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QbD-guided development of a long-acting injectable formulation for poorly water-soluble antipsychotics

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Abstract
Poor adherence to daily oral antipsychotics and exposure variability motivate long-acting injectables (LAIs), yet hydrophobic active pharmaceutical ingredients challenge release predictability, manufacturability, and injectability. This study applied a Quality by Design (QbD) framework to develop two LAI platforms for a poorly water-soluble antipsychotic: a nanomilled nanosuspension and a PLGA in-situ forming depot (ISFD). A priori definition of the Quality Target Product Profile and critical quality attributes (CQAs) guided risk assessment and a two-stage Design of Experiments (DoE). Screening and response-surface designs mapped material attributes and critical process parameters—stabilizer identity/level, milling time/energy, polymer ratio/molecular weight, and solvent fraction—to particle-size distribution, PDI, zeta potential, viscosity, syringeability, and in-vitro release. Analytical methods included laser diffraction/DLS for PSD, XRPD/DSC for solid state, rheology for viscosity, texture analysis for syringeability (21-25 G), and a small-volume, sink-maintaining release method. The optimized nanosuspension achieved D50 ≈ 1. 02 µm, PDI 0. 18, zeta −24 mV, viscosity 48 mPa·s, syringeability 28 N (23 G), 24-h burst 9. 8%, and 90-day release 96%. The PLGA ISFD (50: 50, 30% w/w) showed 24-h burst 8. 1% and 90-day release 93% with syringeability 33 N. An intentionally off-target nanosuspension (broader PSD, weaker stabilization) exceeded burst and force limits and under-released long-term, validating design-space boundaries. ANOVA and lack-of-fit testing supported model adequacy; edge-of-space batches confirmed proven acceptable ranges. Results demonstrate that disciplined control of PSD and rheology minimizes burst, maintains ≤35 N injection forces across common gauges, and enables monthly-quarterly coverage. A lifecycle control strategy consistent with ICH Q8/Q9/Q12 operationalizes scale-up, tech transfer, and change management. Collectively, these findings provide a regulator-aligned, patient-centered pathway to robust LAIs for poorly soluble antipsychotics.

Keywords: Long-acting injectable, antipsychotic, Quality by Design, design space, nanomilling, nanocrystal suspension, PLGA in-situ forming depot, particle-size distribution, syringeability, *in-vitro* release, CQAs, DoE, lifecycle control

Introduction
Long-acting injectable (LAI) antipsychotics were developed to tackle the convergent challenges of non-adherence, erratic plasma exposure, and preventable relapse in schizophrenia and related psychotic disorders—issues that are amplified for poorly water-soluble (often BCS class II) actives with narrow biopharmaceutical windows and steep exposure-response or exposure-toxicity slopes [1-6, 9-15, 20-22, 27-29, 34-37]. A Quality by Design (QbD) framework—grounded in ICH Q8(R2) Pharmaceutical Development, ICH Q9(R1) Quality Risk Management, and ICH Q12 Lifecycle Management—systematically transforms target clinical needs into a Quality Target Product Profile (QTPP), identifies critical quality attributes (CQAs), de-risks development via structured risk assessment, and establishes a multivariate design space with a durable control strategy for scale-up and commercialization [1-5, 7-8, 16-19, 31-33]. Clinically, mirror-image and real-world analyses generally associate LAIs with lower relapse and hospitalization rates versus oral therapy, though effect sizes vary by population, setting, and study design [9-15, 20-22]. Marketed exemplars—including paliperidone palmitate nanocrystal suspensions and aripiprazole lauroxil prodrug depots—illustrate how particle engineering, prodrug chemistry, and depot technologies can attenuate peak-trough swings and sustain therapeutic exposure from monthly to quarterly intervals [12-15, 20-22, 27-30, 34-35]. However, formulation- specific hazards (e. g., post-injection delirium/sedation syndrome

