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Review Article

Nanotechnology-Enabled Niosomal Nasal Sprays: Unlocking New Therapeutic Avenues for Alzheimer's Disease

Charde Yugali*, Dhapake Pankaj, Dhoble Nilakshi, Padole Nitin, Baheti Jagdish

Kamla Nehru College of Pharmacy, Borkhedi Gate, Butibori, Nagpur, India – 441108

ABSTRACT

To determine the viability of using niosome-based nasal sprays as a new delivery method for therapeutic use in Alzheimer's disease. Through searches of current peer-reviewed publication materials through study of nanotechnology drug delivery systems, intranasal delivery and therapeutics used in the treatment of Alzheimer's. Relevance to niosomal formulations, pathway of nose-to-brain administration and previous or ongoing studies (preclinical)/clinical studies on therapeutics developed to treat Alzheimer's. Alzheimer's is a progressive neurodegenerative disorder with limited options for therapy, due largely to the inability of drug molecules to effectively pass through the blood-brain barrier (BBB). Intranasal administration provides non-invasive delivery of therapeutics, eliminating the need for crossing through the BBB (via olfactory/trigeminal nerves). Niosomes formulated from non-ionic surfactants and cholesterol provide improved stability, bioavailability and sustained-release of active ingredients. Niosomal form would improve delivery of therapeutics into the brain, decrease the incidence of systemic adverse effects from drugs used to treat Alzheimer's and enhance therapeutic effectiveness in an Alzheimer's patient. Preliminary clinical trials for the use of niosomes demonstrate improved pharmacokinetics of the drug, cognitive improvement for patients receiving niosomal therapy and greater safety of niosomal therapies over traditionally formulated products. The use of niosomal nasal sprays for the targeted administration (i.e., brain) of therapeutics for treating Alzheimer's represents a powerful and innovative approach to address Alzheimer's disease and will require additional clinical evidence and methods to support large-scale niosome production.

Keywords: Alzheimer's disease, niosomes, nasal delivery, nose-to-brain, nanocarriers, intranasal therapy.

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*Address for Correspondence:

Charde Yugali, Kamla Nehru College of Pharmacy, Borkhedi Gate, Butibori, Nagpur, India – 441108

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disorder and a leading cause of dementia worldwide, characterised by progressive cognitive decline and neuronal degeneration.⁽¹⁻⁴⁾ The blood-brain barrier (BBB) makes it hard for traditional oral medications for AD, including donepezil, to work. They also have low oral bioavailability and systemic side effects. These challenges underscore the need for direct brain-delivery strategies⁽⁵⁾.

Rationale for Nose-to-Brain Drug Delivery

Bypassing the blood-brain barrier, the intranasal route enables therapeutic agents to enter the central nervous system directly through the trigeminal and olfactory pathways.⁽⁶⁾ For chronic conditions like AD, intranasal delivery is particularly appealing because it enhances brain targeting,

minimises peripheral exposure, and permits non-invasive administration⁽⁷⁾.

Alzheimer's Disease and Current Therapeutics

Pathophysiology of AD

Alzheimer's Disease is a fatal, progressive neurodegenerative disease characterised primarily by mental decline (cognitive) and memory loss. The classical pathological features are extracellular amyloid-beta ($A\beta$) plaques and intraneuronal neurofibrillary tangles, which consist of hyperphosphorylated tau protein.⁽⁸⁾ The accumulation of $A\beta$ plaques leads to neuronal damage and, in turn, activates a cascade that instigates tau pathology and neurodegeneration. Tau pathology is more related to cognitive decline and disease course. In addition, neuroinflammation, induced by activated microglia and astrocytes, is a major player in the exacerbation of the AD process, favouring tau

phosphorylation and secondary neuronal damage. The crosstalk between Aβ, tau pathology, and neuroinflammation

is the pathological foundation of disease progression in AD. (9-11,12)

