Niosome as a promising carrier targeting Alzheimer's disease across the Blood Brain Barrier

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Abstract

Targeted delivery has gained much attention in recent years among pharmaceutical industries and pharmacy researchers. Unlike normal drug delivery, tissue targeted drug delivery requires a special technology and techniques to manufacture the final product. In particular, delivering a drug to brain tissue poses various problems like penetration and availability of the drug on brain tissue is ever challenging. The drug delivery to the CNS is always challenging among researchers worldwide. Unlike other organ systems, the human brain architecture is so complex, and also various restrictions exist in the brain tissue inorder to access it. The concept of niosome loaded drug delivery system has gained much attention in recent years because of its high lipophilic nature and also it can easily attract lipophilic drugs and attract the brain tissue. Keeping the idea of explaining niosomes as a drug carrier for delivering drug candidates to the brain target, an attempt was made to review the niosome loaded drugs for Alzheimer's Disease (AD) which is considered to be the most common neurological disorder. This review emphasises the drugs used for AD with their mechanism of actions and its characteristic features to get formulated with niosome with the formulation criteria. In addition to that, it emphasises the future perspective of niosome loaded drug delivery for the treatment of AD.

Key Words: Niosome, Alzheimer disease, Pathology, Acetyl cholinesterase inhibitors

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Introduction

The human brain is a delicate neuronal organ system that requires a steady supply of fuels such as glucose and ketone bodies, gases such as oxygen and hydrogen, and nutrients such as lipids, proteins, and micronutrients to maintain homeostasis and other critical bodily activities. The lacuna of equilibrium in the essential components of the brain or any microbial infection leads to various neurological diseases and disorders. There are several neurological diseases and disorders such as Meningitis, Brain abscess, Eclampsia, Myasthenia Gravis, and cognitive related conditions such as Dementia, Alzheimer's disease, Parkinson's syndrome, *etc* that need attention for their treatments and management.[1] In Order to deal with the treatment of such pathological conditions, delivering the drugs surpasses the Blood Brain Barrier which is composed of the non-fenestrated membrane.[2]The non-fenestrated membrane of the brain consists of astrocytic terminal appendages, endothelial cells, basal lamina, pericytes, and Tight Junctions (TJ). TJ is composed of various transmembrane proteins, *per se* Junctional Adhesion Molecules (JAMs), occludin, and claudins.[3]The transportation is based on the selectivity towards lipophilic materials. To overcome this extensive barrier towards delivering the drug to the brain, several invasive and noninvasive approaches are being carried out by several researchers. One such noninvasive physical approach is known as Niosomal drug delivery. Niosomes are the bilayer vesicles enclosed by the aggregation of cholesterol and insoluble non-ionic surface acting agents of the alkyl polyglycol ether class with subsequent hydration in aqueous media. The recent research says that Niosomes are more stable than the liposomes in concern with the membrane rigidity. Thus, the drug delivery for the treatment of Neurological diseases such as Meningitis, Brain abscess, and Multiple sclerosis are being developed by means of nano particulate drug delivery, especially Niosomes. This article reviews how the Niosome has been used as a carrier for targeting Alzheimer's disease by surpassing the drugs through the Blood Brain Barrier.

Alzheimer's Disease (AD)

First case of AD was reported in 1907 by German physician Alois Alzheimer. Due to the buildup of extracellular plaques in the brain, AD is a prevalent multifactorial neurodegenerative disorder that results in memory loss, cognitive impairment, behavioural changes, and a decrease in one's ability to perform daily tasks. AD is responsible for the dementia of an estimated 50 million persons globally.. By the year 2050, this number is predicted to have risen to over 150 million.[4],[5]There are many factors that contribute to Alzheimer's, including genetics, education, age, and the environment. The cholinergic hypothesis is one of the oldest hypotheses that have laid the groundwork for understanding the disease's aetiology.

AD is characterised by the deposition of amyloid (A) in the form of plaques outside of the brain and the formation of neurofibrillary tangles inside the brain (NFT). The FDA has only approved four drugs for the treatment of AD as of this writing. Donepezil, galantamine, and rivastigmine are all AChE inhibitors, while NMDA receptor antagonist (memantine) rounds out the list.[6] However, only modest improvements in symptom management can be attributed to these medications. Furthermore, they have no effect on neuronal loss, brain atrophy, or cognitive decline.

