Developing oral drug delivery systems using formulation by design: Vital precepts, retrospect and prospects

Article *in* Expert Opinion on Drug Delivery · July 2011

DOI: 10.1517/17425247.2011.605120 · Source: PubMed

4 authors, including:

Bhupinder Singh
Panjab University
243 PUBLICATIONS **2,070** CITATIONS

SEE PROFILE

Expert Opinion

informa
healthcare

Developing oral drug delivery systems using formulation by design: vital precepts, retrospect and prospects

Bhupinder Singh[†], Rishi Kapil, Mousumi Nandi & Naveen Ahuja
[†]*Panjab University, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Studies, Dean Alumni, Chandigarh, India*

Introduction: Over the past few decades, the domain of drug formulations has metamorphosed from the conventional tablets and capsules to advanced and intricate drug delivery systems (DDS), both temporal and spatial. Formulation development of the oral DDS, accordingly, cannot be adequately accomplished using the traditional 'trial and error' approaches of one variable at a time. This calls for the adoption of rational, systematized, efficient and cost-efficient strategies using 'design of experiments (DoE)'. The recent regulatory guidelines issued by the key federal agencies to practice 'quality by design (QbD)' paradigms have coerced researchers in industrial milieu, in particular, to use experimental designs during drug product development.
Areas covered: This review article describes these principles of DoE and QbD as applicable to drug delivery development using a more apt expression, that is, 'formulation by design (FbD)'. The manuscript describes the overall FbD methodology along with a summary of various experimental designs and their application in formulating oral DDS. The article also acts as a ready reckoner for FbD terminologies and methodologies. Select literature and an extensive FbD case study have been included to provide the reader with a comprehensive portrayal of the FbD precept.
Expert opinion: FbD is a holistic concept of formulation development aiming to design more efficacious, safe, economical and patient-compliant DDS. With the recent regulatory quality initiatives, implementation of FbD has now become an integral part of drug industry and academic research.

Keywords: design of experiments, drug delivery, experimental design, product development, quality by design, response surface methodology, systematic optimization

Expert Opin. Drug Deliv. [Early Online]

1. Introduction

In an endeavor to combat various pathological states, drugs have been administered through various possible routes. Oral intake, amongst these routes, has unambiguously been the most sought after by the patients and manufacturers alike [1]. Development of an effective oral drug delivery system (DDS), however, invariably involves rational blending of diverse functional and non-functional polymers and excipients. Optimizing the formulation composition and the manufacturing process of such a drug delivery product to furnish the desired quality traits is, therefore, a Herculean task. The traditional approach of optimizing a formulation or process essentially involves studying the influence of one variable at a time (OVAT), while keeping all others as constant. Using this OVAT approach, the solution of a specific

10.1517/17425247.2011.605120 © 2011 Informa UK, Ltd. ISSN 1742-5247

challenging property can be achieved somehow, but attainment of the true optimal composition or process can never be guaranteed [2]. This may ostensibly be ascribed to the presence of interactions, that is, the influence of one or more variables on others. The final product though may be satisfactory, but mostly sub-optimal, as a better formulation might still prevail for the studied conditions.

Design of experiments (DoE), on the other hand, is an optimization technique meant for products and/or processes, developed to evaluate all the potential factors simultaneously, systematically and speedily. Its implementation invariably encompasses the use of statistical experimental designs, generation of mathematical equations and graphic outcomes, portraying a complete picture of variation of the response(s) as a function of the factor(s), which can never be obtained using the traditional OVAT approach [3-7].

Lately, a holistic DoE-based philosophy of quality by design (QbD) has been slowly permeating into the mindset and practice in the industrial environs [8-12]. This popularity of QbD in pharma circles is largely attributable to the recent impetus provided by the ICH, FDA and EMEA through their respective federal guidance [13-17]. Because DoE has much wider domain of application, we propose, on the heels of QbD, a terser jargon, that is, 'formulation by design (FbD)', applicable specifically to the use of DoE in drug formulation development. **Table 1** succinctly enumerates the merits of FbD over the OVAT methodology.

Owing to such numerous benefits of FbD methodology, the recent years have witnessed a spurt in the development of various DDSs, both oral and non-oral, optimized using FbD [18-25]. **Figure 1** pictographically depicts the number of FbD studies reported in literature in the past 5 decades.

2. FbD terminology

Specific terminology, both technical and otherwise, is usually used during FbD practice. To facilitate better clarity of precepts of FbD of oral DDS, important terms have been compiled in **Box 1**.

As a prelude to the application of FbD, it is essential to be aware of the FbD terminology and previous multidisciplinary knowledge on various possible product and process variables ahead. A 'knowledge space', that is, an entire worth exploring realm, therefore, has to be identified from the possible vast ocean of scientific information based on previous knowledge. A 'knowledge space', thereby, encompasses all those product and process variables that may even minutely affect the overall product quality. A 'design space' has to be demarcated as a subset construct of 'knowledge space' ensuring optimal product quality or process performance involving 'selected few' influential variables. 'Control space' is further deduced from this 'design space' as the experimental domain earmarked for detailed studies during studies within the refined ranges of input variables. It is also sometimes referred to as 'control strategy'. 'Design space' applies a systematic approach on archival data to convert the 'knowledge space' to 'control space' [26]. Extensive experimentation may be necessary for relatively intricate DDSs in order to reduce uncertainty and justify a design space than that required for conventional formulation systems such as tablets. As working within the design space is not considered as a 'change', it would not initiate any post-approval change process as per the federal guidelines [27]. **Figure 2** portrays the hierarchy of knowledge, design and control space.

3. FbD methodology

Verily, FbD hits the bull's eye using five key strengths, that is, apt choice of experimental designs, accurate computer-aided optimization, meticulous drug product development, precise definition of design and control space, and identification of critical quality attributes (CQAs), critical formulation attributes (CFAs) and critical process parameters (CPPs). **Figure 3** pictorially illustrates the concept.

The theme of DoE optimization methodology provides complete information on diverse DoE aspects organized in a five-step sequence.

- The FbD study begins with **Step I,** where an endeavor is made to explicitly ascertain the drug delivery objective (s). Various CQAs or response variables, which pragmatically epitomize the objective(s), are earmarked for the purpose. All the independent product/process variables are also listed.
- In **Step II,** the response variables which directly represent the product quality (e.g., particle size for nanoparticles, emulsification time for self-emulsifying systems) are selected. Also, selection of a 'prominent few' influential factors among the 'possible many' input variables is conducted using experimental designs through a process, popularly termed as 'screening' [28]. The formulators, at times, can even bypass the rigors of screening process to choose these factors, that is, CFAs and/or CPPs by virtue of their experience, wisdom and previous knowledge. Factor influence studies are usually conducted later to quantify the effect of factors and determine the interactions, if any. Experimental studies are also undertaken to define the broad range of factor levels.
- During **Step III,** a suitable experimental design is worked out to map the responses on the basis of the study objective(s), responses being explored, number and the type of factors, and factor levels, that is, high, medium or low. The niceties of important experimental designs along with their pros and cons are discussed in subsequent sections. A design matrix is subsequently generated to guide the drug delivery scientist. The

Table 1. Comparison of OVAT and FbD methodology.

Attribute	OVAT	FbD
Choice of optimum formulation	May result only in sub-optimal solutions	Yields the best possible formulation
Interaction among the ingredients	Inept to reveal possible interactions	Estimates any synergistic or antagonistic interaction among constituents
Scale-up and post-approval changes	Very difficult to design formulation slightly differing from the desired formulation, especially beyond Level II	Changes in the optimized formulation can easily be incorporated, as all response variables are quantitatively governed by a set of input variables
Resource economics	Highly resource-intensive, as it leads to unnecessary runs and batches	Economical, as it furnishes information on product/process performance using minimal trials
Time economics	Highly time-consuming, as each product is individually evaluated for its performance	Can simulate the product or process behavior using model equations

FbD: Formulation by design; OVAT: One variable at a time.

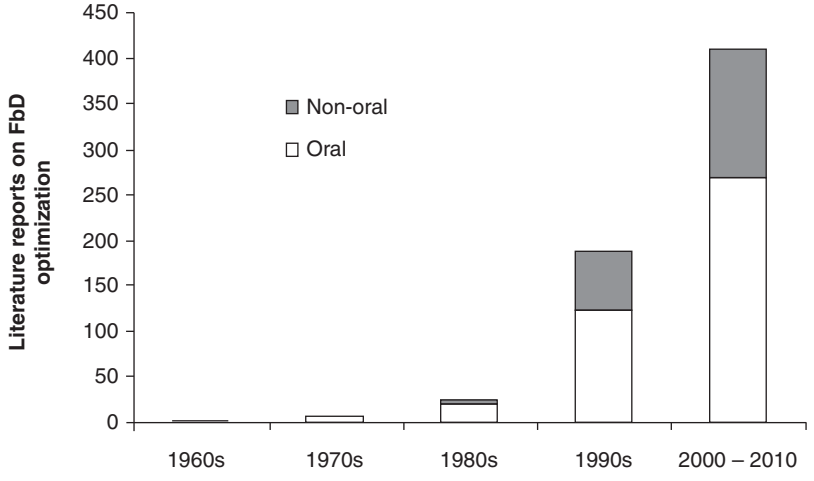


Figure 1. Oral and non-oral drug delivery formulations optimized using FbD.
FbD: Formulation by design.

drug delivery formulations are experimentally prepared according to the chosen experimental design, and the chosen response variables are evaluated meticulously.

- In **Step IV**, a suitable numeric model is proposed on the basis of experimental data thus generated, and its statistical significance is discerned. Response surface methodology (RSM) is used to relate a response variable to the levels of input variables. Optimum formulation compositions are searched within the experimental domain, using graphical or numerical techniques.
- **Step V** is the ultimate phase of the FbD exercise, involving validation of response predictive ability of the proposed design model. Drug delivery performance of some studies, taken as the confirmatory runs, is assessed in relation to that predicted using RSM, and the results are critically compared. The optimum formulation is scaled-up and set forth ultimately for the production cycle.

3.1 Experimental designs used during FbD of oral DDS

An experimental design constitutes the gist of FbD exercise. Systematic FbD optimization of DDS includes a careful 'screening' of influential variables and subsequent response surface analysis using experimental designs. Out of all of the experimental designs, factorial and central composite designs have extensively been used to optimize oral DDS [29-34]. **Table 2** provides a comparative account of key experimental designs used for optimization of oral DDS, listing their advantages and disadvantages.

