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A REVIEW ON OPTIMIZATION IN PHARMACEUTICAL FORMULATION

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ABSTRACT

In today's pharmaceutical industry, optimization has arisen as a technique for finding the best compromise response to a specific problem. The term optimization refers to the process of improving something or making it work better. Finding a perfect, effective, or functional solution is what optimization is all about. The present review article aims at determining the various possible techniques available to enhance the quality, safety and efficacy of pharmaceutical formulations by exploring most suitable and practically applicable experimental designs (ED) and optimization techniques The screening methods discussed here include factorial design, fractional factorial designs, full factorial design, mixture designs etc. Experimental designs and optimization techniques are the tools that are simultaneously and systematically used to identify various types of problems that may influence research, development and production of pharmaceutical formulations.

Key words Optimization, Experimental Design, Variables, Factors.

INTRODUCTION

It is not always easy to get the solution of problems directly or instantly, so in those cases, we precede towards the various optimization methods in search of our answer. But as we know optimization is not as easy, as we have written. To optimize means to make something ideal, effective, or as functional as feasible. It is the process of determining the most effective use of available resources while taking into account all of the factors that can influence decision-making in any experiment.[1]Optimization is selecting the most suitable element from available resources considering all the factors which influence decisions in any experiment[2].The term optimization has been derived from optimize, that means to make as perfect, functional or effective as possible.[3]Optimization can be defined as the implementation of systemic approaches to obtain the best combination of product and/or processes characteristics under a given set of conditions or it can also be said as choosing the best element from some set of available alternatives[20]To improve formulation irregularities, modern pharmaceutical optimization uses a systematic design of experiments (DoE).[1]The main aim of designing quality formulations is achieved by implementing various Optimization techniques (OT) like.

Experimental Design (ED):

A statistical design that prescribes or advises a set of combinations of variables is known as an experimental design. The number and location of design points inside the experimental region are determined by the number of effects to be estimated [5]

- **Quality by Design (QbD):**

Quality by Design enhances the assurance of safe and effective drugs to consumer &promise to improve manufacturing quality performance [6]

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The following steps represent the latest optimization techniques for drug delivery system in pharmaceuticals:

- Defining objectives of the study and planning the experiment.
- Screening of factors and factors influencing studies.
- Response surface methodology using experimental designs.
- Formulation and evaluation of drug delivery systems as per experimental design.
- Computer-aided modelling and search for an optimum.
- Validation of design of experiments methodology.
- Scale-up and implementation in pharmaceutical production.
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- Scale-up and implementation in pharmaceutical production.[9]

Terminology used in optimization:

- **Variables**:
  These are the measurements or values that are characteristics of the data. Dependent and independent variables are the two sorts of variables. Independent variables are variables that are not dependent on any other value, such as lubricant concentrations, drugto polymer ratios, and so on.
- **Factor:**
  The factor is an assigned variable like concentration, temperature, lubricating agent, drug-polymer ratio, polymer-polymer ratio etc. A factor can be qualitative or quantitative.

1. Quantitative:

A quantitative factor has a numerical value to it Example: Concentration-1%, 2%. [3]

2. Qualitative:

These are non-numerical, that is Qualitative factors are those that are not numerical. The nature of them is discrete. Example-Polymer grade, humidity condition etc., [3].

- **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.
- **Response:**
  The majority of the time, a response is interpreted as the result of an experiment. It is the effect that we will analyse, such as disintegration time, buoyancy duration, thickness, and so on [1]
- **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. [7,8]
- **Interactions:**
  It's also related to the term effect, which refers to the combined effect of two or more variables in a response. For instance, consider the combined influence of lubricant and glidant on tablet hardness. [19]

Optimization parameters:

The optimization parameters are broadly divided into two types: Problem type and Variables

1) Problem type

2) Variables.

1) Problem type:

In this problem type, it is again categorized into Constrained and Unconstrained parameters.

Constrained: In this restriction is based on the physical limitations on the system. Unconstrained: In this there are no restrictions based on the physical limitations on the system.

2) Variables:

Variables are categorized into Independent variables and Dependent variables.

a. **Independent**: Independent variables are under the control of formulator. Ex mixing time.[3]
b. **Dependent:** Dependent variables are not directly under the control of formulator. They are dependent on independent variables. These are responses. Ex-homogeneity of mixed granules.[3]

Experimental design:

A statistical design that prescribes or advises a set of combinations of variables is known as an experimental design.[1]Depending on the factors, levels, Interactions and order of the model various experimental designs are chosen.[2]It is an approach where the process variables are first screened to determine which are important to the outcome (excipients type, percentage, disintegration time (DT) etc.,[12,16]

The second step is the 'optimization', when the best settings for the important variables are determined. It involves the use of 'mixture designs' for changing mixture composition and exploring how such changes will affect the properties of the mixture. [7]

Advantages of Experimental Design:

- Because of the ability to improve procedures, there will be more innovation.
- Regulatory confidence in stable products is higher.
- Technology transfer to production that is more efficient.
- There are fewer batch failures.

