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Review Article

# Optimization techniques: An introductory overview

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## ABSTRACT

In today's pharmaceuticals optimization is emerged as a technique for the best compromising answer to a particular question. The term optimization means to optimize something, or use something at its best. Optimization is finding a perfect, effective or functional answer. There is no single solution to design optimization tasks. Many techniques are available for this. In this article an attempt is made to give an introduction to the various parts and methods related to the optimization techniques such as terms used in optimization, optimization parameters, process of optimization and methods used in the optimization. Here a special emphasis is given to the factorial design which is the most used technique in the area of formulation development.

**Key words**: Optimization, factorial design, formulation development.

## INTRODUCTION

***OPTIMIZATION:***

Many a times finding the correct answer is not a simple and straight forward, in such cases using an optimization procedure for best compromise is the smatter way to solve the problem. But optimization is not easy as stated[1].

The word optimize is defined as to make as perfect, effective, or functional as possible. During a development of a new project one generally experiments by a series of logical steps carefully controlling the variable & changing one at a time until a satisfactory result is produced. But under the circumstances the best one is often simply the last one prepared. It is satisfactory but how close is it to the optimum (i.e. best)

***Terms used in Optimization:***

***Variables:*** These are the measurements, values, which are characteristics of the data. There are two types of variables, dependent and independent variables. Independent variables are the variables, which are not dependent on any other value e.g., concentration of lubricants, drug to polymer ratio, etc. Dependent variables are dependent on the concentration of independent variable used.

***Factor:*** Factor is an assigned variable such as concentration, temperature, lubricating agent, drug-to-polymer ratio, polymer-to-polymer ratio or grade. A factor can be qualitative or quantitative. A quantitative factor has a numerical value to it e.g., concentration (1%, 2% so on), drug to polymer ratio (1:1, 1:2 etc). Qualitative factors are the factors, which are not numerical, e.g., Polymer grades, humidity condition, type of equipment etc. These are discrete in nature.

***Levels:*** The levels of a factor are values or designation assigned to the factor, e.g., concentration (factor) 1% will be one level, while 2% will be another level. Two different plasticizers are levels of grade factor. Usually levels are indicated as low, middle or high level. Normally for ease of calculation the numeric and discrete levels are converted to

-1 (low level) and +1 (high level).

The general formula for this conversion is

X — the average of the two levels

Level =Half the difference of levels

Where 'X' is the numeric value.

***Response:*** Response is mostly interpreted as the outcome of an experiment. It is the effect, which we are going to evaluate i.e., disintegration time, duration of buoyancy, thickness, etc.

***Effect:*** The effect of a factor is the change in response caused by varying the levels of the factor. This describes the relationship between factors and levels.

***Interaction:*** It is also similar to the term effect, which gives the overall effect of two or more variables (factors) of a response. For example, the combined effect of lubricant (factor) and glidant (factor) on hardness (response) of a tablet.

From the optimization we can draw conclusion about

- Effect of a factor on a response i.e., change in dissolution rate as the drug to polymer ratio changes.
- The relationship between various factors and response i.e.,

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quantitative change of a response as we change the factors and its levels.

- The contribution effect i.e., whether two factors are contributing additively or antagonistically for a response, e.g., any relationship between concentration of lubricant and glidant on hardness of the tablet or flow property of the granules.
- The best formulation (according to our need).

***OPTIMIZATION PARAMETERS***[2]

The optimization parameters are classified into two types-

A) Problem type

B) Variables

A) Problem type

The problem type of parameters again grouped

a) Constrained type

Constrained types are, restrictions placed on the system by means of a physical limitations or perhaps by simply practical based. This can best explained by taking hardness of tablet and its disintegrate time in less than 15 min.

b)Unconstrained type

In unconstrained type there are no restrictions placed on the system by means of a physical limitations or perhaps by simply practical based.

But in pharmaceuticals, there is always a limitation of a means of a physical limitation or perhaps by simply practically the formulator wishes to place or must place on a System. So, in pharmaceuticals the unconstrained optimization problem is almost nonsexist.

