A REVIEW ON OPTIMIZATION TECHNIQUES IN PHARMACEUTICAL FORMULATION AND PROCESSING

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***Abstract*- This review devotes a large amount of space to the ideas involved in creating drug goods in all of their forms. The choice of ingredients and manufacturing procedures for that dosage form must take into account all of the components' physical, chemical, and biological characteristics. [1] The final product must satisfy the practical mass production criteria for process and product repeatability as well as the demands imposed on it from the perspective of bioavailability. In reality, during these inspections, development reports for both the formulation and the process are scrutinized. The theoretical formulation and target processing parameters, as well as the ranges for each excipient and processing parameter, should all be understood by the pharmaceutical scientist. The use of optimization techniques enables the exploration and defence of ranges for formulation and processing parameters as well as a depth of understanding. One chooses a formulation by applying logic to the choice of the various excipients and manufacturing processes for a particular product. A formulation that has been qualitatively defined can now be quantitated with the help of optimization. The process of optimization is not screening. [2]**

***Keywords*: Optimization, Formulation, Experiment, Variables**

INTRODUCTION:

The ideas involved in creating drug goods in all of their forms are covered in-depth in this book. The choice of ingredients and manufacturing procedures for that dosage form must take into account all of the components' physical, chemical, and biological characteristics. The final product must satisfy the practical mass production criteria for process and product repeatability as well as the demands imposed on it from the perspective of bioavailability.[3] Preapproval inspections for all new drug applications must include a formulation and process justification due to the present regulatory environment. In reality, during these inspections, development reports for both the formulation and the process are scrutinized. The theoretical formulation and target processing parameters, as well as the ranges for each excipient and processing parameter, should all be understood by the pharmaceutical scientist.[4] The use of optimization techniques enables the exploration and defence of ranges for formulation and processing parameters as well as a depth of understanding. The use of optimization techniques enables the exploration and defence of ranges for formulation and processing parameters as well as a depth of understanding. One chooses a formulation by applying logic to the choice of the various excipients and manufacturing processes for a particular product. A formulation that has been qualitatively defined can now be quantitated with the help of optimization. The process of optimization is not screening.[5]

OPTIMIZATION PARAMETERS:

The optimization technique was divided into two types:
1)Problem Type
2)Variables

1) PROBLEM TYPE

The problem type of parameters again grouped into:

A. CONSTRAINED TYPE:

Constrained types place restrictions on the system as a result of physical limits or purely pragmatic factors. The tablet's hardness and short breakdown time (less than 15 minutes) provide the best explanation for this.

B. UNCONSTRAINED TYPE:

The system is not confined by physical constraints in the unconstrained type, or perhaps even just by pragmatic ones. However, there is always a restriction in the pharmaceutical industry that is imposed by a physical restriction or perhaps just by the formulator's desire to place or requirement to place on a system.[6]

2) VARIABLES:

There are many factors in pharmaceutical formulation and processing, but they can be divided into two types:

A. DEPENDENT VARIABLES:

- What are the responses or features of the materials in process?

