PHARMACEUTICAL SOFTWARE: DESIGN EXPERT SOFTWARE (DOE) ASSESSMENT & DRUG DEVELOPMENT

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Abstract

The pharmaceutical sector is expanding, and its various components call for an integrated strategy. In the field of life sciences, finding new pharmaceuticals is still a big focus, but streamlining other areas, such as a medication's composition and how it is recorded and authorized, may be just as important in defining its value. These areas are crucial for guaranteeing the safety, effectiveness, and quality of medications. In order to make these tasks possible, IT is crucial. Pharmaceutical product control and accounting are provided by specialized software systems in order to maintain appropriate work and adhere to legal standards. Adoption of such software has mostly been driven by government entities' regulatory requirements to retain records and provide quality control. To meet their operational needs, pharmaceutical businesses often employ a range of software tools, including enterprise-wide systems and single applications. Right now, roughly. Different sectors utilize a range of software applications, many of which are found in many larger organizations that may design their proprietary software based on their company's needs, while there are commercially available software programs for small companies as well. Because of the increased enforcement of standards like GCP (Good Clinical Practice), GLP (Good Laboratory Practice), and GMP (Good Manufacturing Practice), these computerized systems are expanding. b) The standards set for production, laboratory testing, and clinical trials provide assurance that a product is high-quality and safe for the general population to ingest.

Keywords: *Pharmaceutical Software, types of software, design expert software, drug development.*

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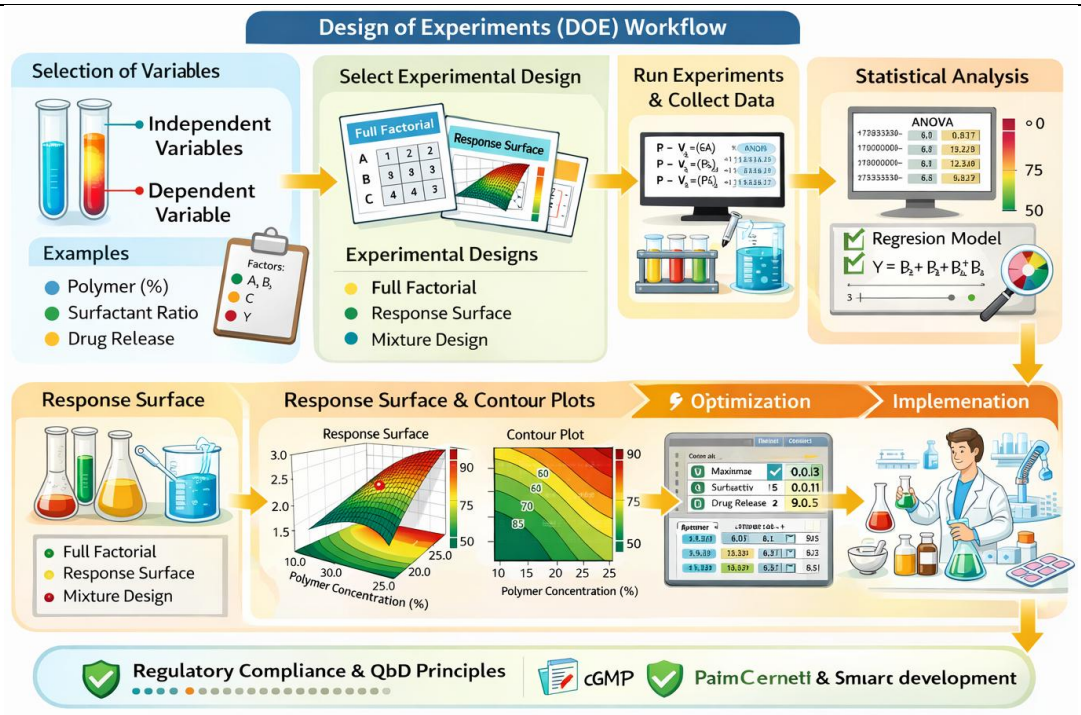

Figure 1: Graphical Abstract

1. Introduction

In order to guarantee product quality, safety, and efficacy, pharmaceutical medication development is a very complicated, multidimensional, and knowledge-intensive process that requires careful management of formulation factors, processing conditions, and analytical parameters. A growing number of people believe that traditional development methods focused on one-factor-at-a-time (OFAT) experiments are ineffective and insufficient for comprehending the factor interactions and variability present in pharmaceutical systems. Consequently, a paradigm shift has occurred toward methodical, statistically driven approaches that allow for a greater understanding of the process while cutting down on development time and expense (Montgomery, 2017; Antony, 2014).

A systematic statistical technique called Design of Experiments (DOE) enables the concurrent examination of several independent variables and their impacts on one or more dependent responses. DOE makes it possible to identify important factors, assess interactions, and create prediction models with fewer experimental runs by utilizing mathematically designed experimental designs. Pre-formulation, formulation optimization, process development, and analytical method validation are just a few of the stages of pharmaceutical development where numerous studies have shown that DOE increases experimental efficiency, improves reproducibility, and supports logical decision-making (Beg et al., 2019; Singh et al., 2020).

The fundamental role of DOE in pharmaceutical research and manufacturing has been further reinforced by the growing adoption of Quality by Design (QbD) concepts. QbD places a strong emphasis on a methodical, risk-and science-based approach to pharmaceutical development in which product quality is included into the design rather than tested in the finished product. The use of DOE for defining design space, identifying critical quality attributes (CQAs), and comprehending the influence of critical material attributes (CMAs) and critical process parameters (CPPs) on product performance is specifically encouraged by regulatory guidelines published by the International Council for Harmonization (ICH), specifically ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System) (ICH, 2009; Yu et al., 2014).

