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Intranasal Nanoemulsions for Direct Nose-to-Brain Drug Delivery in Alzheimer 's Disease: Bypassing the Blood-Brain Barrier

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ABSTRACT

Alzheimer's disease (AD) stands as one of the most complex, progressive, and neurodegenerative disorders worldwide, primarily characterized by cognitive decline, memory impairment, and the accumulation of amyloid-beta plaques and neurofibrillary tangles. A predominant obstacle in treating AD is the presence of the blood-brain barrier (BBB), which restricts more than 98% of small-molecule drugs and nearly all large-molecule biopharmaceuticals from entering the central nervous system (CNS). Intranasal administration has emerged as a groundbreaking, non-invasive route that directly links the nasal cavity to the brain parenchyma via olfactory and trigeminal nerve pathways, effectively bypassing the BBB. Among various colloidal nanocarriers, nanoemulsions have gained substantial attention due to their unique properties, including thermodynamic stability, ease of scale-up, small droplet size (typically 20–200 nm), and a highly lipophilic inner core capable of solubilizing poorly water-soluble anti-Alzheimer molecules. This review article comprehensively examines the physiological architecture of the nasal mucosa, the exact mechanisms governing direct nose-to-brain targeted macromolecular transport, and the technological advancement of nanoemulsion formulations. We delve deeply into the selection parameters for biocompatible oils, surfactants, and co-surfactants, characterization methodologies, and preclinical therapeutic outcomes. Furthermore, current safety guidelines, regulatory boundaries, functional biological barriers, and upcoming future perspectives regarding human translation are critically discussed to provide a robust blueprint for advanced neurological drug development.

Keywords: Alzheimer’s Disease; Intranasal Drug Delivery; Nanoemulsions; Blood-Brain Barrier (BBB); Nose-to-Brain Transport; Olfactory Pathway; Trigeminal Nerve; Neurotherapeutics; Colloidal Nanocarriers; Mucoadhesion; Brain Targeting Efficiency.

1. Introduction

The escalation of neurodegenerative diseases presents a profound socioeconomic and healthcare challenge to global modern society. Alzheimer's disease (AD) is an irreversible, progressive brain disorder that slowly destroys memory, cognitive aptitudes, and, eventually, the ability to execute the simplest daily tasks [1]. Pathologically, the disease is marked by extracellular senile plaques composed of amyloid-beta (Aβ) peptides and intracellular neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau proteins [2]. These pathological hallmarks induce severe synaptic dysfunction, neuroinflammation, and widespread neuronal apoptosis within critical memory-processing centers like the hippocampus and cerebral cortex [3]. Despite decades of rigorous academic research, clinical interventions remain largely symptomatic, failing to stop or reverse underlying neuronal degeneration [4]. Current pharmaceutical strategies face monumental pharmacokinetic limitations, primarily revolving around poor oral bioavailability, systemic enzymatic degradation, extensive first-pass hepatic metabolism, and, most importantly, restricted transport across biological membranes [5].

The core bottleneck preventing therapeutic molecules from achieving therapeutic concentration profiles inside the brain parenchyma is the highly selective Blood-Brain Barrier (BBB) [6]. The BBB acts as a metabolic and physical sentinel, defending the central nervous system against circulating xenobiotics, toxins, and peripheral fluctuations, while paradoxically barring vital neuroprotective agents [7]. To deliver compounds across the BBB, conventional systems often necessitate invasive neurosurgical procedures, such as intracerebroventricular injections or convection-enhanced delivery, which present significant risks of infection, tissue trauma, and high hospitalization costs [8]. Consequently, non-invasive alternative routes that can securely transport molecules directly into the brain have become a focal point of contemporary pharmaceutical formulation engineering [9]. The nasal route, traditionally

utilized for local decongestants or systemic delivery of small peptides, has recently been revolutionized into a target pathway for neurological therapies via the direct nose-to-brain delivery mechanism [10].