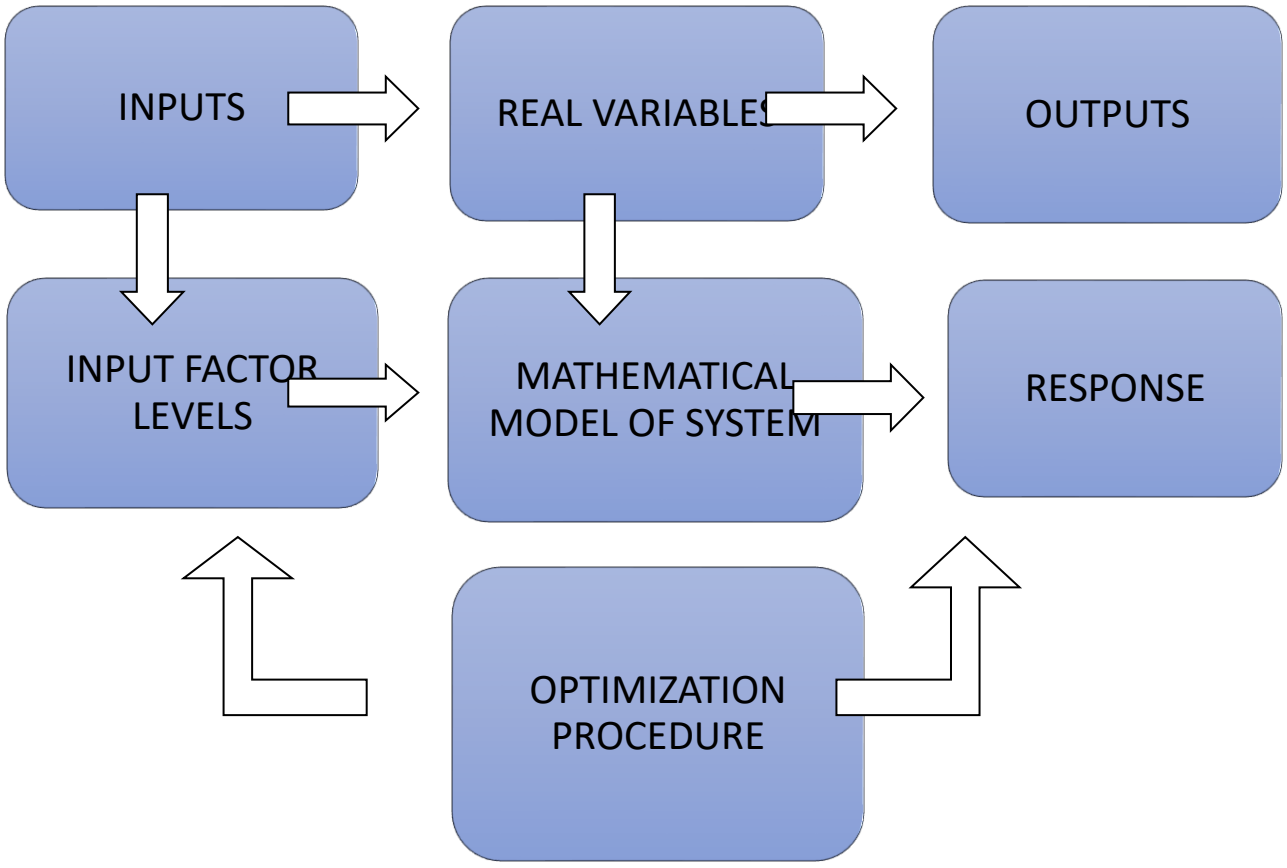
B. INDEPENDENT VARIABLES:

- These are immediately under the control of the formulator.[6]

TABLE 1; EXAMPLES OF DEPENDENT AND INDEPENDENT VARIABLES

DEPENDENT VARIABLES	INDEPENDENT VARIABLES
Disintegration time	Diluent ratio
Hardness	Compressional force
Dissolution	Disintegrant level
Friability	Lubricant level
Weight uniformity	Binder level

FLOW CHART FOR OPTIMIZATION:



TERMS USED IN OPTIMIZATION:

VARIABLES:

These are the data's measurements, values, and properties. Dependent and independent variables are the two sorts of variables. Independent variables include lubricant concentrations, drug-to-polymer ratios, and other variables that are not dependent on any other value. The concentration of the independent variable influences the dependent variables.

FACTOR:

A factor is an assigned variable; examples include grade, temperature, lubricant, drug-to-polymer ratio, polymer-to-polymer ratio, and concentration. You can include either a qualitative or quantitative component. Quantitative components such as concentration (1%, 2%, and so on), drug to polymer ratio (1:1, 1:2, and so on), and so on are assigned a numerical value. Qualitative elements are those that cannot be mathematically quantified, such as equipment kinds, humidity levels, and polymer grades. They have specific characteristics.

LEVELS:

The values or names assigned to a factor are its levels; an example of a level is concentration. One level is 1%, and another is 2%. Two separate plasticizer kinds exist, each with a unique grading factor. Levels are typically classified as low, moderate, or high. For simplicity of calculation (high level), numeric and discrete levels are typically transformed to -1 (low level) and +1 (high level). The standard conversion formula is X, which is the average of the two levels. Level equals half of the level difference where 'X' stands for a number.[7]

RESPONSE:

A reaction is commonly thought of as the result of an experiment. We will investigate the effect of disintegration time, buoyancy duration, thickness, and other parameters.

EFFECT:

The effect is the difference in reaction caused by changing the values of an element. This explains the link between factors and levels.

INTERACTION:

It is also linked to the term effect, which represents the cumulative impact of two or more variables on a response.[8] Consider the combined effect of lubricant and glidant on tablet hardness. We can take conclusions about the optimizations from it.