Pathology of Alzheimer's Disease

The macroscopic pathology of AD includes generalised cortical atrophy, most prominently observed in the medial temporal lobe and hippocampus.[7]This condition is associated with the pathological condition called cardinal lesions. Neurofibrillary tangles and senile plaque are the two main cardinal lesions connected to Alzheimer's disease. The perikaryal cytoplasm of some neurons contains aberrant accumulations of tau that are improperly phosphorylated, which makes up the neurofibrillary tangle. The 4-kD peptide beta-amyloid forms the centre of the senile plaque, which is encircled by improperly shaped neural processes, or neurites. Other lesions include poorly understood alterations including granulovacuolar degeneration and Hirano bodies, which are eosinophilic rod-like structures. Another noteworthy morphological modification that certainly has a big impact on cognitive performance is the loss of synaptic components.[8]Microscopically examining damaged areas of the brain reveals inflammation, granulovacuolar degeneration, Hirano bodies, and the two classic inclusions, neurofibrillary tangles (NFTs) and amyloid plaques.[7]

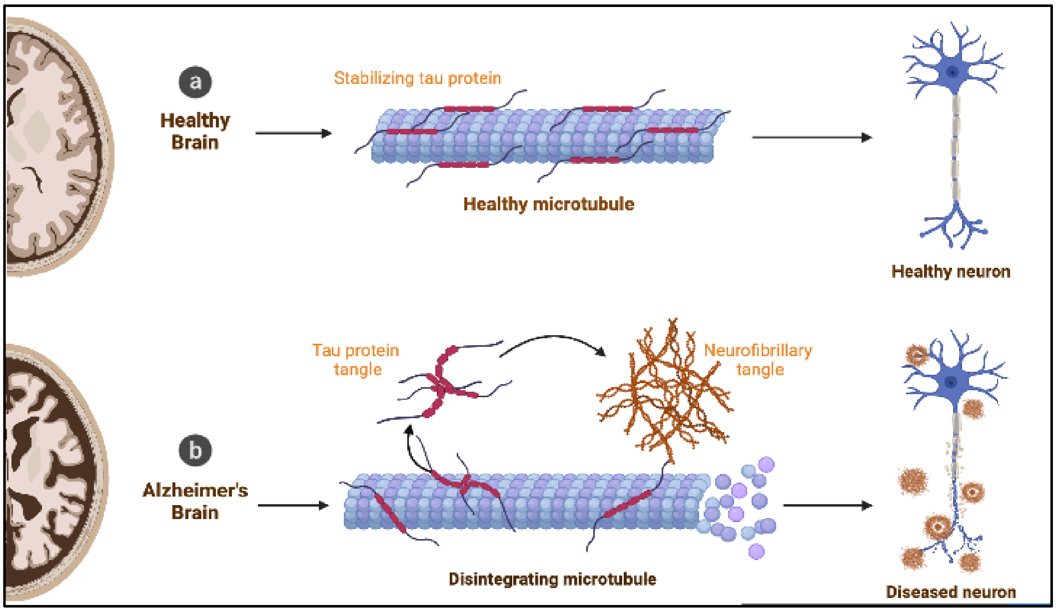

Figure 1: Pathology of Alzheimer disease

Niosomes

Nisomes are the bilayer vesicles enclosed by the aggregation of cholesterol and insoluble non-ionic surface acting agents of the alkyl polyglycol ether class with subsequent hydration in aqueous media.[9],[10]These bilayers are thermodynamically stable only when the temperature is above the gel liquid transition point and the right proportion of surfactants and cholesterol are present in the mixture.[11] There are three main components of niosomes per se: Non-ionic surfactants, aHydration medium, and aLipidic component.[14] They are as follows:

- Nonionic surfactants- They are the class of surfactants which possess uncharged groups in their hydrophilic heads. They are amphiphilic molecules which comprises two different regions such as the hydrophilic head (water soluble) and ahydrophobic tail (lipid soluble).[12][13] Some examples of nonionic surfactants include alkyl ethers, alkyl esters, fatty acids or alcohols, and block copolymers. They are safer and more stable than their anionic, cationic, and amphoteric analogues. Thus they are preferred to be used in niosomes production.[14][12]

- Hydration medium - It imparts substantial effects on the vesicular size and drug loading of vesicles.[13][14](

