WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 17, 1468-1487. Review Article ISSN 2277–7105

BIOAVAILABILITY ENHANCEMENT THROUGH NASAL ROUTES IN ALZHEIMER'S THERAPY

Ms. Tejaswini R. Kulkarni[1*], Ms. Prerana S. Deshmukh[2]

SVS Institute of Pharmacy, Mungase Malegaon (Nashik), India.

Article Received on
21 July 2025,

Revised on 10 August 2025,
Accepted on 30 August 2025

DOI: 10.20959/wjpr202517-38215

***Corresponding Author**

Ms. Tejaswini R. Kulkarni

SVS Institute of Pharmacy,
Mungase Malegaon
(Nashik), India.

ABSTRACT

The pathogenesis of Alzheimer's disease (AD) is complicated and varied. The primary neuropathologic criteria for Alzheimer's disease diagnosis are still the presence of intracellular accumulation of hyperphosphorylated tau as neurofibrillary tangles and extracellular β-amyloid deposition as neuritic plaques. Disease-modifying medicines (DMT) were scarcer in the past because pharmaceuticals, particularly those involving proteins and polypeptides, had a hard time passing across the blood-brain barrier (BBB). Different methods are employed to get the medicine over the blood-brain barrier after developments in drug delivery systems. Alzheimer's disease (AD) is a neurodegenerative brain illness that impairs thinking, memory, judgment, and focus, making it difficult for a person to carry out everyday tasks. The blood-brain barrier and additional barriers to oral and other routes, such as decreased bioavailability, quick metabolism, rapid excretion, and drug breakdown by enzymes and stomach juices, make it difficult to transfer drugs to the brain. The nose-to-brain medication delivery system is one of the innovative methods for targeting the brain that are being developed to get around the drawbacks of oral and other routes of administration. Since it avoids the blood-brain barrier, intranasal medication administration, also known as nose-to-brain drug delivery, is one of the safest, most efficient, and non-invasive ways to target the brain, according to this research. As a result, a variety of innovative methods, such as hydrogels, liposomes, in-situ gels, nanoparticles, and nano-emulsions, are frequently employed to successfully treat Alzheimer's disease by circumventing the blood-brain barrier.

KEYWORDS: Different methods are employed to get the medicine over the blood-brain barrier after developments in drug delivery systems.

INTRODUCTION

One of the most prevalent and deadly neurodegenerative diseases in the world is Alzheimer's disease (AD). [1]Smoking, vascular issues, advanced age, head trauma, family history, insufficient physical activity, and environmental factors are major risk factors for the illness.[2]

According to projections, dementia will affect more than 100 million people globally by 2050, and the costs connected with it are expected to rise to USD 1 trillion in the years to come. One common sign of Alzheimer's disease is dementia, which increases with age, doubling roughly every five years after age 65 and increasing by roughly 50% after age 85. The accumulation of Aβ, which results in senile plaques, excessive tau phosphorylation, which causes neurofibrillary tangles (NFTs), impaired glial function, neuronal inflammation, and abnormalities in vascular activity are among the unique molecular characteristics of Alzheimer's disease.[3,4]

Compared to alternative administration methods, IN delivery has the following benefits: It avoids first-pass metabolism, is comparatively non-invasive, and has fewer adverse effects because the medicinal substance does not come into contact with other healthy organs.[5]

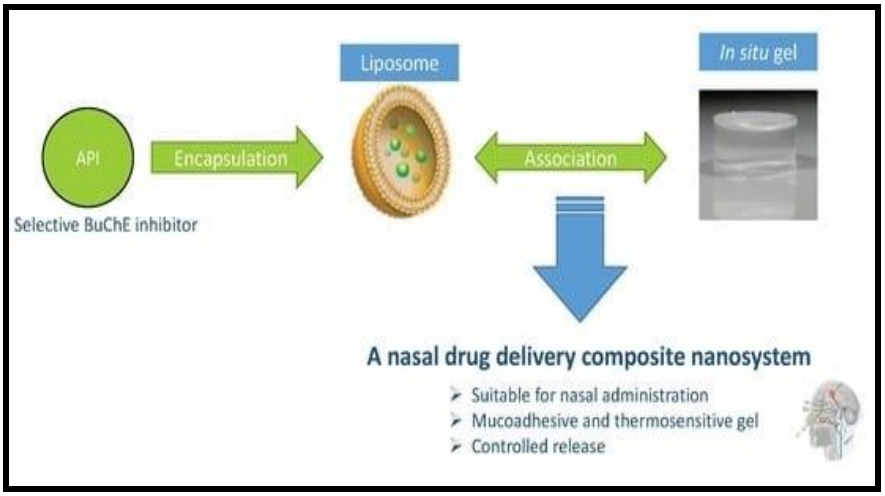
The transport or diffusion of substances directly to the brain via the olfactory mucosa pathway in the olfactory region is the most significant direct channel to the brain.[6]

There are several ways to help transfer drugs from the nose to the brain, including using drug delivery nanosystems and gelling formulations that prevent mucociliary clearance. In order to deliver our active pharmaceutical ingredient (API) to the brain, we decided to combine the two approaches by creating a nasal drug delivery composite nanosystem. Liposomes make up this formulation, which is a thermogelling system. First off, these carriers might give the medication advantageous properties like improved stability, mucoadhesion, and absorption. Second, employing gels improves absorption by lengthening the duration of the drug's residency in the nasal cavity. For the treatment of AD, several APIs packaged into nanoparticles and delivered intranasally were investigated.[7,8,9]

For instance, compared to the commonly used products, the intranasal injection of a liposome laden with donepezil greatly enhanced drug transport to the brain.[10]

Both hydrophilic and hydrophobic medications can be encapsulated in liposomes. Hydrophilic medications are trapped in the aqueous cavity, whereas hydrophobic compounds have affinity for the phospholipid bilayer.[11]

These studies have also suggested a number of possible benefits of intranasal administration. These include the nasal cavity's easy accessibility, which enables self-administration; enhanced patient compliance; a quick onset of action; decreased systemic exposure; and a decreased risk of peripheral side effects. These factors increase the likelihood that a dosage form with several advantages will be clinically developed, in addition to increased drug bioavailability in the brain.[12,13] and based on the encouraging potential of the nose-to-brain route for brain targeting, we will provide an overview on the development of liposomes as a carrier for nose-to-brain drug delivery here. The transport methods by which medications supplied by the nose enter the brain are first summarized in this study. This is followed by a thorough summary of the most recent developments in the formulation of liposomes as an intranasally administered carrier. In order to gain a better understanding and provide insight into the development of liposomal formulations for nose-to-brain medication delivery, consequences and future views will be presented at the end.

