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Recent advancements in the field of nanotechnology for the delivery of anti-Alzheimer drug in the brain region

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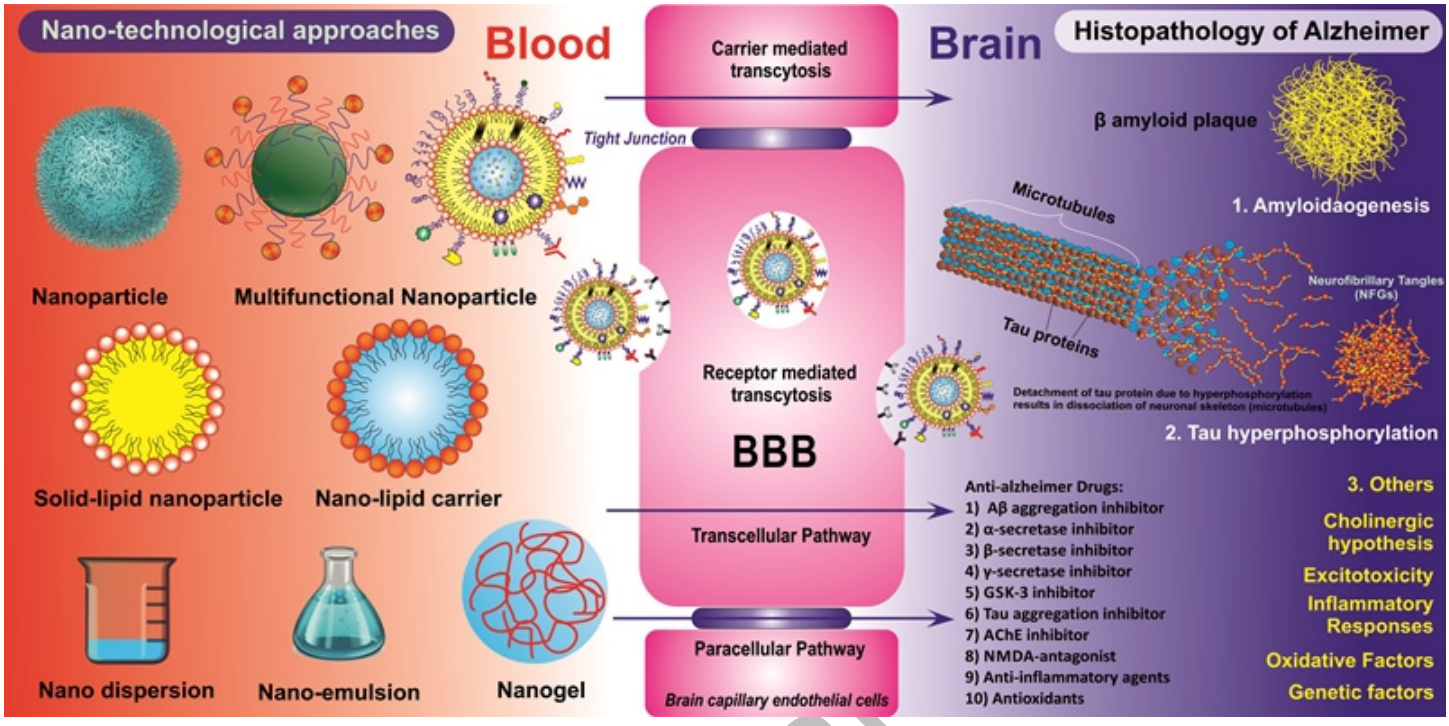
Graphical abstract



The pictorial graphical table of content represents the primary histopathology behind Alzheimer disease (AD) like 1) amyloidogenesis, 2) tau hyperphosphorylation and other pathological factors. On the other hand, it also demonstrates various nanotechnological approaches that can deliver the drug into the brain across blood-brain-barrier (BBB). Also, it shows various drug transport pathways across BBB for different types of anti-Alzheimer drugs.

Abstract

Introduction: Brain is supposed to be the most complicated part of the body which is very far from the reach of drug moieties. The drug entry in to the brain region depends upon various factors, and among those, the blood-brain-barrier remains the most prominent one. This barrier restricts the entry of almost all the drug and most of the essential biological components like proteins, peptides, etc. and hinders treatment of the CNS disorders. Alzheimer Disease (AD) is one such brain disorder, more specifically a neurodegenerative disorder which primarily affects the older adults.

Areas covered: From solubility enhancement to targeted delivery, the nanoparticulate system became the answer for almost all the criticality related to drug delivery. Hence, nanoparticulate drug carrier system has been widely utilizing to remove the hurdles of brain drug delivery. Keeping this in mind, we have underlined the proficiencies of the nanocarrier systems which claim to improve the drug efficacy for the treatment of the AD.

Expert opinion: The nanotechnological approaches are highly exploited by the researchers to enhance the drug permeation across the BBB to improve its bioavailability and efficacy by protecting the drug from peripheral degradation. However, still in this area of drug targeting provides vast scope for discoveries towards the enhancement of drug efficacy through surface modifications, site specification, reduced toxicity of the nanocarrier system and so on.

Keywords: Alzheimer, nanotechnology, BBB, lactoferrin, SLN, NLC.

Article Highlights:

- The summarised pathological factors of Alzheimer's disease.
- The article highlights the available treatments of the AD and future possibilities for effective treatment.
- Nanotechnological approach adapted towards the treatment of AD and its advancements.
- The review summarizes the research done in last ten years in the field of Alzheimer treatment.
- A comparative analysis of the work and future possibilities.

1. Introduction

Cognitive memory loss, behavioral impairment, disturb routine activity like bathing, eating, drinking, general communication, thinking and mental illness recognize Alzheimer, a progressive neurodegenerative ailment[1, 2, 3, 4] the most common cause of dementia in older adults.[5, 6, 7]. As statistics showed around 47 million people worldwide, living with dementia among which nearly about 36 million have Alzheimer [8] which is supposed to increase by 131 million till 2050[9]. Till date, no proper cure or preventive measures are available which can eliminate AD[1] from roots [2, 10]. In general, the AD has two types of treatments; one is symptomatic while another is the targeting approach [11, 12]. Symptomatic treatment is currently utilized to improve the memory and cognition by acting on the cholinergic system. Presently, FDA[2] has approved rivastigmine, galantamine, donepezil (ChEIs[3]) [13] and memantine (NMDA[4] antagonist) [14] responsible for symptomatic action to treat the AD. All these drugs are available in the market as oral preparations except rivastigmine, whose transdermal patch is available. Currently, the available therapies are not enough to act on the physiological causes of AD and such treatments are now under investigations [15].

1.1 AD pathophysiology

The AD is a multifactorial process, and as such, no specific cause for its occurrence is accepted by the scientific fraternity worldwide. [16]. Although, various most accepted theories which explain the basic etiology of AD are discussed below

(a) ***Amyloid cascade hypothesis:*** Amyloid cascade hypothesis is related to the formation of amyloid β plaque and its harmful effect. Generally, a transmembrane glycoprotein, known as APP[5] is express over the surface of brain cells/neurons. The proteolysis of this surface APP is regulated by α, β, and γ secretase enzymes. During the cleavage of APP, some small amyloid β protein fragments are formed which consist of three main components a) Aβ monomer, b) Aβ oligomer and c) Aβ fibrils [17]. Various studies evident that the prior one i.e. the soluble Aβ monomer and oligomers are predominantly responsible for neuronal degeneration instead of the insoluble fibrils [18]. Typically, in the healthy brain, such Aβ fragments get dissolved and cleared from the brain. However, in AD brain the clearance of this Aβ protein gets hindered, resulting in the formation of β amyloid plaque or aggregate **(fig. 1(a))**. This amyloid plaque is neurotoxic and neurodegenerative in nature that produces abnormalities in memory, cognition and behavioural activities which lead to AD condition. There are some drug molecules which selectively reduces the amyloid plaque formation like tarenflurbil [19], semagacestat (γ-secretase inhibitor) [20], solenezumab [21] and aducanumab (anti-Aβ antibody) [22] etc.. Moreover, pioglitazone and rosiglitazone (common anti-diabetic drugs) are selective PPAR-γ[6] agonist which reduces the insulin resistance and also act on AD related inflammatory response, thereby it lower down the amyloid plaque formation, hence, found effective in AD therapy (fails clinical trial phase III on AD patients) [24, 25].

(b) ***Cholinergic hypothesis:*** This is the most commonly accepted and earliest hypothesis to describe AD etiology. According to this hypothesis, the AD represents abnormalities in cholinergic neurons which not only results in a reduced concentration of ACh in the brain but also reduces choline uptake which causes memory and behavioural deficit in the patient. Further, to improve the cholinergic responses, many ChEIs like galantamine, rivastigmine, donepezil are preferred and approved by FDA for the treatment of AD [26].

(c) ***Tau hypothesis:*** In general, the basic structure of a neuron is made up of microtubules. However, these microtubules are sequentially assembled and stabilized with the help of a particular protein known as Tau protein or MAP[7] (MAP1A, MAP1B, and MAP2). The degree of phosphorylation regulates the regular biological activity of tau. In AD patients, the hyperphosphorylation of these tau proteins disturbs the microtubule assemblies which lead to the formation of neurofibrillary tangles (dead neuron) and cause dementia. It has been reported that nicotinamide, lithium, and valproate are the drugs which can reduce this hyperphosphorylation and maintain the neuronal health [27, 28] **(fig. 1(b))**.

(d) ***Excitotoxicity hypothesis:*** The Ca^{++} and Na^{+} channel at the synapse is regulated by NMDA receptor, which is responsible for maintaining the synaptic plasticity and memory function. Some biomolecules like glycine

[1] Alzheimer's disease
[2] Food and drug administration
[3] Cholinesterase inhibitor
[4] N-methyl-D-aspartate receptor
[5] Amyloid precursor protein
[6] Peroxisome proliferator-activated receptor-γ
[7] Microtubule associated protein

and glutamate bind to the NMDA receptor and initiate the Ca^{++}, Na^{+} influx thereof. Hyperexcitability of this NMDA receptor leads to caspase-mediated neuronal cell death due to Ca^{++} overloading at the nerve cells. In this situation, glutamatergic drugs like memantine, an FDA approved non-competitive NMDA antagonist, prescribed for symptomatic treatment of AD [14].

(e) ***Mitochondrial cascade hypothesis:*** Some evidence showed that abnormal mitochondrial energy production might also contribute to AD etiology. Such mitochondrial dysfunctioning can be a result of a genetic mutation which may cause apoptosis, memory deficit, and neurodegeneration. Latrepirdine is a drug that is used to target such mitochondrial abnormalities [29].

Figure 1: Major pathophysiology of Alzheimer disease (a) Amyloidogenesis and (b) Tau hyperphosphorylation.

Apart from these foremost assumptions, the inflammatory mediators, free radicles or reactive oxygen species, nitric oxide, genetic and environmental factors also subsidize with the AD etiology [16, 26] **(fig. 2)**.

1.2 The blood brain barrier

The AD early diagnosis and successful treatment are severely hinder owing to the existence of the BBB[8] [30]. The BBB is an essential protective layer around the brain which protects the brain from the harmful stimuli, pathogens, toxins or any other delirious substances. The BBB consists of endothelial cells, basement membrane, pericytes and astrocytes which in combination with perivascular elements such as the basal lamina, capillaries neurons, and microglia forms a functional or neurovascularunit. This helps to regulate the exchange of essential nutrients and oxygen to the brain [31]. Particular tight junctions between brain epithelial cells restrict the exchange of substances (large molecules as well as several ions) between brain and blood by physical means. In addition to this, some metabolic barriers (enzymes) also exist on the BBB [32, 33]. The primary function of the BBB is to protect the brain by keeping it isolated from harmful toxins potentially present in the bloodstream and to maintain the brain homeostasis. Hence, it restricts the entry of almost all the substance from the periphery into the brain. Though, there are some special provisions for the entry of the essential nutrients, such as amino acid, , and hexoses; proteins, peptides, ions, etc. to assist the normal brain functioning. The transport mechanism or the passage to cross the BBB involves receptor-mediated transcytosis, endocytosis, carrier-mediated transport, adsorption transcytosis, passive diffusion, transcellular lipidic pathway and paracellular aqueous transport [34, 35]. However, in case of drug molecules, only highly lipophilic drugs which are small enough (<500 Da) can cross the BBB [36, 37]. It has been indeed estimating that more than 99.9 % of macromolecules and more than 98% of small molecules cannot penetrate the BBB [38]. Although novel drug molecules for the treatment of AD are under investigation, most of them cannot transform into drug products due to the lack of suitable strategies for transport across the BBB. Many review articles are available for more information about the mechanisms of BBB translocation of molecules [39, 40].

1.3 Nanotechnological Approaches

Ideally, the approaches adopted to facilitate the permeation of AD-therapeutics across the BBB should: (i) be easily controlled; (ii) selectively transport drugs across the BBB following systemic administration; (iii) be fully biodegradable and non-toxic; (iv) not damage the barrier; (v) transport adequate drug amount to achieve therapeutic levels; and (vi) be able to target specific areas of the brain. Among the different suggested approaches to-date, nano
particles offer the best prospects for drug delivery to the brain with improved therapeutic efficacy [41, 42, 43].

Figure 2: Figure showing responsible pathophysiological mechanisms of Alzheimer disease and explored nanoparticulate approaches for the treatment of AD.

Nanotechnology is a science of the study of the ultra-small particulate system which behaves as an individual unit with respect to their properties. These are basically polymeric (natural or synthetic) or lipidic particles (mostly biodegradable in nature) with the size range between 1-100 nm. Nanoparticulate drug delivery represents a very attractive and flexible novel carrier system which targets the drug substances to the particular site of action by protecting its integrity [44, 45, 46]. Nowadays nanotechnology gains very much popularity in diagnostic and therapeutic means [47]. It is most often use as a carrier system to deliver the drug to critical sites (like the brain, tumor cells, etc.) of the body for site-specific delivery of the drug. At the same time, it also

[8] Blood brain barrier

improves the drug solubility, absorption and cellular permeation (owing to its small size) so improves the bioavailability of the drug. Along with this nanoparticle offers various other advantages over conventional drug delivery system like protects the drug from enzymatic degradation and harsh GI environment, improves the stability of the drug in the systemic circulation results in prolong half-life, controls, prolongs and sustained the drug release, and decreases the side effects of the drug. Moreover, it is biodegradable and biocompatible in nature, and so it is supposed that its metabolic products can be easily eliminated from the body [48, 49, 50, 51]. Most of the anti-AD drugs are poorly water-soluble, or membrane impermeable, or exhibit extensive first-pass effect which leads to poor brain delivery. Additionally, the existence of BBB is the major hurdle to treat the CNS disorders hence the researchers focused on nanotechnology based drug delivery system to facilitate the AD therapy. Bases on the composition and method of preparation there are different types of nanoparticles with varying nature like polymeric nanoparticle, nanogels, liposomes, nanoemulsion, nanosuspension, SLN, NLC etc. which are sometimes surface-modified with a ligand to enhance the target specificity [52, 53, 54] **(fig. 2)**.
In this review article, we have mentioned the most recent research strategies applied in the field of nanocarrier design which is brought into line for the treatment of AD by crossing the BBB only. Accordingly, we have structured our review paper into two broad categories which involve firstly, the polymeric nanocarrier and secondly, the lipidic nanocarrier system. In the polymeric nanoparticle design strategies, the importance of the polymer used was discussed in the former section, helping the drug molecule to cross the BBB. The later section highlights the lipid-based nanocarrier systems, helping the drug molecule to cross the BBB for the improvement of its therapeutic efficacy. Therefore, we hope that this review article will be helpful for the researchers and clinicians to understand the proficiencies of the nanocarrier system which are under investigation for the treatment of AD. Moreover, the comprehensive presentation of the recent research will stimulate the idea of implementing these strategies in a more fruitful way for the exploitation of the untouched drug entities available for the treatment of AD. These strategies will help the emerging researchers to open a gateway for the discovery of a new era in the field of nanotechnology towards the brain research.

2. Biomedical Application

As discussed in the previous sections, most of the drug molecules for the treatment of AD possess limitations to access brain region because of the BBB. To overcome this limitation, scientists have redefined the use of nanotechnological approaches to make the drug available in the brain region to improve its efficiency. Some of the attempts/strategies made in this direction to increase the bioavailability of the drug in the brain region are compiled in **table 1**.

2.1 Polymer-based nanocarrier system

2.1.1 Polymeric Nanoparticles

Nanoparticle offers a most versatile and fortunate drug carrier system that can successfully deliver the active drug substance to a critical region of the body like brain [44, 55]. These are microscopic polymeric colloidal particles of a size below 1000 nm. Nanoparticles may be a reservoir or matrix type of carrier systems. Purporting to be made up of biodegradable and biocompatible natural or synthetic polymers[56]. These matrix systems can entrap or encapsulate the active molecule to protect the drug from the harsh, unfavourable environment and can efficiently deliver them to the target site [57, 58, 59, 60, 61, 62, 63, 64, 65]. The toxicological concern of nanoparticulate system is related to the polymers and other ingredients used in its preparation. Hence, the selection of biodegradable and biocompatible polymers is to be made by the FDA guideline to assure safety and efficacy. [66]. In this context, various attempts made using nanoparticles, for successful delivery of drug to the brain for the treatment of AD are discussed below.

As the cholinergic dysfunctioning is the most common and major attribute of AD [67]. The drug molecule with an ability to improve the cholinergic function of the brain can be a potential candidate for the treatment of AD. One such drug is tacrine, a reversible cholinesterase inhibitor that can inhibit both the AChE[9] as well as BuChE[10]. Also, it also acts as a potassium channel blocker which, in combination improves the cholinergic neuronal function [68]. It is the first licensed FDA approved AChE inhibitor to be used for the treatment of AD [69]. The primary disadvantage of tacrine is its poor bioavailability, extensively high first-pass metabolism, rapid clearance and high GI[11] side effects like other ChEIs. To overcome such limitations and to provide an

[9] Acetylcholinesterase
[10] Butyl cholinesterase
[11] Gastro intestinal

efficient drug carrier system for efficient delivery of tacrine, Wilson *et al.* (2010) have prepared a tacrine loaded chitosan nanoparticle coated with polysorbate 80 and studied its effect on biodistribution of drug molecule [70, 71]. Chitosan is a mucoadhesive, cationic natural polysaccharide, commonly used in various novel drug carrier system to enhance the efficacy and potency of the bioactive [72]. Along with this, it is biodegradable, biocompatible and less toxic in nature that releases the entrapped drug through enzymatic degradation in the body[73]. Interestingly, the resulting by-products are non-toxic, non-immunogenic and readily absorbable in the human body. Chitosan can enhance the drug dissolution rate in the biological fluid, can control the rate of release of the carrier system, and can also prolong/ sustained the drug release to improve bioavailability without any harmful effect[61]. Due to these properties of chitosan, there is a high demand of chitosan in various pharmaceutical and biomedical fields like ophthalmology [74], artificial membrane [75], dressing material for wound healing and drug delivery [76]. Also, the rate controlling phenomenon of chitosan has been widely utilized by researchers to improve the solubility, bioavailability, and efficacy of various drug molecules by incorporating them in a suitable nanoparticulate system [77, 78, 79]. In this context, Wilson *et al.* (2010) have selected the natural emulsification method for the preparation of nanoparticle using chitosan as a polymeric phase with a suitable crosslinker [80]. After that, the drug was loaded to the prepared nanoparticle and finally, the nanoparticles coated with polysorbate 80 to alter the distribution of the drug in the body. Coating with polysorbate 80 is a prevalent strategy that enhances the brain uptake of nano drug carrier. At the same time, it increases the drug retention time, improves biodistribution and so enhances drug efficacy. Although, it affects the physicochemical properties of the final formulation, increasing the particle size, reducing the drug loading ability, lowering the drug release, etc. The nanoparticulate system releases around 89% of the drug with an initial burst release followed by sustained release for 12h. The drug release pattern follows Fickanian behavior and obeys Higuchi and Korsmeyer-Peppas kinetic model. The *in vivo* study confirms that the polysorbate 80 coated chitosan nanoparticles increase the half-life, drug retention time and improves the biodistribution and drug concentration in all the vital organs. At the same time, it also reduces renal clearance of the drug from the body. Thus, the polysorbate 80 coated chitosan nanoparticles offer a promising carrier to enhance the bioavailability of tacrine to enhance the cholinergic response for providing a symptomatic treatment of AD by improving the memory and cognitive functions [81].

