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A REVIEW ON QUALITY-BY-DESIGN AN EMERGING TOOLS FOR PHARMACEUTICAL PRODUCT DEVELOPMENT

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Abstract:

The use of quality by design (QbD) in the creation of pharmaceutical products is presently a hot topic among regulatory agencies and the pharmaceutical sector. It mostly entails formulating and creating production processes in order to ensure predetermined product quality. Defining a goal product quality profile, developing product and manufacturing processes, identifying essential quality features, process parameters, and sources of variability, and regulating manufacturing processes to produce consistent quality through time are just a few of the QbD elements. The goal of this article is to explain what pharmaceutical Quality by Design is and how it can help ensure pharmaceutical quality and medication development. The importance of QbD in instilling a science-based approach in pharmaceutical product development is highlighted in this paper.

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INTRODUCTION:

The pharmaceutical regulatory environment has recognized the need to implement a systematic approach to drug product development where quality is built into the process. Quality-by-Design (QbD), a US FDA initiative, promotes the use of engineering tools such as predictive models and optimization techniques to formulate products based on scientific understanding of the process. Product quality is achieved through design of robust processes that are modeled, validated and optimized using knowledge of process principles [1].

Modeling and validation establish a predictive framework using experimental data and physical principles to create predictive mathematical representations of the system. In the process design phase the goal mathematical models is to evaluate the impact operations, equipment and inputs have on product attributes. Such mathematical tools further allow for system study through evaluation of process scenarios, some which have not been experimentally performed [2].

The predictive ability also provides a framework for process control and optimization, where accurate predictions of the system are required in order to provide the best problem solution [3]. Optimization methods are essential tools for:
(1) Experimental design
(2) Analysis and design of processes
(3) Planning, operations research and scheduling
(4) Process control.

In the pharmaceutical literature these methods have been used for experimental and computational design problems surrounding lead drug design and product development. Experimental optimization problems involve development of procedures to test a given hypothesis using the least amount of resources.

In these studies the goal is to reduce the experimental load while maximizing the value of data collected. In the pharmaceutical literature these methods have been used extensively under the design of experiments (DoE) framework. Computational optimization problems use repeated evaluations of mathematical models to determine input effects on the process outcomes and their best combination to reach a desired output [4].

Such methodology provides great benefit to the design of pharmaceutical drug products by further reducing the number of experiments and substituting them with in silico evaluations. A growing powder modeling technology literature has been developing in the past few years given the improved performance of modeling capabilities, which has led to further implementation of optimization methods.

Optimization Methodologies:

Optimization methodologies used in the pharmaceutical modeling literature can be categorized into three groups: direct search, gradient-based and surrogate-based methods. Each group uses different approaches to reach local or global optimum conditions and is used depending on the optimization problem goals. Below, we review some of the methodologies most commonly used in the pharmaceutical manufacturing literature and provide some references on their application.

Heuristic or Direct Search Methods:

Direct search methods are a class of optimization techniques that do not require information from mathematical derivatives to reach an optimum solution. Derived from heuristic methods, these optimization techniques iteratively evaluate a design function to determine input–output effects and obtain optimum values. Various algorithms to improve the sampling give rise to a wide variety of direct search methods, largely described in the optimization literature [5].

Pharmaceutical Optimization Applications:

In the interest of providing the reader with a concise overview of the implementation of direct search methods, the following applications primarily focus on three major areas of solid dose preparation: drug product formulation, drug delivery, and manufacturing processes. Product Formulation Product development involves the design of formulations (recipes) in which active ingredients (i.e., APIs) are combined with pharmacologically inactive excipients to form a product with desired quality attributes. As many drug product attributes are dependent on their composition, this process requires optimal selection of both the type and quantity of materials involved. Excipients in particular play an important role in the absorption, stability and bioavailability of drugs in the body.

Direct search methods have been applied in formulation development and optimization of capsule and tablet drug products, specifically aiming at the selection of excipients ,developed an optimization strategy for design of oral dose dry powder pharmaceutical formulations with little experimental data using a combination of genetic algorithms and simplex lattice methods. In this research, the authors studied blend flow and dissolution properties of API and excipient powders using small laboratory scale

experiments to then formulate an optimal product combination using non experimental methods. [6]

The purpose of the study was to develop a customizable formulation of acetaminophen syrups based on the availability and taste of available co-solvents. The implementation of simulated annealing in the formulation protocol resulted in the selection of an optimal formulation in less computational time than the traditional simplex search method. [7]studied optimal effervescent floating tablets (EFT) composition in order to target a set of product attributes (i.e., specific buoyancy, hardness and floating time). Using a hybrid simplex lattice and multivariate regression approach the authors were able to predict and optimize the EFT properties and develop a first principles approach to the type of tablet matrix erosion. [8] performed a similar protocol by investigating the effects and optimal formulations of melt granulation floating tablet products with minimum experimentation.

