

Central Composite Design (Manual)



Prepared By:
Ruchir Shah, FnD

Index

Basics

- Basics of CCD

Slide 3 - 8

Step 1 & 2

- Define Objective & Identify Variables

Slide 9 - 11

Step 3

- Create Design

Slide 12 - 21

Step 4

- Design Evaluation

Slide 23 - 27

Step 5

- Experimentation

Slide 28 - 31

Step 6

- Analysis & Interpretation

Slide 32 - 39

Step 7

- Diagnostics

Slide 40 - 48

Step 8

- Model graphs

Slide 49 - 53

Step 9

- Knowledge Space

Slide 54 - 57

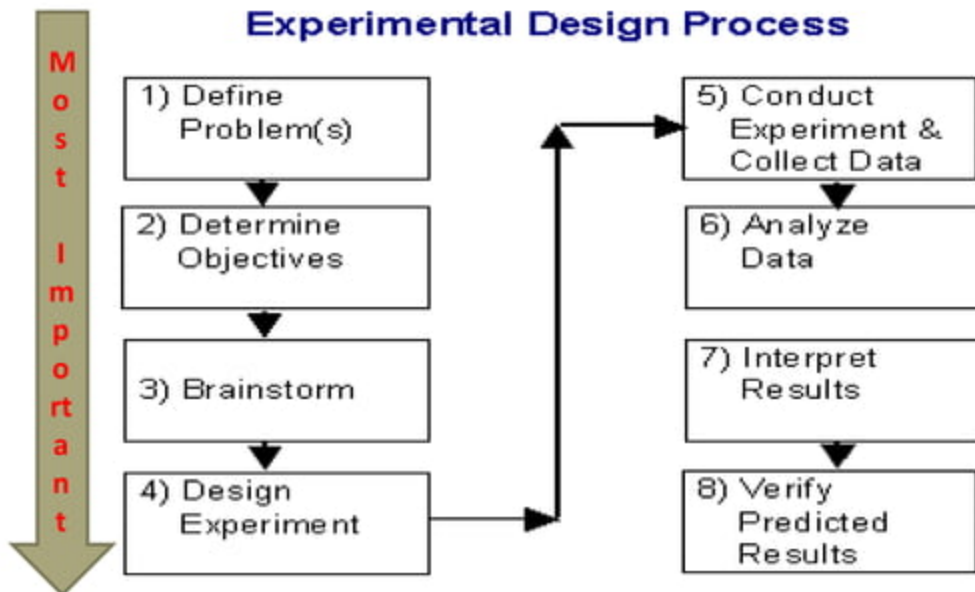
Step 10

- Points to be captured in PDR

Slide 32 - 39

Experiment Design Process

The flow chart below illustrates the experiment design process:

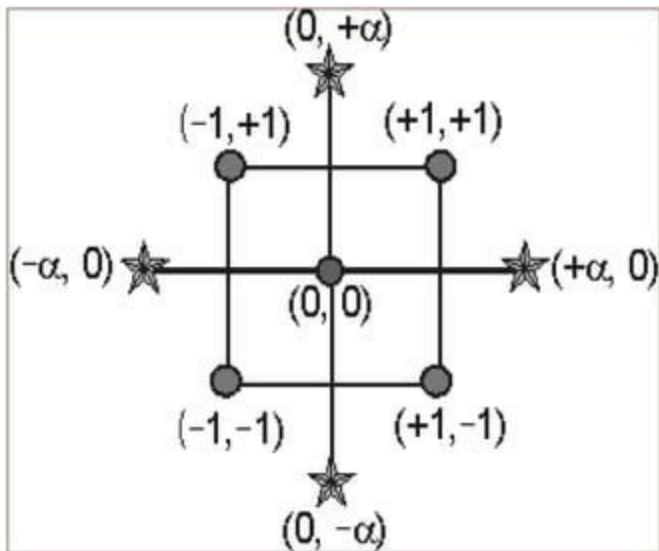


Components of Experimental Design

- There are three components of the Formula/process that are analysed by a design of experiments:
 - **Factors** – Independent Variable will form factors. Variables which can be controlled by an experimenter.
 - **Levels** – Range of each factor in the study or Grade of Excipients
 - **Response** - or output of the experiment.

Response Surface Methodology

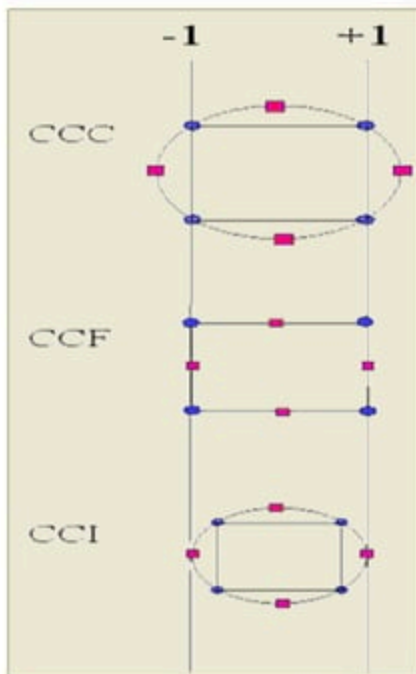
Central Composite Design



Centre Points and Axial Points are added to estimate curvature effect

Types of CCD

1. **CCC – Circumscribed CCD**
 - Each factor studied at 5 level
 - Axial points establishes new high and low ranges
2. **CCF – Face centered CCD**
 - Axial points are at center of each side of factorial space
3. **CCI – Inscribed CCD**
 - For those situations where limit specified for each factor is real limit. Beyond or below that level it is not possible to perform an experiment.
 - Here also Each factor studied at 5 level
 - It is a Scaled down of CCC design



Case Study : Fluid Bed Granulation

- Example

Ingredients	Functional Category	Batch Size	
		mg/tab	%w/w
Dry Mix			
Microcrystalline Cellulose (AVICEL PH 102)	Diluent	90.00	27.27
Silicon dioxide (Aeoperl 300 Pharma)	Adsorbent	10.00	3.03
SSG Type A	Disintegrant	8.00	2.42
Drug Solution			
Drug Substance	Active	90.00	27.27
Povidone K-30	Binder	8.00	2.42
Silicon dioxide (Aeoperl 300 Pharma)	Adsorbent	10.00	3.03
SLS	Surfactant	5.00	1.52
Ethanol	Solvent	qs	
Dichloromethane	Solvent	qs	
Extra Granular			
Microcrystalline Cellulose (AVICEL PH 102)	Diluent	92.00	27.88
Silicon dioxide (Aeoperl 300 Pharma)	Glidant	3.00	0.91
SSG Type A	Disintegrant	8.00	2.42
Talc (M)	Anti-adherent	3.00	0.91
Magnesium Stearate	Lubricant	3.00	0.91
Total Core		330.00	100.00

Step 1 - Define Objective

- **Objective:**
 - **Establishing preliminary formulation component levels and demonstrating the rationale for selection of the excipient levels.** The study can also be utilized to determine if acceptable product attribute are obtained over the range of excipient concentrations studied.

Note: State Objective in Measurable Responses

- ❖ Factor Interaction
- ❖ Formula Optimization
- ❖ Process Optimization

Never Club Formula and Process Optimization in single Study

Step 2 - Identify and Characterize variables

Ingredients	Functional Category	Batch Size	
		mg/tab	%w/w
Dry Mix			
Microcrystalline Cellulose (AVICEL PH 102)	Diluent	90.00	27.27
Silicon dioxide (Aeoperl 300 Pharma)	Adsorbent	10.00	3.03
SSG Type A	Disintegrant	8.00	2.42
Drug Solution			
Drug Substance	Active	90.00	27.27
Povidone K-30	Binder	8.00	2.42
Silicon dioxide (Aeoperl 300 Pharma)	Adsorbent	10.00	3.03
SLS	Surfactant	5.00	1.52
Ethanol	Solvent	qs	
Dichloromethane	Solvent	qs	
Extra Granular			
Microcrystalline Cellulose (AVICEL PH 102)	Diluent	92.00	27.88
Silicon dioxide (Aeoperl 300 Pharma)	Glidant	3.00	0.91
SSG Type A	Disintegrant	8.00	2.42
Talc (M)	Anti-adherent	3.00	0.91
Magnesium Stearate	Lubricant	3.00	0.91
Total Core		330.00	

Identify and Characterize variables.... 2

- Define Variables
- Factors To Be Studied

(Independent Variables - Factors)

- Binder Level - Numerical
- Surfactant Level – Numerical
- Disintegrant Level - Numerical
- Grade of Adsorbent – Categorical (Nominal)
- Responses To Be Measured

