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REVIEW ARTICLE

A Review on Self-Nanoemulsifying Drug Delivery Systems for Intranasal Administration

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Abstract: Poor aqueous solubility and extensive presystemic metabolism restrict the systemic availability and central nervous system accumulation of lipophilic therapeutics classified under the Biopharmaceutical Classification System as Class II and IV entities. Intranasal administration helps in bypassing the hepatic clearance while providing an anatomical route directly into the central nervous system via the olfactory and trigeminal neuronal routes. Self-nanoemulsifying drug delivery systems are isotropic blends of non-ionic surfactants, lipophilic cosurfactants, and structured glyceride oils that spontaneously generate oil-in-water nanoglobules upon contact with endogenous fluids. This can achieve sub-100-nanometer dispersion, protects labile active molecules from mucosal peptidases and cytochrome P450 isoenzymes, and modulates tight junction integrity across the respiratory and olfactory neuroepithelium. Physicochemical optimization depends on thermodynamic boundary mapping via pseudo-ternary phase equilibria and statistical response surface methodologies to evaluate globule diameter, polydispersity, zeta potential, and emulsification kinetics. The use of functional mucoadhesive polymers counteracts rapid nasal mucociliary clearance, prolonging retention against the mucosal epithelial lining. Evaluation of these systems include *ex vivo* transmucosal permeation kinetics across excised tissues, assessments of ciliotoxicity, and pharmacokinetic compartmental modeling of cerebrospinal fluid and brain parenchyma. Self-nanoemulsifying systems provide a non-invasive therapeutic conduit for managing neurodegenerative, psychiatric, and acute neurovascular conditions.

Keywords: Self-nanoemulsifying drug delivery systems; Intranasal delivery; Nose-to-brain targeting; Olfactory pathway; Bioavailability.

1. Introduction

The oral route is the most standard mode of pharmaceutical administration; however, approximately 70% to 90% of newly discovered chemical entities show suboptimal aqueous solubility [1]. Compounds categorized within Class II and Class IV of the Biopharmaceutical Classification System (BCS) exhibit poor oral absorption, aberrant pharmacokinetic variability, and insufficient clinical efficacy due to dissolution rate-limited bioavailability or low intestinal epithelial permeability [2]. Similarly, therapeutic agents targeting the central nervous system (CNS) encounter formidable systemic hurdles, notably high pre-systemic hepatic degradation by cytochrome P450 enzymes and extrusion by endothelial efflux transporters (such as P-glycoprotein) composing the blood-brain barrier (BBB) [3]. These anatomical barriers restrict therapeutic accumulation within cerebral target tissues, necessitating alternative non-invasive delivery pathways [4].

Intranasal administration represents a viable method to achieve systemic therapeutic absorption and direct nose-to-brain targeting [5]. The human nasal cavity presents a vascularized mucosal surface area of roughly 150 cm^2, facilitating rapid absorption into the venous circulation while circumventing first-pass hepatic metabolism [6]. Similarly, the neuroepithelium within the olfactory cleft and the branches of the trigeminal nerve innervating the respiratory mucosa establish an anatomical pathway that bypasses the hematogenous route and the restrictive endothelial junctions of the BBB [7].

Lipid-based formulations, particularly self-nanoemulsifying drug delivery systems (SNEDDS), address the solubility and permeation constraints inherent to lipophilic molecules [8]. SNEDDS are isotropic formulations comprising natural or synthetic oils, solid or liquid non-ionic surfactants, and one or more hydrophilic or lipophilic cosolvents or cosurfactants [9]. Upon introduction to aqueous nasal secretions under low shear, these preconcentrates spontaneously disperse into fine oil-in-water (o/w) nanoemulsions characterized by mean droplet diameters typically beneath 100 nm [10]. The resulting droplet architecture expands interfacial surface area, accelerates drug partitioning, preserves labile molecules from luminal enzymatic degradation, and reversibly alters the fluidity of epithelial phospholipid bilayers to enhance mucosal flux [11]. Figure 1 shows the comparative distribution pathways following intranasal administration, highlighting direct transport along the olfactory nerve bundles and trigeminal branches versus transmucosal systemic vascular uptake.