Out of all the experimental designs, factorial design (FD), central composite design (CCD) and fractional factorial design (FFD) have been most frequently used for systematic optimization of oral DDS. **Figure 4** provides a succinct account of the usage of experimental designs in the development and optimization of oral drug delivery formulations and processes.

Box 1. Vital terminology used during FbD of drug delivery.

Term	Definition
Optimize	Make as perfect, effective or functional as possible
Optimization	Implementation of systematic approaches to achieve 'the best' combination of product and/or process characteristics under a given set of conditions using FbD and computers
Independent variables	Input variables, which are directly under the control of the product development scientist
Quantitative variables	Variables that can take numeric values
Categorical variables	Qualitative variables which cannot be quantified
Runs or trials	Experiments conducted according to the selected experimental design
Factors	Independent variables, which tend to influence the product/process characteristics or output of the process
Design matrix	Layout of experimental runs in matrix form as per experimental design
Knowledge space	Scientific elements to be considered and explored on the basis of previous knowledge as product attributes and process parameters
Design space	Multidimensional combination and interaction of input variables and process parameters, demonstrated to provide quality assurance
Control space	Domain of design space selected for detailed controlled strategy
Levels	Values assigned to a factor
Constraints	Restrictions imposed on the factor levels
Response variables	Characteristics of the finished drug product or the in-process material
Critical quality attributes	Parameters ranging within appropriate limits, which ensure the desired product quality
Critical process parameters	Independent process parameters most likely to affect the quality attributes of a product or intermediates
Critical formulation attributes	Formulation parameters affecting critical quality attributes
Effect	The magnitude of the change in response caused by varying the factor level(s)
Main effect	The effect of a factor averaged over all the levels of other factors
Interaction	Lack of additivity of factor effects
Antagonism	Undesired negative change due to interaction among factors
Synergism	Desired positive change due to interaction between factors
Nuisance factors	Uncontrollable factors which complicate the estimation of main effect or interactions
Orthogonality	A condition where the estimated effects are due to the main factor of interest, but independent of interactions
Confounding	Lack of orthogonality
Resolution	The measure of the degree of confounding
Coding (or normalization)	Process of transforming a natural variable into a non-dimensional coded variable
Factor space	Dimensional space defined by the coded variables
Experimental domain	Part of the factor space, investigated experimentally for optimization
Blocks	A set of relatively homogenous experimental conditions, wherein every level of the primary factor occurs the same number of times with each level of nuisance factor
Response surface	Graphical depiction of the mathematical relationship
Empirical model	Mathematical model describing factor–response relation using polynomial equations
Response surface plot	3D 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, while holding the magnitude of response and other variables as constant

FbD: Formulation by design.

4. Selection of experimental design

Choice of a design amongst the various types of available options depends on 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 experimenter desires. Low-resolution designs such as FFDs, Plackett-Burman designs (PBDs) or Taguchi designs suffice the purpose of simpler screening of a large number of experimental parameters. Screening designs support only the linear responses. Thus, if a nonlinear response is detected, or a more accurate picture of the response surface is required, a more complex design type is necessary. 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 [2]. In a nutshell, the major aspects to be considered while selecting an experimental design can be summarized as:

- All designs can be applied for optimization of product characteristics, but SMD and EVD should not be used for process optimization.
- Any design out of 2^k FD, x^k FD, FFD, PBD or TgD can be used for screening studies.

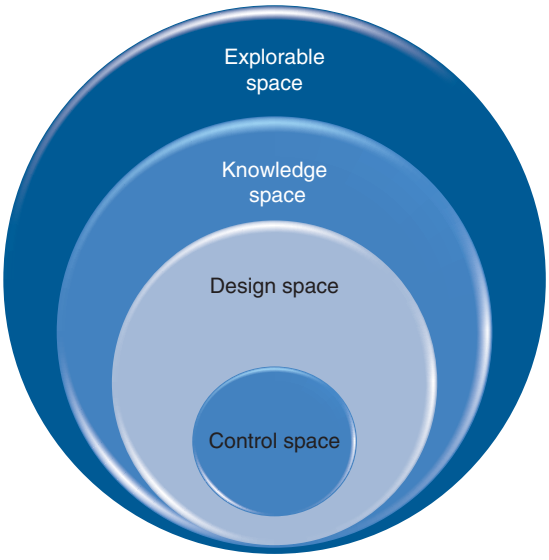


Figure 2. Inter-relationship among knowledge, design and control spaces.

- For estimation of main effects, all 2-level designs except PBD can be used. However, for higher number of factors (> 6), screening should first be used using FFD, PBD or Taguchi design.
- If there are only two factor levels, any design out of 2^k FD, FFD, PBD or mixture design can be used. However, in case of > 3 factor levels, CCD, Box-Behnken design (BBD), equiradial design, simplex centroid and optimal designs are preferred.
- For quadratic models, x^k FD, CCD, BBD or equiradial design is preferred.

5. Model development

A model is an expression defining the quantitative dependence of a response variable on the independent variables. Numeric models can either be empirical or theoretical. An empirical model provides a way to describe the factor–response relationship. Usually, it is a set of polynomials of a given order or degree. The models mostly used to describe the response(s) are first, second and very occasionally, third order polynomials. A first order model is postulated in the first instance. If a simple model is found to be inadequate for describing the phenomenon, the higher order models are followed.

The coefficients for quantitative factors can be estimated using regression analysis. However, in case of qualitative factors, as interpolation between discrete (i.e., categorical) factor values is meaningless, regression analysis is not used. For more factors, interactions and higher order terms, multiple linear regression analysis (MLRA) is usually preferred. Multiple nonlinear regression analysis should be preferred when the factor–response relationship is nonlinear. In multivariate studies, where there are large numbers of variables, the methods of partial least squares (PLS) or principal component analysis can also be used for regression [35]. PLS, an extension of MLRA, is used when there are fewer observations than the number of predictor variables. Model analysis is conducted considering ANOVA, Student's *t* test [36], predicted residual sum of squares and Pearsonian coefficient of determination (r^2). The following account summarizes the basic steps involved in creating and analyzing a mathematical model [37]:

- The data are carefully examined for any outliers and obvious problems. Various graphs such as response distributions, responses versus time order scatter plot, responses versus factor levels, main effects plots and normal or half-normal plots of the effects are plotted.
- The model assumptions are tested using residual graphs. If none of the model assumptions are violated, ANOVA is applied. The model is simplified further, if possible.
- If model assumptions are violated, model transformation is proposed and a new model is generated.
- The results of the model are applied to ascertain important factors, finding optimum settings and so on.

6. Testing and revision of FbD models

The major tools for testing and revising an FbD model are:

- Response versus predictions: Such plots divulge any interaction or involvement between the independent factors.
- Residual lag plots: Randomization of data can be estimated using residual lag plots. Ideally, no particular structures should be present in the plots. Absence of any random patterns points towards interactions or other errors. Lag plots can be generated for any arbitrary lag, the most common being 'lag 1'. A plot of 'lag 1' is a plot of the values of Y_i versus Y_{i-1}.
- Residuals histogram: The purpose of residuals histogram is to graphically summarize the distribution of a univariate data set. The histogram graphically depicts the location, spread, skewness, outliers and multiple nodes of the data.
- Normal probability plot of residuals: The normal probability plot graphically assesses the data for its distribution pattern, whether normal or not. In these plots, the data are plotted against a theoretical normal distribution in such a way that the points should form an approximate straight line. Departures from this straight line indicate departures from normality.

7. Optimum search

From the models thus selected, optimization of one response or the simultaneous optimization of multiple responses needs to be accomplished graphically, numerically, using artificial neural networks (ANNs) and/or through extrapolation outside the domain.

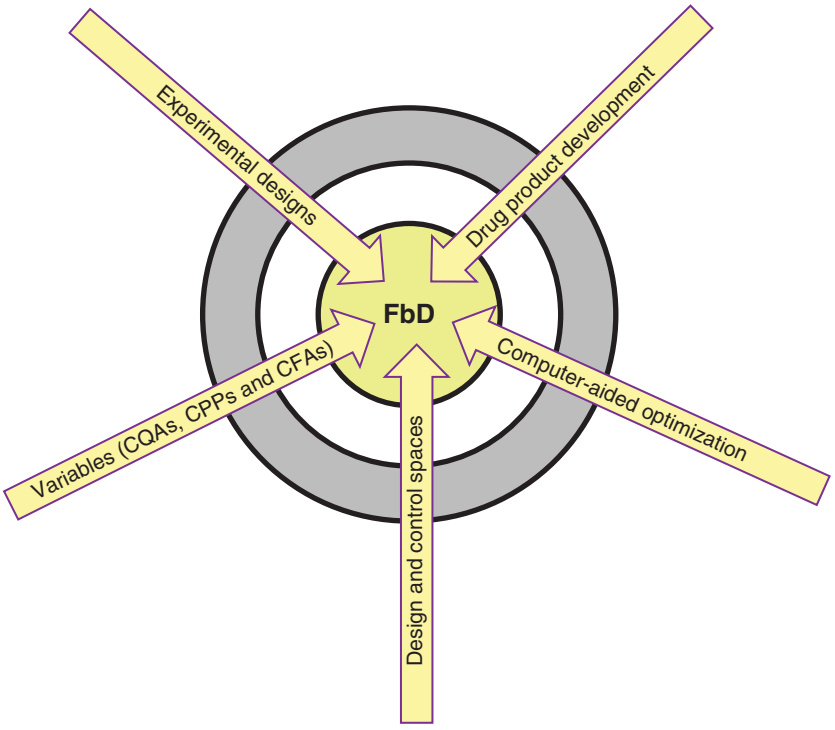


Figure 3. Involving five cardinal elements, FbD aims to hit the bull's eye.
FbD: Formulation by design.

