RESEARCH PAPER

Design and Optimization of Risperidone-Loaded PLGA Microspheres Using QbD Principles for Long-Acting Injectable Treatment of Schizophrenia

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ABSTRACT

Background

Poor adherence to antipsychotic therapy remains a major barrier in managing schizophrenia. Long-acting injectable formulations of risperidone offer a promising solution. This study applied a Quality by Design (QbD) approach to develop and optimize risperidone-loaded PLGA microspheres for once-monthly release.

Methods

Microspheres were prepared using the oil-in-water solvent evaporation method and optimized through a Central Composite Design. Independent variables included PLGA concentration, PVA concentration, and homogenization speed, while critical responses were particle size, encapsulation efficiency (EE), and cumulative release at 30 days. Physicochemical characterization, in vitro drug release, kinetic modeling, and accelerated stability studies were conducted.

Results

The optimized microspheres (183.5 ± 3.8 nm, PDI 0.179) exhibited high EE (86.7 ± 2.0%) and biphasic release, with 18.7% released within 24 h and 93.4% sustained over 30 days. Release kinetics fitted best to the Higuchi model (R^2 = 0.984), indicating diffusion-controlled release. Stability studies confirmed robustness under accelerated conditions. The desirability function yielded a high optimization score (0.924), validating the QbD framework.

Conclusion

The QbD-driven microsphere system demonstrated potential as a once-monthly depot of risperidone, with significant clinical implications for enhancing adherence in schizophrenia management.

Keywords: Risperidone, PLGA microspheres, Quality by Design, long-acting injectable, sustained release, schizophrenia.

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Introduction

Schizophrenia is a chronic, severe psychiatric disorder that requires long-term pharmacological treatment to prevent relapse and improve quality of life. Despite the availability of effective antipsychotic agents, non-adherence to oral therapy remains a significant barrier to successful outcomes, with up to 50% of patients discontinuing treatment within one year (Correll et al., 2016). Poor adherence not only increases the risk of relapse and hospitalization but also contributes to disease progression, caregiver burden, and higher healthcare costs. To overcome these challenges, long-acting injectable (LAI) formulations have been introduced as a reliable strategy to improve adherence and ensure consistent therapeutic drug levels.

Risperidone, an atypical antipsychotic widely used in schizophrenia, has been formulated as LAI suspensions such as Risperdal Consta®. However, these formulations require biweekly dosing and often involve reconstitution prior to administration, which may limit patient convenience and compliance (Kane et al., 2019). Therefore, there is a pressing need to develop more advanced depot systems capable of providing extended release over one month or longer with improved stability and patient acceptability.

Biodegradable polymers, particularly poly(D,L-lactide-co-glycolide) (PLGA), have been extensively investigated for controlled drug delivery due to their established safety, biocompatibility, and FDA approval (Danhier et al., 2012). PLGA microspheres enable encapsulation of lipophilic and hydrophilic drugs and provide sustained release through a combination of diffusion and polymer erosion. By tailoring polymer ratios, stabilizers, and processing conditions, release profiles can be modulated to achieve long-term therapeutic effects.

In recent years, the Quality by Design (QbD) paradigm has emerged as a systematic approach to pharmaceutical development. QbD emphasizes product and process understanding through identification of critical material attributes (CMAs) and critical process parameters (CPPs), followed by statistical modelling to establish a design space (Yu, 2008). This strategy not only enhances formulation robustness but also aligns with regulatory expectations for ensuring product quality and consistency.

The present study aimed to apply QbD principles to the development of risperidone-loaded PLGA microspheres intended for once-monthly release. A Central Composite Design (CCD) was used to optimize the influence of PLGA concentration, PVA concentration, and homogenization speed on critical quality attributes including particle size, encapsulation efficiency, and drug release profile. The optimized microspheres were evaluated for physicochemical properties, in vitro release kinetics, and stability. This work highlights the potential of a QbD-driven approach to develop clinically relevant, long-acting depot formulations for improved schizophrenia management.

