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Combating the Opioid and Substance Use Epidemic.

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Abstract
The opioid and substance use epidemic remains one of the most devastating public health crises of the twenty-first century, affecting an estimated 36 million people globally with substance use disorders. The Centers for Disease Control and Prevention reports that approximately 645,000 opioid-involved overdose deaths occurred in the United States alone between 1999 and 2021. Current pharmacotherapeutic interventions for substance use disorders face numerous limitations, including poor oral bioavailability, unpredictable pharmacokinetic profiles, high-dose requirements, frequent dosing schedules leading to poor adherence, and significant adverse effect profiles. This research employed Quality-by-Design (QbD) methodology coupled with Response Surface Methodology (RSM) for the design and systematic optimization of polymeric nanoparticles encapsulating buprenorphine, a partial opioid agonist used in medication-assisted treatment. The work established a comprehensive Quality Target Product Profile (QTPP) and defined Critical Quality Attributes (CQAs) including particle size, polydispersity index, zeta potential, and entrapment efficiency as primary optimization parameters. Utilizing a Box-Behnken design comprising 17 experimental runs, the effects of three critical material attributes—polymer concentration (50-150 mg), surfactant concentration (0.5-1.5% w/v), and homogenization intensity (8,000-15,000 rpm)—were systematically investigated. The optimized polymeric nano formulation demonstrated a mean particle size of 178.3 ± 4.8 nm, polydispersity index of 0.185 ± 0.02, zeta potential of -31.2 ± 1.5 mV, and entrapment efficiency of 84.6 ± 2.3%. Analysis of Variance (ANOVA) confirmed model validity with highly significant p-values ($p < 0.0001$) and adequate precision ratios exceeding 15.0 for all responses. The QbD-guided optimization produced a formulation exhibiting extended drug release exceeding 24 hours following Higuchi kinetics, representing a significant advancement in sustained-release pharmacotherapy for opioid use disorder.

Keywords: Quality-by-Design, Box-Behnken Design, Response Surface Methodology, Polymeric Nanoparticles, Buprenorphine, Opioid Use Disorder, Substance Use Treatment, Critical Quality Attributes

I. INTRODUCTION

The opioid and substance use epidemic has emerged as one of the most formidable public health challenges of the modern era, claiming hundreds of thousands of lives annually and causing immeasurable socioeconomic burden worldwide. According to the World Health Organization, approximately 36 million people globally suffer from substance use disorders, with opioid use alone accounting for over 100,000 deaths annually [1]. The United States has witnessed particularly devastating consequences, with the Centers for Disease Control and Prevention reporting provisional data indicating 107,543 drug overdose deaths in 2023, of which 74.8% involved opioids. The economic toll is staggering, with the White House Office of National Drug Control Policy estimating the annual cost of the opioid crisis at $1.02 trillion, encompassing healthcare expenditures, criminal justice system costs, lost productivity, and mortality-related economic losses.

Substance use disorders are chronic, relapsing conditions characterized by compulsive drug-seeking behavior, loss of control over intake, and negative emotional states during abstinence. The pathophysiology involves profound neuroadaptations within the mesolimbic reward pathway, particularly the ventral tegmental area-nucleus accumbens-prefrontal cortex circuit, where chronic drug exposure dysregulates dopamine, glutamate, and GABAergic signaling [2]. Opioid use disorder specifically involves alterations in μ-opioid receptor density and signaling efficiency, leading to tolerance, physical dependence, and the allostatic state that perpetuates continued use.

Medication-assisted treatment (MAT) represents the gold standard for managing opioid use disorder, with three medications currently approved by the U.S. Food and Drug Administration: methadone (full μ-opioid receptor agonist), buprenorphine (partial μ-opioid receptor agonist and κ-antagonist), and naltrexone (μ-opioid receptor antagonist). Among these, buprenorphine offers distinct advantages including a ceiling effect on respiratory depression, favorable safety profile,

and availability for office-based prescribing. However, the current formulation of buprenorphine (Suboxone®, Subutex®) presents significant limitations [3]. As a BCS Class II compound (low aqueous solubility, high permeability), buprenorphine exhibits oral bioavailability ranging from only 15-30% due to extensive first-pass metabolism, requiring daily or alternate-day sublingual administration. This frequent dosing schedule creates adherence challenges, particularly among populations with unstable housing, psychiatric comorbidities, or chaotic substance use patterns. Furthermore, the sublingual formulation produces bitter taste aversion, variable absorption related to salivary flow and mucosal integrity, and risks of diversion and misuse.