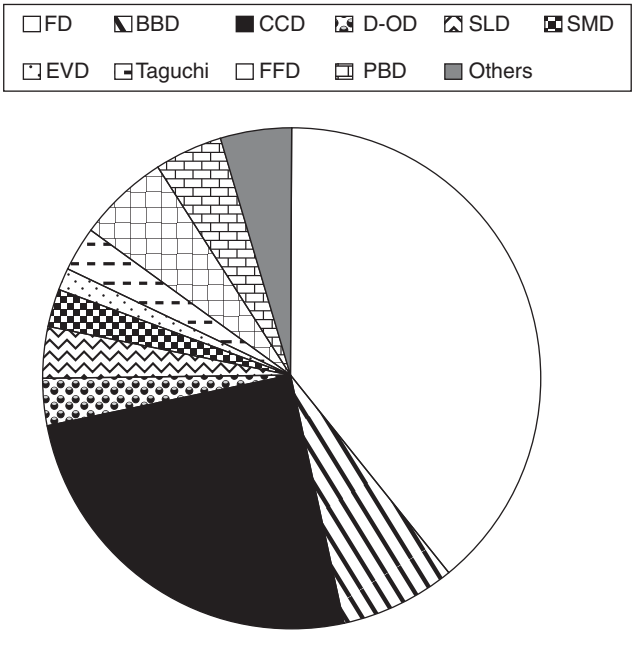


Figure 4. A comparative chart of the proportion of various experimental designs employed during FbD of oral DDSs.
DDS: Drug delivery system; FbD: Formulation by design.

7.1 Graphical optimization

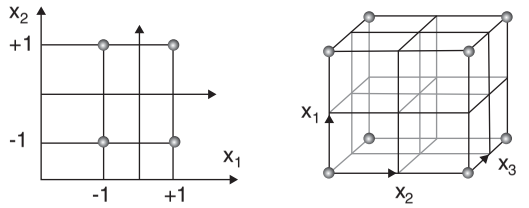
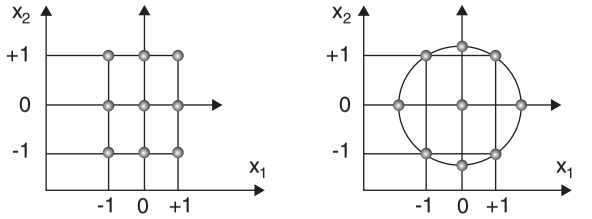
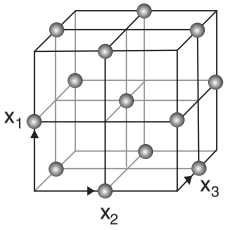
Graphical optimization deals with selecting the best possible formulation out of a feasible factor space region. To do this, the desirable limits of response variables are set, and the factor levels are screened accordingly. Graphical optimization can be accomplished through one or more of the following methodologies:

Other techniques used for optimizing multiple responses are brute-force searches, overlay plots, canonical analysis, ANNs and mathematical optimization.

7.1.1 Brute-force search

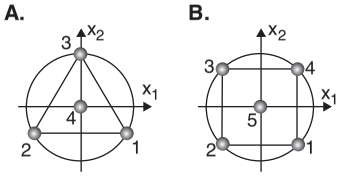
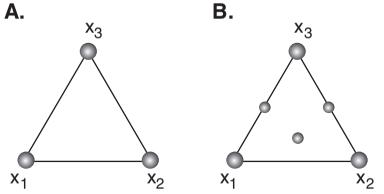
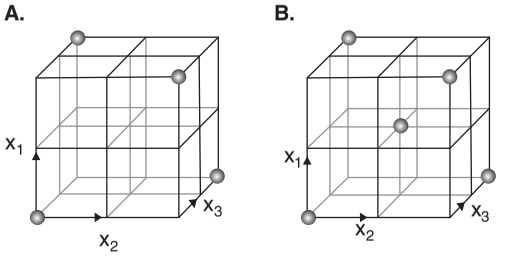
Brute-force search, also known as exhaustive search, is the simplest and most accurate of all possible optimization search methods, as it implies checking every single point in the function space. Herein, the formulations that can be prepared by almost every possible combination of independent factors are screened for their response variables [38]. 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. The advantage of this exhaustive method is that the chances of missing the true optimum formulation are only miniscule.

Table 2. Experimental designs usually used during formulation by design of drug delivery systems.

Design	Description	Diagrammatic representation
Response surface designs		
FD	A factorial experiment is one in which all levels (x) of a given factor (k) are combined with all levels of every other factor in the experiment and the total number of experiments being x^k *Merits:*Efficient in estimating main effects and interactions Maximum usage of data *Demerits:*Reflection of curvature not possible in a 2-level design More experiments are required	**A.** **B.**  **(a)** 2^2 FD; **(b)** 2^3 FD
CCD or Box-Wilson design	For nonlinear responses requiring second order models, CCDs are most frequently used. The 'composite design' contains an imbedded (2^k) FD or (2^{k-r}) FFD, augmented with a group of star points (2k) and a 'central' point. The total number of factor combinations in a CCD is given by $2^k + 2k + 1$ *Merits:*Combines the advantages of FDs and star designs Allows the work to proceed in stages, i.e., if linear 2-level FD does not adequately fit the data, the design can be augmented by adding a center point Requires fewer experiments *Demerits:*Difficult to practice with fractional values of α	**A.** **B.**  **(a)** CCD (rectangular domain) with $\alpha = 1$; **(b)** CCD (spherical domain) with $\alpha = 1.414$
BBD	A specially made design, the BBD, requires only three levels for each factor, i.e., -l, 0 and +1. A BBD is an economical alternative to CCD	 BBD for three factors

BBD: Box-Behnken design; CCD: Central composite design; ErD: Equiradial design; FD: Factorial design; FFD: Fractional factorial design; PBD: Plackett-Burman design.

Table 2. Experimental designs usually used during formulation by design of drug delivery systems (continued).

Design	Description	Diagrammatic representation
ErD	ErDs are first-degree response surface designs, consisting of *N* points on a circle around the center of interest in the form of a regular polygon	 Two-factor ErD **(a)** triangular four-run design; **(b)** square five-run design
Mixture designs	In DDS with multiple excipients, the characteristics of the finished product usually depend not so much on the quantity of each substance present but on their proportions. Mixture designs are highly recommended in such cases. In a two-component mixture, only one factor level can be independently varied, while in a three-component mixture, only two factor levels can be independently varied *Merits:*Suitable for formulations wherein a constraint is imposed on some combination of factor levels *Demerits:*Difficult to comprehend the polynomials generated from mixture design Interactions and quadratic effects are not estimated	 Mixture design **(a)** linear model; **(b)** quadratic model
Optimal designs	When the domain is irregular in shape, optimal designs can be used. These are the non-classic custom designs generated by exchange algorithm using computer. In general, such custom designs are generated based on a specific optimality criteria such as D-, A-, G-, I- and V- optimality criteria *Merits:*Can be used even if the experimental domain is irregular in shape *Demerits:*Involves a relatively complex model	
Screening designs		
FFD	In cases where there are large numbers of factors, it is possible that the highest order interactions have no significant effect. As such, the number of experiments can be reduced in a systematic way, with the resulting design called FFDs or sometimes partial factorial designs. An FFD is a finite fraction ($1/x^r$) of a complete or full FD, where *r* is the degree of fractionation and x^{k-r} is the total number of experiments required *Merits:*Suitable for large number of factors or factor levels *Demerits:*Effects cannot be uniquely estimated, as are confounded with interaction terms Difficult to construct	 **(a)** 2^{3-1} FFD with design points as spheres **(b)** 2^{3-1} FFD with added center point

BBD: Box-Behnken design; CCD: Central composite design; ErD: Equiradial design; FD: Factorial design; FFD: Fractional factorial design; PBD: Plackett-Burman design.

Table 2. Experimental designs usually used during formulation by design of drug delivery systems (continued).

Design	Description	Diagrammatic representation
PBD	PBDs are special two-level FFDs used generally for screening of K factors, i.e., N-1 factors, where N is a multiple of 4. Also known as Hadamard designs or symmetrically reduced 2^{k-f} FDs, the designs can easily be constructed using a minimum number of trials *Merits*:Suitable for very large number of factors, where even FFDs require a large number of experiments *Demerits*:Design structure is complex because of aliasing Results in confounding of effects, as number of experiments is very less	
Taguchi designs	Used to develop the products or processes as robust amidst natural variability. The design is also referred to experimental design as 'off-line quality control' because it is a method of ensuring good performance in the development of products or processes	 Inner 2^3 and outer 2^2 arrays of Taguchi design

BBD: Box-Behnken design; CCD: Central composite design; ErD: Equiradial design; FD: Factorial design; FFD: Fractional factorial design; PBD: Plackett-Burman design.

7.1.2 *Overlay plots*

The bi-dimensional response contour plots are superimposed over each other to search for the best compromise visually. This is termed as an overlay plot or a combined contour plot. 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.

7.1.3 *Canonical analysis*

Canonical analysis indicates the predictability of each of the extracted components of the criterion set of variables from the corresponding components, extracted from the predictor set of variables [39-43]. The technique can only be used for single response optimization.

A saddle point is a point in the domain of a function of two variables which is a stationary point but not a local extremum. At such a point, in general, the surface resembles a saddle that curves up in one direction or curves down in a different direction (like a mountain pass). In terms of contour lines, a saddle point can be recognized, in general, by a contour that appears to intersect itself. The technique can only be used for single response optimization.

Besides, there are other vital methods used for graphically searching the optimum formulation such as Pareto-optimality charts.

7.2 Mathematical optimization

Graphical analysis is usually considered adequate in case of single response. However, in cases of multiple responses, it is usually advisable to conduct mathematical or numerical optimization first to uncover a feasible region.

7.2.1 *Desirability function*

Desirability function is a way of overcoming the difficulty of multiple, sometimes opposing, responses [2]. In this method, each response is associated with its own partial desirability function [44,45]. The point possessing the highest value for desirability is termed as optimum [46]. The experimenter should study the contour plot of desirability surface around the optimum and combine this with contour plots of the most important responses. A large area or volume of high desirability will indicate a robust formulation or set of processing conditions. Although the method requires appropriate computer software, yet it is a highly useful and pragmatic method of optimization.

Besides, the techniques of 'objective function' and 'sequential unconstrained minimization technique' have also been utilized to optimize DDS numerically.

7.3 Artificial neural networks

ANNs are the machine-based computational techniques that attempt to simulate some of the neurological processing abilities of the human brain. The ANNs offer unique advantages of nonlinear processing capacity and the ability to model

poorly understood systems [47-51]. When compared with other optimization methods, the results are comparable with better prognostic abilities. However, they are quite difficult to implement at higher number of factors and/or levels, and no statistical criterion is revealed to declare the degree of aptness of the model.

