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DEVELOPMENT AND CHARACTERIZATION OF QUETIAPINE NANOEMULSION: A COMPREHENSIVE REVIEW OF FORMULATION STRATEGIES, CHARACTERIZATION TECHNIQUES, BRAIN TARGETING, AND THERAPEUTIC APPLICATIONS

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ABSTRACT

Quetiapine is an atypical antipsychotic used to treat schizophrenia, bipolar disorder, and major depressive disorder; however, its clinical effectiveness is limited by poor aqueous solubility, extensive first-pass metabolism, and low oral bioavailability. Nanoemulsion-based drug delivery systems have emerged as an effective approach to enhance quetiapine solubility, absorption, and brain delivery. Their nanoscale droplet size and high surface area facilitate improved drug permeation across the blood–brain barrier and may reduce systemic adverse effects. This review summarizes formulation strategies, including the selection of oils, surfactants, co-surfactants, and preparation methods, along with key characterization parameters such as droplet size, polydispersity index, zeta potential, drug loading, in vitro release, and stability. Recent advances in brain-targeted and intranasal nanoemulsions, pharmacokinetic and pharmacodynamic evaluation, therapeutic applications, and challenges in clinical translation are also discussed. Overall, quetiapine nanoemulsions represent a promising platform for improving the treatment of central nervous system disorders.

KEYWORDS: Quetiapine; Nanoemulsion; Brain targeting; Intranasal delivery; Blood–brain barrier; Drug delivery systems; Bioavailability; Characterization.

INTRODUCTION

Schizophrenia and bipolar spectrum disorders are chronic, relapsing neuropsychiatric conditions affecting an estimated 1% and 2–3% of the global population, respectively, and together represent a substantial component of the global burden of disease attributable to mental illness.[3,4] Pharmacotherapy with atypical (second-generation) antipsychotics remains the cornerstone of management, owing to a more favourable extrapyramidal side-effect profile relative to first-generation agents. Among these, quetiapine fumarate — a dibenzothiazepine derivative acting as an antagonist at dopamine D1/D2, serotonin 5-HT1A/5-HT2A, histamine H1, and adrenergic α1/α2 receptors — is one of the most widely prescribed atypical antipsychotics worldwide, approved for schizophrenia, acute mania associated with bipolar I disorder, bipolar depression, and as adjunctive therapy in major depressive disorder.[1,6]

Despite broad clinical utility, quetiapine is therapeutically constrained by unfavourable biopharmaceutical characteristics. Orally administered quetiapine undergoes extensive first-pass hepatic metabolism, predominantly via cytochrome P450 3A4 (CYP3A4), resulting in an absolute oral bioavailability of approximately 9%.[2,7] This necessitates relatively high oral doses (commonly 300–800 mg/day in maintenance therapy) and twice- or thrice-daily dosing regimens for immediate-release formulations, contributing to reduced patient adherence — a critical concern in a patient population already predisposed to poor treatment compliance due to cognitive impairment and reduced

illness insight characteristic of psychotic disorders.[8,9] Furthermore, even the fraction of drug surviving first-pass metabolism and entering systemic circulation must subsequently cross the blood-brain barrier (BBB) to exert central pharmacological activity, a process limited by P-glycoprotein-mediated efflux and the restrictive nature of BBB tight junctions.[10,11]

These combined pharmacokinetic obstacles — poor oral bioavailability and restricted BBB penetration — have driven research into alternative, non-oral delivery strategies capable of bypassing hepatic first-pass metabolism while enhancing direct CNS drug availability. Among emerging nanotechnology-based platforms, oil-in-water (o/w) nanoemulsions administered via the intranasal route have attracted considerable attention because the nasal mucosa, particularly the olfactory and trigeminal neuroepithelium, provides a direct anatomical conduit from the nasal cavity to the CNS that circumvents both hepatic metabolism and the BBB — the so-called "nose-to-brain" (N2B) pathway.[12,13] Nanoemulsions are thermodynamically or kinetically stabilized colloidal dispersions with globule sizes typically in the range of 20–200 nm, offering high solubilization capacity for lipophilic molecules such as quetiapine (logP ≈ 2.7–3.0), enhanced mucosal permeability, protection from enzymatic and chemical degradation, and the potential for sustained or targeted release when combined with mucoadhesive polymers.[14,15]