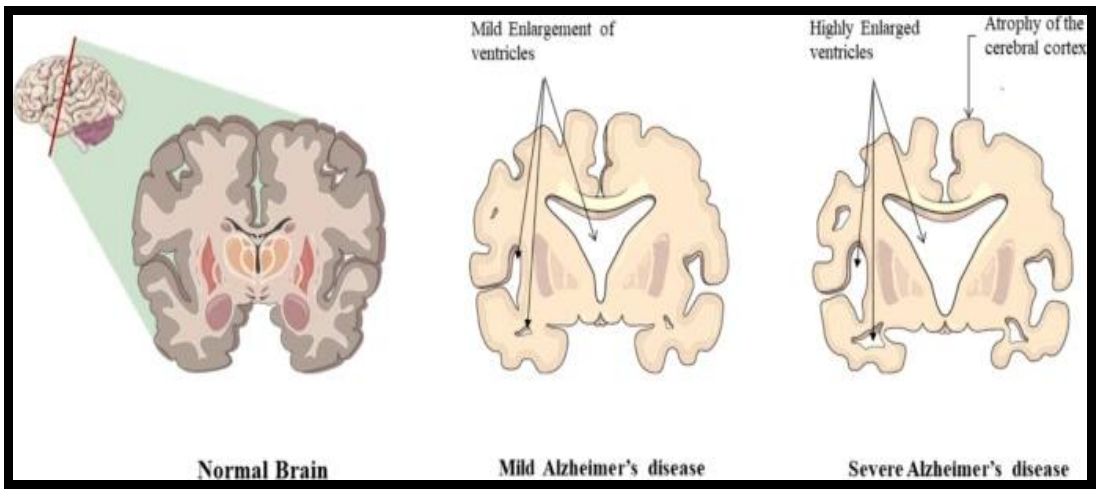


[Fig. 1]: Pharmacotechnical development of a nasal drug delivery composite Nanosystem.

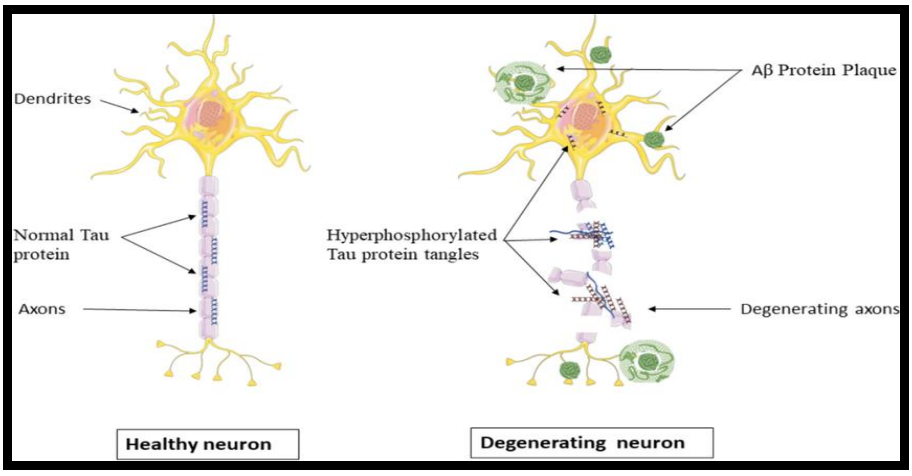
ALZHEIMER'S DISEASE

The hallmarks of AD include behavioral abnormalities, memory loss, and cognitive difficulties. The disease systematically destroys the parts of the brain involved in learning, memory, and higher executive functions. Even though AD was identified over a century ago, the physiological alterations that lead to the illness were not identified for a long time.[14]

Clinically, AD is typified by cognitive deficits and a gradually worsening loss of memory.[15],[16] The abnormal buildup of hazardous protein fragments in the neurological system, specifically intracellular accumulation of microtube-associated Tau protein and amyloid-beta (Aβ) deposition outside of neurons and within senile plaques, is mostly to blame for the patient decline. While Tau neurofibrillary tangles prevent vital nutrients and other substances from passing through neurons, Aβ is thought to contribute to cell death by disrupting neuron-neuron communication at synapses.[17],[18],[19]



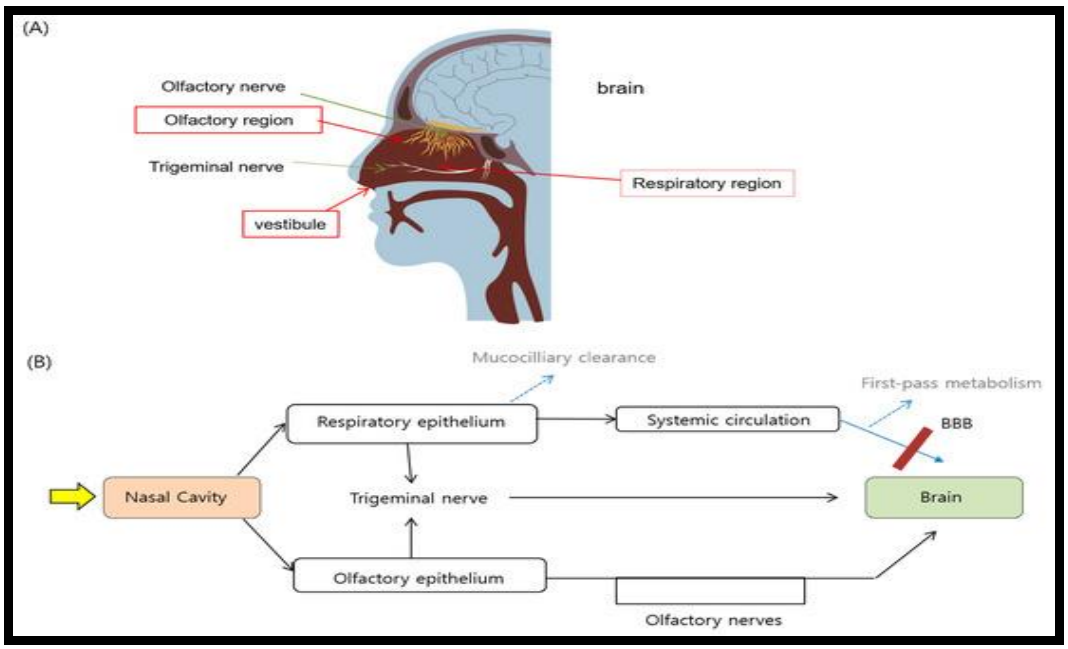
[Fig.2]: Alzheimer's disease development.