Likewise, rivastigmine is also recommend for the treatment of AD. Rivastigmine is a USFDA[12] approved, reversible cholinesterase inhibitor having the ability to inhibit both AChE and BuChE [82]. In various clinical studies, rivastigmine was found useful for the treatment of AD, and it has claimed to improve the behavioral and cognitive functioning of the patient by enhancing the cholinergic responses in the brain [83]. The only problem associated which limits its clinical application is its low brain availability because of its inability to cross the BBB. Exploiting the above-discussed strategy to coat poly(n-butyl cyanoacrylate) nanoparticle by polysorbate 80, Wilson *et al.* (2008) had developed rivastigmine loaded nanoparticle injectable for IV[13] administration [84]. In their work, they had improved the drug efficacy and concentration by using Polysorbate-80 coated poly(n-butyl cyanoacrylate) nanoparticle for the successful delivery of rivastigmine into the brain. This nanoparticulate system delivers the drug moieties to the brain which cannot cross the BBB in its native form and therefore it has been chosen to encapsulate them within Polysorbate 80 coated poly(n-butyl cyanoacrylate) nanoparticles. According to earlier reports, hexapeptide dalargin was the first drug to be successfully delivered into the brain in a time-dependent manner using the same approach [85]. Apart from this, various another drug like dipeptide kyotorphin [86], tubocurarine [87], doxorubicin [88], loperamide [89]and an NMDA receptor antagonist MRZ 2/576 [90] have also been delivered into the brain by the application of Polysorbate-80 coated poly(n-butyl cyanoacrylate) nanoparticle. Wilson *et al.* (2008) had selected an emulsion polymerization technique as a method of choice for the preparation of rivastigmine loaded poly(n-butyl cyanoacrylate) NP[14] followed by coating with 1% polysorbate 80. Also, dextran is also added to impart stearic stability in the formulation, while glucose as cryoprotectant[91]. Moreover, the drug release from the nanoparticles depends on the drug-polymer ratio used in the formulation. The polysorbate 80 coating on nanoparticle surface slightly reduces the drug release rate following a biphasic release pattern. At the initial stage, due to burst effect, a hike in the release of drug occurs which sustained gradually up to 24 h with an overall release up to 86% [78, 92]. *In vivo* study confirms the presence of the drug in the brain region as compared to other peripheral organs like liver, lungs, spleen, kidney, *etc*. Interestingly, the polysorbate 80 coated NPs shows 3.82 folds higher concentration in the brain as compared to the free drug solution. This increase in bioavailability relates to the theory that coating of polysorbate 80 on NPs enhances the targeting

[12] United states food and drug administration
[13] Intravenous
[14] Nanoparticle

ability [85, 93] to a specific apolipoprotein B and E to facilitate the transfer of drug across the BBB via receptor-mediated endocytosis [94]. Hence, polysorbate 80 coating on poly (n-butyl cyanoacrylate) NP represents an efficient drug delivery system to target the drug in the brain that was unable to cross the BBB in its native form.

In general, various metal ions like copper, zinc, iron, etc. are considered as the most critical element for smooth conduction of metabolic processes in the body, responsible for signal transmission from the brain and regulating enzymatic activity. However, the higher concentration of these metal ions could lead to producing toxic effects. Their excessive accumulation in body interferes with the brain function and can increase the risk of various CNS[15] disorders like Alzheimer's disease, Wilson's disease and Parkinson's disease [95, 96]. In case of an AD, these metal ions get interacted with the Aβ[16] plaque and thereby enhance the severity of the disease [97]. However, various metal ion chelators like quercetin, trientine, D-penicillamine, bathocuproine (hydrophilic) [98] and clioquinol (hydrophobic) were proved as potential agents to dissolve the metal-Aβ plaque, therefore deployed for the treatment of Alzheimer's disease [99]. By using this phenomenon of metal ion chelation, a newer approach has been developed by Sun and co-workers (2016) to prevent the metal-peptide interaction through the metal ion chelation [100]. They have prepared a PLGA[17] functionalized quercetin loaded nanoparticles for effective treatment of Alzheimer's disease. Interestingly, quercetin is a natural flavonoid [101]. Quercetin can reduce the neurotoxicity produced by β amyloid peptide [102] as well as it also acts as a chelating agent for metal cations [103]. The limitation associated with quercetin is its poor solubility, extensive first pass metabolism. Hence, it exhibits low oral bioavailability [104]. Therefore, to overcome these limitations, the quercetin is encapsulated into a PLGA nanoparticle that supposed to enhance its therapeutic efficacy [62, 105] by enhanced brain permeation and so the bioavailability [106]. The produced nanoparticles are the result of a double emulsion solvent evaporation method (**fig. 3**) using PVA[18] as an emulsifier to increase the stability of the formulation. The quercetin loaded nanoparticle effectively dissociates the amyloid β plaque when tested on amyloid β aggregates (*in vitro*). The quercetin was released from the carrier system initially in bulk by burst effect for 2 h followed by a sustained release for 48 h. At the same time, it also improves the cell viability and does not produce any cytotoxicity in the *in vitro* cell model. Also, it protects the neuronal cells from the toxic effect of metal-peptide complex and also reduces the aggregate formation. Various behavioral studies (like Morris Water Maze and novel object recognition test) on animal models give the assurance that the quercetin loaded PLGA nanoparticle significantly improves the memory and behavioral abnormalities. At the same time, *in vivo* study assures that it reduces the neurodegeneration by inhibiting metal-peptide complexation. Thus, the author claims that PLGA nanoparticle offers a potential carrier system for the delivery of quercetin into the brain for treatment of Alzheimer's disease [107]. The author mentioned. no evidence to show how the PLGA nanoparticle crosses the BBB. However, the surface modification of nanoparticle with any target-specific ligand could offer a more prominent carrier system to deliver the drug across the BBB.

Figure 3: Diagrammatic representation of the double emulsion method for encapsulating quercetin in PLGA NPs. [Adopted with permission from Sun *et al.*, 2016.]

Similarly, Cui and co-workers (2005) have also done an impressive piece of work; they have prepared D-penicillamine loaded NPs with an objective to treat AD by metal ion chelation therapy [108]. An engineered NP prepared by using MPB-PE[19], PDP-PE[20] and warm microemulsion precursor, a mixture of surfactant (like tween 20, Brij 78) and emulsifying wax. The drug D-penicillamine was conjugated with the prepared nanoparticle through a disulphide or thioether bond, as shown in to clear the concept of conjugation method. The concentration of D-penicillamine in the prepared NP depends upon the amount of MPB or PDP, which increases by increasing amount of MPB or PDP. Also, the higher concentration of MPB or PDP increases the particle size, and it was a known fact that the particle with size less than 100 nm is suitable to cross BBB. At the same time, the thioether or disulphide linkage makes the formulation more stable [109]. The NPs releases the drug by interaction with glutathione (natural reducing agent) expressed over cells of the brain region under a normal physiologic condition which can be enhanced by the addition of a reducing agent DTT[21] [110]. D-penicillamine conjugated NP efficiently crosses the BBB by interrupting its function and integrity and

[15] Central nervous system
[16] Amyloid β peptide
[17] Poly (lactic-co-glycolic acid)
[18] Poly vinyl alcohol
[19] 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine-N-[4-(p-maleimidophe-nyl)butyramide](sodium salt)
[20] 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine-N-[3-(2-pyridyldithio)-propionate](sodium salt)
[21] Dithiothreitol

successfully delivers the metal chelator in the brain under a reducing environment. At the same time, D-penicillamine is capable of resolubilizing the copper- Aβ aggregates in the brain and helps to reduce the severity of the AD-like condition or other CNS disorders [108].

Table 1: Investigated drug-loaded nanoparticles for the treatment of AD

2.1.2 Target specific nanoparticle

To enhance the drug targeting ability, to improve the drug efficacy, and to reduce the undesired side effect of the therapy some targeted specific moieties known as ligands, incorporated on to the surface of nanoparticles. These ligands have an affinity towards specific receptors which are present at the BBB like glucose transporter (GLUT 1), NMDA receptor, transferrin receptor, etc. Such targeting ligands interact with their particular receptors and open a channel for drug transport in the brain. At the same time, some molecules also have an affinity towards site-specific peptides like Aβ peptides which upon interaction exerts their activity to the specific site without any side effect.

In the context of the above strategy, Hu and coauthors (2009) have attempted the development of the brain targeted nanoparticles by preparing noninvasive receptor-mediated drug carrier system [113]. They have prepared an Lf[22] conjugated PEG[23]-PLA[24] nanoparticle (Lf-mNP[25]) to explore the brain targeting ability of Lf as a specific binding vector. Lactoferrin is a cationic iron binding, a mammalian glycoprotein which belongs to transferrin family. It is composed of a single chain polypeptide of 690 AA[26] having two lobes containing iron binding site [114, 115]. Various studies showed that lactoferrin possesses anti-inflammatory, anticancer, antibacterial, antiviral and antifungal activities. At the same time, it is also responsible for the bone growth, wound healing and immunomodulation activity. The BCECs[27] and respiratory epithelial cells are abundant in lactoferrin receptors [116], and therefore, Lf offers a very potential brain targeting ligand because of its high binding affinity towards the Lf receptors of BCECs [116, 117]. Also, the negative charge on the basement membrane of brain facilitates the interaction with positively charged Lf molecule [118]. Hence, for many CNS disorders, lactoferrin can be utilized as a very potent surface-active ligand to deliver the drug into the brain. In this respect, PEG-PLA NPs offers various advantages (like more excellent physical stability, prolong drug release, ease of preparation, less number of excipients needed for preparation thus low cost of preparation) over the other polymeric nanoparticles. Hence, it is selected for conjugation with Lf to successfully delivers any drug molecule into the brain [119]. The Lf-NP prepared with MPEG[28]-PLA and maleimide-PEG-PLA block copolymer using double emulsion solvent evaporation method [120]. Coumarin-6 was loaded as a model drug and as a nanoparticle probe too. The prepared NPs were further surface modified by conjugation with thiolated Lf [121]. The PEG-PLA-Lf-NPs enhanced the cellular uptake through a model bEnd.3[29] cells up to 1.45 as compared to NP. The Lf modified NP improved the cellular uptake in a temperature dependent manner and was found higher at body temperature 37°C as compared to low temperature (4°C). However, at average body temperature, the cell uptake was concentration and time-dependent indicating an active transport of NP across the BBB [116, 117]. It also extensively improves brain distribution of drug as compared to non-modified NP. Additionally, the PEG-PLA-Lf-NP significantly increases the drug concentration and AUC[30]. Further, the cytotoxicity study ensures that the Lf-NP did not possess any toxicity in the body and considered to be safe for the treatment of AD. As per the author, the Lf-NP offers a promising, noninvasive and novel approach for the drug targeting into the brain.

Moving one-step ahead, the drug targeting into the brain involves an innovative approach to formulating a bifunctional or multifunctional NP. This phenomenon describes the decorating the surface of the nanoparticulate system with more than one target active ligand. It facilitates the drug targeting either by triggering multiple receptors of the BBB, resolving the problem of receptor saturation or by reacting with receptors presents at different sites in the brain. Briefly, it firstly opens a passage in the BBB by interacting with the receptor present in BCECs and after that binds to the specific site of action in the brain like β amyloid plaque and the other portion of the brain remains unaffected [122]. By this way, dual functional nanoparticle

[22] lactoferrin
[23] Poly ethylene glycol
[24] Poly lactic acid
[25] Lactoferrin modified nanoparticle
[26] Amino acid
[27] Brain capillary endothelial cell
[28] Methoxy poly (ethylene glycol)
[29] Brain endothelial cell lining
[30] Area under curve

enhances the drug targeting ability of nanoparticle. Using this strategy, Zhang *et al.* (2014) have prepared a cascade targeting drug delivery system made up of PEG-PLA nanoparticle to encapsulate H102. It is surface modified with two different targeting moieties, i.e., TGN[31] and QSH[32]. The first one is responsible for brain targeting and offers 3.6 times greater targeting ability than the non-modified NP, while the later one is responsible for binding with the $A\beta_{42}$ molecules [123]. The H102 is a newer class of oligopeptide or β sheet breaker [124] which became very popular nowadays, because of its unique ability to prevent the formation of senile plaque and to reduce neurotoxicity by interrupting the formation of the β sheet and thus, the causes aggregation [125]. The investigator prefers an emulsion solvent evaporation method for preparation of PEG-PLA NP. The drug loaded into the carrier system at the time of preparation of NP, and after that, the drug-loaded carrier was surface modified with TGN and QSH for active targeting. The surface modification with targeting peptides increases the size of the nanoparticle. The *in vivo* study proves that the dual-targeted PEG-PLA-NP or TQNP[33] enhances the AUC and drug uptake in the brain region. Thus, the overall drug concentration in the brain is approximately 1.8 times as compared to H102/NP. The behavioral study on animal model confirms the neuroprotective ability of TQNP. Therefore, the drug carrier system can be considered as a potential approach to treat AD as it helps in regaining the neuronal dysfunctioning by reducing the plaque formation and restoring the cholinergic functioning [126].

2.1.3 Nano gel

Nano gels can be considered as chemically or physically crosslinked hydrophilic network of specially designed polymers that can get swell by absorbing a significant amount of water or solvent [127]. In other words, nanogel is also referred as hydrogel nanoparticle, composed of a highly hydrated three-dimensional network of either synthetic or natural polymers [128]. The main feature of nanogel is its stimuli-responsive nature, i.e. ability to change own properties in response to any external stimuli (like pH, temperature, light, ionic concentration) [129]. It is a smart nanocarrier system that offers various advantages over the traditional nanoparticles like higher drug loading capacity, higher tissue penetration power, higher elasticity and increased stability due to cross-linked network [130].

The study shows that apart from the aggregation of Aβ peptide the AD etiology also involves the gathering of soluble protein which reduces the clearance of Aβ peptide from the brain [132]. theSuch misfolding of the amyloid peptide can be, therefore, handled by endogenous chaperones molecules [133]. One such useful molecule is CHP[34] that can protect the neuronal cell from toxicity and damage because of its unique protein folding and refolding activity [134]. In this concern, a cationic hydrogel NP of CHP [135], referred as CHP nano gels prepared by Boridy *et al.* (2009). The hypothesis was carried out with an objective to investigate the ability of CHP to reduce the neurotoxicity produced by Aβ plaques. Moreover, the CHP shows the ability to form a monodispersed colloidal nano gels just after self-assembling through hydrophobic interaction; as shown in **(fig. 4)** [134]. Thus, the CHP nano gels preferentially bind to small soluble amyloid β protein in the brain to form an Aβ-CHP complex which reduces the plaque formation thereof. The CHP, therefore, utilizes the immunological attributes of microglial cells and astrocytes of the brain [136] to facilitate the clearance of Aβ monomers, oligomers and fibrils as well as to maintain the homeostasis in the brain. Thus, a microglial cell behaves as the macrophages of the brain and efficiently removes the Aβ-CHP complex without producing any cytotoxic effect. However, the cationic CHP-nano gel is more cytotoxicity as compared to neutral CHP. Recently, various clinical trials have already been performed to assure the feasibility of CHP nano gel system for treatment of various brain disorders. Here, the *in vivo* study demonstrates that the CHP nano gel offers a promising approach for the delivery of various potent bioactive to reduce the Aβ toxicity towards the AD treatment [137].

Figure 4: Self-association of the polymeric nanoparticle, CHP into nano gels by hydrophobic interaction. [Adopted and modified with permission from Boridy *et al.*, 2009]

2.2 Lipid-based nanocarrier system

The lipidic nanoparticles have gained more attention among various types of nano-carriers in the recent years, due to its less or no toxicity, biodegradability, and ability to successfully deliver biomolecules, DNA, RNA, genes, antibodies, etc. The nanoparticulate system in which the polymers are replaced by the lipidic material to provide the necessary assembly for drug loading and ligand binding in case of targeted nanoparticles [138].

[31] BBB targeting peptide
[32] Aβ42 targeting peptide
[33] TGN and QSH conjugated nanoparticles
[34] cholesteryl bearing pullulans

Based on the types of lipids, their physical state, composition and formulation strategy different types of lipid nano-carriers are available like liposome, SLN, NLC, etc. The applications of such lipidic nano-carriers are discussed below.

2.2.1 Liposome

Among all the different lipid carrier system, liposome remains the most popular one. Structurally, it is a small vesicular system made up of a phospholipid bilayer with an aqueous core. This structure contributes to the amphiphilic nature of liposome, i.e. ability to carry both the lipophilic (intercalated with the phospholipid bilayer) and hydrophilic (encapsulated with the aqueous core) moieties. Moreover, it is composed of natural or semisynthetic phospholipid molecule which makes it biocompatible, less toxic and suitable for the delivery of biomolecules [122]. Applications of the liposome as a drug carrier for treatment of AD are compiled in **table 2** and are discussed below.

The excessive accumulation of aluminum ion in any region of the brain and abnormal inflammatory reactions also triggers the neurodegeneration process and significantly reduces the ACh level in the brain (boost up the neuronal dysfunctioning). In such conditions, some AChE inhibitors found effective to improve the amount of ACh in the brain that helps to regain the regular functioning of neurons [143]. By using this approach author (Ismail *et al.* 2013) have prepared a nano-based formulation, i.e., the liposome of a novel AChE inhibitor, rivastigmine [144] for the treatment of AD and tested its effectiveness on $AlCl_3$ induced rats. Rivastigmine is considered as a potential AChE inhibitor, offering advantages over other conventional inhibitors, as it can irreversibly inhibit AChE as well as BuChE [145]. However, it is useful in scopolamine as well as aluminum-induced cognitive dysfunctioning [146]. However, the problem associated with rivastigmine is its shorter half-life and reduced oral bioavailability due to involvement in extensive first-pass metabolism. Interestingly, the authors have followed the passive diffusion principle for drug penetration across the BBB owing to the lipophilic nature of the liposome and have claimed the same for their formulation [32]. Here in this study, the liposome is prepared by two methods lipid layer hydration and a heating method using egg yolk phosphocholine, dihexadecyl phosphate, and cholesterol in different molar ratio and further characterized and evaluated under various parameters to assure the efficacy of carrier system [147]. We know that the particle size of the nano-carrier system dramatically affects its cell permeability and also the brain targeting ability. Here, the study shows that the method of liposome preparation significantly affects the size of the carrier system. For this reason, a lipid layer hydration was preferred overheating method to prepare the liposome at the desired size range. Furthermore, the release study confirms a sustained release of drug over a period of 24h. In particular, the drug release was in a biphasic fashion, it followed fast release behavior for the first 3h and slow release for the next 24h. At the same time, it is also important to mention that the drug release follows the zero order rate kinetics which means that it is independent of the initial drug concentration. Additionally, the *in vivo* study demonstrated a significant improvement in memory of the animal model. Together with this, the liposomal formulation was found amazingly useful in reduction of the amyloidogenic and neurodegenerative effect of $AlCl_3$. However, the work could be more effective if some surface modification would have been done for more prominent site-specific targeting to enhance its therapeutic efficacy. As per the findings, of course, the rivastigmine loaded liposome can serve as a potential candidate for the treatment of AD, but only if the similar results will be observed in human trials.

