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Drug Delivery Methods Based on Nanotechnology for the Therapeutic Management of Alzheimer's Disease

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Abstract:
A neurological disorder named Alzheimer's disease causes cognitive and behavioural deterioration. Because of their poor solubility, low bioavailability, and inability to pass the blood-brain barrier, conventional therapy approaches, especially acetylcholinesterase inhibitor medications, frequently fail. Therapeutics have been improved by the use of nanotechnological treatment approaches that incorporate the design, characterisation, manufacture, and application of nanotechnological drug delivery devices. These nanotechnologies include liquid crystals, solid lipid nanoparticles, polymeric nanoparticles, nanostructured lipid carriers, and micro- and nano emulsions.Each of them is a promising tool for administering therapeutic devices to the nervous system through several pathways, especially the intranasal route. This study's goal is to provide a thorough analysis of Alzheimer's disease drug delivery methods based on nanotechnology.

Keyword: Neurological disorder, Alzheimer's disease, Acetylcholinesterase inhibitor, Polymeric nanoparticles, Nanotechnology.

1. INTRODUCTION:

Alzheimer's disease (AD) is an incurable, debilitating sickness that causes cognitive and behavioural deterioration over a protracted period of time. Plaques form in the cerebral cortex and other regions involved in thought and decision-making in AD, including the hippocampus, a structure located deep within the brain that aids in memory encoding[1]. Worldwide, there are more than 55 million dementia sufferers, 60% of whom reside in low- and middle-income nations. There are around 10 million new cases reported each year. In the world today, dementia is one of the major causes of disability and dependency among older people and the sixth greatest cause of death[2]. Even though dementia risk increases with age, it is not a necessary side effect of aging biologically. Furthermore, young-onset dementia, which is defined as the development of symptoms before the age of 65, accounts for up to 9% of cases and is not just a disease of the elderly. According to studies, staying physically

active, quitting smoking, abstaining from harmful alcohol use, managing one's weight, eating a nutritious diet, and keeping normal blood pressure, cholesterol, and blood sugar levels all help people lower their risk of cognitive decline and dementia. Depression, social isolation, low educational achievement, cognitive inactivity, and air pollution are additional risk factors[2]. Unless medical advances are achieved to prevent, slow down, or stop the disease progression, the number of people 65 years of age and older with AD may nearly quadruple from 5 million to a projected 13.8 million by 2050[3].

There are a number of restrictions with current therapy, and intranasal drug administration appears to be a promising alternative. Neurotransmitter or enzyme modulation is the basis of the currently approved medications for treating the cognitive deficits associated with AD.The most frequent reason for stopping therapy with acetylcholinesterase (AChE) inhibitors is because of gastrointestinal side effects like nausea and vomiting[5,6].Tacrine requires four administrations daily and has a brief half-life[7]. Patients who used the medication also needed routine blood testing owing to hepatotoxicity[8]. Additionally, the half-lives of galantamine and rivastigmine are 7 and 2 hours, respectively. Memantine side effects include drowsiness, disorientation, constipation, and vomiting[9]. Table 1 provides a review of the pharmacokinetic characteristics of medications used to treat AD.

Table 1: A brief overview of the pharmacokinetic factors for memantine and cholinesterase inhibitors.

Drug	**t_{max}(h)**	**Half-life (h)**	**Protein binding (%)**	**Bioavailability (%)**
Memantine[10, 11]	3-7	60-80	45	100
Rivastigmine[5]	0.8–1.7	2	40	40
Tacrine[5]	0.5–3	1.3–7.0	75	17–37
Galantamine[5]	0.5–1.5	5–7	18	85–100
Donepezil[5]	3–5	60–90	96	100

Drug's unfavourable pharmacokinetics and pharmacodynamics commonly cause therapy to fail[12]. Inadequate physical properties of drugs (such as hydrophobicity), unfavourable biological membrane absorption, undesirable pharmacokinetic characteristics (such as intense and plasma metabolic rate), instability of drugs (oxidation, hydrolysis, or photolysis), and tissue toxicity (hepatotoxicity, neurotoxicity, or kidney toxicity) are the causes of pharmacotherapy failure[13, 14].The pharmacokinetics, pharmacodynamics, and potential low toxicity of medications are improved when they are used in nanoplatforms or nanodevices.15,16 The regulated release of medications into illness locations is, on the one hand, a crucial component in the development of nanomedicine[17,18].

Utilizing drug delivery methods based on nanotechnology can improve a treatment's efficacy[19, 20]. Some of these novel platforms work to lessen adverse effects while increasing drug absorption, pharmacokinetics, and pharmacodynamics.

