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DESIGN OF EXPERIMENTS: A MANIFEST APPROACH IN DESIGNING OPTIMIZED DRUG PRODUCTS

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ABSTRACT: The recent scenario of accomplishment with faultlessness indulges a bent towards the techniques that develop the final formulations with the precise use of experimental designs. Also, the application of computer-aided optimization techniques has proved to be favorable in the development of drug delivery systems with reliable results. The optimization techniques have a comprehensive range of designs in total, Design of experiments (DoE) being one, enables a formulator to find a suitable blueprint to formulate a best-optimized formulation. The technology focuses on preparing the drug delivery system with the least expenditure, minimal efforts, and less cost. Using DoE techniques may lead to a perfect combination of a drug product with equivalent excipients. This systematic approach is exclusively constructed for developing optimized pharmaceutical formulations, and processes through phases like screening of factors, different experimental designs along with response surface analysis. The realization of computer-aided optimization techniques has empowered the research within academics and at the industry, level to burgeon the pharmaceutical products of various kinds. The key elements of a DoE optimization methodology encompass planning the study objectives, screening of influential variables, experimental designs, the postulation of mathematical models for various chosen response characteristics, fitting experimental data into these model(s), mapping and generating graphic outcomes, and design validation using model-based response surface methodology. This review endeavors to impart awareness on manifold concepts of DoE and its terminology.

INTRODUCTION: The depiction of a flawless drug delivery system demands various goals and aims, since the time this effort has been accomplished using trial and error method or using conventional approaches. The customary procedures always necessitate using OFAT (one factor at a time) or OVAT (one variable at a time) approach to optimize a formulation.

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Furthermore, the use of these conventional approaches has got certain collapses, like more use of money, many resources are exploited, and the number of experiments increases, and it shows incompetency in producing accurate results, predictability, and compliance [1-2].

Sometimes the formulator being fortunate is able to yield successful results even with such unsystematic approaches. This practice may result in the somewhat near solution to the problem but not a complete resolution and perfect combination with defined properties always. The results of these conventional approaches may predict the interactions among one or more factors, but the perfect formulation my still exit understudied

conditions. With the use of COST (changing one single factor at a time) approach, the prediction is done by fixing one variable at a favorable value, and the next is examined till no fresh improvement is achieved in the response variable [3-4].

Latterly, the utilization of systematic approaches towards the development part in drug delivery systems is supportive in lowering the ever-changing inconsistencies. These techniques demonstrate to be advantageous in comparison to conventional approaches. Such techniques, whenever employed, provide the supreme results without compromising the objective while checking for interactions among factors so as to come up with a perfect combination. With the foregoing skills and practice, the formulator occasionally tends to achieve beneficial results. But again, sometimes due to compact variations, the results obtained are not optimum.

In order to achieve a suitable drug delivery system, a formulator has to fulfill various limits in a formulation, which is not possible with OFAT or OVAT approach [5]. **Table 1** shows the drawbacks of OFAT/OVAT approach.

TABLE 1: LIMITATIONS WITH OFAT/OVAT APPROACH

Limitations with OFAT/OVAT approach
Time Consuming
Demanding
Expensive
Unsuitable to plug errors
Results are not perfect
Solutions are not satisfactory
Number of experiments are large
Detailed study of all factors is not possible
The developed product may also contain the defects as old one

On the other hand, when a drug delivery product has to be formulated, it is mandatory to achieve certain objectives. The systematic optimization methodology promises to accomplish such objectives that a formulator has to fulfill for formulation. The optimization approach reduces the inconsistencies with the use of the principle of DoE, the use of which dates back to 1925 by Sir Ronald Fisher a British statistician. The execution of DoE optimization techniques involves the use of experimental designs with the generation of mathematical equations resulting in graphical outcomes, thus giving the complete picture of differences among the product/process response(s) as a function of the input variable(s) [6-7].

