

A NARRATIVE REVIEW ON OVERCOMING LIMITATIONS OF CONVENTIONAL ALZHEIMER'S THERAPIES: POTENTIAL OF INTRANASAL DRUG DELIVERY

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Abstract : Alzheimer's disease is a slowly advancing disorder of the brain that leads to progressive neuronal degeneration characterized by cognitive decline, memory impairment, and functional deterioration. Despite significant scientific advances, Traditional treatments mainly focus on alleviating symptoms rather than curing the disease and are limited by poor brain targeting, systemic side effects, low bioavailability, and restricted permeability across the blood–brain barrier (BBB). These challenges have driven the exploration of alternative drug delivery strategies aimed at improving therapeutic efficiency and disease management. Intranasal drug delivery has recently gained attention as a promising non-invasive approach capable of facilitating direct nose-to-brain transport via olfactory and trigeminal neural pathways. By partially bypassing the BBB, this route enhances the drug presence in the central nervous system while reducing systemic exposure and associated adverse effects. In addition, the nasal route offers rapid onset of action, improved patient compliance, and suitability for long-term therapy, particularly in elderly populations. Recent advancements in nanotechnology have further expanded the potential of intranasal administration. Nano emulsions, lipid-based carriers, polymeric nanoparticles, and other nano systems enhance drug solubility, stability, mucoadhesion, and controlled release, thereby improving brain targeting and therapeutic outcomes. This review highlights the limitations of conventional Alzheimer's therapies and critically examines the potential of intranasal drug delivery systems as a novel and effective alternative. While challenges related to formulation development, safety, and clinical translation remain, continued research may pave the way for more targeted and disease- modifying treatment approaches in Alzheimer's disease management.

Index Terms -Alzheimer's Disease, Intra Nasal, Nano formulation, Conventional treatments, route of administration

INTRODUCTION

Alzheimer's disease (AD) is a long-term brain disorder that progressively damages neurons and leads to cognitive decline, memory loss, and impaired reasoning^[1]. National surveys indicate that about 7.4% of Indians aged 60 years and older live with dementia, which includes Alzheimer's disease as the most common cause. It is estimated that 70 % of these dementia cases are attributed to Alzheimer's, making it the leading cause of cognitive decline among elderly , and it is the dominant cause of cognitive decline among the elderly in India^[2]. It is a multi-factorial disorder characterized by extracellular deposition of amyloid-beta plaques, oxidative stress, neuroinflammation, neurofibrillary tangles, and degeneration of cholinergic neurons, which influence the disease pathogenesis^[3]. Low acetylcholine levels promote increased amyloid- β ($A\beta$) production and reduced non-amyloidogenic processing of APP. It indirectly contributes to tau pathology and enhances tau phosphorylation ^[4].

oxidative damage and inflammation of neural tissue are interlinked pathological mechanisms that lead to neuronal damage, synaptic loss, and disease progression, as well as the amyloid- β ($A\beta$) and tau pathology. Oxidative stress arises when the accumulation of free radicals exceeds the neutralizing capacity of cellular antioxidants, leading to cellular damage ^[4]. Neuroinflammation is the chronic induction of the brain's immune cells, mainly Microglia and Astrocytes. In Alzheimer's disease, inflammation becomes persistent and damaging, rather than protective ^[5]. Numerous therapeutic agents have been designed to manage Alzheimer's. At present, no disease-modifying drug is available for treatment. All the treatment methods available are symptomatic treatments ^[6]. Conventional treatment approaches for Alzheimer's disease are often inadequate because factors such as the blood–brain barrier, first-pass metabolism, and peripheral side effects restrict the number of medications that are capable of successfully reaching the target tissue ^[7].

PATHOPHYSIOLOGY OF ALZHEIMER'S

Alzheimer's disease represents among the most serious challenges in modern medicine because of its complex underlying mechanisms and the absence of truly effective disease-modifying treatments. The disease develops through a combination of interconnected processes. The accumulation of amyloid-beta ($A\beta$) plaques outside neurons, the accumulation of tau-related neurofibrillary tangles inside neurons, and persistent neuroinflammation operate in coordination to damage synapses and gradually lead to neuronal death^[8].

Beyond the well-known pathological pathways of Alzheimer's disease (such as amyloid plaque formation and tau protein abnormalities), Recent studies have shown that multiple mechanisms that contribute significantly to the progression of the disease. One of these is mitochondrial dysfunction, where the energy-producing units of brain cells fail to function properly, leading to increased oxidative stress and neuronal damage^[9]. Another key factor is impaired autophagy, a process that normally helps cells clear out damaged proteins and cellular waste; when this system becomes defective, toxic proteins accumulate and worsen neurodegeneration^[10].

In addition, accumulating evidence shows that disturbances in the gut–brain axis may contribute to Alzheimer's disease. Imbalances in intestinal microbiota (dysbiosis) can promote widespread inflammatory processes and alter immunological responses which may influence brain health and accelerate disease progression^[11].

Together, these emerging mechanisms highlight the multifactorial and complex nature of Alzheimer's disease, demonstrating that its progression involves not only classical amyloid and tau pathways but also metabolic, immune, genetic, and microbiome-related factors^[12].

