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A REVIEW ON OPTIMIZATION TECHNIQUES IN PHARMACEUTICAL PRODUCT DEVELOPMENT

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ABSTRACT

Optimization plays a pivotal role in modern pharmaceutical product development, ensuring the creation of safe, effective, and high-quality dosage forms with efficient resource utilization. With the growing complexity of drug formulations, particularly those involving nanocarriers, solid dispersions, and controlled-release systems, systematic optimization techniques have become indispensable. This review highlights the various optimization strategies applied across formulation and process development stages, including statistical design of experiments (DoE), response surface methodology (RSM), factorial design, Box–Behnken design, and artificial intelligence (AI)-assisted optimization. Emphasis is placed on the integration of Quality by Design (QbD) principles, where critical quality attributes (CQAs), critical material attributes (CMAs), and critical process parameters (CPPs) are identified and optimized to achieve robust product performance. The article further discusses the role of advanced computational modeling, simulation tools, and multi-criteria decision-making approaches in reducing experimental workload and improving predictability. Collectively, these techniques provide a scientific framework for rational formulation design, efficient scale-up, and regulatory compliance. The review concludes that the adoption of modern optimization methodologies not only accelerates product development timelines but also enhances the quality, reproducibility, and commercial viability of pharmaceutical products.

KEYWORDS: Optimization Techniques, Pharmaceutical Product Development Design of Experiments, Response Surface Methodology, Factorial Design.

INTRODUCTION

In the Pharmacy word "Optimization" is found in the literature referring to any study of formula. In development projects pharmacist generally experiments by a series of logical steps, carefully checking the variables and changing one at a time until satisfactory answers are received. This is how the Optimization done in pharmaceutical manufacture.[1] Optimization is set as follows: "Choosing the best component from some set of available alternatives." It is the procedure of determining the best direction of applying the existing resources while getting into the score of all the elements. that influences decisions in any experiment. The aim of designing quality formulation is achieved by various Optimization techniques like DoE (Design of Experiment). The term FbD (Formulation by Design) and QbD (Quality by Design) indicates that the tone of the product can be made by practicing diverse techniques of DOE (Design of Experiment). This FbD has replaced the OVAT (one variable at a time) strategy for Optimization completely.[2]

Terminologies[3]

- **Variable:** There are of two types of variables Independent variables or primary variables formulations and process variables directly under control of the formulator. These include ingredients dependent or secondary variables. These are the responses of the in progress material or the resulting drug delivery system. It is the termination of

independent variables.

- **Factor:** It is Assigned and Independent variables, which touch on the product or output of the operation. It is an assigned quantitative and qualitatively.
- **Quantitative:** Numerical factor assigned to it, Ex. Concentration- 1%, 2%, 3% etc.
- **Qualitative:** This is not numerical, Ex. Polymer grade, humidity condition and so on.
- **Level:** Levels of a factor are the values or designations assigned to the element.
- **Response Surface:** Response surface representing the relationship between the independent variables X1 and X2 and the dependent variable Y.
- **Run or Trials:** Experiments conducted according to the selected experimental design.
- **Screening:** To sort out something from.
- **Contour Plot:** Geometric illustration of a response obtained by plotting one independent variable against another, while holding the magnitude of response and other variables as constant.
- **Interaction:** It gives the overall effect of two or more variables means lack of additively of factor effects Ex: Combined effect of lubricant and glidant on hardness of the tablet.
- **MLRA (Multiple Linear Regression Analysis):** The technique which express mathematically in form of quadratic equation the linear relationship between various independent variable and dependent variable (Response).
- **Effect:** It is the change in response caused by varying the levels and it gives the relationship between various factors & levels (h) Response: It is an effect of the experimentation.
- **Orthogonality:** When effect is preferable to the main element of interest and no interaction.
- **Confounding:** Lack of Orthogonality is termed as confounding or aliasing.
- **Resolution:** Measurement of degree of confounding.

