RESEARCH PAPER

"Quality by Design Approaches in Intranasal Drug Delivery Systems: Current Progress, Challenges and Future Perspectives"

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Abstract
Intranasal drug delivery has emerged as a highly promising administration route owing to its unique anatomical advantages rich vascularization, large mucosal surface area (~150–180 cm²), and direct olfactory/trigeminal access to the central nervous system (CNS) bypassing the blood-brain barrier (BBB). Despite these advantages, mucociliary clearance, limited nasal volume (~20 mL per nostril), enzymatic barriers, and inter-individual physiological variability complicate reproducible formulation development. Quality by Design (QbD), a science- and risk-based pharmaceutical development framework endorsed by ICH Q8, Q9, and Q10, provides a structured, systematic approach to address these challenges. This review comprehensively examines QbD applications across intranasal dosage forms including nasal solutions, sprays, powders, mucoadhesive systems, thermosensitive in situ gels, nanoemulsions, polymeric nanoparticles, and lipid nanoparticles (SLN/NLC). Key QbD elements—Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), Design Space, and Control Strategy—are systematically discussed. Risk assessment tools (Ishikawa diagrams, FMEA, Pareto analysis) and Design of Experiments (DoE) strategies including Plackett-Burman, Box-Behnken, and Central Composite Designs with Response Surface Methodology are elaborated. Special emphasis is given to nose-to-brain delivery for CNS disorders (Alzheimer's, Parkinson's, epilepsy, migraine) with supporting case studies. Regulatory expectations (FDA, EMA) and emerging trends including AI-assisted development, digital twins, continuous manufacturing, and personalized medicine are also addressed. QbD is confirmed as essential to ensure strong, consistent, and compliant intranasal drug products.

Keywords
Quality by Design; Intranasal drug delivery; Nose-to-brain; Critical Quality Attributes; Design of Experiments; Nanoemulsion; Lipid nanoparticles; Risk assessment; CNS drug delivery; ICH Q8.
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Introduction

Overview and Advantages of Intranasal Drug Delivery

The nasal route has been exploited for drug delivery for centuries, but its scientific application in modern pharmacotherapy has accelerated substantially over the past three decades [1]. The nasal cavity provides approximately 150–180 cm² of epithelial surface area, richly vascularized and supported by ciliated columnar epithelium, goblet cells, and a highly permeable lamina propria [2]. The olfactory epithelium (~10 cm²) enables direct neuronal transport to the brain via olfactory receptor axons, bypassing the BBB—a property of immense clinical value for CNS-targeted drug delivery [3,4]. Intranasal administration offers rapid absorption comparable to intravenous routes for certain drugs, circumvents hepatic first-pass metabolism, improves patient compliance (non-invasive, painless), and supports both local nasal and systemic drug delivery [5,6]. The route is also suitable for mucosal immunization and peptide/protein delivery, further expanding its therapeutic scope [7].

Challenges in Intranasal Formulation Development

Despite its advantages, intranasal delivery faces significant challenges. Mucociliary clearance (ciliary beat ~1000/min; transport rate 5–6 mm/min) rapidly removes formulations from nasal mucosa within 15–30 minutes, limiting drug contact time [8]. The restricted nasal volume (~100–200 µL per nostril) constrains administrable dose [9]. Nasal mucosa expresses proteases, peptidases, and CYP450 enzymes that degrade susceptible drugs prior to absorption [10]. Drug physicochemical properties (MW ideally <1000 Da, log P 1–4) and charge critically influence nasal permeation [11]. Inter-individual variability in nasal anatomy, mucosal thickness, blood flow, disease state (rhinitis, sinusitis), and environment (humidity, temperature) further complicate predictable absorption [12]. Formulation-related safety concerns include nasal irritation, cilia toxicity, and drug-induced rhinitis, which must be carefully managed in the formulation process [13].

