

Design of Experiments in the Formulation and Optimization of Sustained Release Matrix Tablets: A Review

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ABSTRACT

Sustained release (SR) matrix tablets are widely employed oral drug delivery systems due to their formulation simplicity, cost-effectiveness, and ability to maintain therapeutic drug concentrations over extended periods. However, the development of robust SR matrix formulations is challenging, as drug release behavior is governed by multiple interrelated formulation and process variables, including polymer characteristics, drug physicochemical properties, excipient interactions, and manufacturing conditions. Conventional one-factor-at-a-time approaches are inefficient for such complex systems, as they fail to identify interaction effects and often lead to suboptimal formulations. Design of Experiments (DoE) has emerged as a systematic and statistically sound approach for the formulation and optimization of sustained release matrix tablets. This review provides a comprehensive overview of DoE concepts and their application in SR matrix tablet development. Various experimental design strategies, including full and fractional factorial designs, Central Composite Design, Box–Behnken Design, and Taguchi orthogonal arrays, are critically discussed with respect to their roles in screening critical variables, developing predictive models, and optimizing drug release profiles. Particular emphasis is placed on mechanistic insights derived from DoE-based studies, especially in understanding polymer hydration, gel layer formation, diffusion- and erosion-controlled release mechanisms, drug–polymer interactions, and tablet microstructure. The integration of DoE within the Quality by Design framework and its alignment with regulatory guidelines, such as ICH Q8(R2), Q9, and Q10, are also highlighted, demonstrating its importance in defining design space and ensuring consistent product quality. Furthermore, the review discusses key implementation challenges, including experimental complexity, scale-up considerations, and statistical interpretation, while outlining future perspectives involving artificial intelligence, machine learning, digital twins, and continuous manufacturing. Overall, this review underscores the essential role of DoE in enabling robust, predictive, and regulatory-compliant development of sustained release matrix tablets.

Keywords: Sustained release matrix tablets, Design of Experiments (DoE), Quality by Design (QbD), Methodology, Drug release kinetics

INTRODUCTION

Oral drug delivery remains the most widely accepted and preferred route of administration due to its convenience, patient compliance, cost-effectiveness, and ease of large-scale manufacturing. However, conventional immediate-release dosage forms often require frequent dosing to maintain therapeutic plasma concentrations, leading to poor patient adherence and increased risk of dose-related side effects. To overcome these limitations, sustained release (SR) drug delivery systems have been

extensively developed with the objective of maintaining drug concentrations within the therapeutic window for prolonged periods while minimizing dosing frequency and plasma level fluctuations [1,2]. Among the various sustained release systems, matrix tablets have gained significant attention due to their simplicity of formulation, reproducibility, stability, and suitability for industrial manufacturing. In matrix systems, the drug is uniformly dispersed within a polymeric matrix that controls drug release primarily through diffusion, erosion, or a combination of both mechanisms [3,4].

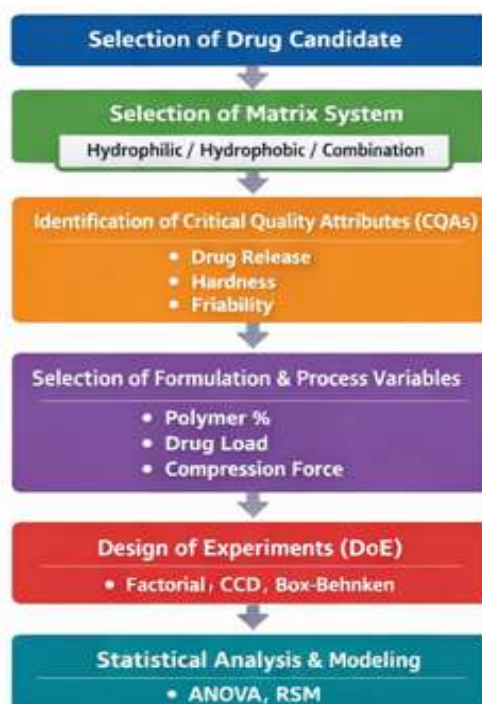
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Commonly used matrix formers include hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), sodium alginate, xanthan gum, and natural gums, as well as hydrophobic polymers like ethylcellulose and waxes. Despite their advantages, the development of sustained release matrix tablets is inherently complex due to the involvement of multiple formulation and process variables that simultaneously influence drug release behavior, mechanical strength, swelling characteristics, and overall tablet performance. Variables such as polymer type and concentration, drug solubility, particle size, compression force, excipient compatibility, and manufacturing conditions often interact in a nonlinear manner, making formulation optimization challenging when using conventional trial-and-error approaches [5]. Traditionally, pharmaceutical formulation development relied on the one-factor-at-a-time (OFAT) approach, where a single variable is changed while keeping others constant. Although simple, this method is time-consuming, resource-intensive, and incapable of identifying interaction effects between variables. As a result, OFAT often leads to sub-optimal formulations and limited scientific understanding of the formulation space [6]. These limitations have driven the adoption of more systematic and statistically robust approaches for formulation development. In this context, Design of Experiments (DoE) has emerged as a powerful and indispensable tool in pharmaceutical research and development. DoE is a structured, multivariate statistical methodology that enables simultaneous evaluation of multiple formulation and process factors and their interactions on critical quality attributes (CQAs) of the dosage form [7]. By applying DoE, formulators can efficiently screen significant variables, build predictive mathematical models, and optimize formulations with a minimal number of experimental runs. The application of DoE in sustained release matrix tablet formulation has been extensively reported in the literature (Table 1-3).