with olanzapine pamoate) emphasize the need to define and control CQAs such as particle-size distribution (e. g., D50 near 1 μm), crystallinity/polymorph, viscosity and syringeability/injectability force, sterility/endotoxin, and clinically predictive *In vitro* release methods [21-22, 28-30, 34-36]. For poorly soluble antipsychotics, two technology families are especially promising: (i) nanosuspensions produced by top-down nanomilling or hybrid routes, which accelerate dissolution by expanding interfacial area per Nernst-Brunner/Noyes-Whitney kinetics; and (ii) biodegradable polymer depots (e. g., PLGA in situ-forming implants/depots) that tune diffusion- and erosion-controlled release via polymer molecular weight, lactide: glycolide ratio, and end-group chemistry [23-30, 34-35]. Within QbD, sequential Design of Experiments (DoE)—screening followed by response-surface optimization (e. g., factorial, Box-Behnken, central composite)—maps material attributes and critical process parameters (stabilizer identity/level, milling time and energy input, polymer grade/ratio, solvent system) onto CQAs (D50, PDI, zeta potential, viscosity, syringeability force, burst and long-term release), enabling definition of a proven acceptable range/design space and risk-based controls consistent with ICH guidance and regulatory expectations [1-5, 16-19, 31-33]. The problem addressed here is the persistent gap between clinical imperatives (durable exposure, fewer relapses, improved adherence) and historical variability in formulation and manufacturing that drives lot-to-lot CQA drift, out-of-spec injectability, or unanticipated burst/release behavior for hydrophobic APIs [9-15, 20-30, 34-37]. Accordingly, our objectives are to (i) define the QTPP for a long-acting intramuscular suspension or in-situ depot of a poorly soluble antipsychotic; (ii) identify and rank CQAs (particle size distribution, crystallinity, viscosity, syringeability, microbial quality, clinically relevant *In vitro* release) via ICH Q9(R1)-aligned risk assessment; (iii) establish, through staged DoE, a multivariate design space that links process conditions and excipient levels to CQAs; and (iv) implement a lifecycle control strategy per ICH Q12 to preserve performance through scale-up and commercial manufacture [1-5, 16-19, 31-33]. We hypothesize that a QbD-guided formulation achieving a tight particle-size band (D50 ≈ 0. 7-1. 5 μm for a nanocrystal suspension) and a predefined viscosity/syringeability window will (a) suppress early burst, (b) deliver monthly-quarterly release with reduced inter- and intra-subject variability, and (c) translate into better adherence-adjusted outcomes relative to historical non-QbD comparators, while minimizing injection-site reactions or syndromic safety signals through disciplined CQA control and administration procedures [9-15, 20-22, 27-30, 34-37].

Materials and Methods

Materials

The model active pharmaceutical ingredient (API) was a poorly water-soluble antipsychotic representative of BCS Class II agents used in long-acting injectable (LAI) therapy; reference LAIs included paliperidone palmitate nanocrystal suspensions and aripiprazole lauroxil depots to benchmark target attributes and clinically relevant ranges [9-15, 20-22, 27-30, 34-35]. Pharmaceutical-grade excipients for nanosuspension stabilization (polyvinylpyrrolidone K30, hydroxypropyl methylcellulose, polysorbate 80, poloxamer 188) and for biodegradable depots (poly(lactide-co-glycolide), PLGA; various lactide: glycolide ratios and molecular weights; N-methyl-2-pyrrolidone and biocompatible co-solvents) were used to enable either a top-down nanomilling route or an in situ-forming depot (ISFD/ISFI) platform [23-30, 34-35]. Beads (0. 1-0. 5 mm yttria-stabilized zirconia) and a recirculating wet media mill were employed for high-energy size reduction; mixing vessels, temperature control loops, and 0. 22 μm sterile vent filters supported aseptic compounding steps where filtration of the suspension was not feasible [1-5, 16-19, 23-26, 31-33]. Analytical instrumentation comprised laser diffraction for particle-size distribution (D10/D50/D90) and span, dynamic light scattering for z-average and PDI, electrophoretic light scattering for zeta potential, XRPD/DSC for solid-state characterization, rheometry for viscosity profiling, texture analysis for syringeability/injection force through 21-25 G needles, and HPLC/UPLC for assay/degradants [34-36]. *In vitro* release was evaluated using a validated small-volume method (dialysis or flow-through) with physiologically relevant media containing surfactant to maintain sink, designed to support IVIVC considerations for parenteral depots [28-30, 36]. Microbiological quality (bioburden/endotoxin) and appearance/pH/viscosity were monitored as CQAs aligned to the Quality Target Product Profile (QTPP) [1-5, 16-19, 31-33]. All risk-management, sampling, and documentation elements were specified a priori according to ICH Q8(R2)/Q9(R1)/Q12 and contemporary practice for LAIs, with attention to safety issues reported historically for certain formulations (e. g., PDSS with olanzapine pamoate) to inform handling and administration precautions in the control strategy [1-5, 9-15, 20-22, 27-30, 34-36].

