QbD in Dissolution Method Development

More than Compliance – It is Survival

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Pharma Consulting

Disso India, Amdavad, July 2016

Contents

- Background
- QbD Process
- Risk Management
- Illustrative Experiments
- FDA Example of IR Product

QbD, Buzz Word ? More chewed than swallowed ?

BLAH,
BLAH,
BLAH…

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?

End Quality Vs Built in Quality

- Both India & China have a large presence in US market both for API's & Drug Formulations
- Many companies have been cited by FDA
- There is not much issue with end quality which is around 6 Sigma
- But there are lots of issues related to built in Quality which is around 3 Sigma
- That is where the problem starts

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?	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 which can impact the dissolution, you need to establish particle size distribution pattern & provide the 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)

PAT is an essential element of QbD.

QbR of QbD

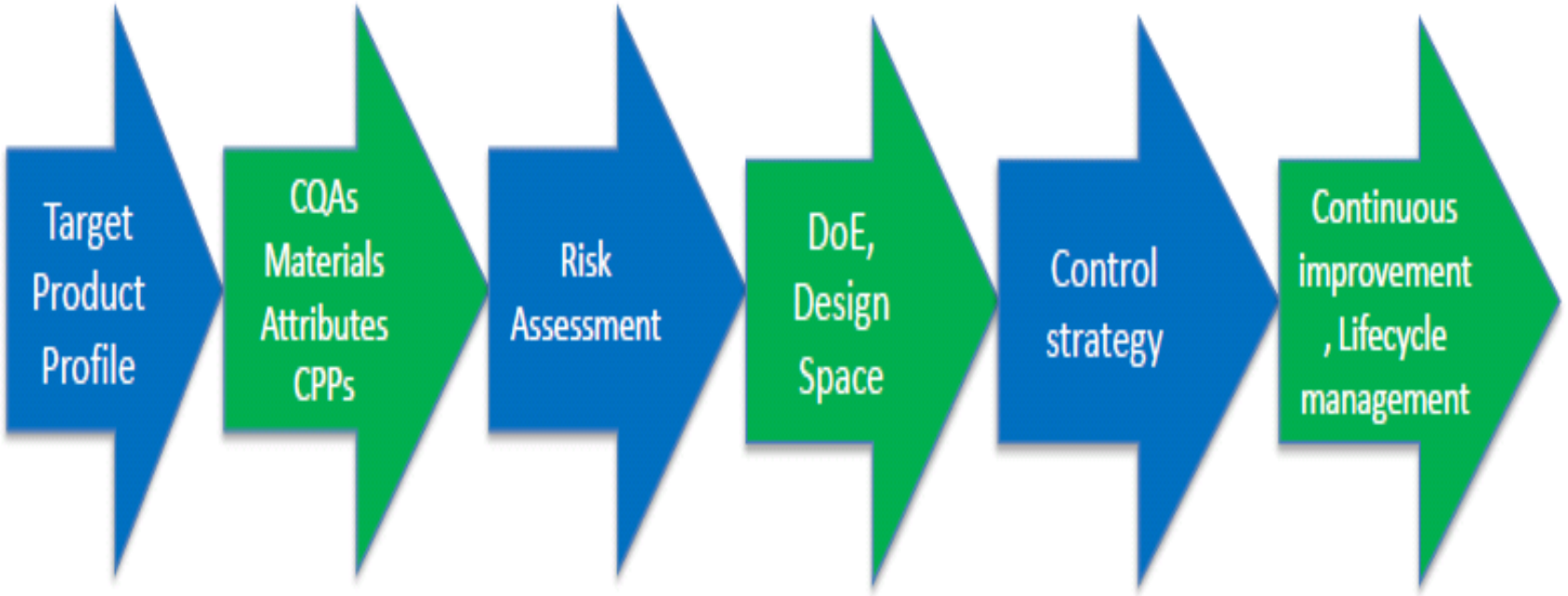
- Is it difficult to follow? How to begin?
- Is it a very costly exercise?
- Is it mandatory?
- Can it be followed by small companies?
- To what extend PAT’s are required?
- Is it only for Product Development?

Do you Have PAT at our company?

Do you have online,

- Temp Indictors
- RPM indicators
- Conductivity meters
- pH meters
- TOC Meters
- Temp record charts
- Continuous monitoring of temp/RH/Differential pressures in manufacturing
- Continuous Particle monitoring

QbD Approach (Important Stages)

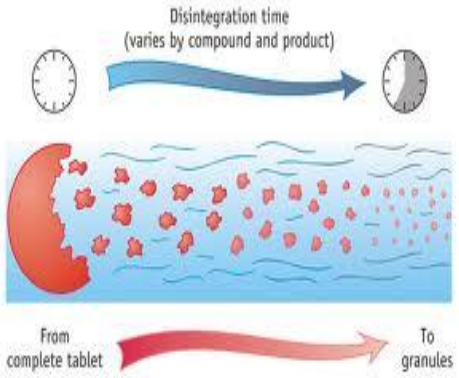


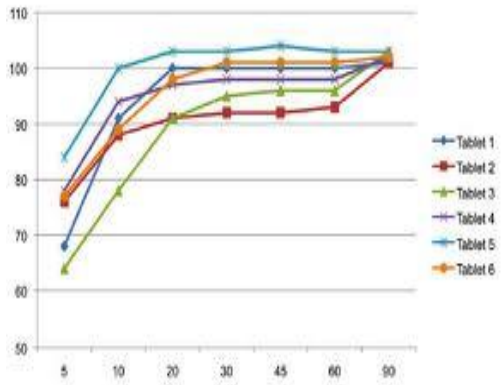
Understanding 4 D's

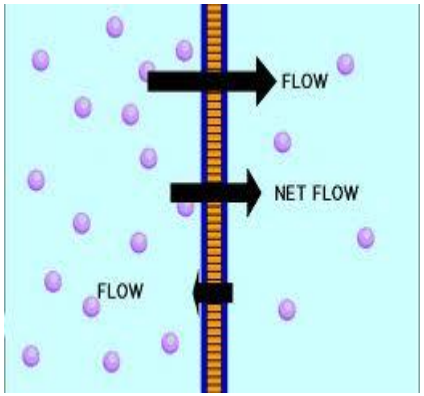
- Disintegration time is the time required for a dosage form to break up in to granules of specified size
- Dispersion is actually meant to distribute the mass evenly thus moving the mass from higher concentration to lower concentration
- Dissolution is the rate of mass transfer from a solid surface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

4D's

- Disintegration
- Dispersion
- Dissolution
- Diffusion







Sink Conditions

- Sink condition refers to the volume of medium which is at least three times that is required 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)

