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Targeted Delivery of Drugs by Intranasal Drug Delivery for Alzheimer's Disease Treatment

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ABSTRACT

Alzheimer's disease (AD) exhibits chronic neuron damaging, characterized by progressive cognitive impairment, memory deterioration, and widespread neuronal destruction, ultimately leading to irreversible brain damage. Current treatments for neurological disorders are hindered by the blood brain barrier's (BBB) selective permeability, which severely restricts the delivery of therapeutic agents to the central nervous system (CNS). Intranasal drug delivery (INDD) has emerged as a promising, non-invasive approach to circumvent the BBB, utilizing the olfactory and trigeminal neural pathways to facilitate direct and targeted delivery of therapeutic agents to brain. This review examines the role of INDD in AD therapy, emphasizing advancements in formulation techniques, including the application of nanoparticles, liposomes, and mucoadhesive polymers, which enhance drug stability, absorption, and retention.Both experimental and human trails have underscored the potential of INDD in facilitating the delivery of treatments such as insulin, neurotrophic factors, and cholinesterase inhibitors, yielding improved outcomes. While INDD offers benefits like rapid brain delivery and reduced systemic side effects, challenges such as limited dose capacity and variability in nasal anatomy persist. Emerging innovations in personalized drug delivery and targeted formulations show promise for optimizing this method in AD care.

Keywords: *Alzheimer's Disease (AD), neuron damaging Disorder, Intranasal Drug Delivery (INDD), Brain Targeting, Nanotechnology.*

1. INTRODUCTION

AD predominantly affects older individuals, manifesting a chronic nuron damaging disorder. It is marked by a gradual decline in cognitive functions, memory loss, and alterations in behaviour and personality, eventually resulting in complete dependence and death. Characterized by the buildup of amyloid-beta deposits, tau protein tangles, and widespread neuronal loss. AD particularly affects hippocampal and cortical regions crucial for memory and cognitive functions. Globally, AD impacts millions, with its prevalence steadily rising due to an aging population. As of 2021, more than six million Americans aged 65 and older were reported to be living with this condition. Despite extensive research over several decades, treatments capable of halting or reversing AD's progression remain elusive. A major obstacle in creating effective treatments for AD is ensuring the proper transport of medications to the brain. The BBB, a specialized endothelial structure, acts as a selective barrier that prevents toxic compounds from accessing brain, additionally restricting the penetration of therapeutic agents. Macromolecular therapeutics such as biologics and genetic materials typically cannot traverse BBB, and even small-molecule drugs often face challenges such as limited brain penetration and rapid elimination, reducing their therapeutic potential. These barriers have fueled the exploration of alternative strategies to overcome the BBB, enabling direct brain delivery of therapeutics. Since AD originates within the brain, accurate delivery of treatment is essential to ensure adequate drug levels at the affected areas while reducing adverse effects on the rest of the body. Traditional systemic drug administration often necessitates high dosages to penetrate the brain adequately, which can lead to toxicity in peripheral organs. In contrast, targeted drug delivery seeks to focus therapeutic agents directly in the brain, thereby improving effectiveness and reducing side effects. Recent technological advancements, such as nanoparticles, liposomes, and antibody-drug conjugates, have demonstrated promise in improving brain-specific drug delivery. However, these approaches still face challenges in effectively crossing the BBB and sustaining therapeutic activity within the brain. IND has emerged as a groundbreaking, non-invasive approach for directly brain delivering of therapeutic agents. This pathway leverages the nasal cavity's unique connection with CNS through olfactory and trigeminal nerve pathways, effectively circumventing the BBB. Medications

delivered intranasally can quickly access the brain, making this approach especially attractive for managing neuro damaging conditions such as AD. INDD also provides multiple benefits, including convenience of use, fast onset of effects, and minimized systemic exposure. Recent research highlights the potential of intranasally delivered compounds, such as peptides, insulin, and nanoparticles, in targeting critical AD-related pathological mechanisms, including Aβ aggregation and tau pathology. These studies suggest that INDD holds significant promise as a platform for delivering various therapeutic agents, including small molecules, biologics and gene therapies offer promising approaches for managing AD, enabling targeted brain delivery[1,2].

ALZHEIMER'S DISEASE: PATHOPHYSIOLOGY AND TREATMENT (Showed in Table 1)

AD is distinguished by two primary neuropathological features: the deposition of fibrillar amyloid aggregates and formation of cytoskeletal inclusions composed of aberrantly phosphorylated tau peptides. The amyloid accumulation hypothesis suggests that the gradual accumulation of these amyloid deposits within the cerebral cortex initiates a complex cascade of molecular events, culminating in neuronal dysfunction and cognitive deterioration. The amyloidogenic fragments, derived from the proteolytic cleavage of a transmembrane glycoprotein, accumulate within the brain's interstitial fluid, compromising cellular homeostasis and eliciting a neuroinflammatory response that exacerbates neuronal degeneration. In addition to Aβ plaques, neurofibrillary tangle compose of tau proteins are key contributors to the pathology of AD. Normally, tau proteins stabilize micro tubules, but in AD, they become hyperphosphorylated, losing this function and forming tangles that impair the neuronal transport system. The convergence of these pathological mechanisms culminates in disrupted neurotransmission, neuronal demise, and widespread cerebral deterioration, predominantly affecting the rhinencephalon and neocortex-neuroanatomical structures pivotal for mnemonic encoding and cognitive processing. Currently, therapeutic options for AD remain limited, with most treatments addressing symptoms rather than targeting the disease's underlying causes. Frequently used treatments involved cholinesterase inhibitors like donazepil, rivastigmine, and galantamine, along with memantine, and NMDA receptor blocker. Cholinesterase inhibitors work by raising acetylcholine concentrations, a neurotransmitter crucial for memory and cognitive functions, while memantine modulates glutamate activity to reduce excitotoxicity. Although these drugs can offer modest improvements in slowing cognitive decline and enhancing daily functionality, their benefits are temporary and do not alter the disease's progression. Consequently, AD continues to advance despite treatment, underscoring the critical need for therapies that address its root causes. The limitations of existing treatments, coupled with the complexity of AD pathology, highlight the urgent demand for innovative therapeutic strategies that act at the molecular level. A significant obstacle in creating efficacious treatment for Alzheimer's disease is ensuring the effective translocation of pharmacological agents across the cerebral vasculature. The hematoencephalic barrier presents a formidable impediment, severely restricting the permeability of various prospective therapeutics, particularly larger biomolecules such as polypeptides, immunoglobulins, and genetic material. Systemic administration often results in sub therapeutic concentrations of drugs within the brain, while the high doses required to achieve sufficient levels can lead to systemic toxicity. To address these challenges, researchers are exploring advanced drug delivery methods, including nanoparticles, gene therapies, and Intranasal delivery systems. These novel approaches aim to improve drug targeting, enhance brain penetration, and minimize systemic side effects, offering new possibilities for more effective AD treatments[3,4,5,6]. The strategies for managing AD were shown in following Table 1.