Advanced statistical software systems have been developed to help the formulation of experimental designs, data analysis, visualization, and optimization in order to facilitate the practical implementation of DOE in pharmaceutical contexts. Among these tools, Design-Expert® software has become quite popular in chemical, pharmaceutical, and biopharmaceutical research because of its extensive statistical capabilities, user-friendly interface, and specific DOE-focused framework. Both early-stage development and late-stage optimization studies can benefit from the software's support for a variety of experimental designs, including as factorial designs, response surface techniques, mixture designs, and screening designs (Anderson & Whitcomb, 2016; Eriksson et al., 2008).

The optimization of solid dosage forms, controlled-release systems, nano-formulations, and herbal and biopharmaceutical medicines have all made substantial use of Design-Expert. For formulation scientists and process engineers in particular, its capacity to produce response surface plots, contour maps, and desirability-based optimization results offers an intuitive portrayal of intricate multivariate connections. Additionally, as part of QbD-driven development strategies, DOE models created with Design-Expert are increasingly being included in regulatory submissions, demonstrating the growing regulatory acceptance of statistically justified experimental designs (Rathore & Winkle, 2009; Politis et al., 2017).

With an emphasis on its theoretical underpinnings, real-world applications, statistical evaluation techniques, and regulatory significance, this review seeks to objectively evaluate the function of Design-Expert software in pharmaceutical drug development. The review aims to offer a thorough and forward-looking assessment of the application of

Design-Expert software as a fundamental instrument in contemporary, quality-driven drug development by fusing DOE concepts with actual pharmaceutical case studies and new digital trends.

2. Design-Expert Software: An Overview

Stat-Ease Inc. created Design-Expert®, a specialized statistical program for experiment design and analysis (DOE). In the pharmaceutical sciences, it is frequently utilized to facilitate methodical testing, process comprehension, and optimization. Design-Expert is especially useful for Quality by Design (QbD)-driven drug development because, in contrast to general statistical packages, it is specifically designed to assist users with experimental design selection, model building, visualization, and numerical optimization (Montgomery, 2019; Anderson & Whitcomb, 2016).

Design-Expert has become well-known in pharmaceutical research because it can effectively assess how formulation variables, process parameters, and their interactions affect critical quality attributes (CQAs) while lowering the cost, duration, and material consumption of experiments (Beg et al., 2019).

2.1 Evolution and Development of Design-Expert

In order to make statistical experimental design easier for scientists and engineers without basic statistical training, Stat-Ease Inc. first released Design-Expert in the late 1980s. Although factorial and response surface designs were the main focus of early versions, later upgrades added mixture designs, optimum designs, split-plot designs, and resilient parameter design (Anderson & Whitcomb, 2016).

Design-Expert included tools in line with regulatory expectations, such as design space exploration, desirability-based optimization, and model diagnostics in accordance with ICH Q8 (R2) recommendations, as pharmaceutical sciences evolved toward QbD and regulatory science (ICH, 2009). Improved regression diagnostics, automatic model selection, improved graphical presentation, and user-friendly workflows that enable both academic research and industry applications are features of recent software versions (Stat-Ease Inc., 2023).

The continual growth of Design-Expert reflects the increasing demand for data-driven, statistically supported decision-making in modern drug development.

2.2 Key Features and Capabilities

Design-Expert offers a comprehensive set of features tailored for DOE-based pharmaceutical research:

Experimental Design Generation

The software supports a wide range of experimental designs, including:

- Full and fractional factorial designs
- Response surface methodologies (central composite, Box–Behnken)
- Mixture and mixture-process variable designs
- Optimal and custom designs for constrained experimental spaces

With fewer experimental runs, these designs allow for effective investigation of formulation and process variables (Myers et al., 2016).

Statistical Modeling and Analysis

Design-Expert uses polynomial regression modeling, analysis of variance (ANOVA), and lack-of-fit testing to determine model significance and suitability. Users can find statistically important elements and interactions with the help of automated model reduction and selection methods (Montgomery, 2019).

Visualization and Interpretation

The software provides interactive graphical outputs, including:

- Response surface plots
- Contour plots
- Perturbation plots
- Diagnostic plots (normal probability, predicted vs. actual)

These visual aids make it easier to comprehend factor-response interactions mechanistically, which is essential for process control and formulation optimization (Beg et al., 2019).

Optimization and Desirability Functions

Design-Expert performs multi-response optimization using desirability functions, enabling the simultaneous optimization of several CQAs. This property is particularly important in pharmaceutical formulation, where trade-offs amongst responses such as solubility, hardness, and stability are typical (Derringer & Suich, 1980).

2.3 Comparison with Other DOE Software Tools

Several statistical software packages are available for DOE applications; however, Design-Expert offers particular advantages for pharmaceutical research when compared to general-purpose tools such as JMP®, Minitab®, and MODDE®.

With built-in regulatory-relevant outputs, guided design selection, and simple graphical interpretation, Design-Expert is especially tailored for DOE workflows. Although JMP

and Minitab provide more extensive statistical capabilities, DOE application frequently necessitates advanced statistical knowledge. Although MODDE is more frequently employed in industrial settings and may have a steeper learning curve, it is equivalent in pharmaceutical applications (Eriksson et al., 2008; Anderson & Whitcomb, 2016).

Design-Expert is one of the most popular DOE tools in pharmaceutical formulation and process development because it strikes a compromise between statistical rigor, usability, and good alignment with QbD concepts.