7.4 Extrapolation outside the domain

Steepest ascent (or descent) methods are direct optimization methods for first order designs [52], especially when the optimum is outside the domain and is to be arrived at rapidly. Optimum path method is just analogous to steepest ascent method and is used where the optimum is searched outside the experimental domain by extrapolation. The technique of evolutionary operations, wherein the production procedure (formulation and process) is allowed to evolve to the optimum by careful planning and constant repetition, is quite popular in several industrial processes.

8. Overall FbD strategy for drug delivery development

The overall approach for conduct of an FbD study in oral DDS can be described by a holistic plan [38,53]. The salient steps involved in this FbD strategy include:

Problem definition: The FbD problem is clearly comprehended and defined.

Selection of factors and factor levels: The independent factors are identified amongst the quantifiable and easily controllable variables.

Design of experimental protocol: Based on the choice of independent factors and the response variables, a suitable experimental design is selected and the number of experimental runs calculated.

Formulating and evaluating the dosage form: Various drug delivery formulations are prepared as per the chosen design and evaluated for the desired response(s).

Prediction of optimum formulation: The experimental data are used for generation of a mathematical model and an optimum formulation is located using graphical and/or numeric methods.

Validation of optimization: The predicted optimal formulation is prepared and the responses evaluated. Results, if validated, are carried further to the production cycle via pilot plant operations and scale-up techniques.

Overall, **Figure 5** depicts the various salient steps involved during an FbD strategy as a whole in the form of a flow chart.

9. FbD optimization of oral DDS: literature instances

Almost all types of orally administered DDS have been reported in literature to be systematically optimized using FbD. Both product and process optimization approaches have been utilized for systematic optimization of oral DDS. **Table 3** provides a succinct account of select literature instances of product optimization of oral DDS.

Selected literature instances for process optimization of various oral DDSs are compiled as **Table 4**.

As evident from the tables, a variety of oral DDS have been systematically optimized using FbD. However, among all the oral DDS, SR tablets and microspheres have most extensively been studied so far. **Figure 6** pictographically depicts the relative proportion of various oral DDSs optimized using FbD.

Apart from product and process optimization, experimental designs have also been used for the purpose of screening of influential factors from various input variables. **Table 5** provides a succinct account of selected literature instances using experimental design for the screening purpose.

10. FbD optimization of oral DDSs: a case study

The investigation [25] aimed at developing oral CR floating-bioadhesive matrices of tramadol hydrochloride, optimized using a CCD. Following extensive preliminary studies among various cellulosic polymers, carbomers and natural polymers, Carbopol 971P (CP) and Methocel K100LV (HPMC) were finally selected for detailed FbD studies to provide optimized drug release extension, bioadhesion and floatational behavior. Any possible incompatibility between the polymers and the drug was ruled out using DSC and FTIR studies. Different tablet formulations of tramadol HCl were formulated using varying amounts of the polymers (i.e., CP and HPMC), magnesium stearate (MST) as glidant and lubricant, and microcrystalline cellulose (MCC) as an inert diluent. All the materials were sieved through fine mesh (80/120), accurately weighed and mixed intimately in a polythene bag for 10 min. The blended mix was subsequently compressed into tablets using flat-faced round punches fitted to a single-punch tablet compression machine.

A CCD for two factors at three levels each (with $\alpha = 1$) was selected to optimize varied response variables. The two factors, CP (i.e., polymer X_1) and HPMC (i.e., polymer X_2), were varied in the polymer blends, as required by the experimental design, and the factor levels coded suitably (**Table 6**). The formulation at central level (0,0) was studied in quintuplicate. The amount of MS was kept as constant at 5 mg, while MCC was used as a diluent in a sufficient quantity to maintain a constant tablet weight of 440 mg. The variations in the values of tablet assay, friability, hardness and tablet weight were all within the limits of pharmacopeia.

The response variables which were considered for systematic DoE optimization included $t_{75\%}$, $rel_{16\ h}$, T_b and ρ. For the studied design, the MLRA method was applied to fit full second order polynomial equation with added interaction

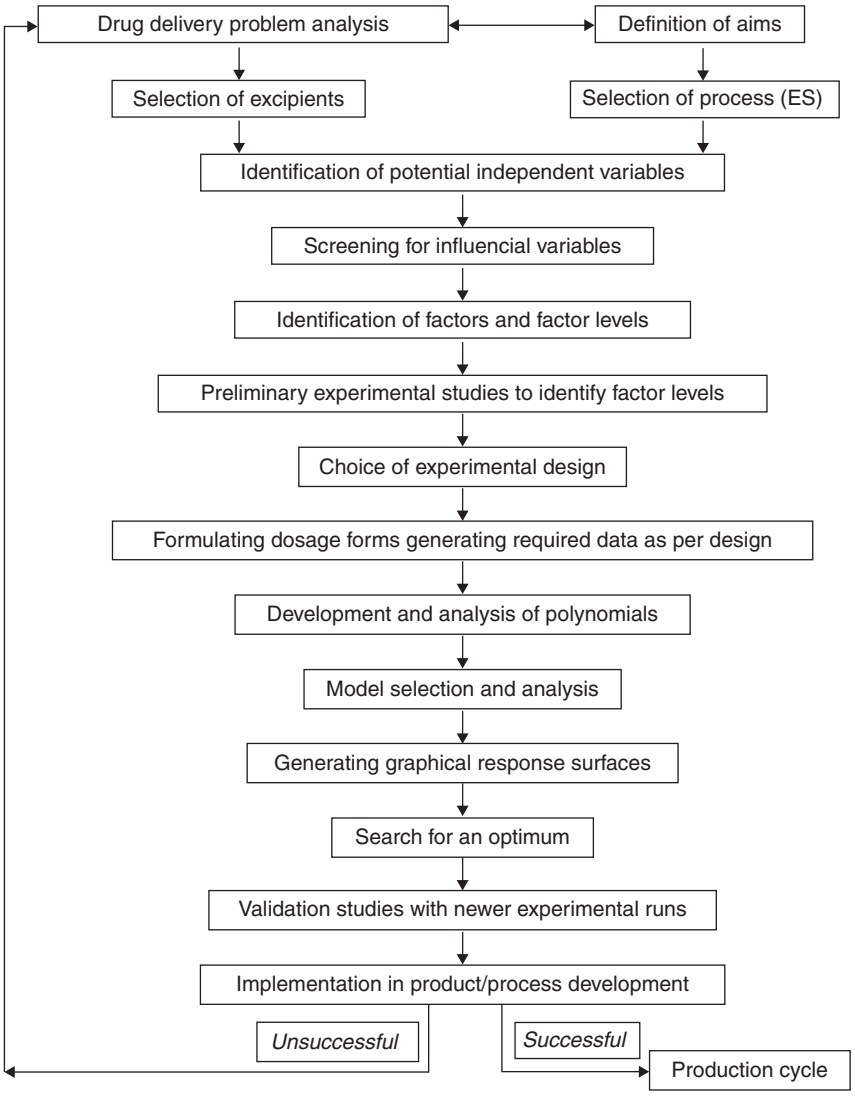


Figure 5. A bird's eye view of the overall FbD strategy during drug delivery development.
FbD: Formulation by design.

terms to correlate the studied responses with the examined variables using Design Expert software. Seven coefficients (β_1 to β_7) were calculated with β_0 representing the intercept, and β_3 to β_7 representing the various quadratic and interaction terms (Equation 1).

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1 X_2^2 + \beta_7 X_2 X_1^2 \quad (1)$$

Quite high values of R^2 of the RSM polynomial coefficients for all four responses, ranging between 0.9853 and 1, vouched their high prognostic ability.

The values of $t_{75\%}$ were found to enhance markedly from 7.1 to 12 h corresponding to the lowest and highest levels of the polymers, respectively. Somewhat linear increasing trends were observed in the values of $t_{75\%}$ with augmentation of CP and HPMC fractions (**Figure 7**). Nevertheless, the influence of CP was found to be distinctly far more significant than that of HPMC, indicating that the former has better release sustaining properties for tramadol. Hence, the higher levels of CP had to be complemented with lower levels of HPMC and vice versa to maintain the value of $t_{75\%}$ at a constant level. *In vitro* tablet dissolution studies showed non-Fickian release behavior. The values of rel_{16h} decreased significantly with increase in the polymer content. The overall rate of drug release tended to decrease with increase in the concentration of either HPMC or CP.

Ex vivo mucoadhesive strength (ρ), determined using porcine gastric mucosa using texture profile analyzer (TAX TEE 32, M/s Stable Microsystems, Surrey, UK), exhibited distinct augmentation with an increase in the amount of either polymer (CP or HPMC). As indicated in **Figure 8**, the

Table 3. Select instances of FbD optimization of various oral DDSs.