Nowadays, the use of DoE techniques is a smooth-running practice for developing new dosage forms and also modify existing ones. In comparison to the COST (changing one single factor at a time) approach, the DoE optimization provides proper and organized methods to connect all runs in a rational manner that enables us to achieve precise results and data with few runs [8]. **Table 2** shows the benefits of the DoE approach.

TABLE 2: MERITS OF DoE APPROACH

Merits of DoE Approach
Lesser experimental runs to obtain a required formulation
Rectification of problem is easy
Resulting of best solution even in the presence of competing objectives
Savior of resources like time, efforts, materials and cost
Simulation of process and product is easy with model equations
Prediction of Performance of Formulation even without preparation

The use of computers as DoE software has enabled numeric calculations an easy part, allowing systematic optimization of DDS. The operation of DoE studies indulged with computers requires an in-depth knowledge of statistical and mathematical concepts [9-10].

The application of DoE in the process development has been increased manifold in the industry over the last 15 years. Following are the reasons for the upward trend in the use of DoE,

1. As a tool, DoE is solving the issues in the optimization of various compressed API.
2. DoE significantly plays an important role in defining process parameters in the validation process. Now, FDA expects the DoE to be considered as a part of NDA submissions.
3. Use DoE has led to maintaining conditions that will lessen the chemical waste and lesser use of reagents and solvents.

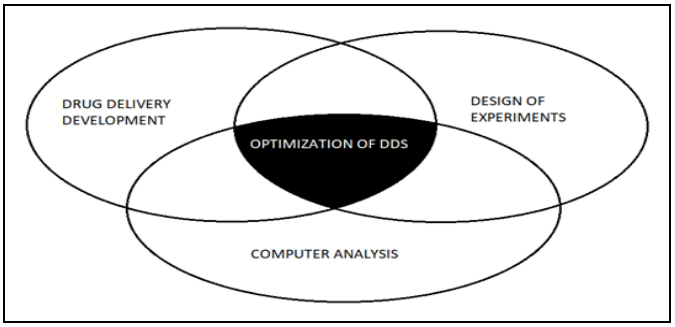

FIG. 1: MAJOR ELEMENTS IN OPTIMIZATION OF DRUG DELIVERY SYSTEMS

These parameters have led to better adoption and DoE as a powerful tool. This review attempts to discuss the detailed information and features of DoE [11-12]. **Fig. 1** shows the main elements of DoE, and **Table 3** shows the difference between conventional and DoE approach.

TABLE 3: DIFFERENCES BETWEEN CONVENTIONAL APPROACH AND DoE APPROACH

Conventional approach (OVAT)	DoE approach
This approach leads to sub-optimal solutions not appropriately able to reveal possible interactions	This approach provides the best possible formulation and gives interactions.
Formulation designing is not very easy to a level of the desired formulation	The optimized formulation can be achieved using input variables
Resource demanding techniques require lots of runs and batches	These techniques are more economical, as it produces information with minimum trials
Time-consuming techniques	Minimal time is required to run

Terminology in Optimization Process: Optimization is an undertaking that produces a faultless feasible combination of drug formulations and pharmaceutical processes or products. The optimization methodology is a blend of various terms that simply means to make as perfect, effective, or functional as possible and to suggest that a product has been improved to accomplish the objectives of a development scientist [13-15].

A. Variables: Any pharmaceutical process requires the involvement of several variables. Like independent variables, which are directly under the control of the product development scientist, *e.g.*, drug and polymer ratio, speed of agitation, temperature, *etc*., having quantitative or qualitative values. Quantitative variables are those that can take numeric values (*e.g.*, time, temperature, amount of polymer, cosmogenic, plasticizer, super-disintegrants) and are continuous [16].

Instances of qualitative variables, on the other hand, include the type of polymer, lipid, excipients, or tableting machine. These are also known as categorical variables. Their influence can be evaluated by assigning discrete dummy values to them. The independent variables, which influence the formulation characteristics or output of the process, are labeled factors [17]. The values assigned to the factors are termed levels, *e.g.*, 100 mg and 200 mg are the levels for the factor, the release-rate-controlling polymer in the compressed matrices. Restrictions imposed on the factor levels are known as constraints [18].

