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A REVIEW ON OPTIMIZATION TECHNIQUES 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 goal of this review article is to identify the many strategies that can be used to improve the quality, safety, and efficacy of pharmaceutical formulations by looking at the most appropriate and practicable experimental designs and optimization techniques, by investigating the most appropriate and practical experimental designs and optimization approaches for pharmaceutical formulations.

KEYWORDS: optimization, formulation, experiments, variables, factor

INTRODUCTION:

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. In the pharmaceutical industry, optimization has always meant changing one variable at a time to solve a problem formulation. To improve formulation irregularities, modern pharmaceutical optimization uses a systematic design of experiments (DoE). To put it another way, we can say that –quantitate a qualitatively specified formulation. It's not a method of screening. As we all know, the pharmaceutical industry is always searching for innovative ways to increase quality through various optimization strategies. characteristics under the given set of conditions.

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 are variables that are not dependent on any other value, such as lubricant concentrations, drug-to-polymer ratios, and so on. The concentration of the independent variable used affects the dependent variables.

Factor: A factor is a variable that has been allocated to it, such as concentration, temperature, lubricant, drug-to-polymer ratio, polymer-to-polymer ratio, or grade. A qualitative or quantitative component can be used. A numerical value is assigned to a quantitative component, such as concentration (1 %, 2%, and so on), drug to polymer ratio, and so on (1:1, 1:2 etc). Qualitative factors are those that are not numerical, such as polymer grades, humidity conditions, equipment type, and so on. The nature of them is discrete.

Levels: A factor's levels are the values or designations attributed to it; for example, concentration 1% is one level, whereas 2% is another. There are two types of plasticizers, each with a different grade factor. Typically, levels are labelled as low, midrange, or high. Normally, numeric and discrete levels are translated to -1 (low level) and +1 (high level) for ease of calculation (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: 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.

Effect: A factor's effect is the change in reaction generated by modifying the factor's values. The link between factors and levels is described in this way.

Interaction: 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 . We can take conclusions about the optimization from it.

- The impact of a factor on a response, such as the change in dissolving rate when the drug-to-polymer ratio varies.
- The contribution effect, i.e., whether two factors contribute additively or antagonistically to a response, such as any relationship between lubricant and glidant concentration and tablet hardness or granule flow property.
- The most effective formulation (according to our need).

Optimization parameters

The optimization parameters are broadly divided into two types:
1)Problem type
2)Variables .

1) Problem type

The problem type of parameters again grouped into:
i. Constrained type: Constrained types are those that impose limitations on the system due to physical constraints or simply practical considerations. This is best explained by considering the tablet's hardness and disintegration period of less than 15 minutes.

ii. Unconstrained type: In the unconstrained type, the system is not restricted by physical limitations or possibly merely by practical considerations. However, in the pharmaceutical industry, there is always a restriction imposed by a physical limitation or perhaps just by the formulator's desire to place or must place on a system.

2) Variables

There are many factors in pharmaceutical formulation and processing, but they can generally be divided into the following categories:

i. Independent variables: These are directly under the formulator's control.for example, mixing time.

ii. Dependent variables: These are not directly under the formulator's control. Example: Homogeneity of mixed granules.

Experimental design

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. Various experimental designs are chosen depending on the number of factors, their levels, probable interactions, and the model's order. Within the experimental domain, each experiment can be represented as a point. In space, a point is defined by its co-ordinate (the value assigned to variables).

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.
- The results have been replicated.

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.

Factorial designs

Factorial designs (FD) were first employed by John Bennet Lawes and Joseph Henry Gilbert in the nineteenth century. With a factorial design, the influence of numerous factors, as well as interactions between them, may be determined with the same number of trials as it takes to determine any one of the effects to the same degree on its own. These are some of the most often utilised reaction surface designs. A factorial experiment combines all levels of a single component with all levels of all other factors in the experiment. The majority of these are based on first-order mathematical models. First, factorial designs should be strong candidates as the designs of choice anytime we are interested in evaluating treatment changes. Factorial designs, on the other hand, are effective. We can effectively merge these research into one rather than doing a series of distinct studies. Finally, this is the only option to investigate interaction effects. The most recent FD application is the optimization of ibuprofen fast dissolving tablets.

Fractional factorial design

For factor screening, a fractional factorial design is commonly utilised. Due to the limited number of runs, this design has a low resolution. 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. Full factorial design (FFD) It's an experimental design that makes use of dimensional factor space at the design space's corner. Factorial designs (FD) are employed in experiments where the effects of several factors or conditions on choice are studied simultaneously to determine the effect of several factors and their interactions. The most basic factorial design is the 2 factorial design, in which two factors are evaluated at two levels each, resulting in four experiments in two-dimensional factor space at the corners of a rectangle. If there are three factors, each with

two levels, eight experiments must be conducted at the four corners of an orthogonal cube in three dimensions. The number of experiments is equal to two times the number of factors, where 'n' is the number of factors. When the number of components and levels in a factorial design is large, the number of experiments required to complete the design is as 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 optimization technique is made easier by fitting an empirical polynomial equation to the experimental result. The following is the general polynomial equation: Y = B0+B1X1+B2 X2+B3 X3++B12 X1X2+B13X1X3+ B23X2X3 —-Where Y is the response, X1, X2, X3 are the levels (concentration) of the 1, 2, 3 factors and B1, B2, B3, B12, B13, B23, are the polynomial coefficients, B 0 is the intercept (which represents the response when the level of all factors is low). Full factorial design was used to generate olmesartan and carbamazepine formulations.