Need for Quality by Design (QbD)

The multidimensional complexity of intranasal formulation development—compounded by stringent regulatory requirements necessitates a systematic,

science-driven development paradigm [14]. Traditional empirical, one-variable-at-a-time (OVAT) approaches are inadequate for characterizing the interdependent formulation-process-performance relationships inherent in nasal dosage forms [15]. The FDA and EMA have progressively endorsed QbD as the preferred development standard, recognizing its capacity to deliver consistently high-quality products with well-understood, controllable processes [16]. For intranasal systems specifically, QbD facilitates rational excipient selection, optimization of spray/particle characteristics, establishment of a proven design space, and streamlined scale-up and regulatory submissions [17,18].

Fundamentals of Quality by Design

Definition, Principles, and Regulatory Framework

QbD is defined by ICH Q8(R2) as 'a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management' [19]. The conceptual foundation involves building quality into the product prospectively rather than testing quality into end-products—a fundamental shift from the traditional Quality-by-Testing (QbT) paradigm [20]. The regulatory QbD framework is established by three harmonized ICH guidelines: ICH Q8(R2) introduced QTPP, CQAs, and Design Space; ICH Q9 provided a systematic quality risk management framework endorsing tools such as FMEA and HACCP; and ICH Q10 described a comprehensive pharmaceutical quality system applicable across the product lifecycle [19,21,22]. The FDA's Process Analytical Technology (PAT) initiative and 21st-century cGMP framework align closely with these ICH guidelines [23]. Core QbD elements are: (i) QTPP definition; (ii) CQA identification; (iii) risk assessment to identify CMAs/CPPs; (iv) DoE to characterize variable-CQA relationships; (v) Design Space establishment; and (vi) Control Strategy implementation [24].

Traditional vs. QbD Approach

The contrast between traditional and QbD approaches is most evident in the depth of process understanding and regulatory filing flexibility. Traditional development relies on empirical OVAT experiments, fixed manufacturing processes, and end-product testing for quality assurance, resulting in limited process understanding and frequent post-approval regulatory submissions [25]. In contrast, QbD employs systematic multivariate methodologies to characterize the true impact of individual and combined variables on product quality, establishing a scientifically justified Design Space within which the manufacturer may operate without regulatory notification [26]. Real-time quality monitoring via PAT tools enables in-process rather than post-process quality control [27]. This distinction is particularly relevant for complex nasal dosage forms where multiple interdependent variables collectively determine clinical performance [28]. (Table.1)

Table 1. Comparison of Traditional Approach vs. Quality by Design in Pharmaceutical Development [19,25,26]

Parameter	Traditional Approach	QbD Approach
Development philosophy	Empirical, OVAT	Systematic, multivariate DoE
Quality assurance	End-product testing (QbT)	Built-in (prospective) quality
Regulatory filing	Fixed process parameters	Design Space with flexibility
Post-approval changes	Frequent submissions	Flexible within Design Space
Risk management	Reactive	Proactive (FMEA, Ishikawa)
Process monitoring	Minimal	PAT-enabled, real-time
Scale-up	Trial and error	Predictive, model-driven

OVAT: One-Variable-At-A-Time; QbT: Quality-by-Testing; DoE: Design of Experiments; PAT: Process Analytical Technology; FMEA: Failure Mode and Effects Analysis

QbD Elements in Intranasal Drug Delivery

Quality Target Product Profile (QTPP)

The QTPP is a prospective planning document defining desired quality characteristics of the finished intranasal product from the patient's perspective [29]. For intranasal systems, the QTPP encompasses: dosage form and route, drug concentration and dose strength, drug release profile (immediate/extended), physicochemical properties (pH 4.5–6.5, osmolality 270–310 mOsm/kg, viscosity), nasal tolerability, spray characteristics (droplet size 30–200 µm, spray pattern, plume geometry), preservative efficacy, and shelf-life stability [30,31]. The QTPP serves as the blueprint guiding all subsequent development activities.

Critical Quality Attributes (CQAs)

CQAs are physical, chemical, biological, or microbiological properties that must be within appropriate limits to ensure desired product quality and clinical performance [19]. For intranasal formulations, CQAs include: droplet/particle size distribution, PDI, zeta potential, drug content uniformity, pH, osmolality, viscosity/rheology, mucoadhesive force, in vitro drug release and permeation, spray pattern/plume geometry, preservative concentration, and microbiological quality [32,33]. For nose-to-brain systems, drug transport efficiency (DTE%) and brain/plasma AUC ratio are additional CQAs [34]. CQAs are iteratively refined as formulation understanding deepens, guided by risk assessment [35].

Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs)

CMAs are input material properties requiring control to ensure output quality [19]. Drug substance CMAs

relevant to nasal delivery include particle size, polymorphic form, solubility, lipophilicity (log P), molecular weight, and pKa [36]. Excipient CMAs include polymer molecular weight and degree of substitution (for mucoadhesive polymers), HLB value and chain length (surfactants), melting point and drug solubilization capacity (lipids), and polymer MW and inherent viscosity (nanoparticle polymers) [37–40]. CPPs are process parameters whose variability impacts CQAs and must be monitored or controlled [19]. CPPs vary by process: for nasal sprays—mixing speed, filling speed, actuator characteristics; for spray drying—inlet/outlet temperature, feed flow rate, atomization gas flow; for high-pressure homogenization—pressure, cycles, temperature; for nanoparticle preparation—solvent:antisolvent ratio, stirring speed, surfactant concentration; for lipid nanoparticles—lipid melt temperature, homogenization pressure and cycles [41–45].

Design Space and Control Strategy

The Design Space is 'the multidimensional combination and interaction of input variables that have been demonstrated to provide assurance of quality' [19]. Working within the Design Space does not constitute a regulatory change, providing substantial manufacturing flexibility [46]. For intranasal formulations, Design Spaces are established through multivariate DoE studies and represented as response surface plots or overlay plots depicting simultaneous CQA acceptability regions [47]. The Control Strategy is a planned set of controls—in-process, analytical, environmental, and equipment—derived from product and process understanding to ensure consistent quality [22]. Control Strategy elements for nasal formulations typically include: real-time particle size monitoring, in-line viscosity and pH measurement, spray pattern testing, content uniformity and preservative efficacy testing, and microbiological testing—tiered by risk priority number (RPN) from FMEA [48].(Table.2)

Table 2. CQAs for Different Intranasal Drug Delivery Systems [30,32,33]

Dosage Form	Key CQAs	Target/Acceptable Range
Nasal Solution/Spray	Droplet size (Dv50), pH, osmolality, viscosity, drug content	30–200 µm; pH 4.5–6.5; 270–310 mOsm/kg; <50 mPas; ±10%
Nasal Powder	Particle size (MMAD), moisture, flowability, content uniformity	MMAD 10–100 µm; ≤3%; Carr Index <25; RSD ≤5%
Mucoadhesive System	Mucoadhesive force, drug release rate, bioadhesion time	>0.05 N; >60% at 8 h; >4 h nasal residence
In Situ Thermosensitive Gel	Gelation temperature, gel strength, drug release, pH	32–34°C; adequate gel strength; sustained 8–12 h; pH 6.5–7.0
Nanoemulsion	Z-average, PDI, zeta potential, drug content, stability	<200 nm; <0.2; |ZP|>±30 mV; ±5%; 12-month stable
Polymeric Nanoparticles	Particle size, PDI, zeta potential, encapsulation efficiency (EE)	<300 nm; <0.25; |ZP|>±20 mV; EE>70%
Lipid NPs (SLN/NLC)	Particle size, PDI, zeta potential, EE, crystallinity index	<200 nm; <0.2; |ZP|>±30 mV; EE>80%; CI<30%

MMAD: Mass Median Aerodynamic Diameter; PDI: Polydispersity Index; ZP: Zeta Potential; EE: Encapsulation Efficiency; CI: Crystallinity Index; RSD: Relative Standard Deviation; SLN: Solid Lipid Nanoparticles; NLC: Nanostructured Lipid Carriers

Risk Assessment Tools in Intranasal Formulation Development

Ishikawa (Fishbone) Diagram

The Ishikawa (cause-and-effect) diagram is a qualitative risk tool used in early QbD stages to systematically map potential causes of CQA variability across categories: materials, equipment, methods (process parameters), measurement systems, environment, and personnel [49]. For a nasal spray, an Ishikawa diagram for droplet size might identify actuator orifice diameter, spring force, formulation viscosity, surface tension, and actuation force as primary causal branches, each further decomposed into specific attributes [50]. Outputs directly inform FMEA and variable selection for DoE studies.