Studies have demonstrated its effectiveness in optimizing polymer concentration, drug-to-polymer ratio, and compression parameters to achieve desired release kinetics and mechanical properties [8,9]. Response surface methodology (RSM) designs such as Central Composite Design (CCD) and Box–Behnken Design (BBD) have been particularly valuable in developing quadratic models that describe complex release behavior and enable visualization through contour and three-dimensional surface plots [10,11]. Furthermore, the integration of DoE aligns closely with the Quality by Design (QbD) paradigm advocated by regulatory agencies such as the US Food and Drug Administration (FDA) and the International Council for Harmonisation (ICH). According to ICH Q8(R2), pharmaceutical development should be based on sound scientific principles and risk-based approaches, with DoE playing a central role in defining design space and ensuring consistent product quality [12]. In sustained release formulations, DoE facilitates a deeper understanding of how formulation variables affect drug release mechanisms, thereby supporting regulatory flexibility and lifecycle management. Recent research has also highlighted the role of DoE in elucidating mechanistic aspects of matrix systems, such as polymer hydration, gel layer formation, erosion dynamics, and diffusion pathways [13]. This mechanistic insight not only aids in optimization but also enhances the predictability and robustness of sustained release formulations under scale-up and manufacturing variations. Therefore, this review aims to provide a comprehensive overview of the application of Design of Experiments in the formulation and optimization of sustained release matrix tablets (Figure 1). Emphasis is placed on experimental design strategies, selection of critical formulation variables, statistical analysis, and practical examples from original research studies, highlighting the indispensable role of DoE in modern pharmaceutical formulation development.

Table 1: Common Design of Experiments (DoE) approaches employed in the formulation and optimization of sustained release matrix tablets [14]

DoE Design	Purpose in SR Matrix Tablets	Typical Factors Studied	Key Advantages	Limitations
Full Factorial Design (2^3 , 3^2 , etc.)	Comprehensive evaluation of main and interaction effects	Polymer concentration, drug load, compression force	Complete interaction analysis; high reliability	Large number of experiments
Fractional Factorial Design	Screening of critical formulation variables	Polymer type, excipient level, lubricant concentration	Reduced experimental runs; efficient screening	Confounding of higher-order interactions
Central Composite Design (CCD)	Optimization and response surface modeling	Drug–polymer ratio, polymer viscosity, compression force	Detects curvature; predictive quadratic models	Requires statistical expertise
Box–Behnken Design (BBD)	Optimization within safe experimental range	Polymer %, binder %, hardness	Fewer runs than CCD; no extreme points	Not suitable for all factor combinations
Taguchi Orthogonal Array	Robust formulation development	Polymer type, manufacturing conditions	Noise factor minimization; economical	Limited interaction information
Mixture Design	Optimization of polymer blends	Ratio of HPMC, EC, natural gums	Ideal for multi-polymer systems	Complex data interpretation

**Figure 1: DoE Workflow for SR Matrix Tablets****Design of Experiments (DoE):**

Design of Experiments (DoE) is a systematic, structured, and statistical approach used to study the relationship between multiple independent variables (factors) and one or more dependent variables (responses). In pharmaceutical formulation development, DoE enables simultaneous investigation of formulation and process variables and

their interactions, thereby providing a comprehensive understanding of the formulation system with a minimal number of experimental runs [14]. Unlike conventional empirical approaches, DoE is grounded in statistical principles that allow the generation of mathematical models capable of predicting product performance across a defined experimental space. This predictive capability is particularly valuable in the development of complex dosage forms such as

sustained release (SR) matrix tablets, where multiple formulation components and processing conditions collectively influence drug release kinetics, mechanical strength, and stability [7,15].

Table 2: Reported original research studies employing DoE for sustained release matrix tablet optimization

Drug	Polymer(s) Used	DoE Design	Factors Investigated	Key Outcomes	Reference
Propranolol HCl	HPMC K15M	Full Factorial	Polymer level, tablet hardness	Controlled release up to 12 h	Ford et al., 1987
Ibuprofen	HPMC	CCD	Polymer %, drug load, compression force	Optimized release kinetics	Khan & Jiabi, 1999
Diclofenac Sodium	HPMC + EC	Box–Behnken	Polymer ratio, binder %, hardness	Zero-order release achieved	Patel et al., 2006
Metformin HCl	HPMC K100M	CCD	Polymer %, lubricant %, hardness	Robust SR profile	Gohel et al., 2000
Diltiazem HCl	HPMC + Xanthan gum	Taguchi L9	Polymer type and ratio	Reduced burst release	Dash et al., 2010
Theophylline	Ethylcellulose	Fractional factorial	Coating level, plasticizer	Extended release > 24 h	Siepmann et al., 2001

Concept of Design of Experiments

The fundamental concept of DoE involves the planned and controlled variation of formulation and process variables to evaluate their individual (main) effects as well as combined (interaction) effects on selected responses. Each experimental run in a DoE matrix represents a unique combination of factor levels, enabling the construction of empirical models that describe cause–effect relationships [16].

Key elements of DoE include:

- **Factors:** Independent variables such as polymer concentration, drug–polymer ratio, compression force, and excipient levels
- **Levels:** Predefined values or ranges at which factors are studied (e.g., low, medium, high)
- **Responses:** Measurable outcomes such as percentage drug release at specific time points, hardness, friability, and swelling index
- **Experimental Design:** The statistical layout determining the number and combination of experimental runs

By systematically varying multiple factors, DoE overcomes the inherent limitations of the one-factor-at-a-time (OFAT) approach, which fails to capture

interaction effects and often leads to misleading conclusions [6].

