



Design Space by Design of Experiments

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Authors' contributions

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ABSTRACT

The quality of methods and products are usually influenced by several input factors. Research has recently focused on understanding the effects of multidimensional and interconnected input factors on the results of pharmaceutical products and analytical methods using Design of Experiment (DoE). Furthermore, it examines how DOE may be implemented, both for students and teachers, as well as highlighting historical perspectives on DOE. A good experimental design can help you make the most use of the available resources and make the analysis of the results easier. Collaborations between researchers and practitioners that are pushing the boundaries of experimental design are examined. It provides an overview of the principles and applications of the most common screening and response surface design, as well as creating mixtures designs.

Keywords: *Design of experiments; design space; screening designs; factorial designs; response surface plots.*

1. INTRODUCTION

Experimental design is not a new concept. In the 1920s, Sir Ronald Fisher, a legendary statistician, laid the foundation for modern statistical research with his contributions to statistics, which have been hailed as "a genius." Research conducted has maintained a proactive stance, which is at the core of the current regulatory system that controls the development of pharmaceutical products [1,2,3]. Walter A. Shewhart, William E. Deming, and Joseph M. Juran extended this work and advocated a process-based culture for incorporating quality into products. A five-step process called "Quality by Design" was coined by Juran to emphasize the need to incorporate Quality into goods and services; this process involves knowing the customer, analyzing his needs, translating them into product features, developing it, and introducing them into operations. W.E. Deming presented his systematic approach to wisdom, using system thinking, understanding variation, theory of knowledge, and psychology, about half a century before Juran. According to him, quality assurance should focus more on the process than the results since "if you can't describe the process, you're not doing it right" and "quality is already in the product [4]." Control charts featuring statistical process control were featured in Schewhart's work on quality improvement. Since the pharmaceutical industry relies heavily on quality and process, it is likely the first sector to adopt these concepts. Thus, regulatory bodies asserted that quality cannot be built into products (that is, made into it by design) early in the millennium [5]. A Design of Experiments (DoE) is used in research and industry contexts to implement Quality by Design (QBD). It is characterized as the primary system of pharmaceutical development because, as a legacy of Fisher's, it demands the application of statistical thinking at the outset. Develop and build quality levels in pharmaceutical products has become increasingly popular. The manufacturing process of pharmaceutical products is the major source of quality problems according to Juran. Studies and tests cannot validate the safety and efficacy of a poorly designed pharmaceutical product [6,7]. Consequently, QbD assumes that more analyses will not improve quality. Another way to put it is that the product's quality must be outstanding to be built in. This approach to pharmaceutical development starts with clearly defined goals and focuses on product and process knowledge. It is based on strong science and risk management of

high quality. Using QbD for pharmaceutical production results in knowledge and understanding. a) Achieving meaningful product quality criteria b) Stabilizing processes and reducing variability c) Improving pharmaceutical development efficiency d) Improving cause-effect analysis and regulatory flexibility. Worldwide, most regulatory bodies have endorsed risk-based approaches and comprehensive quality assurance in pharmaceutical development. There have been several publications discussing how the QbD methods were used in the development of analytical procedures. By utilizing analytical quality management, robust and cost-effective analytical procedures are developed and refined. QbD implementation that uses analytical methods provides more accurate results while also reducing the probability of failure. For centuries, pharmaceutical firms have focused on enhancing one factor at a time (OFAT). All variables are unchanged, apart from one variable that is altered in a reasonable range (or level). The OFAT method does not recognize factor interactions, which could lead to insufficient development and optimization. There is a possibility that if you design experiments properly, you can achieve superior results within a few tests. DoE's collection of statistical techniques includes screening and optimization designs. In pharmaceutical and analytical QbD, a DoE is the most important component [8,9]. As a result, the current study discusses theoretical and practical issues for using DoE in pharmaceutical and analytical QbD.

2. RESEARCH

Among several publications, including more than 500 in 2005, as summarized by Singh et al., the Marlow and Shangraw study is regarded as the first publication on DoE application to the design of pharmaceutical dosage forms. There are currently 5200 results on Scopus for the keywords "Design of Experiments" and "pharmaceutical," covering the period from 1978-2009. The adoption of these strategies is becoming more common in books and articles about statistics and quality, but the industry has not made use of them as frequently as it should. In 2006, we also surveyed manufacturers in the Basque Country. Business experiments are used by 94 percent of businesses, with the majority following OFAT tactics, and only 20 percent applying a predetermined statistical methodology [10]. A methodology is also necessary, with 76 percent of respondents agreeing that the lack of a defined approach is the most significant

obstacle to DoE deployment. With the advent of the International Council Harmonization (ICH) Q8 guideline, which provided a conducive environment for the use of dose-equivalent engineering, there has been significant progress in research and industrial applications related to this technology. Additionally, user-friendly software has been available to ensure easy design composition and analysis [11,12].