- A factor's effect on a reaction, such as how a change in the drug-to-polymer ratio affects the dissolving rate.
- The contribution effect, which determines whether two components contribute to a response in an additive or antagonistic manner, such as any relationship between tablet hardness or granule flow quality and lubricant and glidant concentration.
- The formulation that, in our opinion, works best. [9]

EXPERIMENTAL DESIGN:

A statistical method that proposes or prescribes a specific set of variable combinations is known as an experimental design. The number and location of design points within the experimental zone are determined by the number of impacts that must be estimated. Several experimental designs are used depending on the number of elements, their levels, likely interactions, and the order of the model. Each experiment can be represented graphically as a point within the experimental domain.[10] The co-ordinate of a point, or the value assigned to variables, defines it in space.[11][12]

TYPES OF EXPERIMENTAL DESIGN:

Experimental deign can be divided into many types:

1) Completely Randomized Design
2) Randomized Block Design
3) Factorial Design

A. Full
B. Fractional

4) Response Surface Methodology

A. Central Composite Design
B. Box Behnken Design

5) Adding Centre Points
6) Three Level Full Factorial Design

ADVANTAGES OF EXPERIMENTAL DESIGN:

- There will be more innovation as a result of the opportunity to improve procedures.
- Regulatory trust in stable products is higher.
- More efficient production technology transfer.
- Batch failures are reduced.
- These findings have been replicated.

USES OF EXPERIMENTAL DESIGN:

It is used to determine the reasons for response variability, to determine the conditions under which the optimal (highest or lowest) response is attained, to evaluate responses at various levels of controlled variables, and to construct a response prediction model.[13]

1) COMPLETELY RANDOMIZED DESIGN:

For the experimental units, this approach to optimization employs randomized block designs or random sequence runs. For example, if the principal component has three levels and each level is to be performed thrice, we must set up nine trials. For example, the process temperature can be adjusted to be the least temperature (1), mean temperature (0), or maximal temperature (1). Eqn.2 can define all completely randomized designs with one or more primary components.[14][15]

$$N = k \times L \times n \quad \ldots\ldots\ldots\ldots (1)$$

Where,

k = the number of factors,
L = the number of levels, and
n = the number of replications.

The experimental plans for randomized block designs must have 18 tests for two components with three levels, each of which must be repeated thrice. For example, we can use the randomized block design to determine whether a change in feed material throughout the pyrolysis process has a significant impact on yields given a specific set of fixed process settings.[16][17]

2) RESPONSE SURFACE METHODOLOGY:

The experiments in this approach are designed to provide the form of the response surface, which is then used to investigate the local functions as well as estimate the interactions and quadratic effects (if they exist). This strategy is commonly known as 'RSM design,' and it can be applied to

- Enhance and optimize process conditions
- Resolve process issues and identify weak point
- Increase the process's resistance to external and uncontrollable influences.

RSM is one of the most widely used and well-liked design-of-experiment approaches for managing and optimizing a wide range of technical processes, including chemical technology [35]. RSM provides various advantages, including the ability to extract relevant data on the correlations and interactions between variables that affect yield (such as chemicals, catalysts, and process parameters).[19][20]

The central composite design, also known as the Box-Wilson central composite design, can be used to develop an experimental approach. The tested variables are translated into their corresponding coded values xi) using Eq.

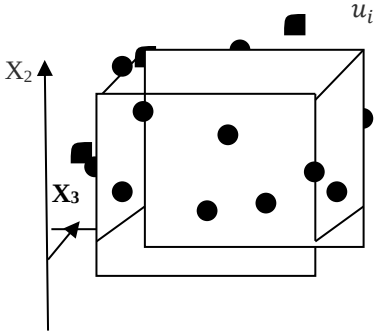
$$X_i = \frac{(ui - ui0)}{2}$$

$$u_i^0 = \frac{\left(u_i^{max} - u_i^{min}\right)}{2}$$

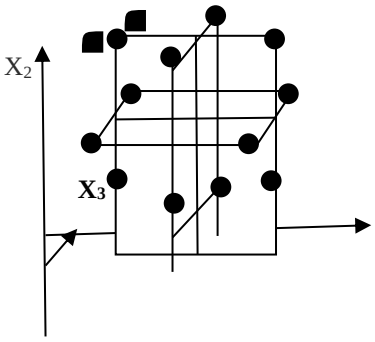
$$\Delta u_i = \frac{\left(u_i^{max} - u_i^{min}\right)}{2}$$ [21]

Where u_i^0 is the central point of the new coordinate system (basic level) and Δu_i is the planned change in the value of the factor u (variation intervals). After conducting all scheduled experiments in accordance with the prepared design of experiments (DOE), the coded values can be returned to the original variables for easier interpretation.[22] For this process, the data should be subjected to the inverse transformation using Eq.