- Lipidic components- The major lipid component used here is cholesterol. It binds with the hydrophilic head of a non-ionic surfactant by forming hydrogen bonds.[13] It improves the vesicular rigidity and inhibits the leakage by decreasing the permeability of vesicles for entrapped molecules. It also prevents the niosomes from the destabilising effects persuaded by plasma and serum components. The example for cholesterol used here is l-α-Soya phosphatidylcholine.[14]

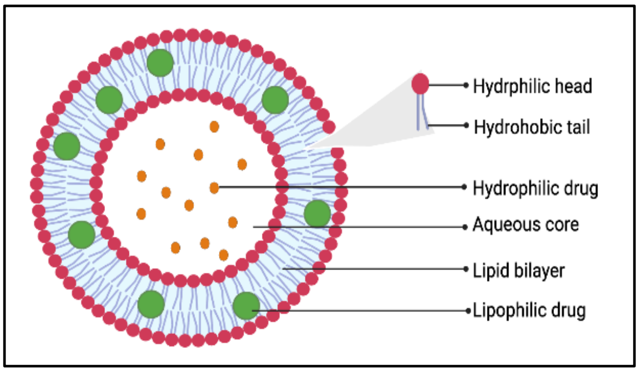

Figure 2: Structure of Liposome

Similar to liposomes, these vesicular structures can be utilised to transport both amphiphilic and lipophilic pharmaceuticals. The preparation methods of niosome is based on liposome technology.Niosomes are prepared by using various methods including, Thin Film Hydration (TFH) method, Ether Injection Method (EIM), Micro fluidization method, supercritical carbon dioxide fluid, proniosome, transmembrane pH gradient heating method, The 'Bubble' method, and Reverse Phase Evaporation (RPE) method, Sonication, *et cetera.* [15][11][16]

Formulation criteria for niosome

The hydrophilic-lipophilic balance value (HLB), the gel-liquid transition temperature (TC), and the critical packing parameter (CPP), are the main requirements for the formulation of niosomes. When designing niosomes, it is crucial to take these considerations into account when selecting a non-ionic surfactant and other agents.[11][15][18][19][20].

Table 1: Formulation criteria for liposomes

Formulation criteria	Properties
Hydrophilic-lipophilic balance value (HLB)	● In determining the size of niosomes. ● The nonionic surfactant's alkyl chain length impacts the niosome's vesicular size, which in turn affects the HLB value. ● In order to prevent the production of niosomal vesicles, surfactant with an HLB value of 14–17 cannot be used. ● In surfactants with an HLB value lower than 6, cholesterol must be added to create vesicles with optimal stability.[21]
Gel-liquid transition temperature (TC)	• Entrapment performance is directly related to the surfactant's (TC). • The lowest temperature at which the lipid transforms from an ordered gel state to a disordered liquid crystalline phase is referred to as the transition temperature.[22] • The Tc can be affected by a variety of factors, including chain length, unsaturation, charge, and head group species. • In addition, hydration must be performed at a temperature higher than the gel-liquid transition temperature (TC) in order to avoid lump formation.[21]
Critical Packing Parameter (CPP)	● CPPs have a significant influence in the variety of surfactants that are available. ● It provides a quick overview of vesicle generation and stability. ● The following equation can be used to calculate CPP. ● **CPP = v ic × a0** ● Here, v is the volume, ic is the chain length of the hydrophobic group, and a0 is the hydrophilic head's surface area. ● Niosomes' structure can be predicted using CPP's established values. ● Less than 0.5- Spherical vesicles ● 0.5-1 Bilayered vesicles ● More than 1- Inverted micelles.[21][23]