2.1 Definitions and Terminologies

Quality by Design (QbD) is defined as 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. It is a method that structures and organizes information about the relationship between process factors and output factors. Also called "Design of Experiments" (DoE). Essentially, it is the process of establishing how inputs influence outputs that develops a process knowledge.

Treatment - Various treatment combinations.

Treatment levels - Intensity of treatment during the experiments

Treatment factors (variables) - A controlled condition in an experiment.

Experimental unit - The subject upon whom treatment will be applied and from which a response will be measured. Also referred to as a measurement of responses.

Responses - Results obtained after treatments are applied to experimental units

Experimental design - Treatment level assignment.

Analysis of variance (ANOVA) - Method for identifying the causes of variability in responses.

Replication - Under identical experimental conditions, observing the responses of multiple experimental units.

Randomization - Choosing experimental units not systematically.

Confounding - An experiment in which the effect of one factor or treatment cannot be distinguished from the effect of another factor or treatment

Independent variables: Directly controlled by formulation scientists

Dependent variables: Result variables

Factors: Qualitative and quantitative factors.

Level: Value assigned to a factor

Responses surface plot: A plot of the relationship between the independent factor and the dependent factor in a 3-D

Interaction: It provides the net effect of two or more variables without requiring additivity of their effects

Effect: Amount of the change

Contour plot: An outline of one independent variable plotted against another while keeping the response constant

Contour lines: calculated contour lines over a counterplot

Orthogonality: When no interaction occurs due to the main factor of interest

Resolution: Measuring confounding

3. DESIGN OF EXPERIMENTS: STEPS TO TAKE

The design of experiments must follow the following steps to produce good findings.

- i. Plan how to achieve your goal
- ii. Determine the variables in the process
- iii. Consider a design that allows for experimentation
- iv. Work on a design
- v. Make sure the experimental assumptions match the data
- vi. The findings should be examined and analyzed.

4. CONDUCTING EXPERIMENTS ACCORDING TO A METHOD

4.1 Levels and Selections of Variables

A process variable includes both inputs and outputs, such as factors and responses. This type of experimental design is very popular since it provides ample information for screening

designs, is easy and cheap, and provides the information needed to proceed to multilayer response surface studies in the future as needed. The choice here is based on the DoE's goal, and it should ensure that the entire design serves its purpose. Therefore, the type and level of numeric and categorical factors are suitable (i.e. the values within the design) [13,14,15]. In a quantitative study, the independent variables (factors) influence the response variable. It is possible to identify components that may affect a response variable using a fishbone diagram.

4.2 Design of Experimental Studies

When selecting an experimental design, consider various aspects, such as the goals, the quantities of components and interactions to be investigated, the statistical validity, as well as the effectiveness. To better understand experimental design, two categories are available: a) Designing for screening; b) Designing for optimization. The type of experiment to be conducted depends on two factors: what the experiment's goals are and how many variables are being examined. There are several types of designs to choose from, including factorial, mixed and process-based designs. All replication, randomization, and blocking decisions should be considered. The factor-response function can be optimized, and the number of test samples can be determined after a screening design identifies significant factors [16].

5. HOW CAN EXPERIMENT DESIGN BENEFIT YOU?

5.1 Treatment Comparison

This involves contrasting different levels of a single element. Introducing statistics classes typically explain a range of different statistical studies applicable to this instance.

5.2 Variable Screening

As a result, fewer variables are used in an experiment. Whenever there are too many factors chosen to consider (more than 8) and they cannot be reduced based on current process information. Utilizing an innovative design taking advantage of fewer runs, it identifies as few variables as possible worth investigating.

5.3 Variable Characterization

To quantify each variable's impact, this step must be carried out. There are usually fewer variables

to consider when using this type of analysis. Simple orthogonal designs are often chosen because they facilitate the development of a risky prediction model.