$$u_i = u_{i0} + x_i . \Delta u_i$$



A)The cube of BBD method



B) three interlocking 2^2 Factorial design

For the **BBD method**, the number of experiments (*N*) can be defined as Eq.2

$$N = 2k\,(k - 1) + C_0 \quad \text{..... (2)}$$

Where,

k is the number of factors and

C_0 is the number of central point's [23]

In the same way as in the preceding scenario, each parameter can be coded at three levels: 1 (minimum), 0 (centre), and +1 (maximum), spanning the whole study range. Several chemical and physical processes have been optimized using this method.[24][25]

3) RANDOMIZED BLOCK DESIGN:

- One factor or variable is of key relevance in this case.
- To control non-significant components, an important technique known as blocking can be used to limit or eliminate their contribution to experimental error.[26]

4) FACTORIAL DESIGN:

Factorial design is a statistical research approach that recognizes the interactive effect of every possible combination of variables in a set of trials. A full factorial experiment is a statistical design that includes two or more factors, each with a discrete possible value or "level," and the experimental units include all conceivable combinations of these levels across all such factors.[27] A fully crossed design is another name for a fully factorial design. Through an experiment, the researcher was able to investigate the effects of the individual components and their interactions on the response variable. In factorial experiments, each component normally has only two levels. A factorial experiment with two components, each taking two levels, would have four treatment combinations, and is known as a 2x2 factorial design.

Factorial Modifications and Designs The mathematical model of the experimental design consists of two or more "factors" that act on two or more "levels." [28]

These come into two varieties. Fractional factorial design vs. full factorial design.

FULL FACTORIAL DESIGN:

YX :22 ,23 ,32,3 3 X=Factors and Y= levels Factorial Designs First-degree mathematical models serve as the foundation for factorial designs (full or fractional).

Each factors(n) influence at different levels (x), as well as their interactions, with the total number of experiments as Xn.

Factorial design (FD), often known as experimental designs for first degree models, is the most widely used technique. A design of experiments (DOE) is most easily created by testing two or more variables (n) at different levels. In a full factorial approach, all factors are connected on all levels, and the number of experiments is f n, where f is the factor and n is the level. The 32 full factorial design employs nine experiments, the 42 employs sixteen, and the 52 employs twenty-five. When the level is raised to 3, 33, 43, and 53 experiments will be carried out. Naturally, the number of experiments increases and exceeds what is reasonable. As a result, levels 2 are often used to limit the number of studies. If each factor has the same number of levels, for example, 22, 33, etc., the design is said to be symmetric. If the number of levels differs from the factor, for example, 23 or 32, the design is considered to be asymmetric. However, if it is necessary to carry out the design for all necessary experiments, fractional factorial design (FFD) can be considered. Experiments are routinely terminated early in this setting. FFD is a subset (1/Xp) of full FD, where p specifies the fractionation degree. The total number of experiments for FFD is given by F n-p. A "trial" or "run" is the name given to each experiment. Tables 2, 3, and 4 list common symbols, data interpretation, experimental design representation, and interactivity, in that order.[29][30]

Table 2. Standard symbols for a particular ratio of drug: excipients

Formulations	Standard symbols	Effect (%drug release)
Low drug + low excipients	1	10%
Low drug + high excipients	A	10%
High drug + low excipients	B	20%
High drug + high excipients	Ab	30%

Note: low and high value refers to the low and high concentrations presented for the drug and excipients. Interaction = [ab-b]- [a-(1)] / 2 = 5%

TABLE 3. Experimental Matrix

Experiment	f_1	f_2	f_3	Interpretation
1	-1	-1	-1	Zero level interaction
2	-1	+1	-1	Main factor effect f_2
3	+1	-1	-1	Main factor effect f_1
4	-1	-1	+1	Main factor effect f_3
5	+1	+1	+1	Interaction between f_1, f_2, f_3

2^2 design (4 experiments can be conducted) and 2^3 design (8 experiments can be carried out). Low (-1) and high (+1) levels are combined together.