DDS	Drug	Factors	Design	Year
Nanosuspension	Simvastatin	Amounts of polymers and solvents	CCD	2011 [29]
NLCs	Valproic acid	Concentrations of aqueous and organic phases, and relative ratios of solvents	Taguchi	2010 [54]
Stomach-specific CR beads	Amoxicillin trihydrate	Amounts of drug and constituent gums	FD	2010 [55]
Pellets	Isoniazid	Amounts of granulating fluid and binder, and spheronization speed	FD	2010 [56]
Colon-targeted systems	Mesalamine	Amounts of polymers in compression coating, coating mass and coating force	BBD	2010 [57]
SR SLNs	Amikacin	Amount of lipid phase, ratio of drug:lipid and volume of aqueous phase	CCD	2010 [58]
SLNs	Vitamin K_1	Relative concentrations of surfactants	CCD	2010 [59]
Superporous hydrogel SNEDDS	Carvedilol	Amounts of lipid and HCl	FD	2010 [60]
SMEDDS	Patchoulic alcohol	Ratios of lipid, surfactant and solvents	CCD	2010 [61]
Floating-bioadhesive tablets	Tramadol	Amounts of constituents polymers	CCD	2010 [25]
Floating microspheres	Aspirin	Amount of calcium alginate	ANN	2010 [62]
SR matrix tablets	Metronidazole	Amounts of HPMC, Carbopol and Psyllum	FD	2010 [63]
SR zero order release tablets	Nimodipine	Amounts of PEG-4000, PVP K30, HPMC K100 and HPMC E50LV	ANN	2010 [50]
CR nanoparticles	Paclitaxel	Amounts of polymer and duration of ultrasonication	CCD	2010 [37]
Micro/nanoporous osmotic pump tablets	Propranolol hydrochloride	Molecular mass of pore formers (PVP K30 and PVP K90)	FD	2010 [33]
Cubosomes	Dacarbazine	Amounts of polymer and drug	BBD	2009 [64]
Proliposomes	Vinpocetine	Amounts of soybean phosphatidylcholine, cholesterol and sorbitol	CCD	2009 [65]
Ion-exchange resin beads	Losartan potassium	Drug resin complex/chitosan and percent of tripolyphosphate	FD	2009 [66]
Nanoparticles	Insulin	Concentrations of calcium chloride, chitosan, albumin	BBD	2009 [67]
Floating osmotic pump	Dipyridamol	Amounts of pore former, sodium chloride, polyoxyethylene	CCD	2009 [68]
Fast dissolving tablets	Diazepam	Amounts of PEG 4000 and PEG 6000	FD	2009 [69]
Taste-masked mouth dissolving tablet	Tramadol	Amounts of superdisintegrant and mouth-melting binder	FD	2009 [70]
SEDDS	Genistein	Amounts of lipid and surfactant	BBD	2009 [71]
Binary solid dispersions	Meloxicam	Drug:polymer ratio, kneading time	FD	2009 [72]
Mucoadhesive microspheres	Lacidipine	Polymer conc., volume of glutaraldehyde, stirring speed, crosslinking time	CCD	2009 [73]
Gastroretentive microspheres	Rosiglitazone maleate	Polymer:drug ratio, concentration of polymer, stirring speed	FD	2009 [74]
Ion exchange SR tablets	Venlafaxine HCl	Amounts of HPMC and EC	CCD	2009 [75]
Mouth dissolving film	Salbutamol	Amounts of HPMC, PVP, PVA	SLD	2009 [45]
Bioadhesive tablets	Hydralazine	Amounts of carbomer and HPMC	CCD	2009 [1]
Orodispersible tablets	Roxithromycin	Levels of modified polysaccharides	FD	2008 [76]
Polymeric microspheres	Flurbiprofen	Percentage of polyvinyl alcohol, aqueous phase conc.	CCD	2008 [77]
Gastroretentive microballoons	Famotidine	pH, drug: Eudragit S100, ethanol: dichloromethane	CCD	2008 [78]
Floating tablets	Domperidone	Amounts of HPMC, carbopol, sodium alginate	BBD	2008 [79]
Time-dependent tablets	Isosorbide 5-mononitrate	Coating levels of tablets and pellets	BBD, ANN	2008 [80]
SNEDDS	Cyclosporine	Amounts of Emulphor EI-620, Capmul MCM-C8 and 20% (w/w) CyA in sweet orange oil	BBD	2007 [81]
Solid dispersions	Rofecoxib	Drug: polymer ratio, temperature	FD	2007 [82]
SR microspheres	Enzyme	Amounts of dichloromethane and Tween 20, 40, 80	FD	2007 [83]
Coated tablets	Metoprolol tartarate	Amounts of polymer film formatting and pore generating excipients	FD	2007 [84]
Bilayer floating tablets	Metoprolol tartarate	Polymer content:drug ratio, polymer:polymer ratio	FD	2006 [85]

ANN: Artificial neural network; BBD: Box-Behnken design; CCD: Central composite design; CR: Controlled release; DDS: Drug delivery system; EC: Ethyl cellulose; FbD: Formulation by design; FD: Factorial design; HPMC: Hydroxypropylmethyl cellulose; NLC: Nanostructured liquid carrier; PVA: Polyvinyl alcohol; PVP: Polyvinyl pyrollidine; SEDDS: Self emulsifying drug delivery systems; SLD: Simplex lattice design; SLN: Solid lipid nanoparticles; SMEDDS: Self micro-emulsifying drug delivery systems;SNEDDS: Self nano-emulsifying drug delivery systems; SR: Sustained release.

Table 4. Select FbD literature instances for process optimization of various oral DDSs.

System	Drug	Factors	Design	Year
Phospholipid complex	Oxymetrine	Temperatures used in preparation of phospholipid complex	CCD	2010 [86]
Pellets	Lithium carbonate	Rotor speed, slit air flow rate, spray air rate	FD	2008 [87]
Osmotic pump	Propranolol hydrochloride	Rotation speed, ionic strength, pH	SSD	2008 [88]
Dual-CR tablets	Insulin	Rate of addition of eudragit, volume of antisolvent, compression pressure	BBD	2008 [89]
Liposomes	Lidocaine hydrochloride	Dripping rate of solution on the liposome colloidal dispersion, stirring rate	FD	2007 [90]
Floating microspheres	Cinnarizine	Stirring rate, time of stirring	FD	2007 [91]
SR tablets	Ketoprofen	pH, dissolution medium volume, stirring speed	PBD	2003 [92]

BBD: Box-Behnken design; CCD: Central composite design; CR: Controlled release; DDS: Drug delivery system; FbD: Formulation by design; FD: Factorial design; PBD: Plakett-Burman design; SR: Sustained release; SSD: Spherical symmetric design.

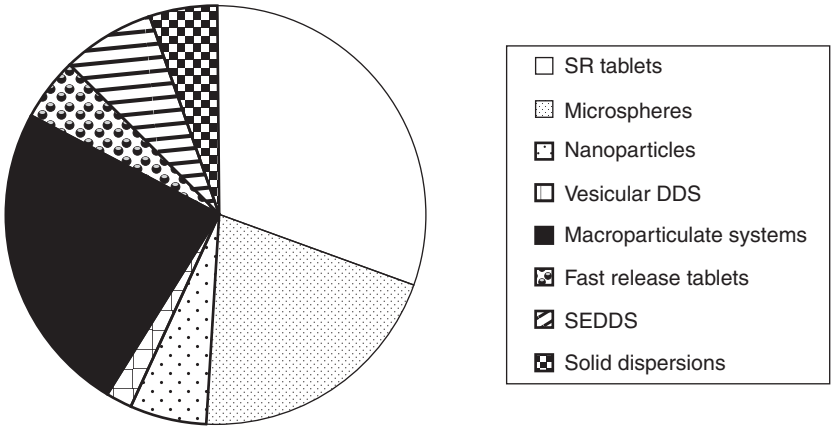


Figure 6. A comparative chart of the proportion of various oral DDSs systematically optimized using FbD.
DDS: Drug delivery system; FbD: Formulation by design.

maximum value of ρ was attained at the highest levels of both the polymers, the effect of CP being more pronounced. Buoyancy time (T_b) of the tablets increased in a linear fashion with increase in HPMC content, owing ostensibly to swelling (i.e., hydration) of the hydrocolloid particles on the tablet surface, resulting ultimately in an increase in the bulk volume. The air entrapped in the swollen polymer maintained a density less than unity and conferred buoyant character to these dosage forms. With increase in CP content, however, buoyancy time tended to decrease in a linear trend, probably due to higher density of CP (1.76 g/cc) than that of HPMC (1.28 g/cc). Maximum value of buoyancy time was discernible at the highest levels of HPMC and the lowest levels of CP, while the converse was also true to attain the minimum.

Finally, the prognosis of optimum formulation was conducted using a two-stage brute force technique using MS-Excel spreadsheet software. First, a feasible space was located and second, an exhaustive grid search was conducted to predict the possible solutions. Eight formulations were selected as the confirmatory check-points to validate the FbD. The observed and predicted responses were critically compared. Linear correlation plots and residual graphs between predicted and observed responses were constructed for the chosen eight optimized formulations. On comparison of the observed responses with those of the anticipated ones, the percent bias (= prediction error) varied between –6.9 and 5.4% with overall mean ± s.d. as -0.06 ± 0.37%. Linear correlation plots (**Figure 9**), drawn between the predicted and observed responses after forcing the line

Table 5. Select literature FbD instances using experimental design for the screening purpose.

Type	Drug(s)	Factors	Design	Year
Nanocapsules	Benzocaine	Size, polydispersion index, ζ potential, drug loading	FFD	2011 [93]
Beads	Caffeine	PEO content, microcrystalline cellulose content, water content, spheronizer speed and spheronization time	FFD	2010 [94]
Solid lipid nanoparticles	Buspirone HCl	Lipid type, surfactant percentage, speed of homogenizer, acetone:DCM ratio	Taguchi	2010 [95]
Orodispersible tablet	Ondansetron HCl	Concentrations of glycine, chitosan and drug, and tablet crushing strength	PBD	2009 [96]
Fast disintegrating tablet	Ondansetron HCl	Concentrations of aminoacetic acid and carmellose, and tablet crushing strength	PBD	2008 [97]
CR tablets	Paroxetine hydrochloride	Ratio of POLYOX:Avicel, the amount of POLYOX and Avicel, hardness, HPMCP amount, Eudragit L100 amount, and citric acid amount	PBD	2008 [98]

CR: Controlled release; DCM: Dicholoromethane; FbD: Formulation by design; FFD: Fractional factorial design; PBD: Plackett-Burman design; PEO: Polyethylene oxide.

Table 6. Factor combinations as per the chosen experimental design.

Experimental trial no.	Coded factor levels	
	X_1	X_2
1	-1	-1
2	-1	0
3	-1	1
4	0	-1
5	0	0
6	0	1
7	1	-1
8	1	0
9	1	1
10	0	0
11	0	0
12	0	0
13	0	0

Translation of coded levels in actual units

Coded Level	-1	0	1
X_1: CP (mg)	80	120	160
X_2: HPMC (mg)	125	150	175

through the origin, also demonstrated high values of r (0.9819 – 0.9981), indicating excellent goodness of fit in each case ($p < 0.001$). The corresponding residual plots showed nearly uniform and random scatter around the mean values of response variables.

The formulation containing the optimized polymer blend was selected by 'trading off' various response variables and adopting the following maximizing criteria: $t_{75\%} \geq 7.1$ h; $rel_{16\ h} > 89\%$; $\rho > 8.0$ g and $T_b > 8.5$ h. On comprehensive evaluation of grid searches, the formulation (CP: 80 mg and HPMC: 125 mg) fulfilled the optimal criteria of best regulation of the release rate, floating and bioadhesive characteristics.

Drug release from the optimized formulation at 12 h (88.15%) was found to be quite comparable to that of the marketed brand, Dolfre™ SR (88.41%). Also, the release parameters such as $t_{70\%}$, $rel_{16\ h}$, MDT, K and *n* were quite analogous to each other. Further, the values of similarity factor, f_2, at periodic intervals of 8 h of both the marketed formulations with relation to the optimized formulation, ranged between 70.16 and 75.49, unambiguously corroborating the sameness of the release profiles. Thus, the studies indicated successful development of CR formulation of tramadol capable of maintaining comparable drug release profile to that of the marketed CR product, and possessing definite gastroretentive potential to retain the drug at its preferred site of absorption in the GI tract.