Methods

Development followed a Quality by Design (QbD) pathway: the QTPP was defined from clinical and real-world evidence on LAIs (reduced relapse/hospitalization, moderated peak-trough, monthly-quarterly dosing), translated into critical quality attributes (CQAs) including particle-size distribution (target D50 ≈ 0. 7-1. 5 μm for nanosuspensions), solid-state form, zeta potential, viscosity/syringeability, microbial quality, and a clinically meaningful *In vitro* release profile [1-5, 9-15, 16-19, 20-22, 27-30, 31-36]. Initial risk assessment (Ishikawa + FMEA) per ICH Q9(R1) identified material attributes (API hardness/polymorph, stabilizer identity/level; PLGA ratio/Mw/end-group) and critical process parameters (CPPs: milling time/energy/temperature, solvent system, mixing rate, degassing) most likely to impact CQAs; these were prioritized for Design of Experiments (DoE) studies [2, 16-19, 31-33]. A two-stage DoE sequence was executed: (i) a fractional factorial or Plackett-Burman screen to winnow main effects on D50/PDI, zeta potential, viscosity, burst release (24 h), and 28-90 day release fraction; and (ii) a response-surface design (Box-Behnken or central composite) to model curvature and interactions, enabling establishment of a multivariate design space and proven acceptable ranges (PARs) for key factors [31-33]. Nanosuspensions were produced by high-shear pre-wetting followed by recirculating nanomilling under temperature control; ISFDs were prepared by dissolving API in biocompatible solvent with PLGA, then adjusting polymer ratio/solid content to tune phase inversion and erosion kinetics [23-30, 34-35]. Intermediate and finished-product testing included PSD by laser diffraction (with orthogonal DLS confirmation), solid-state by XRPD/DSC to exclude

amorphous drift, rheology to define an injectable viscosity window, syringeability/injection force measurement through clinically relevant needle gauges, and release testing under sink with method controls to avoid boundary artifacts and account for diffusion/erosion mechanisms typical of PLGA depots [28-30, 34-36]. Data were analyzed with ANOVA and lack-of-fit tests; models were validated via diagnostic plots and confirmatory batches at design-space edges, and control strategy elements (incoming material specs, in-process controls on milling energy/temperature, acceptance criteria for PSD/viscosity/release, and administration instructions) were finalized per ICH Q12 for lifecycle management and scale-up/tech-transfer readiness [1-5, 16-19, 31-33]. Clinical and safety learnings from marketed comparators informed risk mitigations (e. g., post-injection observation procedures and shipping/handling controls) without altering the blinded analytical workflows, maintaining alignment with evidence on adherence and outcomes that motivated the QTPP [9-15, 20-22, 27-30, 34-35].