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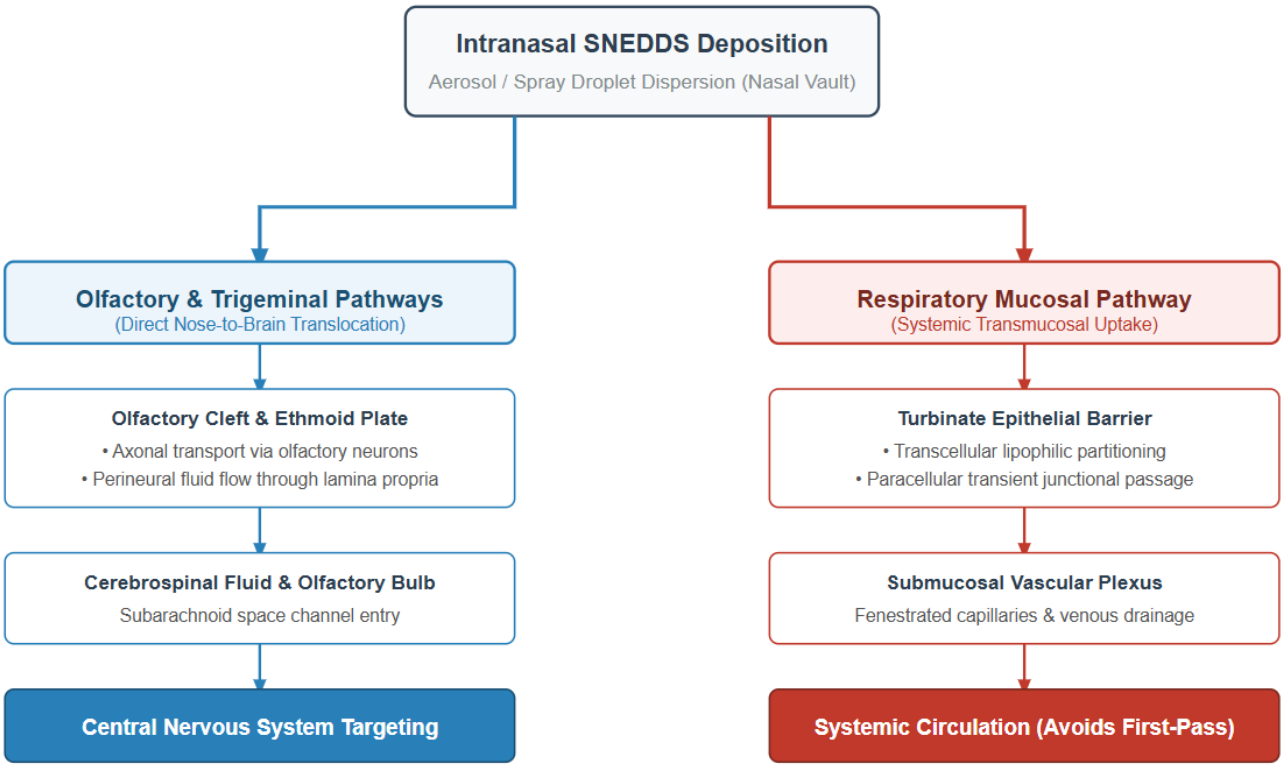

Figure 1. Nose-to-brain Translocation and the Comparative Systemic Uptake of Drugs from the Nasal Cavity

2. Composition of Intranasal SNEDDS

The development of intranasally administered SNEDDS requires an exacting selection of excipients to achieve spontaneous emulsification while maintaining biocompatibility with sensitive nasal mucosa.

2.1. Lipophilic Core and Oil Selection

The lipid phase solubilizes the therapeutic agent, determines drug loading efficiency, and establishes the core of the dispersed nanodroplets [12]. Lipids are structurally categorized into medium-chain triglycerides (MCT, C8–C12 fatty acid esters) and long-chain triglycerides (LCT, C14–C20 fatty acid esters), along with their corresponding mono- and diglyceride derivatives [13]. MCT derivatives, exemplified by glyceryl tricaprylate/caprate (Labrafac Lipophile WL 1349) and propylene glycol monocaprylate (Capryol 90), display higher solvent capacities for poorly water-soluble lipophilic drugs compared to LCTs such as soybean oil or castor oil [14]. The reduced hydrocarbon chain length decreases overall viscosity, reduces interfacial tension, and accelerates self-dispersion kinetics upon dilution with nasal fluid [15]. Additionally, mono- and diglycerides possess polar hydroxyl moieties that impart intrinsic surface-active properties, facilitating the spontaneous generation of sub-50 nm globules [16].