B) Variables

There are several Variables in pharmaceutical formulation and processing but generally variables can be classified into

a) independent variables

b) dependent variables

a) independent variables

These are the variables which are directly under the control of the formulator, such as mixing time etc.

b) dependent variables

These are the variables which are not directly under the control of the formulator, these variables are the responses or the characteristics of the in process materials or the results. These are a direct result of any change in the formulation or a process such as homonogenicity of the mixed granules.

***Optimization Process:***

In general the optimization process involves the following steps:

1. Analysis and define the problems

a) What are the objectives?

b) What is the nature of problem?

c) What is not known?

d) What is already known?

2. Based on previous Knowledge and data, a preliminary choice can be made such as which process is to be adopted and which excipients are to be used.

3. Selection of a model, based on the results of the factor screening.

4. The experiments are designed accordingly and are executed.

5. The responses are analyzed for statstics by ANOVA. Test on lack of fit is done to get an empirical mathematical model for each individual responses.

6. The responses are screened by using multiple criteria to get the values of independent variables. For example restriction of hardness to 6-8 kg/cm$^2$ and disintegration time < 5 min for a tablet formulation to get the most probable values of the independent variables such as type of lubricants or their concentration, disintegrating agent, etc.

**EXPERIMENTAL DESIGNS** [3,4]:

Experimental design is a statistical design that prescribes or advises a set of combination of variables. The number and layout of these design points within the experimental region depends on the number of effects that must be estimated. Depending on the number of factors, their levels, possible interactions and order of the model, various experimental designs are chosen. Each experiment can be represented as a point within the experimental domain. The point being defined by its co-ordinate (the Value given to variables) in the space.

***I) Factorial Design:***

***Histroy***[5]

Factorial designs were used in the 19th century by John Bennet Lawes and Joseph Henry Gilbert.Ronald Fisher argued in 1926 that "complex" designs (such as factorial designs) were more efficient than studying one factor at a time. A factorial design allows the effect of several factors and even interactions between them to be determined with the same number of trials as are necessary to determine any one of the effects by itself with the same degree. First, whenever we are interested in examining treatment variations, factorial designs should be strong candidates as the designs of choice. Second, factorial designs are efficient. Instead of conducting a series of independent studies we are effectively able to combine these studies into one. Finally, factorial designs are the only effective way to examine interaction effects.

***a) Full factorial design***

It is an experimental design, which uses dimensional factor space at the corner of the design space. Factorial designs are used in experiments where the effects of different factors or conditions on choice for simultaneous determination of the

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effect of several factors and their interactions.

The simplest factorial design is the 2 factorial designs, where two factors are considered each at two levels, leads to four experiments, which are situated in 2-dimensional factor space at the corners of a rectangle.

If there are 3 factors, each at two levels, eight experiments are necessary which are situated at the corners of an orthogonal cube on a 3 dimensional space. The number of experiments is given by 2, where 'n' is the number of factors.

If the number of factors and levels are large, then the number of experiments needed to complete a factorial design is large. To reduce the number of experiments, fractional factorial design can be used (i.e., ½ or ¼ of the original number of experiments with full factorial design).

The fitting of an empirical polynomial equation to the experimental result facilitates the optimization procedure. The general polynomial equation is as follows:

$Y = B_0 + B_1X_1 + B_2 X_2 + B_3 X_3 + + B_{12} X_1X_2 + B_{13}X_1X_3 + B_{23}X_2X_3$ —-

Where Y is the response, $X_1$, $X_2$, $X_3$ are the levels (concentration) of the 1, 2, 3 factors and $B_1$, $B_2$, $B_3$, $B_{12}$, $B_{13}$, $B_{23}$, are the polynomial coefficients, $B_0$ is the intercept (which represents the response when the level of all factors is low).

**b. *Plackett-Burman Design***

It is a fractional factorial design with K = m*4 experiment, for screening of (K-i) variables. Where K is the number of variables and m is the number of levels.

**c. *Star Design***

Star design is simply a $2^2$ factorial design rotated over 45° angle in the space. A center point is usually added, which may be replicated to estimate experimental error, so there will be three levels for each factor where quadratic effect can be measured, but the interaction effect cannot be measured as in case of the full factorial design. In star design, 2k factorial designs are rotated over 45° in (k-i) direction in k-dimensional space with a replicated center point. k is the number of factors in the design. This results in 2k+R experiments, where R is the replicate of the center point.