Table 1. Strategies for managing AD

S.No.	Therapeutic Approach	Mechanism of Action	Examples of Treatments	Limitations
1.	Cholinesterase Inhibitors	Increase acetylcholine levels by inhibiting the enzyme that breaks it down, improving cognitive function.	Donepezil, Rivastigmine, Galantamine	Provides only symptomatic relief, short-term efficacy.
2.	NMDA Receptor Antagonist	Regulate glutamate activity to prevent excitotoxicity and protect neurons.	Memantine	Limited long-term benefits, does not modify disease progression.
3.	Nanoparticle-based Drug Delivery	Use nanoparticles to bypass the BBB for targeted brain delivery	Polymeric nanoparticles, Liposomes, Solid lipid nanoparticles	Challenges in formulation, potential toxicity, still under investigation.
4.	Gene Therapy	Modifies or replaces faulty genes to target molecular mechanisms involved in AD.	CRISPR-based therapies, Viral vectors	Safety and ethical concerns, requires more research.

5.	Intranasal Drug Delivery	Targeted cerebral drug delivery via nasal neurovascular route, circumventing the hematoencephalic barrier.	Insulin, Peptides, Small molecules	Limited dose capacity, variability in absorption, still in early stages of development.
6.	Monoclonal Antibodies	Target and neutralize beta-amyloid plaques in the brain to reduce their accumulation.	Aducanumab, Donanemab	Expensive, potential for immune reactions, mixed efficacy in clinical trials.
7.	Stem Cell Therapy	Use stem cells to regenerate neurons and restore brain function	Mesenchymal stem cells and reprogrammed pluripotent stem cells	Ethical concerns, potential for tumor formation, still experimental.
8.	Anti-Amyloid Agents	Inhibit the aggregation of beta-amyloid plaques to slow down or halt disease progression.	Solanezumab, Bapineuzumab	Limited efficacy in late stages of AD, still under clinical investigation.
9.	Anti-Tau Agents	Focous on tau proteins to inhibit hyperphosphorylation and neurofibrillary tangle formation	TauRX, Semorinemab	Still under investigation, requires more clinical trials for safety and efficacy.

2. OBSTACLES IN DRUG ADMINISTRATION OF THE CNS

The BBB as a Barrier for Traditional Drug Delivery Methods

The BBB functions with stringent selectivity, forming, a protective interface that separates cerebral blood vessels from the CNS. It is composed of closely joined endothelial cells, with support from astrocytes and pericytes, forming both a physical and biochemical barrier that restricts the passage of most substances into brain. Although this process is essential for maintaining brain stability, it also poses a significant obstacle to administering medications to the CNS. Large therapeutic agents, including peptides, antibodies, and nucleic acids, typically cannot penetrate the BBB. Even smaller compounds may face limited access due to active efflux mechanisms, such as P-glycoprotein, which actively remove drugs from brain. The BBB's selective permeability creates a major challenge in designing effective therapies for neurological conditions like AD, Parkinson's, and brain tumors, where targeted delivery of treatments to the brain is critical[7].

Systemic Side Effects of CNS Drugs

Administering CNS drugs systemically often requires higher doses to reach therapeutic levels in the brain, owing to the limiting properties of the BBB.

This approach increases the likelihood of systemic side effects, as the drugs may interact with non-CNS organs and tissues. For instance, cholinesterase inhibitors, commonly employed in the treatment of AD, can causes unwanted effects such as gastrointestinal disturbances, bradycardia, and muscle cramps due to their systemic activity. Similarly, anti-psychotic medications prescribed for neuropsychiatric symptoms often cause side effects like sedation, weight gain, and metabolic issues. Balancing the delivery of adequate drug concentrations to the brain while minimizing these non specific effects remains a formidable ta in CNS drug therapy[8].

Potential of Non-Invasive Delivery Methods

Non-invasive drug delivery methods have gained attention as effective strategies to overcome the challenges of the BBB while minimizing systemic side effects. Among these approaches, INDD stands out as promising technique for delivering drugs within the CNS. Via nasal neurovascular pathways, this approach circumvents the hematoencephalic barrier, enabling pharmacological agents to access the cerebral tissue directly. This pathway facilitates swift and targeted drug deliver to the CNS, minimizing the reliance on high systemic doses and limiting undesirable effects on peripheral tissue. Other innovative non-invasive techniques include trans-cranial focused ultrasound, which temporarily disrupts the BBB to facilitate drug entry, and nasal-to-brain nanoparticles designed to improve drug delivery efficiency. These advanced strategies offer significant potential for enhancing CNS drug delivery, especially in managing disorders like Alzheimer’s disease, where precise targeting of specific brain regions is critical for therapeutic success[9].

3. INDD: MECHANISM AND PATHWAYS

The nasal cavity is a critical anatomical structure with key roles in both respiratory function and drug delivery, particularly for Intranasal drug delivery (INDD) applications. The nasal passage is divided into two symmetrical compartments by nasal

divide, a composite framework comprising osseous and chondral tissues. Every compartment is subdivided into three distinct regions: the anterior recess, the aeriferous zone, and the osmotic zone, each performing specific roles. The vestibule serves as the primary filtration area for incoming air, the respiratory region is responsible for conditioning the air by warming and humidifying it, and the olfactory region enables the sense of smell. Moreover, the osmotic zone offers a direct conduit to the central neuroaxis, rendering it especially crucial for intranasal neurodelivery modalities[10,11,12,13].

Nasal Vestibule

The nasal vestible, located just inside the nasal apertures, represents outermost segment of the nasal passage. It is lined with skin and features small hairs known as vibrissae, which act as a primary defense mechanism by trapping large particles from inhaled air. Due to its relatively limited surface area and thicker epithelial lining, the nasal vestibule plays a minimal role in drug absorption compared to other regions of the nasal cavity.