[Fig.3]: Pathological changes of neurons in AD.

THE ROUTE TAKEN BY DRUGS FROM THE NOSE TO THE BRAIN

The mechanisms behind the direct nose-to-brain drug transport pathway remain unclear despite increased interest. However, it is generally accepted that drugs can enter the brain through both direct and indirect channels from the intranasal cavity.[20,21] One is that drugs enter the brain directly through the olfactory or trigeminal pathways, and the other is that drugs enter the systemic circulation and then cross the blood-brain barrier to enter the brain.[22] Intranasal (IN) injections offer a number of benefits for treating neurodegenerative diseases by delivering drugs straight to the brain. Due to considerations including drug size and cost, the BBB restricts the effectiveness of new treatments meant to treat memory loss and neurodegeneration by preventing them from penetrating the brain.[23] As an alternative to the conventional parenteral and oral routes for the direct delivery of pharmaceuticals to the brain, intranasal (IN) administration has been proposed as a desirable method of achieving high drug levels in the brain. Because of the nasal cavity's special anatomical features, drugs can be delivered through this minimally invasive route with a quick onset of action and no hepatic first pass-effect.[24] A therapeutic formulation must pass through the vestibular region's mucociliary clearance once it has been placed into the nose. Once within the nasal cavity, the medication can enter the central nervous system (CNS) directly through the olfactory or trigeminal nerves, or indirectly through the systemic circulation.[25]



[Fig.4] (A) Intranasal structure involved in the possible drug transport and (B) the potential drug transport routes leading to brain uptake following intranasal administration.

Advantages of the nasal route

The intranasal route has several benefits over other routes there, including[26]

• The blood-brain barrier is circumvented.

• It is a non-invasive, practical, and safe method of drug delivery.

• It stops the gastrointestinal tract (GIT) from breaking down drugs.

• It does not go through the liver's first-pass metabolism.

• It makes medications with low molecular weight more bioavailable.

INNOVATIVE MEDICATION DELIVERY TECHNIQUES ARE EMPLOYED TO IMPROVE BIOAVAILABILITY IN THE TREATMENT OF AD

To counteract the drawbacks of conventional and alternative drug delivery methods to the brain through the nose, a number of innovative drug delivery systems are being developed.

1) Nanoparticles

The nanoparticles are colloidal solid particles with sizes ranging between 1 and 1000 nm. Penetration through the mucosal membrane by the paracellular transport via tight junction can be done only by the smallest nanoparticles of 1 to 100 nm size range Chitosan is produced when the crustacean cell's chitin is deacetylated. Chitosan is employed in intranasal delivery due to its bioadhesive qualities, which lengthen the drug's nasal residence period by preventing nasal evacuation.[27] (Polymer-based nanoparticles) Poly (lactic-co-glycolic acid) (PLGA) is another polymer that is utilized to deliver nanoparticles through the intranasal route. Intranasal delivery of PLGA nanoparticles loaded with olanzapine improves medication absorption.[28]

2) Liposomes

These are phospholipid vesicles with lipid bilayers encasing one or more aqueous portions. Depending on the medications' water and lipid solubility, they are either encased in a lipid or water layer.[29]

For example-Quercetin liposomes administered via the nasal route, for instance, have been shown to diminish the degeneration of cortical and cholinergic neurons in the hippocampus in a mouse model study of AD.

3) In-situ gelling system

Prior to administration, they are liquid, but they go through a sol-to-gel transformation that can be brought on by any external factor, such as temperature, pH, ion change, magnetic fields, or biological environments.[30,31]

4) Hydrogels

These are cross-linked 3-dimensional (3D) networks capable of absorbing high-water content and are compatible with biological systems.[32,33]

5) Nano-emulsions

Both nanoscale globules and the nasal mucosa can absorb these lipophilic complexes. NEs come in two varieties: water-in-oil (w/o) emulsions and oil-in-water (o/w) emulsions. The primary purposes of oil-in-water (o/w) emulsions are to encapsulate lipophilic medications, shield them from enzymatic breakdown, increase their solubility in liquid media, control drug release, and boost bioavailability.[34,35]

For example-Rivastigmine-loaded nano-emulsion demonstrated a noticeably higher drug concentration in the brain than the solution in in vitro, drug release, and ex vivo diffusion investigations. Studies on nasal ciliotoxicity in goat nasal mucosa demonstrated that the optimized formulation did not cause nasal ciliotoxicity.

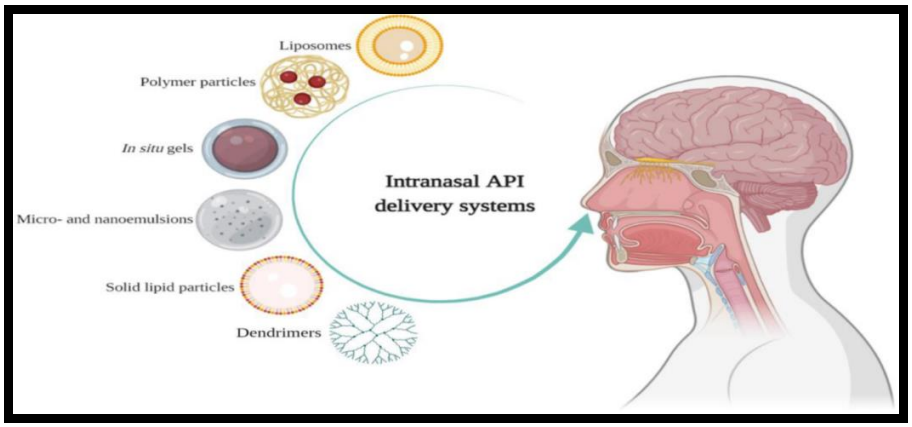
6) **Dendrimers**

Water-soluble or -insoluble, high- or low-molecular-weight compounds can be delivered by dendrimers, the most symmetric, hyperbranched, and homogenous nanosized carriers, by passive or active mechanisms via intravenous, intraperitoneal, or intranasal modes of administration. Due to the diffusion mechanism, in situ mucoadhesive gels demonstrated increased radioactivity in the brain following intranasal administration of aqueous, radio-labeled siRNA-dendrimer complexes (dendriplexes).[44] This study suggests that intranasal administration, which is used to treat AD, can reduce CNS side effects by lowering the plasma drug concentration.[45]

[Table 1]: Several cutting-edge approaches to AD treatment.