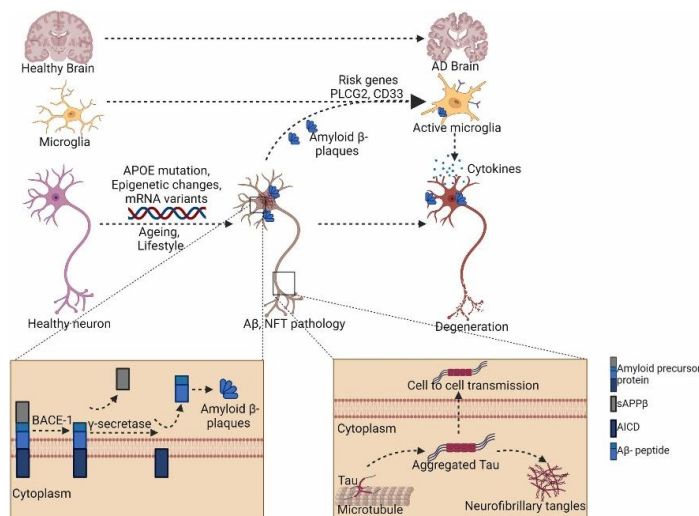


Figure 1: Shows the Pathophysiology of AD

The Limitations of Approved Drugs.

Cholinesterase inhibitors like donepezil, rivastigmine, and galantamine, as well as the NMDA receptor antagonist memantine, are currently approved medications for AD. Cholinesterase inhibitors temporarily improve neurotransmission and cognitive function by stopping the breakdown of acetylcholine. Nevertheless, these medications alleviate symptoms without stopping the course of the illness. They are linked to adverse effects like gastrointestinal problems and frequently exhibit only modest efficacy for six to twelve months.⁽¹³⁾ Memantine, which is used to treat moderate-to-severe AD, modulates glutamatergic neurotransmission but does not change the underlying mechanism of the disease. All things considered, systemic toxicity and restricted blood-brain barrier (BBB) permeability present serious obstacles to existing treatments.^(14,15)

Advanced Delivery Systems Are Necessary.

Research into novel drug delivery systems that can improve brain targeting, increase bioavailability, and lessen systemic side effects has been prompted by the shortcomings of traditional AD therapies. Many therapeutic molecules cannot reach the brain in effective concentrations when the blood-

brain barrier is intact. Delivery systems based on nanotechnology, such as niosomes and nanoparticles, have demonstrated promise in getting pass the BBB's restrictions and allowing for controlled, targeted, and prolonged drug release straight into the brain. Intranasal administration is especially beneficial because it allows for direct nose-to-brain delivery, bypassing the blood-brain barrier through the olfactory and trigeminal nerve pathways. These tactics have the potential to revolutionise AD treatment modalities because they seek to increase therapeutic efficacy, decrease dosage frequency, and minimise side effects^(16,17)

Nose to brain drug delivery

Drug Delivery Through the Nose to the Brain. The vestibular, respiratory, and olfactory systems make up the nasal cavity. Rapid systemic drug absorption is facilitated by the respiratory region's rich vascularisation and large surface area. Sensory neurons in the olfactory region, which is situated at the nasal cavity's roof, have direct connections to the brain's olfactory bulb. By passing through the olfactory and trigeminal nerve pathways, drugs administered intranasally can cross the blood-brain barrier and directly target the brain within minutes. Drugs are transported to the brainstem and related regions by the trigeminal nerve, which innervates the respiratory and olfactory epithelia.^(18,19,20)

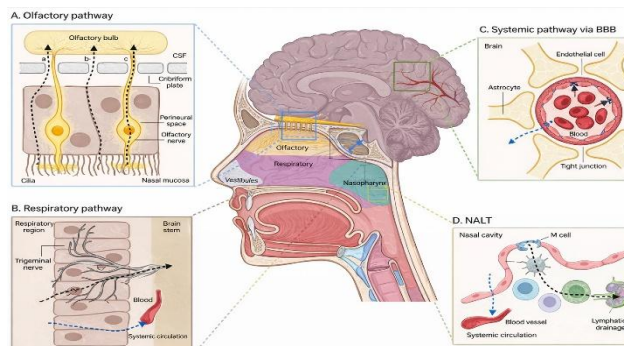


Figure 2: Nose-to-brain drug delivery pathway

Advantages of intranasal drug delivery ^[21]

