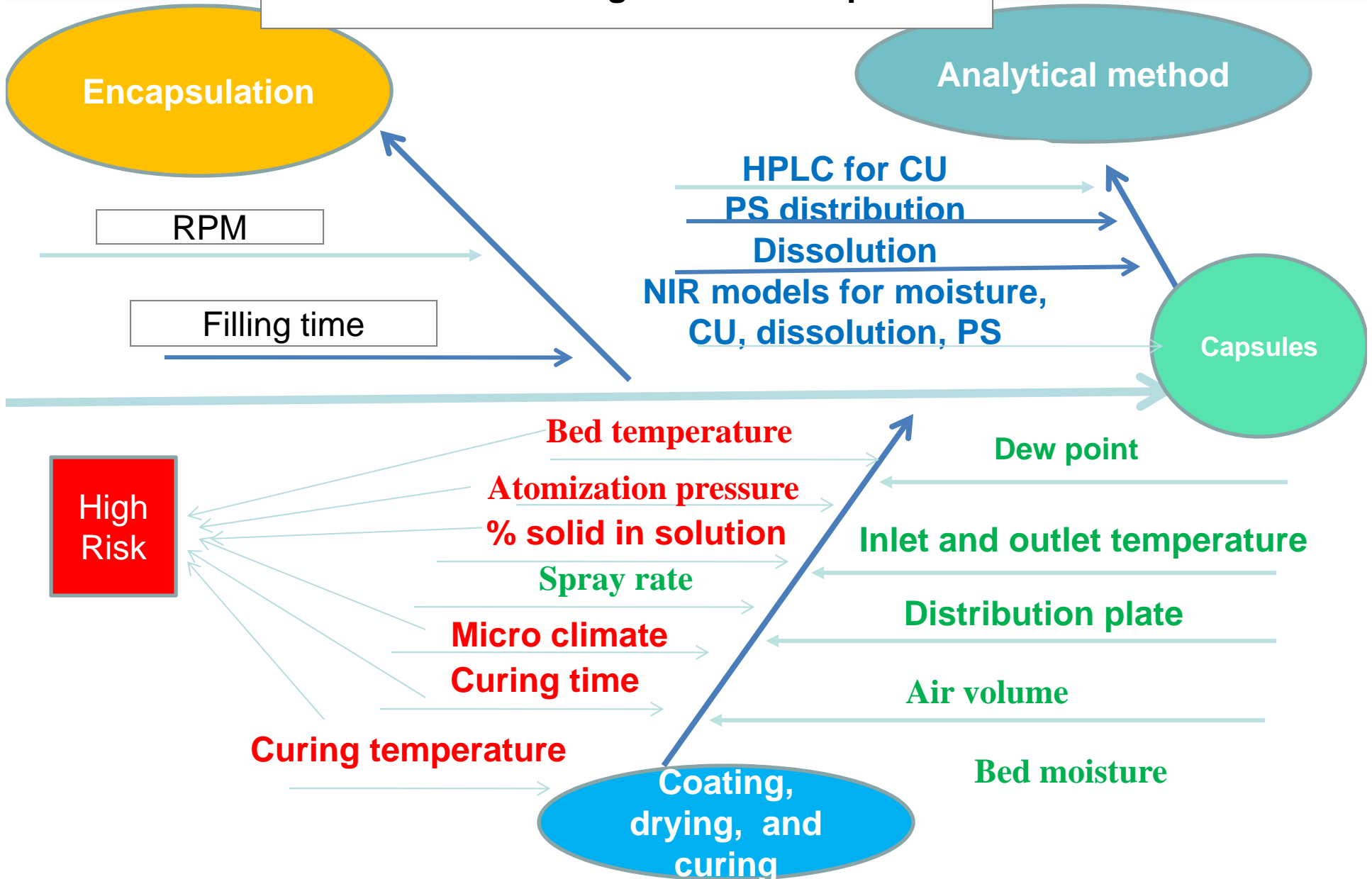
Manufacturing Process Flow Chart for Cipro Capsules







Cause and effect Diagram for unit operation





Conclusions

- Used cause and effect risk model to identify all the variables, based on our experience, science, and data obtained from the preliminary DOE the number of variables were reduced to 6 variables based on the quality of the beads which effect the CQA of the product.
- Based on the data , and response factors, **Critical Process Parameters** were Product temperature, Curing time, Curing temperature, Microclimate, % solids, and atomization pressure. These factors were subject to further study, DOE resolution V



Screening Studies

Objective: Screening studies were coupled with risk models “cause and effect diagram, and FMEA” to Study the thermodynamics and fluid dynamic of the fluid bed and establish initial process ranges and optimize the spray rate.

- Due to the limited amount of the drug layered beads, all the screening studies were performed using MCC to save
- A total of 20 experiments were conducted using resolution V, five factors at two levels with 4 center points ($2^{5-1} + 4 = 20$) which clearly estimated the main effect independently.
- Response factors: efficiency, yield, weight gain, PSD, and % of agglomerations.



Design Range Layout for the coating Process

Factor	Variables	Units	Minimum	Maximum	Mean
A	Microclimate	Bar	0.2	0.4	0.3
B	Atomization Pressure	Bar	0.6	1.0	0.8
C	Air Volume	m ³ /h	20	30	25
D	Product Temperature	°C	40	50	45
E	% Solids	%	15	25	20



FMEA – Risk Assessment Summary

Unit Operation	Failure Mode	Impact of Change	S	Potential Cause or route of failure	O	Detection	D	RPN
Drug Layered Beads	Particle Size	Content Uniformity, Dissolution	3	Material Variation	3	NIR	1	18
	Surface Morphology	Poor Quality of Coated Beads	4	Material Variation	3	Optical Microscopy	3	36
	Assay	Content Uniformity	2	Poor Development	5	HPLC	4	40
	Dissolution	Coat Weight Gain	2	Poor Development	5	Dissolution apparatus	3	30
Fluid Bed Equipment	Nozzle tip diameter	Poor Quality of Coated Beads	2	Operator's error	2	Visual inspection	3	12
	Nozzle cap	Poor Quality of Coated Beads	2	Operator's error	2	Visual inspection	3	12
	No of Nozzles	Process Run Time	1	Operator's error	2	Visual inspection	3	6
	Filter Type	Assay, Dissolution	1	Operator's error	2	Visual inspection	3	6
Coating Dispersion	% Solids in the Solution	Particle Size	3	Operator's error	5	Malvern	5	75
	Viscosity	Poor Quality of Coated Beads	2	Material Variation	3	Viscometer	4	24
	Mixer type/speed	Content Uniformity, Dissolution	1	Equipment Failure	1	Visual inspection	3	3
	Pump/tubing	Dissolution	1	Operator's error/Equipment Failure	2	Visual inspection	3	6
Coating Process	Inlet Air Temperature	Dissolution	4	Operator's error/Equipment Failure	2	Data loggers	3	24
	Product Temperature	Assay, Dissolution	5	Equipment Failure	5	Sensor calibration	5	120
	Microclimate	Dissolution	4	Operator's error/Equipment Failure	4	Equipment calibration	4	64
	Atomization Pressure	Dissolution	4	Operator's error/Equipment Failure	4	Equipment calibration	4	64
	Air Volume	Assay, Dissolution	5	Operator's error/Equipment Failure	5	Sensor calibration	5	125
	Inlet Air Dew Point	Dissolution	5	Operator's error/Equipment Failure	3	Data Loggers	4	60
	Shaking Interval	Assay	2	Operator's error/Equipment Failure	1	Visual Inspection	3	6
	Exhaust Temperature	Assay, Dissolution	3	Equipment Failure	3	Data Loggers	3	27
	Curing Temperature	Dissolution	5	Operator's error/Equipment Failure	4	Sensor Calibration	5	100
	Curing Time	Dissolution	5	Operator's error	4	Visual Inspection	3	60
Spray Rate	Content Uniformity, Assay	3	Operator's error/Equipment Failure	2	Pump calibration	3	18	



Method used to score risk parameters

S = Severity,

O = Probability of Occurrence,

D = Detection;

1 = Low, 3 medium risk and 5 = High;

RPN (Risk Priority Number) = S X O X D

Low Risk Factors = 0-30,

Medium Risk Factors = 31-59,

High Risk Factors = 60 -125



ANOVA Analysis

Responses	Curvature	MC (Bar)	AP (Bar)	AV (m ³ /h)	PT (°C)	% Solids
% Agglomeration	NS	S	S and 2FI	S	S and 2FI	
Aspect Ratio	NS	2FI	2FI		S and 2FI	2FI
Median Particle Size (d50)	NS	S	S		S	
<p>MC = Microclimate, AP=Atomization Pressure, AV=Air Volume, PT=Product Temperature NS = Not Significant, S = Significant, 2FI= Factor Interaction</p>						



Conclusion

- Based on ANOVA analysis % of agglomeration, PSD, Aspect ratio were modeled and CPP were identified
- Resolution V and FMEA risk model suggested that all the factors studied effect the CQA of the final beads, product temperature was found to be the most critical coating parameters effecting the final beads.
- this study allowed us to understand the process and provided input for process ranges of the CPP for the subsequent study.



Critical thinking for process understanding

- How variability influence the quality of the product
- Multivariate analysis
- Multistage risk models (qualitative or quantitative) can be used to rationally determine the number of experiments needed for process development and defining the design.
- develop a predictive model for the system that can be used to find useful operating conditions (design space) using
 - response surface
 - contour plots, mathematical optimization.
 - Qualitative and quantitative risk models.



Critical Process Parameters for coating and curing

Objective: To study the influence of the coating and curing parameters on the critical quality attributes and the quality of film curing.

