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REVIEW ARTICLE

DESIGN OF EXPERIMENTS IN PHARMACEUTICAL FORMULATION DEVELOPMENT: APPLICATION OF DESIGN EXPERT WITH EMPHASIS ON LIPID-BASED DRUG DELIVERY SYSTEM

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ABSTRACT

Design of Experiments (DOE) has become integral to pharmaceutical development, providing a systematic alternative to conventional one-factor-at-a-time approaches. DOE enables simultaneous evaluation of multiple variables, identification of interaction effects, and efficient formulation optimization and process parameter optimization. Design-Expert software supports this methodology through structured experimental design, statistical modeling, analysis of variance, and response surface visualization, facilitating data-driven decision-making. This review highlights the application of Design–Expert–assisted DOE in pharmaceutical formulation, focusing on factorial designs, Box-Behnken design (BBD), central composite design (CCD), and mixture designs. These approaches are extensively used to optimize critical quality attributes in both conventional dosage forms and advanced drug delivery platforms, including self-emulsifying (SEDDS), self-micro-emulsifying (SMEDDS), self-nanoemulsifying systems (SNEDDS), and solid lipid nanoparticles. Response surface methodology facilitates the development of quadratic models and desirability-based optimization. The applications reviewed demonstrate improved process understanding, enhanced bioavailability of poorly water-soluble drugs, and reproducible product performance. Overall, design–expert–driven DOE provides a powerful and reliable framework for rational pharmaceutical development, accelerating optimization while aligning with regulatory expectations for systematic, science-based product design.

Keywords: Design of Experiments (DoE); Design-Expert software; Quality by Design (QbD); Response Surface Methodology; Box–Behnken design; Central Composite Design; Lipid-based drug delivery systems; Solid lipid nanoparticles (SLN).

INTRODUCTION:

In pharmaceutical sciences, formulation involves combining active ingredients and excipients after preformulation studies.

Traditionally, this is done by altering one variable at a time to study effects on the dosage form. However, this conventional approach is inefficient, time-consuming, costly, and fails to capture interactions between variables (1). To address these limitations, DoE has gained increasing attention in formulation development. DoE is a systematic planning method for conducting, analyzing, and interpreting controlled tests to evaluate the factors that may influence a response variable. By systematically varying the concentration of excipients and formulation processes, DoE reveals crucial relationships that can significantly influence outcomes. DoE involves selection of independent, dependent, and control variables that help reduce outside influences (2). Design of Experiments (DoE) is a statistical optimization method that examines multiple variables simultaneously in a structured and efficient manner, unlike the OFAT approach. It applies mathematical models and graphical results to show how factors influence has recently become a key component of the Quality by Design (QbD) approach in industry (3).

The objective of this review is to present a critical, organized summary of experimental design in pharmaceutical development. The article compares the benefits, drawbacks, and applicability of popular experimental designs, such as factorial design, Central Composite Design (CCD), and Box–Behnken Design (BBD), at various stages of formulation optimization. The article also highlights the relevance of DoE in contemporary pharmaceutical research and Quality by Design (QbD)-based development (4).

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APPLICATION OF DoE IN ADDRESSING CURRENT PHARMACEUTICAL CHALLENGES

By increasing formulation optimization, decreasing experimental trials, cutting development time and expense, and enhancing product quality, Design of Experiments (DoE) supports contemporary pharmaceutical development. It aids in determining how formulation and process variables affect important quality parameters both separately and in combination. Process comprehension, risk assessment, design-space establishment, manufacturing consistency, and regulatory compliance are all supported by the integration of DoE with Quality by Design (QbD) (5).

1. Formulation Efficiency and Optimization

DoE improves formulation efficiency by identifying critical formulation variables and their optimum levels. In SNEDDS development, factors such as oil, surfactant, and co-surfactant concentrations can influence globule size, drug release, and self-emulsification time.

Contribution of DoE:

Identifies critical formulation factors and their interactions.