The characteristics of the finished drug product or the in-process material are known as dependent variables, *e.g.*, drug release profile, percent drug entrapment, pellet size distribution, moisture uptake. Popularly termed response variables, these are the measured properties of the system to estimate the outcome of the experiment. Usually, these are direct function(s) of any change(s) in the independent variables [19].

The drug formulation (product), with the optimization process, is called as a system in which the output (Y) is affected by different input variables with a function of the variable (T). These types of variables can either be controlled known as (X), signal factors, or uncontrolled known as (U), noise factors. **Fig. 2** explains the same relationship,

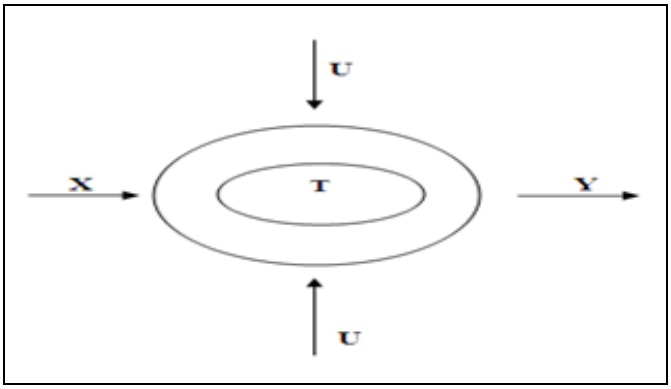

FIG. 2: RELATIONSHIP AMONG VARIABLES, INPUT VARIABLES (*X*), UNCONTROLLABLE INPUT VARIABLES (*U*), TRANSFER FUNCTION (*T*) AND OUTPUT VARIABLES (*Y*)

B. Effect and Interaction: The visibility of effect is seen when the response occurs after varying factors at different levels. The resultant effect is mainly showed upon all other factors. The term interaction refers to factors involved that are dependent on each other. The resultant of change can be positive or negative, which is called as synergism or antagonism [20].

C. Coding: When a variable has to be changed into a non-dimensional coded variable, this is known as

coding. The process of transforming a natural variable into a non-dimensional coded variable; this is known as coding. Different levels can be assigned to the factors from low to high as –1, 0, and +1, and zero can be shown as the arithmetic means of the two extremes (12). Normally different levels of a particular factor are denoted by -1, 0, and +1 showing low, medium, and high levels that has to be investigated [21].

For example, if a hydrophilic polymer like sodium carboxymethylcellulose is studied in the range between 120-240 mg, the codes -1 and +1 will show the value of 120 mg, and 240 mg and the medium value will be 180 mg. Also, for instance, a factor can be denoted by a capital letter A, and the high level by a, with low level (-1). **Table 4** shows the coding used alphabetically for the factors and the combination of factors at different levels. Coding shows the effects and interaction with the help of (+) and (-) signs. It allows equal importance to each axis and allows easy calculation of different coefficient variances with easy responses [22-23].

TABLE 4: VARIOUS LEVELS OF TWO FACTORS

Factor	Low Level	High Level
A	-1	a
B	-1	b
AB	1	ab

D. Experimental Design: The execution of experiments with organized way results into assumptions, which are vital properties of the experimental performance, and the design used for the experiment will give precise information with minimal experimentation. The design type of experiment depends on the model and objective of study [24]. The trials or runs are conducted on the basis of the type of design selected, and the trials are so performed in the design space that precise information is attained with minimal experimentation. The design selection is based on the model proposed and the objectives of the study. Basically, the experimental designs are based on the randomization principles, replication principle and error control principle [25].

F. Response surfaces: After execution of DoE, various types of data are explored, which results in mathematical equations showing interactions among independent variable and dependent variable. The graphical representation of these relationships is known as the response surface. These graphs are in 3-D form, which is plotted between two independent variables and one response variable called response surface plots. The graph which holds one independent variable against others is called contour plot [26]. The contour plots show the 2-D presentation of the particular 3-D response surfaces, and the curves in the plots are termed as contour lines.

