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Review Article

Optimization as an effective tool in pharmaceutical development: A review

Sohail Y. Sayyed*, Ravindra A. Karande, Pravin G. Morankar

Department of Pharmaceutics, St. John Institute of Pharmacy and Research, Palghar (E), Maharashtra, India

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ABSTRACT

Pharmaceutical industry is industry of complex processes and procedures. Development of a new dosage form in formulation and development takes a lot of efforts, the effect of various process variables and different parameters involved in the process. It becomes very difficult to study the process outputs while performing the process, so there is a need to understand the process variables initially at the start of the process and keep an eye on those parameters affecting the outputs throughout the process. Optimization is defined as, to make as functional, perfect, as effective as possible. It is used in formulation and processing, to find the best way of analyzing the effect of process variables, their influence on process and process outputs. Optimization is process of finding the best way of using the existing resources while considering of all factors that influence decisions in any experiment. Optimization technique provides both an ability to explore and depth of understanding and define ranges for formulation and processing factors. Optimization technique is a beneficial tool to quantitate a formulation that has been qualitatively determined. The current review tries to enlighten the potential use and application of optimization technique as an effective tool in designing pharmaceutical dosage form.

Keywords: Optimization, Variables, Design of experiment, Factorial design, Randomized design, Systematic approach.

INTRODUCTION

The pharmaceutical dosage should be designed to meet the patients need and indented product performance. Pharmaceutical companies adopt certain strategies to meet their requirement for example empirical approach or systematic approach or combination of both. The systematic approach to development is also referred as quality by design which includes certain aspects of use of incorporation of prior knowledge, quality risk management, and use of knowledge management throughout the life cycle of product. The quality by design approach enhances the percentage of expected desired quality of product and reduces the risk associated with the formulation and development. QbD is referred as Quality by design which is a systemic approach to development. It begins with the predefined objectives and highlight product and process understanding and controls

Address for Correspondence: Mr. Sohail Sayyed, St. John Institute of Pharmacy and Research, Palghar, Maharashtra, India; E-mail: Sayyadsohail520@gmail.com

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based on enriched science and quality risk management. The concept of QbD is an approach which covers the better scientific understanding of the critical process and product qualities. QbD describes a pharmaceutical development approach referring to manufacturing processes and formulation design and development to maintain the intended product quality. The term optimized is defined as to make "as perfect as efficient as functional as possible" It is the process of finding the best way of using existing resources while taking in to account of all the factors that influences decision in any experiment. Optimization increases the ease of the pharmaceutical scientist to understand theoretical formulation and the target processing parameters which range for each experiment and processing factors.[1][2]

ASICS OF OPTIMIZATION

Design variable: These are the measurement or values that are characteristic of the data. The parameters which describe the design of the system are called as design variables. Optimization process starts with the identifying the design variables. Design variables are generally bound i.e they have value of maximum and minimum values. There are some criteria which one should take into consideration while identifying the design variables.[1][2]

I. The design variables should be independent of each other.
II. The numbers of variable should be kept minimum as far as possible.
III. At the initial formulation stage, some independent parameters are considered as design variable later on that can be gives fixed value.

Table. 1: Types of variables[1][2]

Dependent variables	**Independent variables**
Are the responses or characteristics that are	Are under control of formulator
Developed due to concentration of independent variables.	Variables which are not dependent on any value
e.g. Dissolution time, friability, Hardness	e.g. concentration of lubricant, drug to polymer ratio, compression force, mixing time etc.

Factors: Factors are assigned variable such as the concentration, temperature, lubricating agents, drug polymer ratio, polymer polymer ratio. A factor can be qualitative or quantitative. Quantitative factor has a numerical value to it: e.g. concentration (1%, 2%) a drug polymer ratio (1:1, 1:2). Whereas qualitative factors are no numerals e.g. Polymer grades, humidity or type of equipment. These are discrete in nature.[1][2]

Level: The levels are the values which are assigned to the factors, e.g. in drug to polymer ratio 1:1 will be one level whereas 1:2 will be another level. The levels are indicated as high, low and medium level and there are assigned the code for ease of calculation as shown in table.2 [1][2]

Table. 2: Factors and their coded forms[1][2]

Factors	**Levels and their coded forms**		
Compression speed (RPM)	20 rpm	25 rpm	30 rpm
	Low level (-1)	Medium Level (0)	High level (+1)
Spray rate (in case of coating)	5mg/minute	10mg/minute	15mg/ minute
	Low level (-1)	Medium Level (0)	High level (+1)