S.No	Drug	Delivery system	Results of the study	Reference
01	Rivastigmine (Cholinesterase inhibitor)	Nano-emulsions	Rivastigmine-loaded nano-emulsion demonstrated a noticeably higher drug concentration in the brain than the solution in in vitro, drug release, and ex vivo diffusion investigations. Studies on nasal ciliotoxicity in goat nasal mucosa demonstrated that the optimized formulation did not cause nasal ciliotoxicity.	[36,37]
02	Donepezil (Cholinesterase inhibitor)	Nano-emulsions	Studies on drug diffusion in vitro and drug penetration in vivo revealed that donepezil penetrates the body very well through the intranasal route when compared to other methods. Polymers are a useful strategy for enhancing medication bio-adhesion and nasal mucosal penetration, which eventually raises donepezil's bioavailability.	[38,39]
03	miR-132	Nanoparticles	Neuron survival and morphological homeostasis are maintained by miR-132. Additionally, it improves the microenvironment of hematoma lesions, reduces cell death following cerebral bleeding, and exhibits protective effects following cerebral ischemia. When administered intranasally to mice models, wheat germ agglutinin (WGA)-nanoparticles (NPs)-miR132 significantly increased the levels of synaptic protein expression in AD mouse models.	[40]
04	Donepezil HCl	Hydrogels	When compared to the oral donepezil tablets, the optimized hydrogel improved the average peak drug concentration and area under the curve (AUC) by 46% and 39%, respectively, when administered intranasally to the rabbit in the pharmacokinetics study.	[41]
05	Donepezil	In situ-gelling system	By extending the medication's nasal retention period and examining the impact of many factors on formulation creation, including temperature, pH, drug content,	[42]

			viscosity, and others, the formulation was created to improve the drug's nasal bioavailability.	
06	Quercetin	Liposomes	Quercetin liposomes administered by nasal route have been shown to prevent the degeneration of cortical and cholinergic neurons in the hippocampus, according to a mouse model study of AD.	[43]

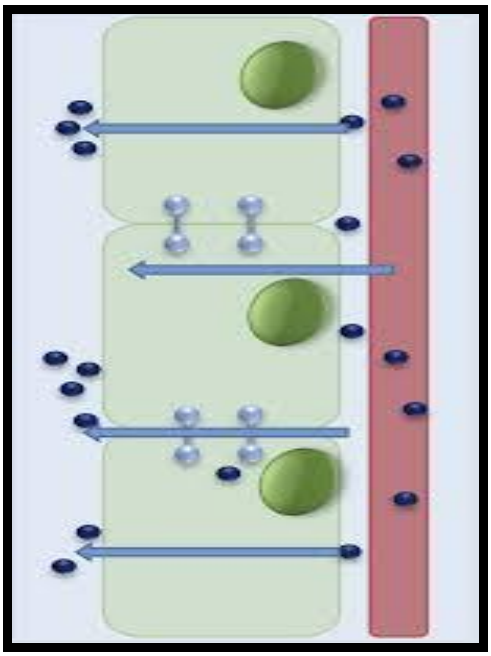


[Fig.5]: The graphical representation delineates the primary hallmarks of Alzheimer's disease, elucidates the mechanisms underlying current treatment strategies, and outlines various intranasal treatment approaches for Alzheimer's disease management based on nanocarriers.

NEED FOR NANOTECHNOLOGY AS A THERAPEUTIC STRATEGY ACROSS THE BBB

Promising medications exist to prevent Aβ toxicity.[46] However, nanocarriers must be used in order to investigate their greatest impact on CNS cells. The main problem in the realm of treatments for AD is the availability of medications in the central nervous system. The primary cause is the existence of a fully functional semipermeable blood-brain barrier (BBB), which acts as a barrier to the transmigration of neurotherapeutic molecules (such as medications, peptides, vectors, and molecules) into the central nervous system. Effective delivery of therapeutic medicines is thwarted by the BBB and its selective transport of molecules into the brain. Furthermore, because high dosages of medications are required to achieve levels beyond the brain's minimum effective concentration, the BBB also has a detrimental impact on drug efficacy and tolerance. These issues can be resolved by using nanotechnology, which includes nanoparticulate systems, which can operate as Trojan horses

for moving active chemicals across the blood-brain barrier, lowering toxicity and enhancing therapeutic effectiveness.[47,48]



[Fig.6]: Semipermeable blood–brain barrier and transmigration route of the nanoparticles.

Drugs' pharmacokinetics and pharmacodynamics are improved and their toxicity is decreased when they are used in nanoplatforms or nanodevices. Drug transport and controlled release into disease areas are crucial components of the development of nanomedicine. Therefore, using drug-delivery systems based on nanotechnology can improve a treatment's efficacy. These novel platforms seek to decrease adverse effects while enhancing drug pharmacokinetics, pharmacodynamics, and bioavailability across the blood-brain barrier.