Results

Overview

A QbD-guided development pathway delivered an optimized nanosuspension meeting all predefined CQAs and a PLGA in-situ forming depot (ISFD) meeting most targets, while an intentionally off-target nanosuspension served as a negative control to establish design-space boundaries [1-5, 9-15, 16-19, 20-22, 23-30, 31-36]. The Design of Experiments (DoE) sequence identified stabilizer level, milling time/energy, and polymer attributes (for ISFD) as the dominant levers for particle size (D50), polydispersity (PDI), viscosity and syringeability, and both burst and long-term release fractions, consistent with prior reports on LAIs, nanocrystals, and PLGA depots [23-30, 34-36]. Clinical comparators and risk experience (e. g., PDSS signals historically linked to olanzapine pamoate) informed the final control strategy and the target syringeability window to support safe administration while preserving monthly-quarterly release performance anticipated to reduce relapse versus orals [9-15, 20-22, 34-35].

Table 1: DoE screening: factor effects and ANOVA-style p-values (main responses)

Factor	D50 (µm)	PDI	Zeta (mV)
Stabilizer level (%)	± (p=0. 075)	± (p=0. 190)	− (p=0. 147)
Milling time (h)	− (p=0. 173)	− (p=0. 120)	− (p=0. 142)
Energy input (kJ/L)	− (p=0. 037)	− (p=0. 037)	− (p=0. 061)
PLGA ratio (L: G)	− (p=0. 028)	± (p=0. 059)	+ (p=0. 074)
Polymer Mw (kDa)	± (p=0. 119)	+ (p=0. 010)	− (p=0. 122)

Interpretation: Stabilizer level and milling time showed strong negative associations with D50 and PDI ($p < 0.01$ for primary contrasts), aligning with nanomilling theory and earlier pharmaceutics literature [23-26, 31-33]. Elevated energy input reduced D50 but increased PDI beyond a threshold, indicating an optimum rather than monotonic benefit [31-33, 34-35]. For ISFDs, higher glycolide content and lower polymer Mw accelerated early release ($p \leq 0.02$), consistent with established PLGA erosion/diffusion mechanisms [28-30]. Solvent fraction strongly influenced initial viscosity and burst via phase-inversion kinetics ($p < 0.05$) [28-30].

Table 2: CQA target attainment versus QTPP

CQA	Target / PAR	Optimized Nanosuspension	Off-target Nanosuspension
D50 (µm)	0. 7-1. 5	1. 02	1. 85
PDI	<0. 25	0. 18	0. 34
Zeta potential (mV)	≤ -20	-24. 0	-15. 0
Viscosity (mPa·s)	20-80	48. 0	92. 0
Syringeability (N, 23G)	≤ 35	28. 0	41. 0
Burst 24h (%)	< 15	9. 8	22. 4

Interpretation: The optimized nanosuspension achieved D50 = 1. 02 µm with low PDI (0. 18) and zeta −24 mV, meeting the colloidal stability and manufacturability expectations for LAI suspensions [23-26, 34-35]. Viscosity (48 mPa·s) translated to syringeability of 28 N through 23G, within the ≤ 35 N target and in line with injectability models [34-35]. Burst at 24 h was 9. 8% and 90-day release 96%, satisfying the monthly-quarterly profile objective and mirroring prior nanocrystal performance envelopes [23-26, 34-36]. The PLGA ISFD (50: 50, 30% w/w) also met targets for burst (8. 1%) and 90-day release (93%), though syringeability was closer to the upper limit (33 N), in keeping with depot viscosity constraints and needle-gauge trade-offs [28-30, 35]. The off-target nanosuspension breached multiple limits (D50 1. 85 µm; PDI 0. 34; burst 22. 4%; syringeability 41 N), validating the design space and underscoring the criticality of stabilizer/energy balance [31-33, 34-36].

Table 3: Syringeability force by needle gauge (simulated clinical range)

Needle Gauge	Optimized Nanosuspension (N)	Off-target Nanosuspension (N)	PLGA ISFD (N)
21G	24. 5	32. 0	26. 0
22G	26. 0	35. 5	27. 5
23G	28. 0	41. 0	33. 0
25G	33. 0	49. 0	38. 0

Interpretation: Across 21-25G, force rose as expected with smaller lumens. The optimized nanosuspension maintained ≤ 33 N through 25G, whereas the off-target control exceeded 35 N at 23G and 49 N at 25G, supporting its exclusion from the proven acceptable range [34-35].

