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Nanotechnology-based Drug Delivery Systems for Alzheimer's Disease Management: Technical, Industrial, and Clinical Challenges

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Keywords: Nanotechnology; Alzheimer's Disease; nanocarriers; clinical trials; nanoparticles; industrial perspectives

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Nanotechnology-based Drug Delivery Systems for Alzheimer's Disease Management: Technical, Industrial, and Clinical Challenges

Abstract

Alzheimer's disease (AD) is a neurodegenerative disease with high prevalence in the rapidly growing elderly population in the developing world. The currently FDA approved drugs for the management of symptomatology of AD are marketed mainly as conventional oral medications. Due to their gastrointestinal side effects and lack of brain targeting, these drugs and dosage regiments hinder patient compliance and lead to treatment discontinuation. Nanotechnology-based drug delivery systems (NTDDS) administered by different routes can be considered as promising tools to improve patient compliance and achieve better therapeutic outcomes. Despite extensive research, literature screening revealed that clinical activities involving NTDDS application in research for AD are lagging compared to NTDDS for other diseases such as cancers. The industrial perspectives, processability, and cost/benefit ratio of using NTDDS for AD treatment are usually overlooked. Moreover, active and passive immunization against AD are by far the mostly studied alternative AD therapies because conventional oral drug therapy is not yielding satisfactorily results. NTDDS of approved drugs appear promising to transform this research from 'paper to clinic' and raise hope for AD sufferers and their caretakers. This review summarizes the recent studies conducted on NTDDS for AD treatment, with a primary focus on the industrial perspectives and processability. Additionally, it highlights the ongoing clinical trials for AD management.

Keywords:

Nanotechnology; Alzheimer's Disease; nanocarriers; clinical trials; nanoparticles; industrial perspectives

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1. Introduction

Alzheimer's disease (AD) is the most common type of dementia within the elderly population [1]. It is a progressive neurodegenerative disease which can be diagnosed in elderly patients affected with memory loss. Other symptoms include thinking disorders**,** impaired communication**,** changes in behavior**,** ill orientation**,** or difficulties in coordination and eating. Up-to-date, AD represents the leading cause of death in Europe and the sixth cause of death in the US and it affects the normal life of the patients and their families with huge economic consequences. In the US, it is estimated that annual societal and economic cost of dementia is $818 billion, and it is expected to become a trillion dollar in just three years' time [2]. This very high cost is due to the expensive treatments in addition to financial burdens for caregivers or hospital care in advanced cases.

AD diagnosis is rapidly progressing due to the increasing prevalence. AD patients manifest symptoms in three stages consisting of mild, moderate and severe dementia. Sperling and coworkers recommended in 2011 a new classification [3] where preclinical AD stage and mild cognitive impairment (MCI) stage were included before the aforementioned three dementia stages. In the MCI stage, people are diagnosed with brain changes, such as atrophy, indicating onset of AD symptoms within 15-20 years. During MCI, people suffer from mild thinking disorders that does not affect their ability to perform their daily activities (i.e. without needing help). In the later dementia stages, some patients show classical AD symptoms and then start requiring assistance.

2. Alzheimer's disease: neuropathogenesis, therapeutic targets and treatments.

AD progression is gradual and slow, and may begin 20 or more years before clinical symptoms are apparent [4, 5]. AD might run in some families and is defined as 'familial AD', which accounts for nearly 5-10% of all AD cases [6]. The primary genes implicated in familial AD are those for

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presenilins 1 and 2, alpha-2 macroglobulins, and Apo-E. On the other hand, sporadic (non-familial) AD, accounting for about 70% of AD cases, and are due to a combination of genetic, environmental, and lifestyle factors [6].

Several hypotheses were proposed to explain AD pathogenesis on a molecular level. Understanding all the key players in AD neuropathogenesis will help identify possible therapeutic targets. AD could therefore be managed using symptomatic or targeted disease-modifying treatments. Symptomatic treatment strategies improve cognition and memory; hence recover a better quality of life [7]. The proposed theories of AD pathogenesis include three different approaches based on cholinergic, amyloid, and tau hypotheses. Besides these major hypothesis, there is evidence that reactive oxygen species (ROS), nitric oxide, and inflammatory mediators might also contribute to the pathogenesis of AD [8].

2.1. Amyloid cascade hypothesis

Amyloid precursor protein (APP) is a type 1 transmembrane glycoprotein that is expressed in several cell types. The proteolysis of APP is regulated by α-, β- and γ-secretases (**Figure 1: A)**. The amyloid cascade hypothesis proposes that altered APP proteolysis drives the accumulation of amyloid proteins [$A\beta_{(1\rightarrow40)}$ and $A\beta_{(1\rightarrow42)}$]; which progressively aggregate into oligomers, fibrils and plaques. These accumulated protein aggregates are toxic, inducing neurodegeneration, cytotoxicity, and inevitably leading to dementia manifestations (**Figure 1: A)** [9, 10]. In 1984, Glenner and Wong successfully identified and purified amyloid protein in the cerebrospinal fluid of AD patients [11]. Based on this hypothesis, several anti-amyloid therapies have been proposed and studied including rosiglitazone, pioglitazone, and semagacestat [12].

2.2. Cholinergic hypothesis

It is the earliest hypothesis explaining AD pathogenesis. Discovery of reduced choline uptake and acetylcholine release of AD patients brain samples indicated substantial presynaptic cholinergic deficit, thus leading to memory impairment and cognition defectiveness [8]. Cholinergic drugs are

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usually cholinesterase inhibitors (ChEIs) that enhance the cholinergic neurotransmission by inhibiting acetylcholine esterase **(Figure 1: B)**. The FDA-approved ChEIs include donepezil, rivastigmine, and galantamine [13].

2.3. Excitotoxicity hypothesis

N-methyl-D-aspartate (NMDA) receptor is essential for controlling synaptic plasticity and memory function [14]. It is activated when glutamate and glycine bind to it, allowing Ca^{2+} and Na^{+} influx **(Figure 1: C)**. It has been reported that the hyperexcitability of NMDA receptors induces Ca^{2+} overload, triggering a cascade of events, and leading eventually to apoptosis [14]. Glutametergic drugs, such as the FDA-approved memantine, are uncompetitive NMDA receptor antagonists for the symptomatic treatment of moderate to severe AD [14] **(Figure 1: C)**.

2.4. Tau hypothesis

A normal mature neuron has three microtubule-associated protein (MAP) taus; MAP1A, MAP1B, and MAP2. They are responsible for promoting the assembly and stability of microtubules [15]. The biological activity of tau is regulated by its degree of phosphorylation [16]. In AD brains, tau is abnormally hyperphosphorylated, which impairs its binding to microtubules; leading to the accumulation of neurofibrillary tangles and dementia [16]. Several anti-tau therapies have been studied including lithium, valproate, and nicotinamide [12] **(Figure 1: D)**.

2.5. Mitochondrial cascade hypothesis

Substantial growing evidence suggests that a defective energy metabolism in the mitochondria might contribute to the pathogenesis of AD [17]. Genetic mutations altering the regulation of the electron transport chain complex enzymes are capable of generating ROS; leading to cell apoptosis and neurodegeneration [17]. Several drugs targeting the mitochondrial dysfunction have been investigated such as latrepirdine [18].