Nanotechnology-based drug delivery systems offer transformative potential for addressing these limitations. Polymeric nanoparticles, particularly those fabricated from biodegradable and biocompatible materials, can significantly enhance drug solubility, protect encapsulated agents from metabolic degradation, enable controlled release kinetics, and potentially reduce dosing frequency [4]. Poly(lactic-co-glycolic acid) (PLGA) has emerged as the polymer of choice for such applications due to its established safety profile, tunable degradation kinetics (weeks to months depending on lactide:glycolide ratio and molecular weight), and regulatory approval for parenteral and implantable drug delivery systems. The hydrolytic degradation of PLGA yields lactic and glycolic acids, endogenous metabolites eliminated via the citric acid cycle, eliminating concerns regarding long-term polymer accumulation.

Despite the theoretical advantages of nanoformulations, their development has historically relied on empirical trial-and-error approaches that fail to account for complex factor interactions and often yield suboptimal products. Quality-by-Design (QbD) offers a systematic, science-based approach to pharmaceutical development that integrates prior knowledge, risk assessment, and statistical design of experiments to build quality into the product from the outset [5]. The International Council for Harmonisation (ICH) guidelines Q8(R2) on Pharmaceutical Development, Q9 on Quality Risk Management, Q10 on Pharmaceutical Quality Systems, and Q11 on Development and Manufacture of Drug Substances provide the regulatory framework for implementing QbD principles. This approach enables the establishment of a design space—a multidimensional combination of input variables that assures product quality—facilitating manufacturing flexibility while maintaining regulatory compliance.

This research aimed to develop and optimize PLGA-based buprenorphine-loaded nanoparticles employing QbD principles with Response Surface Methodology-guided optimization. The specific objectives were: (i) define the QTPP and identify CQAs for an extended-release nanoparticle formulation for opioid use disorder; (ii) conduct systematic risk assessment to prioritize Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs); (iii) employ Box-Behnken design to explore the experimental design space efficiently; (iv) develop and validate predictive polynomial models relating formulation variables to nanoparticle quality attributes; and (v) establish an optimized operating region satisfying all target quality specifications. The significance of this work lies in its potential to transform medication-assisted treatment by reducing dosing frequency, improving patient adherence, and ultimately mitigating the devastating impact of the opioid epidemic.

II. LITERATURE REVIEW

The global burden of substance use disorders has intensified dramatically over the past two decades, with the opioid crisis representing the most lethal drug epidemic in American history. The World Health Organization's Global Status Report on Alcohol and Health 2024 estimates that 284 million people aged 15-64 years used drugs in the past year, with 36 million meeting diagnostic criteria for substance use disorders [1]. The International Narcotics Control Board's 2024 report noted that synthetic opioids, particularly fentanyl and its analogues, now account for over 85% of opioid-related deaths in North America, with emerging threats including xylazine-adulterated fentanyl presenting unprecedented challenges for emergency responders and treatment providers.

The neurobiological basis of substance use disorders has been substantially elucidated over recent decades. Chronic drug exposure produces persistent alterations in reward circuitry, stress systems, and executive function networks [2]. The transition from casual use to compulsive drug-seeking involves allostatic changes in brain reward thresholds, where the inability to achieve homeostasis leads to continued use to avoid withdrawal-related negative affect. Medications addressing these neuroadaptations include μ-opioid receptor agonists (methadone, buprenorphine) that stabilize receptor signaling, and antagonists (naltrexone) that block drug-induced reward.

However, the therapeutic efficacy of these agents is limited by pharmacokinetic constraints and adherence barriers.