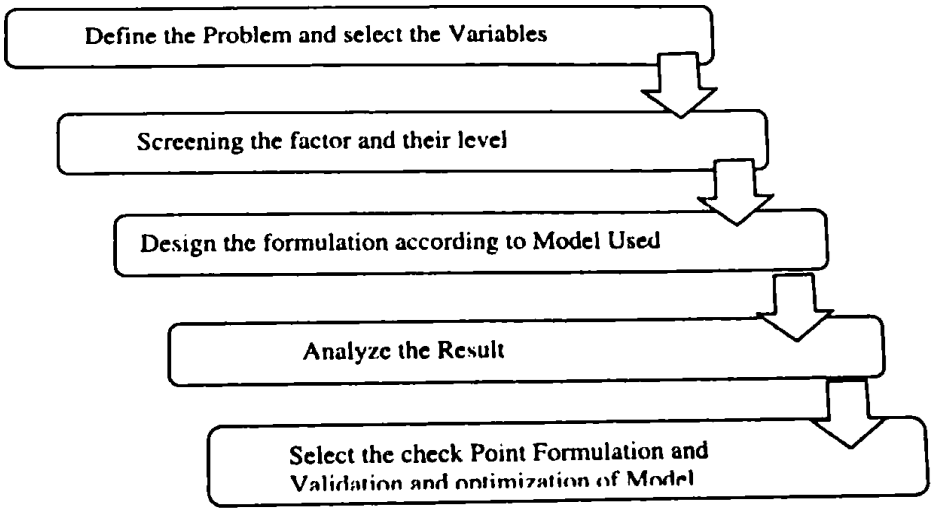


Figure 1: Formulation Optimization using Design of Experiment.[4]

Benefits for Industry[5]

- Better understanding of the process.
- Less batch failure.
- More efficient and effective control of change.
- Return on investment or cost savings.
- Provides opportunities for more flexible regulatory approaches.
- Manufacturing changes within the approved design space without further regulatory review.
- Reduction of post-approval submissions.
- Better innovation due to the ability to improve processes without resubmission to the FDA when remaining in the Design Space.

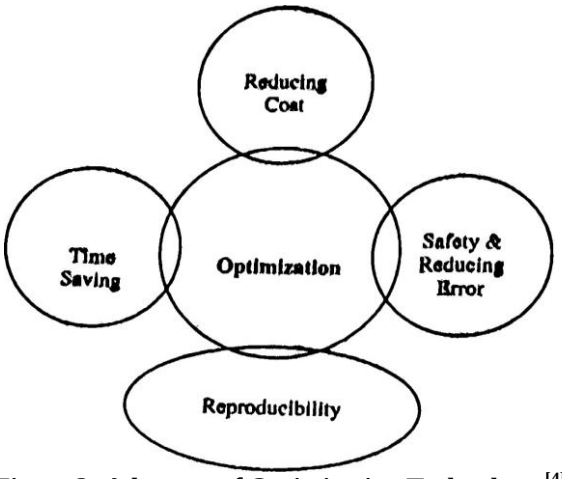


Figure 2: Advances of Optimization Technology.[4]

Various Optimization Techniques[5]

- Continuous optimization
- Discrete optimization
- Unconstrained optimization
- Constrained optimization
- Deterministic optimization
- Stochastic optimization
- Graphical optimization
- Brite-force Search
- Numerical optimization
- **Continuous Optimization:** In continuous optimization, the variables in the model are allowed to take on any value within a range of values, usually real numbers. This property of the variables is in contrast to discrete optimization, in which some or all of the variables may be binary (restricted to the values 0 and 1), integer (for which only integer values are allowed), or more abstract objects drawn from sets with finitely many elements. An important distinction in continuous optimization is between problems in which there are no constraints on the variables and problems in which there are constraints on the variables.[6]
- **Discrete Optimization:** In discrete optimization, some or all of the variables in a model are required to belong to a discrete set; this is in contrast to continuous optimization in which the variables are allowed to take on any value within a range of values. Here, we consider two branches of discrete optimization. In integer programming. the discrete set is a subset of integers. In combinatorial optimization, the discrete set is a set of objects, or combinatorial structures, such as assignments, combinations, routes, schedules, or sequences.[6]
- **Unconstrained Optimization**: Unconstrained optimization problems consider the problem of minimizing an objective function that depends on real variables with no restrictions on their values. Mathematically, let XR XER" be a real vector with n≥1n21 components and let f: R^n Rf: R^n R be a smooth function. Then, the unconstrained optimization problem is, Min, f(x)