2.2. Non-Ionic Surfactants and Interfacial Mechanics

Surfactants lower the interfacial free energy between the immiscible lipid and aqueous domains, providing steric or electrostatic repulsion that prevents globule coalescence [17]. For mucosal applications, non-ionic surfactants are preferred over ionic variants due to their reduced propensity to cause histological irritation and epithelial cell lysis [18]. Polyoxyethylene sorbitan fatty acid esters (Polysorbate 20 and Polysorbate 80), polyoxyl hydrogenated castor oil derivatives (Kolliphor RH40, Kolliphor EL), and caprylocaproyl polyoxyl-8 glycerides (Labrasol) are extensively utilized [19]. Surfactants suitable for o/w nanoemulsion stabilization display hydrophilic-lipophilic balance (HLB) values exceeding 10 [20]. Beyond interfacial stabilization, high-HLB non-ionic surfactants transiently modulate tight junction proteins (e.g., claudins, occludins, and zonula occludens-1), fluidize epithelial membranes, and suppress apical efflux transporters such as P-glycoprotein, enhancing transmucosal permeation [21].

2.3. Cosurfactants and Cosolvents

Cosurfactants intercalate between the primary surfactant molecules at the nanodroplet boundary, introducing curvature flexibility to the interfacial film and reducing interfacial tension toward zero [22]. Short- to medium-chain polyols and glycol ethers, such as diethylene glycol monoethyl ether (Transcutol P), propylene glycol, and polyethylene glycol 400 (PEG 400), are commonly chosen

[23]. These cosolvents disrupt surfactant packing, enhance the mobility of the hydrocarbon tails, and accelerate phase inversion and emulsification [24]. Transcutol P acts as a classical permeation enhancer by solubilizing intercellular lipids within the epithelial matrix, facilitating passive paracellular and transcellular diffusion of dissolved drug molecules [25].

3. Thermodynamic Mechanisms of Spontaneous Self-Nanoemulsification

Self-nanoemulsification is governed by equilibrium thermodynamics and interfacial physical chemistry. The thermodynamic free energy change associated with dispersion is defined by the following expression:

$$\Delta G = \Delta A \cdot \gamma - T\Delta S$$

where ΔG represents the total Gibbs free energy of the system, ΔA is the expanded surface area resulting from nanoglobule generation, γ is the interfacial tension between the lipophilic core and the external aqueous continuous phase, T denotes absolute temperature in Kelvin, and ΔS corresponds to the change in system entropy [26].

Because the generation of billions of sub-micron droplets increases the interfacial area ΔA by several orders of magnitude, the term $\Delta A \cdot \gamma$ is inherently positive and energetically unfavorable [27]. In conventional macroemulsions, this positive energy penalty requires high mechanical input (such as high-pressure homogenization or microfluidization) to drive droplet breakup [28]. Conversely, in optimized SNEDDS compositions, the combination of high-affinity surfactants and penetrating cosurfactants lowers the equilibrium interfacial tension γ to values approaching or below 10^{-2} mN/m [29]. Under these circumstances, the energetic barrier defined by $\Delta A \cdot \gamma$ is drastically attenuated, allowing the positive entropic contribution ($T\Delta S$), which arises from the dispersion of independent nanoglobules throughout the medium, to exceed the interfacial work [30]. Consequently, ΔG becomes zero or negative, making dispersion spontaneous upon gentle hydration [31].

At the microscopic scale, rapid dispersion is driven by diffusion and stranding phenomena occurring at the phase interface [32]. When aqueous fluid meets the preconcentrate, water rapidly diffuses into the hydrophilic domains of the surfactant-cosurfactant matrix, generating localized liquid crystalline phases [33]. Continued water infiltration causes swelling and dynamic instability at the lipid boundaries, detaching swollen structures into the continuous phase as self-assembled nanoscopic oil cores surrounded by a continuous surfactant-cosurfactant shell [34].

4. Phase Equilibrium and Formulation Optimization

The identification of functional SNEDDS requires an accurate mapping of multi-component phase equilibria paired with statistical response surface methodologies.