Respiratory Region

The respiratory region, forming largest segment of the nasal passage, fulfills vital function in conditioning inspired air prior to pulmonary arrival. This area is converted by pseudo stratified ciliated columnar epithelium, which includes goblet calls responsible for mucus production. The mucus has several essential functions, including trapping pathogens and particles, maintaining moisture, and supporting the immune defense of the respiratory tract. Within this region are three bony structures called the nasal conchae or turbinates (superior, middle, and inferior), which significantly increase the nasal cavity's surface area. These turbinates create airflow turbulence, ensuring that inhaled air passes over the mucosal surfaces for effective warming and humidification. The aeriferous zone’s expansive mucosal interface and copious vascularization render it an optimal site for pharmacological assimilation, particularly for systemic distribution of therapeutic agents.

Olfactory Region

Suited at the superior aspect of nasal passage, subjacent to the cribrous lamina of the ethmodial osseus structure, the osmotic zone assumes a pivotal function in intranasal pharmacological administration, particularly for neurotargeting applications. Although smaller than the respiratory region, its importance lies in its direct connection to the brain. This area contains olfactory receptor neurons that connect to the olfactory bulbs, which are part of the brain's limbic system responsible for memory and emotion. The olfactory epithelium within this region consists of three primary cell types:

(a) Olfactory sensory neurons: These specialized cells identify scent molecules and send signals directly to the brain. Their neuronal projections traverse the cribrous lamina to converge with the osmotic ganglia, providing a direct conduit for pharmacological agents to circumvent the hematoencephalic barrier

(b) Supporting cells: These cells provide structural integrity and metabolic support to the olfactory neurons, ensuring their proper function.

(c) Basal cells: Acting as stem cells, basal cells have the capacity to regenerate olfactory neurons throughout a person’s lifetime.

The direct linkage of olfactory neurons to brain provides a distinct pathway for drug delivery within CNS, bypassing BBB. This characteristics makes the olfactory region an essential target for therapeutic delivery, especially for neurodegenerative disorders such as AD.

Nasal mucosa & Its Role in Absorption

The nasal mucosa, which lines the entire nasal cavity, plays a vital role in drug absorption. Its high vascularization enables rapid uptake of medications directly into the bloodstream. Due to this dense network of blood vessels, drugs administered via the nasal passage can enter the blood stream within minutes. The nasal epithelium, particularly in respiratory region, relatively thin, facilitating the efficient absorption of both small and large molecules. However, the mucosa also contains enzymes, such as cytochrome P450, which can metabolize drugs before they reach the bloodstream. This biochemical reactivity constitutes a crucial consideration in intranasal pharmacological composition, as it potentially diminishes the biologic accessibility of specific therapeutic agents.

Mucociliary Clearance

The nasal cavity is equipped with a mucociliary clearance system, plays a key role in safeguarding respiratory tract by trapping and removing inhaled particles, pathogens, and drugs. Kinociliated cells in the aeriferous zone propel mucoid secretions and entrapped particles posteriorly for ingestion or expectoration. Mucociliary elimination, while important for respiratory health, can hinder intranasal drug delivery by quickly removing therapeutic agents from the nasal passage, thereby shortening duration of therapeutic agent contact with the mucosal surface. To counter this, drug formulations often incorporate bioadhesive agents that enhance the drug's ability to adhere to the mucosa, extending its retention time and improving absorption.

Surface Area and Permeability

The nasal vestibule possesses an extensive mucosal interface, estimated to be approximately 150 cm^2 in adults, which supports efficient drug absorption. The semipermeable nature of the olfactory mucosa facilitates the transciliary absorption of pharmacological agents, especially those with compact, hydrophobic molecular configurations. However, macromolecules, such as polypeptides and protean structures, may face challenges in crossing nasal epithelium and reaching their target sites in the brain. In such cases, permeation enhancers or nanoscale vehicular architectures may be needed to facilitate transmucosal conveyance of substantial bioactive complexes.

Blood Supply

The nasal cavity's abundant vascular network enhances its suitability for drug delivery. Blood vessels, predominantly supplied by the sphenopalatine and facial arteries, are located just beneath the nasal mucosa, enabling the quick availability of drugs to blood supply. To access the cerebrovascular axis, these neuropharmaceutical agents can exploit the nasal neuroepithelial interface, utilizing the first cranial nerve and the fifth cranial nerve for direct cerebral access, thereby evading the hematoencephalic barrier and facilitating pinpoint delivery to designated neuroanatomical loci.

Routes of Drug Delivery to the Brain: Olfactory and Trigeminal Pathways

INDD leverages the distinctive rhinencephalic merphology to convey neurotherapeutic entities directly to the cerebrum, circumventing the hematoencephalic barrier. This modality primarily exploits two predominant neurovascular conduits: the rhinencephalic pathway and the trigeminal neural conduit[14,15,16].

Olfactory Pathway

The rhinencephalic conduit offers a direct portal for neuropharmaceutical delivery from the nasal vault to the cerebrum. Specialized neurosensory cells in the rhinencephalic mucosa project axons to the cerebral olfactory nucleus, circumventing the hematoencephalic barrier. This enables direct axonal transport of substance into brain. The process of drug transport through the olfactory pathway involves the following steps:

(a) Absorption: Upon intranasal administration, drugs are absorbed into the olfactory epithelium. Lipophilic drugs can readily diffuse across the neuronal membranes, while hydrophilic drugs may need specialized delivery systems, such as nanoparticles, to facilitate their transport.

(b) Intraneuronal Transport: Following absorption, drugs are moved along the olfactory sensory neurons via intracellular transport mechanisms. Neurosensory cells project axonal extensions through the ethmoidal foramen, a porous osseus septum delineating the rhinencephalic interface.

(c) Entry to the Brain: Once the drug crosses the cribriform plate, it reaches the olfactory bulbs, where it can diffuse into various regions of the brain. From there, it can spread to the hippocampus, cortex, and other brain areas.

The olfactory pathway provides notable advantages for reaching brain region involved in memory, learning, and emotions, making it a potential strategy for treating neurodegenerative diseases like AD.