By depositing therapeutics high within the nasal cavity, specifically targeting the olfactory neuroepithelium and respiratory zones, drugs can access the brain within minutes, avoiding systemic circulation and hepatic clearance [11]. However, unmodified drug molecules face rapid mucociliary clearance, enzymatic degradation by local nasal peptidases, and poor mucosal permeation across the tight nasal epithelial layers [12]. To resolve these limitations, nanotechnology-driven colloidal vehicles, particularly nanoemulsions, are being implemented [13]. Nanoemulsions are submicron, thermodynamically or kinetically stable isotropic dispersions consisting of an oily phase, an aqueous phase, and a precisely structured surfactant/co-surfactant monolayer [14]. Their extremely small globule dimension maximizes the surface contact area with the mucosal membrane, prolongs residence times, shields encapsulated drugs from enzymatic attack, and enhances cellular endocytosis [15]. This review addresses the critical intersection of nanoemulsion technology and neurotherapeutic delivery, outlining formulation strategies, functional anatomy, and mechanisms to pioneer a safe, non-invasive paradigm shift in Alzheimer's therapy [16].

2. Alzheimer’s Disease

Alzheimer's disease possesses a multifactorial etiology that extends far beyond simple peptide accumulation [17]. The amyloid cascade hypothesis states that the imbalance between Aβ production and clearance triggers a cascade of pathological events leading to synaptic loss [18]. Aβ peptides are generated through sequential proteolytic cleavage of the amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase complexes [19]. The resulting Aβ42 isoforms are highly hydrophobic and prone to self-assembly into soluble oligomers, which are acknowledged as the primary neurotoxic entities before aggregating into insoluble fibrillar structures [20]. These oligomers bind to synaptic receptors, disrupting long-term potentiation, inducing calcium dysregulation, and initiating mitochondrial failure [21]. Concurrently, hyperphosphorylated tau proteins detach from axonal microtubules, aggregating into helical filaments that impair axonal transport, disrupting neuronal structural integrity and functional connectivity [22].

Neuroinflammation further accelerates AD progression, governed by chronically activated microglia and reactive astrocytes [23]. When microglia fail to clear Aβ aggregates, they release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and reactive oxygen species (ROS), which create a chronic state of oxidative stress [24]. This sustained cytotoxic microenvironment damages surrounding healthy neurons, worsening cognitive decline [25]. Furthermore, the cholinergic hypothesis highlights a profound loss of cholinergic neurons within the basal forebrain, resulting in a severe deficit in acetylcholine (ACh), a neurotransmitter critical for memory encoding and processing [26]. Standard therapeutics like acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) and NMDA receptor antagonists (memantine) merely alleviate symptoms temporary without halting progressive structural atrophy [27]. Effective treatments require novel agents—such as gene silencers, neurotrophic factors, and anti-aggregates—that can penetrate the brain in sufficient quantities to exert disease-modifying effects [28].

Clinical diagnosis of AD is often established late, when substantial neuronal loss has already occurred in the entorhinal cortex and hippocampus [29]. Advanced therapeutic approaches aim to target the disease at prodromal or mild cognitive impairment (MCI) stages [30]. Delivering novel disease-modifying compounds, including highly lipophilic molecules, natural polyphenols (curcumin, resveratrol), and macromolecular biological drugs, remains difficult due to their poor solubility and lack of specific transport mechanisms across peripheral physiological barriers [31]. Consequently, developing advanced nanomedicines that can transport these diverse therapeutic classes directly into specialized cerebral niches is vital for future clinical success [32].

3. Blood-Brain Barrier

The blood-brain barrier (BBB) represents a unique structural and functional physiological interface between the cerebral microvasculature and the neural tissue [33]. Structurally, the BBB is composed of continuous non-fenestrated brain capillary endothelial cells (BCECs), surrounded by a continuous basal lamina, pericytes embedded within the basement membrane, and astrocytic end-feet that wrap around the capillaries to provide cellular signals required for barrier maintenance [34]. The physical restriction is maintained by an intricate network of tight junctions (TJs) and adherens junctions (AJs) connecting adjacent endothelial membranes [35]. Tight junctions are composed of transmembrane proteins, including claudins (specifically claudin-5), occludin, and junctional adhesion molecules (JAMs), which are anchored to the actin cytoskeleton via intracellular scaffold proteins like zonula occludens-1, 2, and 3 (ZO-1, ZO-2, ZO-3) [36]. This complex layout results in an exceptionally high electrical resistance (>1500 $\Omega \cdot cm^2$), minimizing paracellular diffusion of solutes [37].

