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OPTIMIZATION TECHNIQUES: AN OVERVIEW FOR FORMULATION DEVELOPMENT

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ABSTRACT

The pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality by Design (QbD) is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance. Quality refers to product free of contamination and delivers the therapeutic benefit promised in the label to the consumer. The Quality of the pharmaceutical product can be evaluated by in vivo or in vitro performance tests "QbD" assures in vitro product performance and In vitro product performance provides assurance of in vivo product performance. "Hence QbD relate to Product Performance".

Key words: Quality of the pharmaceutical product, Quality by Design, Contamination.

INTRODUCTION

In 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 controlling the variables and changing one at a time until satisfactory results are obtained. This is how the optimization done in pharmaceutical industry.

Optimization is defined as follows: "Choosing the best element from some set of available alternatives". It is the process of finding the best way of using the existing resources while taking in to the account of all the factors that influences decisions in any experiment. The objective of designing quality formulation is achieved by various Optimization techniques like DoE (Design of Experiment).

The term FbD (Formulation by Design) & QbD (Quality by Design) indicates that quality in the product can be built by using various techniques of DOE (Design of Experiment).

This FbD has replaced the OVAT (one variable at a time) strategy for Optimization completely [1].

Quality by Design (Qb D)

The pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality by Design (QbD) is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance [2].

Application of QbD in Pharmaceutical Industry

Quality refers to product free of contamination and delivers the therapeutic benefit promised in the label to the consumer. The Quality of the pharmaceutical product can be evaluated by in vivo or in vitro performance tests "QbD" assures in vitro product performance and In vitro product performance provides assurance of in vivo product performance. "Hence QbD relate to Product Performance".

Benefits for Industry

- Better understanding of the process.
- Less batch failure.
- More efficient and effective control of change.
- Return on investment / cost savings.
- Provides opportunities for more flexible regulatory approaches.
- Manufacturing changes within the approved design space without further regulatory review.

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Asian J. Pharm. Res. Vol 5, Issue 3, 217-221, 2015.

- 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.

DOE (Design of Experiment)

It is a mathematical tool for systematically planning and conducting scientific studies that change experimental variables together in order to determine their effect on a given response [3-8]. It makes controlled changes to input variables in order to gain maximum amounts of information on cause and effect relationships with a minimum sample size for optimizing the formulation

There are mainly four steps associated with DOE:

1. The design of the experiment (By using various models)
2. The collection of the data
3. The statistical analysis of the data and
4. The conclusions reached and recommendations made as a result of the experiment.

In Optimization Method various types of Model used from preliminary screening of factors to select their level and for finally study of their effect so it's depend upon the formulator to choose a suitable model for study and help in minimizing the experimenting time.

IMPORTANT TERMINOLOGY USED IN DOE FOR OPTIMIZATION

1. Variable

There are of two types of variables

Independent variables or primary variables

Formulations and process variables directly under control of the formulator. These includes ingredients

Dependent or secondary variables

These are the responses of the in progress material or the resulting drug delivery system. It is the result of independent variables

(b) Factor

It is Assigned and Independent variables, which affect the product or output of the process. It is an assigned quantitative and qualitatively like this

***Quantitative*:** Numerical factor assigned to it. Ex; Concentration- 1%, 2%, 3% etc.

***Qualitative*:** Which are not numerical. Ex; Polymer grade, humidity condition etc

(c) Level: Levels of a factor are the values or designations assigned to the factor

(d) Response surface: Response surface representing the relationship between the independent variables X_1 and X_2 and the dependent variable Y

(e) Run or trials: Experiments conducted according to the selected experimental design

(f) Screening: To sort out something from

(g) 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

(h) Interaction: It gives the overall effect of two or more variables means lack of additivity of factor effects Ex: Combined effect of lubricant and glidant on hardness of the tablet

(i)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)