4.1. Pseudo-Ternary Phase Equilibrium Mapping

Pseudo-ternary phase diagrams map the thermodynamic transitions that occur when oil, surfactant-cosurfactant mixtures (S_{mix}), and aqueous phases interact [35]. The surfactant and cosurfactant are blended at defined weight ratios (e.g., 1:1, 2:1, 3:1, and 4:1) to generate pseudo-components [36]. Pre-calculated mixtures of the selected lipid and S_{mix} covering ratios from 9:1 to 1:9 are systematically titrated with aqueous medium at physiological temperatures (37°C) under consistent, gentle agitation [37].

Phase transitions are tracked visually and verified via light scattering to demarcate isotropic, transparent or translucent regions with high transmittance (>95% at 638 nm) from biphasic, turbid macroemulsions or liquid crystalline mesophases [38]. The boundary lines define the nanoemulsification region. A broad nanoemulsion zone indicates a resilient formulation space that tolerates physiological aqueous dilution without precipitation or phase separation [39]. An optimal S_{mix} ratio (frequently observed at 2:1 or 3:1) supplies sufficient surfactant packing density to decrease interfacial tension while maintaining sufficient cosurfactant-driven interfacial flexibility [40].

4.2. Statistical Optimization via Quality by Design (QbD)

Modern formulation development uses statistical Design of Experiments (DoE) under Quality by Design paradigms to model non-linear interactions across formulation variables [41]. Response Surface Methodologies (RSM), including Central Composite Design (CCD) and Box-Behnken Design (BBD), evaluate critical formulation variables—such as the concentration of oil (X_1), concentration of surfactant (X_2), and ratio of surfactant to cosurfactant (X_3)—against Critical Quality Attributes (CQAs) [42].

The mathematical correlation linking independent variables and designated responses is typically fitted using a second-order polynomial model:

$$Y = \beta_0 + \sum_{i=1}^{k} \beta_i X_i + \sum_{i=1}^{k} \beta_{ii} X_i^2 + \sum_{i<j} \beta_{ij} X_i X_j + \varepsilon$$

where Y is the measured quantitative response, β_0 represents the intercept, β_i, β_{ii}, and β_{ij} are the linear, quadratic, and interaction regression coefficients respectively, X_i and X_j represent the coded independent variables, and ε is experimental residual error [43].

Primary response variables include mean hydrodynamic globule diameter (Y_1), polydispersity index (Y_2), self-emulsification time (Y_3), and cumulative percentage drug permeation across excised mucosal tissue at specific time intervals (Y_4) [44]. Analysis of Variance (ANOVA) validates the statistical models, confirming model significance via Fischer's F-test ($p < 0.05$), non-significant lack-of-fit parameters, and high coefficients of determination ($R^2 > 0.90$) [45].

Overlay plots delineate the sweet spot or design space, where all predefined criteria (e.g., globule size < 100 nm, PDI < 0.25, emulsification time < 60 seconds, permeation > 75%) are simultaneously satisfied [46]. Experimental validation is finalized using checkpoint formulations inside the design space, comparing experimental values with software-predicted outputs using percentage prediction bias:

$$\text{Bias (\%)} = \left| \frac{\text{Experimental Value} - \text{Predicted Value}}{\text{Predicted Value}} \right| \times 100$$

A bias below 5% confirms model accuracy and reproducibility [47].

5. Physiological Barriers to Intranasal Delivery and Nose-to-Brain Transport

Effective intranasal delivery requires navigating the physiological, enzymatic, and anatomical features of the nasal cavity.

5.1. Anatomical Characteristics and Mucociliary Movement

The nasal cavity possesses three distinct anatomical zones: the vestibular, respiratory, and olfactory regions [48]. The vestibular zone, situated adjacent to the anterior nares, is lined with stratified squamous epithelium and coarse vibrissae that trap airborne particulates, providing little utility for drug absorption [49].

The respiratory region comprises roughly 80% to 90% of total nasal surface area. It is lined by a pseudostratified ciliated columnar epithelium populated by ciliated cells, non-ciliated intermediate cells, basal cells, and mucus-secreting goblet cells [50]. The underlying lamina propria contains an extensive vascular capillary network supplied by the sphenopalatine and ethmoidal arteries, which enables rapid systemic absorption of lipophilic entities and facilitates fast therapeutic onset [51].

