Systematic Optimization of Drug Delivery Systems using Experimental Designs

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ABSTRACT

The customary approach of developing an optimized formulation or process essentially calls for studying the influence of the corresponding composition and process variables by changing one variable at a time, while keeping others as constant. This traditional approach has been proved to be not only too expensive in terms of time, money and effort, but also unfavorable to fix errors, unpredictable and at times even unsuccessful. Drug delivery optimization using design of experiments (doe), accordingly, has recently gained wide recognition in the development of drug delivery systems. "doe" is an organized approach to determine the relationship between independent product and/or process variables and their effect on the response variable of that product or process. The objective of compiling this review is to familiarize the readership with the fundamentals of doe approach, choice of experimental designs amongst various designs available for drug delivery optimization, various methodologies employed, their experimental validation, and of course, the vital role of pertinent computer interface. The article can serve as a beacon to guide the novice in producing "designed" drug delivery formulations and pharmaceutical processes.

Keywords: *Design of experiments, drug delivery system, optimized, validation, OVAT*

Introduction

Design of an ideal pharmaceutical product invariably comprises multiple objectives. Such is particularly true for more intricate drug delivery systems (DDS) involving a variety of drugs, excipients, polymers and processes. For decades, this task has been conducted through trial and error, supplemented with the previous experience, knowledge, and wisdom of the formulator. The traditional approach of optimizing a formulation or process essentially entails studying the influence of the corresponding composition and process variables by changing One Variable at a Time (OVAT), while keeping others as constant. The technique, at times, is also referred to as Changing One Single (or Separate) variable or factor at a Time (COST) or OFAT (i.e., One Factor at a Time) or "shotgun" approach. During the OVAT studies, the first variable is fixed at a favorable value, and the next is examined until no further improvement is attained in the response variable. This customary OVAT approach has been proved to have various limitations as enumerated in Box 1. On the other hand, the modern formulation optimization approaches, employing systematic Design of Experiments (DoE), can be used in the development of diverse kinds of drug delivery devices to improve such irregularities. Such systematic approaches are far more advantageous (1), as enlisted explicitly in Box 2.

Of late, DoE optimization techniques are becoming a regular practice globally, not only in the design and development of an assortment of new dosage forms, but also for modifying the existing ones. Be it a drug industry, institutional drug delivery resource or federal compliance with USFDA, ICH, NIH or ISO, DoE is being frequently sought after in drug discovery and development. Faster emerging area of quality by design (QbD) also leads to employment of DoE precept in different quality procedures.

Basic terminology

The word, ***optimize*** simply means to make as perfect, effective or functional as possible. The term ***optimized*** has been used in the past to suggest that a product has been improved to accomplish the objectives of a development scientist.

With respect to drug formulations or pharmaceutical processes, ***optimization*** is a phenomenon of finding ***"the best"*** possible composition or operating conditions. Accordingly, ***optimization*** (2) has been defined as the implementation of systematic approaches to achieve the best combination of product and/or process characteristics under a given set of conditions. Of the numerous technical terms

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Box 1: Various limitations of One Variable at a Time approach

- ☒ Strenuous, uneconomical, time consuming and unsuitable to plug errors
- ☒ Inapt to reveal interactions, isolated and unconnected studies
- ☒ Pseudo-convergent to untrue optimum
- ☒ Result only in "just satisfactory" solutions
- ☒ Detailed study of all variables is prohibitive
- ☒ Prone to misinterpretation or faking of results
- ☒ Futile when all variables change simultaneously
- ☒ Unable to establish "cause and effect" relationship
- ☒ Ineffectual as leads to unnecessary runs and batches
- ☒ Irreproducible as infers randomly on the basis of origin
- ☒ New product may retain defects inherent in the old one

employed during DoE optimization, the vital ones are summarized in Box 3.

