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Review Paper

A Review on Optimization Techniques Used in Pharmaceutical Formulations

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ABSTRACT

Optimization of pharmaceutical products is a crucial aspect of drug development, ensuring that formulations are not only effective but also safe, cost-efficient, and compliant with regulatory standards. Over the years, various optimization techniques have emerged to address challenges in drug formulation, manufacturing, and delivery, with the goal of improving product quality, enhancing bioavailability, and reducing time-to-market. This review explores key strategies used in the optimization of pharmaceutical products, focusing on formulation optimization, manufacturing process improvements, and drug delivery system innovations. Techniques such as the selection of appropriate excipients, the use of nanotechnology for enhanced drug solubility, and the application of controlled release systems are discussed in detail. In manufacturing, advancements like continuous processing, Process Analytical Technology (PAT), and Quality-by-Design (QbD) principles have contributed significantly to improving product consistency and scalability. Furthermore, the role of computational modeling, in optimizing drug formulations and predicting pharmacokinetic properties is examined. This review highlights the ongoing efforts to optimize pharmaceutical products and underscores the importance of a multidisciplinary approach to meet the evolving needs of the pharmaceutical industry and patients alike.

INTRODUCTION

Direct or immediate solutions to problems are often not readily available. In such situations, we rely on various optimization techniques to find an effective solution. However, optimization is rarely straightforward; it can be complex, challenging, and time-consuming. Despite these difficulties, these methods ultimately lead us to a practical and viable conclusion (Lachman L, 1990). The word "optimization" is derived from the verb "optimize," which implies to make anything as efficient, useful, or ideal as possible. The term

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"optimized" was first used in pharmacy to refer to a product that has been enhanced to meet development scientist objectives. The process of identifying the optimal composition, formulation, or experimental circumstances to produce the desired outcomes is referred to as optimization in the context of pharmaceutical formulations and processes. The use of methodical techniques to determine the best possible mix of process and/or product attributes under certain circumstances is known as optimization.Alternatively, it can be described as selecting the best option from a range of available alternatives (Singh B, 2008). In order to ensure that a predetermined level of quality is consistently achieved, QbD requires a thorough understanding of how formulation and process variables impact product quality. Traditionally, the development of new pharmaceutical formulations involved studying the effects of composition and process variables on dosage form characteristics by changing one factor at a time while keeping others constant. QbD is an organised approach to pharmaceutical development that begins with clear, predefined goals and focusses on understanding both the product and process, as well as controlling the process through solid scientific principles and quality risk management. This "one factor at a time" approach could address certain issues, but it often failed to determine the true optimal concentration or process, leading to suboptimal products. The traditional method has several limitations, including unpredictability, inefficiency, high resource and time consumption, an inability to correct errors, and a failure to detect interactions between variables. It often yields only workable solutions rather than the best possible outcomes (Bhupinder Singh, 2005). To overcome these limitations, a novel approach known as the optimization technique was introduced. The main objective of developing high-quality formulations is achieved by using various optimization techniques (OT), including Experimental Design (ED). The principles of Formulation by Design (FBD) and Quality by Design (QBD) emphasize that product quality can be attained through the application of various ED methods (Alam1, 2016). In the past, new pharmaceutical formulations were developed by examining the impact of composition and process variables on the characteristics of the dosage form. This was done by changing one factor at a time while keeping others constant, a method known as "changing one variable at a time" (OVAT). Although this approach could solve problems, it didn't ensure the identification of the optimal concentration or process, and the resulting product might be suboptimal. Some of the limitations of traditional methods include unpredictability, inefficiency, high time and energy consumption, difficulty in detecting errors, providing only workable solutions, inability to uncover interactions, and overall resource wastage (Singh B, 2008). To address these limitations, a new approach called the optimization technique was implemented. This approach utilizes a structured experimental design (ED) process, enabling more efficient and precise identification of optimal conditions (Bhupinder Singh, 2005).

1.	Defining the study objectives and planning the experiment
2.	Screening relevant factors and identifying those that influence the study.
3.	Applying response surface methodology (RSM) through experimental designs.
4.	Formulating and evaluating drug delivery systems based on the experimental design.
5.	Utilizing computer-aided modeling to identify the optimum conditions.
6.	Validating the design of experiments (DOE) methodology.
7.	Scaling up and implementing the findings in pharmaceutical production.

