Chapter

Formulation by Design: An Overview

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Abstract

Quality is the most important and necessary attribute for pharmaceutical product development, and it has become the focus of regulatory bodies in order to approve safe, efficacious, stable, patient-compliance, and cost-effective drug delivery systems. QbD-based formulation development is discovered to be an immerging technique in this context. FbD is a formulation development concept that aims to create more effective, safe, robust, cost-effective, and patient-compliant drug delivery systems. This chapter will provide an overview of Formulation by Design (FbD), different terminologies, design of experiment (DoE) and quality by design (QbD), types of experimental design, QbD applications, and FbD methodology along with benefits.

Keywords: formulation by design (FbD), quality by design (Qbd), Design of Experiment (DoE), drug delivery systems

1. Introduction

Quality is the most crucial and essential attribute for pharmaceutical product development, and it has become the thrust area for the regulatory bodies to approve safe, efficacious, stable, patient-compliance and economical drug delivery systems. It is important to recognize that "The Quality cannot be tested into products; i.e., quality should be build in by design". In this context, QbD-based formulation development is found to be an immerging technique. Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach, published in 2004, describes the Quality by Design approach, which was approved by the FDA. Detailed specifications for pharmaceutical product quality are provided in International Conference on Harmonization (ICH) Q8 pharmaceutical development, Q9 quality risk assessment, and Q10 pharmaceutical quality system. QbD and DoE strategies aid in the implementation of ICH/Q8 and ICH/Q9 [1]. Pharmaceutical Quality by Design (QbD) begins the systematic development of product(s) and process(es) with desired quality based on the Juran's Quality philosophy. The QbD philosophy, which is a patient-centric approach, prioritizes patient safety by designing drug products with enhanced quality and decreased manufacturing costs by planning quality early to prevent quality crises [2]. ICH guidance Q8 (R2) describes QbD as, "a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and

process control, based on sound science and quality risk management" [3]. Quality by design is an approach that aims to ensure the quality of medicines by employing statistical, analytical and risk-management methodology in the design, development and manufacturing of medicines. The identification, justification, and management of all sources of variability impacting a process are some of the objectives of quality by design. This enables the finished medicine to consistently meet its predefined characteristics from the start - so that it is 'right first time' [4]. The OFAT-method (one-factor-at-a-time) was the conventional strategy for ensuring and sustaining product quality. It was an empirical technique based on trial and error and built on the *ceteris paribus* principle. This method included the risk of accounting for the potential occurrence of unanticipated, out-of-specification results due to inadequate product and process understanding, both during process optimization and at the validation stage [5]. In these OVAT experiments, the first variable is fixed at a specified value, and each subsequent variable is investigated until no more improvement in the response variable is shown (s). In a summary, the OVAT technique has shown to be insignificant in terms of effort, time, and money as well as unable to offer the true answer by correcting the errors; the results continue to be unpredictable and sometimes even unsuccessful [6]. Recently, whether in industrial practice or in the research milieu, a comprehensive and rigorous approach of pharmaceutical quality by design (QbD) has become popular throughout drug product development [3, 6–9]. **Table 1** provides a brief representation of the advantages of FbD over OVAT methodology. DoE along with QbD having much wider applicability in recent trends in the Pharma industrial as well as in the research milieu, an appropriate term has evolved specifically in development of pharmaceutical dosage form, that is, "Formulation by Design (FbD)". The FbD methodology, therefore, tends to encompass in its purview a rational usage of DoE approach to design more efficacious, safe, robust, economical and patient-compliant Drug Delivery System to accomplish the QbD objectives. The FbD technique is remarkable for its ability to forecast formulation performance as well as

Attributes	OVAT	FbD
Choice of optimum formulation	May result only in sub-optimal solutions	Produces the optimum formulation possible.
Interaction among the ingredients	Inept to reveal possible interactions	Estimates any synergistic or antagonistic interaction among constituents
Scale-up and postapproval changes	Extremely challenging to design formulations that just slightly deviate from the ideal formulation, especially after Level II	All response variables are quantitatively controlled by a set of input variables, making it simple to incorporate changes in the optimal formulation
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	Incredibly time-consuming because each product must have its performance analyzed independently	Can use model equations to simulate the behavior of the product or process

Table 1.
Comparison of OVAT (one-factor-at-a-time) and FbD (formulation by design) methodology.

identify and calculate potential interactions and synergy between variables. FbD helps to fully comprehend the formulation system, and can trace and rectify a "problem" in a remarkably easier manner. As a result, the FbD technique frequently includes a reasonable application of the DoE approach to create high-quality drug products in an efficient and economical manner, endeavoring ultimately to achieve the QbD objectives [10].

2. FbD Teminology

During FbD practice, specific terminology, both technical and non-technical, is usually used. Important terms have been compiled in **Table 2** to facilitate better understanding of FbD of oral DDS precepts. Prior to applying FbD, it is critical to be familiar with FbD terminology and have prior multidisciplinary knowledge on various possible products and process variables. Therefore, it is necessary to separate a "knowledge space," or a whole worth exploring area, from the potential large ocean of scientific material based on prior knowledge. As a result, a "knowledge space" includes all the product and process variables that could even slightly affect the final product's quality. A "design space" must be defined as a subset construct of a "knowledge space" to ensure the best possible performance of a process or product using a "chosen few" key variables. This "design space" is used to further derive the "control space," which is the experimental area reserved for in-depth research when studies are conducted within narrower ranges of input variables. It is also known as "control tactic" on occasion. The knowledge space is transformed into the control space using a methodical strategy on archived data in the "design space" [11]. For relatively complex DDSs, extensive experimentation may be required to eliminate uncertainty and justify a design space greater than that needed for traditional formulation systems like tablets. Working within the design space would not begin any post-approval change process in accordance with federal regulations because it is not regarded as a "change" [3]. **Figure 1** depicts the order of importance in the knowledge, design, and control spaces.

3. FbD methodology

The theme of FbD optimization methodology provides thorough and thought-through information on diverse aspects, organized in a five-step sequence, as schematically depicted in **Figure 2**.

- **Step I: Ascertaining Drug Product Objective(s):** A quality target product profile (QTPP) is embarked upon encompassing the fundamental information of the product to be prepared or aspired as "goal-setting" exercise through brain storming among the team members cutting across industrial disciplines. Various critical quality attributes (CQAs), or response variables, which pragmatically epitomize the objective(s), are earmarked for the purpose. All the independent product/process variables are also listed likewise.

- **Step II: Prioritizing Input Variables for Optimization:** The critical material attributes (CMAs) and critical process parameters (CPPs), which directly influence the CQAs, represent the product quality are prioritized. Prioritization

Term	Definition
Antagonism	Undesired negative change due to interaction among factors.
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.
Categorical variables	Qualitative variables which cannot be quantified.
Coding (or normalization)	Process of transforming a natural variable into a non-dimensional coded variable.
Confounding	Lack of orthogonality.
Constraints	Restrictions imposed on the factor levels.
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.
Control space	Domain of design space selected for detailed controlled strategy.
Control strategy	A planned set of controls that ensures process performance and product quality and is derived from current product and process information. Controls may include facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. They may also include parameters and attributes related to drug substance and drug product materials and components.
Critical Formulation Attributes	Formulation parameters affecting critical quality attribute.
Critical Process Parameters	A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.
Critical Quality Attributes	A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
Design Matrix	Layout of experimental runs in matrix form as per experimental design.
Design Space	The demonstrated multidimensional combination and interaction of process factors (such as material qualities) and input variables that can guarantee quality. Change is not regarded as occurring when working within the design space. Exiting the design space is seen as a change and ordinarily starts a regulatory post-approval change process. The applicant submits a design space proposal, which is subject to regulatory review and approval.
Effect	The magnitude of the change in response caused by varying the factor level(s).
Empirical Model	Mathematical model describing factor–response relation using polynomial equations.
Experimental Domain	Part of the factor space, investigated experimentally for optimization.
Factors	Independent variables, which tend to influence the product/process characteristics or output of the process.
Factor Space	Dimensional space defined by the coded variables.
Formal Experimental Design	A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as "Design of Experiments".
Independent Variables	Input variables, which are directly under the control of the product development scientist.