The earliest dedicated investigation of a quetiapine-loaded nanoemulsion for intranasal brain targeting was reported by Boche and Pokharkar in *AAPS PharmSciTech* (2017), who developed a Capmul MCM/Tween 80-based nanoemulsion (mean globule size 144 ± 0.5 nm) and demonstrated superior brain-targeting efficiency following intranasal administration relative to intravenous delivery in Wistar rats.[16,17] Closely related work by Shah, Khunt, Misra, and Padh examined quetiapine-loaded chitosan nanoparticles and mucoadhesive microemulsions for intranasal brain delivery, providing comparative pharmacokinetic and gamma-scintigraphic evidence supporting the N2B hypothesis.[18,19] More recent work published in the *Indian Journal of Pharmaceutical Sciences* (IJPS Online) has further explored ultrasonication-prepared quetiapine nanoemulsions using isopropyl myristate as the oil phase, again confirming enhanced brain drug concentration via the intranasal route relative to oral and intranasal free-drug controls.[20]

Notwithstanding this encouraging body of work, the literature base specific to quetiapine nanoemulsions remains comparatively limited relative to other CNS-active molecules (e.g., olanzapine, risperidone, duloxetine). A consolidated, critical synthesis of formulation strategy, characterization methodology, mechanistic rationale, and translational status has not previously been compiled. This review therefore aims to: (i) critically summarize the physicochemical and pharmacological rationale for nanoemulsion-based quetiapine delivery; (ii) systematically describe formulation components and preparation methods reported in the literature; (iii) detail QbD-based optimization and characterization techniques applied to these systems; (iv) mechanistically describe nose-to-brain transport and BBB interaction; (v) tabulate and critically compare published quetiapine nanoemulsion/ microemulsion/ nanoparticle studies, supplemented by closely analogous CNS nanoemulsion literature where necessary; (vi) assess the regulatory and patent landscape; and (vii) identify research gaps and future opportunities. Where direct quetiapine-specific evidence is unavailable for a given sub-topic, this review explicitly states so rather than extrapolating unsupported claims, consistent with rigorous scientific reporting standards.

Quetiapine: Physicochemical Properties

Quetiapine is marketed as its fumarate salt (quetiapine fumarate, QTF) to improve aqueous solubility and processability relative to the free base. Chemically, it is 2-.[2-(4-dibenzo.[b, f].[1,4] thiazepin-11-yl-1-piperazinyl) ethoxy] ethanol fumarate, with a dibenzothiazepine core substituted with a piperazinyl-ethoxyethanol side chain.[1,21] The molecule is a weakly basic, lipophilic compound classified under the Biopharmaceutics Classification System (BCS) as Class II (low solubility, high permeability) in its free-base form, although the fumarate salt exhibits pH-dependent solubility that is appreciably higher in acidic media than at physiological or alkaline pH.[21,22] This pH-dependent solubility profile is mechanistically important for nanoemulsion design, since the aqueous continuous phase, co-surfactant choice, and any pH-adjusting buffer can materially affect both drug solubilization and chemical stability of the formulation.

Quetiapine's moderate lipophilicity (logP reported in the range of 2.7–3.0) favours partitioning into the oil phase of an oil-in-water nanoemulsion and is consistent with the general principle that nanoemulsion technology is best suited to BCS Class II/IV lipophilic drugs requiring solubility enhancement.[14,23] The presence of an ionizable piperazine nitrogen renders the molecule susceptible to pH-dependent ionization, which affects its partitioning behaviour between oil and aqueous phases and its electrostatic interactions with anionic mucoadhesive polymers (e.g., carbopol, chitosan derivatives in protonated form) commonly co-formulated with nanoemulsions for nasal application.[18,24]

Physicochemical properties of Quetiapine (fumarate salt unless otherwise stated)

Property	Value / Description
Chemical class	Dibenzothiazepine derivative, atypical antipsychotic
Molecular formula (free base)	C21H25N3O2S
Molecular weight (fumarate salt)	≈ 883.1 g/mol (fumarate salt, 2:1)
logP (octanol/water)	≈ 2.7–3.0 (lipophilic)
BCS classification	Class II (low solubility, high permeability), free base
Aqueous solubility	pH-dependent; higher in acidic media, low at physiological/alkaline pH
pKa	Weakly basic; piperazine nitrogen ionizable
Oral bioavailability	≈ 9% (extensive first-pass hepatic metabolism)
Plasma protein binding	≈ 83%

These physicochemical attributes — moderate lipophilicity, BCS Class II behaviour, pH-dependent solubility, and extensive first-pass metabolism — collectively constitute the rational basis for selecting nanoemulsion technology, particularly via a non-oral (intranasal) route, as a delivery strategy for quetiapine.

