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Review Article

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Optimization Techniques in Designing of Pharmaceutical Dosage Form

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Abstract

Pharmaceutical dosage form design and development usually involves multiple objectives. In past, this task has been through trial and error, supplemented by the previous experience, knowledge and wisdom of the formulator. The final product may be satisfactory but sub-optimal, as a better formulation might still exist for the studied conditions by using traditional approach. Thus, in the traditional approach the primary aim of the formulator may not be in designing the best formulation, but finding a suitable solution under the given set of restrictions. These drug product inconsistencies are generally due to inadequate knowledge of causal factor and response relationship. Nowadays, systematic approaches, usually called as optimization techniques, are being widely practiced to alleviate such inconsistencies. In the present article the insight of optimization techniques is given with respect to its comparison with traditional approach, fundamental concepts, mathematical model, graphic presentation of optimization results, optimization methodologies etc.

Key words: Optimization, dosage form, approach

Introduction

Dosage Form Design: Traditional Vs Systematic Approach

Design and development of an immaculate drug product or pharmaceutical process usually involves multiple objectives under its ambit. For decades, this task has been endeavored through trial and error, supplemented by the previous experience, knowledge and wisdom of the formulator. The modification of a formulation is carried out by the analysis of its composition and influence of process factors on dosage form characteristics, changing any one at a time. Using this approach, the solution of a specific problematic property can be achieved, but attainment of the true optimum composition or process can never be guaranteed. The final product may be satisfactory but sub-optimal, as

a better formulation might still exist for the studied conditions. Thus, in the traditional approach the primary aim of the formulator may not be in designing the best formulation, but finding a suitable solution under the given set of restrictions[1]. The aforementioned drug product inconsistencies are generally due to inadequate knowledge of causal factor and response relationship. Nowadays, systematic approaches, usually called as optimization techniques, are being widely practiced to alleviate such inconsistencies. These encompass experimental designs, mathematical equations and graphic outcomes, depicting a complete picture of variation of the response as a function of the factor[2].

Systematic approaches are thus far more advantageous, possess greater benefits and overcome various pitfalls inherent to the traditional approaches as these are require fewer experiments to achieve an optimum formulation, reveal interactions, yield the best solution in the presence of competing objectives, make problem tracing and rectification quite easier, simulate the product or process performance using model equation, comprehend the process to assist in formulation development and subsequent scale-up[3].

Optimization: Fundamental Concepts

The optimization of pharmaceutical formulations with regard to one or more attributes has always been a subject of importance and attention for pharmaceutical scientists in formulation research. The word *optimized* simply implies to make as perfect, effective or functional as possible. Hence, *optimization* of a product or process is the determination of the experimental conditions resulting in its optimal performance[4].

Objective

The term *objective* has been used to indicate either the property of interest (also called as *criterion*) or the goal of an optimization experiment. The term *criterion* has also been used in isolated cases to indicate a measure of the realization of a target value of the objective, expressed as a single value or range of values[5].

Variables

The development of a pharmaceutical formulation and the associated process usually involves several variables. These are the constituents or process characteristics of a formulation that can be altered to influence its performance. The *independent variables* are the formulation and process variables directly under the control of the formulator, e.g., drug content, polymer composition etc. On the other hand, the *dependent variables* are the responses or characteristics of the finished product (e.g., tablet). These are usually a direct function of the independent variables, e.g., content uniformity, release profile, etc. Formulation variable may be either quantitative or qualitative. *Quantitative variables* are those that can take numerical values (e.g., temperature, amount of bioadhesive etc.) and are continuous. Instances of *qualitative variables*, on the other hand, include the type of a carrier or polymer like bioadhesive. Their influence can be evaluated by assigning dummy values to them.