Term	Definition
Interaction	Lack of additivity of factor effects
Knowledge Space	Scientific elements to be considered and explored on the basis of previous knowledge as product attributes and process parameters.
Levels	Values assigned to a factor.
Lifecycle	All phases in the life of a product from the initial development through marketing until the product's discontinuation.
Main Effect	The effect of a factor averaged over all the levels of other factors.
Nuisance Factors	Uncontrollable factors which complicate the estimation of main effect or interactions.
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 Formulation by Design and computers.
Orthogonality	A condition where the estimated effects are due to the main factor of interest, but independent of interactions.
Process Analytical Technology (PAT)	A system for planning, evaluating, and managing production through timely measurements of key performance and quality characteristics of raw and in-process materials and processes, with the aim of ensuring the quality of the finished product.
Process Robustness	Ability of a process to withstand material variability, changes in the process, and equipment modifications without negatively affecting quality.
Proven Acceptable Range	A defined range of a process parameter that, when used while maintaining other parameters constant, would produce materials that fulfill the necessary quality standards.
Quality	The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as the identity, strength, and purity.
Quality by Design (QbD)	A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.
Quality Target Product Profile (QTPP)	A future summary of the qualities of a drug product that should be attained to assure the intended quality, taking into account the product's safety and efficacy.
Quantitative Variables	Variables that can take numeric values.
Resolution	The measure of the degree of confounding.
Response Surface	Graphical depiction of the mathematical relationship.
Response Surface Plot	3D graphical representation of a response plotted between two independent variables and one response variable.
Response Variables	Characteristics of the finished drug product or the in-process material.
Runs or Trials	Experiments conducted according to the selected experimental design.
Synergism	Desired positive change due to interaction between factors.

Table 2.
Important terms used in the formulation by design of pharmaceutical drug delivery:

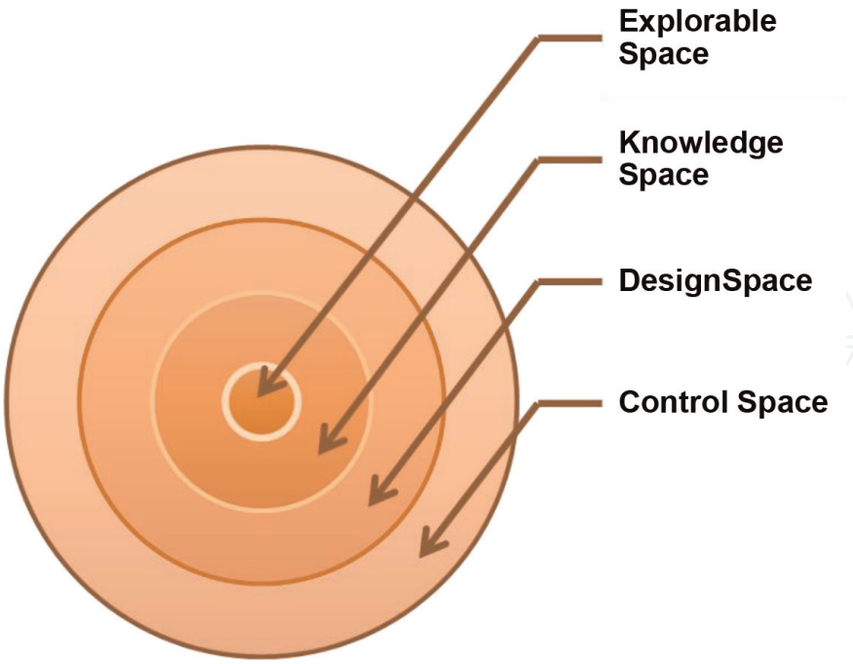


Figure 1.
Inter-relationship among knowledge, design and control spaces.

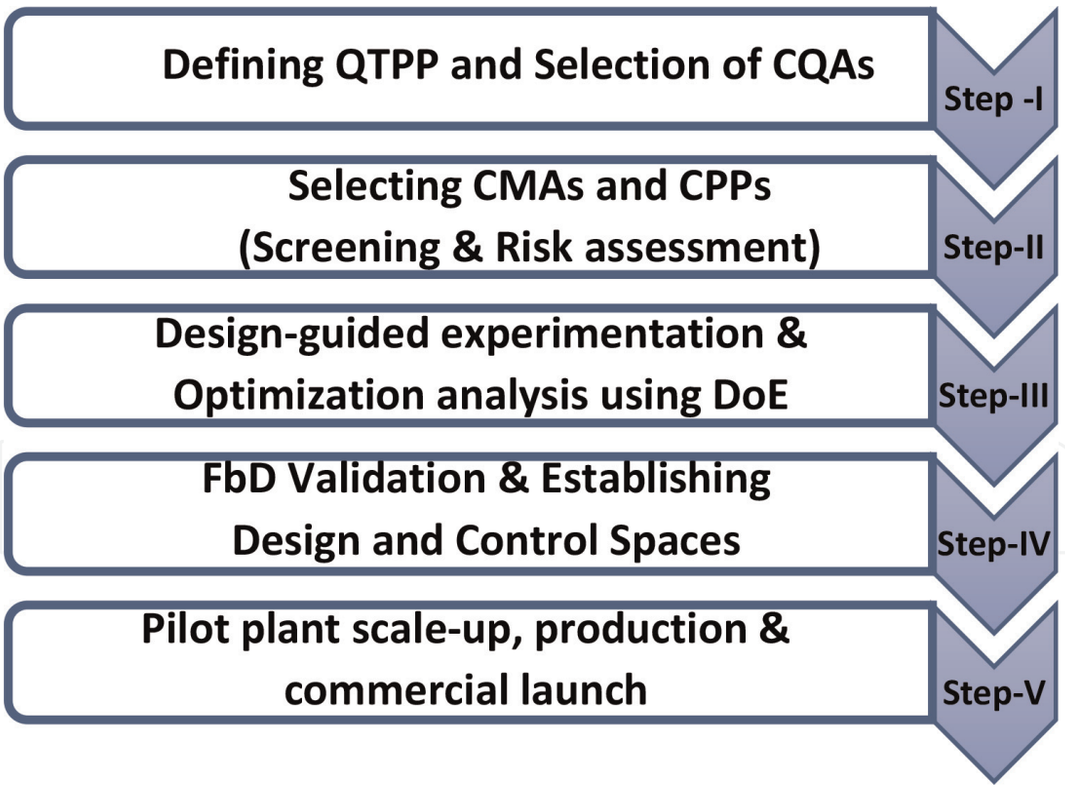


Figure 2.
Schematic representation of FbD optimization methodology.

may be accomplished by carrying out the risk assessment and quality risk management (QRM) approach by earmarking the severity of risk, its frequency of occurrence and detectability associated with each input variable. For that, the

moderate to high risk factors are chosen from patient perspectives through brainstorming among the team members using techniques like risk estimation matrix (REM), failure mode effects analysis (FMEA). These techniques help in identifying and sorting the potential risk associated with each CMA as applicable to the identified CQAs. Selection of "vital few" influential factors among the "possible many" input variables is invariably conducted using experimental designs through a process, popularly termed as factor screening. In a nutshell, screening exercise tends to help the scientist in opting the "leader" variables, while weeding out the "idler" ones. By and large, low-resolution first-order designs (like full-factorial and fractional factorial, Plackett-Burman, Taguchi designs) suffice the purpose of screening of a large number of experimental parameters. Experimental studies are also undertaken to define the broad range of factor levels. Apt use of screening designs, in this regard, helps to identifying the potential CMAs actually affecting the CQAs and reducing their number.

