Implementing QbD in Dissolution
An option or Must?

Vijay Kshirsagar
Director

SPDS, Disso India, June 2017

Contents

- Background of QbD
- DoE's – Theory, Examples & Control Strategy
- FDA IR Tablet QbD Example

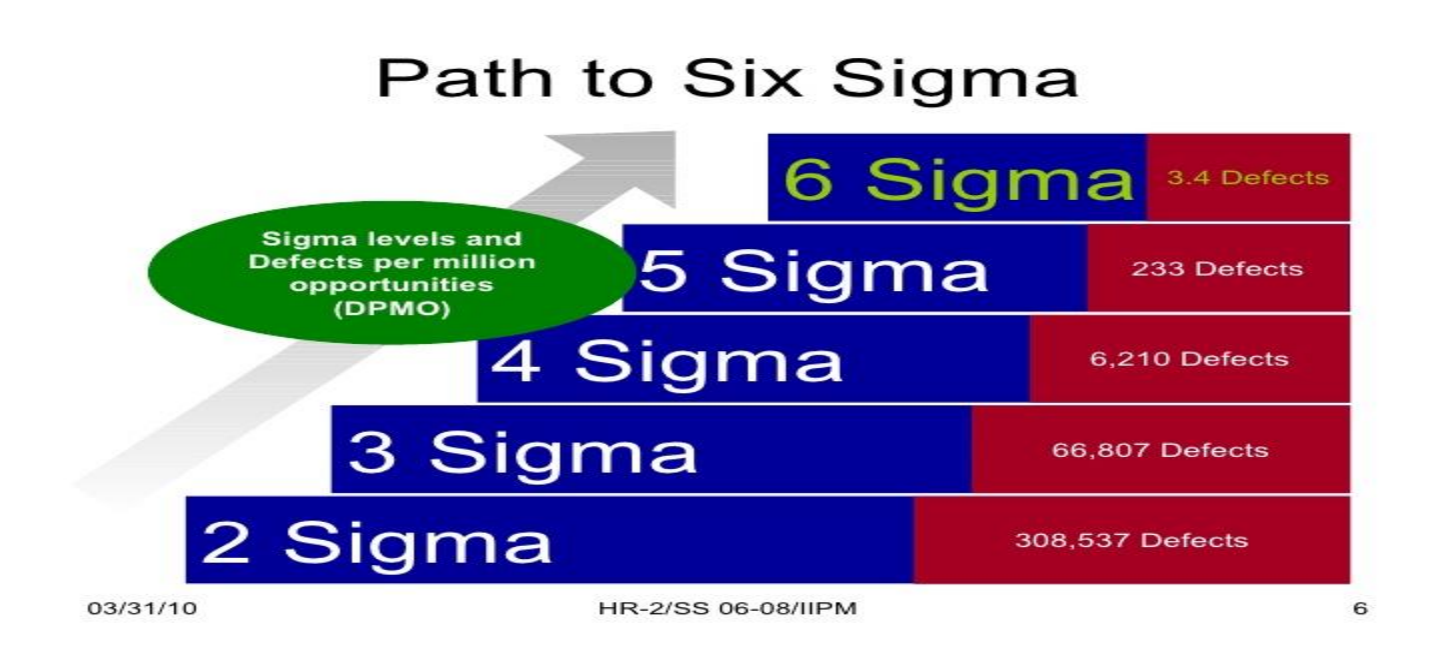
Disclaimer

Every care is taken to base all presentations on current regulatory guidelines & own experiences but finally these are presenters thoughts & can not be construed as a regulatory or SPDS opinion.

Regulators Dilemma

End Quality 6 Sigma Vs **Built in Quality 3 Sigma**

Defects 3.4 PPM **Defects 66807 PPM**



Where do we come from?

- 1980: What happened when the product failed in dissolution testing? It was dissolved forcefully.
- 2015: Now not only that product failure at specified time point is a concern but variation at even one time point during profile study is a cause of concern?
- What has been the cause of this transformation?
- Can the sample of 6 tablets collected from a batch of 1 M tablets predict correct dissolution pattern for the entire batch?

Regulatory Query, Then & Now

2006	2014
Your API specification has the particle size specification of 85% less than 40 micron. What is the permitted size for remaining 15% particles? **Reply:** Remaining 15% are between 40-100 micron. Accepted by the agency.	Your API specification mentions the particle size specification of 85% less than 40 micron & 15% between 40 to 100 micron. Considering the low solubility of the molecule , you need to establish particle size distribution pattern & provide the dissolution results of experiments carried out to prove the entire specified design space.

Driving Force Behind QbD

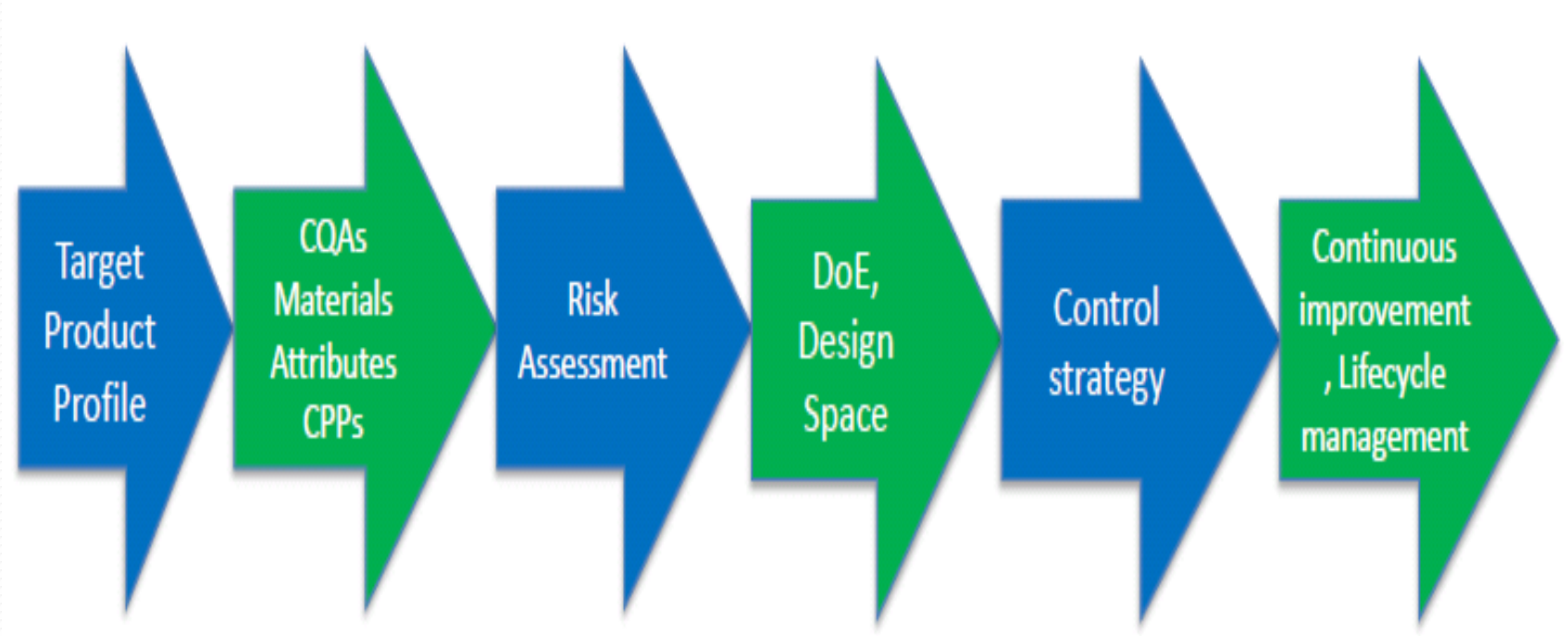
“Quality can not be tested into products; it has to be built in by design”(ICH Q8/ Q11 on product/ drug substance development)

What is Quality By Design ?

As per ICH Q8/Q11 :

"QbD is a systemic approach to development that begins with predefined objectives & emphasizes product & process understanding and process control, based on sound science & quality risk management."

