Quality-by-Design-Based Mucoadhesive Intranasal Nanoemulsion of Lumateperone: A Review

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***Abstract*—Lumateperone is an oral antipsychotic approved for schizophrenia and bipolar depression. Intranasal nanoemulsions have been studied for several other antipsychotics as a way to reach the brain through the nose. This review asks whether a mucoadhesive intranasal nanoemulsion of lumateperone, developed by Quality by Design (QbD), is a reasonable next step. We read the abstracts of 45 papers on lumateperone pharmacology and clinical trials, nose-to-brain delivery, nanoemulsion science, mucoadhesive antipsychotic formulations and design of experiments. In animals, intranasal nanoemulsions of risperidone, paliperidone and quetiapine gave higher brain uptake or better behavioural effects than their comparators, and chitosan was the usual mucoadhesive agent. We found no lumateperone nanoformulation of any kind, no abstract that reports its solubility or lipophilicity, and no nasal study of the drug. We propose a QbD pathway with a target product profile, critical attributes, a Box-Behnken design and a set of in-vitro tests. The design is conceptual and no experimental data are reported.**

***Index Terms*—Lumateperone; intranasal nanoemulsion; mucoadhesion; chitosan; nose-to-brain delivery; Quality by Design; Box-Behnken design; schizophrenia**

I. INTRODUCTION

Schizophrenia and bipolar disorder are treated first with oral antipsychotics, but these drugs cause adverse reactions and adherence is often poor [1]. The blood-brain barrier also stops most drugs meant for the brain. Intranasal delivery with advanced carriers may place drug in the brain while keeping systemic exposure low [2]. The olfactory mucosa lies close to the central nervous system, so the nose offers a minimally invasive path that avoids the barrier [3].

Lumateperone is an oral drug described as a first-in-class selective and simultaneous modulator of serotonin, dopamine and glutamate [4]. It was approved in the USA in December 2019 for adults with schizophrenia and in December 2021 for bipolar depression [4,5]. We found no report of a lumateperone nanoformulation, nasal or otherwise.

A nanoemulsion is a surfactant-stabilised dispersion of one liquid in another, with droplets of tens to a few hundred nanometres [6,7]. For the nose, a mucoadhesive polymer such as chitosan can be added to slow clearance [8]. QbD adds a planned, statistical route to the formulation: the target product is defined first, and the factors that move its critical attributes are then studied by designed experiments [9].

This review asks what the literature supports for a QbD-developed mucoadhesive intranasal nanoemulsion of lumateperone, and where it is silent. We read abstracts only. The proposed design is conceptual.

II. LUMATEPERONE: PHARMACOLOGY, CLINICAL PROFILE AND FORMULATION QUESTIONS

Receptor profile and mechanism

Lumateperone is a tosylate salt that binds 5-HT2A, dopamine D2 and D1 receptors and the serotonin transporter [10]. One review reports high affinity for 5-HT2A, moderate affinity for D2 and low affinity for H1 and 5-HT2C receptors. It describes the drug as a presynaptic D2 agonist and a postsynaptic D2

antagonist, a profile linked to fewer extrapyramidal symptoms [11]. Another review describes partial D2 agonism together with effects on the dopamine transporter, NMDA receptor and serotonin transporter [12]. The reviews word the D2 action differently.
In drug-naive rats, lumateperone enhanced NMDA- and AMPA-receptor-mediated currents in the medial prefrontal cortex in a dopamine D1-dependent manner and increased dopamine and glutamate release. The authors state that translation to humans is not established [13]. A PET study in 10 patients with schizophrenia found a mean peak dorsal striatal D2 occupancy of 39% at 60 mg, one hour after dosing. The authors regard this as lower than most antipsychotics at efficacious doses [14].

Clinical profile
Table 1 lists the main clinical and analytical reports. A meta-analysis of seven randomised trials (2,480 participants) found a small benefit in bipolar depression (MADRS standardised mean difference -0.36, 95% CI -0.59 to -0.13) and a smaller, borderline one in schizophrenia (PANSS standardised mean difference -0.14, P = .051). Extrapyramidal symptoms did not differ significantly from placebo [15]. In a pooled analysis of 42 mg/day, the number needed to treat for a 20% PANSS reduction was 9 (95% CI 5-36), and the number needed to harm for somnolence or sedation was 8 [16].

