



Review article

Alzheimer's disease current therapies, novel drug delivery systems and future directions for better disease management



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ABSTRACT

Alzheimer's disease (AD), is a neurodegenerative disorder that escalates with time, exerting a significant impact on physical and mental health and leading to death. The prevalence of AD is progressively rising along with its associated economic burden and necessitates effective therapeutic approaches in the near future. This review paper aims to offer an insightful overview of disease pathogenesis, current FDA-approved drugs, and drugs in different clinical phases. It also explores innovative formulations and drug delivery strategies, focusing on nanocarriers and long-acting medications (LAMs) to enhance treatment efficacy and patient adherence. The review also emphasizes preclinical evidence related to nanocarriers and their potential to improve drug bioavailability, pharmacokinetics, and pharmacodynamics parameters, while also highlighting their ability to minimize systemic side effects. By providing a comprehensive analysis, this review furnishes valuable insights into different pathophysiological mechanisms for future drug development. It aims to inform the development of treatment strategies and innovative formulation approaches for delivering existing molecules in Alzheimer's disease, ultimately striving to improve patient compliance.

1. Introduction

More than a century ago, Alois Alzheimer defined Alzheimer's disease (AD) as "senile dementia," a progressive neurological condition that leads to a gradual decline in both physical and mental health, ultimately leading to death [1]. It is believed that dementia begins to develop 20 years or even more before the onset of apparent symptoms. The World Alzheimer's Report 2019 reveals that there are currently 6.7 million Americans living with Alzheimer's disease, and this number is projected to rise to 14 million in the United States alone by 2050. The total estimated cost of Alzheimer's treatments in 2019 was 340 billion US dollars, and by 2050, this figure could reach 1.1 trillion US dollars [2]. In the Australian continent, the Australian Institute of Health and Welfare (AIHW) delineated about 472,000 individuals with Alzheimer's disease and this number is projected to increase to 589,000 by 2028 [3]. The data revealed that dementia related to Alzheimer's disease is the second leading cause of death in the country and the economic burden of care and treatment amounted to approximately 3.0 billion dollars during the 2018–2019 fiscal year. Also, it is predicted that this cost will double by 2058, with a total of 849,300 cases of dementia, including 533,800 women [4]. Approximately 70% of all dementia cases in the

country are attributed to AD. The total annual cost of dementia in the country is estimated to be around 15 billion dollars, encompassing healthcare expenses, aged care services, and informal care provided by family and friends [3]. These demographic trends and economic implications highlight the significance of Alzheimer's disease for physicians and healthcare systems worldwide.

In managing AD, the FDA has approved two categories of drugs. Cholinesterase inhibitors (ChEIs) are used in the early stages of the disease to inhibit the degradation of acetylcholine. For moderate to severe conditions, a *N*-methyl-D-aspartate (NMDA) receptor blocker can be used in combination with AChE inhibitors to improve disease progression [5,6]. These drug classes are available in tablet and capsule forms on the market. Clinical and preclinical data have demonstrated significant reductions in disease burden and cognitive improvement with these medications. However, while they have the potential to slow down disease progression, their therapeutic value and effectiveness can be further enhanced by incorporating them into advanced delivery vehicles specifically targeted to the brain. Furthermore, the current discrepancies in central nervous system disorders emphasize the need for efficient and targeted drug delivery to the brain to enhance therapeutic efficacy [7]. Recently, two antibodies, aducanumab and lecanemab, have received

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accelerated approval from the FDA. They are believed to clear A β plaques and aggregates [8,9]. However, there is controversy surrounding their role in modifying the disease.

Besides these advancements in therapeutic molecules, overall patient health in brain disorders has not shown significant improvement. Concerns such as patient adherence to therapy, lack of efficacy, adverse effects, and polypharmacy can contribute to relapse and reduce treatment effectiveness. Additionally, oral dosing presents challenges, particularly in elderly patients with dementia and other psychotic disorders, who may struggle with forgetfulness and difficulty swallowing tablets and capsules. In such cases, long-acting medications or injections that deliver a therapeutic dose over an extended period have shown promise in minimizing disease relapse. These parenteral drug products have been explored in various disease conditions, ranging from HIV and schizophrenia to paradigms such as contraception, bronchial asthma, and cancer [10–13]. Furthermore, the use of long-acting medications in the management of chronic conditions holds great promise due to various advantages like improved patient adherence to therapy, prevention of relapse, better maintenance of drug concentration in the bloodstream, and reduced adverse effects through proper drug dose adjustment [14].

This review article provides a comprehensive discussion on the pathophysiology of Alzheimer's disease, including the various pathways involved and approved drugs for its treatment. It also explores FDA-approved drugs and their innovative formulations, using preclinical data on nanocarriers to evaluate their impact on disease treatment and modification. Although numerous combinations of these drugs have been experimented with, only the Donepezil-Memantine combination, administered as an extended-release tablet taken once daily, has received FDA approval in managing moderate-to-severe dementia [15]. These drug delivery vehicles are further investigated to enhance the therapeutic efficacy via improving pharmacokinetics/pharmacodynamics profiling of these drugs while minimizing their systemic side effects. To the best of our knowledge, this work unprecedentedly discusses preclinical data of drug delivery systems of all FDA-approved drugs (memantine, donepezil, rivastigmine and galantamine) for development of better therapy for AD. In the following section, the pathology, risk factors and primary therapy of AD will be discussed, to build a mechanistic picture into the understanding of this disease, aiding the development of more efficacious and innovative therapeutic alternatives for AD.

2. Background

As mentioned in previous section, AD is a neurological disorder with continuous deterioration of cognitive function and memory. The prevalence of AD is increasing globally, posing significant challenges to healthcare systems and societies.

2.1. Pathology

Understanding different pathways involved in the mechanisms of AD pathogenesis are crucial for the development of effective treatment options. Unfortunately, the precise mechanisms underlying AD pathogenesis are unknown till date. It is believed that the less soluble forms of beta-amyloid plaques and tau tangles accumulates, hence resulting into disruption of normal neuronal function and communication within the brain. The beta-amyloid plaques are formed by the aggregation of insoluble forms of these beta-amyloid peptides, formed in the amyloidogenic pathway by the cleavage of the amyloid precursor proteins (APP) [16]. These plaques accumulation inside and outside the neurons, interferes with the synaptic communication, where it promotes conditions like inflammation and oxidative stress, contributing to neuronal degeneration. Tau tangles, on the other hand, result from the aggregation after abnormal phosphorylation of these proteins, resulting in disruption of axonal transport via destabilization and disintegration of microtubules [17].

Out of several factors, genetic also plays a crucial role in the development of AD. While most cases are sporadic, with no clear genetic cause, a small percentage of cases are familial or early-onset AD (EOAD), caused by specific gene mutations. For example, mutations in the presenilin 2 (PSEN2) gene on chromosome 1, APP gene on chromosome 21, and presenilin 1 (PSEN1) gene on chromosome 14 have been linked to EOAD [18–20]. These mutations disrupt normal protein processing and lead to the formation of beta-amyloid plaques and tau tangles, a hallmark pathological features of the AD. Whereas, in sporadic AD, a common genetic risk factor is the apolipoprotein E (ApoE) gene of different forms ApoE2, ApoE3, and ApoE4, is involved in lipid metabolism and plays a role in maintaining brain homeostasis. Among these, the most consistent gene associated with earlier onset of AD is ApoE4 allele [21]. Individuals carrying the ApoE4 allele have a higher likelihood of developing beta-amyloid plaques and experiencing cognitive decline. The genes involved with EOAD, and their prevalence are demonstrated in the Table 1 below.

The progression of AD is associated with the gradual loss of neurons and brain atrophy. Brain imaging studies have shown significant shrinkage in regions critical for memory and cognition, such as the hippocampus and cerebral cortex [24]. The loss of neuronal cells and synaptic connections contributes to cognitive impairment and the decline in various cognitive domains [25]. Understanding the underlying mechanisms of AD pathogenesis is crucial for the development of effective therapeutic strategies. Current research focuses on targeting beta-amyloid and tau protein to prevent their accumulation and promote the clearance of these abnormal protein aggregates. Novel approaches, including immunotherapies and precision medicine, are being explored to address the complex nature of AD.

Moreover, AD is a multifaceted disease influenced by both genetic and environmental factors. Advances in our understanding of the genetic and molecular basis of AD offer hope for the development of innovative therapies to alleviate the burden of this devastating disease. The interplay between beta-amyloid plaques, tau tangles, and neuroinflammation contributes to the progressive neurodegeneration observed in AD and are described in Fig. 1.

2.2. Tau protein

The hypothesis regarding neurofibrillary tangles (NFTs) in AD was initially described by a German psychiatrist named "Alois Alzheimer" in 1907. The relationship of NFTs with AD and structural understanding was elucidated in 1968 and 1988, respectively [26,27]. Tau protein is a microtubular protein that plays a crucial role in axonal growth and neuronal development by maintaining the stability of microtubule assembly [28]. Understanding the role of tau protein and its pathological

Table 1
EOAD with prevalence and gene involved [22,23].

| Gene associated | Percentage Prevalence of EOAD and onset of Age |
|-----------------|---|
| APP | APP is prevalent in approximately 10–15% of cases. The typical age of onset for individuals with this gene mutation is usually in their 40s and 50s, although it can occasionally occur in their 60s (with a range of onset between 30 and 65 years) |
| PSEN1 | Higher prevalence, accounting for around 20–70% of cases. Most commonly individuals between 40–50s show mutation in PSEN1 gene (with an onset range between 30 and the early 60s). Cases of EOAD associated with PSEN1 mutations after the age of 65 are considered rare. |
| PSEN2 | However, The PSEN2 gene is responsible for approximately 5% of EOAD cases, and individuals with this gene mutation typically experience onset between the ages of 40 and 75 |
| Unknown | Around 20-to-40% of early-onset Alzheimer's cases have an unknown genetic cause, meaning the specific gene responsible has not yet been identified. |

APP = amyloid precursor protein; PSEN1 = presenilin 1; PSEN2 = presenilin 2.

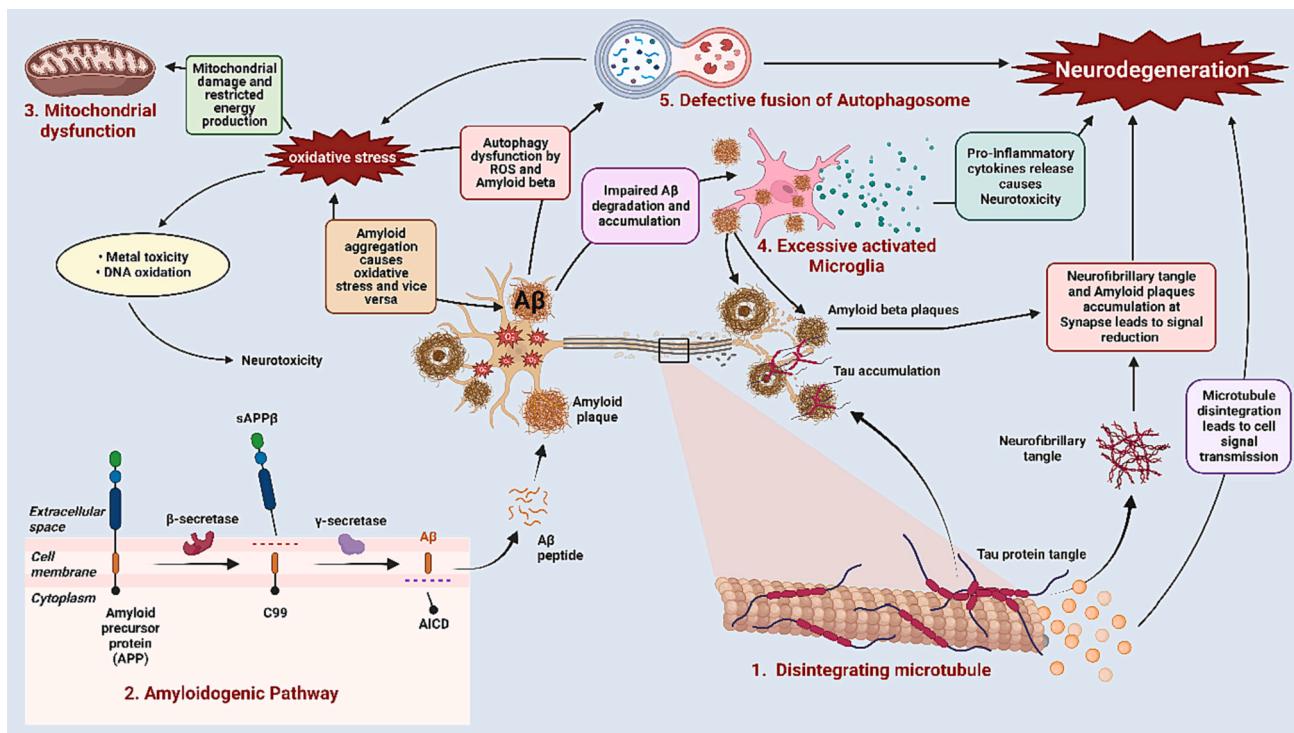


Fig. 1. Illustration explains different mechanisms involved in the pathogenesis of AD. 1) CE) Microtubule disintegration; downregulation of phosphatases causes formation of neurofibrillary tangles. Normal tau protein and hyper phosphorylated tau protein are also depicted. 2) In amyloidogenic pathway, the formation of beta-amyloid from the β -amyloid precursor protein (APP) cleavage by α - and γ -secretase, and accumulation inside and outside the cell. 3) Mitochondrial dysfunction, metal toxicity and DNA oxidation through oxidative stress pathway also shown in the figure. Also, 4) Excessive microglia activation and pro-inflammatory mediators release leads to the neurotoxicity. Finally, 5) Defective autophagic pathway due to oxidative stress. All the described pathways precipitate the dementia like conditions through neurodegeneration of brain cells. "Created with Biorender.com".

alterations in AD is crucial for developing targeted therapies aimed at mitigating tau-related neurotoxicity and preventing disease progression.

Under normal neural conditions, kinase and phosphatase enzymes regulate the balance of phosphorylation and dephosphorylation of tau protein, which regulate the addition or removal of phosphate groups from tau protein and are associated with microtubules [29–31]. However, in pathological conditions, this balance is disrupted due to the upregulation of kinases and downregulation of phosphatases. Consequently, tau proteins undergo hyperphosphorylation, leading to the formation of clumps and insoluble filaments called NFTs [17,32], as illustrated in above Fig. 1. The exact mechanism by which NFTs cause neural dysfunction and cell death is still not fully understood. However, tauopathies, or the presence of NFTs in the brain serves as a pathological marker to assess AD severity. Various experimental evidence suggests that the A β accumulation precedes and triggers the formation of tauopathies [33].

Furthermore, it has been noted that heightened oxidative stress, compromised protein-folding function within the endoplasmic reticulum, and deficiencies in proteasome-mediated and autophagy-mediated removal of damaged proteins, all of which are linked to the aging process, can expedite the build-up of amyloid and tau proteins in Alzheimer's disease [34,35]. All these factors cause the aggregation and formation of NFTs, ultimately leading to neuronal dysfunction and cell death.