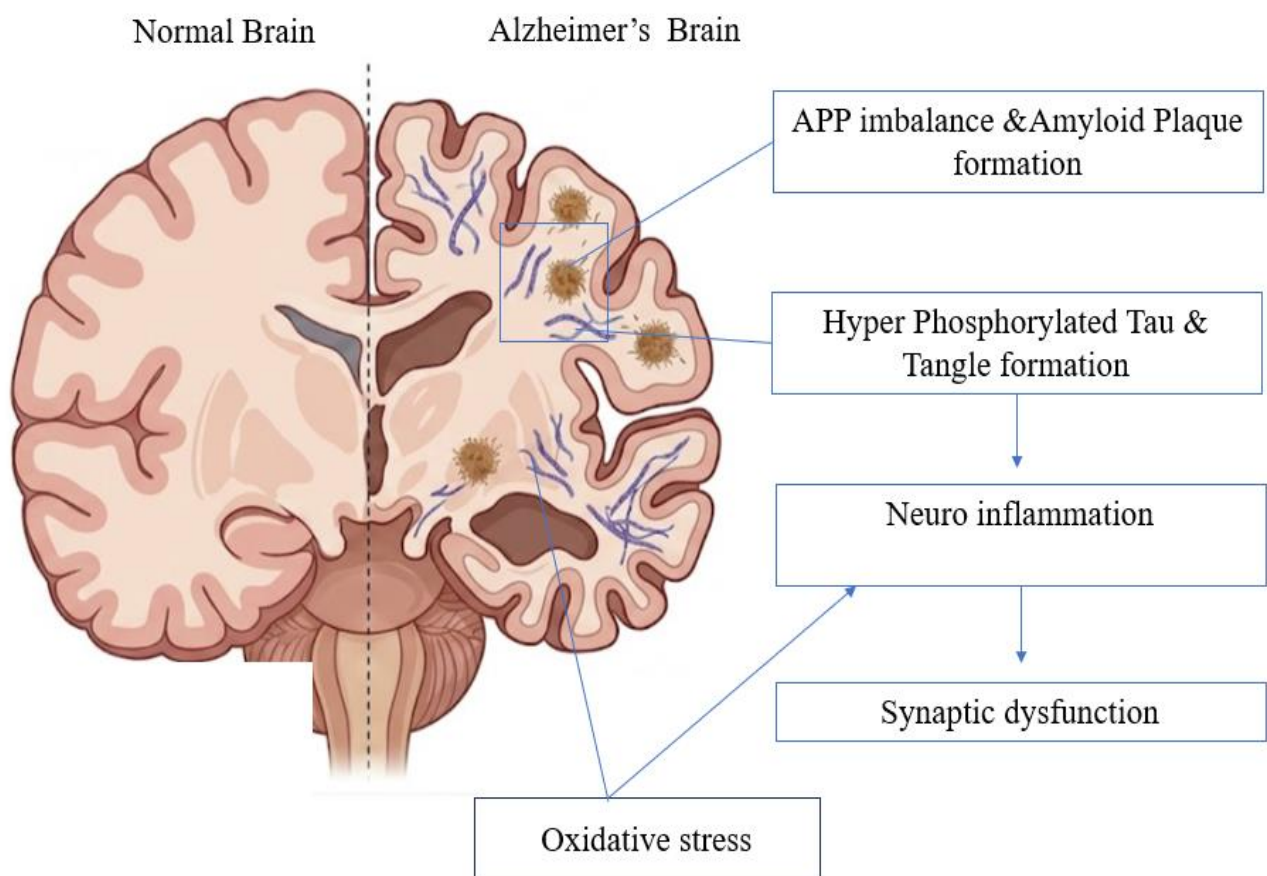


Figure 1: Pathophysiology of Alzheimer's Disease

TREATMENT OPTIONS FOR AD

Existing drugs	Current treatment	Drugs in clinical trials	Recent advanced therapies
1.AcetylcholinesteraseInhibitors (AChEIs)  Donepezil  Rivastigmine  Galantamine 2.NMDA Receptor Inhibitors  Memantine	1.Monoclonal Antibodies in AD  Aducanumab  Lecanemab 2.Supplements Enhancing Cognition & Slowing AD Decline  Melatonin  Eicosapentaenoic Acid  Alpha-Tocopherol (Vitamin E)  Caprylidene	1.Upcoming innovative monoclonal antibody treatments  Donanemab  Semorinemab 2.Tau and Amyloid-targeting treatments  Methylthioninium Moiety  Tramiprosate 3.Anti neuroinflammation, Antidiabetic, and Miscellaneous Agents  NE3107  Metformin  Immunoglobulin  Masitinib 4.Phase2Anti-inflammatory Agents  Atomoxetine  Losartan  Genistein  Trans-resveratrol  Benfotiamine 5.BACE1 Inhibitors  Verubecestat 6.Other investigated drugs  Vafidemstat	1.Nanotechnology in AD Treatment  Nanoliposome  Exosomes  Inorganic Nanoparticles 2.Gene Therapy Strategies →Gene Editing Approaches  Antisense  Oligonucleotides (ASOs)  Epigenetic Modifications  MicroRNAs (miRNAs) 3.Stem Cell Therapy 4.Combination Therapies 5.____Complementary and Alternative Medicine (CAM) Therapies

Table 1:Treatment for Alzheimer's

ROUTE OF DRUG ADMINISTRATION FOR EXISTING THERAPY

The route of drug administration has a significant role in determining therapeutic efficacy, safety, patient adherence, and overall treatment outcomes in Alzheimer's disease (AD). Currently available therapies are administered primarily through oral, transdermal, and intravenous routes. Among these, the oral route remains the most widely used; however, it presents several pharmacokinetic and clinical limitations, particularly in elderly populations ^[13].

Oral Route of Administration

Oral delivery is the most prevalent and convenient route for symptomatic pharmacotherapy in AD. Approved oral medications include cholinesterase inhibitors such as Donepezil, Galantamine, and Rivastigmine, in addition to this the NMDA receptor antagonist Memantine. Such agents are typically delivered once or twice daily in tablet, capsule, or oral solution form ^[13,14].

Advantages of Oral Administration

- Non-invasive and convenient
- High patient acceptance
- Suitable for long-term therapy
- Cost-effective compared to parenteral routes

- Easy dose titration

Despite these advantages, the oral route has significant limitations, particularly in elderly patients with neurodegenerative disease ^[15,16].

Limitations of the Oral Route in Alzheimer's Disease

➤ Gastrointestinal Adverse Effects

Cholinesterase inhibitors commonly lead to digestive side effects such as nausea, vomiting, diarrhoea, anorexia, and weight loss. These effects occur due to peripheral cholinergic stimulation and often limit dose escalation. Poor tolerability frequently results in discontinuation or non-adherence ^[17].

➤ Swallowing Difficulties (Dysphagia)

As AD progresses, patients frequently develop dysphagia and impaired motor coordination, making tablet or capsule intake difficult. This becomes particularly problematic in moderate to severe stages, increasing the risk of aspiration ^[17,19].

➤ First-Pass Hepatic Metabolism

Orally administered drugs undergo hepatic first-pass metabolism, which reduces bioavailability. Variability in cytochrome P450 enzyme activity (especially in elderly individuals) may result in unpredictable plasma drug levels, influencing both efficacy and toxicity ^[17,18].

➤ Blood–Brain Barrier (BBB) Limitations

Although small-molecule drugs like donepezil and memantine cross the BBB, orally it does not specifically target the brain. Systemic distribution reduces the level of the drug reaching the brain-centered nervous system, potentially limiting therapeutic efficiency while increasing peripheral adverse effects ^[20].

➤ Polypharmacy and Drug Interactions

Elderly AD patients mostly experience multiple coexisting conditions (e.g., hypertension, diabetes, cardiovascular disease), leading to polypharmacy. Oral drugs are more susceptible to pharmacokinetic interactions, especially those metabolized by hepatic enzymes. This increases the risk of adverse drug reactions ^[21].

➤ Compliance Issues

Cognitive impairment directly affects medication adherence. Forgetfulness, confusion, and lack of insight into illness may lead to missed doses or incorrect administration, particularly in patients without caregiver supervision ^[22].

Transdermal Route of Drug Administration in Alzheimer's disease

The transdermal route of drug administration has emerged as an important alternative to oral treatment of Alzheimer's disease (AD), particularly among geriatric patients with digestive intolerance or problems with swallowing. Transdermal therapeutic systems administer medication across the skin into systemic circulation through controlled-release patches. In AD therapy, this approach is primarily utilized for symptomatic treatment ^[23].

Approved Transdermal Therapy

Currently, the most widely used transdermal therapy in AD is the Rivastigmine patch. Rivastigmine, a cholinesterase inhibitor, enhances cholinergic neurotransmission by inhibiting acetylcholinesterase and butyrylcholinesterase. This formulation allows for prolonged drug release over 24 hours and is approved for covering mild through moderate stages of Alzheimer's disease ^[24].