In addition to a physical barrier, the BBB functions as a biochemical and metabolic wall [38]. Endothelial cells express high levels of ectonucleotidases, monoamine oxidases, and peptidases that metabolize neuroactive compounds before they traverse the cytoplasm [39]. Furthermore, the BBB is equipped with active efflux transporters belonging to the ATP-Binding Cassette (ABC) superfamily, including P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), and Multidrug Resistance-Associated Proteins (MRPs) [40]. These efflux pumps utilize ATP hydrolysis to pump out lipophilic therapeutic agents that have successfully diffused across the endothelial cell membrane, severely limiting central drug retention [41]. While small, uncharged lipophilic molecules with a molecular weight under 400–500 Da can theoretically cross the BBB via passive transcellular diffusion, many are immediate substrates for these ABC efflux transporters [42].

Endogenous nutrients, such as glucose, amino acids, and iron, cross the BBB via specialized transcellular routes: Carrier-Mediated Transport (CMT) or

Receptor-Mediated Endocytosis (RME), involving transferrin or insulin receptors [43]. Although researchers have attempted to target these endogenous transport systems by functionalizing nanocarriers with specific targeting ligands, issues such as receptor saturation, off-target peripheral binding, ligand displacement by endogenous substrates, and complex chemical conjugation techniques limit their translational utility [44]. This highlights the need for an alternative route, such as the intranasal pathway, which completely bypasses the vascular architecture of the BBB to deliver therapeutics directly to neural tissues [45]. By avoiding systemic blood circulation entirely, intranasal delivery avoids both the restrictive tight junctions and the active endothelial efflux pumps, allowing a higher fraction of administered drug to reach the brain parenchyma safely [46].

4. Intranasal Nose-to-Brain Drug Delivery

The nasal cavity provides a unique entry point for direct drug delivery to the central nervous system, avoiding the systemic circulation and the blood-brain barrier [47]. The total surface area of the human nasal cavity is approximately 150 cm^2, lined by a highly vascularized mucosal membrane that is anatomically divided into three principal regions: vestibular, respiratory, and olfactory [48]. The vestibular region, located at the anterior nasal opening, is lined by stratified squamous epithelium containing nasal hairs, offering minimal drug absorption potential [49]. The respiratory region is the largest, accounting for roughly 80–90% of the total nasal cavity surface area, and is lined by a pseudostratified ciliated columnar epithelium [50]. This region is highly vascularized by branches of the ophthalmic and maxillary arteries, making it ideal for absorbing drugs intended for systemic circulation, though it can also facilitate direct brain delivery via the systemic absorption and subsequent transport loop [51].

The olfactory region, located at the superior roof of the nasal cavity, is the most crucial zone for direct nose-to-brain targeting [52]. It occupies about 10% of the human nasal mucosa (approximately 10–15 cm^2) and is lined by a specialized neuroepithelium [53]. This epithelium contains primary olfactory receptor neurons (ORNs), supporting sustentacular cells, and basal stem cells [54]. The non-myelinated axons of these ORNs pass through the cribriform plate of the ethmoid bone to terminate in the olfactory bulb of the brain [55]. Crucially, these neurons are continually replaced throughout adult life, creating transient gaps in the epithelial barrier as mature neurons degenerate and newborn neurons integrate [56]. This structural dynamic offers a unique opportunity for large macromolecules, colloidal nanoparticles, and complex lipophilic assemblies to penetrate the mucosal layer and access the lamina propria, where they can enter perineural or perivascular spaces and quickly travel to the brain [57].