11. Expert opinion

Oral DDSs, both novel and conventional, have proved their immense worth in regulating drug release behavior, targeting drug molecules to particular organ(s), augmenting rate and/or extent of bioavailability and improving patient compliance. Formulation development of such systems, however, has become much more intricate, involving greater deal of resources. To circumvent these developmental hiccups, formulation of such systems using experimental designs is prudently called for. With rising awareness of their knowhow, the utility of experimental designs has now permeated tangibly into myriad disciplines of medicine, dentistry, engineering, technology, industry and research, both fundamental and applied., DoE together with QbD being the terms widely applied today to diverse technologies, we propose an apposite cliché specific to drug formulation development, that is, FbD. The FbD methodology, therefore, tends to encompass in its ambit a

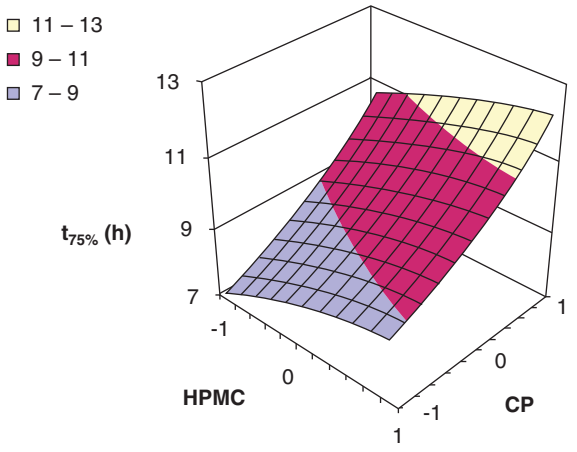


Figure 7. Response surface plot showing the influence of CP and HPMC on the value of $t_{75\%}$ of floating-bioadhesive tablet formulations of tramadol [25].

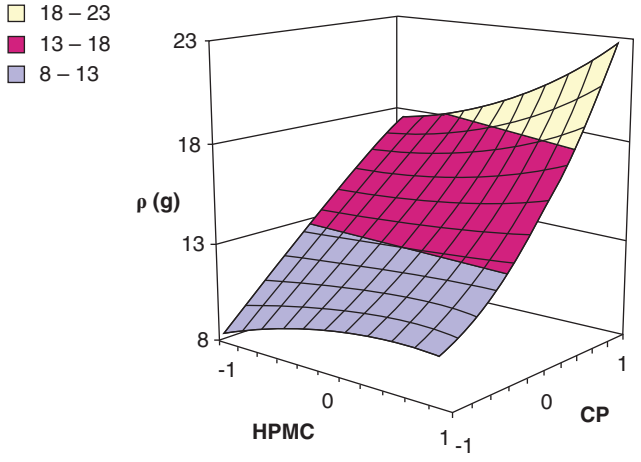


Figure 8. Response surface plot showing the influence of CP and HPMC on the value of bioadhesive strength (ρ) of floating-bioadhesive tablet formulations of tramadol [25].

rational usage of DoE approach to formulate quality DDS effectively and cost-effectively and ultimately endeavoring to accomplish the QbD objectives.

FbD using experimental designs has been applied with fruition almost on all the kinds of oral DDS, for optimizing not only the 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) excipient or process parameter(s). In the pharma industrial set up, in particular, a product development scientist can derive unique benefits of FbD for the development of innovator's brand name as well as the generic drug products. Understanding the formulation or process variables rationally, using FbD, can greatly help in achieving the desired goals with phenomenal ease. As a rule, when finding the correct compromise is not straightforward, a pharmaceutical scientist should mandatorily consider the use of FbD.

As with any other coherent scientific methodology, FbD also requires a thorough envisioning of the formulation development exercise as a whole, from the transition of laboratory scale development to pilot plant, and to scale-up into a robust and stable drug product. The more the formulators know about the system, the better they can define it, and the higher precision they can monitor it with. The difficulties in optimizing an oral DDS using FbD are due to the difficulties in understanding the real cause and effect relationship. The 'process understanding' is the keystone of FbD initiatives. Execution of FbD techniques, therefore, allows gaining the requisite conception of how CFAs and CPPs tend to impact CQAs, and eventually, the holistic product performance during laboratory scale, scale-up and production of exhibit batches. Defining such relationships between these formulation or process variables and quality traits of the formulation is almost an impossible task without apt application of an FbD model. Trial and error OVAT methods, in this regard, would have never allowed the formulator to know how close any particular formulation is to the optimal drug delivery solution.

Notwithstanding the enormous benefits of FbD, one should not consider it as a magic potion for all the product development problems. Despite the well-established applications of FbD in drug delivery development, its successful execution will not only depend on the precision and enormity of the input data, but also on the choice of suitable experimental design and experimental domain. An inept experimental design can adversely affect the predictive ability, while an unsuitable experimental range may either miss the optimum or require much greater experimentation to locate it. A 'designed' product or process, therefore, enhances the system information, instead of merely acting as a surrogate to the experience. The capabilities of FbD, accordingly, have to be amalgamated with the human prowess of the formulation scientist, leading eventually to the 'best' product and economics, in terms of money, human resources, materials, machines and time. Many a time, the rigors of screening and factor influence studies can also be evaded, as the influential variables can be selected using experience and observation as the twin surrogates. Thus, FbD tends to expedite the formulation process by augmenting (rather than replacing) the much-needed formulation skills, creativity and product knowledge. Principally, while working in an industrial milieu, it is highly advisable to confine within the chosen 'design space'; else, it may call for

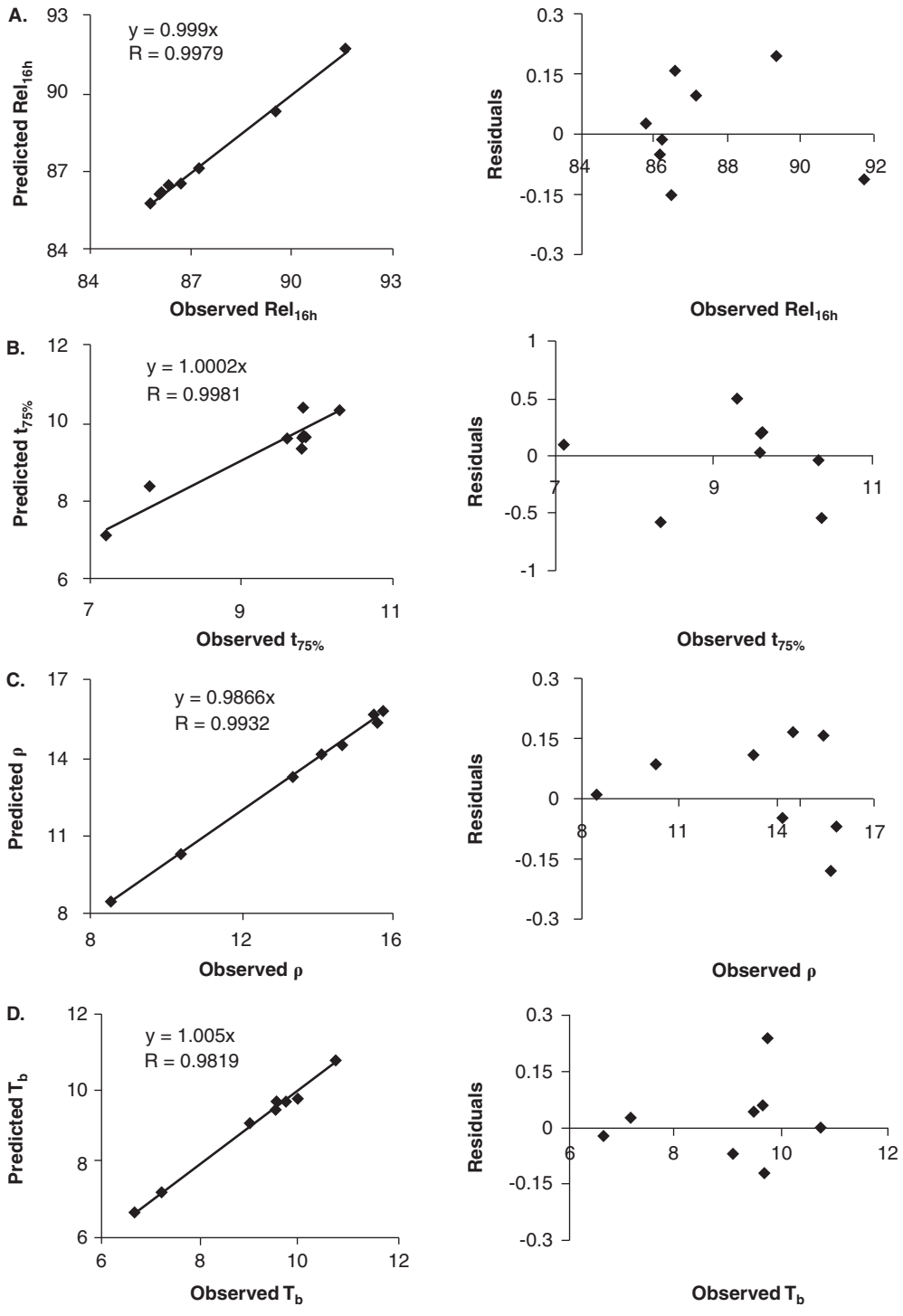


Figure 9. Linear and residual plots between observed and predicted values of (**A**) Rel_{16h}, (**B**) $t_{75\%}$, (**C**) ρ and (**D**) T_b [25].

compliance to the regulatory post-approval change requirements.