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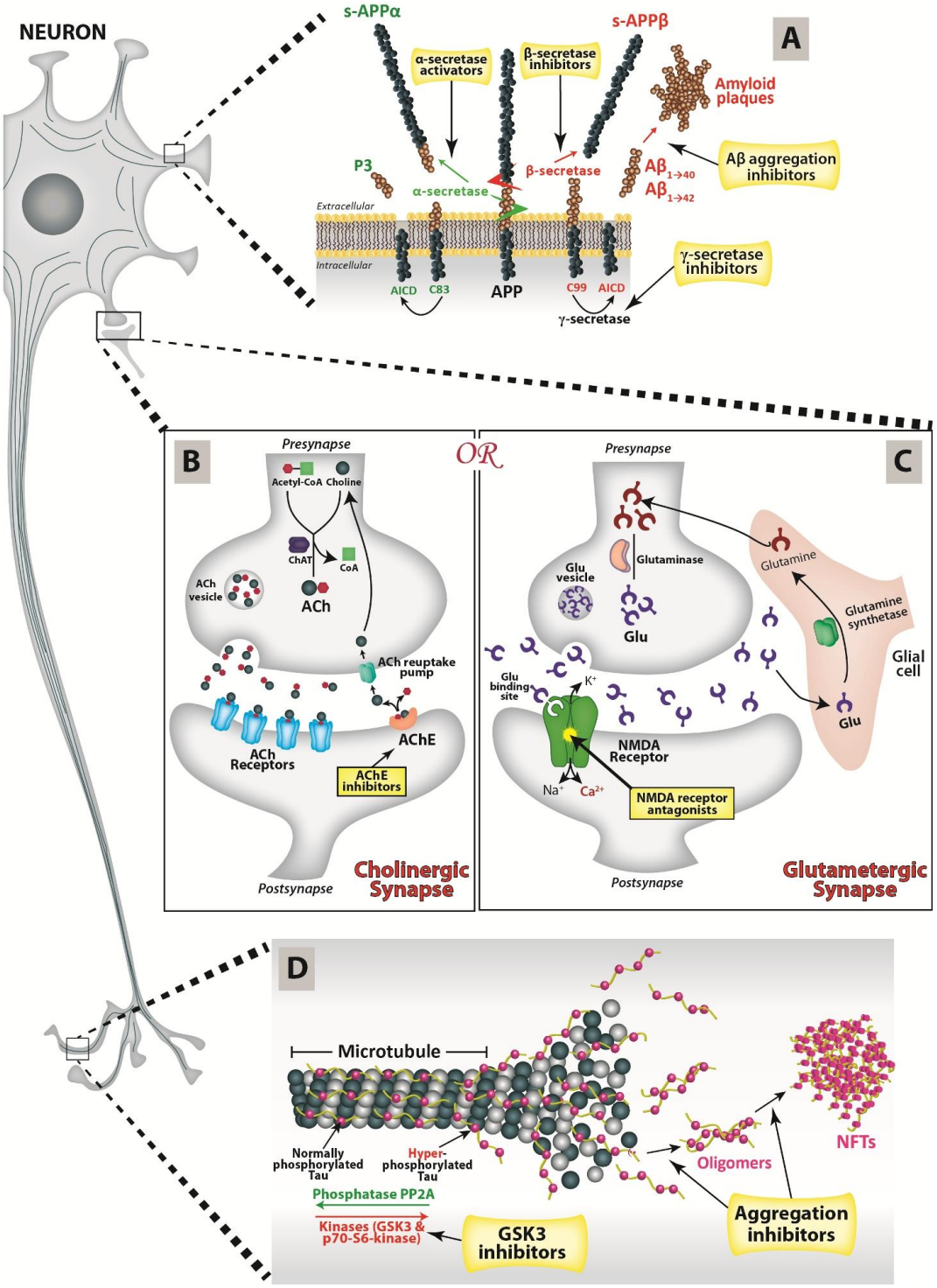

Figure 1: Summary of the main pathogenesis hypotheses for Alzheimer's disease, and treatment strategies targeting them. (A) Amyloid cascade hypothesis, (B) Cholinergic hypothesis, (C) Excitotoxicity hypothesis, (D) Tau hypothesis

ACh, acetylcholine; AChE, acetylcholinesterase; AICD, Amyloid precursor protein Intracellular C-terminal Domain; APP, amyloid precursor protein; Aβ, beta-amyloid protein; ChAT, choline acetyltransferase; CoA, coenzyme A; Glu, glutamate; GSK3, Glycogen Synthase Kinase 3; NFTs, neurofibrillary tangles; NMDA, N-methyl-D-aspartate

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3. Drug delivery strategies for AD

As observed from the above data, all therapeutic targets aiming to control AD progress or symptoms should act centrally in the brain. Up till now, all the approved FDA drugs (donepezil, galantamine, memantine, and rivastigmine) are marketed as oral formulations (except for rivastigmine; which is also available as a transdermal patch). Oral formulations for centrally acting drugs necessitate using comparatively high doses so that the fraction reaching the brain, after overcoming oral barriers of absorption, hepatic metabolism, distribution and finally traversing the blood-brain barrier (BBB), has therapeutic significance. Additionally, most of these dosage forms show high incidence of side effects due to their action in the peripheral tissues such as nausea, vomiting, and diarrhea[19]. Minimizing these side effects improves the patient's quality of life. Furthermore, administered free drugs have to bind to serum albumin to have effective half-lives in the blood circulation. In contrast, nanocarriers do not rely on albumin binding for their half-lives [20]. Besides, some of these nanocarriers can be administered intranasally, completely bypassing the BBB, which maximizes their therapeutic outcomes and minimizes the side effects [21].

Recent advances in nanotechnology have provided superior opportunities in the management of CNS diseases. Loading a drug in a suitably formulated nanocarrier can increase drug concentrations in the brain cells in comparison to drug alone if this nanocarrier is able to cross the BBB and accumulate in the correct neuronal cell [22]. This increase can be attributed to specific functionalities within the nanocarrier that make them have better ability to cross the BBB than the drug on its own. Moreover, nanocarriers have been proposed for theranosis delivering both imaging and therapeutic agents simultaneously [23]. That way, nanocarriers can be modified with targeting moieties to bind preferentially putative receptors or transporters expressed at the BBB,

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thus enhancing CNS selectivity and permeability [24]. **Figure 2** summarizes the different nanocarriers that have been used to target AD brain; which will be discussed in the following sections.

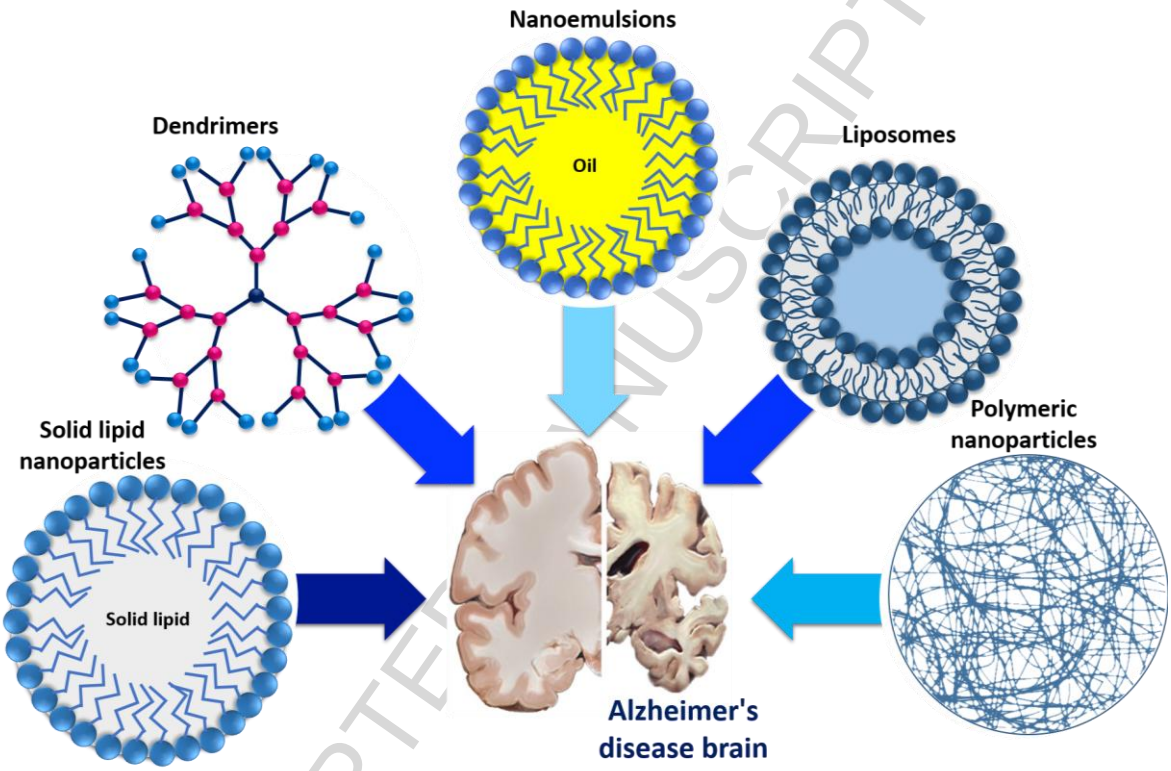

Figure 2: Different promising nanocarriers used for targeting Alzheimer's disease brain