In summary, new developments in nanotechnology provide promising medicinal and diagnostic alternatives. With the help of NPs that are 100 nm in size, targeted medication delivery can successfully raise drug bioavailability across the blood-brain barrier and into the central nervous system with little to no adverse effects. Additionally, these nanoparticles are made to be biocompatible, which lowers toxicity. Additionally, when their magnetic and optical qualities improve, they could be effective substitute agents for early detection.[49]

Additionally, magnetoelectric nanoparticles (MENPs) are among the most effective nanocarriers. They have been extensively researched for their ability to deliver medications to target locations on-demand without causing side effects and noninvasively across the blood-

brain barrier. The on-demand release capability is crucial because it guarantees the delivery of precise dosages of medications that are physiologically effective without being harmful[50-53]

CHALLENGES FOR CLINICAL TRANSLATION

Since the invention of NPs, a variety of forms—including silica, hydrogels, liposomes, metal NPs, silver NPs, gold NPs, and magnetic NPs—have been used quickly in drug-delivery research. At the clinical level, NPs are being investigated for CNS medication delivery. The idea of individualized nanomedicine, which could revolutionize drug transport across the blood-brain barrier and lead to better health care and more options to battle CNS illnesses, is being supported by the US Food and Drug Administration (FDA) and National Institutes of Health.[54] The effectiveness of CNS nanomedicine preclinical research[55-58] could serve as a foundation for a clinical examination of these tactics to investigate availability, toxicity, efficacy, and biocompatibility at the human-patient level. Numerous factors, including as patient variability, genetic and environmental impacts, the co-occurrence of numerous disorders, toxicity, effectiveness, and bioavailability in the brain, influence the clinical translation of these NPs against CNS diseases at the patient level. These NPs can be created and altered to deliver personalized nanomedicine, which may be more advantageous for the individual, based on the patient-disease profile. This necessitates a thorough comprehension of the illness mechanism; bioinformatics-based predictive techniques can even be used to comprehend the course of the disease and then develop a treatment plan appropriately. Regarding CNS treatment.

The significance of using nanotechnology for medication delivery, disease diagnosis, and therapeutic applications has been emphasized in a number of studies. The effectiveness of these preclinical and in vivo investigations has encouraging potential to be converted to clinical levels, even if the majority of present research is at the preclinical level. The main obstacles to the clinical application of tailored nanomedicine for the treatment of CNS disorders are safety, effectiveness, and regulatory concerns. Although new techniques like ultrasound-mediated BBB disruption, which involves noninvasively opening the BBB and applying external stimulation like focused ultrasound or electromagnetic fields, may show promise, they may also have unintended consequences like neurobehavioral abnormalities or infection due to the entry of undesirable molecules.[59] Because they can alter the intrinsic properties of the introduced NPs by heating them or changing their surfaces, controlled

parameters of these stimulations are crucial at the clinical level. They can also upset the CNS's homeostasis by disrupting the permeability of the blood-brain barrier, which allows unwanted circulating molecules to flow inward and cause neurotoxicity, dysfunction, immunohyperactivation, inflammation, reactive oxygen species release, synaptic damage, and oxidative stress, all of which can result in neuronal injury.[60,61] As a result, although research based on nanotechnology shows promise, there is still much work to be done before it can be applied to bedside therapy. For clinical trials to be effective, the problems of toxicity, bioavailability, pharmacokinetics, clearance, and metabolism of NPs must be addressed immediately. The FDA has identified several problems, including those related to NP biodistribution, modalities of administration, NPs' capacity to transport multiple medications, effective transmigration across the blood-brain barrier, risk assessments, toxicity, standards, safety, protocols, and validation.[62] By introducing surface functionalization, preservation techniques to reduce the negative effects of external stimulation, and extending the duration of drug availability in the central nervous system, efforts are being made to address the problems of biocompatibility, surface functionalization, endosomal entrapment, enzymatic degradation, and off-targeting. Making nanotherapeutics accessible at the patient level is essential for the success of upcoming clinical trials, but the transition to personalized nanomedicine is difficult.

FUTURE PERSPECTIVES IN TREATMENT OF ALZHEIMER'S DISEASE

Since powder dosage forms and specially made devices can get past the nasal vestibule and nasal valve, the two main obstacles in the olfactory epithelium, they are currently being investigated for improved nasal delivery of essential actives. According to reports, particles with sizes between 1 and 10 μm are best suited for improved olfactory deposition.[63] The translational phase of clinical studies for the promising administration of insulin and sumatriptan has begun for several of these specialized intranasal targeting devices. Insulin is delivered from the nose to the brain without contamination thanks to an aero pump system (Aero Pump, Germany) that uses a spring mechanism and an incorporated backflow barrier. For long-term, daily dosing, the finger-actuated, metered nasal dispenser (PharmaSystems, Canada) is a reliable intranasal delivery system that is primarily advised for peripheral effects. Hydrofluoroalkane is used as a gas propellant in the semi-disposable, unit-dose Precision Olfactory Delivery® (Impel Neuropharma, USA) device to transport liquids and powders to the olfactory epithelium, ensuring uniform dosage with improved brain bioavailability. With the least amount of pharyngeal deposition, electronic atomizers create a

vortex of nebulized particles to improve uptake in the upper nasal cavity. ViaNaseTM (Kurve Technology, Inc., Lynnwood, WA, USA) is one such device that has been designed for better insulin delivery from the nose to the brain and precise dosing. This device enhances cortical blood flow, vasoreactivity, and cognition.

The possibilities for AD treatments are growing as a result of additional pharmaceutical and biotechnological developments. Because mesenchymal stem cells (MSCs) release neurotrophic factors, they have been shown to have neuroprotective properties that can help cure intractable neurological diseases.[64] By avoiding direct implantation, the intranasal mode of delivery enhances the therapeutic potential of MSCs. In APP/PS1 AD mice, intravenous treatment of MSC secretome showed cell-mediated neuroreparative effects, resulting in a week-long transient memory recovery. Therefore, a long-term intranasal treatment plan was evaluated and demonstrated sustained memory recovery with a notable reduction in plaques surrounded by β-amyloid oligomers. To improve the viability, success rate, and clinical effectiveness of gene delivery, vaccines, and simulated nasal casts in neurotherapies for AD, dementia, or Parkinson's disease, researchers are currently investigating the nose-to-brain administration method. summarizes clinical research on intranasal administration of vaccinations, chemicals, and stem cells. based on information retrieved from the ClinicalTrials.gov database (ClinicalTrials.gov database). Phase 1/2/3 trials number over 130. More proof is needed, nevertheless, that intranasal neurotherapeutic formulations are simple to clinically translate and introduce to the market. This might be achieved through the use of nanoformulation and an understanding of immunological and mechanistic elements.

CONCLUSIONS

Since the intranasal route offers many benefits over traditional routes of administration, including direct transport from the nasal cavity to the brain without crossing the blood-brain barrier, it has a lot of potential as an alternate route of administration in the treatment of AD. Mucoadhesive polymers, prodrugs, absorption promoters, and other technological solutions must be used to optimize the formulations' physicochemical properties in order to achieve good bioavailability in the brain. in order to prevent the physiological processes of removal from the nasal cavity and to be appropriate for this mode of transportation. Lipid-based nanosystems, in particular nanostructured lipid carriers, have demonstrated the greatest promise as efficient systems for obtaining medication access to the brain from the nasal canal among the numerous technical approaches studied to optimize intranasal formulations.

