Chapter 2
Literature Review

2 Literature Review

2.1 Literature Review related to Memantine

Prior to the licensure of memantine, individuals with mild to moderate stages of Alzheimer's disease (AD) had limited therapy options that included cholinesterase inhibitors (ChEI). For the treatment of mild to severe AD, alternative therapies were not approved. As the number of patients experiencing symptoms of AD advance to later stages of the illness, new treatment modalities are required. The pathways involved in cognition, memory, and learning are frequently investigated as prospective therapeutic targets [106]. Memantine was discovered in 1968 and patented by Eli Lilly. It was later developed by Merz in collaboration with Neurobiological Technologies; Inc. Forest Labs was later approved for its development in the United States and Lundbeck for other international markets. The proprietary names of memantine are: Axura® and Akatinol® (Merz), Namenda® (Forest Laboratory), Ebixa® and Abixa® (Lundbeck) and Memox® (Unipharm) [107]. Memantine is involved in central learning mechanisms and improvement of long-term memory (LTP). LTP is mediated by the neurotransmitter glutamate via the NMDA receptor [108–110]. NMDA receptors are widely distributed in the brain. Yet, in the cortex and hippocampus, they develop thick pyramidal cell dendrites (areas involved in cognition, learning and memory). Elevated glutamate levels are linked to excitotoxicity in addition to the association between LTP and learning. It has been demonstrated that NMDA receptor agonists at low dosages cause necrosis while at large doses they induce apoptosis. It has also been demonstrated that glutamate receptor activation promotes glutamate release [111]. Thus, a large accumulation of glutamate can occur and lead to a massive accumulation of Ca^{2+}, leading to apoptosis. Beta-amyloid (AB) plaques have also been observed to increase the susceptibility of neurons to excitotoxicity. It has been shown to induce depolarization of astrocytes, accumulation of extracellular glutamate and intracellular Ca^{2+} deposition. Therefore, the glutamate-mediated excitotoxicity pathway is an ideal target for AD therapy [112]. The commemorative approval allows it to be used alone or in combination with ChEI. Other diseases and conditions currently used to treat moderate to severe AD are potential targets for reminiscence therapy. Reisberg B *et.al.*, investigated the variable efficacy of primary and secondary effects of memantine for the treatment of randomly assigned moderate to severe AD patients. Patients treated with memantine at a daily dose of 20 mg daily for up to 28 days had shown significant reduction in the functional stage of Alzheimer's disease as measured by the functional assessment stage score ($P = 0.02$ with the last observation, $P = 0.007$ for last observation) including weight loss, and other cognitive, functional, and behavioral measures

based on the contribution of the Clinician-Based Assessment Interview for Treatment Modification Plus (CIBIC-Plus) and Alzheimer's Disease Collaborative Study on lifestyle change from the Life Inventory for Severe Dementia (ADCS) -). ADLsev) [113].

In patients with moderate to severe AD, Howard R. *et al.* demonstrated the safety, tolerability, and cognitive advantages of memantine when it was given 3 months after the end of cholinesterase inhibitor medication [114]. Tariot NP *et al.*, 2004 compared the efficacy and safety of memantine (5-20 mg) with placebo in 404 patients with moderate to severe AD on stable treatment with donepezil. and compared the effectiveness and safety of memantine (5-20 mg) with placebo. Memantine significantly performed well in patients with moderate to severe AD receiving stable doses of donepezil in terms of cognition, activities of daily living, overall outcomes, and behavior. It was also well tolerated, indicating that memantine may represent a novel treatment strategy amongst these patients, with moderate to severe AD [115]. However, Dysken W.M *et al.*, 2014 found that vitamin E and memantine may help individuals using acetylcholinesterase inhibitors delay the onset of mild to moderate AD in order to avoid synaptic degradation and slow the progression of neurodegeneration [116], Turcu L.A *et al.*, 2022 created a novel memantine analogue and observed better working memory in an AD 5XFAD mice model by stimulating CREB signaling to prevent synaptic dysfunction to modulate the development of neurodegeneration [117]. Memantine and donepezil combination therapy was shown to be effective by Guo J *et al.* They also showed improved results in cognition, overall evaluation, activities of daily living, and neuropsychiatric symptoms, combination therapy was found more effective and useful in the treatment of AD than monotherapy, and placebo [118]. Sestito S. *et al.*, 2019 has identified a new chemical entity called memmite that has the ability to release H_2S through a cysteine-mediated mechanism to produce memantine. In addition, this novel hybrid molecule provides a protective effect against neuroinflammation and induces a significant reduction in ROS production, which contributes to the reduction of self-induced Aβ aggregation Aβ(1-42) and provides a cytoprotective effect against higher oligomer damage from Aβ in both human neurons and mouse microglial cells, and also promote autophagy to maintain cell homeostasis in cell survival due to changes in neurodegenerative diseases [119].