Table 2: Investigated drug-loaded liposomes for the treatment of AD.

2.2.2 Target specific liposome

As we have previously discussed, the excessive aggregation of Aβ monomer and oligomer is the main cause of neurodegeneration. the are,Hence, by shifting the Aβ equilibrium towards periphery can reduce the Aβ population in the brain. This phenomenon, in turn, would lessen the formation of Aβ plaque and thus reduces the neurodegeneration [148]. Using such phenomenon/strategy, Mancini *et al.* (2016) worked on the formation of a multifunctional lipidic nanoparticulate system (liposome), i.e., mApoE[35]-PA[36]-lip[37] **(fig 5)** to extract the Aβ peptide out of the brain by explicitly binding with it. However, the sphingomyelin and cholesterol (1:1) offer a suitable lipid phase for the preparation of liposome. The prepared liposome was further surface modified with PA (Aβ binding domain) and mApoE derivative (BBB binding domain) [10, 18, 122] while the surface modifications with targeting ligand increase the size of the liposome as compared to the non-functionalized one.

[35] Apolipoprotein E
[36] Phosphatides'
[37] Liposome

The *in vitro* study on a transwell BBB model demonstrates that mApoE-PA-lip increases the efflux of Aβ oligomer from BBB as compared to other formulations. Accordingly, the *in vivo* study shows a significant increase in Aβ level in blood or peripheral compartment as compared to the brain region [149].

Figure 5: Illustration of the bi-functional liposome, surface modified with mApoE and PA

Although only small soluble Aβ oligomers were able to cross the BBB and not the Aβ fibrils, still a significant reduction in Aβ oligomers in the brain is sufficient to prevent the aggregate formation. However, it accentuates the realization that a sink effect created by the multi-functionalized nanoparticles have facilitated the removal of Aβ peptide from the brain and because of this, it prevents the formation of Aβ plaque. Hence, it offers an attractive approach to treat AD [149]. Besides this, ample of works not only focused on the delivery of some bioactive like curcumin, peptides, monoclonal antibodies, etc. as a therapeutic agent but also been utilized as a targeting ligand to bind Aβ [150, 151].

Another strategy in the series of treatment for the AD is the biomedical application of lactoferrin modified nano lipid carrier system. Precisely, it mimics the LDL[38] loaded with drug (like curcumin) for brain targeting, and some exemplary examples of this are demonstrated by Meng *et al.* (2015). The LDL or low-density lipoprotein is one of the most important lipoproteins in the body which is composed of phospholipid core, cholesteryl ester, and ApoB-100[39] which remain compatible with both hydrophilic and hydrophobic molecule and also is nonimmunogenic in nature [152, 153]. The NLC[40] was prepared in a fashion to mimic the LDL by electrostatically binding with Lf[41] which is furthermore responsible for the brain targeting of the drug. The NLC was prepared with phosphatidylcholine, cholesterol, S100-COOH[42], and glycerol trio to be modified with Lf and further loaded with curcumin by solvent evaporation method thereof. The Lf added to the formulation because of its ability to cross the BBB through Lf receptor at endothelial lining. Undoubtedly, S100-COOH was responsible for increasing electrostatic charges so that more enormous amount of Lf could absorb on the surface of NLC. On the other hand, ApoB-100 was accountable for stabilizing the formulation. Additionally, curcumin is a phytoconstituent which is reported to reduce the neurodegeneration by slowing down the Aβ aggregate formation in the brain [10]. Interestingly, the particle size of the nanocarrier decreases with increase in the amount of S100-COOH because of tightening effect of the PEG chain which in turn limits the vesicular size [154, 155]. At the same time, the concentration of Lf also affects the particle size. However, the entrapment efficiency decreases with increasing amount of S100-COOH only and not affected by Lf level. Among various release kinetic models, the Weibull model was found to fit best to describe the release pattern. On the contrary, the Lf concentration reduces the rate of drug release. Despite this, the NLC and Lf-mNLC formulations provide a slower release rate of the drug after 4 h. At last, the *in vivo* study supports the hypothesis that Lf-mNLC significantly increases the AUC and MRT while reducing the drug clearance from the body. At the same time, the Lf-mNLC also enables the drug molecules to cross the BBB efficiently. It all boils down to the fact that, the Lf-mNLC offers a potential carrier system which not only efficiently delivers the drug into the brain without affecting its integrity but also improves its pharmacokinetic behavior [2].

2.2.3 Nanoemulsion

Nanoemulsion is thermodynamically stable, nano-sized, colloidal droplet system in which two immiscible liquid phases are mixed together with the help of suitable emulsifying agent to form a uniform isotropic system [156]. The droplet size falls in nano range (20 to 200 nm) hence it overcomes the of instability issue of the conventional emulsion [156, 157, 158]. At the same time, the smaller droplet size and its larger surface area facilitate the drug absorption which not only to improves the bioavailability of the drug [159]. Along with this, the use of natural oil in the formulation of nanoemulsion makes it biocompatible and biodegradable in nature and does not produce any cytotoxic effect [157]. However, the limitation associated is the instability of the formulation upon storage which may leads to phase separation (especially when highly insoluble oil is used) and immediate drug release. An ample of studies report about the nanoemulsions to be a suitable carrier system for delivery of the drug into the brain [160] for the treatment of various CNS disorders like an AD, PD[43], glioma, tumor, etc.

[38] low-density lipoprotein
[39] Apo-lipo-protein-B-100
[40] Nano-lipid carrier
[41] Lactoferrin
[42] Carboxylated polyethylene glycol (100) monostearate
[43] Parkinsons disease

As noted earlier, the most unfortunate fact associated with the brain disorders is the neurodegeneration which causes permanent loss of nerve cells that can't be retrieved further by any treatment. However, the treatment just prevents the further progression of the disease and save the subject from a severe fatal condition. Accordingly, to maintain a healthy society, efforts should be made towards not only finding any compounds or strategy that can inhibit the manifestation of disease but also be able to slow down the disease progression in its early diagnostic stage. The treatment should point towards the critical factor that initiates the misfolding for an abnormal pathogenic response [161, 162]. Surprisingly, most of the CNS disorders like an AD, PD, CJD[44] and genetic prion disease share some common pathogenesis including neurodegeneration, inflammatory response, oxidative impairment, etc. [163]. In fact, lipid oxidation [164] and oxidative stress are the primary attributes of the brain diseases which stimulate the protein misfolding process leading to neurodegeneration. For this reason, a potent antioxidant molecule along with neuroprotective activity could be beneficial for the management of the brain disorders. In this regard, PSO[45] is one such compound having a potent anti-oxidant and neuroprotective ability which can be beneficial for the treatment of CNS disorders. Furthermore, it is a natural antioxidant consisting of a punicic acid and has conjugated polyunsaturated fatty acid (linoleic acid) [165] and β-sitosterol in significantly higher concentration than any other plant sources [166]. Indeed, PSO is also referred as a potent antioxidant to exhibit anti-inflammatory and neuroprotective effect [167]. However, like other natural compounds, it faces the problem of poor bioavailability and low brain permeability. To resolve this, Mizrahi *et al.* (2014), have attempted to incorporate PSO in a soluble nanoemulsion which supposed to elevate the bioavailability and can improve the safety and efficacy of the drug in the brain [168]. The soluble NE[46] enhances the bioavailability, prolongs the circulation time, improves the drug targeting ability and also assists to cross the BBB [169]. As a result, the study supports the theory that natural antioxidant delayed the disease progression. In a nutshell, the Nano-PSO slows down the disease onset at a low dose at a faster rate. Additionally, the nanoemulsion improves the brain permeation ability and bioavailability of PSO in the brain. At the same time, it also reduces the effective dose of the drug and improves the safety of its long-term administration without producing any harm to human body. Undoubtedly, the nano-PSO serves as a useful strategy to prevent lipid oxidation, neuronal loss, i.e., neurodegeneration and offers a promising treatment for an AD with decidedly less adverse effect [170].

Yang *et al.* (2014) explain the similar piece of work done in the field of the nanoemulsion. They have prepared an oil body nanoemulsion (ONE[47]) of an anti-Alzheimer drug ginkgolide B (GB). Reportedly, GB[48] is a terpenoid, extracted from *Ginkgo biloba* [171] has proved to have the ability to hinder the Aβ induced neurotoxicity in moderate dementia [157, 172, 173]. As discussed above, the problem associated with the bioactive is its poor aqueous solubility resulting in low bioavailability, and its shorter half-life tends to limit its application in the AD. Further, not only to resolve such limitations but also to improve the drug efficacy and stability, the GB was loaded into ONE. ONE is an oil based novel nanoemulsion system consisting of two opposite oil phase (O/W and W/O emulsion) to overcome the incompatibility and phase separation issue. The formulation GB-ONE contains ed by using soyabean oil, soya lecithin, ethyl lactate as outer phase and ethanol, 1,2-propanediol as an internal phase. Besides that, GB imparts more to the inner phase. The nanoemulsion makes the formulation more stable in any of the physiological environment. Additionally, the GB loaded ONE significantly increases the AUC (10 folds) and $t_{1/2}$ (7 to 20 folds) as compared to free GB. Moreover, an increase in biodistribution and tissue binding ability improves the drug targeting ability too. Some notable examples have underlined the research outcome of many behavioral studies to support the theory that GB loaded ONE causes a significant increase in memory and reduced behavioral abnormalities. In addition to this, the drug also increases the ChAT[49] activity thereby increasing the ACh concentration in the brain when administered as GB-ONE. From this point of view, the study confirms that the GB-ONE formulation remains a promising drug carrier system for the treatment of AD [157].

2.2.4 Solid lipid nanoparticle

In addition to the previous discussions, a new generation nanoparticles SLN[50], are also gaining much attention to deliver the drug into the brain region. For the formulation, the polymers are substituted with solid lipid

[44] Creutzfeldt Jacob disease
[45] Pomegranate seed oil
[46] nanoemulsion
[47] Oil body emulsion
[48] Ginkgolide B
[49] Choline acetyl transferase
[50] Solid lipid nanoparticles

content to overcome the limitations of conventional polymeric nanoparticles like safety concerns, non-biodegradability and use of high cost of biodegradables polymer [174, 175, 176]. In fact, it is a sub-micron size nano-colloidal drug carrier system, discovered by Muller and co-workers (1993) as an alternative vehicle over polymeric nanoparticles, nanoemulsions, liposomes, etc. [177, 178]. SLN not only offers various benefits (like biocompatibility) over the traditional drug carrier system but also improves the drug bioavailability, protects the drug molecules from first pass effect, GI degradation [179], increases drug loading ability, offers control release of drug and reduced cytotoxicity thereof. Apart from this, it is suitable for drug targeting on to a particular site. [180]. At the same time, the stealth nature of SLN increases the retention and circulation time thereby enhancing the contact time with the BBB and reduces the RES[51] uptake [181]. All these inherent qualities and behavior of SLN make it a prominent drug carrier system to deliver the drug into the brain for treatment of various CNS disorders. As discussed in the earlier section, quercetin, a secondary plant metabolite which falls under flavonoids, has recently renowned as a potential neuroprotective agent [182, 183]. Quercetin possesses a strong anti-oxidant and anti-inflammatory activity, and in this respect, it mitigates the neurodegeneration in Alzheimer's disease [184, 185]. Typically, the use of quercetin in the treatment of AD is challenging because of its limited BBB permeability [186]. Thus, in this respect, an attempt has been made by Dhawan *et al.* (2011) to enhance the brain delivery and therapeutic efficacy of quercetin towards the treatment of AD. In this context, they have prepared a quercetin-loaded SLN for IV administration to improve the drug permeation across the BBB [187, 188]. The SLN prepared by using compritol 888 (a solid lipid) and tween 80 (a surfactant), in varying ratios. Also, the compritol and tween 80 helps to improve the drug entrapment efficiency and brain targeting ability of the SLN. Subsequently, the lipid-surfactant ratio affects the physicochemical behavior of the formulation. Interestingly, the SLN possesses uniform spherical particles below a 200nm size which makes it more suitable to cross the BBB. The SLN releases the drug initially by burst effect, followed by prolonged drug release up to 48 h. Further, to confirm the drug efficacy and neuroprotective effectiveness of the quercetin-loaded SLN, the study was conducted on aluminum chloride induced neurodegenerative rat model. According to the observations, as compared to pure quercetin, the SLN loaded quercetin significantly improves the memory functioning of the animal model. In conclusion, the SLN increases the brain permeability and antioxidant activity of quercetin and offers an effective drug carrier system to reduce the aluminum induced neurotoxicity [189]. One more similar approach is adopted by Yusuf *et al.* (2013), for the treatment of AD using another natural anti-oxidant piperine. It is a plant alkaloid which not only reduces the oxidative stress in the brain but also increases the cholinergic transmission by inhibiting AChE activity. By all these means, it reduces the neurodegeneration process and improves the memory. Surprisingly, the PIP[52] is still not much explored as an anti-AD drug till now because PIP extensively engaged in first pass metabolism, pH-mediated metabolism, and photo-isomerization [190]. The SLN overcomes the boundaries of the conventional dosage forms henceforth, increases the drug efficacy and the brain targeting ability [180]. As an illustration of this, Yusuf *et al.* (2013) have prepared PIP loaded SLN with an objective to provide effective treatment at low doses. The PIP-SLN formulated with GMS[53], Epikuron 200 by using emulsion solvent diffusion method and the prepared SLN finally coated with polysorbate-80. Of course, an additional coating of polysorbate 80 increase the particle size of SLN and at the same time reduce the drug entrapment efficiency. Then also, it is preferred for the formulation which can further increase the brain targeting ability and the bioavailability thereof. Similarly, GSM also increases the bioavailability by increasing the drug solubility. Furthermore, the *in vivo* study reveals that the PS-80-PIP-SLN efficiently crosses BBB through adsorption transcytosis, by interacting with the LDL receptors of brain endothelial cell [191]. An earlier study demonstrated the efficiency of PS-80 coated methotrexate NP to improve the bioavailability in the brain. Similarly, the PS-80-PIP-SLN also demonstrates the same improved drug concentration in the brain [192]. Likewise, it also significantly reduces the formation of Aβ plaque and neurofibrillary tangles that lessens the severity of the disease. In short, it is proved to be effective against AChE and improve the acetylcholine function in the brain. Thus, the piperine SLN formulation offers a promising drug carrier system for the treatment of Alzheimer disease [193]. In the same fashion, Sachdeva *et al.* (2015) have also worked on a natural anti-oxidant, Sesamol to provide efficient treatment for the AD. Sesamol (5-hydroxy-1,3-benzodioxole or 3,4-methylene-dioxyphenol) is a naturally originated polyphenolic compound. Nowadays, it receives greater attention for the treatment of various CNS disorders like AD, because of its ability to reduce oxidative degeneration of neurons [194]. Along with the anti-oxidant nature [195] sesamol also exert neuroprotective, hepatoprotective, anti-inflammatory [196] and anti-ageing activity [197]. On the other hand, it also suffers from the common limitation of the natural compounds

[51] Reticuloendothelial system
[52] Piperine
[53] Glycerol monostearate

i.e. poor cell permeability and low bioavailability. So as to enhance the drug efficacy and targeting ability, it should be associated with a suitable carrier system. For this reason, Sachdeva *et al.* (2015) worked on the strategy to entrap Sesamol in SLN with a prime objective to explore the drug activity in ICV-STZ[54] treated animal model. The author preferred emulsion solvent diffusion method for the preparation of the S-SLN[55] by using Polysorbate-80 and soy lecithin as lipid phase. The in vitro release profile shows that the SLN prolongs the drug release and the drug was released in diffusion controlled manner. Furthermore, the *in vivo* study shows that SLN not only reduces the AChE activity in brain but also inhibit the inflammatory mediators like TNF-α, thus diminishes the inflammatory responses. So as a matter of fact it clearly improves the memory and cognitive disorder in the brain. Altogether, the study reveals that the Sesamol loaded in SLN gives far better neuroprotective action than the native Sesamol and serves as a potential carrier for treatment of AD [177]. Another similar attempt has been made by Misra *et al.* (2015), they have prepared Galantamine loaded SLN formulation to overcome the precincts associated with the drug molecule and enhance its efficacy for treatment of AD. Galantamine hydrobromide is an alkaloidal compound, either synthetically derived or obtained naturally from the plants of *Amaryllidaceae* family. Galantamine is a first line drug of AD which is primarily act as a reversible and competitive AChE inhibitor [198]. Together with this it also have an ability to specifically binds with nicotinic receptors hence, it is considered as a potent drug for treatment of AD [199]. On the contrary, the drug is poorly lipophilic and having low brain permeability which restrict the brain targeting ability and resulting in poor bioavailability. The cholinergic side effect and frequent dosing, needs a better approach to overcome the hurdles associated with such a potential anti-Alzheimer drug [174]. In like manner, Misra *et al.* (2015) have prepared different GH[56]-SLN formulations by microencapsulation method using biodegradable and biocompatible components (like Compritol), surfactant and the varying ratio of co-surfactant. In the study it was observed that, the increasing concentration of co-surfactant decreases the particle size and drug entrapment efficiency of the formulation get decreases with increasing concentration of co-surfactant. The *in vitro* release study shows initial fast release of the drug followed by a slow and prolonged release from the inner core of the carrier system [200]. Also the *in vivo* study depict that the carrier system increases the drug distribution and tissue binding ability hence the overall bioavailability. A significant improvement in cognitive dysfunctioning and restoration of memory impairment in rat model was observed after ICV administration of GH-SLN as compared to native GH. On the whole, the SLN offers a better carrier system to enhance the efficacy and drug permeability of a potent drug molecule for the treatment of AD [174]. One more interesting work is the preparation of stealth SLN. Laserra *et al.* (2015) have prepared LM-SLN[57] by incorporating the Lipoyl-memantine codrug into stealth SLN, to improve the intestinal drug absorption thus the bioavailability. LA-MEM[58] is a synthetic antioxidant and NMDA antagonist possesses a potent anti-Alzheimer activity. The LA-MEM codrug is synthesized by combining memantine with α-lipoic acid (a natural neuroprotective agent) [201]. The drug is found effective in mild to moderate AD as a symptomatic approach of treatment [26, 202]. Despite the various advantages the drug is suffering from poor aqueous solubility owing to poor bioavailability that further affect the drug efficacy. In order to overcome such limitation, the codrug is needed to encapsulate in a suitable drug carrier system. In the present study, the LM-SLN was prepared by the emulsification-evaporation-solidifying method at varying ratio of drug and lipid phase [203]. As like other nano-carrier systems, the stealth SLN also releases the drug by initial burst for an hour followed by 20% release up to 2 and 4h while the 80% of the drug remain entrapped in the carrier system that is supposed to be delivered at the target site. Additionally, the stealth SLN was found stable at any condition of pH and temperature hence it protects the drug from GI degradation. At the same time, it is non-toxic to the nerve cells and other body tissues thus considered safe for treatment of brain disorder. In short, it can be said that the SLN offers effective drug carrier to improve the drug solubility and absorption and can be further stabilized after *in vivo* and clinical study [178].