The term *factor* implies an assigned variable, i.e., independent variables influencing the response. The *levels* of the factor are the values assigned to the factor. For example, 100, 200 and 300 mg represent the low level, intermediate, and high levels respectively for the factor polymer. *Constraints* are the restrictions placed on the levels of the factors. *Coding* (also termed as normalization) is the transformation of a natural variable to a non-dimensional coded variable X_i such that the central value of experimental domain is zero. To circumvent any anomaly in factor sensitivity with change in levels, it is recommended that the factors coding must be carried out appropriately. For instance, if one factor is temperature (say within the range of 20-80°C) and the other pH (say within the range of 1-5), a change of 1 pH unit is far more significant than a change of 1°C[5].

Response

Response is the measured property of the process (e.g., bioadhesive strength, dissolution rate, etc.), sometimes referred to as dependent variable. It is interpreted either as an outcome of an experiment or the set of outcomes of experiments, arranged according to some design or a mathematical relationship (usually termed as an *objective function*) between the controllable factors and the magnitude of the outcome. *Effect* is the change in response caused by varying the level(s) of the factor(s). The main effect is the effect of the factor averaged over all levels of other factors. *Interaction* is the lack of "additivity of factor effects". This implies that if the factor level is repeatedly increased by a constant amount, the response does not change by a constant amount. In other words, the effect of a factor on the response is nonlinear. Also, interactions are said to take place when the effect of factor A depends on the level given to the factor B. During interaction, the measured property not only depends on the level of fundamental variables but also on the degree of interaction between them[6].

Experimental domain

The term *factor space* is used for the 'k' dimensional space defined by 'k' coded variables X_i for the continuous factors being investigated. For two factors, it is represented as a (two dimensional) plane. Part of the factor space enclosed by upper and lower levels of the variables is the *experimental domain*, also known as the region of interest[2].

Experimental design

Experimental design involves the arrangement of experiments in the design space such that the reliable and consistent information is achievable with minimum number of experiments. No experimental design exists on its own, but is influenced by the previous phase of experimentation and the projected future steps, i.e., the choice of the design depends upon the proposed model, shape of the domain and the objective of the study. Experimental designs are based on the principles of *randomization*, *replication* and *error control*. *Experimental run or trial* is a practical manipulation or series of manipulations carried out under defined conditions, resulting in the data for each of the response to be measured[2].

Mathematical model

Simply referred to as the *model*, it is an expression defining the dependence of a response variable on the independent variables. Mathematical models can either be empirical or theoretical. An *empirical model* provides a way to describe this factor-response relationship[3,6]. It is most frequently, but not invariably, a set of polynomials of a given order. Most commonly used linear models are shown in Equations 2-3:

$$E(y) = \beta_o + \beta_1 X_1 + \beta_2 X_2 \quad \ldots (2)$$

$$E(y) = \beta_o + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1X_2 \quad \ldots(3)$$

$$E(y) = \beta_o + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 \quad \ldots(4)$$

Where E(y) represents the measured response and X_i (n = 1, 2), the value of the factors. β_o, β_i, β_{ii} and β_{ij} are the constants representing the intercept, coefficients of first-order terms, coefficients of second-order quadratic terms and coefficients of second-order interaction terms, respectively. The coefficients are calculated either by multiple linear regression analysis (MLRA) or by the method of contrasts. Equation 2 and 3 are linear in variables, representing a flat surface and a twisted plane in 3-D space, respectively. Equation 4 represents a linear second-order model that describes a twisted plane with curvature, arising from the quadratic terms.

Graphic presentation of optimization results

Usually, the results of an optimization are graphically depicted using one or more of the following plots:

Contour plots are the geometric illustration of responses, obtained by plotting one independent variable *versus* another while holding the magnitude of response level and other variables constant[5]. The resulting curves are called *contour lines*. Figure 1 depicts different types of contour plots:

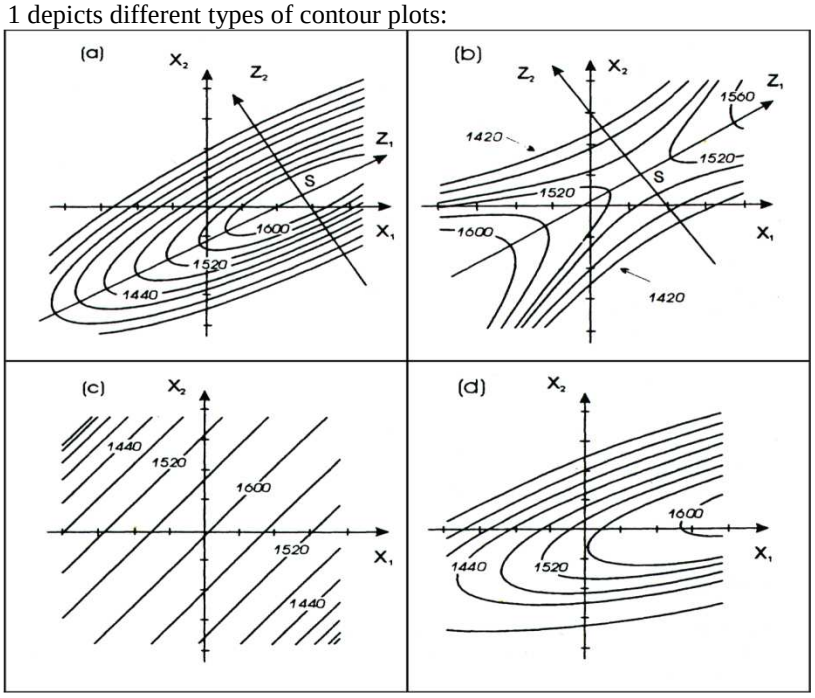


Figure 1.Contour lines (a) maximum; (b) saddle point; (c) ridge; and (d) rising ridge[7]

Response surface plots are three dimensional (3-D) graphical representation of a response plotted between two independent variables and one response variable (Figure 2). The use of 3-D response surface plots allows understanding of the behaviour of the system by demonstrating the contribution of the independent variables[8]. The slices of response surface are represented by the contour plots.

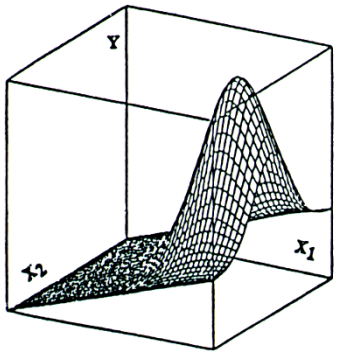


Figure 2. A typical response surface plotted between two factors X_1 and X_2 and a response variable Y[7].

Optimization Methodologies

Broadly, optimization methodology can be categorized into two classes, i.e., *simultaneous optimization*, where the experimentation is completed before the optimization takes place and *sequential optimization* where experimentation continues as the optimization study proceeds. The entire optimization programme is attempted in several stages. The whole endeavor encompasses various steps commencing from the screening for the influential factors, factor influence studies followed by implementation of various techniques to reach an optimum[2,9].