QbD Approach (Important Stages)

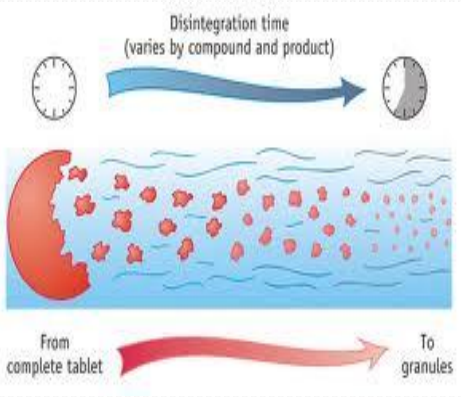


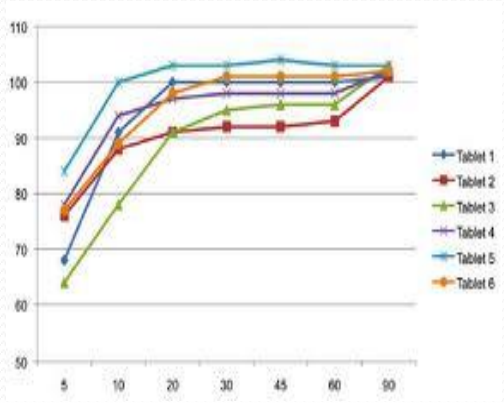
Pay Attention to 4 D's

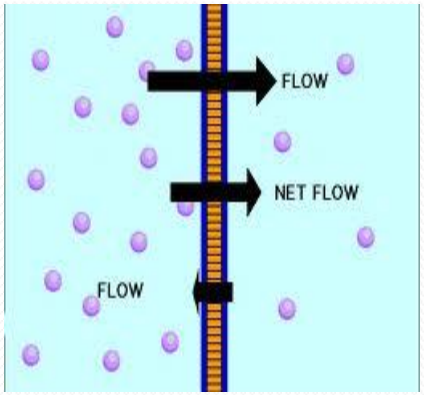
- Disintegration time is the time required for a dosage form to break up in to granules of specified size
- Dispersion is actually meant to distribute the mass evenly thus moving the mass from higher concentration to lower concentration
- Dissolution is the rate of mass transfer from a solid surface into the dissolution medium
- Diffusion refers to the process by which molecules separated by a partition, intermingle as a result of their kinetic energy of random motion.

Understanding Dissolution Science

- Disintegration
- Dispersion
- Dissolution
- Diffusion







Sink Conditions

- Sink condition refers to the volume of medium which is at least three times that is required in order to form a saturated solution of API
- In the absence of sink conditions, investigate methods to enhance solubility, e.g. use of a surfactant
- If a surfactant is used, its concentration should be properly justified (e.g. <2% SLS).

Quality Target Product Profile

QTPP Element	Target	Justification
Dosage Form	Tablet	To match innovator
Dosage design	Immediate Release	To match innovator
Route of Admin.	Oral	To match innovator
Pharmacokinetics	Matching Cmax/Tmax	To pass BE studies
Container/Closure	Must provide adequate protection & Cost Efficient	For stability of product & financial viability of the firm
Stability	Stable for 36 Months	To match innovator
Score Line	To have a deep score	Tablet should break in 2 equal halves

QA's of API (Related to Dissolution)

Quality Attributes	Target	Is this CQA ?	Justification
Appearance	Color & Shape	No	Not linked to Safety & Efficacy
Assay & Particle Size	100% w/w & matching spread	Yes	Impacts dissolution
Moisture Content	< 0.5%	No Exceptions ?	Higher moisture leads to polymorphic change in some cases
Intrinsic Dissolution	NLT 80%(Q) in 20 Mts	Yes	Impacts Bioavailability of Drug Product
Individual unknown Impurities	NMT 0.1%	No	Does not impact dissolution of the API/Drug Product

QA's of DP (Related to Dissolution)

Quality Attributes	Target	Is this CQA ?	Justification
Score line	To have similar dissolution for 2 halves	Yes	Patient should get same drug content
Hardness	To have optimum hardness	Yes	To facilitate disintegration & dissolution of product
Content Uniformity	To have similar drug content in all units	Yes	Impacts dissolution

Establishing Better Linkage

DP CQAs	Drug Substance Attributes		
	Particle Size	Polymorphic Nature	Moisture Content
Assay	Medium	Low	High
CU	High	Low	Low
Dissolution	High	Medium	Low
Impurities	Low	Low	High

Risk Assessment of Method (Scale of 1-5)

Risk	Probability	Severity	Detection	RPN
Improper IVIVC	3	5	4	60
Non discriminative method	3	4	3	36
Improper Deaeration	3	3	3	27
Improper Filter	3	2	2	18

Prerequisite of successful DoE

- Basic statistical knowledge
- Specialized training on software
- Mimic the real life scenario
- Use similar equipments, Instruments in terms of MOC & principle of operation
- Similar measurement tools

* **Thanks to Minitab for granting me free DOE software license for making hypothetical experiments shown in later slides.**

Conventional v/s DoE approach

CONVENTIONAL APPROACH

- Changing one factor at a time.
- May not give real optimum output
- Leads to many experiments and little information.
- Variability may not addressed
- No quantification of interactions.

DOE APPROACH

- Changing all factors same time.
- Investigates entire region in a organized way & provide reliable basis for decision making.
- Provides more precise info. with fewer experiments.
- Variability is addressed
- Quantification of interactions.

Design of experiments (DoE)

Definition:

"*A structured, organized method for determining the relationship between factors affecting a process and the output of that process.*"

Applications :

- Development of new products/processes
- Development of Analytical Methods
- Enhancement of existing products & processes.
- Screening important factors.
- Optimization of production costs

Steps involved in DOE

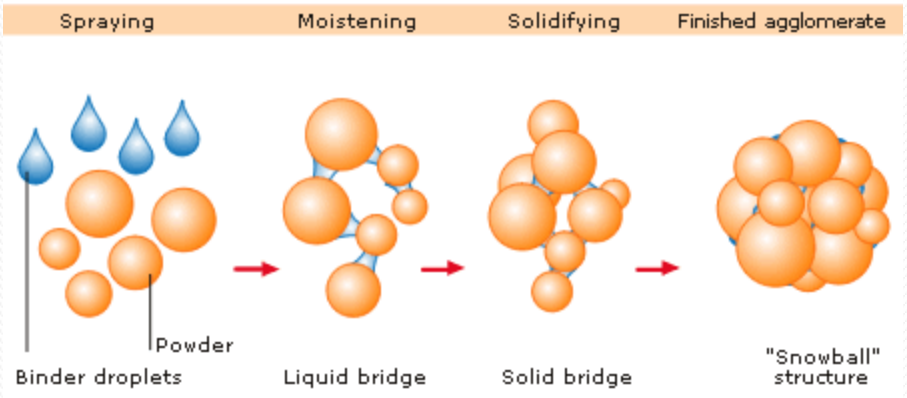
- Define Factors

  (material, process, equipment, environment)
- Define Responses

  (critical quality attributes)
- Create Design
- Construct Model
- Evaluate Model
- Interpret & Use Model (Make Decisions)

Process Attributes

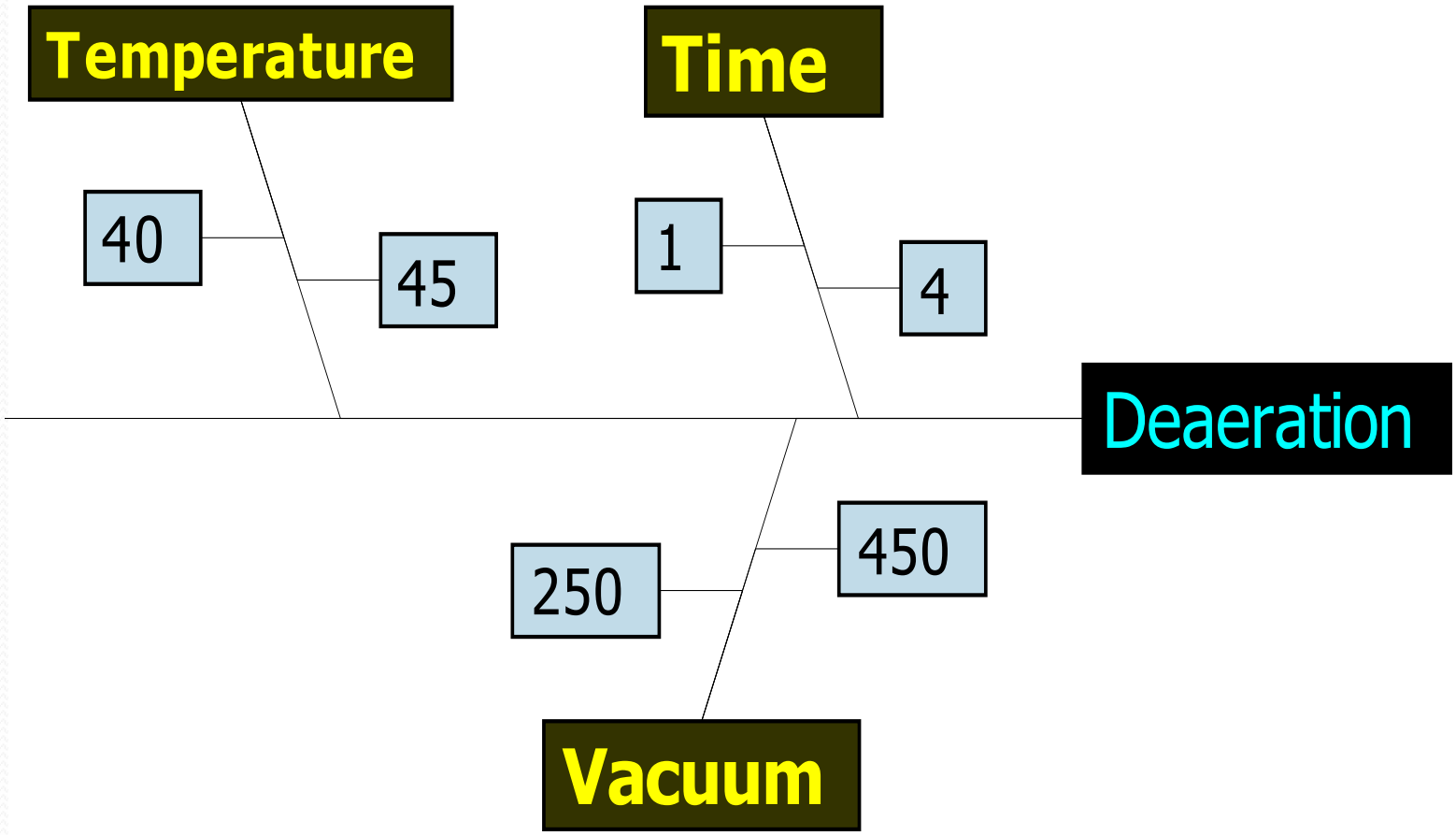
- Qualitative and quantitative excipient changes
- Manufacturing parameters
  - Granulation
  - Lubrication
  - Blend time
  - Compression force
  - Drying parameters



