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Review Article

Unlocking the potential of micelles: DoE and QbD strategies for formulation development and optimization

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ABSTRACT

Micelles have emerged as promising nanocarriers, enhancing drug solubility, stability, and targeted delivery. This review explores the integration of Design of Experiments (DoE) and Quality by Design (QbD) methodologies in optimizing micellar formulations, emphasizing in critical quality attributes (CQAs) and process parameters (CPPs). Nanoscale polymeric, mixed, and stimuli-responsive micelles are mainly evaluated, with Factorial, Central Composite and Box-Behnken designs enabling systematic optimization of particle size, encapsulation efficiency, zeta potential, polydispersity index and release kinetics. Case studies highlight therapeutic advancements in cancer, ocular delivery, and neurological disorders, demonstrating improved bioavailability and reduced systemic toxicity. Additionally, DoE-driven approaches enhance formulation robustness and reproducibility, aligning with regulatory standards. However, large-scale production, long-term stability, and physiological variability challenges persist. This review underscores the transformative role of systematic methodologies in advancing micellar nanomedicines while emphasizing the need for standardized protocols to address manufacturing and regulatory barriers through analysing multiple recent research-oriented case studies.

Glossary – Abbreviations List – may be changed accordingly, only includes most frequently used abbreviations // perhaps needs a different document (from guide-to-authors: "Please provide definitions of field-specific terms used in your article, in a separate list")

BBD	Box-Behnken Design
CCD	Central Composite Design
CMA	Critical Material Attribute
CMC	Critical Micellar Concentration
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DE	Dissolution Efficiency
Dh	Hydrodynamic Diameter
DL	Drug Loading
DoE	Design of Experiments
EE	Entrapment/Encapsulation Efficiency
LE	Loading Efficiency
MD	Median Diameter
MIE	Micellar Incorporation Efficiency
PDI	Polydispersity Index
PS	Particle Size
QbD	Quality by Design
QTPP	Quality Target Product Profile
Tsol-gel or PTT	Phase Transition Temperature
ZP	Zeta Potential

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1. Introduction

Interdisciplinary research in fields such as polymer science, pharmaceutical technology, and molecular biology has led to the development of innovative drug delivery systems. Among these, micelle-based formulations (Scheme 1) have gained popularity for their ability to enhance drug solubility, permeability, and metabolic stability. The success of micellar nanomedicines in clinical and commercial applications is evident. Notable examples include Fungizone® (Ben Venue

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Laboratories Inc., 1966), encapsulating amphotericin B for antifungal therapy [1], Estrasorb® (Novavax, 2003), a topical lotion of micellar oestradiol for menopausal symptoms management [1,2], and Genexol-PM® (Samyang Corporation, 2007), a micellar paclitaxel formulation for breast and non-small cell lung cancers [1–3]. Additionally, PegIntron® and Pegasys® are marketed micellar formulations. Namely, PegIntron® (Merck & Co., 2000) along with Pegasys® (Roche Diagnostics GmbH, 2002) deliver PEGylated interferon alpha-2B for Hepatitis B and C treatment [1–3], while Cequa® (Sun Pharmaceutical Industries Inc., 2018) addresses chronic dry eye disease treatment through its micellar cyclosporine formulation [3]. Concurrently, ongoing clinical trials of micellar formulations for various cancers, pain management and bio-imaging illustrate the expanding scope of this technology (see Figs. 3 and 4).

Polymeric micelles are nanoscopic colloidal carriers typically ranging from 10 to 200 nm in size, depending on their polymeric structure and surface modifications [4,5]. These micelles form through the self-assembly [6–11] of amphiphilic copolymers in aqueous environments as the hydrophobic segments of the amphiphilic polymers aggregate to form a core capable of encapsulating hydrophobic drug molecules [7,11–16]. In contrast, the hydrophilic segments form a stabilizing shell that interacts with the environment and biological substrates [17]. This unique structure enables the incorporation of poorly water-soluble and low-permeability drugs into the micellar hydrophobic core while utilizing the hydrophilic shell for solubilization and biological interaction [18]. Moreover, advances in nanoengineering have further enhanced the functionality of polymeric micelles leading to specific tissue targeting and stimuli-responsive drug release systems characterized by thermosensitive or pH-responsive mechanisms with broad applicability in personalized medicine [5,19,20].

Polymeric micelles offer significant advantages, making them a highly effective platform for advanced drug delivery. Generally, polymeric micelles are used for water solubility enhancement and delivery of poorly water-soluble drugs and hydrophobic molecules. These hydrophobic drugs are incorporated into a polymeric core, since hydrophilic molecules can be attached to a hydrophilic corona [13,15,18,21,22]. Additionally, polymeric micelles enhance drug bioavailability via bypassing enzymatic degradation [19,23] and avoiding rapid clearance by the mononuclear phagocyte system [16,24]. This way, therapeutic drug levels at targeted sites are sustained while minimizing systemic side effects and the risk of adverse reactions [6,11,14,19]. Importantly, their adaptability to tissues with both hydrophilic and lipophilic properties, including sensitive areas like ocular tissues [12,25], highlights their versatility and safety. Furthermore, their cost-effective and straightforward manufacturing processes facilitate scalability and clinical use [26,27].

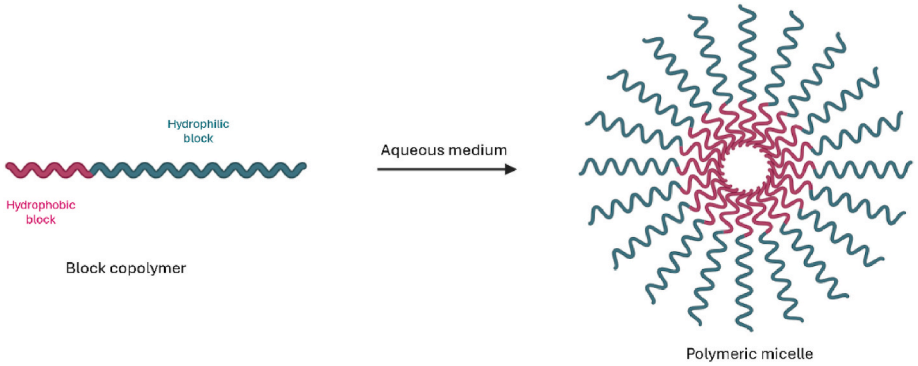
The routes of administration for polymeric micelles are diverse and flexible. Ocular delivery via topical eye drops and gels is particularly effective for treating anterior and posterior ocular diseases [12,20,21,28]. Intranasal administration offers non-invasive access to the brain and systemic circulation [5,9,18,22,24,29], while cutaneous and vaginal applications enable localized treatment [17]. Oral delivery provides a convenient option for systemic therapies, and topical application is suitable for localized pathological conditions. This versatility highlights their potential to address a wide range of therapeutic challenges, such as ocular disorders [11,14,16,17,19,27,31–37]), chronic neurological disorders [5,9,18,38]), and other diseases (AIDS-HIV [39], plaque psoriasis [40], burn injuries [35,41], reflux esophagitis [29], oropharyngeal candidiasis [42]).

Quality by design (QbD) is a regulatory mandated systematic industrial approach for incorporating quality into pharmaceutical products, ensuring they consistently meet predefined quality standards [20,41]. This concept emphasizes that quality cannot be assured through final testing alone but must be systematically incorporated during the product's design and development [32]. The QbD model ensures a proactive approach to pharmaceutical quality, combining scientific understanding with robust design practices to achieve consistent product performance and foster continuous improvement.

According to the International Council for Harmonisation (ICH) guidelines—specifically Q8 to Q11—the establishment and control of quality must be founded on risk-based concepts and principles [18]. Essential elements in a QbD approach include determination of the quality target product profile (QTPP), selection of the critical quality attributes (CQAs) and critical process parameters (CPPs) or/and critical material attributes (CMAs) [8,14,19,23,32,39,40]. These elements are further supported by risk assessment, the application of Design of Experiments (DoE), the development of a Design Space, implementation of a comprehensive control strategy, lifecycle management of the product, and continuous improvement throughout the product's lifecycle [18]. According to the ICH Q8 Guidance for Industry on Pharmaceutical Development [43], defining the quality target product profile (QTPP) is mandatory as it relates to quality, safety and efficacy in order to gain a more systematic and enhanced understanding of the product and process under development. The following Table 1 illustrates in a systematic way the most frequent dosage forms of polymeric micelles in association with their therapeutic applications and relevant QTTP considerations.

In the DoE framework, CQAs (outputs) are linked to the safety and efficacy profiles of the product, while CMAs and CPPs (inputs) correspond to the specific production methods employed in the process. By utilizing a risk estimation matrix, a knowledge-based and risk-driven quality management strategy can be implemented [18,19,23,32]. This approach ranks CQAs and CPPs according to their impact on the desired product quality, guiding the prioritization of parameters.

In micellar drug formulation, the application of QbD begins with defining the QTPP based on therapeutic needs, target patient population, administration route, and drug release profile [8]. CQAs for micellar formulations typically include particle size, polydispersity index, drug loading efficiency, and zeta potential (essentially connected to the charge of the micellar particles). These parameters are optimized



Scheme 1. Schematic representation of micelle structure and formation.

Table 1
Administration routes of micelles and their alignment with QTTP attributes.

Route of Administration	QTTP	Dosage Forms	Therapeutic Applications	References
Ocular	Increased ocular residence time Sterility Osmolality Viscosity Topical application to the targeted tissue Reduced dosing frequency Enhanced corneal penetration Minimized irritation and vision obstruction	Eye drops in situ gels	Inflammations Glaucoma Allergic conjunctivitis Diabetic Macular Edema Diabetic retinopathy Fungal or bacterial eye infections	[7,12,20,21,28,30]
Intranasal	Increased CNS bioavailability Mucociliary clearance resistance Non-invasive brain targeting Rapid drug release and absorption Bypass of the blood-brain barrier Decreased side effects Reduced dosing frequency Rapid release First-pass metabolism protection Patient compliance and safety Nasal mucosa compatibility	Mucoadhesive nanoemulsions Nasal drops Nasal sprays Intranasal gels In situ gels	Schizophrenia Bipolar disorder Multiple sclerosis Neuroinflammations Alzheimer's disease Osteoporosis Reflux esophagitis disease	[5,9,18,22,24,29]
Vaginal	Mucoadhesion Controlled release Minimized irritation	Gels	Vulvovaginal candidiasis	[17]
Cutaneous	Localized treatment Minimal systemic exposure Increased adherence Reduced irritation	Creams Gels	Skin cancer Plaque psoriasis Burn injuries	[35,40,41]
Oral	Simplicity Patient compliance Enhanced intestinal permeability Controlled release Precise dosage Decreased side effects	Self-microemulsifying tablets Hard gelatin capsules Granules Orodispersible Films Microsuspensions Lyophilized powders for reconstitution Aqueous dispersions	AIDS-HIV Cancer Alzheimer's disease HIV protease inhibition Hypertension Oropharyngeal Candidiasis	[11,13,23,42,49]
Intravenous	Sterility Osmolality pH Decreased side effects Enhanced cellular uptake Improved targeting	Lyophilized powders for reconstitution Nanoparticulate Dispersions Vacuum foam-dried products	Cancer Inflammation Melanoma Pancreatic Ductal adenocarcinoma Antimicrobial	[14,16,19,33]

through DoE to explore the formulation space efficiently, minimizing experimental trials and ensuring robust product quality. This approach improves the control of formulation variability, facilitated scalability, and reproducibility [12]. Additionally, resources are used efficiently, reducing development time while maintaining rigorous quality standards [8]. As research progresses, polymeric micelles possess the potential to transform drug delivery, providing safer, more effective, and personalized therapeutic solutions.

This work aims to present a comprehensive literature review and investigate the critical aspects of implementing the Quality by Design (QbD) framework in the development and optimization of micellar pharmaceutical products. To achieve this, peer-reviewed research articles of the last ten years were analyzed. The review focuses on identifying key critical quality attributes (CQAs), their influencing parameters, and the most effective types of design of experiments (DoE) methodologies employed in optimization studies of micelle formulations. Additionally, special attention is given to the added value of the QbD approach in micelle development, and the most effective DoE methods for micelle optimization are described properly. In other words, this review aims to be a roadmap for formulation scientists who aim to design, develop, and scale up micellar nanosystems for drug delivery purposes.

2. Methods: systematic review methodology

An extensive search was performed in the electronic databases PubMed, Scopus, and Google scholar for English-language publications. Publications from the past decade (2014–2024) served as a comprehensive guide for the systematic investigation of the Quality by Design types used in research and the major critical quality attributes and critical process parameters studied in academia for the development of micellar products. The search was based on the following terms: micelles design of experiments and micelles quality by design. The authors performed the literature search excluding studies with full text unavailable and publication language other than English. After the screening of titles and abstracts, 47 full-text studies were included in the aforementioned project.

3. DoE and QbD strategies for formulation development and optimization

Experimental designs used for the development and optimization of micellar products may be categorized into three types: screening designs, optimization designs, and robustness testing designs. Usually, screening and robustness testing designs are two-level fractioned factorial designs or special designs, such as Plackett-Burman or Taguchi designs. Optimization or Responses Surfaces Methodology (RSM) designs are full factorial or/and fractioned designs with three or more levels, to optimize the responses or identify the "best compromise" using quadratic and cubic models. The design focuses on optimization proposals or Design Space identification.