Trigeminal Nerve Pathway

The trigeminal neural conduit serves as a vital ancillary pathways for cerebrovascular drug delivery from the rhinencephalic vault. Unlike the rhinencephalic route, which primarily targets the prosencephalon, the trigeminal neural conduit innervates both the respiratory and rhinencephalic mucosae, facilitating access to diverse cerebral domains. This conduit comprises three primary rami, with the ophthalmic and maxillary rami possessing sensory neuroreceptors within the rhinencephalic mucosa. These nerve endings are responsible for detecting chemical and mechanical stimuli and also act as conduits for drug transport to deeper brain structures, including the brainstem. The process of drug transport via the trigeminal nerve occurs in the following stages:

(a) Peripheral Nerve Uptake: Drugs are absorbed through the sensory nerve endings of trigeminal nerve within nasal mucosa.

(b) Axonal Transport: Following assimilation, pharmaceutical entities are conveyed along the neurofilaments of the cranial nerve V and mesencephalic nucleus. This pathway can also extend to the thalamus and spinal cord, facilitating broader CNS access.

(c) Distribution: Once the drugs reach the brainstem, they are distributed to other parts of the CNS. This pathway complements the olfactory route, providing a means of distributing drugs more extensively throughout the CNS, including areas that may be harder to reach via the rhinencephalic pathway alone.

The cranial nerve V conduit amplifies the efficacy of neuropharmaceutical delivery to diverse cerebral territories, rendering it a pivotal tactic for cerebrocentric interventions.

Bypassing the BBB Using INDD

The BBB is a highly specialized and protective structure that controls passage of most therapeutic substances into the brain, creating major obstacles for treating neurodegenerative and psychiatric disorders.The hematoencephalic partition comprises a compact ensemble of angiocytes, astrogliocytic pedicels, and mural cells, collectively constituting a selective diffusion barrier that restricts solute translocation from the vascular compartment to the cerebral parenchyma. Only small, fat soluble molecules or those equipped with specific transport mechanisms can penetrate the BBB[17].

(a) Rapid Drug Action: Intranasal drug delivery (INDD) allows drugs to reach the brain within minutes of administration. This rapid onset of action provides faster therapeutic effects compared to traditional delivery methods like oral or intravenous administration, which require drugs to be absorbed and metabolized before reaching the brain.

(b) Increased CNS Drug Concentrations: Since INDD bypasses the BBB, neuropharmaceuticals can be administered directly to the cerebrum, avoiding peripheral metabolism and degradation that often reduces drug efficacy. As a result, elevated pharmacological concentrations can accumulate in the cerebral target zones, enhancing its therapeutic potential and improving outcomes for conditions that require targeted brain treatment.

(c) Treating Neurodegenerative Disorders: INDD is particularly advantageous in treatment of neuron damaging disorders such as AD, Parkinson's disease, where targeted delivery to specific brain areas is crucial for effective therapy. Bypassing the BBB, INDD also reduces the need for high systemic doses, minimizing the risk of systemic side effects like gastrointestinal issues or metabolic disturbances. This makes INDD a promising strategy for managing these challenging disorders, offering more precise and effective treatment options.

Advantages of INDD

The nasal cavity's rich vascularization, particularly in the respiratory region, allows for rapid absorption of intranasal drugs, facilitating quick transport to the brain, often within minutes of administration. This expedited pharmacodynamic response is particularly beneficial for cerebrovascular emergencies necessitating prompt therapeutic modulation, such as hyperacute neuropathic episodes or cranial vasculature disorders. Additionally, INDD skips primary hepatic biotransformation that occurs within liver, enhancing bioavailability of the drug. This allows for the administration of lower doses to achieve effective therapeutic outcomes, reducing the potential for liver-related side effects. Intranasal drug delivery provides a direct pathway to brain through the olfactory nerve and trigeminal nerve, bypassing the BBB to target areas such as the hippocampus and cortex, which are vital in neurogenerative diseases like AD. Direct targeting of the brain offers more effective treatment of CNS disorders while minimizing off-target effects that are common with systemic drug administration. For instance, oral CNS drugs can interact with peripheral organs, resulting in side effects such as gastrointestinal distress, cardiovascular issues, or hepatic toxicity. INDD reduces systemic exposure to the drug, concentrating its effects on the brain while avoiding these peripheral side effects. Moreover, because INDD bypasses systemic circulation, it minimizes systemic exposure, making it particularly advantageous for the treatment of CNS disorders. For example, cholinesterase inhibitors, which are generally used in the management of AD, can cause peripheral side effects like nausea, diarrhea, and bradycardia when administered orally. By delivering these drugs intranasally, the systemic concentrations can be kept low, reducing the likelihood of such adverse reactions. Additionally, cerebroselective administration modalities provide a transmucosal alternative to more interventional neuropharmaceutical paradigms, such as intrathecal or intracerebroventricular injections, which require direct administration into the CNS via needles. INDD avoids the discomfort and risks associated with these procedures, making it a more patient-friendly approach for CNS drug delivery[18].

4. FORMULATION STRATEGIES FOR INDD

Formulation strategies for INDD are crucial for enhancing drug efficacy, stability, and absorption. Key considerations include drug solubility, particle size, and formulation type[19,20,21].

Drug Solubility

Drug solubility in the mucus layer is vital for absorption through the nasal epithelium. Poorly soluble drugs may need to be modified (e.g., as salts) or combined with solubilizers like surfactants to improve solubility.

Particle Size

The particle size of a drug significantly influences its absorption. Formulations with particles smaller than 10 microns are generally more effective, as they can penetrate deeper into the nasal mucosa for improved absorption.

Formulation Types

Solutions and Suspensions

These are often used for small-molecule drugs, providing easy absorption and a relatively straightforward formulation approach.

Nanoparticles and Liposomes

These advanced drug delivery systems are utilized for larger, more complex molecules such as peptides, proteins, or nucleic acids. They offer benefits such as protection from degradation, enhanced absorption, and controlled release of drugs over time.

Gels

Gels are preferred for INDD due to their ability to increase the duration of stay in nasal passages. This prolonged contact enhances the absorption of drug and leads better therapeutic results.

Bioadhesive Agents

Bioadhesive substances like chitosan, carbopol, or polylactic acid are employed to extend drug's residence in the nasal passage and minimize its removal by mucus and ciliary action. These agents help the drug adhere to the nasal mucosa, increasing its contact time and improving absorption.