Importance of DoE in Pharmaceutical Formulation Development

The importance of DoE in pharmaceutical sciences lies in its ability to generate scientifically sound, reproducible, and robust formulations. In sustained release matrix tablets, drug release behavior is rarely governed by a single variable; instead, it is the result of complex interactions among polymer characteristics, formulation composition, and manufacturing conditions. DoE provides a rational framework to study these complexities [5,17].

Key advantages of DoE include:

- **Reduction in experimental trials:** Efficient exploration of formulation space with fewer experiments
- **Identification of critical factors:** Determination of variables that significantly affect product performance
- **Understanding of interactions:** Detection of synergistic or antagonistic effects between factors
- **Optimization:** Identification of optimal factor levels to achieve predefined product objectives

These advantages make DoE an essential tool in modern dosage form design, especially for modified and controlled release systems [18].

Role of DoE in Sustained Release Matrix Tablets

In sustained release matrix tablets, DoE plays a crucial role in optimizing formulation composition and processing parameters to achieve desired release profiles. Variables such as polymer viscosity grade, polymer concentration, drug solubility, tablet porosity, and compression force often interact in a nonlinear manner, influencing drug diffusion, matrix swelling, and erosion mechanisms [4,19].

DoE enables:

- Quantification of the impact of polymer concentration on gel layer formation
- Evaluation of the combined effect of compression force and polymer level on tablet porosity
- Prediction of drug release kinetics over extended durations
- Optimization of mechanical properties without compromising release behavior

Such systematic analysis is difficult to achieve using traditional trial-and-error methods [8].

DoE as a Foundation for Quality by Design (QbD)

Regulatory agencies strongly advocate the use of DoE as part of the Quality by Design (QbD) paradigm. According to ICH Q8(R2), pharmaceutical development should be based on scientific understanding and risk management, with DoE serving as a central tool for defining design space and ensuring consistent product quality [12].

Within a QbD framework, DoE contributes to:

- Identification of Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs)
- Establishment of a multidimensional design space
- Development of robust control strategies
- Enhanced regulatory flexibility and lifecycle management

For sustained release matrix tablets, this translates into improved batch-to-batch consistency and predictable in-vivo performance [20].

Table 3: Typical independent variables and responses used in DoE for SR matrix tablets

Category	Variables / Responses
Independent Variables (Factors)	Polymer type, polymer concentration, drug-polymer ratio, compression force, excipient level
Dependent Variables (Responses)	% Drug release (2, 8 & 12 h), MDT, hardness, friability, swelling index
Statistical Tools	ANOVA, regression analysis, response surface plots
Optimization Criteria	Target release profile, mechanical strength, robustness

Statistical and Predictive Power of DoE

Another significant importance of DoE lies in its statistical rigor. DoE employs tools such as analysis of variance (ANOVA), regression analysis, and response surface methodology (RSM) to validate model significance and reliability. Statistical parameters such as p-values, F-values, R^2 , and lack-of-fit tests ensure that conclusions drawn from experimental data are scientifically valid [7,16].

Predictive models generated through DoE allow formulators to:

- Simulate formulation behavior within the design space

- Anticipate the impact of formulation changes
- Reduce development time and cost
- Improve scale-up success

This predictive strength is particularly valuable during technology transfer and commercial manufacturing [21].

Industrial and Regulatory Significance

From an industrial perspective, DoE supports faster product development, reduced material wastage, and improved decision-making. It enhances formulation robustness, reduces post-approval changes, and minimizes the risk of regulatory non-compliance. Consequently, DoE has become a standard

expectation rather than an optional tool in pharmaceutical product development [18,22].

Fundamental Design Types Used in Matrix Tablet Optimization

Design of Experiments (DoE) encompasses several experimental designs that differ in complexity, efficiency, and applicability depending on the formulation objective. In the optimization of sustained release matrix tablets, the choice of experimental design is dictated by the number of formulation and process variables, the need to evaluate interactions, and the requirement for optimization and prediction within a defined experimental domain. The most commonly employed designs include factorial designs, response surface designs, and robust parameter designs, each offering distinct advantages in pharmaceutical formulation development.

Full Factorial Design

Full factorial design is one of the most fundamental and widely used DoE approaches in pharmaceutical formulation studies. In this design, all possible combinations of factors and their respective levels are investigated, allowing comprehensive evaluation of main effects as well as interaction effects between variables. For a formulation involving k factors studied at n levels, a full factorial design requires (n^k) experimental runs. For example, a 2^2 factorial design evaluates two factors at two levels, whereas a 3^2 design investigates two factors at three levels. This exhaustive nature makes full factorial designs particularly valuable during the early stages of matrix tablet development, where a thorough understanding of formulation variables is essential [23]. In sustained release matrix tablets, full factorial designs are commonly applied to evaluate the influence of:

- Polymer concentration
- Polymer viscosity grade
- Drug-to-polymer ratio
- Compression force

These variables directly affect matrix integrity, porosity, swelling behavior, and drug diffusion pathways. Importantly, full factorial designs allow identification of synergistic or antagonistic

interactions such as the combined influence of polymer level and compression force on drug release rate which cannot be detected using OFAT approaches [24]. However, the major limitation of full factorial designs is the rapid increase in experimental runs as the number of factors increases, making them less practical for systems involving multiple variables.