2.2.5 Nano lipid carrier

The NLC is modified or hybridized form of SLN [204], made up of the combination of solid lipid (fatty substance) and liquid lipid (oils) at normal room temperature [205]. The NLC is firstly developed by Muller *et al.* in the 1990s to overcome the limitations of SLN and other lipid-based nanocarriers. It contains partially crystallized lipid droplet or oil incorporated into the amorphous solid lipid core. The drug is encapsulated previously in the oily core [206, 207]. Notably, the NLC offers various advantages over other lipidic drug

[54] Intracerebroventricular streptozocin
[55] Sesamol-solid lipid nanoparticle
[56] Galantamine
[57] Lipoyl-memantine solid lipid nanoparticle
[58] Lipoyl-memantine

careers like; firstly, it improves the drug stability by protecting the bioactives from the harsh external environment. Secondly, it increases the bioavailability of the active drug substances. Thirdly, enhances the encapsulation efficiency and finally increases the drug loading efficiency [208]. The controlled release behavior of NLC is an attribute of its ability to hold the solid particulate state by controlling the liquid content of the formulations [24, 205]. Hence, it is considered as a second generation SLN or smarter nano lipid carrier system [205]. Some natural phytoconstituents can improve the α-secretase activity in the brain. The α-secretase cause's cleavage of APP in a manner that does not produce β amyloid peptide fragment thereby prevents the amyloidogenesis. Thus, it inhibits the formation of Aβ plaque and prevents neurodegeneration thereof. Utilizing this hypothesis, Smith *et al.* (2010), have prepared a nano lipidic carrier of EGCG[59]. It is a phytochemical that boosts the activity of α-secretase in the brain thus, stimulates the non-amyloidogenic pathway of APP cleavage [209, 210, 211]. Some preclinical and clinical studies have been conducted previously to ensure the potency and efficacy of EGCG in the treatment of AD. However, the drug is not found suitable for clinical practices because of its poor bioavailability. For this reason, the nanocarrier system is used to enhance the oral bioavailability of EGCG. The author has prepared the NLC by complexation of drug (green tea derived EGCG) with a suitable lipid by using the co-solubilization method. For instance, the drug-carrier system is found suitable to cross the BBB as an attribute to its smaller size [212]. The earlier studies have reported the need of other co-drug to enhance the bioavailability of EGCG by inhibiting the glucuronidation [213]. However, such additions tend to increase the cost and complexity of the research. Instead, the lower particle size like NLC overcomes this problem and avoids the expensive strategy of the co-drug formation resulting in an improved pharmacokinetic profile. This study proves the NLC as a better and potential candidate than liposome due to its ability to efficiently cross the BBB. In essence, the EGCG loaded NLC offers promising approaches to treating Alzheimer's disease [214]. Some enzyme, coenzyme, vitamins and other bioactive possess an excellent antioxidant and anti-inflammatory activity. For this reason, such bioactive sometimes found very useful in the treatment of various neurodegenerative disorders like amnesia, AD, etc. as a supplemental therapy [215]. One of such compound is ubiquinone (coenzyme Q10), the first lipid soluble 1,4-benzoquinone derivative acting as strongest anti-oxidant in the body [216]. To enhance the potency and pharmacokinetic properties of ubiquinone, Nanjwade *et al.* (2013) have prepared a newer NLC system by mixing the solid lipid with the incompatible liquid lipid [24, 205, 217]. Ubiquinone was used as a model drug to reduce the oxidative stress in various neurodegenerative disorders. The drug-loaded NLC was prepared with glyceryl stearate and glyceryl behenate (Precirol ATO 5 and Compritol 888 ATO) as solid lipid and glyceryl triacetate (Captex 500) as liquid lipid by using solvent diffusion method [218]. The *in vitro* drug release study demonstrated that the drug was released from the NLC by initial bursting followed by a prolonged release up to 24 h, which releases almost 91% of the drug. The drug was released from the NLC by diffusion control mechanism which is aligned with Higuchi release kinetic equation. Further, the NLC preparation found to increases the anti-oxidant potency of the drug as compared to the drug solution. Moreover, the *in vivo* study shows a significant improvement in the pharmacokinetic behavior of the drug when loaded into the NLC. It also improves the overall bioavailability and drug potency. On balance, the study ensures Co Q10-NLC as a promising antioxidant for the treatment of AD with improved bioavailability [215]

3. Toxicological challenges

Till now we have discussed about the application and advantages of nanotechnology in brain drug delivery. In last two decades, an increase application of the nanocarrier system or nanotechnology in the health sector fascinates the new researchers. Although, there is always a darker side and so it is important to estimate the toxicological and safety profile of the nano carrier system. Indeed, it is unjustified to draw a common statement for the safety profile of the nanoparticles because of its diverse nature. The toxicity or safety issues in the nanoparticles originates due to the preparation methods and components (polymers, solvents, etc.) used for the preparation of nanoparticles. So, to evaluate the safety profile of nano carriers there are various methods (*in vitro* or *in vivo*) available like ELISA for cellular inflammatory response, LDH[60] to test cell membrane integrity, cytotoxicity assessment in different cell line (SK-N-MC, BCECs cell line for brain drug delivery) according to the research area etc. [219]. The major flaw is, there is no universal method available for toxicity evaluation which makes it very difficult to judge the safety profile of any nanoparticle. The safety assessment is purely based on the type of research area. Nevertheless, a proper in vitro and in vivo investigation of toxicity profile and surface modification or selective targeting assures the safety of nano carriers to a greater extent [47].

[59] Epigallocatechine-3-gallate
[60] Lactate dehydrogenase

4. Conclusion

Treatment of CNS disorders remains a challenge for the researchers because of the BBB. A numerous research and strategies on novel approaches have already explored, and some of them are under investigation. These investigations aligned with the development of a suitable drug delivery system that not only assures the brain targeting but also improves the effectiveness of drug delivery system to treat CNS disorders. Here, in this article, we concern about a significant neurodegenerative disorder AD. Nanoparticulate drug carrier system offers most possible strategy with a variety of different forms and can easily modify to facilitate the drug targeting to eliminate various boundaries associated with it. The most common polymeric nanoparticle may be a good choice, but sometimes the polymers are toxic due to its non-degradability and non-compatibility. In addition to this, some surface modification has also been done with specific targeting ligands on the surface of nanoparticles to improve the brain targeting ability. To remove the toxicological effect sometimes, the polymers replace with lipidic material offers excellent biocompatibility and biodegradability. Such nano drug delivery systems are an advanced form of the drug carriers and are known as SLN and NLCs. Among the various forms of nanocarriers like polymeric nanoparticle, nanoemulsion, nano gel, SLN, NLC and surface modified/targeted/lactoferrin mediated nanoparticles; the last two are the most advanced carrier systems that offer a potential targeted drug carrier system. At the same time, some smart nanocarriers such as a magnetic nanoparticle, stimuli-responsive nanoparticle, biosensors, etc. are under investigation which would assure effective treatment of AD. Instead of all these findings, insufficient clinical practices are available to date, and most of the attempts have not even under clinical investigation. So to provide a potential treatment for the Alzheimer, first of all, the researchers need to move one step ahead and let their innovation to cross the clinical phase successfully. So that it can be available for real practice and become beneficial for the society and not only remains just as a database for the future scientific work.

5. Expert opinion

Various bioactive like proteins, peptides, antibodies, nucleic acid, growth factors, and plant metabolites including some of the active drug compounds of synthetic origins have proven to have potent anti-Alzheimer activity. After so much scientific claims, no proper treatment of such epidemic disorder is available till now. The reason behind such failure is the inaccessibility of brain, physiological instability of drug, poor drug penetration through BBB, low bioavailability, poor drug targeting and last but essential, the high cost of production and limited research conductions. Various nanotechnological approaches have been utilized nowadays to overcome the hurdles mentioned above, but still, some prospects left behind. Therefore, there is a need for attention to preparing a promising drug delivery system. First of all, most of the works that claim to treat AD have only passed the *in vivo* animal studies and not the human clinical trials. So, it fails to get recognition and finally remains at the laboratory only (not approved for market). At the same time, the study of toxicological profiles of the polymer or other materials and drug used to prepare the novel drug carrier should consider its fundamental aspects towards the development of drug delivery system related to the brain disorder. Similarly, the cost of the prepared formulation is equally significant to maintain its economic range. In case of the novel drug delivery system, the high cost of the formulation is frequently an observed issue, and this makes it more difficult for any low-income person to bear the cost of the treatment. The cost is mostly affected by the polymers or other materials used in the formulation along with novel targeted strategies. Hence, it is imperative for one to consider this economic factor during the development of nanocarrier systems by the implication of novel strategies, so that it can be made cost-effective and available to everyone. In a nutshell, there is a massive scope in the development of a nanocarrier system for the neurological disorders to make it available for clinical application and also to give relief to the sufferers.

References

1. Wen MM, El-Salamouni NS, El-Refaie WM, et al. Nanotechnology-based drug delivery systems for Alzheimer's disease management: Technical, industrial, and clinical challenges. Journal of controlled release : official journal of the Controlled Release Society. 2017 Jan 10;245:95-107. doi: 10.1016/j.jconrel.2016.11.025. PubMed PMID: 27889394; eng.

* this review provide a good illustration about pathophysiology of AD. it a very relevent piece of work which gives a brief of most of nano drug drug delivery system can be used in for AD.

2. Meng F, Asghar S, Gao S, et al. A novel LDL-mimic nanocarrier for the targeted delivery of curcumin into the brain to treat Alzheimer's disease. Colloids and surfaces B, Biointerfaces. 2015 Oct 01;134:88-97. doi: 10.1016/j.colsurfb.2015.06.025. PubMed PMID: 26162977; eng.

**they have prepared the Lf modified LDL mimicking curcumin loaded NLC and demonstrated the effect of surface modification on particle size, release rate, in vivo pharmacokinetic parameters and ability to cross the BBB.

3. Friedrich RP, Pottler M, Cicha I, et al. Novel nanoparticulate drug delivery systems. Nanomedicine (London, England). 2016 Mar;11(6):573-6. doi: 10.2217/nnm.16.18. PubMed PMID: 26911384; eng.
4. Klimova B, Kuca K. Alzheimer's disease: Potential preventive, non-invasive, intervention strategies in lowering the risk of cognitive decline – A review study. Journal of Applied Biomedicine. 2015 2015/11/01/;13(4):257-261. doi: http://dx.doi.org/10.1016/j.jab.2015.07.004.
5. 2015 Alzheimer's disease facts and figures. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2015 Mar;11(3):332-84. PubMed PMID: 25984581; eng.

**it is the annual report published by Alzhiemer's Association which covers all the statistics and facts related to the AD world wide.

6. Di Stefano A, Iannitelli A, Laserra S, et al. Drug delivery strategies for Alzheimer's disease treatment. Expert opinion on drug delivery. 2011 2011/05/01;8(5):581-603. doi: 10.1517/17425247.2011.561311.
7. Pezzini I, Mattoli V, Ciofani G. Mitochondria and neurodegenerative diseases: the promising role of nanotechnology in targeted drug delivery. Expert opinion on drug delivery. 2017 2017/04/03;14(4):513-523. doi: 10.1080/17425247.2016.1218461.
8. Gregori M, Taylor M, Salvati E, et al. Retro-inverso peptide inhibitor nanoparticles as potent inhibitors of aggregation of the Alzheimer's Abeta peptide. Nanomedicine : nanotechnology, biology, and medicine. 2017 Feb;13(2):723-732. doi: 10.1016/j.nano.2016.10.006. PubMed PMID: 27769888; eng.
9. Martin Prince, Adelina Comas-Herrera, Martin Knapp, et al. Improving healthcare for people living with dementia. World Alzheimer Report 2016. London2016. p. 140.

* World Alzheimer Report by Alzheimer's Disease Inernational, London; gives a globle facts and report on AD.

10. Kaushik A, Jayant RD, Bhardwaj V, et al. Personalized nanomedicine for CNS diseases. Drug discovery today. 2017 Nov 15. doi: 10.1016/j.drudis.2017.11.010. PubMed PMID: 29155026; eng.
11. Gauthier S, Molinuevo JL. Benefits of combined cholinesterase inhibitor and memantine treatment in moderate-severe Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2013 May;9(3):326-31. doi: 10.1016/j.jalz.2011.11.005. PubMed PMID: 23110864; eng.
12. Nagpal K, Singh SK, Mishra DN. Drug targeting to brain: a systematic approach to study the factors, parameters and approaches for prediction of permeability of drugs across BBB. Expert opinion on drug delivery. 2013 2013/07/01;10(7):927-955. doi: 10.1517/17425247.2013.762354.
13. Contestabile A. The history of the cholinergic hypothesis. Behavioural brain research. 2011 Aug 10;221(2):334-40. doi: 10.1016/j.bbr.2009.12.044. PubMed PMID: 20060018; eng.
14. Dong XX, Wang Y, Qin ZH. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta pharmacologica Sinica. 2009 Apr;30(4):379-87. doi: 10.1038/aps.2009.24. PubMed PMID: 19343058; PubMed Central PMCID: PMCPmc4002277. eng.
15. Conti E, Gregori M, Radice I, et al. Multifunctional liposomes interact with Abeta in human biological fluids: Therapeutic implications for Alzheimer's disease. Neurochemistry international. 2017 Feb 24. doi: 10.1016/j.neuint.2017.02.012. PubMed PMID: 28238790; eng.

16. Brambilla D, Verpillot R, Le Droumaguet B, et al. PEGylated nanoparticles bind to and alter amyloid-beta peptide conformation: toward engineering of functional nanomedicines for Alzheimer's disease. ACS nano. 2012 Jul 24;6(7):5897-908. doi: 10.1021/nn300489k. PubMed PMID: 22686577; eng.
17. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science (New York, NY). 2002 Jul 19;297(5580):353-6. doi: 10.1126/science.1072994. PubMed PMID: 12130773; eng.
18. Bana L, Minniti S, Salvati E, et al. Liposomes bi-functionalized with phosphatidic acid and an ApoE-derived peptide affect Abeta aggregation features and cross the blood-brain-barrier: implications for therapy of Alzheimer disease. Nanomedicine : nanotechnology, biology, and medicine. 2014 Oct;10(7):1583-90. doi: 10.1016/j.nano.2013.12.001. PubMed PMID: 24333591; eng.
19. Sano M. Tarenflurbil: mechanisms and myths. Archives of neurology. 2010 Jun;67(6):750-2. doi: 10.1001/archneurol.2010.94. PubMed PMID: 20558395; PubMed Central PMCID: PMCPmc3526376. eng.
20. Doody RS, Raman R, Farlow M, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. The New England journal of medicine. 2013 Jul 25;369(4):341-50. doi: 10.1056/NEJMoa1210951. PubMed PMID: 23883379; eng.
21. Crehan H, Lemere CA. Chapter 7 - Anti-Amyloid-β Immunotherapy for Alzheimer's Disease A2 - Wolfe, Michael S. Developing Therapeutics for Alzheimer's Disease. Boston: Academic Press; 2016. p. 193-226.
22. Sevigny J, Chiao P, Bussiere T, et al. The antibody aducanumab reduces Abeta plaques in Alzheimer's disease. Nature. 2016 Sep 1;537(7618):50-6. doi: 10.1038/nature19323. PubMed PMID: 27582220; eng.
23. Hardy J. The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. Journal of neurochemistry. 2009 Aug;110(4):1129-34. doi: 10.1111/j.1471-4159.2009.06181.x. PubMed PMID: 19457065; eng.

* Covers all the critical prospects and detailed information about amyloid hypothesis of AD pathology which helps to drwan a proper structural illustration of pathophysisology.

24. Castelli F, Puglia C, Sarpietro MG, et al. Characterization of indomethacin-loaded lipid nanoparticles by differential scanning calorimetry. International journal of pharmaceutics. 2005 Nov 04;304(1-2):231-8. doi: 10.1016/j.ijpharm.2005.08.011. PubMed PMID: 16188405; eng.
25. Miller BW, Willett KC, Desilets AR. Rosiglitazone and pioglitazone for the treatment of Alzheimer's disease. The Annals of pharmacotherapy. 2011 Nov;45(11):1416-24. doi: 10.1345/aph.1Q238. PubMed PMID: 22028424; eng.
26. Parihar MS, Hemnani T. Alzheimer's disease pathogenesis and therapeutic interventions. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2004 Jun;11(5):456-67. doi: 10.1016/j.jocn.2003.12.007. PubMed PMID: 15177383; eng.
27. Iqbal K, Alonso Adel C, Chen S, et al. Tau pathology in Alzheimer disease and other tauopathies. Biochimica et biophysica acta. 2005 Jan 03;1739(2-3):198-210. doi: 10.1016/j.bbadis.2004.09.008. PubMed PMID: 15615638; eng.
28. Martin L, Latypova X, Wilson CM, et al. Tau protein kinases: involvement in Alzheimer's disease. Ageing research reviews. 2013 Jan;12(1):289-309. doi: 10.1016/j.arr.2012.06.003. PubMed PMID: 22742992; eng.

* A interesting piece of work which details about the tau hypothesis of AD, another major cause of disease.

29. Swerdlow RH, Burns JM, Khan SM. The Alzheimer's disease mitochondrial cascade hypothesis: progress and perspectives. Biochimica et biophysica acta. 2014 Aug;1842(8):1219-31. doi: 10.1016/j.bbadis.2013.09.010. PubMed PMID: 24071439; PubMed Central PMCID: PMCPmc3962811. eng.
30. Wohlfart S, Gelperina S, Kreuter J. Transport of drugs across the blood-brain barrier by nanoparticles. Journal of controlled release : official journal of the Controlled Release Society. 2012 Jul 20;161(2):264-73. doi: 10.1016/j.jconrel.2011.08.017. PubMed PMID: 21872624; eng.

* The work illustrates about different nanotechnological approaches to deliver the drug across BBB and suitable for treatment of varous brain disorders.

31. Begley DJ. Delivery of therapeutic agents to the central nervous system: the problems and the possibilities. Pharmacology & therapeutics. 2004 Oct;104(1):29-45. doi: 10.1016/j.pharmthera.2004.08.001. PubMed PMID: 15500907; eng.

