Computer-Aided Formulation Development and Optimization

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INTRODUCTION

- Formulation and development is an art of selection of pharmaceutical substances and processing. Recently, use of computer tools in the formulation and development of pharmaceutical product has increased.
- "Optimization" makes the perfect formulation & reduce the cost.
- Generally optimization in pharmaceuticals refer changing one variable at a one time, so to obtain remedy of a problematic formulation.
- To identify the correct solution of problematic formulation use of computer tools (optimization procedure) is smarter way to solve problem.

Why Optimization necessary ?

- To reduce the cost of formulation
- Safety and reduce the error
- Save the time
- Reproducibility
- Innovation
- Efficacy

Fundamentals of Optimization And Its Term

Optimization means:- Optimization means choosing the best element from some set of available alternatives.

Factor:- It is an assigned & independent variables, Such as temperature and concentration. Those are quantitative & qualitative.

Level:-Those are designation assigned to the factor. Level indicated as high, low, medium such as excipient ratios.

Response:- It is an outcome of an experiment. Eg:- Disintegration time Dissolution time

Response surface:- Response surface representing a relationship between the independent variables X1 & X2 and dependent variables Y

VARIABLES DURING TABLET FORMULATION

INDEPENDENT VARIABLES	DEPENDENT VARIABLES
X1 Diluent Ratio	Y1 Disintegration time
X2 Compression Force	Y2 Hardness
X3 Disintegrant Level	Y3 Dissolution
X4 Binder Level	Y4 Friability
X5 Lubricant Level	Y5 Weight uniformity

Design of Experiment For Formulation And Development

- All pharmaceutical products are formulated to specific dosage form drugs to be effectively delivered to patient typical pharmaceutical dosage form include tablets, capsules, solution suspension, etc.
- Different dosage form required different technology usually present different technological challenge for formulation & development .
- Due to complex challenges, formulations scientist used effective methodology like as design of experiment and statistical analysis for formulation and development .
- Formulation scientist used this method for process optimization and process validation .

Computer Software

Software	Silent feature
Design Expert	Powerful & compressive package used for optimizing pharmaceutical formulation
Minitab	Powerful DOE software for automated data analysis MS Excel compatibility.
DOE PRO XL	MS-Excel compatible DOE software for automated data analysis
CARD	Powerful DOE software for data analysis include graphics and help feature

SOP of Design Expert Software

1) File new design

2) Click response surface

3) Add numeric factor

4) Write name of independent variables

5) Add low limit and high limit

6) Continue

7) Add response

8) Run will be generated

Applying DOE to Formulation And Development

Factor	Low Level (mg)	High Level (mg)	Effect on
Diluent ratio	10	15	Disintegration time
Disintegrant level	5	10	Dissolution
Binder level	4	6	Friability
Lubricant level	6	8	Weight uniformity

Major Technical Challenges In Tablet Formulation Development

Major challenge	Potential process Technologies
Uniformity	Fluid Bed Granulation
Compatibility	Highly Compressible excipient
Flow ability	Free Flowing excipients
Dissolution	Tablet Matrix containing polymer

Common Formulation Factor For The Tablet And Applicable Design of Experiment

Factor	Response	DOE approaches
%API	Uniformity	Factorial
% Binder	Compactibility	Fractional factorial
%Disintegrant	Flowability	Central composite
%Glidant	Dissolution	Central composite mixture
%Lubricant	Stability	Box -Behnken

STEP IN FORMULATION AND DEVELOPMENT

1) Excipient compability-

First step in formulation and development is campactability study

those select the excipient .

- Those are physically and chemically compatible with the API
- It should be biodegradable and compatible
- By applying doe we can understand interaction effect with API over a time.
- By applying DOE we can understand the interaction effect of excipient with API .

Feasibility Study

- Excipient are selected from excipient compability study and next step is the feasibility study.
- Those conducted to determine the manufacturing process that enable the
- Formulation development.
- Those evaluated technical challenges associated with the formulation and
- development
- In next slide potential process are given to overcome the challenges in formulation and development.
- As technical challenges overcome the next step is selection of manufacturing process.