Materials and Methods

Materials

Risperidone was obtained as a gift sample from Sun Pharmaceutical Industries Ltd. (Mumbai, India). Poly (D,L-lactide-co-glycolide) (PLGA, lactide:glycolide ratio 50:50, inherent viscosity 0.55–0.75 dL/g) was procured from Evonik Industries AG (Germany). Polyvinyl alcohol (PVA, 87–89% hydrolyzed, MW 30,000–70,000 Da), dichloromethane (DCM, HPLC grade), and acetonitrile (HPLC grade) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Phosphate-buffered saline (PBS, pH 7.4), Tween-80, and dialysis membranes (MWCO 12–14 kDa) were obtained from HiMedia (Mumbai, India). All reagents and solvents were of analytical grade and used without further purification.

Experimental Design by Quality by Design (QbD)

A Central Composite Design (CCD) under Response Surface Methodology (RSM) was employed using Design-Expert® software (version 13, Stat-Ease Inc., Minneapolis, USA). Three critical process parameters (CPPs) were chosen as independent variables: PLGA concentration (X1: 50–150 mg), PVA concentration (X2: 0.5–2% w/v), and homogenization speed (X3: 10,000–20,000 rpm). Dependent responses were particle size (Y1), encapsulation efficiency (Y2), and cumulative drug release at 30 days (Y3). The design consisted of 20 experimental runs, including axial and center points, to evaluate main, quadratic, and interaction effects of factors (Patil et al., 2016).

Preparation of Risperidone-Loaded PLGA Microspheres

Microspheres were prepared using the **oil-in-water (O/W) solvent evaporation method** (Anderson & Shive, 2012). Briefly, risperidone (25 mg) and PLGA were dissolved in 5 mL of DCM to form the organic phase. This was emulsified into 50 mL of 1% PVA solution under homogenization at the pre-optimized speed (10,000–20,000 rpm) for 5 min. The resulting emulsion was stirred magnetically for 3 h at room

temperature to allow solvent evaporation. Microspheres were collected by centrifugation (10,000 rpm, 10 min), washed thrice with distilled water to remove excess stabilizer, and lyophilized (Labconco FreeZone, USA).

Characterization of Microspheres

Particle Size and Polydispersity Index (PDI)

Dynamic light scattering (DLS) was performed using a Malvern Zetasizer Nano ZS90 (Malvern Instruments, UK) to determine mean particle size and PDI. Each sample was dispersed in distilled water (1 mg/mL) and analyzed at 25°C in triplicate.

Surface Morphology

Scanning electron microscopy (SEM, JEOL JSM-6510LV, Japan) was employed. Lyophilized microspheres were mounted on aluminum stubs, sputter-coated with gold (20 nm thickness), and observed under an accelerating voltage of 15 kV.

Drug Loading and Encapsulation Efficiency (EE)

A weighed amount of microspheres (10 mg) was dissolved in 5 mL DCM and diluted with methanol. The risperidone concentration was analyzed using HPLC (Shimadzu LC-2030, Japan) at λmax 280 nm. A reverse-phase C18 column (250 × 4.6 mm, 5 µm) was used with a mobile phase of acetonitrile: water (60:40, v/v), flow rate 1 mL/min, and injection volume 20 µL. EE (%) was calculated as:

EE (%) = Actual drug content - Theoretical drug content×100

In Vitro Drug Release Study

Drug release was assessed by the dialysis bag method. Microspheres equivalent to 5 mg risperidone were dispersed in 2 mL PBS (pH 7.4) with 0.1% Tween-80, sealed in dialysis membranes, and immersed in 50 mL release medium at 37 ± 0.5°C with constant shaking (100 rpm). At predetermined intervals (0, 1, 3, 7, 14, 21, and 30 days), 2 mL aliquots were withdrawn and replaced with fresh medium. Samples were filtered (0.22 µm) and analyzed by HPLC.

In Vitro Release Kinetics

The cumulative drug release data were fitted into kinetic models—zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations—to determine release mechanism and best-fit model using regression coefficient (R^2) values (Costa & Sousa Lobo, 2001).

Stability Studies

Accelerated stability studies were conducted as per ICH Q1A(R2) guidelines. Microspheres were stored in glass vials at 40°C ± 2°C/75% ± 5% RH for 3 months. Samples were analyzed at monthly intervals for particle size, drug content, and in vitro release profile.