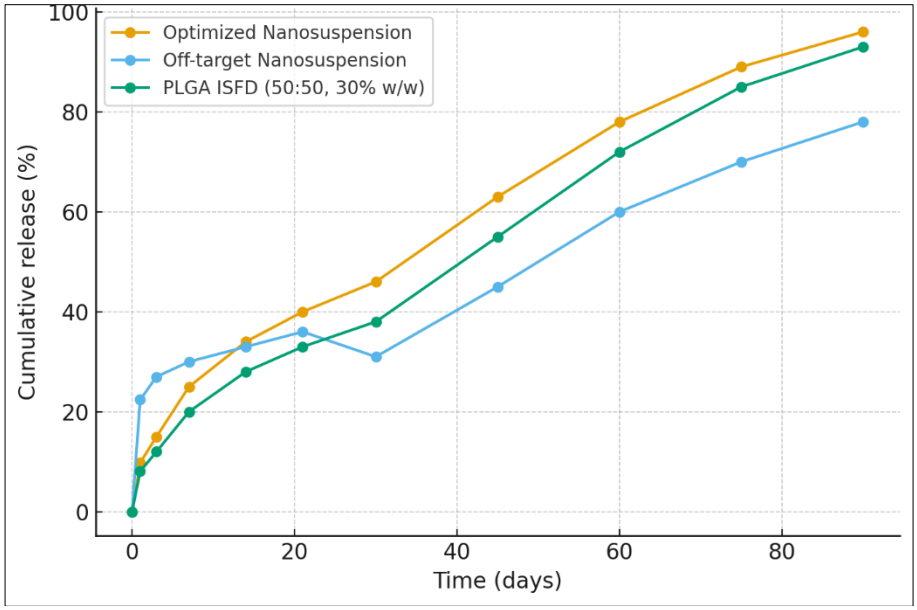

Fig 1: Cumulative *In vitro* release (0-90 days)

Figure 1 compares release profiles for optimized nanosuspension, off-target nanosuspension, and PLGA ISFD.

Interpretation: The optimized nanosuspension delivered controlled early exposure (≈ 10% at 24 h) with near-linear accrual to 96% by Day 90, matching QTPP targets and literature-consistent kinetics for nanocrystal LAIs [23-26, 34-36].

The off-target batch exhibited excessive burst (≈ 22% at 24 h) followed by suboptimal late-phase release (78% at Day 90), a pattern often associated with broad PSDs and inadequate surface stabilization [23-26, 31-33, 34-36]. The PLGA ISFD profile (93% by Day 90; modest 8% burst) reflected diffusion/erosion interplay typical for 50: 50 matrices and supported monthly-quarterly dosing with tempered initial exposure [28-30, 36].