Total 4 Factors
3 Numerical
1 Categorical

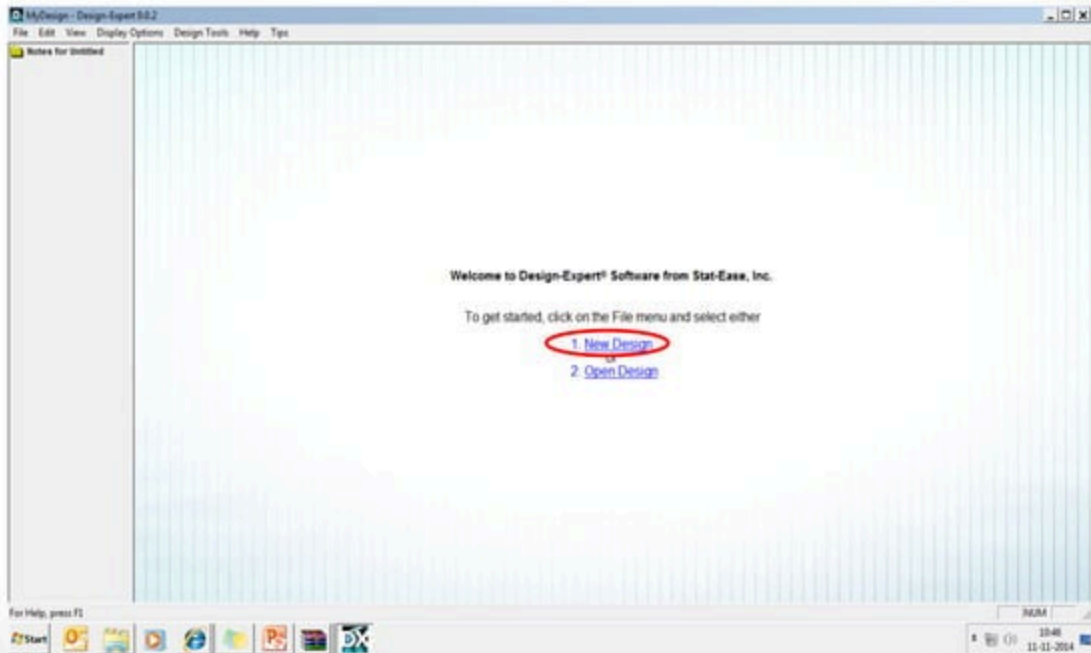
(Dependent Variables - Responses)

- Dissolution at 30 min (Should Be in Line with Specification)
 - Disintegration Time
 - Polymorphic Form
 - Hardness
-
- Only the Factors having impact on CQAs should be selected
 - Only those Responses having direct/indirect link with CQAs should be selected

Step 3: Create Design

Central Composite Design

- Start Design Expert Software



MyDesign - Design-Expert 9.0.2

File Edit View Display Options Design Tools Help Tips

Central Composite Design

Each numeric factor is set to 5 levels: plus and minus alpha (axial points), plus and minus 1 (factorial points) and the center point. If categorical factors are added, the central composite design will be duplicated for every combination of the categorical factor levels.

Numeric factors: 3 (2 to 50) Horizontal
 Categorical factors: 1 (5 to 10) Vertical

	Name	Units	Low	High	+alpha	-alpha
A (Numeric)	Surfactant Level	%	2	8	0.00414	7.99586
B (Numeric)	Detergent Level	%	2	8	0.077011	0.92299
C (Numeric)	Surfactant Level	%	0.5	2	-0.211340	

Enter factor ranges in terms of +/- 1 levels
 Enter factor ranges in terms of alpha

Type: Full Blocks: 1

Points:
 Not center points: 14
 Center points: 6

alpha = 1.68179 Options... 28 Runs

Execution of trial with (-) Surfactant level??

By default Software will take "Rotatable Alpha Value"

Cancel Continue >>

NUM | 11:26 | 13-11-2014

1. Select Response Surface then Select Central Composite
2. Select no. of Numerical and Categorical factors.
3. Write Name of Factor, Units.
4. Put low and high value of factor in **Actual**. Never use coded values.
 1. Check for any negative values in +/- Alpha.
 2. If any of the Factor range is displaying Negative Values, Follow step mentioned on next slide.

Always check : Alpha values should not be in Minus as it is not possible to execute trials with minus values.

Children/Polic/Document/01/01/01/Design/Design-Expert 13.2

File Edit View Display Options Design Tools Help Top

Central Composite Design

Each numeric factor is set to 5 levels: plus and minus alpha (axial points), plus and minus 1 (factorial points) and the center point. If categorical factors are added, the central composite design will be duplicated for every combination of the categorical factor levels.

Number factors: 3 (2 to 10) Horizontal
 Categorical factors: 1 (0 to 10) CCD Options


Name	Units	Min	Low	Hi
A (Factor)	Stroke Level	%	-1	1
B (Factor)	Overhang Level	%	-1	1
C (Factor)	Curvature Level	%	-1	1

Enter factor ranges in terms of ± 1 levels
 Enter factor ranges in terms of alpha

Type: Full Block: 1

Points:
 Std center points: 14
 Center points: 6
 Alpha: 1.68179

Options... 20 Runs



- Alpha value determines the **position of axial run**.
- Default is **Rotatable** for up to 5 factors:
- Adv.: will have equal std. error of prediction

Replication: Replicates of factorial points: 1
 Replicates of axial (star) points: 1
 Center points: 6

Alpha:
 Rotatable ($\phi = 0$): 1.68179
 Spherical: 1.73205
 Orthogonal quadratic: 1.52465
 Practical ($\phi = 0$): 1.31687
 Face centered: 1.0
 Other: 1.31687

20 Runs

Cancel Continue >>

NUM 1
 11:25
 11-11-2014

For Help, press F1

Start

Curvature is best estimated by Rotatable Design

Rotatable: Each factor will be tested at 5 level
*“Recommended when all factor ranges are within allowable operating condition”
 i.e. Alpha range is positive for all factors*

Face Centered: Each factor will be tested at 3 level
 Use when region of interest and region of operability are nearly same.

For Negative Alpha Values – Option 1 (Face Centered – Covers Entire Factor Range)

MyDesign - Design Expert 10.2

File Edit View Display Options Design Tools Help Tips

Central Composite Design

Each numeric factor is set to 5 levels: plus and minus alpha (axial points), plus and minus 1 (factorial points) and the center point. If categorical factors are added, the central composite design will be duplicated for every combination of the categorical factor levels.

Numeric factors: 2 (2 to 50) Horizontal
Categorical factors: 1 (0 to 10) Vertical

Name	Units	Low	High	alpha	-alpha	
A (Factor)	Factor Level	%	2	6	2	0
B (Factor)	Disintegrant Level	%	2	9	2	0
C (Factor)	Surfactant Level	%	0.5	2	0.5	2

Enter factor ranges in terms of +/- 1 levels
 Enter factor ranges in terms of alphas

Type: Full Blocks: 1

Points
Total center points: 14
Center points: 0

alpha = 1 Options 20 Runs

CCD Options

Replication
Replicates of factorial points: 1
Replicates of axial (star) points: 1
Center points: 0

Alpha
 Rotatable (k + 6): 1.68179
 Spherical: 1.73205
 Orthogonal quadrates: 1.52465
 Practical (k + 5): 1.51957
 Face centered: 1.0
Other: 1.68179

Cancel Help

Cancel Continue >>

1

2

For Help, press F1

Start

15:34 15-11-2014

Steps:

1. First click on Option and select Face centered design.
2. Factor ranges will be automatically displayed in Alpha Columns

For Negative Alpha Values – Option 2 (Rotatable – Restricted Operating Range)

MyDesign - Design-Expert 9.0.2

File Edit View Display Options Design Tools Help Tips

Central Composite Design

Each numeric factor is set to 5 levels: plus and minus alpha (axial points), plus and minus 1 (factorial points) and the center point. If categorical factors are added, the central composite design will be duplicated for every combination of the categorical factor levels.

Numeric factors: 3 (2 to 50) Horizontal
Categorical factors: 1 (0 to 10) Vertical

	Name	Units	Low	High	alpha	alpha
A (Numeric)	Stirrer Level	%	2.21079	5.10002	2	
B (Numeric)	Overnight Level	%	2.80000	4.20119	2	5
C (Numeric)	Surfactant Level	%	0.00407	1.00001	0.5	2

Enter factor ranges in terms of +/- 1 levels
 Enter factor ranges in terms of alpha

Type: Full Blocks: 1

Points
Full center points: 14
Center points: 0

alpha = 1.60179 Options 20 Runs

Cancel Continue >>

NUM

11:39
11-11-2014

For Help, press F1

Windows taskbar icons: Start, Internet Explorer, Firefox, Chrome, Edge, Word, PowerPoint, Outlook

Enter same values which you have entered in Low & High Column

inscribing restricts the actual design region to the defined variable ranges by locating the axial points at the lower and upper bounds of the variable ranges

Steps:

1. First click on Option "Enter Factor Ranges in Terms of Alpha".
2. Enter Factor ranges you want to study in alpha columns

Selected Option 1 (Face Centered – Covers Entire Factor Range)

MyDesign - Design-Expert 10.2

File Edit View Display Options Design Tools Help Tips

Central Composite Design

Each numeric factor is set to 5 levels: plus and minus alpha (axial points), plus and minus 1 (factorial points) and the center point. If categorical factors are added, the central composite design will be duplicated for every combination of the categorical factor levels.