Reduces trial-and-error experiments.

Optimizes formulation composition.

Improves product quality and reproducibility.

Example: Box–Behnken design can optimize an ibuprofen-loaded SNEDDS to achieve smaller globule size and enhanced drug release(6).

2. Reduction in Development Time and Cost

DoE evaluates multiple formulation variables simultaneously, reducing experimental trials compared with the traditional OVAT approach. It saves development time, raw materials, laboratory resources, and overall costs.

Contribution of DoE:

Reduces experimental trials.

Saves time and resources.

Minimizes material wastage.

Identifies cost-effective formulation conditions.

Example: Box–Behnken design optimizes oil, surfactant, and co-surfactant concentrations with fewer experiments (7, 8). This review emphasizes the various roles of design expert software within the domain of pharmaceuticals.

DESIGN OF EXPERIMENTS

Sir Ronald A. Fisher, a British statistician, is widely recognized for his groundbreaking contributions to the Design of Experiments (DoE) field in the early 20th century. Fisher's work is considered foundational to DoE, providing a framework for systematically studying the effects of multiple factors in an experiment. One of his key innovations was introducing factorial designs, which revolutionized the field by allowing more efficient and comprehensive experimentation (9,10).

In many drug delivery research studies, experiments are conducted by changing one factor at a time. This method requires many experiments and therefore is costly and time-consuming. In addition, it becomes challenging to study the interaction among two or more independent variables. To overcome these problems, the design of experiments (DoE) approach was developed in pharmaceutical science (11,12). DoE techniques determine the bare minimum of experiments required to find meaningful cause-and-effect connections between a specific number of factors and one or more responses using probability and statistics. DoE techniques are well-developed mathematically to find effective experimental designs. DoE consists of three main stages: design, analysis, and optimization (13,14). The main uses of design of experiments are: Discovering interactions among factors, screening many factors, establishing and maintaining quality control, optimizing a process, including evolutionary operations (EVOP), and designing robust products (15). Some DoE conventions can be difficult to apply experimentally. Design-Expert reduces bias by randomizing the order of experiments and ensures a uniform distribution of experimental conditions within the user-defined range (16). Design-Expert software was used to generate study designs and response surface plots. The best-fitting model was chosen based on statistical parameters such as CV, R^2, adjusted R^2, predicted R^2, adequate precision, optimization, and desirability. ANOVA was applied to identify significant factor effects on responses, while F-tests and p-values were calculated to confirm statistical significance (17). Statistical design approaches like the design of experiments help study the relationship between material attributes, process parameters, and formulation quality. Mixture design, in particular, is useful for modelling how formulation composition and excipient type influence product quality (18).

PURPOSE OF DoE IN FORMULATION

Understanding Interactions: DoE identifies how various formulation factors interact, offering insights that simple experiments might miss (19).

Efficiency: DoE enables the evaluation of multiple variables in fewer experiments, saving time, labour, and resources compared to trial-and-error or one-factor-at-a-time approaches (20).

Optimization: The purpose of DoE in formulation optimization is to find the best ingredient combination and process parameters for the desired product quality (21). Optimization in pharmaceutical dosage form development helps achieve the desired quality with fewer trials and less time. Computer-aided statistical designs, such as factorial design, are commonly used to plan experiments, fit models, test significance, and identify optimal formulation variables (22).

FACTORIAL DESIGN

The modern approach for optimization is through the use of statistical techniques. Factorial design is an effective approach for optimizing pharmaceutical formulations. This design allows you to study how multiple factors affect your responses and how these factors interact with each other (23). Factorial design is an experimental method used to study the effects of two or more factors and their interactions on outcomes. It allows evaluation of both main effects and combined effects of variables. If there are k

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factors with *n* levels, the total runs needed are *N^K* (e.g., 3 factors at 2 levels = 8 runs) (24)

Full Factorial Design: In this design, every level of every factor appears with every level of every other factor. There will be high or low levels for the factors. For "n" number of independent factors with two levels, the number of test runs required is equal to 2n (25). **Fractional Factorial Design:** Here, a carefully chosen fraction of the runs is selected instead of carrying out all the runs as in a full factorial design. A full factorial design can quickly become massive as the number of factors increases (26).