Methodology

The conduct of an experiment and the subsequent interpretation of its experimental outcome are the twin essential features of the general scientific methodology. This can be accomplished only if the experiments are carried out in a systematic way and the inferences are drawn accordingly. The theme of DoE optimization methodology provides thought-through and thorough information on diverse DoE aspects organized in a seven-step sequence as described in Figure 1.

Box 2: Various meritorious features of systematic DoE optimization techniques

- ☑ Require fewer experiments to achieve an optimum formulation.
- ☑ Yield the "best solution" in the presence of competing objectives.
- ☑ Can trace and rectify a "problem" in a remarkably easier manner.
- ☑ Lead to comprehensive understanding of the formulation system.
- ☑ Help in finding the "important" and "unimportant" input variables.
- ☑ Tests and improves "robustness" amongst the experimental studies.
- ☑ Can change the formulation ingredients or processes independently.
- ☑ Aid in determining experimental error and detecting "bad data points".
- ☑ Can simulate the product or process behavior using model equation(s).
- ☑ Save a significant amount of resources *viz.* time, effort, materials and cost.
- ☑ Evaluate and improve the statistical significance of the proposed model(s).
- ☑ Can predict the performance of formulations even without preparing them.
- ☑ Detect and estimate the possible interactions and synergies among variables.
- ☑ Facilitate decision-making before next experimentation by response mapping.
- ☑ Provide reasonable flexibility in experimentation to assess the product system.
- ☑ Furnish ample information on formula behavior from one simultaneous study.
- ☑ Can decouple signal from background noise enabling inherent error estimation.
- ☑ Comprehend a process to aid in formulation development and ensuing scale-up.

Box 3: Key terms used in DoE optimization

- ***Independent variables***: The input variables which are directly under the control of the product development scientist
- ***Factor:*** Experimentally controlled independent variable affecting the performance of a product or process
- ***Categorical Factor:*** Qualitative input factor, e.g., type of polymer, tablet machine, etc.
- ***Signal Factor:*** Controllable input variables influencing a response
- ***Nuisance Factors:*** Uncontrollable factors which complicate the estimation of effects and interactions
- ***Robust:*** A product or process which is less variable to external uncontrollable influences
- ***Quantitative Factor:*** Input variable with continuous numeric value
- ***Levels:*** Values assigned to factor
- ***Constraints:*** Restrictions imposed on levels of a factor
- ***Response:*** Measured system property to estimate experimental outcome
- ***Effect:*** Magnitude of change in response by varying factor level(s)
- ***Main Effect:*** Factor effects averaged at all other factor levels
- ***Interaction:*** Lack of additivity of factor effects
- ***Orthogonality:*** Sole dependence on main factor(s) and independence from interactions
- ***Confounding:*** Aliasing, equaling or lack of orthogonality or independence of variables
- ***Response Surface Plot:*** A 3-D graphical representation of a response plotted between two independent variables and one response variable
- ***Contour Plot:*** Geometric illustration of a response obtained by plotting one independent variable against another, holding the magnitude of response and other variables as constant
- ***Contour Lines:*** Curves drawn on a contour plot corresponding to a response value
- ***Factor Space:*** Dimensional space defined by the coded variables
- ***Experimental Domain:*** Part of the factor space, investigated experimentally for optimization
- ***Experimental design***: A statistical strategy for organizing the experiments in such a manner that the required information is obtained as efficiently and precisely as possible
- ***Randomization:*** An unbiased way of treatment allocation to experimental units
- ***Replication:*** Number of units employed for each treatment