Product Formulation:
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Manufacturing Processes:
Examples of optimization in manufacturing processes have been focused on finding the best process settings using the methodologies described in this section. Ranging from the selection of process conditions to the arrangement of manufacturing plants, direct search methods have played a role in finding the most beneficial process settings. [9]optimized the formulation and the critical process parameters used in tablet products for colon therapies using simplex lattice methods. In the research, the authors established optimal operational conditions of the coater, providing a framework for the design of other coating processes. Coating spray rate and batch time were studied and optimized to reduce final product variability and process.

Gradient-Based Methods:
Extensively used for solving linear and nonlinear programming optimization problems, these methods use information from derivative-based tools in order to reach an optimum solution. Among some of the derivative tools are the Hessian matrix and gradient-vector. They are used to compute the slopes and convexity of functions to determine the direction needed for finding an optimum. Movement towards anoptimum isachieved by iteratively moving along the function using slope and concavity information. While obtaining direction information from previously performed steps, movements are sized based on individual method techniques. The main difference between the various gradient methods is based on the mathematical functions used to find the point from which a next step is made [10]. They are used extensively for solving many linear and nonlinear programming problems

Drug Delivery Systems:
The development and optimization of many drug delivery systems (DDS) has been described in the literature using direct search methods. Most of the work for optimization of DDS focuses on sustained release oral formulations, yet some research points to their use in nontraditional methods of drug delivery such as transdermal devices. [11]successfully formulated an optimized mathematical model for the design and manufacturing of sustained-release pellets using particle swarm theory (PSO) as the optimization algorithm. [12] designed extended release oral drug products using other modeling techniques being optimized with PSO. The random search algorithm was used to elucidate the shape of functions being modeled without the need of experimentation. This method was shown to reduce the number of experiments needed to develop valuable datasets and generate best potential routes for experimentation.

The authors used the simplex lattice design to optimize formulation parameters such as concentration of excipients and relative amounts of drug per unit dose. [13]developed a prediction algorithm for the release of antihypertensive drug compounds from nanoparticle-based formulations using a genetic algorithm (GA) approach. GA methodology was implemented to optimize nanoparticle formulation regarding size and number of particles to enhance in vivo absorption. The method was proven to be successful in the optimum selection of both formulation and manufacturing parameters while reducing the number of experimental trials.

The proposed algorithm automatically determined the appropriate network structure more efficiently than single RBF methods. Optimization of process parameters affecting chromatographic separation selectivity and efficiency of vitamins in

pharmaceutical formulations was also accomplished using GA methods [14]. Investigators established an exponential unit model, including key process parameters such as surfactant concentration, temperature and pH. The process parameters were minimized to improve chromatographic responses between all analytes, simultaneously. The method was shown to greaten differences in resolution and analysis time between samples and pointed to optimal operational parameters for the separation of each compound. [15] used PSO methods to find multiple constant parameter values used in modeling high shear batch granulation processes. The researchers solved the multiobjective optimization problem by implementing a constraint framework: while one of the objective functions is being minimized, other objective functions are incorporated in the form of a constraint. This is done to dictate.

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 [16]. 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:

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

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

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

Response surface: Response surface representing the relationship between the independent variables X_1 and X_2 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 additivity 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

Response: It is an outcome of the experiment.

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

Confounding: Lack of Orthogonality is termed as confounding or aliasing

Resolution: Measurement of degree of confounding

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[17].

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.

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 2^3 the total Number of run will be =08
When we study two factors at three level 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 twolevel FFDs used generally for screening of factors. This design is generally used when we want to screen high number of factors [18]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 32 FD with rectangular experimental domain at $\alpha = \pm 1$, On the other hand, the experimental domain is spherical in shape.

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.

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.

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 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.

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

CONCLUSION:

The concepts of QbD in the new ICH guidance, ICH Q8 (R2), will aid industry in developing successful products and obtaining regulatory approval more quickly. A solid understanding of QbD principles and the tools for building a QbD plan is required for a successful product development strategy. QbD is used to carry out science- and risk-based product development strategies. This approach allows the establishment of priorities and flexible boundaries in the process. As such QbD is becoming a promising scientific tool in quality assurance in pharmaceutical industry.

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