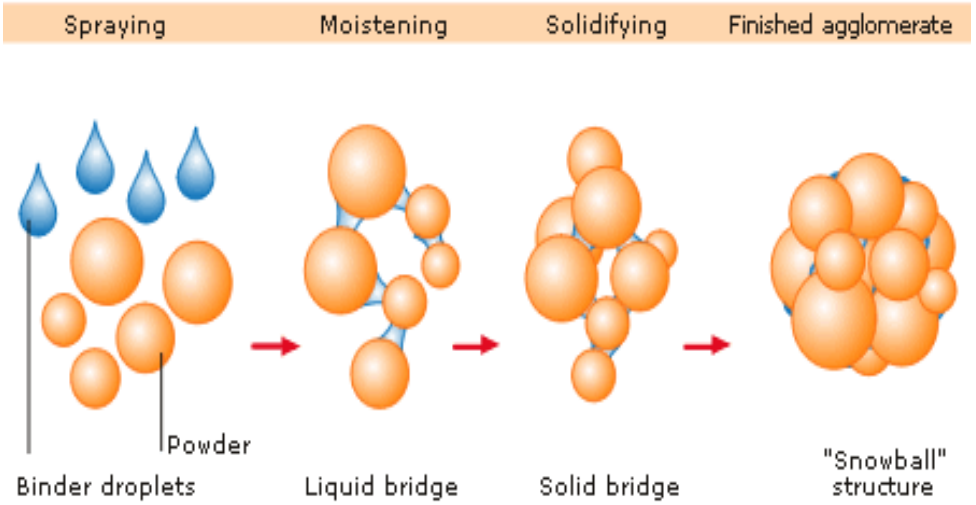
Quality Attributes	Target	Is this CQA ?	Justification
Appearance	Color & Shape	No	Not linked to Safety & Efficacy
Assay & Particle Size	100% w/w & matching spread	Yes	Impacts dissolution
Moisture Content	< 0.5%	Yes Exceptions	Higher moisture leads to polymorphic change in some cases
Intrinsic Dissolution	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 **(Could become a new requirement)**
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

Process Attributes

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



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 Factors of Dissolution Testing

- Proper Deaeration of media
- Calibration of Apparatus
- Selection of filters
- Finding out Discriminatory media
- HPLC or UV method

Risk Factors of Dissolution Testing

- Collection of samples
- Result reporting
- Investigation of stability failures
- Method validation/ method verification
- In Vivo/ In Vitro correlation

Let us learn from case studies!

Risk Assessment of Method (Scale 1-5)

Risk	Probability	Severity	Detection	RPN
Improper IVIVC Correlation	3	5	4	60
Non discriminative method	3	4	3	36
Improper Deae-ration	3	3	3	27
Improper Filter	3	2	2	18

Importance of Deaearation

	Aceclofenac Tablets 100mg					
		With degassing		Without degassing		
	Jar -1	98		99		
	Jar -2	97		86		
	Jar -3	102		94		
	Jar -4	94		104		
	Jar -5	98		92		
	Jar -6	99		98		
	RSD					
	Mean	**98**		**96**		

- **RSD** **2.7 %** **6.5 %**

Importance of proper calibration

Buprenorphine tablets 8mg							
Jar -1	89						
Jar -2	86						
Jar -3	**100**	(Paddle wobbling)					
Jar -4	91						
Jar -5	88						
Jar -6	87						

Importance of proper filter

Name	Losartan Potassium and Amlodipine tablets					
Dissolution Medium	Buffer pH 4.5					
Component	**Losartan Potassium**			**Amlodipine**		
Type of filters used	**NYLON**	**PTFE**	**PVDF**	**NYLON**	**PTFE**	**PVDF**
	% Release			% Release		
Tab 1	6	99	99	68	98	98
Tab 2	16	103	102	69	101	97
Tab 3	26	99	99	71	102	101
Tab 4	33	98	100	77	99	102
Tab 5	43	100	100	79	101	102
Tab 6	47	102	102	81	99	101
Mean	29	100	100	74	100	100
SD	15.76	1.94	1.37	5.53	1.55	2.14
% RSD	**54.34**	1.94	1.37	**7.47**	1.55	2.14
Min	6	98	99	68	98	97
Max	47	103	102	81	102	102
Remarks	PVDF – Polyvinylidene fluoride membrane filter PTFE - Polytetrafluoroethylene membrane filter					

Deaeration Method

USP/BP: Heat the medium while stirring gently to filter having a porosity of 0.45 micron or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated techniques for deaeration can be used .

IP too mentions the requirement of deaeration.

How many of you have validated your Deaeration Technique?

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/ analytical methods.
- Enhancement of existing products & processes.
- Screening important factors.
- Minimization of production costs & pollution
- Development of Analytical Methods