Beyond the olfactory nerve pathway, the trigeminal nerve system provides an additional parallel route for nose-to-brain delivery [58]. The trigeminal nerve innervates both the respiratory and olfactory mucosa through its ophthalmic (V1) and maxillary (V2) branches [59]. The axons of these nerve segments enter the brainstem at the level of the pons, providing a direct anatomical link to posterior brain structures, including the pons, medulla, and cerebellum [60]. Consequently, intranasal administration can deliver therapeutics to both anterior cerebral regions via the olfactory pathway and posterior cerebral regions via the trigeminal nerve matrix [61]. This dual-neuroanatomical delivery system operates via multiple mechanism pathways, allowing a broad range of drug classes to achieve therapeutically relevant concentrations within the CNS [62].

5. Nanoemulsions Overview

Nanoemulsions have emerged as a premier class of submicron colloidal vehicles in advanced drug delivery systems [63]. Formally defined as heterogeneous dispersions of two immiscible liquids stabilized by a surfactant film, these systems exhibit a mean droplet diameter ranging between 20 and 200 nm [64]. Unlike microemulsions, which are thermodynamically stable systems that form spontaneously, nanoemulsions are typically thermodynamically unstable but highly kinetically stable [65]. This kinetic stability prevents typical colloidal breakdown mechanisms such as flocculation, sedimentation, and coalescence over extended periods, making them ideal for pharmaceutical formulations [66]. The submicron scale of the droplets provides a clear translucent or transparent visual profile and creates a large surface-to-volume ratio, significantly accelerating drug dissolution and cellular uptake processes [67].

The structural architecture of a nanoemulsion comprises an inner core (the dispersed phase), an outer continuous phase, and an interfacial monolayer of surfactant and co-surfactant molecules [68]. Depending on the specific orientation of these phases, they can be categorized as oil-in-water (o/w) or water-in-oil (w/o) systems [69]. For intranasal applications, oil-in-water (o/w) nanoemulsions are preferred [70]. In these formulations, lipophilic drugs are completely solubilized within the inner oil core, while the outer aqueous phase remains fully miscible with the hydrophilic nasal mucus layer [71]. This design allows poorly water-soluble molecules to be safely presented to the mucosal surface in a highly solubilized, finely dispersed state, bypassing the typical dissolution step that limits the absorption of conventional suspensions or lipophilic solutions [72].

The fabrication of nanoemulsions generally employs either high-energy or low-energy emulsification methods [73]. High-energy techniques utilize mechanical devices, such as high-pressure homogenizers, microfluidizers, or ultrasonic probes, to apply disruptive hydrodynamic shear forces that break large macroemulsion droplets into submicron structures [74]. While highly effective, these methods can generate substantial heat, potentially degrading thermolabile therapeutic molecules or biological materials [75]. Conversely, low-energy methods, such as Phase Inversion Temperature (PIT), Phase Inversion Composition (PIC), or spontaneous self-emulsification, leverage the intrinsic physicochemical properties of the components to form ultra-fine droplets during phase transition [76]. These low-energy processes require minimal mechanical energy, making them highly suitable for industrial scale-up and protecting sensitive active ingredients [77].

6. Intranasal Nanoemulsions for Alzheimer's Disease

Developing intranasal nanoemulsions tailored for Alzheimer's disease therapeutics requires addressing specific physiological constraints [78]. Many promising anti-Alzheimer compounds, such as cholinesterase inhibitors, BACE1 inhibitors, natural antioxidants, and neuroprotective peptides, possess unfavorable physicochemical properties: high lipophilicity, low aqueous solubility, or rapid peripheral metabolism [79]. By encapsulating these compounds within the lipophilic core of an oil-in-water nanoemulsion, they are shielded from enzymatic degradation by nasal peptidases and cytochrome P450 enzymes present in the nasal mucosa [80]. Furthermore, the small droplet size allows for rapid transport across the nasal epithelial lining, avoiding rapid mucociliary clearance and increasing overall brain targeting efficiency [81].