Fractional Factorial Design

Fractional factorial designs are derived from full factorial designs but involve only a carefully selected subset of experimental runs. These designs are particularly useful during screening studies, where the primary objective is to identify the most influential factors from a large pool of variables. By assuming that higher-order interactions (e.g., three-factor or four-factor interactions) are negligible, fractional factorial designs significantly reduce experimental workload while still providing reliable information on main effects and selected interaction effects [16]. In matrix tablet optimization, fractional factorial designs are frequently used to screen variables such as:

- Types of matrix-forming polymers
- Lubricant concentration
- Granulation method
- Compression parameters

For instance, a 2^{4-1} fractional factorial design can efficiently evaluate four factors using only eight experimental runs instead of sixteen. This efficiency is particularly beneficial when dealing with expensive polymers or limited drug substances [25].

Despite their efficiency, fractional factorial designs may suffer from aliasing, where the effects of two or more factors become confounded. Therefore, these designs are generally used as preliminary tools, followed by more sophisticated optimization designs.

Central Composite Design (CCD)

Central Composite Design (CCD) is a response surface methodology (RSM)–based design widely employed for formulation optimization and process modeling. CCD is particularly suitable when the relationship between independent variables and responses is nonlinear.

A typical CCD consists of:

- Factorial points
- Axial (star) points
- Center points

This structure enables estimation of linear, interaction, and quadratic effects, allowing the construction of second-order polynomial models. In sustained release matrix tablets, CCD is extensively used to optimize formulation variables affecting drug release kinetics and tablet mechanical properties [26].

Common applications of CCD in matrix tablets include:

- Optimization of polymer concentration and viscosity
- Evaluation of compression force and tablet hardness
- Control of drug release at specific time points

CCD is especially valuable in identifying optimal formulation regions where sustained release is achieved without compromising tablet integrity. However, CCD may require experiments at extreme factor levels (axial points), which can sometimes result in impractical or unstable formulations.

Box–Behnken Design

Box–Behnken Design (BBD) is another response surface design that is highly efficient and economical compared to CCD. Unlike CCD, BBD does not include combinations where all factors are simultaneously at their extreme levels, making it safer and more practical for pharmaceutical formulations. BBD typically requires fewer experimental runs and is particularly suitable when three to four factors are involved. The design is constructed using mid-level and extreme-level combinations, enabling accurate estimation of quadratic models without excessive experimentation [27]. In sustained release matrix tablet development, BBD has been successfully applied to:

- Optimize polymer blend ratios
- Balance swelling and erosion mechanisms
- Achieve target drug release profiles

BBD is often preferred in pharmaceutical research due to its ability to minimize formulation failures while still providing robust predictive models. However, its applicability becomes limited when studying more than four factors.

Taguchi Orthogonal Arrays

Taguchi designs focus on robust parameter design, emphasizing the development of formulations that are insensitive to variability caused by uncontrollable factors, also known as noise factors. Unlike traditional DoE approaches, Taguchi methods prioritize quality improvement and process robustness rather than precise optimization [28]. Taguchi orthogonal arrays use predefined experimental matrices that allow the evaluation of multiple variables with a minimal number of experimental runs. These designs are particularly useful in early formulation development stages and scale-up studies. In the context of sustained release matrix tablets, Taguchi designs have been employed to:

- Optimize polymer selection and concentration
- Enhance batch-to-batch consistency
- Improve robustness of drug release profiles

However, Taguchi designs are limited in their ability to model interactions and nonlinear responses, making them less suitable for detailed optimization compared to RSM-based designs such as CCD and BBD [29].

Comparative Significance of Design Types in Matrix Tablet Optimization

Each DoE design serves a specific purpose in the formulation and optimization of sustained release matrix tablets. Screening designs such as fractional factorial and Taguchi arrays are ideal for identifying critical factors, while response surface designs such as CCD and BBD enable fine-tuning and optimization of formulation variables. A rational combination of these designs ensures efficient development, enhanced product understanding, and improved regulatory compliance within a Quality by Design framework [30-32].

Application of Design Of Experiments In Sustained Release Matrix Tablets

The application of Design of Experiments (DoE) in the development of sustained release (SR) matrix tablets has transformed pharmaceutical formulation from an empirical trial-and-error approach into a systematic, science-driven process. SR matrix tablets are inherently complex systems in which multiple formulation and process variables interact to control drug release kinetics, mechanical integrity, and in-vivo performance. DoE enables a holistic understanding of these interactions, allowing formulators to rationally design, optimize, and control matrix systems with improved efficiency and reproducibility.

Screening of Critical Formulation and Process Variables

One of the primary applications of DoE in SR matrix tablet development is the identification and screening of critical formulation and process variables that significantly influence product performance. Early-stage formulation typically involves numerous potential factors, including polymer type, polymer concentration, drug particle size, compression force, lubricant level, and granulation method. Screening designs such as fractional factorial and Plackett–Burman designs are commonly employed to evaluate these variables with a minimal number of experimental runs. Studies have demonstrated that polymer concentration and viscosity grade are among the most influential factors affecting drug release rate and matrix integrity, while variables such as lubricant concentration primarily affect tablet hardness and friability [30]. By identifying statistically significant factors, DoE reduces experimental burden and focuses optimization efforts on truly critical variables.