Classification of Anti-Alzheimer's drugs

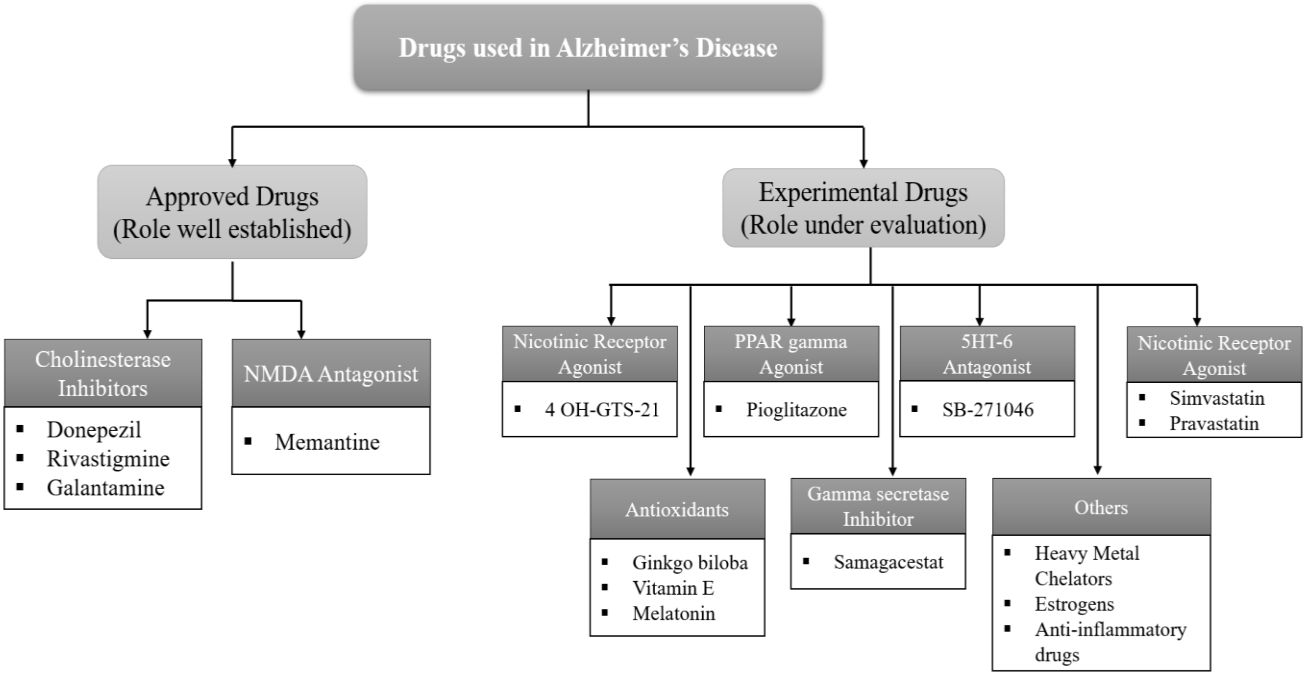

Figure 2: Flow chart of drugs used for Alzheimer disease

Mechanism of niosomes across BBB

The blood-brain barrier (BBB) is a system of brain microvascular endothelial cells (BMVEC) that filters potentially hazardous molecules out of the brain and into the bloodstream. These functions are carried out by the blood-brain barrier.Neural tissues are protected from neurotoxic chemicals and blood structure variations required for normal neuronal functions by the BBB.[24]Capillaries lined with endothelial cells perfuse most of our body's organs, with the exception of the brain and spinal cord, which require small pores to allow small molecules from the circulation to enter swiftly into the interstitial fluid of the organ. A zonula occludens (TJ) connects each EC to the next in the brain arteriole and covers the paracellular route.[16][25]The BBB is part of the CNS's neurovascular unit. It hinders brain cell substance exchange. BBB's major components include endothelial cells, astrocytic end-feet connections, basal lamina, TJ, and pericytes.Endothelial cells in the BBB are distinct from those in the rest of the body.[26][27] TJ is composed of many transmembrane proteins, such as occludin, claudins, and junctional adhesion molecules (JAMs) and the metabolic barrier is tightly controlled by the various enzymes of BBB.[24][28]

Free polar solutes can be effectively blocked from paracellular routes, preventing their entry into the brain interstitial fluid. Therefore, the BBB allows small particles, such as lipophilic solutes or those molecules that enter the brain through an active transport system, to flow over the brain via the bloodstream, usually containing essential nutrients, precursors, and cofactors. Several systems, such as BBB peptide transport pathways, can carry BBB into the brain endothelium for processing.[16] (Endothelial cells and pericytes include a number of important transporters, receptors, and channels that help facilitate transport over the BBB, which is facilitated by endogenous-carrier-mediated transport (CMT) or receptor-mediated transport (RMT). In this sense, the BBB serves as a physical and physiological barrier as well as a secretory and transport interface to the brain and CNS.[29][30]Systemic absorption through the blood-brain barrier (BBB), nasal, and intracerebroventricular (ICV) injection are the most common routes for drugs to reach the brain.[16]

Since Niosomes are vesicles, they may readily pass through the non-fenestrated BBB, which plays a crucial part in the BBB's passage.