2. PATHOPHYSIOLOGY OF ALZHEIMER DISEASE

Extracellular beta-amyloid deposits (seen in neurotic plaques) and intracellular neurofibrillary tangles (paired helical filaments) are the two pathologic hallmarks of Alzheimer's disease[21, 22]. The loss of synapses and neurons caused by beta-amyloid deposition and neurofibrillary tangles causes extensive atrophy of the afflicted parts of the brain, which commonly begins in the mesial temporal lobe. Uncertainty surrounds how beta-amyloid peptide and neurofibrillary tangles harm the brain in this way[23, 24]. Numerous theories exist. According to the amyloid hypothesis, the gradual buildup of beta-amyloid in the brain results in a complicated series of actions that cause neuronal cell death, synaptic loss, and

progressive neurotransmitter deficiencies, all of which contribute to the clinical symptoms of dementia[25]. Alzheimer disease sufferers' brains have been found to have an ongoing immune response and inflammation[26]. According to some researchers, inflammation is the third primary pathologic characteristic of Alzheimer disease[27]. Alzheimer's disease has been linked to abnormal glucose metabolism, which may be a significant contributing factor. Alzheimer's disease has been linked to prion processes[28-32]. A normal cell-surface brain protein known as prion protein is misfolded into a harmful form known as a prion in prion disorders[33]. Brain damage results from the prion's subsequent induction of identical protein misfolding in other prion proteins, which produces a significant rise in aberrant proteins[34]. The beta-amyloid in cerebral amyloid plaques and the tau in neurofibrillary tangles are hypothesized to exhibit prion-like, self-replicating qualities in Alzheimer's disease[35-39].

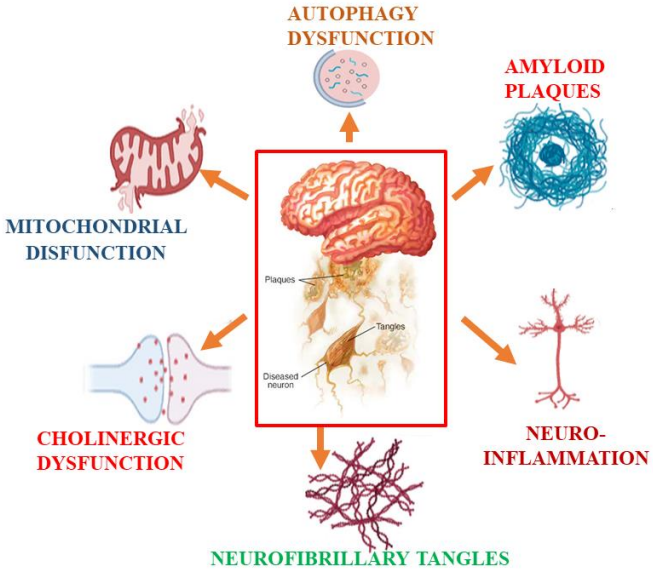

Figure 1: shows the many elements that contribute to the development of Alzheimer's disease. The two main ones are tau hyperphosphorylation and amyloid plaques. Senile plaques are produced as a result of extracellular amyloid deposition. Microtubules become disassembled as a result of hyperphosphorylated tau, which also harms the cytoskeleton and signal transduction in neuronal cells. The progression of the disease is also significantly influenced by other factors such neuroinflammation, oxidative stress, cholinergic insufficiency, mitochondrial dysfunction, and autophagy failure[40,41].

3. ALZHEIMER'S DISEASE: DIAGNOSIS AS WELL AS TREATMENT:

Understanding your symptoms and how they relate to the disease is crucial to making an accurate diagnosis of Alzheimer's. It helps to get feedback about your symptoms and how they affect your everyday life from a close family member or friend. Memory and cognitive tests can also be used to identify Alzheimer's[42]. Other possible causes of the symptoms can be ruled out using blood and imaging testing[43]. They might also aid your doctor in recognizing the dementia-causing illness symptoms[44]. In earlier times, Alzheimer's disease was only definitively identified after death when a microscope examination of the brain revealed plaques and tangles[45]. Researchers and medical professionals can now more accurately diagnose Alzheimer's disease in its early stages. Plaques and tangles can be found using biomarkers[46]. Tests that assess amyloid and tau proteins in the fluid component of blood and cerebral spinal fluid are examples of biomarker tests, as are specific kinds of PET scans[47]. A variety of procedures, including a physical and neurological examination, laboratory tests, mental status and neuropsychological evaluations, brain imaging, and others, are likely to be used to diagnose Alzheimer's disease[48]. Reflexes, muscle strength and tone, the capacity to

stand up from a chair and walk across the room, sense of sight and hearing, coordination, balance, and other factors may be tested as part of a neurological examination[49]. Blood testing might help rule out further potential reasons of forgetfulness and confusion, such as a thyroid condition or inadequate vitamin levels[50]. Beta-amyloid and tau protein levels can also be determined by blood testing, however access to these procedures may be restricted. A quick mental state exam was once used to evaluate one's capacity for memory and other types of thought[37]. Longer versions of this type of test may offer more information about mental function that can be compared to that of individuals of a comparable age and educational level. These tests can aid in making a diagnosis and act as a springboard for further symptom monitoring. Images of the brain are frequently employed to identify observable alterations in illnesses other than Alzheimer's disease that may result in symptoms comparable to those of the disease, such as strokes, trauma, or tumors[51]. The use of new imaging tools, which are primarily found in academic medical institutes or clinical trials, may assist identify particular brain alterations brought on by Alzheimer's disease[52].