Permeation Enhancers

Surfactants, bile salts, and cyclodextrins are commonly used in INDD formulations to loosen the tight connections among nasal epithelial cells, enabling the transport of larger or hydrophilic molecules into the blood stream or brain.

Enzyme Protection

Nasal formulations often incorporate agents to stabilize therapeutics from enzymatic break down by nasal enzymes such as peptidases and esterases. Enzyme inhibitors or encapsulation techniques like nanoparticles and liposomes can protect drugs, particularly peptide- and protein-based drugs, from degradation before they are absorbed.

Challenges in Intranasal Drug Delivery

Despite these advancements, several challenges still exist in formulating drugs for intranasal administration:

Nasal Clearance

Mucosa and cilia naturally remove foreign substances from the nasal cavity, limiting drug absorption time. This can be mitigated by using bioadhesive or high-viscosity formulations to prolong retention.

Enzymatic Degradation

Macromolecules are more susceptible to enzymatic breakdown in nasal passage. Enzyme inhibitors or protective carriers, such as nanoparticles, help prevent this degradation.

Limited Volume of Administration

Intranasal administration is restricted to 200 microliters per nostril, limiting the dose that can be delivered. This can be challenging for drugs that require larger doses for efficacy.

Patient Variability

Differences in nasal physiology and mucus production among individuals can affect the absorption and efficacy of the drug. Personalized formulation approaches may be necessary to optimize drug delivery for individual patients.

5. THERAPEUTIC APPROACHES FOR INDD IN AD

Nanoformulations for intranasal delivery

INDD has gained attention as an innovative strategy for managing AD by bypassing the BBB and enabling targeted drug delivery. Notable advancements in INDD include the use of nanoformulations like nanoparticles, liposomes, and micelles. These nanocarriers offer several benefits for brain targeted delivery, such as protecting drugs from degradation, enhancing absorption, and enabling controlled release, which helps sustain effective drug levels in the brain over time. Nanoparticles have shown considerable promise in enhancing brain drug delivery. They are versatile carriers that can encapsulate both hydrophilic and hydrophobic drugs, improving the solubility and stability of drugs that would typically degrade quickly in the body. Polymeric nanoparticles (PNPs) are widely studied for INDD to the brain. Typically made from biodegradable and biocompatible polymers like polylactic-co-glycolic acid (PLGA), chitosan, or polycaprolactone, these particles enable controlled and prolonged drug release, improving therapeutic efficacy and reducing administrating frequency. Furthermore, PNPs can be designed with mucoadhesive properties, allowing them to attach to nasal mucosa, which enhances drug retention and absorption. Research indicates that PNPs can significantly boost drug bioavailability in the brain, leading to improved treatment outcomes for AD patients. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are studied for INDD, offering controlled release and protection of lipophilic drugs from degradation. These carriers increase drug penetration through the nasal mucosa, facilitating enhanced delivery to the brain. SLNs and NLCs have been used to deliver AD drugs like rivastigmine and donepezil. Their lipid composition ensures sustained therapeutic concentrations in the brain.

Liposomes, made of phospholipid bilayers, are biocompatible vesicles that can enclose water soluble and lipid soluble drugs. They protect drugs from early metabolism in the nasal cavity and enhance brain penetration by fusing cell membranes. Liposomes are used to deliver a range of drugs for AD, including curcumin, which has antioxidant and anti-inflammatory properties, and has shown potential in reducing amyloid-beta plaques in brain. In addition to nanoparticles and liposomes, micelles have also been explored as nanocarriers for INDD. Micelles, formed from amphiphilic molecules, encapsulate hydrophobic drugs in their core, facilitating transfer through the nasal mucosa for brain delivery. They enhance solubility of hydrophobic therapeutics, enhance bioavailability, and efficiently penetrate nasal epithelium because of their small size. Targeted delivery systems in INDD for AD use nanoparticles conjugated with ligands like antibodies or peptides to bind specific receptors on brain cells, enabling precise drug delivery. Antibody-conjugated nanoparticles can specifically target amyloid-beta plaques, a hallmark of AD, and deliver drugs directly to the affected areas in the brain. For example, nanoparticles conjugated with anti-amyloid antibodies have been used to deliver BACE1 inhibitors, which reduce the production of amyloid-beta peptides. Similarly, peptide-based delivery systems can target specific brain regions involved in AD, such as the hippocampus, to enhance drug efficacy[22, 23, 24, 25].

Use of targeted delivery systems (antibody-conjugated nanoparticles, peptide delivery systems)

Targeted drug delivery systems represent a key advancement in INDD for AD treatment. The system use molecular targeting to deliver drugs directly to specific brain cells, enhancing efficacy and reducing side effects. Antibody-conjugated nanoparticles, designed to bind proteins like amyloid-beta or tau, enable precise drug delivery to affected regions. For instance, nanoparticles targeting amyloid plaques have shown potential to reduce their buildup and improve in AD models. In addition to antibody conjugation, peptide-based delivery systems have gained traction in AD treatment via the intranasal route. Peptides can be engineered to mimic naturally occurring molecules in the body and target specific receptors in the brain. Peptide-conjugated nanoparticles can deliver neuroprotective drugs directly to the hippocampus, a region heavily impacted in AD. Peptide-based systems not only facilitate drug delivery but can also contribute actively to neuroprotection and regeneration. These targeting strategies enhance the precision and therapeutic efficacy of INDD, making it a promising approach for neurodegenerative diseases like AD[26].