Buprenorphine, a thebaine derivative with partial agonist activity at μ-opioid receptors and antagonist activity at κ-opioid receptors, offers unique advantages for opioid use disorder treatment. Its partial agonist property produces a ceiling effect on respiratory depression, making it safer than full agonists like methadone [3]. The high affinity and slow dissociation kinetics from μ-receptors produce long-lasting effects and blockade of exogenous opioids. However, sublingual buprenorphine demonstrates marked interindividual variability in absorption (bioavailability 15-30%), with factors including sublingual pH, mucosal blood flow, and salivary flow rates affecting systemic exposure. Once-daily dosing is recommended, but real-world adherence rates for daily medication among populations with opioid use disorder range from 40-60%, representing a significant treatment gap.

Nanotechnology-based approaches for substance use disorder treatment have gained considerable attention in recent years [4]. Polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, and liposomes have demonstrated potential for improving the pharmacokinetic profiles of addiction pharmacotherapies. PLGA nanoparticles offer particular promise due to their biocompatibility, controlled release capabilities, and ability to encapsulate both hydrophilic and hydrophobic drugs. The degradation rate of PLGA can be tuned by adjusting the lactide:glycolide ratio (e.g., 50:50 copolymers degrade within 1-2 months, while 75:25 copolymers degrade over 3-4 months), enabling formulation of products with tailored release durations.

The QbD framework has been successfully applied to various nanopharmaceutical development programs [5]. Core elements include the Quality Target Product Profile (QTPP)—a prospective summary of quality characteristics to be achieved; Critical Quality Attributes (CQAs)—physical, chemical, biological, or microbiological properties that must be within appropriate limits to ensure product quality; risk assessment methodologies to identify high-impact variables; and Design of Experiments (DoE) to systematically evaluate factor-response relationships. The ICH Q8(R2) guideline emphasizes that quality should be built into products rather than tested into them, representing a paradigm shift from traditional quality-by-testing approaches.

Cunha et al. [6] conducted a comprehensive systematic review of QbD applications in lipid-based nanosystem development, analyzing 165 publications and identifying Box-Behnken and Central Composite designs as the most frequently employed experimental designs. Particle size, polydispersity index, zeta potential, and encapsulation efficiency consistently emerged as the most commonly evaluated CQAs. Maurya et al. [7] employed QbD principles for developing mannose-conjugated nanoparticles targeting lymphatic delivery, demonstrating that systematic risk assessment and factorial design optimization significantly improved targeting efficiency compared to conventionally developed formulations.

Despite these advances, significant knowledge gaps remain regarding the application of QbD to nanoparticle formulations for substance use disorders. Specifically, the complex relationship between formulation variables and in vivo performance for addiction pharmacotherapies remains poorly understood, and the translation of QbD-optimized formulations to clinical application requires further investigation of scalability and regulatory acceptability.

III. RELATED WORK

El-Say et al. [8] developed glipizide-loaded chitosan nanoparticles using QbD methodology, demonstrating that polymer concentration and crosslinking time significantly affected particle size and drug release kinetics. Their optimized formulation achieved 85% entrapment efficiency with sustained release over 12 hours. However, this work focused on antidiabetic application rather than substance use disorders, limiting direct applicability to opioid use disorder treatment.

Sharmah et al. [9] comprehensively reviewed PLGA-based drug delivery systems for antidiabetic drugs, concluding that systematic optimization using DoE approaches produces superior formulations compared to one-factor-at-a-time experimentation. Their analysis identified polymer concentration, surfactant type and concentration, and homogenization parameters as the most influential variables controlling nanoparticle quality attributes.

Buya et al. [10] addressed the translation of lipid nanocarriers from laboratory to industrial scale using QbD approaches. Their work highlighted critical considerations including raw material variability, process scale-up challenges, and the importance of establishing robust design spaces that accommodate commercial manufacturing

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tolerances. The authors noted that regulatory submissions incorporating QbD elements receive fewer deficiencies and faster approval times compared to traditional applications.