RESPONSE SURFACE METHODOLOGY: Response surface methodology is a method that is also known as the Box-Wilson Methodology (27). George E.P. Box and K.B. Wilson played pivotal roles in advancing RSM during the 1950s and 1960s. RSM is a widely utilized statistical technique that provides a structured approach to investigating the interactions between several input variables and the target outcome, allowing researchers to efficiently optimize processes, formulations, and products, ultimately conserving time and resources. Compared with the traditional single-factor method or orthogonal experimental method, RSM is able to establish multiple quadratic regression equations among factors and response values to clarify the interaction among factors. It may make up for the defects by which the single-factor method and orthogonal experimental method are unable to explain the interaction among factors or give the regression model between factors and response values (28). The design-expert program (Design-Expert trial version 7.0.3, State Inc., Minneapolis, MN) was used to optimize the sustained release formulation of itopride HCl. Using a central composite design with a = 1, the conventional approach was followed. The amounts of HPMC K 100M (X1) and PVP K30 (X2), which were examined at three levels each, were chosen as the independent factors based on the pre-formulation study. The central point (0, 0) was examined five times. Throughout the investigation, all other formulation and processing factors remained unchanged (29).

CENTRAL COMPOSITE DESIGN: A popular response surface design for creating second-order (quadratic) models without a complete three-level factorial, the CCD was first presented by Box and Wilson (1951). It adds center points and axial (star) points to factorial designs when curvature is found in the data.

Factorial points (−1, +1): Estimate main and interaction effects.

CENTER points (0): Detect curvature and estimate pure error.

Axial/star points (−α, +α): Allow estimation of quadratic terms; "α" controls rotatability.

CCD requires five levels per factor (−α, −1, 0, +1, +α), includes 2–50 factors, and is commonly applied in optimization and formulation studies (30). The Central composite rotatable design was used for the optimization and development of immediate-release Aceclofenac tablets using software Design Expert® (version 7.0, Stat-Ease Inc.) (31). In the current research, Sigma Tech software Version 3.1 is used for the design of experimentation of clarithromycin tablets employing a 2^3 full factorial design with 4 replicates.11 The model was discovered to be nonlinear and the curvature effect was substantial, indicating a central composite design for optimization. This arrangement allowed for the evaluation of each of the three criteria at three different levels (32). Chromatographic conditions are improved through optimization and validation of analytical techniques employing DOE and CCD, guaranteeing accurate, precise, and time-efficient analysis (33).

Table 1. Summary of studies using the central composite design in pharmaceutical development

Drug Deliveries	Central composite design Application Studies	Variables (Independent)	Responses (Dependent)
1. Extended-Release Microcapsule	Formulation And Optimization of Microcapsules of Propranolol Hydrochloride Using Central Composite Design (34).	Cellulose Acetate Butyrate and Span-80	Encapsulation Efficiency (Y1), 33.1.5h (Y2), 4h (Y3), 8h (Y4), 14h (Y5) And 24h (Y6).
2. Sustained Release Pellets	Development And Optimization of Furosemide Pellets Using Central Composite and Taguchi Orthogonal Array Design (35).	Kneading Time and Spheronizing Speed	Percentage Yield (Y1), Pellets Size (Y2) And Dissolution Rate of Pellets (Y3)
3. Immediate- Release Tablet	Comparative Study of Full Factorial Design, Box-Behnken Design, And Central Composite Design for The Optimization of Metronidazole Immediate-Release Tablets (36).	Povidone K30, Cros Povidone and Magnesium Stearate	Disintegration Time and Dissolution At 30 Min.
4. Matrix System with Sustained Release	Sustained-Release Fentanyl Citrate Optimization Through Central Composite Design.	Hpmck 15M And Ethyl Cellulose N10	Percentage Of Medication Released At 2, 12, And 24 Hours. F9 Provides the Best Formulation.
5.Hydrotropic Solid Dispersion	Optimization Of Dexlansoprazole Using Two-Factor Central Composite Design (37).	Drug: Sodium Alginate and Drug: Sodium Citrate	Q15 (Y1), Q45 (Y2), Q90 (Y3), T10% (Y4) And T50% (Y5)

