ejpmr, 2020,7(7), 482-487

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ON OPTIMIZATION TECHNIQUE IN PHARMACEUTICAL FORMULATION

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Article Received on 12/05/2020 **Article Revised on 02/06/2020** **Article Accepted on 23/06/2020**

ABSTRACT

The term Optimize is defined as making perfect, efficient or functional as possible. It is the process of finding the best way to use existing resources while taking into account all the factors that influence decisions in any experience Traditionally, optimization in pharmaceutical products refers to the modification of a variable at the same time, in order to obtain the solution of a problematic formulation. Modern pharmaceutical optimization involves systematic design experiments (DoE) to improve formulation irregularities. In the other word, we can say that - quantity a formulation which has been qualitatively determined. It is not a screening technique. In pharmacy, the word "optimization" is found in the literature referring to any formula study. In development pharmacist projects usually experiment with a series of logical steps, carefully controlling the variables and change one at a time until satisfactory results are achieved got. This is how the optimization performed in pharmaceutical industry Optimization is defined as follows: "Choose the best part of a set of alternatives available." It is the process of finding the best way to use the resources while considering all factors that influences decisions in any experience.

KEYWORD: optimization, factorial design.

INTRODUCTION

The objective of the design of the quality formulation is carried out by various Optimization techniques like DoE (Design of Experiment). The term FbD (Formulation by Design) & QbD(Quality by Design) indicates that the quality of the production be constructed using various DOE techniques (Design experience).This FbD replaced the OVAT (a variable to a time strategy) for optimization completely.[1] The word " Optimize" means to make as perfect, effective or functional as possible. Optimization of product or process is determination of experimental conditions resulting in its optimal performance.[2] Optimization has been defined as the implementation of systemic approaches to achieve the best combination of product and/or process characteristics under a given set of conditions. With respect to the drug formulations or pharmaceutical process, optimization is a phenomenon of finding "the best" possible composition or operating conditions. Although several optimization procedures are available to the pharmaceutical scientist, in general the procedure consists of preparing a series of formulations, varying the concentrations of formulation ingredients in some systemic manner. These formulations are then evaluated according to one or more attributes, such as hardness, dissolution, appearance, stability, taste and so on. Based on the results of these tests, a particular formulation (or series of formulations) may be predicted to be optimal.[3]

DOE (Design of Experiment)

It is a mathematical tool for systematically plan and conduct changing scientific studies set of experimental variables to determine their effect on a given response.[8]

He does controlled modifications of the input variables in order to gain the maximum amount of information on cause and effect relationships with minimum sample size to optimize formulation.

There are mainly four steps associated with DOE

1. The design of the experiment (using various models)
2. Data collection
3. Statistical analysis of the data
4. Conclusions and recommendations made as a result of the experience. In the optimization method, different types of model used from preliminary factor screening to select their level and to finally study their effect so it dependson the formulator to choose an appropriate model for the study and help minimize experimentation time.[4]

- **Advantages of ED**

❖ Better innovation due to the ability to improve

processes.
- ❖ Less batch failures.
- ❖ Greater regulator confidence of robust products.
- ❖ More efficient technology transfer to manufacturing.
- ❖ Replications of results are obtained.

- **Uses of ED**

- ❖ It is used to determine the causes of variation in the response, to determine the conditions under which the optimal (maximum or minimum) response is achieved, to compare responses at different levels of controlled variables and to develop a model for predicting response.
- ❖ Key steps for experimental design
- ❖ To obtain good results from ED the following steps are followed:
- ❖ Set objective
- ❖ Select process variables.
- ❖ Analyze and interpret the results.

- **Selection of ED**

The choice of an experimental design depends on the objectives of the experiments and the number of factors to be investigated.