- **Step III: Design-guided Experimentation & FbD Analysis:** An experimental design constitutes the pivot of the entire FbD exercise esp. for RSM analysis. A suitable experimental design is worked out to map the responses on the basis of the study objective(s), CQAs being explored, number and the type of factors, and factor levels viz. high, medium or low. Out of several experimental designs, the factorial, Box-Behnken, composite, optimal and mixture designs are most extensively and frequently to optimize various drug products esp. those capable of handling second order nonlinear responses. For the purpose of directing the drug delivery scientists, a design matrix—a matrix-based architecture of experimental runs—is afterwards created. The design matrix is followed in the experimental preparation of the medication formulations, and the selected response variables are carefully assessed.

- **Step IV: FbD Modelization & Validation:** The quantitative dependence of a response variable on the independent variables is defined by a model, which can be expressed mathematically or graphically. Primarily, first, second, and very infrequently third order polynomials are used as models. Response surface methodology (RSM) uses the interaction of RSM polynomials, the required constraints/criteria for optimum search, and the design constraint to connect a response variable to the levels of input variables. Additionally, 2D-contour and 3D-response surface plots, which are incredibly helpful in revealing the pertinent scientific nitpicking and interactions between the input variables, are used in the Response surface modeling and analysis. As a component of knowledge and an explorable space, a design space is entered into in order to find the best formulation composition.

- **Step V: FbD Validation, Scale-up and Production:** The FbD methodology's validation is an important milestone in determining how well the polynomial models under investigation can predict the future. Different drug formulations are chosen from the many experimental domain regions, created, and tested following with the standard operating procedures established for the formulations created earlier, usually described as checkpoints or confirmatory runs. The residual analysis is then carried out after comparing the findings from these checkpoints with those that were projected.

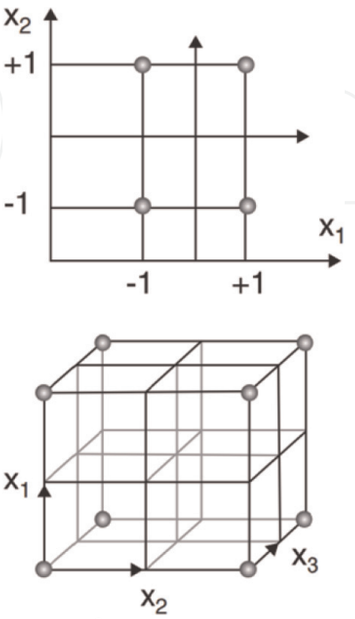
The optimum formulation is scaled up through a pilot plant, an exhibit, and production scale to confirm FbD performance. This phase is carried out in an industrial setting to guarantee that the performed drug product optimization study is reliable and reproducible. The entire process results in a thorough grasp of the product and process at the production and/or commercial scale, in addition to the final product being made available in an "optimized" form compatible with product excellence and federal compliance. A comprehensive and adaptable "control plan" is painstakingly developed and put into practice, ultimately leading to the objective of "continuous improvement" of drug delivery.

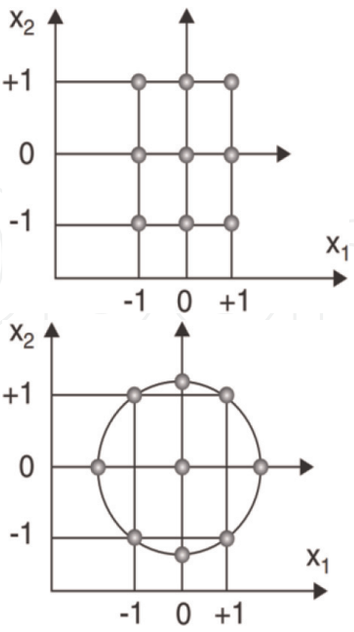
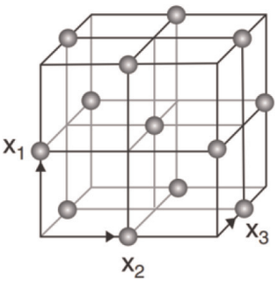
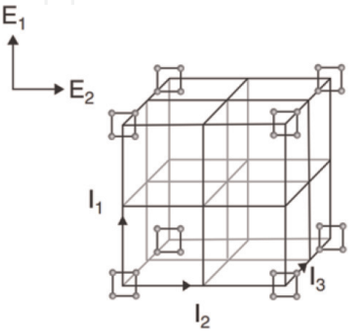
3.1 Experimental designs used during FbD of oral DDS

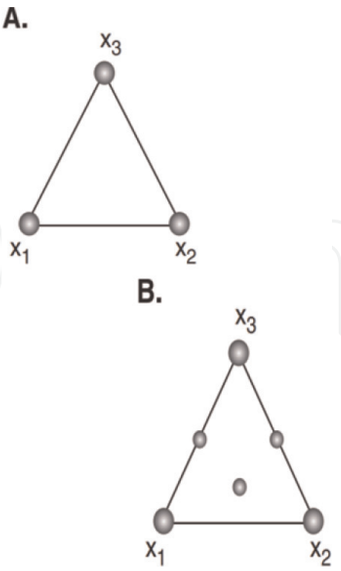
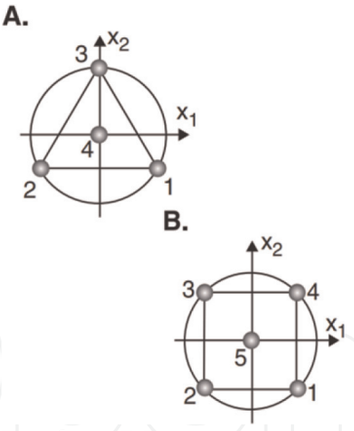
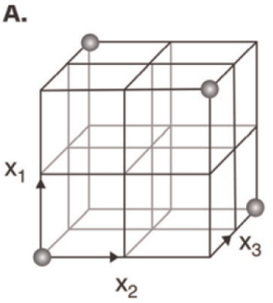
An experimental design serves as the basis of the FbD exercise. In systematic FbD optimization of DDS, a thorough "screening" of crucial variables is followed by a study of the experimental design-based response surface. Out of all experimental designs, oral DDS has been widely optimized using factororial and central composite designs [12–17]. The main experimental approaches used for oral DDS optimization are compared in **Table 3**, along with their advantages and disadvantages. Full factorial designs (FDs), including two-level and three-level FDs, fractional factorial designs (CCD), Box-Behnken designs (BBD), Plackett-Burman designs (PBD), Taguchi methods, and mixture designs, are among the several types of experimental designs (**Figure 3**) [19].