Numeric factors: 5 (2 to 50) Horizontal
Categorical factors: 1 (0 to 10) Vertical

	Name	Units	Lo	Hi	alpha	replicates
A (Dimension)	Slider Level	%	-2	8	2	5
B (Dimension)	Detergent Level	%	-2	5	2	5
C (Dimension)	Surfactant Level	%	-0.5	2	-0.5	2

Enter factor ranges in terms of +/- 1 levels
 Enter factor ranges in terms of alphas

Type: Full Blocks: 1

Points:
Not center points: 14
Center points: 6

alpha = 1 Options... 20 Runs

CCD Options

Replication:
Replicates of factorial points: 1
Replicates of axial (star) points: 1
Center points: 6

Alpha:
 Rotatable (k + 1): 1.68179
 Spherical: 1.73205
 Orthogonal quadratic: 1.52485
 Practical (k + 1): 1.31607
 Face centered: 1.8
1.68179

Cancel Continue

For Help, press F1

Start

NUM 15:34 15-11-2014

Steps:

1. First click on Option 1 and select Face centered design.
2. Factor ranges will be automatically displayed in Alpha Columns
3. Click "**Continue**"

MyDesign - Design-Expert 9.0.2

File Edit View Display Options Design Tools Help Tips

Central Composite Design

Numeric factors: 2 Horizontal
Categorical factors: 1 Vertical

	Name	Units	Type	Levels	L(1)	L(2)
1	Grade of silicon Oil		Nominal	3	Level 1 of 3	Level 2 of 3

Central Composite
Box-Behnken
One Factor
Mondrian-based
Optimal (random)
User Defined
Historical Data

Put Name, type and levels of categorical factor

-- Back Continue --

NUM

15:54
13-11-2014

For Help, press F1

Start

MyDesign - Design-Expert 9.0.2

File Edit View Display Options Design Tools Help Tips

Central Composite Design

Responses: 1 (1 to 999)

Name	Units
Dissolution at 30 min	% Drug release
Hardness	MPa
Q ²	100% Dev ²
Polynomial Form	

Central Composite
Box-Behnken
One Factor
Miscellaneous
Optimal (custom)
User Defined
Historical Data

Recheck the responses, Correct if required and Click on finish

For Help, press F1

Start

NUM

16:33
13-11-2014

File Edit View Display Options Design Tools Help Tips

Notes for WyDesign

Design (Active)

Summary

Graph Columns

Evaluation

Analysis

R1 Description of 3D

R2 Handles (Empty)

R3 DT (Empty)

R4 Polymorphic Form

Optimization

Numerical

Graphical

Post Analysis

Post Prediction

Confirmation

Coefficients Table

Design Tool

Design Layout

Run Sheet

Column Info Sheet

Pop-Out View

Select	Std	Run	Factor 1 A Binder Level %	Factor 2 B Dairings %	Factor 3 C Surfactant %	Factor 4 D Silicone Di. Grade	Response 1 Description & % Drug relea.	Response 2 Hardness kg	Response 3 DT Min Sec	Response 4 Polymorphic
	17	1	4	3.5	1.25	Aersol 200				
	24	2	6	5	0.5	Aersol 200				
	23	3	2	5	0.5	Aersol 200				
	15	4	4	3.5	1.25	Aersol 200				
	20	5	4	3.5	1.25	Aersol 200				
	25	6	2	2	2	Aersol 200				
	19	7	4	3.5	1.25	Aersol 200				
	26	8	4	3.5	1.25	Aersol 200				
	9	9	2	3.5	1.25	Aersol 200				
	31	10	4	2	1.25	Aersol 200				
	3	11	2	5	0.5	Aersol 200				
	16	12	4	3.5	1.25	Aersol 200				
	2	13	6	2	0.5	Aersol 200				
	6	14	6	2	2	Aersol 200				
	26	15	6	2	2	Aersol 200				
	28	16	6	5	2	Aersol 200				
	39	17	4	3.5	1.25	Aersol 200				
	7	18	2	5	2	Aersol 200				
	22	19	6	2	0.5	Aersol 200				
	30	20	4	3.5	1.25	Aersol 200				
	13	21	4	3.5	0.5	Aersol 200				
	27	22	2	5	2	Aersol 200				
	40	23	4	3.5	1.25	Aersol 200				
	10	24	6	3.5	1.25	Aersol 200				
	32	25	4	5	1.25	Aersol 200				
	20	26	4	3.5	1.25	Aersol 200				
	21	27	2	2	0.5	Aersol 200				
	14	28	4	1.4	1	Aersol 200				

For Help, press F1

Start

15-11-2014

**1. Design Layout will be displayed.
(Notice that -alpha and +alpha match the low and high levels in FCD)**

Step 4: Design Evaluation

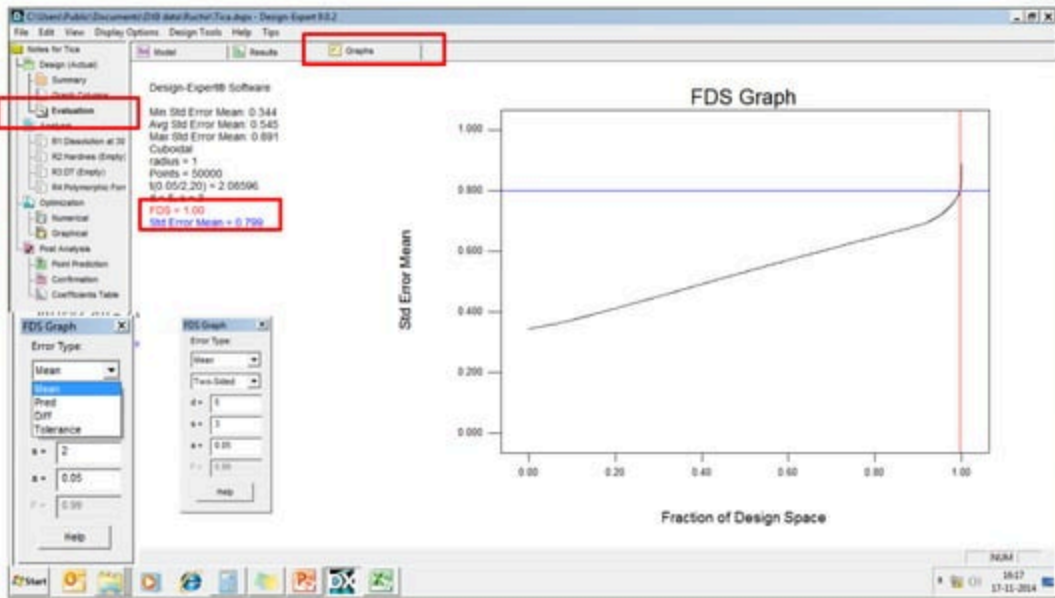
(Before Initiating Experimentation)

Evaluate Precision (Slide 1 of 3)

- Use the FDS graph to see if the responses can be estimated precisely enough: (Calculate Signal/Noise ratio)
 - Dissolution:
 - Want to estimate Mean Within $\pm 5\%$
 - Estimated Std. Deviation is 3% $5/3=1.7$
 - Hardness:
 - Want to estimate Mean Within ± 2 kp
 - Estimated Std. Deviation is 0.6 kp $2/0.6=3.33$
 - Disintegration Time:
 - Want to estimate Mean Within ± 2 min
 - Estimated Std. Deviation is 0.5 min $2/0.5=4$

Before running the experiments make sure the design meets your needs

Evaluate Precision (Slide 2 of 3)



When you have multiple responses, look at worst case first (min. ratio). If its OK, all others will also be good. In this case Dissolution ($\Delta/\sigma = 5/3 = 1.7$) is harder to realize than other responses.

Minimum FDS should be 0.8

Evaluate Precision (Slide 3 of 3)

- Use the **Mean error type** if the goal of the experiment is to provide an optimization model.
- Use the **Pred error type** if the goal of the experiment is to provide accurate predictions.
- Use the **Diff error type** as a substitute for power on response surface and mixture designs.
- Use the **Tolerance setting** if you need to meet tolerance specifications.
- FDS should be at least 0.8 or 80% for exploration, and 100% for robustness testing. FDS can be improved by adding runs, reducing the "s", increasing the "d", and increasing the "a".

Step 5: Perform Experiments and Input Data

Run Experiments

- Since design is precise enough, run the experiments and note the responses in response column.

The screenshot shows the Design Expert 8.0.2 software interface. A red box labeled '1' highlights the 'Design (Actual)' tab in the top-left corner. Another red box labeled '2' highlights the 'Run Sheet' button in the 'Design Tools' panel on the left. The main window displays a design table with columns for 'Run #1', 'Run #2', and 'Run #3'. The table contains various factors and their levels, such as 'Block', 'Binder Level', 'Dexamethasone LA', 'Surfactant LA', and 'Silicone Dioxide'. The 'Response at 2 min' column shows '% Drug release' values for each run.