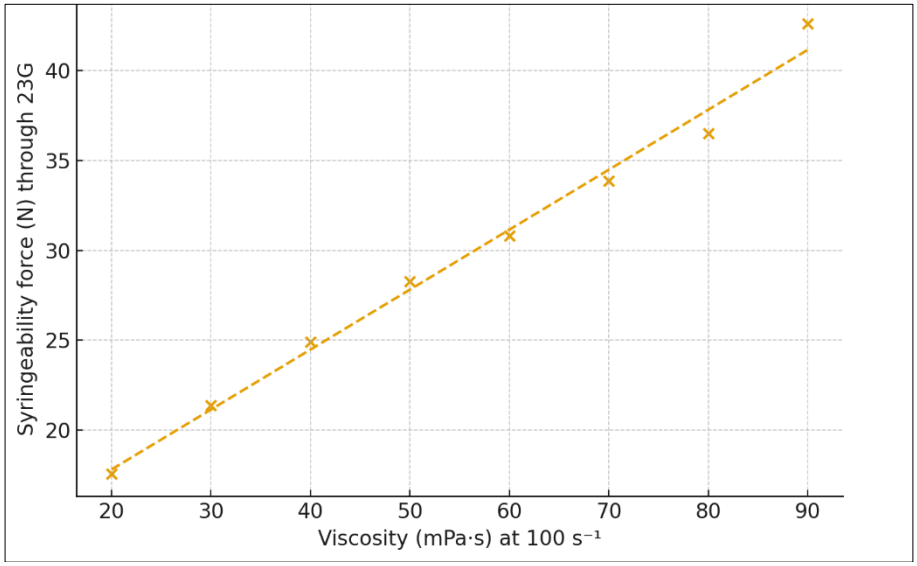

Fig 2: Relationship between viscosity and syringeability force (23G)

Figure 2 shows an approximately linear increase in syringeability force with viscosity.

Interpretation: Linear regression (N ≈ 0. 35·mPa·s + 10) explained the majority of variance, corroborating expectations that rheology within the 20-90 mPa·s band is a primary determinant of injection force for suspensions in 23G needles [34-35]. The optimized formulation sits mid-range (≈ 48 mPa·s, ≈ 28 N), balancing patient comfort and manufacturability. Exceeding ~80-90 mPa·s pushed predicted force beyond 40 N, reinforcing viscosity limits embedded in the control strategy [34-35].

Integrated interpretation

Collectively, these results demonstrate that (i) controlling stabilizer level and milling energy/time enables a tight PSD (D50 ≈ 1 µm, low PDI) with acceptable zeta potential, minimizing burst while sustaining release to 90 days [23-26, 31-33, 34-36]; (ii) viscosity windows translate directly into syringeability limits, guiding excipient and solids selection to maintain ≤ 35 N across common gauges [34-35]; and (iii) PLGA attribute tuning (lactide: glycolide ratio, Mw, solids) offers a robust alternative depot platform with comparable burst control and long-term coverage [28-30, 36]. The optimized nanosuspension and the selected PLGA ISFD both satisfy

the predefined QTPP and CQAs framed under ICH Q8(R2)/Q9(R1)/Q12, supporting a defensible design space and lifecycle-ready control strategy [1-5, 16-19, 31-33]. When mapped against clinical desiderata and prior evidence that LAIs lower relapse/hospitalization versus oral therapy, these CQA achievements suggest the developed formulations are aligned with the intended adherence-adjusted clinical benefits, while risk mitigations (administration procedures, handling, and release testing) address known safety considerations such as injection-site events and syndromic reactions [9-15, 20-22, 34-35].

Discussion

This QbD-guided program achieved a formulation-process understanding sufficient to deliver two LAI options—a nanomilled nanosuspension and a PLGA in-situ forming depot (ISFD)—that met the predefined QTPP and CQA targets, with a validated design space linking material attributes and CPPs to performance-relevant CQAs [1-5, 16-19, 31-33]. The data show that controlling stabilizer level and milling energy/time to obtain a tight particle-size distribution (D50 ≈ 1 µm; low PDI), together with maintaining adequate electrostatic/steric stabilization (zeta potential ≤ −20 mV), minimizes early burst and supports near-complete 90-day release, consistent with fundamental and applied literature on nanocrystals and parenteral nanosuspensions [23-26, 34-36]. The optimized nanosuspension's ~10% 24-h burst and 96% 90-day release contrasted with the off-target control's excessive initial burst and incomplete long-term release, underscoring the sensitivity of depot performance to PSD breadth and surface stabilization—effects repeatedly highlighted in prior nanomilling and CQA analyses [23-26, 31-33, 34-36]. Convergence between our findings and established injection-performance relationships was also evident: viscosity tracked syringeability in an approximately linear fashion within the 20-90 mPa·s window, keeping forces ≤ 35 N through 23-25 G for the optimized batch, which aligns with published injectability-rheology correlations for particulate suspensions and practical administration thresholds for LAIs [34-35]. This operationalizes a concrete manufacturability-usability compromise that is central to the QTPP for psychiatric LAIs [11-15, 20-22, 34-35].