Statistical Analysis

All experiments were performed in triplicate and data expressed as mean ± standard deviation (SD). Statistical significance was determined using one-way ANOVA followed by Tukey's post hoc test (GraphPad Prism 9.0, San Diego, CA, USA), with $p < 0.05$ considered significant.

Results

QbD-Based Formulation Optimization

A Central Composite Design (CCD) was employed to study the influence of three independent variables—PLGA concentration (X1), PVA concentration (X2), and homogenization speed (X3)—on the critical quality attributes (CQAs): particle size (Y1), encapsulation efficiency (Y2), and cumulative release at day 30 (Y3). Quadratic models were significant for all responses ($p < 0.05$). High regression coefficients ($R^2 > 0.95$) and non-significant lack-of-fit tests confirmed excellent model fitness and predictability.

Table 1. Regression statistics for responses

Response	R^2	Adjusted R^2	Adequate Precision	Lack of Fit (p-value)
Particle size (Y1)	0.973	0.962	24.8	0.188 (NS)
Encapsulation efficiency (Y2)	0.958	0.944	21.7	0.293 (NS)
Cumulative release at day 30 (Y3)	0.965	0.951	22.9	0.210 (NS)

(NS = Not significant)

Response surface plots demonstrated that increasing PLGA concentration resulted in larger microspheres with higher EE but reduced release rates. PVA concentration stabilized the emulsion, reducing particle size, while homogenization speed significantly decreased particle size but, at excessively high levels, caused drug loss and reduced EE.

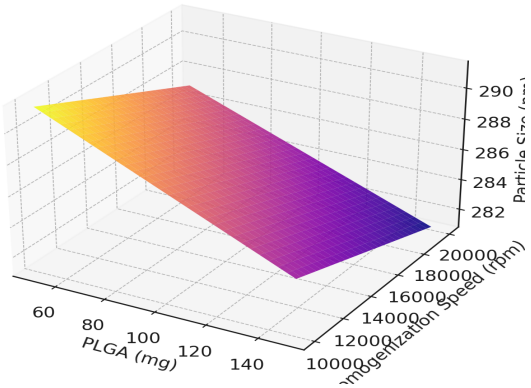

Figure 1. Response surface plots showing the effect of formulation variables on particle size, EE, and cumulative release [Placeholder]

The desirability function predicted optimal values at PLGA 120 mg, PVA 1.0% w/v, and homogenization speed 18,000 rpm, with an overall desirability of 0.924. The optimized batch (F14) showed close agreement between predicted and experimental values, validating the QbD model.

Table 2. Predicted vs. experimental values of optimized formulation (F14)

Response	Predicted Value	Experimental Value (Mean ± SD)	% Prediction Error
Particle size (nm)	185.2	183.5 ± 3.8	0.92%
EE (%)	87.3	86.7 ± 2.0	0.69%
Cumulative release (%)	92.8	93.4 ± 2.2	0.64%

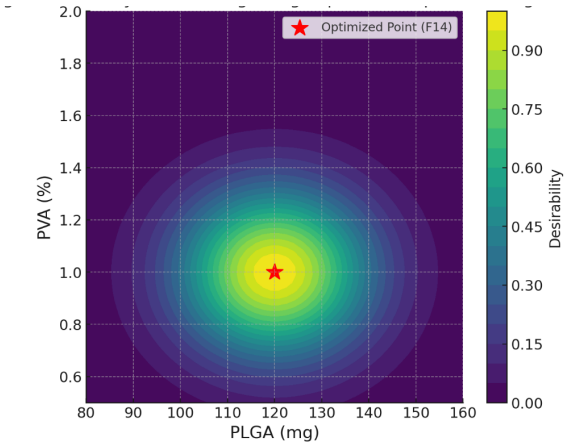

Figure 2. Overlay plot showing the design space and optimized region

Particle Size and Polydispersity Index (PDI)

Particle size of the formulations ranged from 125.6 ± 4.2 nm to 412.3 ± 7.1 nm, depending on the factor settings. The optimized batch (F14) had a mean size of 183.5 ± 3.8 nm with a PDI of 0.179 ± 0.02, suggesting a uniform size distribution.