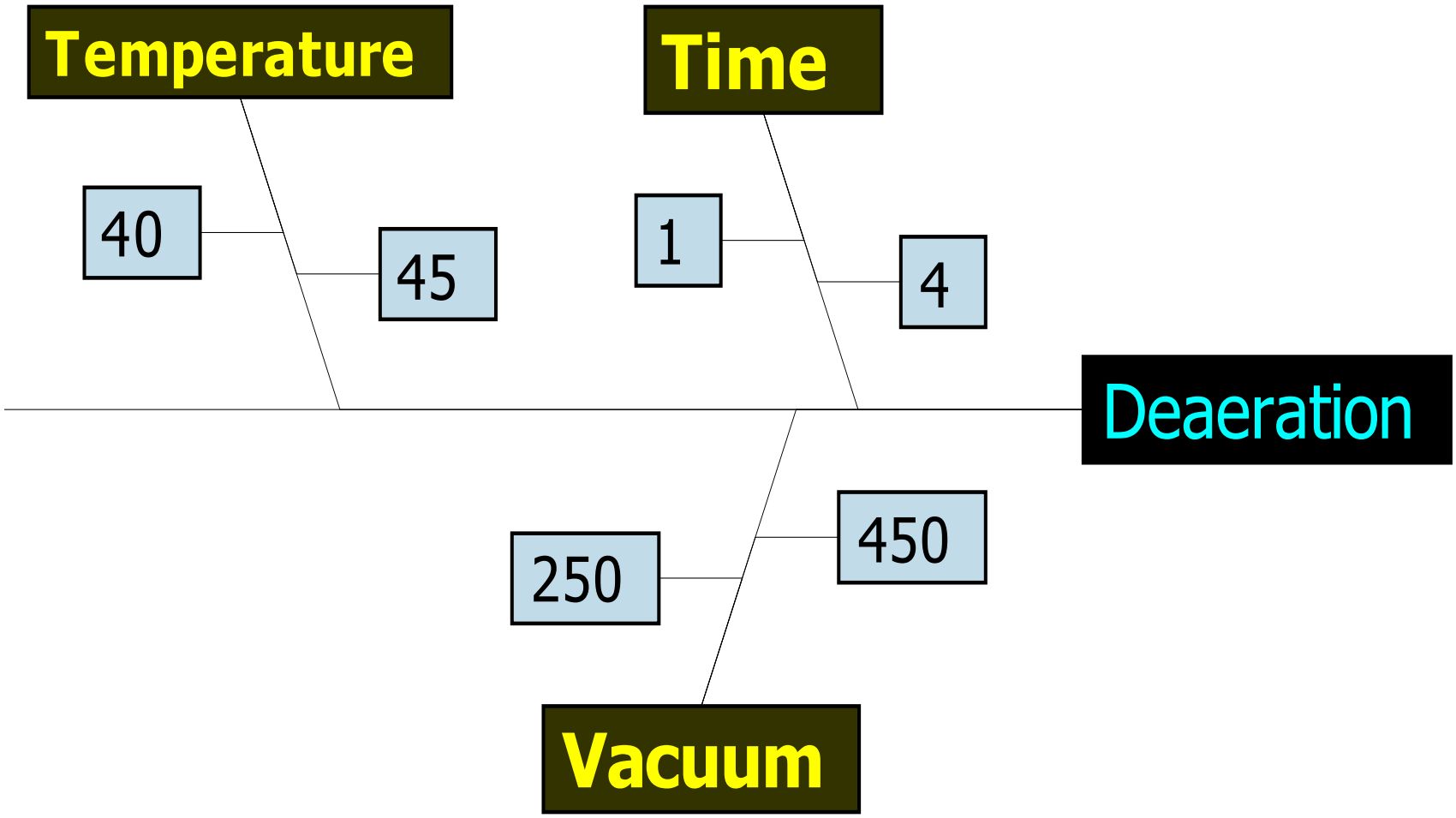
Steps involved in DOE

- Define Factors
  (material, process, equipment, environment)
- Define Responses
  (critical quality attributes)
- Create Design
- Construct Model
- Evaluate Model
- Interpret & Use Model (Make Decisions)

SOME DoE EXAMPLES

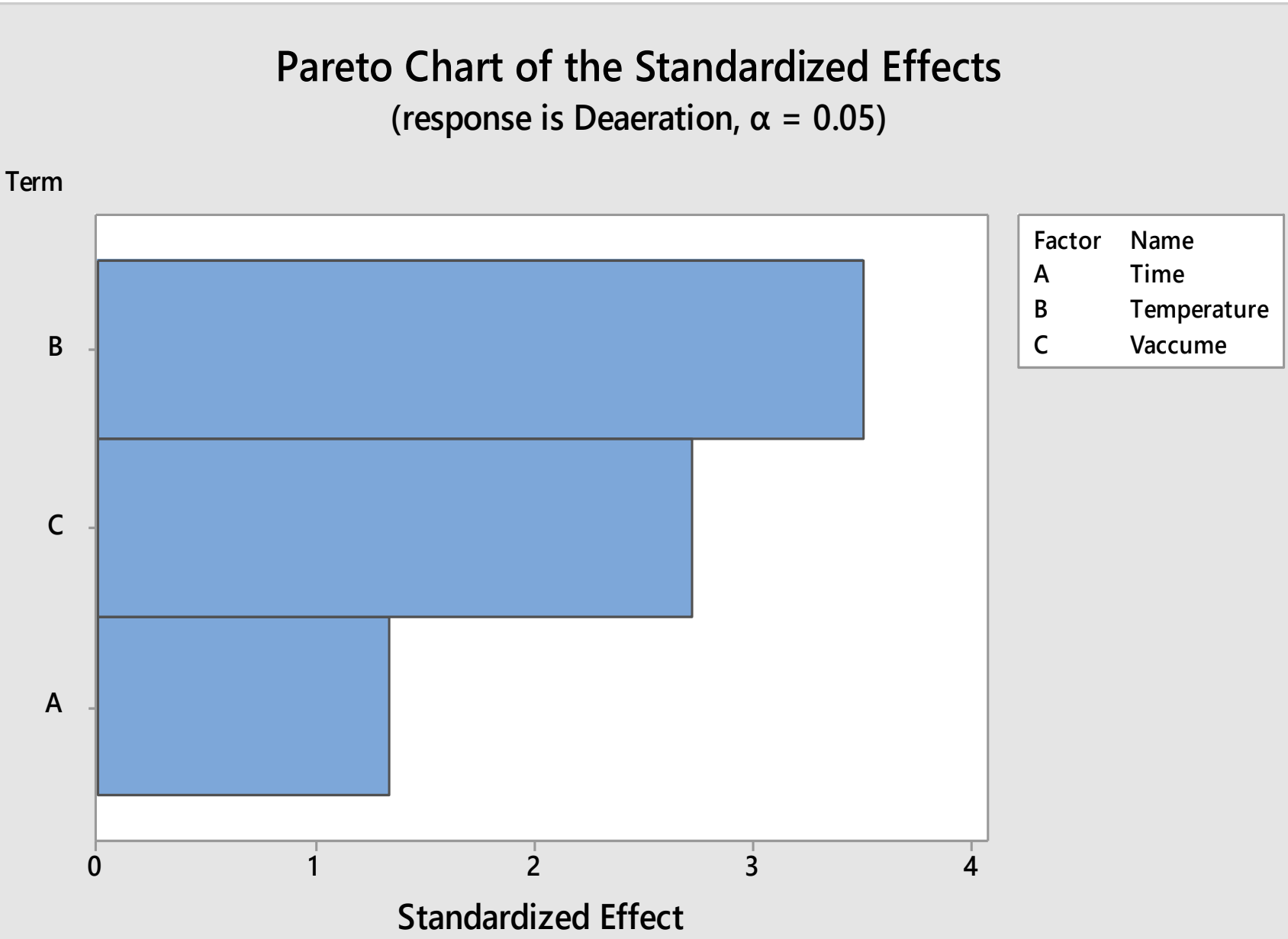
(CREATED ON PAPER JUST FOR ILLUSTRATION)