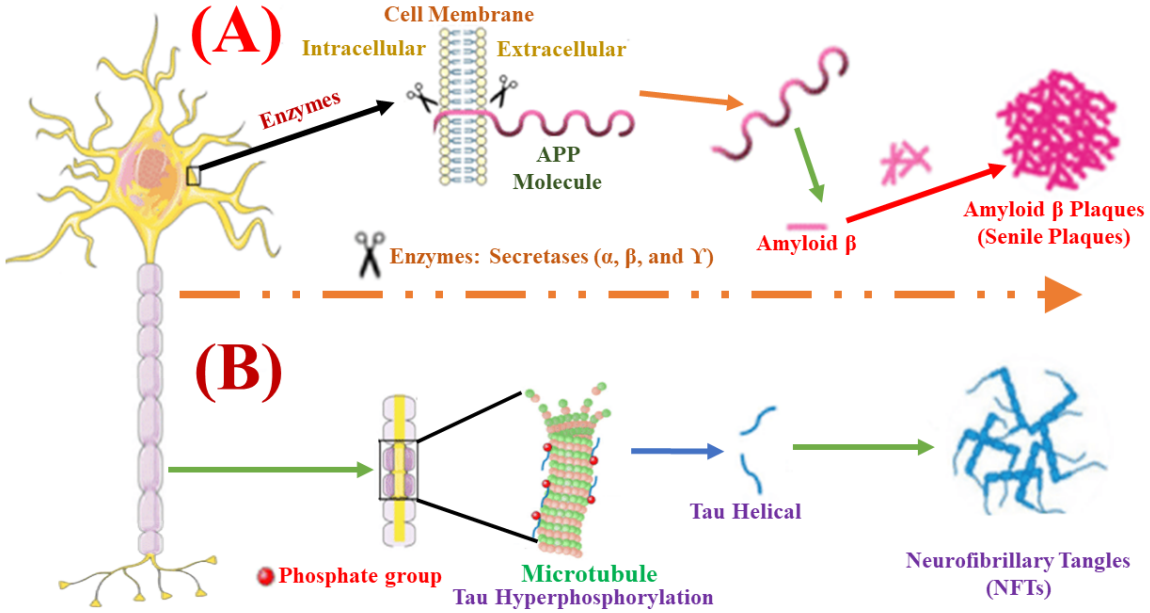

Figure 2: shows the development of amyloid plaques (A) and tangles of neurofibrillary fibres (B) in neurons affected by Alzheimer's disease (AD).

A powerful magnetic field and radio waves are used in magnetic resonance imaging (MRI) to create precise images of the brain. MRI scans not only rule out other illnesses, but they may also reveal shrinkage of particular brain regions linked to Alzheimer's disease. In general, an MRI is preferred to a CT scan when assessing dementia. Cross-sectional images of your brain are created by a computerized tomography (CT) scan, a sophisticated X-ray technology[53]. Usually, it's used to rule out brain traumas, strokes, and malignancies[50]. Brain regions with inadequate food metabolization are seen on fluorodeoxyglucose (FDG) PET imaging images. Differentiating between Alzheimer's disease and other forms of dementia can be made easier by looking for patterns in the regions with poor metabolism[54]. The number of amyloid deposits in the brain can be accessed via amyloid PET imaging[55]. This test is primarily used in research;however, it might be applied in cases where a person exhibits very early or late onset dementia symptoms. Tau PET imaging, which typically only utilized in research settings, measures the tangles in the brain[55].

Alzheimer's disease has no known cure,[56] however some drugs can momentarily prevent the symptoms of dementia from getting worse[57]. Behavioural symptoms can also be helped by

drugs and other treatments. It may be feasible to retain everyday functioning for a while by starting Alzheimer's treatment as soon as possible[58-62]. Current treatments, however, cannot halt or reverse AD[63]. Treatment is extremely customized because AD has varied effects on each individual[64]. To choose the most effective course of therapy, medical professionals consult with Alzheimer's patients and the individuals who care for them. Cholinesterase inhibitors and NMDA antagonists are two classes of medications that the U.S. Food and Drug Administration (FDA) has licensed to treat the signs and symptoms of Alzheimer's disease. Aducanumab, the first Alzheimer's disease disease-modifying treatment, has received accelerated FDA approval.The brain's amyloid deposits are lessened with the aid of the drug. Researchers examined the impact of the novel drug aducanumab on patients with early-stage Alzheimer's disease. As a result, it might only benefit those who are just starting off. Donepezil, Rivastigmine, Galantamine, and other cholinesterase inhibitors can be used to treat mild to moderate Alzheimer's disease symptoms. Acetylcholinesterase, the enzyme that breaks down acetylcholine, is inhibited by these medications[65]. One of the substances that facilitates communication between nerve cells is acetylcholine[66]. Some of the symptoms of Alzheimer's disease are thought to be caused by low levels of acetylcholine, according to researchers[67].These medications can lessen some behavioural signs of Alzheimer's disease and help with some memory issues[67-69]. These drugs don't treat Alzheimer's disease or stop it from getting worse. Memantine is an FDA-approved NMDA antagonist for the treatment of moderate to severe Alzheimer's disease[70-73]. It keeps some brain cells in better health. Memantine users with Alzheimer's disease do better in ordinary everyday tasks like eating, walking, using the restroom, bathing, and clothing themselves, according to studies[74, 75].
Antipsychotics (neuroleptics), antidepressants, anxiety medications, anticonvulsants, and other medications are occasionally used in specific situations[76]. Healthcare practitioners normally only administer these drugs for brief periods when behavioural issues are severe since they can have unpleasant or potentially harmful side effects (such dizziness, which could result in falls)[77, 78]. Or just after your loved one has first tried less risky non-drug treatments.