There are several advantages to using Intranasal Drug Delivery, including its non-invasive nature and ease of administration, which provide increased comfort and compliance for patients. Intranasal Drug Delivery provides fast absorption through the nasal mucosa with rapid drug action, whereas it avoids the first pass (or hepatic) metabolism of drugs in the liver, promoting higher bioavailability of the drug. In addition, intranasal delivery enables direct access to the central nervous system (CNS) by bypassing the blood-brain barrier. However, challenges exist with intranasal administration, including rapid clearing by mucociliary action and degradation of drugs by enzymes, making it difficult to deliver or maintain therapeutic concentrations of the drug at the site of action in the nasal cavity. The amount of drug that can be delivered via this route is limited by the volume of the dosage form, which may also contribute to inconsistent absorption due to variability between patients and the type of condition being treated. To improve the efficacy of intranasal delivery, formulation optimisation and selection of the appropriate delivery device should be considered and tailored to individual patient needs.

Challenges specific to AD patients (age-related nasal changes, olfactory degeneration)

In Alzheimer's disease, ageing processes that affect the nose, such as olfactory neuron degeneration, olfactory bulb atrophy, and epithelial abnormalities, impair the efficacy of nose-to-brain delivery. However, mucosal dryness and elderly Alzheimer's disease-induced changes in structures may affect the absorption and clearance of drugs in this population, necessitating special formulations adapted for intranasal delivery to elderly patients with AD. ^{[22] [23]}

According to one study Chronic rhinosinusitis and airway disease review from 2021 details structural and functional changes due to increasing age: decreased ability to clear the nasal passages through the mucociliary clearance mechanism in older airways; thinning of the nasal epithelium associated with decreased perfusion and decreased secretion of mucus; and decreases in tendon surface area and therefore decreased efficacy for drug delivery systems (e.g., inhalers and nebulizers) to achieve an optimal effect in the nasal cavity. ^[42]

One more study state that the 2023 review "The Benefits of Multiple Routes of Administration" outlines the following barriers faced by individuals suffering from Alzheimer's-Type Dementia (ATD) using the intranasal route: the mucus layer barrier, and mucociliary clearance that are also worsened by the physiological barriers of senescence: the low permeability of the nasal cavity, as well as variability between individuals. ^[43]

Niosomes: an overview

Niosomes are small vesicular systems made of non-ionic surfactants, cholesterol, and sometimes an extra additive (such as charge inducers or stabilisers) to enhance their lipid formulation. Often surfactants are taken from either the Span or Tween series and self-assemble in an aqueous environment, while the transition to cholesterol increases the rigidity and stability of the resultant bilayer system. This combination means that niosomes can encapsulate

hydrophilic drugs into the aqueous core and lipophilic drugs into the bilayer membrane. ^{[23][24]}. Niosomes also have distinct advantages over other vesicular carriers, including liposomes and nanoparticles, such as increased chemical stability due to the use of non-ionic surfactants, being less costly than other carriers, ease of preparation, and less demand to oxidative degradation. Niosomes can also demonstrate improved loading and controlled release, which means they are very versatile carriers for drug delivery, particularly for mucosal routes such as the nasal. ^{[25][26]}.

The process of drug encapsulation in niosomes is achieved through their entrapment into either the aqueous core, resulting in the formation of a hydrophilic drug-containing niosome, or through their incorporation into the lipid bilayers of the niosomes for lipophilic substances. Drug release kinetics occurs through either (i) diffusion, (ii) niosome degradation, or (iii) upon fusion with biological membranes, thereby enabling controlled and sustained drug delivery. The bilayer nature of niosomes also protects the drug from enzymatic degradation to increase bioavailability at the site of action. ^[26] as shown in Fig. 3 ^[36]