2.2 Literature review on the development of memantine-loaded nanocarriers.

Advances in nanomedicine will revolutionize therapeutic approaches in AD management. Recent studies have reported the efficacy of PEGylated nanoparticles in improving memory with a significant reduction in Aβ plaque deposition [120]. Meng *et al.*, 2018 designed a nanocarrier for intranasal delivery of huperzine, from PLGA nanoparticles coated with chitosan

and conjugated to N-trimethyllactoferrin for sustained release and targeted delivery of AD drugs [121]. The components incorporated in the nanocarrier, their physico-chemical properties and the route of administration determine the immunogenicity of nanocarrier. Thus, surface functionalization of PLGA nanoparticles is essential to transport drugs across the BBB with the aim of increasing drug bioavailability in the brain, reducing immunosuppression and achieving site-specific targeting [122].

Recently, a number of memantine-containing nanocarriers have been constructed for the treatment of AD. Despite their decreased bioavailability and toxicity in the body, gamma-irradiated chitosan-memantine nanoparticles have been developed and upon cerebral administration, significant therapeutic efficacy was observed [123]. Furthermore, memantine-loaded nanoparticles (MEM-PEG-PLGA) for oral administration to treat Alzheimer's disease-related memory loss have been developed. Histological studies confirmed that MEM-PEG-PLGA NPs reduced β-amyloid plaques and the associated inflammation characteristic of Alzheimer's disease [124]. Nevertheless, oral administration of memantine is linked to low bioavailability and a variety of side effects, which in extreme cases can result in liver and kidney damage due to decreased metabolism and clearance via liver and kidneys, respectively (creatinine clearance 5-29 ml/minus) [125–127]. Memantine-loaded magnetic nanoemulsion, have been developed for the treatment and diagnostics of AD, produced utilizing a microwave-assisted polyol modification technique with multiple imaging and magnetic properties to provide multimodal preparations for MRI, fluorescence imaging, and drug carriers [128]. Besides their benefits, magnetic nanoemulsion have significant drawbacks like poor stability and subsequent toxicity because inorganic metals and fluorescent materials like zinc, iron, and other synthetic chemicals can linger in the body and are not appropriate for a long-term medication.

Memantine-loaded chitosan nanocrystals developed by Saleh M. A. *et al.*, 2022 demonstrated less cytotoxic effect on goat nasal mucosa and human nasal RPMI 2650 cells than pure MEM. These findings mark some of the first developments in nasal drug delivery devices for the treatment of AD and other neurodegenerative illnesses [129]. Mahmoudi M. *et. al.*, 2021 has developed memantine-loaded polycaprolactone nanocapsules, as effective nanocarriers with 80% entrapment efficiency, and have demonstrated promising outcomes for the treatment of AD [130]. Memantine, tacrine, and (E)-N-(3-aminopropyl) cinnamide were combined to create a drug-polymer conjugate that Naki T. *et al.*, 2023 found to be more effective than tacrine (IC50 = 1698.8 m) at inhibiting the activity of acetylcholinesterase (AChE), which was also supported

by. docking tests [131].

Multitarget Donepezil, memantine, and curcumin loaded nanocarriers with synergistic effects for sublingual administration developed by Topal F *et al.*, 2022, when administered daily sublingually to rats treated with intracerebroventricular streptozotocin (icv-STZ), showed improvement in short-term memory impairments and memory, learning, and exploratory capacities. Also, compared to the AD group, the data showed significantly lower levels of the proteins: Aβ, Tau (τ), APP, GSK-3, AChE, TNF-α and BDNF increased in DO/MM/CUR-loaded NFs treated group. Rats receiving NF with a DO/MM/CUR load did not exhibit neuritic plaques or neurofibrillary tangles as observed in histopathological examination of the cortex and hippocampus [132].

Intrathecal administration of memantine-loaded nanocarriers can help them permeate across BBB. Further, they imitate the extracellular matrix, creating a milieu for neuronal growth [133–135].

2.3 Literature Review: Self-assembled nanocarriers

Researchers' attention has been sparked by developments in nanotechnology and the efficient localization of active moieties in self-assembled nanocarriers. According to a number of literature findings, self-assembled delivery systems and other nanocarrier-based drug delivery methods have less side effects and higher efficacy. These constructed nanosystems exhibit many forms of interactions, including hydrogen bonds, electrostatic interactions, hydrophobic interactions, and van der Waal interactions, are produced by the grouping of atoms or molecules. Surfactant-based nanoparticles, polymer-based polymers, multi-organ lecithin, mixed self-assembly, and phospholipid self-assembly are a few examples of these systems [136]. These nanosystems are employed in a variety of medicinal applications, including regenerative biology, tissue engineering, and vaccination, to deliver medication payloads to specific regions.

