REVIEW OF LITERATURE ON DESIGNING AND SYNTHESIS OF POLYMERIC NANO PARTICLES AND THERAPIES FOR ALZHEIMER'S DISEASE STUDY

Kaluram Patel and Dr. Nikhil Dadarao Amnerkar
[1]Research Scholar, Department of Pharmacy, SunRise University, Alwar, Rajasthan (India)
[2]Professor, Department of Pharmacy, SunRise University, Alwar, Rajasthan (India)

Abstract: Alzheimer's disease (AD) is an irreversible neurodegenerative disorder, in which there is a progressive deterioration of intellectual and social functions, memory loss, personality changes and inability for self-care, and has become the fourth leading cause of death in developed countries. Pathogenesis of AD, there is a progressive deposition of β-amyloid (Aβ)- peptide in the hippocampal and cerebral cortical regions. This deposition is associated with the presence of neurofibrillary tangles (NFTs) and senile plaques. The senile plaques deposited between the neurons consist mainly protein β amyloid. Neurofibrillary tangles deposited inside the neurons fabricated from Tau protein. Diagnosing Alzheimer's requires careful medical evaluation thorough medical history, mental status testing, physical and neurological examination tests (such as blood tests and brain imaging), two classes of medications approved to treat AD· Cholinesterase inhibitors: Donepezil, Rivastigmine, Galantamine, NMDA receptor antagonists: Memantine. The major goal in designing nanoparticles as a delivery system are to control particle size, surface property and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutic optimum rate and dose regimen of the agent to the CNS, but also the ability of the agent to access the relevant target site within the CNS. Many strategies have been developed to deliver the drug into brain by crossing the BBB: chemical delivery systems, magnetic drug targeting or drug carrier systems such as antibodies, liposomes or nanoparticles. Among those, nanoparticles have got a great concentration as the potential targeted drug delivery systems in the brain recently.

[Patel, K. and Amnekar, N.D**. REVIEW OF LITERATURE ON DESIGNING AND SYNTHESIS OF POLYMERIC NANO PARTICLES AND THERAPIES FOR ALZHEIMER'S DISEASE STUDY.** The International Journal of Interpretation, Observation and Analysis, 2023; Volume 1, Issue 1:32-35 (January-March). ISSN 2349-0713, Peer-reviewed (online/offline), Refereed, Indexed and International Journal (Since 2013), Global Impact Factor: 5.776

Keywords: Alzheimer's disease, β-amyloid, cholinesterase inhibitors, Curcumin nanoparticles

Introduction: Alzheimer's disease, β-amyloid, cholinesterase inhibitors, Curcumin nanoparticlesZoonoses have affected human health throughout times, and wildlife has always played a role. For example, bubonic plague, a bacterial disease for which rats and fleas play a central role in transmission, has caused substantial illness and death around the world since ancient times (4). A possible epidemic of bubonic plague was described in the Old Testament, in the First Book of Samuel. The socalled Black Death emerged in the 14th century and caused vast losses throughout Asia, Africa, and Europe. The epidemic, which originated in the Far East, killed approximately one third of Europe's population. However, bubonic plague still occurs in Asia, Africa, and the Americas, and the World Health Organization annually reports 1,000–3,000 cases. In the western United States, acquisition of plague in humans is linked to companion animals infested with Yersinia pestis–carrying fleas in areas of endemic sylvatic disease (5). Rabies was described in Mesopotamia, in hunting dogs, as early as 2,300 BC. Recognizable descriptions of rabies can also be traced back to early Chinese, Egyptian, Greek, and Roman records (6). In Europe in the medieval age, rabies occurred in both domestic animals and wildlife. Rabid foxes, wolves, badgers, and bears have been described in the literature as well as in figurative art. Ancient accounts and modern hypotheses suggest that Alexander the Great, who died in Babylon in 323 BC, died of encephalitis caused by West Nile virus (7), a virus that has a wild bird reservoir. Marr and Calisher reported that as Alexander entered Babylon, a flock of ravens exhibiting unusual behavior died at his feet (7). In 1999, West Nile virus was introduced into the United States, where it caused the ongoing epizootic in birds with a spillover of infections to humans and equines.

Review of literature:

Alzheimer's disease (AD) is a prominent neurodegenerative disorder marked by progressive deterioration of memory, cognitive abilities, and related behavioral and psychological symptoms of dementia. The prevalence of AD rises substantially

with advancing age, predominantly impacting individuals over 60 years. With the rapid aging of the global population, the number of individuals affected by AD is projected to reach approximately 131 million by 2050. The World Health Organization (WHO) predicts that AD will likely become the fourth leading cause of death by 2030 due to the lack of effective diagnostic and treatment options. The substantial personal, family, and socioeconomic challenges associated with AD highlight the urgent need for advances in managing the disease. Although significant progress has been made in understanding the mechanisms behind AD, its exact pathogenesis remains unclear, posing a substantial obstacle to developing effective therapies. Numerous hypotheses have been proposed to explain the disease's development, each emphasizing different pathological hallmarks of onset and progression that could serve as potential therapeutic targets.