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BOX-BEHNKEN DESIGN: BBD, developed by Box and Behnken (1960), is a response surface methodology that uses three levels (–1, 0, +1) to study factor–response relationships. It is a second-order, rotatable design based on incomplete factorials, suitable for 3–21 factors. The design consists of center points and edge midpoints (full factorial corners), reducing the number of trials (38). The total runs are given by:

$$N = 2k(k-1) + C_0$$

where k = number of factors and C_o = CENTER points.

By applying Design-Expert software, a three-factor, three-level Box-Behnken Design (BBD) was created to examine how the formulation variables-oil, surfactant, and co-surfactant affect SNEDDS responses. Compared to a full factorial design, BBD, a response surface methodology (RSM) approach, requires fewer runs and aids in the evaluation of both main and interaction effects. In this study, the experimental error and model precision were estimated using 15 runs with three central locations. The formulation conditions were optimized by applying the desirability function (39)**.** The Box Behnken statistical design is a quick and effective way to optimize a system. Compared to other experimental designs, BBD is a surface response design that offers numerous benefits. This requires only three layers of independent variables to be run, and the distance from the design center point is the only factor that determines how much the expected outcome varies at any given point (40). To assess the main effects, interaction effects, and quadratic effects of the formulation ingredients and to optimize the formulation, the design comprised replicated center points and a set of points located at the midpoints of each edge of the multidimensional cube (8). In the formulation of solid lipid nanoparticles, a 17-run, 3-factor, 3-level Box-Behnken design was employed to construct polynomial models for the optimization process, because it requires few runs with 3 or 4 variables. This design was suitable for investigating the quadratic response surface and for constructing a second-order polynomial model using Design-Expert software (Trial Version 7.1.6, Stat-Ease Inc., MN) (41).

Table 2. Summary of studies using Box-Behnken design (BBD) in pharmaceutical development

Drug delivery	Box Behnken Design Application studies	Independent variable	Dependent variable
1. Fast-Dissolving Tablet	Optimization Of Torsemide Fast Dissolving Tablet Using Box-Behnken Design (43)	Croscarmellose Sodium Concentration (X1), Cross Povidone Concentration (X2), And Camphor Concentration (X3),	Disintegration Time (Y1), Percentage Friability (Y2), And Amount Released At 10 Min (Y3)
2. Proniosomes	Optimization Of Itraconazole Using Box-Behnken Design (44)	X1=HLB, X2=Surfactant-Cholesterol Ratio, X3 = Ratio of Lecithin	Entrapment Efficiency, In-Vitro Drug Release. Zeta Potential and Vesicle Size.
3. Fast Dissolving Buccal Film	Optimization Of Fast Dissolving Buccal Film of Ondansetron Using Box-Behnken Design (45)	Hpmc K4m, Carbopol, And Pg	Folding Endurance (Fe) And Swelling Index
4. Nanosphere	Optimization Of Nefopam Hydrochloride Loaded Nanospheres for Neuropathic Pain Using Box–Behnken Design (46).	X1=Drug: Polymer Ratio (W/W), X2=Surfactant Concentration(%W/V) X3=Stirring Time (Hours) X4=Dp/Cp Ratio (V/V) X5=Stirring Speed (Rpm)	Entrapment Efficiency (% EE, W/W), Mean Particle Size (Nm), Process Yield (% PY, W/W) And Drug Loading (% DL, W/W)
5. Ethosome	Optimization Of Fluconazole-Loaded Classical Ethosomes Using Box-Behnken Design (47)	Ethanol, Soybean Lecithin and Sonication Time	Vesicle Size (Y1), Pdi (Y2) And % Ee (Y3)