Because of their stability, physiological compatibility, and capacity to overcome obstacles related to other nanocarriers, they have attracted a lot of attention. No medications currently on the market have been approved for intranasal administration in the treatment of AD.

By avoiding the blood-brain barrier, the nose-to-brain drug delivery system effectively targets the brain, improving efficacy, permeability, retention, absorption, and bioavailability while posing a much lower risk of side effects than traditional drug delivery methods. This makes it an advantageous treatment option for Alzheimer's disease. It is anticipated that new nasal products, including medications for chronic illnesses, novel nasal vaccines, and medications that directly target the brain and guarantee a therapeutic effect on the central nervous system with fewer side effects, will continue to enter the market due to the broad interest in nasal drug delivery and its potential advantages. Thus, there will be a lot of research and development of new technologies in this growing business in the upcoming years.

REFERENCES

1. Fish PV, Steadman D, Bayle ED, Whiting P. New approaches for the treatment of Alzheimer’s disease. Bioorganic Med Chem Lett., 2019; 29: 125–33.
2. Atri, Alireza.” The Alzheimer’s Disease Clinical Spectrum.’’ Medical Clinics Of North America, mar, 2019; 103(2): 263-93, https://doi.org/10.1016/j.mcna.2018.10.009
3. Wang, L.; Yin, Y.-L.; Liu, X.-Z.; Shen, P.; Zheng, Y.-G.; Lan, X.-R.; Lu, C.-B.; Wang, J.-Z. Current understanding of metal ions in the pathogenesis of Alzheimer’s disease. *Transl. Neurodegener,* 2020; *9*: 10. [Google Scholar] [CrossRef] [PubMed]
4. Haque, R.U.; Lwvey, A. I. Alzheimer’s Disease : a clinical prspective and future nonhuman primate research opportunities proc. Natl Acad. sci. USA, 2019; 116: 26224-26229. [Google Scholar] [CrossRef] [PubMed]
5. Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. Adv Drug deliv rev., 2012; 64: 614-628. Doi:10.1016/j.addr.2011.11.002.[DOI] [PubMed] [Google scholar]
6. Crowe, T.P.; Greenlee, M.H.W.; Kanthasamy, A.G.; Hsu, W.H Mechanism of intanasal drug delivery directly to the brain Life Sci., 2018; 195: 44-52. [google Scholar] [cross Ref]
7. Martins, P.P.; Smyth, H.D.C.; Cui, Z. strategies to facilitate or block nose-to-brain drug delivery directly to the brain. Life Sci., 2018; 195: 44-52. [google scholar] [[CrossRef]

8. Misra, A.; Jogani, V., Jinturkar, K.; Vyas, T. Recent patents review on intranasal administration for CNS drug delivery. Recent Pat. Drug Deliv., 2008; 2: 25-40. [Google Scholar] [Cross Ref]
9. Fonseca-Santos, B.; Gremião, M.P.D.; Chorilli, M. Nanotechnology-based drug delivery systems for the treatment of Alzheimer's disease. *Int. J. Nanomedicine*, 2015; *10*: 4981–5003. [Google Scholar] [CrossRef] [Green Version]
10. AI Asmari, A.K.; ullah, Z.; Tariq, M.; Fatani, A. Preparation, characterization, and in vivo evaluation of intranasally administered liposomal formulation of donepezil. Drug Des. Devel., 2016; 10: 205-215. [Google Scholar]
11. Bulbake, U.; Doppalapudi, S.; Kommineni, N.; Khan, W. Liposomal Formulations in clinical Use: An Updated Review. Pharmaceutics, 2017; 9: 12. [Google Scholar] [CrossRef]
12. Bourganis, V.; Kammona, O.' Alexopoulos, A.; Kiparissides, C Recent advances carrier mediated noe-to-brain delivery of pharmaceutics. Eur. J. Pharm. Biopharm., 2018; 128: 337-362. [Google Scholar] [CrossRef] [PubMed]
13. Bonferoni, M.C.; Rossi, S.; Sandri ,G.; Ferrari, F; Gavini, E.; Rassu, G.; Giunchedi, P. Nanoemulsions for ''Nose-to-Brain'' Drug Delivery. Pharmaceutics 2019; 11: 84. [Google Scholar] [CrossRef]
14. Sex and Gender Differences in Alzheimer's Disease. Recommendations for future research. J Women's Health, 2012; 21: 1018–23. https://doi.org/10.1089/jwh.2012.3789
15. J.L. Haines Alzheimer disease: Perspectives from epidemiology and genetics J. Law Med. Ethics, 2018; 46: 694-698. View in Scopus Google Scholar
16. L. Mucke Lots of people are forgetful. Are there any particular warning signs of Alzheimer's disease? Neuroscience, 2009; 461: 895-897. View at publisher Crossref View in Scopus Google Scholar.
17. Alzheimer's disease facts and figures, Alzheimer's Dement, 2019; 15: 321–387. Google Scholar
18. J.L. Haines Alzhemer disease: Perspective from epidemiology and genetics J.Law Med. Ethics, 2018; 46: 694-698. View at publisher Crossref View View in Scopus Google Scholar
19. L. Mucke Lots of people are forgetful. Are there any particular warning signs of Alzheimer's disease? Neuroscience, 2009; 461: 895-897. View at publisher Crossref View in Scopus Google Scholar