Run #1	Run #2	Run #3
Block Block 1	Block 1	Block 1
Binder Level 4 %	6 %	2 %
Dexamethasone LA 3.5 %	5 %	5 %
Surfactant LA 1.25 %	0.5 %	0.5 %
Silicone Dioxide Aerospan 300 Grade	Aerosol 200 Grade	Aerosol 200 Grade
Response at 2 min % Drug release	% Drug release	% Drug release
Hardness N	N	N
DT N	N	N
Polymorphic Form N	N	N

You can use **“Run Sheet”** while execution of trial but not mandatory

Fill The Response Data.....

1

- Option 1: Enter data manually in Software
- Option 2: Export the file to excel, feed the data and simulate/import to your existing design

1

2

Factor 1 Enter Level %	Factor 2 B Dosegrs. %	Factor 3 C Surfactant %	Factor 4 D Soluone Di. Grade	Response 1 Dissolution % % Drug relea.	Response 2 Hardness kp	Response 3 DT Min Sec**	Response 4 Polymorphic		
4	3.5	0.5	Aeroperl 200	75	10.2	12	1		
4	3.5	0.5	Aeroperl 300	87	9.8	5	1		
6	5	0.5	Aeroperl 200	76	9.5	11	1		
2	2	0.5	Aeroperl 200	75	9.8	11	1		
6	5	0.5	Aeroperl 200	90	9.5	4.3	1		
2	2	0.5	Aeroperl 300	85	10	5	1		
3	5	0.5	Aeroperl 300	82	9.5	4	1		
6	2	0.5	Aeroperl 300	88	10	6	1		
6	2	0.5	Aeroperl 200	78	10.2	13	1		
2	5	0.5	Aeroperl 200	78	10.5	10	1		
4	3	1.25	Aeroperl 300	93	10.8	10.5	1		
4	3.5	1.25	Aeroperl 200	98	9.4	19	1		
4	3.5	1.25	Aeroperl 300	95	10.2	7.5	1		
6	3.5	1.25	Aeroperl 200	97	10.2	19	1		
2	3.5	1.25	Aeroperl 300	95	10	8	1		
4	5	1.25	Aeroperl 200	90	10.5	9	1		
4	3.5	1.25	Aeroperl 200	97	10.8	30	1		
4	3.5	1.25	Aeroperl 200	99	9.7	18	1		
4	5	1.25	Aeroperl 300	97	10.2	7	1		
4	3.5	1.25	Aeroperl 200	99	9.9	19	1		
4	3.5	1.25	Aeroperl 300	94	9.8	8	1		
4	3.5	1.25	Aeroperl 300	98	10.2	7.5	1		
4	3.5	1.25	Aeroperl 300	96	9.8	8	1		
4	3.5	1.25	Aeroperl 200	98	10.1	18	1		
3	3.5	1.25	Aeroperl 200	90	10.8	22	1		
3	3.5	1.25	Aeroperl 300	92	9.7	9	1		
3	10	4	2	1.25	Aeroperl 200	87	10.8	18	1
11	8	4	1.74	Aeroperl 300	94	10.4	16	1	

Fill The Response Data.....

2

C:\Users\Public\Documents\DOE data\Ruchi\Tica.dogs - Design-Expert 9.0.2

File Edit View Display Options Design Tools Help Tips

Notes for Tica

- Design (Codect)
 - Summary
 - Graph Columns
 - Evaluation
 - Analysis
 - R1 Dissolution at 30
 - R2 Hardness
 - R3 DT
 - R4 Polymorphic For
 - Optimization
 - Numerical
 - Graphical
 - Post Analysis
 - Point Prediction
 - Confirmation
 - Coefficients Table
- Design Tool
 - Design Layout
 - Run Sheet
 - Column Info Sheet
 - Pop-Out View

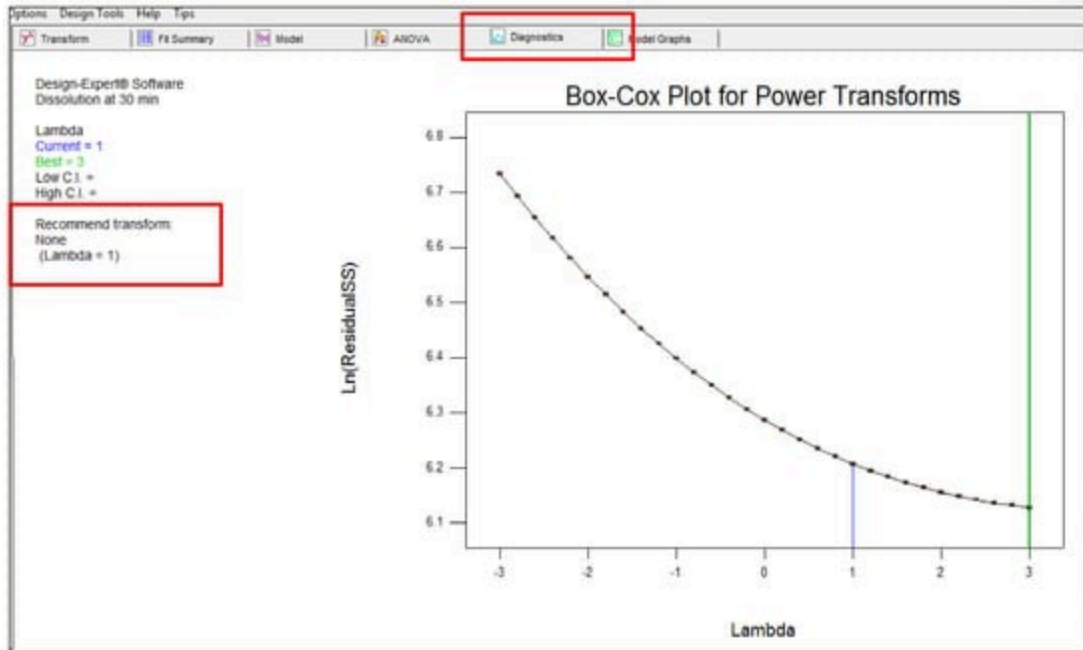
Std	Run	Factor 1 A Binder Level %	Factor 2 B Diameters %	Factor 3 C Surfactant %	Factor 4 D Silicone Di- Grade	Response 1 Dissolution a- % Drug relea	Response 2 Hardness kp	Response 3 DT Min/Sec"	Response 4 Polymorphic	
1	25	-1.000	0.000	0.000	(-1)	95	10	8	1	
2	35	27	-1.000	-1.000	1.000	(-1)	100	10	25	1
3	31	29	1.000	0.000	0.000	(-1)	92	9.7	9	1
4	28	30	0.000	0.000	0.000	(-1)	96	10.2	8	1
5	36	33	1.000	1.000	1.000	(-1)	97	9.8	25	1
6	3	34	0.000	-1.000	0.000	(-1)	93	10.5	10	1
7	2	40	0.000	0.000	-1.000	(-1)	87	9.9	5	1
8	34	2	1.000	1.000	1.000	(1)	99	10.5	26	1
9	1	3	0.000	0.000	-1.000	(1)	75	10.2	12	1
10	21	4	-1.000	1.000	1.000	(1)	97	10.4	25	1
11	33	8	0.000	-1.000	0.000	(1)	87	10.8	18	1
12	11	9	0.000	1.000	0.000	(1)	90	10.5	9	1
13	12	11	0.000	0.000	0.000	(1)	97	10.6	19	1
14	8	12	-1.000	0.000	0.000	(1)	97	10.2	19	1
15	37	18	0.000	0.000	0.000	(1)	98	10.5	19	1
16	18	19	0.000	0.000	0.000	(1)	94	9.9	22	1
17	20	20	1.000	-1.000	1.000	(1)	99	10.8	29	1
18	29	24	0.000	0.000	0.000	(1)	98	10.1	18	1
19	14	26	0.000	0.000	0.000	(1)	92	10.8	23	1
20	32	26	-1.000	-1.000	1.000	(1)	96	10.5	27	1
21	10	31	1.000	1.000	-1.000	(1)	76	9.5	11	1
22	40	32	-1.000	1.000	-1.000	(1)	78	10.5	10	1
23	27	35	1.000	-1.000	-1.000	(1)	70	10.2	13	1
24	4	36	0.000	0.000	1.000	(1)	97	10.6	28	1
25	13	37	-1.000	-1.000	-1.000	(1)	75	9.8	11	1
26	5	38	0.000	0.000	0.000	(1)	99	9.9	19	1
27	30	39	1.000	0.000	0.000	(1)	90	10.6	22	1

For Help, press F1

Start [Icons]

Step 6: Analysis & Interpretation

Data Transformation



1. Go to diagnostic tab
2. In Box-Cox plot, check for recommended transformation

Response: 1 Dissolution a Transform: None

--- WARNING: The Cubic Model and higher are Aliased ---

Summary (detailed tables shown below)

Model	Lack of Fit	Adjusted	Predicted
Source	p-value	R-Squared	R-Squared
Design Model	< 0.0001	0.8188	0.8222
Linear	< 0.0001	0.1593	0.5681
2FI	0.1562	0.2115	0.5074
Quadratic	0.0192	0.6245	0.7561
Cubic	0.2171	0.6225	0.7922

--- Design Model is recommended over Suggested Models ---

Sequential Model Sum of Squares (Type III)

Source	Sum of Squares	df	Mean Square	F Value	p-value
Mean vs Total	3.402E+005	1	3.402E+005		
Linear vs Mean	1057.12	4	414.28	17.95	< 0.0001
2FI vs Linear	210.39	6	35.06	1.70	0.1662
Quadratic vs 2	156.81	2	62.27	3.98	0.0192
Cubic vs Quad	200.55	10	20.05	1.53	0.2171
Residual	210.11	16	13.13		
Total	3.427E+005	40	8567.68		

"Sequential Model Sum of Squares (Type III)" Select the highest order polynomial where the additional terms are significant and the model is not aliased.