32. Brasnjevic I, Steinbusch HW, Schmitz C, et al. Delivery of peptide and protein drugs over the blood-brain barrier. Progress in neurobiology. 2009 Apr;87(4):212-51. doi: 10.1016/j.pneurobio.2008.12.002. PubMed PMID: 19395337; eng.
33. Su Y, Sinko PJ. Drug delivery across the blood–brain barrier: why is it difficult? how to measure and improve it? Expert opinion on drug delivery. 2006 2006/05/01;3(3):419-435. doi: 10.1517/17425247.3.3.419.
34. Rip J, Schenk GJ, de Boer AG. Differential receptor-mediated drug targeting to the diseased brain. Expert opinion on drug delivery. 2009 2009/03/01;6(3):227-237. doi: 10.1517/17425240902806383.
35. Gaillard PJ, Visser CC, de Boer AG. Targeted delivery across the blood–brain barrier. Expert opinion on drug delivery. 2005 2005/03/01;2(2):299-309. doi: 10.1517/17425247.2.2.299.
* illuatrated the role of BBB in brain drug delivery and approaches to taregt the drug to the brain. Also, describe various challenges of brain drug delivery.
36. Pardridge WM. CNS drug design based on principles of blood-brain barrier transport. Journal of neurochemistry. 1998 May;70(5):1781-92. PubMed PMID: 9572261; eng.
37. Choonara YE, Kumar P, Modi G, et al. Improving drug delivery technology for treating neurodegenerative diseases. Expert opinion on drug delivery. 2016 2016/07/02;13(7):1029-1043. doi: 10.1517/17425247.2016.1162152.
38. Pardridge WM. Drug targeting to the brain. Pharmaceutical research. 2007 Sep;24(9):1733-44. doi: 10.1007/s11095-007-9324-2. PubMed PMID: 17554607; eng.
39. Pardridge WM, Boado RJ. Reengineering biopharmaceuticals for targeted delivery across the blood-brain barrier. Methods in enzymology. 2012;503:269-92. doi: 10.1016/b978-0-12-396962-0.00011-2. PubMed PMID: 22230573; eng.
40. Soni V, Jain A, Khare P, et al. Potential approaches for drug delivery to the brain: past, present, and future. Critical reviews in therapeutic drug carrier systems. 2010;27(3):187-236. PubMed PMID: 20540687; eng.
41. Jain KK. Nanobiotechnology-based strategies for crossing the blood-brain barrier. Nanomedicine (London, England). 2012 Aug;7(8):1225-33. doi: 10.2217/nnm.12.86. PubMed PMID: 22931448; eng.
42. Jain A, Jain SK. Ligand-Appended BBB-Targeted Nanocarriers (LABTNs). Critical reviews in therapeutic drug carrier systems. 2015;32(2):149-80. PubMed PMID: 25955883; eng.
43. Antimisiaris SG, Mourtas S, Markoutsa E, et al. Nanoparticles for Diagnosis and/or Treatment of Alzheimer's Disease. Advanced Healthcare Materials: John Wiley & Sons, Inc.; 2014. p. 87-179.
* A very interesting piece of work which demonstrates the application of nanoparticles in treatment and diagnosis of Alzheimer's disease.
44. Saraiva C, Praca C, Ferreira R, et al. Nanoparticle-mediated brain drug delivery: Overcoming blood-brain barrier to treat neurodegenerative diseases. Journal of controlled release : official journal of the Controlled Release Society. 2016 Aug 10;235:34-47. doi: 10.1016/j.jconrel.2016.05.044. PubMed PMID: 27208862; eng.
45. Kumaraswamy P, Sethuraman S, Krishnan UM. Development of a dual nanocarrier system as a potential stratagem against amyloid-induced toxicity. Expert opinion on drug delivery. 2014 2014/08/01;11(8):1131-1147. doi: 10.1517/17425247.2014.912211.
46. Sahni JK, Doggui S, Ali J, et al. Neurotherapeutic applications of nanoparticles in Alzheimer's disease. Journal of controlled release : official journal of the Controlled Release Society. 2011 Jun 10;152(2):208-31. doi: 10.1016/j.jconrel.2010.11.033. PubMed PMID: 21134407; eng.
47. Wolfram J, Zhu M, Yang Y, et al. Safety of Nanoparticles in Medicine. Current drug targets. 2015;16(14):1671-81. PubMed PMID: 26601723; PubMed Central PMCID: PMCPmc4964712. eng.
48. Bonifacio BV, Silva PB, Ramos MA, et al. Nanotechnology-based drug delivery systems and herbal medicines: a review. International journal of nanomedicine. 2014;9:1-15. doi: 10.2147/ijn.s52634. PubMed PMID: 24363556; PubMed Central PMCID: PMCPmc3862741. eng.
49. Sunasee R, Adokoh CK, Darkwa J, et al. Therapeutic potential of carbohydrate-based polymeric and nanoparticle systems. Expert opinion on drug delivery. 2014 2014/06/01;11(6):867-884. doi: 10.1517/17425247.2014.902048.
50. Lorscheidt S, Lamprecht A. Safety assessment of nanoparticles for drug delivery by means of classic in vitro assays and beyond. Expert opinion on drug delivery. 2016 2016/11/01;13(11):1545-1558. doi: 10.1080/17425247.2016.1198773.
* Covers all the toxicity and safety profile of nanoparticles. *In vitro* and *in vivo* assesment of toxicity.51. Weissig V, Guzman-Villanueva D. Nanocarrier-based antioxidant therapy: promise or delusion? Expert opinion on drug delivery. 2015 2015/11/02;12(11):1783-1790. doi: 10.1517/17425247.2015.1063611.

52. Lajoie JM, Shusta EV. Targeting receptor-mediated transport for delivery of biologics across the blood-brain barrier. Annual review of pharmacology and toxicology. 2015;55:613-31. doi: 10.1146/annurev-pharmtox-010814-124852. PubMed PMID: 25340933; PubMed Central PMCID: PMCPmc5051266. eng.
53. Barbu E, Molnàr É, Tsibouklis J, et al. The potential for nanoparticle-based drug delivery to the brain: overcoming the blood–brain barrier. Expert opinion on drug delivery. 2009 2009/06/01;6(6):553-565. doi: 10.1517/17425240902939143.
54. Tosi G, Costantino L, Ruozi B, et al. Polymeric nanoparticles for the drug delivery to the central nervous system. Expert opinion on drug delivery. 2008 2008/02/01;5(2):155-174. doi: 10.1517/17425247.5.2.155.
55. Baeza A, Colilla M, Vallet-Regí M. Advances in mesoporous silica nanoparticles for targeted stimuli-responsive drug delivery. Expert opinion on drug delivery. 2015 2015/02/01;12(2):319-337. doi: 10.1517/17425247.2014.953051.
56. Sagar V, Nair M. Near-infrared biophotonics-based nanodrug release systems and their potential application for neuro-disorders. Expert opinion on drug delivery. 2017:1-16. doi: 10.1080/17425247.2017.1297794.
57. Alexander A, Ajazuddin, Patel RJ, et al. Recent expansion of pharmaceutical nanotechnologies and targeting strategies in the field of phytopharmaceuticals for the delivery of herbal extracts and bioactives. Journal of controlled release : official journal of the Controlled Release Society. 2016 Nov 10;241:110-124. doi: 10.1016/j.jconrel.2016.09.017. PubMed PMID: 27663228; eng.

* Demonstrated the application of nano carrier system in targeting of various bioactives and challenges in the nano drug delivery.

58. Alexander A, Saraf S, Saraf S. Understanding the Role of Poloxamer 407 based Thermoreversible In Situ Gelling Hydrogel for Delivery of PEGylated Melphalan Conjugate. Current drug delivery. 2016;13(4):621-30. PubMed PMID: 26845559; eng.
59. Jeswani G, Alexander A, Saraf S, et al. Recent approaches for reducing hemolytic activity of chemotherapeutic agents. Journal of controlled release : official journal of the Controlled Release Society. 2015 Aug 10;211:10-21. doi: 10.1016/j.jconrel.2015.06.001. PubMed PMID: 26047758; eng.
60. Alexander A, Saraf S, Saraf S. A comparative study of chitosan and poloxamer based thermosensitive hydrogel for the delivery of PEGylated melphalan conjugates. Drug development and industrial pharmacy. 2015;41(12):1954-61. doi: 10.3109/03639045.2015.1011167. PubMed PMID: 25678314; eng.
61. Alexander A, Ajazuddin, Khan J, et al. Formulation and evaluation of chitosan-based long-acting injectable hydrogel for PEGylated melphalan conjugate. The Journal of pharmacy and pharmacology. 2014 Sep;66(9):1240-50. doi: 10.1111/jphp.12262. PubMed PMID: 24824413; eng.
62. Alexander A, Ajazuddin, Khan J, et al. Poly(ethylene glycol)-poly(lactic-co-glycolic acid) based thermosensitive injectable hydrogels for biomedical applications. Journal of controlled release : official journal of the Controlled Release Society. 2013 Dec 28;172(3):715-29. doi: 10.1016/j.jconrel.2013.10.006. PubMed PMID: 24144918; eng.
63. Sahu S, Saraf S, Kaur CD, et al. Biocompatible nanoparticles for sustained topical delivery of anticancer phytoconstituent quercetin. Pakistan journal of biological sciences : PJBS. 2013 Jul 01;16(13):601-9. PubMed PMID: 24505982; eng.
64. Ajazuddin, Alexander A, Khan J, et al. Advancement in stimuli triggered in situ gelling delivery for local and systemic route. Expert opinion on drug delivery. 2012 Dec;9(12):1573-92. doi: 10.1517/17425247.2013.734806. PubMed PMID: 23075325; eng.
65. Alexander A, Dwivedi S, Ajazuddin, et al. Approaches for breaking the barriers of drug permeation through transdermal drug delivery. Journal of controlled release : official journal of the Controlled Release Society. 2012 Nov 28;164(1):26-40. doi: 10.1016/j.jconrel.2012.09.017. PubMed PMID: 23064010; eng.
66. Grabrucker AM, Ruozi B, Belletti D, et al. Nanoparticle transport across the blood brain barrier. Tissue barriers. 2016 Jan-Mar;4(1):e1153568. doi: 10.1080/21688370.2016.1153568. PubMed PMID: 27141426; PubMed Central PMCID: PMCPmc4836460. eng.
67. Coyle JT, Price DL, DeLong MR. Alzheimer's disease: a disorder of cortical cholinergic innervation. Science (New York, NY). 1983 Mar 11;219(4589):1184-90. PubMed PMID: 6338589; eng.
68. Adem A, Mohammed AK, Winblad B. Multiple effects of tetrahydroaminoacridine on the cholinergic system: biochemical and behavioural aspects. Journal of neural transmission Parkinson's disease and dementia section. 1990;2(2):113-28. PubMed PMID: 2222779; eng.

69. Reichman WE. Current pharmacologic options for patients with Alzheimer's disease. Annals of general hospital psychiatry. 2003 Jan 29;2(1):1. PubMed PMID: 12605726; PubMed Central PMCID: PMCPmc149431. eng.
70. Hartvig P, Askmark H, Aquilonius SM, et al. Clinical pharmacokinetics of intravenous and oral 9-amino-1,2,3,4-tetrahydroacridine, tacrine. European journal of clinical pharmacology. 1990;38(3):259-63. PubMed PMID: 2340845; eng.
71. Luppi B, Bigucci F, Cerchiara T, et al. Chitosan-based hydrogels for nasal drug delivery: from inserts to nanoparticles. Expert opinion on drug delivery. 2010 2010/07/01;7(7):811-828. doi: 10.1517/17425247.2010.495981.
72. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM. Recent advances on chitosan-based micro- and nanoparticles in drug delivery. Journal of controlled release : official journal of the Controlled Release Society. 2004 Nov 05;100(1):5-28. doi: 10.1016/j.jconrel.2004.08.010. PubMed PMID: 15491807; eng.
73. Duceppe N, Tabrizian M. Advances in using chitosan-based nanoparticles for in vitro and in vivo drug and gene delivery. Expert opinion on drug delivery. 2010 2010/10/01;7(10):1191-1207. doi: 10.1517/17425247.2010.514604.
74. Felt O, Furrer P, Mayer JM, et al. Topical use of chitosan in ophthalmology: tolerance assessment and evaluation of precorneal retention. International journal of pharmaceutics. 1999 Apr 15;180(2):185-93. PubMed PMID: 10370189; eng.
75. Amiji MM. Permeability and blood compatibility properties of chitosan-poly(ethylene oxide) blend membranes for haemodialysis. Biomaterials. 1995 May;16(8):593-9. PubMed PMID: 7548609; eng.
76. Mittal S, Cohen A, Maysinger D. In vitro effects of brain derived neurotrophic factor released from microspheres. Neuroreport. 1994 Dec 20;5(18):2577-82. PubMed PMID: 7696608; eng.
77. Aktas Y, Andrieux K, Alonso MJ, et al. Preparation and in vitro evaluation of chitosan nanoparticles containing a caspase inhibitor. International journal of pharmaceutics. 2005 Jul 25;298(2):378-83. doi: 10.1016/j.ijpharm.2005.03.027. PubMed PMID: 15893439; eng.
78. Wu Y, Yang W, Wang C, et al. Chitosan nanoparticles as a novel delivery system for ammonium glycyrrhizinate. International journal of pharmaceutics. 2005 May 13;295(1-2):235-45. doi: 10.1016/j.ijpharm.2005.01.042. PubMed PMID: 15848008; eng.
79. Begum AN, Jones MR, Lim GP, et al. Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. The Journal of pharmacology and experimental therapeutics. 2008 Jul;326(1):196-208. doi: 10.1124/jpet.108.137455. PubMed PMID: 18417733; PubMed Central PMCID: PMCPmc2527621. eng.
80. Genta I, Costantini M, Asti A, et al. Influence of glutaraldehyde on drug release and mucoadhesive properties of chitosan microspheres. Carbohydrate Polymers. 1998 1998/07/01/;36(2):81-88. doi: http://dx.doi.org/10.1016/S0144-8617(98)00022-8.
81. Wilson B, Samanta MK, Santhi K, et al. Chitosan nanoparticles as a new delivery system for the anti-Alzheimer drug tacrine. Nanomedicine : nanotechnology, biology, and medicine. 2010 Feb;6(1):144-52. doi: 10.1016/j.nano.2009.04.001. PubMed PMID: 19446656; eng.

** They have prepared tacrine loaded chitosan nanoarticle and studied the effect of polysorbate 80 coating on drug biodistribution. Chiosan nanoparticle controlled the rate of drug release and improved the bioavailability of the drug.

82. Nordberg A, Svensson AL. Cholinesterase inhibitors in the treatment of Alzheimer's disease: a comparison of tolerability and pharmacology. Drug safety. 1998 Dec;19(6):465-80. PubMed PMID: 9880090; eng.
83. Williams BR, Nazarians A, Gill MA. A review of rivastigmine: a reversible cholinesterase inhibitor. Clinical therapeutics. 2003 Jun;25(6):1634-53. PubMed PMID: 12860489; eng.
84. Wilson B, Samanta MK, Santhi K, et al. Poly(n-butylcyanoacrylate) nanoparticles coated with polysorbate 80 for the targeted delivery of rivastigmine into the brain to treat Alzheimer's disease. Brain research. 2008 Mar 20;1200:159-68. doi: 10.1016/j.brainres.2008.01.039. PubMed PMID: 18291351; eng.

** Author have prepared the rivastigmine loaded polysorbate coated poly(n-butylcyanoacrylate) injectable nanoparticle for targeting to the brain. The resulting formulation increases the concentration of drug on the brain 3.8 folds in comparison to the drug solution.

85. Kreuter J, Alyautdin RN, Kharkevich DA, et al. Passage of peptides through the blood-brain barrier with colloidal polymer particles (nanoparticles). Brain research. 1995 Mar 13;674(1):171-4. PubMed PMID: 7773690; eng.

86. Schroeder U, Sommerfeld P, Ulrich S, et al. Nanoparticle technology for delivery of drugs across the blood-brain barrier. Journal of pharmaceutical sciences. 1998 Nov;87(11):1305-7. doi: 10.1021/js980084y. PubMed PMID: 9811481; eng.
87. Alyautdin RN, Tezikov EB, Ramge P, et al. Significant entry of tubocurarine into the brain of rats by adsorption to polysorbate 80-coated polybutylcyanoacrylate nanoparticles: an in situ brain perfusion study. Journal of microencapsulation. 1998 Jan-Feb;15(1):67-74. doi: 10.3109/02652049809006836. PubMed PMID: 9463808; eng.
88. Gulyaev AE, Gelperina SE, Skidan IN, et al. Significant transport of doxorubicin into the brain with polysorbate 80-coated nanoparticles. Pharmaceutical research. 1999 Oct;16(10):1564-9. PubMed PMID: 10554098; eng.
89. Alyautdin RN, Petrov VE, Langer K, et al. Delivery of loperamide across the blood-brain barrier with polysorbate 80-coated polybutylcyanoacrylate nanoparticles. Pharmaceutical research. 1997 Mar;14(3):325-8. PubMed PMID: 9098875; eng.
90. Friese A, Seiller E, Quack G, et al. Increase of the duration of the anticonvulsive activity of a novel NMDA receptor antagonist using poly(butylcyanoacrylate) nanoparticles as a parenteral controlled release system. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV. 2000 Mar;49(2):103-9. PubMed PMID: 10704892; eng.
91. Verdun C, Couvreur P, Vranckx H, et al. Development of a nanoparticle controlled-release formulation for human use. Journal of Controlled Release. 1986 1986/01/01/;3(1):205-210. doi: http://dx.doi.org/10.1016/0168-3659(86)90081-7.
92. Reddy LH, Murthy RS. Pharmacokinetics and biodistribution studies of Doxorubicin loaded poly(butyl cyanoacrylate) nanoparticles synthesized by two different techniques. Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia. 2004 Dec;148(2):161-6. PubMed PMID: 15744366; eng.
93. Kreuter J. Nanoparticulate systems for brain delivery of drugs. Advanced drug delivery reviews. 2001 Mar 23;47(1):65-81. PubMed PMID: 11251246; eng.
94. Kreuter J, Shamenkov D, Petrov V, et al. Apolipoprotein-mediated transport of nanoparticle-bound drugs across the blood-brain barrier. Journal of drug targeting. 2002 Jun;10(4):317-25. doi: 10.1080/10611860290031877. PubMed PMID: 12164380; eng.
95. Atwood CS, Obrenovich ME, Liu T, et al. Amyloid-beta: a chameleon walking in two worlds: a review of the trophic and toxic properties of amyloid-beta. Brain research Brain research reviews. 2003 Sep;43(1):1-16. PubMed PMID: 14499458; eng.
96. Dong J, Atwood CS, Anderson VE, et al. Metal binding and oxidation of amyloid-beta within isolated senile plaque cores: Raman microscopic evidence. Biochemistry. 2003 Mar 18;42(10):2768-73. doi: 10.1021/bi0272151. PubMed PMID: 12627941; eng.
97. Ehmann WD, Markesbery WR, Alauddin M, et al. Brain trace elements in Alzheimer's disease. Neurotoxicology. 1986 Spring;7(1):195-206. PubMed PMID: 3714121; eng.
98. Cherny RA, Barnham KJ, Lynch T, et al. Chelation and intercalation: complementary properties in a compound for the treatment of Alzheimer's disease. Journal of structural biology. 2000 Jun;130(2-3):209-16. doi: 10.1006/jsbi.2000.4285. PubMed PMID: 10940226; eng.
99. Nguyen M, Robert A, Sournia-Saquet A, et al. Characterization of new specific copper chelators as potential drugs for the treatment of Alzheimer's disease. Chemistry (Weinheim an der Bergstrasse, Germany). 2014 May 26;20(22):6771-85. doi: 10.1002/chem.201402143. PubMed PMID: 24797103; eng.
100. Franz KJ. Clawing back: broadening the notion of metal chelators in medicine. Current opinion in chemical biology. 2013 Apr;17(2):143-9. doi: 10.1016/j.cbpa.2012.12.021. PubMed PMID: 23332666; PubMed Central PMCID: PMCPmc3634900. eng.
101. Jagota S, Rajadas J. Effect of phenolic compounds against Abeta aggregation and Abeta-induced toxicity in transgenic C. elegans. Neurochemical research. 2012 Jan;37(1):40-8. doi: 10.1007/s11064-011-0580-5. PubMed PMID: 21858698; eng.
102. Ohta K, Mizuno A, Li S, et al. Endoplasmic reticulum stress enhances gamma-secretase activity. Biochemical and biophysical research communications. 2011 Dec 16;416(3-4):362-6. doi: 10.1016/j.bbrc.2011.11.042. PubMed PMID: 22115781; eng.
103. Sun S, Chen W, Cao W, et al. Research on the chelation between quercetin and Cr(III) ion by Density Functional Theory (DFT) method. Journal of Molecular Structure: THEOCHEM. 2008 7/15/;860(1–3):40-44. doi: https://doi.org/10.1016/j.theochem.2008.03.020.