To further improve therapeutic outcomes, researchers are engineering functionalized nanoemulsions that provide dual-action targeting and prolonged mucosal residence times [82]. Incorporating mucoadhesive polymers—such as chitosan, sodium carboxymethylcellulose, or alginate—into the aqueous phase yields mucoadhesive nanoemulsions (or mucoemulsions) [83]. These positively charged polymers interact electrostatically with the negatively charged sialic acid residues present in the nasal mucus layer [84]. This structural bonding retards normal mucociliary clearance (which typically clears foreign substances within 15–20 minutes), extending the formulation's residence time to several hours [85]. This sustained contact window maintains a concentration gradient across the epithelial barrier, promoting continuous, long-term drug absorption into cerebral compartments [86].

Furthermore, surface modification of nanoemulsions with brain-specific targeting ligands represents a cutting-edge approach in neuro-nanomedicine [87]. Conjugating cell-penetrating peptides (CPPs) like TAT, penetratin, or specific antibodies against transferrin or lactoferrin receptors onto the nanoemulsion interface enhances receptor-mediated or absorptive endocytosis into nasal neuronal pathways [88]. These engineered nanovehicles have demonstrated the capacity to rapidly achieve effective therapeutic concentrations within critical AD anatomical locations, including the hippocampus, frontal cortex, and olfactory bulb [89]. Consequently, intranasal nanoemulsions provide a versatile, highly controllable platform capable of improving the pharmacokinetic and pharmacodynamic profiles of diverse anti-Alzheimer therapeutics [90].

7. Mechanism of Nose-to-Brain Delivery

Transport of therapeutics from the nasal cavity into the central nervous system occurs via three main pathways: the olfactory pathway, the trigeminal pathway, and the systemic circulation pathway [91]. Within the olfactory and trigeminal nerve systems, molecules can travel via intracellular or extracellular mechanisms [92]. The intracellular mechanism begins with endocytosis of the nanoparticles or dissolved drug molecules into the primary olfactory receptor neurons or trigeminal nerve endings, followed by retrograde axonal transport along the nerve fibers directly to the olfactory bulb or brainstem [93]. Once there, the drug is released via exocytosis into the surrounding brain tissue [94]. While this mechanism provides a direct, highly insulated route to the brain, axonal transport velocities are relatively slow (ranging from 0.1 to several mm/hour), meaning molecules may take several hours or days to reach therapeutic levels in distant cerebral structures via this pathway alone [95].

Conversely, the extracellular mechanism provides a much faster transport pathway, typically delivering drugs to the brain within minutes of administration [96]. This mechanism involves passive diffusion or bulk flow transport across the nasal epithelium into the underlying lamina propria [97]. From the lamina propria, molecules travel through the perineural spaces surrounding the olfactory or trigeminal nerves, which are continuous with the subarachnoid space and cerebrospinal fluid (CSF) of the brain [98]. The driving force for this transport is primarily governed by the hydrostatic pressure gradients generated by regular arterial pulsations within the nasal blood vessels [99]. Once the drug enters the CSF, it rapidly distributes throughout the brain parenchyma via perivascular spaces (the glymphatic system) and passive diffusion, avoiding the physical restrictions of the blood-brain barrier [100].

The third pathway involves systemic absorption from the highly vascularized respiratory mucosa into the nasal blood vessels, where the drug enters the systemic circulation [101]. From there, it can theoretically reach the brain by crossing the blood-brain barrier via conventional circulatory transport [102]. While this systemic loop contributes to the overall pharmacokinetics, it exposes the drug to systemic clearance organs and can cause off-target peripheral side effects [103]. Nanoemulsions are engineered to maximize direct perineural extracellular transport while minimizing systemic absorption [104]. Their small droplet size and lipophilic properties allow them to interact with lipid rafts on nerve membranes, shifting the distribution balance toward direct nose-to-brain pathways and away from systemic capillary uptake [105].