G. Mathematical Models: These are termed as the simple algebraic expressions explaining the relationship among different variables. Mathematical models are described in two types empirical and theoretical. Former ones are mostly in the form of linear models, and the latter ones in nonlinear form [27]. The empirical type model depicts the relationship between a response and a factor with the help of the polynomial equation of the given order. Commonly used liner type models are equation 1-3 are,

$$Y= \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \varepsilon \ldots\ldots\ldots (1)$$

$$Y= \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1X_2 + \ldots + \varepsilon \ldots\ldots\ldots (2)$$

$$Y= \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1X_2 + \beta_{11}X_1^2 + \beta_{22} X_2^2 \ldots + \varepsilon \ldots\ldots\ldots (3)$$

Y represents the approximated response and is also denoted using E(y), and Xi shows the value of different factors with β0, βi, βii, and βij as constants symbolizing the intercept, coefficients of first-order, coefficients of second-order and also the coefficients of second-order interaction values. The ε depicts the error. The 1 & 2 equations are linear in nature with flat surface and braided area in 3-D space, and equation 3 depicts a second-order linear model that shows braided curves. A theoretical model can also exist, which is usually nonlinear [27-30].

Design of Experiments:

Methodology: The use of DoE approach in drug delivery systems for optimization encompasses different phases which can be classified into seven steps. **Fig. 3** explains these steps pictographically.

- In Step I, with an attempt to accomplish the objective for a drug delivery system. Various parameters for response are chosen [31-33].

- In Step II, the experimenter has to select factors at various levels, by employing relevant techniques and study into various input variables. An influence study has to be carried out to identify the interactions and effects [34].

- During Step III, after the investigation of factors with levels in detail the experiment design selection is an important step along with the response surface design usage to connect the response variable with input variable [35].

- In Step IV, next step involves the preparation of formulations with the designed approach experimentally prepared according to the approved experimental design, and the chosen responses are evaluated [36].

- Later in Step V, proper experimental design is employed to search the optimum formulation compositions and data is obtained and is analyzed a suitable mathematical model for the objective(s) accordingly under investigation is proposed, the experimental data thus obtained are analyzed accordingly, and the statistical significance of the proposed model discerned.

  Optimal formulation compositions are searched within the experimental domain, employing graphical or numerical techniques. This entire exercise is invariably executed with the help of pertinent computer software.

- Step VI is the penultimate phase of the optimization exercise, involving the validation of response prognostic ability of the model put forward. Drug delivery performance of some studies, taken as the checkpoints, is assessed vis-a-vis that predicted using RSM, and the results are critically compared.

- Finally, during Step VII, which is carried out in the industrial milieu, the process is scaled up and set forth ultimately for the production cycle.