Unconstrained optimization problems arise directly in some applications but they also arise indirectly from reformulations of constrained optimization problems. Often it is practical to replace the constraints of an optimization problem with penalized terms in the objective function and to solve the problem as an unconstrained problem.[6]

- **Constrained Optimization:** Constrained optimization problems consider the problem of optimizing an objective function subject to constraints on the variables. Where f and the functions ci (x), cif (x) are all smooth, real-valued functions on a subset of R^n R^n and EE and II are index sets for equality and inequality constraints, respectively. The feasible set is the set of point's xx that satisfy the constraints. Constrained optimization covers a large number of subfields, including many important special cases for which specialized algorithms are available.[6]
- **Deterministic Optimization:** In deterministic optimization, it is assumed that the data for the given problem are known accurately. However, for many actual problems, the data cannot be known accurately for a variety of reasons. The first reason is due to simple measurement error. The second and more fundamental reason is that some data represent information about the future (e.g., product demand or price for a future time period) and simply cannot be known with certainty.[6]
- **Stochastic Optimization:** In optimization under uncertainty, or stochastic optimization, the uncertainty is incorporated into the model. Robust optimization techniques can be used when the parameters are known only within certain bounds; the goal is to find a solution that is feasible for all data and optimal in some sense. Stochastic programming models take advantage of the fact that probability distributions governing the data are known or can be estimated; the goal is to find some policy that is feasible for all (or almost all) the possible data instances and optimizes the expected performance of the model.[6]
- **Graphical Optimization:** Graphical optimization deals with picking out the best possible formulation out of a feasible factor space region. To answer this, the desirable limits of response variables are ready, and the ingredient levels are screened accordingly with the help of overlay plot.[6]
- **Brute-force Search (Feasibility and Grid Search):** Brute-force search technique is the simple and exhaustive search optimization technique. It contains each and every single point in the office space. Herein, the formulations that can be made by almost every possible combination of autonomous factors and screened for their response variables. Afterwards, the acceptable limits are set for these answers, and an exhaustive search is again led by further narrowing down the feasible part. The optimized formulation is searched from the final feasible space (termed as grid search), which carry out the maximum standards set during experimentation.[6]
- **Numerical Optimization:** It deals with picking out the best possible formulation out of a suitable factor. To answer this, the desirable limits of response variables are ready, and the ingredient levels are exposed by the software. Other techniques used for optimizing multiple responses are canonical analysis, ANNs and mathematical optimization.[6]

DESIGN OF EXPERIMENT (DOE)

Introduction: Experimental design is a statistical design that prescribes or advises a lot of combination of variables. The number and layout of these design details within the experimental part, depends on the number of

effects that must be judged.[7]

Depending on the number of ingredients, their grades, potential interactions and order of the mannequin, the various experimental designs are preferred.[7]

Each experiment can be represented as a point within the experimental domain; the point being defined by its coordinates (the value given to the variables) in the space. It is a mathematical tool for systematically planning and leading scientific studies that change experimental variables together in society to define their effect on a given response. It makes controlled changes to input variables in society to pull in maximum amounts of information on cause and effect relationships with a minimum sample size for optimizing the formulation.[7]

At that place are mainly four steps associated with DoE.[8]

- The design of the experiment (By applying various models).
- The ingathering of the information.
- The statistical analysis of the data and
- The conclusions reached and recommendations made as an upshot of the experimentation.