The Suggested model is selected because:

1. Quadratic model is significant, p-value < 0.05
2. Lack of fit is insignificant, p-value > 0.10
3. Having highest adjusted and predicted R-squares.

Never Select Aliased Model

View

Source	Std.	R-Squared	Adjusted	Predicted	PRESS	
	Dev.		R-Squared	R-Squared		
Linear	4.00	0.6723	0.6348	0.5681	1064.60	
2FI	4.54	0.7576	0.6740	0.5074	1214.14	
Quadratic	3.92	0.8334	0.7501	0.6270	919.39	Suggested
Cubic	3.62	0.9148	0.7922	0.5005	1216.40	Abased

"Model Summary Statistics": Focus on the model maximizing the "Adjusted R-Squared" and the "Predicted R-Squared"

Bookmarks 2

- Top
- Summary
- Sum of Squares
- Lack of Fit
- R-Squared

Start | [Icons] | [Icons] | [Icons] | [Icons] | [Icons] | [Icons] | [Icons] | [Icons]

- Focus on the Model maximizing the "Pred R-Squared", or equivalently minimizing the "PRESS"
- The diff. between Adjusted R-squared and Pred. R-Squared should be < 0.2

Analysis: Selection of Model

The screenshot shows the Design-Expert 9.0.2 interface. The 'Model' tab is selected, and the 'Selection' dropdown is set to 'Backward'. The list of terms in the model includes Intercept, A-Blender Level, B-Couplant Level, C-Surfactant Level, D-Silicone Dioxide, and various two-factor interactions (AB, AC, AD, AE, AF, AG, AH, AI, AJ, AK, AL, AM, AN, AO, AP, AQ, AR, AS, AT, AU, AV, AW, AX, AY, AZ, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BN, BO, BP, BQ, BR, BS, BT, BU, BV, BW, BX, BY, BZ, CA, CB, CC, CD, CE, CF, CG, CH, CI, CJ, CK, CL, CM, CN, CO, CP, CQ, CR, CS, CT, CU, CV, CW, CX, CY, CZ, DA, DB, DC, DD, DE, DF, DG, DH, DI, DJ, DK, DL, DM, DN, DO, DP, DQ, DR, DS, DT, DU, DV, DW, DX, DY, DZ, EA, EB, EC, ED, EE, EF, EG, EH, EI, EJ, EK, EL, EM, EN, EO, EP, EQ, ER, ES, ET, EU, EV, EW, EX, EY, EZ, FA, FB, FC, FD, FE, FF, FG, FH, FI, FJ, FK, FL, FM, FN, FO, FP, FQ, FR, FS, FT, FU, FV, FW, FX, FY, FZ, GA, GB, GC, GD, GE, GF, GG, GH, GI, GJ, GK, GL, GM, GN, GO, GP, GQ, GR, GS, GT, GU, GV, GW, GX, GY, GZ, HA, HB, HC, HD, HE, HF, HG, HH, HI, HJ, HK, HL, HM, HN, HO, HP, HQ, HR, HS, HT, HU, HV, HW, HX, HY, HZ, IA, IB, IC, ID, IE, IF, IG, IH, II, IJ, IK, IL, IM, IN, IO, IP, IQ, IR, IS, IT, IU, IV, IW, IX, IY, IZ, JA, JB, JC, JD, JE, JF, JG, JH, JI, JJ, JK, JL, JM, JN, JO, JP, JQ, JR, JS, JT, JU, JV, JW, JX, JY, JZ, KA, KB, KC, KD, KE, KF, KG, KH, KI, KJ, KK, KL, KM, KN, KO, KP, KQ, KR, KS, KT, KU, KV, KW, KX, KY, KZ, LA, LB, LC, LD, LE, LF, LG, LH, LI, LJ, LK, LL, LM, LN, LO, LP, LQ, LR, LS, LT, LU, LV, LW, LX, LY, LZ, MA, MB, MC, MD, ME, MF, MG, MH, MI, MJ, MK, ML, MM, MN, MO, MP, MQ, MR, MS, MT, MU, MV, MW, MX, MY, MZ, NA, NB, NC, ND, NE, NF, NG, NH, NI, NJ, NK, NL, NM, NN, NO, NP, NQ, NR, NS, NT, NU, NV, NW, NX, NY, NZ, OA, OB, OC, OD, OE, OF, OG, OH, OI, OJ, OK, OL, OM, ON, OO, OP, OQ, OR, OS, OT, OU, OV, OW, OX, OY, OZ, PA, PB, PC, PD, PE, PF, PG, PH, PI, PJ, PK, PL, PM, PN, PO, PP, PQ, PR, PS, PT, PU, PV, PW, PX, PY, PZ, QA, QB, QC, QD, QE, QF, QG, QH, QI, QJ, QK, QL, QM, QN, QO, QP, QQ, QR, QS, QT, QU, QV, QW, QX, QY, QZ, RA, RB, RC, RD, RE, RF, RG, RH, RI, RJ, RK, RL, RM, RN, RO, RP, RQ, RR, RS, RT, RU, RV, RW, RX, RY, RZ, SA, SB, SC, SD, SE, SF, SG, SH, SI, SJ, SK, SL, SM, SN, SO, SP, SQ, SR, SS, ST, SU, SV, SW, SX, SY, SZ, TA, TB, TC, TD, TE, TF, TG, TH, TI, TJ, TK, TL, TM, TN, TO, TP, TQ, TR, TS, TT, TU, TV, TW, TX, TY, TZ, UA, UB, UC, UD, UE, UF, UG, UH, UI, UJ, UK, UL, UM, UN, UO, UP, UQ, UR, US, UT, UU, UV, UW, UX, UY, UZ, VA, VB, VC, VD, VE, VF, VG, VH, VI, VJ, VK, VL, VM, VN, VO, VP, VQ, VR, VS, VT, VU, VV, VW, VX, VY, VZ, WA, WB, WC, WD, WE, WF, WG, WH, WI, WJ, WK, WL, WM, WN, WO, WP, WQ, WR, WS, WT, WU, WV, WW, WX, WY, WZ, XA, XB, XC, XD, XE, XF, XG, XH, XI, XJ, XK, XL, XM, XN, XO, XP, XQ, XR, XS, XT, XU, XV, XW, XX, XY, XZ, YA, YB, YC, YD, YE, YF, YG, YH, YI, YJ, YK, YL, YM, YN, YO, YP, YQ, YR, YS, YT, YU, YV, YW, YX, YY, YZ, ZA, ZB, ZC, ZD, ZE, ZF, ZG, ZH, ZI, ZJ, ZK, ZL, ZM, ZN, ZO, ZP, ZQ, ZR, ZS, ZT, ZU, ZV, ZW, ZX, ZY, ZZ.

To reduce the model use Backward selection

- **Select finalized model. In this case it is "Quadratic".**

Note:

There are four algorithms for selection, 1) Backward, 2) Forward, 3) Stepwise and 4) All-hierarchical.

For experiments with little or no collinearity all four will lead to a same reduced model. When the factors are correlated with one other, the reduced model differ depending on the selection method used.

Backward selection has the advantage of starting with all terms in the model.

Analysis: Anova with backward selection

ANOVA for Response Surface Reduced Quadratic model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	1968.55	4	492.14	34.70	< 0.0001 significant
C-Surfactant	1462.05	1	1462.05	103.08	< 0.0001
D-Silicone D	148.23	1	148.23	10.45	0.0027
CD	186.05	1	186.05	13.12	0.0009
C ²	172.23	1	172.23	12.14	0.0013
Residual	496.43	35	14.18		
Lack of Fit	351.59	25	14.06	0.97	0.5521 not significant
Pure Error	144.83	10	14.48		
Cor Total	2464.98	39			

- The least significant terms will be removed automatically
- Model P-value < 0.05
- Model Lack-of-fit > 0.10

Analysis: Full Vs Reduced Quadratic model

Full Model

Pop-Out View 3

View

Use your mouse to right click on individual cells for definitions.