Advantages of Experimental Designs (ED) (Figure 4)

- Increased innovation as a result of process improvement.
- Fewer batch errors.

Design	Description	Diagrammatic representation
1. Full Factorial Designs (FDs): a. two-level full FDs; b. three-level full FDs	A factorial experiment is one in which all of the levels (x) of a particular factor (k) are coupled with all of the levels of every other factor in the experiment, with xk total experiments. **Merits:** • Maximizing the use of data while being effective in estimating major effects and interactions **Demerits:** • In a 2-level architecture, curvature reflection is not conceivable • Additional trials are needed.	 a. 2^2 FD; b. 2^3 FD

Design	Description	Diagrammatic representation
2. Central Composite Design (CCD) or Box-Wilson Design	CCDs are most typically employed for nonlinear responses needing second order models. A (2 k) FD or (2 k-r) FFD is embedded in the "composite design," which is further enhanced by a group of star points (2 k) and a "centre" point. 2 k + 2 k + 1 equal the total number of factor combinations in a CCD. **Merits:** • Combines the benefits of star and FD designs. • Enables the work to be done in stages; for example, if a linear 2-level FD is unable to effectively fit the data, a centre point may be added to the design. • Requires fewer tests. **Demerits:** • Fractional value (α) practice is challenging.	 a. CCD (rectangular) with α = 1; b. CCD (spherical) with α = 1.414
3. Box-Behnken Design (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
4. Plackett- burman Designs (Hadamard Design)	PBDs are unique two-level FFDs that are typically employed for K factor screening, or N-1 factor screening, where N is a multiple of 4. The designs, which are also known as Hadamard designs or symmetrically reduced 2 k-r FDs, are simply created with a few numbers of attempts. **Merits:** Suitable for a very broad range of factors, including those requiring a large number of experiments for FFDs **Demerits:** Design structure is complicated as a result of aliasing.	
5. Taguchi Designs	Used to create processes or products that are resilient to natural variability. Because it is a technique for assuring successful performance throughout the creation of products or processes, the design is also known as experimental design as "off-line quality control."	 Inner 2^3 and outer 2^2 arrays of Taguchi design

Design	Description	Diagrammatic representation
6. Mixture Designs	The properties of the final product in DDS containing numerous excipients typically depend more on the quantities of the ingredients than their individual amounts. In these circumstances, mixture designs are highly advised. Only one factor level can be individually varied in a two-component combination, but only two factor levels can be freely varied in a three-component mixture. **Merits:** Ideal for formulations where a constraint is placed on a certain combination of factor levels. **Demerits:** Understanding the polynomials produced by mixture design is challenging. Quadratic effects and interactions are not estimated.	 Mixture Design (a) linear model; (b) quadratic model.
7. Optimal Designs	The adoption of optimal designs is possible when the domain has an irregular form. These are the non-traditional custom designs produced by a computer exchange programme. These unique designs are typically created using an optimality criterion, such as the D-, A-, G-, I-, or V- optimality criteria. **Merits:** Can be applied even if the experimental domain is asymmetrical. **Demerits:** Uses a comparatively complicated model.	
8. Equiradial Design (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 fiverun design
9. Screening designs: Fractional Factorial design (FFD)	It is possible that the highest order interactions have no discernible impact when there are several elements at play. As a result, the quantity of experiments can be decreased in a methodical manner. The resulting designs are known as FFDs or occasionally partial factorial designs. An FFD is a discrete portion (1/xr) of a full or complete FD, where xk-r is the total number of necessary experiments and r is the degree of fractionation. **Merits:** Compatible with a wide range of factors or factor levels.	

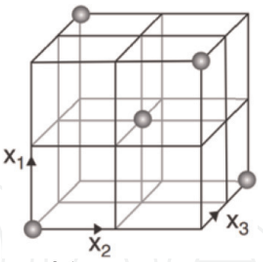
Design	Description	Diagrammatic representation
	Demerits: Effects are difficult to build, cannot be assessed in a singular manner, and are muddled by interaction terms.	 (a) 2^{3-1} FFD with design points as spheres (b) 2^{3-1} FFD with added center point.

Table 3.
Experimental designs used during formulation by design (FbD) [18].

- A higher level of regulator confidence in durable products.
- More effective manufacturing technology transfer.
- Results are acquired with replications.

Uses of Experimental Designs (ED).

It is used to discover the causes behind the variance in the response, to identify the circumstances in which the desired (maximum or minimum) response is obtained, to contrast responses at various levels of controlled variables, and to create a model for predicting response.

4. Selection of experimental design

The quantity of resources available and the degree of control desired by the experimenter over making poor decisions (i.e., Type I and Type II errors for testing hypotheses) determine which design is chosen among the numerous sorts of alternatives. For the objective of a more straightforward screening of many experimental factors, low-resolution designs like FFDs, Plackett Burman designs (PBDs), or Taguchi designs are sufficient. Only linear replies are supported by screening designs. Therefore, a more complicated design type is required if a nonlinear response is observed or if a more precise depiction of the response surface is needed. Therefore, response surface designs that can detect curvatures are used 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 [20]. In a nutshell, the important factors to take into account when choosing an experimental design are as follows:

- All designs can be applied for optimization of product characteristics, but SMD and EVD should not be used for process optimization.
- For screening studies, any design from 2 k FD, xk FD, FFD, PBD, or TgD may be used. The exception to this rule is all 2-level designs.

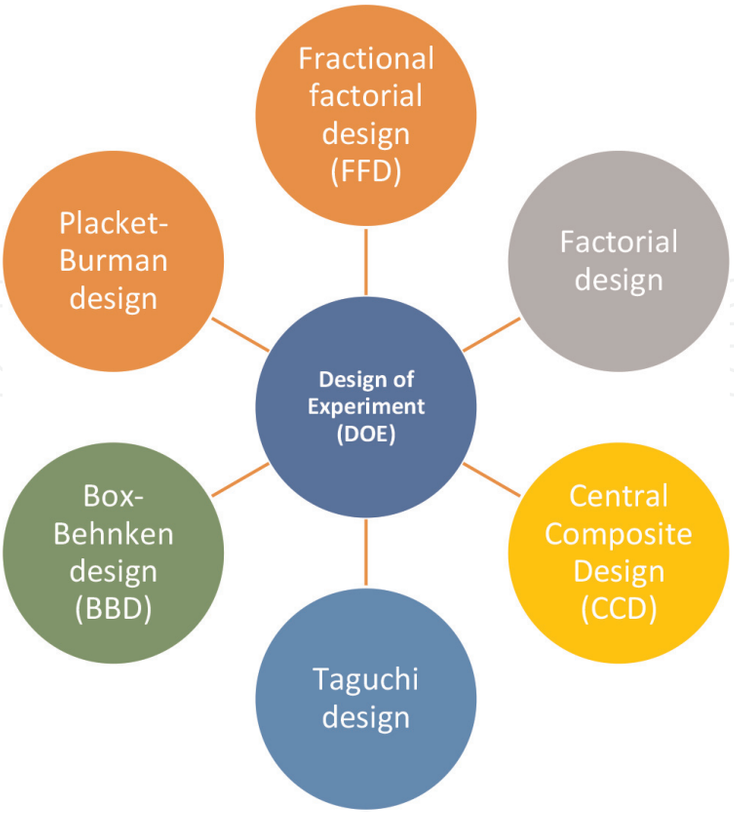


Figure 3.
Classification of Design of Experiments techniques.