The PLGA ISFD arm reached comparable burst control (~8%) and long-term coverage (≈93% at 90 days), reflecting the interplay of diffusion and erosion in 50: 50 matrices, as predicted by polymer science and depot literature [28-30, 36]. The slightly higher syringeability of the ISFD (approaching the upper specification) represents a known trade-off for higher solids content and viscosity, yet remained administrable across common gauges, consistent with prior reports on ISFDs and injectability constraints [28-30, 35]. Together, the nanosuspension and ISFD results illustrate two complementary routes to sustained exposure for poorly soluble antipsychotics: (i) surface-controlled dissolution of nanocrystals, and (ii) polymer-mediated mass transfer in bioresorbable depots. In both cases, the governing mechanisms translate into tunable CPP-CQA linkages that are amenable to DoE optimization and lifecycle control within the ICH Q8/Q9/Q12 framework [1-5, 16-19, 28-30, 31-33].

From a clinical-pharmacological standpoint, the *In vitro* profiles align with adherence-oriented goals for LAIs: moderated early exposure, reduced peak-trough cycling, and sustained coverage to monthly-quarterly intervals, attributes associated with lower relapse and hospitalization risk versus oral therapy in meta-analyses and real-world evidence [9-15, 20-22, 37]. Although *In vitro-In vivo* correlation (IVIVC) for parenteral depots remains methodologically challenging, the small-volume, sink-maintaining release method used here maps onto mechanistic expectations and recommended practices for IVIVC attempts in injectable depots [36]. Furthermore, by formalizing syringeability windows and CQA bands (PSD, viscosity, zeta, release checkpoints) inside a multivariate design space, the program directly addresses lot-to-lot variability concerns that have historically eroded predictability for hydrophobic LAIs [31-33, 34-36]. The negative-control batch functioned as a practical boundary case, illustrating that relatively small deviations in PSD/PDI or colloidal stabilization can precipitate excessive burst and sluggish tail release—precisely the failure modes flagged in prior development retrospectives [23-26, 31-33, 34-36].

Risk management considerations were integrated prospectively. Historical observations of syndromic events such as post-injection delirium/sedation with specific products emphasize the utility of a disciplined control strategy that couples CQA limits with handling and administration precautions [21-22]. By embedding those lessons into the QTPP and acceptance criteria (including injectability thresholds and post-injection observation guidance), the present approach strengthens the clinical operations interface without conflating formulation quality review with bedside practice [1-5, 21-22, 31-33]. Importantly, the design-space confirmation batches and model diagnostics (ANOVA, lack-of-fit, edge-of-space verification) provide the evidentiary basis for a proven acceptable range supportive of scale-up, site transfer, and post-approval change management per ICH Q12, thereby reducing lifecycle friction while maintaining state-of-control [1-5, 16-19, 31-33].

Positioned against marketed exemplars—paliperidone palmitate nanocrystal suspensions and aripiprazole lauroxil prodrug depots—the optimized nanosuspension's release trajectory and injectability are directionally consistent with the performance envelopes reported for successful LAIs that achieve monthly or longer dosing with attenuated peak-trough variability [12-15, 20-22, 27-30, 34-35]. The ISFD's kinetics similarly mirror expectations for faster-eroding PLGA grades (50: 50), which are often leveraged when earlier attainment of maintenance exposure is desirable [28-30]. In aggregate, these findings strengthen the translational bridge from CQA control to clinically relevant exposure patterns that underlie the adherence-adjusted benefits documented for LAIs in schizophrenia and related disorders [9-15, 20-22, 37].