DEMONSTRATION OF FACTORIAL DESIGN:

Adetoun GE et al. has reported the implementation of factorial designing, in his experiment. To study the type of gum as a binding agent (B), its concentration (C) and relative density (D) of the tablet on tensile strength (TS), brittle fracture index (BFI), disintegration time (DT) and crushing strength-friability/ disintegration time ration (CSFR/ DT) of paracetamol tablets, experiments were performed in a factorial design, formulations statistics. Here each of high variables were utilized as "high-level" (subscript H) and "low- level" (subscript L). Number of experiments were 2^3 i.e., 8. [31][32][33]

Thus the combinations were:

$B_LC_LD_L$, $B_LC_LD_H$, $B_LC_HD_L$, $B_LC_HD_H$
$B_HC_HD_H$, $B_HC_HD_L$, $B_HC_LD_H$, $B_HC_LD_L$

B_L: represents the formulation with binding agents Delonix regia seed gum + tragacanth or acacia gum + tragacanth.
B_H: represents the formulation with binding agent's tragacanth + acacia gum or delonix regia seed gum + acacia gum.
C_H and **C_L** represents high (5% w/w) and low concentration (2% w/w) of gum binding agent respectively.
D_L and **D_H** represents tablet relative densities of 0.80 and 0.90 respectively.[34][35]

It was possible to analyse the effects of each of the three factors (B, C, D) on the mechanical/disintegration qualities of the tablets by combining the findings from the combinations into a number of sets and determining if the variables were interacting independently of one other.

By adding all "high" values of B and subtracting the sum of "low" levels of B, the impacts of raising B from low to high levels on mechanical/ disintegration characteristics were discovered.

¼ {($B_HC_HD_H$ + $B_HC_HD_L$ + $B_HC_LD_H$ + $B_HC_LD_L$) – ($B_LC_LD_L$ + $B_LC_LD_H$ + $B_LD_HD_L$ + $B_LC_HD_H$)}

C and D were treated in the same way. The outcomes of combinations in which they exist at "high" and "low" levels were then added together, and the sum of the sums was removed to give the interaction coefficient. As an example, for B and C:

¼ {($B_LC_LD_L$ + $B_LC_LD_H$ + $B_LC_HD_L$ + $B_LC_HD_H$) – ($B_HC_HD_H$ + $B_HC_HD_L$ + $B_HD_LD_H$ + $B_HC_LD_L$)}[36][37][38]

A zero result indicates no interaction; however, if the interaction coefficient departs from zero, the two variables in question were interacting. The greater the difference between the coefficient and zero, the stronger the interaction. At a 5% probability level, the data were subjected to analysis of variances (ANOVA).[39]

DEMERITS OF FACTORIAL DESIGN:

- Insignificant factors may be difficult to identify over time.
- It is impossible to separate the aliased effects.
- If the outcome demonstrates unfavourable impacts, all experiments conducted at that level are rendered useless.
- In the worst-case scenario, the entire experimental plan must be rebuilt and repeated.
- It may not be cost effective and takes extra time.

THREE LEVEL FULL FACTORIAL DESIGN:

The Three Level Design is abbreviated as 3k factorial design. It indicates that k factors are considered at three levels. These are typically classified as low, intermediate, and high level. The digits 0, 1, and 2 symbolize these levels. One might consider utilizing the digits -1, 0 and +1, although this could be confusing for a two-level design because 0 is used only for centre points. As a result, we will use the 0,1,2 scheme. Three-level designs were created to handle the case of nominal factors at three levels and to account for probable curvature in response functions. A third level enables the examination of a quadratic relationship between the answer and each continuous parameters.[40]

Unfortunately, due to the limited number of runs, the three-level concept is unworkable in terms of cost and effort.[35] A two-level design with centre points, for example, is significantly less expensive while still providing a very effective (and representational) means of detecting whether or not there is curvature.[41]

APPLICATIONS:

- High Performance Liquid Chromatographic
- Formulation and Processing
- Culture Medium Analysis Formulation in Virological Studies
- Pharmacokinetic Parameter Study
- Chemistry in Clinical Practise Pharmaceutical Chemistry

USES:

- During the microencapsulation process.
- Offer solutions to large-scale production issues.
- The modification improves the physical and biological qualities.
- Provides regulatory bodies with stringent assurances of outstanding pharma product quality.
- During the microencapsulation process.

ADVANTAGES OF OPTIMIZATION:

- It is more clarity,
- It saves time,
- It improves formulation irregularities,
- It changes one variable at a time to solve a problem function,
- It is easier to improve and glow,
- You operate more effectively, and
- You better comply with the laws and regulations.

DISADVANTAGES OF OPTIMIZATION:

- It requires more repetition to find the genuine optimum,
- It is impractical and expensive to used,
- It is not a substitute for proper laboratory scale inquiry, and
- It is more difficult to troubleshoot than rule-based simulations.

CONCLUSION:

The levels of variables for achieving the best reaction were assessed. For different optimization challenges, different optimization approaches are utilised. Optimization strategies are employed during the development process. The better the product, the more profit the corporation makes.[42][43] Optimization aids in the manufacture of an optimal product with the specified bioavailability parameters.

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