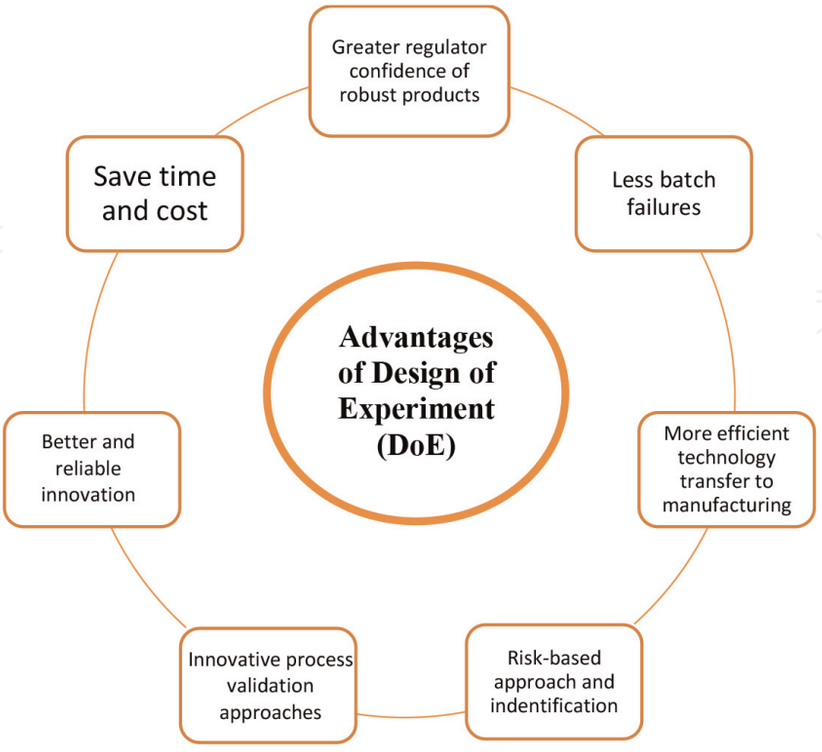


Figure 4.
Advantages of Design of Experimentation techniques.

- PBD is an option. However, screening using FFD, PBD, or Taguchi design should be used first for higher number of factors (> 6).

- Any 2 k FD, FFD, PBD, or mixture design can be used if there are only two factor levels. However, CCD, Box-Behnken (BBD), equiradial, simplex centroid, and optimal designs are preferred when there are more than three factor levels.

- xk FD, CCD, BBD, or equiradial design are preferred for quadratic models.

5. Model development

A model is an expression that shows how quantitatively dependent the independent variables are on a response variable. Both theoretical and empirical numerical models are possible. A way to explain the relationship between factors and responses is through an empirical model. It is typically a collection of polynomials of a certain order or degree. First, second, and sporadically third order polynomials are the models most frequently used to describe the response(s). The initial hypothesis is a first order model. Higher order models are used if a simple model is found to be insufficient for explaining the phenomenon.

Using regression analysis, the coefficients for quantitative factors can be estimated. Regression analysis is not used in the case of qualitative factors, however, because interpolation between discrete (i.e., categorical) factor values is meaningless. Multiple linear regression analysis (MLRA) is typically preferred for situations where there are more factors, interactions, and higher order terms. When the factor-response relationship is nonlinear, multiple nonlinear regression analysis is advised. The techniques of partial least squares (PLS) or principal component analysis can also be used for regression in multivariate studies where there are numerous variables [21]. When there are fewer observations than there are predictor variables, PLS, an extension of MLRA, is used. ANOVA, Student's t test [22], predicted residual sum of squares, and Pearsonian coefficient of determination When there are fewer observations than there are predictor variables, PLS, an extension of MLRA, is used. ANOVA, Student's t test [22], predicted residual sum of squares, and Pearsonian coefficient of determination are all taken into account when conducting model analysis (r2) are all taken into account when conducting model analysis. The essential stages required in developing and examining a mathematical model is outlined in the narrative that follows [23]:

- The data are meticulously checked for any anomalies and evident issues. The results are presented in a variety of graphs, including response distributions, responses vs. time order scatter plots, responses versus factor levels, main effects plots, and normal or half-normal plots of the effects.

- Remainder graphs are used to test the model's presumptions. ANOVA is used if none of the model presumptions are broken. If possible, the model is further condensed.

- Model transformation is suggested and a new model is developed if model assumptions are broken.

- The model's findings are used to determine critical elements, identify ideal conditions, and other things.

6. FbD models testing and revision

The main variables for evaluating and improving a FbD model are:

- Response versus predictions: These charts show how the independent variables interact or are involved.
- Residual lag plots: These graphs can be used to determine how random the data are. In a perfect world, the plots would have no specific structures. In the absence of any random patterns, interactions or other errors are likely. Latency plots can be produced for any arbitrary lag, with "lag 1" being the most typical. A plot comparing the values of Yi versus Yi-1 is known as a "lag 1" plot.
- Residuals histogram: A univariate data set's distribution is graphically summarized by a residuals histogram. The histogram visually represents the data's distribution, skewness, outliers, and many nodes.
- Normal probability plot of residuals: The normal probability plot evaluates the data's distribution pattern, whether normal or not, in a visual way. These graphs plot data against a hypothetical normal distribution so that the dots should roughly form a straight line. This straight line is a good indicator of deviations from normality.

7. Search optimization

The optimization of a single answer or the simultaneous optimization of several responses from the thus chosen models must be carried out graphically, numerically, with artificial neural networks (ANNs), and/or by extrapolation outside the domain.

7.1 Graphical optimization

The goal of graphical optimization is to choose the optimum formulation from a feasible factor space region. To do this, the factor values are screened in accordance with the desired limits of the response variables. A combination of the following approaches can be used to optimize graphics: ANNs, canonical analysis, overlay plots, brute-force searches, and mathematical optimization are further methods for optimizing numerous replies.

7.1.1 Brute-force search

The simplest and most precise optimization search technique is brute-force search, commonly referred to as exhaustive search because it involves looking at every single point in the function space. Here, the response variables of the formulations that can be created by practically every feasible arrangement of independent factors are

filtered [24]. Then, by further reducing the possible region, the acceptable boundaries are established for these responses, and a thorough search is once more carried out. The final viable space (also known as the grid search), which satisfies the most requirements established during experimentation, is searched for the optimum formulation. The benefit of using this thorough approach is that there is very little risk of missing the actual best formulation.

7.1.2 Overlay plots

To visually find the optimal compromise, the bi-dimensional response contour plots are stacked over one another. An overlay plot or integrated contour plot is what this is known as. The permissible range of objective values is defined with minimum and maximum values. The area that contains all acceptable responses is highlighted. By balancing several reactions, an optimum is found within this region.

7.1.3 Canonical analysis

According to canonical analysis, each of the extracted components from the criterion set of variables may be predicted from the corresponding components from the predictor set of variables [25–29]. The method is restricted to single response optimization. A saddle point is a stationary point that is not a local extremum in the domain of a function of two variables. The surface at such a location typically resembles a saddle that curves up in one direction or down in another (like a mountain pass). A saddle point on a contour line is typically identified by what appears to be an intersection of the contour with the line. The method is restricted to single response optimization. Additionally, there are additional crucial techniques for graphically locating the best formulation, including Pareto-optimality charts.

7.2 Mathematical optimization

Typically, when there is only one response, a graphic analysis is deemed sufficient. But when there are several responses, it is typically wise to perform mathematical or numerical optimization first to identify a workable area.