20. Erdo, F.; Bors, L.A.; Farkas, D.; Bajza, A.; Gizurarson, S. Evaluation of intranasal delivery route of drug administration for brain targeting. *Brain Res. Bull.*, 2018; *143*: 155–170. [Google Scholar] [CrossRef]
21. Crowe, T.P.; Greenlee, M.H.W.; Kanthasamy, A.G.; Hsu, W.H. Mechanism of intranasal drug delivery directly to the brain. *Life Sci.*, 2018; *195*: 44–52 . [Google Scholar] [CrossRef] [PubMed]
22. Illum, L. Transport of drugs from the nasal cavity to the central nervous system. *Eur. J. Pharm. Sci.*, 2000; *11*: 1–18. [Google Scholar] [CrossRef]
23. Dhanda DS, Frey W, Leopold D, Kompella U. Approaches for drug deposition in the human olfactory epithelium. Drug Deliv Technol., 2005; 5: 64–72.
24. C.P. Costa, J.N. Moreira ,J.M. Sousa Lobo, A.C. Silva Intranasal delivery of nanostructured lipid carriers, solid lipid nanoparticles and nanoemulsions: a current overview of *in vivo* studies Acta Pharm. Sin. B, 2021; 11: 925-940. 10.1016/j. apsb.2021.02.012 View PDFView article View in Scopus Google Scholar
25. V. Bourganis, O. Kammona, A. Alexopoulos, C. Kiparissides Recent advances in carrier mediated nose-to-brain delivery of pharmaceutics Eur. J. Pharm. Biopharm., 2018; 128: 337-362. 10.1016/j.ejpb.2018.05.009 View PDF View article View in Scopus Google Scholar
26. Thakur, P.K. Singh, S.S. Biswal, N. Kumar, C.B. Jha, G. Singh, C. Kaur, S. Wadhwa, R. Kumar Drug delivery through nose : a non-invasive technique for brain targeting J. Rep. Pharm. Sci., 2020 Jan 1; 9(1): 168, 10.4103/jrptps.JRPTPS_59_19
27. R.J. Soane, M. Hinchcliffe, S.S. Davis, L. Illum Clearance characteristics of chitosan based formulations in the sheep nasal Cavity Int. J. Pharm., 2001 Apr 17; 217(1–2): 183-191,10.1016/S0378-5173(01)00602-0
28. U. Seju, A. Kumar, K.K. Sawant Development and evaluation of olanzapine -loaded PLGA nanoparticles for nose-to-brain delivery: in vitro and in vivo studies Acta Biomater., 2011 Dec 1; 7(12): 4169-4176. 10.1016/j.actbio.2011.07.025
29. Ganeshpurkar A., Ganeshpurkar A., Agnihotri A., Pandey V., Vishwakarma N., Bansal D., Dubey N. Chondroitin Sulfate Surface Engineered Docetaxel-Loaded Liposomes for Tumor Targeting: design, Development, and Charaticterizaon. InProceedings of All India Seminar on Biomedical Engineering 2012 (AISOBE 2012) 2013; 77–82. Springer, Google Scholar.

30. S. Al Harthi, S.E. Alavi, M.A. Radwan, M.M. El Khatib, I.A AlSarra Nasal delivery of donepezil HCl-loaded hydrogels for the treatment of Alzheimer's disease Sci. Rep., 2019 Jul 2; 9(1): 1-20. 10.1038/s41598-019-46032-y
31. F.C. Carvalho, M.L. Bruschi, R.C. Evangelista, M.P. Gremião Mucoadhesive drug delivery systems J. Pharm. Sci., 2010 Mar; 46(1): 1-7, 10.1590/S1984-82502010000100002
32. S. Al Harthi, S.E. Alavi, M.A. Radwan, M.M. El Khatib I.A AlSarra Nasal delivery of donepezil HCl-loaded hydrogels for the treatment of Alzheimer's disease Sci. Rep., 2019 Jul 2; 9(1): 1-2010.1038/s41598-019-46032-y
33. F.C. Carvalho, M.L. Bruschi, R.C. Evangelista, M.P. Gremião Mucoadhesive drug delivery systems J. Pharm. Sci., 2010 Mar; 46(1): 1-7, 10.1590/S1984-82502010000100002.
34. S. Bahadur, D.M. Pardhi, J. Rautio, J.M. Rosenholm, K.Pathak Intranasal nanoemulsions for direct nose-to-brain delivery of actives for CNS disorders Pharmaceutics, 2020 Dec; 12(12): 1230. 10.3390/ pharmaceutics12121230
35. M. Sessa, M.L. Balestrieri, G. Ferrari, L. Servillo, D. Castaldo, N. D'Onofrio, F. Donsì, R Tsao Bioavailability of encapsulated resveratrol into nanoemulsion-based delivery systems Food Chem., 2014 Mar 15; 147: 42-50, 10.1016/j.foodchem2013.09.088
36. S. Bahadur, D.M. Pardhi, J. Rautio, J.M. Rosenholm, K. Pathak Intranasal nanoemulsions for direct nose-to-brain delivery of activesFor CNS disorders Pharmaceutics, 2020 Dec; 12(12): 1230, 10.3390/ pharmaceutics12121230
37. M.F. Haider, S. Khan, B. Gaba, T. Alam, S. Baboota, J. Ali, A. Ali Optimization of rivastigmine nano-emulsion for enhanced brain delivery: in-vivo and toxicity evaluation J. Mol. Liq., 2018 Apr 1; 255: 384-396, 10.1016/j.molliq. 2018.01.123
38. S. Bahadur, D.M. Pardhi, J. Rautio, J.M. Rosenholm, K. Pathak Intranasal nanoemulsions for direct nose-to-brain delivery of activesFor CNS disorders Pharmaceutics, 2020 Dec; 12(12): 1230, 10.3390/ pharmaceutics12121230
39. L.C. Espinoza, M. Silva-Abreu, B. Clares, M.J. Rodríguez-Lagunas, L. Halbaut, M.A. Cañas, A.C. . Calpena Formulation strategies to improve nose-to-brain delivery of donepezil Pharmaceutics, 2019 Feb; 11(2): 64, 10.3390/pharmaceutics11020064
40. Y. Su, B. Sun, X. Gao, X. Dong, L. Fu, Y. Zhang Z. Li, Y. Wang, H. Jiang, B. Han Intranasal delivery of targeted nanoparticles loaded with mir-132 to brain for the treatment of neurodegenerative diseases Front. Pharmacol., 2020 Aug 6; 11: 1165, 10.3389/fphar. 2020.01165