Notably, mutations in the tau gene located on chromosome 17 have been detected in frontotemporal dementia with Parkinsonism, but they are not present in Alzheimer's disease. This implies that there are separate genetic mechanisms contributing to various neurodegenerative disorders [36]. Further research is needed to elucidate the intricate mechanisms involved in tau pathology and explore potential therapeutic interventions targeting tau protein in Alzheimer's disease.

2.3. β -Amyloid (A β)

A β peptides, consisting of 39 to 43 amino acids, naturally occur in the brain [37]. These peptides are generated through the cleavage of their precursor, amyloid protein precursor (APP), which occurs via two pathways. Fig. 1 depicts the process of β -amyloid formation in the amyloidogenic pathway, where full-length APP is cleaved by β -secretase and γ -secretase enzymes [16], resulting in the production of a secreted C-terminal fragment comprising 83 residues.

The APP is a polypeptide that is naturally present in the endoplasmic reticulum (ER) during its co-translational insertion [38]. Overexpression of APP proteins can be beneficial for cell growth. These APP proteins undergo cleavage by membrane-bound β -secretase and γ -secretase enzymes [39,40]. Growth factor deprivation has been identified as a trigger for this cleavage, and it is suggested that the ectodomain produced after β -secretase cleavage may have different properties compared to the α -secretase ectodomain [41]. The beta amyloid produced by the β -secretase (BACE1) is transported to the extracellular space for degradation by lysosomes or vesicles [42].

Physiologically, A β peptides are produced in low concentrations and have been considered as waste products, with their precise functions in the brain yet to be fully understood. However, it has been found that A β can exert positive effects on synapses at picomolar concentrations, although the specific ligand to which A β binds at synapses has not been identified. Some experiments have isolated oligomers from AD brains and shown their relation to long-term potentiation (LTP) inhibition, long-term depression (LTD) increase, and dendritic spine density reduction [43,44]. It has also been observed that A β oligomers act through glutamate receptors.

Among the A β peptides, A β 1–40 is soluble, less toxic to the brain, and commonly found in a healthy brain. On the other hand, A β 1–42 is generally considered insoluble and forms aggregates in neurons to cause

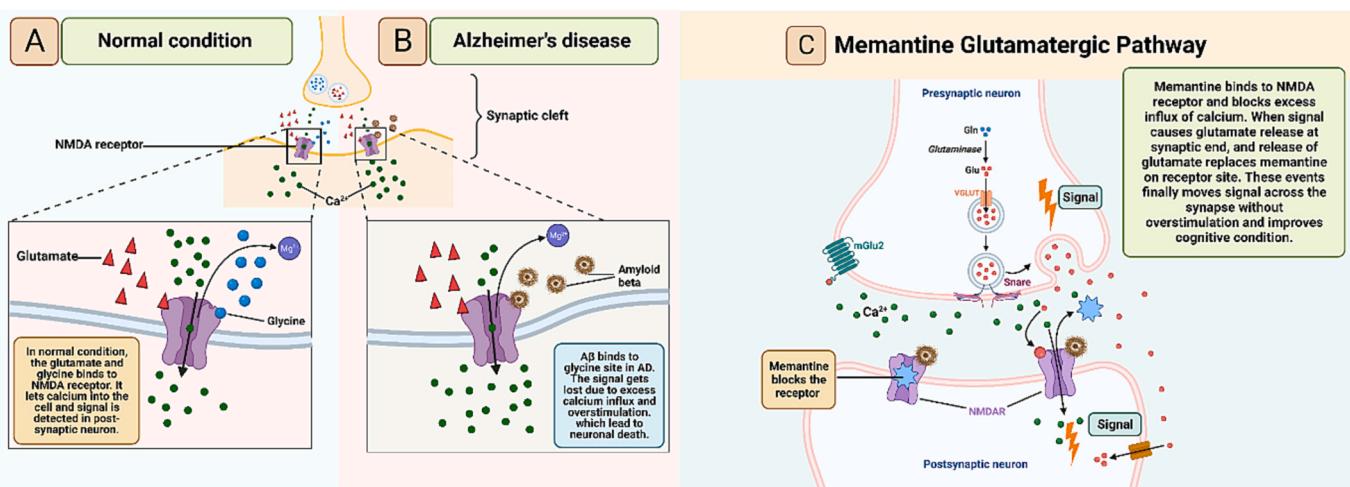


Fig. 2. The glutamate and glycine help in NMDA receptor activation by binding to receptor complex. Glutamate has an activity-dependent role, whereas glycine is a modulator of the effect. A) This activation leads to long term synaptic plasticity, which is important for learning, memory, and cognition. B) In disease condition like dementia the amyloid beta binds to the receptor complex and reduces the signal by overstimulation or excess calcium influx. The glutamate-dependent excitotoxicity can be managed by Memantine. C) The drug binds to receptor complex helps in noise reduction and signal enhancement. “Created with Biorender.com”.

toxicity. A β peptides can exist in multiple physical forms, including oligomers (consisting of 2 to 6 peptides) and intermediate assemblies. Another characteristic that contributes to the toxicity of β -amyloid is its propensity to form fibrils or arrange themselves into insoluble fibres known as β -pleated sheets, which are found in advanced amyloid plaques [45,46]. In brain-slice preparations of Alzheimer's-induced brains, it has been observed that synaptic toxicity is primarily attributed to A β dimers and trimers.

Interestingly, the presence of amyloidogenic proteins in the brain can lead to the overactivation of microglia. Initially, microglia help in clearance of A β via phagocytosis. However, when these proteins accumulate inside the microglia, they disrupts the enzymatic degradation of A β [47]. This disruption activates the immune response and releases pro-inflammatory mediators reactive species, nitric oxide, and cytokines. Moreover, the studies have revealed that compromised A β clearance and release of inflammatory mediators causes neuroinflammation leading to neurodegeneration, which is associated with AD [48].

2.4. Mitochondrial dysfunction

Mitochondrial dysfunction is another mechanism that contributes to the development of Alzheimer's disease (AD) through the toxic effects of A β on synapses [49,50]. A β attacks enzymes within the mitochondria, with cytochrome c oxidase being particularly affected [51]. This leads to disruptions of electron transport chain reaction, oxygen cycle, and mitochondrial membrane potential. To understand the role of mitochondrial dysfunction, researchers have investigated the release of amyloid beta by platelets into the bloodstream.

Casoli et al. observed a 73% increase in A β_{40} levels in the test group, along with swollen mitochondria, indicating a potential association between A β_{40} and mitochondrial dysfunction [52]. Similarly, Sheng et al. found lower expression of various proteins (PGC-1 α , NRF1, NRF2 α , NRF2 β , and TFAM) in the hippocampal brain region compared to the cerebellum region and impaired mitochondrial biogenesis in APPswe M17 cells [53]. In another study by Jadiya et al. demonstrated that NCLX-cKO \times 3xTg-AD mice exhibited spatial memory decline, calcium dysregulation, 60% increase in amyloid deposits, and AD pathogenesis [54]. Additionally, oxidative stress, cytochrome c release, and apoptosis were linked to superoxide radicals and hydrogen peroxide (H_2O_2) formation [55,56].

2.5. Oxidative stress

Oxidative stress plays a significant role in the AD pathology and the aging process. In the Alzheimer's brain, mitochondrial dysfunction [57] and A β are known to generate reactive oxygen species (ROS) [58] and reactive nitrogen species (RNS) [59], which have damaging effects on neuronal brain cells. These oxygen species are responsible for causing significant damage to important cellular components such as DNA, proteins, carbohydrates, and cell membranes, ultimately leading to cellular dysfunction and death shown in Fig. 1 [60].

Several experimental studies have focused on the formation ROS and RNS and its role in AD. For example, one such study demonstrated a connection between lipid peroxidation, protein, and nucleic acid oxidation. The researchers observed a significant decline in the expression of malondialdehyde (MDA), a marker of lipid peroxidation, supporting the hypothesis of lipid peroxidation-induced oxidative stress as a pathogenic mechanism in Alzheimer's disease [61]. These findings highlighted the importance of oxidative stress in AD, emphasizing its role in the progression of the disease and its potential as a therapeutic target for intervention. By understanding and targeting the mechanisms involved in oxidative stress, it may be possible to develop novel strategies for preventing or treating Alzheimer's disease.

3. Therapeutics interventions for AD

As discussed in the previous section, the diverse pathological pathways observed in AD suggest that combination therapy, rather than monotherapy [62], is more advantageous in improving patients' disease condition and reducing the burden of behavioural and social aspects on their lives. The primary objective is to improve cognition and memory by targeting various neuronal factors involved in the progression of the disease. FDA approved two categories of drugs for Alzheimer's treatment: acetylcholinesterase (AChE) inhibitors (donepezil, galantamine, and rivastigmine) and NMDA receptor blockers (memantine). The clinical effectiveness of these anti-Alzheimer drugs can be assessed using scales such as the Alzheimer's Disease Assessment-Cognitive Subscale and the Disability Assessment in Dementia (DAD) scale [63]. These drug classes operate through distinct mechanisms, which are discussed in length in the following section. Important information regarding the chemical composition, pharmacological (pharmacodynamic), pharmaceutical (pharmacokinetic), and safety parameters essential for therapeutic intervention will also be presented.

Table 2
Both classes of Drugs, NMDA receptor and AChE inhibitors are summarized below and defined with different parameters.

| Drug | Memantine | Donepezil | Rivastigmine | Galantamine |
|-----------------------|---|---|--|---|
| Class | NMDA receptor blocker | AChE inhibitors | AChE inhibitors | AChE inhibitors |
| Chemical formula | C ₁₂ H ₂₁ N | C ₁₂ H ₂₂ N ₂ O ₃ | C ₁₇ H ₂₁ NO ₃ | C ₁₇ H ₂₂ N ₂ O ₂ ·C ₄ H ₈ O ₄ |
| Log P | 3.3 | 4.3 | 1.8 | 2.3 |
| Solubility | 8.495 (mg/mL) | 2.93 (mg/mL) | 31 (mg/mL) | 2.04 (mg/mL) |
| Structure | | | | |
| PK profile | V _d (L/Kg) T _{max} | 9–11 3–7 h | 12–16 3–4 h | 175 1 h |
| Metabolites | 6-hydroxy memantine, 4-hydroxy-memantine, 1-nitro deaminated memantine. | O-methylation and N-oxidation. | Epi-galantamine, nor-galantamine, and O-desmethyl-galantamine. | 0.8 to 167 h |
| Available formulation | Oral tablets (5–10 mg), oral solutions (1 mg/mL), and once-a-week transdermal patch (5 and 10 mg). | 57% unchanged in urine. | NAP226-90 and ZNS 144–666 | 1.8 to 2.7 |
| Marketed brand names | Aldriarty, Aricept, Namzaric, Alzepil, Donecept, Axura, Ebixa, Marinovo, Namenda, Donepex, Depzil, and Memac. | 48% unchanged in the urine. | Renal clearance (2.1–2.8 L/h) | 0.8 to 167 h |

3.1. NMDA receptor antagonist

The cognitive behaviour in central nervous system is regulated by glutamate, an excitatory neurotransmitter. It binds to ionotropic Non-competitive N-Methyl-D-aspartate (NMDA) receptor and helps in learning and memory, neuroplasticity, and neuronal regulation. In neuronal conditions like AD, the overexcitation of these neurons due to excess calcium inflow can damage the cognitive flow and hence worsens the patient's condition. Here, the NMDA receptor antagonists can help in calcium regulation and signal transmission at synapse, finally improving the cognition [64]. The mechanism by which NMDA receptor blocker acts is explained in Fig. 2.

3.1.1. Memantine

Memantine is an uncompetitive, open channel *N*-methyl-D-aspartate receptor blocker, and structurally closest to amantadine (anti-parkinsonian drug) [65]. It is a primary aliphatic amine derived from the 3,5-dimethyl derivative of 1-aminoamadamantane. The chemical structure of memantine (free base) with amantadine like nucleus. Even though it can be used in various neurological conditions like traumatic brain injuries, dementia, chemical brain lesions, epilepsy, and drug addiction for its neuroprotective effect [66,67], however, within the context of this work only the application in AD will be discussed.

When administered orally, the drug is readily absorbed through the gastrointestinal tract and follows a linear pharmacokinetic profile. Metabolism of memantine occurs partially in the liver through the CYP450 enzyme generating different metabolites listed in Table 2 [68].

Memantine acts by blocking NMDA receptors, which are voltage-gated cation channels, thereby preventing their overstimulation and reducing calcium influx into the cells [69,70]. Glial cells in the brain contain glutamate transporters that help maintain the transmembrane gradient of sodium (Na⁺) and potassium (K⁺) ions [71]. Calcium plays a critical role in dementia pathology by inducing excitotoxicity-induced neuronal cell death and hyperphosphorylation of tau proteins [72,73]. It is generally well tolerated when taken orally and has demonstrated good clinical efficacy in various randomized studies. Common side effects associated with the drug therapy include dizziness, headache, constipation, confusion, urinary infections, somnolence, and agitation.

3.2. Acetylcholinesterase (AChE) enzyme inhibitors

AChE enzyme inhibitor is another class of drugs which helps in maintaining acetylcholine levels at synaptic cleft by inhibiting the cholinesterase enzyme. In this category FDA has approved three drugs: donepezil, galantamine, and rivastigmine. In cholinergic neurons present in the different regions of the brain like forebrain, hippocampus, and cortex, acetylcholine (ACh) binds to the cholinergic receptors and helps in learning and synaptic plasticity leading to memory production. The patients with dementia experiences lack in connection between the forebrain cholinergic neurons and the hippocampus and cortex of the CNS [74]. These synaptic failure between hippocampus and forebrain causes memory and learning related problems followed by cognitive decline. However, this condition can be modified increasing the levels of ACh at synapse, so AChE inhibitors prevent the degradation of acetylcholine by binding to cholinesterase enzyme [75]. The increase in the levels of ACh enhances the signal quality and duration of neurotransmitter action which is explained in Fig. 3 below.

3.2.1. Donepezil

In year 1996, FDA-approved donepezil for the treatment of mild, moderate, and severe Alzheimer's. It is a piperidine derived molecule with a reversible selectivity towards acetylcholinesterase, which is involved in the metabolism of acetylcholine [76].

The other pharmacological uses of donepezil are suggested in cerebrovascular disease related cognitive treatment [77], in traumatic brain injury (TBI) condition [78], dementia related to lewy bodies [79], in

nondemented Parkinson's disease [80], dementia related to down syndrome [81], and autism spectrum disorder (ASD) [82].