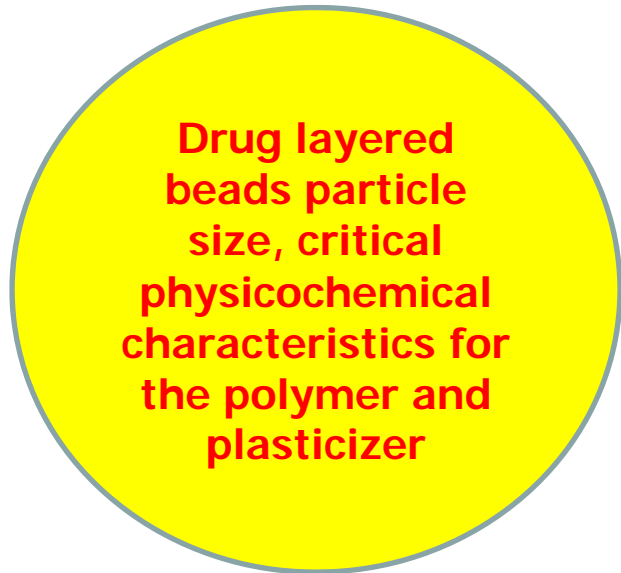
Resolution IV study design conducted in two parts

- Part I (without center points) = $2^{7-3} = 16$ experiments
- Part II (with center points) = $2^{7-3} + 4 = 20$ experiments
- A novel process analytical tool Pyrobuttons[®], a data logger was utilized to record real time temperature and humidity changes occurring at different locations in the fluid bed equipment.
- Used Drug layered beads, therefore we needed to optimize the spray rate with separate set of experiment.



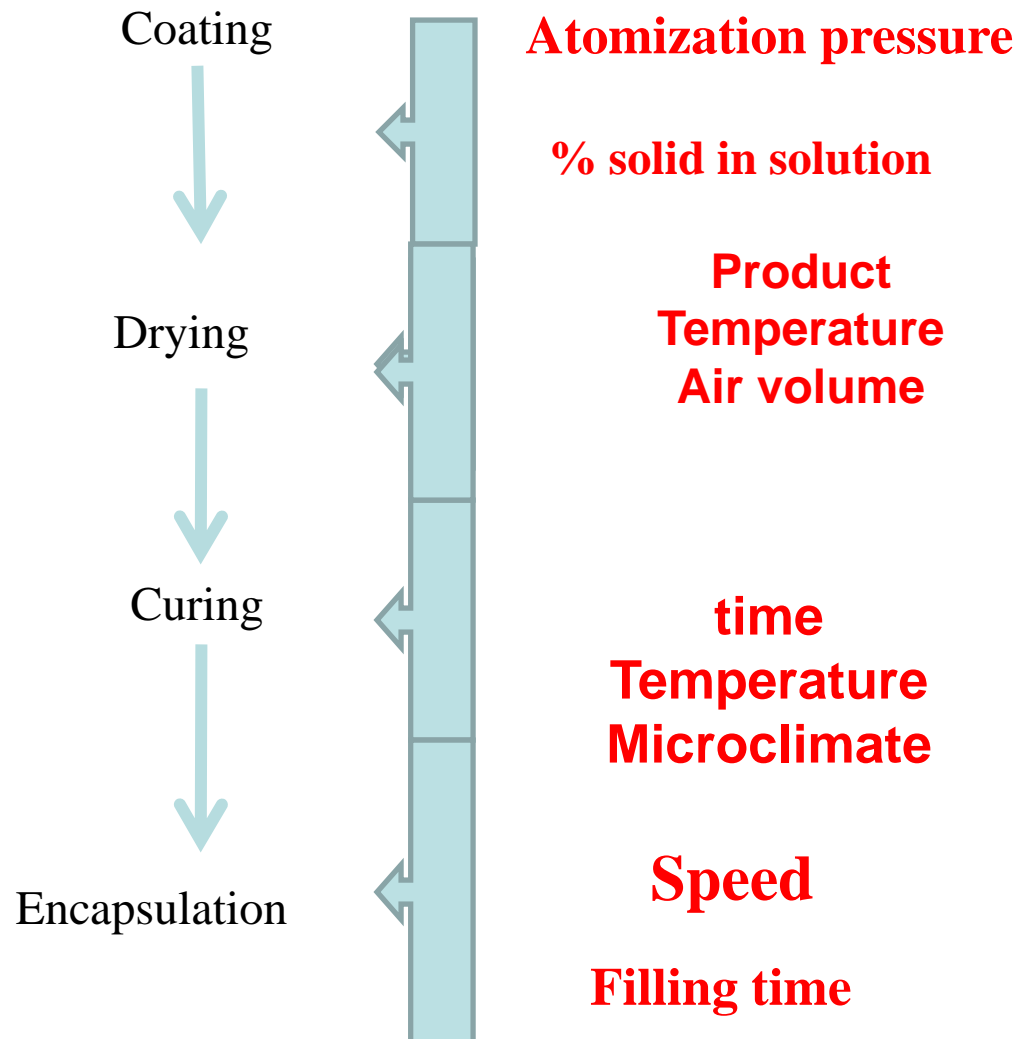
Risk Assessment

Formulation



Red – high risk

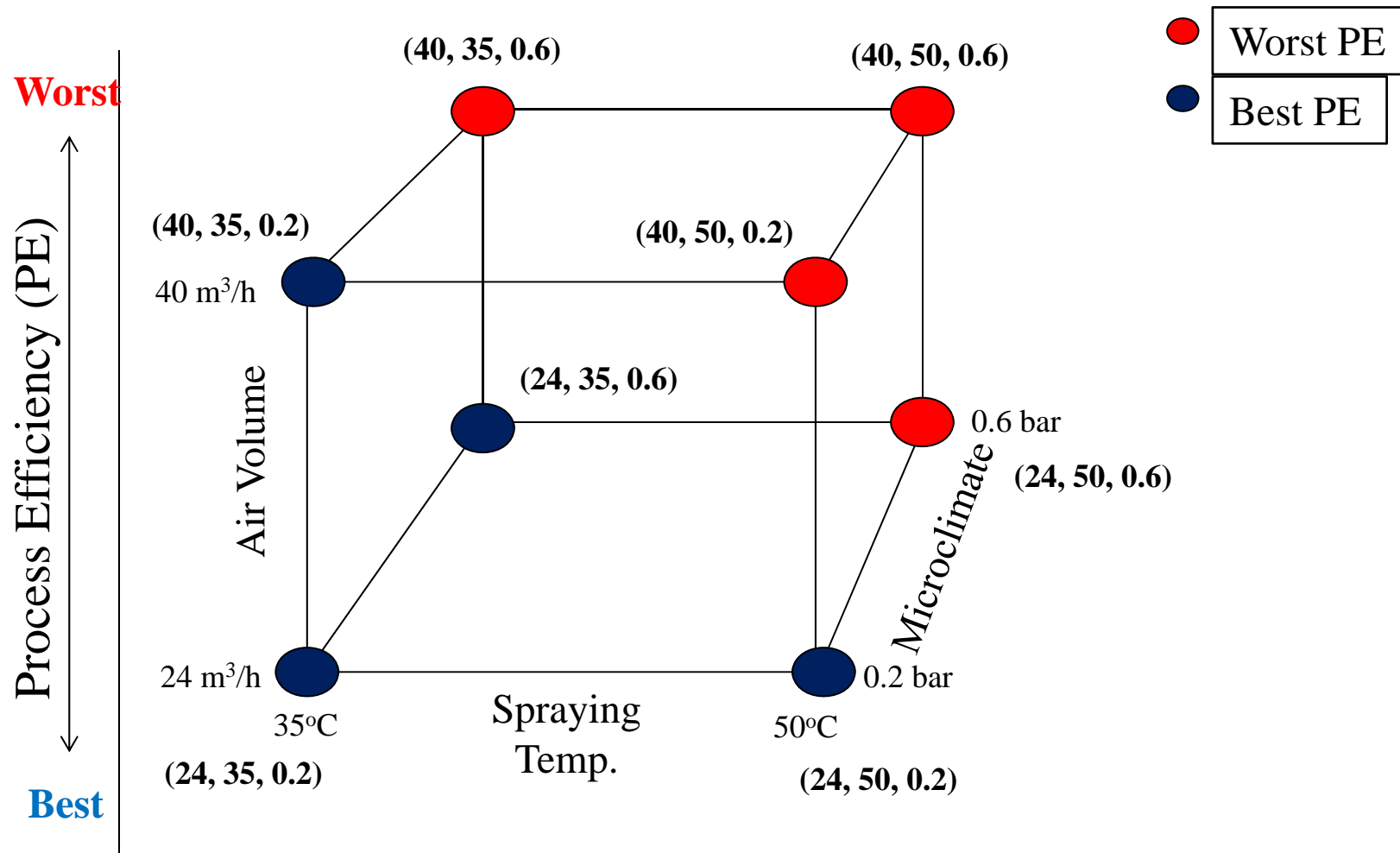
Manufacturing process





Resolution IV – Design Range Layout

Factor	Variable	Units	Minimum	Maximum	Mean
A	Microclimate	Bar	0.2	0.6	0.4
B	Atomization Pressure	Bar	0.6	1.2	0.9
C	Air Volume	m ³ /h	24	40	32
D	Product Temperature	°C	35	50	42.5
E	% Solids	%	15	25	20
F	Curing Time	Hours	1	4	2.5
G	Curing Temperature	°C	50	70	60