Case studies of drug molecules and formulations used in INDD for AD (e.g., insulin, peptides, small molecules) (Showed in Table 2)

Case studies highlight INDD's effectiveness in delivering AD treatments, with insulin being key focus. Insulin enhances memory and cognitive function in mild cognitive impairment and AD, likely by regulating brain glucose metabolism and reducing neuroinflammation. Clinical trails show intranasal insulin improves cognition with minimal systemic side effects, making it a promising AS therapy . Another important category of molecules studied for INDD in AD treatment includes peptides. Vasoactive intestinal peptide (VIP) and neuropeptide Y (NPY) has demonstrated neuroprotective activities when delivered intranasally in animal models of AD. VIP is known to protect neurons from oxidative stress and inflammation, while NPY have been shown to minimize amyloid-beta accumulation in brain. These peptides not only mitigate AD pathology but also promote neuronal survival, making them promising therapeutic agents. Small molecules like donepezil, rivastigmine, and galantamine, which are cholinesterase inhibitors commonly used to manage AD symptoms, have also been effectively delivered via the intranasal route. These molecules enhance cholinergic transmission in the brain, improving cognitive function in AD patients. Intranasal formulations of these drugs offer superior brain bioavailability compared to traditional oral administration, making INDD a more efficient method of delivering these therapeutics. Additionally, compounds such as curcumin and resveratrol, known for their anti-inflammatory and neuroprotective properties, have been studied for intranasal delivery in AD models. These molecules not only reduce amyloid-beta accumulation but also protect neurons from oxidative damage, a key contributor to AD progression. These case studies underscore the versatility and efficacy of INDD in delivering a broad spectrum of therapeutic molecules for AD management[27]. Case Studies of INDD for AD Treatment were shown in Table 2 in detailed as follows,

Table 2. Case Studies of INDD for Alzheimer's Disease Treatment

S.No.	Study/Therapeutic Molecule	Effectiveness/Outcome
1	Intranasal Insulin	Enhanced memory and cognition in individuals with mild cognitive impairment and AD.
2	Vasoactive Intestinal Peptide (VIP)	Neuroprotective effects; improved cognitive function in animal models
3	Neuropeptide Y (NPY)	Neuroprotection and reduction in amyloid-beta levels in animal models
4	Oxytocin	Improved social memory and reduced AD-like pathology in animal models
5	Leptin	Reduction in amyloid plaques and improvement in cognitive function in *in*

		vivo models
6	Nerve Growth Factor (NGF)	Improved cholinergic neuron survival and Cognitive function in preclinical models.
7	Brain-Derived Neurotrophic Factor (BDNF)	Neuroprotection and improvement of memory function in AD models
8	Donepezil	Improvement in cholinergic transmission and cognitive function in AD patients
9	Rivastigmine	Reduced amyloid-beta levels and cognitive improvement in clinical trials
10	Curcumin	Anti-inflammatory and neuroprotective effects; reduced amyloid-beta accumulation in AD models
11	Galantamine	Cognitive improvement in AD patients
12	Resveratrol	Reduction of neuroinflammation and oxidative stress in preclinical models
13	Liraglutide	Neuroprotection and improved glucose metabolism in AD models
14	Tacrine	Cognitive improvement and reduction in amyloid-beta levels
15	Tocopherol (Vitamin E)	Antioxidant effects and reduction in oxidative stress in AD models

6. PHARMACOKINETICS AND PHARMACODYNAMICS OF INTRANASAL DRUGS IN AD

Pharmacokinetics of INDD in the context of AD

The pharmacokinetics of IND encompass absorption, distribution, metabolism, and elimination, especially for brain targeted therapies like AD. INDD bypass the BBB, enabling direct and efficient CNS delivery compared to systemic methods[28,29].

Absorption

The absorption of intranasally administered therapeutics begins in the nasal passage, where the drug is deposited onto the mucosal surface. Drugs can be absorbed through two main routes: the respiratory epithelium for main blood stream and the olfactory pathway and trigeminal pathway for direct access of brain. In AD trearment, the pathways allow direct brain delivery, bypassing the restrictive BBB that limits oral and IV drugs. Rapid absorption occurs due to the nasal mucosa's rich vasculization and epithelium.

Distribution

Drugs absorbed through olfactory and trigeminal pathways reach targeted brain regions. This transport avoids systemic circulation, leading to higher drug concentrations in the brain relative to peripheral tissues. This feature of INDD is particularly beneficial for treating AD, where targeting the hippocampus and cortex—the areas most affected by the disease—is critical. Drug distribution via these pathways results in relatively rapid onset of action, as the drug reaches the CNS more quickly than through traditional systemic routes.

Metabolism

The nasal passage is with a variety enzymes, including cytochrome P450 enzymes and peptidases, that can metabolize drugs before they enter systemic circulation or reach the brain. This enzymatic activity can limit the bioavailability of some drugs; however, INDD allows direct brain delivery via olfactory and trigeminal pathways, partially avoiding enzymatic breakdown. In cases where nasal enzymes do affect the drug, formulation strategies such as using enzyme inhibitors or nanoencapsulation can protect the drug from premature metabolism.

Elimination

Intranasally administered drugs that are absorbed into the bloodstream are subject to elimination through the liver and kidneys, similar to systemically administered drugs. However, drugs that reach the brain by the olfactory pathway and trigeminal pathway typically avoid significant first-pass metabolism, enhancing their therapeutic efficacy. The elimination half-life of intranasally administered drugs can vary depending on the formulation, the drug’s chemical properties, and the rate of mucociliary clearance, which gradually removes substances from the nasal cavity. Bioadhesive formulation prolong nasal retention, boosting absorption and minimizing dosing frequency.

Clearance and Bioavailability

The nasal cavity's defense mechanism moves mucus and trapped particles, including drugs, toward the pharynx for expulsion or swallowing. While this system helps protect the respiratory tract, it can reduce the systemic availability of drug delivered via nasal route by limiting time drug remains in contact with the mucosa. To improve bioavailability, bioadhesive

formulations or absorption enhancers are often used to extend residence of drugs in nasal cavity and improve their chances of being absorbed into the brain.

7. CLINICAL STUDIES AND PRECLINICAL MODELS

Preclinical studies on INDD in AD

Preclinical studies highlight the potential of INDD for AD treatment, with rodent models mimicking AD pathology, like amyloid-beta plaques and neurofibrillary tangles, used to assess therapeutic efficacy and safety. Preclinical studies have focused on delivering a range of drugs, including insulin, peptides, neurotrophic factors, and small molecules, to the brain via intranasal route. For example, intranasal insulin has been demonstrated to maximize cognitive function and minimize amyloid-beta deposition in mouse models of AD. Similarly, neurotrophic factors like brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) have shown neuroprotective effects when delivered intranasally in AD models, promoting neuronal survival and improving memory. These studies highlight the ability of INDD to circumvent the BBB, and convey therapeutic concentrations of drugs straight into brain. Additionally, nanoparticle-based delivery systems have been explored in preclinical studies to maximize bioavailability and brain specific delivery of intranasally delivered drugs. For instance, nanoparticles encapsulating donepezil and other cholinesterase inhibitors have been tested in AD models, demonstrating improved brain delivery and cognitive outcomes compared to traditional administration methods. These preclinical studies strongly support INDD as a promising strategy for AD treatment[30].