The oral formulation of donepezil is slowly absorbed through the gastrointestinal tract half-life of approximately 70 h [83], with 96% plasma protein binding to albumin and α -glycoproteins [84]. Only about 15.7% of the total drug readily crosses the blood-brain barrier and reaches the cerebrospinal fluid to exert its therapeutic effect. The primary site of metabolism for donepezil is the liver [85,86]. However, patients with liver conditions such as cirrhosis may experience more than a 20% decrease in clearance when taking the oral dose [87], although no clinically significant effect on potency has been observed.

The pharmacodynamic profile of donepezil reveals that the drug specifically and reversibly inhibits the acetylcholinesterase enzyme responsible for the breakdown of acetylcholine in the brain cells [88]. Acetylcholine is a primary neurotransmitter that regulates cognitive functioning in various brain regions. Lesion formation in the basal region of the forebrain is most affected in the pathogenesis of Alzheimer's disease, leading to a decline in episodic and semantic memories [89]. The uncompetitive and competitive blockade of receptors by the drug prevents acetylcholine degradation, thus improving memory and cognition in AD patients. Clinical data from erythrocyte membrane studies have shown that daily doses of 5–10 mg produce a significant inhibition of AChE activity ranging from 63.6% to 77.3% [85].

3.2.2. Galantamine

Another drug in AChE inhibitor class is galantamine, a plant based tertiary alkaloid obtained from *Galanthus nivalis* [90]. It was approved by FDA in year 2001 for the management of mild to moderate dementia related to Alzheimer's disease. Despite its therapeutic effects in cognitive impairment, it was first used in other neuropathic conditions like myopathies and polio-related paralysis and later was approved for AD. The chemical structure of galantamine contains three chiral centres with two ortho aromatic protons on ring A on its tricyclic skeleton [2].

Additionally, its potential use in other diseases such as neuromuscular blocking in the surgeries, Vaso protection in glaucoma [91], Inflammation [92], and antidiabetic effect [93].

Galantamine (Razadyne) given orally gets readily absorbed through GI tract and depicts dose dependent linear profile [94,95]. Moreover,

the studies have shown that the primary metabolism of galantamine is through hepatic CYP3A4 and CYP2D6 enzymes [96].

The galantamine acts through two pathways firstly, through reversible binding with acetylcholinesterase and increasing the concentration of ACh in affected region and secondly, by positive allosteric modulation of the nicotinic receptors and creates a configurational change. This dual action in cholinergic neurons in the hippocampus, cortex and forebrain increases memory and behavioural function and overall, DAD and ADAS upscale recovery [97]. The gastrointestinal related side effects with galantamine therapy are nausea, cramping, salivation, and vomiting. However, the other effects are hypotension, weakness in muscles, depression in respiration, convulsions, and heart conditions like bradycardia and hypotension, are common in all other anticholinesterase drug treatment. A meta-analysis report published by kobayashi et al. 2016 and lie et al. 2019, the findings revealed that the drug was considered safe and effective in patients with mild to moderate dementia [98,99].

3.2.3. Rivastigmine

Rivastigmine is the last drug in the quiver of mild to moderate anticholinesterase inhibitor AD treatment and was approved by FDA in year 1997. Unlike the galantamine, rivastigmine is a synthetic physostigmine based derivative. It is a carbamate ester with non-competitive and long-acting reversible inhibition towards acetylcholinesterase enzyme [100]. Rivastigmine is a synthetic physostigmine derivative used for mild-to-moderate AD.

The orally administered rivastigmine gets rapidly absorbed approx. 90% of the total dose following linear kinetics and its T_{max} varies from 0.8 to 167 h, and oral bioavailability of around 0.355. After crossing blood brain barrier, it gets metabolized by cholinesterase enzymatic (competes with ACh) hydrolysis and finally by *N*-demethylation reaction in liver [101].

The mechanism of action of rivastigmine is through binding to cholinesterase enzyme (forms G1, G2 and G4) present in the synapse of the cholinergic neuron and gets hydrolysed, preventing the degradation of ACh [100]. Oral formulation with dose 6–12 mg has shown better cognition and improvement on mini-mental state examination (MMSE) scale [100].

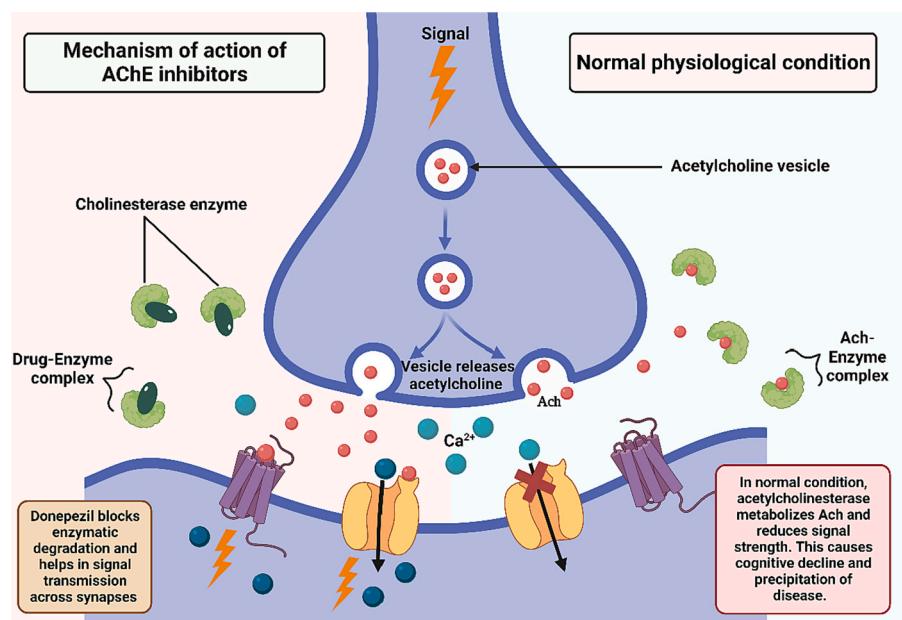


Fig. 3. Acetylcholinesterase (AChE) enzyme present at the synapse breaks down the acetylcholine and reduces signal strength. The AChE inhibitor drugs block the pathway by reversible binding to enzyme and helps in signal transmission across synapse. Both normal physiological condition and mechanism of AChE inhibitors is illustrated in the figure. "Created with Biorender.com".

3.3. Combination therapy and associated problems

Alzheimer's disease requires ongoing support and medication to improve the patient's condition and quality of life. A combination therapy of memantine and donepezil has been approved for managing moderate to severe AD [102]. Numerous studies have shown promising results for this combination therapy, one such study by Guo et al. conducted a meta-analysis of 54 trials from Asia, Europe, and North America, assessing the therapeutic efficacy of monotherapy and combination therapy in dementia. The results indicated that the combination therapy was the most effective in improving social and cognitive aspects in AD patients. However, it was also found that the combination therapy was more expensive than monotherapy and increased the economic burden. Overall, the combination therapy was found to be reducing disease burden and slow disease progression [102]. Another study by Glinz et al., reported the significance of combination of memantine (NMDA receptor blocker) and cholinesterase inhibitor in moderate to severe dementia. The study included nine controlled trials with a total of 2604 participants and concluded that the combination therapy was more effective than using AChE inhibitors. However, adverse event reporting was poor in all the trials, so the collection of these adverse and analysis need to be improved in the future studies [103].

Similarly, meta-analysis report by Chen et al. on supporting the hypothesis that the combination of both drugs resulted in significant improvement in disease condition. The study also reported various adverse reactions, with nausea, vomiting, and diarrhea being the major digestive system-related adverse events. In conclusion, it is well-established from these studies that combination therapy is highly effective for moderate to severe AD [104]. Matsunaga et al. also conducted a meta-analysis for understanding the effect of combination therapy on dementia. The author included seven studies, with a total sample size of 2182 participants and examined treatment outcomes in

terms of cognition, behavioural and day-to-day activities. The results indicated that combining memantine with the cholinesterase inhibitor has overall beneficial effect on all the parameters compared to monotherapy, of note the treatment regimen was well tolerated in the patients [105].

Although the data from various studies supports the efficacy of combination therapy of memantine and AChE inhibitor in different stages of Alzheimer's, there are several challenges associated with it. For example, the adverse effects on the digestive tract, cost burden, and frequent dosing can make it less patient compliant, particularly in elderly patients who are more sensitive to these factors [106]. The innovative viewpoint recognizes that the progressive forgetfulness associated with the disease can lead to non-adherence to therapy, resulting in disease relapse. Introducing long-acting injectable (LAI) have emerged as an alternative approach to increase the effectiveness of combination therapy, enhance patient compliance, and reduce the prevalence of the disease and relapse, but also holds the promise of mitigating the economic burden associated with the traditional combination therapy.

In essence, the innovative perspective suggests that incorporating long-acting formulations into the existing combination therapy for Alzheimer's disease could revolutionize treatment approaches. By optimizing effectiveness, improving patient adherence, and reducing side effects, this approach aims to elevate the overall quality of life for individuals battling Alzheimer's while potentially reducing the prevalence of the disease and relapse.

3.4. Antibodies for amyloid clearance

The available NMDA receptor antagonist and AChE inhibitor therapies are symptomatic relief for AD and do not slow the progression of disease. Two main hallmarks of AD, beta amyloid plaques and tau

Table 3

The investigational drugs under Phase 3 clinical trials for the treatment of AD.

| Drug | CADRO target class | Trial with a completion year | Mechanism of action | Patient characteristics |
|--|-------------------------|--|--|---------------------------------|
| • Disease-modifying biological products | | | | |
| Aducanumab | Anti-amyloid | NCT05310071 (2025) | Monoclonal antibodies targeting plaques and oligomers | Prodromal stage |
| Donanemab | Anti-amyloid | NCT05026866 (2027) NCT05508789 (2027) | Monoclonal antibodies targeting pyroglutamate plaques | Preclinical and prodromal stage |
| E2814 | Anti-tau | NCT01760005 (2027) NCT05269394 (2027) | Monoclonal antibodies targeting tau aggregates | Preclinical and prodromal stage |
| Gantenerumab | Anti-amyloid | NCT01760005 (2027) NCT05552157 (2029) NCT05256134 (2023) | Monoclonal antibodies targeting plaques and oligomers | Preclinical and prodromal stage |
| Lecanemab | Anti-amyloid | NCT01760005 (2027) NCT03887455 (2027) NCT04468659 (2027) NCT05269394 (2027) | Monoclonal antibodies targeting protofibrils and plaques | Preclinical and prodromal stage |
| Remternetug | Anti-amyloid | NCT05463731 (2024) | Monoclonal antibodies targeting pyroglutamate plaques | Prodromal stage |
| Semaglutide | Anti-inflammatory | NCT04777396 (2025) NCT04777409 (2025) | GLP-1 agonist with anti-inflammatory activity | Prodromal stage |
| Solanezumab | Anti-amyloid | NCT01760005 (2027) | Monoclonal antibodies for monomeric amyloid proteins | Preclinical and prodromal stage |
| Tertomolide | Neuroprotective | NCT05303701 (2025) | hTERT agonist | Mild-moderate-severe dementia |
| • Small molecules as disease-modifying agents | | | | |
| Blarcamesine | Neuroprotective | NCT04314934 (2024) | Targeting sigma-1 and M2 receptors | Prodromal stage |
| Masitinib | Anti-inflammatory | NCT05564169 (2025) | Tyrosine kinase inhibitor | Mild-moderate dementia |
| Metformin | Metabolic activity | NCT04098666 (2026) | Increasing insulin sensitivity | Prodromal stage |
| Nilotinib BE | Proteostasis | NCT05143528 (2025) | Autophagy enhancer and Abl tyrosine kinase inhibitor | Prodromal stage |
| Omega-3 | Anti-oxidative activity | NCT03691519 (2023) | Antioxidant | Healthy volunteers |
| Piromelatine | Miscellaneous | NCT05267535 (2024) | Targeting melanin and serotonin receptors | Prodromal stage |
| Simufilam | Neuroprotective | NCT05026177 (2024) NCT05575076 (2026) | Targeting Filamin A protein receptor | Mild-moderate dementia |
| Tricaprilin | Metabolic activity | NCT04187547 (2023) | Ketosis inducer to generate energy units | Mild-moderate dementia |
| Valitramiprosate | Anti-amyloid | NCT04770220 (2024) | Tramiprosate prodrug | Prodromal stage |
| • Drugs used to enhance cognition | | | | |
| AR1001 | Neuro-receptors | NCT05531526 (2025) | Increasing neuroplasticity via PDE5 inhibition | Prodromal stage |
| Caffeine | Neuro-receptors | NCT04570085 (2024) | Adenosine antagonist | Prodromal stage |
| Donepezil | Neuro-receptors | NCT04661280 (2024) NCT05592678 (2027) | AChE inhibitor | Mild-moderate dementia |

CADRO- Common Alzheimer's Disease Research Ontology; hTERT- Human telomerase reverse transcriptase; GLP- glucagon like peptide; PDE- Phosphodiesterase.

aggregates are mainly responsible for disease progression? as mentioned above, therefore developing an anti-amyloid therapy can be a game changing in the treatment of Alzheimer. However, the central nervous system and anatomical regions of the brain are naturally less immune responsive, illustrating the potential area of treatment. In this line FDA has approved two disease modifying monoclonal antibodies (MABs) including aducanumab and lecanemab [107]. These MABs targets different forms of the amyloid and exhibit activity via selective pathways. Once the antibodies reach the brain, they bind to the fibrillar aggregates through fragment antigen binding site. The complex formed then got recognized by microglia (macrophages present in the CNS) and binds through Fc receptors leading to phagocytic process [108]. In addition to this, another microglia independent pathway accounts for A β clearance, where the antibodies can cause dissolving of protein aggregates along with efflux from the brain [109]. Third mechanism opted by antibodies is peripheral sink pathway. The antibodies in the peripheral blood bind to the fibrillar proteins creating a change in equilibrium between the brain and peripheral circulation. This leads to the efflux of beta proteins from the brain and reduces the levels [110,111]. All these pathways contribute to A β clearance, however the efficacy of the antibodies used as anti-amyloid is debatable.

Aducanumab, a human IgG1 antibody was approved in June 2021 and produced by Biogen, depicted a 10 K fold more selectivity towards protein aggregates than monomeric units [112]. It prevents the aggregation and removes the insoluble as well soluble A β in dose dependent manner in the human brain. Another IgG1 monoclonal antibody, lecanemab was approved in January 2023 for AD. Lecanemab have a higher selectivity for larger soluble protofibrils of beta amyloid and reverts the progression of the AD in both human and mice models [113]. Both these antibodies need to be given slowly through intravenous route. The MAB dosing suggests that aducanumab should be given in every four weeks with a minimum of 21 days gap. Also, the lecanemab need to be administered after every two weeks. The recommended injectable volume must be diluted prior administration.