SOME DoE EXAMPLES

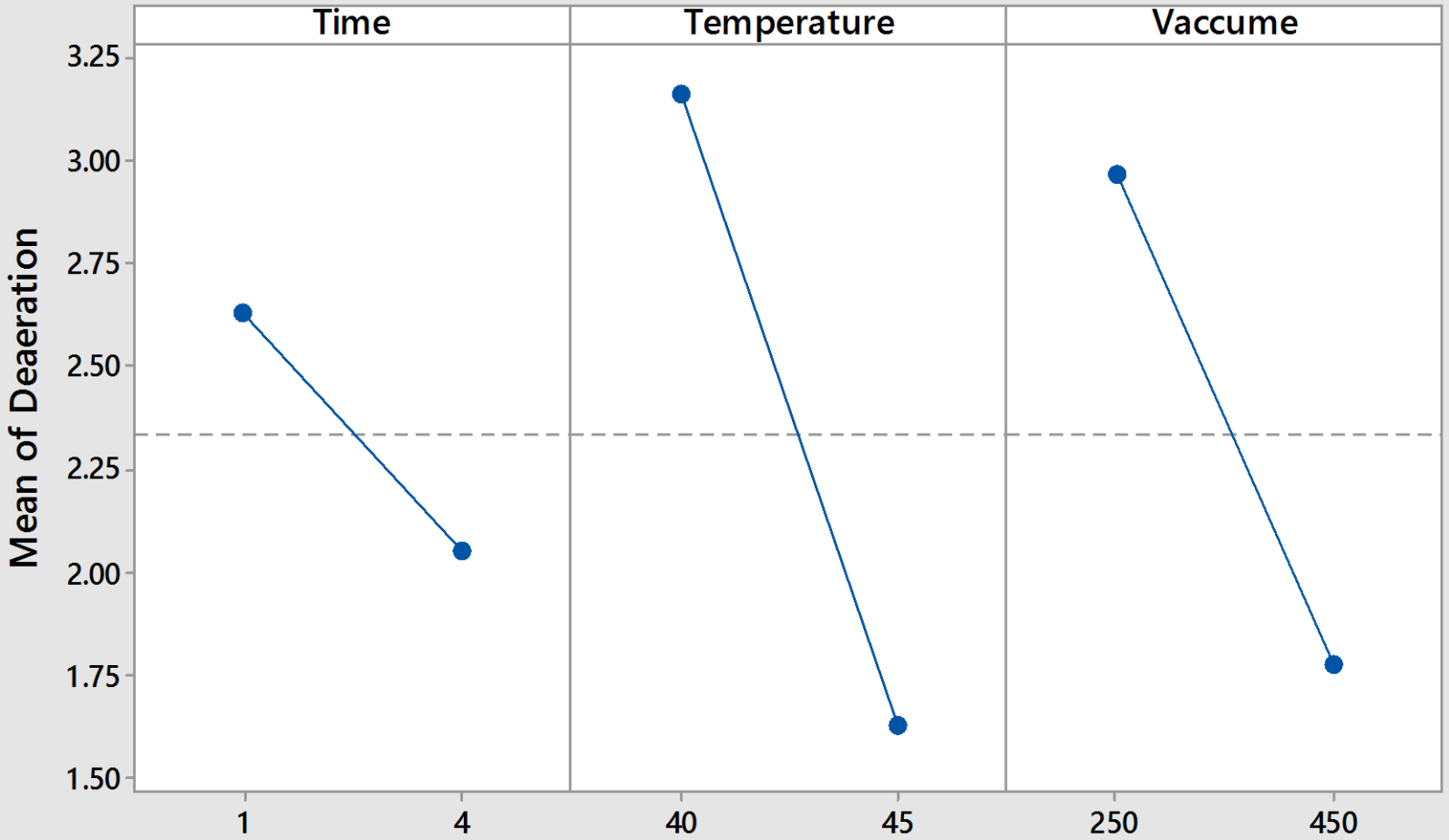
(CREATED ON PAPER JUST FOR ILLUSTRATION)