104. Spencer JP, Chowrimootoo G, Choudhury R, et al. The small intestine can both absorb and glucuronidate luminal flavonoids. FEBS letters. 1999 Sep 17;458(2):224-30. PubMed PMID: 10481070; eng.
105. Jain AK, Das M, Swarnakar NK, et al. Engineered PLGA nanoparticles: an emerging delivery tool in cancer therapeutics. Critical reviews in therapeutic drug carrier systems. 2011;28(1):1-45. PubMed PMID: 21395514; eng.
106. Ansari MA, Abdul HM, Joshi G, et al. Protective effect of quercetin in primary neurons against Abeta(1-42): relevance to Alzheimer's disease. The Journal of nutritional biochemistry. 2009 Apr;20(4):269-75. doi: 10.1016/j.jnutbio.2008.03.002. PubMed PMID: 18602817; PubMed Central PMCID: PMCPmc2737260. eng.
107. Sun D, Li N, Zhang W, et al. Design of PLGA-functionalized quercetin nanoparticles for potential use in Alzheimer's disease. Colloids and surfaces B, Biointerfaces. 2016 Dec 01;148:116-129. doi: 10.1016/j.colsurfb.2016.08.052. PubMed PMID: 27591943; eng.
** They have developed PLGA functionalized quercetin nanoparticles which reduces the neurotoxicity by metal ion chelation. the PLGA nanoparticle releases the drug in a sustained manner and improves the bioavailability of the drug.
108. Cui Z, Lockman PR, Atwood CS, et al. Novel D-penicillamine carrying nanoparticles for metal chelation therapy in Alzheimer's and other CNS diseases. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV. 2005 Feb;59(2):263-72. doi: 10.1016/j.ejpb.2004.07.009. PubMed PMID: 15661498; eng.
109. Martin FJ, Papahadjopoulos D. Irreversible coupling of immunoglobulin fragments to preformed vesicles. An improved method for liposome targeting. The Journal of biological chemistry. 1982 Jan 10;257(1):286-8. PubMed PMID: 7053372; eng.
110. Kato N, Nakamura M, Uchiyama T. 1H NMR studies of the reactions of copper(I) and copper(II) with D-penicillamine and glutathione. Journal of inorganic biochemistry. 1999 Jun 15;75(2):117-21. PubMed PMID: 10450606; eng.
111. Hartig W, Paulke BR, Varga C, et al. Electron microscopic analysis of nanoparticles delivering thioflavin-T after intrahippocampal injection in mouse: implications for targeting beta-amyloid in Alzheimer's disease. Neuroscience letters. 2003 Feb 27;338(2):174-6. PubMed PMID: 12566180; eng.
112. Klein WL, Krafft GA, Finch CE. Targeting small Abeta oligomers: the solution to an Alzheimer's disease conundrum? Trends in neurosciences. 2001 Apr;24(4):219-24. PubMed PMID: 11250006; eng.
113. de Boer AG, Gaillard PJ. Strategies to improve drug delivery across the blood-brain barrier. Clinical pharmacokinetics. 2007;46(7):553-76. doi: 10.2165/00003088-200746070-00002. PubMed PMID: 17596102; eng.
114. Hu K, Li J, Shen Y, et al. Lactoferrin-conjugated PEG-PLA nanoparticles with improved brain delivery: in vitro and in vivo evaluations. Journal of controlled release : official journal of the Controlled Release Society. 2009 Feb 20;134(1):55-61. doi: 10.1016/j.jconrel.2008.10.016. PubMed PMID: 19038299; eng.
** They have prepared lactoferrin conjugated PEG-PLA nanoparticle which crosses the BBB via receptor mediated transcytosis and increases the drug concentration in the brain. It also improves the cellular uptake and brain distribution of drug.
115. Huang R, Ke W, Liu Y, et al. The use of lactoferrin as a ligand for targeting the polyamidoamine-based gene delivery system to the brain. Biomaterials. 2008 Jan;29(2):238-46. doi: 10.1016/j.biomaterials.2007.09.024. PubMed PMID: 17935779; eng.
116. Suzuki YA, Lopez V, Lonnerdal B. Mammalian lactoferrin receptors: structure and function. Cellular and molecular life sciences : CMLS. 2005 Nov;62(22):2560-75. doi: 10.1007/s00018-005-5371-1. PubMed PMID: 16261254; eng.
117. Huang RQ, Ke WL, Qu YH, et al. Characterization of lactoferrin receptor in brain endothelial capillary cells and mouse brain. Journal of biomedical science. 2007 Jan;14(1):121-8. doi: 10.1007/s11373-006-9121-7. PubMed PMID: 17048089; eng.
118. Zhong ZR, Liu J, Deng Y, et al. Preparation and characterization of a novel nonviral gene transfer system: procationic-liposome-protamine-DNA complexes. Drug delivery. 2007 Mar;14(3):177-83. doi: 10.1080/10717540601067471. PubMed PMID: 17454038; eng.
119. Olivier JC. Drug transport to brain with targeted nanoparticles. NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics. 2005 Jan;2(1):108-19. doi: 10.1602/neurorx.2.1.108. PubMed PMID: 15717062; PubMed Central PMCID: PMCPmc539329. eng.
120. Lu W, Zhang Y, Tan YZ, et al. Cationic albumin-conjugated pegylated nanoparticles as novel drug carrier for brain delivery. Journal of controlled release : official journal of the Controlled Release

Society. 2005 Oct 20;107(3):428-48. doi: 10.1016/j.jconrel.2005.03.027. PubMed PMID: 16176844; eng.
121. Olivier JC, Huertas R, Lee HJ, et al. Synthesis of pegylated immunonanoparticles. Pharmaceutical research. 2002 Aug;19(8):1137-43. PubMed PMID: 12240939; eng.
122. Agrawal M, Ajazuddin, Tripathi DK, et al. Recent advancements in liposomes targeting strategies to cross blood-brain barrier (BBB) for the treatment of Alzheimer's disease. Journal of controlled release : official journal of the Controlled Release Society. 2017 May 24;260:61-77. doi: 10.1016/j.jconrel.2017.05.019. PubMed PMID: 28549949; eng.
123. Zhang C, Wan X, Zheng X, et al. Dual-functional nanoparticles targeting amyloid plaques in the brains of Alzheimer's disease mice. Biomaterials. 2014 Jan;35(1):456-65. doi: 10.1016/j.biomaterials.2013.09.063. PubMed PMID: 24099709; eng.
124. Xu YL, Zhao J, Ma RY, et al. [Influence of H102 on the expression of amyloid protein and amyloid precursor protein in the hippocampus of APP695 transgenic mice]. Zhongguo ying yong sheng li xue za zhi = Zhongguo yingyong shenglixue zazhi = Chinese journal of applied physiology. 2010 Aug;26(3):302-6. PubMed PMID: 21038675; chi.
125. Soto C, Estrada L. Amyloid inhibitors and beta-sheet breakers. Sub-cellular biochemistry. 2005;38:351-64. PubMed PMID: 15709488; eng.
126. Zhang C, Zheng X, Wan X, et al. The potential use of H102 peptide-loaded dual-functional nanoparticles in the treatment of Alzheimer's disease. Journal of controlled release : official journal of the Controlled Release Society. 2014 Oct 28;192:317-24. doi: 10.1016/j.jconrel.2014.07.050. PubMed PMID: 25102404; eng.
127. Kabanov AV, Vinogradov SV. Nanogels as Pharmaceutical Carriers. In: Torchilin V, editor. Multifunctional Pharmaceutical Nanocarriers. New York, NY: Springer New York; 2008. p. 67-80.
128. Soni G, Yadav KS. Nanogels as potential nanomedicine carrier for treatment of cancer: A mini review of the state of the art. Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society. 2016 Mar;24(2):133-9. doi: 10.1016/j.jsps.2014.04.001. PubMed PMID: 27013905; PubMed Central PMCID: PMCPmc4792897. eng.
129. Eckmann DM, Composto RJ, Tsourkas A, et al. Nanogel Carrier Design for Targeted Drug Delivery. Journal of materials chemistry B. 2014 Dec 14;2(46):8085-8097. doi: 10.1039/c4tb01141d. PubMed PMID: 25485112; PubMed Central PMCID: PMCPmc4251498. eng.
130. Dorwal D. Nanogels as novel and versatile pharmaceuticals. Int J Pharm Pharm Sci. 2012;4(3):67-74.
131. LaFerla FM, Green KN, Oddo S. Intracellular amyloid-beta in Alzheimer's disease. Nature reviews Neuroscience. 2007 Jul;8(7):499-509. doi: 10.1038/nrn2168. PubMed PMID: 17551515; eng.
132. Muchowski PJ, Wacker JL. Modulation of neurodegeneration by molecular chaperones. Nature reviews Neuroscience. 2005 Jan;6(1):11-22. doi: 10.1038/nrn1587. PubMed PMID: 15611723; eng.
133. Ikeda K, Okada T, Sawada S, et al. Inhibition of the formation of amyloid beta-protein fibrils using biocompatible nanogels as artificial chaperones. FEBS letters. 2006 Dec 11;580(28-29):6587-95. doi: 10.1016/j.febslet.2006.11.009. PubMed PMID: 17125770; eng.
134. Morimoto N, Endo T, Iwasaki Y, et al. Design of hybrid hydrogels with self-assembled nanogels as cross-linkers: interaction with proteins and chaperone-like activity. Biomacromolecules. 2005 Jul-Aug;6(4):1829-34. doi: 10.1021/bm050156x. PubMed PMID: 16004415; eng.
135. Ayame H, Morimoto N, Akiyoshi K. Self-assembled cationic nanogels for intracellular protein delivery. Bioconjugate chemistry. 2008 Apr;19(4):882-90. doi: 10.1021/bc700422s. PubMed PMID: 18336000; eng.
136. Pilakka-Kanthikeel S, Raymond A, Atluri VS, et al. Sterile alpha motif and histidine/aspartic acid domain-containing protein 1 (SAMHD1)-facilitated HIV restriction in astrocytes is regulated by miRNA-181a. Journal of neuroinflammation. 2015 Apr 8;12:66. doi: 10.1186/s12974-015-0285-9. PubMed PMID: 25890101; PubMed Central PMCID: PMCPmc4410490. eng.
137. Boridy S, Takahashi H, Akiyoshi K, et al. The binding of pullulan modified cholesteryl nanogels to Abeta oligomers and their suppression of cytotoxicity. Biomaterials. 2009 Oct;30(29):5583-91. doi: 10.1016/j.biomaterials.2009.06.010. PubMed PMID: 19577802; eng.
** Boridy et al. have prepared cationic CHP nanogel which forms a complex with Aβ peptide in brain and facilitates the clearance of Aβ protein from brain and reduces he neurotoxicity.
138. Puri A, Loomis K, Smith B, et al. Lipid-based nanoparticles as pharmaceutical drug carriers: from concepts to clinic. Critical reviews in therapeutic drug carrier systems. 2009;26(6):523-80. PubMed PMID: 20402623; PubMed Central PMCID: PMCPmc2885142. eng.

139. Sinha S, Lieberburg I. Cellular mechanisms of beta-amyloid production and secretion. Proceedings of the National Academy of Sciences of the United States of America. 1999 Sep 28;96(20):11049-53. PubMed PMID: 10500121; PubMed Central PMCID: PMCPmc34239. eng.
140. Akiyama H, Barger S, Barnum S, et al. Inflammation and Alzheimer's disease. Neurobiology of aging. 2000 May-Jun;21(3):383-421. PubMed PMID: 10858586; PubMed Central PMCID: PMCPmc3887148. eng.
141. Garcia T, Esparza JL, Nogues MR, et al. Oxidative stress status and RNA expression in hippocampus of an animal model of Alzheimer's disease after chronic exposure to aluminum. Hippocampus. 2010 Jan;20(1):218-25. doi: 10.1002/hipo.20612. PubMed PMID: 19405147; eng.
142. Cummings JL, Cole G. Alzheimer disease. Jama. 2002 May 08;287(18):2335-8. PubMed PMID: 11988038; eng.
143. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet (London, England). 2006 Jul 29;368(9533):387-403. doi: 10.1016/s0140-6736(06)69113-7. PubMed PMID: 16876668; eng.
144. Raschetti R, Albanese E, Vanacore N, et al. Cholinesterase inhibitors in mild cognitive impairment: a systematic review of randomised trials. PLoS medicine. 2007 Nov 27;4(11):e338. doi: 10.1371/journal.pmed.0040338. PubMed PMID: 18044984; PubMed Central PMCID: PMCPmc2082649. eng.
145. Camps P, Munoz-Torrero D. Cholinergic drugs in pharmacotherapy of Alzheimer's disease. Mini reviews in medicinal chemistry. 2002 Feb;2(1):11-25. PubMed PMID: 12369954; eng.
146. Wang RH, Bejar C, Weinstock M. Gender differences in the effect of rivastigmine on brain cholinesterase activity and cognitive function in rats. Neuropharmacology. 2000 Jan 28;39(3):497-506. PubMed PMID: 10698015; eng.
147. Ismail MF, Elmeshad AN, Salem NA. Potential therapeutic effect of nanobased formulation of rivastigmine on rat model of Alzheimer's disease. International journal of nanomedicine. 2013;8:393-406. doi: 10.2147/ijn.s39232. PubMed PMID: 23378761; PubMed Central PMCID: PMCPmc3558309. eng.
148. Matsuoka Y, Saito M, LaFrancois J, et al. Novel therapeutic approach for the treatment of Alzheimer's disease by peripheral administration of agents with an affinity to beta-amyloid. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2003 Jan 01;23(1):29-33. PubMed PMID: 12514198; eng.
149. Mancini S, Minniti S, Gregori M, et al. The hunt for brain Abeta oligomers by peripherally circulating multi-functional nanoparticles: Potential therapeutic approach for Alzheimer disease. Nanomedicine : nanotechnology, biology, and medicine. 2016 Jan;12(1):43-52. doi: 10.1016/j.nano.2015.09.003. PubMed PMID: 26410276; eng.
** They have prepared a multifunctional liposome surface functionalized with mApoE and PA to target the BBB and Aβ peptide in the brain and exert more precise effect on the target site inside the brain. it significantly reduces the Aβ level in the brain.
150. Mourtas S, Canovi M, Zona C, et al. Curcumin-decorated nanoliposomes with very high affinity for amyloid-beta1-42 peptide. Biomaterials. 2011 Feb;32(6):1635-45. doi: 10.1016/j.biomaterials.2010.10.027. PubMed PMID: 21131044; eng.
151. Mohanty C, Das M, Sahoo SK. Emerging role of nanocarriers to increase the solubility and bioavailability of curcumin. Expert opinion on drug delivery. 2012 2012/11/01;9(11):1347-1364. doi: 10.1517/17425247.2012.724676.
152. Sarkar G, Curran GL, Mahlum E, et al. A carrier for non-covalent delivery of functional beta-galactosidase and antibodies against amyloid plaques and IgM to the brain. PloS one. 2011;6(12):e28881. doi: 10.1371/journal.pone.0028881. PubMed PMID: 22216132; PubMed Central PMCID: PMCPmc3244419. eng.
153. Gabathuler R. Approaches to transport therapeutic drugs across the blood-brain barrier to treat brain diseases. Neurobiology of disease. 2010 Jan;37(1):48-57. doi: 10.1016/j.nbd.2009.07.028. PubMed PMID: 19664710; eng.
154. Shi Y, Su Z, Li S, et al. Multistep Targeted Nano Drug Delivery System Aiming at Leukemic Stem Cells and Minimal Residual Disease. Molecular Pharmaceutics. 2013 2013/06/03;10(6):2479-2489. doi: 10.1021/mp4001266.
155. Lim S-J, Kim C-K. Formulation parameters determining the physicochemical characteristics of solid lipid nanoparticles loaded with all-trans retinoic acid. International journal of pharmaceutics. 2002 2002/08/28/;243(1):135-146. doi: http://dx.doi.org/10.1016/S0378-5173(02)00269-7.

156. Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech. 2015 Apr;5(2):123-127. doi: 10.1007/s13205-014-0214-0. PubMed PMID: 28324579; PubMed Central PMCID: PMCPmc4362737. eng.
157. Yang P, Cai X, Zhou K, et al. A novel oil-body nanoemulsion formulation of ginkgolide B: pharmacokinetics study and in vivo pharmacodynamics evaluations. Journal of pharmaceutical sciences. 2014 Apr;103(4):1075-84. doi: 10.1002/jps.23866. PubMed PMID: 24496859; eng.
158. Kuo F, Subramanian B, Kotyla T, et al. Nanoemulsions of an anti-oxidant synergy formulation containing gamma tocopherol have enhanced bioavailability and anti-inflammatory properties. International journal of pharmaceutics. 2008 Nov 03;363(1-2):206-13. doi: 10.1016/j.ijpharm.2008.07.022. PubMed PMID: 18718513; eng.
159. Wu H, Zhou A, Lu C, et al. Examination of lymphatic transport of puerarin in unconscious lymph duct-cannulated rats after administration in microemulsion drug delivery systems. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 2011 Mar 18;42(4):348-53. doi: 10.1016/j.ejps.2010.12.010. PubMed PMID: 21216284; eng.
160. Gaoe H, Pang Z, Pan S, et al. Anti-glioma effect and safety of docetaxel-loaded nanoemulsion. Archives of pharmacal research. 2012 Feb;35(2):333-41. doi: 10.1007/s12272-012-0214-8. PubMed PMID: 22370788; eng.
161. Aguzzi A, O'Connor T. Protein aggregation diseases: pathogenicity and therapeutic perspectives. Nature reviews Drug discovery. 2010 Mar;9(3):237-48. doi: 10.1038/nrd3050. PubMed PMID: 20190788; eng.
162. Morales R, Green KM, Soto C. Cross currents in protein misfolding disorders: interactions and therapy. CNS & neurological disorders drug targets. 2009 Nov;8(5):363-71. PubMed PMID: 19702573; PubMed Central PMCID: PMCPmc2804467. eng.
163. Ashe KH, Aguzzi A. Prions, prionoids and pathogenic proteins in Alzheimer disease. Prion. 2013 Jan-Feb;7(1):55-9. doi: 10.4161/pri.23061. PubMed PMID: 23208281; PubMed Central PMCID: PMCPmc3609051. eng.
164. Perluigi M, Coccia R, Butterfield DA. 4-Hydroxy-2-nonenal, a reactive product of lipid peroxidation, and neurodegenerative diseases: a toxic combination illuminated by redox proteomics studies. Antioxidants & redox signaling. 2012 Dec 01;17(11):1590-609. doi: 10.1089/ars.2011.4406. PubMed PMID: 22114878; PubMed Central PMCID: PMCPmc3449441. eng.
165. Schubert SY, Lansky EP, Neeman I. Antioxidant and eicosanoid enzyme inhibition properties of pomegranate seed oil and fermented juice flavonoids. Journal of ethnopharmacology. 1999 Jul;66(1):11-7. PubMed PMID: 10432202; eng.
166. Kaufman M, Wiesman Z. Pomegranate oil analysis with emphasis on MALDI-TOF/MS triacylglycerol fingerprinting. Journal of agricultural and food chemistry. 2007 Dec 12;55(25):10405-13. doi: 10.1021/jf072741q. PubMed PMID: 18004807; eng.
167. Shi C, Wu F, Zhu XC, et al. Incorporation of beta-sitosterol into the membrane increases resistance to oxidative stress and lipid peroxidation via estrogen receptor-mediated PI3K/GSK3beta signaling. Biochimica et biophysica acta. 2013 Mar;1830(3):2538-44. doi: 10.1016/j.bbagen.2012.12.012. PubMed PMID: 23266618; eng.
168. Friedman-Levi Y, Meiner Z, Canello T, et al. Fatal prion disease in a mouse model of genetic E200K Creutzfeldt-Jakob disease. PLoS pathogens. 2011 Nov;7(11):e1002350. doi: 10.1371/journal.ppat.1002350. PubMed PMID: 22072968; PubMed Central PMCID: PMCPmc3207931. eng.
169. Sawant RR, Torchilin VP. Multifunctionality of lipid-core micelles for drug delivery and tumour targeting. Molecular membrane biology. 2010 Oct;27(7):232-46. doi: 10.3109/09687688.2010.516276. PubMed PMID: 20929339; eng.
170. Mizrahi M, Friedman-Levi Y, Larush L, et al. Pomegranate seed oil nanoemulsions for the prevention and treatment of neurodegenerative diseases: the case of genetic CJD. Nanomedicine : nanotechnology, biology, and medicine. 2014 Aug;10(6):1353-63. doi: 10.1016/j.nano.2014.03.015. PubMed PMID: 24704590; eng.
** They have prepared a soluble nanoemulsion of PSO which improves the brain permeability and bioavailabilty of PSO in brain. Along with this, it also reduces the effecive dose of drug and prevent the lipid oxidation.
171. Yankner BA. Mechanisms of neuronal degeneration in Alzheimer's disease. Neuron. 1996 May;16(5):921-32. PubMed PMID: 8630250; eng.
172. Shi C, Zhao L, Zhu B, et al. Protective effects of Ginkgo biloba extract (EGb761) and its constituents quercetin and ginkgolide B against beta-amyloid peptide-induced toxicity in SH-SY5Y cells. Chemico-

biological interactions. 2009 Sep 14;181(1):115-23. doi: 10.1016/j.cbi.2009.05.010. PubMed PMID: 19464278; eng.
173. Xiao Q, Wang C, Li J, et al. Ginkgolide B protects hippocampal neurons from apoptosis induced by beta-amyloid 25-35 partly via up-regulation of brain-derived neurotrophic factor. European journal of pharmacology. 2010 Nov 25;647(1-3):48-54. doi: 10.1016/j.ejphar.2010.08.002. PubMed PMID: 20709055; eng.
174. Misra S, Chopra K, Sinha VR, et al. Galantamine-loaded solid-lipid nanoparticles for enhanced brain delivery: preparation, characterization, in vitro and in vivo evaluations. Drug delivery. 2016 May;23(4):1434-43. doi: 10.3109/10717544.2015.1089956. PubMed PMID: 26405825; eng.
** They have prepared GLN loaded SLN using compritol to increase the drug distribution and bioavailability of the drug in the brain. th formulation is biodegradble and biocompatible in nature because fo the use of compritol for SLN preparation.
175. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: a modern formulation approach in drug delivery system. Indian journal of pharmaceutical sciences. 2009 Jul;71(4):349-58. doi: 10.4103/0250-474x.57282. PubMed PMID: 20502539; PubMed Central PMCID: PMCPmc2865805. eng.
176. Patel M, Souto EB, Singh KK. Advances in brain drug targeting and delivery: limitations and challenges of solid lipid nanoparticles. Expert opinion on drug delivery. 2013 2013/07/01;10(7):889-905. doi: 10.1517/17425247.2013.784742.
177. Sachdeva AK, Misra S, Pal Kaur I, et al. Neuroprotective potential of sesamol and its loaded solid lipid nanoparticles in ICV-STZ-induced cognitive deficits: behavioral and biochemical evidence. European journal of pharmacology. 2015 Jan 15;747:132-40. doi: 10.1016/j.ejphar.2014.11.014. PubMed PMID: 25449035; eng.
178. Laserra S, Basit A, Sozio P, et al. Solid lipid nanoparticles loaded with lipoyl-memantine codrug: preparation and characterization. International journal of pharmaceutics. 2015 May 15;485(1-2):183-91. doi: 10.1016/j.ijpharm.2015.03.001. PubMed PMID: 25747452; eng.
179. Esposito E, Fantin M, Marti M, et al. Solid lipid nanoparticles as delivery systems for bromocriptine. Pharmaceutical research. 2008 Jul;25(7):1521-30. doi: 10.1007/s11095-007-9514-y. PubMed PMID: 18172580; eng.
180. Kaur IP, Bhandari R, Bhandari S, et al. Potential of solid lipid nanoparticles in brain targeting. Journal of controlled release : official journal of the Controlled Release Society. 2008 Apr 21;127(2):97-109. doi: 10.1016/j.jconrel.2007.12.018. PubMed PMID: 18313785; eng.
181. Uner M, Yener G. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. International journal of nanomedicine. 2007;2(3):289-300. PubMed PMID: 18019829; PubMed Central PMCID: PMCPmc2676658. eng.
182. Dhawan K, Dhawan S, Sharma A. Passiflora: a review update. Journal of ethnopharmacology. 2004 Sep;94(1):1-23. doi: 10.1016/j.jep.2004.02.023. PubMed PMID: 15261959; eng.
183. Cacciatore I, Ciulla M, Fornasari E, et al. Solid lipid nanoparticles as a drug delivery system for the treatment of neurodegenerative diseases. Expert opinion on drug delivery. 2016 2016/08/02;13(8):1121-1131. doi: 10.1080/17425247.2016.1178237.
184. Huber A, Stuchbury G, Burkle A, et al. Neuroprotective therapies for Alzheimer's disease. Current pharmaceutical design. 2006;12(6):705-17. PubMed PMID: 16472161; eng.
185. Richard PU, Duskey JT, Stolarov S, et al. New concepts to fight oxidative stress: nanosized three-dimensional supramolecular antioxidant assemblies. Expert opinion on drug delivery. 2015 2015/09/02;12(9):1527-1545. doi: 10.1517/17425247.2015.1036738.
186. Kitagawa S, Tanaka Y, Tanaka M, et al. Enhanced skin delivery of quercetin by microemulsion. The Journal of pharmacy and pharmacology. 2009 Jul;61(7):855-60. doi: 10.1211/jpp/61.07.0003. PubMed PMID: 19589226; eng.
187. Bondi ML, Craparo EF, Giammona G, et al. Brain-targeted solid lipid nanoparticles containing riluzole: preparation, characterization and biodistribution. Nanomedicine (London, England). 2010 Jan;5(1):25-32. doi: 10.2217/nnm.09.67. PubMed PMID: 20025461; eng.
188. Wong HL, Chattopadhyay N, Wu XY, et al. Nanotechnology applications for improved delivery of antiretroviral drugs to the brain. Advanced drug delivery reviews. 2010 Mar 18;62(4-5):503-17. doi: 10.1016/j.addr.2009.11.020. PubMed PMID: 19914319; eng.
189. Dhawan S, Kapil R, Singh B. Formulation development and systematic optimization of solid lipid nanoparticles of quercetin for improved brain delivery. The Journal of pharmacy and pharmacology. 2011 Mar;63(3):342-51. doi: 10.1111/j.2042-7158.2010.01225.x. PubMed PMID: 21749381; eng.

190. Bhat BG, Chandrasekhara N. Studies on the metabolism of piperine: absorption, tissue distribution and excretion of urinary conjugates in rats. Toxicology. 1986 Jul;40(1):83-92. PubMed PMID: 3715893; eng.
191. Kreuter J. Influence of the surface properties on nanoparticle-mediated transport of drugs to the brain. Journal of nanoscience and nanotechnology. 2004 May;4(5):484-8. PubMed PMID: 15503433; eng.
192. Wagner S, Zensi A, Wien SL, et al. Uptake mechanism of ApoE-modified nanoparticles on brain capillary endothelial cells as a blood-brain barrier model. PloS one. 2012;7(3):e32568. doi: 10.1371/journal.pone.0032568. PubMed PMID: 22396775; PubMed Central PMCID: PMCPmc3291552. eng.
193. Yusuf M, Khan M, Khan RA, et al. Preparation, characterization, in vivo and biochemical evaluation of brain targeted Piperine solid lipid nanoparticles in an experimentally induced Alzheimer's disease model. Journal of drug targeting. 2012 Dec 11. doi: 10.3109/1061186x.2012.747529. PubMed PMID: 23231324; eng.
194. Parihar VK, Prabhakar KR, Veerapur VP, et al. Effect of sesamol on radiation-induced cytotoxicity in Swiss albino mice. Mutation research. 2006 Dec 10;611(1-2):9-16. doi: 10.1016/j.mrgentox.2006.06.037. PubMed PMID: 17045515; eng.
195. Prasad NR, Mahesh T, Menon VP, et al. Photoprotective effect of sesamol on UVB-radiation induced oxidative stress in human blood lymphocytes in vitro. Environmental toxicology and pharmacology. 2005 Jul;20(1):1-5. doi: 10.1016/j.etap.2004.09.009. PubMed PMID: 21783559; eng.
196. Hou RC, Chen YS, Chen CH, et al. Protective effect of 1,2,4-benzenetriol on LPS-induced NO production by BV2 microglial cells. Journal of biomedical science. 2006 Jan;13(1):89-99. doi: 10.1007/s11373-005-9039-5. PubMed PMID: 16308662; eng.
197. Sharma S, Kaur IP. Development and evaluation of sesamol as an antiaging agent. International journal of dermatology. 2006 Mar;45(3):200-8. doi: 10.1111/j.1365-4632.2004.02537.x. PubMed PMID: 16533216; eng.
198. Maelicke A, Samochocki M, Jostock R, et al. Allosteric sensitization of nicotinic receptors by galantamine, a new treatment strategy for Alzheimer's disease. Biological psychiatry. 2001 Feb 01;49(3):279-88. PubMed PMID: 11230879; eng.
199. Hernandez CM, Kayed R, Zheng H, et al. Loss of alpha7 nicotinic receptors enhances beta-amyloid oligomer accumulation, exacerbating early-stage cognitive decline and septohippocampal pathology in a mouse model of Alzheimer's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2010 Feb 17;30(7):2442-53. doi: 10.1523/jneurosci.5038-09.2010. PubMed PMID: 20164328; PubMed Central PMCID: PMCPmc2947456. eng.
200. Corrigan OI, Li X. Quantifying drug release from PLGA nanoparticulates. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 2009 Jun 28;37(3-4):477-85. doi: 10.1016/j.ejps.2009.04.004. PubMed PMID: 19379812; eng.
201. Sozio P, Cerasa LS, Laserra S, et al. Memantine-sulfur containing antioxidant conjugates as potential prodrugs to improve the treatment of Alzheimer's disease. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 2013 May 13;49(2):187-98. doi: 10.1016/j.ejps.2013.02.013. PubMed PMID: 23454012; eng.
202. Anand R, Gill KD, Mahdi AA. Therapeutics of Alzheimer's disease: Past, present and future. Neuropharmacology. 2014 Jan;76 Pt A:27-50. doi: 10.1016/j.neuropharm.2013.07.004. PubMed PMID: 23891641; eng.
203. Shahgaldian P, Da Silva E, Coleman AW, et al. Para-acyl-calix-arene based solid lipid nanoparticles (SLNs): a detailed study of preparation and stability parameters. International journal of pharmaceutics. 2003 Mar 06;253(1-2):23-38. PubMed PMID: 12593934; eng.
204. Khan S, Baboota S, Ali J, et al. Nanostructured lipid carriers: An emerging platform for improving oral bioavailability of lipophilic drugs. International journal of pharmaceutical investigation. 2015 Oct-Dec;5(4):182-91. doi: 10.4103/2230-973x.167661. PubMed PMID: 26682188; PubMed Central PMCID: PMCPmc4674999. eng.
205. Muller RH, Radtke M, Wissing SA. Nanostructured lipid matrices for improved microencapsulation of drugs. International journal of pharmaceutics. 2002 Aug 21;242(1-2):121-8. PubMed PMID: 12176234; eng.
206. Varshosaz J, Eskandari S, Tabakhian M. Production and optimization of valproic acid nanostructured lipid carriers by the Taguchi design. Pharmaceutical development and technology. 2010 Jan-Feb;15(1):89-96. doi: 10.3109/10837450903013568. PubMed PMID: 19552542; eng.

207. Lancelot A, Sierra T, Serrano JL. Nanostructured liquid-crystalline particles for drug delivery. Expert opinion on drug delivery. 2014 2014/04/01;11(4):547-564. doi: 10.1517/17425247.2014.884556.
208. Pardeike J, Hommoss A, Muller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. International journal of pharmaceutics. 2009 Jan 21;366(1-2):170-84. doi: 10.1016/j.ijpharm.2008.10.003. PubMed PMID: 18992314; eng.
209. Kim JO, Kabanov AV, Bronich TK. Polymer micelles with cross-linked polyanion core for delivery of a cationic drug doxorubicin. Journal of controlled release : official journal of the Controlled Release Society. 2009 Sep 15;138(3):197-204. doi: 10.1016/j.jconrel.2009.04.019. PubMed PMID: 19386272; PubMed Central PMCID: PMCPmc2728168. eng.
210. Liu J, Lee H, Allen C. Formulation of drugs in block copolymer micelles: drug loading and release. Current pharmaceutical design. 2006;12(36):4685-701. PubMed PMID: 17168772; eng.
211. Huynh NT, Passirani C, Saulnier P, et al. Lipid nanocapsules: a new platform for nanomedicine. International journal of pharmaceutics. 2009 Sep 11;379(2):201-9. doi: 10.1016/j.ijpharm.2009.04.026. PubMed PMID: 19409468; eng.
212. Wissing SA, Kayser O, Muller RH. Solid lipid nanoparticles for parenteral drug delivery. Advanced drug delivery reviews. 2004 May 07;56(9):1257-72. doi: 10.1016/j.addr.2003.12.002. PubMed PMID: 15109768; eng.
213. Lambert JD, Hong J, Kim DH, et al. Piperine enhances the bioavailability of the tea polyphenol (-)-epigallocatechin-3-gallate in mice. The Journal of nutrition. 2004 Aug;134(8):1948-52. PubMed PMID: 15284381; eng.
214. Smith A, Giunta B, Bickford PC, et al. Nanolipidic particles improve the bioavailability and alpha-secretase inducing ability of epigallocatechin-3-gallate (EGCG) for the treatment of Alzheimer's disease. International journal of pharmaceutics. 2010 Apr 15;389(1-2):207-12. doi: 10.1016/j.ijpharm.2010.01.012. PubMed PMID: 20083179; eng.
215. Nanjwade BK, Kadam VT, Manvi FV. Formulation and characterization of nanostructured lipid carrier of ubiquinone (Coenzyme Q10). Journal of biomedical nanotechnology. 2013 Mar;9(3):450-60. PubMed PMID: 23621001; eng.
216. Arroyo A, Navarro F, Gomez-Diaz C, et al. Interactions between ascorbyl free radical and coenzyme Q at the plasma membrane. Journal of bioenergetics and biomembranes. 2000 Apr;32(2):199-210. PubMed PMID: 11768753; eng.
217. Jores K, Mehnert W, Drechsler M, et al. Investigations on the structure of solid lipid nanoparticles (SLN) and oil-loaded solid lipid nanoparticles by photon correlation spectroscopy, field-flow fractionation and transmission electron microscopy. Journal of controlled release : official journal of the Controlled Release Society. 2004 Mar 05;95(2):217-27. doi: 10.1016/j.jconrel.2003.11.012. PubMed PMID: 14980770; eng.
218. Hu FQ, Jiang SP, Du YZ, et al. Preparation and characterization of stearic acid nanostructured lipid carriers by solvent diffusion method in an aqueous system. Colloids and surfaces B, Biointerfaces. 2005 Nov 10;45(3-4):167-73. doi: 10.1016/j.colsurfb.2005.08.005. PubMed PMID: 16198092; eng.
219. Bahadar H, Maqbool F, Niaz K, et al. Toxicity of Nanoparticles and an Overview of Current Experimental Models. Iranian biomedical journal. 2016;20(1):1-11. PubMed PMID: 26286636; PubMed Central PMCID: PMCPmc4689276. eng.
220. Sanchez-Lopez E, Ettcheto M, Egea MA, et al. New potential strategies for Alzheimer's disease prevention: pegylated biodegradable dexibuprofen nanospheres administration to APPswe/PS1dE9. Nanomedicine : nanotechnology, biology, and medicine. 2017 Apr;13(3):1171-1182. doi: 10.1016/j.nano.2016.12.003. PubMed PMID: 27986603; eng.
221. Liu Y, An S, Li J, et al. Brain-targeted co-delivery of therapeutic gene and peptide by multifunctional nanoparticles in Alzheimer's disease mice. Biomaterials. 2016 Feb;80:33-45. doi: 10.1016/j.biomaterials.2015.11.060. PubMed PMID: 26706474; eng.
222. Loureiro JA, Gomes B, Fricker G, et al. Cellular uptake of PLGA nanoparticles targeted with anti-amyloid and anti-transferrin receptor antibodies for Alzheimer's disease treatment. Colloids and surfaces B, Biointerfaces. 2016 Sep 01;145:8-13. doi: 10.1016/j.colsurfb.2016.04.041. PubMed PMID: 27131092; eng.
223. Bondi ML, Montana G, Craparo EF, et al. Ferulic Acid-Loaded Lipid Nanostructures as Drug Delivery Systems for Alzheimer's Disease: Preparation, Characterization and Cytotoxicity Studies. Current Nanoscience. 2009;5(1):26-32.