Fig. 1illustrates the six types of Design of Experiments (DoE) and

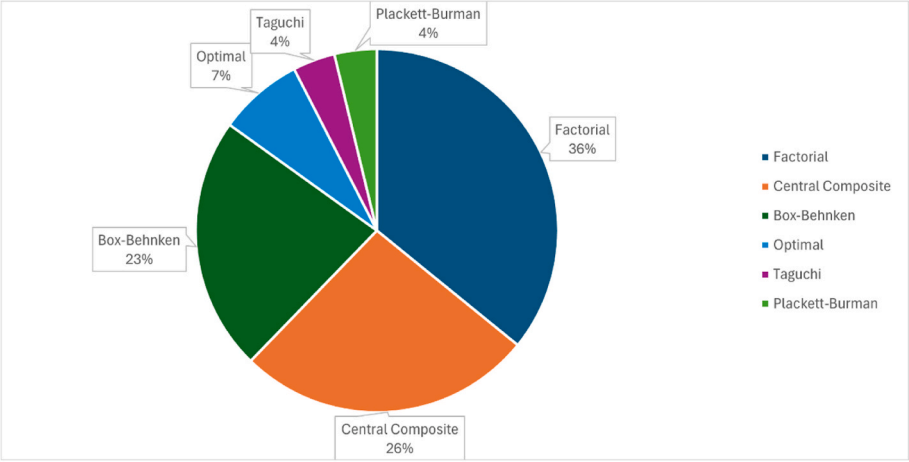


Fig. 1. Chart of the DoE types utilized in chosen literature indicating each design's popularity, ease of use and applicability in micellar products development and optimization. The chart was created by the authors based on the data extracted from the reviewed *studies*.

their usage percentages in research papers. The Factorial method is predominant (36 %), likely due to its simplicity and efficiency in analysing factor interactions. Central Composite and Box-Behnken designs jointly represent 49 %, favoured for their adaptability and response-optimization capabilities. Optimal Designs, at 7 %, are suited for irregular experimental spaces while Taguchi and Plackett-Burman, each at 4 %, see limited application, typically in screening or robustness studies (see Fig. 2).

Table 2 summarizes the CQAs, CPPs/CMAs, DoE Type and the most influential/studied process parameters and/or formulation factors.

3.1. Factorial design

Factorial Designs systematically investigate the influence of multiple factors on a response variable by simultaneously and independently varying each factor's levels. These designs are particularly useful when the number of factors and levels is relatively small, allowing for the comprehensive study of all possible interactions and the development of empirical models that describe the relationship between factors and the response. While efficient in exploring a moderate number of factors, the number of experimental runs required increases exponentially with the number of factors, limiting their applicability to larger systems. Moreover, the use of a factorial design allowed the authors to systematically evaluate the combined influence of formulation variables on the

A

CQA \ QTPP	Dosage form	Nanocarrier	Indication	Target population	Administration route	Drug release profile	Drug permeation profile
LCST	MEDIUM	HIGH	MEDIUM	LOW	HIGH	HIGH	HIGH
Micelle size	HIGH	HIGH	MEDIUM	LOW	HIGH	HIGH	HIGH
Micelle size distribution	HIGH	HIGH	MEDIUM	LOW	HIGH	HIGH	HIGH
Zeta potential	MEDIUM	MEDIUM	LOW	LOW	MEDIUM	LOW	MEDIUM
Encapsulation efficiency	MEDIUM	HIGH	MEDIUM	LOW	MEDIUM	HIGH	HIGH
Thermodynamic solubility	MEDIUM	HIGH	MEDIUM	LOW	MEDIUM	HIGH	HIGH
Viscosity	HIGH	MEDIUM	LOW	MEDIUM	HIGH	HIGH	MEDIUM
pH	HIGH	MEDIUM	LOW	MEDIUM	HIGH	HIGH	HIGH
Ionic strength	MEDIUM	LOW	LOW	LOW	MEDIUM	LOW	LOW

B

CQA \ CMA/CPP	Ratio of polymers	Polymer concentration	API concentration	Dissolution volume	Freeze-drying time	Freeze-drying temperature	Freeze-drying pressure
LCST	HIGH	HIGH	HIGH	MEDIUM	LOW	LOW	LOW
Micelle size	HIGH	HIGH	HIGH	LOW	MEDIUM	MEDIUM	MEDIUM
Micelle size distribution	HIGH	HIGH	MEDIUM	LOW	MEDIUM	MEDIUM	MEDIUM
Zeta potential	HIGH	MEDIUM	MEDIUM	LOW	LOW	LOW	LOW
Encapsulation efficiency	HIGH	HIGH	HIGH	LOW	LOW	LOW	LOW
Thermodynamic solubility	MEDIUM	HIGH	HIGH	LOW	LOW	LOW	LOW
Viscosity	MEDIUM	MEDIUM	LOW	HIGH	LOW	LOW	LOW
pH	MEDIUM	MEDIUM	LOW	HIGH	LOW	LOW	LOW
Ionic strength	LOW	LOW	LOW	MEDIUM	LOW	LOW	LOW

Fig. 2. Interdependence rating amongst CQA–QTPP (A) and CQA–CMA/CPP elements (B). Adapted from Ref. [5].

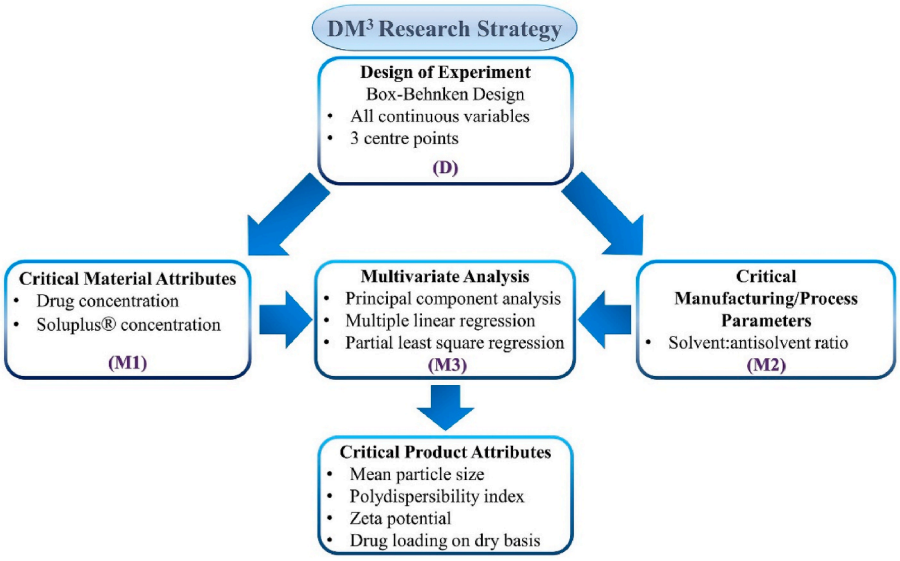


Fig. 3. Modelling scheme for DM3 research strategy: Application of design of experiments (D) and multivariate analysis (M3) to understand the interplay between critical material attributes (M1) and the critical manufacturing parameters (M2), and their impact on critical product attributes (CPAs). Adapted from [39].

Name of factor	Severity score (S)	Occurrence score (O)	Detection score (D)	RPN = S × O × D
Phospholipid conc. (%)	5	5	5	125
Surfactant conc. (%)	5	4	5	100
Stabilizer conc. (%)	2	3	3	18
Permeation enhancer conc. (%)	4	4	4	64
Cryoprotectant conc. (%)	4	3	5	60
Homogfcenization speed (rpm)	4	4	5	80
Homogenization time (min)	3	3	3	27
Ultrasonication frequency (kHz)	3	4	3	36
Ultrasonication time (min)	4	5	5	100

Risk ranking	0 to 50	51-100	101-125

Fig. 4. FMEA analysis performed for nanomixed micelles of OLM. Adapted from Ref. [23].

micelles characteristics, rather than assessing one factor at a time.

Gupta et al. [6] developed polymeric micelles containing curcumin, poly (ethylene glycol)-b-poly (ε-caprolactone) (mPEG-PCL) diblock copolymer and trehalose via a continuous processing method of co-axial turbulent jet in co-flow technology. For their study, a 3 × 3 × 4 full Factorial Design of experiments with six centre-points and three repeats was used aiming to optimize the micelles' particle size and poly-dispersity index. The chosen CPPs were the aqueous medium flow rate, the aqueous medium temperature and the polymer concentration of the formulations. For this purpose, a total of 36 formulations were prepared leading to optimized micelles with a particle size of 29.1 ± 0.51 nm and PDI equal to 0.05 ± 0.02, when the CPPs were adjusted at 70 mL/min, 60 °C and 4 mg/mL, respectively. Moreover, the solubility of curcumin was significantly increased, about 2.7 × 10^3 times higher than its plain solubility in water. Ultimately, the research group supports the advancement of a continuous processing approach that could enhance the manufacturing and quality of complex drug products, offering improvements over the traditional batch manufacturing methods currently employed in the pharmaceutical industry.

Trinh et al. [25] utilized the design of experiments approach to develop a mixed nanomicellar formulation for delivering triamcinolone acetonide as a topical ocular drop formulation. The formulation was designed with two main surfactants, hydrogenated castor oil 60 (HCO-60) and octoxynol-40 (Oc-40). Using a 2-factors, 3-levels full-Factorial Design, the study evaluated a total of 10 formulations to optimize entrapment efficiency, loading efficiency, and critical micellar concentration for effective drug delivery. HCO-60 and Oc-40 wt% ratio was chosen as the main CMA of the experiments and identified as optimal at 5 % HCO-60 and 1.5 % Oc-40, resulting in an entrapment efficiency of 46 %, loading efficiency of 0.697 %, and a low CMC of 0.0216, enhancing the stability and drug solubility. The results showed that both HCO-60 and Oc-40 affect loading efficiency, whilst the CMC is

Table 2
CQAs, CPPs/CMAs and DoE type of micelles.

REFERENCE	INGREDIENTS	DoE TYPE	CQAs	CPPs	CMAs	RESPONSES	NOTES
[6]	mPEG-PCL Curcumin Trehalose	3 × 3 × 4 Full Factorial Design with 6 center-points and 3 repeats	PS PDI	Aqueous Flow Rate: 40 mL/min Aqueous Temperature: 60 °C Ethanol Flow Rate: 70 mL/min Ethanol Temperature: 45 °C Storage temperature: 20°C–25 °C	Polymer/drug ratio: 100:15 Trehalose/polymer ratio: 20:100	PDI: 0.11 + 0.02 PS: 20–35 nm	1) Higher Re (mixture) number increases PDI and decreases EE.
[25]	Hydrogenated castor oil 60 (HCO-60) Octoxynol-40 (Oc-40) Triamcinolone acetonide	2-factors, 3-levels Full Factorial Design with 1 center point	EE DL CMC		HCO-60 wt%: 5.0 Oc-40 wt%: 1.5	EE: 44 % DL: 0,676 %, CMC:0,0216	1) Both HCO-60 and Oc-40 affect loading EE 2) CMC is only affected by Oc-40
[30]	mPEG-PCL Methazolamide	2-factors 3-levels Full Factorial Design	PS EE ZP		Polymer molecular weight (MW): 3 kDa Drug/Polymer ratio: 1:10	PS: 60.39 nm EE: 93.91 % ZP: 9.27 ± 1.54 mV	1) Increasing polymer MW increases PS and the level of ZP while it decreases EE. 2) D/P ratio positively influences both EE and negative values of ZP.
[46]	Calcipotriol Paclitaxel PEGMA-500 Anhydrous ε-caprolactone	CCD & Fractional Factorial Design with defined center and axial points	2-h DR at pH 6 2-h DR at pH 7.4 PS		PEGMA-500 units: 40, Anhydrous ε-caprolactone units: 6 Crosslinking density: 75 % PTX/CAL ratio: 5:1	CAL: 2-h DR at pH 6: 6 % 2-h DR at pH 7.4: 24 % PS: 51 nm PTX: 2-h DR at pH 6: 20 % 2-h DR at pH 7.4: 18 % PS: 51 nm	1) Increasing PEGMA-500 amount decreases drug release at pH = 6 but increases it at pH = 7,4 2) PEGMA-500 amount is negatively correlated to PS. 3) Increasing CPL amount increases DR and decreases PS.
[4]	Pullulan Tween-80 Sitagliptin	2-factors, 3-levels Full CCD	DL EE DR		Drug Concentration: 6 mg Polymer concentration: 10 mg	DL: 38.67 ± 0.23 %, EE: 79.67 ± 0.54 %, DR: 82,34 ± 0.78 %	1) Increasing polymer concentration increases DL. 2) Increasing sitagliptin concentration decreases EE and increases DR. However, at higher drug content, DR is independent of the amount of drug present in the formulation.
[44]	Dexamethasone ε-Caprolactone mPEG 2.000	2-factor, 3-level Factorial Design	Solubility		1st method: Polymer amount: 50 mg Dexamethasone amount: 5 mg 2nd method: Polymer amount: 53,8 mg Dexamethasone amount: 3 mg	1st method: SOLUBILITY: 0,37 mg/mL 2nd method: SOLUBILITY: 1,36 mg/mL	Increasing polymer concentration affects solubility based on DEX levels: at high DEX concentrations, solubility increases with higher polymer levels, while at low DEX concentrations it

(*continued on next page*)

Table 2 (*continued*)