3.1. Polymeric nanoparticles

Polymeric nanoparticles (NPs) are colloidal carriers into which drugs are loaded in either solid state or solution, adsorbed non-covalently or chemically linked to the surface [25]. These delivery systems offer good stability, biocompatibility, biodegradability, low toxicity and immunogenic response, sustained drug release and ease in production [26]. Several polymers have been used to produce NPs for CNS delivery using different preparation techniques [27] depending on polymer and drug features. Interestingly, aiming to increase their circulation lifetime and improve drug delivery across BBB, NPs surface properties can be modified by either adsorption or chemical grafting of polyethylene glycol (PEG), poloxamers or other molecules, that increase their

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circulation lifetime and improve drug delivery across the BBB. PEG reduces the immunogenicity of the NPs by limiting phagocytosis by the reticuloendothelial system thus increasing their circulation lifetime and improving drug delivery across the BBB [(28)]. Some of the recent studies conducted on delivering FDA-approved drugs for AD using polymeric NPs are summarized in **Table I**.

PEGylated poly[α,β-(N-2-hydroxyethyl)-d,l-aspartamide] (PHEA) NPs prepared by UV irradiation of polymers as an inverse microemulsion were reported to release rivastigmine in simulated extra-cellular fluid and in human plasma with a rate-controlled delivery by both the incorporation procedure and the drug form, thus suggesting an improved parenteral administration[(29)]. Fornaguera et al.[(30)] prepared galantamine loaded poly(lactic-co-glycolic acid) (PLGA) NPs with high encapsulation efficiency and sustained drug release, maintaining galantamine pharmacological activity for intravenous delivery using nanoemulsion templating from oil-in-water (O/W) nanoemulsions. The high versatility of the nano-emulsification approach was previously reported[(31)]. Nanoemulsions can be prepared by the phase inversion composition method to obtain tailored NPs with the required physicochemical properties.

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Table I: Recent studies on nanocarriers delivering FDA-approved drugs for Alzheimer's disease.

Carrier type	Drug	Carrier material	Route of administration	Ref
Polymeric nanoparticles	Donepezil	Chitosan	Intranasal	(32)
		PLGA (Polysorbate 80-coated)	Intravenous	(33)
		PLGA-b-PEG	Intravenous	(34)
	Galantamine	Chitosan	Intranasal	(35)
		PLGA	Intravenous	(30)
	Rivastigmine HCl	Chitosan	Intranasal	(36)
	Rivastigmine Tartrate	PLGA, PBCA	Intravenous	(37)
		Chitosan (Polysorbate 80-coated)	Intravenous	(38)
Solid lipid nanoparticles	Galantamine	Glycerylbehnate (Compritol)	Oral	(39)
	Lipoyl–Memantine	Stearic acid	Oral	(40)
	Rivastigmine HCl	Compritol 888 ATO	Intranasal	(41)
Liposomes	Rivastigmine HCl	Phosphatidylcholine; Dihexadecyl phosphate; cholesterol; glycerol	Subcutaneous	(42)
	Donepezil	Carboxymethyl cellulose, 1,2-distearyl-sn-glycero-3-phosphocholine, cholesterol, PEG	Intranasal	(43)
CPP-modified liposomes	Rivastigmine HCl	EPC, cholesterol, DSPE-PEG-CPP	Intranasal	(44)
Flexible liposomes	Galantamine	Soya phosphatidylcholine, cholesterol, and propylene glycol as edge activator	Intranasal	(45)

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CPP, cell-penetrating peptide; DSPE, 1,2-Distearoyl-*sn*-glycero-3-phosphoethanolamine; EPC, Egg phosphatidylcholine; PEG, polyethylene glycol; PBCA, polybutyl cyano acrylate; PLGA, poly lactide-co-glycolic acid

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Since an increase in the production and accumulation of beta-amyloid protein aggregates occurs in AD and leads to neuronal dysfunction, a study based on the reported anti-amyloid activity of curcumin [46] was conducted. Amyloid binding aptamers conjugated with PLGA-coated curcumin NPs prepared by single emulsion solvent evaporation technique were used to bind to the amyloid plaques and an *in vitro* decrease in the protein aggregate size was reported.

In another study, polysorbate 80 coated PLGA NPs loaded with donepezil [33] were prepared by solvent emulsification diffusion-evaporation technique for sustained release and efficient brain targeting through parenteral route. The high donepezil uptake and sustained concentrations in the brain due to coated NPs may help in AD treatment. However, more extensive clinical studies are needed to confirm the efficacy of the prepared delivery system.

Joshi et al. [37] prepared sustained release PLGA and PBCA (Poly (butyl cyanoacrylate)) NPs of rivastigmine tartrate by nanoprecipitation and emulsion polymerization techniques, respectively. The pharmacodynamic performances of the prepared NPs were evaluated after parenteral administration for brain targeting and memory improvement in scopolamine-induced amnesic mice, using Morris Water Maze Test. The pharmacodynamics studies demonstrated faster regain of lost memory in amnesic mice with both formulations compared to rivastigmine solution, indicating a rapid and high extent of drug transport into the mice brain. Even if both formulations could be considered as potential carriers for sustained rivastigmine brain delivery, further studies are needed to support these findings and to confirm their *in vivo* performance. Recently, Baysal et al. [34] prepared donepezil loaded PLGA-block-PEG NPs for intravenous administration by double emulsion method. This study reported that the prepared carrier could enhance the efficacy of donepezil and reduce its side effects for AD treatment. The prepared NPs have destabilizing effect on Aβ fibril formation and are able to reduce tissue distribution. Moreover, the NPs proved to cross the BBB *in vitro* using both human brain microvascular endothelial cells and human astrocytes and their neuroprotective effect was reported [34].

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Fazil et al.[36] formulated rivastigmine-loaded chitosan NPs by ionic gelation method to improve their bioavailability and enhance their brain uptake intranasally. The biodistribution and pharmacokinetic study in Wistar rats proved the superiority of direct nose to brain delivery (bypassing the BBB) of the developed NPs over intravenous rivastigmine solution.

Moreover, qualitative biodistribution studies confirmed nose-to-brain transport of the prepared NPs compared to solution attributed to the mucoadhesive nature of the chitosan NPs which decreases the mucociliary clearance of the formulation and enhances its residence time. However, clinical data is needed to evaluate the risk / benefit ratio.

A recent study formulated polysorbate-80 coated chitosan NPs loaded by rivastigmine, using spontaneous emulsification method for brain targeting [38]. The prepared NPs increased the rivastigmine concentration in mice brain by 3.82 folds compared to free drug following intravenous administration [38].

Hanafy et al.[35] prepared galantamine hydrobromide-loaded cationic chitosan NPs by ionic gelation for intranasal delivery. Complexation was investigated as an approach to enhance the galantamine hydrobromide entrapment. The prepared NPs were delivered successfully to different brain regions shortly after administration suggesting the potential of this delivery system for AD management.