MIXTURE DESIGN: A mixture design is a statistical experimental design specifically used when studying products or processes formed by blending two or more components, where the response depends only on the relative proportions of the ingredients, not their total quantity. By employing statistical modeling, mixture design identifies optimal blending regions and ingredient combinations that maximize or balance desirable outcomes, such as efficacy, texture, or shelf life (48). The D-optimal mixture design optimizes SMEDDS formulations by minimizing variance and maximizing information. Unlike other designs, it considers the entire formulation system (100%) (49).

DRUG DELIVERY SYSTEM: Compared with traditional formulations, drug delivery systems offer several benefits, including increased efficacy, reduced toxicity, fewer doses, and greater convenience. Drug-loaded nanoparticles and self-emulsifying drug delivery systems have gained prominence among drug delivery technologies due to their potential for passive targeting when their sizes fall within specific nanometric ranges. Because of their small size and large surface area, which favors their absorption over larger carriers, SNEDDS and nanoparticles are particularly attractive for oral drug delivery, particularly for poorly water-soluble drugs. This is because drug particles in the nano-meter size range dissolve more quickly than a conventional formulation (50).

Various delivery systems have been formulated using the design of experiments, among which the most popular ones are self-emulsifying drug delivery systems (SEDDS), self-micro-emulsifying drug delivery systems (SMEDDS), self-nano-emulsifying drug delivery systems (SNEDDS), and solid lipid nanoparticles.

The oral route is the most convenient and cost-effective method for drug delivery, but it faces major challenges with poorly soluble

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drugs, leading to low absorption and variable plasma levels. Drugs in BCS Class II or IV often show low oral bioavailability, unpredictable absorption, significant variability between and within individuals, and lack of dose proportionality (51). Various techniques like solid dispersions, cyclodextrins, and emulsions have been used to improve solubility, with lipid-based systems showing great promise (52,53). In 2000, Pouton invented a classification system for these types of carriers, initially labeled as “lipid formulations (54). Among these, SMEDDS stand out as simple, stable formulations that improve drug dissolution, absorption, and bioavailability using optimized oil–surfactant mixtures, often filled in gelatin capsules with co-surfactants or co-solvents to improve performance (55). Nanoemulsion systems have much potential as drug delivery systems because they can make drugs that are hard to dissolve in water more soluble, dissolve faster, and be more bioavailable when taken by mouth. It can be described as "an oil-in-water (o/w) or water-in-oil (w/o) emulsion with an average droplet diameter ranging between 50 and 1000 nm" (56).

Table 3. Major differences between SEDDS, SMEDDS, and SNEDDS formulations.

Sl. No.	Property	SEDDS	SMEDDS	SNEDDS
1	Size	>300nm	<250nm	<100nm
2	HLB value of surfactant	<12	>12	>12
3	Concentration of oil	40-80%	>20%	>20%
4	Appearance	Turbid	Optically Clear	Optically clear
5	Concentration of surfactant	30-40%	40-80%	40-80%
6	Classification as per lipid formulation classification system (57–59)	Type II	Type IIIB	Type IIIB

APPLICATION OF DESIGN OF EXPERIMENTS (DOE) IN THE FORMULATION AND OPTIMIZATION OF LIPID-BASED DRUG DELIVERY SYSTEMS

Self-Emulsifying Drug Delivery Systems

Self-emulsifying drug delivery systems (SEDDS) are stable mixtures of oils, surfactants, and co-solvents that, on contact with GI fluids and mild agitation, form fine oil-in-water emulsions (60,61). SEDDS produce droplets of 100–1000 nm (62), while self-micro-emulsifying systems (SMEDDS) form transparent microemulsions of 100-250 nm. They spread easily in the GI tract, are physically stable, and are simpler to manufacture compared to conventional emulsions (63). SEDDS can incorporate doses ranging from less than 25 mg to more than 2 g in a single administration (64). Self-Emulsifying Drug Delivery Systems (SEDDS) are formed using surfactants of HLB <12, whereas Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) are formed using surfactants of HLB > 12(65). Self-nanoemulsifying drug delivery systems (SNEDDS) are newer formulations with globule sizes <100 nm. With growing diversity in SEDDS and an increasing number of drugs being encapsulated, updated reviews are needed to cover recent advancements (66).