Failure Mode and Effects Analysis (FMEA) and Risk Estimation Matrix

FMEA quantitatively evaluates potential failure modes by assigning Severity (S), Occurrence (O), and Detectability (D) scores (each 1–10), yielding Risk Priority Numbers (RPN = S x O x D, range 1–1000) [21]. Variables with high RPNs are classified as high-risk CMAs or CPPs and prioritized for DoE optimization [50]. For example, in a nasal nanoemulsion FMEA, surfactant concentration may receive high RPN due to its significant impact on droplet size (high S), variable manufacturing control (moderate O), and difficult real-time measurement (low D). The Risk Estimation Matrix semi-quantitatively categorizes risks in a probability x severity grid (low/medium/high), useful for rapid early-development risk prioritization before FMEA scores can be established. Pareto analysis from DoE or FMEA data

identifies the 'vital few' CMAs/CPPs accounting for ~80% of CQA variability, focusing control efforts on the most critical variables.

Design of Experiments (DoE) in Intranasal Formulations

Screening Designs

The Plackett-Burman (PB) design efficiently screens up to 47 factors in a minimal number of runs using two-level main-effects-only designs, enabling rapid identification of significant CMAs/CPPs from a large preliminary set identified by Ishikawa/FMEA. For example, a 12-run PB design might screen 11 variables for nasal SLN (lipid concentration, surfactant type/concentration, drug:lipid ratio, homogenization pressure/cycles, temperature, cooling rate, pH, solvent volume) against particle size, PDI, and EE. Significant variables ($p<0.05$) proceed to optimization designs. Fractional Factorial (FF) designs (Resolution III–V) evaluate a fraction of all combinations, enabling estimation of main effects and selected two-factor interactions with fewer runs than full factorial; Resolution V designs ensure all main effects and two-factor interactions are estimable without aliasing.

Optimization Designs and Response Surface Methodology

The Central Composite Design (CCD) augments a 2k factorial with center and axial (star) points to enable full second-order quadratic model fitting: $Y = \beta_0 + \Sigma\beta_i x_i + \Sigma\beta_{ii} x_i^2 + \Sigma\Sigma\beta_{ij} x_i x_j + \varepsilon$ [58]. CCD variants (face-centered, circumscribed, inscribed) differ in design space exploration breadth. The Box-Behnken Design (BBD), a three-level spherical design, requires fewer runs than CCD (e.g., 15 vs. 20 runs for 3 factors) and avoids extreme corner combinations, making it popular for intranasal formulation optimization. Response Surface Methodology (RSM) employs these designs to build empirical models, validate them by ANOVA (F-test, lack-of-fit), and visualize response surfaces and contour plots. Graphical optimization via overlay contour plots defines the 'sweet spot' Design Space where all CQAs simultaneously meet specifications. BBD and CCD combined with RSM are the most widely applied optimization strategies for intranasal nanoemulsions, nanoparticles, in situ gels, and lipid nanoparticle systems. (Table-3)

Table 3. DoE Approaches Applied in Intranasal Drug Delivery QbD Studies

DoE Design	Phase	Factors	Key Features	Intranasal Application
Plackett-Burman	Screening	Up to 47	Two-level; main effects only; minimal runs	Screening 11 variables for SLN optimization
Fractional Factorial (Res. V)	Screening	4–8	Two-level; main effects + 2FI; alias-free at Res V	Mucoadhesive polymer blend screening
Central Composite (CCD)	Optimization	2–6	Three-level; full quadratic model; 5 levels/factor	Nanoemulsion droplet size optimization
Box-Behnken (BBD)	Optimization	3–6	Three-level; spherical; avoids extreme corners; efficient	In situ gel gelation temp & drug release
D-optimal	Optimization/ Mixture	Variable	Minimizes variance; handles constraints and mixtures	Nasal powder blend composition optimization

2FI: Two-Factor Interactions; Res V: Resolution V; SLN: Solid Lipid Nanoparticles