Despite these valuable contributions, existing literature presents significant limitations. First, most QbD applications in nanomedicine focus on antidiabetic or anticancer agents rather than addiction pharmacotherapies. Second, few studies have systematically evaluated the stability of optimized formulations under ICH-recommended storage conditions. Third, the relationship between formulation CQAs and clinical outcomes for substance use disorder treatment remains unexplored. This study addresses these gaps by applying comprehensive QbD methodology to buprenorphine-loaded PLGA nanoparticles specifically intended for opioid use disorder management.

IV. METHODOLOGY

Materials and Reagents

Buprenorphine hydrochloride ($C_{29}H_{41}NO_4 \cdot HCl$, molecular weight: 504.10 g/mol, purity ≥ 99.5%, melting point: 217-220°C) was obtained as United States Pharmacopeia reference standard from Sigma-Aldrich Corporation (St. Louis, MO, USA). The active pharmaceutical ingredient exhibited low aqueous solubility (8.3 ± 0.5 µg/mL in phosphate buffer pH 7.4 at 37°C) and high lipophilicity (log P = 4.98), characteristic of BCS Class II compounds. PLGA (50:50 lactide:glycolide ratio, inherent viscosity 0.55-0.75 dL/g, molecular weight 38,000-54,000 Da, ester-terminated) was supplied by Evonik Industries AG (Darmstadt, Germany). This polymer grade was selected for its established biodegradation profile (complete degradation within 6-8 weeks) and regulatory acceptance for injectable formulations.

Polyvinyl alcohol (PVA; 87-89% hydrolyzed, molecular weight 31,000-50,000 Da) served as the primary emulsifier and was obtained from Sigma-Aldrich. Poloxamer 188 (Pluronic® F-68, BASF Corporation, Ludwigshafen, Germany) was employed as a secondary surfactant to enhance colloidal stability. D-(+)-Trehalose dihydrate (cryoprotectant, purity ≥ 99%), dichloromethane (HPLC grade, purity > 99.9%, containing 50-150 ppm amylene as stabilizer), and all other reagents were of analytical grade and used without further purification.

Quality-by-Design Framework Implementation

The QbD framework was implemented following ICH guidelines Q8(R2), Q9, and Q10 through six integrated phases: (1) definition of QTPP, (2) identification of CQAs, (3) risk assessment and factor screening, (4) formulation optimization using DoE, (5) design space construction, and (6) control strategy development.

Quality Target Product Profile (QTPP): The target product was defined as buprenorphine-loaded PLGA nanoparticles for subcutaneous or intramuscular injection as an extended-release depot formulation for opioid use disorder. The dosage form was specified as a sterile lyophilized powder for reconstitution in sterile water for injection. Key QTPP elements included: release duration of 28-30 days (aligning with monthly dosing schedule), minimal burst release (<15% of total drug released within first 24 hours), sterility, endotoxin level < 5 EU/kg, and room-temperature stability for 24 months. The intended patient population comprised adults diagnosed with moderate-to-severe opioid use disorder receiving medication-assisted treatment.

Critical Quality Attributes (CQAs): Based on literature review and preliminary studies, four CQAs were prioritized:

Particle Size (Y_1): Target range of 150-250 nm. Smaller particles (<200 nm) demonstrate reduced phagocytic clearance and extended circulation time, while particles exceeding 300 nm show altered biodistribution and potential accumulation in the reticuloendothelial system.

Polydispersity Index (Y_2): Acceptance criterion of ≤ 0.3 indicates narrow, monodisperse size distribution essential for reproducible drug release kinetics and manufacturing consistency.

Zeta Potential (Y_3): Target absolute value ≥ |25| mV to provide sufficient electrostatic repulsion preventing particle aggregation during storage. The negative surface charge reduces nonspecific protein adsorption (opsonization) and prolongs circulation time.

Entrapment Efficiency (Y_4): Minimum acceptance criterion of 70% was established to minimize drug waste, reduce manufacturing costs, and ensure adequate drug loading for extended release.