Clinical trials on INDD for management of AD

Clincal trails have explored INDD's efficacy in AD patients, building on promising preclinical findings. A notable clinical trail demonstrated that intranasal insulin enhances memory and cognitive function in AD and MCI patients. The results from these trials suggest that insulin modulates glucose metabolism in the brain and has neuroprotective effects, reducing neuroinflammation and potentially slowing the progression of AD. Other clinical trials have focused on the intranasal delivery of peptides and neurotrophic factors. Intranasal delivery of neuropeptide Y and vasoactive intestinal peptide has shown potential in enhancing cognition and reducing amyloid-beta in small human studies. Additionally, studies on intranasal BDNF delivery have shown potential for enhancing memory and cognitive performance in AD patients. Although these trails suggest the potential of INDD for AD, full scale studies are required to validate its safety and effectiveness. Further research will likely enhance its precision and applicability in AD treatment[31].

Limitations and Considerations for Translating Animal Studies to Human Use

Despite the success of preclinical studies, translating these findings from animal models to human use poses several challenges. One of the primary limitations is the difference in nasal anatomy between humans and animal models like rodents. The structure, surface area, and clearance mechanisms of the nasal cavity vary significantly between species, which can affect drug absorption and distribution in the brain. In humans, mucociliary clearance and nasal enzymatic activity may alter the bioavailability of intranasally delivered drugs, making it challenging to replicate the same results observed in animal studies. Another limitation is the dose scaling between animal models and humans. Preclinical studies allow precise dose control and detailed monitoring of cognitive effects and AD pathology. However, translating these doses to human use requires careful adjustment to ensure both efficacy and safety, particularly given the limited volume that can be administered intranasally in humans (usually no more than 200 microliters per nostril. Additionally, individual variability in human nasal physiology, including differences in nasal airflow, mucosal surface area, and the presence of co-morbidities such as sinusitis, can affect drug absorption and treatment outcomes. This variability must be considered when designing clinical trials and optimizing intranasal formulations for human use. Lastly, one of the major challenges in translating preclinical findings to clinical practice is the lack of long-term safety data. While INDD has shown potential for transporting drugs to brain efficiently, there is still a need for comprehensive studies on the long-term effects of chronic intranasal administration, particularly with respect to nasal irritation, potential toxicity, and the risk of over-stimulation of certain receptors in the brain[32].

MERITS AND LIMITATIONS OF INTRANASAL DRUG DELIVERY IN ALZHEIMER'S DISEASE (Showed in Table 3)

Intranasal drug delivery (INDD) offers several significant advantages, particularly in the AD treatment. One of the most notable benefits is the ease of use. INDD is a non-invasive and relatively simple method of drug administration, making it highly accessible for patients, including those with cognitive impairments like AD. Patients can self-administer medications via nasal sprays or drops, which improves overall treatment adherence. Unlike invasive methods such as intravenous or intrathecal administration, INDD does not require medical personnel or specialized equipment. Another key benefit is the capacity for precise brain delivery. INDD bypasses the BBB by utilizing the olfactory pathway and trigeminal nerve pathway, which allows direct drug transport to the brain. This not only enhances the therapeutic efficacy of drugs designed to treat AD but also reduces systemic side effects, as the drug primarily concentrates in the brain rather than circulating throughout the

body. The rapid absorption associated with INDD ensures that drugs reach their target sites in the brain quickly, offering faster symptom relief compared to oral administration. Aditinally, INDD has demonstrated potential in enhancing patient adherence owing to its simplicity and reduced necessity for frequent medical visits for drug administration. For patients with neurodegenerative diseases like AD, who often struggle with complicated medication regimens, the simplicity of INDD can improve the likelihood of adherence to treatment plans. Despite its many advantages, INDD also has certain limitations that must be addressed for it to be fully effective in treating AD. A key constraint is the restricted volumetric payload. The nasopharyngeal compartment's diminutive dimensions impose a ceiling on the quantity of therapeutic agents that can be concurrently administered via this route (typically up to 200 microliters per nostril). This restricts the use of larger doses or drugs with low potency that require higher doses for therapeutic effect. Additionally, some large molecules may not be efficiently absorbed intranasally without the use of permeation enhancers or advanced formulations like nanoparticles. Another significant issue is the potential for nasal irritation. Repeated administration of drugs intranasally, particularly those containing permeation enhancers or other excipients, can cause irritation or injury to the nasal mucosa. This may leads to discomfort, dryness, or even inflammation, which could deter patients from adhering to the treatment. Moreover, certain individuals may have preexisting nasal conditions, such as rhinitis or sinusitis, which can further exacerbate these issues and reduce the effectiveness of INDD. Variability in absorption is also a critical concern with INDD. Factors such as individual differences in nasal anatomy, mucociliary clearance rates, and the presence of nasal congestion or infections can affect drug absorption. These variations may result in inconsistent drug delivery and efficacy across different patients. Additionally, enzymatic activity in the nasal cavity can metabolize certain drugs before they are absorbed, further reducing their bioavailability. To overcome the limitations associated with INDD, ongoing research and development are focused on enhancing drug formulations and delivery systems. One potential solution to the issue of limited dose capacity is the use of nanoformulations, such as nanoparticles, liposomes, or micelles, which can encapsulate drugs and improve their stability, absorption, and bioavailability. These systems enabke the administration of higher drug concentrations within the confined volume of nasal cavity; while also offering sustained or controlled release, reducing the need for frequent dosing. The problem of nasal irritation could be addressed by developing bioadhesive formulations that minimize the need for permeation enhancers. These formulations allow the drug to adhere to the nasal mucosa for extended periods, improving absorption without causing irritation. Additionally, using excipients that are less irritating or modifying the pH of nasal formulations to be more compatible with the nasal environment may help reduce irritation and improve patient tolerance. To reduce variability in absorption, personalized medicine approaches could be applied. Tailoring INDD treatments based on individual nasal anatomy and physiology through imaging or diagnostic tools could help optimize drug delivery for each patient. Furthermore, the use of permeation enhancers and enzyme inhibitors in conjunction with nanocarriers can improve drug stability and absorption across a wider population, making INDD more consistent and reliable.