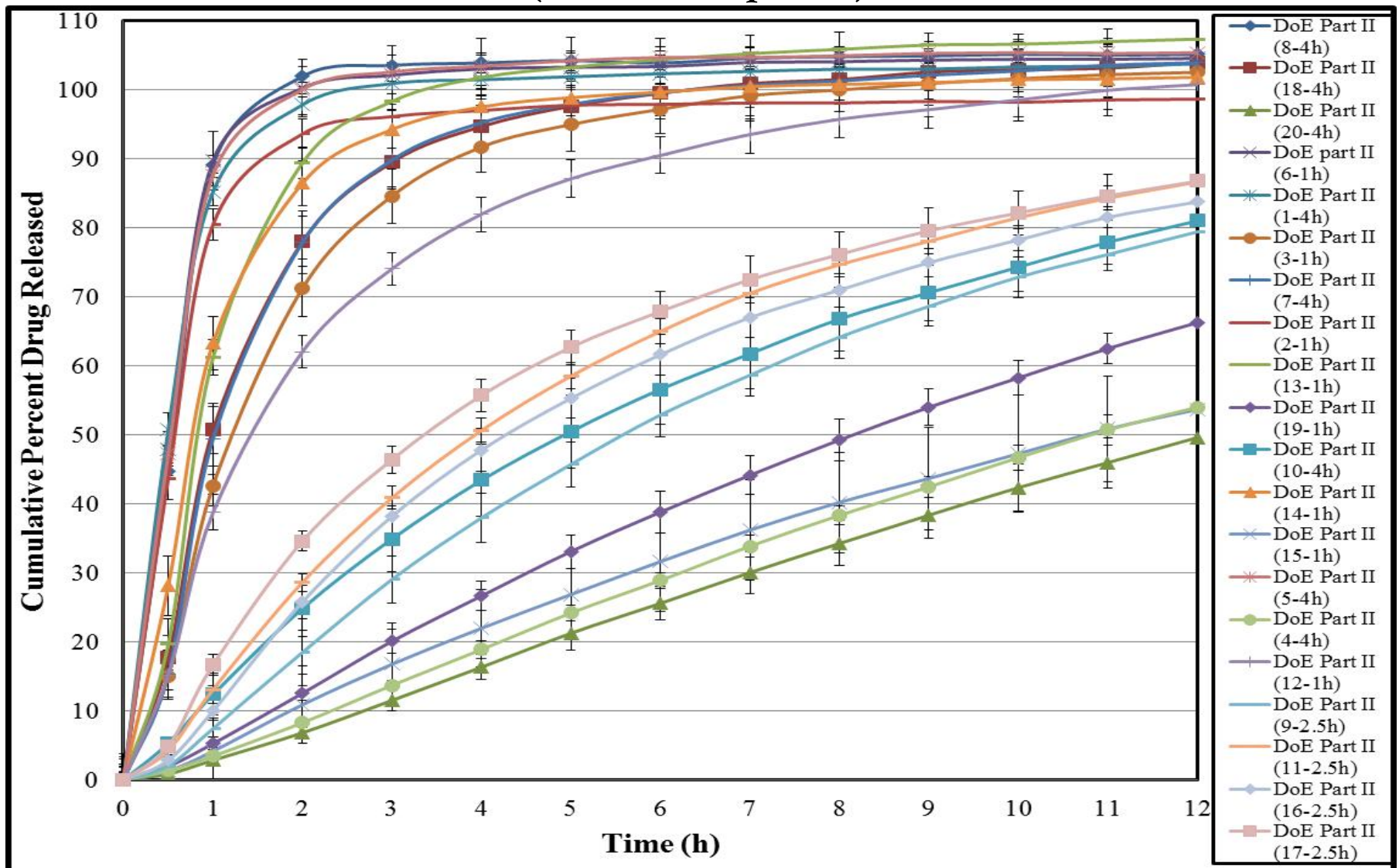


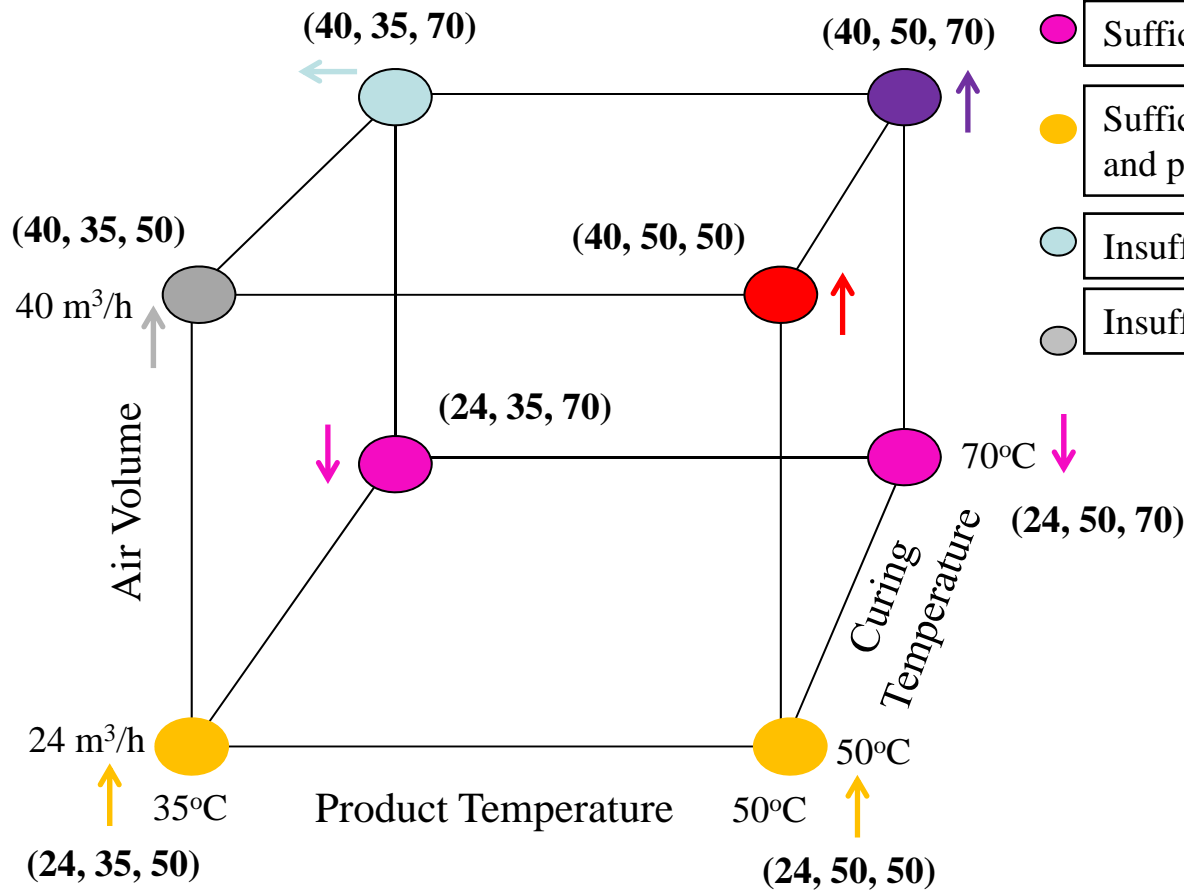
Effect of Critical Process Parameters - Coating Conditions

% Process Efficiency = Amount of Coating Polymer deposited on the drug layered beads compared to its theoretical amount



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





- Spray Drying and Incomplete Curing
- Spray Drying and Curing effect
- Sufficient Polymer film - Curing time effect
- Sufficient Polymer film - Incomplete Curing and potential to detect Humidity effect
- Insufficient Polymer film - Curing Effect
- Insufficient Polymer film - Incomplete Curing

↑ Fast dissolution ↓ Slow dissolution ← Intermediate dissolution

Interdependence of Processing Parameters, Process Efficiency and Curing Conditions on Dissolution



Conclusion

- Conformed the CPP and identified 2FI terms,
- Wide range of Process Parameters enabled to Understand Coat Variability (Process Efficiency)
- Correlation was Established between Critical Process Parameters and Critical Quality Attribute
- % of agglomeration, % yield, and LOD were not significant on the ANOVA analysis.
- Information obtained from Resolution IV study utilized for Response Surface Study to Establish Design Space
- **Critical Parameters: Product temperature, curing temperature, and curing time are critical. Further investigation should be done on curing temperature.**
- The independent process parameters like microclimate (cloud of air surrounding the nozzle to prevent its clogging), atomization pressure (to form fine droplets of the solution), inlet air temperature and air volume are controlled by the equipment setting.