A network meta-analysis of 12 trials (4,584 patients) compared lumateperone with cariprazine, asenapine and xanomeline-trospium. The lumateperone estimate for PANSS change did not reach significance, and the authors call for head-to-head trials [17]. A systematic review of four studies found placebo-level weight gain, metabolic change, prolactin rise, extrapyramidal symptoms and akathisia in short trials [18]. In bipolar depression, a post hoc analysis of 376 patients found improvement on all 10 MADRS items [19], a pooled analysis supported benefit in bipolar II disorder [20], and a further trial tested the drug added to lithium or valproate [21]. Reviews still ask for long-term data [12].

Formulation-relevant data that were not found
The abstract of the first-approval review gives no bioavailability, half-life or metabolism data [4]. No abstract that we read gave the aqueous solubility, lipophilicity or oral bioavailability of lumateperone. The case for a nanoemulsion therefore rests on an assumption that the drug is poorly soluble and cleared by first-pass metabolism. Both points must be tested before oils and surfactants are chosen. For comparison, quetiapine has an oral bioavailability of 9% because of first-pass metabolism, and an intranasal nanoemulsion raised its brain levels in rats [22].

Assay methods exist for biological samples. One HPLC-MS/MS method was validated for volumetric absorptive microsampling [23]. Another, a UPLC-MS/MS method for rat plasma, used 10 mM ammonium acetate buffer (pH 3.2) and acetonitrile (80:20) as mobile phase [24]. These support later pharmacokinetic work. A release or permeation assay for a nasal nanoemulsion would still need its own validation.

Table 1. Key lumateperone reports whose abstracts were read. Values are as stated by the authors; "none" means the abstract gives no numbers.

Report type	Population or system	Finding	Ref.
Review	Receptor pharmacology	High 5-HT2A, moderate D2, low H1 and 5-HT2C affinity; presynaptic D2 agonist and postsynaptic antagonist	[11]
Rat study	Medial prefrontal cortex	NMDA and AMPA currents enhanced in a D1-dependent way; dopamine and glutamate release increased	[13]
PET study	10 patients, 60 mg orally	Mean peak dorsal striatal D2 occupancy 39% at 1 h	[14]
Meta-analysis	7 trials, 2,480 participants	MADRS SMD -0.36 (bipolar depression); PANSS SMD -0.14, P = .051 (schizophrenia)	[15]

Report type	Population or system	Finding	Ref.
Pooled analysis	Schizophrenia, 42 mg/day	NNT 9 for 20% PANSS reduction; NNH 8 for somnolence or sedation	[16]
Network meta-analysis	12 trials, 4,584 patients	Lumateperone PANSS difference not significant; head-to-head trials requested	[17]
Systematic review	4 studies, short term	Placebo-level weight gain, metabolic change, prolactin, extrapyramidal symptoms	[18]
Post hoc and pooled analyses	Bipolar I and II depression	All 10 MADRS items improved (376 patients); bipolar II benefit in pooled trials	[19,20]
Analytical method	Rat plasma	UPLC-MS/MS; range 1.5-100 ng/mL for lumateperone tosylate; applied to an interaction study	[24]

III. NOSE-TO-BRAIN DELIVERY AND NANOEMULSIONS AS CARRIERS

Drug placed in the upper nasal cavity can reach the brain along the olfactory and trigeminal nerves and avoid first-pass metabolism [8,25]. Nanocarriers may improve the transfer [26]. The architecture and mucociliary clearance of the olfactory mucosa shape formulation design [3]. A review of biologics concludes that the route and the interaction of excipients with the drug and nasal physiology are not yet well understood [27]. Another review lists liposomes, polymeric and solid lipid nanoparticles, micelles, nanoemulsions and nanogels as carriers, and notes that surface modification can reduce nanoparticle toxicity to the nasal mucosa [28]. Figure 1 sets out the route and the nanoemulsion structure.

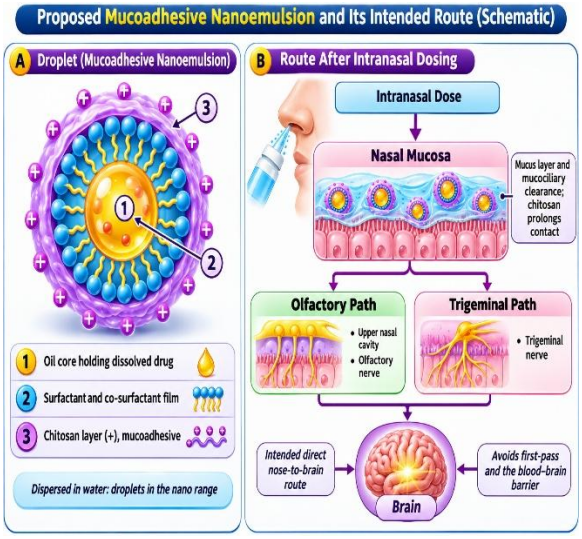


Figure 1. Schematic of the proposed system. Left, a mucoadhesive oil-in-water nanoemulsion droplet. Right, the intended route after intranasal dosing. The drawing is conceptual and not to scale; it shows no data.