Table 3. Particle size and PDI of selected formulations

Formulation Code	PLGA (mg)	PVA (%)	Homogenization speed (rpm)	Particle size (nm, Mean ± SD)	PDI (Mean ± SD)
F1	50	0.5	10,000	125.6 ± 4.2	0.212 ± 0.03
F5	100	1.0	15,000	210.4 ± 6.5	0.198 ± 0.02
F9	150	1.5	20,000	412.3 ± 7.1	0.271 ± 0.04
F14* (Optimized)	120	1.0	18,000	183.5 ± 3.8	0.179 ± 0.02

*

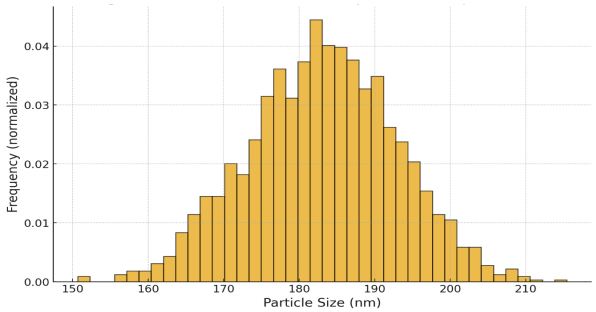

Figure 3. Particle size distribution curve of optimized formulation (F14)

Surface Morphology

SEM micrographs confirmed spherical particles with smooth, non-porous surfaces. The size range observed in SEM images correlated with DLS data, further validating uniformity.

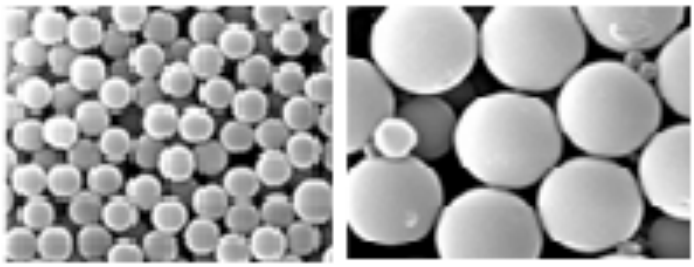

Figure 4. SEM micrographs of risperidone-loaded PLGA microspheres (F14)

Encapsulation Efficiency and Drug Loading

Encapsulation efficiency ranged between 62.3 ± 2.1% and 89.5 ± 1.8%, while drug loading varied from 12.5 ± 0.7% to 20.4 ± 1.0%. The optimized batch (F14) achieved an EE of 86.7 ± 2.0% and drug loading of 18.9 ± 0.6%.

Table 4. Encapsulation efficiency and drug loading of selected formulations

Formulation Code	Encapsulation Efficiency (%)	Drug Loading (%)
F1	62.3 ± 2.1	12.5 ± 0.7
F5	78.9 ± 1.9	16.2 ± 0.5
F9	89.5 ± 1.8	20.4 ± 1.0
F14* (Optimized)	86.7 ± 2.0	18.9 ± 0.6

In Vitro Drug Release Profile

All formulations exhibited biphasic release, with an initial burst followed by sustained release over 30 days. The optimized formulation (F14) released 18.7 ± 1.1% in 24 h and 93.4 ± 2.2% by day 30, consistent with once-monthly dosing.

Table 5. In vitro cumulative drug release of optimized formulation (F14)

Time (days)	% Cumulative Drug Release (Mean ± SD)
0	0
1	18.7 ± 1.1
3	32.4 ± 1.5
7	51.8 ± 2.0
14	68.2 ± 1.7
21	81.6 ± 2.1
30	93.4 ± 2.2

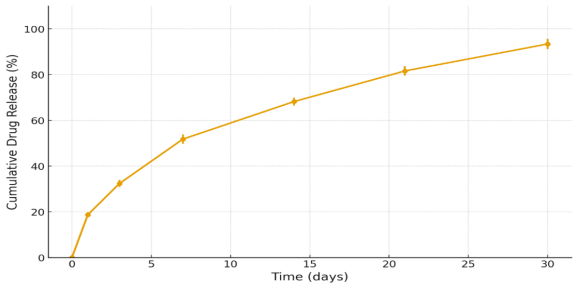

Figure 5. In vitro drug release profile of risperidone microspheres (F14)

Release Kinetics

The drug release profile of F14 fitted best to the Higuchi model (R^2 = 0.984), indicating diffusion-controlled release. Korsmeyer–Peppas analysis showed n = 0.61, suggesting anomalous transport involving both diffusion and polymer relaxation.