Early detection of AD and prompt interventions are crucial yet unresolved challenges in its management. The ideal therapeutic window—especially during the preclinical symptomatic phases—remains unclear due to the lack of reliable confirmatory diagnostic tools. Current diagnostic methods mainly focus on identifying pathological biomarkers, such as amyloid-β (Aβ) aggregates and hyperphosphorylated tau (p-tau), which form amyloid plaques and neurofibrillary tangles (NFTs), respectively, the hallmark features of AD. However, assessments of cerebrospinal fluid (CSF) and neuroimaging techniques provide only supportive, rather than definitive, diagnostic information, as the relationship between biomarker levels and disease progression remains debated. Therefore, integrating multimodal diagnostic approaches that combine biochemical, imaging, and genetic markers could significantly enhance diagnostic accuracy and facilitate early therapeutic interventions. In this context, theranostic methods that integrate therapeutic and diagnostic functions into a single platform hold considerable promise by enabling real-time monitoring of drug efficacy and disease progression. Despite some encouraging early results from a limited number of theranostics agents, this field remains relatively new and requires extensive research before widespread clinical use. Additionally, the Blood–Brain Barrier (BBB), a highly selective and dynamic neurovascular interface comprising endothelial cells, pericytes, astrocytes, and supporting glial cells, presents a significant obstacle for effective AD treatment by blocking most therapeutic agents from reaching the brain.

The build-up of extracellular Aβ plaques and NFTs made of hyperphosphorylated tau is a hallmark of AD pathogenesis. These aggregates impede synaptic transmission and disturb the integrity of neuronal microtubules. Neuronal loss and cognitive decline are also caused by oxidative stress, mitochondrial dysfunction, and neuroinflammation. Despite significant advances in elucidating genetic risk factors and molecular pathways, the precise etiology of AD remains unresolved. Current treatments primarily provide symptomatic relief without modifying disease progression. Recently developed disease-modifying antibodies, such as aducanumab, lecanemab, and donanemab, which target Aβ aggregates, have demonstrated potential to slow cognitive decline; however, their long-term safety and efficacy remain under evaluation. The BBB presents a significant obstacle, blocking over 98% of small molecules and nearly all macromolecular therapeutics, thereby underscoring the urgent need for innovative drug delivery strategies. Only a small proportion of hydrophobic molecules can cross the BBB, limiting the delivery of many potentially effective therapeutics. Nanoparticle-based drug delivery systems represent a promising approach to enhance drug stability, increase BBB permeability, and facilitate targeted administration to affected neuronal regions. The application of nanotechnology in future AD therapies may facilitate not only symptomatic relief but also direct intervention in underlying molecular mechanisms to modify disease progression. Biosensor technologies have recently emerged as effective tools for early diagnosis and monitoring of AD by enabling sensitive detection of key biomarkers, including Aβ peptides, tau protein, and phosphorylated tau. Smart nanomaterials are central to advancing these biosensors, as they enhance biorecognition efficiency, signal transduction, and analytical sensitivity through their high surface area, distinctive electrical properties, and biocompatibility. In addition to improving biosensor performance, smart nanomaterials facilitate the development of multifunctional theranostic platforms that combine biomarker detection with targeted drug delivery across the BBB. Consequently, progress in nanomaterial design is intrinsically linked to biosensor development, underscoring the importance of nanotechnology-driven biosensing strategies for AD diagnosis and therapeutic intervention presents

emerging strategies to enhance drug delivery across the BBB in AD.

The pathogenesis of AD has not yet been fully explored, but Aβ is considered to be an important factor. This substance is derived from the amyloid precursor protein (APP), a neuronal membrane protein. Abnormal postsynaptic acetylcholine receptor locations and excessive sprouting of nerve endings have been reported in APP-deficient mice. These clues suggest a role for APP in neural development (**Wang et al., 2005**). APP is degraded during metabolism by either α-secretase and γ-secretase or β-secretase and γ-secretase, the latter produces two different amino acid chain lengths, namely, $A\beta_{40}$ and $A\beta_{42}$, depending on the shear position of γ-secretase (**Huse et al., 2002**). $A\beta_{42}$ is thought to be the more neurotoxic sequence among the two. The detailed shearing process is shown in **Figure 2**. In summary, $A\beta_{42}$ accumulates in the brain, forming amyloid plaques. This is followed by the activation of glial cells and the pathological phosphorylation of tau (**Andronie-Cioara et al., 2022**). During this process, Aβ is recognized by pattern recognition receptors in microglia, which produce neurotoxic cytokines and chemokines, such as CCL-4, TNF, IL-6 and IL-1β. This illustrates the importance of neuroinflammation in the development of AD pathology (**Martin et al., 2017**). Furthermore, Aβ has been demonstrated to impede long-term potentiation (LTP) and dendritic spine density in a manner that is dependent on the activation of NMDAR. The aberrant activation of extrasynaptic NMDARs has been identified as a significant contributor to the substantial decline in synapse number observed in patients with AD (**Fani et al., 2021**).