Star Design

A 22 factorial design rotated over a 45° angle in space is known as a star design. A centre point is frequently included, which may be reproduced to assess experimental error, 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.

Plackett-burman designs (Hadamard designs)

Plackett-Burman designs (PBD) are two-level FFDs that are commonly employed for factor screening. This design is commonly employed when screening a large number of factors; for example, if we wish to analyse the influence of seven factors, we must show four dummy factors. 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. They discover big main effects in a cost-effective manner, assuming that all interactions are trivial when compared to a small number of main effects. These designs are also called as saturated designs as it investigates n*4 experiments i.e. 8, 12, 16, 20, etc that is suitable for studying up to 7, 11, 15, 19, etc factors respectively.

Central composite design (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). It's made up of +2k Factorial or Fractional Factorial designs. Central composite designs (CCDs) are the most commonly used for nonlinear responses that require second-order models. A two-factor CCD is identical to a 32 FD with the rectangular experimental domain at $\alpha = \pm 1$, On the other hand, the experimental domain is spherical in shape for $\alpha = \sqrt{2} = 1.414$. During the development of pharmaceutical products, the CCD is often used in response surface optimization. The formulation of glipizide is a practical application of CCD.

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. An orthogonal balanced incomplete block design is the name of the pattern. 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.

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.

Taguchi design (TD)

Because it is a way of assuring good performance in the development of products or processes, Taguchi refers to experimental design as "off-line quality control." It's also used for factor screening, and it comes with eight experimental runs for seven different factors. The preparation of glicalazide is an example of TD.

Mixture design (MD)

These illustrations depict the amount of each substance present, as well as their proportions. The sum of all the excipients' proportions is unity, and none of the fractions can be negative. As a result, the levels of various components can be changed as long as the cumulative total does not exceed one. The features of the completed product in pharmaceutical formulations with several excipients are usually determined by the proportions of each component rather than the quantity of each substance. The aggregate total of all excipient proportions is unity, and none of the fractions can be negative. 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. 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. FD and CCD designs are preferred for process optimization. Mixture designs come in a variety of shapes and sizes, with simplex designs being the most prevalent. In a (n-1) dimensional space, a simplex is the simplest feasible n-sided figure. For two components, it is represented as a straight line, for three components as a 2-D triangle, for four components as a 3-D tetrahedron, and so on. The lattice is made up of

design points that are evenly dispersed across the factor space. The usage of Mixture design (MD) in practise can be seen in a celecoxib solubilization study.

Simplex Lattice design

Simplex The inside and borders of the simplex are explored using lattice patterns. Its dimensions are determined by the number of components. The arrangement of design points in the factor space, as well as their number, are determined by the model's degree (highest order term). 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.

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.

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. Observations are made at the corners of the limited design space, the middle of the edges, and the centre of the design space in an Extreme Vertices design. These can be used to determine the composition of the mixture as well as in conjunction with factorial designs.

Sequential optimization design (SOD)

Despite the obvious advantages of simultaneous techniques, there are times when little prior knowledge of the impacts of variables is available. Such circumstances need the use of sequential procedures. The sequential technique takes a step-by-step approach to optimization. The experiment is initiated at any point in the experimental domain, and the results are analysed. Knowing when the aim has been met is a key feature of sequential designs.

D-optimal design (DOD)

This design demonstrates that these designs optimize the information in a chosen set of experimental runs when compared to a given model. The D-Optimal design (DOD) maximises the determinant, which is a broad measure of information. This refers to maximising the volume of a dimensional space geometrically. 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. With more than two levels and no mixed level design available, or the mixed level design indicates too many runs to be acceptable, there are qualitative factors. Response Surface Matter (RSM) is the goal, and there are qualitative elements to consider. The number of experimental runs that may be afforded is less than any existing classical design's number of runs.

Optimization of important factors

Model development

A model is a mathematical formulation that expresses the quantitative relationship between the response variable and the independent variables. It's usually a collection of polynomials of a certain order or degree. We use the principal of MLRA(Multiple Linear Regression Analysis) 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. The optimization of one response or the simultaneous optimization of several responses must be optimised graphically, mathematically, and employing Brute force search technology from the models thus selected.

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.

Brute-force search (Feasibility and Grid search)

The brute-force search methodology is a straightforward and thorough search optimization method. Every single point in the function space is checked. The formulations that can be made from practically any combination of independent factors and screened for their response variables are presented here. The acceptable boundaries for these responses are then defined, and an exhaustive search is undertaken again by further limiting down the possible region. The optimum formulation is found by doing a grid search on the final feasible space, which meets the maximum requirements given during experimentation.

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 analysis, ANNs, and mathematical optimization are some of the other strategies used to optimise numerous answers.

Applications

High Performance Liquid Chromatographic
Formulation and Processing
Analysis Formulation of Culture Medium in Virological Studies.

Study of Pharmacokinetic Parameters.
Clinical Chemistry Medicinal Chemistry

Uses

In microencapsulation process.
Provide solution to large scale manufacturing problems.
Improvement of physical & biological properties by modification.
Provides string assurances to regulatory agencies superior drug product quality.
In microencapsulation process.

CONCLUSION

The levels of variables for getting optimum response is evaluated.
Different optimization methods are used for different optimization problems.
Optimization techniques are a part of development process.
More optimum the product = More the company earns in profits
Optimization helps in getting optimum product with desired bioavailability criteria as well as mass production.

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