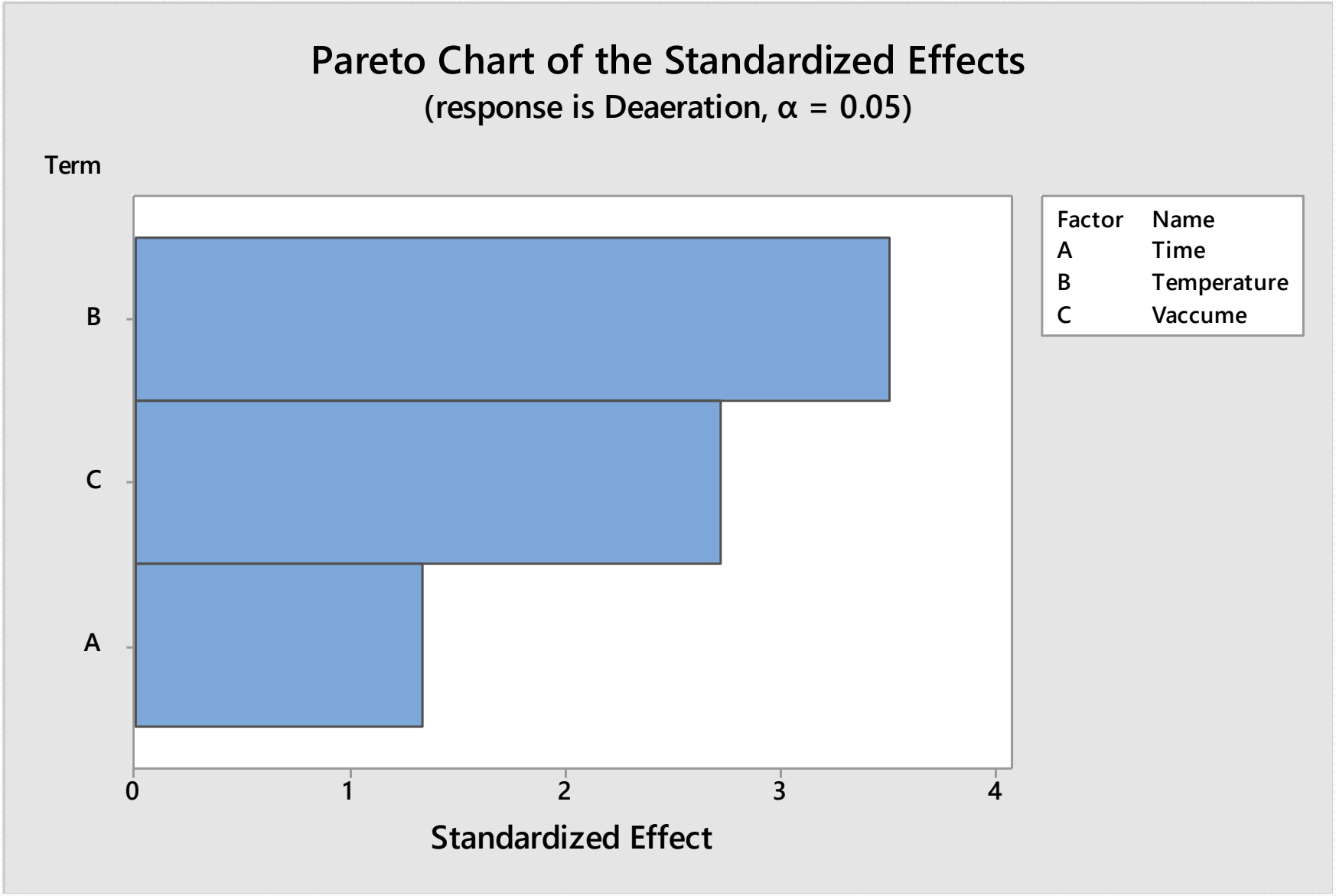
Optimization of Deaeration Procedure



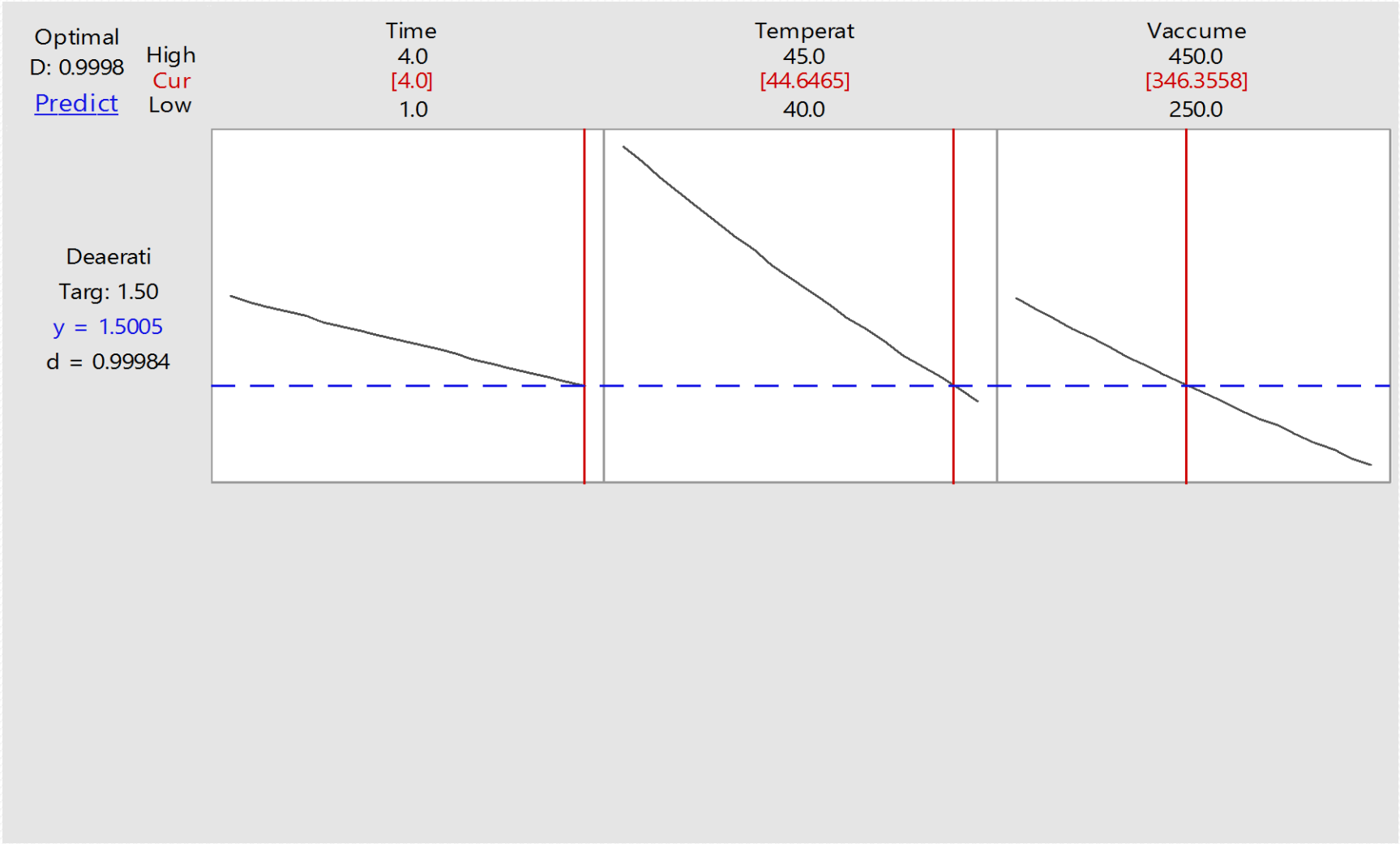
Full factorial Design, 3 factors/2 levels

C1	C2	C3	C4	C5	C6	C7	C8
StdOrder	RunOrder	CenterPt	Blocks	Time	Temperature	Vaccume	Deaeration
4	1	1	1	4	45	250	4.0
5	2	1	1	1	40	450	3.0
2	3	1	1	4	40	250	5.0
1	4	1	1	1	40	250	4.0
3	5	1	1	1	45	250	7.0
7	6	1	1	1	45	450	3.5
6	7	1	1	4	40	450	5.0
8	8	1	1	4	45	450	3.0

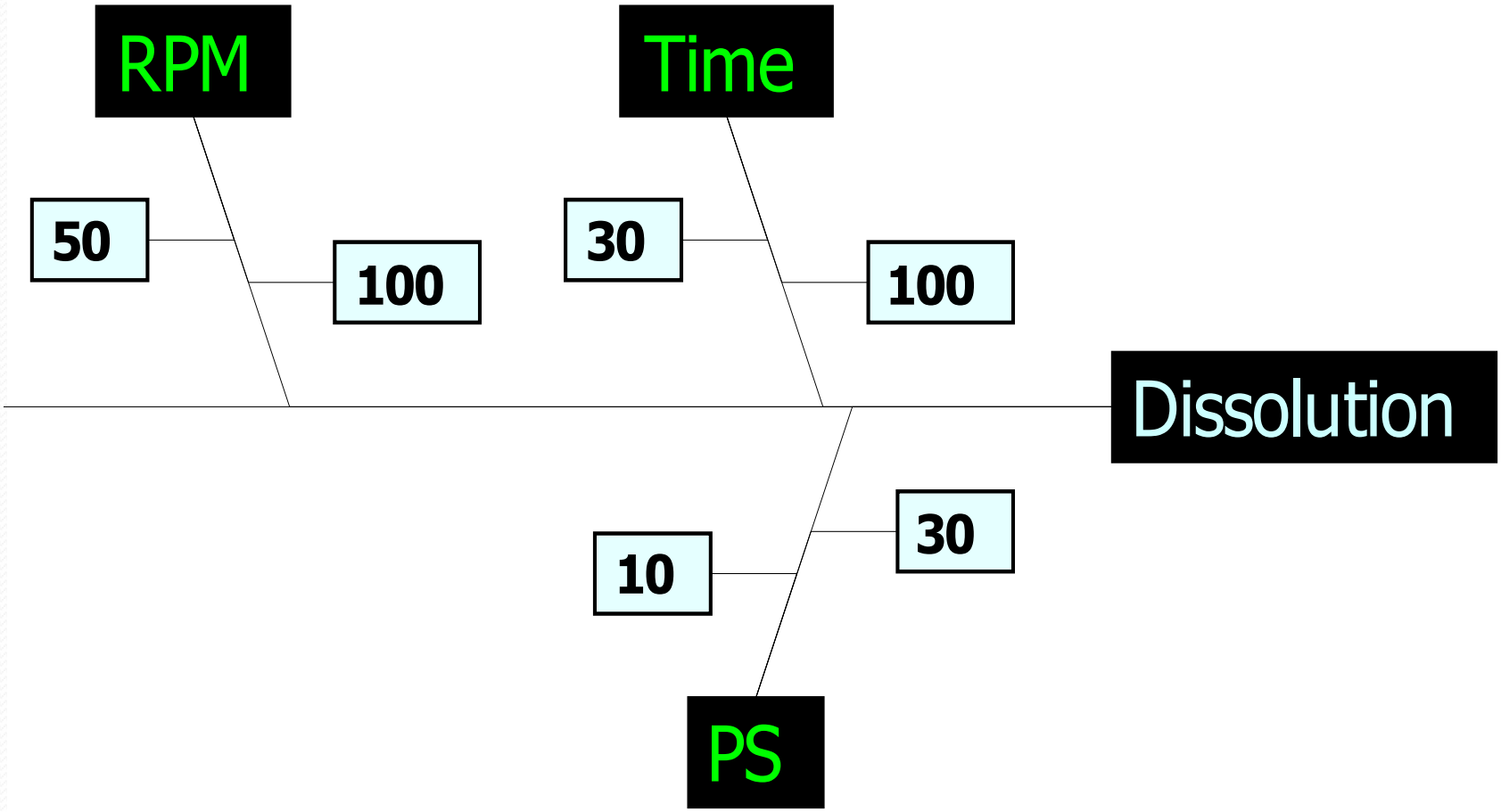

Main Effects Plot for Deaeration
Fitted Means
Time
Temperature
Vaccume
Mean of Deaeration
3.25
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1
4
40
45
250
450