REFERENCE	INGREDIENTS	DoE TYPE	CQAs	CPPs	CMAs	RESPONSES	NOTES
							decreases as polymer levels rise.
[38]	Galantamine DSPE-PEG 2000 & 4000 Cremophor RH 40 Phospholipon Soy lecithin Acconon CC 6 & MC8-2 Tween 20 & 80	CCD	EE PS		DSPE-PEG 2000 amount: 10,75 mg/mL Soy lecithin amount: 9,5 mg/mL Ethanol concetration: 10 mg/mL	EE: 86 % PS: 175 nm	1) Intermediate levels of DSPE-PEG and high levels of lecithin maximize EE, while low levels of lecithin and moderately low levels of DSPE-PEG increase DR. 2) Increasing the phospholipid amount reduces PS. 3) Decreasing polymer concentration increases the value of ZP.
[12]	Poloxamer-407 Poloxamer-188 TPGS Hydroxypropyl methylcellulose, Methylcellulose Sodium carboxymethylcellulose Posaconazole	CCD	Gelling capacity DL Tsol/gel		Poloxamer 407: 20 % w/v Poloxamer 188: 0.404 % w/v Polymer types	GELLING CAPACITY: immediate gelation and stay for several hours, DL: 90.97 % Tsol/gel: 31.56 ± 1.40 °C	1) Increasing Poloxamer 407 decreases Tsol/gel leading to instant gelation. 2) Both Poloxamer types influence Tsol/gel and DL.
[18]	Meloxicam Soluplus	3-factors, 3-levels BBD	Z-average PDI ZP	Mixing time Rotation pressure Rotation temperature Rotation speed	Meloxicam/Soluplus ratio: 1:4 Ethanol volume NaOH volume	Z-AVERAGE: 100.47 ± 0.87 nm PDI: 0.149 ± 0.01, ZP: 26.7 ± 0.6 mV	1) Increasing Soluplus concentration decreases PDI. 2) Higher Soluplus levels combined with ethanol volume increase PS.
[39]	Ritonavir Soluplus HPMC HPC Kollidon VA 64	BBD with 3 central points - DM3 framework	Mean PS PDI ZP		Ritonavir Concentration: 54.55 mg/mL Soluplus Concentration: 1.0 % w/v Solvent/Antisolvent ratio: 1:10	MEAN PS: 154.8 ± 0.7 nm PDI: 0.181 ± 0.009, ZP: 20.4 ± 0.8 mV	
[35]	Quercetin Salicylic acid Phospholipid Tweens 20-40-60-80	3-factors, 3-levels BBD	PS Permeation Transmittance Retention		Phospholipid amount Tween amount Ethanol amount QCT/SA ratio: 1:2	PS: <50 nm PERMEATION: 78.12 ± 0.47 % TRANSMITTANCE: 99,5 % RETENTION:12.63 ± 0.37 %	1) Increasing drug concentration increases PS and decreases PDI and ZP negative value. 2) Soluplus concentration decreases PS and ZP negative value.
[26]	Magniferin Vitamin E TPGS PEG-200 Phospholipid 90G	I-Optimal Mixture Design	DR in 15min DE PS Temul		Phospholipid 90G amount Vitamin E TPGS amount PEG-200 amount	DR in15min: 82 % DE:26 % PS: 25 nm Temul: 39s	1) Emulgent affects DR, PS, and Temul, while co-emulgent and cosolvent influence PS, and Temul. 2) At high levels of PEG-200, PS decreases. 3) PS is minimized at intermediate-high levels of vitamin E TPGS, and at

(*continued on next page*)

Table 2 (*continued*)

REFERENCE	INGREDIENTS	DoE TYPE	CQAs	CPPs	CMAs	RESPONSES	NOTES
							intermediate levels of PEG 200. 4) Phospholipid 90G negatively affects DR. 5) DE declines with increase in Phospholipid 90G and PEG 200 conc. while it increases in vitamin E TPGS higher levels. 6) Permeation maximizes at lower levels of Phospholipid 90G and decreases with higher levels of vitamin E TPGS and PEG-200. 7) Increasing Phospholipid 9G and PEG concentration decreases ZP, while increasing vitamin E TPGS increases it.
[37]	Salinomycin Pluronic F127	3-factors, 2-level Factorial Design + CCD	PS PDI EE	Evaporation Temperature & Pressure Flask Rotating speed & geometry & capacity, & Water Temperature Agitation time & speed	Polymer Concetration: 10 mg/mL, SAL Concetration: 200 μg/mL Solvent Type & Volume Water Volume	PS: 26 nm PDI: 0,22 EE: 97,9 %	1) Decreasing drug concentration increases EE. 2) Increasing polymer concentration neutralizes ZP.
[27]	Docetaxel Soluplus Pluronic F108	2-factors, 3-level Full Factorial Design	EE PS		Soluplus Concentration: 365 mg Pluronic PF108 Concentration: 45 mg	EE: 74.81 % PS: 71.4 nm	1) Increasing PF108 and Soluplus concentration to intermediate levels increases EE. 2) After a certain concentration, further increases in PF108 and Soluplus content result in larger PS.
[5]	Risperidone Pluronic F108 Pluronic F127 Chitosan HPMC	3-factors, 2-level Factorial Design	PS PDI	pH: 5–7,5 Freeze-drying Time Freeze-drying temperature & pressure	Risperidone amount: 5,0 mg, Combined amount of F127 and F108: 100,0 mg F127/F108 ratio: 4:1 Dissolution volume	PS: 21.15 ± 0.8 nm PDI: 0.098 ± 0.007	
[17]	Clotrimazole Sodium hyaluronate (HA) Dodecyl amine Hexadecyl amine (HDA) Cholesterol	3-factors, 2-level Full Factorial Design	PS ZP Clotrimazole concentration	Preparation temperature	HA/HDA ratio: 1:0.93 Cholesterol amount: slightly higher than 20 %	HDA micelles were preferred PS: 148–207 nm ZP: 34.83 ± 0.32 mV Clotrimazole concentration: 18.37 g/mL	1) A HA/HDA ratio close to 1:1 leads to the highest Clotrimazole concentration. 2) Increasing HA decreases Clotrimazole concentration. 3) Dimensions are independent of the CPPs.
[45]	Ketoprofen PEG-1000 ε-caprolactone	2-factors, 2-level Full Factorial Design	PS PDI EE		PCL/PEG ratio: 2.0:1	PS: 235.70 ± 6.03 nm PDI: 0.30 ± 0.06 EE:87.08 ± 0.06 %	1) CL increases PS, PDI, and EE. 2) PEG and

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Table 2 (*continued*)

REFERENCE	INGREDIENTS	DoE TYPE	CQAs	CPPs	CMAs	RESPONSES	NOTES
							interactions between CL and PEG decrease PS, PDI and EE.
[33]	Erlotinib Pluronic F127 TPGS	BBD	PS EE		F127 Amount: 90 mg TPGS Amount: 10 mg, Solvent (EtOH) Volume: 7,5 mL	PS: 3.22 ± 1.45 nm EE: 82.13 % ± 0.11	1) All three independent variables negatively impact micellar size. 2) TPGS highly impacts the CQAs, namely: High TPGS concentration decreases core radius. 3) Increased polymer concentration increases EE.
[7]	Fexofenadine Pluronic F127 Pluronic P123 Polysorbate 80	2-factors, 3-level Factorial Design	EE PS ZP DR after 6h		PL90G amount Pluronic (F127 and P123) mixture ratio	EE: 62.15 ± 2.75–90.25 ± 1.48 % PS 291.35 ± 6.43–467.95 ± 3.60 nm ZP: 5.41 ± 0.12 - (−) 9.23 ± 0.23 mV DR after 6h: 50.27 ± 1.11–95.38 ± 0.92 %	1) Increasing PL90G increases EE. 2) Increasing P123 increases EE. 3) Increasing F127 increases PS whereas increasing P123 decreases PS. 4) Increasing F127/P123 ratio increases DR.
[34]	Cisplatin Quercetin PLGA Span-80	CCD	EE PS		PLGA amount Span-80 amount Organic solvent volume	PS: <250 nm EE: 80 %	1) PLGA and Span-80 amounts affect EE. 2) Increasing PLGA amount increases EE & decreases PS. 3) Increasing Span-80 amount increases PS.
[23]	Olmesartan medoxomil Soy Lecithin Tween 80 Poloxamer P123	BBD	PS ZP DL	Ultrasonication Time: 4,9750s Homogenization speed & time Ultrasonication frequency	Soy lecithin amount: 2481 Surfactant amount: 0,574 Stabilizer amount Permeation enhancer amount Cryoprotectant concentration	PS: 168 nm ZP: 22.4 mV DL: 70 %	1) PS increases with higher soy lecithin concentration but decreases with increased surfactant concentration and ultrasonication time. 2) ZP and DL are both influenced by phospholipid and surfactant concentrations, as DL is also being decreased with extended ultrasonication.
[40]	Resveratrol Poloxamer F127 & P123	Face Centered CCD	PS Skin Deposition		%Pluronic P123 in Pluronic mixture: 73.5 % Resveratrol Amount: 51.5 mg	PS: 142.67 ± 6.98 nm Skin Deposition: 51.63 ± 1.97 %	1) Increasing P123 increases EE and increases PS. 2) Decreasing Resveratrol amount increases MIE and decreases PS. 3) Intermediate levels of CMAs increase skin deposition.

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Table 2 (*continued*)

REFERENCE	INGREDIENTS	DoE TYPE	CQAs	CPPs	CMAs	RESPONSES	NOTES
[13]	Exemestane Pluronic L121 Pluronic F127 Chrysin Gelucire 44/14 (GL44)	3-factor, 3-level BBD	PS PDI DL EE		CHS-L121 concentration: 2.00 F127 concentration: 1.50 GL44 concentration: 1.00	PS: 33.04 ± 2.62 nm PDI: 0.145 ± 0.02 DL: 5.2 ± 2.2 % EE: 89.6 ± 2.5 %	1) Increasing CHS-L121 reduces PS while also enhancing DL and EE. 2) Increasing F127 leads to larger particles with reduced EE and DL. 3) Increasing GL44 conc. increases PS but also improves EE and DL.
[41]	Silver Sulphadiazine Phospholipon 90G Egg oil Pluronic F127	Taguchi orthogonal array design (7-factors, 2-levels)	PS DR Viscosity PTT	Temperature Mixing time	PF-127 concentration: 25 % Organic solvent (ethanol) concentration: 30 % Egg oil concentration: 25 % Surfactant concentration: 20 % Phospholipon/ Surfactant ratio Organic phase ratio Phospholipid type Surfactant type	PS: 256.5 ± 1.24 nm DR: 78.06 % VISCOSITY: 295.02cps PTT: 40.9 ± 0.5 °C	1) Viscosity is influenced by organic phase ratio, oil concentration, type of phospholipid and temperature. 2) Physical stability is influenced by organic phase ratio, surfactant concentration and type and mixing time. 3) Increasing ethanol levels increases DR and PS but reduces viscosity. 4) Lower PF-127 conc. decreases viscosity and yields intermediate DR. 5) Intermediate levels of phospholipid/ surfactant and PF-127 increases PTT, with maximum PTT observed at low ethanol levels
[47]	Hydrochlorthiazide Oleic acid Tween 20 Propylene glycol (PG)	CCD	DR in 15 min PS		Oil concentration: 11.22 % w/w Tween 20 concentration: 69.8 % w/w Propylene glycol concentration: 0.27 % w/w	DR at 15 min: 99.32 % and 97.67 % PS: 175 ± 23 nm	
[19]	Raloxifene Hydrochloride Pullulan Carbamoylethyl-grafted-Palmitic acid (CP-g-PA)	CCD	PS EE		Raloxifene concentration CP-g-PA concentration	PS: <100 nm EE: 77.02 %	RA-PMs exhibit a distinguished pH-responsive DR characteristics at acidic conditions influencing PS
[14]	Curcumin PLGA Levan Tween 80	Plackett–Burman Design & BBD	PS ZP	Dropping rate	Levan molecular weight:134 kDa PLGA amount: 51.51 mg Acetone volume:10 mL Levan amount, Surfactant type & concentration	PS: 91.93 nm ZP: 25.7 mV	1) PS is influenced by Levan MW, PLGA amount and acetone volume. 2) The interaction between Levan MW and PLGA amount reduces PS, while the combination of Levan MW and

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Table 2 (*continued*)

REFERENCE	INGREDIENTS	DoE TYPE	CQAs	CPPs	CMAs	RESPONSES	NOTES
							acetone volume increases it. 3) ZP was positively influenced by PLGA MW, surfactant type and concentration, and acetone volume, but was negatively impacted by Levan MW. 4) EE is driven by the curcumin amount, surfactant type, and higher PLGA MW, which enhances EE. 5) PDI is influenced by the surfactant type, PLGA amount, and stirring speed.
[49]	Valsartan Capmul MCM Tween 80 Gelucire 44/14 Poloxamer 40 Florite PS-10 Low-substituted hydroxypropyl cellulose B1	BBD	PS DE in 15min Angle of repose		Surfactants ratio (T80/G44): 0.63, Carriers ratio (FLO/HPC):0.41, Total solid mass carrier: 177.6 mg	PS:191.9 nm DE in 15min: 55.0 % Angle of repose: 32.4°	1) PS is negatively influenced by G44 proportion and carriers ratio. 2) DE is positively influenced by HPC but negatively by total solid mass of carriers.
[15]	Glycyrrhizic acid Baicalein	BBD	EE DL PS PDI ZP	Water bath shaking time:12 h Ultrasonication time:10 min	Glycyrrhizic acid amount: 90 mg Baicalein amount: 8 mg	EE: 80.95 ± 1.11 % DL: 9.15 ± 0.04 % PS: 196.2 ± 22.5 nm PDI: 0.254 ± 0.012 ZP: 55.0 ± 2.6 mV	1) Increased GA concentration enhances EE, DL, and ZP while reducing PS. 2) Raising Baicalein amount decreases EE but increases DL and ZP. 3) Extending the water bath shaking time leads to reductions in EE and DL and an increase in ZP.
[8]	mPEG (5kD)-PCL(2kD) mPEG (10kD)-PCL (4.1kD) mPEG (20kD)-PCL (8kD) mPEG (2kD)-PLA Paclitaxel Lactose Anhydrous	Full Factorial Design	PS	Ethanol flow rate: 40 mL/min Ethanol phase temperature: 60 °C Temperature	Polymer concentration in ethanol: 8,4 mg/mL Polymer concentration: 0.75 mg/mL Organic/aqueous flow rate ratio Drug-polymer interaction Drug/polymer ratio Polymer MWs	PS: 22.6 ± 0.2 nm	1) Polymer molecular weight and conc. influence PDI. 2) Higher polymer molecular weights increase PS and crystallinity. 3) Low aqueous phase flow rates favour monodispersed micelles. 4) Solvent temperatures above the glass transition (Tg) improve polymer solubility and