The optimization study begins with Step I, where an endeavor is made to ascertain the initial drug delivery objective(s) in an explicit manner. Various main response parameters, which closely and pragmatically epitomize the objective(s), are chosen for the purpose. In Step II, the experimenter has several potential independent product and/or process variables to choose from. By executing a set of suitable screening techniques and designs, the formulator selects the vital few influential factors among the possible "so many" input variables. Before going to the more detailed study, experimental studies are undertaken to define the broad range of factor levels as well. During Step III, an apposite experimental design is worked out on the basis of the study objective(s), and the number and the *type* of factors, factor levels, and responses being explored. Working details on variegated vistas of the experimental designs, customarily required to implement DoE optimization of drug delivery, have been elucidated in the subsequent section. Afterwards, response surface methodology (RSM) is characteristically employed to relate a response variable to the levels of input variables, and a design matrix is generated to guide the drug delivery scientist to choose optimal formulations (3). In Step IV, the drug delivery formulations are experimentally prepared according to the approved experimental design, and the chosen responses are evaluated (4). Later in Step V, a suitable mathematical model for the objective(s) under exploration 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 validation of response prognostic ability of the model put forward. Drug delivery performance of some studies, taken as the checkpoints, is assessed vis-à-vis that predicted using RSM, and the results are critically compared (5). 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 (6).

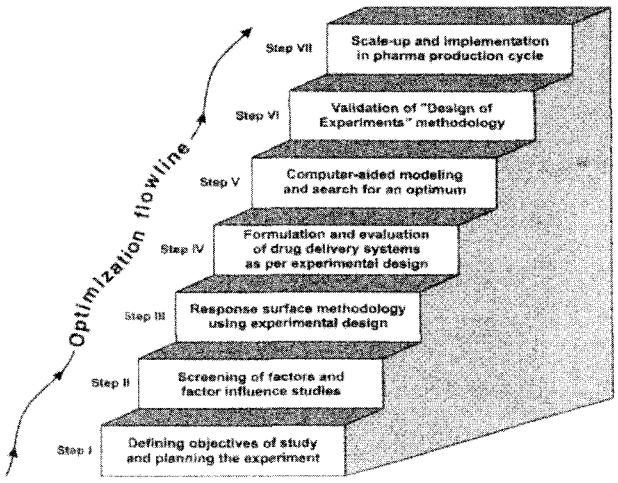

Figure 1: Seven-step ladder for optimizing drug delivery systems

Experimental designs

An experimental design constitutes the pith of entire DoE exercise. Before the selection of an experimental design, it is essential to demarcate the experimental domain (i.e., the area to be investigated) within the factor space (i.e., the broad range of factor studies). To accomplish this task, first a pragmatic range of experimental domain is embarked upon and the levels and their number are selected so that the optimum lies within its realm. While selecting the levels, one must see that the increments between them should be realistic. Too wide increments may miss finding the useful information between the levels, while a too narrow range may not yield accurate results.

There are numerous types of experimental designs to choose from. Various commonly employed experimental designs for RSM (7), screening and factor-influence studies during pharmaceutical product/ process development includes factorial, fractional factorial, Plackett-Burman, star, central composite, Box-Behnken, center of gravity, equiradial, mixture, Taguchi, Rechtschaffner and Cotter designs. The salient features of some of above mentioned designs are briefly stated in Table 1.

Selection of Experimental Design

Choice of a design amongst the various types of available options depends upon the amount of resources available and the degree of control over making wrong decisions (i.e., Type I and Type II errors for testing hypotheses) that the

Hence, when the investigator is interested in estimating interaction and even quadratic effects, or intends to have an idea of the local shape of the response surface, the response surface designs, capable of detecting curvatures, are used. The compilation in Table 2 acts as a help guide while selecting an experimental design, based upon the desired motive of the study.

Search for Optimum

Optimization of one response or the simultaneous optimization of multiple responses can be accomplished either graphically or numerically.