41. S. Al Harthi, S.E. Alavi, M.A. Radwan, M.M. El Khatib I.A AlSarra Nasal delivery of donepezil HCl-loaded hydrogels for the treatment of Alzheimer's disease Sci. Rep., 2019 Jul 2; 9 (1): 1-20. 10.1038/s41598-019-46032
42. J.A. Trejo-Lopez, A.T. Yachnis, S. Prokop Neuropathology of Alzheimer's diseases Neurotherapeutics, 2021; 1-13, 10.1007/s13311-021-01146-y
43. 43) W. Phachonpai, J. Wattanathorn, S. Muchimapura, T. Tong-Un, D. Preechagoon Neuroprotective effect of quercetin encapsulated liposomes: a novel therapeutic strategy against Alzheimer's diseaseAm. J. Appl. Sci., 2010; 7(4): 480-485, 10.3844/ajassp.2010.480.485
44. Perez A. P., Mundina-Weilenmann C., Romero E. L., Morilla M. J. (2012). Increased brain radioactivity by intranasal P-labeled siRNA dendriplexes within *in situ*-forming mucoadhesive gels. Int. J. Nanomedicine, 7: 1373–1385. 10.2147/IJN.S28261[DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
45. Aliev G., Ashraf G., Tarasov V. N., Chubarev V. N., Leszek J., Gasiorowski K., et al. (2019). Alzheimer's disease - future therapy based on dendrimers. Curr. Neuropharmacol., 17(3): 288–294. 10.2174/1570159X16666180918164623 [DOI] [PMC free article] [PubMed] [Google Scholar]][Ref list]
46. Tiwari S, Atluri VSR, Yndart Arias A, et al. Withaferin a suppresses beta amyloid in APP expressing cells: studies for tat and cocaine associated neurological dysfunctions. *Front Aging Neurosci*. 2018; 10: 291. doi: 10.3389/fnagi.2018.00291 [DOI] [PMC free article] [PubMed] [Google Scholar] [Ref list]
47. Hsiao IL, Hsieh YK, Chuang CY, Wang CF, Huang YJ. Effects of silver nanoparticles on the interactions of neuron-and glia-like cells: toxicity, uptake mechanisms, and lysosomal tracking. *Environ Toxicol*., 2017; 32(6): 1742–1753. doi: 10.1002/tox.22397[DOI] [PubMed] [Google Scholar]
48. Hsiao I-L, Hsieh Y-K, Wang C-F, Chen I-C, Huang Y-J. Trojan-horse mechanism in the cellular uptake of silver nanoparticles verified by direct intra-and extracellular silver speciation analysis. *Environ Sci Technol*., 2015; 49(6): 3813–3821. doi: 10.1021/es504705p [DOI] [PubMed] [Google Scholar]
49. Leszek J, Md Ashraf G, Tse WH, et al. Nanotechnology for Alzheimer disease. Curr Alzheimer Res. 2017; 14(11): 1182–1189. doi: 10.2174/1567205014666170203125008 [DOI] [PubMed] [Google Scholar]

50. *Lammers T, Rizzo LY, Storm G, Kiessling F. Personalized nanomedicine. Clin Cancer Res. 2012; 18(18): 4889–4894. doi: 10.1158/1078-0432.CCR-12-1414* [DOI] [PubMed] [Google Scholar]
51. *Tietjen GT, Saltzman WM. Nanomedicine gets personal. Sci Transl Med., 2015; 7(314): 314fs347. doi: 10.1126/scitranslmed aad3106*[DOI] [PubMed] [Google Scholar]
52. *Yu D, Khan OF, Suvà ML, et al. Multiplexed RNAi therapy against brain tumor- initiating cells via lipopolymeric nanoparticle infusion delays glioblastoma progression Proc Natl Acad Sci., 2017; 114(30): E6147-–E6156. doi: 10.1073/pnas.1701911114* [DOI] [PMC free article] [PubMed] [Google Scholar]
53. *Jayant RD, Atluri VS, Tiwari S, et al. Novel nanoformulation to mitigate co-effects of drugs of abuse and HIV-1 infection: towards the treatment of NeuroAIDS J Neurovirol., 2017; 23(4): 603–614. doi: 10.1007/s13365-017-0538-8* [DOI] [PMC free article] [PubMed] [Google Scholar]
54. *Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med., 2010; 363(4): 301–304. doi: 10.1056/NEJMp1006304* [DOI] [PubMed] [Google Scholar]
55. *Theek B, Rizzo LY, Ehling J, Kiessling F, Lammers T. The theranostic path to personalized nanomedicine Clin Transl Imaging., 2014; 2(1): 67–76. doi: 10.1007/s40336-014-0051-5* [DOI][PMC free article] [PubMed] [Google Scholar]
56. *Jain KK, Jain KK. The Handbook of Nanomedicine. 404 Heidelberg: Springer; 2008.* [Google Scholar]
57. *Fornaguera C, García-Celma M. Personalized nanomedicine: a revolution at the nanoscale. J pers med., 2017; 7(4): 12. doi: 10.3390/jpm7040012*[DOI] [PMC free article] [PubMed] [Google Scholar]
58. Mura S, Couvreur P. Nanotheranostics for personalized medicine. Adv Drug Deliv Rev., 2012; 64(13): 1394–1416. doi: 10.1016/j.addr.2012.06.006[DOI] [PubMed][Google Scholar]
59. Yang F-Y, Lin Y-S, Kang K-H, Chao T-K. Reversible blood–brain barrier disruption by repeated transcranial focused ultrasound allows enhanced extravasation. J Control Release., 2011; 150(1): 111–116. doi: 10.1016/j.jconrel.2010.10.038[DOI] [PubMed] [Google Scholar]
60. Jain KK, Jain KK. The Handbook of Nanomedicine. Vol. 404 Heidelberg: Springer; 2008. [Google Scholar]

61. Fornaguera C, García-Celma M. Personalized nanomedicine: a revolution at the nanoscale. J pers med., 2017; 7(4): 12. doi: 10.3390/jpm7040012[DOI] [PMC free article] [PubMed][Google Scholar]
62. Sanhai WR, Sakamoto JH, Canady R, Ferrari M. Seven challenges for nanomedicine. Nat Nanotechnol., 2008; 3(5): 242. doi: 10.1038/nnano.2008.114*[DOI] [PubMed [Google Scholar]*
63. Trevino J. T., Quispe R. C., Khan F., Novak V. (2020). Non-invasive strategies for nose-to-brain drug delivery. J. Clin. Trials, 10(7): 439. [PMC free article] [PubMed] [Google Scholar]
64. Santamaria G., Brandi E., Vitola P., Grandi F., Ferrara G., Pischiutta F., et al. (2021). Intranasal delivery of mesenchymal stem cell secretome repairs the brain of Alzheimer's mice. Cell Death Differ. 28: 203–218. 10.1038/s41418-020-0592-2 [DOI] [PMC free article] [Google Scholar]