5.4 System Optimization

A process "ideal" requires determining how processes should be run. Alternatively, the goal is to determine the levels of each aspect that allow the process to produce the best results. In cases when the process is understood sufficiently and the factors affecting its outcome are minimal, the procedure is frequently carried out. These cases, which allow for the estimation of quadratic terms of second-order, are common. Usually, non-linear zones exist near an optimum, so this improves forecast accuracy.

5.5 System Robustness

By doing so, you need to determine what level of the fundamental factors reduces the unpredictability principally caused by the noise. As a result, it's only employed in situations with an exceptional level of crowd noise. On the other hand, it necessitates special protocols known as Robust Parameter Designs (RPD). By using this interaction between the main (control) and secondary (noise) components, these schemes employ the advantages of dual-component modeling [17].

6. CONCEPTS

To increase the efficacy of experiments in industrial trials, three principles of experimental design are employed: randomization, replication, and blocking.

6.1 Randomization

In randomized experiments, noise factors (unwanted variations) like temperature fluctuations or fluctuations in power supply have an equal chance of affecting all levels of a parameter. All experimental materials are allocated at random, as well as the order in which they are conducted. This is critical for the following three reasons:

- a. The assumption that observations (or errors) are independent random variables is usually validated by randomization.
- b. It makes it possible to "average out" any additional factors; and

- c. There may be a learning process involved or it may be important to have the experiments conducted in the correct order where the operation is repetitive. Systematic bias can be eliminated with randomization.

However, Randomization cannot eliminate the variability resulting from uncontrollable variables, although it can help to "average out" their impacts. By blocking, we reduce or eliminate 'nuisance' variability, such as batch variances in raw materials, that may influence the response to an experiment but are of no direct significance. In this way, the experimental error is smaller, and the variability caused by these factors is separated from the experimental error, allowing for more precise conclusions.

6.2 Replication

To estimate experimental errors and main and interaction effects more precisely, it includes repeating an experiment, all, or part of it, in random order. Rather than performing an experiment once and getting several measurements, replication involves repeating it under the same conditions. A probability density function can be utilized to explain the differences between two sample sizes, which may be used as a measure of statistical significance. Because the variance of the sample means is less than that of the individual observations, replication allows the researcher to acquire a more precise estimate of the influence of a factor in the experiment. Repetition of measurements however leads to an increase in variability, which is a consequence of the inherent variability of the measuring system or gauge [18].

6.3 Blocking

To spread out the effect of changes in blocking factors, such as batch size, machine type, and time of day, it is the practice of grouping similar testing runs into blocks (or groups). All experiments should be managed to avoid confounding (confusions over which changes in the output are a result of changes in the block or factor levels).

7. DESIGN OF EXPERIMENTS

Historically, DoE has been an instrument that has contributed to improving product quality and reliability. Different industries are increasingly using DoE for their decisions, whether for new

products or process improvements. Administration, marketing, hospitals, pharmaceuticals, the food industry, energy and architecture, and chromatography, among other applications, are among its uses. Models both physically and computer-based can be simulated using DoE. An experiment's design, analysis, and interpretation are part of a study's DoE. This type of applied statistics is often used to examine how changing the input variables (X's) affects measuring the response variable (Y) in a system, process, or product. Using the DoE technique, variables are initially screened to determine those that have significant impacts on results (excipient kind, proportion, disintegration time (DT), etc.) [19]. Optimizing the procedures involves determining which are the best settings for each of the essential variables [20]. This research involves investigating how changes in mixture composition affect the mixture's attributes using mixture designs. Chemical, physical, and manufacturing stability are fundamental to product development and manufacturing. To ensure product safety and efficacy, different quality criteria must be fulfilled [21]. To ensure a targeted formulation effort, a target product profile (TPP) must be identified. In TPP (appearance), one frequently finds information about the formulation, methods of administration, maximum and minimum doses, and characteristics of pharmaceutical elegance. Formulation scientists are assisted by the TPP in developing formulation strategies as well as directed and efficient efforts. Developing a formulation requires many investigations after the TPP is clearly defined. DoE can be very useful to formulation scientists during all phases of the formulation process since it helps them make informed decisions. There are many important steps in this process, including product optimization, excipient compatibility, formulation and scale-up, and process characterization. A DoE may be generated and analyzed rapidly using appropriate statistical software. Statistical packages for this purpose can be found as both freeware and commercial software. Minitab, Statistica, Statistical Package for the Social Sciences (SPSS), Statistical Analysis System(SAS), Design-Expert, STATGRAPHICS, Prisma, and other well-known commercial packages are examples [22].