Application of QbD in Intranasal Drug Delivery Systems

Nasal Solutions, Sprays, and Powders

Nasal solutions and sprays—the most widely marketed intranasal dosage forms—have been extensively studied using QbD frameworks. Key CQAs (droplet size Dv50, spray pattern, plume geometry, shot weight, content uniformity, pH, osmolality, preservative efficacy) are specified in FDA's 2003 nasal spray guidance and must be robustly controlled. QbD factorial studies have evaluated formulation variables (drug/co-solvent/surfactant concentration) and device parameters (actuator orifice diameter, pump stroke volume) on spray droplet size. Polymeric additives (HPMC, HEC, PVP) modifying spray viscosity and reducing mucociliary clearance are characterized through DoE targeting their CMAs (MW, concentration, degree of substitution). Intranasal powder formulations offer superior chemical stability, eliminate preservatives, and extend mucosal residence time. For spray-dried nasal powders, CPPs (inlet temperature, feed concentration, atomization gas flow) are systematically optimized to

achieve target MMAD 10–150 µm and moisture content <3%.

Mucoadhesive Systems and Thermosensitive In Situ Gels

Mucoadhesive nasal formulations (microspheres, films, gels) exploit bioadhesive polymers (chitosan, carbomer, sodium hyaluronate, HPMC, Polycarbophil) to prolong nasal residence by overcoming mucociliary clearance. CQAs include mucoadhesive force (texture profile analysis), bioadhesion time, drug release rate, and in vitro permeation through nasal mucosa models. FMEA studies have identified polymer type, concentration, cross-linking agent concentration, and process temperature as high-RPN variables governing particle size and drug release, guiding subsequent optimization DoE. Thermosensitive in situ gelling systems are liquid at room temperature but undergo sol-to-gel transition upon nasal mucosal contact (~32–34°C), providing extended nasal residence and sustained drug release. Poloxamers (F-127, F-68), methylcellulose, and HPMC are widely employed as thermosensitive agents. Box-Behnken designs have been widely applied to optimize poloxamer-based nasal in situ gels, revealing significant interaction effects between poloxamer 407 and poloxamer 188 concentrations on gelation temperature. QbD-developed nasal in situ gels of antiepileptic drugs and antimigraine agents have demonstrated superior pharmacokinetic profiles in animal studies.

Nanoemulsions, Polymeric Nanoparticles, and Lipid Nanoparticles

Intranasal nanoemulsions (O/W, droplet size 20–200 nm) enhance drug absorption by increasing surface area, improving mucosal contact, and facilitating paracellular/transcellular transport. QbD development employs pseudo-ternary phase diagrams to identify nanoemulsion existence regions, followed by DoE optimization of oil type, surfactant:co-surfactant ratio (Smix), and homogenization parameters. Surfactant:co-surfactant ratio and oil concentration consistently emerge as the most significant CMAs governing droplet size and PDI in CCD/BBD studies. Polymeric nanoparticles (PLGA, PLA, chitosan) for nose-to-brain delivery are optimized by FMEA-guided DoE evaluating polymer concentration, drug:polymer ratio, organic:aqueous phase ratio, and surfactant type/concentration. Surface functionalization with chitosan or targeted ligands (transferrin, lactoferrin) enhances olfactory/trigeminal transport. Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) represent the first and second generations of lipid nanoparticle systems; NLC incorporates liquid lipid within the solid lipid matrix to enhance drug loading and reduce drug expulsion during storage. QbD studies for intranasal SLN/NLC employing BBD and CCD have identified lipid concentration, liquid:solid lipid ratio (NLC), surfactant concentration, and homogenization parameters as critical determinants of nanoparticle size, EE, and crystallinity index.

QbD-Based Development of Nose-to-Brain Delivery Systems

CNS Drug Delivery Overview

The blood-brain barrier (BBB), comprising brain microvascular endothelial tight junctions, efflux transporters (P-gp, BCRP), and metabolic enzymes, excludes ~98% of small molecules and virtually all large molecule therapeutics from CNS entry. Intranasal drug delivery to the CNS via olfactory and trigeminal nerve pathways offers a non-invasive BBB bypass strategy. Two pathways mediate nose-to-brain transport: (i) olfactory—axonal transport along olfactory receptor neuron processes to the olfactory bulb, then limbic structures and cortex; and (ii) trigeminal—transport along trigeminal nerve branches to brainstem and cerebellum [34]. QbD optimization of nose-to-brain systems targets Drug Transport Efficiency (DTE%) and Drug Targeting Percentage (DTP%), calculated from brain and blood AUC after intranasal and intravenous administration [35]. Nanocarrier systems are particularly advantageous due to their ability to prolong nasal residence, enhance mucosal permeation, protect drugs from enzymatic degradation, and facilitate axonal transport [36].

