Short Review Article

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OPTIMIZATION TECHNIQUES IN DESIGNING PHARMACEUTICAL FORMULATIONS

Pusukuri Navya	G.Pulla Reddy College of Pharmacy, Hyderabad , Telangana, India.
Priyarini k	G.Pulla Reddy College of Pharmacy, Hyderabad, Telangana, India.
Tejaswi k	G.Pulla Reddy College of Pharmacy, Hyderabad, Telangana, India.
Prasanthi D*	Associate Professor, G.Pulla Reddy College of Pharmacy, Hyderabad, Telangana, India. *Corresponding Author

ABSTRACT This review determines various optimization techniques which are used commercially for pharmaceutical formulations. A glance on the terminology used in optimization, about the software which is used for design of experiments and information regarding optimization parameters.In this various experimental designs are listed such as Factorial design, fractional factorial design,mixture design, star design, Plackett-Burmann design,Central composite design, Box-Behnken design, Taguchi design, D-Optimal design,sequential optimization design etc.In this it describes about the future scope of the optimization techniques and also various types of experimental designs used for various research works were listed. Thus optimization techniques plays key role in the formulation of various pharmaceutical formulations which brings profits and save time for pharmaceutical industry.

KEYWORDS : Optimization Techniques, Design Of Experiment, Quality By Design

INTRODUCTION

Optimization is selecting the most suitable element from available resources considering all the factors which influence decisions in any experiment. Designing quality formulation is obtained by the use of various techniques of optimization [1].Quality by Designenhances the assurance of safe and effective drugs to consumer and promise to improve manufacturing quality performance and also product free of contamination and gives the desired benefit as in the label to the consumer. Design of experiment is systemic planning and performing studies that change the experimental variables to determine their effect on a given response. Optimization techniques and Experimental design are used specifically to examine various problems that occur during the research. If the experiments in the production are carried out randomly then results obtained will be random, so we need to plan the experimental process such that relevant information is obtained. In pharmaceutical industry optimization techniques used for the drug delivery systems are designed accordingly which include,

Defining the objectives

⇩

Planning the experiment

⇩

Factors which influence the study is screened

⇩

Selecting the experimental design

⇩

Formulation and evaluation of the drug delivery system as instructed by the experimental design

⇩

Search for the optimum by using computer aided modeling

⇩

Design of experiments methodology should be validated

⇩

Scale up and the obtained steps by this entire process is implemented in production of the desired pharmaceutical drug delivery system.

Optimization Of Important Factors

Model development: It is set of polynomials of given order.We can know the effect of excipients and their interaction, contour plot etc.

Graphical Optimization or Response surface analysis: In this obtaining the best possible formulation is carried out.

Brute-force search (Feasibility and Grid search): This technique checks each and every point in the experiment and it is very simple and exhaustive technique.

Numerical Optimization: The desirable limits of response variables and factor levels are set by the software such that we can select the best possible formulation out of suitable factor.

TERMINOLOGY USED IN OPTIMIZATION[2].

Variable: Measurements or values that are characteristics of the data.

Factor: It is an assigned variable like concentration, temperature.

Level: Values assigned for the factors are levels

Response surface: It represents the relationship between the independent variables and the dependent variable.

Run or trials: Experiments conducted according to the selected experimental designs.

Screening: Screening is sorting out something from the given mixture.

Contour Plot: contour plot is the geometric illustration of response obtained by plotting one independent variable versus another by keeping magnitude and other variables as constant.

Interaction: Interaction means the overall effect of two or more variables.

MLRA (Multiple Linear Regression Analysis): MLRA express mathematically in the form of quadratic equation the linear relationship between various independent variable and dependent variable.

Effect: Effect is the change in the response which is caused by different levels

Response: Response is the outcome of an experiment.

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

Confounding: Also known as Aliasing, it arises when there is lack of orthogonality

Resolution: It is the measurement of degree of confounding.

Software For Designs And Optimization:

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

Software's For Experimental Designs

Design Expert:

Design expert screens important components and factors. It also characterizes interactions, achieve optimal product manufacturing process and also set the process steps.

Other softwares are MATLAB,OPTIMUS PLATFORM etc.

Software For General Statistical Nature

SAS: Software suite developed by SAS Institute for advanced analytics (statistics, forecasting, machine learning, optimization, etc.) risk management, business intelligence, data management, customer intelligence, and so on.

Others are MINITAB, SYSTAT etc.

Future Scope:

The scope of optimization technique is intended to support innovation and efficiency in pharmaceutical industry. Pharmaceutical companies need to adopt new technologies, processes and collaborations. Researchscientists need to work in collaboration as virtual drug discovery teams. Standardized tools and processes are delivered through drug discovery portals e.g. gene mapping.

OPTIMIZATION PARAMETERS:[2]

Optimization parameters are classified into Problem type and Variables

Problem Type: In this problem type, it is again categorized into Constrained and Unconstrained parameters.

Constrained: In this restriction is based on the physical limitations on the system.

