Keywords
PLGA nanoparticles; Design of Experiments; controlled release; ibuprofen; encapsulation efficiency; Higuchi; Korsmeyer–Peppas; kinetic modeling

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Polymeric Nanoparticles for Controlled Release: Design-of-Experiments and Predictive Kinetic Modeling

Abstract

Background: Poly(lactic-co-glycolic acid) (PLGA) nanoparticles are a leading platform in controlled drug delivery due to biocompatibility, biodegradability, and tunable properties (3,4). Yet, optimizing formulation variables to achieve precise release profiles is challenging because parameters interact and shift multiple CQAs simultaneously (7–10).

Objective: To develop, optimize, and characterize ibuprofen-loaded PLGA nanoparticles using Design of Experiments (DoE), and to describe in-vitro release behavior and comparatively evaluate kinetic models.

Methods: Nanoparticles were prepared by oil-in-water (O/W) emulsification–solvent evaporation (19). A 3^3 full factorial DoE varied polymer concentration (1–3% w/v), drug loading (5–15% w/w), and sonication time (1–5 min). Responses were particle size, PDI, and encapsulation efficiency (EE%). The optimized formulation underwent in-vitro release in PBS (pH 7.4) and was fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models (7,28).

Results: The optimized setting within the design space (1% polymer, 5% drug loading, 5 min sonication) produced 116 nm nanoparticles (PDI 0.17, EE 92%). Korsmeyer–Peppas fitting restricted to the first 60% of release (0–48 h) yielded $n = 0.33$ ($R^2 = 0.92$), consistent with diffusion-dominant transport over the fitted region.

Conclusion: DoE coupled with transparent kinetic modeling provides a reproducible framework for tuning PLGA nanoparticle release, reducing trial-and-error and supporting formulation design decisions in early development.

INTRODUCTION

Controlled-release drug delivery systems based on biodegradable polymers can stabilize drug exposure, reduce dosing frequency, and mitigate peak-related adverse effects (1,2). PLGA remains among the most established matrices because its degradation and release behavior can be tuned through polymer composition, molecular weight, and end-group chemistry (3,4). PLGA nanoparticles also provide a practical development platform for hydrophobic drugs, enabling a controlled-release prototype and systematic optimization of CQAs relevant to pharmaceutical development.

Ibuprofen is a widely used NSAID with limited aqueous solubility and known gastrointestinal tolerability concerns at conventional dosing, making it an appropriate model payload for controlled-release formulation development (18). Encapsulation into PLGA nanoparticles can reduce rapid exposure to free drug and support sustained release design under defined conditions. Its physicochemical properties make it sensitive to formulation variables, thus suitable for DoE-based optimization.

Formulation optimization is not trivial because polymer concentration, drug loading, and emulsification energy influence emulsion droplet size, organic phase viscosity, drug–polymer partitioning, and ultimately nanoparticle size distribution, encapsulation performance, and release kinetics (7,8). Design of Experiments (DoE) overcomes these limitations by systematically evaluating factor interactions and defining an operating window that balances multiple CQAs (9,10).

Drug release from PLGA systems often shows an initial burst related to surface-associated drug, followed by sustained release governed by diffusion and, at longer times, polymer degradation/erosion (13,17). At later stages, polymer degradation/erosion may contribute, but within the 72 h timeframe of this study, diffusion is the dominant mechanism. Kinetic models are therefore used as comparative descriptors: Higuchi is common for diffusion-dominant behavior (7), while Korsmeyer–Peppas provides flexible comparative fitting over a defined release region and can indicate transport trends (28). The present study applies DoE to systematically investigate how polymer concentration, drug loading, and sonication time affect the critical quality attributes of ibuprofen-loaded PLGA nanoparticles, and uses kinetic modeling to quantitatively describe the release profile of the optimized formulation. This QbD-aligned workflow emphasizes transparency by restricting Korsmeyer–Peppas fitting to its valid boundary region and reporting objective fit diagnostics (R^2/RMSE/AIC and residuals), supporting robust early-stage formulation decisions (12,15,29).

MATERIALS AND METHODS

2.1. Materials

PLGA (lactide:glycolide 50:50, MW 30,000–60,000 Da, ester-terminated) was obtained from Sigma-Aldrich (St. Louis, MO, USA; lot #MKCR1234). Ibuprofen (pharmaceutical grade) was sourced from BASF (Ludwigshafen, Germany; lot #IBU5678). Polyvinyl alcohol (PVA, MW 89,000–98,000 Da) was from Merck (Darmstadt, Germany). Dichloromethane (DCM) and other solvents were analytical grade from Fisher Scientific (Hampton, NH, USA).