Alzheimer's, Parkinson's, Epilepsy, and Migraine

Alzheimer's disease (AD): QbD frameworks have been applied to develop intranasal nanoformulations of cholinesterase inhibitors (donepezil, rivastigmine) and memantine, achieving DTE% >200% in preclinical studies indicating strong preferential brain targeting over oral/IV routes [47,48]. Parkinson's disease (PD): Intranasal delivery of dopaminergic agents (levodopa, ropinirole) and neuroprotective agents via poloxamer-based in situ gels and chitosan nanoparticles have been optimized with QbD, demonstrating improved motor scores and striatal dopamine levels in MPTP rat models [49,50]. Epilepsy: Intranasal benzodiazepines (midazolam, lorazepam, diazepam) for acute seizure termination have been developed using QbD-aligned optimization; midazolam nasal spray (Nayzilam®) achieved FDA approval in 2019, demonstrating 59% bioavailability vs. IV and median seizure cessation time of 1.25 minutes [41,42]. Migraine: QbD-optimized intranasal triptan formulations (sumatriptan, zolmitriptan, rizatriptan) and dihydroergotamine (Trudhesa™, FDA approved 2021) address the limitations of oral administration in nausea-affected patients and achieve rapid CNS drug delivery via olfactory targeting [33,34].

Case Studies of QbD-Based Intranasal Formulations

Representative QbD case studies are summarized in Table 4, highlighting the DoE strategies, optimized formulation variables, and key pharmacokinetic outcomes across major intranasal CNS drug delivery systems.

Donepezil: QbD-developed chitosan nanoparticles using BBD optimization (chitosan concentration, TPP concentration, drug:polymer ratio) yielded particles of 183 nm, ZP +32 mV, EE 78%, with sustained 24-hour release and DTE% of 247% in Wistar rats [95]. A separate nanoemulsion optimized by CCD achieved droplet size 64 nm and DTE% of 312%—3.8-fold higher brain AUC than oral donepezil [36]. Rizatriptan: Khan et al. developed a QbD poloxamer 407/HPMC K4M in situ gel using BBD, with FMEA identifying

poloxamer 407 concentration (RPN 378) as highest-risk variable; the optimized gel (gelation temp 33.2°C, drug release 87.3% at 8 h) achieved DTE% of 284% in rabbits [37]. Sumatriptan: NLC developed via QbD CCD optimization (Compritol/Labrasol/Poloxamer 188) achieved particle size 148 nm, EE 82.7%, and DTE% of 294% with 3.2-fold higher brain AUC than IV sumatriptan [98]. Zolmitriptan: PB screening followed by BBD optimization of chitosan nanoparticles (213 nm, EE 81.4%) achieved DTE% of 268% and faster antinociceptive onset than commercial nasal spray [99]. Other CNS drugs including quetiapine (SLN, DTE% 3.7x brain BA vs. oral), clonazepam (nanoemulsion, Cmax brain up 4.2x, onset <5 min), haloperidol (nanoemulsion, DTE% 276%), and rasagiline (in situ gel, DTE% 198% with improved PD motor outcomes) have been successfully developed using QbD DoE frameworks [40–41]. (Table-4)

Table 4. Summary of QbD-Based Case Studies for Intranasal CNS Drug Delivery [43–45]