The enhanced drug permeation to the brain and cerebrospinal fluid was attributed to the cationic nature of chitosan which delays the mucociliary clearance, in addition, chitosan causes a transient opening of the epithelial tight junctions. Moreover, it was hypothesized that the intranasal administration of the NPs could have led to their cellular internalization through several endocytic pathways. Hanafy et al. [21] also investigated the pharmacological and toxicological profiles of the prepared NPs in male Wistar rats when administered intranasally. The NPs showed an improved efficacy, compared to the oral galantamine solution, and no toxicological manifestations were observed. Also, in the determination of its safety profile in Sprague-Dawley rats, donepezil-

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loaded chitosan nanosuspension intended for nose-to-brain targeting proved to be safe through morphological, hematological, and histopathological analyses [32].

The relatively low cost of chitosan compared to other biodegradable polymers in addition to the ease of formulating chitosan NPs by the simple and rapid ionic gelation procedure should be considered to improve the economics of entrapment of drugs like neurotherapeutics into chitosan NPs [35]. However, safety and toxicological studies of NPs as delivery systems alone or in combination with drugs require more investigation.

Also, for CNS delivery using polymeric NPs; a rapid clearance from blood circulation occurs due to carrier's interaction with reticuloendothelial system, however, lipid NPs showed a higher ability to escape this system, thus, prolonging the residence time for brain targeting. It was also reported that, the brain uptake of lipid NPs is an interaction between plasma proteins adsorbed on NPs surface and endothelial cells of BBB, thus facilitating adhesion and activating endocytotic process[41].

3.2. Lipid Nanoparticles

Lipid NPs are colloidal dispersions which may be an alternative to many other larger colloidal carriers including liposomes, nanoemulsions and polymeric NPs [47]. Depending on the composition, lipid NPs could exhibit low toxicity, maintaining the same advantages of other carries, as controlled drug release, drug targeting, drug protection against degradation and amenability to scale up manufacturing [48].

Lipid NPs encompass two generations; the solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) [49]. SLNs are composed of a lipid core, that stays solid at both body and room temperature. On the other hand, NLCs comprise of a mixture of both solid and liquid lipids to overcome some of the limitations of SLNs, including poor drug loading ability and poor long-term stability caused by polymorphic transitions of lipids to more stable forms. The main

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drawback is that drug incorporation into SLNs and NLCs is strongly governed by drug lipophilic character, lipid type, surfactants used and production technique [48].

Studies have been conducted on using lipid NPs for AD drug delivery **(Table I)**. In a study by Bondi, et al. [50], the intravenous administration of SLNs and NLCs prepared by warm O/W microemulsion method, encapsulating ferulic acid, led to a higher protective activity against AD oxidative stress induced in neurons, suggesting the efficiency of these systems in increasing bioavailability. It was reported that, lipid nanoparticles overcome the BBB through endocytotic mechanism and accumulate in the CNS aided by their lipophilic nature. In addition, owing to their small size, lipid nanoparticles could be injected intravenously avoiding macrophage uptake of mononuclear phagocyte system.

Gobbi et al. [51] suggested the application of SLNs for imaging probes and/or drug molecules to target the characteristic beta-amyloid peptide aggregates of AD. *In vivo* studies are required to confirm these applications and also more studies related to the employment of different drug molecules are needed.

Misra et al. [39], developed galantamine hydrobromide SLNs by micro-emulsification method. This formulation demonstrated a significant capability of memory restoration in cognitive deficit rats after oral administration and offered 100% bioavailability enhancement compared to plain drug, thus, was found to be promising for safe and effective galantamine delivery. This study presented the preclinical data with desired outcomes in animal model, which is potentially promising in the clinical studies.

Also, lipoyl-memantine co-drug loaded SLNs were prepared by emulsification-evaporation-solidifying method to improve its solubility and absorption through the gastrointestinal tract. *In vitro* cytotoxicity studies against mouse N2a neuroblastoma using MTT assay as well as primary human whole blood cells using lactate dehydrogenase assay suggested that the prepared SLNs have a potential as candidate for *in vivo* investigation for brain targeting, since it proved to be safe

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from a toxicological point of view and devoid of cytotoxicity. In addition, the ability to mitigate the oxidative damage and increase the antioxidant capacity in AD would be enhanced [40].

Shah et al.[41] developed and optimized rivastigmine loaded SLNs by homogenization and ultrasonication method. The prepared SLNs showed an enhanced *ex vivo* diffusion through goat nasal mucosa compared to rivastigmine solution, attributed to the lipidic nature of the carrier. Moreover, the histopathology study of the prepared SLNs performed on goat nasal mucosa showed intact mucosa without any nasociliary damage and/or cell necrosis suggesting its safety for intranasal administration for AD treatment.

Regarding the SLNs preparation technique; the high shear homogenization and ultrasound are widely used, easy and require relatively inexpensive equipment [52, 53]. However, the dispersion quality may be compromised by the presence of larger microparticles. Also, metal contamination should be considered if ultrasound is used. Additionally, both emulsification-evaporation-solidifying method and microemulsion techniques may create toxicological problems due to organic solvent residues, since complete solvent removal is difficult from a technical point of view [48].

Despite the extensive studies on lipid NPs over the last 20 years, no commercial drug formulations are as yet available on the market. However, some companies are performing clinical trials for lipid nanoparticle formulations[25].

3.3. Liposomes:

Liposomes are spherical bilayered phospholipid vesicles enclosing an aqueous inner core. They can be prepared with different sizes ranging practically from 50 nm up to 100 µm. According to the phospholipids type and the manufacturing process, liposomes may have different surface charges and uni-, bi-, or multi-lamellar structures. Moreover, modifications in liposome

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composition result in the emergence of different modified liposomes such as transfersomes, ethosomes, phytosomes, and others [54-57].

Being phospholipids, liposomes are considered biocompatible and non-toxic [54, 58]. They encapsulate drugs within a lipid bubble and can therefore accommodate both hydrophilic and lipophilic drugs, thus protecting the drugs from enzymatic degradation and improving their therapeutic effectiveness [59]. Liposome-based systems were extensively studied as suitable carriers for improvement of AD treatment (**Table I**). Many researchers have investigated the brain bioavailability of liposome encapsulated drugs. As liposomes are highly lipophilic in nature, one would expect them to be ideal brain-targeting carrier systems[60, 61]. However, exact mechanisms of BBB penetration are not fully understood. The endocytic pathway represents an important means of transport for small liposomes with a diameter not larger than 100 nm, as their size is comparable with that of the brain endothelial cell vesicles. On the other hand, larger liposomes (>100 nm) would be unlikely to pass through leaky capillaries of the brain [62]. Also, the charge and the type of the phospholipid affects the distribution and stability of the liposome. Negatively charged liposomes were believed to be more rapidly removed from circulation than neutral or positively charged liposomes [63]. Consequently, scientists have attempted to modify the liposomal structure in order to improve liposomal penetration across biological membranes and into their target organs.

Al Asmari et al. [43] recently developed and evaluated liposomal formulation of donepezil. They compared its brain and plasma pharmacokinetics following intranasal administration in healthy male Wistar rats weighing 200±20 gm. Liposomes containing PEG were prepared by the simple lipid film hydration method and showed high entrapment efficiency and sustained-release behavior. Intranasal administration of these liposomes was found to significantly increase the brain bioavailability of donepezil as compared with the conventional dosage form. In addition, safety of the formulation was demonstrated by absence of histopathological changes in various

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tissues after intranasal administration of the liposomal formulation. They concluded that the nasal administration of their liposomal preparation may provide an efficient and reliable approach of drug delivery to the central nervous system. Rivastigmine loaded liposomes and cell penetrating peptide (CPP) modified liposomes were prepared by Yang et al. for intranasal application [44]. Their results revealed that the concentration of rivastigmine across the BBB was increased significantly when CPP liposomes and liposomes were used compared to the free drug. The average rivastigmine concentration was significantly higher for the modified liposomes in the hippocampus and cortex which are the most affected regions by AD[44]. Other rivastigmine loaded liposomal formulations were developed for treatment of AD [42, 64]. Their results showed significant increase in the exposure and concentration of the drug in the brain of rat models with AD [11]. Up to our knowledge, these studies lack the clinical investigation on humans. However, there is a study of free rivastigmine on patients with AD [64].