In our understanding, besides the potential of approved MABs to clear plaques formed in the brain, their approval has been questioned for the efficacy and safety. The major side effect associated with these monoclonal antibodies is amyloid related cerebral edemas (ARIA). These side effect can lead to microhemorrhages or vasogenic edemas, a condition where blood leakage into parenchymal tissues can cause headaches, dizziness, confusion, seizures, or death of the patients [114,115]. The innovative viewpoint acknowledging that intravenous corticosteroids can be given in combination to MAB to reduce the severity of ARIAs and highlighting the commitment to refining and enhancing the safety profile of these innovative therapies. The most important criteria for treatment with antibodies are: features such as crossing the BBB, improving cognition along with evident cerebral amyloidosis and less side effects are essential to start treatment with antibodies [107].

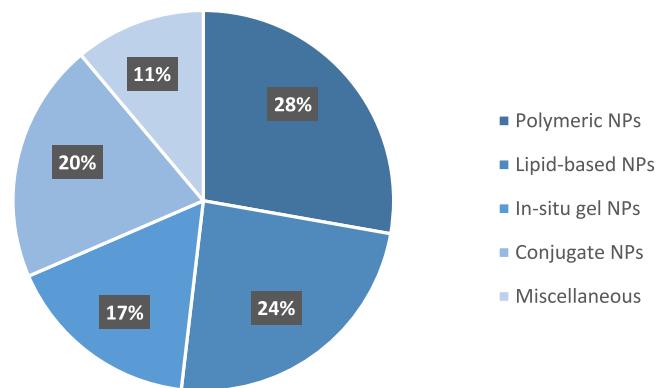


Fig. 5. Preclinical research papers published in last five years on advance delivery systems of all the anti-Alzheimer drugs (memantine, donepezil, rivastigmine and galantamine). The data is distributed according to the delivery systems.

4. Therapeutic compounds under investigation

The pathological complexity and continuous progression of AD impedes the therapeutics efficacy leading to increase in global burden of the disease. Currently clinical data from the companies developing different biologic drugs and small molecules (with molecular weight <1000 Da) targeting various pathways is compiled in this section to increase the understanding of advancement in this area [116]. However, these therapeutic molecules are still under different phases of investigation or trials. The data obtained from the [ClinicalTrials.gov](#) database indicated that total 121 studies of investigational type are in different phases (Phase 1–4) as of 1 January 2024. A total 5, 46 and 39 trials were registered within Phase 1, 2 and 3 respectively, studying biological and small molecules targeting inflammatory, plasticity/neuroprotection, oxidative stress, amyloid and tau clearance pathways to revert the disease progression. **Table 3** shows a summary of clinical trials in Phase 3.

Biological product shows high efficacy in clearing tau and amyloid aggregates via different pathways, associated with disease progression. Two monoclonal antibodies aducanumab and lecanemab received accelerated approval as anti-amyloid agent. Donanemab, a third candidate in this line has not received approval yet probably due to the insufficient data showing efficacy. Besides the therapeutic efficacy, the side effects of these agents such as ARIA can lead to brain atrophy in some cases questioning their safety. There is an increased trend towards the developmental process of biological products (as shown in Fig. 4) these days probably due to the fact that they have higher profits margins as compared to small molecules. Around 2% of total approved drugs are biological molecules whereas they account for 37% of total spendings [117,118]. The small molecules are easy to develop and formulate, but their role in clearing tau and amyloid is still under evaluation. The Fig. 4 showing different category compounds in phase 1, 2 and 3 Fig. 4.

5. Advanced drug delivery systems (ADDS) for AD drugs

Despite the availability of therapeutic drugs such as acetylcholinesterase inhibitors and NMDA receptor blockers for managing dementia associated with Alzheimer's disease, relapse due to age progression and limited permeation across the blood-brain barrier (BBB) remains a challenge. While conventional therapies like tablets and capsules exhibit significant oral bioavailability, their efficacy decreases due to factors like first-pass metabolism, plasma protein binding, and systemic side effects. To address these challenges, different advanced drug delivery systems (ADDS) including lipid and polymer-based nanoparticles (NPs), gel-based systems, and drug-conjugates can be employed. These delivery vehicles have advantages over conventional delivery systems, where they can improve the pharmacokinetic parameters (such as absorption,

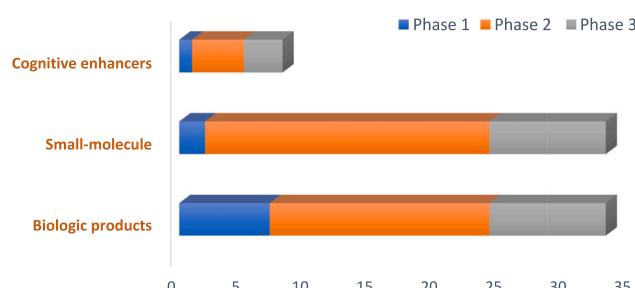


Fig. 4. The bar graph illustrating number of molecules belonging to biologic, small molecule, and cognitive enhancer class in different phases of clinical trials.

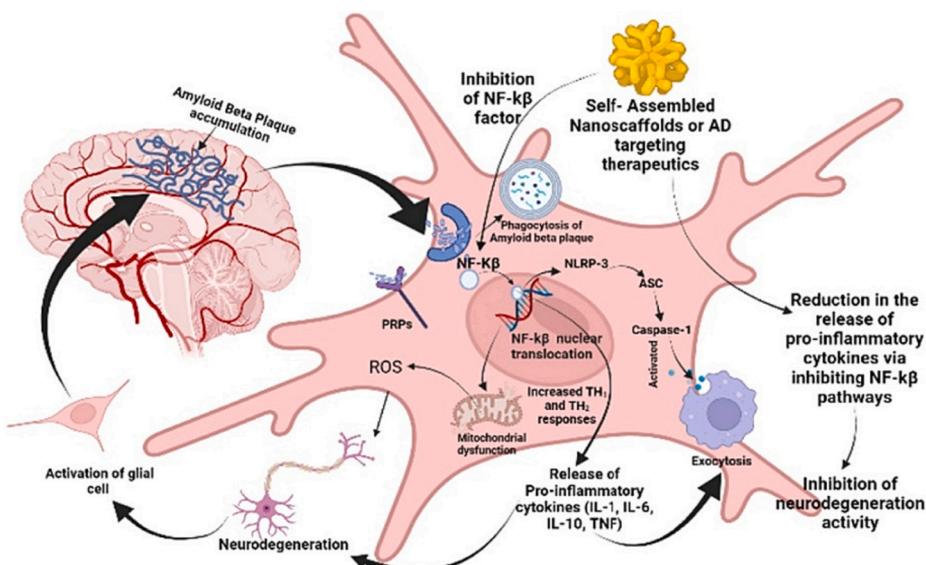


Fig. 6. Graphical images showing self-assembled NPs delivery and pathway followed to treat AD. Nano scaffolds were synthesized by modified non-solvent temperature induced phase separation (N-TIPS) method. Reprint with permission from Rani et al. [119]. Elsevier, 2023.

distribution, metabolism, and clearance) of the drug, and can increase the solubility or permeation from biological membranes (BBB in case of AD, PD etc). Also, these advance delivery systems may improve toxicological or adverse reactions via less exposure of the drug to systemic circulation. Whereas the use of particular ADD system in any disease should be justified in terms of biocompatibility and therapeutic efficacy. Additionally, since diseases like Alzheimer's and Parkinson's require lifelong treatment, achieving prolonged and sustained release of drugs is another approach to enhance treatment efficiency. Pharmaceutical researchers worldwide are actively working on developing ADDS formulations using various techniques and components, achieving varying degrees of success. In the following sections, AADS fabricated to deliver Memantine, Donepezil, Galantamine, and Rivastigmine to the brain for the treatment of AD will be discussed, also the preclinical data these drugs are illustrated in Fig. 5.

5.1. Polymer based nanoparticulate DDS

Wide range of natural and synthetic polymer are available for developing nanoparticles and these particles can be used for targeted delivery. Treating neurological disorders requires continuous therapeutic intervention, where these polymeric NPs seems useful. Various scientific approaches are available to develop these particles. However, optimizing release of drugs from the formulations require further investigations. In this section, we have compiled the preclinical studies including drug delivery systems of FDA approved drugs (memantine, donepezil, rivastigmine and galantamine) and their interventions in disease modification. However, more focus is directed towards studies with prolonged or long-acting medications and their disease modifying potential in length, but we cannot ignore the other drug delivery systems developed as immediate release.

Rani and co-workers prepared self-assembling nano scaffolds (in Fig. 6) loaded with memantine. Modified non-solvent temperature phase separation (N-TIPS) technique was employed and the resulting NPs have particle sizes between 100 and 200 nm, percentage entrapment efficiency of around 92%. Furthermore, these pegylated nano-scaffolds were subjected to invitro release and illustrated 91.52% drug diffusion after 72 h. The slow release of the drug from the matrix was possibly due to cross linking of PLGA. Moreover, the overall mice serum profile of proinflammatory cytokines was improved with 20-fold reduction of IL-1 β levels, 12-fold of IL-6 levels, 4-fold of the TNF- α levels and 10-fold of

IL-10 levels. These cytokines play a significant role in the disease pathology, hence their reduction showed disease modifying behaviour. The author concluded that pegylated scaffolds may have a beneficiary effect due to incorporation of Pluronic as permeation enhancer and PLGA forms a network to facilitate slow drug release, compared to conventional therapies available for Alzheimer's disease [119].

The donepezil was also incorporated in different delivery systems. AD treatment has been challenging due to lack of effective drug delivery and patient compliance. To overcome this challenge, Aydin and team tried to develop nanofibers of donepezil and curcumin loaded poly lactic acid (PLA)/poly caprolactone (PCL) nanofibers (in Fig. 7) for effective delivery into the brain for prolonged action [122]. Nanofibers (NFs) were prepared using electrospinning technique using both natural and synthetic polymers. After optimization, the characterization studies depicted the diameter of fibres as 410 nm. Similarly, the tensile strength of the DNF fibres was higher in comparison to other fibres. As these nanofibers were injected into muscle and formed a depot, pharmacokinetic studies were performed to ensure the effective delivery. The cumulative diffusion of the drug from the NFs was sustain release, where initial burst release with 61.5% of donepezil and 62.4% of curcumin in DNF-12 formulation after 1 h was observed. Furthermore, the total release of the drug from the formulation was up to 14 days. Whereas degradation studies for 45 days suggested that the increase in diameter of the fibre decreases the degradation rate of the system. Fibroblast cells (L929) of the healthy mouse were taken for cytotoxic evaluation and good compatibility of the NF was found, illustrating effectiveness of the formulation. Even though the system had shown a sustain release profile of the drugs form the delivery system, however further evaluation is required in *in vivo* models and clinical trials to ensure efficacy.

Similarly, Bhavna et al. employed the solvent emulsification diffusion-evaporation method to fabricate a nano system containing donepezil as drug of choice. With average particle size of 89.67 nm, the system achieved a drug entrapment efficiency of 88.65%, a drug loading capacity of 15.65% w/w, and zeta potential of -36 mV. A good *in vivo* brain permeability with biphasic sustain release profile from the coated nanoparticles was observed with 87.42% after 25 days. *In vivo* bio-distribution studies were also performed by group to study the distribution of nanoparticles in the brain and blood of the rat model and found higher drug concentration in in brain and blood samples while comparing with drug solution. Which was further confirmed with gamma scintigraph studies. Despite the improved circulation time and

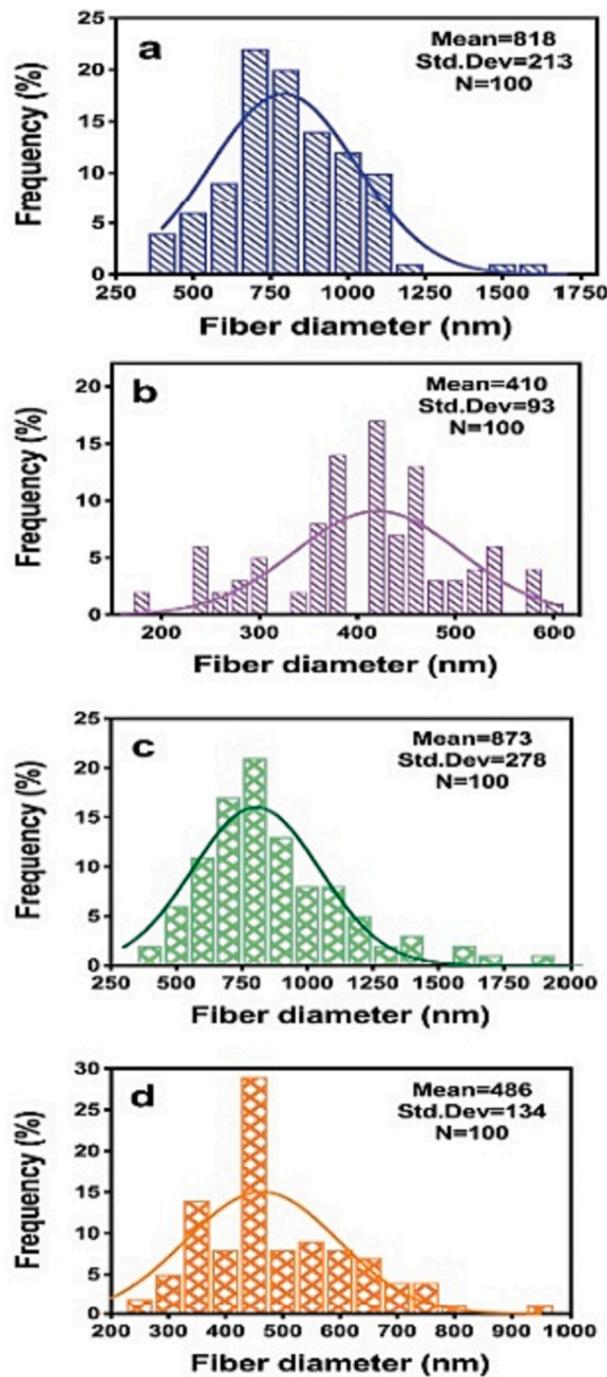
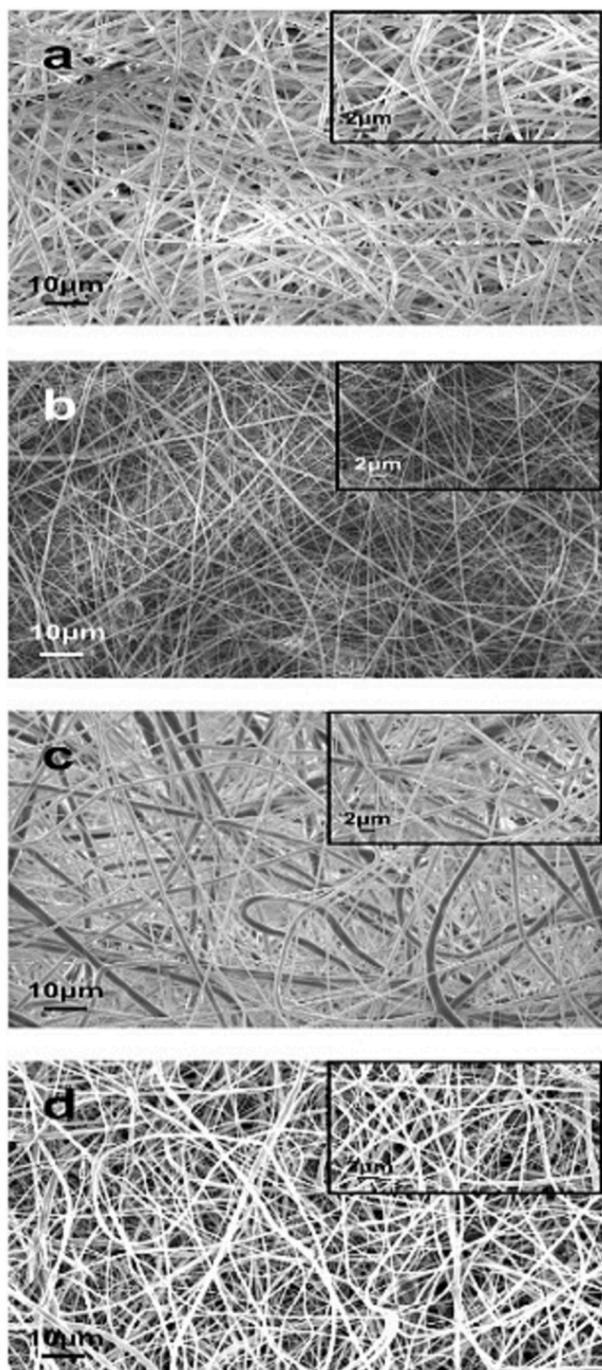


Fig. 7. Scanning electron microscopic illustrations of the nanofibers loaded with donepezil or curcumin. Also, by changing the PLA/PCL polymers concentration causes difference in diameter. Reprint with permission from Aydin et al. [122]. John Wiley and Sons, 2023.

better permeation, improvement is required to control initial burst release. Also, more clinical and extensive in vivo data can be beneficial to ensure safety and efficacy of the NPs [134] Table 4.