Response 1 Dissolution at 30 min

ANOVA for Response Surface Quadratic model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value	Prob > F	significant
Model	2054.32	13	158.02	10.01	< 0.0001		significant
A ²	0.78	1	0.78	0.012	0.9154		
BF	13.53	1	13.53	0.86	0.3633		
C ²	60.56	1	60.56	3.83	0.0610		
Residual	410.66	26	15.79				
Lack of Fit	265.82	16	16.61	1.15	0.4245	not significant	
Pure Error	144.83	10	14.48				
Cor Total	2464.98	39					

Reduced Model

Pop-Out View 2

View

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value	Prob > F	significant
Model	1968.55	4	492.14	34.70	< 0.0001		significant
Residual	496.43	35	14.18				
Lack of Fit	351.59	25	14.06	0.97	0.5521	not significant	
Pure Error	144.83	10	14.48				
Cor Total	2464.98	39					

How do you compare full vs reduced model
Answer: reduction improves lack-of-fit

Analysis: Full Vs Reduced Quadratic model

Full Model

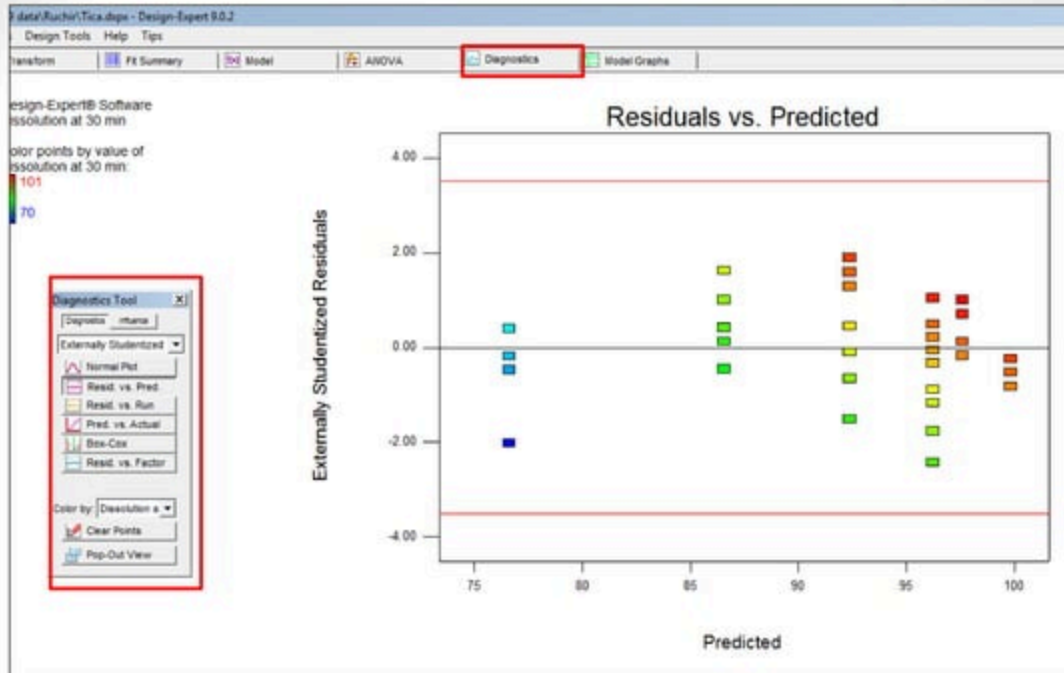
Std. Dev.	3.97	R-Squared	0.8334
Mean	92.22	Adj R-Squared	0.7501
C.V. %	4.31	Pred R-Squared	0.6270
PRESS	919.39	Adeq Precision	11.898

Reduced Model

Std. Dev.	3.77	R-Squared	0.7986
Mean	92.22	Adj R-Squared	0.7756
C.V. %	4.08	Pred R-Squared	0.7466
PRESS	624.61	Adeq Precision	17.424

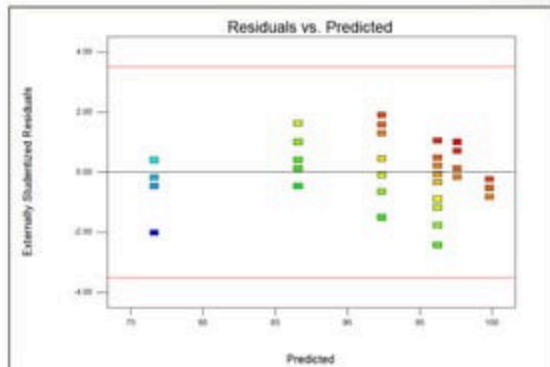
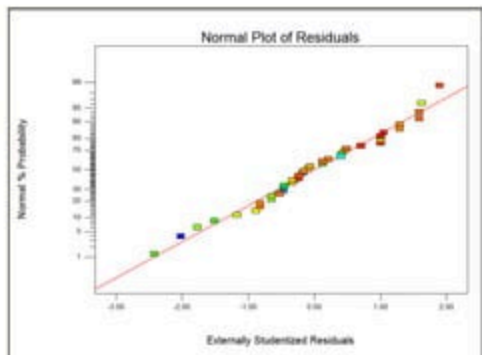
Predicted R-Squared and Adequate Precision improved with Reduced Model

Step 7: Diagnostic



1. Go to diagnostic plot and use diagnostic tool tab to confirm assumptions for ANOVA are met.
2. Check all the plots always

Analysis: Normal Plot & Residual Vs. Predicted Plots



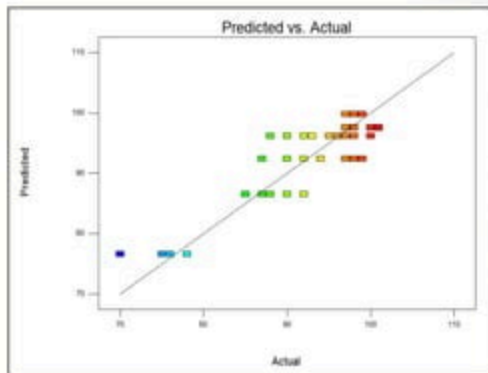
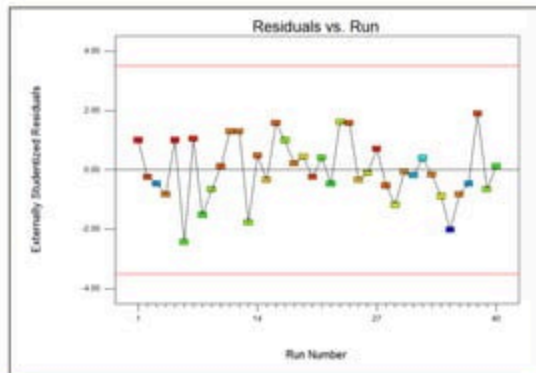
Normal plot of residuals:

- Check for normality of data.
- Residuals should follow a straight line.
- Some scatter is expected.
- Look for definite patterns, e.g. "S Shape".

Residuals Vs. Predicted:

- This plot is used to confirm the **constant variance assumption**
- All the points should be within the 3 sigma limits
- Some scatter is expected
- Look for definite patterns, e.g. **Megaphone "< Shape"**.

Analysis: Residual vs. Run & Predicted Vs Actual



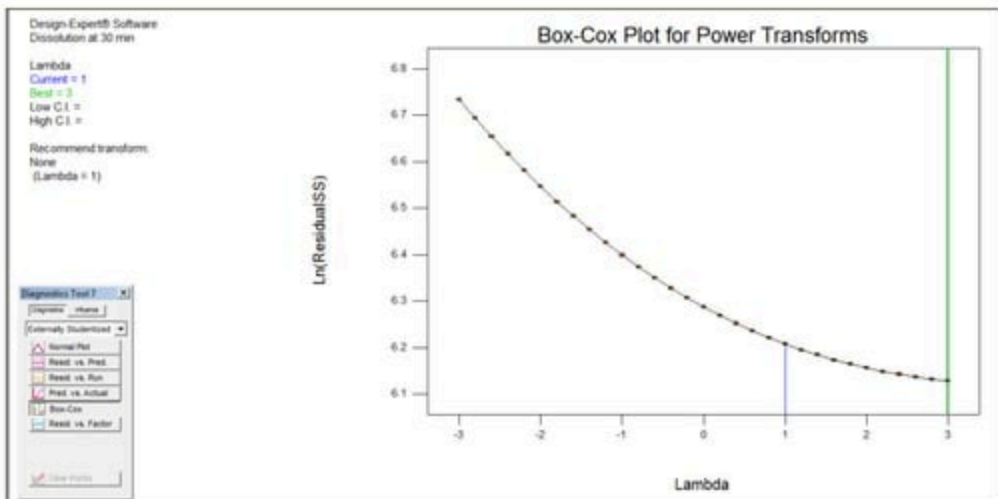
Residuals Vs. Run:

- Used to confirm the independence assumption.
- All the points should be within the 3 sigma limits.
- Some scatter is expected.
- If any point fall outside 3 sigma limit, this points are statistical outlier.
 - Problem with the model
 - Transformation problem
 - Wrong data entered
 - Wrong experiment done

Predicted Vs. Actual:

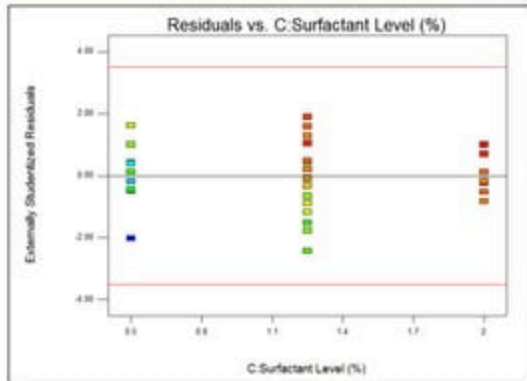
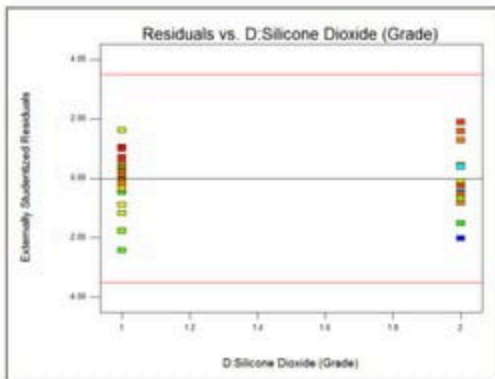
- Use to see how the model predicts over the range of data.
- Some scatter is expected.
- For optimization study it's not very important.
- Its imp. When you want to predict a response based on change in factor level.