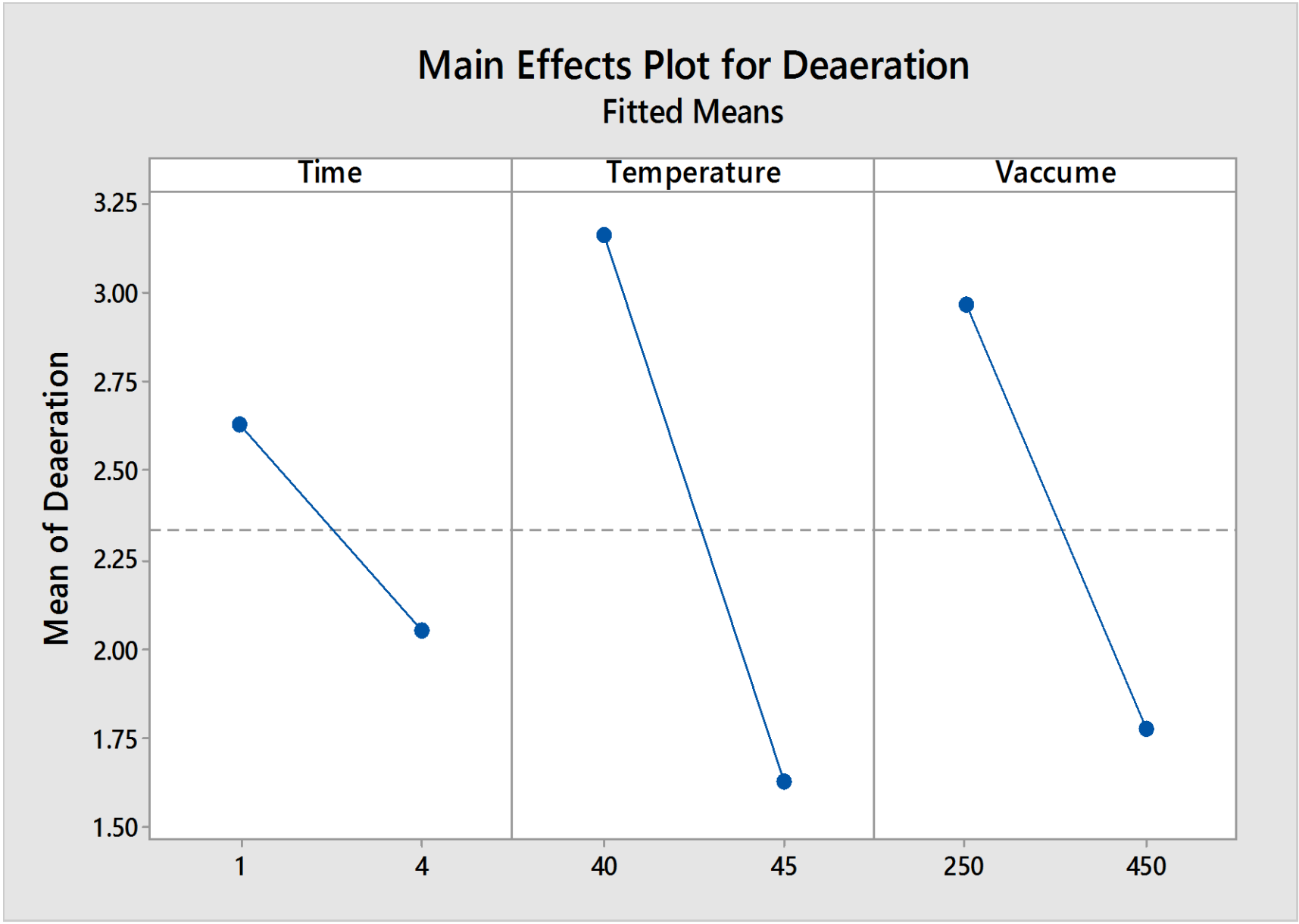
Optimization of Deaeration Procedure



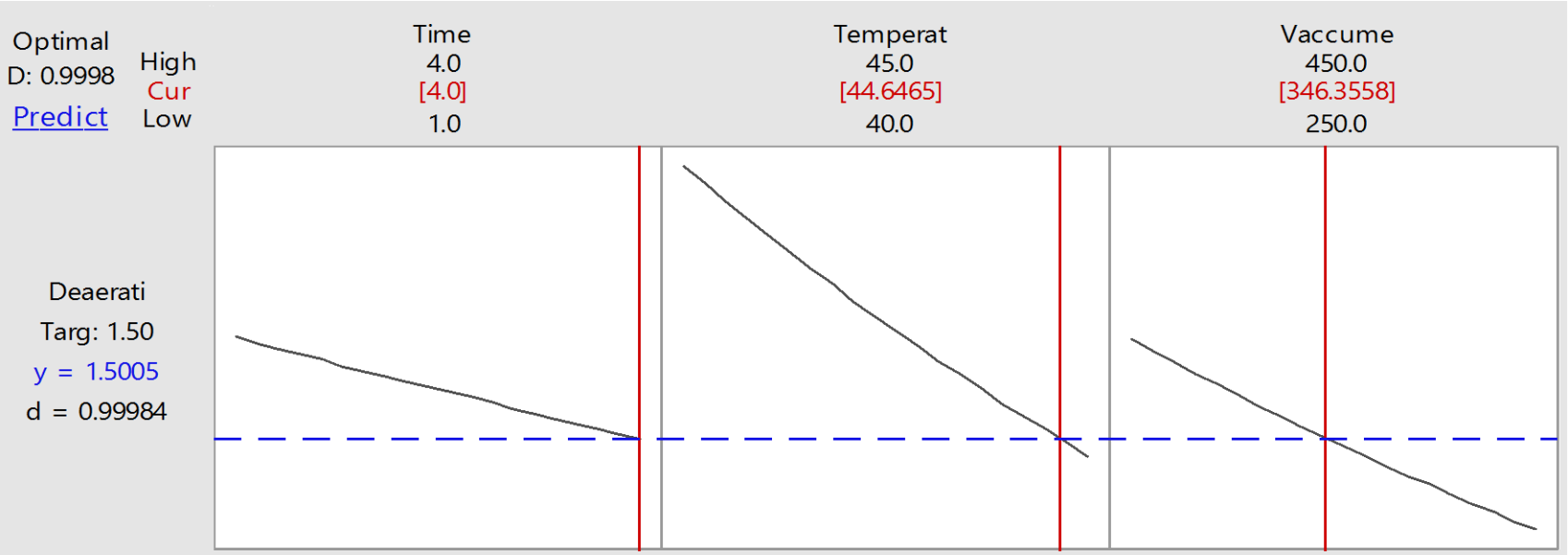
Full factorial Design, 3 factors/2 levels