Pareto Chart of the Standardized Effects
(response is Deaeration, α = 0.05)
Term
B
C
A
0
1
2
3
4
Standardized Effect
Factor Name
A Time
B Temperature
C Vaccume

Deaeration Optimization Plot



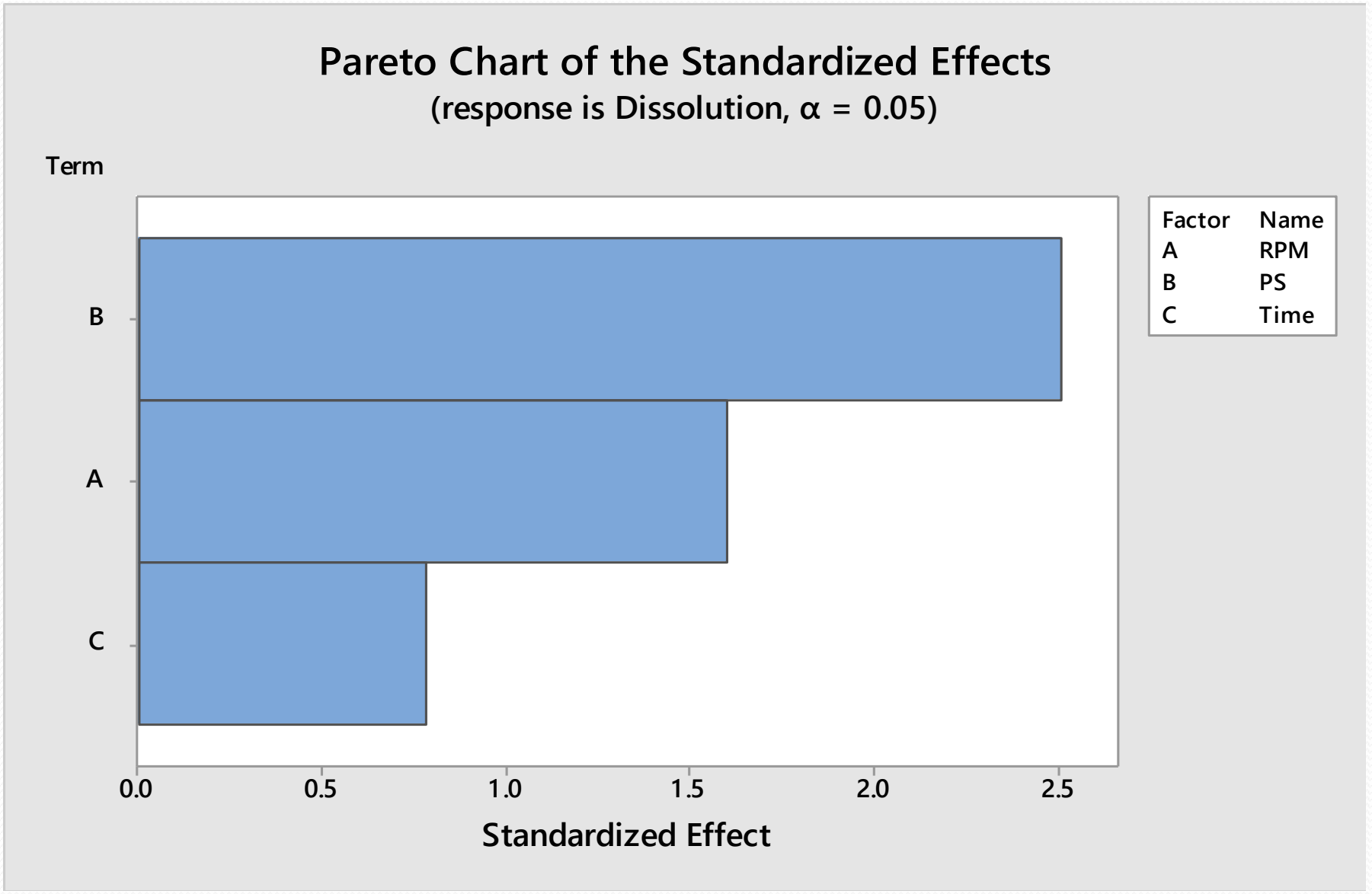
Dissolution Design of Experiments

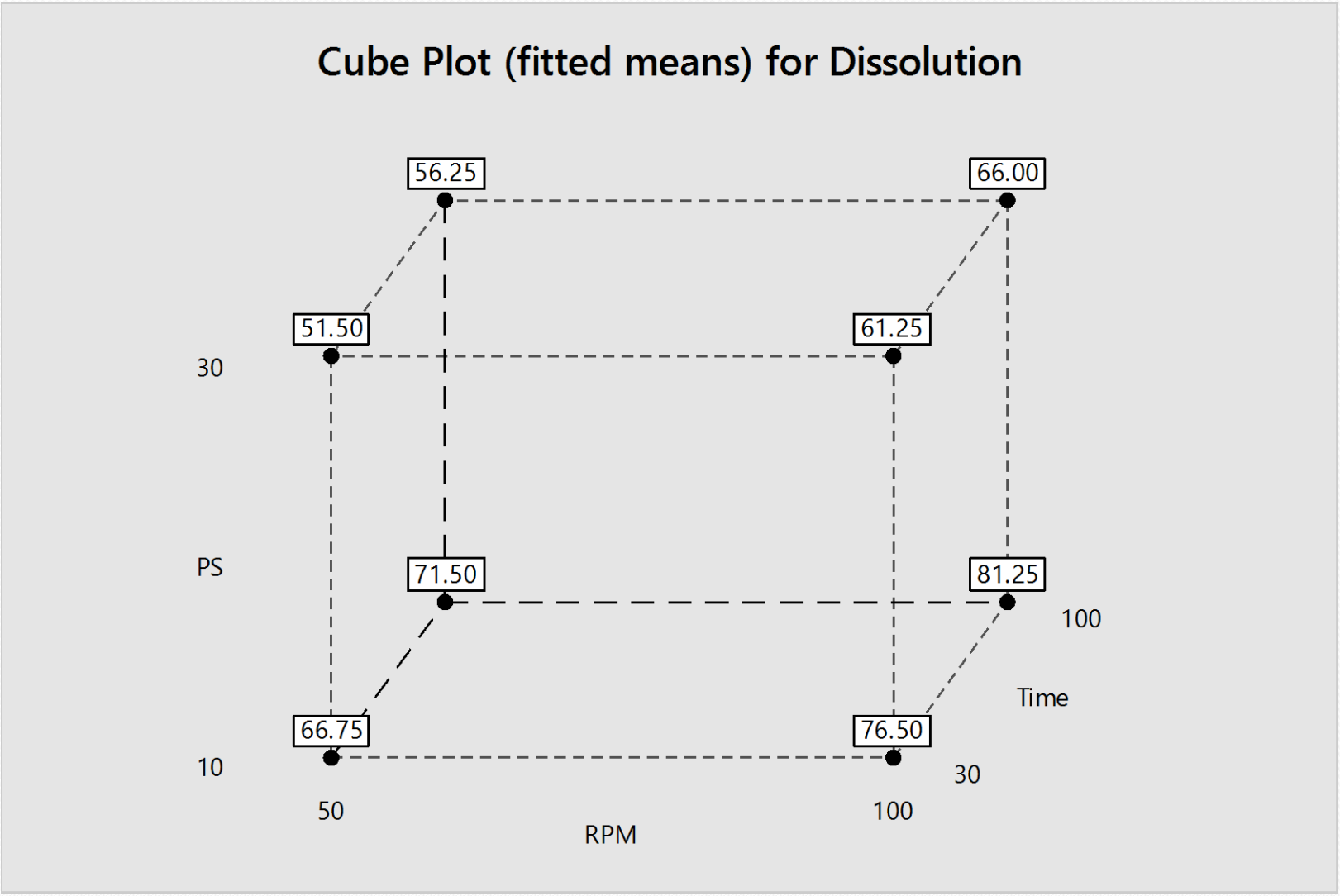


Full factorial Design, 3 factors/2 levels

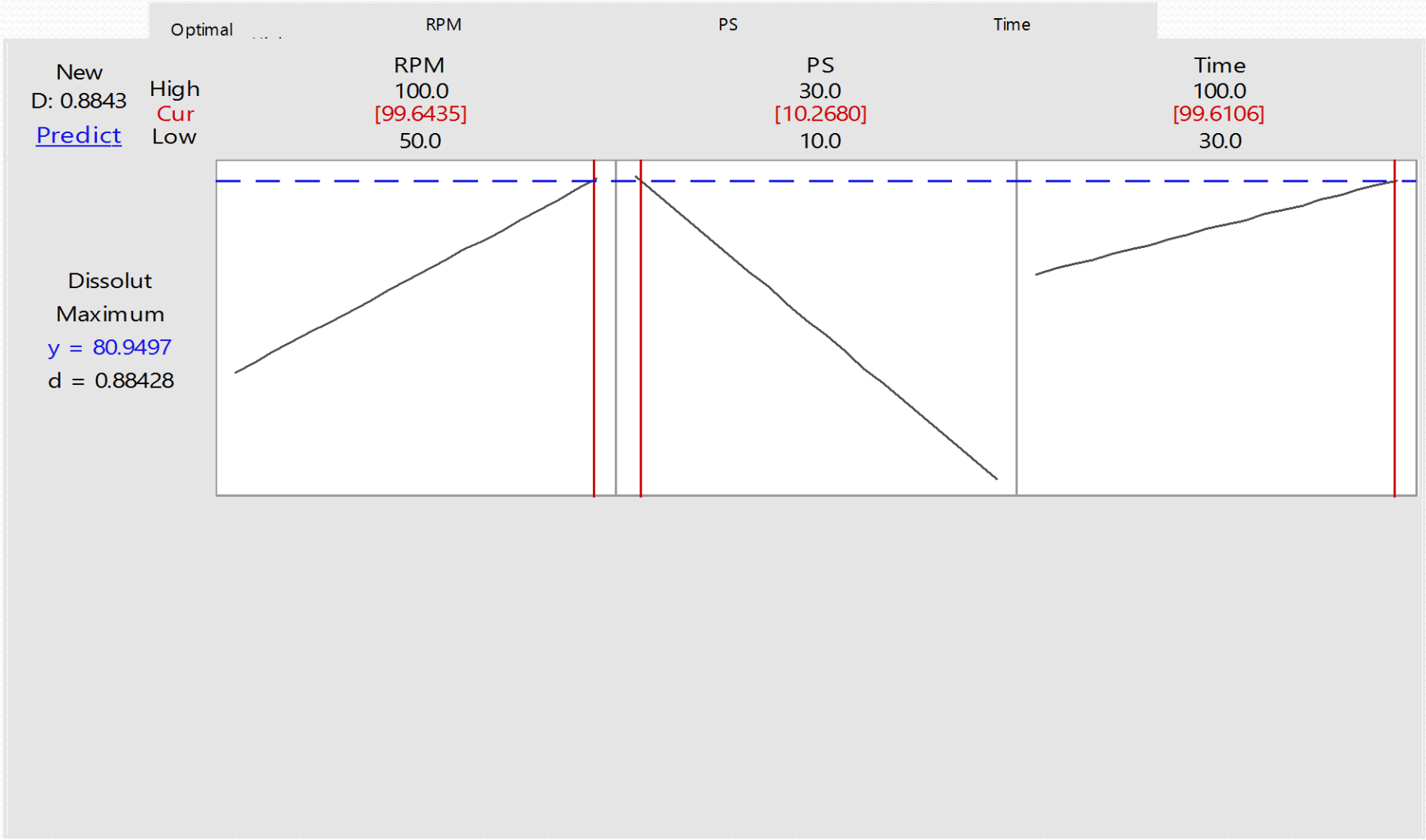
Worksheet 1 ***

	C1	C2	C3	C4	C5	C6	C7	C8
	StdOrder	RunOrder	CenterPt	Blocks	RPM	PS	Time	Dissolution
1	8	1	1	1	100	30	100	65
2	4	2	1	1	100	30	30	55
3	3	3	1	1	50	30	30	50
4	5	4	1	1	50	10	100	60
5	2	5	1	1	100	10	30	80
6	7	6	1	1	50	30	100	65
7	6	7	1	1	100	10	100	85
8	1	8	1	1	50	10	30	71
9								
10								


Pareto Chart of the Standardized Effects
(response is Dissolution, α = 0.05)
Term
B
A
C
0.0
0.5
1.0
1.5
2.0
2.5
Standardized Effect
Factor Name
A RPM
B PS
C Time


Cube Plot (fitted means) for Dissolution
56.25
66.00
51.50
61.25
30
PS
71.50
81.25
100
Time
66.75
76.50
10
30
50
100
RPM

Dissolution Optimization Plot

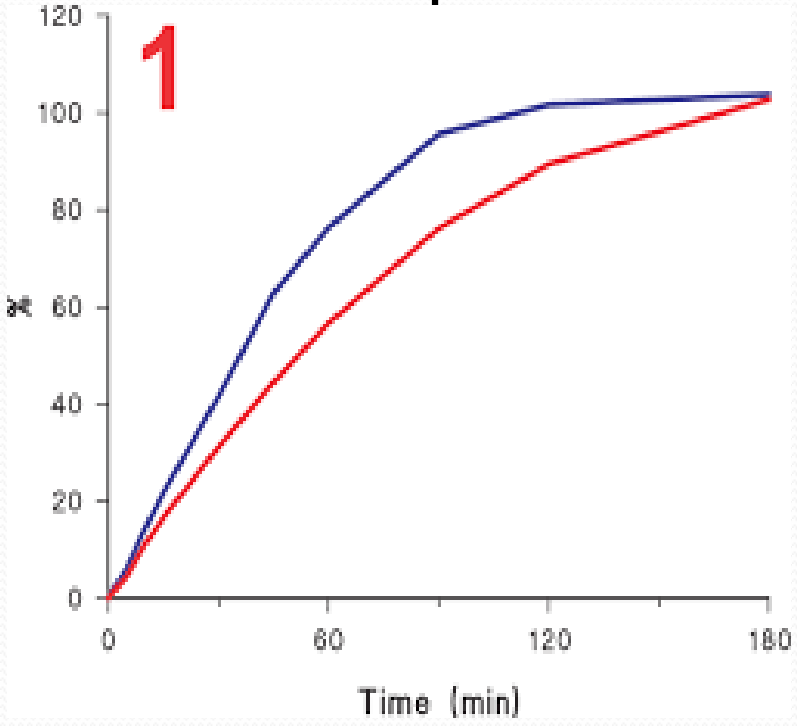


Control Strategy

- Do extensive literature search
- Do not rely solely on Pharmacopeial/OGD methods
- Minimize the number of invalidated OOS's
- Do not over commit on the specifications
- Remember that it is not a magic stick

Here Discrimination is not bad!

- Discrimination in Dissolution simply means that method tells the difference between a good and bad formulation
- What is bad? Non-bioequivalent!



Robustness of Discriminatory Method

- While discrimination is important, your method should not be so sensitive that minor differences in the test lead to different results.
- Analyst to analyst
- Lab to lab
- Vendor differences
- Over sensitive method parameters

What FDA has got to say?

Note to Reader: A pharmaceutical development report should document the selection of the dissolution method used in pharmaceutical development. This method (or methods) may differ from the FDA-recommended dissolution method and the quality control method used for release testing.

Ref: Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms ,US FDA Guideline.