Pharmacokinetic and Therapeutic Advantages

The transdermal route bypasses gastrointestinal absorption and hepatic first-pass metabolism. Drug molecules penetrate the stratum corneum and diffuse into the dermal microvasculature, leading to systemic distribution ^[24]. This method offers several advantages:

- **Reduced Gastrointestinal Adverse Effects** – Compared to oral rivastigmine, the patch significantly lowers the incidence of nausea and vomiting due to gradual drug absorption and lower peak plasma concentrations.
- **Stable Plasma Drug Levels** – Continuous delivery minimizes peak–trough fluctuations, improving pharmacodynamic stability.

- **Improved treatment adherence**– Once-daily application simplifies treatment regimens, which is beneficial for cognitively impaired patients.
- **Suitable for Dysphagic Patients** – As Alzheimer’s progresses, many patients develop difficulty swallowing; the patch eliminates the need for oral intake.
- **Visual Confirmation of Adherence** – Caregivers can easily verify medication administration ^[25].

Limitations of the Transdermal Route

Despite these benefits, the transdermal route has several important limitations:

➤ **Skin-Related Side Effects**

The most common limitation is local dermatological reactions, including erythema, itching, irritation, and allergic contact dermatitis. Improper site rotation may exacerbate these effects and reduce tolerability ^[25,26].

➤ **Limited Drug Permeability**

The skin acts as a strong barrier, particularly the stratum corneum. Only drugs with suitable physicochemical properties (low molecular weight, lipophilicity, and potency at low doses) can be effectively delivered transdermally. Large molecules and biologics are generally unsuitable without advanced enhancement technologies ^[25,26].

❖ **Dose Limitations**

Transdermal systems are constrained by the level of drug that can permeate the skin surface. High-dose medications may not attain the effective plasma concentrations through this route ^[26].

❖ **Slower Onset of Action**

Compared to oral or intravenous administration, transdermal delivery may have a slower onset due to gradual absorption ^[26].

❖ **Adhesion and Application Issues**

Improper patch application, accidental removal, or poor adhesion (especially in humid climates or excessive sweating) can compromise drug delivery ^[27].

Parenteral route of administration

The parenteral route of drug administration involves the delivery of medications by injection, bypassing the gastrointestinal tract. In Alzheimer’s disease (AD), parenteral administration is primarily used for disease-modifying biologic therapies and investigational agents that cannot be effectively delivered orally. This route ensures rapid systemic availability and precise dosing but is associated with important clinical and logistical limitations ^[28].

Types of Parenteral Routes Used in Alzheimer’s Disease

❖ **Intravenous (IV) Administration**

Intravenous infusion is considered the most important parenteral route in AD treatment, particularly for monoclonal antibody therapies targeting amyloid pathology ^[28].

Approved agents include:

- **Lecanemab**
- **Donanemab**

These biologics are administered via periodic IV infusions (typically every 2–4 weeks) in controlled clinical settings. IV delivery ensures 100% bioavailability and controlled plasma concentration profiles ^[28,29].

❖ **Subcutaneous (SC) Administration**

monoclonal antibodies are currently under investigation in subcutaneous formulations to allow easier outpatient or home-based administration. Subcutaneous delivery offers slower systemic absorption compared to IV infusion but may improve convenience ^[29].

❖ Intramuscular (IM) Administration

Currently, intramuscular administration is rarely used in conventional for standard AD therapy but it could be employed for supportive treatments or investigational agents ^[29].

Limitations of the Parenteral Route

Despite its advantages, the parenteral route has several significant limitations in Alzheimer's therapy: ^[30,31]

➤ Invasiveness

Injection-based administration may cause pain, discomfort, anxiety, and risk of local complications such as phlebitis or hematoma.

➤ Risk of Infusion Reactions

Monoclonal antibodies may cause infusion-induced adverse effects, such as fever and chills, including fever, chills, rash, or hypersensitivity responses.

➤ Amyloid-Related Imaging Abnormalities (ARIA)

Anti-amyloid monoclonal antibodies may lead with ARIA, including cerebral edema (ARIA-E) and micro haemorrhages (ARIA-H), requiring routine MRI monitoring.

➤ High Cost

Parenteral biologic therapies are expensive due to manufacturing complexity and healthcare facility requirements.

➤ Need for Clinical Supervision

Intravenous infusions require hospital or specialized centre visits, increasing logistical burden for patients and caregivers.

➤ Limited Brain Penetration

Although administered systemically, monoclonal antibodies must still cross the blood–brain barrier in small fractions, limiting the proportion reaching brain tissue.

Challenges in CNS Drug Delivery

➤ Restricted Drug Permeability

More than 98% of small-molecule drugs and nearly 100% of large biologics fail to cross the BBB in therapeutically relevant amounts. ^[31,32]

➤ Efflux Transporters

ATP-binding cassette (ABC) transporters such as P-glycoprotein actively pump many drugs back into systemic circulation, reducing intracerebral drug concentration. ^[32]

➤ Enzymatic Degradation

Metabolic enzymes in endothelial cells can degrade drugs before they reach brain tissue.

➤ Molecular Size and Polarity

Large molecules such as peptides, proteins, and monoclonal antibodies have poor BBB penetration without specialized transport mechanisms. ^[32]

➤ Systemic Toxicity

High dosage adjustments may be needed to achieve minimal brain exposure, increasing peripheral adverse effects ^[31,33].

➤ Variability in BBB Integrity

Aging and disease-related vascular changes alter BBB permeability unpredictably, complicating dose optimization ^[31].

INTRA NASAL ROUTE STRATEGY IN ALZHEIMER'S DISEASE

The blood–brain barrier (BBB) is a specialized semipermeable barrier that protects the brain-centered nervous system from toxins, pathogens, and fluctuations in systemic circulation. While essential for maintaining neural homeostasis, the BBB presents among the most important obstacles in developing effective therapeutics for neurological disorders, including Alzheimer's disease ^[31].

In Alzheimer's disease, BBB integrity may be partially compromised due to vascular dysfunction, inflammation, and amyloid- β deposition. However, this disruption is inconsistent and does not sufficiently enhance drug penetration. In fact, pathological changes may further impair transport mechanisms, complicating therapeutic delivery ^[33,34].

Intranasal administration has gained attention as emerged as an effective, non-invasive method for delivering drug directly to the central nervous system (CNS). Unlike conventional systemic administration, drug delivery via the nasal route partially bypasses the blood–brain barrier (BBB) by means of anatomical pathways connecting the nasal cavity to the brain. This strategy has garnered substantial attention in AD research because of the limited BBB permeation of most conventional drugs ^[35].