4. DRUG DELIVERY TECHNIQUES BASED ON NANOTECHNOLOGY:

Treatment options are often limited due to drugs' inability to cross the blood-brain barrier (BBB) or their poor solubility when administered orally. Various strategies have been developed to overcome the BBB, including drug delivery systems such as liposomes, polymeric and solid lipid nanoparticles (SLNs), solid lipid carriers, liquid crystals (LCs), microemulsions (MEs), and hydrogels. The physicochemical properties of drugs—such as hydrophilicity, lipophilicity, ionization, high molecular weight, poor bioavailability, extensive metabolization, and adverse effects—can lead to their failure as pharmacotherapeutic agents. However, these limitations can be addressed through intranasal administration, an alternative non-invasive method of drug delivery to the brain. This route allows drugs to bypass the BBB and directly transport to the central nervous system (CNS)[79,80].

4.1. Polymeric nanoparticles (NPs)

Nanoparticles (NPs) are defined as particulate dispersions or solid particles ranging from 1 to 1,000 nm in size. The structural organization of a nano system depends on its composition: nano capsules feature compartments that create oily or aqueous cores surrounded by thin polymer membranes, whereas nanospheres have a matrix-based organization of polymeric chains. NPs can be prepared using various methods, including polymer polymerization, ionic gelation or coacervation, emulsion solvent evaporation, spontaneous emulsification or solvent diffusion, nanoprecipitation, spray drying, supercritical fluid technology, and particle replication in non-wetting templates (PRINT)[81].

Drug delivery across the blood-brain barrier (BBB) to the brain can provide significant advantages over current strategies without damaging the BBB. The transport mechanism of NPs across the BBB involves increased retention of the NPs in brain blood capillaries and their adsorption to capillary walls. This leads to a higher concentration gradient, enhancing transport across the endothelial cell layer and improving delivery to the brain. Transport can also be facilitated by inhibiting the efflux system using polysorbate 80 as a coating agent[82].
NPs may induce local toxic effects on brain vasculature, causing limited permeabilization of brain endothelial cells. Using a surfactant to solubilize the lipids of the endothelial cell membrane can further enhance drug permeability across the BBB. Additionally, NPs can permeate the BBB through tight junctions that open between the endothelial cells of brain blood vessels[83].

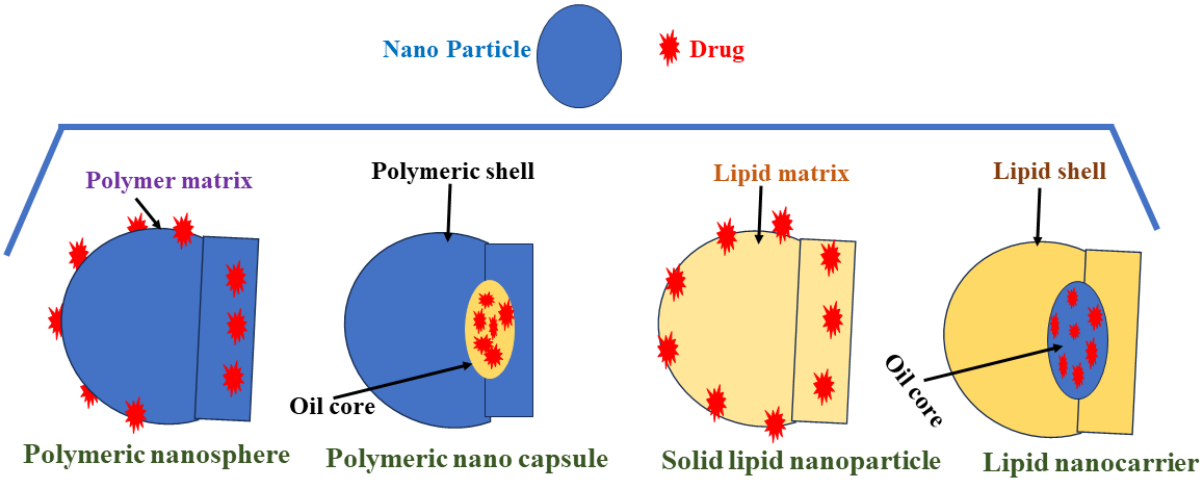

Figure 3:Schematic differences between nano capsule, nanostructured lipid carrier, polymeric nanoparticle, and solid lipid nanoparticle drug delivery systems.

Endocytosis by endothelial cells, followed by the release of drugs within these cells, facilitates delivery to the brain. Transcytosis can also aid in transporting drugs across the endothelial cell layer. A combination of these mechanisms can be utilized for effective drug delivery (Figure 4). NPs can also be administered nasally to enhance absorption and delivery to the brain. Additional strategies include coating NPs with polyethylene glycol (PEG), polymers, or antibodies to improve nasal absorption. Surface modification of NPs with mucoadhesive polymers can increase the retention time of NPs administered via the nasal route[83].