The intranasal administration of galantamine loaded flexible liposomes (transferosomes) was suggested as a successful approach to improve drug brain targeting [45]. Flexible liposomes were prepared with lipid film hydration method using propylene glycol as an edge activator. High entrapment efficiency of the drug (83.6 ± 1.8%) was observed. This was explained by the high lamellarity of the vesicle to the core and the increased hydrophilicity of lipid bilayer. The authors revealed that the efficiency of acetylcholinesterase inhibition by galantamine was greatly enhanced by intranasal administration of their flexible liposomes. In addition, the cytotoxicity of galantamine to cells was noticeably diminished by the flexible liposome delivery [45].

Many techniques have been used to target liposomes across the BBB. Among them, the conjugation of drugs and monoclonal antibodies (mAbs) against endogenous receptors [65, 66] or coating the liposomes with cationic macromolecules, peptides, or antibodies against BBB receptors or Aβ peptides [65-68]. Also, coating liposomes, and SLNs, with polysorbate 80 has been previously studied [69]. The addition of a targeting ligand can increase the rate of liposomal

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penetration across the BBB by targeting certain receptors on it. Moreover, targeting certain receptors that are overexpressed in AD can increase the liposomal uptake and accumulation in the required tissues [65-68]. The following paragraphs summarize examples of the recent most promising studies of targeted liposomes.

Mourtas et al.[70] designed and formulated curcumin-conjugated nanoliposomes using two methods; the conventional synthetic method and the click chemistry technique. The former involved the conjugation of curcumin with functionalized phospholipid, then the use of this lipid conjugate for nanoliposome formation. The second technique allowed conjugation of an appropriate curcumin derivative designed in order to preserve the planarity of the compound. Surface plasmon resonance experiments indicated that the nanoliposomes exposing the curcumin derivative had extremely high affinity for $A\beta_{(1-42)}$ fibrils, likely because of the occurrence of multivalent interactions, whereas those exposing non-planar curcumin did not bind to $A\beta_{(1-42)}$. The curcumin-conjugated nanoliposomes showed significant amounts of labeled Aβ deposits in postmortem brain tissue of AD patients. *In vivo* injection into the hippocampus and the neocortex of transgenic mice, overexpressing AD-related human mutations (APP/PS1mice) and developing numerous Aβ deposits, showed that curcumin-conjugated nanoliposomes were able to specifically stain the Aβ deposits[70]. Since extracellular deposits of Aβ peptide is one of the main histopathological features of AD, these curcumin-conjugated nanoliposomes can be considered the first step in formulating a system with application in AD diagnosis or treatment.

Another study investigated the use of mAbs (anti-transferin Ab) as transport mediator in liposomes loaded with a curcumin analog [71]. The authors showed that both curcumin analog- and curcumin-loaded liposomes demonstrated high affinities for senile plaques on postmortem brain tissue of AD patients. Both liposomes revealed an ability to delay $A\beta_{(1-42)}$ peptide aggregation *in vitro*. Nevertheless, the mAbs- decorated curcumin-derivative liposomes significantly improved the intake by the BBB *in vitro* cellular model [71]. However, there is still a need for more detailed *in vivo* investigations.

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Other studies investigated the effect of liposome functionalization with anti-transferrin receptor antibody [72, 73], cell-penetrating TAT peptide [72], and apolipoprotein peptide analog [73]. They were investigated for BBB-targeting, uptake and permeability studies. This was performed *in vitro* with a BBB model made of human brain capillary endothelial cells hCMEC/D3 [72, 73] and *in vivo* using APP/PS1 mice [74]. Authors revealed that these functionalized liposomes showed higher permeability across the barrier model in comparison to non-decorated liposomes [72-74]. *In vivo* peripheral administration of apolipoprotein peptide analog decorated liposomes significantly increased the plasma Aβ level, suggesting the ability of these liposomes to withdraw amyloid peptides from the brain as a strategy for AD treatment [74]. As noted, most of studies formulated the liposomes by the lipid film hydration technique. However, on small scale production, the lipid film hydration method suffers the major limitation of requiring the use of organic solvents. Traces of these solvents might remain in the final preparations, resulting in cytotoxicity and stability issues [42]. Different procedures have been utilized to reduce the amount of residual solvents in liposomes including gel filtration, dialysis, and vacuum evaporation. However, on a large scale, these techniques would be time-consuming and difficult to apply.

Other techniques were described in the literature for liposomes preparation as microfluidization and heating methods [75]. Both methods show high entrapment efficiencies, although micro-fluidization produces smaller liposomes [75]. Ismail et al. [42] utilized the heating method for liposomes preparation. According to their study, this method could be considered as a safe and scalable method useful for industrial production. Glycerol used in the heating method as an isotonizing agent is a biocompatible and relatively nontoxic solvent. Moreover, it prevented vesicles coagulation or sedimentation, thereby improving liposomes stability. However, it might be considered a tedious multistep procedure as each lipid was hydrated separately.

3.4. Nanoemulsions

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Nanoemulsions or oil-in-water (O/W) nanoemulsions are heterogeneous systems stabilized by surfactant(s) and composed by oil droplets, dispersed in water or in aqueous medium. Oil droplet size of nanoemulsions ranges from 10 to 100 nm, making them interesting systems to improve drug delivery. Furthermore, lipophilic molecules can be solubilized and protected within the oil droplets and laboratorial production methods can be easily transferred to an industrial level. However some such systems suffer some limitations, as instability during storage resulting in phase separation and a consequent and immediate release effect [25, 76, 77]

Despite the above mentioned advantages of nanoemulsions and their application to improve drug delivery [78], only recently few studies reported the use of nanoemulsion system for brain delivery. Sood et al. [79] studied the use of nanoemulsion system to deliver curcumin for AD treatment. The nanoemulsions were prepared using spontaneous nanoemulsification method. The developed formulations were non-toxic and safe as demonstrated by *in vitro* cytotoxicity and nasal ciliotoxicity studies. Mucoadhesive nanoemulsions showed highest flux across sheep nasal mucosa compared to nanoemulsion and drug solution and thus have potential for intranasal delivery of poorly soluble curcumin.

In regard to curcumin, Nasr [80] reported the use of the hyaluronic acid-based lipidic nanoemulsion which proved to be a promising carrier for transnasal brain delivery of the two polyphenols curcumin and resveratrol. Preparation of nanoemulsions was carried out using the spontaneous emulsification method. Albino rats received the selected formula in the left nostril for 7 consecutive days using a micropipette, to assess toxicity related to multiple administrations, with the right nostril considered as the control. The results showed that the integrity of the lining epithelium of the nasal cavity was maintained upon repeated administration. In addition, considerable amount of both drugs reaching the therapeutic level were detected in the brain of the rat.

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In addition, Jaiswal and coworkers [81] showed the use of nanoemulsion to intranasally deliver a *Centella asiatica* plant extract. It is worth mentioning that these studies included biological evaluation depending only on *ex vivo* permeation, *in vitro* antioxidant value, or quantification of drug in the brain, and did not evaluate the pharmacological efficacy of this delivery system for potentially treating AD. Therefore, further studies reporting on this delivery system are needed.

3.5. Microemulsions

Microemulsions are defined as 'a system of water, oil and amphiphile which is an optically isotropic and thermodynamically stable liquid solution.' In practice, the key difference between emulsions and microemulsions is that the former, whilst they may exhibit excellent kinetic stability, is fundamentally thermodynamically unstable and will eventually undergo phase separation [82]. Another important difference concerns their appearance; emulsions are cloudy while microemulsions are clear or translucent. In addition, there are distinct differences in their methods of preparation whereby emulsions require a large input of energy, while microemulsions do not require as much energy, but larger amounts of emulsifiers. The latter point has obvious implications when considering the relative safety and cost of commercial production of the two types of system[83].