Optimization of Polymer Type and Concentration

Polymer selection and concentration play a decisive role in governing drug release mechanisms in matrix tablets. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), sodium alginate, and xanthan gum control release primarily through swelling and diffusion, whereas hydrophobic polymers like ethyl cellulose regulate release through pore formation and erosion. DoE-based response surface methodologies, including Central Composite Design (CCD) and Box–Behnken Design (BBD), have been extensively used to optimize polymer

levels to achieve desired release profiles. Research studies have shown that increasing HPMC concentration leads to the formation of a thicker gel layer, reducing drug diffusion and prolonging release duration [31]. DoE models allow quantification of this relationship and identification of optimal polymer concentrations that balance sustained release with acceptable tablet size and mechanical strength.

Control of Drug Release Kinetics

Achieving a predefined drug release profile is the primary objective of SR matrix tablet development. DoE facilitates the systematic evaluation of formulation variables on key release parameters such as cumulative drug release, release rate constants, and kinetic models (zero-order, Higuchi, Korsmeyer–Peppas). Multiple studies have utilized DoE to optimize formulations targeting near zero-order release by adjusting drug-to-polymer ratio, polymer blend composition, and compression force [32]. The use of mathematical models generated through DoE enables prediction of drug release behavior at untested conditions, significantly reducing experimental trials and enhancing formulation predictability.

Evaluation of Mechanical and Physical Properties

In addition to drug release, SR matrix tablets must exhibit adequate mechanical strength to withstand handling, packaging, and transportation. DoE is widely applied to study the effects of formulation variables on tablet hardness, friability, thickness, and density. Compression force, binder concentration, and polymer content are critical determinants of tablet mechanical properties. DoE-based optimization ensures that tablets possess sufficient hardness without excessively retarding drug release. For example, increasing compression force may improve tablet strength but reduce porosity, thereby slowing drug diffusion [33]. DoE allows identification of optimal compression conditions that balance mechanical robustness and release performance.

Understanding Drug–Polymer and Polymer–Polymer Interactions

Drug–polymer compatibility and polymer–polymer interactions significantly influence matrix behavior, stability, and release mechanisms. DoE facilitates the

systematic investigation of these interactions by incorporating multiple polymers and drug characteristics into experimental models. Studies using mixture designs have demonstrated that blending hydrophilic and hydrophobic polymers can synergistically modulate drug release by combining diffusion-controlled and erosion-controlled mechanisms [34]. DoE enables precise adjustment of polymer ratios to achieve desired release profiles while minimizing formulation variability.

Process Optimization and Scale-Up

Process parameters such as granulation technique, mixing time, and compression speed can profoundly affect matrix tablet performance. DoE is extensively used to optimize these process variables and ensure consistent product quality during scale-up. By integrating formulation and process variables within a single experimental framework, DoE supports robust process development and minimizes batch-to-batch variability. Studies have reported successful scale-up of SR matrix tablets by defining a design space wherein critical quality attributes remain unaffected by minor process variations [35].

Integration with Quality by Design (QbD)

The application of DoE in SR matrix tablet development is closely aligned with the Quality by Design (QbD) paradigm advocated by regulatory authorities. DoE plays a central role in defining critical material attributes (CMAs), critical process parameters (CPPs), and their relationship with critical quality attributes (CQAs). Regulatory guidelines such as ICH Q8(R2) emphasize the use of DoE to establish a scientifically justified design space that ensures consistent product quality and regulatory flexibility [36]. In sustained release formulations, DoE-driven QbD approaches enhance product understanding, reduce development risk, and facilitate lifecycle management.

Mechanistic Insights and Predictive Modeling

Beyond optimization, DoE contributes to mechanistic understanding of matrix tablet behavior. By correlating formulation variables with swelling kinetics, gel layer thickness, erosion rate, and diffusion coefficients, DoE provides valuable insights

into drug release mechanisms. Recent studies have integrated DoE with mathematical modeling and simulation tools to predict in-vivo performance based on in-vitro data, thereby improving in-vitro–in-vivo correlation (IVIVC) for SR matrix tablets [37]. Such predictive capability is invaluable for reducing development timelines and enhancing formulation robustness.

Case Studies Demonstrating DoE Effectiveness

Numerous original research studies have validated the effectiveness of DoE in SR matrix tablet development. For instance, Ford et al. successfully optimized hydrophilic matrix tablets using factorial design, demonstrating controlled release over 12 hours [38]. Similarly, Gohel et al. employed Box–Behnken design to optimize polymer blends and achieved targeted release kinetics with minimal variability [39]. These studies highlight the practical advantages of DoE in achieving reliable, reproducible, and scalable sustained release formulations.

Mechanistic Insights from Design of Experiments (DoE)

While Design of Experiments (DoE) is widely recognized for its efficiency in formulation optimization, its true scientific value lies in the mechanistic insights it provides into sustained release (SR) matrix tablet systems. SR matrix tablets are governed by complex, interdependent phenomena including polymer hydration, gel layer formation, diffusion, erosion, and matrix relaxation. DoE enables systematic dissection of these mechanisms by quantifying how formulation and process variables influence each stage of drug release, thereby transforming empirical observations into predictive, mechanism-based understanding.

Polymer Hydration and Gel Layer Formation

In hydrophilic matrix tablets, drug release is initiated by water penetration into the tablet, leading to polymer hydration and swelling. The hydrated polymer chains form a viscous gel layer that acts as a diffusional barrier, regulating drug transport from the matrix core to the surrounding dissolution medium. DoE studies have consistently demonstrated that

polymer concentration and viscosity grade are the most critical determinants of gel layer thickness and strength. Factorial and response surface designs have revealed nonlinear relationships between polymer level and hydration rate, where incremental increases in polymer concentration result in disproportionately thicker gel layers beyond a critical threshold [40]. These findings explain why minor formulation changes can cause substantial variations in release kinetics and underscore the importance of statistically defined design spaces.