Response: It is an outcome of the experiment, helps to identify the effect of combinations of variables setting that jointly optimize the single response or set of response. Response helps to evaluate the impact of variables and their levels on the response. For e.g. the concentration of disintegrate will have an impact on the disintegration time of the tablet.[1][2]

Effect: The effect of factors is the change in response caused by varying the level of the factors, which describes the relationship between factors and levels e.g. higher compression speed will result in the decrease in thickness of the tablet or decrease in the concentration of the disintigrant will increase the disintegration time of the tablet.[1][2]

Interaction: The interaction term describes the term effect but in a broad manner which means it gives the overall effect of two or more variables on response. The relationship between various factors and response, those are quantitative change of response as we change the factors and their levels. The contribution effect i.e. to test two factors are contributing additively or antagonistically for a response. For e.g. the combined effect of lubricant (factor) and glidant (factor) on hardness (response) of the tablet.[1][2]

Run or trials: Experiments conducted according to selected experimental design.

Contour Plot: Geometric illustrations of a response obtained by plotting one independent variable against another, while holding the magnitude of response and other variables as constant. Multiple linear Regression Analysis: The technique which expresses mathematically in form of the quadratic equation the linear relationship between a various independent variable and the dependent variables.[1][2]

OPTIMIZATION PARAMETERS

There are two general types of parameters/ Problems which one has to deal while making any optimization plan. First parameter is constrained and second is unconstrained.

Table. 3: Types of problems involved in optimization process[3]

Constrained Problems	Unconstrained problems
These are this restriction which are placed upon the system due to physical limitations (e.g., Economic consideration)	The unconstrained problems don't have the restriction
For e.g., Make the hardest tablet possible that disintegrate in 15 minutes	For e.g., make the hardest tablet possible or make lotion with the lowest degree of caking
There is always restriction which formulator wishes to place or must place on the system	Unconstrained problems are nonexistent

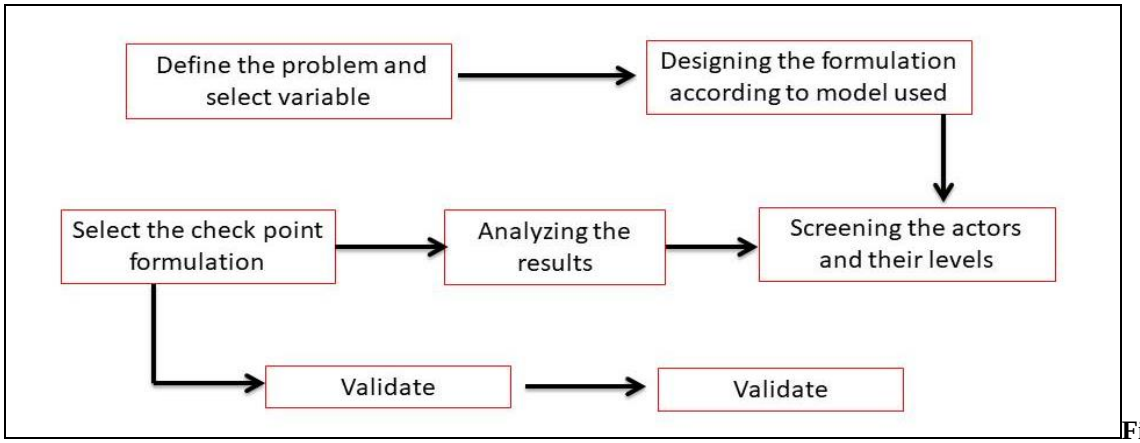

Fig.1: Optimization Parameters [4]

DESIGN OF EXPERIMENT

Drug formulation has been developed by the process of trial-and-error approach also known as COST approach or OVAT (i.e. one variable at one time) or OFAT (i.e. one factor at one time) or shotgun approach. This traditional approach of development used to involve studying the influence of one factor and keeping the other factor constant. During these COST studies the first variable is fixed at favorable value and the next is examined until no further improvement is attained in the response variable. Also COST approach used to get stuck when it comes to study of interaction of the process variables on the response. Accordingly, the COST approach requires many experiments for little gain in information about the system under investigation. Whereas optimization technique has various benefits over the COST approach as described in table. Design of experiment approach was defined by the British statistician, Sir Ronald Fisher in 1925. The implementation of DoE optimization technique invariably encompasses use of experimental design and generation of mathematical equation and graphi-Geometric illustrations of a response obtained by plotting one independent variable against another, while holding the magnitude of response and other variables as constant. Multiple linear Regression Analysis: The technique which expresses mathematically in form of the quadratic equation the linear relationship between a various independent variable and the dependent variable outcomes.[4]