The galantamine is another AChEI used in AD interventions and has been loaded in different systems. Nanaki et al. fabricated a hybrid nanoparticle containing galantamine using solid-oil-water (s/o/w) modified double emulsification method. The outcomes from the characterization revealed that the average particle size of the NPs was 241.60 nm, PDI was 1.00, Zeta potential -19.77 mV, percentage entrapment efficiency- 58.6%, and percentage drug loading- 31.24%. Additionally, the release data suggested that the dissolution occurred in two stages initial burst release (55%) and extended release (90%) for

1.5 days and 9 days respectively. Hippocampal samples of in vivo rat model revealed the presence of NPs through fluorescence photomicrographs. The hybrid NPs may be effective in managing moderate Alzheimer's disease due to extended-release characteristics, however initial burst release and repeated dosing in animal models need to be tested for potential safety along with inflammatory and distribution studies [127].

Guimaraes et al. and colleagues developed an alginate and kappa-carrageenan hydrogel mounted into microneedles (MNs) patch to deliver rivastigmine to the brain. The resulting formulation was compared with marketed Exelon patch. The results from optimization and characterization illustrated 680–770 μm size and having 3-D pyramidal structure as best suited for the transdermal delivery. The skin

Table 4

Polymer-based drug delivery systems of anti-Alzheimer drugs including memantine, donepezil, galantamine and rivastigmine in last five years.

| System | Components | Method | Characterization | Achievements | Ref |
|---|--|---|---|---|-------|
| Memantine | | | | | |
| Self-assembled nano scaffolds | PLGA 50:50 and 75:25, PG and Pluronic F127 | Non-solvent-temperature induced phase separation (N-TIPS) method | Size 100–200 nm %EE- 92.21% | Total release of 91.52% in 72 h, and 20-fold reduction in proinflammatory cytokines. | [119] |
| PLGA NPs | PLGA | Probe-sonication method | Particle size- ~100 nm | MTT and LDH assays suggested least toxicity, and downregulation of lysosomal enzymes like Ctsd and Ctsg. | [120] |
| MEM-NCs | Chitosan | Ionic gelation method | Drug loading- 98.44% %EE- 78.7% Size ranging- 100 to 129 nm | Cumulative release was 87.2% in 24, and dose dependent toxicity in RPMI 2650 cell lines. | [121] |
| Donepezil | | | | | |
| Donepezil-PLA/PCL NFs | Poly lactic acid, polycaprolactone | Electrospinning | Fibre diameter of PNF12 was 486 nm. EE%- 95.3% | Initial burst release (61.5% after 1 h) followed by 14 days sustain release, and L929 cell line assay showed good cell viability. | [122] |
| Chitosan NPs | Chitosan, sodium tripolyphosphate | Ionic gelation technique | Size 135 nm %EE- 70.4 Zeta potential +38 mV PDI- 0.33 | The percentage cumulative release was biphasic with 20% initially and 38% after 24 h. | [123] |
| PLGA-b-PEG NPs | Pluronic F68, Poly (lactic-co-glycolic acid)-block-poly (ethylene glycol), Poly(D, L-lactide-co-glycolide), mannitol | Double emulsion method | | Animal behavioural studies (NOR, EPM, and MWM), and immunochemistry showed improvement in learning and memory function. The Invitro drug release was 96% after 56 days showing sustain release profile. | [124] |
| Microspheres | | Ultrasonic atomizer | Avg diameter- 65 μm % EE- 93% | Moreover, In vivo profile showed a Cmax of 3.3 mg/mL at 21 days (Tmax) | [125] |
| PLGA-Microspheres | Poly(D,L-lactide-co-glycolide) | Double emulsion solvent evaporation technique | Particle size- 138.2 μm %Loading capacity- 15.84% | Release profile showed gradual erosion and 99.5% ± 0.81% drug release within 8 h Additionally, Pharmacokinetic profile revealed Cmax of 0.28 ng/mL. | [126] |
| Galantamine | | | | | |
| PLLA/PLGA NPs | Poly (L-Lactic acid), Poly (lactic-glycolic acid), sodium cholate | solid-oil–water (s/o/w) modified double emulsification method | Avg size- 241.60 nm PDI- 1.00 Zeta potential- -19.77 ± 0.08 mV %EE- 58.6% %Loading capacity- 31.24% | Almost 100% drug release after 11 days was observed. The brain penetration in In vivo rat model was confirmed by fluorescence microscopy. | [127] |
| Chitosan-alginate NPs | Chitosan, sodium triphosphate (TPP), alginic acid | Gelation method | Size- 240 nm Zeta potential- -35.5 mV % Loading efficiency- 67% | Invitro release data showed prolonged release for 8 h period and negligible burst release. | [128] |
| Chitosan particles | Chitosan, polysorbate 80, TPP | Ionic gelation method | | Animal studies using NPs as treatment for 30 days treatment illustrated less oxidative stress and decrease in pro inflammatory levels. | [129] |
| PAA-NPs | Polyacrylic acid, sodium tauro- deoxycholate (TDC) | Spray drying | Size- 185.55 nm PDI- 0.49 Zeta potential- -16.1 mV % Yield- 69.58% | Initial burst release for 30 min and complete release after 2 h. MTT assay in oral epithelial cells confirmed safety. Also, the CLSM and histopathology confirmed the permeation. Further evaluation confirmed that neuroinflammatory mediators were decreased significantly. | [130] |
| Rivastigmine | | | | | |
| Eudragit-coated chitosan NPs | Eudragit EPO, chitosan, Span 80, and glutaraldehyde | Emulsion cross-linking method | Size- 175 nm %EE- 64.83- 69.82% % Drug loading- 11.76% Zeta potential- 20 mV | Total 80% release after 24 h following korsmeyer peppas model. The permeation flux was 40.39 μg.h/cm² maximum in prepared NPs. | [131] |
| Methoxy Poly (ethylene glycol)-co-Poly (ε-caprolactone) NPs | Monomethoxy-poly (ethylene glycol), caprolactone, stannous 2-ethyl hexanoate (SnOct)₂ | Classical ring opening polymerization method followed by nanoprecipitation method | Size- 98.5 nm Zeta potential ranges between 18.5 and 35.1 mV PDI-0.11%EE- 40.2% % Loading- 19.2% | Pharmacokinetic studies suggested higher permeation (3.7-fold) after 60 min and higher circulation time (2.3-fold) in 90 min with I-V injection. | [132] |
| PEG-PLGA NPs | Pegylated polyethylene glycol, pluronic F68 | Nano-precipitation technique | Size- 125.93 nm PDI- 0.197 Zeta potential -11 mV %EE- 69% | Maximum release 61.33% of drug at pH 7.4 in 24 h. Intravenous administration of NPs depicted Cmax 1058 ng/mL and longer circulation time of 17.7 h. The histopathological studies suggested decrease in neuronal damage and inflammation. | [133] |

EE = encapsulation efficiency; CS = chitosan; MEM = memantine; TPP = triphosphate; PDI = polydispersity index.

Table 5

Lipid-based delivery vehicles designed for anti-Alzheimer loaded with different approved drug like memantine, donepezil, galantamine and rivastigmine in last five years.

| System | Excipients | Method | Characterization | Achievement | Ref |
|--|--|---|---|--|-------|
| Memantine | | | | | |
| Nano-emulsion | Cetyl Pyridinium Chloride | Homogenization & ultrasonication methods | Size- 11 nm approx. PDI- 0.080 Zeta potential -19.6 mV | The Invitro release profile in SNF media illustrated total 80% release in 6 h period. Where, the MTT assay showed 95% cell viability. The in vivo animal model assay showed max 99% radioactivity, and 158.78% increase in DTE%. | [138] |
| SLNs | Labrasol and gelucire 43/04 (2:1), tween 80 and labrafil (3:1) | Homogenization-ultrasonication method | %DEE- 99.24% Size- 159.9 nm PDI- 0.149 Zeta potential -6.4 mV | The release profile showed 80% total drug release after 48 h, and pharmacokinetic studies revealed 4-fold increase of drug concentration in brain tissue with better permeability. | [139] |
| Donepezil | | | | | |
| Nano-emulsion | Tween 20, soybean oil, propylene glycol, chitosan | Homogenization and ultrasonication method | PDI- 0.084 Size- 65.36 nm Zeta potential -10.7 mV | The total percentage cumulative release after 4 h was 99.22%. The MTT assay revealed 76.3% cell viability and 98% radiolabeling (3.6%/g) in brain samples after intranasal delivery. | [140] |
| Lyotropic liquid crystal (LLC) mesophases | CETETH-10, oleic acid | Ternary phase diagram | | The percentage release was around 25% after 6 h and followed korsemeye peppas model. Also, In vivo C_{max} and AUC after intranasal delivery of colloidal formulation was 2563.3 ng/g and 14,024 h.ng/g respectively reached after 1.5 h. | [141] |
| NLC gel | Lecithin, oleic acid, sodium taurodeoxycholate hydrate | Hot-microemulsion technique | Size- 177.05 nm PDI- 0.25 Zeta potential -55.35%EE- 99.4 %DL- 12.42 | The release was biphasic in with Initially burst release after 12 h and biphasic release after 48 h following korsemeye peppas. The permeation kinetics followed a zero-order model and high cutaneous permeation. | [142] |
| Nano-emulsion | Lecithin, chitosan | Desolvation method | Size- 278.86 nm PDI- 0.090 Zeta potential -5.53 mV | The complete drug release after 45 days was observed. where, the MTT assay showed total 80% cell viability and good safety. | [143] |
| Chitosan coated NLCs | Compritol 888 ATO, Capryol 90, poloxamer 188 and Chitosan | Homogenization & sonication technique | Size- 192.5 nm PDI- 0.298 Surface charge +38.9 mV | Percentage release from the formulation revealed that initial burst release (29.35%) followed by sustained release (84.82%) up to 24 h The fraction delivered to brain was 74.55% through olfactory region after nasal delivery. | [144] |
| Niosomes | Span 60, cholesterol, Dicetyl Phosphate, Solulan C24 | Thin-film hydration (TFH) method | %EE- 82.15% Zeta potential -24.7 mV PDI- 0.12 Size- 180.1 nm | The release kinetic was pH dependent and illustrated around 95.7% at 7.4 pH after 105 h, whereas at 6.8 pH after 6 h and at 5.4 pH after 3 h were 98.17% and 98.17% \pm 1.65% were observed respectively | [145] |
| Combination therapy (Memantine and Donepezil) | | | | | |
| ApoE targeted-SLNs | Apolipoprotein-E, polyethylene glycol, avidin | Homogenization-sonication method | EE%- 86.44% Size- 147 nm PDI- 0.221 Zeta potential -9.62 | The total Invitro release was 50% in 72 h. MTT study conducted and SH-SY5Y cell lines suggested safe and nontoxic character of NPs in neurons. The drug permeability was 3.2-fold higher than simple SLNs | [146] |
| Galantamine | | | | | |
| Liposomes-embedded polymeric scaffold (LEPS) | distearoyl-sn-glycero phosphatidyl choline, chitosan, DSPE, cholesterol, Eudragit RSPO | Reverse-phase evaporation technique | Size- 100-158 nm Zeta potential- -34 mV | The drug release from the cross-linked LEPS was lowest and showcased an extended-release profile after 50 days. | [147] |
| Rivastigmine | | | | | |
| SLNs | Glyceryl monostearate (GMS), polysorbate 80 | Combination of modified solvent-evaporation diffusion method and probe sonication technique | Size- 110.2 nm, PDI- 0.309, % EE- 82.56%, % drug content- 99% and zeta potential -28 mV was observed. | The total drug release was 94.86% after 24 h following Higuchi model. Ex vivo data confirmed the permeation through nasal mucosa. Similarly, the brain PK studies illustrated the C_{max} - 73.99 ng/mL and t_{max} - 0.667 h. | [148] |
| Transferrin-NLCs | Capmul MCM C8, poloxamer 188, poloxamer 407 | Modified w/o/w double emulsion method | Size- 84 nm PDI- 0.142 Zeta potential- -3.5 mV | Initial burst release of 25.3% in 2 h and followed by controlled release (approx. 80%) for 24 h. The antioxidant and haemolytic activity revealed 95.1% and | [149] |

(continued on next page)

Table 5 (continued)

| System | Excipients | Method | Characterization | Achievement | Ref |
|------------------------|----------------------------------|------------------------------|---|--|-------|
| Nasal delivery of NLCs | Phospholipon 90G, polysorbate 80 | High pressure homogenization | %EE- 40.3% %Drug loading- 1.5% Size- 109.00 nm PDI- 0.196 Zeta potential- -30.466 mV %EE- 97.174 pH -6.21 | 1.13% respectively. Brain uptake studies were analysed and confirmed by confocal laser scanning microscopy Total cumulative release was 89.25% after 48 h, following korsmeyer peppas and non-fickian release mechanism | [150] |

DEE = drug entrapment efficiency; GH = galantamine hydrobromide; SLN = solid lipid nanoparticles.

permeation comparison studies between marketed and prepared microneedle patch revealed an enhanced sustain release pattern from experimental patch. Also, the formulation exhibited less irritation while exposing to pig ear after 24 h comparison to exelon patch, showing good compatibility and permeation [135]. However in vivo inflammatory studies (inflammatory mediators are most important parameter in AD pathogenesis) and organ drug distribution need to be conducted to ensure efficacy. Interestingly, another drug formulation as PEGylated polymeric NPs were prepared by Craparo et al., using reverse phase microemulsion. The author tried to incorporate different forms of rivastigmine including the free base and salt form. The formulation showed maximum release from tartrate salt (around 90.8%) followed by free base with 79.8% after 24 h, illustrating slow-release characteristics. The higher release from these pegylated NPs can be due to the soaking method adopted for loading the drug onto the particles. Whereas the pegylated nanoparticles with drug entrapped into the matrix showed slow release with 32% in 24 h. The haemolytic activity in myelogenous leukemia cell line (K-562) ensured safety and higher cell viability. Based on all the previous results, the pegylated NPs could be safe and effective to use in the physiological conditions like AD [136].