However, absorption across this respiratory surface is limited by the mucociliary clearance (MCC) mechanism [52]. Coordinated ciliary beating (10–15 Hz) propels the overlying mucus layer toward the nasopharynx at transit rates between 5 and 20 mm/min, sweeping foreign particulates, unformulated suspensions, and solutions into the gastrointestinal tract within 15 to 20 minutes [53]. Consequently, simple aqueous solutions experience limited residence times, curtailing the window available for trans-epithelial absorption [54].

5.2. Direct Pathways: The Olfactory and Trigeminal Axes

The olfactory region, located at the superior aspect of the nasal vault directly beneath the cribriform plate of the ethmoid bone, covers an area of approximately 10 to 15 cm^2 [55]. It is lined by a specialized neuroepithelium containing bipolar olfactory sensory neurons interspersed with sustentacular supporting cells, microvillar cells, and basal stem cells [56]. The apical dendritic knobs of the olfactory neurons terminate in non-motile cilia that project into the luminal mucus, while their non-myelinated basal axons coalesce into bundles (fila olfactoria) [57]. These axon bundles traverse the fenestrations of the cribriform plate to synapse directly within the olfactory bulb inside the cranial vault [58].

This structural orientation forms a direct anatomical conduit between the external environment and the central nervous system, circumventing the continuous capillary endothelial walls and astrocyte foot processes of the BBB [59]. Drug transport along the olfactory axis occurs via two main mechanisms as shown in Figure 2.

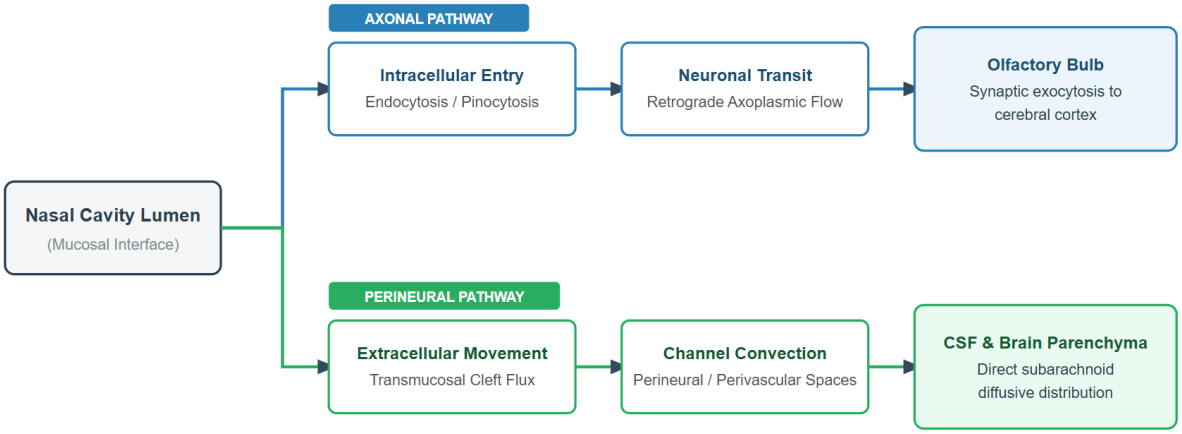

Figure 2. Direct Nose-To-Brain Translocation Routes

The intracellular axonal route involves endocytosis or pinocytosis at the apical dendritic process, followed by retrograde axoplasmic transport toward the olfactory bulb [60]. While selective, this pathway is slow, requiring hours to days for macromolecular transport [61]. Conversely, the extracellular paracellular pathway involves rapid fluid movement through the gaps between sustentacular cells and olfactory neurons, moving into the perineural channels continuous with the subarachnoid space [62].

Small lipophilic molecules and nanoglobules (<100 nm) leverage these perineural spaces to access the cerebrospinal fluid (CSF) and brain interstitial spaces within minutes [63]. A secondary direct route is mediated by the trigeminal nerve system, whose ophthalmic (V_1) and maxillary (V_2) branches innervate the respiratory and caudal olfactory epithelium [64]. Solutes enter the brainstem at the pons through perineural routes along trigeminal nerve fibers, dispersing throughout caudal and rostral brain regions [65].