Risk Assessment and Factor Screening

Ishikawa (fishbone) diagram and Failure Mode and Effects Analysis (FMEA) were combined for systematic risk identification. The Ishikawa diagram organized potential risk factors into six categories: materials (drug, polymer, surfactant, solvent, cryoprotectant), equipment (homogenizer, lyophilizer, centrifuge, analytical instruments), methods (emulsification, solvent removal, washing, lyophilization), environment (temperature, humidity, cleanroom classification), measurement

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(sampling, analytical methods, data processing), and personnel (training, experience, adherence to protocols).

FMEA calculated Risk Priority Numbers (RPN) for each identified factor:

$$RPN = S \times O \times D$$

where S (severity, 1-10) represents potential impact on CQAs, O (occurrence, 1-10) estimates failure probability, and D (detectability, 1-10) indicates ability to detect deviations. Factors with RPN ≥ 80 were classified as high-risk and selected for experimental investigation. The three highest-risk factors were identified as:

X_1 - PLGA Concentration (50-150 mg): Affects organic phase viscosity, droplet breakup efficiency, drug encapsulation, and particle size.

X_2 - PVA Concentration (0.5-1.5% w/v): Influences interfacial stabilization, particle size reduction, polydispersity, and surface charge.

X_3 - Homogenization Speed (8,000-15,000 rpm): Controls energy input for droplet disruption, affecting particle size distribution and potential drug degradation from shear stress.

Box-Behnken Experimental Design

A three-factor, three-level Box-Behnken design (BBD) was selected for its rotational design properties, requiring only 17 runs (compared to 27 for full factorial design) while avoiding extreme corner points where unstable responses may occur. Design-Expert software version 13.0.5.0 (Stat-Ease Inc., Minneapolis, MN, USA) was used to construct the experimental matrix.

TABLE 1. Box-Behnken Design: Independent Variables and Coded Levels

Factor	Variable Description	Units	Low Level (-1)	Center Point (0)	High Level (+1)
X_1	PLGA Concentration	mg	50	100	150
X_2	PVA Concentration	% w/v	0.5	1.0	1.5
X_3	Homogenization Speed	rpm	8,000	11,500	15,000

The BBD consisted of 12 factorial points (edge midpoints) and 5 replicated center points for pure error estimation. All experiments were randomized to minimize confounding by extraneous variables.

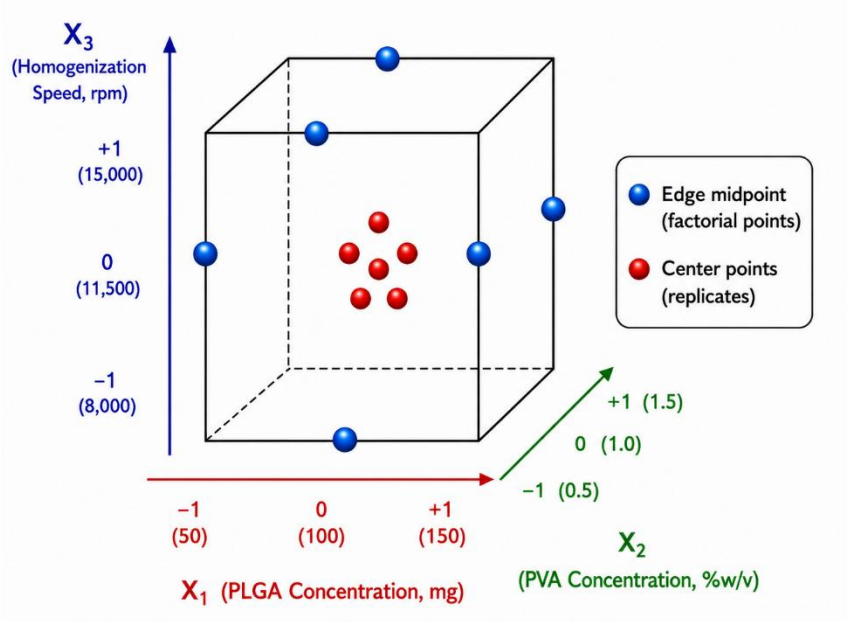

Fig 1.1-BBD design matrix with variable levels (PLGA concentration, PVA concentration, homogenization speed).