Another study by Shah and coworkers [84] demonstrated the preparation of rivastigmine as microemulsion using titration method. The formed emulsion was designed to be administered intranasally nasal ciliotoxicity and was found to be stable for three months. However, further *in vivo* and biodistribution studies were not performed to demonstrate the potential of the developed system to confirm pharmacokinetics and transport pathway for rivastigmine to the brain when intranasally administered.

In a Shi et al. [85] study, a bioadhesive microemulsion-based patch was developed simultaneous transdermal delivery of huperzine A and ligustrazine phosphate (LP) . *In vitro* permeation and release results of huperzine A and LP suggested that the skin was the rate limiting step for both

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drugs when applying the microemulsion-based patches. Furthermore, the pharmacodynamic studies in male Sprague–Dawley rats indicated that the transdermal combination therapy of huperzine A and LP showed great improvements in the cerebral cholinergic function and oxidative systems that further slowdown the progression of AD, which significantly surpassed those of the rats treated with either one alone. The effects were also confirmed in scopolamine-induced amnesia rats after transdermal administration at multiple doses for 9 consecutive days with efficacy showing dose-dependence.

3.6. Dendrimers

Dendrimers, originally referred to as cascade molecules and arborols, have now been known for two decades [(86)]. The term dendrimer (greek: dendron. tree, meros. part) graphically describes the architecture of this new class of molecules. Although the earlier name 'cascade molecule' is more suitable to design their own nomenclature [(87)], the expression 'dendrimers' has been established in the meantime. Generally, these molecules emanate from a core and like a tree they more and more ramify with each subsequent branching unit. There are two fundamentally different construction concepts:

1) The divergent method [(88)] in which one branching unit after another is successively attached to the core molecule, hence the multiplication of the number of peripheral groups is dependent on the branching multiplicity (usually 2 or 3). This way the dendrimer can be built up step by step until steric effects prevent further reactions of the end groups.

2) The convergent method, which takes the opposite course. The skeleton is constructed stepwise starting from the end groups towards the inside and is finally treated with a core molecule to yield the dendrimer [(88)].

According to the amyloid cascade hypothesis, amyloid peptide aggregation is related to the onset and development of AD. Amyloid formation is a complex phenomenon involving many different

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intermediate aggregated species. Fibrils, the end product of this process and the structural basis of amyloid plaques, would be nontoxic. One way of action against the damaging effects of amyloid peptides on neuronal functioning consists in finding molecules which are able either to block the formation of the toxic oligomers, to disrupt their structure, or to lock the amyloid into what may be a noncytotoxic form of the aggregate.

It has been shown that the globular branched polymers known as dendrimers have a great potential as anti-amiloydogenic agents. In this regard, Oxana Klementieva and colleagues in their studies [(89)], showed that fourth carbohydrate (PPIG4- Mal) and fifth (PPI-G5-Mal) generated glycodendrimers display the capacity of interfering with Alzheimer's amyloid peptide $A\beta_{(1-40)}$ fibrilization. The interaction is dependent on the terminal carbohydrate groups: PPI-G5-Mal blocks amyloid fibril formation generating granular nonfibrillar amorphous aggregates, whereas PPI-G4-Mal generates clumped fibrils at low dendrimer-peptide ratios and amorphous aggregates at high ratios.

Both PPI-G4-Mal and PPI-G5-Mal are nontoxic to PC12 and SH-SY5Y cells. PPI-G4-Mal reduces amyloid toxicity by clumping fibrils together, whereas the amorphous aggregates are toxic to PC12 cells. This study showed that glycodendrimers could be promising nontoxic agents as anti-amyloidogenic compounds. Fibril clumping may become an anti-amyloid toxicity strategy.

Klajnert et al. [(90)] investigated the effect of a GATG (gallic acid-triethylene glycol) dendrimer decorated with 27 terminal morpholine groups ([G3]-Mor) on the aggregation process of Alzheimer's peptide. Prefibrillar species were more toxic than mature fibrils. [G3]-Mor significantly reduced the toxicity of Aβ, which was attributed to lowering the amount of prefibrillar forms in the system by speeding up the process of fibril formation.

Wasiak et al.[(90)] demonstrated that phosphorus-containing dendrimers (CPDs) are able to affect β-amyloid and MAP-Tau aggregation processes. The authors used a neuro-2a cell line (N2a) to test cytotoxicity of formed fibrils and intermediate products during the $A\beta_{(1-28)}$ aggregation. They

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showed that CPDs might have a beneficial effect by reducing their toxicity. The results presented suggest that phosphorus dendrimers may be used in the future as agents regulating the fibrilization processes in AD.

4. Clinical need and challenge in drug delivery for Alzheimer's disease

Current treatment of AD is mainly based on these FDA approved medicines, including galantamine, donepezil, rivastigmine and memantine with etanercept, a tumor necrosis factor blocker, is prescribed as off label use for AD. Tacrine was discontinued in the US since 2013 due to its clinically apparent hepatotoxicity [(91)]. These drugs are delivered predominantly through oral route. Dosage forms prepared for drug delivery include tablet, capsule, solution and oral disintegrating tablet. Rivastigmine is also available as transdermal patch for extended release, and etanercept is given as subcutaneous injections. Current ongoing clinical trial on the new drug E2609 (Eisai Inc.) is in phase 2 study which is also to be administered orally [(92)].

Efficient transport of these and other medicines through the BBB still presents a bottle-neck in pharmaceutical research. With very limited delivery systems available on the market, one can realize the urgent clinical need and challenge in this area to improve drug delivery. **Table II** summarizes the most relevant advantages and disadvantages of the nanocarriers employed for the management of AD.

Intranasal delivery of drugs targeting the brain, exploiting the olfactory pathway, has been a trending research topic for quite some time now. The results of many recently published studies were mostly positive towards intranasal compared to intravenous administration for chronic drug delivery because of the BBB bypassing advantage for effective brain targeting and the noninvasiveness of intranasal administration; which improves the patient compliance[(93)]. Interestingly, in preclinical studies the development of new nanocarriers for AD drugs through intranasal route depends mainly on animal models. Comparing the anatomy of the nasal cavity of these commonly used lab animal and human revealed that the rabbit's nasal cavity was quite

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similar to that of the human; especially with regard to the hair follicles in nasal mucosa. However, the ciliated respiratory epithelium usually seen in rats immediately posterior to the upper incisor teeth is not located at the same area in the rabbit, but rather in deeper parts of the nasal cavity. It is worth noting that the olfactory epithelium occupies a significant area of the nasal cavity in rabbits in comparison with humans [(94)]. However, the results obtained from conducting such studies on animal models may predict and reflect the nose-to-brain transport in humans to some extent.

Another consideration in the clinical challenge of AD treatment is associated with severe side-effects of the drug therapy, especially given that most of these therapies require long-term use and involve the elderly population. Common side effects experienced by patients using this group of medicines are diarrhea, nausea, vomiting and headache leading to loss of appetite, weight loss and fatigue [(95)] which is mainly attributed to their oral route of administration. Therefore, other drug delivery strategies such as extended release, orally disintegrating, sublingual, intranasal, intramuscular, transdermal forms and NTDDS are being researched in the hope to improve the patient compliance and assist caretaker in the process of patient caring.