5.3. Enzymatic and Permeability Barriers

In addition to physical clearance, drugs encounter an active enzymatic barrier within the nasal mucosa, colloquially termed the nasal metabolic sieve [66]. Luminal and intracellular environments possess high levels of cytochrome P450 isoenzymes (primarily CYP1A, CYP2E1, and CYP4A), aldehyde dehydrogenases, glutathione S-transferases, carboxylesterases, aminopeptidases, and endopeptidases [67]. Peptide-based structures and oxidizable drugs risk rapid presystemic cleavage prior to mucosal transit [68]. The paracellular transit of hydrophilic molecules is hindered by intercellular junctional complexes, including tight junctions (TJ), adherens junctions, and desmosomes, which hold apical intercellular spaces to widths below 1 nm [69].

6. Mucoadhesion and Surface Modulation

To overcome rapid mucociliary transport, SNEDDS can be modified into mucoadhesive nanoplatforms or structured as in situ gelling systems.

6.1. Polymeric Mucoadhesion

Incorporating functional polymers into the self-nanoemulsifying preconcentrate or external phase extends residence time along the nasal epithelium [70]. Chitosan, a linear polysaccharide obtained from the deacetylation of chitin, is used for this purpose [71]. Chitosan displays primary amine residues that protonate at physiological nasal pH ($\approx 5.5 - 6.5$), imparting a net positive charge [72]. These cationic motifs interact with negatively charged sialic acid and sulfate groups on mucosal mucin glycoproteins via electrostatic forces, hydrogen bonding, and polymer-chain interpenetration [73]. Beyond physical mucoadhesion, chitosan transiently reorganizes tight-junctional proteins such as zonula occludens-1, widening paracellular gaps without inducing irreversible mucosal damage [74]. Thiolated polymers (thiomers), synthesized via the covalent conjugation of thiol-bearing ligands (such as cysteine or thioglycolic acid) to polymeric backbones, further enhance interfacial adhesion [75]. Thiomers establish covalent disulfide bonds with cysteine-rich domains of mucin glycoproteins, generating stronger mucoadhesive bonds than non-covalent electrostatic interactions alone [76].

6.2. Temperature- and Ion-Triggered In Situ Gelling Systems

A practical challenge of liquid intranasal sprays is formulation runoff from the anterior nostrils or rapid posterior clearance into the pharynx [77]. In situ gelling SNEDDS remain free-flowing liquids at room temperature ($20 - 25°C$) to facilitate accurate spray atomization, but undergo rapid sol-to-gel transitions upon contact with nasal physiological conditions [78].

Thermosensitive systems frequently use poloxamers (e.g., Pluronic F-127 and F-68) [79]. At lower temperatures, poloxamer molecules exist as unassociated unimers in aqueous environments [80]. As temperature rises to physiological levels ($34 - 37$°C within the nasal vault), dehydration of hydrophobic polyoxypropylene blocks drives the spontaneous self-assembly of spherical micelles into ordered, closely packed cubic or hexagonal liquid crystalline lattices, converting the fluid into a rigid, non-flowing gel [81].

Ion-responsive platforms use polysaccharides such as gellan gum or sodium alginate [82]. Deacylated gellan gum undergoes conformational transitions from disordered coils into double helices in the presence of mono- and divalent cations (Na^+, K^+, Ca^{2+}) present in human nasal secretions (approximately 150 mM Na^+ and 4 mM Ca^{2+}), forming a crosslinked hydrogel network that traps the dispersed nanodroplets against the mucosal surface [83].

7. Characterization and Physicochemical Evaluation Matrix

The evaluation of intranasal SNEDDS requires assessing droplet physics, colloidal stability, and membrane transport kinetics. The physicochemical specifications, analytical testing protocols, and biological significance of the optimized nanocarriers are summarized in Table 1.