1. Table 1: Comparison of DOE Software Tools Used in Pharmaceutical Development

Software Tool	Key Features	Types of Designs Supported	Advantages	Limitations
Design-Expert®	User-friendly GUI, response surface plotting, optimization, model diagnostics	Full Factorial, Fractional Factorial, RSM, Mixture Designs, Screening Designs	Easy visualization, strong statistical analysis, widely accepted in pharma	Limited integration with AI tools (older versions), cost
Minitab	Advanced statistics, regression, DOE, Six Sigma tools	Full Factorial, Fractional Factorial, RSM	Powerful statistical engine, widely used in industry	Less specialized for DOE than Design-Expert
JMP	Interactive dashboards, predictive modeling, visualization	Full Factorial, Fractional Factorial, RSM, Custom Designs	Dynamic graphs, integration with analytics	Requires high computing resources
MATLAB (with Statistics Toolbox)	Flexible programming environment, advanced modeling	Custom factorial, RSM	Highly flexible, programmable	Steep learning curve for non-programmers

3. Principles of Design of Experiments (DOE)

A structured statistical method called Design of Experiments (DOE) is used to efficiently and methodically examine how various input variables affect one or more outcome

responses. DOE is essential to pharmaceutical research and development because it helps minimize experimental trials while comprehending intricate formulation and process interactions. In contrast to traditional one-factor-at-a-time testing, DOE permits simultaneous factor variation, which makes it possible to identify interactions and nonlinear effects that are frequently crucial for product quality. As a result, DOE supports the regulatory requirements specified in ICH Q8 (R2) for pharmaceutical development and serves as the scientific foundation for Quality by Design (QbD) (ICH, 2009; Montgomery, 2019).

3.1 Fundamentals of DOE

The core idea of DOE is the systematic and intentional manipulation of experimental variables to assess their impact on measured responses. While responses relate to dependent variables, which are frequently critical quality attributes (CQAs) like dissolving rate, hardness, particle size, or stability, factors reflect independent variables like excipient concentration, processing temperature, or mixing speed. In order to draw significant conclusions, each factor is examined at predetermined levels and the aggregate impact of these factors is examined using statistical models.

A fundamental feature of DOE is its capacity to detect interaction effects, where the influence of one element depends on the level of another. Although these interactions are commonly seen in pharmaceutical formulations and production processes, conventional experimental methods are unable to identify them. Regression modeling and analysis of variance (ANOVA) are commonly used in statistical analysis of DOE data to evaluate factor significance, experimental variability, and model suitability. Risk assessment, optimization, and the creation of a design space that complies with regulatory requirements are all supported by the knowledge produced by DOE (Beg et al., 2019; Myers et al., 2016).

3.2 Types of Experimental Designs

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requirements are all supported by the knowledge produced by DOE (Beg et al., 2019; Myers et al., 2016).

3.2.1 Full Factorial Designs

Full factorial designs involve the examination of all conceivable combinations of factor levels and provide complete information on both main effects and interaction effects. The number of experimental runs grows exponentially in a study that examines several parameters at two or more levels. Despite this drawback, full factorial designs are quite instructive and especially helpful in the early phases of development when a mechanical grasp of the system is needed.

Full factorial designs are frequently employed in pharmaceutical applications to determine key process parameters (CPPs) and critical material attributes (CMAs) influencing product performance. Researchers can thoroughly assess factor interactions with these designs, which is crucial for sound formulation and process development. However, their use is frequently restricted to studies with a limited number of parameters because of the high number of experimental runs needed (Montgomery, 2019).

3.2.2 Fractional Factorial Designs

Fractional factorial designs are a subset of full factorial designs and are created to reduce the experimental effort while keeping critical information regarding main effects and selected interactions. These designs allow for effective screening of many parameters with fewer experimental runs by deliberately confusing higher-order interactions.

Fractional factorial designs are frequently used in pharmaceutical research to find important formulation elements or process factors in the first screening stage. When there are limitations on time, money, or material availability, these designs are especially beneficial. Fractional factorial designs offer a useful mix between information content and experimental efficiency, making them appropriate for early-stage risk assessment and factor prioritization even though certain interactions may be aliased (Anderson & Whitcomb, 2016; Montgomery, 2019).

3.2.3 Response Surface Methodology (RSM)

A collection of statistical methods called Response Surface Methodology (RSM) is used to simulate, examine, and optimize responses that are impacted by several quantitative variables. RSM focuses on investigating curvature and nonlinear interactions within the experimental domain and is usually used once important parameters have been found

through screening designs. Box-Behnken Designs (BBD) and Central Composite Designs (CCD) are typical RSM designs.

RSM is widely utilized in pharmaceutical formulation and process development to maximize product performance attributes like stability, bioavailability, and drug release. Response prediction and the determination of ideal operating conditions are made possible by the second-order polynomial models produced by RSM. Under QbD frameworks, graphical tools like contour plots and three-dimensional response surface plots help construct a design space and make factor-response interactions easier to understand (Myers et al., 2016; Beg et al., 2019).

3.2.4 Mixture Designs

When experimental factors are components of a formulation whose proportions add up to a constant total, specific DOE techniques known as mixture designs are used. Because the response is dependent on the relative proportions of components rather than their absolute numbers, this feature sets mixture designs apart from factorial designs. In pharmaceutical systems that contain excipients, polymers, lipids, or solvents, mixture designs are very important.

Mixture designs are frequently employed in pharmaceutical development to optimize emulsions, suspensions, tablet formulations, nanoformulations, and herbal preparations. Simplex lattice and simplex centroid designs are common mixture design techniques that enable methodical investigation of formulation composition and its influence on important quality attributes. These designs promote logical formulation creation and optimization by offering insightful information about component compatibility and synergistic effects (Cornell, 2011; Eriksson et al., 2008).