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Table II: The most relevant advantages and disadvantages of nanocarriers employed for the management of Alzheimer's disease

Nanocarrier	Advantages	Disadvantages
Polymeric nanoparticles	• Good stability, biocompatibility, biodegradability, with low toxicity and immunogenic response [96] • Sustained drug release • Chitosan NPs can be easily produced by ionic gelation method with a considerably low cost [35]. • NPs made of hydrophilic polymers offer prolonged circulation in blood, facilitating passive targeting[97].	• Polymers may have possible toxicity and slow degradability. • Difficult modification and handling [96] • In the absence of surface modification, polymeric NPs have limited capability to cross the BBB [98].
Lipid nanoparticles	• Good loading of lipophilic drugs [96] (NLCs are advantageous in drug loading and long term stability compared to SLNs [48]) • Low biotoxicity, drug protection against degradation, controlled drug release [48] • Easy and low cost scaling up by high shear homogenization and ultrasound [48], avoiding the use of organic solvents [99]. • Easy surface modification and sterilization [49, 96]. • Their lipophilic nature facilitates overcoming the BBB via endocytosis [99].	• Poor loading of hydrophilic drugs [96]. • Drug incorporation is highly affected by drug lipophilic property, lipid type, surfactant used and production method [48]. • Poor *in vivo* stability [96] • Metal contamination may occur upon using ultrasound in production [48]. • Production by emulsification-evaporation solidifying and microemulsion methods may cause toxicological problems due to the organic solvent residual [48].
Liposomes	• Good loading of both hydrophilic and lipophilic drugs. • Biocompatible and non-toxic due to their phospholipid nature. • Protect incorporated drugs from enzymatic degradation and improve therapeutic effectiveness [59]. • Simply prepared by film hydration method or by microfluidization and heating methods yielding high entrapment efficiency [75]. • Heating method is one of the safest and most scalable techniques for the industrial production of liposomes [100].	• Poor *in vivo* stability [96] • Production by film hydration method may result in organic solvents residual in the final product; which can be cytotoxic and may affect its stability. Residual solvents can be removed by time consuming gel filtration, dialysis and vacuum evaporation [75]. • Production by heating method is a tedious, multistep procedure since each lipid is separately hydrated [100].

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Nanoemulsions	• Good solubilization and protection of lipophilic drugs in the oil droplets • Easy large scale production [76, 101]	• Poor stability upon storage, resulting in phase separation and immediate release effect [76, 101]
Dendrimers	• High drug loading capacity in both the internal cavity and dendrimer surface, offering capability of use in both imaging and theranosis [96]. • Their size, molecular weight and chemical composition can be easily controlled by the proper selection of monomers and polymerization degree. [102]	• Polymers used may have possible toxicity issues [96].

BBB, blood-brain barrier; NLCs, nanostructured lipid carriers; NPs, nanoparticles; SLNs, solid lipid nanoparticles

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5. Clinical trials and Alzheimer's Disease

Many studies showed that nanotechnology enables drug delivery into the brain with high efficiency and accuracy [103]. From clinical neuroscience point of view, many questions need to be answered before clinical trials of these NTDDS. For example, can nanomedicine be internalized efficiently by olfactory sensory neurons in the epithelium cells to further entry into the brain? Or can they be safe for long-term use? Most literature related to NTDDS is based on non-primate animal models. It still remains a long road to reach the clinical trial stage to address potential efficacy and toxicity issues.

Several systemic reviews in Cochrane support the evidence that significant improvement in cognitive function and overall clinical outcomes occurs in patients with mild to moderate AD treated with ChEIs such as donepezil, rivastigmine, and galantamine [104-106]. While results from large randomized clinical trials showed the evidence of therapeutic efficacy of memantine in cognition, function, and overall clinical outcome in patients with moderate to severe AD, but not for treatment of mild to moderate stages of the condition [107, 108]. Although the clinical value of the extended release formulation in AD was conclusive, only limited studies are available [109]. These clinical trials were all based on the conventional oral delivery route, leaving room for future NTDDS to improve their extended release.

Natural medicines are also worth exploring in the application of nanotechnology such as Huperzine A. Most of the research publications found so far are mainly in the Chinese literatures which have included only small numbers of patients and for short treatment periods. More evidence of long-term safety and effectiveness are needed before it can be recommended as mainstream therapy. One Cochrane review of Huperzine A in 6 randomized controlled trials showed little evidence of the beneficial effects of oral administration on improvement of cognitive function, global clinical status, behavioral disturbance and functional performance, but they had no obvious serious adverse events [110].

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Unfortunately, up till now, no relevant clinical trials are ongoing on the employment of nanocarriers in AD management. Thus, the point to be focused on is the translatability of this approach from bench to bedside. Giving the NTDDS the chance to come into clinical use is quite related to their industrial impact and costs; which might be inevitably high. However, the advantages of such NTDDS should not be overlooked; especially when they are properly engineered to cross the BBB, characterized by a decreased invasiveness, and are able to be used for diagnosis as well as treatment. They are not only multifunctional systems, but there is also a huge possibility that they improve the efficacy of these drugs as proposed by some studies [(21)]. Therefore, simplifying the preparation methods and searching for low-cost approaches for the scaling up of such nanocarriers could be the real challenge needed to overcome to convey these nanocarriers from paper to clinic.

6. The future of nanotechnology-based drug delivery to brain

Biological drugs such as proteins, peptides, monoclonal antibodies, growth factors and nucleic acids are presently a subject undergoing intense studies and have shown unique abilities in restoring damaged cells and slowing the progression of AD [(111)]. However, no biologics have been successfully introduced into the clinical market so far. Their route of administration, along with *in vivo* instability, poor penetration across the BBB and high cost of manufacturing are hurdles that have hindered immediate studies on their beneficial effects [(112)].

In the meantime, AD research has been exploring other therapeutic avenues including generating an immune response against amyloid. Generating an immune response against "self" proteins have been criticized. Dr. Pardridge predicted in 2009 that "current trials of passive immunity against β-amyloid peptide will likely fail, whereas past trials of active immunization exhibited trial-ending side effects, in part because of disruption of the integrity of the blood-brain barrier"[(113)]. There are many AD vaccines, passive and active type, clinical trials currently undergoing and some have completed phase 2 after his remarks. The results of these clinical

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trials, mostly active vaccines targeting Aβ or tau proteins, have yet to be announced. **Table III** provides a summary of these recent clinical trials on passive and active immunization against AD[114]. This table reflects the wide gap existing between the advances achieved in the clinical trials on immunotherapy in AD compared to the lack of such trials on the extensively researched nanocarriers employed for brain targeting in AD.

It is worth mentioning that active and passive vaccines are used to prevent Aβ plaques from building up before the functional damage of the brain. Recently, 'nanovaccines' employing NPs as vehicles protecting antigens from degradation and improving their efficacy have been gaining attention [115]. Therefore, vaccinology for AD aided by nanotechnology is thought to have a great potential to become a future leading streamline of development.

On the other hand, nanotoxicity studies are far less researched compared to the efficacy studies. Potential danger of nanoparticle treatment may hinder the speed of alternative drug delivery development. Recent nanotoxicity studies have primarily depended on non-primate animals and a limited number of healthy adult humans. However, in diseased and aged populations such as AD patients, NPs may aggravate disease conditions by inducing further oxidative stress and inflammation [116].

In conclusion, conventional drug therapy focus on improving the symptoms is falling short of the expectations of many clinicians. More specific and effective strategies are urgently needed to halt or slow the development of the disease. Overall, clinical activities involved in nanomedicine for AD are still low compared to other diseases such as cancers. To transform the research from 'paper to clinic' and from 'bench to bedside', NTDDS appears promising to address this challenge and raise hope for AD sufferers and their caretakers. Moreover, connecting multifunctional properties such as bioactivity, targeting, imaging and gene delivery into these systems and minimize off-target side effects can further enhance the treatment outcomes [117].