As a result, it is anticipated that the next generation of supramolecular self-assembly systems would enhance human healthcare by utilizing cutting-edge technology and producing significant therapeutic results. The methods for creating self-assembled nanocarriers are highlighted in this chapter, along with their classification and medical uses. In addition, the chemistry underlying supramolecular structure formation and their larger function in biomedical applications are emphasized. For the therapy of neoplasms, researchers have developed self-assembling nanocarriers [137]. A three-in-one adamantine nanocarrier functionalized with ruthenium complex monomer ([Ru(phen-ad)3] (PF6)2,Ru) and cyclodextrin (-CD) was

developed by Yang G. *et al.*, 2018 to perform dual drug administration, photon imaging, and synergistic chemophotodynamic therapy for the treatment of cancer. Double-edged 5-fluorouracil/LD@RuCD nanoparticles exhibit effective cancer cell penetration and preferentially aggregate in lysosomes, and RuCD nanocarriers exhibited significant photodynamic therapeutic potential when exposed to visible light. They produce reactive oxygen species and harm lysosomes, which allows 5-fluorouracil and londamine to bypass them and reach the cancer cells' mitochondria and cause apoptosis [138].

For accurate and deep penetration into 3D ESCCs (esophageal cells), Xiang Li et al, 2021, created RNA-mediated self-assembly chemotherapeutic nanocarriers with molecular targeting for the treatment of esophageal squamous cell carcinoma [139]. Neurodegenerative disorders can now be treated using self-assembled nanocarriers. Xue R *et al.*, 2018 created Lithium Ion Nanocarriers Self-Assembled from Amphiphiles with Aggregation-Induced Emission Activity to treat bipolar illnesses. Lithium salts are frequently used to treat bipolar disorder, but due to the accumulation of lithium ions in peripheral organs, patients frequently have undesirable side effects [140]. Since traditional nanocarrier preparation methods are not suitable for Li-ion preparation, amphiphiles with two ethylene oxide tetramers attached to a hydrophobic core that prevent aggregation-induced light emission (IEA) have been developed to successfully prepare Li-ion nanocarriers in water [140]. Koss *et al.*, 2016 developed a self-assembled Nanoscaffold containing peptide Matrix Metalloproteinase 2 (MMP-2) for neural tissue engineering (RADA) and was able to promote neural differentiation for PC-12 cells following the release of ciliary neurotrophic factor analogs methionine-valine-guanine and aspartic acid-guanine-guanine-leucine. Thus, a fully synthetic self-assembled biomimetic nanoscaffold, biocompatible with microglia and intracellular components can serve as a tunable drug delivery system capable of inducing neural differentiation through peptide cleavage [141].

Polyaniline Composite Scaffolds, which are self-assembled peptide nanoribbons, were created by Smith AM *et al.*, 2018 and employed them as templates for conjugating with particular proteins that are known to be crucial for the formation of neural tissue. Tetramethylene glutaric acid and isoleucine were conjugated to create the model (Ile-TMG-Ile), and the amphiphilic sphere's capacity to self-assemble was tested in the pH range of 4 to 9. In the presence of rat neural cortex cells, cell proliferation and brief neurite outgrowth followed, demonstrating the viability of scaffolds for the regeneration of neural tissue [142]. Yang L. *et al.*, 2018 created a biodegradable inorganic MnO_2 scaffold that can be an effective tool for enhancing human neural stem cell (NSC) transplantation and control cell differentiation in rat models of spinal cord

injury and traumatic brain injury [143].