- **Objective of ED**

- ❖ Comparative analysis.
- ❖ Optimal fitting of regression model estimation.
- ❖ Response surface method determination.
- ❖ Optimizing response when factors are proportions of a mixture

- **Screening**

Select an experimental design. Execute the design.
Check that the data are consistent with the experimental Assumption

- **Choice of experimental design**

The most important part of a DoE process, choosing an appropriate experimental design, is critical for the success of the study. The choice of experimental design depends on a number of aspects, including the nature of the problem and/or study (e.g., a screening, optimization, or robustness study), the factors and interactions to be studied (e.g., four, six, or nine factors, and main effects or two-way interactions), and available resources (e.g., time, labour, cost, and materials). Using previous knowledge of a product or previous experiments to identify possible interactions among the input process parameters before performing an experiment also plays a key part in selecting an appropriate experimental design.[5]

- **Factorial design**

Factorial designs are effective. Instead of conducting a series of independent studies we are able to effectively combine these studies in one. Finally, these are the only effective ways to examine interaction effects. Many experiments involve the study of the effects of two or more factors. Factorial designs are most efficient for this type of experiment. In a factorial design, all possible combinations of the levels of the factors are investigated in each replication. If there are a levels of factor A, and b levels of factor B, then each replicate contains all ab treatment combinations.

- **Main Effects** -The main effect of a factor is defined to be the change in response produced by a change in the level of a factor. The main effect of A is the difference between the average response at A1 and A2.

		FACTOR B	
		B_1	B_2
FACTOR A	A_1	20	40
	A_2	50	12

		FACTOR B	
		B_1	B_2
FACTOR A	A_1	20	30
	A_2	40	52

Interaction

Interaction graphs

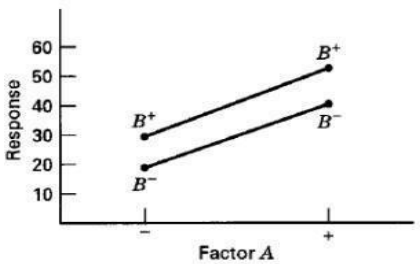


Figure 5-3 A factorial experiment without interaction.

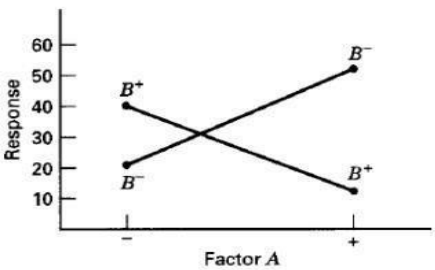


Figure 5-4 A factorial experiment with interaction.

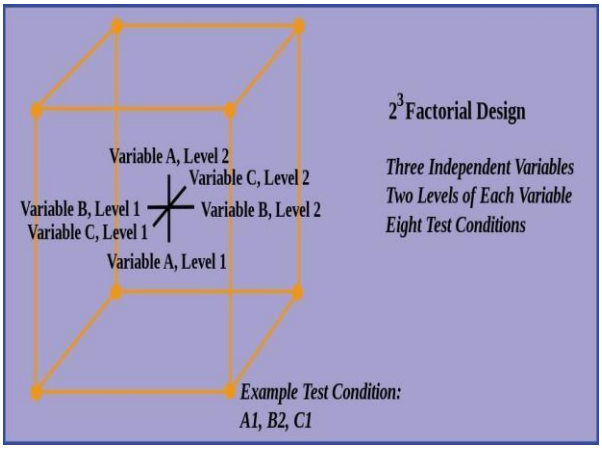
In some experiments we may find that the difference response between the levels of one factor is not the same at all levels of the other factor. When this occurs, there is an interaction between the factor Graphics are often useful for interpreting meaningful interactions

- When an interaction is important, the main effects have little practical sense.
- Significant interaction will often mask the significance of main effect.[6]

Example: The simplest factorial experiment contains two levels for each of the two factors. Suppose that an engineer wishes to study the total power used by each of the two different motors, A and B, operating at each of the two different speeds, 2000 or 3000 rpm. The factorial experiment would include four experimental units: motor A at 2000 rpm, motor B at 2000 rpm, motor A at 3000 rpm and motor B at 3000 rpm. Each combination of a single level selected from all factors is present once. This experiment is an example of a factorial experiment of 22 (or 2 × 2), so named because it considers two levels (the base) for each of the two factors (the power or the exponent), or levels factors, producing 22 = 4 factor points. Designs can involve many independent variables. As another example, the effects of three input variables can be evaluated under eight experimental conditions represented as the corners of a cube. this can be done with or without replication, depending on its purpose and the resources available. It will provide the effects of the three independent variables on the dependent variable and the possible interactions.