Diffusion-Controlled Drug Release

Drug diffusion through the hydrated polymeric matrix is a primary release mechanism in many SR matrix systems. DoE allows quantification of how diffusion coefficients vary as a function of polymer concentration, drug solubility, and tablet porosity. Regression models generated through DoE often reveal that drug release follows Higuchi or Korsmeyer–Peppas kinetics within specific factor ranges, with the diffusion exponent (n) shifting as formulation variables change [41]. For instance, DoE-based studies have shown that increasing compression force reduces matrix porosity, thereby decreasing effective diffusion pathways and slowing drug release. Such mechanistic interpretation would be difficult to derive using conventional trial-and-error experimentation.

Erosion and Matrix Relaxation Dynamics

In addition to diffusion, matrix erosion and polymer relaxation contribute significantly to drug release, particularly in formulations containing swellable or biodegradable polymers. DoE has been instrumental in distinguishing erosion-dominated systems from diffusion-dominated ones. By simultaneously evaluating polymer type, concentration, and dissolution medium conditions, DoE models can identify conditions under which erosion becomes the rate-limiting step. Studies employing response surface methodology have demonstrated that lower viscosity polymers and higher dissolution agitation speeds promote surface erosion, leading to near zero-order release profiles [42]. These insights enable rational polymer selection based on desired release mechanisms.

Drug–Polymer Interactions at the Molecular Level

Drug–polymer interactions, including hydrogen bonding, ionic interactions, and hydrophobic associations, significantly influence drug release behavior. DoE facilitates systematic evaluation of these interactions by incorporating drug physicochemical properties and polymer characteristics into multivariate models. Research combining DoE with spectroscopic and thermal analyses has shown that strong drug–polymer interactions can retard drug diffusion by stabilizing the matrix structure and reducing drug mobility [43]. DoE-derived interaction terms provide statistical evidence for these molecular-level phenomena, enhancing mechanistic credibility and formulation robustness.

Influence of Tablet Microstructure and Porosity

Tablet microstructure, including pore size distribution and tortuosity, plays a critical role in governing water ingress and drug diffusion. DoE enables correlation of compression parameters with microstructural attributes and release performance. Studies using factorial designs have demonstrated that increased compression force reduces tablet porosity and increases tortuosity, resulting in prolonged diffusion pathways and sustained drug release [44]. DoE models allow visualization of these relationships through contour plots, offering intuitive mechanistic interpretation of how processing conditions shape matrix architecture.

Transition Between Release Mechanisms

One of the most valuable mechanistic contributions of DoE is its ability to identify transitions between different drug release mechanisms. By mapping formulation variables against kinetic parameters, DoE can pinpoint regions where release shifts from diffusion-controlled to erosion-controlled behavior. For example, response surface analysis has revealed that polymer concentration beyond a critical level lead to dominant diffusion control, whereas lower concentrations favor erosion-driven release [45]. Such mechanistic mapping is essential for designing formulations with predictable and reproducible release characteristics.

Predictive Modeling and In-Vitro-In-Vivo Correlation (IVIVC)

DoE-driven mechanistic models contribute significantly to predictive formulation science by linking in-vitro release behavior with in-vivo performance. By identifying mechanistically relevant variables, DoE improves the reliability of IVIVC models for SR matrix tablets. Recent studies integrating DoE with physiologically based pharmacokinetic (PBPK) modeling have demonstrated enhanced predictability of plasma concentration–time profiles based on in-vitro release data [46]. This mechanistic predictability reduces dependence on extensive in-vivo studies and accelerates formulation development.

Contribution to Robustness and Scale-Up

Mechanistic understanding derived from DoE supports robust formulation design and successful scale-up. By identifying mechanistically critical variables and their acceptable ranges, DoE minimizes sensitivity to manufacturing variability. For sustained release matrix tablets, mechanistic DoE models ensure that polymer hydration, diffusion, and erosion processes remain consistent across batch sizes and equipment scales, thereby enhancing product quality and regulatory confidence [47].

Implementation Challenges in Applying DOE to Sustained Release Matrix Tablets

Despite the significant advantages of Design of Experiments (DoE) in the formulation and optimization of sustained release (SR) matrix tablets, its practical implementation is associated with several scientific, technical, and organizational challenges.

Selection of Critical Variables and Responses

One of the primary challenges in DoE implementation is the correct identification of critical material attributes (CMAs) and critical process parameters (CPPs). In SR matrix tablets, numerous variables—polymer type, polymer viscosity, drug solubility, excipient compatibility, compression force, and granulation method—can influence drug release behavior. Inappropriate selection of variables may result in statistically valid but mechanistically

irrelevant models, limiting the interpretability and applicability of the results.

Experimental Complexity and Resource Constraints

Although DoE reduces the total number of experiments compared to conventional approaches, advanced designs such as Central Composite Design (CCD) or Box–Behnken Design (BBD) may still require substantial experimental effort, particularly when multiple factors are involved. Resource limitations related to materials, time, analytical capacity, and skilled personnel often restrict the practical adoption of higher-order designs in academic and small-scale industrial settings.