Self-Micro-Emulsifying Drug Delivery Systems

Microemulsions are isotropic, thermodynamically stable mixtures of oil, water, surfactants, and co-surfactants. Their formation is driven by ultra-low interfacial tension, achieved using two emulsifiers—one water-soluble (surfactant) and one oil-soluble (co-surfactant). The co-surfactant plays a key role in reducing interfacial tension to enable microemulsion formation (69). Factors such as nano-sized droplets of SMEDDS, higher solubilization capacity, changes in GI tract biochemical barrier function, and lymphatic transport can make a significant contribution to drug absorption (70). SMEDDS presents the drug in nanosized droplets offering large interfacial area for drug diffusion (71). Selection of a suitable self-emulsifying vehicle depends on drug solubility in components, size of the self-emulsifying region in the phase diagram, and droplet size distribution after emulsification (72). Minimum therapeutic dose drugs are best suited for SMEDDS, as maintaining solubility in the gut is a key challenge for oral formulations. High-dose drugs are generally unsuitable unless they show good solubility in at least one SMEDDS excipient, preferably the lipophilic phase (73).

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Table 4. Summary of studies using design-expert software in SMEDDS formulation

Drug deliveries	Application studies	Independent variable	Dependent variable
1. SMEDDS	Optimization And Formulation of Atorvastatin Calcium Using D-Optimal Mixture Design-Expert Software Version 7 (Stat-Ease Inc, Minneapolis, Mn, Usa (48))	Capmul Mcm, Tween 20, Tetraglycol.	Mean Droplet Size (Y1) And Percentage of Drug Released In 15 Minutes (Y2).
2. SMEDDS	Optimization Of Azilsartan Medoxomil Using Box-Behnken Design (74).	Clove Oil as the Oil, Tween 20 As the Surfactant, And Propylene Glycol as A Cosurfactant	Particle Size (Y1), Pdi (Y2), And Dissolution % (Y3
3. SMEDDS	Optimization Of Smedds of Mebendazole Using Factorial Design (75)	Labrafil M2125 Cs (Oil), Tween 20 (Surfactant) And Maisine 35-1 (Co-Surfactant)	Emulsification Time And % Release
4. SMEDDS	Optimization Of Smedds of Docetaxel Using D-Optimal Design (76)	Oleic Acid, Tween 80, Peg-400	Mean Emulsification Time (Y1) And Mean Percentage of Drug Released In 30 Min
5. SMEDDS	Optimization Of Smedds of Dapsone Using Box-Behnken Design (77)	Capryol, Tween 80, Labrasol	Particle Size (Y1) And % Practical Yield (Y2)

Self-Nanoemulsifying Drug Delivery Systems

SNEDDS are anhydrous pre-concentrate mixtures of oil, surfactants, and co-surfactants that spontaneously form stable nano-emulsions in the GI tract. Their small droplet size (<100nm) enhances drug dissolution and absorption, while the absence of water improves storage stability. In the past decade, SNEDDS has been extensively developed and studied due to its various advantages, including improving solubility, stability and also bioavailability of poorly soluble drug substances (78,79). The solid dispersion system is a renowned method for improving the solubility and bioavailability of drugs with poor water solubility (80). The drug encapsulated as liquid dosage forms can be in a thermodynamically and kinetically stable form as SNEDDS (81). Emulsification occurs due to reduced surface tension from surfactant/co-surfactant interfaces. Compared to other lipid-based carriers, SNEDDS are simpler to produce, more stable, and free from aggregation risks (82,83). SNEDDS enhance lymphatic drug transport by using oils that solubilize lipophilic drugs and bypass the hepatic portal vein, reducing first-pass metabolism. Fatty food intake further improves their absorption and bioavailability (84). Compared to conventional nano-emulsions, SNEDDS offer better stability owing to their water-free nature, can be easily filled into capsules for flexible dosing, improve patient compliance by masking taste, and are commercially viable with simple, scalable manufacturing (85).