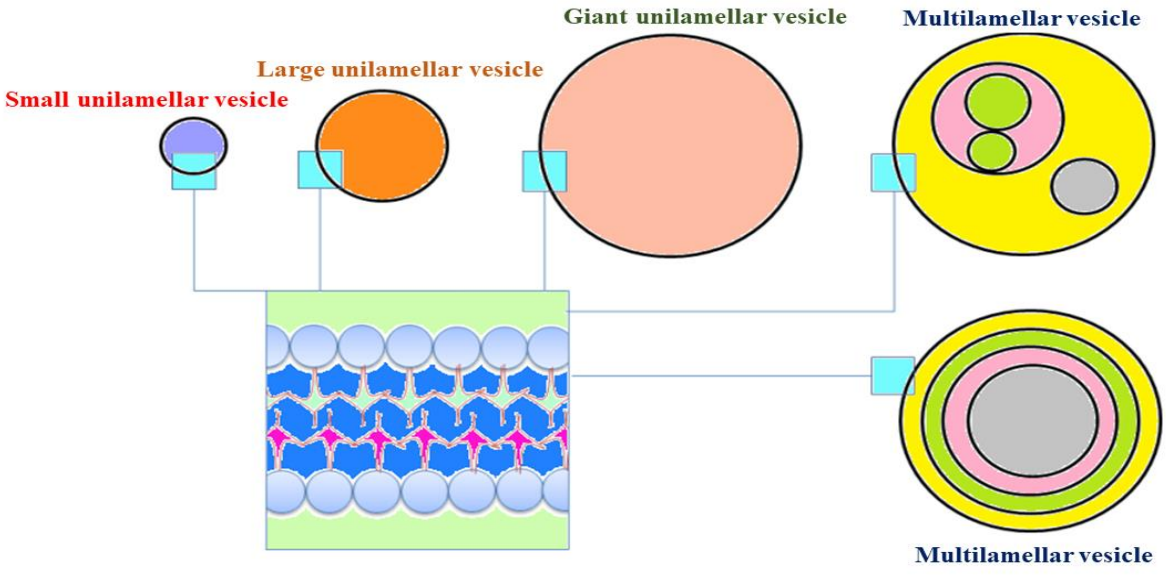

Figure 4: Schematic representation of different types of liposomes and an enlarged view of the phospholipid layers.

Polysorbate 80-coated poly (n-butyl cyanoacrylate) nanoparticles (NPs) loaded with tacrine were prepared using emulsion polymerization. The concentrations of tacrine in the lungs and kidneys were not significant compared to other groups. The authors suggested that the delivery mechanism of the coated polysorbate 80 NPs to the brain involved the interaction between the polysorbate 80 coating and the endothelial cells of the brain microvessels[84].

In another study, poly(n-butyl cyanoacrylate) NPs coated with polysorbate 80 were developed for the targeted delivery of rivastigmine to the brain to treat Alzheimer's disease (AD). Animal studies involved injecting the NPs into mice[85]. The concentration of tacrine in the brain was approximately 170 ng/mL when the coated NPs were used, which was significant ($P < 0.001$) compared to using uncoated NPs or the free drug. The authors proposed that the delivery mechanism of the coated polysorbate 80 NPs to the brain was the interaction between the polysorbate 80 coating and the endothelial cells of the brain micro vessels. This specific role of the polysorbate 80 coating in targeting NPs to the brain was studied by *Sun et al*.

Zhang et al. developed a dual-functional NP drug delivery system based on a PEGylated poly (lactic acid) polymer containing two targeting peptides, TGN and QSH, conjugated to the surfaces of the NPs. TGN specifically targets ligands at the BBB, while QSH has good affinity for Aβ1-42, the main component of amyloid plaques. The optimal maleimide/peptide molar ratio was 3 for both TGN and QSH on the surface of the NPs. These NPs were delivered to amyloid plaques with enhanced and precisely targeted delivery in the brains of AD model mice[85].

Zhang et al. also studied the use of intranasal NPs to deliver basic fibroblast growth factor (bFGF) to the brain for treating AD. In this study, bFGF was entrapped in NPs conjugated with PEG, polylactide-polyglycolide (PLGA), and Solanum tuberosum lectin (STL), which selectively binds to N-acetylglucosamine on the nasal epithelial membrane to facilitate brain delivery. The NPs were prepared using the emulsion solvent evaporation method. Intranasal administration of STL-modified NPs (STL-bFGF-NPs) resulted in a 1.7-5.17-fold greater distribution in the brain compared to intravenous administration of the NPs. The distribution using intranasally administered STL-bFGF-NPs was also 0.61-2.21-fold greater than an intranasally administered drug solution and 0.19-1.07-fold greater than intranasally administered unmodified NPs[86-90]. The activity of ChAT in mice significantly increased ($P < 0.05$) in the group treated with NPs via the intranasal route compared to the AD control group. These findings indicated that ChAT activity in the hippocampus of AD rats treated with bFGF-loaded STL-conjugated NPs was higher than in rats treated with unconjugated NPs. The STL-conjugated NPs effectively facilitated direct transport of bFGF into the rat brain with reduced peripheral adverse effects following intranasal administration[90-93].