Table 2: Application of important experimental designs depending upon the nature of factor, models, and strategies

	2^kFD	x^kFD	FFD	PBD	CCD	BBD	EQD	SMD	EVD	TGD	DOD
Factor type											
Formulation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Process	✓	✓	✓	✓	✓	✓	✓	---	---	✓	✓
Both	✓	✓	✓	✓	✓	✓	✓	---	---	✓	✓
Number of factors											
≤3	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
4 – 6	✓	✓	✓	✓	✓	✓	✓			✓	✓
> 6			✓	✓						✓	
Factor level											
2	✓	---	✓	✓	---	---		✓		✓	✓
≥ 3	---	✓		---	✓	✓	✓	✓	✓	✓	✓
Model proposed											
Linear model	✓	✓	✓	✓				---	---	✓	
Interaction model	✓	✓	✓	✓	✓	✓	✓	✓	---	✓	
Quadratic model	---	✓		---	✓	✓	✓	---	---		
Mixture model	---	---	---	---	---	---	---	✓	✓	---	
Custom made model	---	---	---	---	---	---	---	---	---	---	✓
Screening and Factor influence study	✓	✓	✓	✓	---	---	---	✓	---	✓	✓
Response surface mapping		✓	✓		✓	✓	✓	✓	✓	✓	✓

FD: Fractional Design; FFD: Fractional Factorial Design; PBD: Plackett-Burman Design; CCD: Central Composite Design; BBD: Box-Benkhen Design; EQD: Equiradial Design; SMD: Simplex Mixture Design; EVD: Extreme Vertices Design; TGD: Taguchi Design; DOD: D-Optimal Design

a. *Graphical Optimization*

Known popularly as *response surface analysis,* graphical optimization (11) displays the area of feasible response values in the factor space. One or more of the following techniques may be employed for this purpose.

Location of the stationary point: After completing the experimental work, often the goal of the formulation scientist is to locate the optimum. Figure 2 (a, b) shows the location of the stationary points in case of a maximum and minimum, respectively. The case in which the stationary point is not a maximum or minimum is known as the *saddle point,* as shown in Figure 2c.

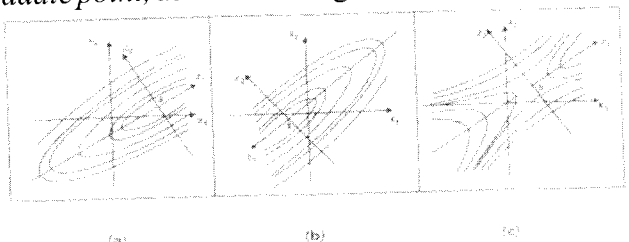

Figure 2: Diagrammatic representation of contour lines for location of the stationary point, S. (a) Maximum; (b) minimum; (c) saddle point

When the number of factors investigated is large, i.e., more than two, use of a graphical procedure cannot be interpreted with dexterity.

Search methods: Search *brute force* methods are employed for choosing the upper and lower limits of the responses of interest. The response surfaces in these search methods, as defined by the appropriate equations, are searched to find the combination of independent variables yielding the optimum. Two major steps are used—*feasibility search* and *grid search.* The feasibility search method is used to locate a set of response constraints that are just at the limit of possibility. Subsequently, the exhaustive grid search is applied, wherein the experimental range is further divided into a grid of specific size and searched methodically.

Overlay plots: The response surfaces or contour plots are superimposed over each other to search for the best compromise visually, as depicted in Figure 3. Minimum and maximum boundaries are set for acceptable objective values. The region is highlighted wherein all the responses are

acceptable. Within this area, an optimum is located, trading off different responses. An *overlay plot* can also be termed as *combined contour plot.*