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Table 2 (*continued*)

REFERENCE	INGREDIENTS	DoE TYPE	CQAs	CPPs	CMAs	RESPONSES	NOTES
							chain mobility. 5) Increasing MW increases polymer crystallinity.
[48]	PEG-2000 PLGA	CCD	PS PDI ZP		PLGA amount.:43.79 mg PEG concetration:12.61 PLGA MW: 30,000–60,000	PS: 69 nm PDI: 0.124 ZP: 0.23−(-36.80) mV	1) Increasing PLGA amount increases the PS. 2) Higher PLGA MW, combined with PEG contributed to PS increment
[29]	Pluronic P123 Pluronic F127 Xyloglucan	2-factor, 3-level Full Factorial Design	PS PDI EE DL		Pluronic P123/P127 ratio: 1:5 (or 30:70) Drug/Pluronic ratio: 1:2 Xyloglucan concentration: 1 % wt	PS: 64.6 5 ± 1.77 to 108.31 ± 1.37 nm PDI: 0.14 ± 0.01 to 0.28 ± 0.05 EE: 42.19 ± 1.47 % to 80.07 ± 2.42 % DL: 7.03 ± 0.24 % to 26.69 ± 0. 81 %,	
[20]	Dexamethasone Sodium Phosphate Tobramycin Sulphate Poloxamer 188 & 407 Hydroxyl propyl methyl cellulose Benzalkonium chloride	2-factor, 3-level CCD	DR after 9h		Poloxamer 407 concentration: 16.75 % HPMC K4M concentration: 0.54 %	Dexamethasone DR in 9h: 0.1 % Tobramycin DR in 9h: 3 %	1) Increasing P407 and HPMC K4M concentration enhances gel strength. 2) The synergistic effect between the type and concentration of polymers improves the mucoadhesive index. 3) Formulations lacking HPMC K4M fail to maintain DR for 9 h.
[21]	Fluoroquinolone Poloxamer 407 PVA Chitosan	3-factor, 2-level Factorial Design	EE		Polymer concentration: 28 % Drug concentration: 1–2 mg PVA concentration: 0,50 %	EE: approx. 99 %	1) Higher Poloxamer and PVA concentrations increase EE.
[24]	Raloxifene hydrochloride Poloxamer 407 Carbopol 934	D-Optimal Mixture Design	PS PDI ZP		Oil volume: 10 μL Surfactant volume: 47 μL Co-surfactant volume: 30 μL Water volume: 1913 μL	PS: 98.64 nm PDI: 0.195 ZP: 9.10 mV	
[51]	D-Xylitol (XYL) D-mannitol PEG 6000 Cremophor RH 40 Soluplus Megestrol acetate	3-level design	PS PDI ZP		Polymer type: Cremophor or Soluplus	Cremophor PS: 27.82 ± 0.87 nm PDI: 0.205 ± 0.010 ZP: 1.15 ± 0.55 mV Soluplus PS: 102.27 ± 2.06 nm PDI: 0.259 ± 0.006 ZP: 12.99 ± 0.11 mV	
[42]	Amphotericin B Dextran Maltodextrin, Sorbitol Avicel 200 PEG-400 Glycerol Hydroxypropylmethyl cellulose acetate succinate Hydroxypropyl cellulose	Taguchi L8 orthogonal array (7-factors, 2-levels factorial mixture design)	Disintegration Time Release in saliva Burst Strength Flexibility Adhesion		Dextran concentration: 25 % Maltodextrin concentration: 25 % Sorbitol concentration: 5 % Avicel 200 concentration: 10 % PEG-400 concentration:10 %, Glycerol concentration: 10 % Hydroxypropylmethyl cellulose acetate succinate concentration: 3 % Hydroxypropyl	DISIDINTEGRATION TIME: 60±3s RELEASE IN SALIVA: >80 % in 10 min BURST STRENGHT: 2190 ± 140 mN mm FLEXIBILITY: “good” ADHESION: “medium”	1) Reducing Avicel or increasing plasticizers decreases disintegration time. 2) Higher Avicel and HPMC with methanol use increases burst strength. 3) A smoother film appearance is attained using maltodextrin and high Avicel and

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Table 2 (*continued*)

REFERENCE	INGREDIENTS	DoE TYPE	CQAs	CPPs	CMAs	RESPONSES	NOTES
					cellulose concentration: 12 %		cellulose-former content.
[28]	Cyclosporine A (CyA) D-α-Tocopherol polyethylene glycol succinate (VitE-TPGS) ctylphenoxy poly (ethyleneoxy)ethanol (OPEE) Hyaluronic acid (HA)	Full Factorial Design with 3x3 quadrature points	Solubilized Cyclosporine A (CyA-In) Dh CMC		Total amount of Vit E-TPGS & OPEE (at ratio 2.25:1): 1.0 % w/w HA amount: 0.01 % w/w	CyA-In: 0.082 ± 0.005 % Dh: 22.95 ± 5.60 CMC: 0.057 ± 0.005 %	
[22]	Clozapine (CLZ) Bile salt sodium deoxycholate SDC Soy lecithin (SPC)	2-factors, 3-levels Factorial Design	PS ZP EE DL		Ingredients ratio: CLZ: SPC:SDC: 1:3:10	PS: 12.23 ± 4.76 nm ZP: 38 mV EE: 93.00 ± 0.05 % DL: 6.47 %	
[32]	Docetaxel trihydrate (DTH) Long-chain glycerides (LCG): Maisine 35-1 Medium-chain glycerides (MCG): Capmul MCM Tween 80 Transcutol HP	Placket-Burman Design & Fractional Factorial Design & I-/D-Optimal Mixture Designs	PS Emulsification time DR in 15 min		LCG Glyceride amount: 338 mg Tween 80 amount: 434 mg Transcutol HP amount: 227 mg MCG Glyceride amount: 353 mg Tween 80 amount: 440 mg Transcutol HP amount: 205 mg	LCG PS: 60,4 nm Emulsification time: 1,3min DR in 15 min: 75 % MCG PS: 70,7 nm Emulsification time: 1,2min DR in 15 min: 84 %	PS is decreased by decreasing lipid concentration, increasing surfactant concentration, and adjusting co-solvent levels to an intermediate concentration, with a higher surfactant concentration notably reducing emulsification time and enhancing DR.
[31]	Poly (styrene-*alt*-maleic anhydride) (PSMA) mPEG Cystamine Arginine Histidine Bovine Serum Albumin (BSA)	CCD	PS PDI ZP		Drug/polymer ratio: 4,50 Solvent/Non solvent ratio: 0,18	PS: 98,54 nm PDI: 0,203 ZP: 4.1 ± 0.21 mV	
[16]	Gefitinib Poloxamer 407 α-Tocopherol PEG1000 succinate	BBD	PS PE	Temperature: 40–50 °C	Drug amount: 0.5–1.5 mg Poloxamer 407 ratio: 1-5 TPGS ratio: 0.5–1.5	PS: 22.34 ± 0.18 nm EE: 95.67 ± 0.34 %	1) Increasing the drug content while reducing poloxamer 407 minimized PS, while increasing drug content with reduced TPGS levels led to larger particles. 2) Higher drug content and lower temperature increase PS and reduce EE. 3) The sustained release follows a first-order diffusion model, improving DR through polymer matrix swelling and erosion from water molecules.
[9]	Ibudilast Surfactin Dopamine hydrochloride Tris (hydroxymethyl aminomethane)	3-level Factorial Design	PS DR in 6h		Surfactin amount: 34.43m Drug amount: 9.81 mg PDA coating: 70.3 ± 5.2 %	PS: 174.6 ± 15.7 nm DR in 6h: 52.9 ± 2.9 %	1) Increasing the amount of surfactin enlarges the PS. 2) Higher ibudilast concentrations slightly enhance DL. 3) The nano-sized micellar formulations have a larger

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Table 2 (*continued*)

REFERENCE	INGREDIENTS	DoE TYPE	CQAs	CPPs	CMAs	RESPONSES	NOTES
							surface area, which enhances the DR rate through intra-nasal pathway. 4) The PDA coating increases PS across all conditions, indicating effective micelle formation. 5) The thickness and PDA coating features can be changed by solvent type, coating time, pH and dopamine concentration.
[10]	Posaconazole Pluronic F68 Soluplus	2-factors, 3-levels Full Factorial Design	PS EE		PF68 concentration: 0.8 Soluplus concentration: 0.06	PS: 66.3 ± 2.1 nm EE: 94.88 ± 2.4 %	1) Increasing PF68 and Soluplus concentrations negatively affects EE but positively influences PS. 2) Lyophilization effectively prevents particle aggregation and maintains uniform particle dispersion.
[11]	O-Carboxymethyl Chitosan (OCMC) Cholesterol Succinic Acid Monoester (CHS) O-Carboxymethyl Chitosan-g-Cholesterol Succinic Acid Monoester (CCMC)	Plackett–Burman Design & BBD	PS	Activation time: 80min, Ultrasonic power: 350W, Ultrasonic time: 7min	OCMC concentration: 10 mg/mL OCMC/CHS ratio: 1.5:1	PS: 173.9 ± 2.3 nm	1) Increasing ultrasonic power and time initially decreases PS, however, excessive conditions lead to PS increase. 2) Medium-power sonication minimizes PS. 3) The most influential factors on PS and PDI in order are the activation time, ultrasonic power, and mass ratio.
[36]	Dasatinib Soluplus TPGS 1000	CCD	EE PS		DAS/polymer ratio: 1:30 TPGS ratio: 1:2	EE: 64.479 ± 1.45 % PS: 74.477 nm	
[50]	Capsaicin Stearic Acid Glycyrrhetinic Acid Chitosan	BBD	EE PS	Dialysis time: 126 min Stirring time: 95 min	Organic/Aqueous phase ratio: 2.01	EE: 67.85 % PS: 167.54 nm	1) Dialysis time significantly affected EE and PS: increasing dialysis time initially raised EE but caused a decline at higher durations. 2) The organic-to-aqueous phase ratio displayed an antagonistic quadratic effect on EE and PS, where increases initially enhanced EE and PS before reversing. 3) Stirring time reduced PS, with

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REFERENCE	INGREDIENTS	DoE TYPE	CQAs	CPPs	CMAs	RESPONSES	NOTES
							lower and higher durations showing diminished effects.

only affected by Oc-40. Overall, the DoE concluded in suitable mathematical models connecting EE and LE to the CMAs and lead to micelle formulations in line with QTPP aiming to treat ocular inflammation in a non-invasive way, compared to current invasive methods. Possible limitations include potential scalability challenges of the method.

Elmowafy et al. [30] applied a comprehensive design of experiments framework to optimize crystalline-core micelles of methoxy poly (ethylene glycol)-b-poly (ε-caprolactone) (mPEG-PCL) for the ocular delivery of methazolamide, an anti-glaucoma drug with poor solubility. More specifically, a 2-factors 3-levels full Factorial Design was employed to study the effect of mPEG-PCL molecular weight and drug-to-polymer ratio on the identified CQAs, such as particle size, entrapment efficiency and zeta potential. For this purpose, 10 formulations were prepared using the thin film hydration procedure and resulted in optimized micelles with particle size of 60.39 nm, entrapment efficiency of 93.91 % and zeta potential equal to −9.27 ± 1.54 mV when the polymer's MW was low, at 3 kDa, and the drug-to-polymer ratio was adjusted at 1:10. During the study, mathematical models were developed and indicated that increasing polymer MW increases the particle size and the level of negative zeta potential while it decreases the entrapment efficiency. At the same time, the drug-to-polymer ratio seemed to positively influence both entrapment efficiency and negative values of zeta potential. Altogether, the study highlights the potential of the optimized formulation for providing a non-invasive, sustained-release treatment for glaucoma. Nonetheless, challenges related to scalability and long-term stability remain.

Other studies, such as the on conducted by Vaishya et al. in Ref. [44] optimized a dexamethasone (DEX)-loaded nanomicelle system with ε-caprolactone and mPEG-2000 for ocular treatment of intermediate and posterior segment uveitis. Using a 2-factor, 3-level response surface methodology, the study evaluated critical process parameters (CPPs), such as polymer and drug concentrations and heating during preparation, to enhance DEX solubility (particle size and polydispersity index were also monitored). Two sets of experiments were conducted, each consisting of 9 formulations. The first experiment utilized a standard film hydration technique, which resulted in a limited DEX solubility of 0.37 mg/mL and an average nanomicelle size of approximately 50 nm due to crystallization during film formation. The second experiment introduced a heating step at 65 °C which significantly improved the CQAs by reducing polymer crystallization and enhancing DEX encapsulation with drug-polymer interactions. This optimized method achieved a DEX solubility of 1.36 mg/mL, with the nanomicelles being 27.32 nm in size and showing a PDI of 0.135 by DLS. Particularly, it was found that increasing polymer concentration affects solubility based on DEX levels: at high DEX concentrations, solubility increases with higher polymer levels, while at low DEX concentrations it decreases as polymer levels rise. These findings suggest that precise control of heating and concentration parameters is crucial for developing a stable and effective nanomicelle system for non-invasive ocular drug delivery. Nonetheless, further evaluation for long-term stability and scalability is needed.