Nonlinear and Time-Dependent Release Behavior

Sustained release systems exhibit dynamic, time-dependent mechanisms involving swelling, erosion, and diffusion. Conventional DoE models often assume steady-state behavior, which may not adequately capture temporal changes in drug release mechanisms. This limitation necessitates the integration of kinetic modeling and time-dependent response analysis, which increases statistical and computational complexity.

Model Overfitting and Statistical Misinterpretation

Overfitting of DoE models remains a critical concern, particularly when the number of experimental runs is limited relative to the number of factors studied. High regression coefficients and statistically significant terms may not always translate into practical or mechanistic relevance. Misinterpretation of interaction effects without physicochemical justification can lead to misleading conclusions and suboptimal formulation decisions.

Scale-Up and Manufacturing Translation

DoE models developed at laboratory scale may not directly translate to pilot or commercial-scale manufacturing due to changes in equipment geometry, mixing dynamics, compression behavior, and heat and mass transfer phenomena. Ensuring scalability of DoE-derived design spaces requires

additional confirmatory studies and scale-sensitive modeling approaches.

Regulatory Perspective on DoE In Sustained Release Matrix Tablets

Regulatory agencies increasingly recognize DoE as a cornerstone of modern pharmaceutical development, particularly within the framework of Quality by Design (QbD).

Alignment with ICH Guidelines

The International Council for Harmonisation (ICH) guidelines, including ICH Q8(R2) (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System), strongly encourage the use of DoE for systematic formulation development. DoE facilitates the establishment of a scientifically justified design space, within which regulatory flexibility is granted for post-approval changes without additional regulatory submissions.

Establishment of Design Space for SR Matrix Tablets

In sustained release matrix tablet development, DoE enables identification of formulation and process parameter ranges that ensure consistent drug release profiles and product quality. Regulatory authorities accept DoE-generated design spaces provided that they are supported by sound scientific rationale, robust statistical validation, and adequate risk assessment.

Support for Lifecycle Management

DoE plays a vital role in lifecycle management by enabling continuous improvement and post-approval optimization. Regulatory agencies view DoE-based knowledge as evidence of enhanced process understanding, which supports change management, scale-up, site transfer, and formulation modifications with reduced regulatory burden.

Challenges in Regulatory Submissions

Despite regulatory acceptance, challenges remain in effectively communicating DoE findings in regulatory dossiers. Clear justification of factor

selection, statistical model validation, and mechanistic relevance is essential. Poorly documented or inadequately validated DoE studies may lead to regulatory queries or rejection of proposed design spaces [48,49].

FUTURE PERSPECTIVES

The application of DoE in sustained release matrix tablet development is expected to evolve significantly with advances in data science, modeling, and manufacturing technologies. Future DoE frameworks are likely to incorporate machine learning (ML) and artificial intelligence (AI) algorithms to handle high-dimensional datasets and nonlinear relationships. Hybrid DoE–ML models can enhance predictive accuracy, reduce experimental burden, and enable real-time optimization of SR formulations. The development of digital twins' virtual representations of formulation and manufacturing processes combined with DoE will allow simulation-based optimization of matrix tablets. These approaches will enable rapid exploration of formulation space and improved prediction of scale-up behavior. Emerging research emphasizes the need for mechanism-based DoE models that integrate polymer physics, drug diffusion theory, and erosion kinetics. Time-resolved DoE approaches will improve understanding of dynamic release processes and enhance in-vitro–in-vivo correlation (IVIVC). With the shift toward continuous manufacturing, DoE will play a critical role in optimizing continuous processes and enabling real-time release testing (RTRT). Multivariate models derived from DoE will support real-time monitoring and control of SR matrix tablet quality. Future DoE applications will also focus on sustainability by optimizing formulations to reduce material usage and energy consumption. Additionally, patient-centric design considerations such as tablet size, dosing frequency, and release customization will increasingly influence DoE strategies.

CONCLUSION

Design of Experiments has emerged as a transformative approach in the formulation and optimization of sustained release matrix tablets. Beyond its role in experimental efficiency, DoE provides profound mechanistic insight into drug release behavior, enabling rational selection of

polymers, excipients, and processing conditions. By systematically evaluating the effects and interactions of multiple variables, DoE facilitates the development of robust, reproducible, and regulatory-compliant sustained release formulations. Despite challenges related to model complexity, scale-up, and statistical interpretation, continued advancements in computational tools, mechanistic modeling, and regulatory science are expected to further strengthen the role of DoE in pharmaceutical development. The integration of DoE with Quality by Design principles, artificial intelligence, and continuous manufacturing represents a paradigm shift toward data-driven, knowledge-based formulation science. In conclusion, DoE is no longer an optional optimization tool but an essential component of modern sustained release matrix tablet development, supporting innovation, regulatory flexibility, and improved therapeutic outcomes.