Though the practice of systematic development of oral DDSs has undoubtedly spiced up over the past a few decades, it is far from being adopted as a standard practice. Several more initiatives, therefore, need to be undertaken to underscore the growing utility of FbD before this can happen perceptibly. The current paper highlights the FbD applications, methodology and potential cautions and is an endeavor towards the same.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Singh B, Pahuja S, Kapil R, et al. Formulation development of oral controlled release tablets of hydralazine: optimization of drug release and bioadhesive characteristics. Acta Pharm 2009;59(1):1-13
2. Singh B, Kumar R, Ahuja N. Optimizing drug delivery systems using "Design of Experiments" Part 1: fundamental aspects. Crit Rev Ther Drug Carrier Syst 2005;22:27-106

•• **Deals with all the salient aspects of DoE such as extensive explanation of terms used, the experimental designs, optimization methodology and application of computers in DoE.**

3. Dhawan S, Kapil R, Singh B. Formulation development and systematic optimization of solid lipid nanoparticles of quercetin for improved brain delivery. J Pharm Pharmacol 2011;63:342-51
4. Doornbos DA, Haan P. Optimization techniques in formulation and processing. In: Swarbrick J, Boylan JC. editors. Encyclopedia of Pharmaceutical Technology. Marcel Dekker; New York; 1995. p. 77-160
5. Schwartz JB, Connor RE. Optimization techniques in pharmaceutical formulation and processing. In: Banker GS, Rhodes CT. editors. Modern Pharmaceutics. Marcel Dekker; New York; 1996. p. 727-52

• **An excellent reference for using systematic optimization techniques.**

6. Singh B, Mehta G, Kumar R, et al. Design, development and optimization of nimesulide-loaded loiposomal systems for topical application. Curr Drug Deliv 2005;2:143-53

• **A discussion of numerous applications of Design of Experiments specifically to drug delivery systems including oral drug delivery systems.**

7. Lewis GA. Optimization methods. In: Swarbrick J, Boylan JC. editors. Encyclopedia of Pharmaceutical Technology. Marcel Dekker; New York; 2002. p. 1922-37
8. Yu LX. Pharmaceutical quality by design: product and process development, understanding, and control. Pharm Res 2008;25(4):781-91

• **Deals with salient aspects of QbD as applicable to drug delivery development.**

9. Huang J, Kaul G, Cai C, et al. Quality by design case study: an integrated multivariate approach to drug product and process development. Int J Pharm 2009;382(1-2):23-32
10. Skrdla PJ, Wang T, Antonucci V, et al. Use of a quality-by-design approach to justify removal of the HPLC weight % assay from routine API stability testing protocols. J Pharm Biomed Anal 2009;50(5):794-6
11. Verma S, Lan Y, Gokhale R, et al. Quality by design approach to understand the process of nanosuspension preparation. Int J Pharm 2009;377(1-2):185-98
12. Cogdill RP, Drennen JK. Risk-based Quality by Design (QbD): A taguchi perspective on the assessment of product quality, and the quantitative linkage of drug product parameters and clinical performance. J Pharm Innov 2008;3:23-39
13. International Conference on Harmonisation; guidance on Q8(R1) pharmaceutical development; addition of annex; availability. Notice. Fed Regist 2009;74(109):27325-6
14. Nasr MN. Implementation of quality by design (QbD): status, challenges, and next steps. FDA advisory committee for pharmaceutical science. Available from: http://wwwfdagov/ohrms/dockets/ac/06/slides/2006-4241s1_6ppt [Acessed on 30 December 2010]
15. Yu LX. Implementation of quality-by-design: OGD initiatives. FDA advisory committee for pharmaceutical science. Available from: http://wwwfdagov/ohrms/dockets/ac/06/slides/2006-4241s1_8ppt [Acessed on 03 January 2011]
16. ICH Draft consensus guideline: pharmaceutical development annex to Q8. Available from: http://www.ich.org/LOB/media/MEDIA4349.pdf [Acessed on 29 December 2010]
17. Lionberger RA, Lee SL, Lee L, et al. Quality by design: concepts for ANDAs. AAPS J 2008;10(2):268-76
18. Ivic B, Ibric S, Cvetkovic N, et al. Application of design of experiments and multilayer perceptrons neural network in the optimization of diclofenac sodium extended release tablets with Carbopol 71G. Chem Pharm Bull (Tokyo) 2010;58(7):947-9
19. Nekkanti V, Muniyappan T, Karatgi P, et al. Spray-drying process optimization for manufacture of drug-cyclodextrin complex powder using design of experiments. Drug Dev Ind Pharm 2009;35(10):1219-29
20. Cahyadi C, Heng PW, Chan LW. Optimization of process parameters for a quasi-continuous tablet coating system using Design of Experiments. AAPS PharmSciTech 2011;12(1):119-31
21. Patel MM, Amin AF. Design and optimization of colon-targeted system of theophylline for chronotherapy of nocturnal asthma. J Pharm Sci 2011;100(5):1760-72
22. Shamma RN, Basalious EB, Shoukri RA. Development and optimization of a multiple-unit controlled release formulation of a freely water soluble drug for once-daily administration. Int J Pharm 2011;405(1-2):102-12
23. Barmpalexis P, Kachrimanis K, Georgarakis E. Solid dispersions in the development of a nimodipine floating tablet formulation and optimization by artificial neural networks and genetic programming. Eur J Pharm Biopharm 2011;77(1):122-31
24. Sharma S, Sharma N, Das Gupta G. Optimization of promethazine theoclate fast dissolving tablet using pore forming technology by 3-factor, 3-level response surface-full factorial design. Arch Pharm Res 2010;33(8):1199-207
25. Singh B, Rani A, Babita, et al. Formulation optimization of hydrodynamically balanced oral controlled release bioadhesive tablets of

tramadol hydrochloride. Sci Pharm 2010;78:303-23

- **Described as the case study.**

26. Huang J, Goolcharran C, Ghosh K. A Quality by Design approach to investigate tablet dissolution shift upon accelerated stability by multivariate methods. Eur J Pharm Biopharm 2011;78(1):141-50
27. Q8R2: Pharmaceutical Development. ICH Harmonised Tripartite Guideline: International Conference on Harmaonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2009

- **Provides information on federal perspectives of QbD.**

28. Murphy JR. Screening designs. In: Chow SC. editor. Encyclopedia of Biopharmaceutical statistics. Marcel Dekker; New York: 2003
29. Shah M, Chuttani K, Mishra AK, et al. Oral solid compritol 888 ATO nanosuspension of simvastatin: optimization and biodistribution studies. Drug Dev Ind Pharm 2011;37(5):526-37
30. Shirsand SB, Suresh S, Jodhana LS, et al. Formulation design and optimization of fast disintegrating Lorazepam tablets by effervescent method. Indian J Pharm Sci 2010;72(4):431-6
31. Gohel MC, Parikh RK, Nagori SA, et al. Fabrication and evaluation of bi-layer tablet containing conventional paracetamol and modified release diclofenac sodium. Indian J Pharm Sci 2010;72(2):191-6
32. Aboelwafa AA, Basalious EB. Optimization and in vivo pharmacokinetic study of a novel controlled release venlafaxine hydrochloride three-layer tablet. AAPS PharmSciTech 2010;11(3):1026-37
33. Tuntikulwattana S, Mitrevej A, Kerdcharoen T, et al. Development and optimization of micro/nanoporous osmotic pump tablets. AAPS 2010;11(2):924-35
34. Zhang Y, Geng Y. Preparation of sinomenine hydrochloride delayed-onset sustained-release tablets. Zhongguo Zhong Yao Za Zhi 2010;35(6):703-7
35. Westerhuis JA, Coenegracht PMJ. Multivariate modelling of the pharmaceutical two step process of wet granulation and tabletting with multiblock partial least squares. Chemometrics 1997;11:372-92
36. Bolton S. Factorial designs. Pharmaceutical statistics: practical and clinical applications. 3rd edition. Marcel Dekker; New York: 1997
37. Kollipara S, Bende G, Movva S, et al. Application of rotatable central composite design in the preparation and optimization of poly(lactic-co-glycolic acid) nanoparticles for controlled delivery of paclitaxel. Drug Dev Ind Pharm 2010;36(11):1377-87
38. Singh B, Ahuja N. Response surface optimization of drug delivery systems. In: Jain NK. editor. Progress in controlled and novel drug delivery systems. 1st edition. CBS Publishers; New Delhi; 2004. p. 470-509
39. Kincl M, Turk S, Vrecer F. Application of experimental design methodology in development and optimization of drug release method. Int J Pharm 2005;291(1-2):39-49
40. Sousa JJ, Sousa A, Moura MJ, et al. The influence of core materials and film coating on the drug release from coated pellets. Int J Pharm 2002;233(1-2):111-22
41. Sousa JJ, Sousa A, Podczeck F, et al. Factors influencing the physical characteristics of pellets obtained by extrusion-spheronization. Int J Pharm 2002;232(1-2):91-106
42. Lundqvist AE, Podczeck F, Newton JM. Compaction of, and drug release from, coated drug pellets mixed with other pellets. Eur J Pharm Biopharm 1998;46(3):369-79
43. Hogan J, Shue PI, Podczeck F, et al. Investigations into the relationship between drug properties, filling, and the release of drugs from hard gelatin capsules using multivariate statistical analysis. Pharm Res 1996;13(6):944-9
44. Vaghani SS, Patel SG, Jivani RR, et al. Design and optimization of a stomach-specific drug delivery system of repaglinide: application of simplex lattice design. 2010; In print
45. Gohel MC, Parikh RK, Aghara PY, et al. Application of simplex lattice design and desirability function for the formulation development of mouth dissolving film of salbutamol sulphate. Curr Drug Deliv 2009;6(5):486-94
46. Shah PP, Mashru RC, Rane YM, et al. Design and optimization of artemether microparticles for bitter taste masking. Acta Pharm 2008;58(4):379-92
47. Leonardi D, Salomon CJ, Lamas MC, et al. Development of novel formulations for Chagas' disease: optimization of benznidazole chitosan microparticles based on artificial neural networks. Int J Pharm 2009;367(1-2):140-7
48. Zhang XY, Chen DW, Jin J, et al. Artificial neural network parameters optimization software and its application in the design of sustained release tablets. Yao Xue Xue Bao 2009;44(10):1159-64
49. Gohel M, Nagori SA. Fabrication and evaluation of captopril modified-release oral formulation. Pharm Dev Technol 2009;14(6):679-86
50. Barmpalexis P, Kanaze FI, Kachrimanis K, et al. Artificial neural networks in the optimization of a nimodipine controlled release tablet formulation. Eur J Pharm Biopharm 2010;74(2):316-23
51. Miyazaki Y, Yakou S, Yanagawa F, et al. Evaluation and optimization of preparative variables for controlled-release floatable microspheres prepared by poor solvent addition method. Drug Dev Ind Pharm 2008;34(11):1238-45
52. Lewis GA, Mathieu D, Phan-Tan-Luu R. Pharmaceutical experimental design. In: Singh B, Ahuja N, editors. Book Review on "Pharmaceutical Experimental Design". 1st edition. Marcel Dekker, New York. 2000. Int J Pharm 1999;195:247-8
53. Myers WR. Response surface methodology. In: Chow SC. editor. Encyclopedia of Biopharmaceutical statistics. Marcel Dekker; New York: 2003
54. Varshosaz J, Eskandari S, Tabakhian M. Production and optimization of valproic acid nanostructured lipid carriers by the Taguchi design. Pharm Dev Technol 2010;15(1):89-96
55. Narkar M, Sher P, Pawar A. Stomach-specific controlled release gellan beads of acid-soluble drug prepared by ionotropic gelation method. AAPS PharmSciTech 2010;11(1):267-77
56. Pund S, Joshi A, Vasu K, et al. Multivariate optimization of formulation and process variables influencing physico-mechanical characteristics of

site-specific release isoniazid pellets. Int J Pharm 2010;388(1-2):64-72

57. Patel NV, Patel JK, Shah SH. Box-Behnken experimental design in the development of pectin-compritol ATO 888 compression coated colon targeted drug delivery of mesalamine. Acta Pharm 2010;60(1):39-54