Furthermore, various other polymer-based nanoparticulate systems were developed using PLGA, PLGA-PGA, PLGA-PEG, chitosan, PCL, hyperbranched chitosan, poly(n-butyl cyanoacrylate) polymers by different working groups using different techniques. Where, the release from these NPs illustrated a controlled release profile ranging from a few minutes to hours. However, we can achieve the desired release by modifying the concentration and blend of polymers for effective

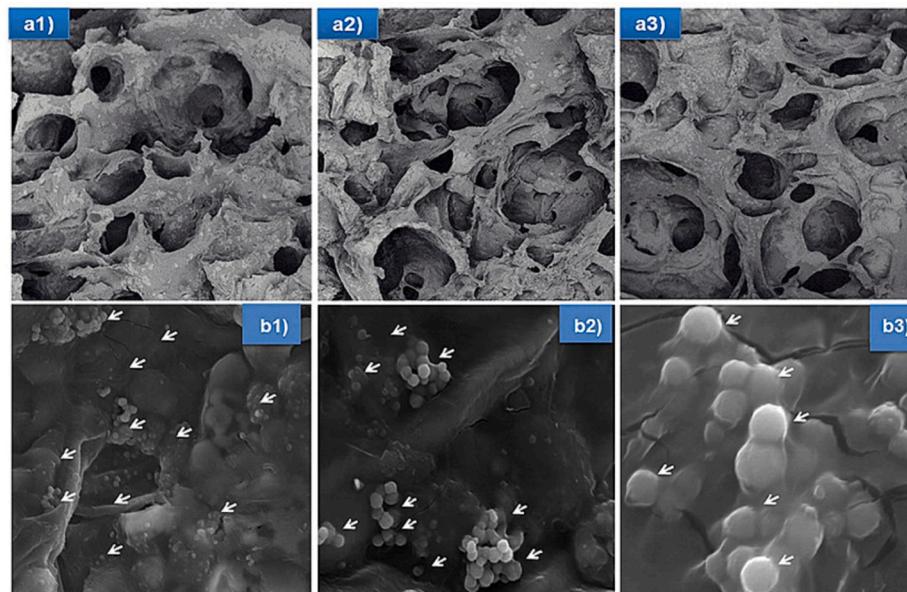
treatment of neurodegenerative disease like Alzheimer to increase the patient compliance.

5.2. Lipid-based DDS

Lipidic nanoparticles, such as liposomes and solid lipid nanoparticles (SLNs), have gained attention in Alzheimer's to deliver therapeutic molecules due to their biocompatibility, versatility, and ability to encapsulate both hydrophobic and hydrophilic drugs. These nanoparticles can be modified to improve their stability, prolong circulation time, and enhance brain uptake through surface modifications or ligand conjugation.

Kaur et al. developed an intranasal delivery system of lipid based nano emulsion loaded with memantine by homogenization and ultrasonication method using oils as lipid phase. The formulation showed a particle size of around 11 nm, PDI of 0.080 and zeta potential of -19.6 mV. The cumulative release in different buffer systems like PBS, ACSF and SNF revealed maximum release in SNF media of around 80% in 6 h probably due to the smaller globule size. Similarly, the antioxidant assay, cell toxicity assay and FRAP assay confirmed the efficacy of the formulation. In vivo studies illustrated successful treatment output via high radiolabelling efficiency (around 99%), drug treatment efficiency (DTE%) (158%) and drug transport percentage (DTP%) (37%) [137] Table 5.

The lipid-based carriers are effective in delivery of wide range of drugs including anti-Alzheimer drugs. For example, Bhandari et al. tried to load donepezil into soy lecithin and chitosan based nano emulsion



Label: SEM micrographs of (a1-a3) lyophilized CEP scaffold and (b1-b3) nanoliposomes embedded into the CEP scaffold.

Fig. 8. Lyophilized CEP scaffold micrographs by SEM showed liposomes embedded into 3-D structure. “Reprint with permission from Mufamadi et al.” [147]. Elsevier, 2023.

(NEs) using desolvation method. These prepared NEs showed average size of 278.86 nm, polydispersity of 0.090, negative zeta potential of 5.53 mV. The loading efficiency was acceptable with a value of 8.77% and 0.46% for different concentration (4 mg/mL and 8 mg/mL). Additionally, the prolonged release diffusion pattern in acidic conditions at pH 5.5 was seen with a total drug release of 36.33% after 45 days. This sustain release profile can be very beneficial to improve compliance. MTT assay using L929 fibroblast cell line revealed 80% cell viability [143]. Despite, the nontoxic nature of the formulation, animal testing for inflammatory mediators, tissue distribution and brain permeability should be arranged in future studies to ensure its clinical application.

Subsequently, Topal and colleagues investigated better brain penetration potential of Apo-E targeted solid lipid nanoparticles for mild-moderate dementia. These SLNs were prepared by homogenization and sonication method and were of size 147.5 nm and surface charge of -9.62. Whereas the PDI value of NPs was 0.221, percentage entrapment efficiency was 86.44%. The release from SLN was biphasic in nature, initially burst release (presented challenges) followed by sustain release. Cell viability studies in brain endothelial cell lines (RBEC) and human endothelial cell lines (hCMEC/D3) revealed 10 µg/mL as safer concentration, further confirmed in SH-SY5Y cell lines. The permeability in BBB co-culture model also confirmed the efficacy and 3.2-fold higher brain concentration (P_{app} - 133.4×10^{-6} cm/s). The findings from the study suggested that the targeted SLNs might show higher permeability in the brain, however inflammatory mediators level and tissue distribution using *in vivo* models could be explored [146].

Galantamine was incorporated into different lipidic nanocarriers for prolonged release and better intervention in AD. Mufamadi et al. prepared an extended-release polymeric scaffold containing liposomes loaded with galantamine for AD. Different scaffolds (as shown in Fig. 8) were prepared and optimized using different polymers. The final formulation was subjected to swelling, particle size, erosion, and diffusion studies. Addition to this the release studies and PC12 neuronal cell proliferation, cytotoxicity and surface damage were studied. The results of the chitosan scaffold characterization found that the porosity was decreased with increasing the Eudragit concentration. Similarly, the texture analysis suggested high resilience and hardness in pre-hydrated condition, while the post hydration caused the softening and gradual erosion of the scaffold. The release illustrated the extended release for almost 50 days. Furthermore, the scaffold-PC12 neuronal cell adhesion was significant. The neuronal cells showed low cell membrane deformation and high liposomal accumulation (due to surface functionalisation) into the cells. In conclusion, the author depicted that this system may have high efficacy and low toxicity of liposomal nanoparticles with extended-release profile up to 50 days [147].

Rivastigmine was used in formulations to evaluate for preclinical studies in different models, where Chauhan et al. 2019 employed a nano lipidic carrier (NLCs) system for transdermal delivery in moderate Alzheimer condition. The NLCs were prepared by high pressure homogenization method and particle size was 134.60 nm, PDI- 0.286, surface charge-11.80 mV with high encapsulation efficiency- 70.56%. After incorporating NLCs into the patch system, the weight variation of 87 mg

Table 6
In situ drug loaded Gel-forming drug delivery systems.

| System | Constituents | Method | Characterization | Achievements | Ref |
|--|---|--|---|---|-------|
| Donepezil | | | | | |
| Ethosomal gel | Phospholipon 90G, Poloxamer 407 and 188, Carbopol 934 | Ethanol injection method | EE%- 70.02 Size- 110.06 nm T_{gel} - 31.7 °C %EE- 62.52% Size- 438.7 nm | The Invitro release was 98.76% in 24 h and ex vivo permeation release studies depicted 99.33% in 24 h | [153] |
| Chitosan hydrogel containing liposomes | Thiolated chitosan, | Liposomes were prepared by reverse phase evaporation technique and incorporating slowly by mechanical mixing in gel "cold" procedure | | Invitro release from liposomes was 94.7% in 6 h and followed Korsmeyer-Peppas model. PK studies suggested that about >2-fold brain conc in comparison to marketed product | [154] |
| DPZ Gel | Pluronic F-127, chitosan and Transcutol® P | | T_{gel} - 32.5 °C % Porosity- 80.90% | RPMI 2650 cell line studies revealed 80% cell viability. Moreover, around total 98% drug release was observed and significant permeation flux across nasal mucosa | [155] |
| Cubosomes NPs | Glycerol monooleate, Poloxamer 407 and gellan gum | Emulsification method | Size- 143.6 nm PDI- 0.38%EE- 48.48% Surface charge- -40mV | Around 72.83% drug release was after 6 h, and in vivo studies suggested C_{max} and T_{max} as 24.01 µg/ml and 60 min respectively | [156] |
| Liposomal gel | Hydrogenated soy phosphatidyl choline (HSPC), cholesterol | Ammonium sulfate gradient-based active loading technique | Size- 103 nm %EE- 93% PDI- 0.108 T_{gel} - 28 s | The permeation profile revealed 80.11% into nasal mucosa. Subsequently, PK studies revealed drug targeting efficiency as 314.29% with reduction in SOD, AChE and MDA levels | [157] |
| Nanocrystal hydrogel | Cellulose nanocrystal (CNCS) | | pH was well within the physiological range- 7.7 | The PK profile of subcutaneously applied formulation showed C_{max} and T_{max} values as 255.39 ng/mL and 0.90 h respectively. Biodegradation studies illustrated 73% remaining formulation at the site of injection after 14 days. | [158] |
| Galantamine | | | | | |
| Proniosome gel | Lecithin, cholesterol, and tween 20 | Coacervation-phase separation method | Vesicle size- 3.495 µm %EE- 76.92% pH- 6.52 | The drug release was maximum in tween formulation around 99.24% after 360 mins. Whereas the permeation coefficient was 4.835 | [159] |
| GelMA hydrogel | Methacrylated gelatin, ascorbic acid, and glutathione | Radical cross-linking | | Behavioural (MWM, PA and Y-maze test) and biochemical (AChE, GSH, SOD, CAT and LPO) assays confirmed clinical significance. Moreover, the histopathological and immune histopathological assay revealed $A\beta$ degradation | [160] |
| Rivastigmine | | | | | |
| Long-acting gel | PLGA (50:50), sodium azide | Homogenous mixing | | The optimized formulation (5% w/v) 180 mg/mL showed longer release profile. Whereas the free base formulation release was maintained to 42 days. Similar results were observed in the <i>in vivo</i> studies. | [161] |

Glutathione (GSH) = glutathione; Superoxide Dismutase (SOD) = superoxide dismutase; Lipid Peroxidation (LPO) = lipid peroxidation; ANOVA = analysis of variance.

and drug content 99.70% was observed. The selected optimized patches subjected to release studies showed that the drug release was 98.12% after 72 h, which was higher than marketed formulation in similar conditions. Furthermore, the *In vivo* pharmacokinetic studies in rats showed 1.5-fold higher plasma concentration than marketed formulation, which could have potential superiority of NLC-patch system in dementia management [151].

5.3. *In situ* gel-based DDS

Gel-based drug delivery systems have gained considerable attention in the field of Alzheimer's research due to their unique properties. These systems offer controlled release, improved drug stability, and targeted drug delivery directly to the affected brain regions. The gel matrix can encapsulate variety of drugs, providing sustained release and protecting them from degradation, ensuring a consistent and optimal therapeutic effect.

Memantine was incorporated into gel-based delivery vehicles for better prolonged delivery. In such study by Bagul and co-workers, they synthesized *in situ* gel for nose to brain delivery using the Design-Expert software-based Box-Behnken design for optimization. The gel was prepared from poloxamer 407 and HPMCK4M using cold method. The gel obtained after optimization was clear with shorter gelation time (48 s), lower gelation temperature (at nasal physiological temperature) (lower than 35 °C) and higher gel strength (3867 mpa). However, by changing the concentration of both gelling agent and thermo-responsive polymer, these parameters can be increased or decreased. The pH of the system was ranging 5.2 to 5.7, and drug content between 80.11 and 84.77%. Finally, the gel was subjected to *invitro* diffusion release studies and results suggested that the increase in the concentration of gelling and thermosensitive polymer decreases the cumulative release from the gel matrix. Where, the release of memantine from the gel matrix was around 75–80% in 7 h [152].

Similarly, the donepezil was loaded in gel delivery systems, where Gagopadhyay et al., developed a thermos-reversible ethosomal gel for better BBB transport through intranasal route, using the ethanol injection method. Poloxamer 407 (18%) and poloxamer 188 (6%) as thermosensitive polymer, along with Carbopol 934 (0.1–0.5%) as gelling agent and produced size- 110.7 nm and entrapment efficiency-70.02%. Total percentage drug content entrapped was 93.78 and gelation temperature 31–34 °C (well within nasal physiological temperature range). It also showed good mucoadhesion strength as well higher viscosity possibly due to usage of Carbopol. Furthermore, 98.76% drug diffusion was observed after 24 h in *invitro* release studies following Higuchi-diffusion model. Similarly, *ex vivo* permeation was maximum in C4 formulation (around 99%) after 24 h study period. In conclusion, the drug-ethosomes can effectively deliver through nasal mucosa, but further *in vivo* evaluation will serve better delivery [153] Table 6.

Galantamine is another AChEI incorporated into Carbopol gel for transdermal patch by Woo et al., as the prolonged delivery of drug from a reservoir system can increase patient adherence to therapy. The study proclaimed transdermal delivery over 8 h period with better permeation flux. The gel was prepared using Carbopol 940, triethanolamine and propylene glycol by homogenous mixing. Cumulative release from formulation was 16.93 mg/cm² and permeation flux of 2.32 mg·cm⁻²/h. Furthermore, patch was also subjected to release studies, revealed drug content of 96.97, and slow release-68.71% after 8 h probably due to the use of Carbopol and PG. The patch demonstrated a good permeation flux with value 0.75, however it is still lower than gel prepared. This decrease signifies the sustain release of drug from patch and might have potential as prolonged release system in AD [162].

These gel-based systems were also used for rivastigmine delivery, where Salatin and co-workers employed the sol-gel transition temperature and mucoadhesive strength of the hydrogel to prepare a nano intranasal delivery system. The NPs obtained average particle size in between 118 and 158 nm, and surface charge 22.5–30.8 mV.