Table 2: Common Experimental Designs in DOE for Pharmaceutical Applications

Design Type	Description	Applications in Drug Development	Advantages	Limitations
Full Factorial	All possible combinations of factors and levels	Pre-formulation studies, formulation optimization	Complete interaction data, highly reliable	Large number of experiments for many factors
Fractional Factorial	Subset of full factorial combinations	Screening experiments, early-stage optimization	Fewer experiments, identifies significant factors	May miss higher-order interactions

Response Surface Methodology (RSM)	Models the relationship between factors and responses	Optimization of dosage forms, nanoformulations	Visualizes factor-response relationships, allows prediction	Complex model fitting may be required
Mixture Designs	Factor levels sum to a constant (e.g., excipients in a formulation)	Herbal formulations, nanoemulsions	Effective for formulation compositions	Limited for non-mixture applications

4. Application of Design-Expert Software in Drug Development

In order to facilitate systematic testing, optimization, and risk-based decision-making, Design-Expert® software has been widely used throughout several phases of drug development. It is especially useful in pharmaceutical research, where formulation and process variables are highly interrelated, because of its capacity to combine statistical rigor with intuitive visualization. In accordance with regulatory Quality by Design (QbD) principles, the program facilitates the effective identification of essential factors, the creation of ideal conditions, and the production of scientifically supported data (Beg et al., 2019; Anderson & Whitcomb, 2016).

4.1 Pre-Formulation Studies

The first stage of medication development is known as pre-formulation research, which focuses on characterizing the physicochemical characteristics of active pharmaceutical ingredients (APIs) and how well they work with excipients. At this point, a lot of people use Design-Expert software to methodically assess how factors like particle size, polymorphic form, pH, and excipient type affect important responses like solubility, stability, and dissolution behavior.

By utilizing screening designs such as full or fractional factorial designs, Design-Expert permits speedy identification of critical material attributes (CMAs) that significantly affect medication performance. The software's statistical analysis and visualization tools help researchers comprehend interaction effects and variability, which lowers the possibility of formulation failure in subsequent phases of development (Montgomery, 2019; Singh et al., 2020).

4.2 Formulation Optimization

One of the most popular and significant uses of Design-Expert software in pharmaceutical development is formulation optimization. The software is widely used to optimize the composition of sophisticated drug delivery systems, liquid formulations, semi-solids, and solid dosage forms. To attain the required product properties, variables including polymer concentration, surfactant levels, binder type, and compression force are methodically investigated.

Several key quality characteristics (CQAs), including medication release, hardness, friability, and stability, can be optimized simultaneously using Response Surface Methodology (RSM) and mixture designs created with Design-Expert. The desirability function methodology permits multi-response optimization, offering an objective and quantitative mechanism for identifying optimal formulation conditions. Several research have shown how Design-Expert can improve formulation robustness while reducing experimental effort (Beg et al., 2019; Myers et al., 2016).

4.3 Process Optimization and Scale-Up

Process optimization and scale-up are crucial processes in transferring laboratory-scale formulations to commercial manufacture. Critical process parameters (CPPs) like mixing time, granulation speed, drying temperature, and compression force can be systematically evaluated with Design-Expert software. The program makes it possible to identify process characteristics that guarantee consistent product quality by using DOE-based methodologies.

Design-Expert is used to analyze the influence of scale-dependent variables and process resilience in scale-up studies. ANOVA analysis and statistical modeling are useful tools for identifying important variables and interactions that could affect a product's performance during manufacturing. This data-driven strategy facilitates the creation of scalable and repeatable pharmaceutical processes while lowering batch-to-batch variability (Montgomery, 2019; Yu et al., 2014).

4.4 Analytical Method Development and Validation

Design-Expert software is increasingly applied in analytical method development and validation under the context of Analytical Quality by Design (AQbD). It permits systematic study of analytical factors such as mobile phase composition, pH, flow rate, column temperature, and detection wavelength on technique performance characteristics.

Analytical techniques can be adjusted for factors like resolution, retention time, sensitivity, and robustness using DOE techniques incorporated in Design-Expert. By

making it easier to identify method operable design regions (MODR), the program guarantees dependable analytical performance under a variety of circumstances. This strategy lowers the need for revalidation, improves method robustness, and synchronizes analytical development with regulatory needs (Ribeiro et al., 2018; Rozet et al., 2011).

4.5 Quality by Design (QbD) Implementation

A methodical, risk- and science-based approach to pharmaceutical development is emphasized by Quality by Design (QbD). By facilitating organized experimentation, risk assessment, and design space establishment, Design-Expert software is essential to QbD implementation. The software facilitates the identification of CMAs and CPPs and their interactions with CQAs through statistically proven models.

Using response surface models and contour plots, Design-Expert enables design space exploration and offers both quantitative and visual support for operating ranges. The software is a useful tool for regulatory submissions since it can produce reliable, repeatable data that complies with ICH Q8 (R2), Q9, and Q10 criteria. As a result, Design-Expert is extensively used as a fundamental platform for QbD-driven pharmaceutical development in both academic and commercial contexts (ICH, 2009; Yu et al., 2014).

Table 3: Applications of Design-Expert Software in Pharmaceutical Drug Development

Stage	Purpose	DOE Approach Used	Example
Pre-formulation	Identify optimal excipient ratios, solubility enhancement	Full Factorial, Screening Designs	Solid dispersion of poorly soluble drugs
Formulation Optimization	Maximize drug release, stability, and bioavailability	RSM, Mixture Designs	Self-nanoemulsifying drug delivery systems (SNEDDS)
Process Scale-up	Determine critical process parameters for manufacturing	Fractional Factorial, RSM	Tablet compression optimization
Analytical Method Development	Optimize HPLC conditions, peak resolution	Box–Behnken Design	RP-HPLC method for herbal extract
QbD Implementation	Establish design space and control strategy	RSM, Desirability Function	Nanosystem optimization for oral delivery

5. DOE Assessment Using Design-Expert Software

A thorough framework for evaluating experimental designs, creating statistical models, and refining pharmaceutical formulations and procedures is offered by Design-Expert® software. The DOE assessment phase is crucial because it establishes the created models' predictability, interpretability, and dependability. Design-Expert integrates experimental design generation, statistical analysis, and graphical interpretation into a unified workflow, enabling systematic evaluation of factor–response relationships and supporting data-driven decision-making in drug development (Anderson & Whitcomb, 2016; Montgomery, 2019).