Nanoemulsions are kinetically stable liquid-in-liquid dispersions with droplets of about 100 nm [6]. Another review gives a range of 20 to 500 nm [7]. For nasal use they are usually oil-in-water systems stabilised by surfactants, with droplets of 100 to 300 nm or less. The authors of that review conclude that nasal nanoemulsions appear effective, non-invasive and safe for poorly soluble, poorly bioavailable or enzyme-labile drugs [8]. A second review sorts the work by brain disorder and names three needs: the total dose reaching the target region, biodistribution studies and long-term toxicity studies [25]. A survey of more than 100 articles covers schizophrenia and depression and notes that hydrophilic and hydrophobic drugs may both use these paths [29].

Antipsychotics suit the format because many are lipophilic and hard to formulate at high strength. In one review, emulsions raised solubility by up to 4796-fold compared with water, and in animals they outperformed drug solutions or suspensions. The authors found no single composition to be clearly the best, given the many variables [30].

IV. MUCOADHESIVE AND ANTIPSYCHOTIC PRECEDENTS

The closest precedent is a risperidone study in rats. It compared a nanoemulsion, a mucoadhesive nanoemulsion and a solution. At 0.5 h the brain-to-

blood ratios were 0.617 (intranasal solution), 0.754 (intranasal nanoemulsion), 0.948 (intranasal mucoadhesive nanoemulsion) and 0.054 (intravenous nanoemulsion). The mucoadhesive version also had the highest drug transport efficiency and direct transport percentage [31]. Table 2 collects this and later precedents.

Paliperidone nanoemulsions have been made by phase-diagram screening [32] and by ultrasonication with a central composite design. In the latter, a chitosan-coated version gave higher brain AUC and Cmax in rats than the uncoated emulsion and a suspension, and did better in behavioural tests [33]. A quetiapine nanoemulsion gave higher brain levels and a longer brain half-life than oral or intranasal free drug [22]. A mucoadhesive quetiapine microemulsion with globules under 50 nm was compared with chitosan nanoparticles of 131 nm. It gave about 1.9-fold higher nasal bioavailability, which the authors link to the tight-junction action of chitosan and the small globules [34]. Chitosan nanoparticles of olanzapine raised absolute systemic bioavailability in rabbits to 51 +/- 11.2%, from 28 +/- 6.7% for the intranasal solution [35]. This is systemic absorption, not brain uptake.

Other carriers show the same direction. An aripiprazole nanostructured lipid carrier, optimised by a 3^2 factorial design, improved ex vivo nasal permeation and gave biphasic release over 72 h [36]. An olanzapine polymersome made with poloxamer 401 and optimised by a Box-Behnken design gave a 2.7-fold higher Cmax and a 5.7-fold higher AUC in rats than oral dosing [37]. An ion-triggered in situ gel holding a naringin nanoemulsion gave higher brain targeting efficiency in rats and no notable mucosal damage [38]. A chitosan review describes better brain delivery, with scalability still a problem [39].

The most recent precedent is an intranasal asenapine mucoadhesive nanoemulsion made by high-pressure homogenisation and optimised by a central composite design. It showed the highest inhibition of compulsive behaviour (72.24%) and locomotor activity (65.22%) among the formulations tested. Its abstract also reports that ex vivo permeation was higher for the non-mucoadhesive microemulsion and nanoemulsion than for the mucoadhesive version [40]. Mucoadhesion is therefore a trade-off to be measured and not assumed.

Table 2. Intranasal antipsychotic and related precedents from the abstracts read. Findings are as stated by the authors; no lumateperone study exists among them.