Process Optimization – Response Surface Methodology Using Central Composite Design to Establish Design Space of the Critical Process Parameters (CPP)

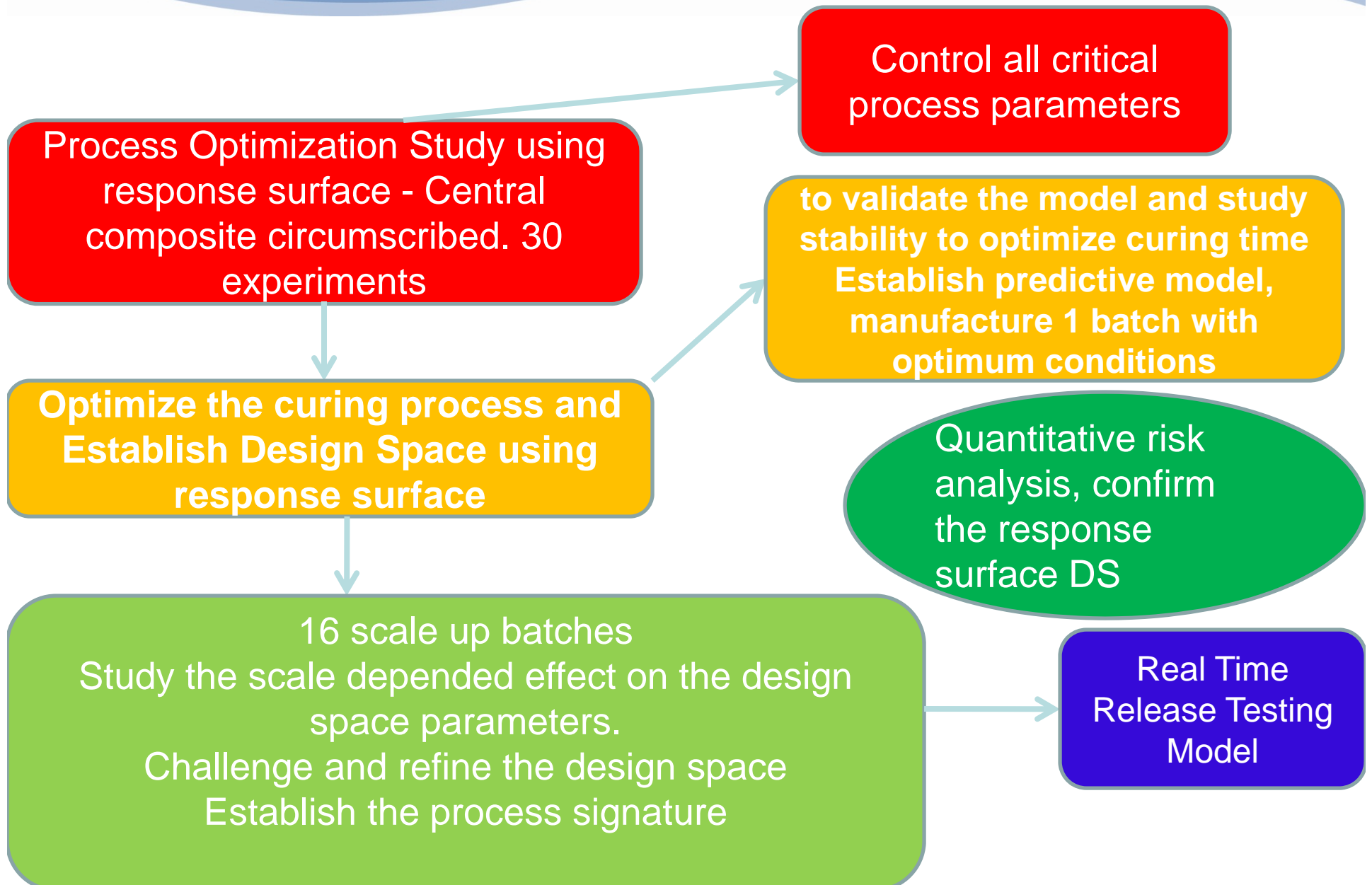


Critical thinking when optimizing the formulation and manufacturing process

- Strategy for optimization formulation and manufacturing during the development.
- Number of experiment too much or too little
- Relationship between the formulation and the process to the QTPP
- keep the DOE dynamic (central composite, full factorial, fractional factorial,,,,,,)
- mechanism of studying independent variables from formulation and process and how they affect the critical quality attributes with the least number of experiments



Design of Experiment for Process Optimization





Process Optimization – Response Surface Central

Composite Rotatable Design

- Objective: Optimize the process and gain more information to establish the Design Space.
- Parameters studied: Air volume, product temperature, curing time, and curing temperature
- Design consists of the following points
 - Factorial Points (two levels)
 - Center Point (one level)
 - Axial Points or star points (two levels)
- Purpose of the DoE
 - Estimate clear main effects and 2FI
 - Estimate quadratic terms to address curvature effect or non-linearity
- Processing parameters (factors) kept constant
 - Microclimate: 0.2 bar
 - Atomization pressure: 0.8 bar
 - Spray rate: 0.7-1.2 gm./min
 - % solids (15%)

Response factors: assay, dissolution @ 1, 2, 7 Hrs.

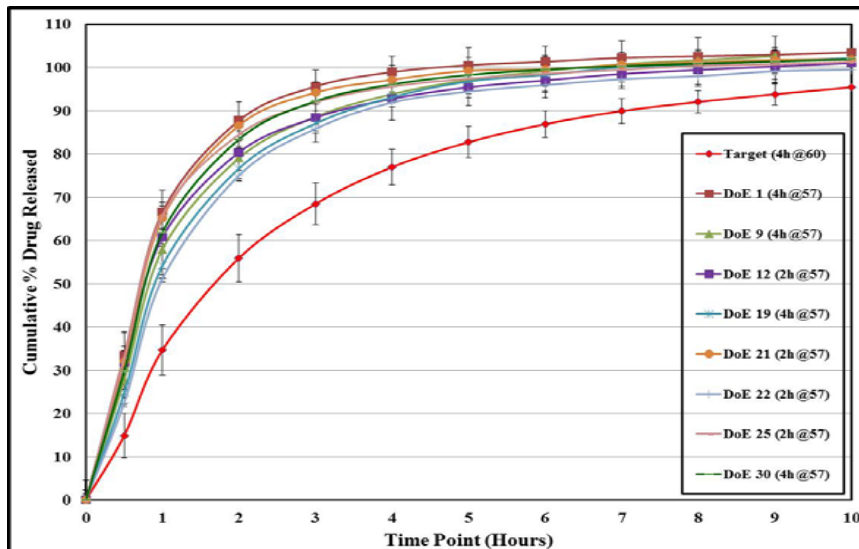


RSM – Design Range Layout

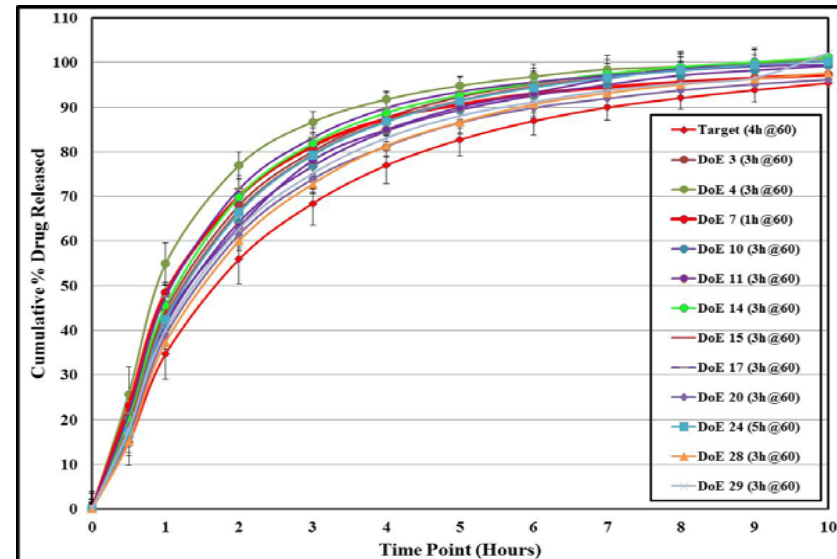
Factor	Variable	Units	Minimum	Maximum	+ Alpha	- Alpha	Mean
A	Air Volume	m ³ /h	28	32	26	34	30
B	Product Temperature	°C	40	44	38	46	42
C	Curing Time	Hours	2	4	1	5	3
D	Curing Temperature	°C	57	63	54	66	60



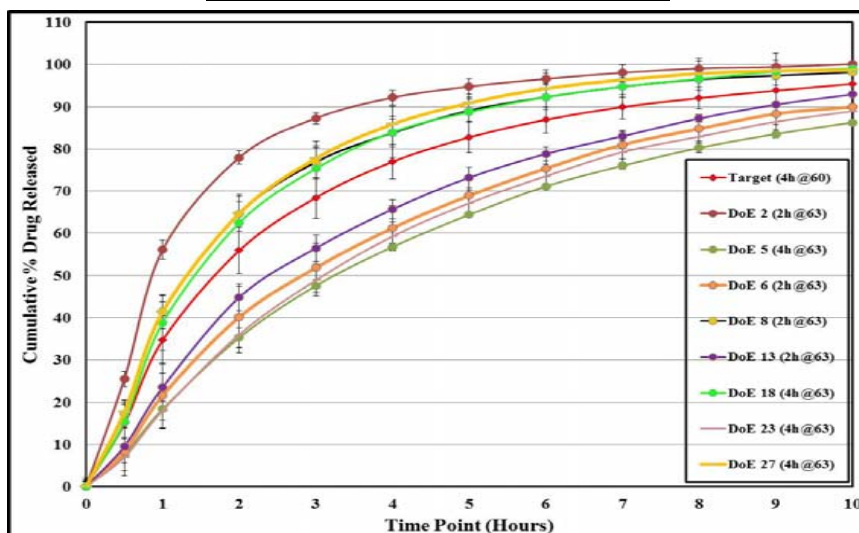
**Dissolution Profiles of Ciprofloxacin HCl Coated Beads, 257 mg/g
Cured@57°C – Different Curing Time**