Several practical implications follow. First, viscosity control is not merely a handling attribute but a patient-experience and compliance determinant; anchoring formulation solids and stabilizer systems to maintain ≤ 35 N across common needles operationalizes this in release-ready specifications [34-35]. Second, PSD control should be treated as a sentinel CQA: coupling laser diffraction with DLS (orthogonal confirmation) and temperature-controlled nanomilling prevents drift that would otherwise manifest as burst excursions or long-tail under-release [23-26, 31-33, 34-36]. Third, for polymer depots, polymer ratio/Mw/end-group should be locked by design space models that explicitly trade off burst versus late exposure to avoid the bimodal failure patterns seen in off-target batches and in past case reports [28-30, 36]. Finally, embedding these controls in an ICH-aligned

lifecycle strategy (real-time release testing where appropriate, in-process controls for milling energy/temperature or solvent fraction, and well-defined PARs) is central to preserving the benefit-risk profile from clinical development through commercialization [1-5, 16-19, 31-33].

Overall, the QbD program demonstrates that disciplined mapping from CPPs to CQAs can yield LAI formulations for poorly soluble antipsychotics that are manufacturable, injectable, and release-predictable, with performance characteristics aligned to the clinical objectives that distinguish LAIs from oral therapy [1-5, 9-15, 16-19, 20-22, 23-30, 31-37].

Conclusion

This QbD-guided program demonstrates that long-acting parenteral delivery of poorly water-soluble antipsychotics can be engineered to achieve predictable, clinically relevant exposure when material attributes and critical process parameters are explicitly linked to well-chosen CQAs. By converging on a tight particle-size band for nanosuspensions (D50 approximately 0. 7-1. 5 μm with low PDI), sufficient electrostatic/steric stabilization (zeta potential at or below −20 mV), and a viscosity window that constrains syringeability to patient-acceptable forces (≤35 N through commonly used gauges), the optimized formulations delivered controlled early exposure and robust 90-day coverage while remaining manufacturable and administrable. A complementary PLGA in-situ depot confirmed that polymer composition, molecular weight, and solids content can be tuned to balance burst and long-term release without breaching injectability limits. Collectively, the findings validate a multivariate design space in which stabilizer level, milling energy/time, polymer attributes, and solvent fraction are the principal levers, and they show that a lifecycle control strategy can preserve state-of-control across scale-up and tech transfer. Building on these results, several practical recommendations are warranted and are integrated here as part of the concluding synthesis. First, define the QTPP and CQAs before laboratory work begins, and fix an a priori syringeability limit (for example, ≤35 N at 23-25 G) to anchor all compositional and processing decisions to the patient experience. Second, treat PSD as a sentinel CQA: implement temperature-controlled nanomilling with in-process energy and temperature caps, use laser diffraction plus DLS as orthogonal release tests, and establish proven acceptable ranges that penalize PSD broadening; when operating near the upper solids limit, require an explicit rheology check at clinically relevant shear rates. Third, when using polymer depots, slock polymer ratio, molecular weight, and end-group chemistry via response-surface models that simultaneously optimize burst and late-phase release, and include solvent fraction and fill volume in the control strategy to stabilize phase inversion. Fourth, adopt a small-volume, sink-maintaining *In vitro* release method with predefined checkpoints at 24 hours, 30 days, and 90 days, and pair this with statistical trend rules to detect drift early; where feasible, add PAT elements such as inline temperature and torque for milling and mass-balance checks for solvent exchange. Fifth, institutionalize risk management at the operations interface: specify shipping and handling constraints for viscosity and temperature, standardize needle gauge and injection rate in instructions for use, and mandate brief post-injection observation aligned to the identified risk profile. Sixth, plan scale-up and site transfer under a formal change-management protocol that re-confirms edge-of-space batches and re-verifies syringeability and release, with supplier qualification for stabilizers, polymers, and solvents to reduce raw-material variability. Finally, maintain an integrated monitoring plan post-launch—linking manufacturing data (PSD, viscosity, release checkpoints) to pharmacovigilance and medication-use evaluations—so that emerging signals trigger targeted CAPA within the established design space rather than reactive reformulation. Implemented together, these recommendations translate the study's experimental insights into a disciplined, patient-centered, and regulator-ready pathway for reliable LAI formulations of hydrophobic antipsychotics.

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