Drug	System and design	Main finding reported	Ref.
Risperidone	Nanoemulsion and mucoadhesive nanoemulsion; rats, scintigraphy	Brain-to-blood ratio at 0.5 h 0.948 for the mucoadhesive form, against 0.754 and 0.617 for the plain emulsion and solution	[31]
Paliperidone	Nanoemulsion; phase diagrams; ex vivo permeation	Globules 28.8-43.2 nm; Higuchi release; no ciliotoxicity; stable for 6 months at room temperature	[32]
Paliperidone	Chitosan-coated nanoemulsion; ultrasonication; central composite design	Higher brain AUC and Cmax than uncoated emulsion and suspension in rats	[33]
Quetiapine	Nanoemulsion; ultrasonication; rats	Higher brain levels and longer brain half-life than oral or intranasal free drug	[22]
Quetiapine	Mucoadhesive microemulsion and chitosan nanoparticles	About 1.9-fold higher nasal bioavailability for the microemulsion	[34]
Olanzapine	Polymersomes; Box-Behnken design	Intranasal Cmax 2.7-fold and AUC 5.7-fold higher than oral in rats	[37]
Asenapine	Mucoadhesive nanoemulsion; high-pressure homogenisation; central composite design	Highest inhibition of compulsive behaviour (72.24%); lower ex vivo permeation than non-mucoadhesive forms	[40]
Bilastine	Nanoemulsion; Box-Behnken design	Globules 129.1 nm; higher ex vivo permeation than the comparison formulation	[41]

V. PREPARATION, STABILISATION AND THE PROPOSED QBD PATHWAY

Preparation and stability

High-energy methods such as high-pressure homogenisation and ultrasonication, and low-energy methods such as phase inversion temperature and emulsion inversion point, are the usual routes to nanoemulsions [6]. The precedents used ultrasonication [22,33] or high-pressure homogenisation [40]. Paliperidone solubility was measured in oils, emulsifiers and co-emulsifiers, and phase diagrams located the nanoemulsion region [32]. Bilastine work used pseudo-ternary diagrams and thermodynamic stability tests [41], and asenapine work used ternary diagrams of Capmul MCM EP and Cremophor EL [40]. Lumateperone needs the same screening, and suitable excipients cannot be named without its solubility data.

Physical instability appears as creaming, flocculation, coalescence and Ostwald ripening [42]. Chitosan is the mucoadhesive agent of choice in the precedents because it slows nasal clearance [8,33].

A proposed QbD pathway

QbD uses statistical experimental design to optimise attributes such as particle size, zeta potential, polydispersity index (PDI), entrapment efficiency and release [9]. The nasal precedents used several designs. A central composite design served for paliperidone and asenapine [33,40]. A Box-Behnken design served for bilastine and olanzapine [37,41]. A 3^2 factorial design served for aripiprazole [36], a 2^3 factorial design for rivastigmine nanoparticles [43], and a mixture design for an aripiprazole nanoemulsion [44]. One study of rivastigmine carriers used a central composite design for formulation and then a Box-Behnken design to compare ultrasound with high-pressure homogenisation [45].

We propose the staged route in Figure 2. A Box-Behnken design needs fewer runs than a full three-level factorial and avoids the extreme corners of the factor space. Three factors would be studied, for example oil proportion, surfactant and co-surfactant proportion, and chitosan concentration. Their ranges would come from the solubility and phase-diagram work. Table 3 sets out the proposed elements. They are proposals and not results.

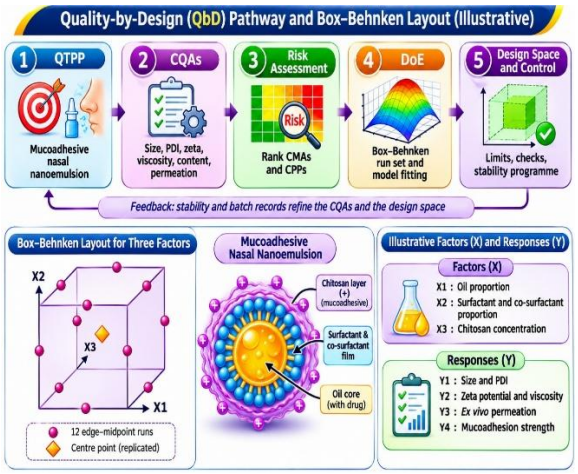


Figure 2. Illustrative QbD pathway (top) and a three-factor Box-Behnken layout (bottom). The factors and responses are examples drawn from the precedents and are not experimental results. QTPP, quality target product profile; CQA, critical quality attribute; CMA, critical material attribute; CPP, critical process parameter.

Table 3. Proposed QbD elements and in-vitro tests for the lumateperone nanoemulsion. All entries are proposals based on the precedents; no results are reported.