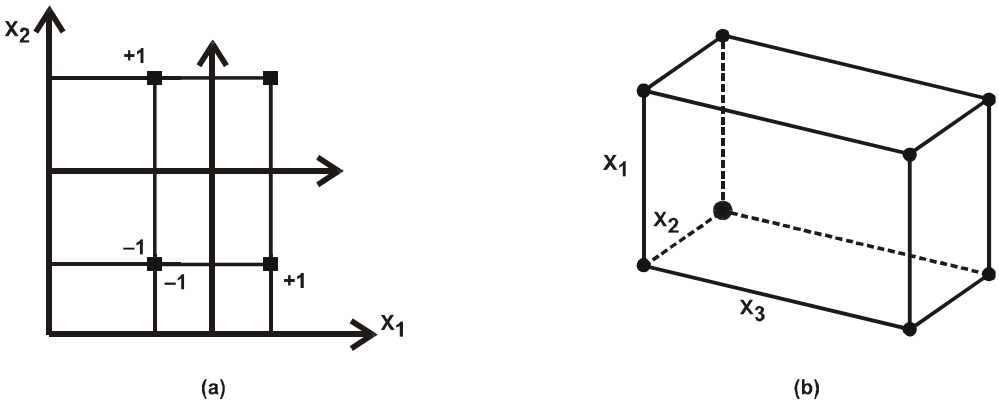
Simultaneous (Model-dependent)methods

In simultaneous methods, usually called as *response surface methodology (RSM)*, one or more selected experimental responses are recorded for a set of experiments, carried out in a systematic way, to predict the optimum and the interaction effects. These approaches involve the postulation of empirical mathematical model, for each response, which adequately represents changes in the response within the zone of interest. Rather than estimating the effects of each variable directly, fitting the coefficients in the model equation to the response and mapping of the response over the whole of the experimental domain in the form of a surface is done[1,5].

For implementation of the simultaneous optimization, one or more of the following statistical designs can be adopted:

Factorial designs

Factorial designs (FD, full or fractional), also known as experimental designs for the first-degree models, are the most popular response surface designs. Full factorial designs involve studying the effect of all factors (n) at various levels (x), including the interactions amongst them with total no. of experiments as x^n. The simplest class of FDs involves factors at two levels with factor levels suitably coded. The design is said to be *symmetric*, if each factor has same number of levels and *asymmetric*, if the number of levels for each factor differs. Pictorially, design of FD is presented in Fig. 3, where each point represents the individual experiment.



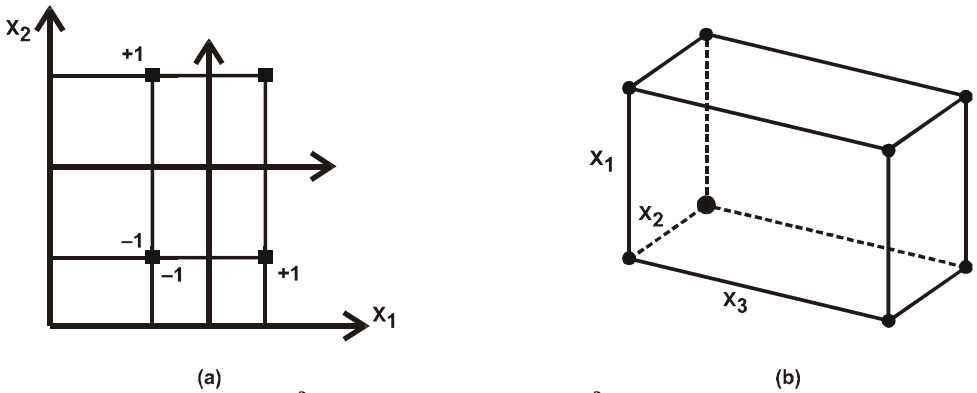


Figure 3. (a) 2^2 full factorial design (b) 2^3 full factorial design.

For convenience, the factors and their levels are denoted by a notation (symbol) to express various combinations required for an FD. For a 2^n design, a factor is denoted by a capital letter, the levels of a factor for expressing a combination by (1) for low level and the corresponding small letter for high level, e.g., for factor A the high level is denoted by the letter a[5].Although the terminology for factors as A, B, etc. and there levels as (1), a, b, etc. is comprehensive in the text format, yet their translation into mathematical equation is neither practical nor easy to comprehend. Therefore, the symbol X_n is normally used for representing the factor, where the subscript n depicts the number of factor. Similarly the subscripted B values are employed to denote the coefficient values in such equations.