Media Cautions

- Be careful with water
- Quality can differ b/w sites
- Quality can differ b/w DI systems, filters, etc.
- Check pH before and after run to ensure buffering capacity is acceptable
- Beware of methods needing tight pH limits
- Do not use SLS with Potassium Phosphate Buffers – Sodium Phosphate Only

Media Degassing

- Media should be degassed per USP unless another approach is validated
- Heat to 41-45 C
- Vacuum degas through 0.45um filter
- Hold under vacuum 5 minutes after media has passed through
- Helium sparging is acceptable but not Nitrogen, sonication is not desired

Agitation Rate

- Should be sufficient to allow for media to interact with dosage form
- Too much agitation can result in non-discriminatory profiles
- Baskets – 50-100 RPM
- Paddles – 25-100 RPM

Use of Sinkers

- Dosage forms should not float or move during the dissolution as this will greatly increase variability. A Sinker is necessary if it is floating or moving is seen
- Sinkers should be chosen based on:
  - •Media access •Weight •Reproducibility
  - •Hydrodynamic Impact

Coning Phenomenon

- Coning is a normal and expected occurrence for disintegrating dosage forms,
- Coning may still be present if drug is fully dissolved.
- Cone should be moving somewhat,
- If Severe, Peak Vessel or Apparatus 3 (Reciprocating Cylinder) can be used with justification

Cross Linking

- Cross-linking of capsule shells can result in hardened and chemically resistant shells.
- Delay opening
- Trap Drug Product
- Pellicle Formation. If Cross-Linking is seen, testing with pepsin or pancreatin should be performed
- Opening time important regardless of cross-linking

QbD for IR Tablet – US FDA Example

Background

- BCS Class II compound Acetryptan
  (Low Solubility/High Permeability)
- Poor Aqueous solubility (less than 0.015 mg/Lt)
- Method to act as best predictor of equivalent pharmacokinetics to the RLD
- Immediate release product
- Dissolution in the stomach & absorption in the upper small intestine is expected which suggests the use of dissolution medium with low pH

Recommended USP Method

- 900 ml of 0.1N HCl with 2% SLS
- USP Apparatus 2
- RPM : 75
- Initial developed formulation exhibited rapid dissolution of >90% in 30 Mts, comparable to RLD
- So a challenge to make a formulation which will perform same as RLD in vivo.
- So solubility in different media was checked

Solubility in different media

Media	Solubility (mg/ml)
*Biorelevant FaSSGF	0.12
Biorelevant FaSSIF-V2	0.18
0.1N HCl with 0.5 % SLS	0.075
0.1N HCl with 1.0 % SLS	0.15
0.1N HCl with 2.0 % SLS	0.3

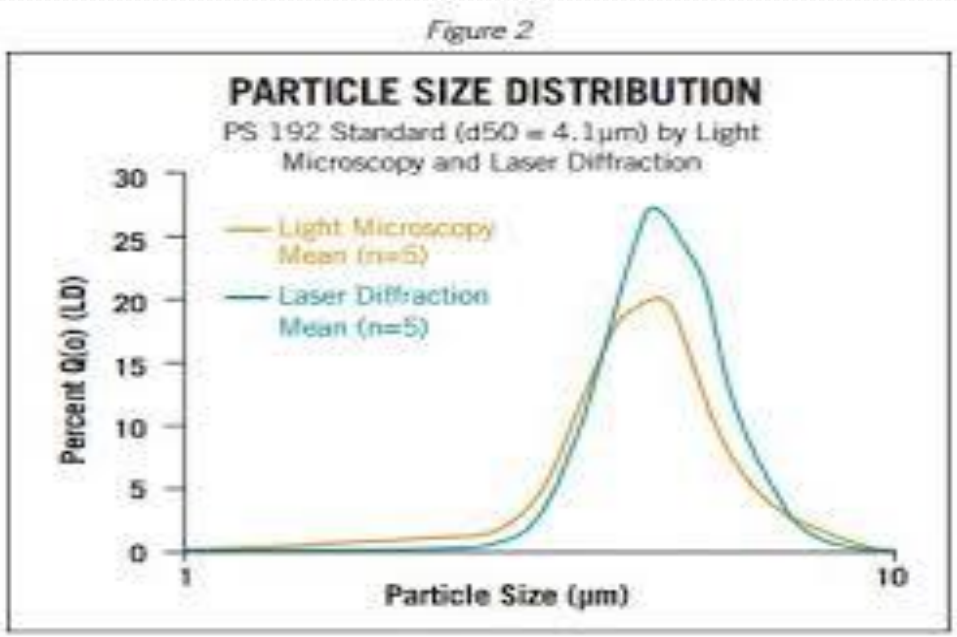
*Janatratid et al, Dissolution Media simulating conditions in Gastrointestinal tract, Pharm Res 25, 2008

Conclusion from Solubility Study

- Solubility of API in 0.1N HCl with 1.0% w/v SLS is similar to its solubility in Biorelevant media.
- Here it was observed that dissolution is not sensitive to pH , similar in 0.1N HCl, pH 4.5 buffer & pH 6.8 buffer.
- Method selected for product development:
  - 900ml of 0.1N HCl with 1.0% SLS
  - 75 RPM
  - UV 282 nm (maxima with negligible interference)

Additional Studies Performed

- Particle size was deliberated changed.
- Drug product made out of these changes resulted in change in dissolution values
- Particle size was found critical for optimal dissolution



Formulation Details

Table 7. Formulation of Generic Acetriptan Tablets, 20 mg, used in Pilot BE Study #1001

Ingredient	Function	Composition	
		(mg per tablet)	(% w/w)
Acetriptan	Active	20.0	10.0
Intragranular Excipients			
Lactose Monohydrate, NF	Filler	79.0	39.5
Microcrystalline Cellulose (MCC), NF	Filler	79.0	39.5
Croscarmellose Sodium (CCS), NF	Disintegrant	10.0	5.0
Talc, NF	Glidant/lubricant	5.0	2.5
Extragranular Excipients			
Magnesium Stearate, NF	Lubricant	1.2	0.6
Talc, NF	Glidant/lubricant	5.8	2.9
Total Weight		200.0	100

Pilot Bioequivalence studies

- Being low soluble drug, Pilot BE studies were considered essential
- Pilot BE study should support control on critical attributes like particle size & establish relation between in vivo & in vitro relationship
- Pilot BE study was performed in 6 healthy subjects (4 way cross over, 3 prototypes & RLD of 20mg/tab)

Pilot Bioequivalence studies

- Formulation used for 3 prototypes was same except the particle size distribution (d90 of 20, 30 & 45 microns)
- General understanding used: Mean Cmax & AUC responses of 2 drug products should not differ by >12-13% to meet BE limit of 80-125%
- Target was to have both Cmax ratio & AUC ratio for test to reference between 0.9 to 1.11

Pilot Bioequivalence studies

Results of PK study showed that drug product with API of d90 of 30 micron met this criteria but not 45 micron. Results with 20 micron were within the window but not as close as 30 micron.

PK Parameters

Table 8. Pharmacokinetic parameters (geometric mean) from Pilot BE Study #1001

Pharmacokinetic Parameters	Lot #2 (d_{90} 20 µm)	Lot #3 (d_{90} 30 µm)	Lot #4 (d_{90} 45 µm)	N/A (RLD)
Drug Product Batch No.	18	19	20	A6971R
AUC_{∞} (ng/ml h)	2154.0	2070.7	1814.6	2095.3
AUC_{0-t} (ng/ml h)	1992.8	1910.6	1668.0	1934.5
C_{max} (ng/ml)	208.55	191.07	158.69	195.89
T_{max} (h)	2.0	2.5	3.0	2.5
$t_{1/2}$(h)	6.0	6.0	6.0	6.0
Test/Reference AUC_{∞} Ratio	1.028	0.988	0.866	--
Test/Reference AUC_{0-t} Ratio	1.030	0.988	0.862	--
Test/Reference C_{max} Ratio	1.065	0.975	0.810	--

Mean PK profiles from Pilot BE

The pharmacokinetic results are presented in Figure 3 and Table 8.