REFERENCE

1. Langer R. New methods of drug delivery. *Science*. 1990;249(4976):1527–1533.
2. Robinson JR, Lee VHL. *Controlled Drug Delivery: Fundamentals and Applications*. 2nd ed. Marcel Dekker; 1987.
3. Alderman DA. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. *Int J Pharm Tech Prod Mfr*. 1984; 5:1–9.
4. Colombo P, Bettini R, Santi P, Peppas NA. Swellable matrices for controlled drug delivery. *Pharm Sci Technol Today*. 2000;3(6):198–204.
5. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on HPMC. *Adv Drug Deliv Rev*. 2001;48(2–3):139–157.
6. Lewis GA, Mathieu D, Phan-Tan-Luu R. *Pharmaceutical Experimental Design*. Marcel Dekker; 1999.
7. Montgomery DC. *Design and Analysis of Experiments*. 9th ed. Wiley; 2017.
8. Ford JL, Rubinstein MH, Hogan JE. Prolonged release of drugs from HPMC matrices. *Int J Pharm*. 1987;40(3):223–234.
9. Khan GM, Jiabi Z. Formulation and evaluation of ibuprofen sustained release matrix tablets. *J Control Release*. 1999;57(2):151–159.
10. Gohel MC, Panchal MK. Optimization of modified release formulations using factorial design. *Drug Dev Ind Pharm*. 2000;26(10):1139–1146.
11. Patel VF, Patel NM. Statistical evaluation of influence of formulation variables on diclofenac sodium release. *AAPS PharmSciTech*. 2006;7(3): E1–E9.
12. ICH Q8(R2). *Pharmaceutical Development*. International Council for Harmonisation; 2009.
13. Siepmann J, Siepmann F. Mathematical modeling of drug delivery. *Int J Pharm*. 2012;418(1):42–53.
14. Box GEP, Hunter JS, Hunter WG. *Statistics for Experimenters*. Wiley; 1978.
15. Eriksson L, Johansson E, Kettaneh-Wold N, et al. *Design of Experiments: Principles and Applications*. Umetrics; 2008.
16. Montgomery DC. *Design and Analysis of Experiments*. Wiley; 2017.
17. Shah RB, Tawakkul MA, Khan MA. Comparative evaluation of flow for pharmaceutical powders and granules. *AAPS PharmSciTech*. 2008;9(1):250–258.
18. FDA. *Pharmaceutical Quality for the 21st Century: A Risk-Based Approach*. 2004.
19. Colombo P, Peppas NA. Swelling-controlled release in hydrogel matrices. *J Control Release*. 1995; 37:151–160.
20. Yu LX. Pharmaceutical quality by design: Product and process development, understanding, and control. *Pharm Res*. 2008; 25:781–791.
21. Lionberger RA, Lee SL, Lee L, et al. Quality by design: Concepts for ANDAs. *AAPS J*. 2008;10(2):268–276.
22. ICH Q9. *Quality Risk Management*. International Council for Harmonisation; 2005.
23. Bolton S, Bon C. *Pharmaceutical Statistics: Practical and Clinical Applications*. Marcel Dekker; 2004.
24. Peppas NA, Siepmann J. Modeling of drug release from delivery systems. *Adv Drug Deliv Rev*. 2012; 64:163–174.
25. Myers RH, Montgomery DC, Anderson-Cook CM. *Response Surface Methodology*. Wiley; 2016.
26. Montgomery DC. *Design and Analysis of Experiments*. Wiley; 2017.
27. Box GEP, Behnken DW. Some new three level designs for the study of quantitative variables. *Technometrics*. 1960; 2:455–475.



28. Taguchi G. Introduction to Quality Engineering. Asian Productivity Organization; 1990.
29. Phadke MS. Quality Engineering Using Robust Design. Prentice Hall; 1989.
30. Lewis GA, Mathieu D, Phan-Tan-Luu R. Pharmaceutical Experimental Design. CRC Press; 1999.
31. Colombo P, Bettini R, Santi P, Peppas NA. Swellable matrices for controlled drug delivery. *Pharm Sci Technol Today*. 2000; 3:198–204.
32. Khan GM, Zhu JB. Evaluation of drug release kinetics from matrix tablets using factorial design. *Int J Pharm*. 1999; 183:123–131.
33. Hancock BC, Mullarney MP. Compression physics of pharmaceutical tablets. *Pharm Technol*. 2005; 29:56–66.
34. Siepmann J, Siepmann F. Mathematical modeling of drug delivery. *Int J Pharm*. 2008; 364:328–343.
35. Montgomery DC. Design and Analysis of Experiments. Wiley; 2017.
36. ICH Q8(R2). Pharmaceutical Development. International Council for Harmonisation; 2009.
37. Siepmann J, Peppas NA. Modeling of drug release from delivery systems. *Adv Drug Deliv Rev*. 2012; 64:163–174.
38. Ford JL, Rubinstein MH, Hogan JE. Formulation of sustained release tablets. *Int J Pharm*. 1987; 40:223–234.
39. Gohel MC, Patel MM, Amin AF. Box–Behnken design in controlled release formulations. *Pharm Dev Technol*. 2000; 5:491–500.
40. Colombo P, Bettini R, Santi P, Peppas NA. Swellable matrices for controlled drug delivery. *Pharm Sci Technol Today*. 2000; 3:198–204.
41. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release. *Int J Pharm*. 1983; 15:25–35.
42. Siepmann J, Peppas NA. Hydrophilic matrices for controlled drug delivery. *Adv Drug Deliv Rev*. 2001; 48:139–157.
43. Qiu Y, Zhang GGZ. Design and characterization of drug–polymer matrices. *Adv Drug Deliv Rev*. 2005; 57:1199–1215.
44. Hancock BC, Mullarney MP. The influence of compression on tablet porosity. *Pharm Technol*. 2005; 29:56–66.
45. Siepmann J, Siepmann F. Modeling of drug release from delivery systems. *Int J Pharm*. 2008; 364:328–343.
46. Dressman JB, Reppas C. In vitro–in vivo correlations. *Eur J Pharm Sci*. 2000; 11: S73–S80.
47. Montgomery DC. Design and Analysis of Experiments. Wiley; 2017.

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