5.1 Selection of Independent and Dependent Variables

A fundamental stage in DOE assessment with Design-Expert software is the selection of suitable independent and dependent variables. Polymer concentration, surfactant ratio, mixing speed, drying temperature, and other formulation elements or process parameters that are purposefully changed during research are examples of independent variables, also known as factors. Drug release, particle size, assay, hardness, stability, and other critical quality characteristics (CQAs) are examples of dependent variables that correlate to measured responses.

Design-Expert ensures that the variables chosen are both practically manageable and scientifically relevant by facilitating systematic factor selection through screening designs and risk-based techniques. The reliability of subsequent statistical analysis and optimization results is improved by correctly identifying factors and responses, which also improves model interpretability and lowers experimental noise (Beg et al., 2019; ICH, 2009).

5.2 Model Building and Statistical Analysis

Fitting experimental data to mathematical models that explain the relationship between causes and responses is the process of model creation in Design-Expert. To capture both main effects and higher-order interactions, linear, interaction, or quadratic polynomial models are created, depending on the experimental design. The program offers automatic model selection capabilities that make it possible to compare several model orders according to goodness-of-fit and statistical significance standards.

Regression analysis is used by Design-Expert to estimate model coefficients and evaluate how they affect response variability. Diagnostic tools, including residual analysis and model adequacy tests, assist evaluation of assumptions such as normality and

homoscedasticity. This methodical approach guarantees that the chosen model may be utilized for prediction and optimization with reliability and appropriately depicts the experimental system (Myers et al., 2016; Montgomery, 2019).

5.3 ANOVA and Regression Analysis

A key statistical tool in Design-Expert for assessing the importance of created models and specific model terms is analysis of variance (ANOVA). ANOVA provides statistical measures like F-values and p-values for hypothesis testing by dividing total variability into components related to model effects and experimental error. A statistically significant model suggests that the specified factors meaningfully influence the answer under examination.

By measuring the strength and direction of factor effects, regression analysis enhances ANOVA. Coefficient estimates, coefficient of determination (R2), adjusted R2, anticipated R2, and lack-of-fit statistics are among the important statistical parameters that Design-Expert reports. These measures are critical for measuring model robustness and prediction performance. In pharmaceutical research, regression analysis and ANOVA together offer a strong statistical foundation for evaluating DOE results (Montgomery, 2019; Anderson & Whitcomb, 2016).

5.4 Response Surface and Contour Plot Interpretation

One of Design-Expert's main advantages is its ability to interpret DOE data graphically. An intuitive grasp of interaction effects and nonlinear trends is made easier by response surface plots and contour plots, which graphically depict the relationship between two or more factors and a response. In pharmaceutical development, where a variety of formulation and process variables interact to affect product quality, these graphs are especially useful.

Three-dimensional response surface plots provide a thorough depiction of factor–response interactions, whereas two-dimensional contour plots allow identification of favorable locations within the experimental domain. Dynamic interaction with these plots is made possible by Design-Expert, which helps with result interpretation and communication. These graphical tools facilitate the regulatory justification of operating ranges under QbD frameworks and are essential for design space exploration (Myers et al., 2016; Beg et al., 2019).

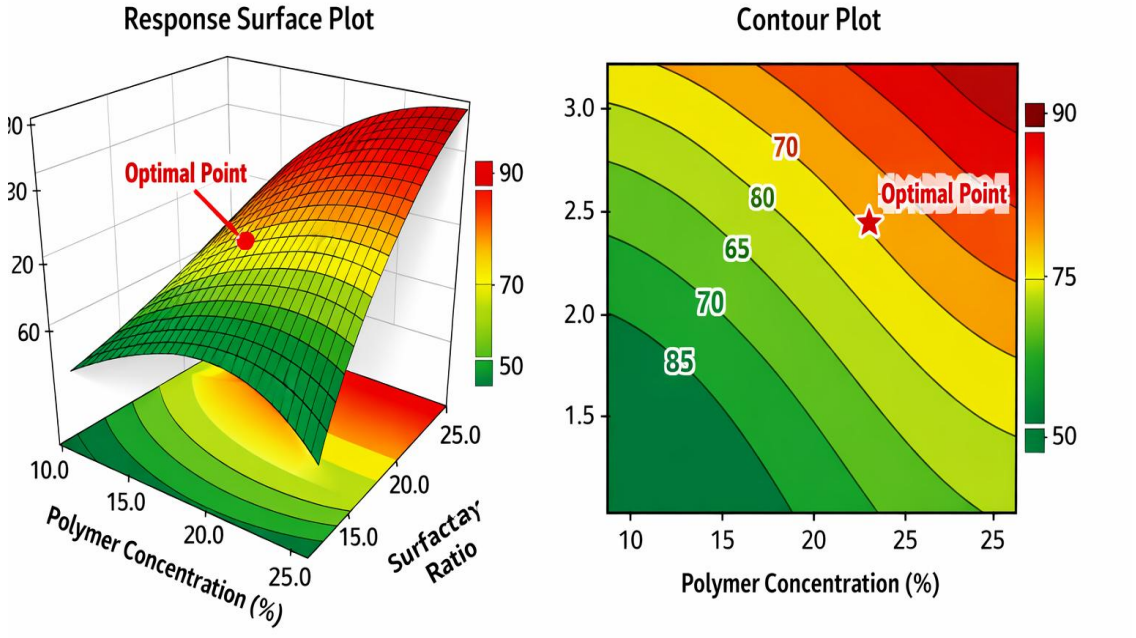

Figure 2: Response Surface and Contour Plot Example

5.5 Optimization and Desirability Function

One of the main results of DOE evaluation with Design-Expert software is optimization. Pharmaceutical development frequently entails the simultaneous optimization of several reactions, some of which may have conflicting goals. The desirability function approach, which transforms individual responses into dimensionless desirability values between zero and one, is how Design-Expert tackles this problem.