Table. 4: Comparison of various approaches in optimization process[4]

COST approach	Systemic approach (DoE)
➢ Strenuous, ➢ uneconomical, ➢ time consuming, ➢ no results on interaction of variables, ➢ too many trials, ➢ Isolated and unconnected studies, ➢ detailed study of all variables is prohibitive	➢ Require fever experiment to achieve optimum formulation ➢ study of interaction of variables is possible ➢ Various variables can be studies at one time ➢ Save significant amount of resources viz time, effort, material and cost ➢ Detection of error is easy ➢ Detection of synergistic and antagonistic interaction ➢ Can predict the performance of formulation even without preparing them

DoE is structured and organized method for determining the relation between input factors (x_1-independent variable) affecting one or more output response through the establishment of mathematical models ($y=f(x_1)$). In DoE approach the controlled input factors are systematically varied to determine their effects on the output response.

Selection and preparation of experimental design: Selection of the best experimental design is based on various aspect which include defined objectives, the number of factors involved in study, different levels of factors, various interaction to be studied and effectiveness of each factor, and its each level and also statistical validity and effectiveness of each design. While designing the experimental design the process variables are screened to determine which are important to outcomes. The second step is the optimization when the best settings for the important variables are determined. Experimental design is the statistical design that prescribes or advises a set of combination of results. The number and layout.

Table. 5: Objectives and uses of Experimental design[4]

Objectives of ED	Uses of ED
➢ Comparative analysis ➢ Optimal fitting of regression model estimation ➢ Response surface method determination ➢ Optimizing response when factors are proportions of mixture ➢ Screening	➢ To determine the causes of variations ➢ Studying the effect of individual effect or combinational effect of variables ➢ Compare response at different levels.

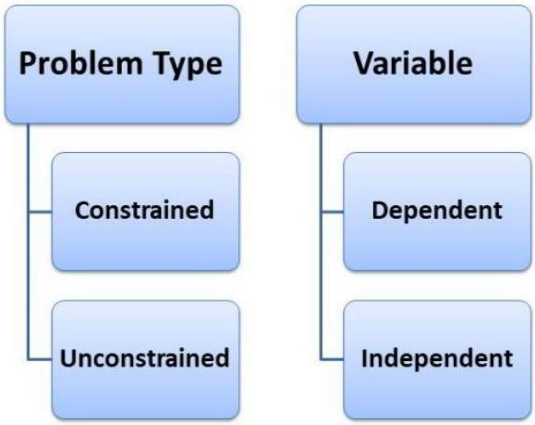

Fig. 2: Basic steps involved in optimization[4]

TYPES OF EXPERIMENTAL DESIGN [5][6]

- Completely randomized design
- Randomized block design
- Factorial design
  - Full
  - Fractional
    - Homogenous fractional,
    - mixed level fractional
    - box-hunter,
    - Plackett-Burman,
    - Taguchi,
    - Latin square

- Response surface design
- Central composite design
- Box-Behnken design
- Three level factorial design

Completely randomized design: The complete randomized design is the simplest of all design based on randomization and replication. In CRD, all treatments are randomly allocated among all experimental subjects. Which allows every experimental unit, to have an equal probability of receiving treatment. The complete randomized design, includes one treatment factor, *n* experimental units are divided randomly into *t* group. Each group is then subjected to one of the unique level or values of the treatment factor. In CRD there is a complete flexibility in the number of treatments and number of replications which may vary from treatment of treatment.[5][6]

Randomized block design: In order to reduce the natural variation as possible and increase the sensitivity of experiment, it is advisable to choose the experimental units to be as homogeneous (that means to reduce the variance of experimental errors) and increase the power of detecting treatment factor effect. Blocking can be used in situation to achieve both objectives randomized block experimental design has wider applicability in agricultural and industrial streams. They are more powerful, have higher external validity and produce more reproducible results. The 'randomized block' design is generic name for a family of experimental design in which the experimental material is split up into number of 'mini-experiments' that are recombined in final statistical analysis. Typically, in each block there is a single experiment unit to each treatment is assigned. They include cross over design and Latin square design.[7]