Subsequently, the hydrogel showed pH ranging 5.8 to 6.1 (well within the compatible nasal pH), optimum sol-to-gel transition temperature between 32 and 34 °C, and percentage loading capacity between 1.98% to 2.43%. However, the release assay followed peppas model with cumulative percentage release of 81.73%, 73.41% and 65.35% from three selected formulations. The cytotoxic MTT assay on A549 cells depicted the low toxicity and safety through limiting adverse effects. The permeability of the NP-hydrogel was confirmed through both fluorescence photomicrographs and higher permeation flux (24×10^{-4} mg/cm²·min) across nasal mucosa, indicating the potential use of this system as safe and effective mean of AD management through nasal route [163].

Vintiloiu et al., prepared an *in-situ* N-stearoyl L-alanine methylester (SAM) oleogel (oil as continuous phase in the gel) loaded with rivastigmine free base (RFB) and tartrate salt (RTS) through different methods. The gels were prepared by suspending the salt form of the drug into the gel (dispersed—RTS gel) or by dissolving the free base of the drug into the gel (dissolved-RFB gel). The prepared gel was waxy and soft, and the difference of G' (storage modulus) and G'' (loss modulus) in RTS and drug free gel was around 15-fold. This difference in mechanical strength of the gel was due to dispersed RHT molecules. While comparing RTS, RFB gels and drug solution, the dispersed drug formulation exhibited significant lower in burst release, where the release was 15% after first day exhibiting prolonged release characteristic, which was prerequisite. The *In vivo* pharmacokinetic studies after subcutaneous injection of formulation in the rat animal model showed a sustain release profile with plasma levels within the permissible therapeutic window (1–400 ng/mL) for about 11 days. The modified release from the depot was attributed to the high density of the SAM network and smaller surface area [164].

5.4. Conjugates based DDS

Drug-conjugates are other class of nanocarriers widely used as advance systems for effective delivery across brain barriers. These conjugates can be synthesized by attaching different functional groups to both drug and polymers and then chemically combining both the molecules by selected reactions. Such conjugated nanoparticles show slow release of therapeutic molecules after esterase cleavage, hence increasing the efficacy. Park et al., studied the effect of nanofabricated reactive oxygen sensitive NPs incorporated with memantine for the Alzheimer's disease depicted in Figure. The nanoparticles were prepared by conjugation reaction of succinyl β-cyclodextrin (bCDsu) with thio-ketal diamine and memantine with thio-ketal carboxylic acid. Both reagents were then with each other to form bCDsu-MEM conjugates and confirmed by NMR spectroscopy. The particle size of conjugates was 82.8 ± 12.3 nm and spherical in shape confirmed by TEM photographs. However, the addition of NP conjugates into PBS solution with H₂O₂ can alter the particle size distribution. Whereas the release of memantine form the conjugates in lower H₂O₂ concentration (1 mM) was around 20% w/w and in higher H₂O₂ concentration (5 mM and 10 mM) was >80% w/w. Similarly, in *in-vivo* biodistribution studies, the brain uptake was higher than other organs and illustrated high fluorescence intensity. The *invitro* cell line oxidative studies in SH-SY5Y and U87MG cells revealed time dependent increase in the expression of NMDAR1 receptor when exposed to reactive oxygen species, however this was reversed by introducing memantine conjugates as treatment. These results were also confirmed from the fluorescent microscopy as well. In conclusion, the ROS-dependent anti-Alzheimer's activity of bCDsu-MEM conjugates may be effective and further *in vivo* studies are required [165].

In another study by Naki et al., nanoparticles containing memantine conjugated with polyamidoamine were prepared through conjugation reaction. The objective was to increase brain bioavailability and efficacy of the therapy. In this, the optimized particles showed the size 243.9 nm, polydispersity index of PDI- 0.515 and surface charge of 5.45 mV. The

Table 7

Drug-conjugated delivery systems containing memantine, donepezil, galantamine and rivastigmine for AD in last five years.

| System | Constituents | Method | Characterization | Achievements | Ref |
|--------------------------------------|---|--|---|--|-------|
| Memantine | | | | | |
| bCDsu-thioketal conjugates | succinyl β-cyclodextrin, Thioketal diamine | Thioketal linkage conjugation | Size- 82.8 nm | The in vitro release was <20% after 96 h, showing slow release from the formulation. Th animal In vivo- biodistribution using Ce6 dye in MTT assay using SH-SY5Y Neuroblastoma and U87MG Cell line confirmed the effective delivery. | [165] |
| Drug-polymer conjugates | Propane-1,2-diamine, <i>N,N</i> -methylenebisacrylamide | Aqueous Michael's addition polymerization technique | Size- 243.9 nm PDI- 0.515 Surface charge- 5.45 mV | The cumulative in vitro release 20% in 72 h. Whereas the Insilco AChE inhibition was 12.8 μM at 50% relative concentration | [166] |
| PAMMAM-Lf conjugates | Poly[N-(4-[4-(aminophenyl)methylphenylmethacrylamide])], Lactoferrin | Amidation reaction | Size- 131.72 nm Surface charge -20.13 mV PDI- 0.16%EE- 71.1% | Initially burst release with total 51.23% in 48 h 4.73-fold overall enhanced residual time In vivo biodistribution was higher in bEnd3 cell studies | [167] |
| CNDs | Carbon nitride, sinapinic acid | Coupling reaction | Average size ~2.2 nm (lower than 5 nm) | The ThT fluorescence aggregation assays illustrated that the drug-conjugate has greater effect on tau protein aggregation and degradation. | [168] |
| Self-assembling conjugate | Docohexaenoic acid | Amide coupling reaction | Size- 144.30 nm PDI- 0.181 Zeta potential -6.82 mV | The SH-SY5Y cell line assay for oxidative stress studies depicted good efficacy of the NPs | [169] |
| Donepezil | | | | | |
| Lipoprotein conjugated polymeric NPs | Polyethylene glycol, polycaprolactone | Nano precipitation technique | %EE- 84.12% Size- 159.31 nm Zeta potential -3.62 mV PDI- 0.24 | Neuroblastoma (SH-SY5Y) cell line studies, ThT assay and behavioural studies were used to study the effectiveness of conjugates. Where the results suggested better efficacy than plain drug. | [170] |
| Lipoprotein biomimetic nanodrug | Apolipoprotein A-I, high density lipoprotein (HDL), low density lipoprotein (LDL) | Bioinspired disassembly-reassembly strategy | %EE- 90.47% Zeta potential -29.06 mV PDI- 0.160 Size- 45.8 nm | Total in vitro release observed was 79% in 96 h. SH-SY5Y cell viability assay and in vivo assay were performed | [171] |
| dcHGT NPs | Human serum albumin, Monosialo tetrahexosyl ganglioside (GM1), transcriptional activator protein (TAT) | Electrostatic and hydrophobic interaction followed by amide conjugation reaction | Size- 14.6 nm % Drug loading-35% Zeta potential was neutral. | The percentage release of drug from the conjugate was 15% in 10 days period. TNF-α and IFN-γ and were decreased in dcHGT NPs treated group, also Aβ aggregation and Aβ induced apoptosis was reduced | [172] |
| Galantamine | | | | | |
| Cysteine-chitosan conjugate | L-cysteine, chitosan (low molecular weight), sodium tripolyphosphate (TPP) | Covalent bonding of chitosan and L-cysteine followed by ionic gelation | Size- 527 nm PDI- 0.88 Zeta potential- 44.0 mV % Drug loading- 19.37% %EE- 42.36% | The release from the selected formulation was in two phases 1) initially burst release and 2) second phase was completed in 12 days | [173] |
| Rivastigmine | | | | | |
| TAT functionalized P (MMA-co-AA) NPs | Methyl methacrylate (MMA), acrylic acid (AA), sodium dodecyl sulfate (SDS) and transcription activator peptides (TAT) | Mini-emulsion polymerization | Size range- 65- 80 nm PDI- 0.080-0.239 Zeta potential -39.4%EE- 73.20 to 95.78% | Pharmacokinetic studies in Caco-2 cells confirmed the cellular uptake and permeability, concentration ranging from 23.64 to 27.20, whereas the cytotoxic effects were observed in homomer and copolymer formulation. | [174] |
| Lectin-conjugated microspheres | Ethyl cellulose, chitosan, polyvinyl alcohol, and ammonium chloride | Carbodiimide activation reaction | Size 19.1 μm %EE range- 77.8% Zeta potential- 20.5 mV | The release profile predicted non-fickian release with high $T_{80\%}$ value ranging between 5.86 and 9.73 h. however, the optimum $T_{80\%}$ value obtained was 7.3 h. In vivo behavioural improvement was confirmed with MMW and EPM assessment. Similarly, the biochemical activity after nasal delivery revealed reduced levels of glutathione, malondialdehyde and nitrile. | [175] |

cumulative invitro release was performed at buffer media pH 5.5 and total drug diffusion was around 20% following korsemeye-peppas model. Moreover, the acetylcholinesterase inhibitory analysis also suggested the IC₅₀ value of different formulation between 13 and 44.4 μM and was beneficial in reversing the AD progression. The findings from

the study concluded that the NPs loaded with drug may effectively inhibit the AChE, however further evaluation is still required to understand and utilize the system full potential [166] Table 7.

Transcriptional activator protein-surface modified human serum albumin NPs containing donepezil were developed by Yang et al. for

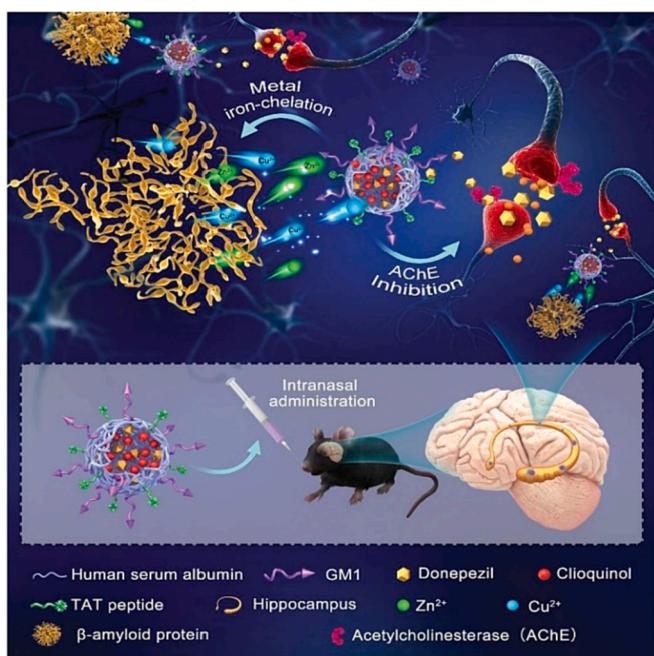


Fig. 9. Graphical abstract showing the dc-HGT NPs delivered through nose to brain exhibiting neuroprotective and AChE inhibitory action. Reprint with the permission from Yang et al. [172].

intranasal delivery. The nanoparticles were prepared by electrostatic interaction and conjugated surface modification. These NPs were spherical in shape with size ranging between 13.2 and 14.6 nm, cationic surface charge of 9.52 mV, and the drug loading was 35% as further evaluated with MALDI-TOF. The release of drug loaded dc-HGT NPs was tested in buffer of pH 7.4 and revealed a sustain release 15% donepezil release after 10 days. Subsequently, the beta amyloid inhibition,

biocompatibility, cellular uptake, and inflammatory inhibition in BV-2 cell MTT assay, were performed for safety evaluation. The results suggested strong inhibition and degradation of beta amyloid. Additionally, the NPs showed 2.15 times high fluorescence signals, 14.1% reduction of TNF- α and 3.82% decrease of IFN- γ . The biodistribution of dc-HGTs in in vivo model was significantly higher (1.9 times) than other nanoparticles in hippocampal region. The conclusion of the study attributed that donepezil conjugated human serum albumin NPs can be highly efficient in both in vitro and in vivo models including neuroprotective action by metal chelation [172]. Also, suggesting the efficiency of combination therapy for neurodegenerative disorders Fig. 9.

Galantamine was loaded into L-cysteine modified chitosan NPs for their effectiveness in dementia caused by Alzheimer's by Nanaki et al. The optimization revealed size Particle size- 527.24 nm, PDI- 0.88, zeta potential of 44.0 mV, Drug loading of 19.37% and entrapment efficiency of 42.36%. The in vitro release was in two phases, initially burst release was observed for 15–30 min and in second phase the slow release for 12 days. The slow release proclaimed swelling and erosion of the polymer matrix diffusing drug into the media. The data from the study depicted that surface modified CS-NPs may have prolonged action, however it is essentially that in vivo pharmacokinetic studies need to be further conducted to predict its therapeutic outcome in humans [173].

The BBB permeation is important in the management of AD, where it can be achieved by various approaches, one such approach developing drug conjugates was used by Gothwal et al. [176]. The author tried to incorporate rivastigmine in the polyamidoamine (PAMAM) dendrimers coated with lactoferrin (Lf) for targeted delivery. The PAMAM-PEG-Lf nanoparticles were synthesized using dimethyl suberimidate linker in conjugation reaction. The prepared nanoparticles were characterized for particle size, zeta potential and PDI, where results showed values as 216.13 nm, 23.33 mV and 0.2. addition to this the entrapment efficiency and percentage drug loading of the particles were 60% and 10.5%, depicting sufficient drug entrapped and loaded. The release profile in media at physiological pH 7.4 was carried in dialysis bag. Where the findings depicted slow release of drug (around 82% followed

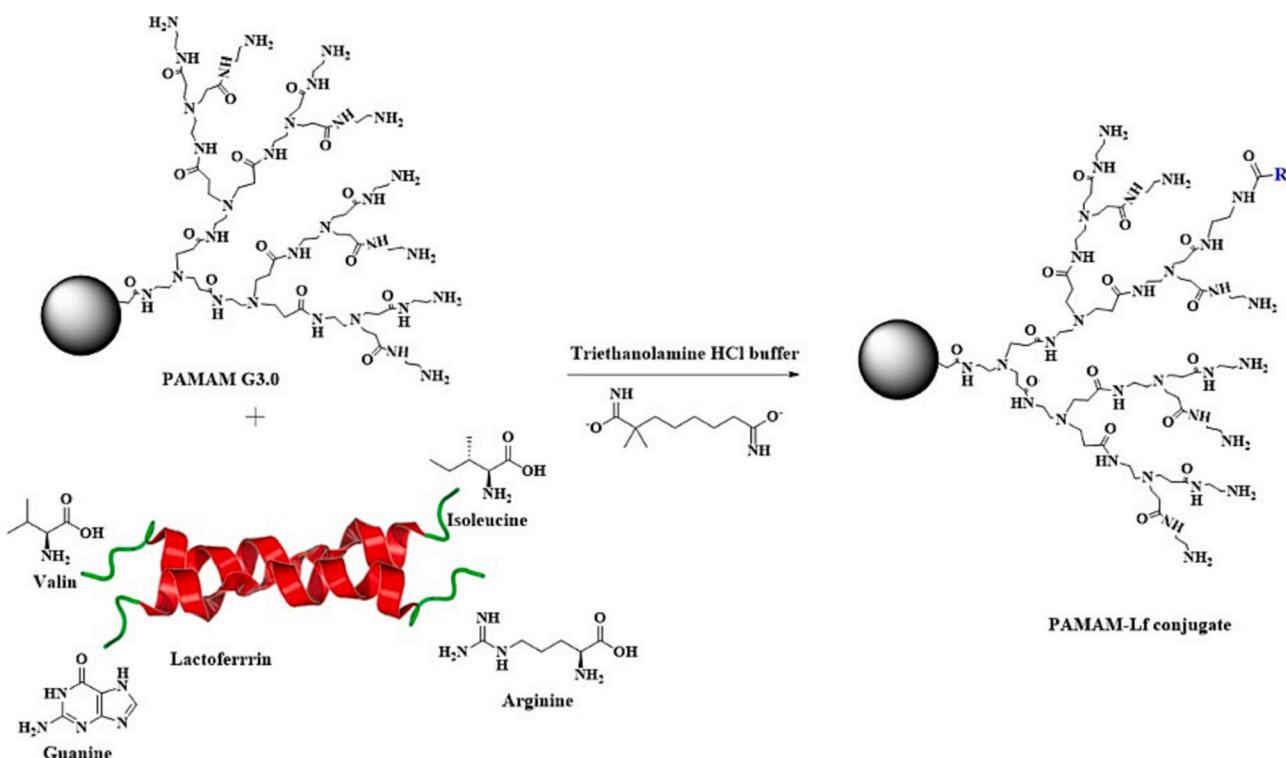


Fig. 10. Lactoferrin and PAMAM G3.0 dendrimers were conjugated in the presence of triethanolamine and dimethylsuberimidate. The PAMAM-lactoferrin conjugates were used for drug (rivastigmine) loading. Reprint with the permission from Gothwal et al. [176]. American Chemical Society, 2023.