Objective of the study and experimental planning include the following steps (Table.1)

The goal of optimization techniques is to uphold the quality, cost-effectiveness, and safety for both the public and industry. In the context of

pharmaceutical product optimization, it focuses on identifying key variables, finding more affordable and efficient formulation methods, and enhancing the consistency and effectiveness of the quality specifications in the formulation. Optimization techniques offer a deeper understanding and the ability to examine and justify the ranges for formulation and processing factors. At this stage, optimization becomes a valuable tool for quantifying the formulation that has already been qualitatively defined. It is important to note that optimization is not a screening technique (Joseph B.Schwartz, 2002). Optimization Techniques (OT) and Experimental Design (ED) are tools specifically designed to address various challenges encountered during research, development, and production. It goes without saying that experiments carried out at random will likewise yield unpredictable findings. As a result, rigorous experiment planning is essential to guaranteeing that pertinent and significant data is collected.

Fundamental Terms in Optimization:-

Every optimization problem consists of three key elements- an objective function, decision variables, and constraints. Formulating an optimization problem refers to the process of converting a "real-world" issue into mathematical equations and variables that define these three components in table 2 (Boyles, 2015).

Component	Description	Example
Objective function	A mathematical expression that represents the goal of the optimization problem (maximize or minimize).	Maximize profit Profit=50x+30y\text{Profit} = 50x + 30yProfit=50x+30y (where x and y are quantities of two products)
Decision Variables	Variables that you can control or adjust to achieve the optimal solution.	x and y (quantities of products to produce)
Constraints	Restrictions or limitations that define the feasible region for the decision variables.	2x+3y≤100 (labour hours) and x+y≤50x + y \liq50x+y≤50 (maximum production capacity).

Terms used in Optimization (Tabel.2)

Variable:-

Variables are the measurable characteristics or values that define the data in an experiment. There are two main types of variables .Independent Variables: These are the factors that are manipulated or controlled in the experiment. For example , ingredients or formulation variables controlled by the formulator. Dependent (or Secondary) Variables: These represent the outcomes or responses that result from changes in the independent variables. In the context of drug formulation, dependent variables could be the properties of the in-progress material or the final drug delivery system, which depend on the independent variables.

Factors:-

A factor is a designated variable that affects how a procedure turns out. Concentration, temperature, lubricants, drug-polymer ratio, and polymer-polymer ratio are a few examples of variables. There are two types of factors: quantitative and qualitative. Quantitative factors are variables that have numerical values, like the drug-to-polymer ratio (e.g., 1:1, 1:2) or concentration (e.g., 1%, 2%).The Qualitative Aspects These are non-numerical and describe attributes or classifications, including equipment type, humidity levels, or polymer grade. Usually, these

are distinct in character. A factor is a quantitative or qualitative independent variable that has a direct impact on the process's output or final product. Both quantitative and qualitative values can be attributed to factors:

Quantitative: These factors are assigned numerical values. For example, concentration could be 1%, 2%, 3%, and so on.

Qualitative: These are non-numerical factors that describe categories or characteristics. For instance, polymer grade, humidity conditions, etc (JB, 1981 VOL. 32; NO 5; PP.;).

Level: of a factor refers to the specific values or designations assigned to it. For example, if concentration is the factor, 1% could represent one level, while 2% represents another level. Similarly, two different plasticizers might be considered as levels for the polymer grade factor. Levels are typically described as low**,** middle**,** or high. For ease of calculation, these levels are often coded as -1 (for low level) and +1 (for high level). The general formula for converting levels is.

$$\text{Level} = \text{X} - \frac{\text{Average of the two levels}}{\text{Half of the diffrence level}}$$

Where X represents the numeric value.

Response: refers to the outcome or effect of an experiment, which is typically evaluated to measure the success of the process. Examples of responses include disintegration time, buoyancy duration, tablet thickness, etc. Response surface: represents the relationship between two or more independent variables (e.g., X_1, X_2) and a dependent variable (e.g., Y). It is often used to visualize how changes in independent variables affect the response.

Runs or trials: refer to the individual experiments conducted based on the experimental design chosen for the study.

Screening: is the process of identifying significant factors or variables that influence the response or outcome of an experiment.