**Dissolution Profiles of Ciprofloxacin HCl Coated Beads, 257 mg/g
Cured@60°C – Different Curing Time**



**Dissolution Profiles of Ciprofloxacin HCl Coated Beads, 257 mg/g
Cured@63°C – Different Curing Time**



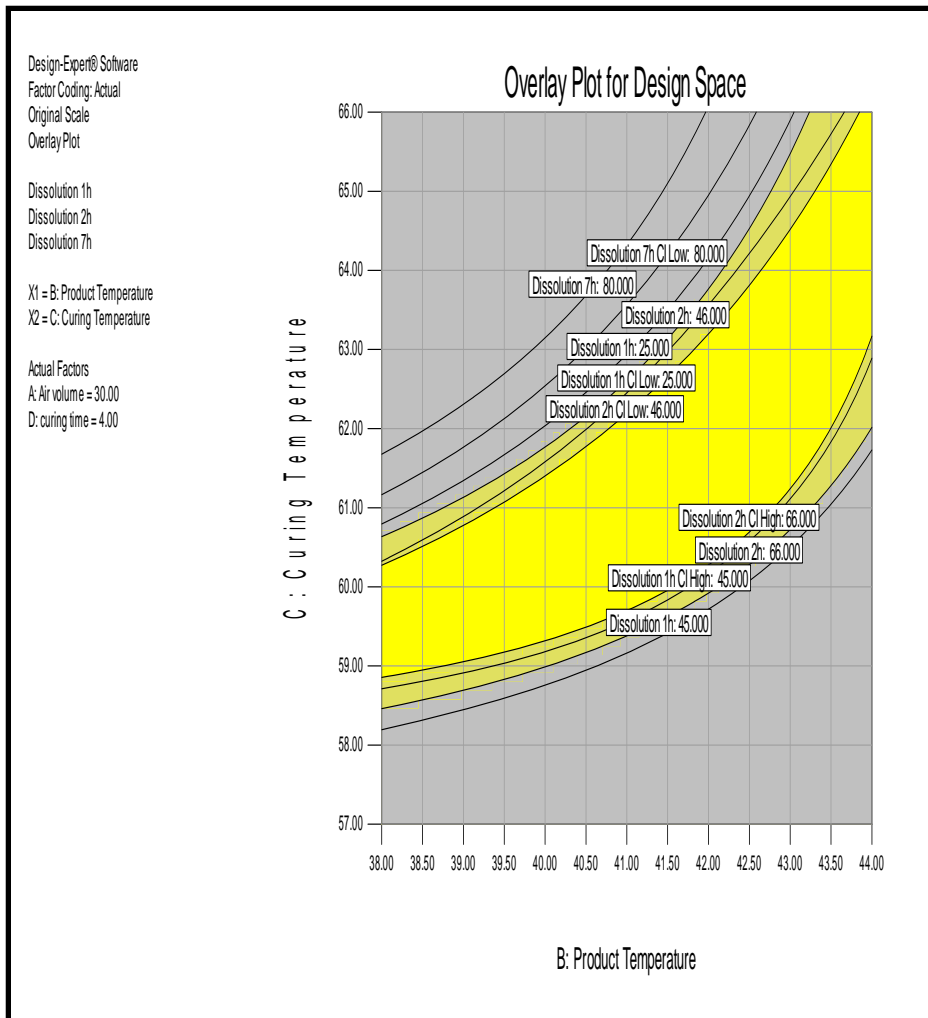
- Batches cured at 57°C - Faster Dissolution (Process efficiency and Incomplete Film Formation)
- Batches cured at 60°C - close to target dissolution (effect of Humidity)
- Batches cured at 63°C – slower (dense film)and faster dissolution (spray drying)



Response Surface – Statistical Models

ANOVA for Response Surface Reduced 2FI Model					
Dissolution 1 hour		Dissolution 2 hour		Dissolution 7 hour	
Terms	Status	Terms	Status	Terms	Status
Model	significant	Model	significant	Model	significant
A - Air Volume	not significant	A - Air Volume	not significant	B-Product Temperature	significant
B-Product Temperature	significant	B-Product Temperature	significant	C-Curing Temperature	significant
C-Curing Temperature	significant	C-Curing Temperature	significant	BC	significant
D-curing time	significant	D-curing time	significant	CD	significant
AC	significant	AC	significant	Lack of Fit	not significant
BC	significant	BC	significant		
Lack of Fit	not significant	CD	significant		
		Lack of Fit	not significant		

Dissolution Design Space {Target Product Temperature and Curing Time}



- Response surface suggested that the most critical parameters for the design space were
 - **Product temperature: 40-42**
 - **Curing time: 4 hours**
 - **Curing temperature: 59-61**
- We are monitoring and controlling other critical parameters using pyro bottom for the humidity and other machine capabilities, and using the optimize ranges.
- This case study is an example for Cipro modified release at the level of 3% polymer coating.



Scaling up Design

- Study Design: at full scale
- Model Utilized: 2FI based on the RSM data
- Study 3 factors (product temperature, curing time, and curing temperature) at two levels $2^3 = 8$ experiments
- Number of Replicates: Two - to ensure enough power of the design and study the design space based on tolerance limit determined from fraction of design space (FDS) i.e.
- Number of experiments = $8 * 2 = 16$ experiments