The development of docetaxel-loaded Soluplus-PF108 mixed micelles (DSP-MMs) took place by the team of Chougale et al. [27] who employed a QbD approach, optimizing key factors like particle size, encapsulation efficiency (EE), and drug loading to improve stability and therapeutic efficacy against melanoma. Using a 3^2 Factorial Design, the concentrations of Soluplus and PF108 were identified as critical material attributes. Dynamic and electrophoretic light scattering were employed to assess particle size and zeta potential. The study revealed that increasing the concentrations of PF108 and Soluplus to intermediate levels enhanced EE. However, after a certain concentration, further increases in PF108 and Soluplus content resulted in larger micelle sizes. The optimal DSP-MM formulation achieved a particle size of 71.4 nm and EE of 74.81 %, indicating effective docetaxel encapsulation. This formulation-maintained stability under accelerated storage conditions, showcasing its potential for stable, high-efficacy cancer treatment. However, challenges such as aggregation during extended storage remain a limitation for clinical application.

In a similar way, Kurane et al. [10] utilized a 3^2 full Factorial Design aiming to optimize the formulation of posaconazole-loaded mixed micelles (POS-MMs), assessing two independent variables: Pluronic F68 (PF68) and Soluplus concentrations and their effect on critical quality attributes such as particle size (PS) and entrapment efficiency (%EE). Following nine experimental trials, the results demonstrated that increasing PF68 and Soluplus concentrations affected negatively %EE, but positively influenced PS, leading to larger micelle sizes. The optimized formulation exhibited a PS of 66.3 ± 2.1 nm and a %EE equal to 94.88 ± 2.4 %. The optimal critical process parameters were determined as PF68 at 0.8 mg and Soluplus at 0.06 mg, which minimized particle size and enhanced entrapment efficiency. Furthermore, lyophilization effectively prevented particle aggregation and maintained uniform dispersion, with a zeta potential of −51.1 ± 2.4 mV, indicating good colloidal stability. Altogether, this approach improved the solubility and stability of posaconazole, but further in vivo studies are needed to validate the enhanced therapeutic efficacy of the obtained micelles.

In [5] Sipos et al. used a Quality by Design approach to optimize risperidone-loaded thermosensitive polymeric micelles for nasal delivery, aiming to enhance bioavailability. The initial design involved a risk assessment to identify critical quality attributes, including particle size and size distribution. The critical material attributes were risperidone amount, the combined amounts of F127 and F108, and their ratio, while the critical process parameters included pH, dissolution volume, freeze-drying time, temperature, and pressure. Thereafter, the researchers conducted a 2^3 Factorial Design of 9 experiments, through which, the optimized micelles achieved an average particle size of 118.4 ± 3.1 nm with a polydispersity index of 0.315 ± 0.009 at ambient temperature, shrinking to 20.47 ± 1.2 nm with a PDI of 0.096 ± 0.014 at 36.5 °C, showing a monodisperse profile ideal for nasal administration. The formulation exhibited rapid burst drug release and high permeation under nasal conditions, promoting immediate therapeutic effects. Stability tests confirmed that variables such as pH and viscosity did not significantly affect the micelles' properties, indicating robustness for nasal application. Nonetheless, maintaining consistent performance under varying nasal conditions remains a potential limitation. This QbD-guided micellar system offers a promising approach to improving risperidone bioavailability for central nervous system treatments.

During the study by Catenacci et al. [17] the Design of Experiments approach was used to optimize clotrimazole-loaded ionic polymeric micelles based on hyaluronic acid (HA) for improved solubility and bioavailability of the antifungal drug. A 2^3 full Factorial Design of 8 experimental formulations was initially applied, assessing the impact of variables such as the HA-to-hexadecyl amine (HDA) ratio, cholesterol concentration, and preparation temperature on particle size, zeta potential and clotrimazole concentration. Further optimization involved a

rotatable central composite design of five experiments, enabling precise adjustments to achieve desired nanoparticle dimensions and drug concentration. Specifically, adjusting the HA-to-hexadecyl amine ratio to 1:0.93 and cholesterol amount slightly higher than 20 % of HDA amount results in size ranging between 148 and 204 nm, since micelle dimensions seemed to be independent of the process parameters, and zeta potential equal to −34.83 ± 0.32 mV. Moreover, the solubility of clotrimazole was significantly improved at 18.37 μg/mL, compared to the pure drug solubility in water equal to 0.5 μg/mL. In general, the optimized micellar system confirmed a stable ionic interaction between HA and HDA, forming a core-shell structure ideal for encapsulating the hydrophobic drug. This approach demonstrated robust outcomes in drug loading and particle size, though challenges in maintaining colloidal stability under varied storage conditions suggest a need for future stability studies.

In the study of Prasetyo et al. [45] PCL-PEG-PCL triblock copolymer micelles were prepared and optimized to enhance the solubility of simvastatin (SIM), a hydrophobic drug. Key optimization was achieved through a 2^2 full Factorial Design of 12 formulations where critical process parameters such as the PCL-PEG-PCL copolymer ratio and preparation temperature were adjusted in order the micellar particle size, polydispersity index and drug entrapment efficiency to be optimal. This way, when the PCL-to-PEG ratio was set to 2:1 the system's micelle size was 235.70 ± 6.03 nm, the PDI was equal to 0.30 ± 0.06, and EE reached 87.08 ± 0.06 %. Furthermore, simvastatin's solubility was significantly improved, reaching 96.80 ± 2.39 μg/mL-10.6 times higher than its solubility in pure form. The results of the study indicated that an increased PCL ratio enhanced PS, PDI, and EE, while the inclusion of PEG, along with its interactions with PCL, reduced these values. Briefly, although this micellar system demonstrated enhanced solubility and efficient drug loading, future work is recommended to improve stability under varied storage and physiological conditions.

El-Shahed et al. in Ref. [7] applied a 3^2 Factorial Design to develop a polymeric mixed micelle (PMM) formulation that enables sustained ocular delivery of fexofenadine (FEX) for allergic conjunctivitis treatment. Key formulation variables included the amount of PL90G and the ratio of Pluronic F127-to-P123, which influenced critical quality attributes such as entrapment efficiency, particle size, zeta potential, and drug release percentage over 6 h. Specifically, through 9 experimental formulations, the study found that increasing both PL90G and P123 led to a rise in EE, indicating an improved capacity for drug encapsulation. Conversely, while an increase in F127 concentration raised PS, increasing P123 reduced it, allowing fine-tuning of particle size through their ratios. Furthermore, a higher F127/P123 ratio enhanced the percentage of fexofenadine released over a 6-h period, supporting sustained drug delivery. Optimized PMMs achieved EE ranging from 62.15 ± 2.75 % to 90.25 ± 1.48 %, particle sizes of 291.35 ± 6.43 nm to 467.95 ± 3.60 nm, zeta potential values between −5.41 ± 0.12 mV to −9.23 ± 0.23 mV, and a sustained drug release of up to 95.38 ± 0.92 % within 6 h. Blending PMMs into a hydrogel base created a stable, effective, and safe FEX delivery system, as confirmed by the Draize test for ocular safety. In vivo evaluations demonstrated that the FEX-PMM hydrogel accelerated recovery in induced allergic conjunctivitis cases, surpassing the performance of a free drug hydrogel, thus highlighting the formulation's potential for improved therapeutic outcomes in ocular drug delivery.

Interestingly, Gupta et al. [8] developed a continuous processing system using a co-axial turbulent jet in co-flow technology to create uniform paclitaxel-loaded polymeric micelles across different polymer molecular weights. A full Factorial Design of Experiments approach was conducted with four setups, evaluating critical material attributes like polymer concentration and molecular weight, alongside process parameters such as temperature and flow rates. Thirty-six formulations were prepared, optimizing micelle characteristics like particle size, polydispersity index, and drug loading efficiency. Higher polymer molecular weights increased particle size and crystallinity, while lower aqueous phase flow rates favoured monodisperse micelles. Solvent temperatures above the glass transition (Tg) improved polymer solubility and chain mobility. The optimized formulation achieved a particle size of 22.6 ± 0.2 nm, low PDI of 0.18 ± 0.02, and drug loading of 15.1 ± 0.3 %, with key CPPs including a 60 °C aqueous phase temperature, 40 mL/min ethanol flow rate, and 8.4 mg/mL polymer concentration. This continuous method minimized batch variability and enhanced scalability. Remarkably, the optimized micelles demonstrated comparable or superior characteristics to the marketed Genexol PM, although high initial costs and further scale-up challenges remain.

Hammad et al. [29] utilized a 2^3 full Factorial Design of experiments to optimize the formulation of mosapride-loaded cross-linked xyloglucan-Pluronic micelles (MOS-XPMs). The three independent variables considered were the Pluronic P123 ratio, drug-to-Pluronic ratio, and xyloglucan concentration. Eight formulations were prepared, leading to an optimal formulation identified with a desirability value of 0.952. The optimized critical quality attributes included minimized particle size (64.65 nm), maximized entrapment efficiency (80.07 %), and enhanced drug loading (26.69 %) when the CMAs were adjusted as: Pluronic ratio of 30:70, drug-to-Pluronic ratio of 1:2, and xyloglucan concentration equal to 1 %. The study demonstrated improved bioavailability and nasal permeation but faced limitations related to potential variations in mucoadhesive properties across different nasal environments. The enhanced stability and controlled release profile were key added values, supporting its application for intranasal delivery in reflux esophagitis treatment.

A 2^3 Factorial Design was also applied in Ref. [21] by Akhtar et al. in order to optimize nano-micelle formulations for ocular drug delivery. A total of 8 formulations were prepared, varying concentrations of Poloxamer 407, PVA, and drug load. The optimization focused on enhancing critical quality attributes like drug entrapment efficiency (EE) and loading capacity. It was observed that increasing Poloxamer concentration significantly improved both EE and loading capacity, as did an increase in PVA concentration. The optimal critical process parameters included a Poloxamer concentration of 28 %, PVA at 0.5 %, and varying drug concentrations based on formulation needs yielding formulations with high EE (up to 99 %) and loading capacity, suitable for prolonged ocular drug delivery. The study highlighted the fact that higher concentrations of these excipients enhance micelle stability and drug release efficiency. Despite its successes, limitations included potential scale-up challenges and variability in ocular residence time due to physiological factors.

In Terreni et al.'s study [28] a full-Factorial Design was employed to optimize nanomicellar formulations for cyclosporine A (CyA) delivery, focusing on the effects of surfactant and hyaluronic acid (HA) concentrations on three critical quality attributes: CyA solubilization (CyA-In), hydrodynamic diameter (Dh), and critical micellar concentration (CMC). Nine formulations were developed with varying surfactant and HA ratios to identify the most effective balance for ocular bioavailability and stability. The optimized formulation achieved a CyA-In of 0.105 % w/w, a Dh of 14.41 ± 0.41 nm, and a CMC of 0.045 % w/w, indicating high drug encapsulation and optimal micelle formation for ocular application. Critical process parameters included a surfactant concentration of 1.0 % w/w and HA at 0.01 % w/w to minimize ocular side effects while maintaining drug delivery efficacy. This formulation demonstrated enhanced CyA encapsulation and bioavailability comparable to commercial formulations, with the added benefits of a simpler and controlled production process. However, while promising, the study highlighted that the addition of HA, while beneficial for cytocompatibility, had limited impact on CyA solubilization at lower concentrations. Overall, this study provides an optimized, biocompatible nanocarrier system that improves upon traditional formulations by enhancing encapsulation and ease of production.

Elsharkawy et al. [22] utilized a 3^2 Factorial Design to enhance lecithin-based polymeric micelles (LbPM) for nose-to-brain delivery of clozapine. This design assessed the impact of clozapine, soy

phosphatidylcholine (SPC) and sodium deoxycholate (SDC) levels on four critical quality attributes: particle size (PS), zeta potential (ZP), encapsulation efficiency (EE), and drug loading (DL). Nine formulations were generated to obtain the most optimal one based on its high desirability score (0.845), resulting from maximum EE% and ZP, and minimal PS. The optimized formula presented desirable CQAs: PS (12.23 ± 4.76 nm), ZP (−38.6 mV), EE% (93.00 ± 0.05 %), and DL% (6.47 %) when the drug-to-SPC-to-SDC ratio was adjusted to 1:3:10 mg. The study highlighted the potential of LbPMs in targeting the brain through intranasal delivery, showing significantly higher brain uptake of clozapine in animal studies. Nonetheless, limitations included potential formulation stability challenges and the need for further optimization to ensure consistent drug delivery across a broader dosage range.

Similarly, Sharifian et al. [9] used a 3-level Factorial Design to optimize ibudilast-loaded surfactin micelles. The group investigated the effects of surfactin and ibudilast concentrations on key quality attributes such as particle size, drug loading efficiency, and release rate. The critical process parameters such as the amount of dopamine (for poly-dopamine coating), solvent type, and coating time were optimized, resulting in a final micellar particle size of 174.6 nm and a drug release efficiency of 52.9 %. A total of 14 formulations were prepared, with the optimal formulation containing 34.43 mg of surfactin and 9.81 mg of ibudilast. The study found that increasing the amount of surfactin enlarged the particle size, while higher ibudilast concentrations slightly enhanced loading efficiency. Furthermore, the poly-dopamine (PDA) coating increased particle size across all conditions, indicating effective micelle formation, while enhanced drug release is due to the increased surface area of nano-sized micelles, and modulation of PDA coating properties by variables such as pH and dopamine concentration. Overall, the prepared micelles showed potential for improved brain delivery of ibudilast but require further in vivo testing for conclusive therapeutic benefits.