In optimization Method various types of Model used for preliminary screening of factors to select their level and for finally study of their effect, so it is depended upon the formulator to choose a suitable model to study and help in minimizing the experimenting time.[8]

Types of Experimental Design: There are diverse types of Experimental design methods:

1. Screening Designs: Cover Designs are used for distinguishing the important gene and their level, which affects the Quality of Formulation. Screening Designs generally support only the linear responses. Response Surface Designs are applied when we required exact image of response, estimating interaction and even quadratic effects.[9]

2. Response Surface Designs: Response surface designs generally support nonlinear and quadratic response and capable of detecting curvatures.[9]

3. Factorial Designs: Factorial designs (FDs) are really frequently used response surface designs. A factorial experiment is one in which all strata of a given factor are combined with all stages of every other ingredient in the experimentation. These are mostly founded upon first-degree mathematical models. Full FDs involve studying the outcome of all the factors (k) at various levels (x), including the interactions among them, with the total number of experiments being x k. If the number of points is the same for each gene in the optimization field, the FDs are said to be symmetric, whereas in cases of a different number of layers for different factors, FDs are termed asymmetric. "When we study three factors at two level 2^3 the total Number of runs will be 08 & When we study two factors at three level 3^2 the total Number of run will be 9.[10]

4. Fractional Factorial Design (FFD): Fractional factorial design is generally employed for the screening of factor. This design has low resolution due to less number of foot races. Although these plans are economical in terms of number of experiments, the ability to recognize some of the factor effects is partly sacrificed by a decrease in the number of experimentations.[10]

5. Plackett-Burman Designs (Hadamard Designs): Plackett-Burman designs (PBD) are special two level FFDs used generally for screening of genes. This pattern is mostly utilized when we want to screen a high figure of factors if we want to study the effect of 7 factors then we have to show four dummy factors. The interpretations of outcomes in the FFD, Plackett-Burman Designs & Taguchi design are traced with the help of Pareto chart and half normal plot.[10]

6. Central Composite Design (Box-Wilson design): For nonlinear responses requiring second-order models, central composite designs (CCDs) are the most frequently used. A two-factor CCD is identical to a 3^2 FD with the rectangular experimental domain at a ±1, On the other hand, the experimental domain is spherical in shape for a = 1.414. The CCD is quite popular in response surface Optimization during pharmaceutical product development.[10]

7. Box-Behnken Designs: A specially made design, the Box-Behnken design (BBD), takes only three points for each facto -1, 0 and +1. It employs 15 experiments run with three agents at three points. It is economical then CCD because it calls for less number of trial.

8. Taguchi Design: Taguchi refers to experimental design as "off-line quality control" because it is a method of assuring good performance in the development of products or processes. It is likewise utilized for screening of genes and it provides 8 experimental runs for 7 genes.[11]

9. Mixture Design: Mix designs are applied when the characteristics of the finished product (drug delivery system) usually depend not so much on the amount of each substance present but on their balances. The sum total of the proportions of all the excipients is unity, and none of the fractions can be negative. Thus, the levels of different elements can be changed with the limitation that the sum total should not exceed one.[11]

OPTIMIZATION BY FACTORIAL DESIGNS

Introduction: In statistics, a full factorial experiment is an experiment whose design consists of two or more factors, each with discrete possible values or "levels", and whose experimental units take on all possible

combinations of these levels across all such factors. A full factorial design may also be called a fully crossed design. Such an experiment allows the investigator to study the effect of each factor on the response variable, as well as the effects of interactions between factors on the response variable. For the vast majority of factorial experiments, each factor has only two levels. For example, with two factors each taking two levels, a factorial experiment would have four treatment combinations in total, and is usually called a 2x2 factorial design. If the number of combinations in a full factorial design is too high to be logistically feasible, a fractional factorial design may be done, in which some of the possible combinations (usually at least half) are omitted.[11]

The advantage of a factorial experiment.[11]

- More efficiency than on-factor-at-a-time experiments,
- All data are used in computing both effects. (Note that all 4 observes are used in determining the average effect of factor A and the average of factor B),
- Some information is provided on possible interaction between the 2 factors.