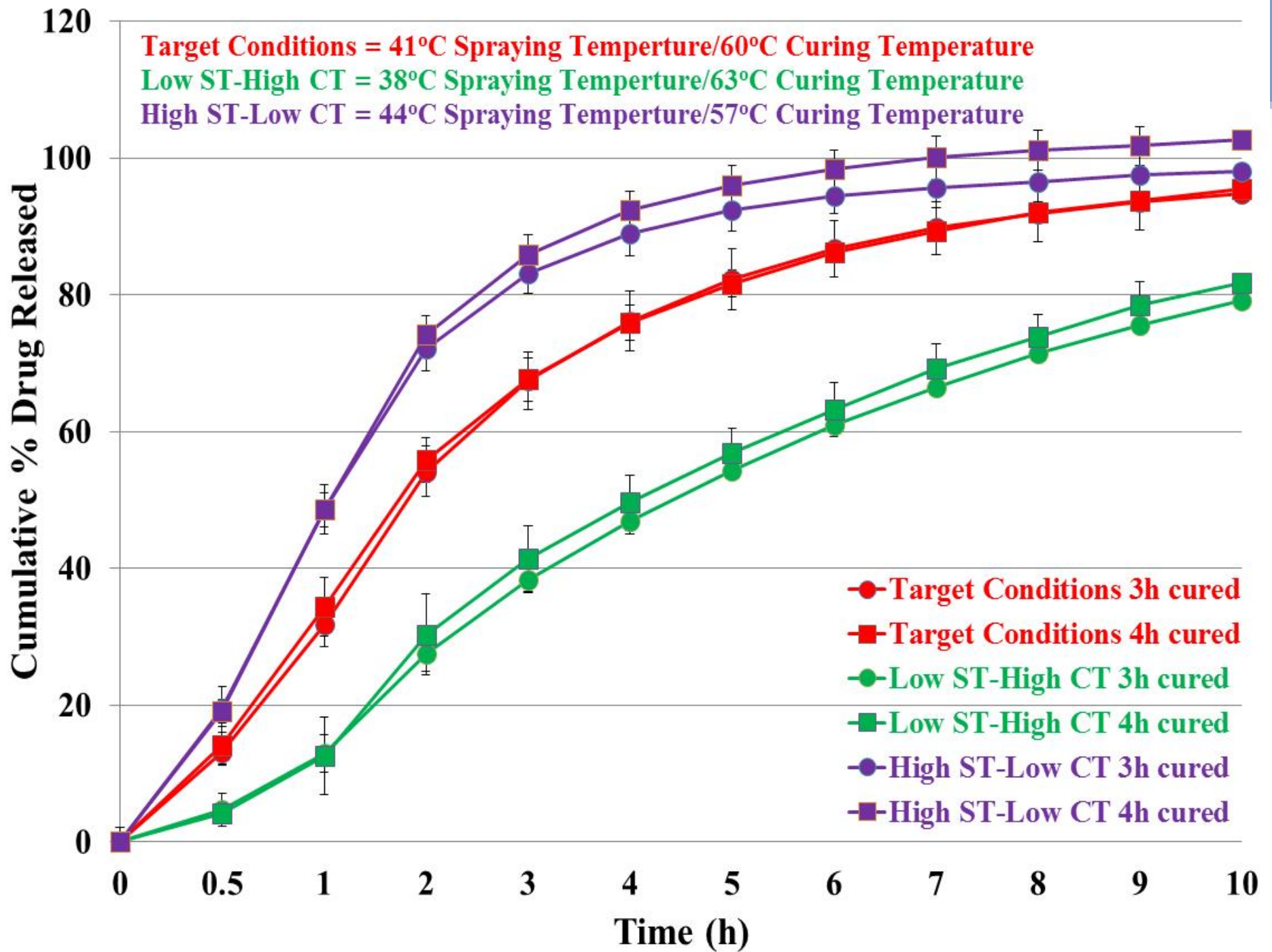


Parameters and Responses

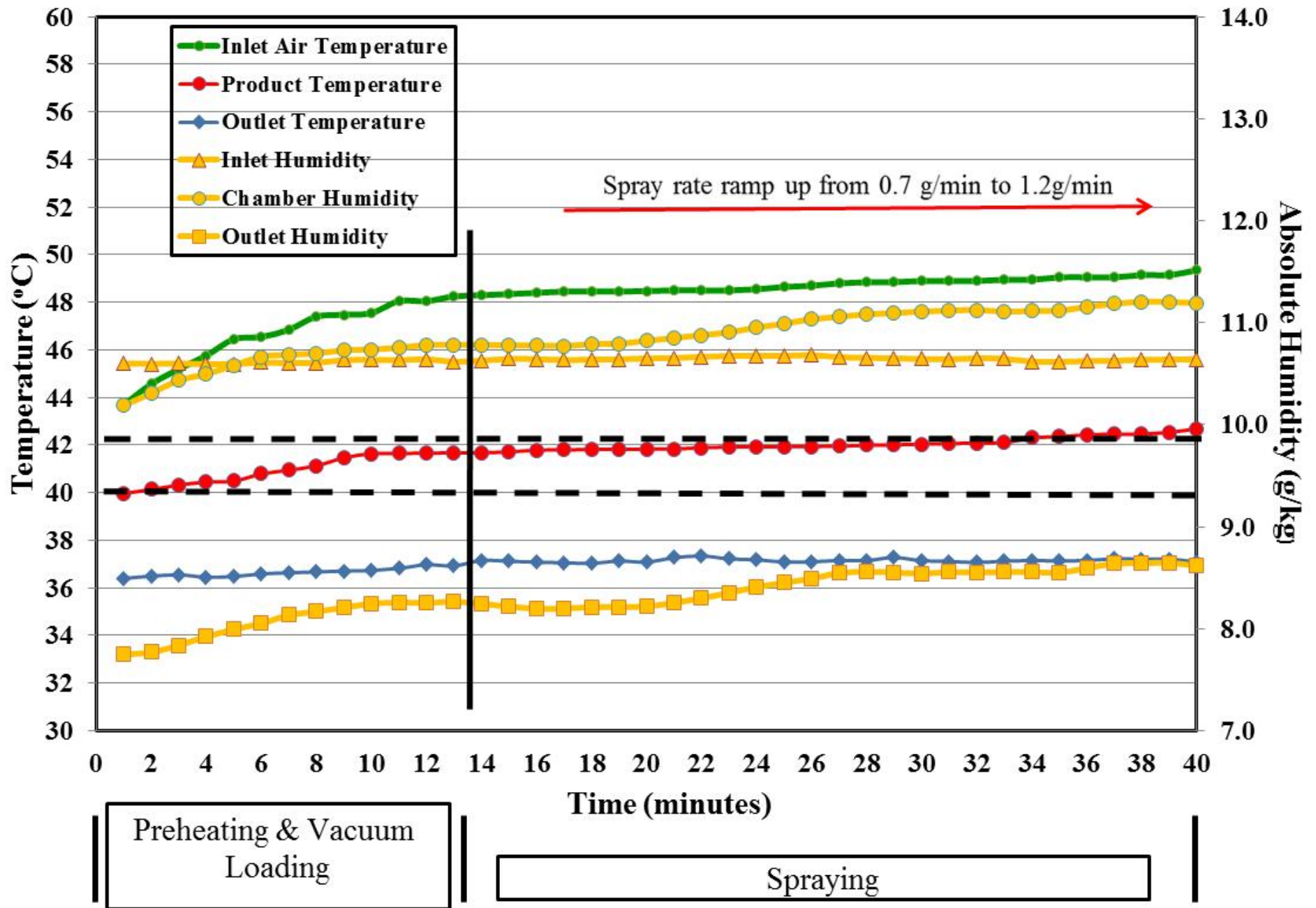
Variable Tested	Unit	Low	High
Product Temperature	°C	40	44
Curing Temperature	°C	57	63
Curing Time	hr	3	4

Responses

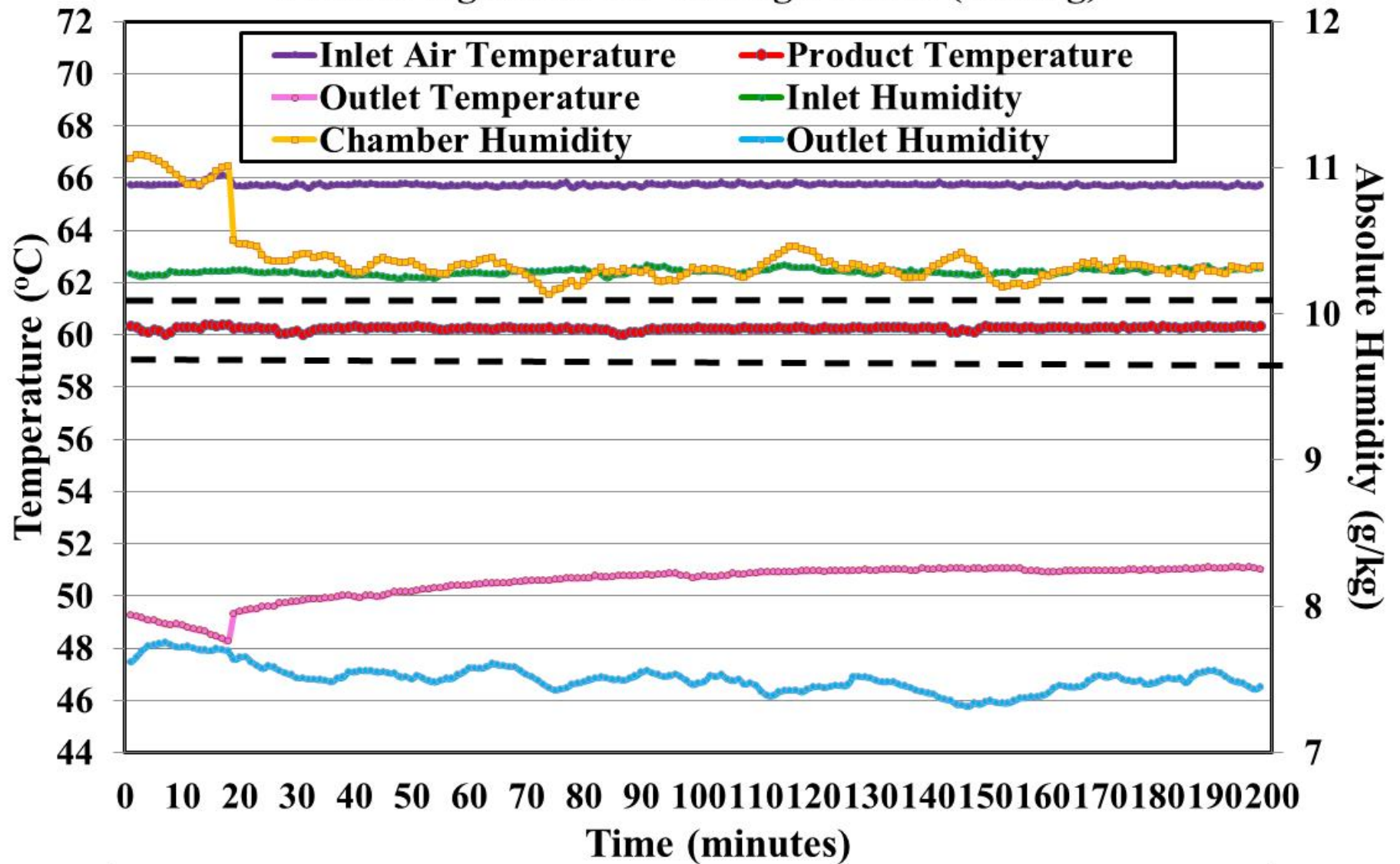
Percent Agglomeration	%	Response	NMT 1%
Percent Yield	%	Response	NLT 98-100%
Assay	%	Response	95-101%
Dissolution 1h	%	Response	NMT 40%
Dissolution 2h	%	Response	NMT 70%
Dissolution 7h	%	Response	NLT 85%



Process Signature for Coating Process - (Spraying)



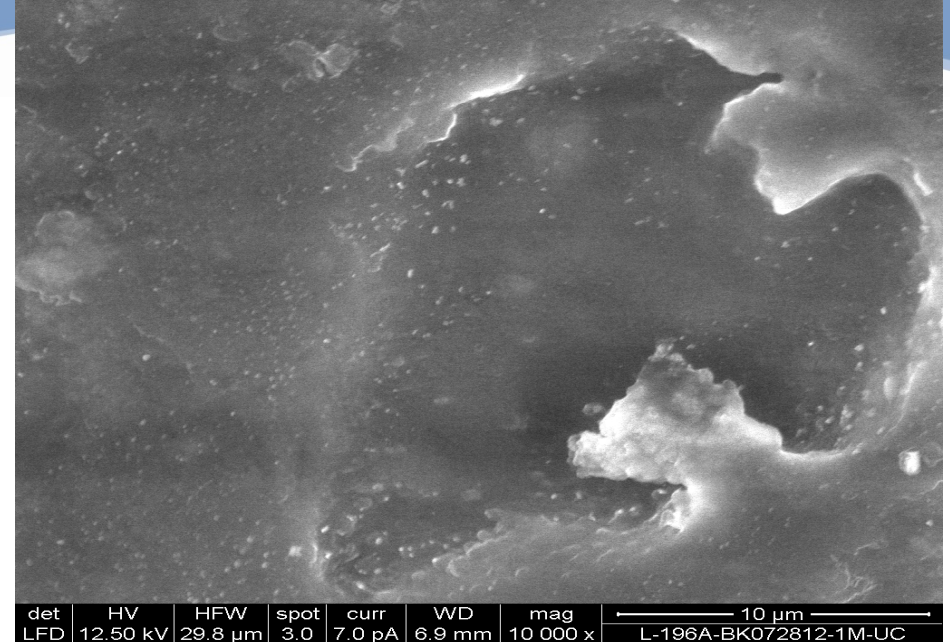
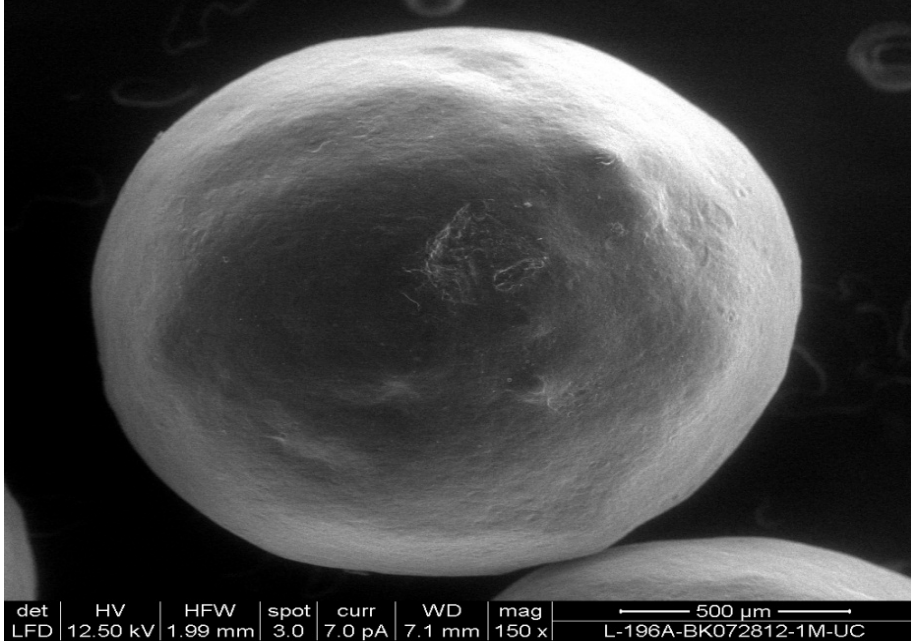
Process Signature for Curing Process (Curing)