Unconstrained: In this there are no restrictions based on the physical limitations on the system.

Variables: Variables are categorized into Independent variables and Dependent variables.

Independent: Independent variables are under the control of formulator.

Dependent: Dependent variables are not directly under the control of formulator. They are dependent on independent variables. These are responses.

EXPERIMENTAL DESIGN:[3]

It is a statistical design that advises a set of combination of variables. Depending on the factors, levels, Interactions and order of the model various experimental designs are chosen. Includes

FACTORIAL DESIGN: A factorial design allows the effect of several factors and even interactions between them to be determined with the same number of trials. These designs are very frequently used response surface designs.

FRACTIONAL FACTORIAL DESIGN: Fractional factorial design is generally used for screening of factor. Fractional factorial design is economical as it reduces the number of experimental runs which ultimately leads to low resolution.

FULL FACTORIAL DESIGN: It uses dimensional factor space at corner of design space. In which the effects of different factors leads to determination of the effect of several factors and their interactions.

PLACKETT-BURMAN DESIGN (Hadamard designs): Plackett-Burman designs are special two-level Fractional Factorial Designs used for the screening of factors. It is used when only main effects are of interest. Plackett-burman design is also called as saturated designs as they detect large main effects, assuming other interactions as negligible.

CENTRAL COMPOSITE DESIGN (CCD) (Box-Wilson design): This design was developed for nonlinear responses requiring second-order models. The CCD is popular in response surface optimization during pharmaceutical product development.

BOX-BEHNKEN DESIGN: Box-Behnken Design requires only three levels for each factor. It is economical than CCD because requires less number of Trial.

TAGUCHI DESIGN:It promises the best performance in the development of processes and products also, so Taguchi design is also known as off-line quality control. It is also used for screening of factors.

MIXTURE DESIGN: The quantity of each substance is represented in this design but not their proportions where excipients proportions are unity. Sum total should not exceed one for excipients.

STAR DESIGN: It is simply a 22 factorial design rotated over 45° angle in space, in which a center point is added which replicate to estimate experimental error.

BOX DESIGN: It is also known as Orthogonal balanced incomplete block design. Box design is preferred when three or more factors are used.

UNIFORM SHELL DESIGN (Doehlert uniform shell design): In this it starts with an equilateral triangle which is mirrored in one side to hexagon which is expandable in 2-D space which upon mirroring at the center point towards the outward sides, it can be expanded in 3-dimension to centric spherical shells.As it has uniform distribution it gives good basis for interpolation.

SIMPLEX LATTICE DESIGN: Simplex Lattice Designs are used to know Interior and boundaries of the simplex. Number of factors determines its dimensions. The points are distributed over the factor space, forming a lattice which can be controlled precisely.

D-OPTIMAL DESIGN: D-Optimal design (DOD) maximizes the determinant Information. That is maximizing the volume in a dimensional space. No other classical designs can investigate an irregular region then D-Optimal Design is preferred, as DOD makes efficient use of full experimental space.

SEQUENTIAL OPTIMIZATION DESIGN: Optimization is done in a step-wise fashion, started at an arbitrary point in experimental domain and responses are evaluated.

EXTREME VERTICES DESIGN: We can notice that Some Times in formulation studies whole factor space is not accessible or not giving expected responses in formulation studies.In Extreme Vertices design, observations are shown at corners of bounded design space,used for the mixture composition as well as in combination with factorial designs.

EVOLUTIONARY METHODS: In evolutionary methods it includes very small changes in the formulation process in which the improvement analysis done more times.Evolutionary method is useful where there is a continuous production.

Table: 1 Various Drug Formulations Formulated Using Different Optimization Technique

DRUG	EXPERIMENTAL DESIGN	FORMULATION TYPE	REFERENCE NUMBER
Provastatin	Factorial design	Fast Dissolving Tablets	[4]
Lornoxicam	Central composite design	Multi particulate sustained release drug delivery	[5]
Furosemide	Taguchi orthogonal array design and central composite design	Pellets	[6]
Ivabradine hydrochloride	Response surface methodology (minitab)	Floating pulsatile microspheres	[7]
Dipyridamole	Box–benhken design	Floating micro balloons	[8]
Alfuzosin hydrochloride	Taguchi orthogonal array design	Ethosomes	[9]
Tolterodine tartrate	Taguchi orthogonal array design	Transdermal gel	[10]
Finasteride	Taguchi orthogonal array design	Invasomes	[11]
Fluconazole	Taguchi orthogonal array design	Pickering emulsion	[12]

CONCLUSIONS

In this article we conclude that optimization techniques are very helpful in formulation developments such as in reducing the cost of the product by minimizing the experimental trails and also it enhances the safety, quality and efficacy of the products thus delivering the required benefits to the consumers by the product.In this article brief information on different types of experimental designs in which Factorial design and CCD are most preferred. Various software used for optimization used were discussed. The most preferred software is Design expert. Optimization is vast and it has several applications, various techniques are used according to the need.

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