Pharmacology of Quetiapine

Quetiapine exerts its antipsychotic and mood-stabilizing effects through a multi-receptor antagonist profile. It demonstrates moderate-to-high affinity antagonism at serotonin 5-HT2A and dopamine D2 receptors, a combination characteristic of atypical antipsychotics that is thought to underlie reduced extrapyramidal symptom liability compared with first-generation agents.[1,5] Additionally, quetiapine and its active metabolite norquetiapine exhibit affinity for 5-HT1A (partial agonism), histamine H1, and adrenergic α1/α2 receptors, contributing respectively to anxiolytic/antidepressant effects, sedation, and orthostatic hypotension.[1,6] Norquetiapine, formed via CYP3A4-mediated metabolism, has independent pharmacological activity, notably as a norepinephrine transporter inhibitor, which is believed to contribute to quetiapine's antidepressant efficacy in bipolar depression and adjunctive MDD use.[6,7]

Clinically, quetiapine is dosed in immediate-release (IR) and extended-release (XR) oral formulations. Due to its short elimination half-life (≈6–7 hours) and dose-dependent sedative/hypotensive effects, dose titration is required at treatment initiation, and steady-state plasma levels show considerable inter-individual variability attributable to variable first-pass metabolism and CYP3A4 polymorphism/drug-interaction susceptibility.[2,6,7] Because dopaminergic and serotonergic antipsychotic efficacy is governed by central receptor occupancy, the fraction of administered dose that ultimately achieves adequate brain concentration — rather than total systemic exposure — is the pharmacologically relevant determinant of therapeutic response, reinforcing the rationale for brain-targeted delivery strategies that maximize CNS drug availability per unit dose administered.[10,11]

Limitations of Conventional Quetiapine Dosage Forms

Conventional oral quetiapine tablets (IR and XR) are associated with several clinically significant limitations:

1. **Low and variable oral bioavailability (~9%)** due to extensive first-pass hepatic metabolism, requiring high doses to achieve therapeutic plasma concentrations.[2,7]
2. **Frequent dosing** for IR formulations (commonly twice or thrice daily), reducing adherence in a patient population frequently affected by cognitive impairment, anosognosia, or disorganized behaviour associated with psychotic illness.[8,9]
3. **Dose-dependent adverse effects** including sedation, weight gain, dyslipidaemia, and orthostatic hypotension, which are partly attributable to high systemic doses needed to compensate for poor bioavailability and partly to off-target receptor binding (H1, α1).[1,6]
4. **Delayed onset of central action**, since oral absorption, hepatic first-pass processing, and subsequent BBB crossing are sequential rate-limiting steps before therapeutic brain concentrations are achieved.[10,11]
5. **Inability to bypass the BBB**, meaning that even drug surviving hepatic metabolism is subject to P-glycoprotein-mediated efflux and restricted paracellular transport at the BBB, further reducing effective brain exposure relative to plasma concentration.[10,11]
6. **Risk of non-adherence-related relapse**, a well-documented concern in chronic antipsychotic therapy, which has independently motivated long-acting injectable antipsychotic development, though injectables carry their own limitations of invasiveness and injection-site reactions not further reviewed here.[9]

These limitations collectively underscore an unmet need for delivery technologies capable of improving brain-targeted bioavailability while reducing total systemic drug burden and dosing frequency.

Need for Nanoemulsion Drug Delivery

Nanoemulsion-based delivery directly addresses several of the limitations outlined above. By solubilizing lipophilic quetiapine within nanoscale oil globules

stabilized by surfactant/co-surfactant films, nanoemulsions can enhance apparent solubility and dissolution rate severalfold compared with free drug, as demonstrated experimentally (more than twofold increase in in vitro dissolution for an optimized quetiapine nanoemulsion relative to pure drug).[16,17] When administered intranasally rather than orally, nanoemulsions avoid hepatic first-pass metabolism entirely, since absorption occurs across nasal mucosa directly into systemic circulation and, more importantly, via direct olfactory/trigeminal neuronal and perivascular pathways into the CNS, bypassing the BBB.[12,13,20]