- **Fixed and Random Effects**

Fixed Effect



- The levels of a factor are pre-determined
- The inference will be made only on the levels used in the experiment

Random Effect

- The levels of a factor are randomly chosen
- The inference will be drawn about a population, from which the factors are chosen.

- **Method of Analysis**

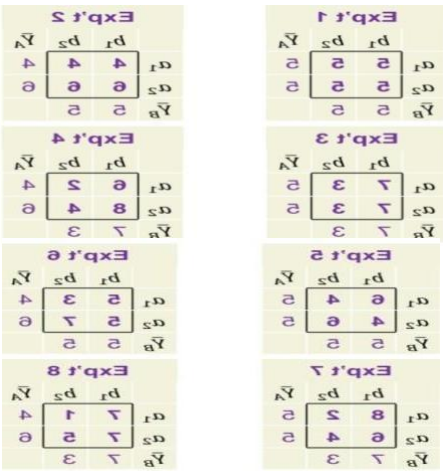
A factorial experience can be analysed using an ANOVA or regression analysis.

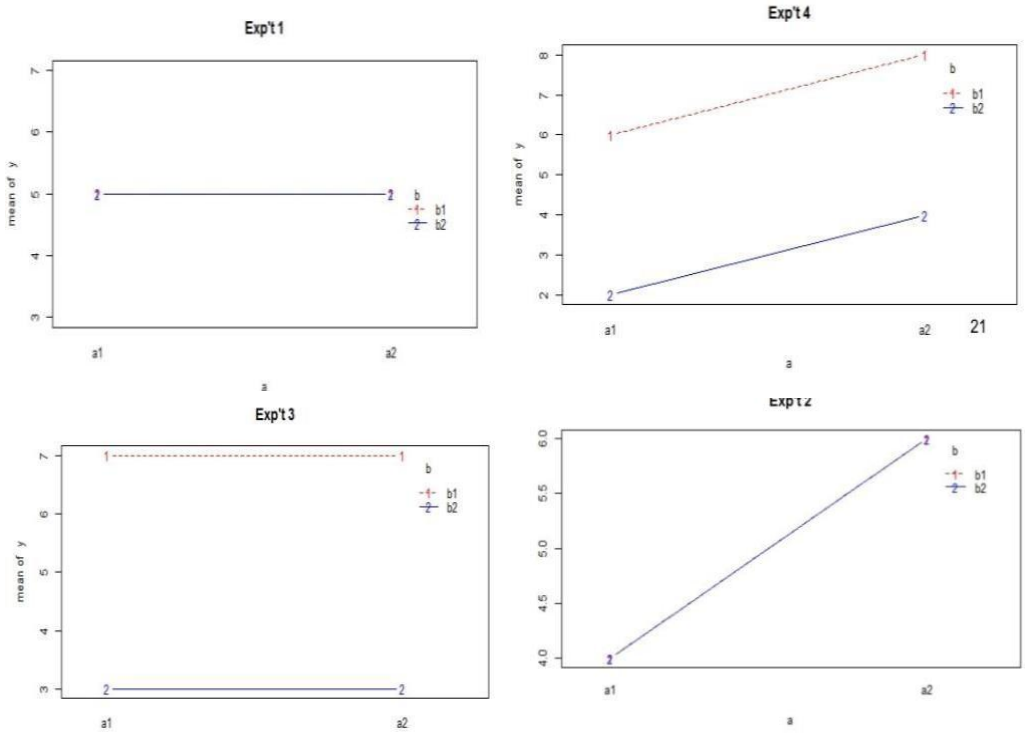
To calculate the main effect of a factor "A", subtract the average response of all the experimental series for which A was at its low (or first) level from the average response of all the experimental series for which A was at its high level (or second level). Other exploratory analysis tools useful for factorial experiments include graphs of main effects, interaction graphs, Pareto graphs, and a normal probability graph of estimated effects.