Lastly, studies reported in Ref. [37] by Sousa et al. utilized a combination of a screening 2^3 Factorial Design followed by an optimization central composite one in order to develop polymeric micelles containing salinomycin (PM-SAL)and Pluronic F127 block copolymer with enhanced antimicrobial and anticancer effects. The factorial screening design identified salinomycin and polymer concentration as the most influential factors on the formulation's critical quality attributes like micelles mean diameter (MD), size distribution (PDI), encapsulation efficiency (EE%) and zeta potential (ZP). Later on, the Central Composite Design refined the optimization, testing drug and polymer concentrations over a broader range. Results showed that decreasing salinomycin concentration would increase encapsulation efficiency, while increasing Pluronic F127 amount would neutralize the zeta potential value. After the development of 15 formulations, the final optimized CQAs were: mean particle size of 26 nm, PDI equal to 0,22, ZP of −10,7 mV and EE% equal to 97,9 %. significantly enhancing antimicrobial action against MRSA over free salinomycin. Moreover, the PM-SAL system notably reduced cell viability, impaired cell migration, and effectively downregulated vimentin, a marker linked to epithelial-to-mesenchymal transition critical for tumour progression in cancer cells, while increasing the drug's intracellular concentration. All the above studies described in this section are used for optimization of micellar formulations.

3.2. Central composite design (CCD)

Central Composite Designs are response surface methodology designs that augment factorial or fractional Factorial Designs with additional axial (star) points and one centre point. This structure allows for the efficient estimation of quadratic effects, enabling the study of curvature in the response surface. All factors are examined at five levels (-α, −1, 0, +1, +α), thus effectively studying the effect of curvature. A key advantage of CCDs is their flexibility and adaptability, as the axial points can be adjusted to achieve desired properties. Nonetheless, while CCDs require fewer runs than full Factorial Designs for studying curvature, they still involve a substantial number of experiments.

In this context Lincha et al. [46] followed the Central Composite Design approach to optimize a polymeric micellar delivery system designed for the co-delivery of calcipotriol (Cal) and paclitaxel (PTX) aiming to treat pancreatic ductal adenocarcinoma. The research team optimized key CPPs such as polymer utilized (PEGMA-500 & Anhydrous ε-caprolactone), number of units in the copolymer chain, crosslinking density and PTX-to-Cal ratio to produce micelles with specific critical quality attributes including particle size and drug release profile of the two APIs at different pH values. After the preparation of 20 formulations, the ideal formulation was identified consisting of 40 repeating units of PEGMA-500, 7 units of ε-caprolactone, 75 % crosslinking density and the two drugs in a 5:1 ratio. This optimized micelle system achieved an average particle size of 53 nm and a 2-h cumulative drug release at pH 6 and 7.4 of 25 % and 22 %, respectively. Through the experiments, mathematical equations were developed showing a negative influence of PEGMA-500 units on the drug release at pH = 6 and particle size. On the other hand, increasing ε-caprolactone seems to be positively correlated to PTX release and decreases size. While the micellar system shows promising pharmacokinetics and tumour accumulation, scalability and the long-term stability of the formulation may present limitations for clinical translation.

Similarly, the team of Sharma et al. [4] based their study on the response surface methodology with a 2-factors, 3-levels full Central Composite Design to optimize a polymeric nanomicelle delivery system for sitagliptin, a DPP-4 inhibitor used in diabetes management. The formulation incorporated pullulan as a biopolymer and Tween-80 as a surfactant. The main CPPs studied were the drug and polymer concentrations and they were accordingly adjusted at 6 mg and 10 mg, respectively to acquire enhanced CQAs such as drug loading, entrapment efficiency, and drug release. The optimized formulation after 13 experiments demonstrated a drug loading of 38.67 ± 0.23 %, with an entrapment efficiency of 79.67 ± 0.54 %, and a sustained drug release of 82.34 ± 0.78 % over 24 h, offering potential for prolonged and safe ocular application. Moreover, the applied DoE resulted in mathematical equations capable of predicting and optimizing the stated CQAs as the models suggest a positive correlation between polymer concentration and drug loading percentage. At the same time, increasing the drug concentration decreases entrapment efficiency and increases drug release. However, at higher drug content, drug release is independent of amount of drug present. All in all, this optimized delivery system represents a novel approach to enhance sitagliptin's permeability and bioavailability for effective diabetes management.

Lohan et al. [38] applied a Quality by Design approach using a Central Composite Design to optimize galantamine-loaded mixed nanomicelles (MNMs) for enhanced brain delivery in Alzheimer's therapy. A total of 30 formulations were prepared, focusing on critical quality attributes such as particle size, zeta potential, entrapment efficiency, and drug release rate. Findings revealed that intermediate levels of DSPE-PEG and high levels of lecithin maximized entrapment efficiency, while low lecithin and moderately low DSPE-PEG levels enhanced drug release rate over 16 h. Additionally, increased phospholipid amounts reduced particle size, contributing to a smaller micelle size of 175 nm, and decreasing polymer concentration improved zeta potential equal to −18 mV, thereby enhancing stability. The optimized formulation achieved an entrapment efficiency of 86 % and cumulative drug release of 73 % over 16 h. Critical material attributes included DSPE-PEG 2000 (10.75 mg) and soy lecithin (9.5 mg), while process parameters were closely controlled to maintain these attributes. This approach provided a valuable framework for neurotherapeutics, though in vivo studies and scalability assessments are needed to confirm therapeutic efficacy and commercial feasibility.

Durgun et al. in Ref. [12] optimized posaconazole-loaded micelle--based in situ gelling systems for ocular delivery, aiming to enhance bioavailability for treating fungal infections. Utilizing a Central

Composite Design, the researchers prepared 15 formulations that focused on several critical quality attributes, including gelation temperature, gelling capacity, and drug release profiles. The study revealed that increasing the concentration of Poloxamer 407 resulted in a decreased sol-to-gel transition (Tsol/gel) temperature, facilitating instant gelation at physiological ocular temperature. The optimal formulation comprised Poloxamer 407 at 20 % w/v and Poloxamer 188 at 0.404 % w/v, achieving a drug release of 71.6 % over 3 h while exhibiting significant antifungal activity without causing ocular toxicity. Notably, both Poloxamer types were found to influence Tsol/gel and drug content. Although this optimized in situ gel represents a promising model for ocular drug delivery, potential challenges in large-scale production and the necessity for further in vivo testing to validate therapeutic efficacy remain as issues to be clarified.

In similar manner, cisplatin (CIS) and quercetin (QCT)-loaded bionanomicelles (BNMs) intended for improved drug delivery were developed by Rana et al. in Ref. [34]. The formulation was optimized focusing on the amount of PLGA and Span-80 concentration as critical process parameters. Key critical quality attributes included particle size and encapsulation efficiency. Results showed that both PLGA and Span-80 concentrations significantly influenced the critical quality attributes: increasing PLGA led to higher encapsulation efficiency and reduced particle size, while increasing Span-80 raised particle size. Through Central Composite Design, 13 experimental runs were conducted, resulting in an optimized formulation with encapsulation efficiency above 80 % and a particle size under 250 nm. The finalized BNM formulation achieved controlled drug release up to 8 h and showed stability in size and surface charge, as confirmed by zeta potential analysis. The added value of the study lies in providing a sustained, targeted delivery system with potential to minimize toxicity associated with CIS.

In their study, Khurana et al. [40] focused on optimizing resveratrol-loaded polymeric micelles (PMs) within a carbomer gel for psoriasis treatment. A Face Central Composite Design was utilized to fine-tune variables across 15 formulations, targeting critical quality attributes such as particle size, micellar incorporation efficiency (MIE), and skin deposition. It was observed that increasing the concentration of Pluronic P123 enhanced both encapsulation efficiency and particle size, while decreasing resveratrol content led to higher MIE and reduced particle size. Additionally, a positive correlation between critical material attributes (CMAs) was noted, with intermediate levels of CMAs maximizing skin deposition. The polymer concentration was optimized at 73.5 % w/w, resulting in a PM formulation with a particle size of 142.67 ± 6.98 nm and encapsulation efficiency of 93.45 ± 2.34 %. This formulation was incorporated into a carbomer gel, showing superior skin permeation and in vitro antioxidant activity. Significant reductions in PASI scores, splenomegaly, and pro-inflammatory cytokines were also observed in an IMQ-induced psoriatic model, suggesting potential for improved topical delivery in psoriasis treatment, though extended clinical trials are needed for long-term benefits evaluation.

In [47], a self-microemulsifying drug delivery system (SMEDDS) and liquisolid compacts of hydrochlorothiazide (HCTZ) were designed to enhance both solubility and processability. A Central Composite Design was used to optimize critical material attributes, focusing on oleic acid, Tween-20, and propylene glycol concentrations in order to enhance critical quality attributes such as %transmission, cumulative drug release in 15 min and drop size. After the development of 15 experimental batches, the optimal formulation presented 99.32 % cumulative drug release in 15 min and a droplet size of 175 ± 23 nm when the values of the aforementioned CMAs were adjusted at 11.22 %, 69.8 % and 0.27 %, respectively. Improved dissolution was likely due to the drug existing in a molecularly dispersed or amorphous state of hydrochlorthiazide. Notably, this approach not only improved hydrochlorothiazide bioavailability but also addressed formulation challenges, presenting a robust manufacturing process.

In their study on carbamoylethyl pullulan-g-palmitic acid (CP-g-PA) polymeric micelles for targeted delivery of raloxifene to breast tumours, Sethi et al. [19] applied a Central Composite Design with response surface methodology to optimize micelles' particle size, polydispersity index, entrapment efficiency and drug loading by controlling the amount of raloxifene and CP-g-PA. For this purpose, a total of 13 formulations were prepared leading to optimized micelles with a particle size less than 100 nm, entrapment efficiency of 77.02 %, ensuring targeted release. Additionally, the micelles exhibited a distinguished pH-responsive drug release characteristics at acidic conditions influencing particle size.

Eskandari et al. [48] developed PEG-PLGA nano micelles for drug delivery by examining the effects of PLGA amount, PEG amount, and PLGA molecular weight, over 26 experimental runs, on particle size, polydispersity index and zeta potential through Central Composite Design. Results demonstrated that increasing the amount of PLGA raised the micelle size, while a higher PLGA MW, combined with PEG, also contributed to size increment. The optimal formulation was achieved using 43.79 mg of high MW PLGA (30,000–60,000) and 12.61 mg of PEG, yielding a particle size of 69 nm with a low polydispersity index of 0.124 and zeta potential ranging between −0.23 and −36.8 mV. This optimized formulation was validated through experiments, maintaining stability at room temperature for six months.

Patel et al. [20] implemented a 2^3 Central Composite Design as part of a Quality by Design approach to optimize an ophthalmic in-situ gel formulation containing dexamethasone sodium phosphate and tobramycin sulphate. A total of 10 formulations were prepared, adjusting the concentrations of Poloxamer 407 and HPMC K4M. The optimized formulation contained 16.75 % Poloxamer 407 and 0.54 % HPMC K4M, achieving targeted critical quality attributes such as gel strength, mucoadhesive index, gelation temperature, and sustained drug release over 9 h. The study identified that increasing concentrations of Poloxamer 407 and HPMC K4M enhanced gel strength. Additionally, the synergistic effect between the type and concentration of polymers improved the mucoadhesive index. Notably, formulations lacking HPMC K4M failed to maintain drug release for 9 h. This study demonstrated enhanced precorneal residence time and sustained drug release, but the limitations included the necessity of balancing polymer concentrations to avoid excessive viscosity, potentially impacting patient comfort and drug diffusion.

A Central Composite Design was also applied by researchers in Ref. [31] where Aji Alex et al.'s team optimized drug-loaded micelles for co-delivery of doxorubicin and siRNA. Thirteen micelle formulations were prepared with a focus on optimizing their characteristics. These enhanced attributes included an average particle size ranging from 98.54 nm, a polydispersity index of 0.203 and zeta potential equal to -4.1 ± 0.21 mV. The optimal conditions for the drug-to-polymer and solvent-to-non solvent ratios were established as 4.50 and 0.18, respectively, so that the formulations achieving a drug loading content of approximately 8.6 % w/w. Overall, the findings suggest a promising avenue for effective cancer therapy through the co-delivery of drugs and genetic materials, however, limitations include challenges in clinical translation due to high manufacturing costs and scalability issues.

Finally, Shaikh et al. [36] utilized a Design of Experiments methodology, including single-factor analysis and Central Composite Design, to optimize the formulation of polymeric micelles loaded with dasatinib for enhanced oral bioavailability. A total of 13 formulations were evaluated to achieve optimal critical quality attributes identified were particle size, drug loading efficiency, and in vitro release profile, focusing on particle size and entrapment efficiency. The optimal critical process parameters included a Soluplus-to-TPGS ratio of 2:1, a dasatinib-to-polymer ratio of 1:30, resulting in an optimized formulation with a particle size of approximately 74.477 nm and an entrapment efficiency of 64.47 %. This formulation demonstrated enhanced drug loading and sustained release over 72 h. The added value of the study lies in its potential to improve dasatinib's therapeutic efficacy by increasing its solubility and stability, particularly for targeting liver

cancer.

3.3. Box-Behnken Design (BBD)

Box-Behnken Designs offer an alternative approach to generating response surface designs, particularly useful for exploring quadratic effects. Box-Behnken designs are 3-levels factorial similar to Central Composite Design described in the previous section, and are used for optimization. BBDs position experimental points on a hypersphere, equidistant from the centre point, and utilize only three levels (−1, 0, +1) for each factor. This design strategy often requires fewer experimental runs than Central Composite Designs for a similar number of factors, scaling as 2k (k-1) + Cp, where k is the number of factors and Cp is the number of central points. The structured arrangement of points in BBDs facilitates efficient estimation of model coefficients and simplifies the experimental process. However, BBDs may not be as flexible in accommodating specific experimental constraints.