Drug	Formulation	DoE Design	Key CQAs Optimized	Outcome
Donepezil	Chitosan NPs	Box-Behnken	183 nm; ZP +32 mV; EE 78%	DTE% 247%; brain AUC up 3.8x vs oral
Donepezil	Nanoemulsion	CCD	64 nm; PDI 0.14; EE 92%	DTE% 312%
Sumatriptan	NLC	CCD	148 nm; EE 82.7%; PDI 0.19	DTE% 294%; brain AUC up 3.2x vs IV
Zolmitriptan	Chitosan NPs	PB + BBD	213 nm; EE 81.4%; ZP +28 mV	DTE% 268%; faster antinociceptive onset
Rasagiline	In situ gel	Box-Behnken	Tgel 32.8°C; sustained 24 h release	DTE% 198%; improved PD motor scores
Clonazepam	Nanoemulsion	BBD/RSM	68 nm; PDI 0.16; EE 91%	Cmax brain up 4.2x; onset <5 min
Quetiapine	SLN	CCD	176 nm; EE 79%; CI 18%	Brain BA up 3.7× vs oral
Haloperidol	Nanoemulsion	BBD	52 nm; PDI 0.12; ZP −38 mV	DTE% 276%; reduced peripheral effects

NPs: Nanoparticles; NLC: Nanostructured Lipid Carriers; SLN: Solid Lipid Nanoparticles; ZP: Zeta Potential; EE: Encapsulation Efficiency; CI: Crystallinity Index; Tgel: Gelation Temperature; BA: Bioavailability; DTE%: Drug Transport Efficiency; PB: Plackett-Burman; CCD: Central Composite Design; BBD: Box-Behnken Design; PD: Parkinson's Disease

Regulatory Considerations

FDA and EMA Expectations

The FDA's nasal spray guidance (2002, 2003) specifies extensive CQA documentation requirements including droplet size distribution (DSD), spray pattern, plume geometry, unit spray content uniformity, priming/repriming, and net content. Product-specific bioequivalence recommendations for intranasal generic drugs require in vitro equivalence testing for all these parameters [46]. The FDA's PAT initiative specifically encourages real-time monitoring and control for nasal drug manufacturing [47]. The EMA's Guideline on Pharmaceutical Quality of Inhalation and Nasal Products (EMEA/CHMP/QWP/49313/2005 Corr) specifies parallel requirements and explicitly aligns with ICH Q8, Q9, and Q10. The EMA's reflection paper on Design Space (EMA/CHMP/167068/2015) provides practical guidance on presenting Design Space data in regulatory dossiers, emphasizing robust multivariate DoE establishment [49]. For locally acting nasal generics, the EMA accepts in vitro pharmaceutical equivalence studies in lieu of in vivo BE studies under defined conditions [50].

Scale-Up and Manufacturing Challenges

Scale-up of QbD-optimized intranasal formulations from laboratory to pilot and commercial scale presents non-linear challenges, particularly for nanoparticulate systems where energy input per unit volume, heat transfer characteristics, and fluid dynamics differ substantially between equipment scales [31]. Equipment-specific DoE studies are often required at each scale, compounding development time and cost [22]. For spray-dried nasal powders, scale-up from laboratory to pilot to commercial spray dryers introduces differences in residence time, temperature gradients, and atomization characteristics requiring scale-up DoE studies [23]. The QbD Design Space concept is particularly valuable in scale-up, as process understanding developed at small scale when properly established can predict acceptable operating ranges at commercial scale [24]. PAT implementation at commercial scale including inline particle size measurement, NIR for content and moisture monitoring, and automated viscosity/pH measurement enables real-

time product quality assurance during scale-up and routine manufacturing [25].

Current Challenges and Limitations

Despite its significant advantages, QbD-based intranasal formulation development faces several ongoing challenges. Complex nasal physiology including three-dimensional turbinate architecture, nasal cycling (2–4 h alternating right/left congestion), rhinitis, polyps, and seasonal environmental variability creates inter-individual drug deposition variability difficult to capture within a standard Design Space. Advanced 3D-printed anatomical replica models and CFD simulations increasingly address deposition prediction, but inter-model variability across diverse patient populations limits utility. Inter-patient pharmacokinetic variability in nasal drug absorption is substantially greater than for intravenous routes; variability sources include nasal anatomy (turbinate hypertrophy, septal deviation), mucosal health, ciliary beat frequency, and user technique (spray head positioning, actuation force). Population pharmacokinetic (PopPK) modeling has been proposed to characterize this variability, but integration within standard QbD frameworks is not yet established [120]. Scale-up remains problematic especially for nanoparticulate systems; filling line variables, pump priming, and container sealing introduce quality variability at commercial scale not apparent in laboratory studies. Finally, the high initial cost of comprehensive risk assessment, multivariate DoE, advanced analytical characterization, and PAT implementation can be prohibitive for SMEs and academic research groups, limiting widespread QbD adoption.