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Table III: Recent Clinical Trials on Passive and Active immunization against Alzheimer's disease (ClinicalTrials.gov) [114]

Status	Title of Study	Nature of the study	Sponsor	Clinical Trial Phase	Target protein	Year of Completion
(1) Passive Immunization						
ongoing	Progress of Mild Alzheimer's Disease in Participants on Solanezumab Versus Placebo	efficacy	Eli Lilly and Company	phase 3	-	estimate in 2016
ongoing	Safety Study of Passive Immunization for Patients With Mild to Moderate Alzheimer's Disease	safety	Pharmacology Research Institute	phase 2	-	estimated in 2008, but not yet complete
completed	Amyloid Imaging And Safety Study Of Subcutaneous Bapineuzumab In Subjects With Mild to Moderate Alzheimer's Disease	safety and efficacy	JANSSEN Alzheimer Immunotherapy Research & Development, LLC	phase 2	-	2013
completed	A Multiple-dose Study of Gantenerumab in Japanese Alzheimer's Disease Patients	safety and efficacy	Chugai Pharmaceutical	phase 1	-	2014
completed	Multiple IV Dose Study of PF-04360365 In Patients With Mild To Moderate Alzheimer's Disease	safety	Pfizer	phase 2	-	2011
completed	A Randomized, Double-blind, Placebo-controlled Study to Assess Safety, Tolerability, Pharmacokinetics, Immunogenicity, and Pharmacodynamic Response of Repeated Intravenous Infusions of BAN2401 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease and Mild Alzheimer's Disease	safety and efficacy	Eisai Co., Ltd.	phase 1	-	2015
(2) Active Immunization						
completed	Study to Evaluate Safety, Tolerability and Immunogenicity of Vaccine (UB 311) in Subjects With Alzheimer's Disease	safety and efficacy	United Biomedical	Phase 1	Aβ	2011
ongoing	18-months Safety Follow-up Study of AADvac1, an Active Tau Vaccine for Alzheimer's Disease	safety	Axon Neuroscience SE	Phase 1	Tau	estimate in 2017
completed	Observational Study to Monitor Long-term Immunogenicity and Efficacy of UB 311 Vaccine in Subjects With Alzheimer's Disease	efficacy	United Biomedical	Phase 1	Aβ	2011
completed	Safety Study of AADvac1, a Tau Peptide-KLH-Conjugate	safety	Axon Neuroscience	Phase 1	Tau	2015

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	Active Vaccine to Treat Alzheimer's Disease		SE			
terminated by the sponsor	Follow-up Study to Assess Safety and Clinical Activity of Continued AFFITOPE® AD02 Vaccinations of Patients Who Participated in AFF006	safety & efficacy	Axon Neuroscience SE	Phase 2		2015
completed	Study Evaluating Single Ascending Doses of AAB-001 Vaccine SAD Japanese Patients With Alzheimer's Disease	safety	Pfizer	Phase 1	Aβ	2010
recruiting	Evaluate the Safety, Tolerability, Immunogenicity and Efficacy of United Neuroscience LtdUB-311 in Mild Alzheimer's Disease (AD) Patients	safety & efficacy	United Neuroscience Ltd.	Phase 2	Aβ	estimate in 2017
completed	Amyloid Imaging And Safety Study Of ACC-001 In Subjects With Mild to Moderate Alzheimer's Disease (ACCTION)	safety	JANSSEN Alzheimer Immunotherapy Research & Development, LLC	phase 2	Aβ	2014
completed	A) Safety/Tolerability, Immunological and Clinical Activity of a Boost Immunization With AFFITOPE AD02	safety & efficacy	Affiris AG	Phase 1	Aβ	2010
terminated	B) Observational Follow-up Extension Study of AFF002 and AFF004A in Patients With Alzheimer's Disease	safety	Affiris AG	Phase 1	Aβ	2013
completed	A)Tolerability and Safety of Subcutaneous Administration of AFFITOPE AD02 in Mild to Moderate Alzheimer's Disease	safety and efficacy	Affiris AG	Phase 1	Aβ	2009
completed	B)Tolerability and Safety of Subcutaneous Administration of Affitope AD01 in Mild to Moderate Alzheimer's Disease	safety and efficacy	Affiris AG	Phase 1	Aβ	2009
not yet open for recruitment	24 Months Safety and Efficacy Study of AADvac1 in Patients With Mild Alzheimer's Disease (ADAMANT)	safety and efficacy	Axon Neuroscience SE	phase 2	tau	estimate in 2018
recruiting	A Study to Evaluate the Safety and Tolerability of a New Drug Named Lu AF20513 in Patients With Mild Alzheimer's Disease	safety	H. Lundbeck A/S	phase 1	Aβ	estimate in 2017
completed	Study Evaluating Safety, Tolerability, And Immunogenicity Of ACC-001 In Subjects With Mild To Moderate Alzheimer's Disease	safety and efficacy	Pfizer	phase 2	Aβ	2013
completed	Safety and Tolerability of Repeated Subcutaneous Injections of CAD106 in Mild Alzheimer's Patients.	safety	Novartis	phase 2	Aβ	2010
completed	A Study of V950 in People With Alzheimer Disease	safety and	Merck Sharp &	phase 1	Aβ	2012

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		efficacy	Dohme Corp.			

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7. Conclusion

AD is one of the major health problems facing the community and health authorities with consequences affecting the life style of the patient with substantial economic cost on individuals, families and society as a whole. The problem will only get worse as the aging population continues to grow. Up till now, approved FDA medications for AD mostly address symptomatic problems and do cease or retard disease progression. The marketed delivery systems for these drugs are also far from optimal. Most are oral formulations requiring high doses with subsequent high incidence of side effects. NTDDS, such as liposomes and SLNs, have shown previous success when marketed, with promising safety and efficacy profiles. However, more safety and toxicity studies are required to confirm these results and gain support for clinical trials. In addition, due to the technology boost in the diagnosis of the AD, early diagnosis may allow for better disease control. Finally, the search is still on for medication to prevent AD which when found will most definitely benefit from the best delivery systems that can deliver it to the most protected target to reach, the brain.

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Declaration of interest

The authors declare no conflict of interest.

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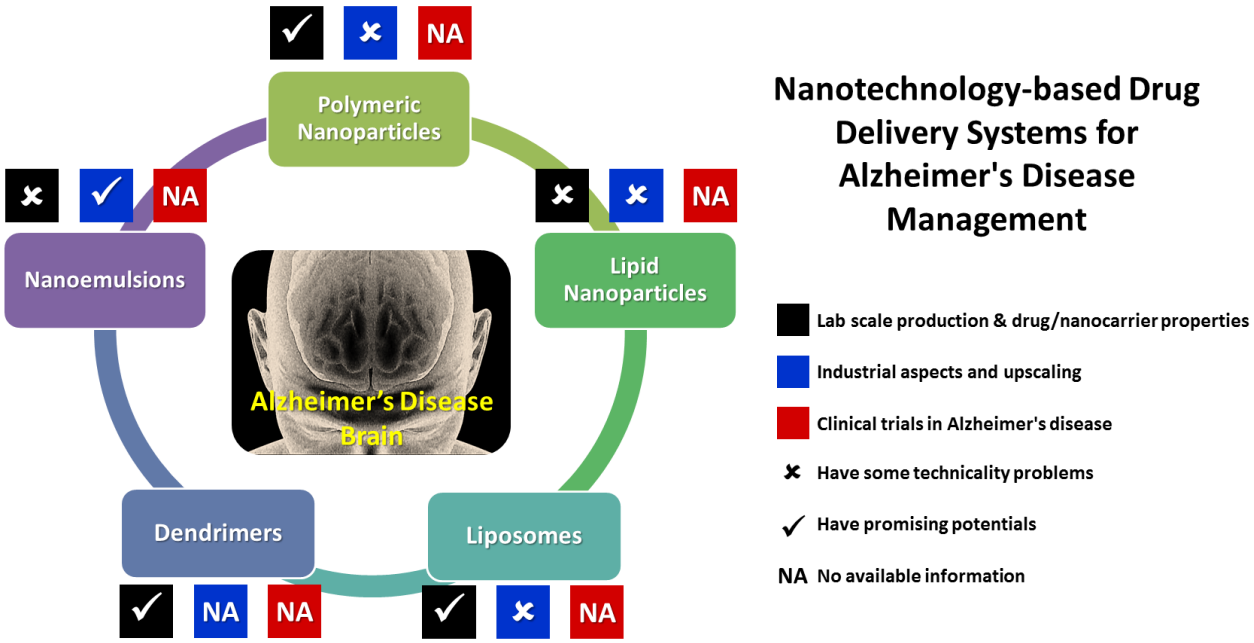

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