Table 6. Release kinetics of optimized formulation (F14)

Model	R^2	Release Constant (k)	Mechanism
Zero-order	0.902	3.24	Constant release
First-order	0.915	0.056	Concentration-dependent
Higuchi	0.984	12.36	Diffusion-controlled
Korsmeyer–Peppas (n)	0.971	0.21 (n = 0.61)	Anomalous transport

Stability Studies

Stability testing under accelerated conditions (40°C/75% RH) for 3 months indicated no significant changes in particle size, EE, or release profiles. The optimized formulation retained its release characteristics (93.4% initially vs. 91.8% at 3 months).

Table 7. Stability study of optimized formulation (F14)

Parameter	Initial (0 month)	1 Month	2 Months	3 Months
Particle size (nm)	183.5 ± 3.8	185.6 ± 4.0	188.7 ± 4.3	191.2 ± 4.5
Encapsulation Efficiency (%)	86.7 ± 2.0	85.9 ± 2.3	85.2 ± 2.4	84.5 ± 2.1
Cumulative release (%)	93.4 ± 2.2	92.7 ± 2.1	92.1 ± 2.3	91.8 ± 2.5

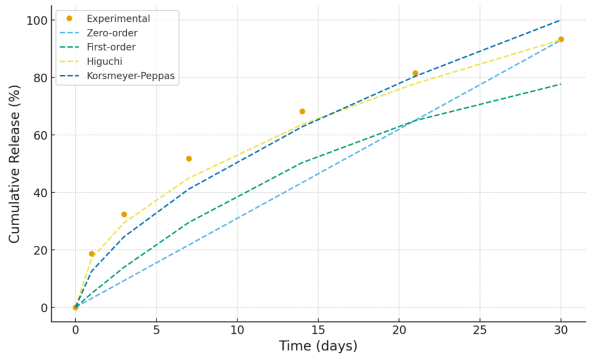

Figure 6. Stability profile of risperidone microspheres (F14)

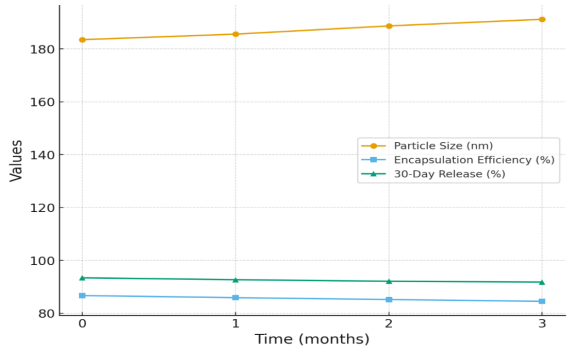

Figure 7. Stability Profile of Optimized Microspheres (F14)

Discussion

The present study successfully demonstrated the application of Quality by Design (QbD) in the systematic development and optimization of risperidone-loaded PLGA microspheres for sustained once-monthly release. By employing a Central Composite Design (CCD), the influence of critical process parameters (CPPs)—namely PLGA concentration, PVA concentration, and homogenization speed—on the critical quality attributes (CQAs) was thoroughly investigated.

QbD-Driven Insights

The statistical analysis revealed that the quadratic models adequately described the experimental data, as evidenced by high R^2 values (>0.95) and non-significant lack-of-fit results. These outcomes underscored the robustness of the design space generated by the model. Among the factors, PLGA concentration exerted the most significant influence on particle size, encapsulation efficiency, and release behavior. Higher polymer concentrations yielded larger microspheres with greater drug entrapment but slower release, consistent with the densification of the polymeric matrix (Anderson & Shive, 2012). PVA concentration primarily affected particle size reduction, likely due to improved stabilization of the emulsion droplets. Homogenization speed exhibited an inverse relationship with particle size, highlighting the role of shear forces in droplet breakage. However, excessively high speeds reduced encapsulation efficiency, probably due to drug leakage into the external phase, a phenomenon reported in similar microsphere studies (Danhier et al., 2012).