When the factors are continuous, two-level factor designs assume that the effects are linear. If a quadratic effect is expected for a factor, a more complicated experiment should be used, such as a central composite design. Optimizing the factors that could have quadratic effects is the main objective of the response surface methodology.[7]

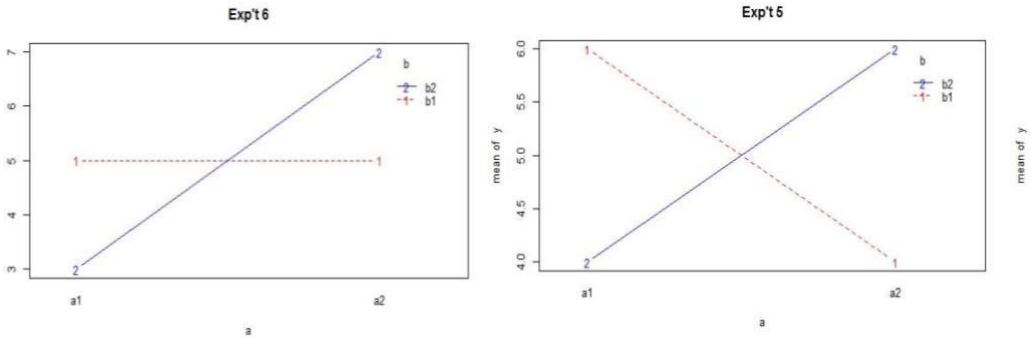
- **Factorial ANOVA**

Consider 8 hypothetical experiments, each involving 2 levels of 2 different factors (A and B) Group means: no interaction.





Interaction



Difference res response between the levels of one factor is

- **Full factorial design(FFD)**

Factorial experiments with two-level factors are used widely because they are easy to design, efficient to run, straightforward to analyse, and full of information. A full factorial design contains all possible combinations of a set of factors. This is the most fool proof design approach, but it is also the most costly in experimental resources. The full factorial designer supports both continuous factors and categorical factors with up to nine levels. Factorial designs with only two-level factors have a sample size that is a power of two (specifically 2^f where f is the number of factors). When there are three factors have a sample size that is a power of three.

N=L^k

Where k = number of variables, L = number of variable levels, N = number of experimental trials, for example, in an experiment with three factors, each at two levels, we have eight formulations, a total of eight response.[8]

- **Fractional factorial design**

Experiment	A	B	C
1	-	-	-
2	+	-	-
3	-	+	-
4	+	+	-
5	-	-	+
6	+	-	+
7	-	+	+
8	+	+	+

Table 3: Description of full factorial design 2^3

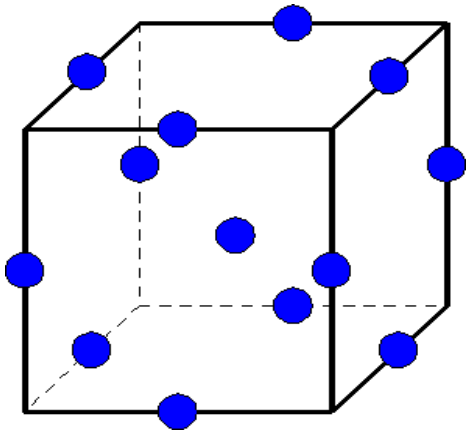
Experiment	A	B	C	AB	AC	BC	ABC
1	-	-	-	+	+	+	-
2	+	-	-	-	-	+	+
3	-	+	-	-	+	-	+
4	+	+	-	+	-	-	-
5	-	-	+	+	-	-	+
6	+	-	+	-	+	-	-
7	-	+	+	-	-	+	-
8	+	+	+	+	+	+	+

Example

Four design variables-A, B, C, D. Lower and upper levels are coded '-' and '+' respectively. First the full factorial design is built with only 3 variables A, B & C (2^3).[9]

- **BOX BEHNKEN DESIGN**

In statistics, Box– Behnken designs are experimental designs for response surface methodology.