7.2.1 Desirability function

Desirability function is a method of getting around the challenge of having various, occasionally conflicting, responses [20]. Each response in this strategy has a unique partial desirability function [30, 31]. The ideal point is the one with the highest value for desirability [32]. The experimenter should combine contour plots of the most significant replies with an analysis of the contour plot of the desirability surface surrounding the optimal. Strong formulation or a combination of processing circumstances will be indicated by a big area or volume of high desirability. Although the method necessitates the use of certain computer software, it is a very helpful and practical approach to optimization. DDS has also been numerically optimized using the "objective function" and "sequential unconstrained minimization technique" techniques.

7.3 Artificial neural networks (ANN)

Machine-based computational methods called Artificial Neural Networks (ANNs) aim to imitate some of the neurological processing capabilities of the human brain. Because of their nonlinear processing power and capacity to simulate complex systems, ANNs have special advantages [33–37]. The results are equivalent with superior prognostic capabilities when compared to other optimization techniques. However, they are rather challenging to apply to more levels or elements, and no statistical criterion is made clear to indicate the level of applicability of the model.

7.4 Extrapolation outside the domain

For first order designs, steepest ascent (or descent) methods are direct optimization techniques [38], particularly when the optimum is external to the domain and needs to be reached quickly. The optimum path method, which is employed for extrapolating the optimum outside of the experimental region, is just like the steepest ascent approach. Several industrial processes use the evolutionary operations technique, which allows the production procedure (formulation and process) to evolve to the best possible state through careful planning and repeated repetition.

8. Benefits of FbD implementation during product development

- High-quality drug product development.
- Improved product and process understanding.
- Astute planning with a team approach.
- Decreased resource use.
- Shortened time to reach the market.
- Few product recalls and rejects.
- A quicker regulatory product review process.
- Excellent returns on investment.
- Decreased consumer-generic skepticism.
- Efficient regulatory oversight.
- Fewer post approval changes.
- Dynamic control technique that increases operational flexibility.

- Complementation with federal question-based reviews (QbR).
- Wide operating ranges.
- End-product testing done solely for validation.

9. Overall FbD approach for drug delivery development

A comprehensive plan can be used to outline the overall strategy for carrying out a FbD study in oral DDS [24, 39]. The key steps in this FbD method include the following:

- **Definition of the problem:** The FbD problem is fully understood and defined.
- **Factor selection and factor levels:** Among the quantifiable and easily controllable variables, the independent factors are found.
- **Design of experimental protocol:** A suitable experimental design is chosen, and the number of experimental runs is determined, based on the independent factors and response variables chosen.
- **Formulating and evaluating the dosage form:** Different drug delivery formulations are created in accordance with the selected design and tested for the desired outcome(s).
- **Prediction of the best formulation:** A mathematical model is created using experimental data, and then the best formulation is found using graphical and/or numerical methods.
- **Validation of optimization:** Responses are assessed when the expected optimal formulation is generated. If results are confirmed, they are then transferred via scale-up methods and activities at pilot plants to the production cycle.

Figure 5 is a flow chart that shows the several key processes that make up a FbD approach as a whole.

10. Software usage in FbD optimization

FbD optimization approaches have several benefits, and their acceptance is optimistic. However, implementing such logical concepts frequently necessitates complex mathematical and statistical procedures. Today's computational snags have been substantially streamlined and simplified because to the availability of strong hardware that is also reasonably priced, as well as the full FbD software. Software for computers is only available to undertake data analysis using the FbD methodology (**Figure 6**).

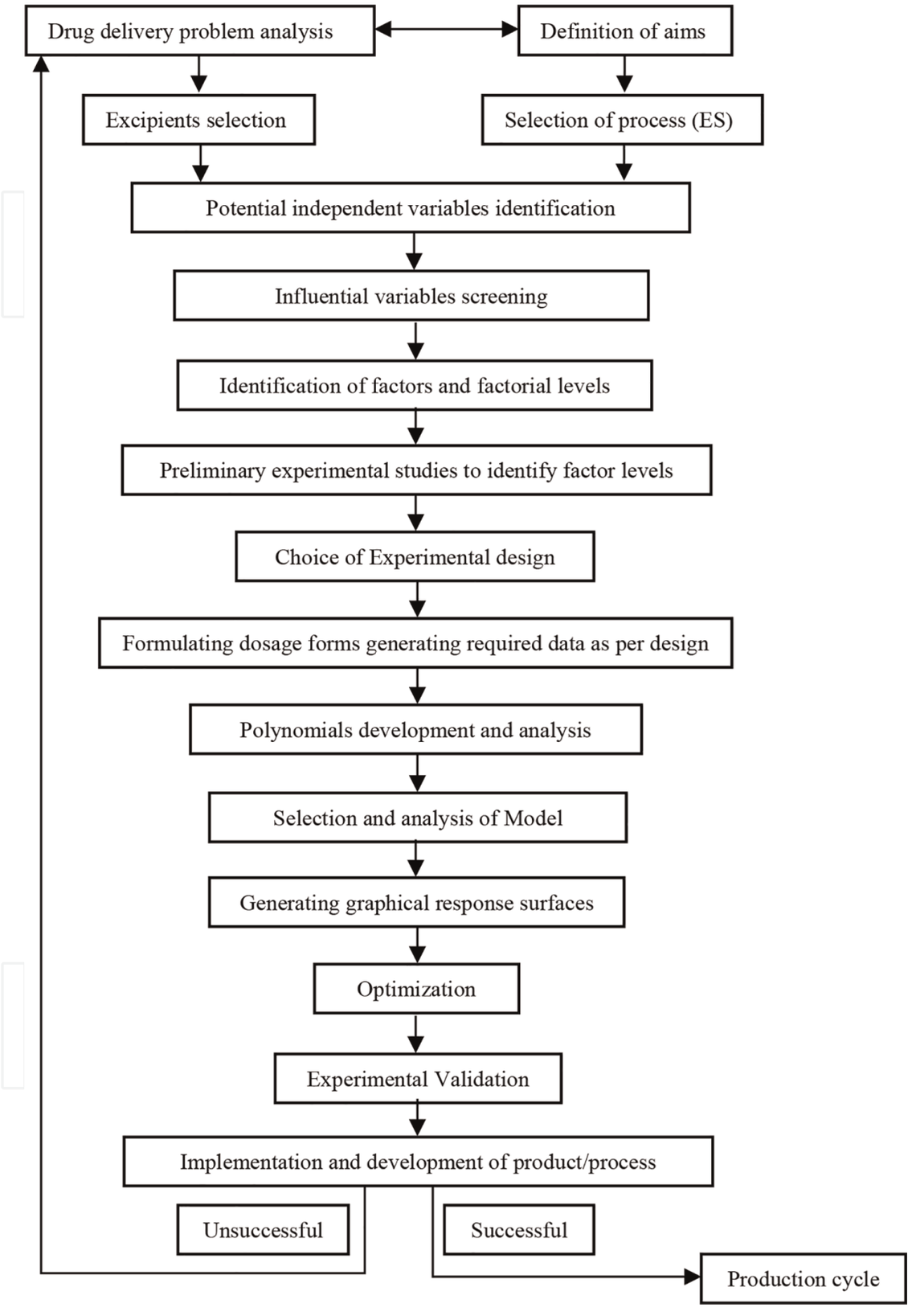


Figure 5.
Overall FbD strategy during drug delivery development.