- Replication of results are obtained.[1]

Uses of Experimental Design:

It is used to establish the sources of response variance, find the conditions under which the ideal (maximum or lowest) response is attained, compare responses at different levels of controlled variables, and construct a response prediction model.

Key steps for experimental design:

To obtain good results from ED the following steps are followed:

- Set objective.
- Select process variables.
- Select an experimental design.
- Execute the design.
- Check that the data are consistent with the experimental assumptions.
- Analyse and interpret the results.[3]

Types of experimental design:

There are various types of ED available out of which method we have to use depends upon the resources we have and the parameters we want to estimate.

1. Factorial design:

Factorial designs (FD) were first employed by John Bennet Lawes and Joseph Henry Gilbert in the nineteenth century.[1] 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[22,23] These designs are very frequently used response surface designs.[2].

2. Fractional factorial design:

Fractional factorial design is generally used for screening of factor. [3] Fractional factorial design is economical as it reduces the number of experimental runs which ultimately leads to low resolution.[2] The capacity to differentiate some of the factor effects is partly sacrificed by the reduction in the number of experiments, despite the fact that these designs are cost-effective in terms of the number of experiments.[1]

3. Full factorial design (FFD):

It is an experimental design, which uses dimensional factor space at the corner of the design space. Factorial designs (FD) are used in experiments where the effects of different factors or used in experiments where the effects of different factors or conditions on choice for simultaneous determination of the effect of several factors and their interactions.[3]

4. Response surface designs (RSD):

These are used when we required exact image of response, estimating interaction and even quadratic effects. RSD generally support nonlinear and quadratic response and capable of detecting curvatures. [3].

5. Plackett-burman design (PBD) (Hadamard designs):

Plackett-Burman designs are special two-level Fractional Factorial Designs used for the screening of factors. It is used when only main effects are of interest. Plackett-burman design is also called as saturated designs as they detect large main effects, assuming other interactions as negligible.[2] This design is generally used when we want to screen a high number of factors if we want to study the effect of 7 factors then we have to show four dummy factors[8]

The Pareto chart and half normal plot are used to generate interpretations of data in FFD, PBD, and taguchi design (TD). When only the principal impacts are of interest, these designs tend to be excellent screening designs. [1].

6. Central composite design (CCD) (Box-Wilson design):

This design was developed by Box and Wilson. The central composite design is a better design that incorporates the benefits of factorial design, fractional factorial design, and the star design (CCD***)***. [1]This design was developed for nonlinear responses requiring secondorder models. The CCD is popular in response surface optimization during pharmaceutical product development.[2].

7. Box-behnken designs (BBD):

A specially made design, BBD requires only three levels for each facto-l, 0 and+1. It employing 15 experiments run with three factors at three levels. It is economical then CCD because it requires less number of Trial [18, 19].

8. Taguchi design (TD):

Taguchi refers to experimental design as "off-line quality control" because it is a method of ensuring good performance in the development of products or processes." It is also used for screening of factors and it provides 8 experimental runs for 7 factors.

9. Mixture design (MD):

The quantity of each substance is represented in this design but on their proportions [2]. The sum total of the proportions of all the excipients is unity, and none of the fractions can be negative. Therefore, the levels of different components can be varied with the restriction that the sum total should not exceed one [3]. In pharmaceutical formulations with multiple excipients, the characteristics of the finished product usually do not depend on the quantity

of each substance but depend on their proportions. Here, the sum total of the proportions of all excipients is unity and none of the fractions can be negative. [3]As a result, the levels of the individual components can be changed as long as the cumulative total does not exceed one. Only one factor level can be individually varied in a two-component combination, while only two factor levels can be separately varied in a three-component mixture.[1]To bring the total to one, the remaining factor level is picked. As a result, they're frequently referred to as ED for formulation optimization.[1].

10. Simplex Lattice design:

Simplex Lattice Designs are used to know Interior and boundaries of the simplex. Number of factors determines its dimensions.[2]The pattern of design points in the factor space and their number depend on the degree (the term of the highest order) of the model that is postulated.[3] A lattice is formed when the points are placed in an ordered manner over the factor space. The variables can be precisely and precisely controlled. The coefficients of model equations are simple to calculate.[1].

11. Screening designs (SD):

These designs support only linear responses and are used to determine crucial factors and their levels that affect the quality of formulation. [1].

12. D-optimal design:

D-Optimal design maximizes the determinant Information. That is maximizing the volume in a dimensional space. No other classical designs can investigate an irregular region then D-Optimal Design is preferred, as DOD makes effcient use of full experimental space.[2]The factor settings are constrained linearly, restricting the experimental region to an irregular polyhedron. If no traditional designs can adequately explore an uneven region, DOD is the best option since it makes efficient use of the full experimental space. The region is an irregular polyhedron due to formulation factors with lower and upper boundaries, as well as maybe extra limitations.[1].