Compared with other nanocarrier platforms applied to quetiapine — namely chitosan-based polymeric nanoparticles and microemulsions — nanoemulsions offer comparatively simple, low-energy or moderate-energy manufacturing, thermodynamic/kinetic stability sufficient for pharmaceutical shelf life when properly formulated, ease of scale-up, and compatibility with mucoadhesive polymer incorporation to extend nasal mucosal residence time.[14,15,19] Comparative pharmacokinetic and gamma-scintigraphic data indicate that mucoadhesive microemulsion/nanoemulsion systems can outperform plain polymeric nanoparticle suspensions in brain-targeting efficiency, attributed partly to smaller, more uniform globule size facilitating transcellular and paracellular nasal mucosal transport and partly to tight-junction-modulating excipients such as chitosan.[18,19]

Fundamentals of Nanoemulsion

A nanoemulsion is a biphasic, optically translucent-to-transparent colloidal dispersion of two immiscible liquids (oil and water), stabilized by an interfacial film of surfactant(s) (and frequently co-surfactant), with droplet (globule) diameters generally cited in the range of 20–200 nm, distinguishing them from coarse (micron-scale) emulsions and from true thermodynamically stable microemulsions, though the precise boundary between nanoemulsions and microemulsions is debated in the literature and is sometimes drawn on the basis of formation mechanism (low-energy, spontaneous, thermodynamically stable for microemulsions, versus high-energy or low-energy kinetically stabilized for nanoemulsions) rather than size alone.[14,15,23] Nanoemulsions can be oil-in-water (o/w), water-in-oil (w/o), or multiple emulsions, with o/w systems being the predominant configuration for solubilizing lipophilic CNS-active drugs intended for intranasal administration, since the continuous aqueous phase is compatible with nasal mucosal physiology and facilitates dilution with nasal secretions without phase inversion.[15,16]

The small globule size confers a large interfacial surface area, enhancing drug dissolution rate, and the nanoscale dimension favours mucosal penetration, since particles below approximately 200 nm are generally considered to traverse mucus layers and nasal epithelium more efficiently than larger particulates, although mucus pore size and rheology vary regionally within the nasal cavity and are influenced by mucoadhesive polymer interactions.[12,13,24] Kinetic stability against Ostwald ripening and coalescence depends on appropriate surfactant film rigidity, oil-surfactant interfacial tension reduction, and globule size distribution narrowness (low polydispersity index, PDI).[14,15]

Components of Nanoemulsion

Oils

The oil phase serves as the primary solubilizing medium for lipophilic quetiapine and substantially influences globule size, drug loading capacity, and permeation-enhancing properties. Medium-chain triglycerides and mono/diglyceride esters such as Capmul MCM (caprylic/capric mono- and diglycerides) have been specifically employed in quetiapine nanoemulsion development due to favourable drug solubility and ability to form stable isotropic regions in pseudoternary phase diagrams with Tween 80.[16,17] Isopropyl myristate, an ester oil with established use in nasal and dermal nanoemulsion systems owing to its low viscosity and good skin/mucosal permeation-enhancing characteristics, has also been used as the oil phase for quetiapine nanoemulsion prepared by ultrasonication.[20] Selection criteria generally include maximal drug solubility in the oil, capacity to form a stable nanoemulsion region with selected surfactants (assessed via pseudoternary phase diagrams), low intrinsic toxicity/irritancy to nasal mucosa, and compatibility with regulatory-acceptable (GRAS or pharmacopoeial) status.[14,15]

Surfactants

Non-ionic surfactants are preferred for nasal nanoemulsion systems due to lower mucosal irritation potential relative to ionic surfactants. Tween 80 (polysorbate 80) is the most consistently reported surfactant in quetiapine nanoemulsion literature, used at the oil-water interface in combination with co-surfactants to achieve sufficiently low interfacial tension for nanoemulsion formation.[16,17,20] Tween 20 has also been used as part of the surfactant/co-surfactant mixture in ultrasonication-based quetiapine nanoemulsion preparation.[20] Surfactant selection is guided by hydrophilic-lipophilic balance (HLB) matching to the oil phase (HLB requirement typically in the range suited to o/w emulsification, generally HLB 10–18 for the overall surfactant blend), as well as by pseudoternary phase diagram construction to identify the isotropic nanoemulsion existence region.[14,16]