An interface like this provides guidance at every stage of the optimization cycle, including the design selection, factor screening, use of response surface designs, generation of the design matrix, plotting of 3-D response surfaces and 2-D contour

Software	Features
Design Expert	Pharmaceutical formulations and processes can be improved; this enables the screening and analysis of key factors for FD, FFD, BBD, CCD, PBD, and mixture designs; gives 2D contour maps and rotateable 3D plots to show the response surfaces; Optimization using numbers and graphics.
DE PRO XL and DE KISS	Software for automated data analysis employing Taguchi, FD, FFD, and PBD that is MS-Excel compatible. However, only one response variable can be used with the reasonably cheap program, DoE KISS.
Mini Tab	Powerful DoE software with practically all RSM designs, graphic and help features, and compatibility with MS-Excel.
MATREX	Software for optimization that works with Excel and has facilities for a number of experimental designs, including the Taguchi design.
OPTIMA	Constructs the experimental design, calculates the data fit to a mathematical equation, and visually displays the response surfaces.
OMEGA	Only a program that enables multi-criteria decision making using Pareto-optimality, up to six objectives, and includes numerous statistical functions is available for mixed designs.
FACTOP	Develops polynomials and grid searches to aid in the optimization of formulation utilizing various FDs and other designs; contains computer-aided-education module for optimization.
GRG2	Using a mathematical optimization program, you can find a function's maximum or minimum with or without restrictions [40].

Table 4.
List of computer Softwares available commercially for formulation by design (FbD) studies.

Figure 6.
Selected computer software used during FbD implementation for product and process optimization.

plots as design spaces, optimum search, partial interpretation of the results, and validation of the methodology. **Table 4** outlines the specific computer software products that are commercially available for conducting FbD studies in an industrial setting. **Tables 5** and **6** illiterates examples of several approaches of FbD in the optimization of micro and nanoformulations and a comprehensive account of the independent variables and response variables used for various DDS.

DDS	Drug	Factors	Design	Year (Ref)
Self-nanoemulsifying	Bosentan	Oil phase percentage, surfactant percentage, and co-surfactant percentage	Box-Behnken	2022 [41]
Floating Gastroretentive	Famotidine	Concentrations of Guar gum and the concentrations of Rice Bran Wax	3^2 factorial	2022 [42]
Self-microemulsifying (SMEDDS)	Teriflunomide	Concentration of oil (Sefsol 218), surfactant (Acrysol EL-135), and cosurfactant (PEG 400)	Mixture design	2022 [43]
Nanoencapsulation	Crocin component of saffron (*Crocus sativus* L.)	pH and the concentrations of CS, ALG, and calcium chloride ($CaCl_2$)	Taguchi	2022 [44]
Gastro-retentive (GRDDS)	Itopride Hydrochloride	Concentrations of Eudragit L 100, PEG, and sodium bicarbonate	Box-Behnken	2022 [45]
Magnetite Nanoparticles	Ciprofloxacin	Concentrations of CIP (35–80 mg/L), adsorbent doses (20–60 mg), and pH values (4–10) at reaction time (80 min)	Box-Behnken	2022 [46]
Nano invasomal gel	Glibenclamide (GLB) and Atenolol (ATN)	Amount of phospholipid (mg), ethanol (%), and terpene (%)	Box-Behnken	2021 [47]
Gastroretentive	Ranitidine Hydrochloride	Concentration of HPMC/NaCMC and Concentration of $NaHCO_3$	Central Composite Design	2021 [48]
Emulsomes	Bifonazole	Phospholipid to Bifonazole ratio; Phospholipid to Tristearin ratio and Phospholipid to Stearylamine ratio	Box-Behnken	2021 [49]
Solid lipid nanoparticle	Eflornithine hydrochloride	Drug: lipid, Surfactant concentration, Stirring time	Central Composite Design	2021 [50]
Microspheres	Pentazocine	Polymer concentration, Stirring speed, Surfactant concentration	Box-Behnken	2021 [51]
Solid lipid nanoparticle	Clarithromycin	Homogenization speed (rpm), Sonication time (min), Amount of lipid (mg), Surfactant ratio, Surfactant concentration (%)	3^2 full factorial design	2021 [52]
Orodispersible films	Vitamin B12	Amount of Glycerine, Menthol and Polymer Soluplus® amount	Box-Behnken	2021 [53]
Cubosomes	Ketoconazole	Stabilizer, Surfactant amount	3^2 full factorial design	2021 [54]

DDS	Drug	Factors	Design	Year (Ref)
Nanoparticles	L-arginine	Oleic acid concentration, Poloxamer 188 concentration, Sonication rate	2^3 full factorial design	2021 [55]
Self-nanoemulsifying (SNEDDS)	Candesartan	Oil percentage (Capmul PG-8), surfactant percentage (Kolliphor EL), and a co-surfactant percentage (Transcutol P)	D-optimal mixture	2020 [56]
Self-nanoemulsifying (SNEDDS)	Andrographolide	Amount of Capryol-90 as the oil phase (20–50%), Kolliphor RH 40 as the surfactant (40–70%), and propylene glycol	Simplex lattice	2020 [57]
Solid lipid nanoparticle	Pioglitazone	Concentration of lipid (Compritol® 888 ATO), surfactant (tween80) and homogenization speed	Box-Behnken	2020 [58]
Nanoparticles	Benzylisothiocynate	Amount of polymer Concentration of surfactant	Central Composite Design	2020 [59]
Microspheres	Epichlorohydrin	Concentration of epichlorohydrin Duration of cross-linking	Two-level full factorial design	2020 [60]
Microbeads	Nitazoxanide	Percentage of chitosan, Percentage of sodium tripolyphosphate	Central Composite Design	2020 [61]
Nanoparticles	Ansamycin	Homogenization speed, Drug/polymer ratio, PVA concentration	Central Composite Design	2020 [62]
Nanoparticles	Clonazepam	PLGA amount, Poloxamer 188 concentration	3^2 full factorial design	2020 [63]
Nanoparticles	Clarithromycin	Time of sonication, Lipid amount	3^2 full factorial design	2020 [64]
Microspheres	Theophylline	Starch:alginate ratio (X1) and polymer:drug ratio (X2)	2 factor, 2 Level CCD	2020 [65]
Polymeric nanoparticle	Zoledronic acid	Zoledronic acid content, PLGA/Pluronic F68 ratio, Organic to aqueous phase ratio	Central Composite Design	2020 [66]
Fast disintegrating oral film	Zolmitriptan	Amount of polymer and Plasticizer	2^2 factorial design	2019 [67]
Magnetic nanoparticles (MNPs)	(3-amino propyl) triethoxy silane (APTES)	Concentration of Fe_3O_4, Tragacanth Gum (TG): Chitosan (CS) ratio, nanocomposite weight, and curcumin weight on the drug loading	Taguchi	2019 [68]