Contour plot: is a graphical representation used to show the relationship between two independent variables by plotting them against each other while keeping the response and other variables constant. It visually illustrates how changes in independent variables affect the response. The combined impact of two or more factors (variables) on a response is referred to as an interaction. For instance, a tablet's hardness is influenced by the interaction between lubricant and glidant. The influence of variations in the drug-to-polymer ratio on the rate of dissolution can be evaluated using optimization study. Factors and reactions may have an antagonistic (factors opposing each other) or additive (factors contributing together) relationship. The qualities of the finished product are impacted by the synergistic or opposing effects of components, which can be ascertained by interaction analysis. The change in response brought about by modifying the levels of a factor is referred to as its effect. It explains the connection between the variables (factors) and the levels that correspond to them. Multiple Linear Regression Analysis: is a statistical technique that models the relationship between multiple independent variables and a dependent variable (response). This relationship is typically represented mathematically by a quadratic equation.

Orthogonality: refers to a situation where the effect of a factor is independent of interactions with other factors. In other words, the main factor of interest influences the response without interference from other factor

Confounding: occurs where orthogonality is not achieved , meaning that the effects of different factors are mixed or intertwined. This can make it difficult to isolate the individual effects of each factor.

Resolution: measures the degree of confounding in an experimental design. It indicates how clearly

the factors' effects can be distinguished from one another in the analysis (RK Garg, 2015).

Optimization model parameter:-

In optimization, optimization parameters are typically divided into two broad categories: 1.ProblemType and

2. Variables (Shelke1, 2021).

1. Problem type:-

There are two main types of optimization problems:

Constrained type: Constrained types refer to systems that are limited by physical factors or practical considerations. For example, this can be illustrated by a tablet's required hardness and the need for it to disintegrate within 15 minutes.

Unconstrained type: In an unconstrained system, there are no physical limitations or, at most, only minor practical restrictions. However, in the pharmaceutical industry, there are always some constraints, whether due to physical limitations or the formulator's specific choices or requirements for the system.

2. Variables:-.

The development of pharmaceutical formulation and processing involve mathematically numerous variables, which can generally be categorized into, Independent variables: The formulator's direct control over formulation and process variables, such as the amount of a particular ingredient or the amount of time needed to mix a particular step in the process, are known as independent variables. However, the characteristics of the final drug delivery system or the in-process material are known as dependent variables, and they are directly impacted by any changes made to the formulation or process (Fonner, 1970). Examples of these include the drug release profile, friability, tablet granule size, disintegration time, and other related attributes (BEHNKEN, 1960). Often called response variables, these are the system's measured characteristics that are used to predict the experiment's outcome. They usually follow directly from any modifications made to the independent variables. In the framework of optimization approaches, a drug formulation (product) can be thought of as a system in which a transfer function (T) influences the output (Y) based on a collection of controllable (X) and uncontrollable (U) input variables. Fig. 1 provides a visual representation of this relationship (Calvin, 1954).

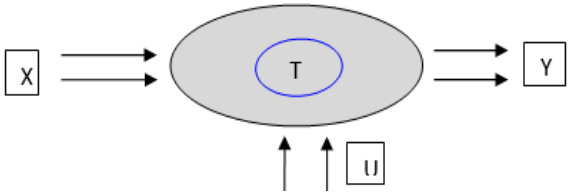

Fig.1 **System consisting of controllable input variables (X), uncontrollable input variables (U), a transfer function (T), and output variables (Y)**

The nomenclature of the transfer function (T) depends on the predictability of the output in response to changes in the input variables. T is referred to as a black box. A white box system, on the other hand, is one with complete predictability, where the output can be accurately determined from the input variables. A gray box represents a system with moderate predictability, where the output is partially predictable but not fully deterministic. Using optimization methods, the formulator's goal is to shift the system from a black or gray box status, as seen in traditional studies, to a white box or near-white box status, where the relationships between inputs and outputs are more clearly understood and predictable.

Experimental Designs (ED):-

Experimental design is a methodology used to identify and evaluate the process variables that significantly impact the outcome. In this approach, process variables are initially screened to determine which ones play a critical role in influencing the results. These variables could include factors such as the type and percentage of excipients, disintegration time (DT), and other

relevant process parameters (Sanford Bolton, 2003).