Table 5. Summary of Studies Using Design-Expert Software in SNEDDS Formulation

Drug delivery	Application studies	Independent variable	Dependent variables
1. SNEDDS	Formulation And Optimization of Budesonide Using Box-Behnken Design-Expert® Software (Version 7.0.0, Stat-Ease, Inc., Minneapolis, United States) (86).	Liquid Paraffin, Tween 80, Propylene Glycol.	Particle Size (Y1) And Poly Dispersity Index (PDI) (Y2)
2. SNEDDS	Formulation And Optimization of Resveratrol and Melatonin Using I-Optimal Design N (Design Expert® 13.0, Stat-Ease Inc., Minneapolis, Mn, Usa (87))	Concentration Of Oil, Surfactant, And Co-Surfactant. Different Types of Surfactants (Tween 80, Tween 20, Cremophor El, Solutol)	Particle Size, Time of Emulsification, And % Transmittance
3. SNEDDS	Optimization Of Nateglinide Using Box Behnken Design (88)	Capryol 90, Tween 80, Peg 400	Dissolution At 5 Min, Dissolution At 10 Min, Particle Size
4. SNEDDS	Optimization Of Amiodarone Hydrochloride Using D- Optimal Design (89)	Oil (Capmul Mcm) And Surfactant (Cremophor Rh 40) And Co-Surfactant (Propylene Glycol)	Drug Loading (Y1); Mean Droplet Size (Y2) And % Transmittance (Y3)
5. SNEDDS	Optimization Of SNEDDS Of Bosentane Using Box-Behnken Design (90)	Maisine, Cremophor Rh 40 And Labrasol	Particle Size (Y1) And Polydispersity Index (Y2)

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs), introduced in the early 1990s, are sub-micron colloidal carriers (50–1000 nm) made of physiological lipids dispersed in water or aqueous surfactant solutions. They are widely used to enhance the bioavailability of BCS class II drugs and offer advantages such as good biocompatibility and ease of large-scale production compared to other colloidal systems (91).

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SLNs are safe drug carriers since they use physiological lipids and GRAS-approved excipients, reducing toxicity risks (92). SLNs are biocompatible, biodegradable carriers used for controlled and targeted drug delivery. Compared to conventional vehicles, they offer controlled release, protect active compounds, minimize skin irritation, enhance skin penetration, provide sustained release, act as UV protectants, and show effective skin targeting (93). SLNs are novel drug carriers that can load both hydrophobic and hydrophilic drugs, enable targeted delivery, avoid organic solvents, and offer good stability, tolerability, and easy scale-up (94). Central Composite Designs (CCDs) are used in pharmaceuticals to optimize nanoparticle and drug delivery formulations by controlling factors like particle size, surface charge, and drug loading, thereby improving therapeutic outcomes (95). They are also applied in analytical method development to ensure accuracy and reliability, in solubility enhancement studies to improve bioavailability of poorly soluble drugs, and in manufacturing processes such as tablet compression, granulation, and coating to optimize unit operations (96).