DDS	Drug	Factors	Design	Year (Ref)
Nanoparticles and nanosuspension	Loratadine	Drug amount, Solvent to anti-solvent ratio, Stabilizer type, Stabilizer concentration, Sonication time, Sonication power	Central Composite Design	2019 [69]
Encapsulated nanoparticle	Sorafenib	Concentration of HPMC, PVP concentration, Poloxamer concentration	Box-Behnken	2019 [70]
Floating matrix tablets	Ciprofloxacin Hydrochloride	Amount of HPMC K100M and Xanthan gum	3^2 factorial	2018 [71]
Encapsulated Eudragit® microspheres	Vildagliptin	Eudragit RS-100 concentration, Span-80 amount, Volume of methanol, Volume of acetone, Stirring speed	Plackett-Burman design	2018 [72]
Encapsulated Chitosan nanoparticle	Cefadroxil	Polymer weight, Polymer concentration	2^2 factorial design	2018 [73]
Mucoadhesive microspheres	Quetiapine fumarate	Ethyl cellulose concentration, Chitosan concentration, Stirring speed, Type of HPMC, HPMC concentration	2^2 factorial design	2018 [74]
Mucoadhesive buccal tablets	Risperidone	Amount of Carbopol® (CP) and sodium alginate (SA)	Response surface methodology	2017 [75]
Multiparticulate pellets	Naproxen	Level of microcrystalline cellulose (MCC), polyvinylpyrrolidone K-90 (PVP K-90), croscarmellose sodium (CCS), and polacrilin potassium (PP)	Mixture design	2017 [76]
Cellulose nanofiber (CNF) aerogels	Bendamustine hydrochloride	Optimization of stirring time varied from 3 to 8 hours and the CNF ratio varied from 0.6 to 3.	Central composite design	2017 [77]
Hot Melt Extrusion Amorphous Dispersion Tablet	Compound X	Type of polymer, filler (microcrystalline cellulose (MCC), lactose, and dicalcium phosphate anhydrous (DCPA)), and disintegrant (Crospovidone, croscarmellose sodium, and sodium starch glycolate (SSG))	Full factorial	2016 [78]
Osmotic	Dicloxacillin sodium and Amoxicillin trihydrate	Screening of three categories of polymers, Optimization of osmotic tablets	Plackett-Burman and Box-Behnken	2016 [79]
Self-microemulsifying (SMEDDS)	Atorvastatin calcium	Concentrations of Capmul MCM, Tween 20, and Tetraglycol	D-optimal mixture design with response	2015 [80]

DDS	Drug	Factors	Design	Year (Ref)
			surface methodology	
Transdermal delivery	Risperidone	Amount of cholesterol, span 60, phospholipid G90, and risperidone	4^3 factorial design	2015 [81]
In situ gel	Glipizide	Concentration of gelling agent, drug release retardant polymers and concentration of drug release retardant polymers	Taguchi	2015 [82]
Sustained Release Mucoadhesive Microcapsules	Venlafaxine HCl	concentration of sodium alginate, HPMC type (i.e., K4M, K15M, HPMC K100M), amount of HPMC K100M and crosslinking time	Plackett-Burman and Box-Behnken	2014 [83]
Oro-dispersible	Clobazam	Amount of disintegrant (crospovidone) and the diluent (MCC)	Response surface methodology	2013 [84]

Table 5.
FbD optimization of various oral DDSs.

Types of drug delivery system	Factors	Response variables
Oral sustained release matrices	Drug loading, polymer type and content, polymer grades, ratio of polymers, ratio of polymer to filler, drug-polymer ratio, heating time, solvent ratio, binder, lubricant, film former, adhesive, amount of water in granulating liquid, volume of granulation solvent, granulation time, compression force, storage temperature, relative humidity, light, punch face tip geometry	Dissolution kinetics, tablet thickness, hardness, moisture uptake, friability, lag time, visual tablet quality, tensile strength, tapped density of granules, weight variation
Sustained release coated tablets	Polymer, solid content, volume of coating dispersion, plasticizer, weight gain, curing time, particle size, hardness, lubricant	Dissolution profile, in vivo plasma profile, lag time
Multiple-layered tablets	Core polymer concentration, lubricant, hardness of compressed core, compression force for complex layer	Drug release, adhesion strength in complex layer
Gastroretentive floating and bioadhesive tablets	Polymer-drug ratio, polymer grades, ratio of polymers, ratio of diluents	Dissolution kinetics, duration of buoyancy, detachment force, shear force, compression force, tablet density
Osmotic tablets	Orifice size, coating level, content of pore former, polymer content, coat weight, plasticizer type and content, cure time and cure temperature	Drug release rate, lag time, burst strength, correlation coefficient of cumulative amount of drug released and time
Buccoadhesive tablets	Amounts of polymer	Drug release, bioadhesion, and diffusion parameters

Types of drug delivery system	Factors	Response variables
Macroparticulates	Drug content, surfactant content, water content, impellar speed, mixing time, plasticizer concentration, polymer coating load, concentration of lacquer in the coating dispersion, extruder speed and screen size, spheronizer speed and load, spheronization time, extrusion rate, spray rate and temperature, curing time and temperature, agitation, osmolality and polarity of the medium	Pellet yield, dissolution time, percentage of stuck pellets, steady state extrusion force, bulk density, friability, flowability, pellet size, morphological characteristics
Microparticulates (microspheres)	Polymer type and content, polymer:drug ratio, polymer grades, molecular weight of polymer, amount of hardening agent, cross linking agent, cross linking time, emulsifier concentration, solvent, pH, phase volume ratio, stirring speed, stabilization time, surfactant, composition of internal phase, emulsifier type, deaggregating agent, dehydrating agent, precipitant, injection rate, needle gauge size	Dissolution kinetics, yield, percent drug loading, particle size, loose surface crystals, drug entrapping efficiency, surface morphology, angle of repose
Microparticulates (microcapsules)	Core-wall ratio, particle size, pH of the medium, surfactant concentration, speed of stirring, ratio of total polymer to total volume of solution	Dissolution time, stability of the capsule walls
Nanoparticulates	Monomer concentration, polymer, surfactant, volume of oily phase, stabilizer, pH, stirring speed, temperature of aqueous phase, oxygen level	Percent yield, drug loading, drug release profile, polydispersity index, particle diameter, zeta potential
Vesicular systems	Average molecular weight, surface affinity, number of additional steps, temperature, phospholipids, stabilizers, inlet pressure of homogenizer, shaking time, incubation time for annealing vesicles, lipid charge, sonication time, pH, solvent, hydration time	Percent encapsulation, average amount of polymer adsorbed per lipid, entrapment volume, size of vesicles, drug leakage, stabilization ratio
Solid dispersions, coevaporates and coprecipitates	Carrier, polymer, disintegrant, lubricant, solvent, spray feeding volume, polymer to drug ratio, diluent, compressional pressure, polymer-lubricant ratio	Release rate, dissolution time, dissolution efficiency, weight variation, hardness, friability, disintegration,
Fast release tablets	Drying time, compression force, particle size, moisture content of wet granules	Distintegration time, tensile strength, tablet porosity
Self-nanoemulsified tablet dosage forms	Amount of copolyvidone, microcrystalline cellulose and maltodextrin, surfactant, cosolvent	Weight, flowability index, tensile strength, friability, disintegration time, drug release

Table 6.
List of various independent variables and response variables chosen for various types of drug delivery system: [85].

11. Conclusions

Today, rather than relying on end-product testing, the federal agencies want assurance of QbD-centric quality that is "built-in" to the system. Therefore, understanding the formulation or process factors utilizing FbD will assist in achieving the

targeted goals of product/process excellence with extraordinary ease and efficiency. Almost all types of oral DDS have successfully utilized FbD employing experimental designs to improve not only the drug formulations but also the development procedures. It has proven effective even if choosing the best formulation is not the main goal because it tends to reveal how much the product qualities improve when (any) excipient or process parameter is changed (s). By enhancing (rather than substituting) the essential formulation abilities, inventiveness, and product knowledge, FbD tends to speed up the formulation process.

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