**d. *Central Composite Design*.**

A better design that encompasses the advantages of factorial design or fractional factorial design or the star design, is the central composite design(CCD). This design is developed by Box and Wilson. It is composed of +2k Factorial design or Fractional factorial design.

***2* k star design.***

This design enables the estimation of a full second-order model. The equation for two factors is given by

$B_0 + B_1 X_1 + B_2 X_2 + B_{12} X_1X_2 + B_{11} X_{12} + B_{22} X_{22}$

**II ) Box design**

In central composite design each factor has five levels. If the number of factors increases, the number of experiments may become too high. The Box designs for three or more factors are economical alternative in which each factor is given three levels. The design is called an orthogonal balanced incomplete block design. It can be split into a set of incomplete blocks, which means that every effect is not estimated in every block, but every factor effect is measured as equal number of times with a balanced partition over the different blocks.

***III) Doehiert Hexagon or Uniform Shell design***

Doehiert proposed uniform shell designs, starting with an equilateral triangle, mirrored in one side to a hexagon. The hexagon is expandable in 2- dimensional space by mirroring the center point in the outward sides. The equally spaced design points are uniformly distributed in concentric circles. It is also expandable in 3-dimension to concentric spherical shells. Due to the uniform distribution, models based on this design provide, a good basis for interpolation. A disadvantage may be that the number of levels is not same for all factors. The design may be started with one side of the hexagon parallel to the most important axis.

***IV) Mixture design:***

For mixtures of components (such as drugs and excipients in the formulation), special models have been derived, based on the mixture constraints. A fraction cannot be negative, and sum of the fractions of the components should be equal to one. An important property is that the number of coefficients to be estimated is reduced. The mixture constraint has consequences for the experimental designs. Factors cannot be chosen freely. In a two-component mixture, only one faction (variable) can be chosen, while in three component mixture only two fractions and so on. The remaining fraction completes the sum to one, which implies a dimension reduction. For k variable, the factor space can be represented geometrically by a (k-1) dimensional regular simplex, for two components a line, for three, a triangle and for four a tetrahedron.

***V) Simplex Lattice design[1]***

Simplex Lattice designs are used to explore the interior and the boundaries of the simplex. The number of factors determines its dimensions. The pattern of design points in the factor space and their number depend on the degree (the term of highest order) of the model that is postulated. The points are distributed orderly over the factor space, forming a lattice. The factors can be controlled accurately and precisely. The coefficients of model equations can be calculated easily.

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**VI) Extreme-Vertices design**

It often occurs in formulation studies that the whole factor space is not accessible for experiment or that some areas are expected not to give useful responses. In an Extreme-Vertices design, observations are made at the corners of the bounded design space, at the middle of the edges and at the center of the design space. These can be used for the mixture composition as well as in combination with factorial designs..

***VII ) Evolutionary methods[2]***

In the method the formulator makes a very small change in the formulation or process, but it makes so many times That he or she can determine statistical whether the product has improved. If it has be makes another change in the same direction many times and notes.The results continues until further change do not improve the product.

This methods is useful where there is a continue production . but due to the reasons like

i) EVOP is not substitute to G.M.P

ii) due to regulatory subject

iii) because of the necessarily small changes utilized, it is not particularly suitable for lab.

***VIII) D-Optimal:[5]***

"D-Optimal" means that these designs maximize the information in the selected set of experimental runs with respect to a stated model.

The D-Optimal design maximizes the determinant, of which is an overall measure of the information. Geometrically, this corresponds to maximizing the volume in a dimensional space.

**A D-Optimal design is suggested when:**

- There is a linear constraint on the factor settings, reducing the experimental region to an irregular polyhedron. There are no classical designs that can well investigate an irregular region. A D-Optimal design is then the preferred choice as it makes efficient use of the entire experimental space.
- There are formulation factors, with lower and upper bounds, and possibly additional constraints, making the region an irregular polyhedron.
- There are qualitative factors, with more than two levels and there is no mixed level design available, or the mixed level design suggests too many runs to be acceptable.
- The objective is Response Surface Matter (RSM) and there are qualitative factors.
- The number of experimental runs affordable is smaller than the number of runs of any available classical design.

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