Selection Of Manufacturing Process

1) Formulation preliminary study:-

- It gives idea about selection of final excipient

2) Formulation optimization study:-

- Those define the optimum level of excipient in the each formulation.
- During this many formulation factor and response are evaluated in tablet formulation and development.
- These problem can be solve by applying doe.
- Those gives idea to understand formulation system and optimize the
- formulation by choosing best combination of excipient.

Design and Conduct a Formulation Optimization Study

FACTOR	EXCIPIENT	LOW SRENGTH %	HIGH STENGTH%
API	-	5	10
Diluent	MCC	59	30
Disintegrant	Crospovidone	5	5
lubricant	Magnesium stearate	1	1

Various variables of Drug & Excipients

VARIABLES	NO. OF LEVELS
API%	2
DILUENT	3
DISINTEGRANT	2
LUBRICANT	2

Combination for excipient in the initial formulation study are evaluated, a full factorial DOE is required 24 study

Table VI: A design-of-experiments example for a tablet formulation preliminary study.

	API %	Diluent	Disintegrant	Lubricant
1	5	Microcrystalline cellulose	Crospovidone	Magnesium stearate
2	5	Microcrystalline cellulose	Crospovidone	Stearic acid
3	5	Microcrystalline cellulose	Sodium starch glycolate	Magnesium stearate
4	5	Microcrystalline cellulose	Sodium starch glycolate	Stearic acid
5	5	Lactose	Crospovidone	Magnesium stearate
6	5	Lactose	Crospovidone	Stearic acid
7	5	Lactose	Sodium starch glycolate	Magnesium stearate
8	5	Lactose	Sodium starch glycolate	Stearic acid
9	5	Starch	Crospovidone	Magnesium stearate
10	5	Starch	Crospovidone	Stearic acid
11	5	Starch	Sodium starch glycolate	Magnesium stearate
12	5	Starch	Sodium starch glycolate	Stearic acid
13	10	Microcrystalline cellulose	Crospovidone	Magnesium stearate
14	10	Microcrystalline cellulose	Crospovidone	Stearic acid
15	10	Microcrystalline cellulose	Sodium starch glycolate	Magnesium stearate
16	10	Microcrystalline cellulose	Sodium starch glycolate	Stearic acid
17	10	Lactose	Crospovidone	Magnesium stearate
18	10	Lactose	Crospovidone	Stearic acid
19	10	Lactose	Sodium starch glycolate	Magnesium stearate
20	10	Lactose	Sodium starch glycolate	Stearic acid
21	10	Starch	Crospovidone	Magnesium stearate
22	10	Starch	Crospovidone	Stearic acid
23	10	Starch	Sodium starch glycolate	Magnesium stearate
24	10	Starch	Sodium starch glycolate	Stearic acid

Table VII: A design-of-experiments example for a tablet optimization study.

	API (%)	Lactose:MCC	Crospovidone (%)	Magnesium stearate (%)
1	5	2:1	5	0.5
2	5	2:1	5	1.0
3	5	2:1	10	0.5
4	5	2:1	10	1.0
5	5	1:1	5	0.5
6	5	1:1	5	1.0
7	5	1:1	10	0.5
8	5	1:1	10	1.0
9	5	1:2	5	0.5
10	5	1:2	5	1.0
11	5	1:2	10	0.5
12	5	1:2	10	1.0
13	10	2:1	5	0.5
14	10	2:1	5	1.0
15	10	2:1	10	0.5
16	10	2:1	10	1.0
17	10	1:1	5	0.5
18	10	1:1	5	1.0
19	10	1:1	10	0.5
20	10	1:1	10	1.0
21	10	1:2	5	0.5
22	10	1:2	5	1.0
23	10	1:2	10	0.5
24	10	1:2	10	1.0

CONCLUSION

- Application of (DOE) design of experiment formulation scientist evaluate the all formulation factors in systematically and timely manner to optimize the formulation and manufacturing process
- Design of experiment & statistical analysis have been used in the formulation development
- Optimization of pharmaceutical process and product by systematic approach facilitate the effective process validation & scale up because of the robustness of the formulation and manufacturing process.

Thank you