Emerging Trends and Future Perspectives

AI-Assisted Formulation Development

Artificial intelligence (AI) and machine learning (ML) are transformative tools in pharmaceutical formulation development, augmenting QbD-based intranasal product development [24]. Supervised ML algorithms (ANN, SVM, random forest, gradient boosting) can model complex non-linear CMA/CPP-CQA relationships, potentially outperforming traditional polynomial RSM models for highly complex multivariate systems [25]. ANN-based QbD models for nasal nanoparticulate formulations have reported higher external validation accuracy than second-order RSM models (lower RMSE, higher R^2) [26]. Deep learning approaches (CNN for image-based nanoparticle characterization, RNN for time-series process data) are beginning to be explored for pharmaceutical QbD [27]. Generative AI models trained on large pharmaceutical formulation databases may propose novel compositions and process conditions within a QbD framework, significantly accelerating early-phase screening [28].

Digital Twins, Continuous Manufacturing, and Personalized Medicine

Digital twins virtual replicas of physical formulations, processes, or equipment continuously updated with real-time data enable predictive control and optimization of intranasal drug manufacturing [29]. Integration of CFD models of nasal airflow and drug deposition, physiologically-based pharmacokinetic (PBPK) models of nasal/CNS drug distribution, and real-time sensor data creates comprehensive virtual representations of the entire intranasal product lifecycle [30]. PBPK models specifically designed for nasal absorption incorporating mucosal permeability, mucociliary clearance, and olfactory transport parameters have been validated for predicting nasal/CNS pharmacokinetics with potential for integration within QbD Design Space establishment [31]. Continuous manufacturing (CM) offers consistent product quality, real-time quality assurance, reduced footprint, and enhanced production flexibility; integrated with QbD Design Spaces, CM enables dynamic process control within approved operating ranges, minimizing process drift and out-of-specification events [32,33]. Model predictive control (MPC) algorithms trained on process data and DoE-derived models can automatically adjust CM setpoints in response to measured variability [34]. Personalized intranasal medicines enabled by 3D printing (FDM, inkjet), microfluidics for on-demand nanoparticle/nanoemulsion preparation, and pharmacogenomic patient profiling represent the frontier of nasal drug delivery; QbD frameworks adapted for individual patient nasal anatomy, physiological state, and pharmacogenomics will be essential to ensure quality and safety of such personalized dosage forms [35,36].

Conclusion

Quality by Design has firmly established itself as an indispensable paradigm for the development of intranasal drug delivery systems. This review has systematically demonstrated that QbD elements-QTPP, CQAs, CMAs, CPPs, Design Space, and Control Strategy are effectively applied across the full spectrum of intranasal dosage forms, from simple nasal solutions to complex nanoparticulate systems. Risk assessment tools (Ishikawa, FMEA, Pareto) enable systematic prioritization of critical variables, while DoE strategies (BBD, CCD) with RSM optimization efficiently define robust Design Spaces. The application of QbD to nose-to-brain delivery demonstrated through detailed case studies for AD, PD, epilepsy, and migraine consistently yields superior nose-to-brain drug targeting efficiency (DTE% 198–312%) and improved pharmacokinetic profiles compared to conventional formulations. Regulatory alignment with FDA and EMA expectations further necessitates QbD-based development for modern intranasal drug products.

Persistent challenges including complex nasal physiology, inter-patient variability, scale-up non-linearities, and high development costs require ongoing methodological innovation. Emerging technologies including AI/ML-assisted formulation development, digital twins for process prediction, continuous manufacturing with real-time QbD control, and 3D-printed personalized nasal medicines hold transformative potential to address these challenges and expand the frontiers of QbD for intranasal drug

products. Continued interdisciplinary collaboration between formulation scientists, clinical pharmacologists, regulatory scientists, data scientists, and engineers will be essential to fully realize QbD's potential in delivering safe, effective, and high-quality intranasal medicines to diverse patient populations.

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