Table 1. Critical Quality Attributes, Analytical Characterization Methodologies, and Clinical Relevance for Intranasal Self-Nanoemulsifying Drug Delivery System

Parameter	Standard Target	Analytical Method	Clinical Application
Self-Emulsification Kinetics	<60 seconds	Visual endpoint tracking in simulated nasal fluid under low-shear mechanical rotation	Predicts *in vivo* dispersion rate upon contact with endogenous nasal secretions.
Hydrodynamic Droplet Diameter (z-average)	<100 nm (typically 20-80 nm)	Dynamic Light Scattering (DLS) / Photon Correlation Spectroscopy	Smaller globules cross perineural olfactory gaps more readily and resist rapid physical coalescence.
Polydispersity Index (PDI)	<0.25	Cumulant analysis of the DLS autocorrelation function	Low values indicate a narrow, monodisperse size distribution that ensures uniform drug diffusion.
Zeta Potential	Negative: ≤-20 mV Positive: ≥+20 mV	Laser Doppler Electrophoresis / Phase Analysis Light Scattering	High absolute surface charge prevents droplet aggregation via electrostatic repulsion; cationic surfaces promote mucoadhesion.
Droplet Morphology	Spherical, uniform borders, absent of micro-aggregation	Transmission Electron Microscopy (TEM) / Cryo-TEM	Confirms the physical integrity and nanoscale dimensions of dispersed oil droplets.
Thermodynamic Robustness	Absence of phase separation, drug precipitation, or creaming	Centrifugation (13,000×g for 30 min) and freeze-thaw thermal cycling (-20°C to +40°C)	Establishes the physical shelf stability of the preconcentrate across real-world temperature variations.
Nasal Mucosal Compatibility (pH)	5.5-6.5	Potentiometric glass-electrode evaluation	Prevents physiological irritation, ciliary stasis, and mucosal necrosis triggered by non-physiological pH extremes.
Kinematic Viscosity	Sprayable: $5 - 50$ mPas In situ gel: $>$ 1000 mPa · s	Cone-and-plate or rheometer shear profiling	Dictates the atomization pattern from standard nasal actuator devices and controls mucosal retention.
Transmucosal Flux (J_{ss})	Target-dependent (>1.5–3.0× increase over unformulated control)	*Ex vivo* Franz diffusion cells utilizing excised nasal respiratory/olfactory tissues	Quantifies the rate of drug transfer per unit area across the epithelial barrier.
Ciliotoxicity Profile	Ciliary beat frequency maintained at >90% of control	Ex vivo microscopy of excised ciliated tissue or in vitro RPMI 2650 cell survival assays	Confirms the safety of formulation excipients on healthy mucosal clearance mechanisms.

8. Preclinical Applications

Intranasal SNEDDS have shown utility across neurodegenerative conditions, psychiatric illnesses, and acute neurovascular emergencies. The clinical and preclinical application spectrum of intranasally delivered nanoemulsions across varying neuropathological conditions is categorized in Figure 3.