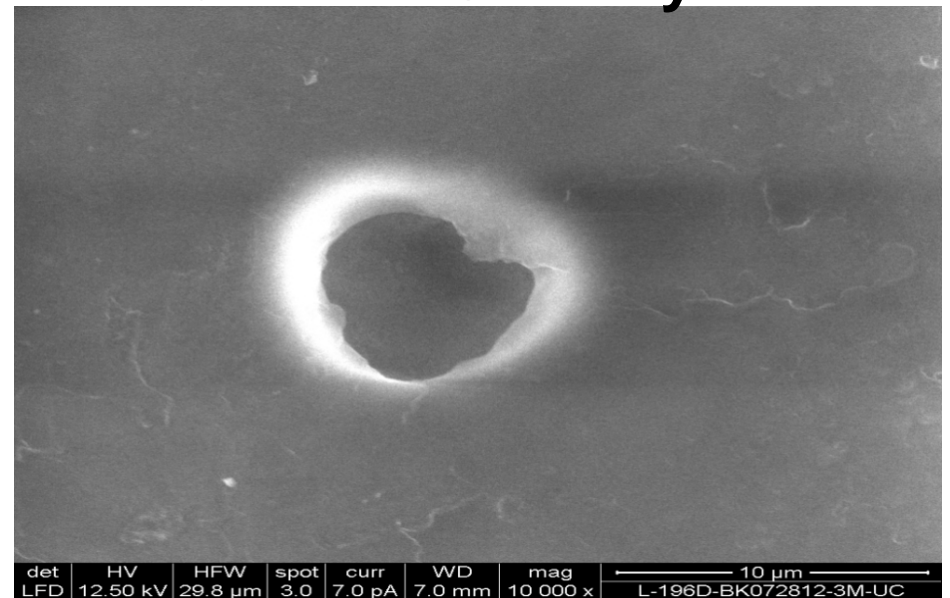
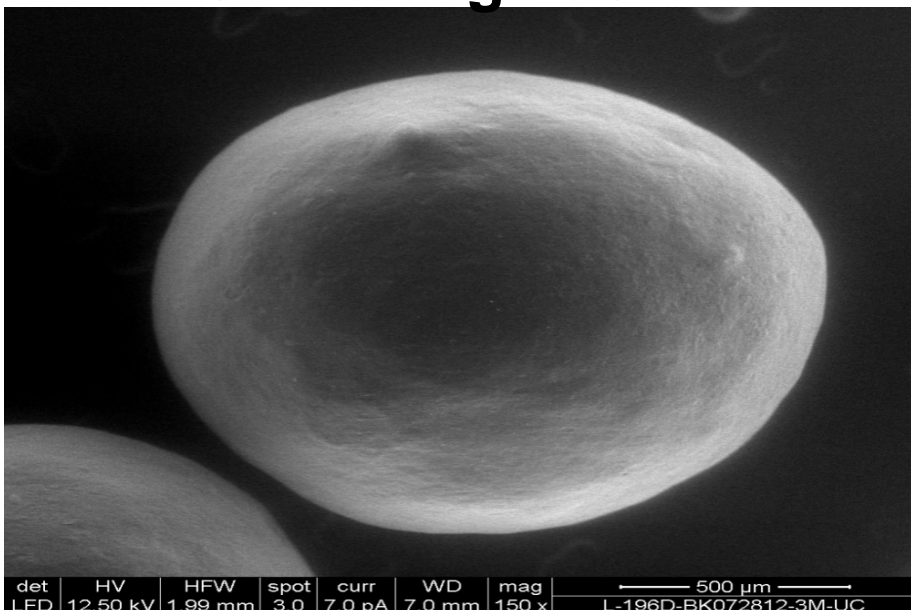
Drying and Curing

SEM Images Uncured Beads – 1 Month Stability

www.fda.gov

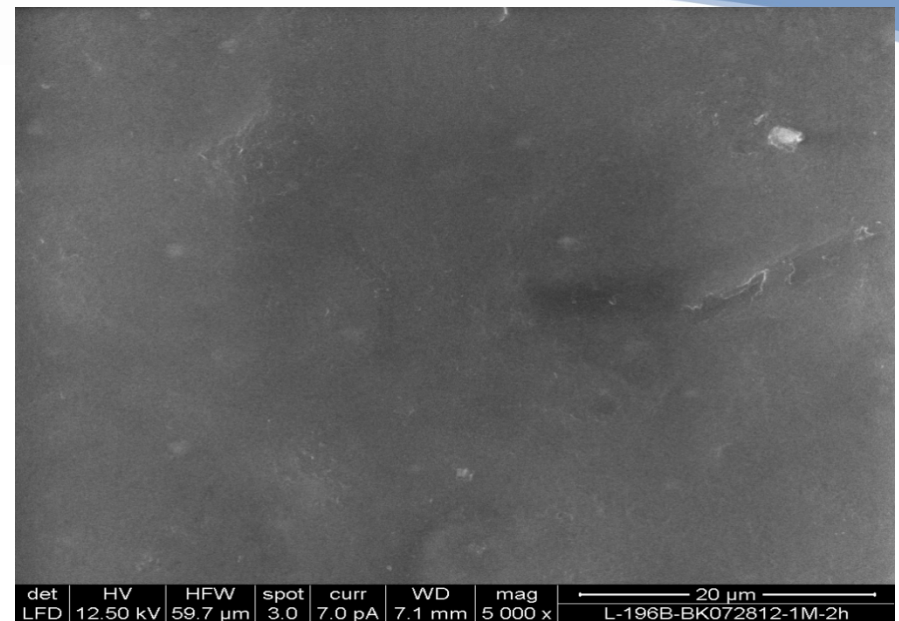
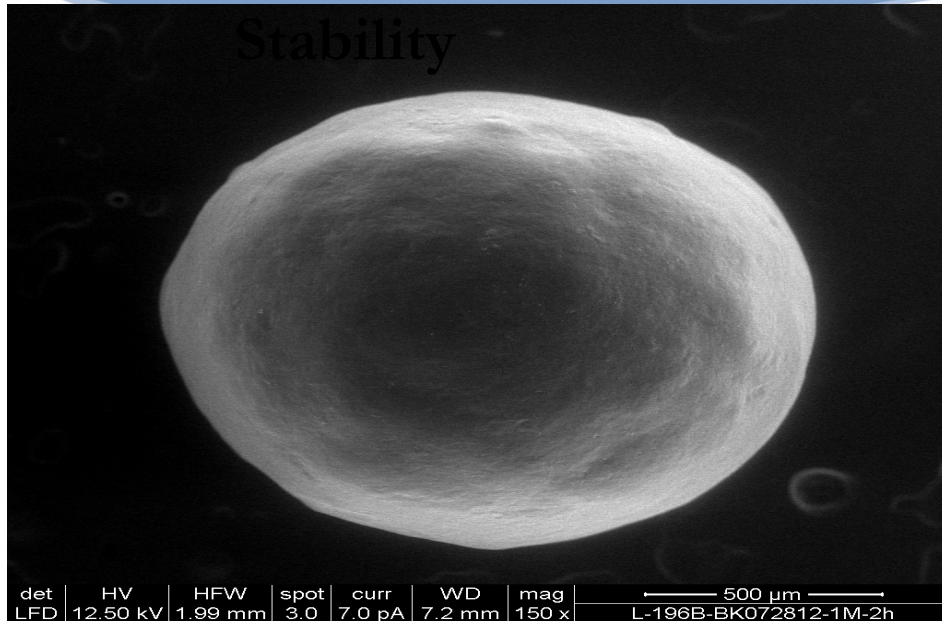