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

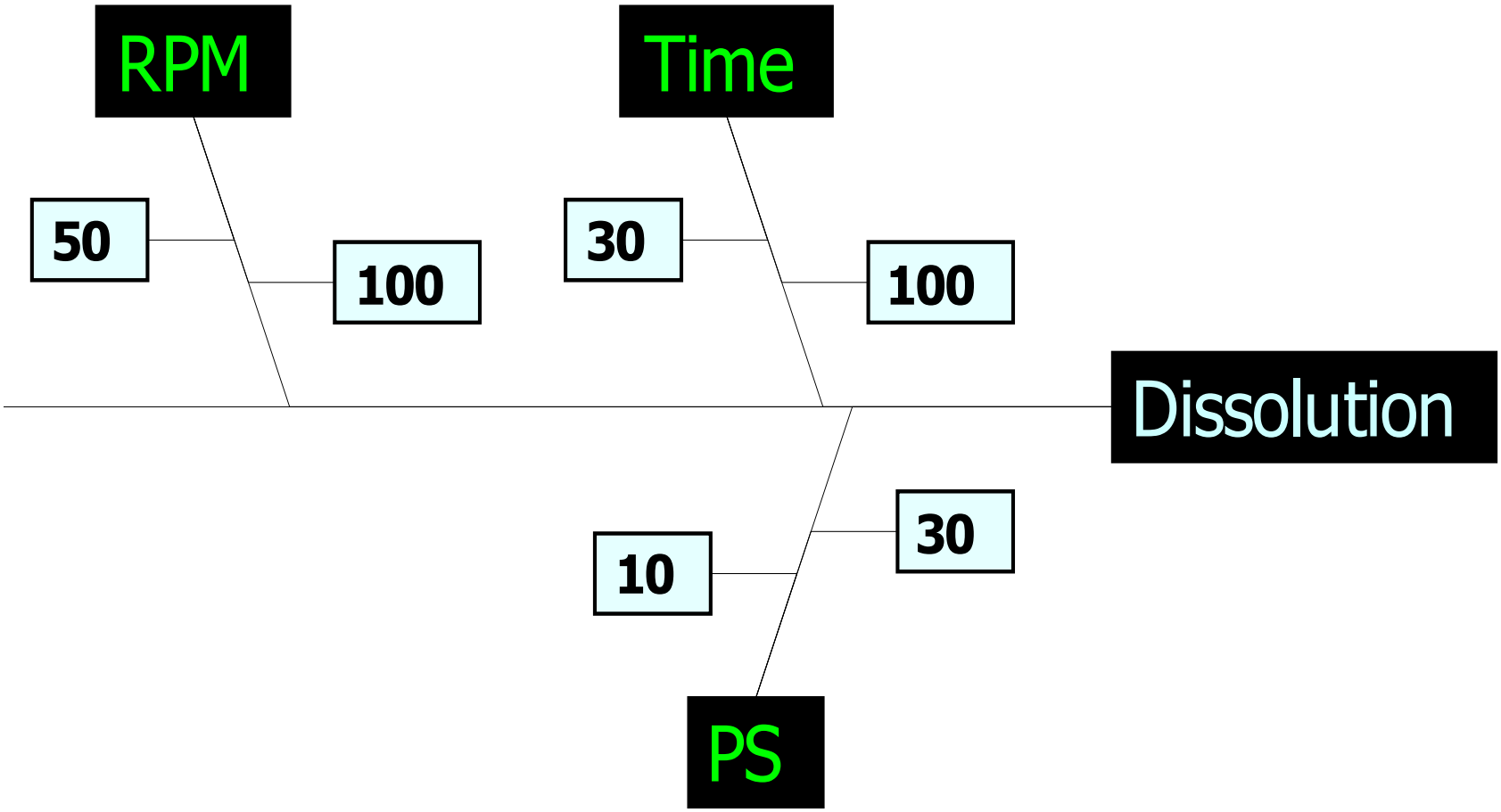

Pareto Chart of the Standardized Effects
(response is Deaeration, α = 0.05)
Term
B
C
A
0
1
2
3
4
Standardized Effect
Factor Name
A Time
B Temperature
C Vaccume