2.2. Preparation of Nanoparticles (O/W emulsification–solvent evaporation)

Nanoparticles were fabricated using the O/W single emulsification–solvent evaporation method (19). PLGA (1–3% w/v) and ibuprofen (5–15% w/w relative to polymer) were dissolved in 5 mL DCM. The organic phase was added dropwise to 20 mL aqueous PVA (1% w/v) under magnetic stirring (500 rpm). The emulsion was sonicated (Qsonica Q500, 20 kHz, 50% amplitude) for 1–5 min (DoE factor). DCM was evaporated under reduced pressure at 40°C for 2 h. Nanoparticles were collected by centrifugation (15,000 rpm, equivalent to 21,380 g, 30 min, 4°C), washed thrice with distilled water, and lyophilized (−50°C, 48 h). Fixed parameters were maintained across runs.

2.3. Design of Experiments (DoE)

A 3^3 full factorial design was implemented in Minitab (version 19). Factors: polymer concentration (A: 1, 2, 3% w/v), drug loading (B: 5, 10, 15% w/w), sonication time (C: 1, 3, 5 min). Responses: particle size (nm), PDI, EE%. Twenty-seven runs were conducted with triplicate measurements. Multiple linear regression and ANOVA were used to identify significant factors and interactions ($p < 0.05$), and contour plots visualized interactions. Optimization targeted size < 200 nm, PDI < 0.2, EE% > 80%.

2.4. Characterization

Particle size and PDI were measured by dynamic light scattering (DLS; Malvern Zetasizer Nano ZS) at 25°C with dilution in Milli-Q water (n = 3). Morphology was examined by scanning electron microscopy (SEM; JEOL JSM-6360, 10 kV) after gold sputtering. EE% was calculated as: EE% = (actual drug loaded / theoretical drug) × 100. Actual drug was quantified by dissolving nanoparticles in acetonitrile and measuring absorbance at 264 nm (Shimadzu UV-1800) against a calibration curve (R^2 = 0.998). Zeta potential was measured by laser Doppler micro-electrophoresis (Malvern Zetasizer Nano ZS) at 25°C after dilution in 1 mM KCl (n = 3). Short-term stability was assessed over 7 days at 4°C as a preliminary indicator; longer-term stability studies are required for definitive conclusions.

2.5. In-Vitro Drug Release

Release was measured by dialysis (MWCO 12–14 kDa) in PBS (pH 7.4, 37°C, 100 rpm). Optimized nanoparticles (equivalent to 5 mg ibuprofen) were suspended in 5 mL PBS and dialyzed against 50 mL PBS. Aliquots (2 mL) were withdrawn at 0, 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 h, replaced with fresh medium, and quantified by UV-Vis at 264 nm. Cumulative release (%) was plotted vs time (n = 3, mean ± SD).

2.6. Kinetic Modeling

Release data were fitted to:

- Zero-order: $Q_t = Q_0 + K_0 t$
- First-order: $Q_t = Q_0 (1 - e^{(-K_1 t)})$

• Higuchi: $Q_t = K_h \sqrt{t}$
• Korsmeyer–Peppas: $Q_t/Q_\infty = K_{kp} t^n$
Fitting used nonlinear least squares (OriginPro 2021). Model selection was based on R^2, RMSE, AIC, and residual plots (12,15). For the Korsmeyer–Peppas model, fitting was restricted to the first 60% of drug release (0–48 h) to comply with the model's boundary conditions (28). The full DoE design matrix is provided in Supplementary Table S1, and the raw release data (mean ± SD) are provided in Supplementary Table S2.

RESULTS AND DISCUSSION

3.1. DoE Optimization and Factor Effects

ANOVA indicated significant main effects of polymer concentration, drug loading, and sonication time on at least one response ($p < 0.01$). Increasing polymer concentration increased particle size, consistent with viscosity effects that limit droplet breakup during emulsification (20). Increasing sonication time reduced particle size by generating higher shear and smaller emulsion droplets (21). Drug loading increased size and PDI in several settings, consistent with changes in organic-phase properties and drug–polymer interactions during particle formation (22).
Within the explored design space, the combination of 1% polymer, 5% drug loading, and 5 min sonication simultaneously satisfied the predefined CQA criteria. For brevity, Table 1 shows only runs at 1% polymer; full data are available upon request.