The software finds experimental settings that offer the optimal compromise between several CQAs by merging individual desirabilities into an overall desirability score. Robust formulation and process development are supported by this numerical optimization approach, which facilitates objective decision-making. The desirability function approach is commonly used in pharmaceutical research and satisfies regulatory requirements for methodical optimization that is supported by science (Derringer & Suich, 1980; Anderson & Whitcomb, 2016).

6. Case Studies and Practical Applications

Pharmaceutical research has made extensive use of Design-Expert® software to solve formulation and process issues across a variety of dosage forms and drug delivery systems. Its efficacy in improving product performance, lowering experimental burden, and bolstering QbD-oriented development strategies is demonstrated by a number of case studies published in the literature. The applications of Design-Expert-based DOE in solid

dosage forms, nano-formulations, and biopharmaceutical and herbal products are highlighted in the following subsections.

6.1 Optimization of Solid Dosage Forms

Because of their stability, ease of administration, and patient compliance, solid dosage forms—such as tablets and capsules—continue to be the most widely used pharmaceutical items. Design-Expert software has been widely used to optimize process parameters that affect tablet quality as well as formulation variables like binder concentration, disintegrant level, lubricant content, and compression force.

The effective application of factorial and response surface designs in Design-Expert to maximize important quality features like hardness, friability, disintegration time, and dissolution profile has been documented in a number of studies. By simultaneously examining formulation components and processing circumstances, researchers have been able to identify significant interactions and build stable formulations with enhanced performance and reproducibility. For immediate-release and modified-release dosage forms, where exact control over drug release kinetics is crucial, such DOE-driven optimization has proven very beneficial (Patel et al., 2017; Dash et al., 2020).

6.2 Nano-Formulations and Novel Drug Delivery Systems

Because of the numerous formulation variables and nonlinear interactions involved, nano-formulations and innovative drug delivery devices provide difficult formulation issues. Optimizing nanoparticle-based systems, such as polymeric nanoparticles, solid lipid nanoparticles, nanoemulsions, self-nanoemulsifying drug delivery systems (SNEDDS), and nanostructured lipid carriers, has been a common application of Design-Expert software.

Particle size, polydispersity index, drug loading, entrapment efficiency, and in vitro drug release have all been optimized in these systems using Design-Expert-based DOE. Researchers can now comprehend how surfactant concentration, lipid content, and processing circumstances affect the performance of nano-formulations thanks to response surface technique and mixture designs. Several case studies have shown that DOE-guided optimization with Design-Expert leads to improved stability, increased bioavailability, and repeatable nanosystems that can be developed further (Jana et al., 2019; Garg et al., 2021).

6.3 Biopharmaceutical and Herbal Formulations

Design-Expert software is being used for biopharmaceutical goods and herbal formulations in addition to traditional small-molecule formulations. Protein stability, encapsulation efficiency, and controlled release from delivery matrices have all been optimized in biopharmaceutical development using DOE-based methods implemented in Design-Expert. Because biologics are sensitive to changes in formulation and procedure, these applications are especially crucial.

Design-Expert has been used in herbal and phytopharmaceutical formulations to improve bioactive content, solubility, and stability by optimizing extraction procedures, excipient quantities, and formulation composition. In the study of multicomponent herbal systems, where synergistic interactions between constituents are critical to medicinal performance, mixture designs have proven particularly useful. These investigations demonstrate the adaptability of Design-Expert software in managing intricate, multivariable pharmaceutical systems that are challenging to optimize using traditional experimental methods (Verma et al., 2018; Mishra et al., 2022).

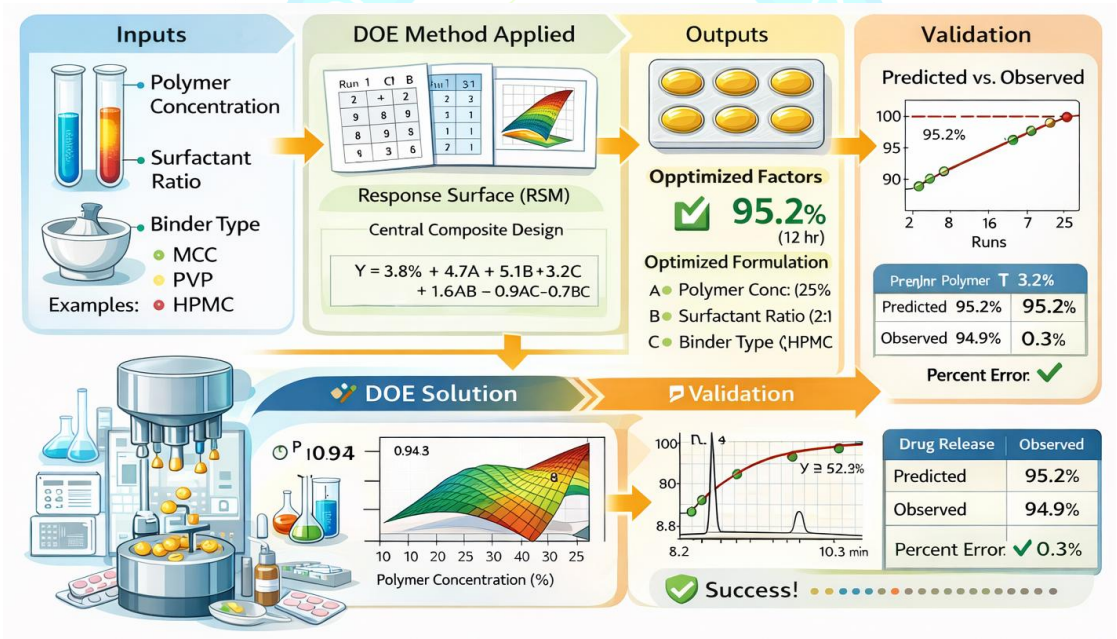

Figure 3: Case Study Summary – DOE in Pharmaceutical Formulation Optimization

7. Advantages and Limitations of Design-Expert Software

The software Design-Expert® is well known for its ability to provide statistical analysis and organized experimentation in pharmaceutical development. While the program offers major advantages in terms of efficiency, interpretability, and regulatory alignment, it also has certain limitations that must be understood. For Design-Expert to be used