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

Deaeration Optimization Plot



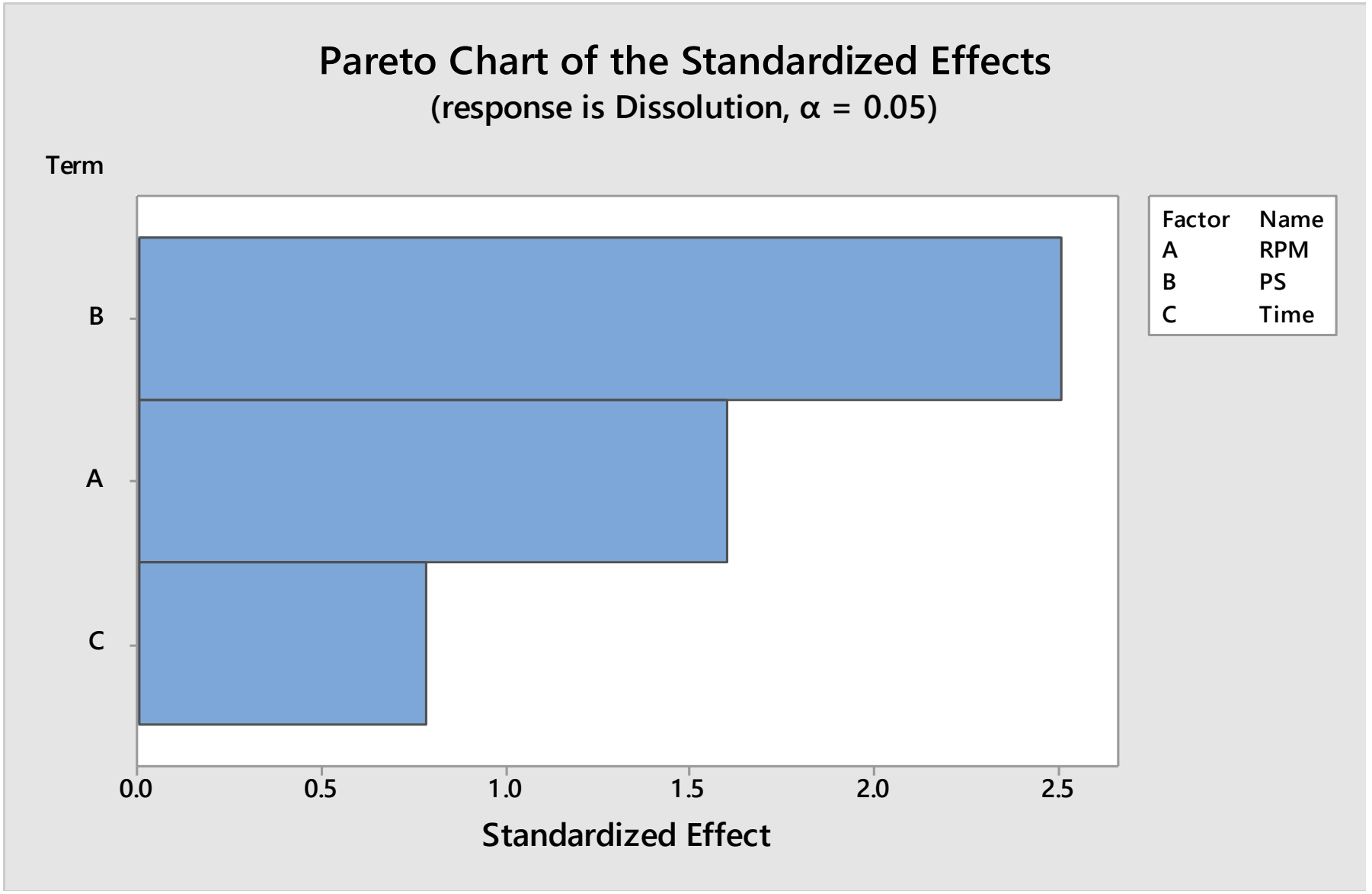
Dissolution Design of Experiments

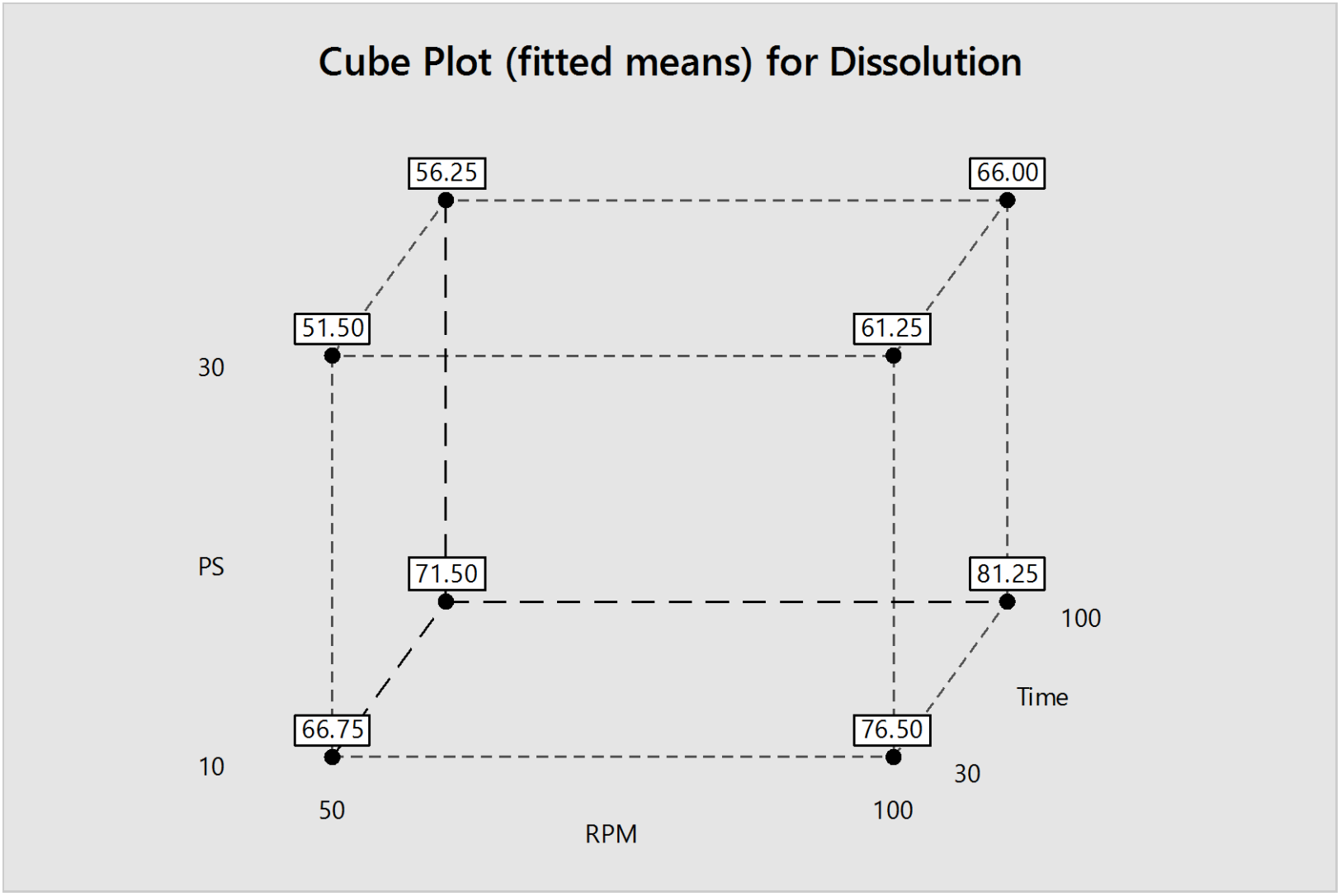


Full factorial Design, 3 factors/2 levels

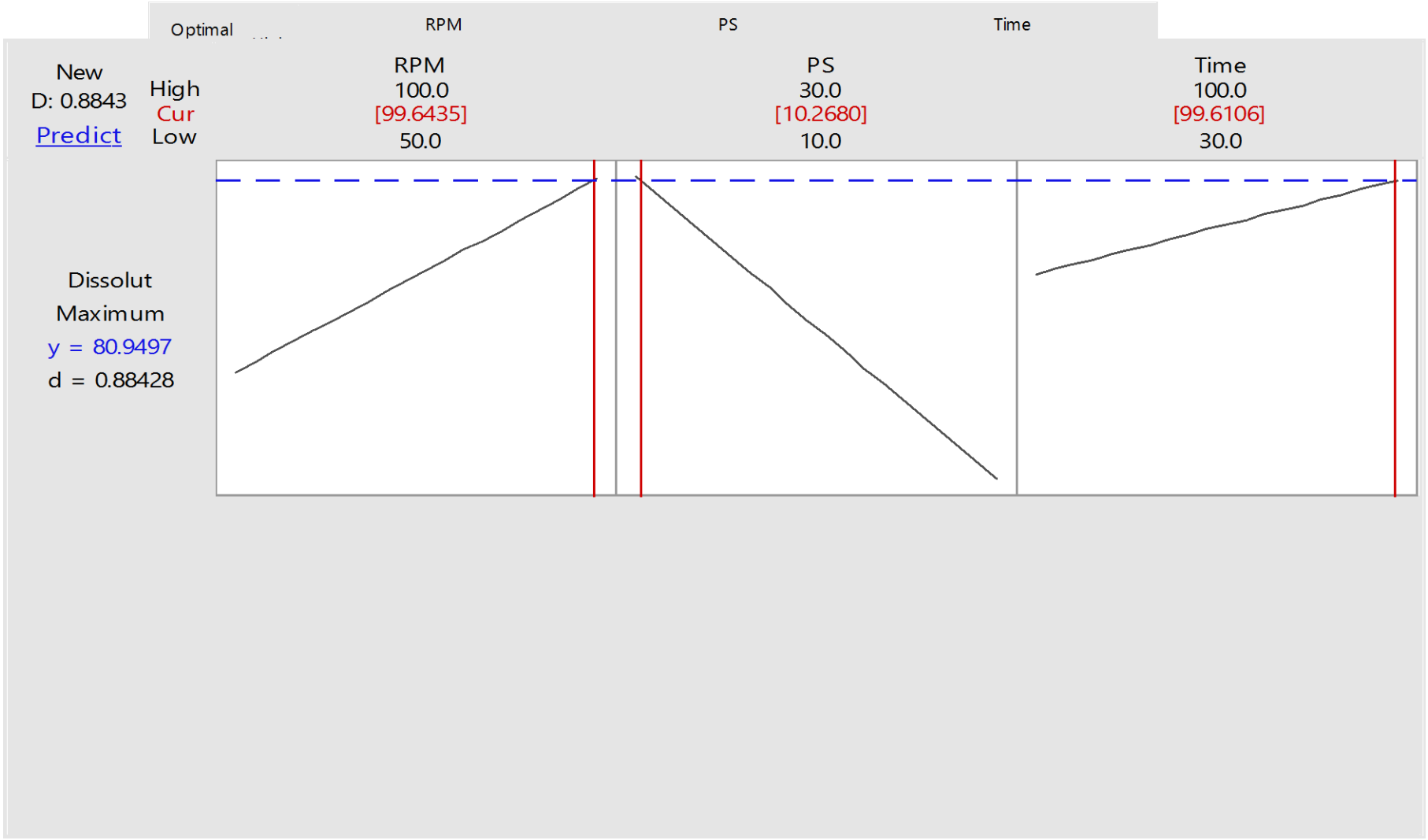
Worksheet 1 ***

	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
71.50
81.25
66.75
76.50
PS
30
10
RPM
50
100
Time
30
100

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
- Implement QbD but remember that it is not a magic stick

Food for thought …

Within specification Investigation?

- Am I crazy?
- But tell me as much as product can fail in analysis by mistake, can it not pass also by mistake ? Think over!
- I feel it will be a future requirement?

Mass Balance application to Dissolution

Food for thought …

OOS Result obtained during BE limit?

Current Scenario?

- Most probably CRO has done a mistake?
- Analysis has been done wrongly?
- BE protocol was not proper?
- There was lack of control on volunteers?
- I am right, you are wrong?

Why not apply OOS to BE failures?