Table 8

Compiled table of miscellaneous delivery systems of anti-Alzheimer drugs in last five years.

| System | Constituents | Method | Characterization | Achievements | Ref |
|-----------------------------------|---|--|--|---|----------------|
| Memantine | | | | | |
| Magnetic nano emulsion (MNE) | ZnxFe3 – xO4, sodium dodecyl sulfate | Modified microwave-assisted polyol process | Size, zeta potential, %EE and %loading was 107 nm, -38 mV, 77.5% and 86.1% respectively. | Invitro release was 97% on 24 h following korsemeye peppas model. | [177] |
| Donepezil | | | | | |
| Polymeric-magnetic NPs PPA NPs | Bismuth ferrite (BiFeO ₃), Polyvinyl alcohol, Poly (amidoamine) (PAMAM) | Co-precipitation method | Size- 164 nm %EE- 91% Zeta potential +19 mV Size- ~ 49 nm | 68.9% invitro release and 75.23% cell viability in L929 lines. Total 50.71% viability in BV-2 cell lines, AMPK/mTOR autophagy pathway. | [178] [179] |
| Rivastigmine | | | | | |
| Transdermal patch system | Ethyl acetate, limonene, and terpineol | Mechanical mixing | Drug content uniformity-99.2% Loading-10% w/w, patch thickness- 154 µm | The cumulative release-10% w/w patch was highest; flux was 12.2 µg/cm ² /h | [182] |
| Galantamine | | | | | |
| Surface functionalized MSN-Ca NPs | 4-amino acetophenone, cetyltrimethylammonium bromide (CTAB) | | Size-100 nm Zeta between -4 to -6 mV % DL-2.6% %EE- 32.5% | Cumulative release 40% and 1.88-fold brain permeation. | [184] |
| Nasal insert | HPMC K4M and K100M, silica gel | Quick melting step | Insert length and width were 23.6 mm and 4.8 mm | Cmax- 1.69 mg/cm ² and Jss of 0.11 mg/cm ² /h after 24 h. Invitro 54.5% release | [185] |

korsemeye peppas model) from the PAMMA-Lf formulation after 72-h period. Additionally, the ex vivo hemotoxic studies were performed to predict the safety of PAMAM-Lf NPs and depicted 9.8-fold safer profile than PAMAM. This reduction in toxicity in comparison to uncoated PAMAM particles was due to Lf coating. Also, the plasma profile and biodistribution studies revealed 7.87 higher area under the curve, 8-fold increase in brain uptake than plain drug and significantly higher circulation time of the NPs. These outcomes were further confirmed by histological and behavioural studies (such as locomotion and novel object evaluation test). While concluding the author illustrated that the PAMAN-Lf conjugates may have good bioavailability and have potential to permeate the brain, however more extensive brain uptake studies will be done in future Fig. 10.

5.5. Miscellaneous

Antonoglou et al. and their colleagues developed a magnetic NEs containing fluorescein-labelled memantine through a modified microwave-assisted polyol process. Resulting NEs showed optimal size and loading and the release over a 24-h period was 50% within the first hour following Korsemeye-Peppas release model. Fluorescence imaging demonstrated prolonged circulation time and reduced clearance. While the preliminary findings may have shown good results, but there is still need for further in vivo studies to validate the effectiveness of this NE system [177].

Various research groups tried to develop different delivery systems like magnetic nanoparticles, surface modified SPIONs, tip loaded microneedles, HAP NPs, and nanocrystals. One such study conducted by Cesur and colleagues presented findings on donepezil loaded polymeric-magnetic nanoparticles formulated using bismuth ferrite (BiFeO₃) and polyvinyl alcohol (PVA) polymer of optimal parameters mentioned in Table 8. The in vitro release was 68.9% and cell viability rate of 75.23% in L929 cells, indicating their good biocompatibility [178]. Another study conducted by Zhong et al., Poly (amidoamine) (PAMAM), angiopep-2 polypeptide, and Gadolinium (III) (Gd3+), were employed for the fabrication of nano system. In cytotoxicity studies using the BV-2 cell lines, 50.71% decrease in cell viability was observed. Additionally, the NPs were found to induce autophagy through the AMPK/mTOR pathway, reduction in inflammatory mediators (IL-1 β and TNF- α), proving their promising use in AD [179]. Simultaneously, Mittapelly and co-workers, investigated the nanocrystals prepared through a high-pressure homogenization process for the encapsulation of donepezil. The parameters from the characterization were satisfactory and having

good stability. The drug release followed a first-order kinetic with a T90% value of 35.7 h, indicating a sustained release profile, and Cmax of 1.07 µg/mL and Tmax o 0.14 days. These findings suggested controlled and sustained release properties, which could be advantageous for drug delivery applications [180]. In addition to this, hydroxyapatite nanoparticles (HAP NPs) were constructed using the co-precipitation method [181]. The HAP NPs exhibited pH-dependent release with 15% and 90% at pH 7.4 and 4.5, respectively, after the first day. Additionally, cytotoxicity assessments using WST-1 and LDH assays demonstrated <4% cytotoxicity, indicating good biocompatibility of the HAP NPs. Overall, all these donepezil containing nanoparticles developed by different teams might have potential as drug delivery carriers due to their controllable drug release behaviour and low cytotoxicity.

Ameen et al., developed a transdermal patch system for galantamine delivery to eliminate GI tract related side effects and to improve compliance. The formulation of the patch system included ethyl acetate, limonene, and terpineol, which were mixed mechanically. The drug content uniformity of the patches was determined to be 99.%, indicating consistent drug distribution within the patches. The optimal drug loading and thickness was observed in the aptch system. The cumulative release from the 10% w/w patch was the highest, with a flux observed at 12.2 µg/cm²/h. These results suggest that the transdermal patch system developed in this study could have a uniform drug content, appropriate drug loading, and controlled drug release, making it a potential candidate for transdermal drug delivery applications [182].

Consequently, Karimzadeh et al. (2017) conducted a study on the utilization of mesoporous silica nanoparticles (NPs) for drug delivery. The synthesized NPs indicated good stability and potential for the control release. The cumulative release of the drug varied between 30.5% and 89.5%. Importantly, cytotoxicity studies conducted on SY5Y cell lines demonstrated no significant toxicity, thereby highlighting the effective drug delivery capabilities of these NPs, which possessed high drug loading capacity, controlled release properties, and low cytotoxicity [183]. Another approach for the effective delivery of rivastigmine was explored by Basharzad et al., in which they focused on surface functionalized MSN-Ca NPs. The release data showed a total drug diffusion of 40%. Notably, the NPs demonstrated good hemocompatibility, suggesting minimal damage due to the Ca coating. In the follow up animal study involving intravenous administration of the NPs, a 1.88-fold increase in brain permeation was observed compared to other systems, highlighting the favourable prospects of these NPs for targeted drug delivery applications [184].

Another interesting was conducted by Shaghil to develop a nasal insert formulation of rivastigmine. The formulation was prepared using a quick melting step, resulting in dimensions of 23.6 mm in length and 4.8 mm in width. The permeation data revealed a maximum concentration of 1.69 mg/cm² and a steady-state flux (J_{ss}) of 0.11 mg/cm²/h after 24 h. Additionally, the invitro release study indicated that the drug release from the insert reached 54.5% after 8 h, demonstrating a sustained release profile. These findings suggest that the nasal insert formulation might have promising drug permeation and release characteristics, positioning it as a potential candidate for nasal drug delivery [185].

6. Conclusion and future directions in management of AD

Long-acting medications (LAMs) are pharmaceutical formulations that are specifically engineered to release therapeutic substances gradually, ensuring consistent and effective drug levels in the body for an extended duration of days, weeks, months, or even years [186]. The primary objective of LAMs is to provide sustained drug delivery, thereby reducing the frequency of dosing required and enhancing patient compliance. Also, by improving the overall effectiveness of treatment they offer patients convenience and an improved quality of life. These medications prove to be especially beneficial in the realm of neurological disorders, where long-term pharmacological interventions are necessary to manage symptoms, halt disease progression, and mitigate the likelihood of relapse [187].

Neurological diseases often require long-term pharmacological and non-pharmacological therapies to improve the disease condition and prevent relapse. To address this need, LAMs were introduced to increase patient adherence in neurodegenerative disorders such as Alzheimer's and Parkinson's [188]. In a study conducted by Borah and colleagues involving 3091 patients with a mean age of 80, non-adherence to oral therapy was observed in 58% of patients, possibly due to pill burden, age, and low formulary tier of the medication [189]. Similarly, a cross-sectional survey by Farrukh et al. found that non-adherence was highest in Alzheimer's patients, followed by those with other brain disorders [190]. By offering patients adherence to therapy without frequent dosing, LAMs overcome the challenges associated with conventional dosing methods in neurological diseases.

One approach to enhancing therapeutic success is the use of long-acting injections (LAIs). LAIs form a depot at the injection site, allowing for slow drug diffusion from the depot into the systemic circulation and at the site of action, maintaining a steady-state concentration [186]. The duration of action of LAIs can vary from a few days to several months. However, several factors, including drug pharmacokinetics, injection site characteristics, formulation characteristics, and patient-related factors such as age, gender, body mass, and physical activity, can significantly influence the overall success of the therapy. Despite these challenges, LAIs offer advantages such as bypassing "first-pass metabolism," improving adherence to therapy by reducing the need for frequent dosing, minimizing side effects (especially gastrointestinal), preventing relapse, and reducing hospitalization, which can increase the overall disease burden [191].

LAIs encompass a range of techniques for delivering therapeutic molecules effectively in neurological conditions. These techniques include in-situ gel-forming implants, microspheres, liposomes, oily solutions, oleo gels, and lipid-based liquid crystal forming systems [192]. Each method offers unique advantages in sustaining drug release and optimizing treatment outcomes. For example, in-situ gel-forming implants ensure a sustained release of drugs, providing a prolonged therapeutic effect and potentially slowing the progression of the disease. Similarly, microspheres and liposomes offer advantages in the delivery of drugs that target specific pathways involved in Alzheimer's pathology. They can encapsulate drugs designed to modulate neurotransmitter levels or reduce neuroinflammation, allowing for targeted and controlled release over an extended period. Whereas, oily solutions, oleo

gels, and lipid-based liquid crystal forming systems can effectively deliver lipophilic drugs or drugs that require localized delivery to the brain. These techniques provide sustained drug release, ensuring consistent therapeutic concentrations and minimizing fluctuations that can affect treatment efficacy in Alzheimer's patients.

Patch as advanced deliver system for prolonged delivery can serve as a drug reservoir (usually multiple doses are loaded) supported by the backing layer resistant to environmental and day to day tasks, whereas other side of the patch is exposed to skin delivering the drug into the skin. It is very popular approach for delivering drugs topically to obtain local action, but the systemic delivery is bit challenging including drug permeability and safety when exposed to skin. Addition to this, there are microneedle (MNs) patches being explored as a delivery option in AD to deliver drugs. These MNs penetrate into the skin barriers and deliver the therapeutic molecules into the systemic circulation with constant sustain release profile. There are five different types of microneedle techniques including dissolving, solid, coating, gel based and hollow, that can be loaded with drug to be used in disease conditions. Moreover, the MNs are generally considered as safe to use, but few challenges are there including control release and biocompatibility along with efficacy of the treatment.

Unlike skin, the nose-to-brain delivery seems more promising approach to deliver drug into the brain. In intranasal delivery high brain bioavailability can be achieved due to high vasculature in nasal epithelium and number of nerve openings. Also, the nasal delivery is considered an excellent route because of the existence of a direct transport pathway through the olfactory region of the nasal cavity which fulfills the demand for effective treatment [193]. Large surface area, porous endothelial membrane, high total blood flow, the avoidance of the first-pass metabolism, and ready accessibility are a few of the major advantages for drug delivery across the nasal mucosa [194]. Besides its advantages, there are major disadvantages like limited absorption, rapid clearance due to mucociliary movement, however these can be avoided by using permeation enhancers and mucoadhesive excipients.

Besides above discussed anti-Alzheimer drugs and utilizing different ADDS strategies, in recent times two monoclonal antibodies including aducanumab (Aduhelm®) and lecanemab (Leqembi®) got accelerated approval. Where they act by binding to beta amyloid protein aggregates, important biomarker in AD and increases their clearance. These agents are considered next gen treatment option in the management of AD. Their biomarker lowering potential in the brain, improves the cognitive and behavioural aspects of the patients in the critical stages of the disease. However, anti-amyloid drugs have some limitations like multiple intravenous administration after every 2–4 weeks, constant MRI screening is required, and side effects [116]. The researchers are trying different strategies like vaccines, plant derived molecules and autophagy inducers as anti-Alzheimer drugs, but the supportive data from clinical studies is needed to ensure their therapeutic benefit in humans.

Overall, these advanced drug delivery techniques have the potential to enhance treatment outcomes and alleviate the symptoms associated with Alzheimer's disease, providing hope for improved care and management of this challenging neurological disorder.

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