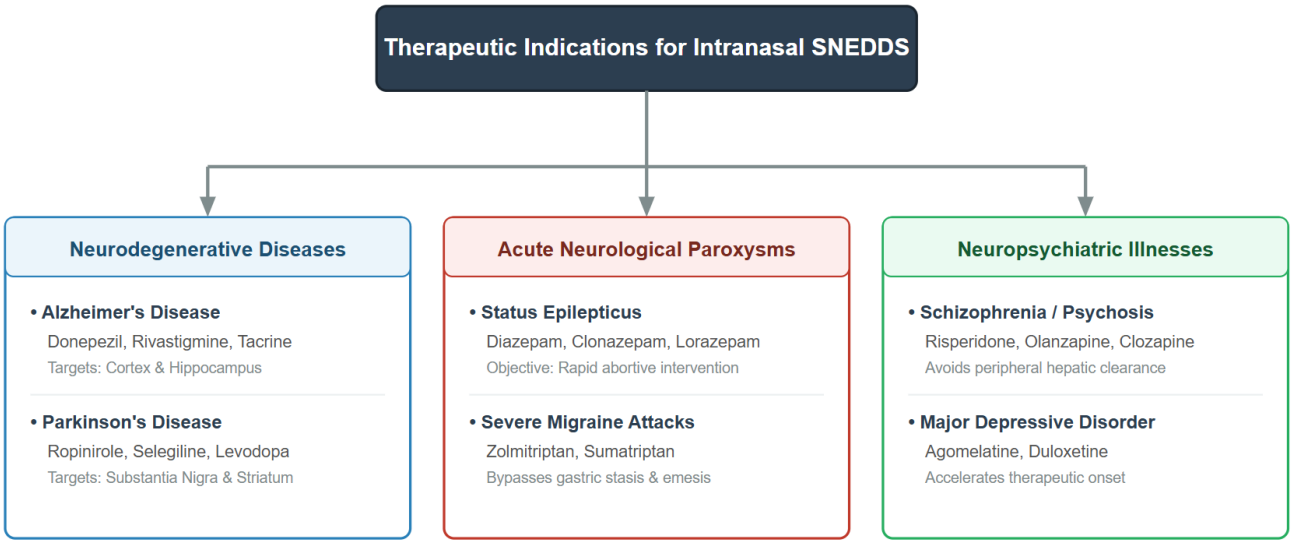

Figure 3. Classification of Preclinical and Translational Applications of Intranasal Self-Nanoemulsifying Drug Delivery Systems

8.1. Neurodegenerative Disorders: Alzheimer's and Parkinson's Disease

Targeting progressive neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease via traditional oral therapy is hindered by low BBB permeability and gastrointestinal side effects [84]. Cholinesterase inhibitors (e.g., donepezil, rivastigmine) and dopamine receptor agonists (e.g., ropinirole) suffer from high systemic clearance [85]. Administering these agents via intranasal SNEDDS concentrates therapeutics within the hippocampus, frontal cortex, and striatum [86]. Preclinical animal models have showed that nanoemulsified ropinirole and selegiline yield higher drug targeting efficiency (DTE%) and direct transport percentage (DTP%) values relative to intravenous controls [87]. This improves motor and cognitive scores in behavioral tests while avoiding high systemic drug exposures that contribute to peripheral cardiac and gastrointestinal adverse events [88].

8.2. Acute Neurological Paroxysms: Status Epilepticus and Migraine

In acute status epilepticus and severe migraine, rapid therapeutic drug onset is critical [89]. Oral absorption is often delayed or compromised by postictal states, altered gastric motility, or acute nausea and vomiting [90]. Lipophilic anticonvulsants (diazepam, lorazepam, clonazepam) and selective serotonin 5-$HT_{1B/1D}$ receptor agonists (zolmitriptan, sumatriptan) formulated as intranasal SNEDDS undergo rapid transmucosal uptake, matching intravenous pharmacokinetic onset profiles ($T_{max} < 10$ minutes) [91]. Bypassing the hepatic bed prevents extensive first-pass glucuronidation and demethylation, maintaining active drug fractions at lower administrative doses [92].

8.3. Neuropsychiatric Illnesses: Antipsychotics and Anxiolytics

The clinical management of schizophrenia, major depressive disorders, and acute agitation often requires ongoing therapy with lipophilic neuroleptics, including risperidone, olanzapine, and clozapine [93]. When administered orally, these compounds encounter substantial metabolism by hepatic CYP2D6 and CYP3A4 enzymes, yielding unpredictable circulating concentrations and variable CNS penetrance [94]. Formulating these lipophilic agents into intranasal SNEDDS allows direct uptake into the brain via olfactory and trigeminal tracks, increasing bioaccumulation within the limbic regions and prefrontal cortex [95]. Consequently, equivalent neuropharmacological efficacy can be attained with lower aggregate dosing, minimizing peripheral metabolic side effects such as extrapyramidal symptoms, weight gain, and cardiovascular changes [96].

9. Conclusion

Intranasal administration of self-nanoemulsifying drug delivery systems provides a viable route to resolve solubility, metabolic, and biological barrier limitations for poorly water-soluble therapeutics. The use of medium-chain glycerides, non-ionic surfactants, and penetrating cosurfactants yields nanoscopic, thermodynamically stable dispersions that accelerate mucosal transfer and enable direct transport into the brain parenchyma through olfactory and trigeminal nerve pathways. Adapting Quality by Design methodologies and pseudo-ternary equilibrium tracking ensures precise control over droplet physics, emulsification kinetics, and mucosal permeation. Combining these systems with functional mucoadhesive polymers or in situ gelling matrices effectively mitigates rapid mucociliary clearance, extending functional residence times along the nasal neuroepithelium. The continued translation of intranasal SNEDDS from preclinical models to clinical practice will depend on evaluating chronic mucosal tolerability, ensuring batch-to-batch structural uniformity, and engineering precise multi-dose nasal delivery devices.

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