In a full factorial design, as the number of factors or level increases, the number of experiments required exceeds manageable levels. Moreover, with a large number of factors, it is plausible that highest-order interactions have no significant effect. In such cases, the number of experiments can be reduced in a systematic way and the resulting design is called the *fractional factorial designs (FFD)*. A FFD is a fraction ($1/x^p$) of a complete or "full" FD, where p is the degree of fractionation, and the total number of experiments required for FFD designs are given by x^{n-p}. For a two level three factor design, for instance, a full FD will require 2^3, i.e., 8 experiments and 8 main effects and the interactions of 3 factors are estimated. A FFD with p=1 will require 2^{3-1}, i.e., 4 experiments and a total of 4 effects are estimated but they are combined effects of factors and interactions. The calculation of effects and interactions, coefficients of the equations, and the statistical significance of coefficients, so generated can be carried out using various methods. The method of contrasts and Yates algorithm can be used for calculating the effects and interactions. The coefficients can be calculated either by regression analysis. The significance of coefficients can be computed by applying ANOVA based on Yates method or by Student's t-test[7].

Sequential (Model-independent) methods

Lack of appropriate knowledge about the effects of variables makes the sequential methods a good choice for optimization. In sequential approach, the optimization is attempted in a step wise fashion, experimentation started at an arbitrary point in experimental domain, responses evaluated and the subsequent experiments are designed based on the results of these studies obtained according to an algorithm that directs these new experiments towards the optimum. Whether the chosen optimum is maximum or minimum, the general term used for this approach is "hill climbing". An important aspect of sequential designs is to know when the procedure has finished. There are many different stopping rules, but sometimes the best method involves the experimenter's skill in judging the true optimum, which is generally a local maximum and minimum [1,2,5]

Search for an optimum

The experimental designs used for optimization enables one to generate a mathematical model by careful planning of the experimentation. The mathematical model so generated is further analyzed for generating response surfaces, contour maps and finally, predict an optimum composition for the desired product using *search methods* and/or *mathematical optimization methods*[1,10].

Search methods

Search methods do not require continuity or differentiability of the function, but only computability. In these methods, the response surfaces, as defined by the appropriate equations, are searched by various methods to find the combination of independent variables yielding the optimum. Two major steps are used *viz. feasibility search* and the *grid search*. The feasibility search method is used to locate a set of response constraints that are just at the limit of possibility. One selects the several values for the responses of interest (i.e., the responses one wishes to constrain)

and a search of the response surface is made to determine whether a solution is feasible. The feasibility search method yields the possibilities satisfying the constraints. The exhaustive grid-search method is later applied in which the experimental range is divided into a grid of specific size and methodically searched. Grid search method can provide a list of possible formulations and the corresponding response values. At this point, the experimenter can trade off one response for another and the most acceptable formulation is selected from the results to complete the optimization objective[6].

Optimization Strategy

The overall approach for conduct of an optimization studies in pharmaceutical dosage forms can be described by an optimization plan. The salient steps involved in an optimization strategy are:

Problem definition: The optimization problem (e.g., release of a drug from dosage form) should be clearly understood and defined.

Selection of factors and levels: The independent variables selected should be quantifiable and easily controllable. The levels of each variable are either established from the prior experience or pilot studies. Factor and level selection should be judicious enough to gather a maximum of information with a minimum of experimental effort. If a large number of independent variables are involved, a preliminary screening study for the influential variables should be carried out. The levels for each factor should neither are too narrow nor too wide.

Design of experimental protocol: Based on the choice of independent variables and the type of response expected a suitable statistical method is selected. If no information is available on the type of response a quadratic model is chosen. The number of experiments required is dictated by the selected design. To measure the inherent variability, a sufficient number of replicates should also be determined.

Formulating and evaluating the dosage form: The dosage form is formulated corresponding to the requisite number of experiments and evaluated for the desired response(s).

Prediction of optimum formula: The experimental data is used for generation of a mathematical model and an optimum formula is determined using search methods and/or mathematical optimization methods. This is usually facilitated with the help of computer software.

Validation of optimization:

The predicted optimal formulation is formulated and the responses evaluated and verified. The results are implemented in the process/product development cycle [5, 11].

Conclusion

Optimization approaches involves experimental designs, mathematical equations and graphic outcomes, depicting a complete picture of variation of the response as a function of the factor. Optimization is becoming a regular practice globally, not only in the design and development of dosage forms, but also for modifying the existing one.

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