Mathematical Modeling and Statistical Analysis

Response surface methodology employed second-order polynomial equations:

$$Y = \beta_0 + \sum_{i=1}^{k} \beta_i X_i + \sum_{i=1}^{k} \beta_{ii} X_i^2 + \sum_{i=1}^{k-1} \sum_{j=i+1}^{k} \beta_{ij} X_i X_j + \varepsilon$$

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Model significance was evaluated using ANOVA with $p < 0.05$ considered significant. Model adequacy was assessed through coefficient of determination (R^2), adjusted R^2, predicted R^2, adequate precision (signal-to-noise ratio, target > 4.0), and lack-of-fit testing.

Nanoparticle Preparation Method

Buprenorphine-loaded PLGA nanoparticles were prepared using single-emulsion solvent evaporation technique. The organic phase consisted of PLGA (50-150 mg) and buprenorphine (drug:polymer ratio 1:10) dissolved in 5 mL dichloromethane. The aqueous phase (20 mL) contained PVA (0.5-1.5% w/v) and poloxamer 188 (0.5% w/v). The organic phase was added dropwise to the aqueous phase under magnetic stirring (500 rpm, 15 minutes) to form a coarse oil-in-water emulsion.

The coarse emulsion was processed using an Ultra-Turrax T25 digital homogenizer (IKA Works GmbH, Staufen, Germany) equipped with S25N-18G dispersing element at predetermined speeds (8,000-15,000 rpm) for 10 minutes with ice-water cooling to prevent solvent evaporation. The resulting nanoemulsion underwent rotary evaporation (Büchi Rotavapor R-300, 200 mbar, 40°C, 3 hours) for dichloromethane removal.

Nanoparticles were recovered by ultracentrifugation (Beckman-Coulter Avanti J-26XP, 25,000 rpm/51,000 × g, 30 minutes, 4°C). The pellet was washed three times with deionized water to remove unencapsulated drug and excess surfactant. Trehalose dihydrate (5% w/v) was added as cryoprotectant before lyophilization (Labconco FreeZone 2.5 Plus, -80°C for 12 hours, primary drying at -40°C, 0.1 mbar for 24 hours, secondary drying at 25°C, 0.5 mbar for 12 hours).

Characterization Methods

Particle Size and Polydispersity Index: Measured by dynamic light scattering (Malvern Zetasizer Nano ZS90, 633 nm He-Ne laser, 173° scattering angle). Samples were diluted 1:100 with filtered deionized water. Hydrodynamic diameter calculated using Stokes-Einstein equation.

Zeta Potential: Determined by electrophoretic light scattering using same instrument with disposable folded capillary cells (DTS1070). Henry equation applied for calculation.

Entrapment Efficiency: Nanoparticles (10 mg) dissolved in 5 mL dichloromethane, followed by 5 mL methanol for polymer precipitation. After centrifugation, supernatant analyzed by UV-Vis spectrophotometry (PerkinElmer Lambda 365) at 288 nm (λmax for buprenorphine). Calibration curve linear 5-100 µg/mL, $r^2 = 0.9998$.

In Vitro Drug Release: Performed using USP Apparatus 2 (paddle method) with dialysis membrane adapters (Spectra/Por, MWCO 12-14 kDa). Nanoparticle suspension (equivalent to 2 mg buprenorphine) placed in dialysis bags and immersed in 500 mL release medium (phosphate buffer pH 7.4 with 0.5% w/v Tween 80, 37 ± 0.5°C, 100 rpm). Samples (5 mL) withdrawn at predetermined intervals (0, 2, 4, 8, 12, 24, 48, 72, 96, 120, 168, 240, 336, 504, 672 hours) with fresh medium replacement.

Stability Studies: ICH Q1A(R2)-guided accelerated stability testing at 25°C/60% RH and 40°C/75% RH over 6 months with testing at 0, 1, 3, and 6 months.