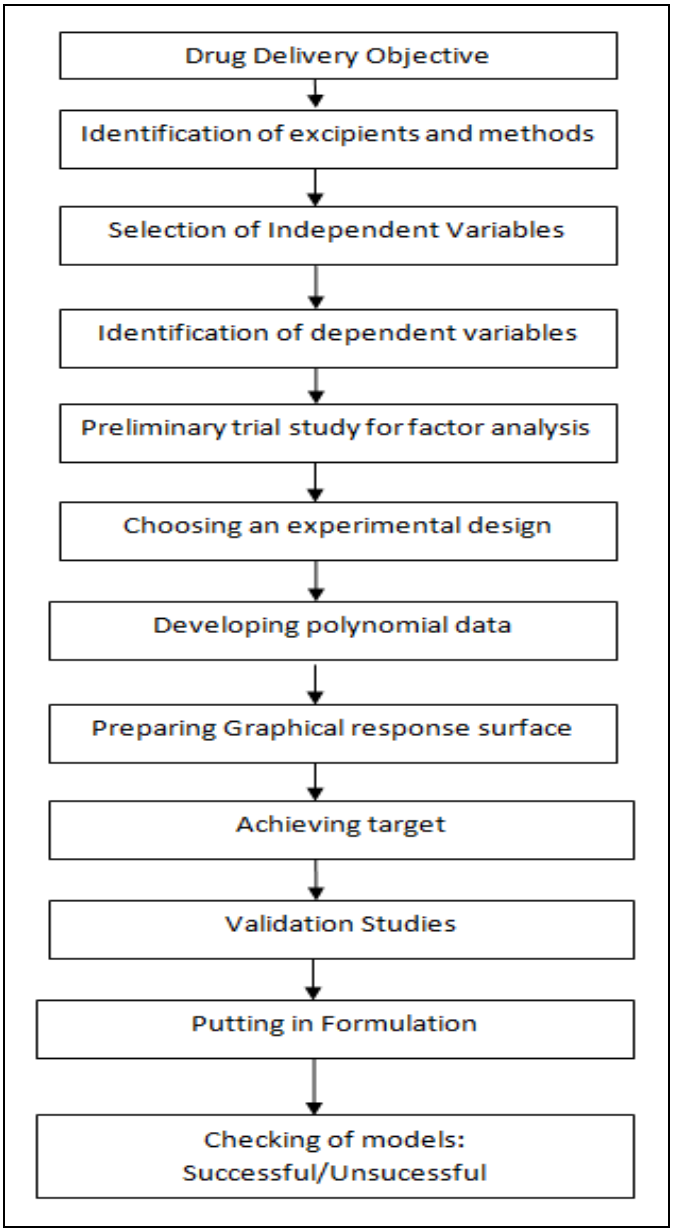

FIG. 3: DoE FEATURES IN OBTAINING DRUG DELIVERY OBJECTIVES

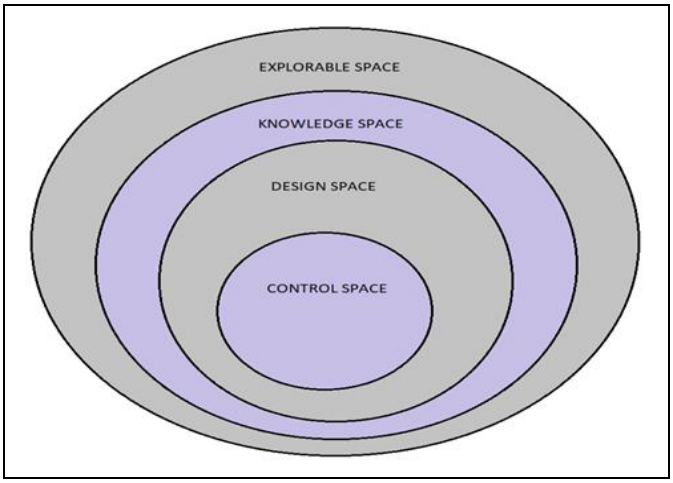

FIG. 4: RELATIONSHIP AMONG KNOWLEDGE, DESIGN AND SPACES

The detailing for each step for process optimization are discussed in detail below,

Step I: Objective: The first step for using DoE technology involves the understanding of objectives in the final product. This part of understanding goes beyond to explore all the concepts till market research. The objectives of a drug delivery system should be clearly discussed and determined among the team members of the optimization experiment. Defining objectives may take a long time and may not produce effective results. The prioritizing of the objectives helps to select the factors, experimental design, and variables. The efforts well done with time leads to appropriate information with minimum experimental runs [37].

Step II: Factor Screening: The next step in the process is the finding of important factors, and studying their effects with the interactions. This finding of factors, along with their influence study, is known as factor screening. This study leads to finding the optimum and important effects. So, the results obtained aims for optimization studies [38].