In a study by Sipos et al. [18] meloxicam-loaded polymeric micelles for intranasal administration were designed using Box–Behnken design. Fifteen formulations were developed, focusing on particle size, polydispersity index, and zeta potential. The optimized formulation achieved a Z-average particle size of 111.6 nm, PDI of 0.114, and zeta potential of −25.2 mV, ensuring stability and effective nasal delivery. Critical process parameters and critical material attributes included the MEL/Soluplus ratio of 1:4, ethanol and NaOH volume, mixing time, rotation pressure, temperature and speed. Key findings showed that increasing Soluplus concentration decreased PDI, promoting uniform micelle formation, while higher Soluplus levels combined with ethanol volume increased particle size. The final system demonstrated high entrapment efficiency (89.4 %) and significantly faster dissolution compared to pure meloxicam, supporting rapid nose-to-brain delivery. Limitations include the need for in vivo testing to confirm efficacy and potential challenges in scaling up production. Overall, this QbD framework provides valuable insights into enhancing drug bioavailability for neuroinflammation therapies through polymeric micelles.

Likewise, in Ref. [39] Rathod et al. employed a QbD-DM^3 framework, to develop an optimal nanoamorphous micellar dispersion of ritonavir, a BCS Class IV drug. A total of three verification batches (15 experiment runs) were used to confirm predictive accuracy for attributes such as particle size, polydispersity index and zeta potential. The optimized formulation focused on specific critical process parameters including drug concentration at 54.55 mg/mL, Soluplus concentration at 1.0 % w/v, and the solvent-to-antisolvent ratio equal to 1:10, each of which significantly impacted the CQAs. The resulting micellar dispersion showed optimized CQA values of 54.8 ± 0.7 nm, 0.181 ± 0.009, and −20.4 ± 0.8 mV for particle size, PDI and ZP, respectively. Moreover, a "spring-hover" dissolution profile at pH 4.5 and a "spring--parachute" profile at pH 6.8 were noticed, indicating enhanced drug release. All in all, while the QbD-DM3 approach provided a rationalized design process, limitations include potential challenges in scale-up and the complexity of the multivariate models used.

Sandhu et al.'s study on surface-tailored nanomixed micelles (NMMs) for quercetin-salicylic acid (QCT-SA) utilized 3^3 Box-Behnken design to optimize various formulation attributes for enhanced therapeutic potential. Fifteen formulations were tested to assess their micelle size, permeation, transmittance, and retention, with statistical analysis validating a significant quadratic model. The optimized formulation exhibited a micelle size of approximately 21 nm, high transmittance (98.53 %), and improved skin retention (12.63 ± 0.37 %), supporting enhanced delivery to target tissues. The identified critical process parameters were defined by the concentrations of phospholipid, surfactant, and ethanol and by the QCT-to-Salicylic acid ratio. Specifically, increasing the drug concentration led to an increase in micelle size, a decrease in the polydispersity index, and a more negative zeta potential value. In contrast, higher Soluplus concentration reduced the micelle size and further decreased the negative zeta potential value. Overall, the study highlighted the high drug loading and consistent drug dispersion throughout the micelles, though challenges may arise in scaling and maintaining consistency in clinical applications. Finally, this QbD-guided strategy underscores the formulation's potential for targeted, efficient drug delivery with minimal side effects [35].

In [33], the researchers developed and optimized erlotinib-loaded self-assembled mixed micelles for enhanced delivery in lung cancer therapy. Using a Box-Behnken design, the researchers varied the ratios of Pluronic F127, tocopheryl polyethylene glycol succinate (TPGS) and ethanol to optimize particle size and entrapment efficiency. All three independent variables were found to negatively impact micellar size, with TPGS notably affecting critical quality attributes: high TPGS concentrations decreased the core radius, significantly impacting micellar compactness. Furthermore, increasing polymer concentration raised entrapment efficiency by providing more carrier space for drug entrapment. Across 15 formulations, the optimized micelles achieved particle sizes between 42 and 133 nm and entrapment efficiencies of 55–82 %. Moreover, the optimized formulation exhibited a sustained drug release profile with 84.91 % of erlotinib released over 72 h. This formulation strategy enhanced the pharmacokinetics of erlotinib, minimizing off-target deposition and improving therapeutic efficacy.

Chary et al. [16] optimized the formulation of gefitinib-loaded polymeric mixed micelles using poloxamer 407 and TPGS. Twenty-three formulations were prepared to assess the impact of drug amount, poloxamer 407, TPGS, and temperature on particle size and entrapment efficiency. The optimal formulation achieved a particle size of 22.34 ± 0.18 nm and an entrapment efficiency of 95.67 ± 0.34 %, while critical process parameters included drug content, poloxamer 407 ratio, TPGS ratio, and temperature were tuned to 1 mg, 3, 1 and 45 °C, respectively. Notably, increasing the drug content while reducing poloxamer 407 minimized particle size, while increasing drug content with reduced TPGS levels led to larger particles. Meanwhile, higher drug content and lower temperature increased particle size and reduced entrapment efficiency. The sustained release followed a first-order diffusion model, improving drug release through polymer matrix swelling and erosion from water molecules.

Beg et al. [23] focused their study on the development of phospholipid-based nanomixed micelles containing olmesartan medoxomil (OLM) aiming to improve lymphatic drug targeting and systemic bioavailability. A Box-Behnken design optimized the formulation by varying three critical process parameters: phospholipid concentration, surfactant concentration, and ultrasonication time. Key critical quality attributes included particle size, zeta potential, and drug loading efficiency. Findings showed that particle size increased with higher phospholipid concentration but decreased with increased surfactant concentration and ultrasonication time. Zeta potential and loading efficiency were both influenced by phospholipid and surfactant concentrations, with loading efficiency also decreasing with extended ultrasonication. The optimized formulation exhibited a particle size of 168 nm, zeta potential of −22.4 mV, and a drug loading efficiency of 70 %, all of which directly influenced OLM's bioavailability. In vitro and in vivo studies revealed that the optimized micelles reduced P-glycoprotein efflux, achieving a 60 % reduction over a pure drug suspension, which substantially increased drug permeability. Pharmacokinetic evaluations showed a 10.62-fold increase in the AUC and a 6.02-fold increase in Cmax compared to a pure drug suspension. Remarkably, the study concluded that phospholipid-based nanomixed micelles enhanced the biopharmaceutical performance of OLM, offering a promising strategy for improving oral bioavailability in hypertension management.

Similarly, a solid self-dispersing micelle (S-SDM) for enhancing the dissolution and oral bioavailability of valsartan using the Box-Behnken design was developed by Goo et al. in Ref. [49]. The independent variables examined were the ratios of surfactants (Tween 80/Gelucire 44/14), solid carriers (Florite PS-10/Hydroxypropyl Cellulose), and the total mass of solid carriers. These variables significantly impacted droplet size, dissolution efficiency at 15 min (DE15), and angle of

repose. The results indicated that droplet size was negatively influenced by the proportion of Gelucire 44 and the ratio of carriers. DE15 was positively correlated with Hydroxypropyl Cellulose but negatively with the total solid mass of carriers. After the development of 15 experimental batches, the optimized formulation achieved a droplet size of 191.9 nm, DE15 of 55 %, and an angle of repose of 32.4°, with a desirability function of 0.636 when the CPPs were adjusted as: surfactants ratio (T80/G44): 0.63, carriers' ratio (FLO/HPC): 0.41, total solid mass carrier: 177.6 mg. The optimized S-SDM showed improved dissolution and a 2-fold increase in oral bioavailability compared to raw valsartan, demonstrating its potential for enhanced drug delivery, though scalability may present a challenge.

Singh et al. [13] utilized a 3-factor, 3-level Box-Behken Design to develop polymeric micelles in which Exemestane (CHS) was incorporated into mixed micelles via physical loading, while chrysin was conjugated to Pluronic L121 (CHS-L121). This experimental design involved 15 different formulations focusing on the concentrations of CHS-L121, Pluronic F127, and Gelucire 44/14 (GL44) to enhance particle size, polydispersity index, drug loading (%DL), and entrapment efficiency (%EE). Findings indicated that increasing CHS-L121 reduced particle size while enhancing %DL and %EE. In contrast, increasing F127 led to larger particles with reduced %EE and %DL. Additionally, raising GL44 concentrations increased particle size but also improved % EE and %DL. The optimized micelles had a size of 33.04 ± 2.62 nm and a polydispersity index of 0.145 ± 0.02, ensuring uniform particle distribution, drug loading of 5.2 ± 2.2 % and entrapment efficiency equal to 89.6 ± 2.5 %, essential for effective drug delivery and bioavailability. The added value of this approach lies in its ability to co-deliver a synergistic combination of synthetic and natural anticancer agents, enhancing therapeutic efficacy against breast cancer.

Box-Behnken design was also applied to optimize glycyrrhizic acid-baicalein (GA-BE) nano-micelles by You et al. [15] focusing on glycyrrhizic acid (GA) concentration, baicalein (BE) dosage, and shaking time as critical material attributes and process parameters and their effect on encapsulation efficiency, drug loading, particle size, polydispersity index, and zeta potential. After the preparation of 17 formulations, the optimization results showed that increasing GA concentration enhanced EE, DL, and ZP while reducing PS. Conversely, raising the BE amount decreased EE but increased DL and ZP. Moreover, extending the water bath shaking time led to reductions in EE and DL and an increase in ZP. The optimal formulation (GA 90 mg, BE 8 mg, shaking time 12 h, ultrasonication 10 min) achieved 80.95 % EE, 9.15 % DL, with a particle size of 196.2 nm, PDI of 0.254, and ZP of −55.0 mV. The nano-micelles improved the solubility of BE by 4600 times and demonstrated controlled release capabilities.

Lastly, in Ref. [50] Mayuri & Sunitha employed Box-Behnken Design, to optimize capsaicin-loaded glycyrrhetinic acid-conjugated stearic acid-grafted chitosan micelles. Seventeen formulations were developed, evaluating critical process parameters (CPPs) such as dialysis time, organic-to-aqueous phase ratio, and stirring time, which influenced critical quality attributes like encapsulation efficiency and particle size. Optimal conditions included a dialysis time of 126 min, an organic-to-aqueous phase ratio of 2.01, and stirring for 95 min, yielding micelles with 67.85 % EE and a particle size of 167.54 nm. Dialysis time significantly affected EE and particle size: increasing dialysis time initially raised EE but caused a decline at higher durations. Similarly, the organic-to-aqueous phase ratio displayed an antagonistic quadratic effect on EE and particle size, where increases initially enhanced EE and size before reversing. Stirring time reduced particle size, with lower and higher durations showing diminished effects. The micelles were biocompatible and exhibited sustained capsaicin release, achieving 86.78 % release over 24 h.

3.4. Optimal designs

Optimal designs utilize algorithmic optimization (e.g., D-optimality) to maximize information efficiency for predefined model forms. They offer flexibility in handling constraints (e.g., budget, factor ranges) and excel in resource-limited settings. While optimal designs can be highly efficient in achieving their specified objectives, they may require specialized software and may be more complex to analyse than traditional designs. It should be underlined that the presented examples in this section are practical D-Optimal designs, DoE with three or more levels, when one or more input variables are qualitative, not quantitative.

Khurana et al. [26] utilized an I-Optimal mixture design to develop self-assembled phospholipidic nano-mixed micellar systems (SPNMS) for Mangiferin, co-loaded with vitamin E TPGS, aiming to enhance biopharmaceutical properties. The study involved 16 formulation runs, optimizing key material attributes—phospholipid 90G, vitamin E TPGS, and PEG 200 concentrations—to achieve optimal micelle size, drug release in 15 min, dissolution efficiency, and emulsification time. The researchers found that emulgent concentration influenced micelle size and emulsification time, while co-emulgent and cosolvent mainly affected micelle size and emulsification time. At the same time, high PEG-200 levels reduced micelle size, whereas intermediate to high levels of vitamin E TPGS and PEG 200 minimized size. Additionally, Phospholipid 90G impacted in a negative way drug release in 15 min, and dissolution efficiency declined with increased Phospholipid 90G and PEG 200, while higher vitamin E TPGS concentrations improved dissolution efficiency. Permeation was highest at low phospholipid 90G concentrations and decreased with higher PEG 200 and vitamin E TPGS levels. Increasing phospholipid 90G and PEG 200 reduced the negative zeta potential, whereas higher vitamin E TPGS increased it. The optimized SPNMS exhibited 25 nm particle size, 82 % drug release in 15 min, 26 % DE, and 39s emulsification time, demonstrating enhanced intestinal permeability and bioavailability.

Correspondingly, D-Optimal mixture design was employed to optimize a thermosensitive nanoemulgel formulation for intranasal delivery of raloxifene hydrochloride by Zakir et al. [24]. Sixteen formulations were prepared to evaluate the effect of surfactant, co-surfactant, and water on critical quality attributes, including droplet size, polydispersity index and zeta potential. The optimized NE achieved a small, uniform droplet size of 98.64 nm, with a low PDI of 0.195 and zeta potential equal to −9.10 mV. Optimized critical process parameters included a 2:1 surfactant-to-co-surfactant ratio which balanced NE formation and reduced micelle content to 2 %. Contributions of the study lie in achieving a nanosized drug delivery system that facilitates improved bioavailability while bypassing hepatic metabolism, adding therapeutic value, especially for intranasal delivery. However, potential variability in batch consistency and the need for stringent control over CPPs during manufacturing pose significant limitations.

3.5. Taguchi designs

Taguchi methods focus on robust design, aiming to identify control factors that minimize the impact of noise factors on product or process performance. These methods utilize inner and outer arrays, where the inner array explores the control factor space, and the outer array systematically varies noise factors. The goal is to find control factor settings that yield consistent performance results despite natural environmental and process variability. While Taguchi methods are widely used, their statistical properties have been subject to debate, and alternative approaches, such as combined arrays, are often considered more efficient and informative.