13. Sequential optimization design:

Optimization is done in a step-wise fashion, started at an arbitrary point in experimental domain and responses are evaluated.[2]Despite numerous merits of simultaneous approaches, there are situations where there is hardly any prior knowledge about the effects of variables. Such situations call for the application of the sequential methods. In sequential approach, optimization is attempted in a step-wise fashion. Experimentation is started at an arbitrary point in the experimental domain and responses are evaluated. An important aspect of sequential designs is to know when the goal has been accomplished.[3]

14. Interpretation of experimental design data:

Assume that we have a final model that has passed all the relevant tests that includes visual and quantitative tests, then we and are ready to make conclusion and decisions. These should be the response to the outputs dictated by the original experimental goals [10,11].

15. Extreme vertices design (EVD):

It is common in formulation studies for the entire factor space to be unavailable for experimentation, or for some areas to be predicted to have no beneficial results. [1]We can notice that Some Times in formulation studies whole factor space is not accessible or not giving expected responses in formulation studies.In Extreme Vertices design, observations are shown at corners of bounded design space,used for the mixture composition as well as in combination with factorial designs.[2].

16. Doehiert Hexagon or Uniform Shell design:

Starting with an equilateral triangle mirrored on one side to a hexagon, Doehiert proposed uniform shell designs. By mirroring the central point on the outward sides, the hexagon can be expanded in two-dimensional space. The design points are evenly spaced and dispersed in concentric rings. It can also be expanded into concentric spherical shells in three dimensions. Models based on this design give a strong basis for interpolation because of the uniform distribution. One downside could be that the number of levels for each element is not the same. One side of the hexagon can be parallel to the most critical axis to begin the design. [1].

17. Star design:

It is simply a 22 factorial design rotated over 45° angle in space, in which a center point is added which replicate to estimate experimental error.[2]resulting in three levels for each factor where the quadratic effect can be evaluated but not the interaction effect, as in the full factorial design. 2k factorial designs are rotated over 45° in the (k-i) direction in k-dimensional space with a duplicated centre point in star design. The number of factors in the design is given by k. This yields 2k+R experiments, where R is the centre point's replication.[1].

18. Box design:

Each element in the centre composite design comprises five levels. The number of experiments may become excessive as the number of factors increases. Box designs with three or more elements are a cost-effective option that assigns three levels to each factor.It can be divided into a series of incomplete blocks, meaning that not every effect is estimated in each block, but each factor effect is measured an equal number of times with a balanced partition across the blocks.[1] It is also known as Orthogonal balanced incomplete block design.[2]

Optimization of important factors:

1. Model development:

A model is a mathematical formulation that expresses the quantitative relationship between the response variable and the independent variables. Usually, it is a set of polynomials of a given order or degree. [1] We use the principal of Multiple Linear Regression Analysis (MLRA)to determine the coefficient from this polynomial equation . We can also analyse the effect of excipients, their interactions, 3D Response plots, Contour Plots, and other things using software. We can simply determine the primary element and their level in screening design using a half normal plot and a Pareto chart. [1]

2. Graphical Optimization (GO):

Response surface analysis (RSA) is the process of choosing the best possible formulation from a feasible factor space area. To do so, the desired response variable limits are determined, and the factor values are screened using an overlay plot.[1]

3. Brute-force search (Feasibility and Grid search):

Brute-force search technique is the simple and exhaustive search optimization technique. It checks each and every single point in the function space. Herein, the formulations that can be prepared by almost every possible combination of independent factors and screened for their response variables. Subsequently, the acceptable limits are set for these responses, and an exhaustive search is again conducted by further narrowing down the feasible region. The optimized formulation is searched from the final feasible space that is called as grid search, which fulfils the maximum criteria set during experimentation. The brute-force search methodology is a straightforward and thorough search optimization method[1]

4. Numerical Optimization:

It is concerned with determining the best possible formulation from a set of factors. To do so, the desired limits of response variables are selected, and the software displays the factor levels. Canonical analysisand mathematical optimization are some of the other strategies used to optimise numerous answers.[1]

Applications:

- High Performance Liquid Chromatographic
- Formulation and Processing
- Analysis Formulation of Culture Medium in Virological Studies
- Study of Pharmacokinetic Parameters.
- Clinical Chemistry Medicinal Chemistry[1]

Conclusion:

After having a detailed study on the effect of OT and experimental designs in pharmaceutical formulations, we can conclude that these parameters are highly influential in enhancing the quality, safety and efficacy of pharmaceutical products. In this article we conclude that optimization techniques are very helpful in formulation developments such as in reducing the cost of the product by minimizing the experimental trails and also it enhances the safety, quality and efficacy of the products thus delivering the required benefits to the consumers by the product.In this article brief information on different types of experimental designs in which Factorial design and CCD are most preferred.

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