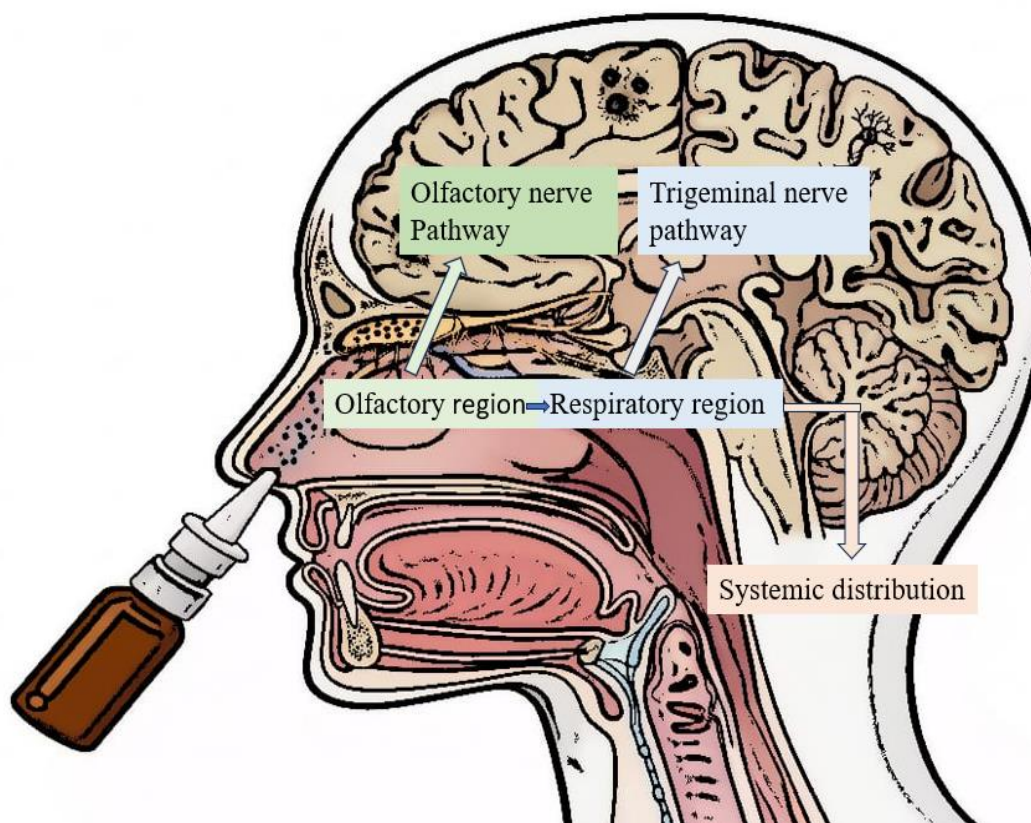


Figure 2: Intra nasal route strategy for Alzheimer's disease

Direct and Indirect Nose-to-Brain Transport

The Intra nasal route of delivery has developed as a effective way to improve transport of drug across the brain and central neural system targeting, particularly in progressive neurological diseases like Alzheimer's disease. The nasal cavity provides both primary and secondary pathways for drug delivery to the brain. Direct transport occurs via the olfactory -trigeminal neural pathways, while indirect delivery occurs through systemic absorption followed by blood–brain barrier (BBB) penetration. ^[35,36]

Direct Nose-to-Brain Transport Pathways

Olfactory Pathway

The nasal-olfactory pathway is considered the most rapid and a reliable route for direct brain targeting after intranasal administration. ^[36,37]

The nasal -olfactory region consists of:

- **Olfactory epithelium**
- **Anterior olfactory nucleus**
- **Olfactory tract**
- **Olfactory bulb**

The nasal-olfactory epithelium is lined by a mucosal layer composed of:

- **Olfactory receptor neurons (ORNs)**
- **Supporting (sustentacular) cells**
- **Basal cells**

Supporting cells help in maintain structural framework and metabolic support to olfactory neurons and contain microvilli that assist in sensory processes. Basal cells are responsible for the regeneration and repair of the olfactory mucosa, ensuring maintenance of epithelial integrity. ^[37]

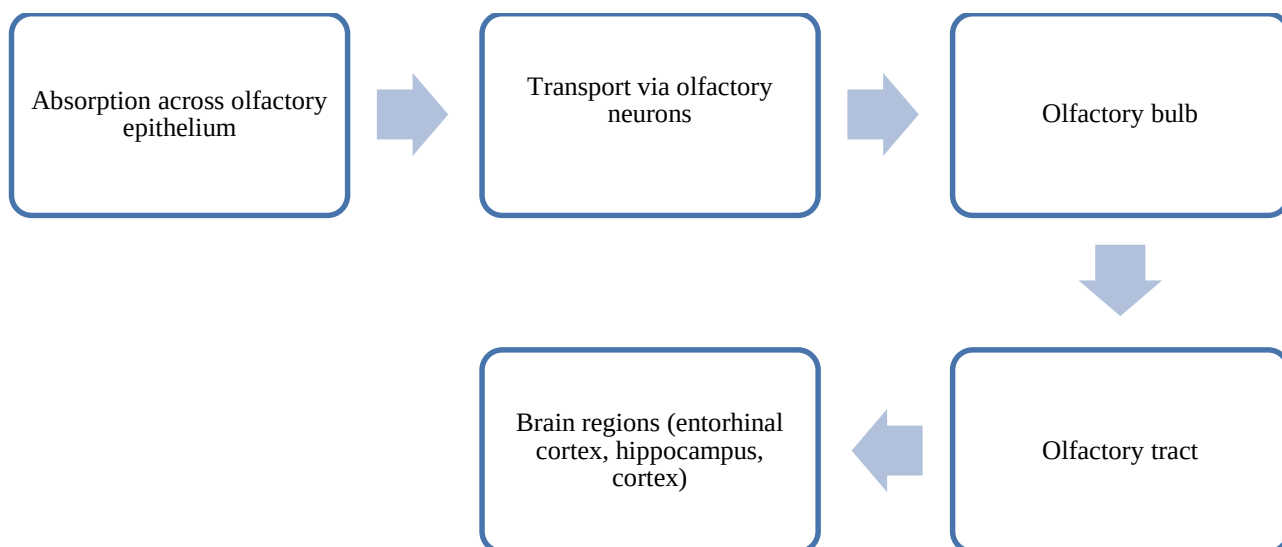


Figure 3: : Flow chart of Olfactory pathway

Mechanism of Drug Transport

Drugs administered intranasally can cross the olfactory mucosa through multiple mechanisms:^[38]

Intraneuronal Transport

- It is relatively slow process and may require hours to days.

Extra neuronal Transport

- It is generally faster and occurs within minutes.

Drug molecules enter olfactory receptor neurons.	- It occurs through 2 transport Paracellular transport: - Drugs pass between cells through tight junctions - Primarily favours hydrophilic molecules.
Transported along axons passing through the cribriform plate of the ethmoid bone.	Transcellular transport: - Drugs cross directly through supporting cells. - Occurs via passive diffusion (lipophilic drugs) or receptor-mediated endocytosis.
Transport continues to the olfactory bulb and subsequently to higher brain regions.	- After crossing the epithelium, drugs reach move toward the olfactory region . - Moves to other CNS regions, including the cortex, cerebrum, and cerebellum.

Table 2: Comparison of Mechanism of Transport of olfactory pathway



Trigeminal Nerve Pathway

The trigeminal nerve pathway represents another major direct route for nose-to-brain delivery.

The trigeminal nerve is the largest cranial nerve and innervates both:^[37,38]

- Olfactory epithelium
- Respiratory epithelium

It has three branches: Ophthalmic, Maxillary, and Mandibular

The ophthalmic and maxillary branches are particularly important for nasal-to-brain drug delivery. These branches converge at the trigeminal ganglion and extend into the CNS, terminating primarily in the brainstem.