58. Varshosaz J, Ghaffari S, Khoshayand MR, et al. Development and optimization of solid lipid nanoparticles of amikacin by central composite design. J Liposome Res 2010;20(2):97-104

59. Liu CH, Wu CT, Fang JY. Characterization and formulation optimization of solid lipid nanoparticles in vitamin K1 delivery. Drug Dev Ind Pharm 2010;36(7):751-61

60. Mahmoud EA, Bendas ER, Mohamed MI. Effect of formulation parameters on the preparation of superporous hydrogel self-nanoemulsifying drug delivery system (SNEDDS) of carvedilol. AAPS PharmSciTech 2010;11(1):221-5

61. You X, Wang R, Tang W, et al. Self-microemulsifying drug delivery system of patchoulic alcohol to improve oral bioavailability in rats. Zhongguo Zhong Yao Za Zhi 2010;35(6):694-8

62. Zhang AY, Fan TY. Optimization of calcium alginate floating microspheres loading aspirin by artificial neural networks and response surface methodology. Beijing Da Xue Xue Bao 2010;42(2):197-201

63. Asnaashari S, Khoei NS, Zarrintan MH, et al. Preparation and evaluation of novel metronidazole sustained release and floating matrix tablets. Pharm Dev Technol 2011;16(4):400-7

64. Bei D, Marszalek J, Youan BB. Formulation of dacarbazine-loaded cubosomes-part I: influence of formulation variables. AAPS PharmSciTech 2009;10(3):1032-9

65. Xu H, He L, Nie S, et al. Optimized preparation of vinpocetine proliposomes by a novel method and in vivo evaluation of its pharmacokinetics in New Zealand rabbits. J Control Release 2009;140(1):61-8

66. Madgulkar A, Bhalekar M, Swami M. In vitro and in vivo studies on chitosan beads of losartan Duolite AP143 complex, optimized by using statistical experimental design. AAPS PharmSciTech 2009;10(3):743-51

67. Woitiski CB, Veiga F, Ribeiro A, et al. Design for optimization of nanoparticles integrating biomaterials for orally dosed insulin. Eur J Pharm Biopharm 2009;73(1):25-33

68. Zhang ZH, Tang X, Peng B, et al. Optimization of a floating osmotic pump system of dipyridamole using central composite design-response surface methodology. Yao Xue Xue Bao 2009;44(2):203-7

69. Giri TK, Sa B. Statistical evaluation of influence of polymers concentration on disintegration time and diazepam release from quick-disintegrating rapid release tablet. Yakugaku Zasshi 2009;129(9):1069-75

70. Madgulkar AR, Bhalekar MR, Padalkar RR. Formulation design and optimization of novel taste masked mouth-dissolving tablets of tramadol having adequate mechanical strength. AAPS PharmSciTech 2009;10(2):574-81

71. Zhu S, Hong M, Liu C, et al. Application of Box-Behnken design in understanding the quality of genistein self-nanoemulsified drug delivery systems and optimizing its formulation. Pharm Dev Technol 2009;14(6):642-9

72. Ghareeb MM, Abdulrasool AA, Hussein AA, et al. Kneading technique for preparation of binary solid dispersion of meloxicam with poloxamer 188. AAPS PharmSciTech 2009;10(4):1206-15

73. Sultana S, Bhavna, Iqbal Z, et al. Lacidipine encapsulated gastroretentive microspheres prepared by chemical denaturation for pylorospasm. J Microencapsul 2009;26(5):385-93

74. Rao MR, Borate SG, Thanki KC, et al. Development and in vitro evaluation of floating rosiglitazone maleate microspheres. Drug Dev Ind Pharm 2009;35(7):834-42

75. Madgulkar AR, Bhalekar MR, Kolhe VJ, et al. Formulation and optimization of sustained release tablets of venlafaxine resinates using response surface methodology. Indian J Pharm Sci 2009;71(4):387-94

76. Sharma V, Philip AK, Pathak K. Modified polysaccharides as fast disintegrating excipients for orodispersible tablets of roxithromycin. AAPS PharmSciTech 2008;9(1):87-94

77. Coimbra PA, De Sousa HC, Gil MH. Preparation and characterization of flurbiprofen-loaded poly(3-hydroxybutyrate-co-3-hydroxyvalerate) microspheres. J Microencapsul 2008;25(3):170-8

78. Gupta R, Pathak K. Optimization studies on floating multiparticulate gastroretentive drug delivery system of famotidine. Drug Dev Ind Pharm 2008;34(11):1201-8

79. Prajapati ST, Patel LD, Patel DM. Gastric floating matrix tablets: design and optimization using combination of polymers. Acta Pharm 2008;58(2):221-9

80. Xie H, Gan Y, Ma S, et al. Optimization and evaluation of time-dependent tablets comprising an immediate and sustained release profile using artificial neural network. Drug Dev Ind Pharm 2008;34(4):363-72

81. Zidan AS, Sammour OA, Hammad MA, et al. Quality by design: understanding the formulation variables of a cyclosporine A self-nanoemulsified drug delivery systems by Box-Behnken design and desirability function. Int J Pharm 2007;332(1-2):55-63

82. Shah TJ, Amin AF, Parikh JR, et al. Process optimization and characterization of poloxamer solid dispersions of a poorly water-soluble drug. AAPS PharmSciTech 2007;8(2):Article 29

83. Rawat M, Saraf S. Influence of selected formulation variables on the preparation of enzyme-entrapped Eudragit S100 microspheres. AAPS PharmSciTech 2007;8(4):E116

84. Tomuta I, Leucuta SE. The influence of formulation factors on the kinetic release of metoprolol tartrate from prolong release coated minitablets. Drug Dev Ind Pharm 2007;33(10):1070-7

85. Narendra C, Srinath MS, Babu G. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. AAPS PharmSciTech 2006;7(2):E34

86. Yue PF, Yuan HL, Li XY, et al. Process optimization, characterization and evaluation in vivo of oxymatrine-phospholipid complex. Int J Pharm 2010;387(1-2):139-46

87. Beretzky A, Antal I, Karsai J, et al. Optimatization of pellet preparation is CF-granulator with factorial design. Acta Pharm Hung 2008;78(1):37-43

88. Wang C, Chen F, Li JZ, et al. Novel osmotic pump tablet using core of drug-resin complexes for time-controlled delivery system. Yakugaku Zasshi 2008;128(5):773-82

89. Agarwal V, Nazzal S, Khan MA. Optimization and in vivo evaluation of an oral dual controlled-release tablet dosage form of insulin and duck ovomucoid. Pharm Dev Technol 2008;13(4):291-8

90. Gonzalez-Rodriguez ML, Barros LB, Palma J, et al. Application of statistical experimental design to study the formulation variables influencing the coating process of lidocaine liposomes. Int J Pharm 2007;337(1-2):336-45

91. Varshosaz J, Tabbakhian M, Zahrooni M. Development and characterization of floating microballoons for oral delivery of cinnarizine by a factorial design. J Microencapsul 2007;24(3):253-62

92. Furlanetto S, Maestrelli F, Orlandini S, et al. Optimization of dissolution test precision for a ketoprofen oral extended-release product. J Pharm Biomed Anal 2003;32:159-65

93. Moraes CM, de Matos AP, Grillo R, et al. Screening of formulation variables for the preparation of poly(epsilon-caprolactone) nanocapsules containing the local anesthetic benzocaine. J Nanosci Nanotechnol 2011;11(3):2450-7

94. Mallipeddi R, Saripella KK, Neau SH. Use of coarse ethylcellulose and PEO in beads produced by extrusion-spheronization. Int J Pharm 2010;385(1-2):53-65

95. Varshosaz J, Tabbakhian M, Mohammadi MY. Formulation and optimization of solid lipid nanoparticles of buspirone HCl for enhancement of its oral bioavailability. J Liposome Res 2010;20(4):286-96

96. Goel H, Vora N, Tiwary AK, et al. Formulation of orodispersible tablets of ondansetron HCl: investigations using glycine-chitosan mixture as superdisintegrant. Yakugaku Zasshi 2009;129(5):513-21

97. Goel H, Vora N, Rana V. A novel approach to optimize and formulate fast disintegrating tablets for nausea and vomiting. AAPS PharmSciTech 2008;9(3):774-81

98. Jin SJ, Yoo YH, Kim MS, et al. Paroxetine hydrochloride controlled release POLYOX matrix tablets: screening of formulation variables using Plackett-Burman screening design. Arch Pharm Res 2008;31(3):399-405

Affiliation

Bhupinder Singh[†1] M Pharm PhD DSt,
Rishi Kapil[3] M Pharm,
Mousumi Nandi[3] M Pharm &
Naveen Ahuja[2] M Pharm PhD
[†]Author for correspondence
[1]Professor (Pharmaceutics and Pharmacokinetics),
Panjab University,
University Institute of Pharmaceutical Sciences,
UGC Centre of Advanced Studies,
Dean Alumni, Chandigarh 160 014,
India
Tel: +91 172 2534103;
E-mail: bsbhoop@yahoo.com
[2]Dr Reddy's Laboratories Ltd,
Hyderabad,
India
[3]Panjab University,
University Institute of Pharmaceutical Sciences,
UGC Centre of Advanced Studies,
Chandigarh 160 014,
India