8. Formulation & Characterization

Developing an effective intranasal nanoemulsion requires careful screening and selection of its core components: oils, surfactants, co-surfactants, and aqueous phases [106]. The choice of the lipid phase is critical, as it determines the total solubilization capacity for the lipophilic drug [107]. Commonly used natural and synthetic oils include medium-chain triglycerides (MCTs like Captex 355 or Miglyol 812), oleic acid, isopropyl myristate, and various vegetable oils [108]. Surfactants are added to reduce interfacial tension and form a protective mechanical barrier that prevents droplet coalescence [109]. For intranasal use, non-ionic surfactants—such as Polysorbates (Tween 20, Tween 80), Sorbitan esters (Span 20, Span 80), and Polyoxyl castor oils (Cremophor EL, Solutol HS15)—are preferred due to their established biocompatibility and low irritation potential compared to ionic surfactants [110]. Co-surfactants, including short-to-medium chain alcohols like ethanol, propylene glycol, and polyethylene glycol (PEG 400), are often paired with surfactants to increase interfacial film flexibility and induce spontaneous emulsification [111].

Characterization of the developed nanoemulsions is essential to ensure physical stability, safety, and efficient in vivo performance [112]. The primary

parameter is average droplet size and polydispersity index (PDI), typically quantified via Dynamic Light Scattering (DLS) or Photon Correlation Spectroscopy [113]. A narrow PDI (<0.2) indicates a highly homogenous size distribution, which is vital for maintaining predictable drug release profiles [114]. Zeta potential, which measures the surface electrical charge of the droplets, provides insight into electrostatic stability; values outside the range of -30 mV to +30 mV generally indicate strong repulsive forces that prevent aggregation [115]. Morphological analysis is conducted using high-resolution imaging techniques, such as Transmission Electron Microscopy (TEM) or Scanning Electron Microscopy (SEM), to verify the spherical structure and uniform size of the nanoemulsion droplets [116].

Beyond structural traits, key rheological and physicochemical properties must be carefully optimized for the nasal cavity [117]. The viscosity of the formulation must be balanced: low enough to allow clean atomization during spray pump actuation, yet high enough to resist immediate drainage from the nasal cavity [118]. The pH must be adjusted to match physiological nasal fluid values (typically 5.5 to 6.5) to avoid mucosal irritation or altering the natural ciliary beat frequency [119]. Drug entrapment efficiency and percentage loading capacity are determined by separating unencapsulated drug via ultrafiltration or centrifugation and quantifying the fractions using validated HPLC or UV-visible spectrophotometry methods [120].

9. Therapeutic Agents & Research Evidence

A wide variety of therapeutic agents have been encapsulated into intranasal nanoemulsions and evaluated in preclinical Alzheimer's models [121]. Cholinesterase inhibitors remain a primary focus; for instance, donepezil-loaded nanoemulsions have been extensively developed to improve brain targeting [122]. Preclinical pharmacokinetic studies in rodents have demonstrated that intranasally administered donepezil nanoemulsions achieve significantly higher Brain Targeting Efficiency (BTE) and Direct Transport Percentages (DTP) than equivalent oral or intravenous solutions [123]. Behavioral studies using Morris water maze and passive avoidance tests showed marked improvements in spatial memory and learning in scopolamine-induced amnesia models, accompanied by a significant reduction in brain acetylcholinesterase enzyme activity [124]. Similarly, galantamine and rivastigmine nanoemulsions have shown enhanced neuroprotective efficacy when delivered via the nasal route [125].

Natural hydrophobic polyphenols and phytochemicals, which often face low oral bioavailability and rapid systemic clearance, benefit significantly from nanoemulsion encapsulation [126]. Curcumin, a potent anti-amyloid and anti-inflammatory agent, has been successfully incorporated into mucoadhesive nanoemulsions [127]. Brain biodistribution studies revealed rapid, high-concentration accumulation of curcumin in the hippocampus, leading to decreased amyloid-beta aggregation, suppressed microglial activation, and reduced levels of pro-inflammatory cytokines like TNF-α [128]. Resveratrol, quercetin, and huperzine A nanoemulsions have similarly demonstrated enhanced neuroprotective profiles, effectively neutralizing intracellular reactive oxygen species (ROS) and restoring endogenous antioxidant enzyme levels (such as superoxide dismutase and catalase) in cortical tissues [129]. These findings highlight the platform's versatility in delivering poorly soluble natural compounds for neuroprotective therapy [130].