Co-surfactants

Co-surfactants reduce interfacial tension further, increase interfacial film flexibility, and expand the nanoemulsion existence region in phase diagrams. In quetiapine nanoemulsion development, Boche and Pokharkar systematically compared the effect of co-surfactants of differing HLB — Emalex LWIS 10, PEG 400, and Transcutol P — on the isotropic nanoemulsion region, finding that co-surfactant HLB significantly influenced phase behaviour and globule size.[16,17] Propylene glycol

has also been used as a co-surfactant component in ultrasonication-prepared quetiapine nanoemulsions.[20] Transcutol P (diethylene glycol monoethyl ether) is additionally recognized in the broader nasal nanoemulsion literature as a permeation enhancer with mucosal-penetration-promoting properties beyond its co-surfactant role.[16,24]

Aqueous phase

The aqueous (continuous) phase is typically purified/double-distilled water, sometimes buffered to a pH compatible with nasal mucosal physiology (nasal mucosal pH is approximately 5.5–6.5) and with quetiapine's pH-dependent solubility and stability profile.[16,21,24] Isotonicity adjustment (e.g., with mannitol or sodium chloride) and inclusion of mucoadhesive polymers (chitosan, carbopol) within or alongside the aqueous phase are reported strategies to extend nasal mucosal residence time and reduce mucociliary clearance of the formulation.[18,19,24]

Methods of Preparation

High-pressure homogenization (HPH)

HPH is a high-energy emulsification technique in which a coarse pre-emulsion is forced through a narrow orifice under high pressure (commonly 500–1500 bar), generating intense shear, cavitation, and turbulence that disrupt oil droplets into the nanometre range.[14,15] While widely used for nanoemulsion manufacture generally, dedicated peer-reviewed reports of HPH specifically applied to quetiapine nanoemulsion are limited in the literature surveyed for this review; most quetiapine-specific nanoemulsion studies identified employed phase-titration/spontaneous-emulsification or ultrasonication approaches rather than HPH.[16,17,20] HPH principles are nonetheless included here for completeness and comparative context, as the technique remains a standard reference method in nanoemulsion pharmaceutics generally.[14,15]

Ultrasonication

Ultrasonication uses high-frequency acoustic cavitation (typically 20–40 kHz) to disrupt a coarse emulsion into nanoscale globules via the implosive collapse of cavitation bubbles, which generates localized high-shear microstreaming. This method was specifically employed for quetiapine nanoemulsion preparation using water, Tween 20, and propylene glycol as the surfactant/co-surfactant mixture with isopropyl myristate as the oil phase, as reported in the IJPS Online study, in which the resulting nanoemulsion demonstrated enhanced brain drug concentration following intranasal administration in rat models relative to oral and intranasal free-drug controls.[20] Ultrasonication is generally regarded as suitable for small-batch/laboratory-scale nanoemulsion preparation, offering good control over globule size via adjustment of amplitude and sonication time, though batch-to-batch reproducibility and potential probe-tip metal contamination/drug degradation from localized heating are recognized limitations.[14,15]

Phase inversion methods

Phase inversion techniques (phase inversion temperature, PIT, and phase inversion composition, PIC) exploit changes in surfactant spontaneous curvature — induced by temperature change (PIT) or by progressive water addition (PIC) — to drive the system through a transient low-interfacial-tension state conducive to fine droplet formation, without requiring high-energy mechanical input.[14,15] Direct peer-reviewed evidence of phase inversion methodology applied specifically to quetiapine nanoemulsion was not identified in the literature surveyed for this review; this technique is described here on the basis of its established role in nanoemulsion pharmaceutics broadly and represents a plausible but currently unvalidated approach for quetiapine-specific development.[14,15]

Spontaneous emulsification (low-energy/phase titration method)

Spontaneous emulsification, including pseudoternary phase diagram-guided low-energy emulsification, relies on the diffusion of a water-miscible co-solvent/surfactant phase into the aqueous phase, generating interfacial turbulence that spontaneously produces fine droplets without significant mechanical energy input. This phase-titration approach, guided by construction of pseudoternary phase diagrams to map the isotropic nanoemulsion existence region as a function of oil: surfactant:co-surfactant:water ratios, was the method employed by Boche and Pokharkar in developing their quetiapine nanoemulsion (Capmul MCM/Tween 80/co-surfactant system), enabling systematic identification of the optimal composition yielding a 144 ± 0.5 nm globule size.[16,17] This approach is widely favoured in academic nanoemulsion research for its low energy requirement, reproducibility once the phase diagram is established, and amenability to QbD-based optimization.[14,16]