Based on these requirements, PEG-PLGA copolymer NPs with a PEG-rich surface around the PLGA core are ideal for intranasal administration because the PEG-rich surface prevents NP aggregation typically observed when uncoated PLGA NPs contact the nasal mucosa. Poly [(hexadecyl cyanoacrylate)-co-methoxypoly(ethylene glycol) cyanoacrylate] NPs were formulated to investigate their effects on slowing down or disrupting the aggregation process of Aβ1-42 peptide or its oligomers through kinetic studies performed with capillary electrophoresis. The capillary electrophoresis experiments showed that these NPs could link the Aβ1-42 peptide both in its monomeric and soluble oligomeric forms, influencing Aβ1-42 peptide aggregation as confirmed by thioflavin-T assays[94,95].

Rivastigmine-loaded PLGA and PBCA NPs were prepared using a modified nanoprecipitation method and an emulsion polymerization method, respectively. Administering rivastigmine formulations to saline-treated animals did not result in noticeable improvements in learning and memory capacities, whereas administering different rivastigmine-loaded NPs to scopolamine-treated mice antagonized scopolamine-induced amnesia, as evidenced by a significant decrease ($P < 0.05$) in escape latency. Chitosan NPs were prepared using an ionic gelation method to enhance the bioavailability and uptake of rivastigmine to the brain via intranasal delivery. Using confocal laser scanning fluorescence microscopy, the concentration of rivastigmine in the brain following intranasal administration was significantly higher at all times compared to the administration of a rivastigmine solution via the intravenous or intranasal route[96-99].

The spray-drying technique was used to develop idebenone-loaded chitosan and N-carboxymethyl chitosan NPs. Although the authors did not study the use of these NPs in AD treatment, the beneficial effects of idebenone for AD treatment and its role as an antioxidant in AD progression have been well documented in clinical trials. Incorporating idebenone in chitosan or N-carboxymethyl chitosan NPs preserved the antioxidant efficiency, especially at higher polymer-to-drug ratios. The NPs showed a tenfold increase in drug stability compared to the free drug. Free idebenone exhibited severe reactivity similar to the positive control, indicating significant potential for corrosion or irritation. Incorporating idebenone in polymeric NPs reduced drug reactivity. Chitosan and N-carboxymethyl chitosan exhibit mucoadhesive properties, revealing that NPs are potential carriers for nasal delivery of hydrophobic and irritating drugs like idebenone due to idebenone's high first-pass metabolism after oral administration[100].

4.2. Solid lipid carriers

Solid lipid nanoparticles (SLNs) are typically spherical with average diameters between 10 and 1,000 nm when dispersed in water. They have a solid lipid core matrix that can solubilize lipophilic molecules. The lipid core typically consists of triglycerides (e.g., tristearin), diglycerides (e.g., glyceryl behenate), monoglycerides (e.g., glycerol monostearate), fatty acids (e.g., stearic acid), steroids (e.g., cholesterol), or waxes (e.g., cetyl palmitate) and is stabilized by surfactants. A combination of emulsifiers may be more efficient at preventing particle agglomeration[101].

Although SLNs are formed using a matrix lipid, a new generation of nanoparticles called nanostructured lipid carriers (NLCs) can be produced using a blend of solid lipids with a liquid lipid to minimize drug expulsion associated with SLNs (Figure 3). SLNs or NLCs are prepared from lipids, an emulsifier, and water or solvent using various methods, including high-pressure homogenization, ultrasonication/high-shear technique, solvent evaporation, solvent emulsification-diffusion, supercritical fluid, microemulsion-based, spray-drying, double emulsion, and precipitation techniques[102].

The blood-brain barrier (BBB) can be overcome using SLNs or lipid nanocarriers for drug delivery to the brain, as these formulations can penetrate the BBB or be administered intranasally to bypass it. Using cationic lipids can enhance mucoadhesion in the nasal cavity by promoting electrostatic interactions with mucus and mediating adsorptive-mediated transcytosis of cationic nanoparticles across the BBB. Coating nanoparticles with surfactants is another strategy for BBB penetration. Transport of surfactant-coated nanoparticles across the BBB may occur through endocytosis mediated by endothelial cells of brain capillaries[103].

Piperine SLNs with a polysorbate 80 coating were prepared using the emulsification-solvent diffusion technique. These nanoparticles were experimentally assessed in an ibotenic acid-induced Alzheimer's disease (AD) model in mice. The results showed an increase in acetylcholinesterase (AChE) activity and improved cognition, which were superior to the

results achieved with donepezil. Histopathology studies also revealed a reduction in plaques and tangles[104].

4.3. Liposomes

Liposomes are vesicles made up of one or more phospholipid bilayers that enclose an aqueous compartment, enabling them to carry both lipophilic and hydrophilic drugs. They can be prepared using various methods such as hydration of a thin lipid film followed by agitation, sonication, extrusion, high-pressure homogenization, or reverse-phase evaporation[105].

Liposomes are classified based on their structure into unilamellar vesicles (single lipid bilayer) and multilamellar vesicles (multiple bilayers). They are further categorized by size into small unilamellar vesicles (20–100 nm), large unilamellar vesicles (over 100 nm), giant unilamellar vesicles (up to 1 μm), oligolamellar vesicles (0.1–1 μm), and multilamellar vesicles (up to 500 nm)[106].