Factorial design depends on independent variables for development of new formulation. Factorial design also depends on levels as well as coding.[11]

There are three types of levels.[11]

1) Low
2) Intermediate
3) High

Simultaneously CODING takes place for levels.[11]

1) For Low = (-1)
2) For Intermediate = (0)
3) For High = (+1)

Factorial Design (FD) is for the evaluation of multiple factors simultaneously.[11]

1) 2^3 means 2 is level while 3 is factor.
2) Factorial Design is divided into two types
3) Full Factorial Design
4) Fractional factorial design

Full Factorial Design: A design in which every setting of every factor appears with setting of every other factor is full factorial design. The design is simple to create, but extremely inefficient. If there is k factor, each at Z level, a Full FD has z ^ K.[12]

Number of Runs (N)

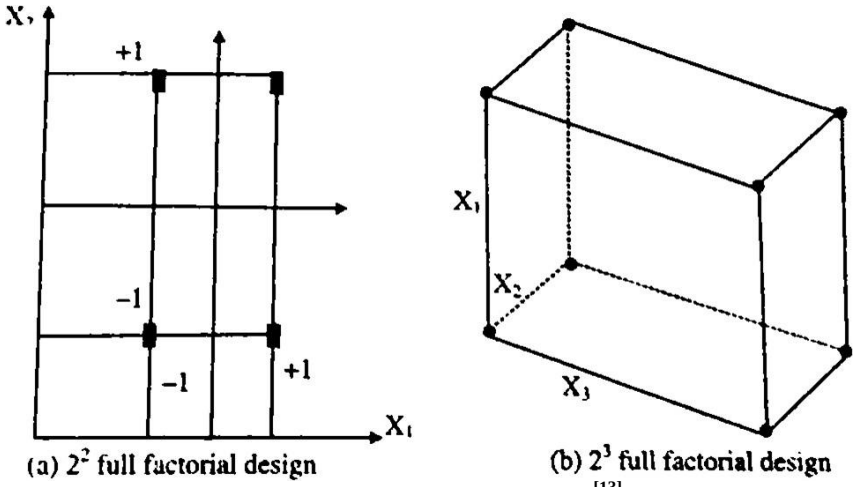
$N = y^x$

Where, y = number of levels, x = number of factors.
Example; 3 factors, 2 levels each,

$N = 2^3 = 8$ runs

Factorial Design: 2^2, 2^3, 3^2, 3^3

22 FD = 2 Factors, 2 Levels = 4 runs
23 FD = 3 Factors, 2 Levels = 8 runs
32 FD = 2 Factors, 3 Levels = 9 runs
33 FD = 3 factors, 3 Levels = 27 runs



(a) 2^2 full factorial design (b) 2^3 full factorial design

Figure 3: Full Factorial Design.[13]

Two Levels Full FD

1) 2 factors: X1 and X2 (Independent variables)
2) 2 levels: Low and High
3) Coding: (-1), (+1)

Three Levels Full FD

In three level factorial design,

1) Factors: X1, X2 and X3
2) levels are use,
i) Low (-1)
ii) Intermediate (0)
iii) High (+1)

Fractional Factorial Design: In Full FD, as a number of factor or level increases, the number of experiment required exceeds to unmanageable levels. In such cases, the number of experiments can be reduced systemically and resulting design is called as Fractional factorial design (FFD). Applied if no. of factor are more than. Means "less than full" Levels combinations are chosen to provide sufficient information to determine the factor effect. It is more efficient method.[12]

Types of Fractional Factorial Design[12]

1) Homogenous Fractional: Useful when large number of factors must be screened.

2) Mixed Level Fractional: Useful when variety of factors needs to be evaluated for main effects and higher level interactions can be assumed to be negligible.

3) Plackett-Burman: It is a popular class of screening design. These designs are very efficient screening designs when only the main effects are of interest. These are useful for detecting large main effects economically, assuming all interactions are negligible when compared with important main effects. Developed in 1946 by statisticians Robin L. Plackett and J.P. Burman, it is an efficient screening method to identify the active factors using as few experimental runs as possible. Placket and Burman showed how full factorial design can be fractionalized in a different manner, to yield saturated designs where the number of runs is a multiple of 4, rather than a power of 2. Only main effects are analyzed in this design. Interaction effects are not included General polynomial obtained Plackett Burman screening is:

$Y=b_0+b_1x_1+b_2x_2+ + b_k x_k$

Where, b(0-k) is the regression coefficients Y is the dependent variable

K number of independent variable X(1-k) independent variables

Validation of Model

The predicted optimal formulation (Check point) is prepared as per optimum factor level and the responses evaluated. On comparison of Results of Observed and predicted response conclusion will be drawn for model validation.[12]