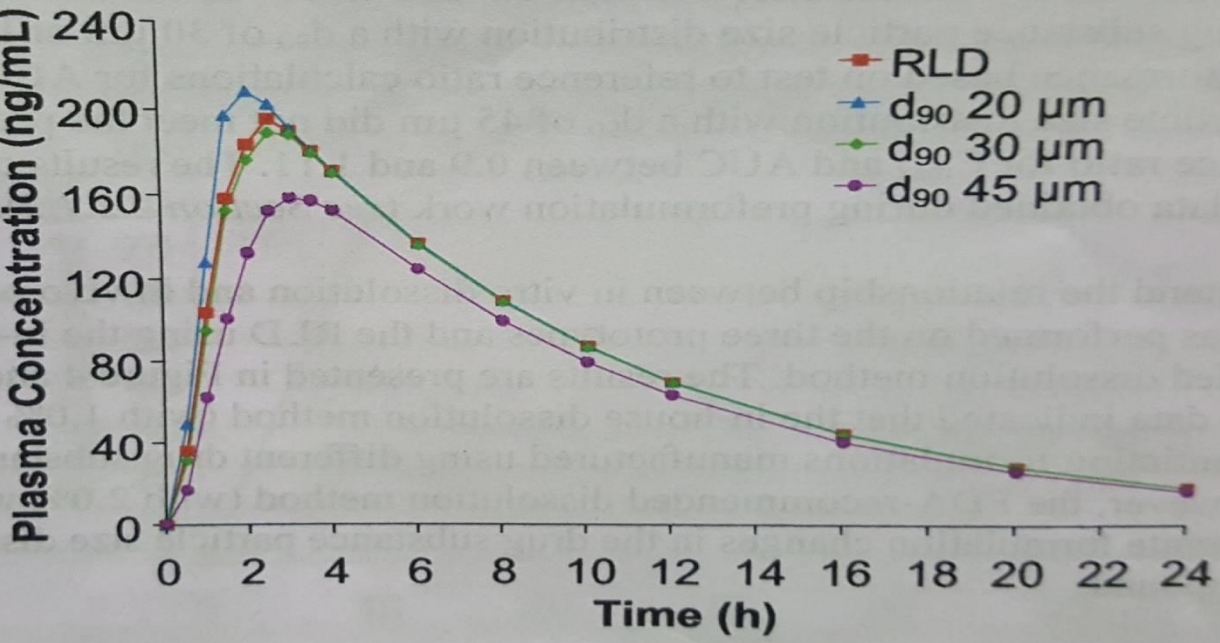


Figure 3. Mean PK profiles obtained from Pilot BE Study #1001

Method Challenge

- To understand the relationship between in vivo & in vitro performance, Dissolution was performed on 3 prototypes & the RLD using the in-house versus the FDA recommended method
- Results showed that medium with 1% SLS & 30 mts time point was found to be predictive of in vivo performance (in-house method)
- Dissolution medium with 2% SLS (USP method) was not found to predict the in vivo performance differences due to different particle sizes

Discriminatory Vs Indiscriminatory

Example QbD IR Tablet Module 3 Quality 3.2.P.2 Pharmaceutical Development

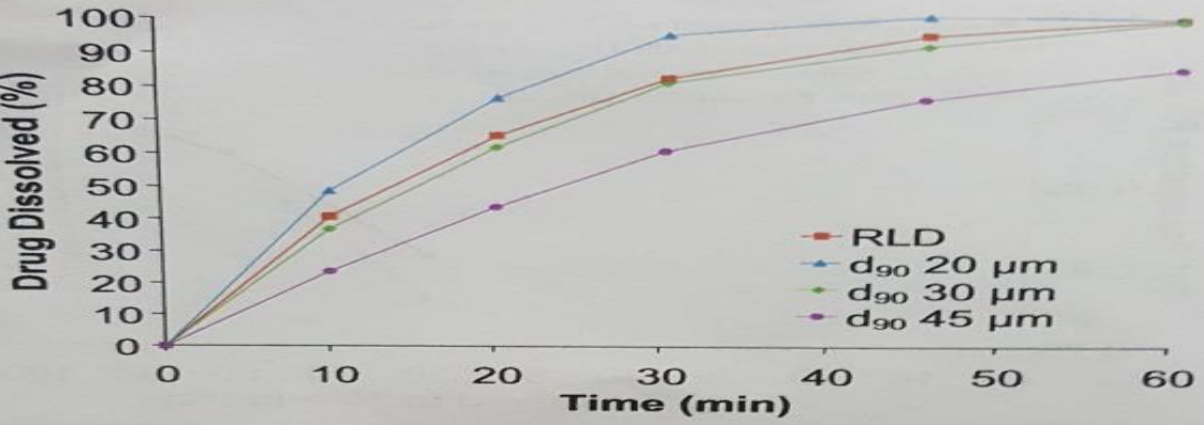


Figure 4. Dissolution of acetriptan tablets (RLD and three prototypes) using in-house method (900 mL of 0.1 N HCl with 1.0% w/v SLS using USP apparatus 2 at 75 rpm)

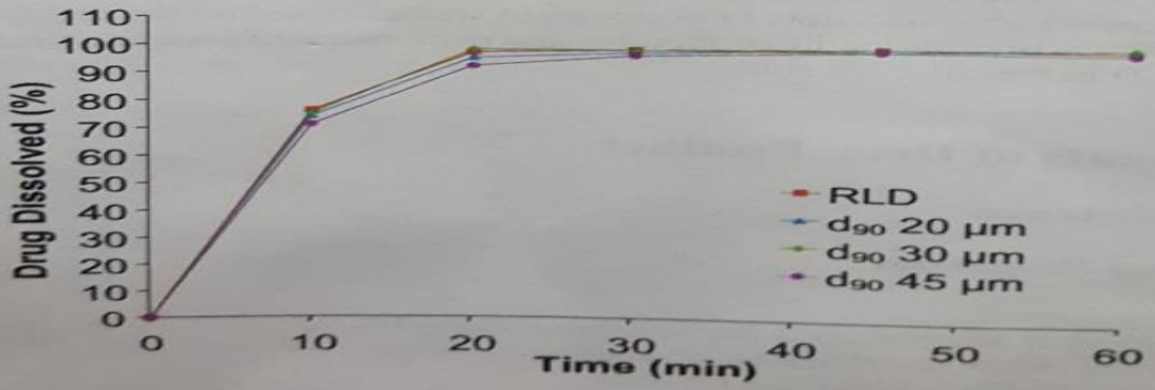


Figure 5. Dissolution of acetriptan tablets (RLD and three prototypes) using FDA-recommended method (900 mL of 0.[illegible]N HCl with 2.0% w/v SLS using USP apparatus 2 at 75 rpm)

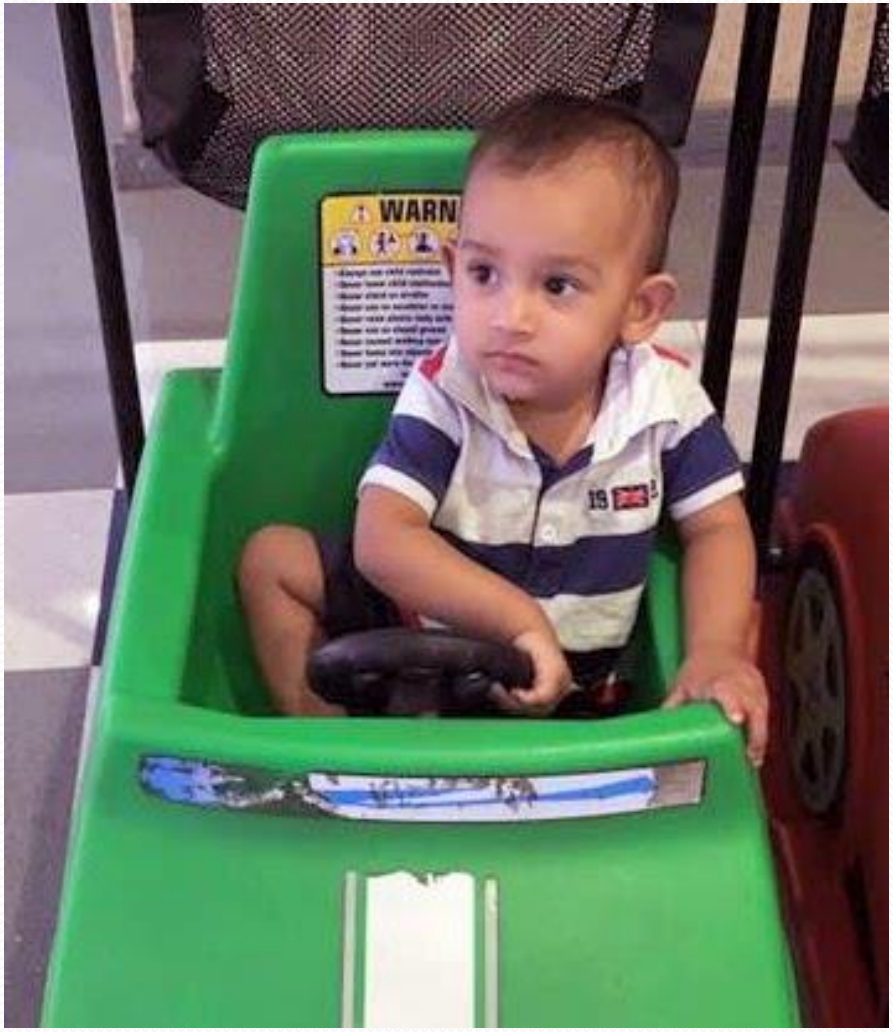
Limit Setting

- A dissolution rate of NLT 80% in 30 mts in 0.1N HCl with 1.0% SLS as one of the 3 batches gave 80.8% dissolution in 30 mts and demonstrated comparable properties to the RLD

Could you Notice?

- QTTP
- CQA's
- CPP's
- Risk Assessment
- DOE's
- Control Strategy

Our First Priority: Our Customer



References

- US FDA, Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms, April 2012
- BCS Guidance (Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System”); August 2000
- IR Dissolution Guidance (Dissolution Testing of Immediate Release Solid Oral Dosage Forms); August 1997
- IVIVC Guidance (Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations); September 1997

vukshirsagar@gmail.com

M: +91 9867650160