Additionally, liposomes can be classified as niosomes, transferosomes, ethosomes, and phytosomes. Niosomes are formed by non-ionic surfactants in an aqueous dispersion, offering more flexibility and stability than traditional liposomes. Transferosomes are deformable vesicles of phospholipids used for transdermal administration. Ethosomes are liposomes or transferosomes containing up to 10% ethanol, aiding in the solubilization of hydrophilic drugs. Phytosomes are formed by binding herbal extract components to phosphatidylcholine[103].

Several techniques are employed to enhance liposome delivery across the blood-brain barrier (BBB). These include conjugating drugs and monoclonal antibodies against BBB receptors, coating liposomes with polysorbate 80, cationic macromolecules, peptides, or antibodies. Liposomes functionalized with an anti-transferrin receptor antibody have shown increased uptake and permeability across the BBB compared to non-functionalized liposomes. Liposomes with a modified cell-penetrating TAT peptide also demonstrated increased permeability of curcumin-loaded liposomes across a BBB model[107].

Dual-functionalized liposomes have been prepared with an anti-transferrin monoclonal antibody (MAb) and a peptide analogue of apolipoprotein (PAA). Studies showed that these liposomes had a higher uptake and transport across human microvascular endothelial cells (hCMEC/D3) compared to non-functionalized liposomes. In vivo studies indicated increased brain targeting with MAb and dual-ligand liposomes. However, a contradiction between in vitro and in vivo results was noted, highlighting the role of serum proteins in targeted nano formulation performance[108,109].

Another study explored liposomes loaded with curcumin analogues. These liposomes showed high affinity for senile plaques in postmortem brain tissue of Alzheimer's disease (AD) patients and delayed Aβ1-42 peptide aggregation. Curcumin-conjugated liposomes were also developed, showing significant labelling of Aβ deposits in the brain. These liposome formulations hold potential for AD diagnosis and targeted drug delivery[105].

Ligand-functionalized nanoliposomes for galantamine delivery were designed, showing improved uptake into PC12 neuronal cells. Rivastigmine-loaded liposomes prepared by lipid hydration showed superior effects in an aluminium chloride-induced AD model compared to rivastigmine solution. Intranasal delivery of rivastigmine-loaded liposomes achieved higher plasma concentration and longer half-life compared to orally delivered free drug[103].

Folic acid niosomes were prepared using non-ionic surfactants and cholesterol, with ex vivo perfusion studies showing nasal absorption. Freeze-dried niosomes loaded with *Ginkgo biloba* extract (GbE) improved oral bioavailability and brain accumulation. However, evidence on the clinical benefits of Ginkgo biloba for dementia or cognitive impairment remains inconsistent.

In summary, liposomes offer a versatile platform for drug delivery, especially for targeting the brain and overcoming the BBB. Advanced functionalization techniques enhance their targeting efficacy and therapeutic potential for diseases like Alzheimer's[110].

4.4. Surfactant-based systems

Surfactant-based drug delivery systems utilize surfactant molecules that self-aggregate, typically in the presence of water, to form various structures. These structures' parameters depend on surfactant concentration, the presence of salts, or temperature. The addition of oils or other surfactants further organizes these aggregates, allowing for the creation of microemulsions (MEs), nano emulsions (NEs), and lyotropic liquid crystal (LC) mesophases with different geometries[111].

Microemulsions (MEs) are thermodynamically stable, isotropic liquids formed by mixing oil, water, and surfactants. In contrast, nano emulsions (NEs) are conventional emulsions with very small particles. MEs have droplet sizes between 10 and 140 nm, making them optically transparent and thermodynamically stable. NEs, with droplet sizes up to 140 nm, are less transparent and less thermodynamically stable. MEs form through self-assembly, while NEs require mechanical shearing[106].

Several parameters distinguish MEs from Nes that were MEs are more stable in long-term storage, MEs can return to their original conditions after agitation, cooling, or heating, whereas NEs cannot, MEs have homogeneous droplet sizes, while NEs have heterogeneous sizes, MEs may not have spherical droplets due to lower interfacial tension, whereas NEs consist of spherical droplets due to high Laplace pressure[112].

The formation of MEs involves spontaneous mixing of oils, water, and surfactants, sometimes requiring stirring or heating to overcome kinetic energy barriers. NEs form through external energy input from high-pressure homogenizers, microfluidizers, or sonication, converting the mixture into a colloidal dispersion or phase inversion. Spontaneous emulsification methods can also form Nes[97].

Curcumin-loaded NEs have been developed for intranasal delivery, showing improved memory and learning in treated groups compared to those given pure curcumin. MEs for transdermal delivery of huperzine A improved cognitive functions in mice compared to oral administration. An ME-based patch combining huperzine A and ligustrazine phosphate demonstrated a synergistic effect against induced amnesia in mice[94].

Intranasal administration of β-asarone-loaded MEs achieved a significantly higher brain-to-plasma concentration ratio compared to intravenous administration. Another study loaded an anticholinesterase alkaloidal extract from *Tabernaemontanadivaricata* into MEs, resulting in good stability and over 80% AChE activity after 180 days. This formulation also increased skin permeation and retention within 24 hours after transdermal delivery[102].

Tacrine-loaded MEs showed rapid absorption and nose-to-brain transmission, doubling the efficiency of an intranasally administered drug solution. These MEs transported more tacrine to the brains of scopolamine-induced amnesic mice, leading to the fastest recovery of memory loss[79].