Polymers are macromolecular compounds formed by the linking of a large number of repeating units through chemical bonds. These assemblies are then subjected to further processing to yield nanomicelles, vesicles, polymers and other products (**Feng et al., 2017**). Polymers can have one or more of these forms at the same time. Structurally, they can be composed of a single monomer arranged in a repeating manner, or a variety of monomers of different structures arranged in a random alternating manner, with a high degree of customization and desirable physicochemical properties such as solubility, amphiphilicity, and biodegradability (**Agrahari and Agrahari, 2018**).

Since Abuchowski et al. first coupled monomethoxy-polyethylene glycol (mPEG) to bovine serum albumin in 1977, researchers have found that it is possible to couple polymers to organic or inorganic drugs. This approach was first approved by the US FDA in 1990 (**Moncalvo et al., 2020**). Although only PEG couplers are commercially available today, much progress has been made with other polymers over the last 3 decades. This is largely due to advances in reversible radical polymerization technology, which has made it possible to control chain length, monomer content and, to some extent, monomer sequence in a precise and reproducible manner (**Guerassimoff et al., 2020**).

Block copolymers, comprising a hydrophilic shell and a hydrophobic core, represent a promising class of carriers for drug delivery (**Pottanam Chali and Ravoo, 2020**).

PLGAs are typically formed by ring-opening copolymerization of lactic acid (LA) and glycolic acid (GA), with the monomers linked by lipid bonds. The ratio of PLA to GA in the composition affects the hydrophobicity, size and rate of biodegradation (**Schliecker et al., 2003**). Incorporating GA reduces the polymer's crystallinity while increasing the water absorption rate of the nanomaterial. Consequently, the degradation rate of PLGA can be finely tuned by adjusting the LA-to-GA ratio in the amorphous polymer. LA is crystalline, while GA exhibits more amorphous characteristics. A higher GA content shifts the ratio of crystalline to amorphous phases in PLGA particles toward the amorphous region, resulting in faster hydrolysis of the polymer particles. The most common ratio in the biomedical field is currently 50:50, because this ratio of polymers has the lowest crystallinity and the highest hydrophilicity, giving this ratio of PLGAs the fastest degradation rate (**Lü et al., 2009**; **Allahyari and Mohit, 2016**). This ratio of PLGA has been demonstrated to be particularly effective in facilitating drug delivery across the BBB. A comparison of the neuronal uptake of Cur, NPs-Cur 50:50, and NPs-Cur 65:35 revealed that SK-N-SH cells exhibited a higher uptake of NPs-Cur 50:50 than NPs-Cur 65:35 or free Cur (**Djiokeng Paka et al., 2016**).

References:

Fan, S.; Zheng, Y.; Liu, X.; Fang, W.; Chen, X.; Liao, W.; Jing, X.; Lei, M.; Tao, E.; Ma, Q.; Zhang, X.; Guo, R.; Liu, J. Curcumin-loaded PLGA-PEG nanoparticles conjugated with B6 peptide for potential use in Alzheimer's disease. Drug Delivery **2018**, 25, 1091– 1102,

Lee, Y.-J.; Choi, D.-Y.; Yun, Y.-P.; Han, S. B.; Oh, K.-W.; Hong, J. T. Epigallocatechin-3-gallate prevents systemic inflammation-induced memory deficiency and amyloidogenesis via its anti-

neuroinflammatory properties. J. Nutr. Biochem. **2013**, 24, 298– 310, DOI: 10.1016/j.jnutbio.2012.06.011

Mittal, G.; Sahana, D. K.; Bhardwaj, V.; Ravi Kumar, M.N. V Estradiol loaded PLGA nanoparticles for oral administration: effect of polymer molecular weight and copolymer composition on release behavior in vitro and in vivo. J. Controlled Release **2007**, 119, 77– 85,

Kaur, A.; Nigam, K.; Bhatnagar, I.; Sukhpal, H.; Awasthy, S.; Shankar, S.; Tyagi, A.; Dang, S. Treatment of Alzheimer's diseases using donepezil nanoemulsion: an intranasal approach. Drug Delivery Transl. Res. **2020**, 10, 1862– 1875,

Qian, Y.; Zha, Y.; Feng, B.; Pang, Z.; Zhang, B.; Sun, X.; Ren, J.; Zhang, C.; Shao, X.; Zhang, Q.; Jiang, X. PEGylated poly(2-(dimethylamino) ethyl methacrylate)/DNA polyplex micelles decorated with phage-displayed TGN peptide for brain-targeted gene delivery. Biomaterials **2013**, 34, 2117– 29,

Wibroe, P. P.; Ahmadvand, D.; Oghabian, M. A.; Yaghmur, A.; Moghimi, S. M. An integrated assessment of morphology, size, and complement activation of the PEGylated liposomal doxorubicin products Doxil®, Caelyx®, DOXOrubicin, and SinaDoxosome. J. Controlled Release **2016**, 221, 1– 8

Kuo, C. Y.; Kohn, D. B. Gene Therapy for the Treatment of Primary Immune Deficiencies. Curr. Allergy Asthma Rep. **2016**, 16, 39,

.