Several commercial software packages offer an intuitive interface and excellent output visuals, such as Minitab and STATISTICA. Using the R (R is a free software environment for statistical computing and graphics) platform, Action

produces graphics using Excel and the R platform. Furthermore, Microsoft Excel can be used to quickly perform DoE design and analysis by utilizing the procedure and formulas provided in the next paragraph. Knowing how to use ANOVA and linear regression as statistical approaches is essential to do any DoE as mentioned above [23].

7.1 Advantages

Compared with OFAT, DoE exhibit numerous advantages. A method to design experiments that maximize process knowledge while minimizing resource use is the experimental design strategy. As much as possible, provide accurate information. Find out how factors interact. Analyze each factor individually to determine its relative significance. Predicting how a process will behave within a design space [24].

OFAT is superior to DoE on several counts. Utilize the least number of resources possible with experimental design methodologies. Data should be provided as accurately and efficiently as possible. Investigate their interactions. Rank each variable according to its relative importance. Within the design space, allow for the prediction of process behavior. (CPPs) Critical Process Parameters and (CQAs) Critical Quality Attributes should be linked in a strong, casual manner. Pharmaceutical products must be optimized simultaneously as they include multiple CQA's. Improve product or process resilience, i.e., make it less susceptible to uncontrollable factors and external events. Identify outliers inside the established experimental matrices to ensure their protection [25].

On the other hand, OFAT methods identify local sub-optimal zones by modifying one aspect at a time. It cannot study multiple factors at once or look at their interconnections, as this antiquated technique requires a lot of time. QbD applications cannot use OFAT due to its flaws. A key advantage of the DoE technique over OFAT experiments is how it clarifies the interaction between input elements. Input elements' effects on output are assessed by plotting interaction effects.

By using this method, an existing design can be enhanced while reducing the number of experimental trials, analyzing, and optimizing the complex interaction between independent variables, and reducing the total amount of data. Therefore, compared to traditional experimental

work, this statistical method is more practical because it incorporates interactions between variables and, therefore, displays the cumulative effects of the variables. In addition, several types of response surface design, such as the Central Composite, Box-Behnken, and Hybrid designs are sometimes useful in practice [10].

8. TYPES OF DoE AND DESIGN SPACE

8.1 Implementing Design Spaces: Challenges and Barriers

The challenges and obstacles associated with implementing Design Space include fear of revenge when expressing all the information and data collected. In terms of design, the "current state" of things is well understood by the industry, which must be associated with higher quality assurance criteria and stricter risk management. There is also the possibility of higher initial development expenses and a longer development period. Planned experiments are part of the experimentation strategy. As a result, the best method is typically used because it relies on guesswork to select input pieces. Although this may seem to be an excellent solution, it has no scientific basis and there is no way of knowing if it is the best. As another option for adjusting one variable at a time, the OFAT method is employed [26,27]. A level can be quantitative (e.g., temperature or voltage) or qualitative (e.g., coolant presence) (such as temperature). When a level changes in a factor, it generates a change in response. On the other hand, the OFAT approach can reveal only one causal effect, and the causal effects of multiple factors are generally not additive, indicating that they interact. This is called interaction when one component's effect on another component's reaction differs on different levels. A single element is changed in the OFAT approach without affecting all the other elements. A scientific study involves simultaneously varying multiple variables to detect the main effect and the interaction effect of the response variable. If factors have discrete values (levels), then the number of levels will define the experimental design. Full factorial experiments involve experimenting with all scenarios of component levels available. As opposed to the full factorial design, fractional factorial experiments only use a portion of the runs in the design [28,29].

8.1.1 Screening designs

In addition to determining which ingredients to include in follow-up studies, these designs are

used to quantify the gradient impact of individual components.

8.1.1.1 Taguchi designs

For the analysis of parameter space, Taguchi uses fractional factorial arrays calculated from a DoE, also known as orthogonal arrays. Since Taguchi believes it is unnecessary to consider interactions between two design variables directly, he invented a method of tabulated designs that requires fewer experiments than a full factorial design. It is advantageous to be able to work in discrete variables. Taguchi ignores parameter interactions, which is a disadvantage. Using these pillars, we established a whole approach that simplifies the implementation of DoE in enterprises. Our goal is to offer businesses a straightforward engineering process that doesn't ignore the issue's complexity or statistics [30]. It is a great advantage that today's software is capable of aiding users in setting up and conducting investigations [31,32].