Quality by Design (QbD) Approach

Quality by Design is a systematic, risk-based pharmaceutical development framework — endorsed within ICH Q8(R2), Q9, and Q10 guidelines — that emphasizes building quality into the product through a predefined understanding of the relationship between Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), and Critical Quality Attributes (CQAs), rather than relying solely on end-product testing.[25,26] Application of QbD to nanoemulsion development typically begins with a risk assessment (e.g., Ishikawa/fishbone diagrams or failure mode and effects analysis, FMEA) to identify formulation and process variables likely to influence globule size, PDI, zeta potential, entrapment efficiency, and in vitro release, followed by systematic Design of Experiments (DoE) to quantitatively model these relationships and define a Design Space within which quality is assured.[25,26,27]

For quetiapine nanoemulsion specifically, Boche and Pokharkar's systematic evaluation of co-surfactant HLB effects on the isotropic nanoemulsion region exemplifies

a QbD-aligned formulation-screening approach, even though the original publication may not have used QbD terminology explicitly.[16,17] More broadly within the quetiapine intranasal nanocarrier literature, Shah, Khunt, Misra, and Padh explicitly applied Box-Behnken experimental design to optimize quetiapine-loaded chitosan nanoparticles for intranasal brain delivery, representing a directly relevant QbD precedent within the quetiapine CNS-delivery literature, even though that specific study concerns a polymeric nanoparticle rather than a nanoemulsion system.[18] This precedent strongly supports the applicability and expected benefit of formal QbD/DoE methodology for future quetiapine nanoemulsion optimization studies.

Characterization Techniques

Comprehensive physicochemical characterization is essential to establish the quality, stability, and biopharmaceutical performance of quetiapine nanoemulsions, and is expected under both academic peer-review standards and regulatory frameworks.

Particle (globule) size

Globule size is most commonly measured by dynamic light scattering (DLS, photon correlation spectroscopy). The optimized quetiapine nanoemulsion of Boche and Pokharkar exhibited a mean globule diameter of 144 ± 0.5 nm,[16,17] within the broadly accepted nanoemulsion size range and consistent with literature expectations for efficient nasal mucosal permeation.[12,13]

Polydispersity Index (PDI)

PDI, derived from DLS cumulant analysis, quantifies globule size distribution homogeneity, with values below approximately 0.3 generally regarded as indicating an acceptably narrow, monodisperse distribution suitable for pharmaceutical nanoemulsions.[14,15] Specific PDI values for the Boche and Pokharkar or IJPS Online quetiapine nanoemulsion formulations were not consistently reported in the source abstracts/summaries available for this review; where primary full-text PDI values cannot be independently verified, this review reports that evidence is limited rather than asserting a specific figure.

Zeta potential

Zeta potential, measured by electrophoretic light scattering, reflects the net surface charge of nanoemulsion globules and is a key predictor of colloidal (electrostatic) stability, with higher absolute values (conventionally $|\geq 30|$ mV, though lower values can suffice when steric stabilization from non-ionic surfactants dominates) associated with reduced aggregation tendency.[14,15] Non-ionic surfactant-stabilized nanoemulsions (e.g., Tween 80-based systems) often exhibit modest absolute zeta potential values because stabilization is predominantly steric rather than electrostatic; mucoadhesive cationic polymer incorporation (e.g., chitosan) can shift zeta potential toward more positive values, which is additionally advantageous for electrostatic interaction with the negatively charged nasal mucosal layer.[18,19]

Morphology (TEM/SEM)

Transmission electron microscopy (TEM) was used by Boche and Pokharkar to confirm the spherical morphology and nanoscale dimension of the optimized quetiapine nanoemulsion, corroborating DLS-derived size data.[16,17] TEM is generally preferred over scanning electron microscopy (SEM) for liquid nanoemulsion systems because of superior resolution at the relevant size scale and the ability to visualize internal globule structure following negative staining, whereas SEM is more commonly applied to solid or lyophilized nanoparticulate systems.[14,15]

Viscosity

Viscosity influences nasal residence time, ease of administration (e.g., via nasal spray device), and mucociliary clearance resistance. Low-viscosity nanoemulsions facilitate uniform droplet spray formation, while mucoadhesive polymer incorporation increases viscosity to prolong mucosal contact time; specific rheological data for quetiapine nanoemulsion formulations were not comprehensively available in the literature surveyed, and this remains an area where reporting in the primary quetiapine nanoemulsion literature is limited.[14,24]

pH

Formulation pH must be compatible with nasal mucosal physiology (approximately pH 5.5–6.5) to minimize irritation while remaining consistent with quetiapine's pH-dependent solubility and chemical stability.[21,24] Explicit pH measurement data for the primary quetiapine nanoemulsion studies were not consistently available in the sources reviewed.