SEM Images Uncured Beads – 3 Month Stability

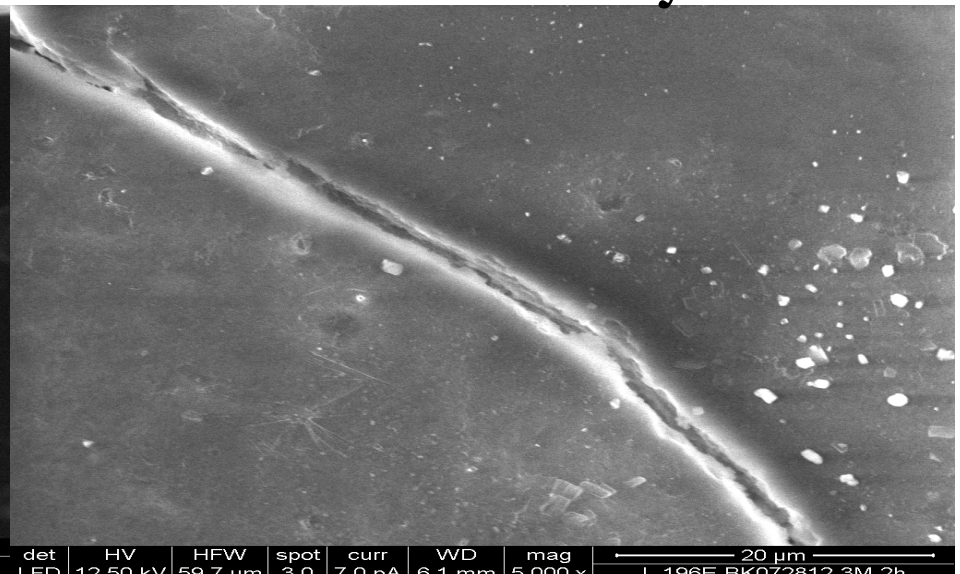
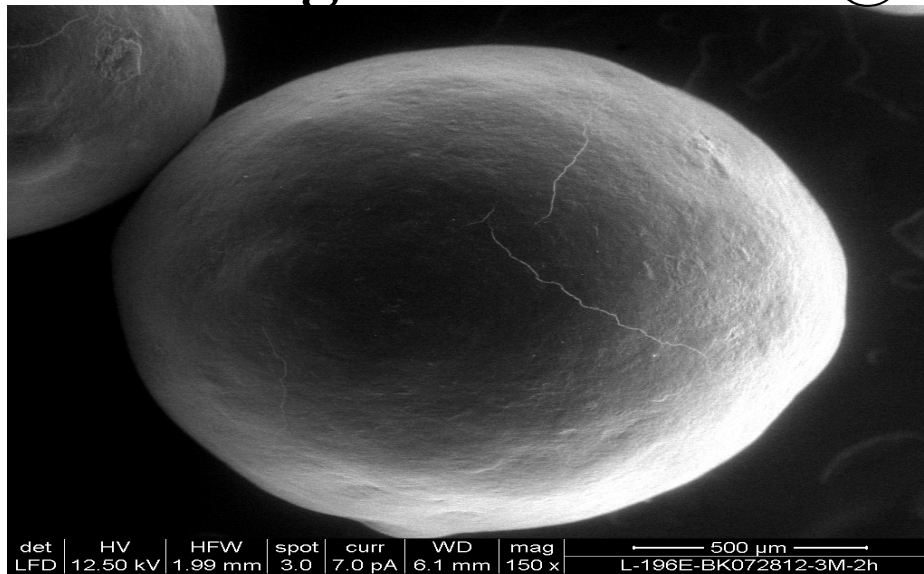




SEM Images Cured Beads @ 2h – 1 Month



SEM Images Cured Beads @ 2h – 3 Month Stability

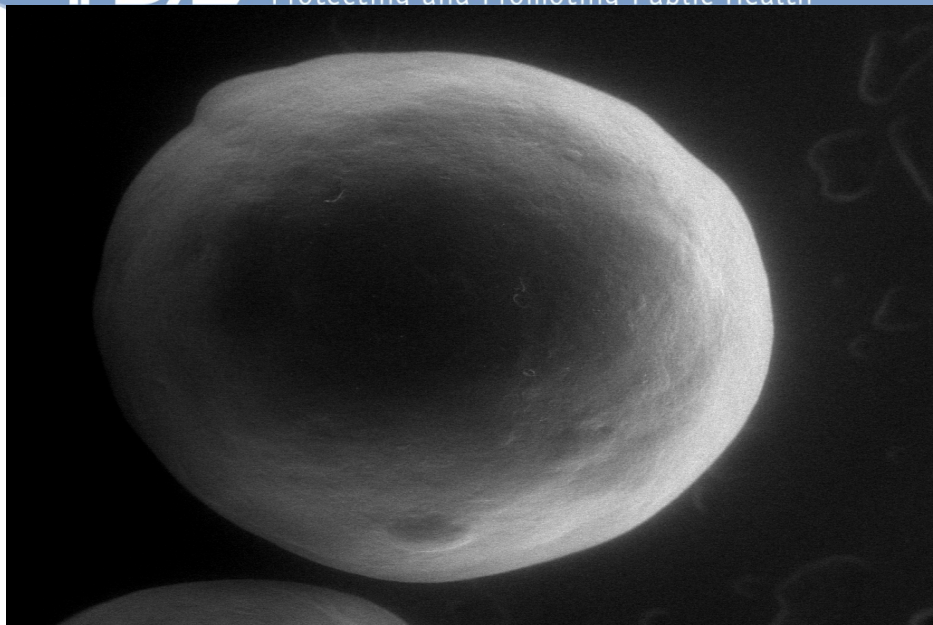




SEM Images Cured Beads @ 4h – 3 Month Stability

U.S. Food and Drug Administration
Protecting and Promoting Public Health

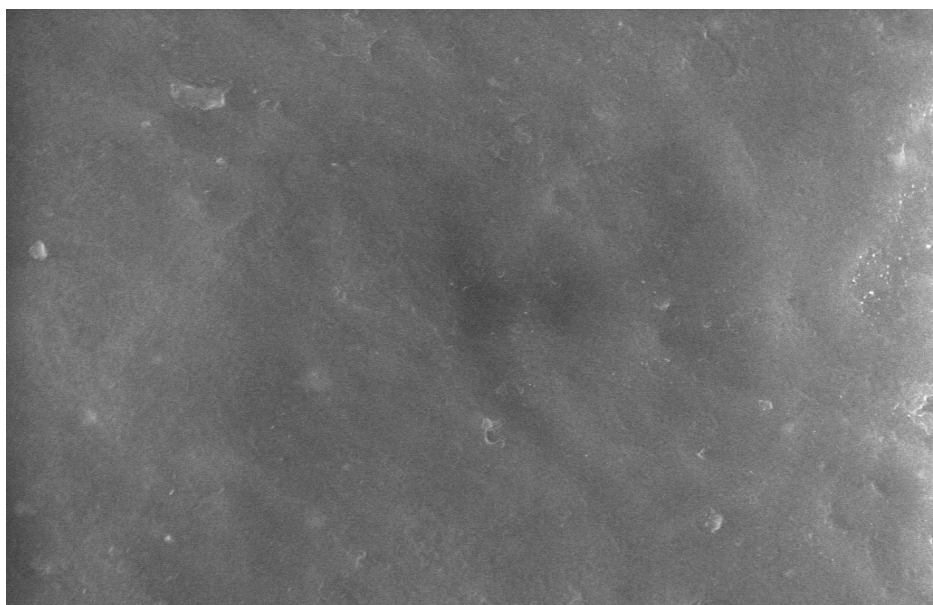
www.fda.gov



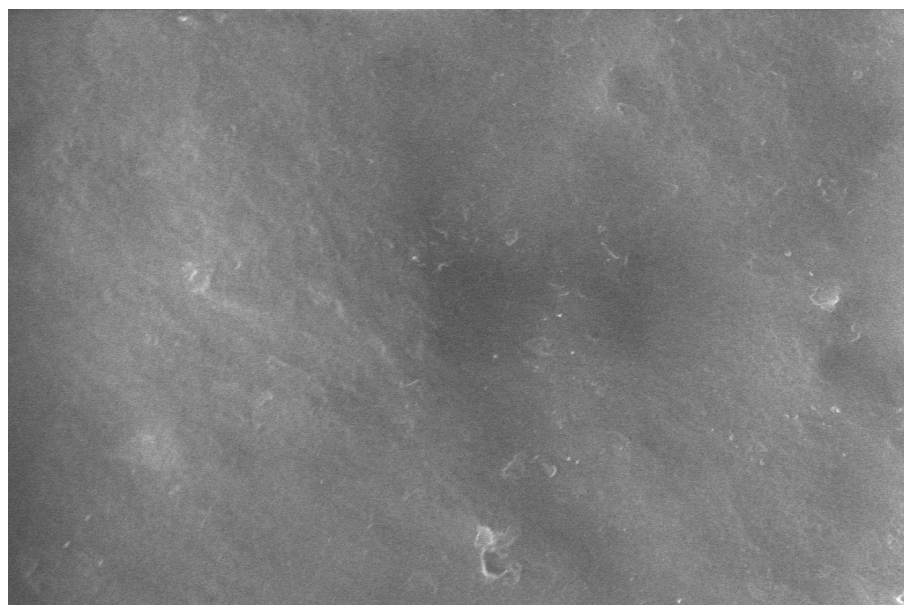
det	HV	HFW	spot	curr	WD	mag	scale
LFD	10.00 kV	1.99 mm	3.0	6.4 pA	6.3 mm	150 x	500 μ m



det	HV	HFW	spot	curr	WD	mag	scale
LFD	12.50 kV	298 μ m	3.0	7.0 pA	6.4 mm	1 000 x	100 μ m



det	HV	HFW	spot	curr	WD	mag	scale
LFD	12.50 kV	59.7 μ m	3.0	7.0 pA	6.4 mm	5 000 x	20 μ m



det	HV	HFW	spot	curr	WD	mag	scale
LFD	12.50 kV	29.8 μ m	3.0	7.0 pA	6.4 mm	10 000 x	10 μ m



Conclusion

- Real time release testing product development can be easily achieved by using a systematic approach where the DOE coupled with risk and statistical models during the development to define the critical process and material parameters, establish the design space and a robust control strategy.



Acknowledgments

- Mr. Bhavesh Kothari
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