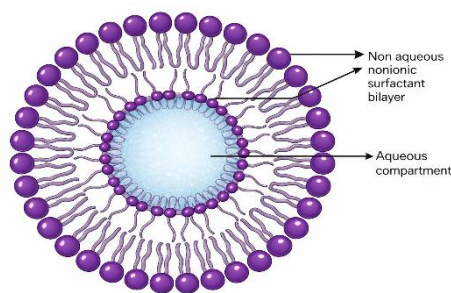


Figure 3: Structure of niosomes

The stability of formulation and biocompatibility are paramount in the design of niosomal drug formulations. Niosomes show good physical and chemical stability and are resilient to aggregation and leakage under physiological conditions. Niosomes inherently also have a low toxicity profile and minimal immunogenicity due to their non-ionic chemical nature, which makes them safe for intranasal and other parenteral routes of administration. Properly selecting surfactants and stabilisers significantly enhances formulation stability, shelf-life, in vivo activity, and the overall performance of niosomal formulations. ^{[25][27]}

Niosomal Nasal Spray Formulations for Alzheimer's disease

Niosomal nasal sprays are commonly developed as suspensions, in situ gels, or mucoadhesive systems to enhance residence in the nasal cavity and brain targeting. Preparation methods include thin-film hydration and reverse-phase evaporation, which allow for control of vesicle size and drug encapsulation. Maximising drug loading and encapsulation of both hydrophilic and lipophilic drugs is critical to dosing. Particle size, surface charge, and mucoadhesive polymers are also leading to enhanced nasal absorption and delivery via the trigeminal and olfactory pathways to deliver therapeutic products directly to the brain for targeted therapy for Alzheimer's Disease (AD) patients. ^[26]

Advantages of Niosomal Nasal Spray in AD Therapy^[28]

Niosomal nasal spray applications have the following advantages in treating Alzheimer's disease (AD). Niosomes will allow drug delivery to the brain directly, through the ability to carry drugs across the blood-brain barrier, thus improving therapeutics. Systemic adverse effects typically associated with oral or parenteral administration can also be reduced using niosomes. Niosomes will provide controlled &

sustained release of drugs, thus increasing the duration of the medication's action, which allows for a longer duration of action without increasing the dose. The patient will accept Niosomes; therefore, they are a non-invasive, painless, and easy-to-use method for administering medication. By using niosomal nasal sprays, patients will have better adherence and be able to maintain long-term treatment for neurodegenerative conditions.

Table 1: Available marketed formulation for AD

Formulation Type	Drug & Brand Name	Limitations
Oral Tablets/Capsules	Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (Razadyne)	Poor blood-brain barrier penetration, first-pass metabolism, gastrointestinal side effects, variable bioavailability
Transdermal Patches	Rivastigmine Patch (Exelon Patch)	Skin irritation, limited brain targeting, and adhesion issues
Injectable Biologics	Aducanumab (Aduhelm), Lecanemab (Leqembi)	High cost, intravenous administration, infusion-related reactions, and uncertain long-term efficacy

Formulations available in the marketplace so far consist exclusively of oral cholinesterase inhibitors (rivastigmine-transdermal patches) or injectables (monoclonal antibodies). Nasal sprays (rivastigmine formulations) are still in development and not marketed, while niosomal nasal sprays represent a newer direction of research.

Preclinical and Clinical Studies

In vitro characterisation of niosomal formulations includes evaluation of particle size, surface charge, and sustained release of the drug that assures optimum stability and interaction with mucosal surfaces. In vivo studies indicate improved targeting to the brain through the nasal route, improved pharmacokinetic and cognitive indications in animal models. Safety assessments indicate good biocompatibility and low toxicity to support tolerability with chronic use. Based on the comparative advantages of stability, cost, and delivery to the brain over other nanocarriers, niosomes represent a promising platform for therapy for AD.^[27]