2.4 Mechanism of action of self-assembled PLGA nanoscaffolds

Self-assembly is the phenomenon of arrangement of nanostructure into closed packed structure by the action inter- and intra-molecular bonding through van der Waals forces or hydrophobic interactions depending on the stimuli present at local site. These close-packed structures may be either colloidal crystals or particle clusters exhibited by the movement of nanostructure depending on condition of stimulus present at the site administration [144]. Polymer-based self-assembled nanostructures are one of the potential nanovehicles for delivering a wide range of pharmaceutical agents [145]. In present study, PEG coated Memantine loaded PLGA nanoscaffolds were developed and studied for their capacity to self-assemble in the damaged brain region in AD. At the site of neurodegeneration, the pH condition is altered and according to a recent study pH in AD brain ranges from 6.3 to 6.8, which is lower than that of the healthy brain with a pH range from 7.1 to 7.38. This low pH is linked to brain acidosis and therefore inflammatory processes associated in AD condition [146]. pH can be used as a stimulus for the self-assembly of the nanoparticles and in our study self-assembly of nanoscaffolds was achieved by the contributory role of Pluronics F-127 and PLGA [147,148]. Pluronics F-127 has unique ability to self-assemble its copolymer into micelles with a hydrophobic PPO center core and a hydrophilic PEO outer shell that interfaces with water in aqueous environment [149]. After intrathecal administration of nanoscaffolds, the nanostructure crosses BBB via paracellular and endocytosis transport mechanism [150], reaches the neurodegenerated site where these nanostructures self-assemble into elongated structures and drug gets released from the PLGA polymeric matrix by following diffusion release mechanism. In addition, the self-assembled nanoscaffolds behave as extracellular matrix which support adhesion, proliferation and differentiation of neuronal tissues and promote neuronal regeneration [151]. In the present study, Bone marrow stem cells were grafted to the PEG coated Memantine loaded PLGA nanoscaffolds, which accelerates the process of neuroregeneration by releasing paracrine and growth factors at neurodegenerated site which results in proliferation and differentiation of neuronal tissues in brain [152]. Mechanism of drug transport via Intrathecal route to Brain Intrathecal (IT) administration wherein the drug is administered directly into the thecal sac that contains cerebrospinal fluid (CSF) is a potentially powerful drug delivery approach. This route of administration can achieve a high concentration of therapeutic agent within the central nervous system (CNS) while minimizing off-target exposure and associated toxicity [153]. Upon intrathecal administration, nanoscaffolds move into the spinal canal, then via

subarachnoid space ultimately reach the cerebrospinal fluid (CSF). After reaching CSF these nanocarriers are paracellularly transported across BBB via transcytosis. Intrathecal route of administration provides an efficient route for delivery of drug to site of action bypassing the blood brain barrier and infusing therapeutic agents into the cerebrospinal fluid. However, when same drug is given orally, very little amount is able to reach the brain region because of its inefficiency to cross BBB. Clinical studies have shown that naturally occurring cerebrospinal fluid pulsations inside the spinal canal accelerate drug transport. To demonstrate the mechanism involved via intrathecal route an experimental model of the human spinal canal was built for infusion tests of a radionucleotide in stagnant and pulsatile flow fields. The distribution of infused Technitium-99 m in the spinal canal model was quantified and validated with computational study. The results show that the oscillatory flow of the cerebrospinal fluid, accelerates dispersion of drug delivery system in the spinal canal [154,155]. Currently, intrathecal route is typically used for three main purposes: treatment of chronic non-malignant pain, muscle spasticity, and cancer-related pain [156]. The intrathecal injection includes intraventricular, intracisternal and lumbar locations with which opens within the subarachnoid space and then CSF. Nanoscaffolds could offer a solution and alter the fate of freely administered drugs to navigate via the subarachnoid space and offer sustained delivery of therapeutic molecules, genes, and imaging agents within CNS [157].

2.5 Selection of Intrathecal route over oral route of administration

The oral route is the most convenient and usually the safest and least expensive most often used route of administration. However, it has limitations for CNS targeting because of absorption (mouth, stomach and small intestine), metabolism (liver) and excretion (kidney) negligible concentration of drug reaches to site of action. The drug passes through the intestinal wall and travels to the liver before being transported via bloodstream to its target site [158]. However, most drugs are usually absorbed from the small intestine. The intestinal wall and liver chemically alter (metabolize) many drugs, decreasing the amount of drug reaching the bloodstream. The first-pass effect is an important consideration for orally administered medications. It refers to the drug metabolism whereby the drug concentration is significantly diminished before it reaches the systemic circulation, often due to metabolism in the liver [159]. For CNS targeting of drugs BBB is main challenge, and most of oral administered drug are unable to reach CSF and cross BBB which reduces the therapeutic effect of drug in the treatment of neurodegenerative disorders [160]. Furthermore, presence of food and other drugs in digestive tract may affect absorption and metabolism of orally administered drug. Intrathecal

administration to the site of action reduces the systemic toxicity and off target exposures of drugs. Also, smaller dose needs to be administered when given by intrathecal route Although memantine does not show first pass metabolism, with 41% oral bioavailability (bioavailability<30% considered as first pass metabolic drug) [161]. In order to improve the overall efficacy and the extravascular side effects, with targeted delivery to the brain tissues, intrathecal route was selected over oral route.