Thakur et al. [41] applied a systematic DoE methodology to optimize an egg oil-based organogel for enhanced dermatokinetics and therapeutic efficacy in burn wound treatment. Utilizing a Taguchi orthogonal array, the researchers examined 15 formulations focusing on critical quality attributes, such as particle size, drug release, viscosity, and phase transition temperature (PTT). The study found that viscosity was influenced by factors like organic phase ratio, oil concentration,

phospholipid type, and temperature, while physical stability was affected by surfactant concentration, type, and mixing time. Increased ethanol concentration enhanced drug release and particle size but reduced viscosity, while lower PF-127 concentrations decreased viscosity and yielded intermediate drug release. Furthermore, intermediate levels of phospholipid/surfactant and PF-127 increased PTT, with maximum PTT observed at low ethanol levels. An optimal formulation was achieved with PF-127, ethanol, egg oil and surfactant in 25 %, 30 %, 25 % and 20 % concentration, respectively, offering favourable dermatokinetic properties with enhanced drug retention, indicating potential efficacy in burn wound management. Possible limitations include challenges in large-scale production and variability in patient responses.

A year earlier, Serrano et al. employed a Taguchi L8 orthogonal array design — an efficient fractional factorial approach for studying seven variables at two levels with 8 experimental runs — to optimize orodispersible films of Amphotericin B. A total of 8 formulations were prepared by varying seven factors: the type and amount of dextrose-derived film formers (maltodextrin and dextran), Avicel (microcrystalline cellulose), plasticizers (PEG 400 and glycerol), and cellulose-derived film formers (HPMC and HPC). Key critical quality attributes optimized were disintegration time, burst strength, and film appearance. Findings indicated that, for disintegration, reducing Avicel or increasing plasticizers decreased time, while for burst strength, higher Avicel and HPMC with methanol use increased strength. The optimal formulation included a 1:1 ratio of dextran and maltodextrin, 10 % Avicel 200, 20 % plasticizers, and a mixture of 3 % HPMC AS with 12 % HPC, achieving a disintegration time of 60±3s and high burst strength (2190 ± 140 mN mm). Additionally, a smooth film appearance was attained using maltodextrin and high Avicel and cellulose-former content. This study's added value lies in its effective use of the solvent casting method and GRAS excipients, but its limitations include the need for further toxicological evaluations [42].

3.6. Plackett-Burman designs

Plackett-Burman designs screen main effects to identify the most influential factors with minimal runs, using two-level (−1, +1) factors and often include "dummy" factors to balance the design. A key advantage is their ability to screen many factors efficiently for preliminary studies. However, they provide limited information about interactions between factors and are unsuitable for modelling curvature in the response surface, restricting their use to initial screening phases prior to detailed optimization.

The study of Bahadori et al. [14] utilized a Design of Experiments approach, incorporating both Plackett-Burman and Box-Behnken designs, to optimize a PLGA-Levan-based drug delivery system for curcumin. The Plackett-Burman design identified critical factors influencing the critical quality attributes, including particle size, zeta potential, encapsulation efficiency, and polydispersity index. For particle size, the key influencing factors were Levan molecular weight, PLGA amount, and acetone volume. Notably, the interaction between Levan MW and PLGA amount reduced PS, while the combination of Levan MW and acetone volume increased it. ZP was positively influenced by PLGA MW, surfactant type and concentration, and acetone volume, but was negatively impacted by Levan MW. EE was driven by the curcumin amount, surfactant type, and higher PLGA MW, which enhanced the encapsulation. PDI was influenced by the surfactant type, PLGA amount, and stirring speed (rpm). The optimization process involved testing 15 formulations, yielding an optimal nanoparticle size of 91.93 nm, ZP of −25.7 mV, and an EE of 100 %. The optimal critical process parameters included 134 kDa Levan, 51.51 mg of PLGA, and 10 mL acetone. The optimized formulation showed enhanced curcumin solubility and stability for up to 60 days. However, the complexity of scaling up remains a limitation of this method.

In a similar way, in Ref. [32] the researchers utilized Design of Experiments through Placket-Burman Design and Fractional Factorial Design for initial factor screening, followed by I- and D-optimal mixture designs to optimize the formulation variables, achieving sixteen runs with five replicates each. A total of 12 formulations for long-chain glycerides (LCG) and eight for medium-chain glycerides were created to optimize globule size (Dnm), emulsification time (Temul), percent drug release in 15 min (Rel15min), dissolution efficiency (%DE), and permeability over 45 min (Perm45min). The optimized LCG formulation showed a Dnm of 98 nm, Temul of 1.3 min, Rel15min of 75 %, and Perm45min of 82 %, while the optimized MCG formulation recorded slightly different CQA values: Dnm of 106 nm, Temul of 1.2 min, Rel15min of 84 % and Perm45min of 60 %. Particle size reduction was achieved by decreasing lipid concentration, increasing surfactant concentration, and adjusting co-solvent levels to an intermediate concentration, with a higher surfactant concentration notably reducing Temul and enhancing drug release. The study's approach demonstrated a significant advantage in understanding the interactions between variables, though limitations included the complex Factorial Design and potential scalability issues.

Li et al. [11] integrated single-factor analysis, Plackett–Burman design, and Box-Behnken response surface methodology to optimize the preparation of O-carboxymethyl chitosan-g-cholesterol succinic acid monoester nanomicelles. A total of 17 formulations were prepared, focusing on optimizing three quality attributes: particle size, polydispersity index, and encapsulation efficiency. The critical process parameters identified were the mass ratio of CCMC to CHS (optimal at 1.5:1), activation time (80 min), and ultrasonic power (350 W). The results indicated that increasing ultrasonic power and time initially decreased the particle size, however, excessive conditions led to size increase. Notably, medium-power sonication minimized particle size. The most influential factors on particle size and PDI in order were the activation time, ultrasonic power, and mass ratio. The optimized nanomicelles demonstrated high drug loading and sustained release characteristics. Limitations include the scalability of the ultrasonic method and potential variability in process reproducibility.

It is worth mentioning that during this literature review we were unable to clearly classify the study by the researchers in Ref. [51] in one of the DoE types, possibly because of the simpler use of the Quality by Design approach. In this study, the researchers aimed to optimize micellar formulations for enhancing the release of megestrol acetate. A risk assessment identified critical factors influencing the drug delivery system, and various formulations were prepared using two surfactants: Cremophor RH 40 (CR40) and Soluplus (SP). A total of six formulations were evaluated to determine optimal characteristics. The critical quality attributes identified included micelle size, drug loading efficiency, and stability. The optimal critical process parameters involved controlling temperature and surfactant concentrations, with SP micelles showing enhanced performance at 2.154 mg/mL solubility and a nanoparticle size of 102.27 nm with uniform distribution (PDI of 0.259) and colloid stability (zeta potential of 12.99 mV). Moreover, SP polymeric micelles demonstrated superior solubilizing efficiency (56.77 %) compared to CR 40 micelles (37.4 %). While the study successfully enhanced drug solubility and release, potential variability in vivo performance due to physiological conditions may pose a significant challenge (see Fig. 5).

4. The added value of QbD approach in micelle development

Micelles is one of the main categories of nanoparticles, especially for tumor-targeting and controlled release purposes [52]. Most frequently studied CQAs in the reviewed literature studies of the last decade (2014–2024) are presented in Fig. 6. It is well known in literature that nanoparticles exhibit challenges in the development of these pharmaceutical products. The complex physicochemical properties, their interactions with biological systems, including interactions with serum proteins and mechanisms for cell internalization, and the variability of formulations outcome due to several factors affecting the manufacturing process make the introduction of QbD in pharmaceutical

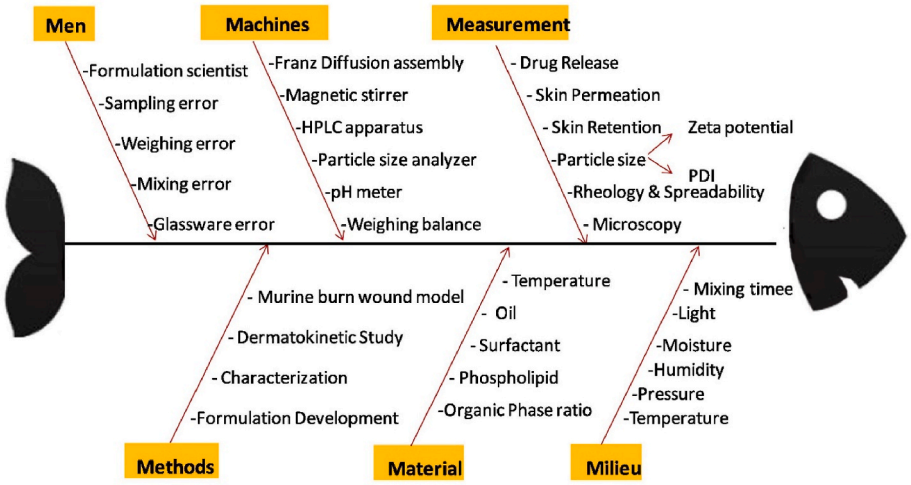

Fig. 5. Ishikawa fish-bone diagram portraying various causes and sub-causes affecting CQAs of organogel formulation. Adapted from Ref. [41].

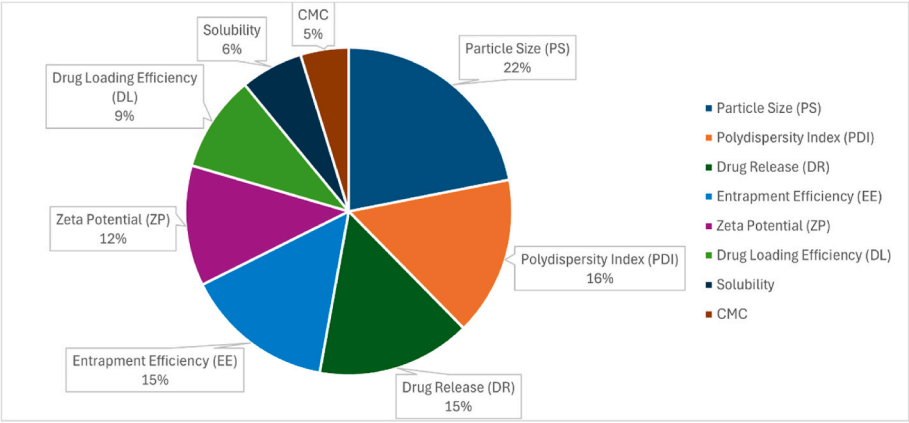

Fig. 6. Most frequently studied CQAs in the reviewed literature studies of the last decade (2014–2024).

nanotechnology of paramount importance [53]. Namely, Troiano et al. (2026) [54] highlighted the importance of the introduction of a risk-based QbD framework for the industrialization of micellar products underlying the manufacturing challenges related to the chemistry, physicochemical characteristics, stability, and biological effectiveness of a micellar product. The systematic optimization, the reduced number of experiments, and the identification of the critical parameters for the effectiveness of the micellar formulation are some of the advantages of the DoE for micellar formulation development. Furthermore, the in-depth understanding of the processes in the micelle preformulation, formulation, and manufacturing phases is ameliorated by QbD. The incorporation of risk assessment tools (i.e., Ishikawa diagrams, control charts, etc.) and the establishment of the design space lead to the mitigation of the possible risks during the life cycle of the pharmaceutical product. For the above reasons, continuous improvement is more effective due to the utilization of continuous quality monitoring. Last but not least, QbD is widely accepted by regulatory agencies, leading to risk-based approvals and fast clinical translation of nanoformulations.

5. Comparative assessment – conclusions

The systematic application of Design of Experiments (DoE) and Quality by Design (QbD) in developing micelle-based drug delivery systems benefits formulation scientists by integrating quality early in the development process. This approach reduces variability, ensures consistent results, lowers resource costs, and facilitates technology transfer to large-scale production while also ensuring regulatory compliance. This work aimed to present a comprehensive literature review and investigate the critical aspects of implementing the Quality by Design (QbD) framework in the development and optimization of micellar pharmaceutical products. DoE was used to optimize micellar formulation parameters with QbD-driven risk management. Several APIs were examined as case studies for micellar development.

Research teams may select various DoE methodologies to achieve CQAs that align with the QTTP. Moreover, combining different DoE types can effectively meet study objectives. The most frequently examined CQAs in the literature included particle size, polydispersity index, drug release, entrapment efficiency, and zeta potential, all pivotal for clinical success, as evidenced by marketed nanomedicines. These attributes are influenced by critical material attributes and critical process parameters such as mixture concentrations, ratios, mixing duration, and ultrasonication power. RSM is useful for identification of the interrelationships between several variables and more than one response, while full factorial is useful for matching all the existing combinations of the factor levels. Fractional factorial design is the most appropriate method for the minimum number of experiments and for this reason is widely used in pre-formulation studies. The most common CQAs are the physicochemical characteristics (size, size distribution, and zeta potential), the drug EE, and the release studies. The most common factors are the API:polymer ratio, stirring time, speed, and temperature.

To the authors' knowledge, this represents the first comprehensive literature review of the most recent DoE and QbD applications in

micellar nanomedicine development. By analysing 47 studies (in the period 2014–2024), the review delineates methodological trends—Factorial Designs for screening and Response Surface Methodology for optimization—and establishes best practices for risk assessment, design space development, and lifecycle management. This holistic approach bridges academic innovation with industrial scalability, offering a roadmap for advancing micellar therapeutics into clinical and commercial applications, ultimately contributing to safer, more effective, and personalized drug delivery.

CRediT authorship contribution statement

Eirini-Zoi Papavasileiou: Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Dimitrios M. Rekkas:** Writing – review & editing, Supervision, Conceptualization. **Paraskevas P. Dallas:** Writing – review & editing, Investigation, Data curation. **Stergios Pispas:** Writing – review & editing, Investigation, Conceptualization. **Natassa Pippa:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data appeared in the main manuscript.

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