Food for thought

Rationality of BE Studies?

- Many people prefer to use the same batch of innovator for product development, analysis of exhibit batch, stability, pilot BE studies, pivotal BE studies etc. Why?
- People have observed difference in innovator product from batch to batch? Why?
- What is the consistency that we are talking about?

Is that the genesis of QbD?

Learning From FDA Example

Background

- BCS Class II (LS HP) compound Acetryptan
- 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 QC Method

- 900 ml of 0.1N HCl with 2% SLS
- USP Apparatus 2 (Paddle)
- 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

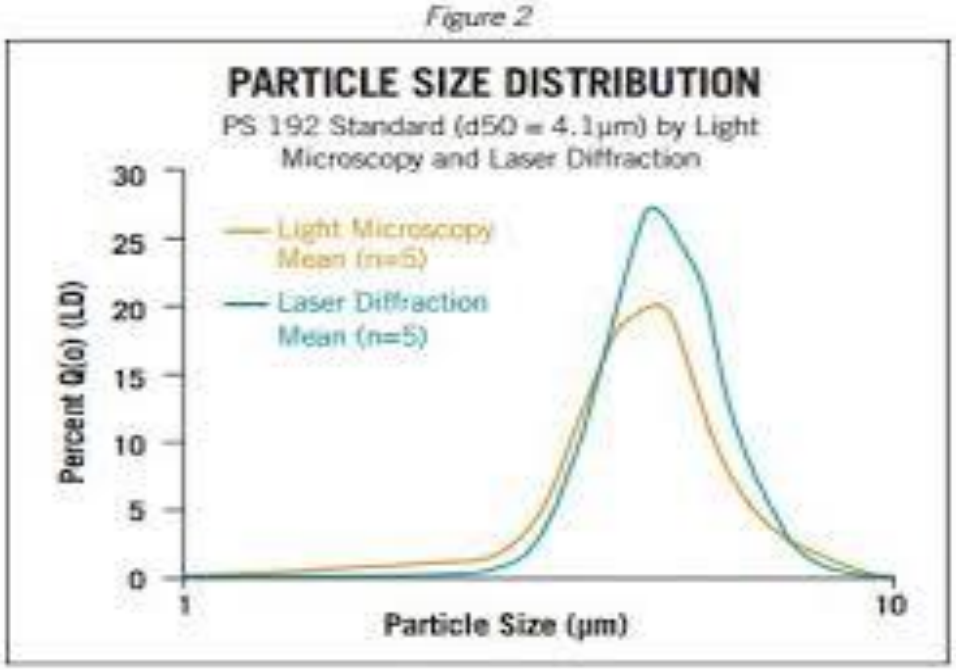
*Janatratid et al, Dissolution Media simulating conditions in Gastrointestinal tract, Pharm Res 25, 2008

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.
- Further 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



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

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

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.