Analysis: Box-Cox



Box-Cox plot tells you whether transformation of data may help. Notice that it says "none" for recommended transformation

Analysis: Residual Vs. Factors

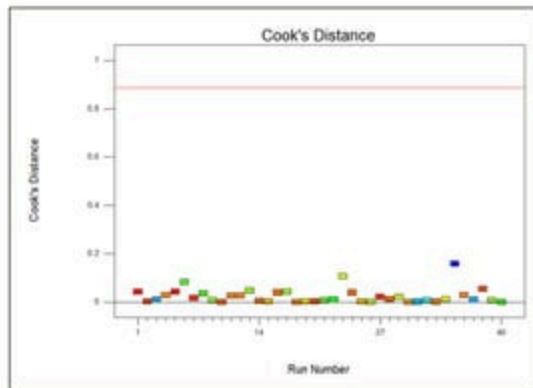


GOOD: Random scatter both ends

BAD: More variation at one end

Watch **ONLY** for very large differences.

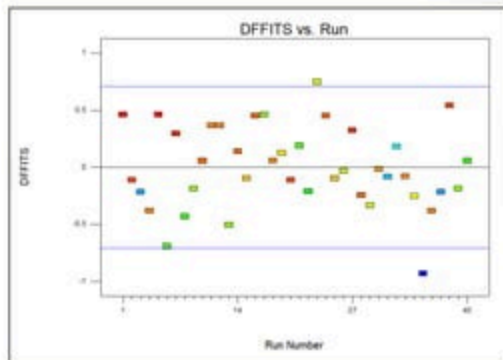
Analysis: Influence – Cook's Distance & DFFITS



Cook's Distance:

- Cases with large values relative to other cases should be investigated.
- They could be caused by recording errors, an incorrect model or a design point far from the remaining cases.

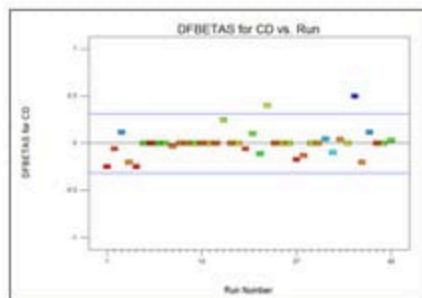
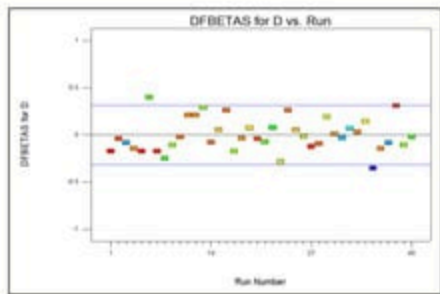
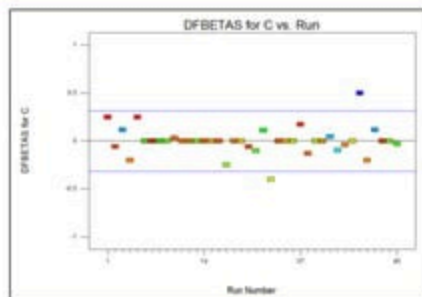
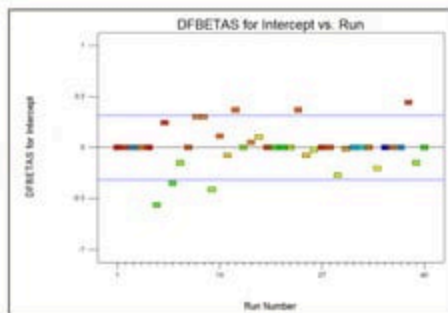
helps if you see more than one outlier in other diagnostic plots. Investigate the run with the largest Cook's Distance first.



DFFITS – Difference in Fits:

- Look for values outside the blue limits.
- A high value indicates the predicted response for a particular run changes when the particular run is removed from the regression.

Analysis: Influence - DFBETAs



DFBetas: Difference in Betas

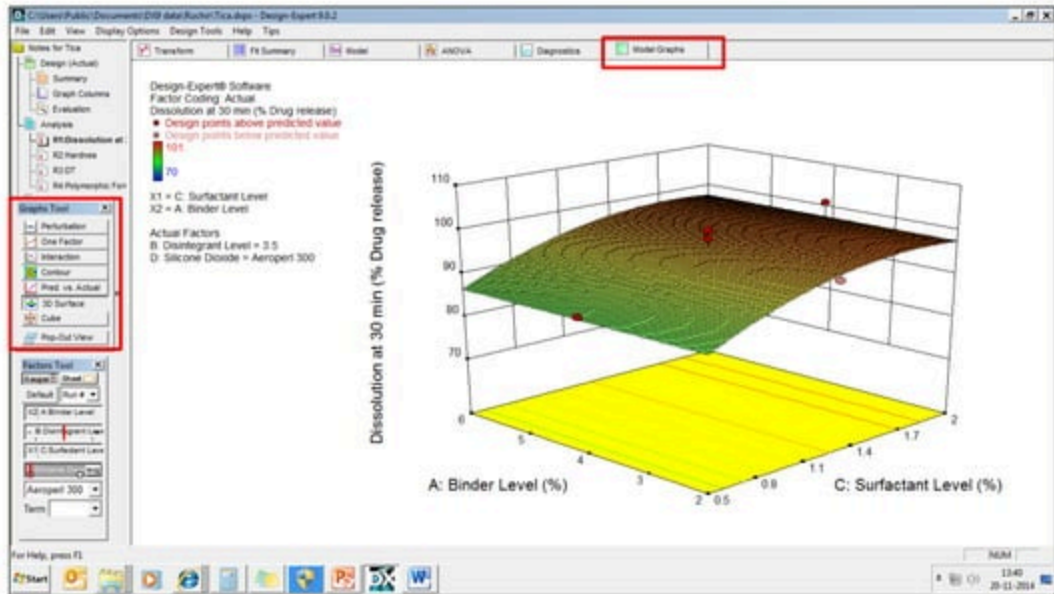
Used to identify model and data problems.

You must click through the Term Pull down menu to look through all this graphs.

Response Surface - Influence

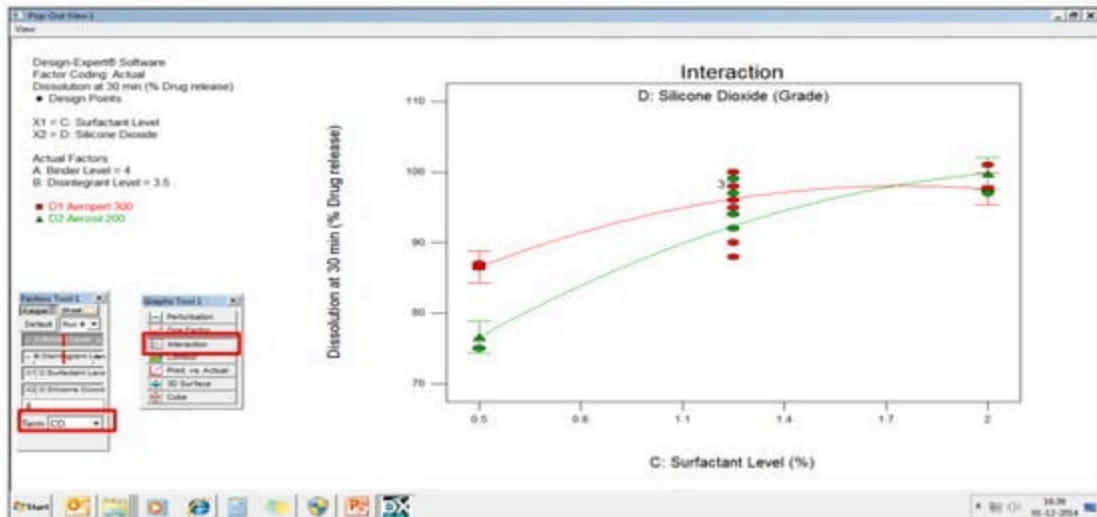
TOOL	Description	WIIFM
Internally Studentized Residuals	Residual divided by the estimated standard deviation of that residuals	Normally constant σ^2
Externally studentized Residuals	Residuals divided by the estimated std dev of that residual, without the i^{th} Case (deletion statistic)	Outlier detection and/or model misspecification
Cook's Distance	Change in joint confidence ellipsoid (regression) with and without a run (deletion statistic)	Overall Influence
DFFits (difference in fits)	Change in prediction with and without a run; the influence a run has on the predictions (deletion statistic)	Influence on fitted value
DFBetas (difference in betas)	Change in each model coefficient(beta) with and without a run (deletion statistic)	Influence on coefficients

Model Graphs



Look at different model graphs, i.e. interaction, 2D, 3D, perturbation to understand the impact of factor on responses.