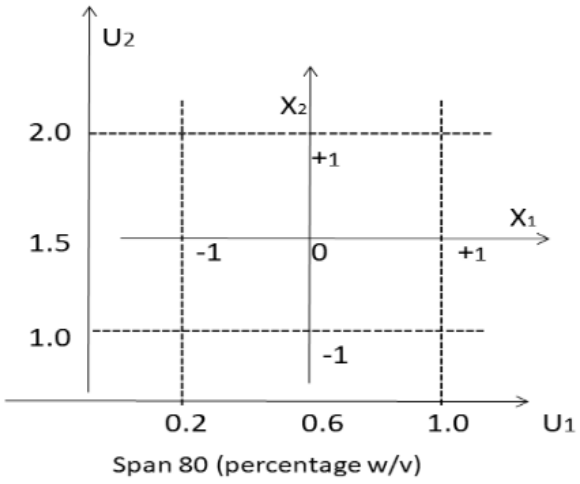

Fig.2 Quantitative factors and the factor space are defined by the natural variables, Ethyl Cellulose Drug ratio and Span 80 concentration, which are represented by U1 and U2, respectively. These natural variables are then transformed into coded variables, X1 and X2, for analysis.

The execution of an experiment and the subsequent analysis of its results are the two fundamental components of the general scientific methodology (Gareth A. Lewis, 1998). This can only be achieved if experiments are conducted in a structured manner, with conclusions drawn based on the results. Experimental design is the statistical approach used to organize experiments in a way that ensures the necessary information is gathered as efficiently and accurately as possible (Kettaneh-Wold, 605-610). Runs or trials refer to the experiments conducted according to the chosen experimental design. These Design of Experiments (DoE) trials are arranged within the design space to ensure reliable and consistent results with minimal experimentation. The arrangement of these experimental runs in a matrix format, based on the experimental design, is called the design matrix (Gareth A. Lewis, 1998).

The selection of the design depends on the proposed model, the shape of the domain, and the study's objectives. In general, experimental (or statistical) designs are based on the principles of randomization (how treatments are assigned to experimental units), replication (the number of units used for each treatment), and error control or local control (grouping specific types of experiments to enhance precision) (M.N. Das, 2003).

Advantages of Experimental Design	Disadvantages of Experimental Design
1. Control over Variables. 2. Increased Precision. 3. Efficient Use of Resource. 4. Analysis. 5. Reproducibility. 6. Identification of Interactions.	1. Complexity in Design. 2. Resource. 3. Intensive Ethical Concerns. 4. Limited Generalizability. 5. Potential for Bias. 6. Over-Simplification

Advantage and Disadvantage of Experimental Design (Table. 3)

Types of Experimental Designs (ED)

There are several types of experimental designs (ED), and the choice of method depends on the available resources and the specific parameters we aim to estimate.

Factorial Designs

Factorial designs (FD) were first introduced in the 19th century by John Bennet Lawes and Joseph Henry Gilbert. A factorial design enables the investigation of the effects of multiple factors, as well as the interactions between them, using the same number of trials required to assess any single effect. These designs are frequently used in response surface methodologies (Borror, 2018). Factorial designs (FDs) are considered symmetric when each factor has the same number of levels and asymmetric when the number of levels varies across the factors (Gareth A. Lewis, 1998). Apart from Response Surface Methodology (RSM), the design is also used for identifying influential variables and analyzing the impact of different factors. Figure.3(a and b) provides a visual representation of 2^2 and 2^3 factorial designs, with each point representing an individual experiment.

In a factorial experiment, all levels of one factor are combined with all levels of every other factor being studied. Typically, factorial designs are based on first-degree mathematical models. There are several key advantages to using factorial designs:

Examination of treatment variations: Factorial designs are ideal for studying variations in treatments, as they allow for the assessment of multiple factors simultaneously.

Efficiency: Factorial designs are efficient because they combine multiple independent studies into one experiment, saving time and resources.

Interaction effects: Factorial designs are the most effective way to examine interaction effects between factors (KUMAR*, 2017).