In terms of future perspectives, INDD could play a significant role in combination therapies for neurodegenerative diseases like AD. By using a combination of drugs delivered intranasally, it may be possible to target multiple pathological pathways simultaneously, providing a more comprehensive approach to treatment. Advancements in nanotechnology may enable the creation of smart delivery systems that release drugs based on brain signals or disease markers, improving the precision and efficacy of INDD[33,34].

Table 3. Advantages and limitation of INDD in treatment of AD

S. No.	Advantages	Limitations
1	Ease of use: Non-invasive and simple administration that improves patient adherence, especially in Alzheimer's patients.	Limited dose capacity: Nasal cavity allows for only small volumes (up to 200 microliters), restricting the dose that can be delivered.
2	Patient compliance: Self-administration reduces the need for frequent clinical visits, leading to better treatment adherence.	Nasal irritation: Repeated administration can cause irritation, dryness, or inflammation of the nasal mucosa.
3	Targeted brain delivery: Direct brain access via the olfactory and trigeminal pathways, circumventing the BBB.	Variability in absorption: Differences in nasal anatomy, mucociliary clearance, and nasal conditions (e.g., congestion) affect drug absorption.
4	Rapid absorption: Faster onset of action as drugs reach the CNS more quickly compared to oral or intravenous routes.	Enzymatic degradation: Nasal enzymes can metabolize drugs before they are absorbed, reducing bioavailability.
5	Minimized systemic side effects: Higher drug concentration in brain lowers the threat of toxicity.	Limited availability of long-term safety data: Deficiency of comprehensive studies on the chronic use of intranasal delivery.

8. REGULATORY & COMMERCIALIZATION ASPECTS OF INDD FOR AD

Regulatory Considerations for Developing INDD Systems for AD. The development of INDDS aimed at AD presents several regulatory challenges because of the complexities involved in targeting the brain. Regulatory bodies such as the FDA and EMA mandate comprehensive preclinical and clinical data to confirm the safety and effectiveness of the treatment. One major requirement is proving that intranasally administered drugs can cross nasal epithelium and reach the CNS at therapeutic levels. Bioavailability studies are critical in this respect, as these drugs must demonstrate that they can escape the BBB and deliver sufficient concentrations to treat AD. Additionally, regulatory authorities must evaluate the potential for nasal toxicity with long-term use, given that AD patients often require chronic treatment. Another regulatory challenge is associated with manufacturing and quality control. Strict guidelines govern the manufacturing process for intranasal formulations, including the consistency of particle size, stability, and delivery mechanism. For formulations involving nanoparticles, specialized toxicology studies are required to assess potential nanotoxicity, as current regulatory frameworks for nanoscale formulations are still developing. From a commercialization perspective, developing and bringing an intranasal AD therapeutic to market faces challenges such as high development costs, competitive pressures, and market acceptance. The cost of developing advanced INDD systems that include nanoparticles or other novel delivery systems can be significant, requiring substantial investment in both R&D and clinical trials. Furthermore, the AD therapeutic market is highly competitive, with a growing number of companies working on various oral, injectable, and intranasal treatments. Despite these challenges, the market outlook for INDD in AD is positive. Intranasal delivery offers several advantages, including ease of administration and the potential for superior brain-targeted delivery, making it attractive to both patients and clinicians. Successful outcomes from clinical trials, such as those involving intranasal insulin, have generated increased interest in this delivery method. As the prevalence of AD continues to grow globally, the demand for more effective treatments is expected to rise, creating significant market potential for INDD[35].

9. FUTURE DIRECTIONS AND INNOVATIONS IN INDD FOR AD

The future of INDD in AD treatment looks promising, fueled by continuous advancements in drug delivery technologies. Scientists are continuously investigating new methods to enhance effectiveness and specificity of brain-targeted delivery via the nasal route, with a particular focus on leveraging innovations in nanotechnology and biologics. These developments aim to overcome current challenges such as limited drug absorption, variability in efficacy, and the need for more precise targeting of therapeutic agents[36,37,38,39,40].

Emerging Technologies (e.g., Mucoadhesive Polymers, Novel Drug Carriers)

Emerging technologies are driving advancements in INDD for AD treatment. Mucoadhesive polymers like chitosan and carbopol are being designed to enhane drug retention in the nasal block by bonding to mucosal surfaces. This aids in extending the duration the drug stays in the system and enhances its uptake. Nanoparticles, including solid lipid nanoparticles (SLNs) and liposomes, are also gaining traction as carriers that protect therapeutic agents from degradation and improve their bioavailability in the brain. These carriers can be engineered to release drug gradually, ensuring prolonged delivery.

Personalized INDD Approaches for AD Treatment

Personalized medicine is increasingly becoming a focus in AD treatment, and this concept is being applied to INDD. The development of personalized INDD formulations involves tailoring drug delivery systems based on a patient's unique nasal physiology and disease characteristics. For example, imaging technologies and biomarker analysis can help identify optimal delivery strategies for each patient. In addition, researchers are exploring customized nanoparticles that can be modified with ligands to bind to specific brain receptors, ensuring targeted and efficient delivery.

Enhancing Brain-Targeted Delivery

The future of INDD for AD treatment looks promising, with ongoing advancements in nanotechnology and biophysics that are expected to enhance brain-targeted delivery. Researchers are developing smart drug delivery systems, that can deliver drugs by response to specific neural or biochemical signals. The combination of INDD with gene therapies and biologic drugs could also pave the way for disease-modifying treatments, going beyond symptomatic relief to address the underlying causes of AD.

10. CONCLUSION

INDD offers a non-invasive and efficient route for directly transporting drugs or therapeutic agents to the brain, revolutioning AD treatment. By avoiding the BBB, INDD enhances treatment effectiveness and minimizes systemic effects. Innovations in drug carriers, such as nanoparticles and mucoadhesive polymers, have already demonstrated promising results in preclinical and early clinical studies. As research continues to advance, the integration of personalized approaches and smart delivery systems will further improve the precision and efficacy of brain-targeted therapies. Despite challenges such as

limited dosing capacity and variability in absorption, ongoing technological advancements are expected to overcome these obstacles, making INDD an essential tool in the management of neurodegenerative diseases. The future of INDD is bright, offering new hope for patients with AD and other CNS ailments, ultimately changing the landscape of neurodegenerative disease treatment.

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