There are various variables through which a product development scientist has to encompass a group of factors with a significant influence on the response, a group of the rest of the non-influential factors. In the optimization process, all variables are explored for their response on the finished product in the initial stages. The important factors like active (influential) and inactive (non-influential) variables are responsible for variability. The identification of the factors is the vital step in optimization, the more active variables are optimized and the inactive variables are kept as constant. The priority in screening process is the identification of effects, termed as main effects. For determining main effects, the approximate runs are four times the number of factors to be estimated. In cases where a larger number of factors need to be screened, the number of runs becomes exorbitantly high. After, the screening of factors a detailed study is required which quantifies interactions, if any [39].

Step III: Response Surface Modeling and Experimental Designs: This is one of the crucial stages in the optimization process, where the experimental designs are utilized for carrying the experimental setup to achieve the data analysis. It involves the use of response surface modeling for predicting particular responses. With careful design and data analysis, a response surface is generated, which gives the levels of independent variables, showing the relationship with the responses. These designs are called response surface designs [40].

Step IV: Formulation of DDS and Their Evaluation: A proper design is predicted with the use of experimental designs, and the drug delivery systems are prepared according to the predicted design in a random manner; randomization assures that the noisy factors are spread in all control factors. The involved factors are varied at levels selected and keeping all other variables constant. Further, the formulated systems are evaluated for parameters and variables. The methods used for analysis give results with precision and reliability.

Step V: Computer-Aided Modeling and Optimization: The next step to experiment conduction is an interpretation of data. Different types of plots are constructed for understanding the working of a system like response versus time order scatter plots as response histograms, main effects mean plots, response(s) versus factor levels plots, and normal or half-normal plots can be plotted. The polynomial equations are generated post plot formations, and tests like ANOVA or Student's *t*-test are applied to test the model and to further simplify it [41].

Step VI: Validation of Optimization Methodology: For further scale-up, a reliable and accurate formulation is required so the validations of the optimization methodology prove to be a crucial step giving the ability of model studied. The polynomial equations so generated are tested for the ability different types of drug delivery systems from the domain of experiment selected, and prepared act as checkpoints around six to eight runs are appropriate to check the variability in a particular region. The conditions of the experiment should mimic the original experiment conditions. The result produced is compared with the predicted one, and the residual analysis is checked. The plot is prepared with the obtained data to check the patterns, and the parameters like r^2, r^2adj are obtained from the linear plot [42-44].

Step VII: Scale-Up and Implementation in Production Cycle: This final step is performed only for the sake of industrial milieu to confirm that the optimization studies performed are precise and robust. The results obtained are executed to a large-scale production cycle [45].

Computer Use in Optimization: The DoE approaches can be used manually, but the related software provides and eases the use of time well with performing the calculations using minimum time. It also provides the results in a graphical manner with numerical tables. The use of DoE involves the major statistics, which acts as an obstacle. With the discovery of different software for DoE, there has been ease of using them statistically. The use of DoE methods does not involve the in-depth knowledge of diverse statistical methodology. Computer software has been used almost at every step during the optimization cycle, ranging from the screening of factors, selection of design, use of response surface designs, generation of the design matrix, plotting of 3-D response surfaces and 2-D contour plots, robustness testing, application of optimum search methods, interpretation of results, and finally, validation of the methodology [46-48].

In particular, optimization is based totally upon the computer interface, tailor-made for the purpose. Many software packages, through helpful wizards, lead the user quite rationally through various phases of design, analysis, graphing, and optimization, even without a mathematical model or statistical equations insight. The use of pertinent software can make the DoE optimization task a lot easier, faster, more elegant, and more economical. Specifically, the erstwhile impossible task of generating varied kinds of 3-D response surfaces manually can be accomplished with phenomenal ease using appropriate software. While selecting the software, following points are to be considered [49]:

1. An array of designs for selection and optimization.
2. The facility to prepare design in accordance with selected experimental design.
3. Selection of suitable model and diagnostic plots.
4. A well-documented software manual with tutorials to get you off to a quick start.
5. A comprehensive glossary of various terms employed and needed during DoE optimization.