Mechanism of Transport

Drugs can reach the brain via:

- Intracellular endocytic transport**
- Axonal transport along trigeminal neurons**

Two main entry routes include:

- Via the respiratory epithelium to the brainstem
- Through the dorsal olfactory epithelium and cribriform plate to the rostral and caudal brain regions

Preclinical studies have demonstrated that biologically active molecules such as insulin-like growth factor-1 (IGF-1) and lidocaine can reach the brainstem and spinal cord within minutes through this pathway. Compared to the olfactory pathway, the trigeminal route primarily targets deeper brain structures such as the brainstem.^[37,38]

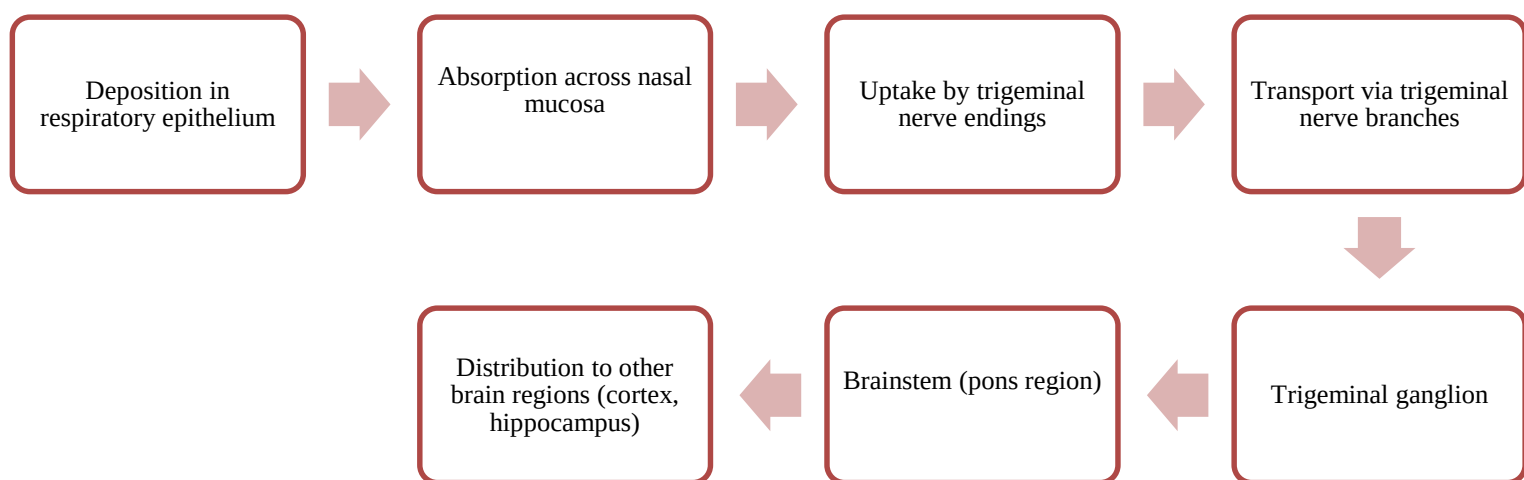


Figure 4: Flow chart of Trigeminal pathway

Systemic Pathway

Systemic pathway is an another way the intranasally administered drugs will follow.^[39]

Mechanism

- Drugs are taken up via the nasal vasculature.
- They enter systemic circulation.
- Subsequently, they must permeate the BBB to reach the brain.

Limitations of Systemic Pathway

- Slower onset of CNS action
- Reduced brain bioavailability due to the BBB restriction
- Greater systemic exposure
- Hepatic and renal elimination
- Interpatient variability in absorption and metabolism

Non polar drugs are more chance to utilize this route, as they can move through the BBB after entering systemic circulation.^[39]

Pathway	Speed	Target Regions	Transport Type
Olfactory (intraneuronal)	Slow	Olfactory bulb → cortex	Axonal
Olfactory (extra neuronal)	Fast	Cortex, cerebrum	Paracellular / transcellular
Trigeminal	Moderate–Fast	Brainstem, spinal cord	Axonal/endocytic
Systemic	Slow	Whole brain (BBB dependent)	Hematogenous

Table 3 : Comparative Overview of Pathways

Benefits of Nasal Route of Administration

The administration of drugs through intra nasal route has increased focus as an alternative and innovative drug delivery pathway, especially for systemic and central neural system therapies, including Alzheimer's disease. Its unique anatomical and physiological characteristics provide several clinical benefits compared to traditional oral and parenteral routes.^[40]

➤ **Rapid initiation of drug action**

The nasal passage is extensively vascularized, enabling fast absorption of drug into systemic circulation. Drugs can permeate the bloodstream quickly, leading to increased pharmacological actions as compared to oral administration. It is beneficial in acute conditions and CNS disorders where prompt action is required.^[40]

➤ **Bypass of First-Pass Hepatic Metabolism**

Unlike oral drugs, intranasally administered drugs avoid gastrointestinal degradation and first-pass biotransformation in the liver. This enhances bioavailability and reduces dose levels needed for drugs that are extensively metabolized when taken orally.^[40]

➤ **Direct Nose-to-Brain Delivery**

A major advantage is its ability to partially bypass the blood–brain barrier (BBB) via the olfactory-trigeminal neural pathways. This facilitates:

- Improved CNS targeting
- High drug concentration in brain tissues
- Reduced systemic exposure
- Enhanced therapeutic efficiency for progressive neurological diseases. ^[40,41]

➤ **Non-Invasive and Patient-Friendly**

The intra nasal route is painless and needle-free, improving patient compliance—especially in:

- Elderly patients
- Paediatric populations
- Chronic therapy cases
- Patients with swallowing difficulties

➤ **Suitable for Peptides and Biologics**

The nasal route protects certain drugs from gastrointestinal enzymatic degradation. Peptides, proteins, hormones (e.g., insulin), and neuronal growth factors can be delivered effectively, which would otherwise be unstable via oral administration.^[41]

➤ **Reduced Systemic Side Effects**

Because some fraction of the drug can reach the target organ directly (e.g., brain), systemic drug exposure may be reduced. This approach helps to reduce side effects associated with peripheral distribution.^[40,41]

➤ **Ease of Administration and Self-Use**

Intranasal formulations such as sprays, drops, and powders are convenient and allow ^[40,41]

- Self-administration
- Reduced need for healthcare professionals
- Lower hospitalization costs

➤ Improved Bioavailability

For drugs with low oral bioavailability or instability in the digestive system, the nasal route may significantly enhance bioavailability.^[41]

➤ Avoidance of Gastrointestinal Irritation

Drugs associated with gastric discomfort or are easily degraded in acidic environments benefit from nasal administration since the gastrointestinal tract is completely bypassed.^[41]

➤ Target based Drug Delivery

Advanced formulations such as:

- Mucoadhesive systems
- Nano emulsions
- Nanoparticles
- In situ gels

can further enhance nasal residence time and targeted delivery, particularly for CNS applications.^[42]