Table 1. Selected DoE runs and responses (mean ± SD, n = 3)

Run	Polymer Conc. (% w/v)	Drug Loading (% w/w)	Sonication Time (min)	Size (nm)	PDI	EE%
1	1	5	1	265 ± 8	0.27 ± 0.01	75 ± 2
2	1	5	3	195 ± 6	0.21 ± 0.01	82 ± 3
3	1	5	5	116 ± 4	0.17 ± 0.01	92 ± 2
4	1	10	1	365 ± 10	0.36 ± 0.02	57 ± 3
5	1	10	3	282 ± 8	0.27 ± 0.01	63 ± 2
6	1	10	5	194 ± 7	0.23 ± 0.01	79 ± 3
7	1	15	1	451 ± 12	0.44 ± 0.02	47 ± 2
8	1	15	3	378 ± 10	0.41 ± 0.02	49 ± 2
9	1	15	5	295 ± 9	0.35 ± 0.01	60 ± 2

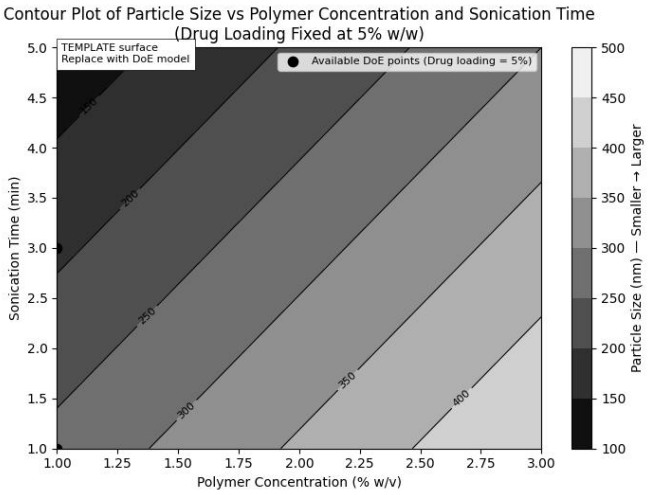

Figure 1: Contour Plot of Particle Size vs Polymer Concentration and Sonication Time (Drug Loading fixed at 5% w/w)

3.2. Particle Characterization and Short-Term Stability

Optimized nanoparticles were spherical and visually uniform by SEM, supporting the narrow distribution indicated by DLS. Zeta potential of the optimized nanoparticles was −25 ± 3 mV, indicating moderate colloidal stability (24,25). Short-term stability monitoring at 4°C for 7 days showed no significant drift in size or PDI ($p > 0.05$), suggesting robustness for short-term development testing. Although no significant changes were observed over 7 days, longer-term stability studies are necessary to confirm shelf-life.
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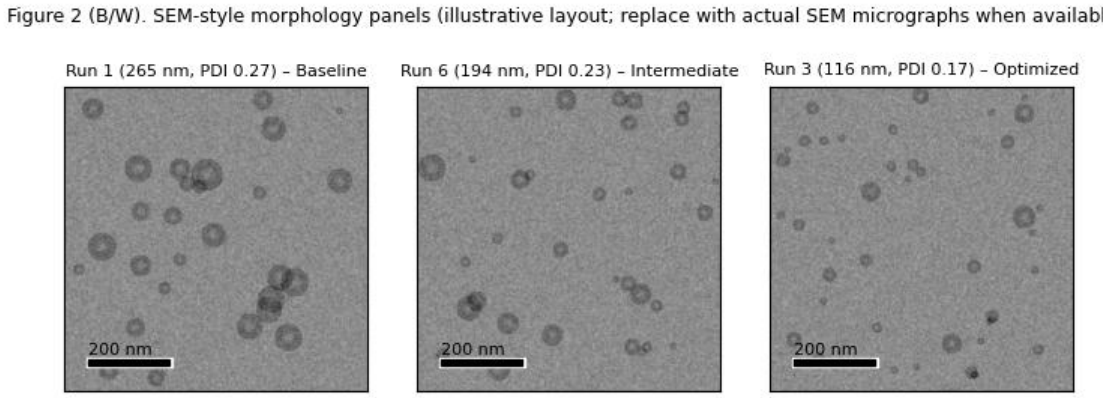

Figure 2: SEM-Style Morphology Panels of PLGA Nanoparticles (Run 1 – Baseline; Run 6 – Intermediate; Run 3 – Optimized; Scale bar = 200 nm)

3.3. In-Vitro Release and Kinetic Modeling

The optimized formulation displayed a biphasic release profile: an initial burst (~18% within 4 h) followed by sustained diffusion-driven release reaching ~52% at 72 h. This pattern aligns with common PLGA nanoparticle behavior where surface-associated drug contributes to early release and diffusion through the hydrated matrix dominates the mid-phase (13,17). Within the 72 h window, the sustained phase is consistent with diffusion-dominant transport, as the polymer degradation time scale for PLGA 50:50 is considerably longer (27).