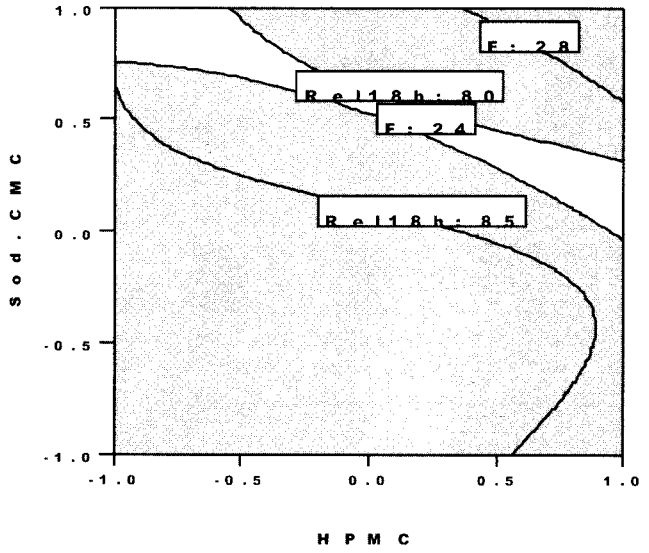

Figure 3: A contour overlay plot, plotted between two excipients, X_1 and X_2 shows the region between the two set criteria, i.e., Release till 18 h should be between 80 and 85% and bioadhesive strength should be between 24 and 28 g.

b. Mathematical Optimization Methods (Numerical Optimization)

Graphical analysis is usually preferred in the case of single response. However, in cases of multiple responses (12-13), it is usually advisable to conduct numerical or mathematical optimization first to uncover a feasible region.

Desirability function involves a way of overcoming the difficulty of multiple, sometimes opposing, responses. *Objective function* methods are used to seek an optimum formulation by solving for a maximum or a minimum in the presence of equality and/or inequality constraints. *Lagrangian method* can be used for optimization of functions expressed by introducing a slack variable for each inequality constraint.

Computer use in optimization

The merits of DoE optimization techniques are galore and their acceptability upbeat. Putting such rational approaches into practice, however, usually involves a great deal of mathematical and statistical intricacies. Today, with the availability of powerful and economical hardware and that of the comprehensive DoE software the erstwhile computational hiccups have been greatly simplified and streamlined. Computer software (14) have been used almost at every step during the entire optimization cycle ranging from selection of design, screening of factors, use of response surface designs, generation of the design matrix, plotting of 3-D response surfaces and 2-D contour plots, application of optimum search methods, interpretation of the results, and finally, the validation of the methodology. Hence, when selecting a DoE software package, it is important to look for not only a statistical engine that is fast and accurate, but also the following:

- A simple graphic user interface (GUI) that is intuitive and easy-to-use
- A well-written working manual with tutorials to get off to a quick start
- A wide selection of designs for screening and optimizing processes or product formulations
- A spreadsheet flexible enough for data entry as well as dealing with missing data and changed factor levels
- Graphic tools displaying the rotatable 3-D response surfaces, 2-D contour plots, interaction plots and the plots revealing model diagnostics
- Facility to randomize the order of experimental runs
- Design evaluation tools that will reveal aliases (i.e., confounded or equal effects) and other potential pitfalls
- After-sales technical support, online help and training offered by manufacturing vendors

Box 4 lists some commonly used computer software packages for DoE optimization, especially in pharma circles, along with their respective web sources.

Epilogue

Use of DoE as a leading edge approach has become an integral and regular phenomenon globally in rational drug delivery. Currently, it has gained acceptance as a pivotal developmental tool in diverse industrial processes. Employing DoE optimization can make it much simpler to modify existing formulations and meet redefined objectives. However, its enormous potential has not been fully harvested in drug delivery

Box 4: Important computer software packages for DoE optimization

MINITAB www.minitab.com	OPTIMA www.optimasostware.co.uk	Omega www.winomega.com
JMP www.jmp.com	DOE PRO XL & DOE KISS www.sigmazone.com	Design Expert www.statease.com
SOLVER www.solver.com	MATREX www.rsd-associates.com/ matrex.htm	iSIGHT www.engenious.com
ECHIP www.echip.com	GRG2 www.fp.mcs.anl.gov	STATISTICA www.statoftinc.com
SPSS www.spss.com	COMPACT www.fp.mcs.anl.gov	

development, research, and industry. Regardless of some reports and publications, we have yet to make the most of this revolutionary practice for routinely optimizing the DDS.

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