8.1.1.2 Plackett Burman design

Regardless of the level of N runs, $k=N-1$ factors can be analyzed at each level of N, where N represents a multiple of four. Screening tests are typically done with resolution III designs. Due to the muddled nature of the alias structure, each significant influence is accompanied by partial effects of several two-factor interactions [33]. To determine the effect of both components on lactase production, Plackett-Burman statistics are commonly used. The 'n+1' test screens "n" variables in the two-factorial (i.e., 1 and +1) design for variables relevant to the production. Plackett-Burman matrices were used to examine all 11 characteristics in this study. Using high (+1) and low (1) measurements of each variable, the primary effect was determined [34]. Plackett-Burman configuration is a useful tool for screening process parameters' effects on yields when using a response surface methodology. Using this method in conjunction with an optimization study can significantly reduce the number of experiments required in the following optimization study [35,36].

The QbD approach was used by Kuchekar et al., to develop polymeric micelles containing capecitabine. Plackett Burman screening design was used to identify the significant formulation and process variables like HP β -CD, ultrasonication time, and drug concentration. The

factors were confirmed using the p-value less than 0.05 to evaluate robustness. The. Finally based on the findings the design space was confirmed. The Plackett Burman screening design was performed using STATGRAPHICS XVI [33].

8.1.2 Factorial design

With factorial designs, a predetermined matrix of factors is used to alter process parameters simultaneously and deliberately. They are distinguished from mixed designs by their ability to alter each aspect separately. Several factors can be used in a factorial experiment. An experiment with only one component is a simple comparative experiment. In these cases, we analyzed the data using a t-test or an ANOVA [37]. Studies with more components have more possible combinations as well. A 2-level design with 8 variables has 256 combinations, which makes constructing and analyzing them challenging. An experiment requiring multiple factors requires a lot of resources, supplies, and time. A second challenge with multiple factorial designs is maintaining experimental conditions across many trials. To avoid the issues associated with multiple factor factorial designs, they may be designed as Full Factorial Design $2k$ or Fractional Factorial Design $2kp$, depending on the circumstances [38]. This example employs a full factorial that consists of 2 levels, k factors, and p fractions. Factorial therapies are based on a combination of factors.

8.1.3 Full factorial design

They show all possibilities of combining the levels of each element with those of the others. Multiplying the number of levels of each factor by the number of levels of each factor determines the number of experimental runs. It is especially valuable to experiment with two levels of components ($2k$) as it is extremely efficient. Full factorial designs with two levels offer the greatest power for screening experiments since they allow one to study the principal effects of the input variables and their interactions on the output responses [39,40]. There are $2k$ experiments needed for full factorial designs with two levels, where k is the number of factors to be investigated. In this study, two levels of factoring are used. An experimental design with two levels always places all input elements at the same level.

Kuchekar et al. developed diltiazem hydrochloride chronotherapeutic tablets using 3^2

full factorial designs with dependent variables selected as t10%, t25%, t75%, and t90% of the cumulative drug. The concentrations of independent variables, xanthan gum, and concentration sodium alginate were varied to check the impact on the selected responses. The study concluded that the drug release pattern changed by the selection of independent variables. DESIGN EXPERT was used to perform the 3^2 full factorial designs [41].

8.1.4 Fractional factorial design

Usually, $1/2$ or $1/4$ are the fractional factorial designs, which are a subset of full factorial designs. The screening method is frequently used when there are more than 4 or 5 components. They are unable to decipher major effects and interactions due to confounding or aliasing. A design's "resolution" refers to its ability to assess effects and interactions without being confounded. Major effects do not alias to other main effects in Resolution III designs, but they may alias with two-factor interactions, some of which may alias to each other. The presence of two-factor interactions that adversely affect the answer can be misleading [42]. A major effect in Resolution IV does not alias into another main effect or a two-factor interaction, but instead, it may alias into a three-factor interaction. Interactions between two factors are also aliased. Due to their clear principal effects, they are a good choice for screening. Compared to full factorial designs, Resolution V (or higher) designs are less expensive and take up less space. There is no aliasing of principal effects or interactions between two factors. To refer to these latter interactions, you could use the term "three-factor interactions.". If interactions between three factors (or higher) are not significant or unlikely, both main effects can be estimated. With decreasing design resolution, it becomes increasingly difficult to understand the results [43]. For factors with just two levels apiece, even a full factorial can have a very large number of runs. To minimize the number of runs, it is possible to select a fraction of the whole factorial, such as half or a fourth. Fractional factorial designs are the same as $2k-p$ factorial designs. What they are, however, is the $1/2^p$ fraction of a $2k$ factorial experiment. Fractional fractionation can cause confounding. Therefore, because the resolution measures how confused the design is, it is a very important factor. The ease of use and high inductive power of factorial designs make them useful [44,45].