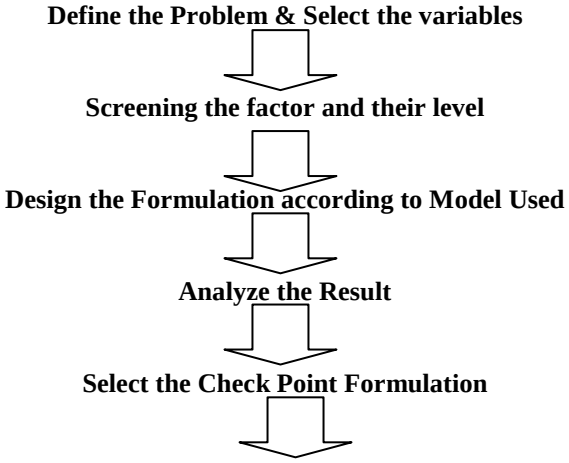
(j) Effect: It is the change in response caused by varying the levels and It gives the relationship between various factors & levels

(h) Response: It is an outcome of the experiment.

(i) Orthogonality: When effect is due to the main factor of interest and no interaction

(j) Confounding: Lack of Orthogonality is termed as confounding or aliasing

(k) Resolution: Measurement of degree of confounding



(Basic Flow Chart for using DOE and optimizing the formulation)

EXPERIMENTAL DESIGN

Experimental design is a statistical design that prescribes or advises a set of combination of variables. The number and layout of these design points within the experimental region, depends on the number of effects that must be estimated. Depending on the number of factors, their levels, possible interactions and order of the model, various experimental designs are chosen. Each experiment can be represented as a point within the experimental domain, the point being defined by its co-ordinate (the value given to the variables) in the space [9-11].

TYPES OF EXPERIMENTAL DESIGN

There are various type of Experimental design methods are available out of which method we have to use depends upon the resources we have and what we want to study.

Asian J. Pharm. Res. Vol 5, Issue 3, 217-221, 2015.

Screening Designs are used for identify the important factor and their level which affect the Quality of Formulation. Screening Designs generally support only the linear responses.

Response Surface Designs are used when we required exact image of response, estimating interaction and even quadratic effects. Response surface designs generally support non linear and quadratic response and capable of detecting curvatures

Factorial Designs

Factorial designs (FDs) are very frequently used response surface designs. A factorial experiment is one in which all levels of a given factor are combined with all levels of every other factor in the experiment. These are generally based upon first-degree mathematical models. Full FDs involve studying the effect 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 levels is the same for each factor in the optimization study, the FDs are said to be *symmetric*, whereas in cases of a different number of levels for different factors, FDs are termed *asymmetric."*

When we study three factors at two level $\mathbf{2^3}$ the total Number of run will be =08 &

When we study two factors at three level $\mathbf{3^2}$ the total Number of run will be =09

Fractional Factorial Design (FFD)

Fractional factorial design is generally used for screening of factor. This design has low resolution due to less number of run. Although these designs are economical in terms of number of experiments, the ability to distinguish some of the factor effects is partly sacrificed by reduction in the number of experiments.

Plackett-Burman Designs (Hadamard designs)

Plackett—Burman designs (PBD) are special two-level FFDs used generally for screening of factors. This design is generally used when we want to screen high number of factors (11-47) if we want to study the effect of 7 factors then we have to show four dummy factors. The interpretations of results in FFD, Plackett-Burman Designs & Taguchi design are drawn with the help of Pareto chart and Half normal plot.

Central Composite Design (Box-Wilson design)

For nonlinear responses requiring second-order models, central composite designs (CCDs) are the most frequently employed. A two-factor CCD is identical to a 3^2 FD with rectangular experimental domain at $\alpha = \pm 1$, On the other hand, the experimental domain is spherical in shape for $\alpha = \sqrt{2} = 1.414$.The CCD is quite popular in response surface optimization during pharmaceutical product development.

Box-Behnken Designs

A specially made design, the Box-Behnken design (BBD), requires only three levels for each facto -l, 0 and +1. It employing 15 experiments run with three factors at three levels. It is economical then CCD because t requires less number of Trial

Taguchi Design

Taguchi refers to experimental design as "off-line quality control" because it is a method of ensuring good performance in the development of products or processes." It is also used for screening of factors and it provides 8 experimental run for 7 factors.

Mixture Design

Mixture designs are used when the characteristics of the finished product (Drug delivery system) usually depend not so much on the quantity of each substance present but on their proportions. The sum total of the proportions of all the excipients is unity, and none of the fractions can be negative. Therefore, the levels of different components can be varied with the restriction that the sum total should not exceed one.