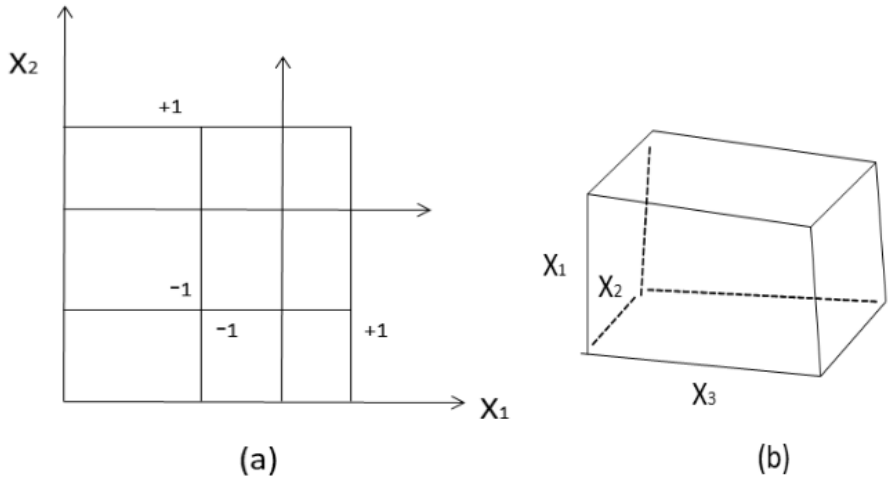

Figure.3 In part (a), each of two factors has 2 levels (a 2^2 design), while in part (b), each of three factors has 2 levels (a 2^3 design). In both cases, the design is "full factorial," meaning all possible combinations of factor levels are tested (Bhupendra singh, 2002).

Fractional Factorial Design (FFD):-

Fractional factorial design is commonly used for screening factors. This design has lower resolution due to a reduced number of experimental runs. While fractional factorial designs are economical in terms of the number of experiments, the ability to clearly distinguish some factor effects may be compromised due to the smaller number of runs (KUMAR*, 2017).

Plackett-Burman Designs (PBD)

One particular kind of two-level fractional factorial design that is typically utilized for screening factors is the Plackett-Burman design. When a lot of factors need to be examined, these designs are perfect. For instance, four dummy factors must be included if you wish to examine the impacts of seven components. Pareto charts and half-normal plots are commonly used to assess

the outcomes of fractional factorial designs, Plackett-Burman designs, and Taguchi designs. When key effects are the focus, these designs work quite well for screening. Assuming that interactions are insignificant compared to the main effects, they are cost-effective in identifying large main effects. Because these designs usually include tests like 8, 12, 16, they are also known as saturated designs, like 8, 12, 16, or 20 runs, which are suitable for studying 7, 11, 15, or 19 factors, respectively (Harrington, 2001).

Central Composite Design (CCD)

The Central Composite Design (CCD), created by Box and Wilson, is a more sophisticated design that incorporates the advantages of the star design, fractional factorial design, and factorial design. CCD is typically used for nonlinear responses requiring second-order models. It often includes a 2k2^k2k factorial or fractional factorial design, augmented with additional star points. A two-factor CCD is essentially the same as a 323^232 factorial design, but the experimental domain is spherical for a value of α=2=1.414\alpha = sqrt{2} = 1.414α=2=1.414, as opposed to the rectangular shape for α=±1\alpha = \pm 1α=±1. CCD is widely used in response surface optimization, especially during pharmaceutical product development. An example application is the formulation of Glipizide (Dash, 2015).

Box-Behnken Design (BBD)

Box- Behnken Design is a specialized experimental design requiring only three levels for each factor: -1, 0, and +1. It uses 15 experimental runs to examine three factors at three levels. Compared to CCD, BBD is more economical because it requires fewer trials. BBD has been applied in the preparation of Tenofovir and the fabrication of Nateglinide nanoparticles.

Taguchi Design (TD)

Taguchi design, also known as "off-line quality control," is a methodology developed by Genichi Taguchi that aims to ensure robust product or process performance. It is commonly used for screening factors and is particularly efficient for studying the effects of multiple factors with minimal experiments. Taguchi design often uses 8 experimental runs to evaluate 7 factors. An example of Taguchi design in pharmaceutical applications is the preparation of Gliclazide (J. Varshosaz, 2009).

Mixture Design (MD)

Mixture designs are used to study the proportions of various components in a formulation rather than their individual quantities. The sum of the proportions of all ingredients is equal to one, and none of the fractions can be negative. In pharmaceutical formulations that involve multiple excipients, the finished product's characteristics depend on the proportions of each excipient rather than their absolute quantities. Therefore, the levels of different components are varied while maintaining the restriction that their total sum remains unity (ENNEFFAH WAFAA1, 2016).