Factorial design: Factorial design was first employed by the John Bennet Lawes and Joseph Henry Gilbert Ronald fisher in 1926 stated using the complex design (such as factorial design) were more efficient than studying one factor at one time. A factorial design allows the effect of several factors and the interaction between them to determine with the same numbers of trials as are necessary to determine any one of the effects by itself with the same degree. Factorial design is choice of design when we are examining the treatment variations and also, they are very efficient. The same precision of effects can be achieved with fewer experiments than would be required if each of the factor was studied one-at-a-time in separate experiments. The more factors included in factorial experiments the greater the efficiency is achieved and also the greater number of interactions can be studied. Factorial designs are very frequently used response surface design. A factorial experiment is in which all levels of a given factors are combined with all levels of every other factor in the experiment. Full FDs involve studying the effect of all the factors (*k*) at various levels (x), including the interaction among them with the total number of experiment being x^k. [8]

2^2 and 2^3factorial design: The two and three level FDs are the simplest design commonly employed for screening and factor influence studies. They involve the study of K factors with two level i.e low and high level whereas in 2^3 three levels are studies as described in table.[9]

Table. 6: Factors and their coded forms involved in 2^2 factorial design [9]

Trial number	Factor (x1)	Factor (X2)	Response
T1	-1	-1	Y1
T2	-1	+1	Y2
T3	+1	-1	Y3
T4	+1	+1	Y4

Table. 7: Factors and their coded forms involved in 2^3 factorial design[9]

Trial number	Factor (x1)	Factor (X2)	Response
T1	-1	-1	-1
T2	1	-1	-1
T3	-1	1	-1
T4	1	1	-1
T5	-1	-1	1
T6	1	-1	1
T7	-1	1	1
T8	1	1	1

Fractional factorial design: This design has low resolution due to lower number of runs. Although these designs are economical in terms of number of experiments, the ability to distinguish some of the factor effects is partly sacrificed by reduction in number of experiments.[9]

Response surface design: Response surface design involves the study of independent variables or factors which are varies over a continuous range. The basic approach behind response surface design is to determine the factor setting that gives or produce maximum or minimum or to map the relationship between the response and the factor. Response surface design are beneficial where the experiment involves more than six factors. In order to locate maximum or minimum in response as a function of the factor settings, at last three levels of each factor should be utilized. Moreover, the response surface design is complete package of statistical analysis tool that are utilized for following three steps.

1. Design and collection of data to fit an equation to approximate the relationship between the factors and response
2. Regression analysis to fit model to describe the data.
3. Examination of the fitted relationship through graphical and numerical technique.

Response surface design has wider application in chemical industry where the reaction yield or cost of production can be optimized as a function of controllable process factors. Also, the design is utilized in food science, engineering, biology, psychology, textiles and education.[9]

Central composite design: Central composite design can fit a full quadratic model. They are often used when plan call for sequential experimentation because these designs can include information from a correctly planned factorial experiment. A better design that encompasses the advantage of factorial design or fractional factorial design or the star design is the central composite design These designs are designs with center points, augmented with a group of axial points (also called star points) Central composite design can be effectively utilized in following cases:

Efficiently estimate first-and second-order terms.
Model a response variable with curvature by adding center and axial point to previously done factorial design. These designs are specially used in sequential experiments because we can build on previous factorial experiments by adding axial and center points.[9]

Box-Behnken Design: Central composite design requires each factor with five level but if the number of factors increases the resulting experiment number will be too high. Box and Behnken (1960) developed some three-level design that will allow to estimate the general quadratic model. The Box design for three or more factors are economical alternative in which each factor is given three levels. The design is also called orthogonal balanced incomplete box 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 balanced partition over the different blocks. These designs consist of 2^2 factorials in each pair of factors with all other factor held constant at their mid-level plus a few centre points.
Box-Behnken design have two advantages over CCD's. The first advantage is that they only require that factor be varied over three levels. That makes experimentation less costly and second advantage is they usually require less total number of runs than CCD. For example, the three factor CCD required 20 runs whereas the three-factor Box-Behnken design only required 15 runs as follows:[10][11]

Table. 8: Factors and their coded forms involved in Box-Behnken Design[10][11]

Run	X1	X2	X3
1	-1	-1	0
2	1	-1	0
3	-1	1	0
4	1	1	0
5	-1	0	-1
6	1	0	-1
7	-1	0	1
8	1	0	1
9	0	-1	-1
10	0	1	-1

11	0	-1	1
12	0	1	1
13	0	0	0
14	0	0	0
15	0	0	0

DISCUSSION

The area of pharmaceutical sciences is involved with the trial and error and their associated risk, as well the formulation and development in pharmaceutical field takes a huge time, in order to reduce this time and tedious work there has to be some methods which will reduce this work. Optimization methodologies are helpful in reducing the cost and minimizing the number of risks involved in the process. In this current review article, an attempt was made to enlighten the potential benefits of various optimization techniques.

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