OPTIMIZATION OF IMPORTANT FACTORS

Model Development

A model is an expression defining the quantitative dependence of a response variable on the independent variables. Usually, it is a set of polynomials of a given order or Degree. From this polynomial equation we calculate the coefficient with the help of Principal of MLRA (Multiple Linear Regression Analysis). By the help of software we can also study here the effect of excipients, their interaction study, 3D Response plot, Contour Plot etc.

In screening design with the help of half normal plot and Pareto chart we can find out easily the main factor and their level

From the models thus selected, optimization of one response or the simultaneous optimization of multiple responses needs to be optimized graphically, numerically and by using Brute force search technology.

(a) Graphical Optimization

Graphical optimization deals with selecting the best possible formulation out of a feasible factor space region. To do this, the desirable limits of response variables are set, and the factor levels are screened accordingly by the help of overlay plot.

(b) Brute-force search (Feasibility and Grid search)

Brute-force search technique is the simple and exhaustive search optimization technique. It checks each and every single point in the function space. Herein, the formulations that can be prepared by almost every possible combination of independent factors and screened for their response variables. Subsequently, the acceptable limits are

Asian J. Pharm. Res. Vol 5, Issue 3, 217-221, 2015.

set for these responses, and an exhaustive search is again conducted by further narrowing down the feasible region. The optimized formulation is searched from the final feasible space (termed as grid search), which fulfills the maximum criteria set during experimentation.

(c) Numerical Optimization

It deals with selecting the best possible formulation out of a suitable factor. To do this, the desirable limits of response variables are set, and the factor levels are displayed by the software. Other techniques used for optimizing multiple responses are canonical analysis, ANNs and mathematical optimization.

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.

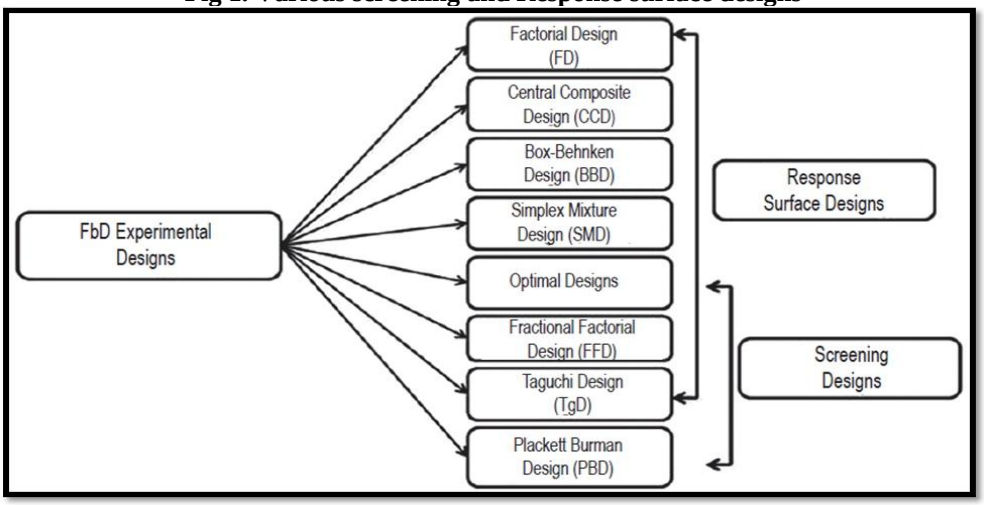
Software for Designs and Optimization

Many commercial software packages are available which are either dedicated to experimental design alone or are of a more general statistical type.

Software's dedicated to experimental designs

- DESIGN EXPERT
- ECHIP
- MULTI-SIMPLEX
- NEMRODW
- Software for general statistical nature
- SAS
- MINITAB
- SYSTAT
- GRAPHPAD PRISM

Fig 1. Various screening and Response surface designs



CONCLUSION

The area of optimization is vary vast and its applications in all areas of pharmaceutical science. Different techniques have been used according to need. In this article, an overview of various techniques was given. Optimization techniques are help full in reducing the cost of product by minimizing the number of experimental trials during formulation development. It is very thirst area of Research now a day in every industry.

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