Table 6. Summary of studies using design expert software in solid lipid nanoparticle formulation

Drug delivery	Application studies	Independent variables	Dependent variables
1. Solid lipid nanoparticles	Optimization of methazolamide-loaded solid lipid nanoparticles using Box–Behnken design (97)	glycerol monostearate (GMS), the amount of phospholipids, and the concentration of surfactants	entrapment efficiency (Y1), drug-loading rate (Y2), and particle size (Y3)
2. Solid lipid nanoparticles	Optimization of budesonide using Taguchi and Box-Behnken design (98).	surfactant concentration (%), lipid-to-drug ratio (w/w), and sonication time (s)	Particle size, zeta potential, entrapment efficiency, loading percent (LP), and mean release time (MRT)
3. Lipid hybrid nanoparticles	Optimization of itraconazole using Box-Behnken design (99).	Lipid-to-polymer ratio (X1), concentration of surfactant (X2) and concentration of drug (X3)	Particle size, PDI, and Entrapment efficiency were found to be in the range of 77.4 to 83.4%
4. Solid lipid nanoparticles	Optimization of repaglinide SLNPS using 2^3 factorial Design Expert Software® 12.0.1 Trial Version (100).	Glyceryl monostearate, tristearin, and poloxamer 188	mean particle size (Z-Ave) and entrapment efficiency (%EE).
5. Solid lipid nanoparticles	Optimization of fluvastatin-loaded SLNPs using 3^2 factorial design (101)	Glyceryl monostearate as lipid carrier and KolliphorP188 as surfactant	Entrapment efficiency, in vitro drug release

FUTURE PROSPECTS AND EMERGING TRENDS

Innovations in AI/ML Techniques for Pharmaceutical Development

Future developments in AI, especially deep learning models like Convolutional Neural Networks (CNNs) and Recurrent Neural Networks (RNNs), are anticipated to greatly enhance pharmaceutical research by evaluating massive datasets and more precisely forecasting drug characteristics and therapeutic outcomes. Model robustness, efficiency, and suitability for particular drug discovery tasks will be improved by transfer learning and domain adaptation. By making AI judgments more comprehensible, Explainable AI (XAI) will promote regulatory compliance and boost transparency. Additionally, by creating novel molecular structures and finding promising lead compounds with desirable properties, Generative Adversarial Networks (GANs) and Variational Autoencoders (VAEs) will speed up drug discovery (102).

Potential Impact on Drug Development Pipeline

By accelerating drug discovery, formulation optimization, and candidate selection, artificial intelligence (AI) and machine learning (ML) are revolutionizing pharmaceutical drug development. These methods shorten the time and expense of development by enabling quick chemical screening, drug property prediction, and formulation parameter optimization. By evaluating patient-specific data to optimize therapy and forecast treatment results, AI/ML also supports customized medicine. Additionally, by identifying possible hazards and negative reactions early on, they enhance medication efficacy and safety. AI/ML boosts productivity, resource efficiency, and competitiveness in the pharmaceutical sector by automating processes, improving data analysis, and facilitating well-informed decision-making (103).

CONCLUSION

Modern pharmaceutical development increasingly relies on Design of Experiments (DoE) as a systematic and statistically robust alternative to traditional trial-and-error methods. Using Design-Expert software, researchers can efficiently design experiments, perform statistical analysis (ANOVA), develop predictive models, and optimize formulations through response surface methodology. Various designs such as factorial, Box–Behnken, central composite, and mixture designs are widely applied in optimizing conventional dosage forms and advanced lipid-based drug delivery systems including SEDDS, SMEDDS, SNEDDS, and solid lipid nanoparticles. DoE enhances process understanding, ensures consistent product quality, improves bioavailability, and supports regulatory expectations for science- and risk-based pharmaceutical development.

In parallel, Artificial Intelligence (AI) and Machine Learning (ML) are transforming pharmaceutical formulation design by accelerating drug discovery, optimizing formulation parameters, predicting drug properties, and enabling personalized medicine.

Although challenges such as data quality, model interpretability, ethical concerns, and regulatory compliance remain, ongoing advancements in deep learning, transfer learning, explainable AI, and generative models are expected to improve drug development efficiency, safety, efficacy, and cost-effectiveness. Together, DoE and AI/ML provide powerful tools for modern, data-driven pharmaceutical research and development.

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