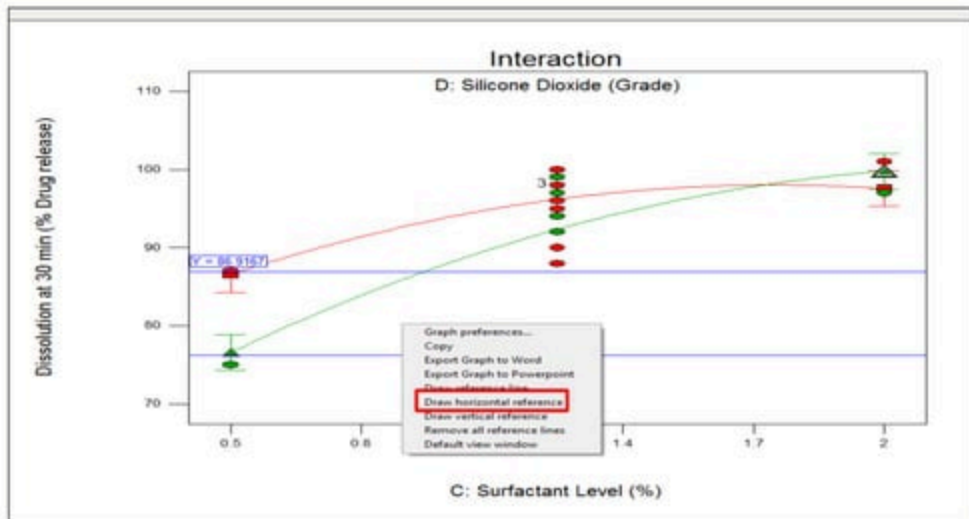
Interaction Graph



With Aerosil 200, increasing Surfactant significantly improves the dissolution. While with Aeroperl 300 there is only a slight increase in dissolution with increase in surfactant level.

If the LSD bars for two means overlap, the difference in those means is not large enough to be declared significant change.

Interaction Graph



To aid in seeing whether the bars overlap, try right clicking on LSD bar and choosing "Draw horizontal reference".

Analysis of Each factor

- Analyze all the factors using similar method

Develop Good Model

- Be sure that the fitted surface adequately represents your process before you use it for optimization
 1. A significant model: Large F-value with $p < 0.05$
 2. Insignificant lack-of-fit: F-value with $p > 0.10$
 3. Adequate precision > 4 .
 4. Well behaved residuals: Check diagnostic plots!

Creating Knowledge Space

- For multiple response optimization, it's better to use Numerical optimization.

The screenshot displays the Design-Expert 9.0.2 software interface. The left-hand navigation pane shows a tree structure with 'Optimization' expanded and 'Numerical' highlighted with a red rectangle. The main window is titled 'A:Binder Level' and contains the following elements:

- Criteria:** A list of response variables: A:Binder Level, B:Disintegrant Level, C:Surfactant Level, D:Silicone Dioxide, Dissolution at 30 min, Hardness, DT, and Polymorphic Form.
- Goal:** A dropdown menu set to 'Around the mean' with a value of 4.
- Limits:** Input fields for Lower (2) and Upper (6).
- Weights:** Input fields for Lower (1) and Upper (1).
- Importance:** A dropdown menu set to '+++'.
- Options:** A button labeled 'Options...'
- Graph:** A plot showing a vertical line at the value 4 on a horizontal axis. The axis is labeled 'A:Binder Level' and has tick marks at 2 and 6.

Data to be captured in PDR

- Goal of the study
- Study name
- Factors studied and corresponding level
- Responses measured
- Design matrix
- Graphs and conclusion – Interaction/Pareto/Contour Etc.
- Result obtained from study as pasted below

Table 19 Results from formulation study#2

Magnesium Stearate Level (%)	Talc Level	Tablet hardness at a fixed compression pressure (kP)	30 min Dissolution (%)	Tablet content uniformity (% RSD)
1	I	10	89	2.0
0.5	I	9.9	92	2.4
0.25	I	Fail to tablet	Fail to tablet	Fail to tablet
1	II	9.8	88	1.9
0.5	II	9.7	93	2.2
0.25	II	Fail to tablet	Fail to tablet	Fail to tablet

Data to be captured in PDR.... 2

- ANOVA

	Coefficient		Standard	t for H₀		
Factor	Estimate	DF	Error	Coeff-0	Prob > t 	VIF
Intercept	86.99	1	0.000			
A-API Part Size	-4.97	1	0.000	-7978.72	< 0.0001	1.00
B-MgSt level	-2.55	1	0.000	-7978.72	< 0.0001	1.00
D-Roler pressur	-3.11	1	0.000	-7978.72	< 0.0001	1.00
AD	-0.50	1	0.000	-7978.72	< 0.0001	1.00
AD	4.15	1	0.000	7978.72	< 0.0001	1.00
ED	-1.61	1	0.000	-7978.72	< 0.0001	1.00
ABD	-0.29	1	0.000	-7978.72	< 0.0001	1.00

Thank you !!!!!

Annexure

Selection Of Design

<u>Number of Factors</u>	<u>Comparative Objective</u>	<u>Screening Objective</u>	<u>Response Surface Objective</u>
1	<u>1-factor completely randomized design</u>	–	–
2 - 4	<u>Randomized block design</u>	<u>Full</u> or <u>fractional factorial</u>	<u>Central composite</u> or <u>Box-Behnken design</u>
5 or more	<u>Randomized block design</u>	<u>Fractional factorial</u> or <u>Plackett-Burman</u>	Screen first to reduce number of factors

Interaction Study

Factorial Design

Curvature Effect

RSM - Central Composite Design

Excerpt of QbD IR

Note to Reader: When center points are included in the factorial DOE, it is possible to test if the curvature effect is significant. The data analysis is done by separating the curvature term from the regression model in an adjusted model. This approach provides the factorial model coefficients as if there were no center points. If the curvature is significant, the design should be augmented to add runs that can estimate the quadratic terms. On the other hand, if the curvature is not significant, the adjusted model and unadjusted model will be similar.

In this mock example, we have not included ANOVA results for each DOE. In practice, please be advised that ANOVA results should accompany all DOE data analysis, especially if conclusions concerning the significance of the model terms are discussed.

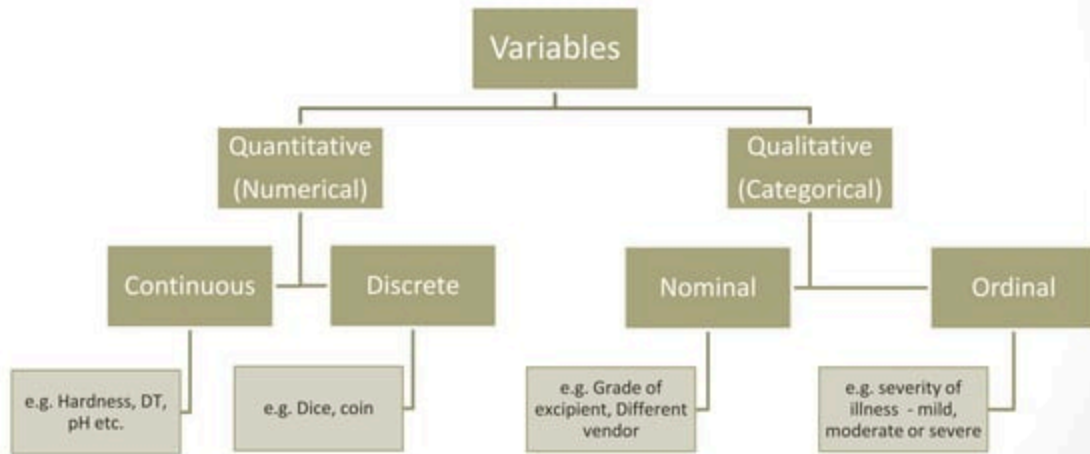
For all DOE data analysis, the commonly used alpha of 0.05 was chosen to differentiate between significant and not significant factors.

Significant factors for $T_{50\%}$ of ER coated beads

Since center points were included in the ER polymer coating optimization DOE, the significance of the curvature effect was tested using an adjusted model. The Analysis of Variance (ANOVA) results are presented in Table 34.

Variables

Variables are attributes that we want to study in the sample



Variables

- Variables can be further classified as:
 - **Dependent/Response.** Variable of primary interest (e.g. Dissolution, Hardness). Not controlled by the experimenter.
 - **Independent/Factor**
 - called a **Factor** when controlled by experimenter. (e.g. Disintegrant level, Binder level, Kneading time, Chopper Speed etc.)