Mechanism of action of Anti-alzheimer drugs

Acetylcholinesterase Inhibitors

AD is best treated with AChEIs (donepezil, galantamine, and rivastigmine). By blocking the acetylcholinesterase enzyme (AChE), the AChEIs attempt to increase ACh levels and so reduce the symptoms associated with the increasing loss of cholinergic function in AD. Cognitive impairment in dementia, including AD, has been linked to poorer ACh production (including lower choline acetyltransferase activity, which is essential for ACh synthesis). Higher levels of ACh in the brain have been linked to enhanced activity of other neurotransmitter systems connected to cognition, such as glutamate, as well as increased expression of nicotinic ACh receptors on cholinoceptive neurons.[31][25]

Three AChEIs show no clinical differences, but their underlying mechanisms can be separated in terms of selectivity to the target protein: Donepezil is a selective and reversible inhibitor of AChE, as well as a neuronal nicotinic ACh receptor antagonist.[32][33] To put this into perspective, rivastigmine is a butyrylcholinesterase-simulating pseudo-irreversible AChE inhibitor (i.e. via a transient covalent link) (BuChE).[34] As the severity of Alzheimer's disease increases, levels of BuChE, a non-specific enzyme that hydrolyzes ACh and other choline esters, rise. BuChE is primarily found outside the central nervous system. (An inhibitor of AChE called galantamine has been shown to boost the intrinsic activity of ACh on nicotinic receptors, which may be linked to the clearance of amyloid-beta. However, this latter effect has been widely disputed.[35] There doesn't appear to be a significant difference in the therapeutic effects of the AChEIs based on these varied specificities.Although tacrine is a reversible inhibitor of both enzymes, it is no longer utilised in clinical practise due to intolerability concerns.[36]

Table 2: Target of the Acetylcholine inhibitors for Alzheimer disease

Drug	Target	Action
Donepezil	Neuronal nicotinic ACh receptor	Inhibition
Galantamine	Nicotinic receptors; amyloid-beta	Inhibition
Rivastigmine	AChE and BuChE	Inhibition

NMDA Receptor antagonist

Till date, Memantine is the only approved NMDA receptor antagonist for treating moderate to severe AD.[37]It has shown strong symptomatic efficacy in large-scale, controlled clinical investigations. Memantine may also lessen agitation and animosity. Memantine is a voltage-dependent NMDA receptor antagonist with modest binding affinity and fast receptor kinetics. Memantine's glutamatergic binding profile alters AD-related NMDA receptor activation. Resting magnesium ions block NMDA receptor channels. The postsynaptic membrane depolarizes in response to a strong, brief glutamate synaptic signal, releasing the blockade of the voltage-dependent Mg2+ channel and opening the NMDA channel to let Ca2+ ions into the cell.[38]Low-level glutamate and amyloid-beta stimulation in AD may lower membrane potential, lowering NMDA receptor channel obstruction by Mg2+ ions, increasing Ca2+ ion flow into the postsynaptic neuron, and creating a 'background noise' of stimulation. Memantine binds to NMDA receptor ion channels, says electrophysiology. Memantine binds with intermediate affinity and voltage dependence, so it continues to block the NMDA receptor channel at moderate levels of protracted stimulation (pathological circumstances). Mg2+. Memantine dissociates from the receptor when glutamate levels are transiently high (a physiological signal).Memantine may lower the "background noise" of glutamate signalling in AD to better distinguish physiological signals. In vivo and in vitro investigations demonstrate this restores NMDA-induced learning deficits. Preclinical research reveals memantine protects neurons against glutamate excitotoxicity. Memantine protects against excitotoxicity in vitro and in vivo. Amyloid-beta exerts pathogenic effects on the glutamatergic system by the inhibition of the astroglial glutamate transporter and reducing glutamate reuptake. NMDA receptors may act as a direct agonist or through interactions with postsynaptic anchoring proteins which can be stimulated by Amyloid-beta peptides according to certain studies. Memantine protects against amyloid-beta-induced degenerative changes and learning impairment. Memantine improved cognition and decreased amyloid-beta levels in triple-transgenic AD-like mice. Memantine prevents amyloid-beta-induced synapse degradation and ROS. Despite these observations, the mechanisms linking memantine's clinical effect in AD are unclear.[31]