appropriately and effectively in drug development, a careful assessment of its advantages and disadvantages is necessary.

7.1 Advantages in Pharmaceutical Research

The capacity of Design-Expert software to simplify the application of Design of Experiments (DOE) for intricate pharmaceutical systems is one of its main benefits. The program offers guided workflows that help researchers define factor ranges, choose suitable experimental designs, and create statistically valid experimental plans. This user-friendly framework preserves analytical rigor while lowering reliance on sophisticated statistical knowledge.

key material attributes (CMAs) and key process parameters (CPPs) that affect product quality can be identified thanks to Design-Expert's simultaneous evaluation of several formulation and process factors. Its sophisticated visualization features, such as response surface and contour plots, help logical decision-making and enable intuitive analysis of multidimensional interactions. Additionally, the desirability-based optimization approach permits simultaneous optimization of many critical quality attributes (CQAs), which is particularly important in pharmaceutical formulation development where trade-offs between responses are common.

From a regulatory standpoint, Design-Expert facilitates the creation of statistically supported data appropriate for regulatory filings and is in line with Quality by Design (QbD) standards. Its capacity to specify and illustrate design space improves process comprehension and resilience, which lowers development risk and post-approval modifications (Yu et al., 2014; Beg et al., 2019).

7.2 Limitations and Challenges

Despite its advantages, Design-Expert software has some drawbacks that, if ignored, could reduce its efficacy. The dependence on the caliber of experimental input data is a significant obstacle. Regardless of software capacity, poor experimental design, improper factor selection, or limited factor ranges can lead to deceptive models and erroneous predictions.

Another limitation is the potential for overfitting statistical models, particularly when higher-order polynomial models are used without sufficient experimental runs. Model dependability may be jeopardized by poor replication or disregard for model validation measures such projected R2 and lack-of-fit. Furthermore, even while Design-Expert is extremely specialized for DOE applications, its usage for exploratory or non-DOE-based

investigations is limited since it lacks the more extensive statistical and data-mining capabilities present in more general-purpose platforms.

Cost and license restrictions can sometimes be problematic, especially in academic or resource-constrained research environments. Additionally, users who lack adequate statistical knowledge may misinterpret statistical results, which highlights the necessity of appropriate training and methodological awareness (Eriksson et al., 2008; Ferreira et al., 2020).

7.3 Common Errors and Best Practices

When using Design-Expert software for pharmaceutical research, a number of frequent mistakes have been documented. These include choosing factors and answers incorrectly, neglecting interaction effects, failing to perform an initial risk assessment, and relying too much on numerical optimization without sufficient scientific support. Ignoring diagnostic plots and model adequacy tests further increases the danger of erroneous findings.

The best ways to use Design-Expert are to carefully organize experiments using risk assessment techniques like failure mode and effects analysis (FMEA) and prior knowledge. For a model to be credible, realistic factor ranges must be chosen, enough experimental runs and replicates must be included, and statistical diagnostics must be carefully assessed. Results are meaningfully interpreted and practically applicable when statistical outputs are combined with pharmacological expertise. Following these best practices improves DOE outputs produced with Design-Expert software in terms of dependability, repeatability, and regulatory acceptability (Ferreira et al., 2020; Rathore & Winkle, 2009).

8. Regulatory Perspective

Regulatory bodies worldwide support the adoption of methodical, science- and risk-based techniques in pharmaceutical development to assure consistent product quality and patient safety. Design of Experiments (DOE), assisted by statistical software such as Design-Expert®, plays a crucial role in satisfying these objectives by enabling structured experimentation, increased process understanding, and robust decision-making. A move away from empirical development and toward knowledge-driven pharmaceutical quality systems is reflected in the incorporation of DOE into regulatory submissions.

8.1 Role of DOE in Regulatory Submissions

Regulators are beginning to acknowledge DOE as a scientifically sound method for producing data to support lifecycle management, process optimization, and formulation

development. DOE-derived data are utilized in regulatory submissions to establish critical material attributes (CMAs) and critical process parameters (CPPs), support formulation component selection, and show control over key quality attributes (CQAs).

The creation of statistically validated models and graphical representations, including response surface and contour plots, which are commonly found in regulatory dossiers, is made easier by Design-Expert software. These results facilitate the construction of a design space and provide regulators with a clear grasp of factor–response interactions. Operating inside an approved design area reduces regulatory burden and improves manufacturing agility by giving manufacturers more freedom for post-approval adjustments without needing further regulatory filings when justified (Yu et al., 2014).

8.2 FDA and ICH Guidelines Related to DOE and QbD

The use of DOE within the Quality by Design (QbD) paradigm is specifically supported by international regulatory frameworks. The fundamental regulatory framework for DOE-driven pharmaceutical development is provided by the International Council for Harmonization (ICH) recommendations. ICH Q8 (R2) promotes the idea of design space, which is frequently generated utilizing DOE approaches, and stresses pharmaceutical development through methodical testing. While ICH Q10 describes a pharmaceutical quality system that combines product and process information across the lifecycle, ICH Q9 concentrates on quality risk management and promotes data-driven risk assessment methodologies (ICH, 2009; ICH, 2005; ICH, 2008).