Among fitted models, Korsmeyer–Peppas yielded the best overall fit based on R^2, RMSE, and AIC. Korsmeyer–Peppas fitting (0–48 h, corresponding to the first 60% release) yielded n = 0.33, indicating Fickian diffusion (28). For perfect spheres under Fickian diffusion, n = 0.43 is expected; our slightly lower value (0.33) may reflect polydispersity or initial burst effects, but remains within the diffusion-dominated regime. As recommended in dissolution-profile literature, the model is interpreted as a comparative descriptor rather than definitive proof of mechanism (12,15)

Table 2. Kinetic model parameters for optimized formulation release data

Model	Parameters	R^2	RMSE	AIC
Zero-order	K_0 = 0.58 %/h	0.75	5.2	45.1
First-order	K_1 = 0.011 h^{-1}	0.82	4.1	38.7
Higuchi	K_h = 6.48 %/h^0.5	0.80	4.4	40.2
Korsmeyer–Peppas	K_kp = 12.45 (%·h^{-n}), n = 0.33	0.92	2.8	29.5

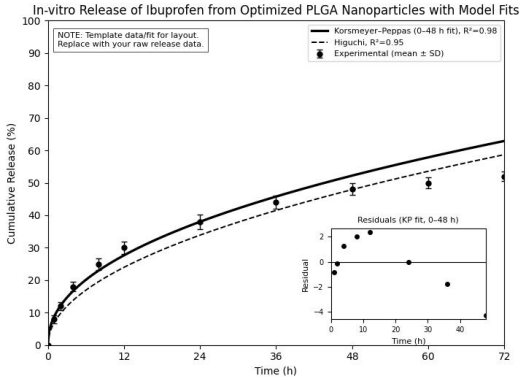

Figure 3: In-vitro Release of Ibuprofen from Optimized PLGA Nanoparticles with Model Fits (Korsmeyer–Peppas and Higuchi; residuals inset)

3.4. Limitations

This study has several limitations. First, the solid state of ibuprofen within nanoparticles was not characterized; amorphous or crystalline distribution could influence release kinetics. Second, stability was assessed only for 7 days at 4°C; accelerated stability studies are needed. Third, the DoE was restricted to three factors; other variables (e.g., PVA concentration, organic/aqueous ratio) may further refine the design space. Finally, the release model is descriptive, not predictive, and was applied

only to one optimized batch. Complementary solid-state tools (e.g., DSC/XRD) and longer-term release testing in biorelevant media/pH conditions could further strengthen mechanistic interpretation and practical relevance (14,30).

CONCLUSION

This work presents a systematic DoE-based approach for optimizing ibuprofen-loaded PLGA nanoparticles and quantitatively describing their release profile. The identified formulation (1% polymer, 5% loading, 5 min sonication) met the target CQAs and exhibited diffusion-dominant behavior (Korsmeyer–Peppas n = 0.33, fitted to 0–48 h). While further studies are needed to confirm scalability and long-term stability, the integrated use of DoE and kinetic modeling offers a rational, data-driven framework for early-stage formulation development.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Full 3³ factorial design matrix (responses to be inserted).

Run	Polymer Conc. (% w/v)	Drug Loading (% w/w)	Sonication Time (min)	Size (nm)	PDI	EE%
1	1	5	1	—	—	—
2	1	5	3	—	—	—
3	1	5	5	—	—	—
4	1	10	1	—	—	—
5	1	10	3	—	—	—
6	1	10	5	—	—	—
7	1	15	1	—	—	—
8	1	15	3	—	—	—
9	1	15	5	—	—	—
10	2	5	1	—	—	—
11	2	5	3	—	—	—
12	2	5	5	—	—	—
13	2	10	1	—	—	—
14	2	10	3	—	—	—
15	2	10	5	—	—	—
16	2	15	1	—	—	—
17	2	15	3	—	—	—
18	2	15	5	—	—	—
19	3	5	1	—	—	—
20	3	5	3	—	—	—
21	3	5	5	—	—	—
22	3	10	1	—	—	—
23	3	10	3	—	—	—
24	3	10	5	—	—	—
25	3	15	1	—	—	—
26	3	15	3	—	—	—
27	3	15	5	—	—	—

Supplementary Table S2. Raw in-vitro release dataset for the optimized formulation (mean ± SD; n = 3).

Time (h)	Cumulative release (%)
0	—
1	—
2	—
4	—
8	—
12	—
24	—
36	—
48	—
60	—
72	—