TABLE 5: SHOWS THE LIST OF COMPUTER SOFTWARE PACKAGES FOR USE IN DoE OPTIMIZATION

Name of the Software	Properties	Source
Design-Expert	Proper package used in optimizing different formulations with numerous designs like Factorial Design, Central Composite Design, Plackett Burman design. 3D plots are easily prepared and can be easily rotated	www.statease.com
NEMROD	Used for factorial designs	www.umt.ciw. uni-karlsruhe.de/22713
DOE WISDOM	Used for design D-Optimal and Taguchi methods	www.launsby.com
OPTIMA	Easily fits the data into equations, explains the response surface plots well	www.optimasoftware.co.uk
iSIGHT	Basic DoE Software with Taguchi. Factorial Designs and Plackett Burman Designs	www.engenious.com/ release1_11isightenhance.Html
DOE PRO XL&DOE KISS	DoE software with Factorial Design, Full Factorial Design and Placket Burman design	www.sigmazone.com

Epilogue:

Cautions in DoE Optimization: The choosing of experimental design plays a vital role in obtaining DoE optimization, whereas the incorrect design results into improper reliability of the prognosis and an unsuitable experimental range requires the lots of experimental runs [50]. The easier experimental designs applied with the mathematical tools give all data results from small experiments.

The improper use of DoE can result into restricted experiments with unsatisfactory results. The scientist can achieve the best formulation within the proper experimental setup. The predictions within the region are helpful but outside the region, they are null and void. The responses are only optimized on the cases with the best domain. If this step is not properly done, then the experimentation is doubled [51-52].

The use of the DoE approach to study the responses and to analyses the model is only possible in the optimal region if, in case this is not done, the experimentation will get increased. Regardless of the meritorious benefits of DoE, the approach should never be considered either a magic wand for product development by the experimenter. But the fact is this, the product knowledge and DoE go hand in hand.

CONCLUSION: The drug delivery systems demonstrate to control the drug release pattern, their targeting to specific organs. Developing such a delivery system requires many resources and time. To overcome various constraints in developing drug delivery systems, one can use an experimental design system. The use of experimental designs has enabled a formulator to achieve the desired objectives well in time. The use of DoE (design of experiments) approach is through various disciplines like medicine, dentistry, engineering, a technology widely applied today to diverse technologies. The DoE technology, therefore, tends to encompass in its ambit a rational usage of approach to formulating quality DDS effectively and cost-effectively and ultimately endeavoring to accomplish the desired objectives. DoE with experimental designs can be applied to almost on all the kinds of oral DDS, for optimizing not only to drug formulations, but also the processes leading to their development. It has proved to be useful even if the primary aim is not the selection of the optimum formulation, as it tends to divulge the degree of improvement in the product characteristics as a function of the change in (any) excipients or process parameter(s). In the pharmaceutical industries, DoE, in particular, are used for benefits in developing the brand name and generic products. The understanding of formulations using DoE helps in obtaining the desired objectives with simplicity. When finding the correct compromise is not straightforward, a pharmaceutical scientist should mandatorily consider the use of DoE. The DoE also requires a thorough understanding of formulation development as in from small lab scale to a big pilot plant scale-up. The appropriate knowledge of this system may help the formulator to apply this system with higher precision. The difficulties in optimization are due to improper understanding of effects relationship.

The trial and error methods like OVAT/OFAT never allow the formulator to guess the optimal drug delivery solution. Even with the well-documented uses of DoE in the development of drug delivery systems, the successful implementation depends on the type of experimental design and experimental domain. An improper design chosen can affect the ability, and an unsuitable range of experimental target may either skip the proper domain or may require much experimentation to obtain it. A properly obtained product or process can improvise the system leading to the formulation of the best possible product and economics.

Thus, DoE tends to explore the formulation process. Mainly, at the industrial point of view, it is considered mandatory to be confined within the chosen ‘design space’; or it may result in post-approval changes. From the last few decades, the systematic development of oral DDS has gained importance. New undertakings are therefore required to be taken to handle the growing utility of DoE. This paper highlights the DoE applications, methodology, and potential cautions and is an endeavor towards the same.

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