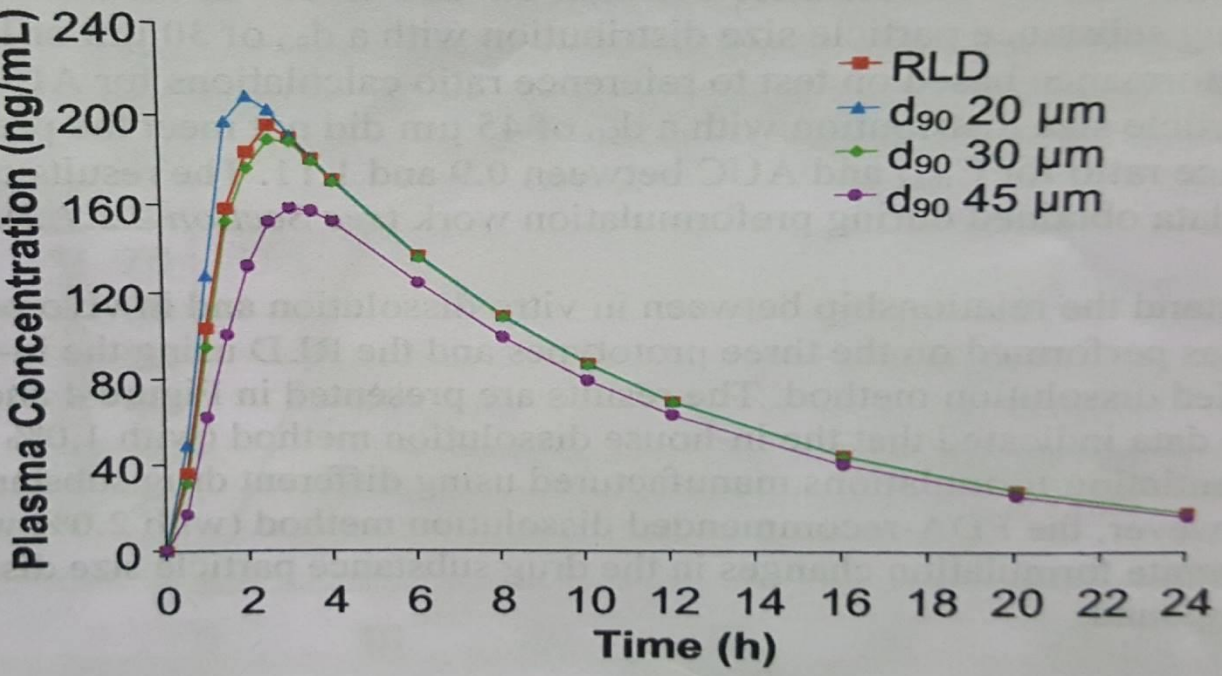


Figure 3. Mean PK profiles obtained from Pilot BE Study #1001

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

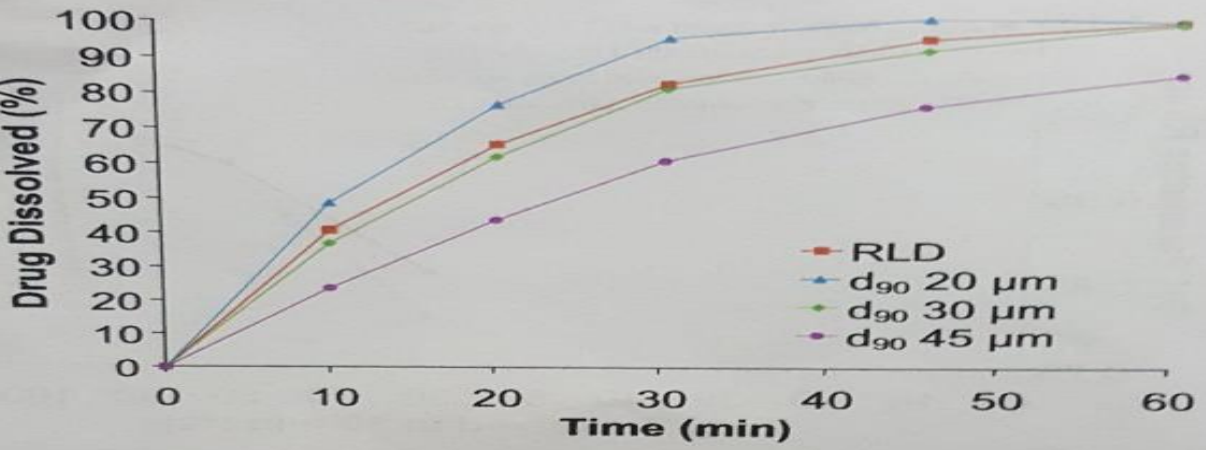


Figure 4. Dissolution of acetriptan tablets (RLD and three prototypes) using in-house method (900 mL of 0.1 N HCl with 1.0% w/v SLS using USP apparatus 2 at 75 rpm)

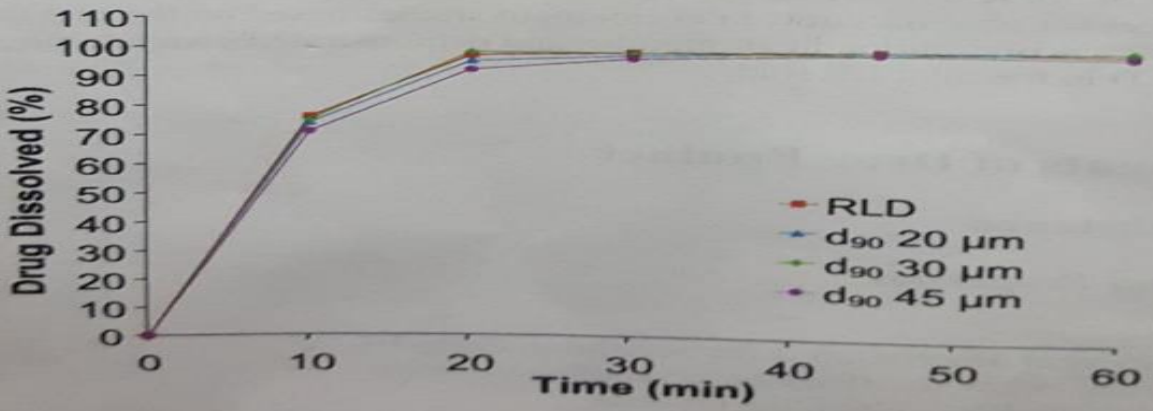


Figure 5. Dissolution of acetriptan tablets (RLD and three prototypes) using FDA-recommended method (900 mL of 0.1 N HCl with 2.0% w/v SLS using USP apparatus 2 at 75 rpm)

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?

- QTPP
- CQA's of DS & DP
- CPP's
- Risk Assessment
- DOE's
- Control Strategy

References

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- USP <711> Dissolution and <724> Drug Release, <1088> In-Vitro and In-Vivo Evaluation of Dosage Forms
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- Quality by Design Approaches to Analytical Methods - FDA Perspective, Yubing Tang, Octo. 11
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Thank You !