Several preclinical studies have evaluated the use of niosomal nasal spray formulations to treat Alzheimer's Disease (AD) with the following parameters typically defined for in vitro evaluation: particle size (approximately 100-300 nm is considered optimal for penetrability through mucosa), zeta potential (an example being -20 to -40 mV assumed as stable), and release profile showing 70-90% drug release over 24 to 48 hours post-application. In vivo preclinical evaluations utilised rat models for determining the bioavailability of niosome-donepezil via the nasal versus oral routes, resulting in 2-3 times greater brain bioavailability through the nasal route, and demonstrated cognitive enhancement through improved performance in the Morris water maze (MWM) test, while demonstrating 60-75% reduction of AChE activity. The safety profiles from preclinical data support low cytotoxicity (cell viability > 90% for the nasal epithelial cell type tested) with minimal irritation to the nasal cavity.^[44]

The translation of these studies to clinical use is still in the early phases, building on the initial promise observed. Phase

1 studies of a similar class of intranasal nano-formulations (i.e., the foralumab nasal spray) used in mild AD patients found good tolerability with no serious adverse events, as well as decreased microglial activation seen during PET imaging and preliminary cognitive stabilisation over six months. Currently, Phase 2 studies are ongoing, evaluating the sustained delivery of rivastigmine using niosome-like carriers that demonstrate improved compliance and brain targeting based on gamma scintigraphy findings, supporting their future utilisation for chronic AD treatment.^[45]

Case study

Rivastigmine Nasal Spray for Alzheimer's disease. A study recently published examined the formulation approach used to develop a rivastigmine nasal spray (RHT-ns) designed for swift nose-to-brain delivery for the treatment of Alzheimer's disease. Oral rivastigmine therapies have a delayed time for absorption and likely involve systemic side effects. The nasal spray formulation aimed to enhance delivery to the brain while lessening exposure to the medication in the periphery.^[30]

The formulation included a viscosity modifier (1% Avicel® RC-591), which was developed in part to maximise drug deposition in the olfactory region.

A 3D-printed nasal cast was utilised to track drug deposition patterns and also demonstrated targeting of the olfactory region.

Brain delivery of rivastigmine was demonstrated using an in vivo model through fluorescent tracing and the use of Desorption Electrospray Mass Spectrometry (DESI-MS), with a strong correlation between olfactory deposition and uptake in the brain.^[30]

In the studies of drug effect, the nasal spray formulation was more effective in improving cognition than oral formulations already commercially available. The researchers reported acceptable tolerability of the formulation with few side effects.

This study provided rigorous confirmation that nasal spray formulations of rivastigmine may lead to increased brain delivery and improved treatment outcomes for Alzheimer's disease models.^[30]

The effective application of advanced nasal delivery technology, such as 3D nasal casts and advanced imaging, supported the nose-to-brain delivery mechanism for treating Alzheimer's disease (AD).^[31]

Further Preclinical Support Research out of Texas A&M University showed that a stem-cell-derived extracellular vesicle nasal spray reduced beta-amyloid plaques and neuroinflammation in Alzheimer's mouse models, and improved cognition and slowed progression.^[32]

Wake Forest University used PET imaging to assess that the intranasal delivery of insulin reached regions of the brain regulating memory and cognition; these studies also demonstrated variable uptake of the insulin nasal spray in cognitively impaired versus cognitively normal subjects.^[33]

These studies provide good evidence for the development of a nasal spray formulation with the potential to be a non-invasive method for targeting AD pathology in the brain, and to offer a potential therapeutic avenue and direction in research for the nasal spray route, including niosomal or advanced nasal sprays. Let me know if you'd like to know more about formulation techniques or other nanocarrier-based AD nasal sprays.^[34]

Challenges and Limitations

Although niosomal nasal sprays have many potential benefits, they also present challenges. Issues related to the stability of formulation and storage may be due to possible aggregation of vesicles and drug leakage over time. The rapid mucociliary clearance from the nasal cavity decreases the residence time of niosomal delivery in the nasal cavity, leading to decreased absorption. Scale-up and reproducibility across the batch process also remain challenging in manufacturing processes. Increased complexity in characterisation and stronger safety and efficacy data also serve as barriers towards regulatory approval and the ability to translate into the clinic. It will be important to overcome these barriers if niosomes are to be commercially available and able to be used in a therapeutic setting for patients with dementia.^{[29][52]}