Liquid crystals (LCs) exhibit properties between conventional liquids and solid crystals, combining the structural rigidity of solids with the mobility and fluidity of liquids. Lyotropic mesophases, characterized by alternating hydrophobic and hydrophilic regions, form micelles with ordered molecular arrangements. Increasing surfactant concentration generates lamellar, hexagonal, and cubic liquid-crystalline forms[100,103].

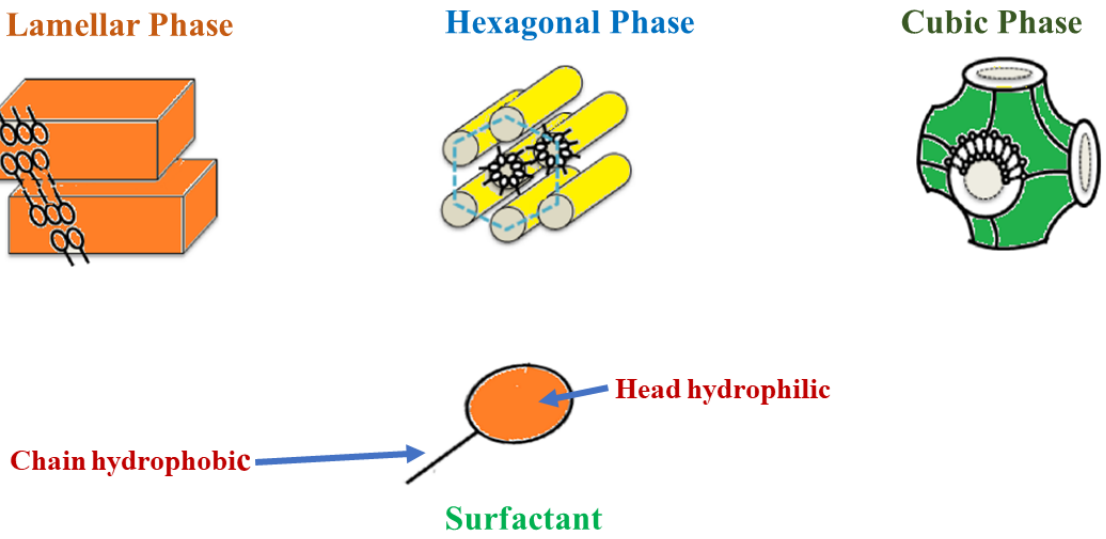

Figure 5: A schematic representation of lamellar, hexagonal, and cubic liquid crystal mesophases formed by surfactant molecules' self-assembly.

The lamellar phase consists of bilayers separated by layers of surfactants and solvents, forming a one- or two-dimensional network. In the hexagonal phase, aggregates are arranged into long cylinders, creating two- or three-dimensional structures. Lyotropic cubic phases are more complex, featuring curved, bi-continuous lipid bilayers extending in three dimensions, forming non-contacting aqueous nanochannels[84].

Self-assembled systems undergo phase transformations and notable in situ thickening upon administration, making them promising for drug delivery to body cavities. Intranasal administration of liquid crystalline (LC) phases is intriguing due to their dilution in nasal fluid, triggering a phase transition to hexagonal or cubic LCs that enhance formulation residence time on mucosa. Mucoadhesion in LC phases likely involve rheological properties akin to in situ gelling vehicles, with hexagonal and cubic phases' high viscosity suggesting potential as mucoadhesive. However, cubic phase viscosity can hinder nasal administration, prompting precursor formulations of liquid crystalline mesophases to address handling challenges. Studies indicate that micellar and lamellar phases can serve as precursors to hexagonal or cubic phases under specific stimuli[82].

LC systems notably enhance transdermal delivery of *T. divaricata* extract over 24 hours, offering an alternative percutaneous formulation to elevate acetylcholine levels in AD patients. Intranasal LC administration for AD treatment and management remains underexplored but holds promise. LCs are well-suited for nasal administration, undergoing in situ gelation upon nasal fluid dilution, thereby prolonging nasal residence time and facilitating brain-targeted drug delivery[95].

5. CHALLENGES&REMARKS

Approximately 15 million people worldwide currently suffer from Alzheimer's disease (AD), a number expected to quadruple by 2050. Nanotechnology offers promising avenues for designing drug delivery systems with unique properties. In the context of AD treatment, these nano systems can effectively transport drugs and neuroprotective molecules to the brain. The intranasal route is particularly promising for bypassing the blood-brain barrier (BBB) and directly targeting drugs to the brain. Additionally, oral, dermal, and intravenous routes can also be utilized to administer nanodevices, enhancing drug bioavailability, pharmacodynamic properties, and reducing adverse effects, thereby maximizing pharmacotherapy for AD patients.

While the number of patents for nanotechnology-based products is increasing, clinical trials are crucial to assess their clinical efficacy and potential toxicological effects on human

health. In the near future, neurologists and patients alike stand to benefit from advanced nanotechnology-based drug delivery systems, potentially leading to improved therapeutic outcomes at reduced costs. Although clinical studies on nanotechnology in AD treatment are lacking, its anticipated impact on neurology promises novel approaches for AD diagnosis and personalized therapeutic strategies.

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