Software for Designs and Optimization: Many commercial software packages are available which are either dedicated to experimental design alone or are of a more general statistical type.[12]

Software dedicated to experimental designs.[12]

- DESIGN EXPERT
- ECHIP
- MULTI-SIMPLEX
- NEMRODW

Software for general statistical nature.[12]

- SAS
- MINITAB
- SYSTAT
- GRAPHPAD PRISM

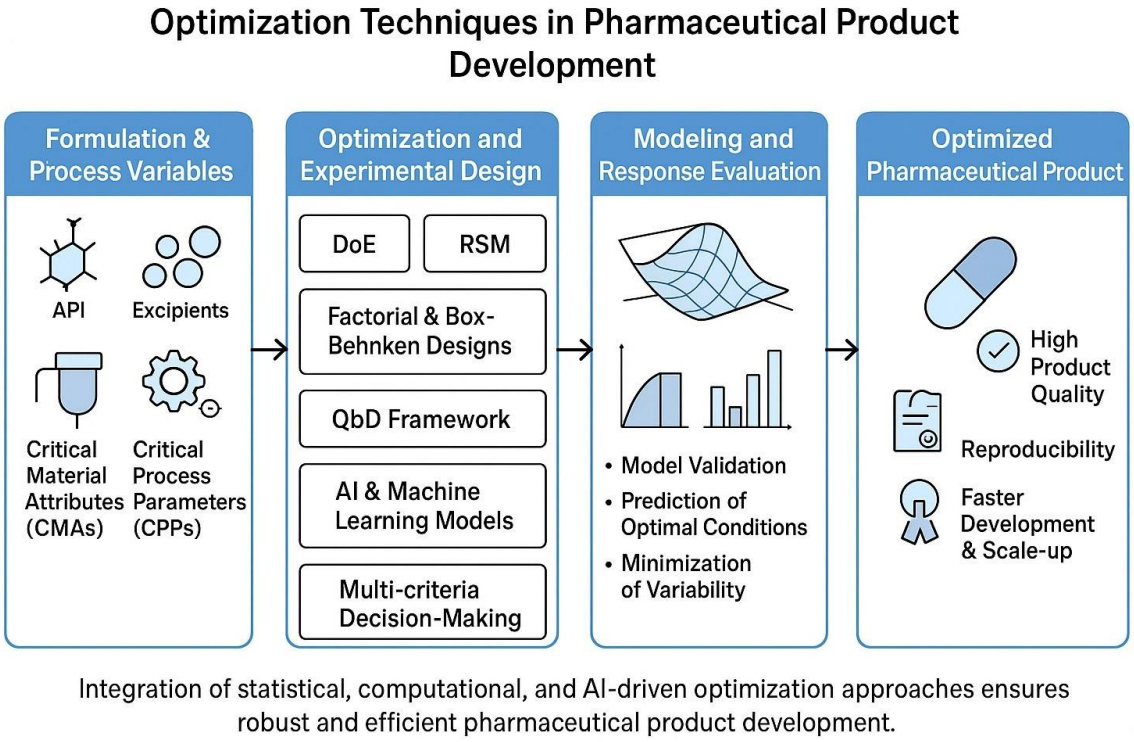


Figure 4: Schematic representation of Optimization Techniques in Pharmaceutical Product Development.[12]

CONCLUSION

Optimization techniques have become an indispensable component of modern pharmaceutical product development, providing a scientific and systematic approach to achieving robust, high-quality, and reproducible formulations. The integration of statistical tools such as Design of Experiments (DoE), Response Surface Methodology (RSM), and Quality by Design (QbD) principles enables a comprehensive understanding of formulation and process variables, ensuring efficient control over product performance. Emerging computational approaches, including artificial intelligence (AI), machine learning, and simulation-based models, further enhance predictive capabilities, minimize experimental trials, and accelerate development timelines. Collectively, these techniques support regulatory compliance, cost-effectiveness, and smooth technology transfer from laboratory to large-scale production. In conclusion, adopting a multidisciplinary optimization framework is essential for future pharmaceutical innovation, fostering the development of safer, more effective, and economically sustainable therapeutic products.

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