To achieve the following goals

- Each factor, or independent variable, is placed at one of three equally spaced values, usually coded as −1, 0, +1. (At least three levels are needed for the following goal.)
- The design should be sufficient to fit a quadratic model, that is, one containing squared terms, products of two factors, linear terms and an intercept.
- The ratio of the number of experimental points to the number of coefficients in the quadratic model should be reasonable (in fact, their designs kept in the range of 1.5 to 2.6).
- The estimation variance should more or less depend only on the distance from the centre (this is achieved exactly for the designs with 4 and 7 factors), and should not vary too much inside the smallest (hyper)cube containing the experimental points. (See "rotatability" in "Comparisons of response surface designs)

Each design can be thought of as a combination of a two-level (full or fractional) factorial design with an incomplete block design. In each block, a certain number of factors are put through all combinations for the factorial design, while the other factors are kept at the central values. For instance, the Box– Behnken design for 3 factors involves three blocks, in each of which 2 factors are varied through the 4 possible combinations of high and low. It is necessary to include centre points as well (in which all factors are at their central values).Most of the designs can be split into groups (blocks), for each of which the model will have a different constant term, in such a way that the block constants will be uncorrelated with the other coefficients.[10]

Example for box behnken design for tablet:-

Box-Behnken Design for Optimization of Formulation Variables for Fast Dissolving Tablet of Urapidil:-

Urapidil is a sympatholytic antihypertensive drug. It acts as an α1-adrenoceptor antagonist and as a 5-HT1A receptor agonist. Although an initial report suggested that urapidil was also an α2- adrenoceptor agonist, this was not substantiated in later studies that demonstrated it was devoid of agonist actions in the dog saphenous vein and the guinea-pig ileum. Guinea pig ileum, unlike some other α1-adrenoceptor antagonists.[11]

Response surface methodology explores the relationships between several control variables and one or more response variables.[12]

However, an experimental design involves choosing the appropriate combination of factors and the levels of each factor to be tested. Since experimental runs cost time and money, it is pertinent to minimize the number of runs while not compromising the desired goals. To achieve this, some strategies such as full factorial, BoxBehnken (BB), and central composite designs are frequently used optimization with factorial designs and analysis of the response surfaces is powerful, efficient, and systematic tools that shorten the time required for the development of pharmaceutical dosage forms and increases research output.[13] BB experimental design allows the designer to utilize three levels of each factor (with each factor placed at one of each equally spaced value to ensure orthogonality and near rotatability) to adequately quantify second-order response models in 17 runs, inclusive of 5-replicated center points of a cubical design region. BB design can be used to construct a second-order polynomial model to describe the mutual dependency of the studied parameters.[14]

CONCLUSION

- Optimization techniques are a part of development process.

- ❖ The levels of variables for getting optimum response is evaluated.
- ❖ Different optimization, methods are used for different optimization problems.
- ❖ More optimum the product = More the company earns in profits !
- ❖ The factorial design is more efficient more than the 1-variables involed in formulation.
- ❖ A factorial design is necessary, when interactions are present, to avoid a misleading conclusion.
- ❖ Estimation of one factor at different levels of the other factor could yield conclusions over a range of conditions for the experiment.

*The Box-Behnken is a good design for response surface methodology because it permits:

(i) Estimation of the parameters of the quadratic model
(ii) Building of sequential designs
(iii) Detection of lack of fit of the model
(iv) Use of blocks. A comparison between the Box-Behnken design and other response surface designs (central composite, Doehlert matrix and three-level full factorial design) has demonstrated that the Box-Behnken design and Doehlert matrix are slightly more efficient than the central composite design but much more efficient than the three-level full factorial designs.

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