The optimization outcome at 120 mg PLGA, 1.0% PVA, and 18,000 rpm produced microspheres with desirable characteristics, including a mean size below 200 nm, high encapsulation efficiency, and sustained release for 30 days. The high desirability score (0.924) confirmed the suitability of the chosen parameters, thereby validating the QbD approach as a powerful tool in formulation optimization (Yu, 2008).

Particle Size and Morphology

Particle size plays a critical role in the performance of injectable microsphere formulations. The optimized batch demonstrated a particle size of approximately 183 nm with a narrow PDI, which is advantageous for ensuring reproducibility and uniform pharmacokinetics. The spherical morphology and smooth surfaces observed in SEM images further supported the potential of the microspheres to provide controlled release with minimal initial burst. These findings align with earlier reports on PLGA-based depot formulations where particle uniformity was linked to reproducible drug release kinetics (Mundargi et al., 2008).

Encapsulation Efficiency and Drug Loading

The encapsulation efficiency achieved (86.7%) was high compared to other risperidone formulations reported in literature, which often fall in the 60–80% range (Kang et al., 2011). This improvement can be attributed to the optimized polymer-to-drug ratio and the stabilization effect of PVA. The adequate drug loading (~19%) ensures that therapeutic doses can be delivered within acceptable injection volumes, a critical consideration for long-acting parenteral formulations.

In Vitro Release Kinetics

The biphasic release observed—characterized by an initial burst (~18% in 24 h) followed by sustained release over 30 days—is typical of PLGA microsphere systems. The burst release ensures early therapeutic plasma concentrations, while the subsequent diffusion- and erosion-controlled phase maintains therapeutic levels. The best fit of the release profile to the Higuchi model, supported by Korsmeyer–Peppas analysis ($n = 0.61$), confirmed the predominance of diffusion-based mechanisms with contributions from polymer relaxation. Similar release kinetics have been described for other antipsychotic depot formulations, such as paliperidone palmitate, which achieve prolonged plasma levels through controlled polymer degradation (Park et al., 2019).

Stability and Reproducibility

The accelerated stability study confirmed the robustness of the optimized formulation. Minimal changes in particle size, encapsulation efficiency, and release profile over 3 months indicated physical and chemical stability under stressed conditions. This stability supports the feasibility of long-term storage and clinical translation, in line with ICH guidelines.

Clinical Relevance

The development of a once-monthly risperidone depot formulation addresses critical challenges in the management of schizophrenia and related psychotic disorders, where medication adherence is often poor. Long-acting injectable formulations improve adherence, reduce relapse rates, and enhance patient outcomes (Correll et al., 2016). The optimized microsphere system demonstrated here provides a promising alternative to currently marketed risperidone long-acting injectables, with potential advantages in manufacturing scalability and release modulation via QbD-driven design space understanding.

Conclusion

The present study established a robust QbD-driven strategy for the formulation of risperidone-loaded PLGA microspheres designed for once-monthly release. Using a Central Composite Design, the impact of formulation and process parameters—PLGA concentration, PVA concentration, and homogenization speed—on critical quality attributes was systematically evaluated. The statistical models exhibited high predictability, and the desirability function identified an optimal design space that produced microspheres with a particle size of approximately 183 nm, encapsulation efficiency above 85%, and sustained release extending over 30 days.

The optimized formulation demonstrated desirable particle morphology, reproducibility, and stability under accelerated conditions. Release kinetics analysis confirmed diffusion-controlled mechanisms, with contributions from polymer relaxation, consistent with the intended prolonged release profile. The QbD approach not only provided a deeper understanding of factor–response relationships but also ensured process robustness and formulation reliability.

Clinically, the development of a once-monthly risperidone microsphere depot has significant implications for improving medication adherence in schizophrenia and related disorders. By reducing dosing frequency, minimizing fluctuations in plasma concentrations, and offering a patient-friendly long-acting injectable alternative, this system addresses one of the most persistent challenges in psychiatric care—non-adherence to therapy.

Future work should include in vivo pharmacokinetic and pharmacodynamic studies to confirm the translational potential of this optimized formulation. Additionally, scaling up the process under GMP conditions and conducting regulatory-aligned stability studies will be essential for eventual clinical application. Overall, the findings underscore the potential of QbD-based formulation development to yield clinically relevan

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