NOVEL DRUG ADMINISTRATION SYSTEMS FOR BRAIN TARGETS THROUGH INTRA NASAL DELIVERY IN AD

Alzheimer's disease (AD) therapy faces a major challenge: the neurovascular barrier, which restricts nearly 98% of therapeutic molecules from entering the brain. Conventional oral drugs often show poor brain bioavailability, systemic adverse effects, and limited efficacy. Therefore, novel drug administration systems are being developed to enhance brain targeting, bioavailability, controlled release, and reduced toxicity.^[43]

The effective approaches are nanoparticle-based drug delivery systems. Biodegradable polymer-based nanoparticles such as PLGA and chitosan allow modulated and gradual release will prevent the chemical degradation of drug or enzymatic degradation. Lipid-based transport systems like lipid-based solid and lipid nano delivery systems enhance the solubility of water-insoluble drugs and improve their effectiveness to penetrate the BBB^[43]. These are examined for delivering conventional anti-Alzheimer drugs like donepezil and rivastigmine, along with natural substances such as curcumin, which otherwise suffer from poor bioavailability.^[43,44]

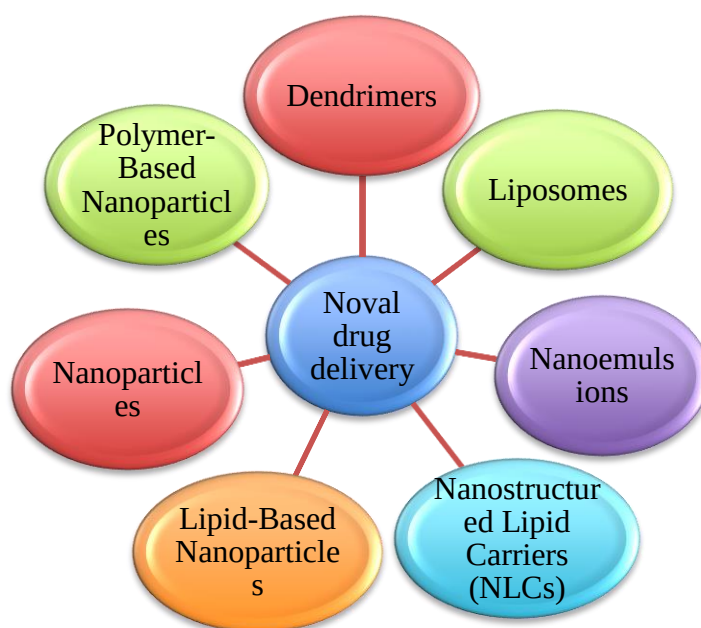


Figure 5 : Novel drug delivery system



Nanoparticles

Nanoparticles are submicron-sized carriers, typically from 1 to 1000 nm, designed to enhance the drug penetration through biological membranes. In Alzheimer's disease, nanoparticles have the significant importance as they can improve the drug dissolution nature, prevent enzymatic degradation of active agents, prolong systemic circulation, and improve targeting across the BBB. Depending on their composition, nanoparticles can be designed to provide the controlled drug release in a prolonged way or to exhibit a particular reaction to corresponding stimuli within the brain environment.^[43]

Nanoparticles may cross the blood–brain barrier via multiple processes, including receptor-mediated endocytosis, adsorptive-mediated transcytosis, or via intranasal delivery pathways like the olfactory and trigeminal nerves. Their outer layer can also be modified with conjugated targeting molecules like transferrin or apolipoprotein E to enhance receptor-specific uptake into brain tissue.^[43,44]



Polymer-Based Nanoparticles

Polymer-based nanoparticles are among the most widely studied systems for Alzheimer's therapy. They are produced from biodegradable and biocompatible molecules like poly(lactic-co-glycolic acid) (PLGA), chitosan, and polyethylene glycol (PEG). Their major advantage lies in their activity to provide modulated and long-lasting release; it helps maintain adequate therapeutic levels of the molecule in the brain over extended periods.^[44]

In Alzheimer's research, polymer-based nano formulation has been studied for delivering cholinesterase inhibitors such as donepezil and rivastigmine. For example, Curcumin has poor solubility in aqueous media and rapid metabolism; encapsulation in polymeric nanoparticles enhances its stability and brain penetration. Furthermore, chitosan-based nano compounds have the important role for intranasal administration because of its adhesive properties on mucosa, which increase the residence time in the intra nasal region and improve direct nose-to-brain transport^[46]

Overall, polymer-based nanoparticles offer improved bioavailability, reduced systemic toxicity, and the capacity for surface functionalization to achieve the site-specific drug delivery in Alzheimer's disease.^[45,46]



Lipid-Driven Nanoparticle Systems

Lipid-Driven Nanoparticle Systems are another important category in Alzheimer's drug delivery. These include lipid-based solid nanoparticles and nanostructured lipid delivery systems. Unlike polymeric nanoparticles, lipid-based systems utilize physiological lipids, which enhance biocompatibility and decrease toxic effects.^[46]

These nano compounds are formed with a solid lipid core structure that cover the lipid soluble drugs, shielding them from degradation and providing controlled release. advanced lipid nanocarriers represent an improved version of SLNs, incorporating a mixture of solid and liquid lipids to increase drug-loading capacity and prevent drug expulsion during storage.

Lipid-based nanoparticles play an important role delivering hydrophobic compounds such as curcumin, resveratrol, and certain essential oils being investigated for neuroprotective effects. Their lipid nature facilitates interaction with cellular membranes, improving BBB penetration. Additionally, when administered intranasally, lipid nanoparticles can directly target the brain by means of the olfactory-trigeminal pathway, thus making them favourable for Alzheimer's treatment^[46,52].



Lipid Carriers for nano compounds

Lipid carriers for nano compounds are an advanced generation of lipid-based nanoparticles that combine solid and liquid lipids to form an imperfect lipid matrix. This structural modification overcomes some of the disadvantages connected with solid lipid nanoparticles, particularly low drug loading capacity^[47].

The inclusion of liquid lipids enhances drug incorporation, stability, and controlled release properties. NLCs also demonstrate improved flexibility in accommodating both hydrophilic and lipophilic compounds. Their nanoscale size and lipid composition support efficient penetration across biological membranes, including the blood–brain barrier^[48].

In Alzheimer's research, NLCs are being developed for the transport of neuroprotective compounds and anti-amyloid agents. Their improved stability makes them a promising alternative to conventional lipid-based systems.^[49]



Nano-sized emulsion systems

Nano-sized emulsion systems are known for the property of stable dispersions consisting of non-polar and aqueous phases emulsified by emulsifiers, to attain the particle sizes typically in the nano meter range. These systems are particularly useful for enhancing the solubility of poorly water-soluble drugs.^[50]

A major advantage of nanoemulsions is their increased inferential area, which attain rapid drug absorption and improved bioavailability. They are useful for intranasal delivery, where they facilitate efficient drug permeation across the nasal mucosa and direct transport to the brain.^[51]

In Alzheimer's disease, Nano-sized emulsion system shave been studied for delivering lipophilic drugs, antioxidants, and natural compounds. Their drug solubility and absorption properties make them an effective approach for brain-targeted therapy.^[51]



Dendrimer-based nanocarriers

Dendrimer-based nanocarriers exhibit extensive branching tree-like macromolecules with a well-defined structure and terminal functional groups. These surface groups can be altered to attach drugs, targeting ligands, or imaging agents.^[54]