Element	Proposed entry	Basis in the literature	Ref.
QTPP	Mucoadhesive oil-in-water nanoemulsion of lumateperone for intranasal use; droplets in the nano range; tolerated by nasal tissue; stable on storage	Nasal nanoemulsions are oil-in-water systems of 100-300 nm or less; chitosan slows clearance	[8]
CMAs	Oil, surfactant and co-surfactant identity and grade; chitosan grade; drug solubility in each oil	Solubility screening and phase diagrams preceded every optimisation	[32,40]
CPPs	Energy method (ultrasonication or homogenisation), time or pressure, stirring speed	Instrument parameters were optimised as well as formulation variables	[41,45]

Element	Proposed entry	Basis in the literature	Ref.
DoE	Phase-diagram screening, then a three-factor Box-Behnken design with replicated centre points	Box-Behnken and central composite designs were used for nasal systems	[33,41]
Physical CQAs	Droplet size, PDI, zeta potential, transmittance, pH, viscosity, drug content, morphology	Reported for paliperidone and bilastine nanoemulsions; spherical on TEM	[32,41]
Release and permeation	In-vitro release with kinetic fitting; ex vivo flux across sheep or goat nasal mucosa	Higuchi and Korsmeyer-Peppas models; sheep and goat mucosa used	[38,40,41]
Safety tests	Ciliotoxicity on sheep nasal mucosa with positive and negative controls; cell viability	Treated tissue matched the negative control in a rivastigmine study; L929 cells used	[38,43]
Stability	Storage at several temperatures; watch for creaming, flocculation, coalescence, ripening	Instability mechanisms; storage studies reported	[42,45]
Assay	Validated chromatographic method for drug content and release samples	Methods exist only for biological samples	[23,24]

VI. CHARACTERISATION AND IN-VITRO EVALUATION

The precedents report droplet size, PDI, zeta potential, transmittance, pH, viscosity and drug content as the core physical set. Paliperidone nanoemulsions had globules of 28.8 to 43.2 nm, PDI of 0.129 to 0.152 and transmittance of 98.33 to 99.33% [32]. The bilastine nanoemulsion had globules of 129.1 +/- 5.97 nm, PDI of 0.214 +/- 0.045 and a zeta potential of +8.405 mV, and was spherical on electron microscopy [41]. These are reference points for other drugs, not targets for lumateperone.

Release data are usually fitted to kinetic models: Higuchi for paliperidone [32] and Korsmeyer-Peppas for asenapine [40]. The aripiprazole carrier fitted Fickian diffusion [36]. In the bilastine study, 24 h release was 82.74 +/- 5.78% against 49.91 +/- 3.48% for a conventional form [41]. Ex vivo permeation used sheep nasal mucosa for the naringin gel [38] and goat nasal mucosa for bilastine, where confocal imaging showed deeper penetration, about 35 um against about 15 um [41]. For paliperidone, the best nanoemulsion reached a flux of 5.072 +/- 0.13 ug/cm2/min, an enhancement ratio of 1.1 over drug solution [32].

Safety and stability tests carry equal weight for a drug used over months. A ciliotoxicity study on sheep nasal mucosa found treated tissue resembling the negative control, while the positive control showed damaged architecture [43]. The paliperidone nanoemulsion was free from ciliotoxicity and stable for 6 months at room temperature [32]. The naringin gel was biocompatible with L929 fibroblasts [38]. The rivastigmine carrier showed no significant change in its critical attributes over 90 days [45], and the aripiprazole carrier was more stable at 5 C than at higher temperatures [36].

In-vitro work cannot show brain targeting. Rat studies have used drug transport efficiency and direct transport percentage with scintigraphy [31], and gamma scintigraphy was also used for quetiapine [34]. The bilastine authors list spray performance, long-term stability and in vivo studies as still needed [41].

VII. GAPS AND CONCLUSION

We found no lumateperone nanoemulsion, nanoparticle or other non-oral formulation. We found no abstract that gives its aqueous solubility, lipophilicity or oral bioavailability, so the premise for a nanoemulsion is unconfirmed. We found no nasal or pre-clinical brain-uptake study of the drug. No abstract that we read gave the volume a nostril can hold, so dose volume and drug loading cannot yet be matched. No review of phase-diagram methods turned up; the diagrams appear only as applied tools [32,40,41]. Most precedents are rodent or rabbit studies, and some abstracts differ from their full texts, so we left out some numbers. Finally, the evidence on lumateperone itself is mainly short-term trials, and reviewers ask for longer data [12,18].

A mucoadhesive intranasal nanoemulsion of lumateperone is a reasonable but unproven idea. The risperidone, paliperidone, quetiapine and asenapine work supports the format, and chitosan has the strongest record as the mucoadhesive agent. The QbD tools are well described. The next steps are to measure the drug's solubility and lipophilicity, screen oils and surfactants, run the proposed design, and test the product for ciliotoxicity, permeation and stability. The design here is conceptual and awaits experimental testing.

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