Through its Pharmaceutical Quality for the 21st Century effort and Process Analytical Technology (PAT) guidelines, the U.S. Food and Drug Administration (FDA) has further emphasized the significance of DOE. These documents encourage producers to use multivariate analysis and statistical techniques to enhance process control and comprehension. According to FDA (2004) and Lawrence & Lee (2020), DOE studies carried out with software systems like Design-Expert closely match these regulatory standards and are generally accepted when backed by solid statistical analysis and scientifically validated experimental designs.

8.3 Data Integrity and Compliance Considerations

Regulatory acceptability depends on data accuracy and adherence to proper documentation methods, even as DOE and sophisticated software tools improve development efficiency. Regulators stress that data produced by DOE must be precise, comprehensive, and traceable at every stage of the experiment. This entails accurately

recording the choice of experimental design, factor ranges, statistical presumptions, and model validation outcomes.

By offering clear statistical results, repeatable studies, and comprehensive reports that can be saved as part of regulatory paperwork, Design-Expert promotes compliance. But in the end, it is the user's job to ensure data integrity. Regulatory confidence may be damaged by insufficient experimental control, selective presentation of positive data, or incorrect statistical interpretation. Maintaining data credibility in regulatory submissions requires adherence to standards like ALCOA+ (Attributable, Legible, Contemporaneous, Original, Accurate, plus completeness and consistency) (WHO, 2016; EMA, 2018).

9. Future Perspectives

Pharmaceutical research and development is being redefined by the quick growth of digital manufacturing, data science, and computational technologies. Predictive accuracy, development speed, and regulatory resilience are anticipated to be greatly improved by combining traditional DOE methods with artificial intelligence (AI), machine learning (ML), and digitalization initiatives. In order to facilitate the shift to intelligent and self-sufficient drug development systems, software platforms like Design-Expert are increasingly positioned as fundamental tools that can interface with sophisticated analytics.

9.1 Integration with Artificial Intelligence and Machine Learning

A revolutionary step in pharmaceutical research is the incorporation of DOE with machine learning and artificial intelligence. While traditional DOE effectively explores experimental design spaces using structured statistical methods, AI and ML algorithms can evaluate huge, multidimensional datasets, identify non-linear correlations, and improve predictive modeling beyond classical regression-based approaches. More precise predictions of formulation behavior and process performance are made possible by hybrid models that combine machine learning techniques with DOE-generated datasets.

In this regard, DOE programs like Design-Expert offer excellent, statistically sound datasets that are perfect for machine learning model training. Combining DOE with support vector machines, random forests, and neural networks has showed promise in speeding up decision-making, minimizing experimental runs, and improving intricate drug delivery systems. This convergence is predicted to increase adaptive experimentation, where models continuously learn and refine experimental tactics in real time (Vamathevan et al., 2019; Wu et al., 2020).

9.2 Digitalization and Smart Drug Development

The pharmaceutical business is moving toward smart drug development frameworks with automation, data integration, and real-time process control due to digitalization. Pharmaceutical processes can be virtually replicated, tracked, and optimized prior to physical implementation thanks to the use of digital twins, cloud-based analytics, and linked production systems. By establishing the experimental logic that supports model-based simulations and process knowledge, DOE plays a critical role in this digital ecosystem.

Design-Expert-generated models can be incorporated into digital development platforms to facilitate continuous improvement and lifecycle management. DOE facilitates proactive risk mitigation and real-time quality monitoring when paired with Industry 4.0 technologies and Process Analytical Technology (PAT). This strategy is in line with the new Pharma 4.0 paradigm, which prioritizes data-driven regulatory compliance, predictive control, and intelligent systems (Islam et al., 2021; Lichtenthaler, 2020).

9.3 Emerging Trends in Pharmaceutical Software

Pharmaceutical software tools are changing quickly to meet the demands of innovation, regulatory scrutiny, and growing data complexity. Cloud-enabled DOE platforms, improved visualization dashboards, compatibility with AI-driven analytics tools, and interaction with laboratory information management systems (LIMS) are examples of emerging developments. Future versions of DOE software are intended to integrate automatic design selection, intelligent factor screening, and real-time optimization capabilities.

Furthermore, as long as data quality and transparency are upheld, regulatory bodies are becoming more open to sophisticated modeling and simulation techniques. This has prompted the creation of software solutions that prioritize analytical power combined with audit trails, repeatability, and regulatory compliance. DOE software like Design-Expert, which supports creativity while guaranteeing quality and compliance, is anticipated to continue to be a crucial part of integrated digital development ecosystems as pharmaceutical research becomes more data-intensive (Kumar et al., 2022; Patel & Shah, 2021).

10. Conclusion

To sum up, Design-Expert® software has become an essential instrument in contemporary pharmaceutical development, allowing for the methodical use of Design of Experiments

(DOE) to effectively and consistently optimize formulations, procedures, and analytical techniques. By supporting multivariate analysis, response surface modeling, and desirability-based optimization, the software allows researchers to identify essential aspects, explain interconnections, and develop scientifically justified design spaces consistent with Quality by Design (QbD) concepts. Its adaptability across solid dosage forms, nano-formulations, biopharmaceuticals, and herbal products, coupled with regulatory approval and intuitive visualization capabilities, highlights its value in both academic and industry settings. Looking ahead, integration with artificial intelligence, machine learning, and digital manufacturing platforms promises to further enhance predictive accuracy, streamline development timelines, and support smart, data-driven pharmaceutical innovation, positioning Design-Expert as a cornerstone of future drug development strategies.

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12. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this review.

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