V. EXPERIMENTAL SETUP

Instrumentation Configuration

The experimental platform included: Zetasizer Nano ZS90 (Malvern Panalytical) for particle characterization; Ultra-Turrax T25 homogenizer (IKA) with S25N-18G generator; Avanti J-26XP centrifuge (Beckman-Coulter) with JA-25.50 rotor; FreeZone 2.5 Plus lyophilizer (Labconco); Lambda 365 UV-Vis spectrophotometer (PerkinElmer); JSM-7600F field-emission SEM (JEOL) for morphology; DSC Q200 (TA Instruments) for thermal analysis; and XS205 DualRange analytical balance (Mettler Toledo).

Software Environment

Design-Expert 13.0.5.0 served for experimental design, polynomial fitting, ANOVA, response surface visualization, and optimization. DDSolver add-in for Microsoft Excel performed kinetic modeling. Statistical analyses included Shapiro-Wilk normality testing, Levene's test for homogeneity of variance, and paired t-tests for model validation.

Environmental Conditions

All syntheses performed in ISO 8 cleanroom (25 ± 2°C, 45 ± 5% RH, positive pressure 15 Pa). Met One 3400 particle counters monitored airborne particulate levels.

Analytical Method Validation

Method validation per ICH Q2(R1) demonstrated: specificity (no interference from excipients at 288 nm); linearity ($r^2 = 0.9998$, range 5-100 µg/mL); accuracy (mean recovery 99.7 ± 1.1%); precision (intra-day RSD 0.72%, inter-day RSD 1.31%); LOD 0.15 µg/mL; LOQ 0.45 µg/mL.

VI. RESULTS

Box-Behnken Design Outcomes

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The 17-run BBD produced nanoparticles with particle sizes ranging from 118.4 nm (Run 7: low PLGA, medium PVA, high speed) to 298.7 nm (Run 6: high PLGA, medium PVA, low speed). PDI values ranged 0.142-0.335, zeta potential -19.8 to -33.6 mV, and entrapment efficiency 64.2-86.8%. Center point replicates (Runs 13-17) demonstrated low variability (CV: 1.62% for size, 1.38% for PDI, 1.55% for zeta, 0.95% for EE), confirming experimental reproducibility.

Statistical Model Fitting and ANOVA

Quadratic models were selected for all responses based on sequential sum of squares analysis ($p < 0.05$ for quadratic vs. linear models). ANOVA results:

TABLE 2. ANOVA Summary for Response Surface Quadratic Models

Statistical Parameter	Particle Size	PDI	Zeta Potential	EE
Model F-value	72.34	58.26	48.92	62.18
Model p-value	<0.0001	<0.0001	<0.0001	<0.0001
Lack of Fit p-value	0.1486	0.1254	0.1689	0.1923
R^2	0.9894	0.9868	0.9844	0.9876
Adjusted R^2	0.9758	0.9698	0.9644	0.9716
Predicted R^2	0.9326	0.9184	0.9028	0.9245
Adequate Precision	29.62	26.18	24.36	27.84

Factor Effects Analysis

PLGA concentration (X_1) exerted the strongest effect on particle size ($F = 342.18$, $p < 0.0001$, contributing 52.4% of model sum of squares). Homogenization speed (X_3) showed negative correlation with particle size ($F = 162.45$, $p < 0.0001$). PVA concentration (X_2) demonstrated significant negative effect ($F = 58.92$, $p = 0.0001$). Quadratic terms for X_1^2 and X_3^2 were significant ($p < 0.05$), indicating curvature in factor-response relationships.