Recent advancements have expanded the use of intranasal nanoemulsions to deliver novel disease-modifying macromolecular therapeutics [131]. Small interfering RNA (siRNA) targeted against the BACE1 gene, neurotrophic factors like Brain-Derived Neurotrophic Factor (BDNF), and various neuroprotective peptides have been successfully encapsulated into surface-modified, cationized nanoemulsions [132]. These advanced formulations protect biological macromolecules from extracellular enzymatic degradation and facilitate transcellular transit across the nasal epithelial barrier [133]. In transgenic AD mouse models, these formulations have demonstrated the capacity to downregulate amyloid precursor protein processing, promote neurogenesis, and preserve synaptic plasticity, providing strong preclinical evidence for disease-modifying therapies [134].

10. Advantages

Intranasal nanoemulsions offer distinct biopharmaceutic and clinical advantages over conventional drug delivery methods [135]. The primary benefit is the non-invasive nature of the route, which eliminates the risks, pain, and specialized medical oversight associated with neurosurgical procedures or intravenous infusions [136]. This significantly improves patient compliance, particularly in elderly Alzheimer's patients who require long-term, chronic therapeutic regimens [137]. Additionally, because these formulations can achieve higher local brain concentrations with lower total doses than systemic therapies, the risk of systemic side effects is greatly reduced [138]. This is especially critical for drugs like acetylcholinesterase inhibitors, which often cause severe gastrointestinal distress and cardiovascular side effects when administered orally at high therapeutic doses [139].

From a pharmacokinetic perspective, the rapid onset of therapeutic action achieved via direct neural pathways is highly advantageous [140]. By completely bypassing the gastrointestinal tract and the hepatic portal system, encapsulated drugs avoid first-pass metabolism, substantially increasing overall bioavailability [141]. The high solubilization capacity of nanoemulsions allows hydrophobic therapeutic agents to remain stable in solution, preventing localized precipitation within the nasal cavity and ensuring uniform, reproducible absorption profiles [142]. Furthermore, nanoemulsions can safeguard sensitive biological molecules from local enzymatic cleavage, extending the functional shelf-life and in vivo stability of advanced bio-therapeutics [143].

From an industrial manufacturing viewpoint, nanoemulsions present favorable structural characteristics [144]. Their inherent kinetic stability extends shelf-life and minimizes the risk of phase separation compared to macroemulsions or unstable suspensions [145]. The availability of low-energy self-emulsification methods simplifies manufacturing processes, reducing energy consumption and facilitating seamless industrial scale-up under sterile conditions [146]. This combination of patient-centric benefits, optimized pharmacokinetics, and scalable production makes intranasal nanoemulsions a highly viable platform for next-generation neurotherapeutics [147].

11. Limitations & Safety

Despite their clear therapeutic potential, intranasal nanoemulsions face physiological and formulation challenges that must be addressed [148]. The primary limitation is the restricted volume capacity of the human nasal cavity, which can typically accommodate only 100 to 200 microliters per nostril per administration [149]. This strict volume limit requires therapeutic agents to have high solubility and potency within the nanoemulsion core to deliver effective doses [150]. Additionally, the continuous action of the mucociliary clearance system can quickly sweep formulations toward the nasopharynx and gastrointestinal tract, limiting the time available for mucosal absorption unless the system is properly optimized with mucoadhesive polymers [151].

Local toxicity and mucosal compatibility represent critical safety criteria for long-term clinical use [152]. Incorporating high concentrations of chemical surfactants and co-surfactants to achieve small droplet sizes can potentially irritate or damage the delicate ciliated nasal epithelium [153]. Severe or prolonged irritation can lead to epithelial desquamation, structural damage to cilia, or localized neurotoxicity along olfactory nerve pathways [154]. Therefore, performing rigorous in vitro cytotoxicity assays on human nasal epithelial cell lines (such as RPMI 2650) and conducting ex vivo ciliotoxicity evaluations using isolated animal nasal mucosa are essential requirements during early-stage formulation screening [155].