8.1.5 Response surface methodology

An empirical model is developed by utilizing response surface methodology (RSM). Experiments designed meticulously have the goal of maximizing an output variable (response) influenced by numerous independent variables (input variables) [46]. The experimental analysis consists of a series of tests, known as Runs, that are used to test the effects of modifications to input variables on output responses. Before moving on to numerical experiment modeling, RSM was initially designed to model experimental response [47]. The difference is in the type of error caused by the response. While measurement error can produce inaccurate results in physical experiments, numerical noise occurs in computational experiments as the result of inaccuracies in iterative processes, round-off errors, or discrete representations of continuous physical phenomena. It is supposed that RSM generates random errors [48].

8.1.5.1 Centre composite design

Central composite designs (CCDs) are among the most popular as they require fewer experiments and use five levels of each input component compared to complete factorial designs with three levels. These aspects of the design are the factorial points of the design, the axial points of the design, and the center point. An axial (or star) point is necessary to estimate second-order effects based on an axiomatic design (the cube's corners). Response surface approaches are the most common [49]. Alpha value 1.0, as measured by a face-centered central composite design, can alter the number of levels for each factor in a typical design. There are only three levels in each aspect of face-centered design. A quadratic model is estimated by using this architecture, which does not depend on missing data [11,50]. CCDs composed of composite factorial data (CCD) include point factorial data, axial data, and center data [51,52].

8.1.5.2 Box Behnken design

As a kind of multilevel fractional factorial design, Box-Behnken can simulate first and second-order response surfaces. Three-level full factorial designs are less efficient than these, especially if there are many input variables. Design that utilizes three levels per element and fewer trials per element than the central composite design, called Box Behnken Design (BBD) [53,54]. Axial

points and corners of the design space are eliminated (or extreme factor combinations are bypassed) to address many of the shortcomings of central composite designs. In addition, this design is completely rotatable, so all its equidistant sites from the design center will display the same prediction variance. With this design, fewer experiments are conducted for an equal number of factors than those with a composite central design. Due to these factors, BBD outperforms central composite designs [55]. It is a second-order, incomplete three-part factorial, rotatable, and not like conventional fractions. BBD is a result of combining blocks with factorials. In q factor block designs of size two, find an incomplete block design for q treatments [56,57,58,59].

Pawar et al. [60] studied the evaluation of Gellan Gum, sodium bicarbonate, and calcium chloride concentration, three independent variables, using a Box Behnken factorial design to determine the floating lag time and t50 (time required for 50% drug release). The BBD was performed using SYSTAT 13 and was subjected to multiple regression analysis.

8.1.6 Mixture designs

8.1.6.1 Simplex lattice

One of the widely used designs. In this design, factors with the same ranges are considered. To generate the design, it imposes an equal distance grid over the design area. To detect its absence, this design needs to be improved.

8.1.6.2 Simplex centroid

In addition to a simplex-lattice design, a simplex-centroid design may be used. It is applicable if all components have the same range of values (between 0 and 1) and no constraints limit the design area. Every run has a center point containing equal amounts of all ingredients [61,62].

9. CONCLUSION

Finally, statistical thinking and knowledge management are useful tools in pharmaceutical development because they support operational excellence within the QbD framework. It is projected that DoE's use trend will slow down in the short term for existing scientific domains, but it will expand very quickly to other areas of science. Factorial trials help develop or enhance

systems, processes, and products by making decisions that are informed and accurate. Design an experiment, conduct it, collect the data, and analyze the results. It has become more popular in recent years to optimize formulations. The optimization would become a much more popular development tool. In all phases of product development, from pre-formulation through clinical trials and beyond, DoE is a significant tool for formulation scientists. A quality breakthrough requires persistence, patience, perseverance, and a thirst for knowledge in computer and statistical fields. Optimizing products reduce the number of trials, reducing the cost and time spent on product development.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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