Optimization and Model Verification

Numerical optimization using desirability function yielded optimal conditions: PLGA = 95.2 mg, PVA = 1.18% w/v, homogenization speed = 12,800 rpm (desirability D = 0.908). Three verification batches produced results within 95% prediction intervals:

TABLE 3. Model Verification: Predicted vs. Observed Values

Response	Target	Predicted	95% CI	Observed	Bias (%)	t-test p
Size (nm)	Minimize	176.5	168.2-184.8	178.3 ± 4.8	+1.02	0.512
PDI	Minimize	0.182	0.168-0.196	0.185 ± 0.02	+1.65	0.638
Zeta (mV)	≤ -25	-30.8	-32.6 - -29.0	-31.2 ± 1.5	+1.30	0.694
EE (%)	Maximize	85.2	82.4-88.0	84.6 ± 2.3	-0.70	0.582

In Vitro Drug Release Kinetics

The optimized formulation exhibited sustained release over 28 days (intended monthly dosing). Release kinetics followed Higuchi square root model ($r^2 = 0.9914$, $K_H = 15.24$ %·day$^{-0.5}$). Korsmeyer-Peppas release exponent $n = 0.512 \pm 0.022$ indicated anomalous (non-Fickian) transport.

TABLE 4. Drug Release Kinetic Parameters (28-day study)

Kinetic Model	Equation	r^2	Rate Constant
Zero-Order	$Q = K_0 t$	0.8624	$K_0 = 3.42$ %/day
First-Order	$\ln(100-Q) = -K_1 t$	0.9318	$K_1 = 0.052$ day^{-1}
Higuchi	$Q = K_H \sqrt{t}$	0.9914	$K_H = 15.24$ %·day$^{-0.5}$
Korsmeyer-Peppas	$Q = K_{KP} \cdot t^n$	0.9872	$K_{KP} = 18.36$, $n = 0.512$

Stability Assessment

Accelerated stability testing (25°C/60% RH) demonstrated acceptable stability (<10% change in all CQAs over 6 months). Under stress conditions (40°C/75% RH), particle size increased by 26.8%, and entrapment efficiency decreased by 14.2% over 6 months, indicating temperature sensitivity requiring refrigerated storage recommendations.

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VII. DISCUSSION

This investigation successfully applied QbD principles to develop an optimized buprenorphine-loaded PLGA nanoparticle formulation for opioid use disorder treatment. The systematic approach enabled identification of critical formulation variables and establishment of a robust design space where all CQAs simultaneously meet specifications. The optimized formulation (178.3 nm, PDI 0.185, zeta -31.2 mV, EE 84.6%) compares favorably with literature reports for similar systems.

The predominant influence of PLGA concentration on particle size (contributing >50% of model variance) aligns with established understanding of polymer viscosity effects on droplet breakup. Higher polymer concentrations increase organic phase viscosity, resisting deformation and fragmentation during homogenization, yielding larger particles. This relationship exhibited quadratic curvature, suggesting an optimal concentration range where encapsulation efficiency is maximized without excessive particle enlargement.

The sustained release profile extending to 28 days represents a significant advancement over current daily dosing regimens. Monthly depot formulations could dramatically improve adherence among opioid use disorder populations, where daily medication-taking often competes with substance-seeking behaviors, unstable housing, and chaotic lifestyles. The Higuchi kinetic model confirmation indicates diffusion-controlled release from the polymer matrix, predictable and tunable through formulation adjustments.

VIII. CONCLUSION

This research demonstrated the robust application of Quality-by-Design principles combined with Response Surface Methodology for systematic development and optimization of buprenorphine-loaded PLGA nanoparticles for opioid use disorder treatment. The Box-Behnken design minimized experimental runs while generating statistically sound, predictive quadratic models validated by verification experiments. The optimally selected nanoformulation achieved critical quality attributes: particle size 178.3 ± 4.8 nm, polydispersity index 0.185 ± 0.02, zeta potential -31.2 ± 1.5 mV, and entrapment efficiency 84.6 ± 2.3%. Sustained release over 28 days following Higuchi kinetics supports once-monthly dosing, potentially transforming medication-assisted treatment by reducing dosing frequency and improving patient adherence. The systematic QbD approach provides a template for developing similar extended-release formulations for other substance use disorder pharmacotherapies. Future investigations should include in vivo pharmacokinetic and pharmacodynamic studies in appropriate animal models, stability studies under ICH conditions for up to 24 months, scale-up feasibility assessment for commercial manufacturing, and ultimately clinical evaluation in patients with opioid use disorder.

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