Pathological changes within the nasal cavity can also introduce pharmacokinetic variability [156]. Common conditions like allergic rhinitis, the common cold, mucosal congestion, or structural abnormalities like a deviated nasal septum can alter nasal fluid volume, tissue permeability, and local pH [157]. These variations can affect the reproducibility of drug absorption, leading to inconsistent therapeutic profiles [158]. Additionally, ensuring long-term physical stability—specifically preventing Ostwald ripening, where smaller droplets diffuse and merge into larger ones over time—requires precise adjustment of surfactant ratios and storage conditions to prevent formulation breakdown [159, 160].

12. Regulatory Considerations

Navigating the regulatory landscape for intranasal nanoemulsions involves adhering to stringent international standards for combination products [161]. Regulatory bodies, such as the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA), evaluate these formulations under combined frameworks that assess both the pharmaceutical nanoemulsion and the nasal delivery spray device [162]. A primary focus is the safety profile of all Excipients, which must be selected from the FDA's Inactive Ingredient Database (IID) or designated as Generally Recognized as Safe (GRAS) to minimize clinical approval hurdles [163]. If a formulation requires surfactant concentrations that exceed standard historic thresholds, extensive long-term preclinical toxicity studies are mandatory to prove safety before human clinical trials can begin [164].

Developing standardized characterization protocols is critical for achieving reproducible clinical batches under Current Good Manufacturing Practices (cGMP) [165]. Manufacturers must implement validated controls for droplet size distribution, stability profiles, and accurate metrological quantification of the spray pattern and plume geometry produced by the mechanical actuation device [166]. Demonstrating clear in vitro-in vivo correlations (IVIVC) regarding drug release and mucosal permeation rates is vital for satisfying regulatory quality mandates [167]. Additionally, safety evaluations must monitor for potential systemic accumulation of nanocarrier materials, ensuring that repeated chronic administration does not lead to unwanted tissue retention or toxicological complications [168].

13. Future Perspectives

The future of intranasal nanoemulsions in treating Alzheimer's disease depends on bridging the gap between successful preclinical animal models and human clinical applications [169]. A major challenge is the structural and scale differences between animal and human nasal anatomy; while rodents possess a highly developed olfactory region covering nearly 50% of their total nasal cavity, the human olfactory zone is restricted to roughly 10% [170]. This anatomical difference requires the development of advanced nasal delivery devices—such as electronic atomizers, breath-powered powder inhalers, or targeted acoustic wave delivery systems—capable of bypassing the restrictive lower nasal turbinates to deposit formulations precisely onto the upper olfactory neuroepithelium [171].

Concurrently, the integration of personalized medicine and smart nanotechnology platforms holds promise for optimizing neuro-therapeutics [172]. Developing stimuli-responsive nanoemulsions that undergo sol-to-gel transformation upon contact with the physiological nasal temperature, ionic strength, or specific mucosal pH values represents a major area of research [173]. These smart systems allow simple, low-viscosity liquid instillation that rapidly converts into a robust, protective mucoadhesive gel network inside the cavity, minimizing premature drainage and supporting long-term, controlled drug delivery [174]. Clinical trials evaluating these multi-functional nanoemulsions will be essential for establishing definitive safety, efficacy, and pharmacokinetic parameters in human patients, potentially transforming the management of Alzheimer's disease [175].

14. Conclusion

Intranasal nanoemulsions represent a highly promising, non-invasive breakthrough in neurotherapeutic delivery, successfully bypassing the restrictive blood-brain barrier to target Alzheimer's disease directly. By utilizing the direct pathways of the olfactory and trigeminal nerves, these submicron colloidal vehicles allow a wide range of therapeutic molecules—including hydrophobic compounds, plant-derived polyphenols, and large biological macromolecules—to achieve effective therapeutic concentrations within critical cerebral compartments. The optimization of formulation variables, such

as selecting biocompatible lipid cores and non-irritating non-ionic surfactant systems, remains vital for ensuring robust stability and preventing mucosal irritation. Preclinical evidence across numerous animal models consistently demonstrates improved cognitive function, reduced amyloid aggregation, and minimized systemic side effects. As research advances, resolving differences in nasal anatomy between species and developing targeted nasal delivery devices will be essential steps for successful clinical translation, offering a viable and effective strategy for managing neurodegenerative disorders.

Declaration

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