Pharmacokinetic and pharmacodynamic profile of Anti-alzheimer's drug [34][39][40][41] [42][43]

Table 3: Pharmacokinetic and Pharmacodynamics profile of Anti Alzheimer drugs

Drug	Bioavailability	Protein binding	Half life	T_{max}	Hepatic metabolism
Donepezil	100	96	60-90	3-5	CYP2D6, CYP3A4
Galantamine	85-100	18	5-7	0.5-1.5	CYP2D6, CYP3A4
Rivastigmine	40	40	1.5	0.8-1.7	Non-hepatic
Memantine	100	45	60-80	3-7	NA

Future perspective of Niosome based drug delivery for Alzheimer's Disease

AD is a global cause of dementia. The challenges of detection and treatment in neurodegenerative disease limit the effectiveness of therapy.. The impermeable BBB has limited the use of oral therapies. AD sufferers lose cognitive function, have impaired language, can't rationalise, and have behavioural impairment. AD impairs quality of life. Quality of life declines for both the patient and the caregiver, resulting in weariness. AD symptom management has few FDA-approved solutions. Rivastigmine is the gold standard for treating AD. Current medications treat symptoms but don't slow disease progression. Nanotechnology advances provide customised medicine delivery. Neurodegenerative diseases may be treated via niosomal medication delivery. Niosomal drug loading reduces reticuloendothelial absorption by macrophages, enhances biological distribution, , and decreases free drug, minimising systemic toxicity. Niosomes can be modified to target the brain and overcome the BBB. Multifunctional liposomes may decrease neurodegenerative disease progression by targeting many pathologies.

In addition to being able to carry hydrophilic, lipophilic, and amphiphilic drug moieties, niosomes also exhibit a wide range of desirable properties, including tunable vesicle size, sustained drug release, high loading capacity, osmotic stability, ease of fusogenicity, and intracellular drug release.[44] Loaded niosomes boost drug efficacy, controlled release, stability, targeted action, and therapeutic index. Niosomes-based drug delivery is more effective, stable, and safe than liposomal drug delivery, although further trials are needed to determine the most effective and safe route of administration. Many uses of Niosomes as a medicine delivery technology lack dosage information. Niosomes induce drug accumulation; clearance must be therapeutically appropriate and non-toxic.

Future research is planned to apply Niosomes' advantages over Liposomes, such as size variation, large load transport capabilities, sustained agent delivery, increased efficacy, enhanced therapeutic index, improved agent stability, selective passive targeting, and reduced toxicity. Niosome composition must vary from batch to batch. Lack of homogeneity in large-scale liposome production increases niosome production costs. Future research will lead to cheaper liposomal medication delivery methods. Reticuloendothelial niosome uptake needs more research. Recent studies have focused on niosomes as inoculations or intranasal drug delivery, however, research on the safe method is necessary.

Niosomes-based medication delivery for AD shows promise and possibility for decreasing AD pathogenesis. Variation in Niosomes and modification enable for precise targeting to breach the BBB focus on multifunctional liposomes that target several brain pathologies. Further study is needed to ensure safe niosomal medication delivery.

Conclusion:

The targeted drug delivery system has evolved as a promising approach for delivering drugs to specific sites in the body, especially to the sites of secured structural arrangements such as the brain, because of its fenestrated, continuous arrangement. The nanoparticle drug delivery strategy has emerged as a wonderful and beneficial drug delivery system to the brain, in which the Niosomes are considered to be the more stable and advantageous drug delivery strategy. The Anti-alzheimer's drug classes such as Acetylcholinesterase inhibitors and NMDA receptors are the least suitable for the delivery of drugs through conventional drug delivery systems. Thus, the vesicular carrier systems like niosomes can surpass the BBB due to its high lipophilicity which can deliver those drugs to provide better treatment and management for Alzheimer's disease. Since Alzheimer's disease is considered to be one of the most widespread brain diseases, it needs the development and treatment strategies that can be achieved by nanoparticles and extensively by niosomes when compared to the conventional treatment strategies. Further research and development need to be centred on the development of more niosome-based anti-alzheimer drugs.

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Conflicts Of Interest

There are no conflicts is declare.

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