Response Surfaces:-

Conducting Design of Experiments (DoE) trials using a chosen statistical design generates a collection of data regarding the response variable under investigation. This information can subsequently be utilized to create a mathematical model that illustrates the connection between the independent variables and the dependent variable. The visual depiction of this mathematical connect on is known as a response surface. A response surface plot is a three dimensional graphical illustration that display the connection between two independent variables and a single response variable. By using 3D response surface plots, one can gain insights into the systems behaviour, illustrating how the independent variables influence the response variable (Gareth A. Lewis, 1998) A contour plot is a geometric representation of a response, created by plotting one independent variable against another while keeping the response level and other variables constant(Singh,

2002). Contour plots represent 2-D slices of 3-D response surfaces, with the resulting curves referred to as contour lines. These plots show the contour lines and response surface for the response variable, such as the percentage of drug entrapment in nimesulide liposomal vesicles. It could be required to create a total of nC2 response surfaces and contour plots in order to sufficiently depict the reaction among 'n' independent variables. In other words, to illustrate each response for 2, 3, 4, or 5 variables, you would need 1, 3, 6, or 10 3-D and 2-D plots, respectively.

Optimization of Important Factors:-

Model Development:

The quantitative link between a response variable and the independent variables is expressed mathematically by a model. Typically, this model takes the form of a set of polynomials of a certain degree. To determine the coefficients of the polynomial, we use techniques like Multiple Linear Regression Analysis (MLRA). Software tools can assist in analyzing the effects of excipients, their interactions, and generating graphical outputs like 3D response plots and contour plots. In screening designs, half-normal plots and Pareto charts help identify the most significant factors and their optimal levels. Once the key factors and their levels are determined, the next step is to optimize one or more responses. This can be done through graphical methods, numerical methods, or by using Brute Force Search Technology (REHA S. CHODANKAR*, 2016).

Optimization Methods:-

Graphical Optimization (GO):-

Also known as Response Surface Analysis (RSA), graphical optimization focuses on selecting the best formulation within a feasible factor space. This method involves setting the desired limits for the response variables, and then adjusting the factor levels accordingly. One common tool for this is the overlay plot, which combines multiple response surfaces to help identify the optimal region for factors (Dahiya, 2005).

Brute-Force Search (Feasibility and Grid Search):-

The brute-force search method is an exhaustive optimization technique. It involves evaluating every possible combination of independent factors to assess their effects on the response variables. The goal is to narrow down the feasible space by setting acceptable limits for the responses, and then conducting another exhaustive search within this narrowed region. The grid search step is the final part of this process, where the optimal formulation is identified from the feasible space (Bhupendra singh, 2002).

Numerical Optimization:-

This method involves using computational techniques to select the best formulation based on the desired limits of the response variables. The factor levels that lead to optimal responses are determined using specialized software. Techniques such as canonical analysis**,** artificial neural networks (ANNs), and other mathematical optimization methods can be used for optimizing multiple responses (REHA S. CHODANKAR*, Optimisaton techniques: a futuristic approach for formulating and processing of pharmaceuticals, 2016).

Model Validation

Once an optimal formulation or checkpoint is identified through the optimization process, it should be prepared according to the optimal factor levels, and the response should be evaluated. The observed responses are then compared to the predicted ones. If the predicted and observed results match closely, the model can be considered validated.

Criteria for Selecting Software for Experimental Designs and Optimization:-

Before selecting software for experimental designs and optimization techniques, the following factors should be considered.

Ease of Use**:** A simple graphical user interface (GUI) that is intuitive and user-friendly.
Documentation: A well-written manual with clear tutorials to help users get started quickly.
Variety of Designs: The software should offer a wide range of designs suitable for both screening and optimize process or product formulations.
Data Management: The software should feature a flexible spreadsheet for data entry, as well as the ability to handle missing data and changes in factor levels. Graphical tools that provide interactive 3D response surface plots**,** 2D contour plots**,** interaction plots, and model diagnostic plots to help visualize and assess the experimental results.
Software that allows randomization of experimental run orders, randomization is essential because it ensures that external or "noisy" factors are evenly distributed across all control factors, minimizing their impact on the results.
Design evaluation features that help identify issues such as aliasing and other potential problems, ensuring the integrity of the experimental design.
Comprehensive after-sales support, including online help and training resources provided by the vendor, ensuring users receive the assistance they need to effectively use the software.