Drug content

Drug content (assay) is typically determined by validated HPLC or UV-spectrophotometric methods, confirming that the labelled/intended drug concentration is accurately achieved and uniformly distributed within the nanoemulsion batch.[14,16]

Stability studies

Physical stability (resistance to creaming, coalescence, Ostwald ripening, and phase separation) and chemical stability (drug degradation) are assessed under ICH-aligned accelerated (e.g., 40°C/75% RH) and long-term storage conditions, as well as via centrifugation and freeze-thaw cycling stress tests, consistent with general nanoemulsion pharmaceutics practice.[14,15,26] Dedicated long-term (≥6 month) stability data specific to quetiapine nanoemulsion formulations were not identified in the literature surveyed for this review, representing a recognized data gap.

Regulatory Considerations (FDA, EMA, ICH)

Nanoemulsion-based intranasal drug products occupy a regulatory space governed both by general pharmaceutical quality guidelines and by nanotechnology-specific and route-specific (nasal) guidance. The **US FDA** evaluates nanomedicine products under existing drug regulatory pathways (typically New Drug Application, NDA, for a novel quetiapine nanoemulsion product, given quetiapine is an already-approved active ingredient via a different route/formulation, potentially via the 505(b) (2) pathway referencing existing quetiapine safety/efficacy data while requiring new data to support the novel nanoemulsion formulation and intranasal route), with attention to nanomaterial-specific characterization expectations articulated in FDA guidance for industry on nanotechnology-related drug products, including emphasis on particle size distribution control, reproducibility, and characterization of physicochemical attributes that may influence biodistribution.[25,30] The **EMA** similarly addresses nanomedicine quality, safety, and efficacy through reflection papers and guidelines emphasizing comprehensive physicochemical characterization, batch-to-batch reproducibility, and nanospecific pharmacokinetic/toxicological assessment, particularly given that nanoscale reformulation can alter the absorption, distribution, metabolism, and excretion (ADME) profile of an established active substance relative to its originally approved formulation.[25,30]

ICH guidelines relevant to quetiapine nanoemulsion development include ICH Q8(R2) (Pharmaceutical Development, underpinning QbD methodology as discussed in Section 9), ICH Q9 (Quality Risk Management, relevant to risk-based identification of CMAs/CPPs), ICH Q10 (Pharmaceutical Quality System), and ICH Q1A(R2)/Q1B (stability testing and photostability, relevant to the long-term and accelerated stability evaluation discussed in Section 11.11).[25,26] For a nasally administered product specifically, additional regulatory expectations relate to nasal spray/aerosol device performance characterization (e.g., droplet size distribution of the emitted spray plume, spray pattern, dose uniformity through container life), consistent with established FDA guidance for nasal spray and inhalation solution/suspension drug products, though such device-specific characterization was not reported in the quetiapine nanoemulsion studies surveyed for this review and represents an additional translational requirement prior to regulatory filing.[30]

Given the preclinical-only status of current quetiapine nanoemulsion evidence (Section 16), substantial additional nonclinical toxicology (nasal mucosal repeat-dose toxicity, systemic toxicology bridging studies), human pharmacokinetic bridging studies, and Chemistry, Manufacturing, and Controls (CMC) development (including formal QbD-derived design space, validated analytical methods, and demonstrated scale-up reproducibility) would be required before a regulatory filing for an intranasal quetiapine nanoemulsion product could reasonably be contemplated.[25,26,30]

Advantages of Quetiapine Nanoemulsion Delivery

Based on the evidence reviewed above, the principal advantages reported or reasonably inferable for quetiapine nanoemulsion delivery, particularly via the intranasal route, include:

7. Enhanced in vitro dissolution/apparent solubility of quetiapine (more than twofold increase reported relative to pure drug).[16,17]
8. Avoidance of hepatic first-pass metabolism via the nasal absorption route, addressing the central bioavailability limitation of oral quetiapine.[2,7,16]
9. Direct nose-to-brain transport bypassing the BBB, demonstrated via higher DTE%/DTP% and shorter brain Tmax relative to intravenous administration.[16,17]
10. Higher brain drug concentrations achieved with intranasal nanoemulsion compared with both oral and intranasal free-drug administration in rodent models.[20]
11. Non-invasive route of administration (compared with intravenous or intracerebroventricular delivery), with potential for improved patient acceptability and self-administration, though this has not been directly evaluated in human quetiapine studies.[12,13]
12. Compatibility with mucoadhesive polymer incorporation to further enhance nasal residence time and brain-targeting efficiency, as demonstrated in the closely related quetiapine mucoadhesive microemulsion system.[18,19]
13. Relatively simple, low-energy manufacturing achievable via spontaneous emulsification/phase titration or ultrasonication, potentially facilitating laboratory-to-pilot scale development.[14,16,20]

Limitations of Quetiapine Nanoemulsion Delivery

Notwithstanding the above advantages, important limitations and unresolved uncertainties remain

14. **Limited primary literature base**: only a small number of dedicated quetiapine nanoemulsion/ microemulsion/ nanoparticle studies have been published, restricting the strength of generalizable conclusions and necessitating cautious extrapolation from related nanocarrier systems.[16,17,18,19,20]
15. **Absence of human clinical data**: no quetiapine nanoemulsion clinical trial was identified; all evidence is preclinical (rodent).[16-20]
16. **Incomplete characterization reporting**: PDI, zeta potential, viscosity, pH, and long-term stability data were not consistently retrievable across the available primary literature sources for this review, limiting cross-study comparability.
17. **Mechanistic uncertainty regarding nanocarrier fate**: whether the nanoemulsion globule remains intact during neuronal/perineuronal transport, or whether drug is released at/near the nasal mucosal surface with subsequent free-drug transport, has not

been definitively established for quetiapine nanoemulsion systems specifically.[12]

18. **Interspecies translational uncertainty**: substantial differences in nasal/olfactory anatomy between rodents and humans complicate direct extrapolation of rodent DTE%/DTP% data to anticipated human brain-targeting efficiency.[12,13]
19. **Device and manufacturing scale-up challenges**: nasal spray device performance characterization and large-scale manufacturing reproducibility (particularly for high-energy methods such as HPH) have not been reported for quetiapine nanoemulsion systems.[14,30]
20. **Absence of dedicated pharmacodynamic/behavioural efficacy data**: enhanced brain drug concentration has been demonstrated, but direct confirmation of superior antipsychotic-like behavioural efficacy for quetiapine nanoemulsion has not been established.
21. **Nasal mucosal safety with repeated dosing**: comprehensive histopathological/ciliotoxicity data following repeated quetiapine nanoemulsion administration were not comprehensively available in the literature surveyed.

CONCLUSION

Quetiapine fumarate's clinical utility in schizophrenia, bipolar disorder, and adjunctive depression treatment is constrained by low oral bioavailability (~9%) secondary to extensive hepatic first-pass metabolism, compounded by restricted blood-brain barrier penetration that limits the efficiency with which systemically available drug reaches its central pharmacological targets. Nanoemulsion-based intranasal delivery, exploiting the direct nose-to-brain anatomical pathway, represents a mechanistically well-justified strategy to address both limitations simultaneously, and the limited but consistent body of available preclinical evidence — principally the work of Boche and Pokharkar, and the closely related quetiapine microemulsion/chitosan nanoparticle studies of Shah, Khunt, Misra, and Padh — demonstrates enhanced in vitro dissolution, favourable brain pharmacokinetics (shorter Tmax, higher DTE%/DTP%), and superior brain drug concentrations relative to oral and free-drug intranasal administration in rodent models. However, this evidence base remains preclinical, methodologically heterogeneous in characterization reporting, and has not yet incorporated formal QbD/DoE optimization, dedicated pharmacodynamic efficacy confirmation, comprehensive nasal mucosal safety evaluation, or any human clinical translation. Realizing the full therapeutic potential of quetiapine nanoemulsion technology will require systematic, standardized, QbD-driven formulation development; mechanistic clarification of nose-to-brain transport pathways specific to nanoemulsion vehicles; rigorous nonclinical safety and human pharmacokinetic bridging studies; and ultimately well-designed clinical trials. This review has sought to consolidate the current, verifiable evidence base while transparently identifying the substantial gaps that must be addressed before quetiapine nanoemulsion technology can progress from a promising preclinical concept to a clinically validated therapeutic platform.

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