Future Perspectives

Niosomal nasal sprays for Alzheimer's disease (AD) are expected to be further developed. They will be even more effective and increase patient compliance to brain-targeted drugs due to their novel formulation technologies and advanced dosage forms. The niosomes surface-modified with targeting ligands, such as transferrin, lactoferrin, or specific peptides, can improve mucosal uptake and receptor-mediated transcytosis to specific regions of the brain. Niosomes containing mucoadhesive polymers, such as chitosan, Carbopol, or hyaluronic acid as the nasal spray matrices or as part of the vehicle, can prolong residence time in the mucosa, overcome rapid mucociliary clearance, and improve

penetration through the nasal mucosa to control drug release and promote sustained release efforts.^[35]

With the advancement of 3D printing technology, personalised nasal delivery systems are becoming more and more likely to be engineered for a person's specific nasal anatomy. The systems often come equipped with smart metered-dose delivery systems, which deliver patient-specific doses tailored to a person's pharmacokinetics or disease progression, enabling optimal outcomes and adherence.^[35]

Incorporating targeted therapy with diagnostic agents, which could be imaging probes or biosensors, into niosomal formulations might permit real-time, simultaneous diagnostic and therapeutic capabilities. With these two functions, therapy plus diagnosis systems would enable reliable dynamic monitoring of drug distribution, uptake by the brain, and therapeutic response by the application of imaging modalities such as MRI, PET, or fluorescence techniques. These readings would enable adjustments in dosing and facilitate timely recognition of the disease's progression, thereby supporting the practice of precision medicine.^[50]

Combination therapies administered via niosomal nasal sprays offer the potential for combined therapeutic benefit in the treatment of AD via the simultaneous targeting of amyloid-beta clearance, tau pathology, and neuroinflammation/pathology. The use of co-encapsulated combination therapies in multifunctional niosomes, or concurrent delivery of multiple nanoformulations via a nasal spray, will improve treatment efficacy. Novel dosage forms (e.g., in situ gelling systems that form a gel during nasal administration) can improve formulation retention and provide controlled drug release, while dry powder nasal formulations can improve formulation stability and shelf life, as well as offer a more convenient patient-use formulation since refrigeration is not required.^[36]

Emerging nasal spray formulations continue to explore enzyme inhibitors that provide protection of drugs against nasal enzymatic degradation, utilise novel penetration enhancers to promote permeation through the mucosa, and employ temperature- or pH-responsive gels to initiate drug delivery once in the nasal environment. Latest delivery strategies also include work on 'smart' delivery devices that provide for individualised dosing and ordering of therapies, in combination with biosensors for precise management of therapies.^[51]

In conclusion, these advancements in delivery device formulation design, personalised delivery devices, and integration with combination therapy may overcome current barriers such as mucociliary clearance of drug solutions, formulation instabilities, and biological variability of dosing that ultimately may transform niosomal nasal spray technology from the experimental laboratory stage to clinical routine. These approaches are expected to provide safer, effective, and convenient treatment options to delay or modify the onset of cognitive decline with Alzheimer's disease and to enhance patient quality of life.^[37]

The recent advancements made with UTMB's nasal spray to target aggregation of tau proteins and Texas A&M's extracellular vesicle treatment via nasal delivery showcase the clinical potential of the nasal delivery route in therapeutic development. Future work will require collaboration from formulation scientists, device engineers, clinicians, and governing agencies to achieve the translational promise of advances in therapies for patients globally.^[38]

CONCLUSION

Niosomal nasal sprays have substantial therapeutic potential in Alzheimer's disease by providing direct, non-invasive delivery to the brain, increased bioavailability, and decreased systemic side effects. Niosomal formulations offer the potential for controlled and sustained drug release, which can enhance drug effectiveness and improve patient compliance. Although preclinical studies provide some evidence of efficacy, further studies in humans and clinical populations are warranted to establish safety, determine dosing, and communicate long-term benefits. The future of niosomal nasal sprays in the treatment of neurodegenerative disorders has great promise, with continued work anticipated in personalised delivery and combination therapies with the potential to change the management of AD.

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