Computer Used in Optimization:-

The principles of optimization, now known as Design of Experiments (DoE), originated in the 1920s through the work of British statistician Ronald Fisher. However, optimization remained largely stagnant for many years due to the cumbersome and time-consuming manual calculations required. It was only with the development of mainframe computers that software emerged, enabling the automation of designed-experiment optimization processes (Anderson-Cook & Lu, 2016). Mainframes, requiring programming expertise beyond the reach of most statisticians, handled complex DoE equations. However, it wasn't until these bulky, room-sized computers shrank into desktop PCs that affordable DoE software became available to non-statisticians. Nowadays, computers are crucial in design and optimization processes, as they handle the complex statistical and mathematical calculations involved (Joseph B.Schwartz, Optimization Techniques in Pharmaceutical Formulation and Processing, 2002). In particular, ANN optimization is fully dependent on a computer interface that is specifically designed for this task.

Optimization method	Model situations for use
Graphical Analysis	Mathematical model for a single response of any kind, usually with no more than four components. Mathematical model that optimizes several replies and has two to six factors of any order. first-order Model for a single response, where the optimum is outside the domain. Second-order model for a single answer, where the optimum is outside the domain. Direct optimization for one or more replies without the need of a mathematical model. Industrial environment with little change
Desirability Function	
Steepest Ascent	
Optimum Path	
Sequential Simplex	
Evolutionary Operations	

Suitability of Different Optimization Methods in Various Situations (Table.4)

Computer software is used at nearly every stage of the optimization process, from selecting the design and screening factors to applying response surface designs, generating the design matrix, creating 3-D response surfaces and 2-D contour plots, using optimum search methods, interpreting results, and finally validating the methodology (Bhandarkar, 1994). Indeed, many software packages now assist users in conducting data analysis without the need for direct interaction with mathematical models or statistical equations (Ravi P. Singh1, 2011). The appropriate software can greatly simplify, accelerate, refine, and make DoE optimization tasks more cost-effective. Notably, tasks that were

once considered impossible, such as manually creating various types of 3-D response surfaces, can now be accomplished with exceptional ease using the right tools (HARPER, 2006).

Table.5 presents a selection of widely used optimization software along with their key features. These commercially available software packages are priced differently, ranging from $99 to $2500, depending on the features they offer. However, the actual number of such software solutions is significantly higher, as the field of optimization continues to expand rapidly (REHA S. CHODANKAR, 2016)

Software	Main features	Source
1.Design Expert	A robust, all-inclusive, and popular program for pharmaceutical formulation and process optimization. For several design types, such as FD, FFD, BBD, CCD, PBD, and mixed designs, it makes it easier to screen and analyze important variables. In addition to numerical and graphical optimization tools, the software provides 2D contour maps and 3D plots that may be rotated to visualize response surfaces.	**www.statease.com**
2. MINITAB	A robust DoE program for automated data analysis that works with MS-Excel and has useful features and visualizations. It encompasses almost every Response Surface Methodology (RSM) design.	**www.minitab.com**
3. CARD	A robust DoE program with useful functions and graphic tools for automated data analysis. It is compatible with MS-Excel and is suitable for automated data analysis using Taguchi, FD, FFD, and PBD;	**www.s-matrix.com**
4. DoE PRO XL & DoE KISS	however, the relatively inexpensive software, DoE KISS, is limited to single response variables only. Appropriate for response surface modeling and assessing the model's fit.	**www.sigmazone.com**
5.MODDE	A comprehensive statistical program that provides tools for implementing experimental designs, specifically for mixture designs.	**www.umetrics.com**
6.SPSS	It is the only program that supports multi-criteria decision-making through Pareto-optimality,	**www.spss.com**
7.Omega	accommodating up to six objectives, and includes a variety of statistical functions	**www.winomega.com**

Key optimization software and their standout features (Table.5)

CONCLUSION: -

In conclusion, the optimization of pharmaceutical products plays a critical role in ensuring that drugs are not only effective but also safe, cost-efficient, and compliant with regulatory standards. Through advancements in formulation, manufacturing processes, and drug delivery systems, the pharmaceutical industry has made significant strides in improving product quality and bioavailability while reducing time-to-market. Techniques like excipient selection, nanotechnology, controlled release systems, continuous processing, and Quality-by-Design principles have enhanced product consistency and scalability. Computational modeling has further supported the optimization of drug formulations and pharmacokinetic predictions. Despite these advancements, challenges such as regulatory constraints and patient-specific needs remain. Future developments, including personalized medicine and sustainable practices, will continue to shape the field, emphasizing the need for a collaborative, multidisciplinary approach to meet the dynamic demands of both the pharmaceutical industry and patients.

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