Their distinct structure facilitates controlled manipulation over size, shape, and drug loading, make them suitable for targeted drug delivery. Dendrimers can cross biological barriers and interact with pathological targets such as amyloid-beta aggregates.^[54,55]

In Alzheimer's therapy, dendrimers are recommended because of their property to reduce amyloid plaque formation, reduce neuroinflammation, and deliver therapeutic molecules directly to affected brain regions. Their multifunctional nature offers significant promise in advanced neurotherapeutics.^[54,55]



Liposomes

Liposomes are nano-sized vesicular carriers consisting of one or more concentric lipid bilayers encasing an internal aqueous compartment, allowing efficient covering of both poplar and non-polar drugs. Because of their unique structural organization, liposomes are useful for entrapping hydrophilic agents in the aqueous core while simultaneously incorporating lipophilic molecules within the lipid bilayer, which contributing the appropriate carriers for Alzheimer's disease management. ^[56]

The major benefits of liposomes is their excellent biocompatibility, as they closely resemble biological membranes. Liposomes can be surface-modified with PEGylated, using polyethylene glycol to increase circulation time and reduce immune recognition. Furthermore, Liposomes can be conjugated with targeting ligands to enhance specificity like transferrin or lactoferrin to promote receptor-mediated delivery across the BBB.^[57]

Liposomes are the potential carriers for delivering anti-amyloid agents, antioxidants, and gene therapies aimed at reducing amyloid-beta accumulation and tau pathology. The effectiveness of these systems to enable site-specific drug delivery while limiting toxicity underscores their significant potential for future clinical translation in Alzheimer's disease therapy.^[57]

CONCLUSION

Alzheimer's disease continues as the major global challenging neurodegenerative conditions worldwide, with current therapeutic options providing only modest and temporary symptomatic improvement. Conventional oral and parenteral treatments are significantly limited by poor brain penetration, systemic side effects, decreased bioavailability, and the protective nature of the blood-brain barrier. As a result, these therapies do not adequately modify disease progression, highlighting the necessity for more efficient and targeted delivery strategies.

The drug transport through nasal region offers a scientifically compelling alternative by enabling direct entry to the brain through olfactory region & trigeminal region of nose . This route minimizes systemic exposure while enhancing central neural system targeting, thereby potentially improving therapeutic efficiency and reducing unwanted side effects. Its non-invasive and patient-friendly nature further supports better compliance, particularly in elderly populations who require long-term treatment.

Recent innovations in nanotechnology have enabled the potential of intranasal therapy. Novel carriers like nano emulsions, lipid-based systems, and polymeric nanoparticles have the property to increase the drug solubility, stability, controlled release, and mucosal retention. These innovations may improve brain bioavailability and open new possibilities for delivering neuroprotective agents, peptides, and disease-modifying compounds sometimes it may become difficult to administer effectively.

Overall, drug transport through nasal region represents a forward-looking strategy with strong potential to remove the major drawbacks of conventional Alzheimer's therapies. Continued multidisciplinary research and clinical validation may lead to safer, more efficient, and targeted treatment approaches capable of enhancing clinical outcomes in patients with Alzheimer's disease.

REFERENCE

- 1) Sochocka M, Donskow-Łysoniewska K, Diniz BS,. The gut microbiome alterations and inflammation-driven pathogenesis of Alzheimer's disease. *Front Aging Neurosci.* 2019;11: 232.
- 2) Knopman DS, Amieva H, Petersen RC,. Alzheimer disease. *Nat Rev Dis Primers.* 2021;7:33.
- 3) Nady DS, Bakowsky U, Fahmy SA. Recent advances in brain delivery of synthetic and natural nano therapeutics: Reviving hope for Alzheimer's disease patients. *J Drug Deliv Sci Technol.* 2023 Nov;89:105047.
- 4) Singh B, Day CM, Abdella S, Garg S. Alzheimer's disease current therapies, novel drug delivery systems and future directions for better disease management. *J Control Release.* 2024 M;367:402–424.
- 5) Vohra M, Amir M, Sharma A, Wadhwa S. Formulation strategies for nose-to-brain drug delivery in Alzheimer's disease. *Health Sciences Review.* 2023;6:100075
- 6) Yiannopoulou KG, Papageorgiou SG. Current and future treatments in Alzheimer disease. *CNS Drugs.* 2020;34:1-14.
- 7) Pathan A. Limitations of Alzheimer's Disease Medications. *NeuroPharmac Journal.* 2023;8(3):11-17.
- 8) Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev.* 2018;6:CD001190.
- 9) Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *British Journal of Clinical Pharmacology.* 2019;57(1):6–14
- 10) Singh B, Day CM, Abdella S, Garg S. Alzheimer's disease current therapies, novel drug delivery systems and future directions. *Journal of Controlled Release.* 2024;367:402-424.
- 11) Rankin A, Cadogan CA, Patterson SM, et al. Interventions to improve the appropriate use of polypharmacy for older people. *BMJ Open.* 2018;8(3):e019012.
- 12) Smith D, Lovell J, Weller C, . A systematic review of medication adherence in people with dementia. *BMC Geriatr.* 2017;17(1):1–12.
- 13) Paudel KS, Milewski M, Swadley CL, Challenges and opportunities in dermal/transdermal delivery. *Therapeutic Delivery.* 2010;1(1):109–131.
- 14) Schurad B, Koch C, Schug B, Morte A, Vaqué A, De la Torre R, et al. Comparative bioavailability study of a novel multi-day patch formulation of rivastigmine (twice weekly) with Exelon transdermal patch (daily): a randomized clinical trial. *Curr Alzheimer Res.* 2022;19(7):541-553.
- 15) Gaikwad SS, Zanje AL, Somwanshi JD. Advancements in transdermal drug delivery: A comprehensive review of physical penetration enhancement techniques. *Int J Pharm.* 2024;652:123856.
- 16) Prausnitz, M. R., & Langer, R. 2020. Transdermal drug delivery. *Nature Biotechnology*, 2020: 38, 1042–1050.
- 17) Brown, M. B. Dermal and transdermal drug delivery systems: Current and future prospects. *Drug Delivery and Translational Research*, 10, 140–158.
- 18) Van Dyck C.H. Lecanemab in Early Alzheimer's Disease. *New England Journal of Medicine*, 388, 9–21.
- 19) Sims.J.R. Donanemab in Early Symptomatic Alzheimer Disease. *Journal of the American Medical Association*, 330(6), 512–527.
- 20) Knopman DS, Jones DT, Greicius MD. Failure to demonstrate efficacy of aducanumab: an analysis of the EMERGE and ENGAGE trials as reported by Biogen. *Nat Rev Neurol.* 2021;17(9):529–530.
- 21) Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood–brain barrier. *Neurobiol Dis.* 2010;37(1):13–25.
- 22) Pardridge WM. Drug transport across the blood–brain barrier. *J Cereb Blood Flow Metab.* 2012;32(11):1959–1972.
- 23) Storck SE, Meister S, Nahrath J, Meißner JN, Schubert N, Di Spiezio A, et al. Endothelial LRP1 transports amyloid-β1–42 across the blood–brain barrier. *J Clin Invest.* 2016;126(1):123–136.
- 24) Lochhead JJ, Thorne RG. Olfactory drug delivery with intranasal sprays after nasal midvault reconstruction. *Int J Pharm.* 2023;644:123341.
- 25) Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. *Life Sci.* 2018;195:44–52.
- 26) Khan AR, Liu M, Khan MW, Zhao G. Progress in brain targeting drug delivery system by nasal route. *J Control Release.* 2017;268:364–389.
- 27) Pina Costa C, Moreira JN, Amaral MH, Lobo JMS, Silva AC. Targeted drug delivery to the brain via intranasal nanoemulsion: Available proof of concept and existing challenges. *Int J Pharm.* 2019;565:258–268.
- 28) Luo D, Ni X, Yang H, Feng L, Chen Z, Bai L. A comprehensive review of advanced nasal delivery: Specially insulin and calcitonin. *Eur J Pharm Sci.* 2024 Jan 1;192:106630. doi:10.1016/j.ejps.2023.106630.

- 29) Keller, L.-A., Merkel, O., & Popp, A. Intranasal drug delivery: Opportunities and toxicologic challenges during drug development. *Drug Delivery and Translational Research*.2022: 12(3), 735–757.
- 30) Safarov R, Fedotova O, Uvarova A, Gordienko M, Menshutina N. Review of intranasal active pharmaceutical ingredient delivery systems. *Pharmaceuticals (Basel)*. 2024;17(9):1180.
- 31) Wei S, Zhai Z, Kong X, Wu C, Zhu B, Zhao Z .Strategies to enhance efficiency of intranasal drug delivery by improving drug absorption. *Int J Pharm*. 2025;676:125584.
- 32) Lombardo R, Musumeci T, Carbone C, Pignatello R. Nanotechnologies for intranasal drug delivery: an update of literature.*PharmDevTechnol*.2021;26(8):824–845.
- 33) Chahat A, Shome A, Chawla PA. Role of novel drug delivery systems in managing Alzheimer’s disease. *Novel Drug Delivery Systems in the management of CNS Disorders*. 1st ed. Elsevier; 2025. p. 199–214
- 34) Lochhead JJ, Thorne RG. Olfactory drug delivery with intranasal sprays after nasal midvault reconstruction. *Int J Pharm*. 2023;644:123341.
- 35) Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. *Life Sci*. 2018;195:44–52.
- 36) Khan AR, Liu M, Khan MW, Zhao G. Progress in brain targeting drug delivery system by nasal route. *J Control Release*. 2017;268:364–389.
- 37) Pina Costa C, Moreira JN, Amaral MH, Lobo JMS, Silva AC. Targeted drug delivery to the brain via intranasal nanoemulsion: Available proof of concept and existing challenges. *Int J Pharm*. 2019;565:258–268.
- 38) Luo D, Ni X, Yang H, Feng L, Chen Z, Bai L. A comprehensive review of advanced nasal delivery: Specially insulin and calcitonin. *Eur J Pharm Sci*. 2024 Jan 1;192:106630. doi:10.1016/j.ejps.2023.106630.
- 39) Keller, L.-A., Merkel, O., & Popp, A. Intranasal drug delivery: Opportunities and toxicologic challenges during drug development. *Drug Delivery and Translational Research*.2022: 12(3), 735–757.
- 40) Safarov R, Fedotova O, Uvarova A, Gordienko M, Menshutina N. Review of intranasal active pharmaceutical ingredient delivery systems. *Pharmaceuticals (Basel)*. 2024;17(9):1180.
- 41) Wei S, Zhai Z, Kong X, Wu C, Zhu B, Zhao Z .Strategies to enhance efficiency of intranasal drug delivery by improving drug absorption. *Int J Pharm*. 2025;676:125584.
- 42) Lombardo R, Musumeci T, Carbone C, Pignatello R. Nanotechnologies for intranasal drug delivery: an update of literature.*PharmDevTechnol*.2021;26(8):824–845.
- 43) Chahat A, Shome A, Chawla PA. Role of novel drug delivery systems in managing Alzheimer’s disease. *Novel Drug Delivery Systems in the management of CNS Disorders*. 1st ed. Elsevier; 2025. p. 199–214
- 44) Alghareeb S, Asare-Addo K, Conway B, Adebisi A. PLGA nanoparticles for nasal drug delivery. *Journal of Drug Delivery Science and Technology*. 2024;95:105564.
- 45) Vohra M, Amir M, Sharma A, Wadhwa S. Formulation strategies for nose-to-brain drug delivery in Alzheimer’s disease. *Health Sciences Review*. 2023;6:100075
- 46) Costa CP, Moreira JN, Sousa Lobo JM, Silva AC. Intranasal delivery of nanostructured lipid carriers, solid lipid nanoparticles and nanoemulsions: A current overview of in vivo studies. *Acta Pharmaceutica Sinica B*. 2021;11(4):925-940.
- 47) Cunha S, Forbes B, Sousa Lobo JM, Silva AC. Improving drug delivery for Alzheimer’s disease through nose-to-brain delivery using nanoemulsions, nanostructured lipid carriers and in situ hydrogels.*Int J Nanomedicine*. 2021;16:4373–4390.
- 48) Vohra M, Amir M, Sharma A, Wadhwa S. Formulation strategies for nose-to-brain drug delivery in Alzheimer’s disease. *Health Sciences Review*. 2023;6:100075
- 49) Tripathi S, Nano-lipidic formulation and therapeutic strategies for Alzheimer’s disease.*J Microencapsul*. 2021;38(8):673–687.
- 50) Sharma N, Bansal M, Visht S, Sharma PK, Kulkarni GT.Nanoemulsion: a new concept of delivery system. *Chron Young Sci*. 2010;1(2):2–6
- 51) Khan SA.Nose-to-brain delivery of nanoemulsions for neurodegenerative disorders: recent progress and challenges .*Int J Nanomedicine*. 2024;19:
- 52) Dighe S, Intranasal drug delivery by nanotechnology: advances in Alzheimer’s disease management. *Pharmaceutics*. 2023;16(1):58.
- 53) Gadhave D ,Gorain B,Tagde P, Nanocarriers for nose-to-brain delivery: a review of recent advances.*Pharmaceutics*. 2022;14(3)
- 54) Mroziak M, Kozłowski G, Kołodziejczyk W, Pszczołowska M, Walczak K, Beszlej JA, .Dendrimers—Novel therapeutic approaches for Alzheimer’s disease. *Biomedicines*.2024;12(8):1899.
- 55) Singh A, Ansari VA, Mahmood T, Ahsan F, Wasim R. Dendrimers: A neuroprotective lead in Alzheimer disease.*DrugResearch*.2022;72(8):417–423.
- 56) Vieira DB, Gamarra LF.Getting into the brain: liposome-based strategies for effective drug delivery across the blood–brain barrier. *International Journal of Nanomedicine*. 2022;17:5381–5403.

57) Battaglini M, Tapeinos C , Ciofani G . Liposome based drug delivery systems in neuro degenerative diseases. *Pharmaceutics*.2023;15(6):1635.



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