224. Patel PA, Patil SC, Kalaria DR, et al. Comparative in vitro and in vivo evaluation of lipid based nanocarriers of Huperzine A. International journal of pharmaceutics. 2013 Mar 25;446(1-2):16-23. doi: 10.1016/j.ijpharm.2013.02.014. PubMed PMID: 23410989; eng.
225. Do TD, Ul Amin F, Noh Y, et al. Guidance of Magnetic Nanocontainers for Treating Alzheimer's Disease Using an Electromagnetic, Targeted Drug-Delivery Actuator. Journal of biomedical nanotechnology. 2016 Mar;12(3):569-74. PubMed PMID: 27280254; eng.
226. Agyare EK, Curran GL, Ramakrishnan M, et al. Development of a smart nano-vehicle to target cerebrovascular amyloid deposits and brain parenchymal plaques observed in Alzheimer's disease and cerebral amyloid angiopathy. Pharmaceutical research. 2008 Nov;25(11):2674-84. doi: 10.1007/s11095-008-9688-y. PubMed PMID: 18712585; PubMed Central PMCID: PMCPmc3766361. eng.
227. Chen ZL, Huang M, Wang XR, et al. Transferrin-modified liposome promotes alpha-mangostin to penetrate the blood-brain barrier. Nanomedicine : nanotechnology, biology, and medicine. 2016 Feb;12(2):421-30. doi: 10.1016/j.nano.2015.10.021. PubMed PMID: 26711963; eng.
228. Tanifum EA, Dasgupta I, Srivastava M, et al. Intravenous delivery of targeted liposomes to amyloid-beta pathology in APP/PSEN1 transgenic mice. PloS one. 2012;7(10):e48515. doi: 10.1371/journal.pone.0048515. PubMed PMID: 23119043; PubMed Central PMCID: PMCPmc3485335. eng.
229. Kuo YC, Chou PR. Neuroprotection against degeneration of sk-N-mc cells using neuron growth factor-encapsulated liposomes with surface cereport and transferrin. Journal of pharmaceutical sciences. 2014 Aug;103(8):2484-97. doi: 10.1002/jps.24081. PubMed PMID: 25041794; eng.
230. Kuo YC, Wang CT. Protection of SK-N-MC cells against beta-amyloid peptide-induced degeneration using neuron growth factor-loaded liposomes with surface lactoferrin. Biomaterials. 2014 Jul;35(22):5954-64. doi: 10.1016/j.biomaterials.2014.03.082. PubMed PMID: 24746790; eng.
231. Kuo YC, Lin CY. Targeting delivery of liposomes with conjugated p-aminophenyl-alpha-d-manno-pyranoside and apolipoprotein E for inhibiting neuronal degeneration insulted with beta-amyloid peptide. Journal of drug targeting. 2015 Feb;23(2):147-58. doi: 10.3109/1061186x.2014.965716. PubMed PMID: 25268274; eng.
232. Chen H, Tang L, Qin Y, et al. Lactoferrin-modified procationic liposomes as a novel drug carrier for brain delivery. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 2010 May 12;40(2):94-102. doi: 10.1016/j.ejps.2010.03.007. PubMed PMID: 20298779; eng.
233. Yu Y, Pang Z, Lu W, et al. Self-assembled polymersomes conjugated with lactoferrin as novel drug carrier for brain delivery. Pharmaceutical research. 2012 Jan;29(1):83-96. doi: 10.1007/s11095-011-0513-7. PubMed PMID: 21979908; eng.
234. Xie F, Yao N, Qin Y, et al. Investigation of glucose-modified liposomes using polyethylene glycols with different chain lengths as the linkers for brain targeting. International journal of nanomedicine. 2012;7:163-75. doi: 10.2147/ijn.s23771. PubMed PMID: 22275832; PubMed Central PMCID: PMCPmc3263409. eng.
235. Rotman M, Welling MM, Bunschoten A, et al. Enhanced glutathione PEGylated liposomal brain delivery of an anti-amyloid single domain antibody fragment in a mouse model for Alzheimer's disease. Journal of controlled release : official journal of the Controlled Release Society. 2015 Apr 10;203:40-50. doi: 10.1016/j.jconrel.2015.02.012. PubMed PMID: 25668771; eng.
236. Lindqvist A, Rip J, Gaillard PJ, et al. Enhanced brain delivery of the opioid peptide DAMGO in glutathione pegylated liposomes: a microdialysis study. Mol Pharm. 2013 May 06;10(5):1533-41. doi: 10.1021/mp300272a. PubMed PMID: 22934681; eng.
237. Rip J, Chen L, Hartman R, et al. Glutathione PEGylated liposomes: pharmacokinetics and delivery of cargo across the blood-brain barrier in rats. Journal of drug targeting. 2014 Jun;22(5):460-7. doi: 10.3109/1061186x.2014.888070. PubMed PMID: 24524555; PubMed Central PMCID: PMCPmc4651142. eng.
238. Balducci C, Mancini S. Multifunctional liposomes reduce brain beta-amyloid burden and ameliorate memory impairment in Alzheimer's disease mouse models. 2014 Oct 15;34(42):14022-31. doi: 10.1523/jneurosci.0284-14.2014. PubMed PMID: 25319699.
239. Mourtas S, Lazar AN, Markoutsa E, et al. Multifunctional nanoliposomes with curcumin-lipid derivative and brain targeting functionality with potential applications for Alzheimer disease. European journal of medicinal chemistry. 2014 Jun 10;80:175-83. doi: 10.1016/j.ejmech.2014.04.050. PubMed PMID: 24780594; eng.

240. Ordonez-Gutierrez L, Re F, Bereczki E, et al. Repeated intraperitoneal injections of liposomes containing phosphatidic acid and cardiolipin reduce amyloid-beta levels in APP/PS1 transgenic mice. Nanomedicine : nanotechnology, biology, and medicine. 2015 Feb;11(2):421-30. doi: 10.1016/j.nano.2014.09.015. PubMed PMID: 25461285; eng.
241. Zheng X, Shao X, Zhang C, et al. Intranasal H102 Peptide-Loaded Liposomes for Brain Delivery to Treat Alzheimer's Disease. Pharmaceutical research. 2015 Dec;32(12):3837-49. doi: 10.1007/s11095-015-1744-9. PubMed PMID: 26113236; eng.
242. Li W, Zhou Y, Zhao N, et al. Pharmacokinetic behavior and efficiency of acetylcholinesterase inhibition in rat brain after intranasal administration of galanthamine hydrobromide loaded flexible liposomes. Environmental toxicology and pharmacology. 2012 Sep;34(2):272-279. doi: 10.1016/j.etap.2012.04.012. PubMed PMID: 22613079; eng.
243. Yang ZZ, Zhang YQ, Wang ZZ, et al. Enhanced brain distribution and pharmacodynamics of rivastigmine by liposomes following intranasal administration. International journal of pharmaceutics. 2013 Aug 16;452(1-2):344-54. doi: 10.1016/j.ijpharm.2013.05.009. PubMed PMID: 23680731; eng.

Figure legends

Figure 1: Major pathophysiology of Alzheimer disease (a) Amyloidogenesis and (b) Tau hyperphosphorylation.

Figure 2: Figure showing responsible pathophysiological mechanisms of Alzheimer disease and explored nanoparticulate approaches for the treatment of AD.

Figure 3: Diagrammatic representation of the double emulsion method for encapsulating quercetin in PLGA NPs. [Reprinted with permission from [107]]

Figure 4: Self-association of the polymeric nanoparticle, CHP into nano gels by hydrophobic interaction. [Reprinted and modified with permission from [137]]

Figure 5: Illustration of the bi-functional liposome, surface modified with mApoE and PA.

Table 1: Investigated drug-loaded nanoparticles for the treatment of AD.

Nanocarrier	Drug	Polymer	Transport mechanism	Method	Animal model	Improvement		Reference
						In vitro	In Vivo (Pharmacokinetics)	
Nanoparticle	Rivastigmine (AChE and BuChE inhibitor)	Poly(n-butylcyano-acrylate), polysorbate 80	Receptor-mediated endocytosis	Emulsion polymerization	Male Wistar rat	• Particle size around 40.5nm • Zeta potential -35.2mV • Drug releases initially by bursting for 30 min followed by sustained release for 24 h, releases overall about 86.40% of drug • Drug release follow Fickanian behavior of release • Kinetics of drug release best fits to Higuchi and Korsmeyer-Peppas model	• 3.82 folds improvement in bioavailability • Very potential for AD treatment	[84]
Nanoparticle	Tacrine (AChE and BuChE inhibitor)	Chitosan	Adsorption mediated transcytosis	Spontaneous emulsification	Wistar Rat	• Particle size around 41 nm • Zeta potential: 34.7 mV • Loading efficiency: 10.86% • Releases 89.31% of drug, initially by burst release for 30 min followed by slow release for 12 h, • diffusion controlled release of drug follow Fickanian movement • Release kinetic: Higuchi and Korsmeyer-Peppas	• Improves drug conc. In brain, • Enhancing targeting efficiency • Enhance the drug retention time, • Increases half-life • Sustained the release of drug • enhance the overall bioavailability	[81]
Nanoparticle	Thioflavin T (Fluorescent molecule / model drug)	Butyl-cyanoacrylate, polystyrene core	-	Emulsion polymerization	C57B6 mice	-	• β sheet breaker • Reduces Aβ accumulation • Reduces neurotoxicity	[111]
Nanoparticle	Quercetin (antioxidant, metal ion chelator)	PLGA	Metal ion chelation	Emulsion solvent evaporation	AD mouse model	• Particle size near about 150 nm • Initial burst release followed by sustained for 48 h	• Reduce metal ion accumulation in brain • Decreases neurotoxicity • Improves cell viability • Reduces aggregate formation • Memory improvement	[107]
Nanoparticle	D-penicillamine	MPB-PE or PDP-PE	Endocytosis/transcytosis or passive	Covalent conjugation via disulphide	AD mouse model	• Particle size around 105nm	• Reduces metal ion accumulation in brain • Decreases Aβ accumulation	[108]

	(metal ion chelator)		diffusion	or thioether bond			and neurotoxicity	
Nanosphere	Dexibuprofen (NSAID[61])	PEG-PLGA	Passive diffusion	Solvent diffusion method	APPswe/PS1dE9	• Size around 166 nm, • PDI 0.074, • Surface charge -9.9 • Entrapment efficiency 99.99%. • Drug released from the Nanosphere initially by bursting followed by prolonged release for 6h • The drug release follows first order release kinetics.	• Non-toxic to the neurons and other body tissues, • Improves cell viability • Enhance brain permeability • Enhance retention time • Improve memory impairment, • Reduces Aβ accumulation • Restore cognitive responses	[220]
Multifunctional nanoparticle	Gene or peptide (RGV29 & D-amino acid peptide sequence)	NHS-PEG-MAL[62], DGLs[63]	Receptor-mediated transcytosis	-	BCECs, C57BL/6J mice	• Particle size range from 97-110nm • PDI less than 0.3 • Surface charge near about 6.11 – 7.72mV	• Reduces amyloid deposit in brain • Improves cell viability • Disrupt the tau fibril formation • Improves memory and behavioral responses • Improved brain targeting ability	[221]
Multifunctional nanoparticle	iAβ_5 peptide (anti-transferrin antibody)	PEG-PLGA, pluronic 127, surface functionalized with anti-transferrin receptor antibody (OX26) & anti-Aβ (DE2B4)	Receptor mediated transcytosis	-	PBCECs[64]	• Average particle size was found 160nm • PDI found less than 0.1 • Zeta potential: -10mV • Around 50% of drug releases initially by burst effect for 5h, followed by followed by slow release for 6 days	• Improves brain uptake of drug • Cellular uptake decreases with increasing conc. of nanoparticle • Increases peptide conc. in brain	[222]
Dual-	H102	PEG-PLA	Receptor-	Emulsification	ICR mice	• Particle size around 120nm	• Increases AUC 1.33-1.49 times	[126

[61] Non-steroidal anti inflammatory drugs
[62] α-Malemidyl-ω-N-hydroxysuccinimidylpolyethyleneglycol
[63] Dendrigraft poly-L-lysines
[64] Porcine brain capillary endothelial cells

functional nanoparticle	peptide (β sheet breaker)		mediated transcytosis	/ solvent evaporation		• Surface charge found -28 mV, assures stability • Entrapment efficiency: 57.68-65.54% • Loading efficiency: 0.54% • In vitro release:65% in plasma	• Increases Drug conc. 1.8 times • Enhances half-life 1.57h • 1.86-2.62 times greater brain uptake • Reduces plaque formation • Restoring cholinergic function • Improved neuroprotective effect	]
Nanoemulsion (oil body nanoemulsion)	Ginkgolide B (Terpenoid, reduces Aβ toxicity)	Soybean oil, soybean lecithin	-	Emulsion method	Sprague-Dawley rat	• Size ranging from 80-100nm • Prolongs the release of drug	• 10 folds increase drug AUC • 7-20 folds increase in $t_{1/2}$ • Higher distribution in brain tissue • Increases tissue binding confirms brain targeting	[157]
Nanogel	Pullulan (reduce Aβ toxicity by protein refolding)	Cholesteryl	-	Self-assembling through hydrophobic interaction	transgenic AD animal model	-	• Reduce the Aβ toxicity • Enhance cell viability	[137]
SLN	Quercetin (antioxidant, metal ion chelator)	Compritol & tween 80	Metal chelator	Microemusification technique	Male Wistar rat	• Surface charge around -25mV • Entrapment efficiency: 92.65% • 90.14 % of drug releases initially by burst effect followed by sustained release for 48 h • Release kinetic: Fickanian, non-Fickanian or zero order release	• Improves brain permeation and therapeutic efficacy • Potent anti-oxidant • Reduces neurotoxicity, • Neuroprotective effect, • Improves learning ability and memory	[189]
SLN	Piperine (antioxidant)	Polysorbate -80	Absorption transcytosis	Emulsification -Solvent Diffusion technique	Albino Wistar rat	• Having particle size around 312.0 nm • PDI: 0.16 • Surface charge (-51.3 mV) assure stability of formulation • Entrapment efficiency: 68.2% • Sustained release for long period	• Increases pharmacokinetic properties of drug (AUC: 46485 ng.min/g, C_{max}: 121 ng/g, and T_{max}: 60 min) • Improves bioavailability • Reduces oxidative stress and cholinergic degradation	[193]
SLN	Ferulic acid (Antioxi	Compritol 888 ATO	Absorption transcytosis	Microemusion technique		• Size ranging from 90-140nm, • Lower PDI range from 0.174 – 0.312	• Nontoxic to human neuroblastoma cells	[223]

	dant)					• High surface charge (-36.40mV) assures the stability (+49.11mV in case of cationic drug) • Drug loading efficiency found 20% • Initially, the drug was released by bursting followed by slow release of 100% drug within 10h	• Protects neurons against oxidative stress • Reduce neurotoxicity • Improves cell viability • Excellent carriers for drug targeting to brain	
SLN	Sesamol (Antioxidant)	Polysorbate-80, soy lecithin	-	Microemusification technique	male Wistar rat	• Particle size ranging from 40-70nm • Entrapment efficiency: 75.9% • Diffusion-controlled prolonged release	• Better neuroprotective effect • Improves memory and learning ability in animal model	[177]
SLN	Galantamine hydrobromide (AChE inhibitor)	Pluronic F-127, Tween 80	-	Microemusification technique	AD Wistar rat	• Particle size ranging from 88-221nm • Entrapment effi: 77.29-90.17% • Drug releases up to 99.83%, Initially fast release followed by slow prolong release for 24 h	• Two folds increase in AUC, • Improves V_d, • Increases bioavailability, • Improves cognitive dysfunction, • Memory restoration	[174]
SLN	Lipoyl–memantine codrug (antioxidant and NMDA antagonist)	Stearic acid	-	Emulsification–evaporation–solidifying method	AD mouse model	• Particle size at a suitable range around 169.90 nm • PDI: 0.072 • Surface charge: -33.80 mV • Entrapment effi: 88% • Loading effi: 12.5% • Initial burst release followed by 20% release up to 2 & h that facilitate 80% release to target site	• Releases free codrug, • Improves drug absorption hence bioavailability, • Increases drug stability, • Reduces neurotoxicity and oxidative stress	[178]
NLC 1:8 ratios	Epigallocatechin-3-gallate (α-secretase booster)	-	-	Co-solubilization method	Male Sprague-Dawley rat	• Particle size at a suitable range near about 100nm	• Improves pharmacokinetic behavior of drug (AUC: 36524, C_{max}: 704.67 µg/ml), • 2.5 folds greater bioavailability, • Enhance α secretase production	[214]
NLC	Huperzine A (improves neuronal function)	Capmul®, glyceryl monostearate	-	Microemulsion template technique	Scopolamine-induced dementia mice model	• Particle size around 137.1 nm • **PDI:** 0.422 • **Surface charge:** -17.5 mV • **In vitro release:** sustained and controlled release of drug	• Increases the ACh level in brain, • Behavioural and memory improvement	[224]
NLC	Ubiquinone	Precirol ATO 5 and	-	Solvent diffusion	Wistar albino rat	• Particle size ranging from 65-80 nm • PDI: 0.291-0.391	• Improves drug pharmacokinetics (AUC:	[215]

	(Coenzyme Q10) (antioxidant)	Compritol 888 ATO		Method		• Surface charge: -32.4 to -37.1 mV • Entrapment effi: 74.99% • Loading effi: 63.57% • Releases around 91% of drug, initially by burst followed by prolonged release up to 24 h • Diffusion-controlled release, best fitted to Higuchi release kinetic equation	63.48, C_{max}: 1.34 m.mol/l, T_{max}: 8.10 h) • Improves bioavailability	
Lactoferrin modified NLC	Curcumin (reduce Aβ plaque formation)	Phosphatidylcholine, cholesterol, S100-COOH	Receptor-mediated transcytosis	Solvent evaporation method	SD rats and ICR mice	• Particle size range from 70-170nm • Sustained drug release follow Ficks' law of diffusion	• 2.5 folds increase in AUC so overall bioavailability • Improves drug permeability • Increases targeting efficacy of drug	[2]
Lactoferrin nanoparticle	Coumarin 6 (Model drug)	PEG-PLA	Receptor-mediated transcytosis	Emulsion solvent evaporation method	KM mice	• Particle size near about 131 nm • **Loading effi:** 0.084% • **In vitro release:** 8% drug release till 1h followed by 20% for 24h	• 2.98 folds increase in AUC • Improves drug conc. in the brain (62.28 ng/ml) • Reduce cytotoxicity on bEnd3 cell line • Improve brain uptake of the drug 1.45 times in a temperature dependent manner	[114]
Magnetic nanocontainer	Fluorescent carboxyl magnetic particles	-	Electro-magnetic drug targeting	-	WT C57BL/6N mice model	-	• Increase in brain uptake and permeation • Improves biodistribution and drug targeting • An effective tool for AD diagnosis and treatment.	[225]
Smart Nano-vehicle(iv)	IgG4.1 (anti Aβ antibody)	chitosan polymeric core	Transcytosis	ionic gelation method	AD mice model	• Sustain the drug release for 18 h	• Increases brain uptake, • Increases AUC, • Enhances volume of distribution, • Increases conc. of drug carrier in various region of the brain, • Reduces drug clearance, • The improved target of cerebral amyloid deposit.	[226]

Table 2: Investigated drug-loaded liposomes for the treatment of AD.

Nanocarrier / Route	Drug	Lipid	Targeting ligand	Transport mech.	Method	Animal model/ Cell line	Improvement Observed		Reference
							In vitro (Dosage form)	In Vivo (Pharmacokinetics)	
Transferrin modified liposome	α-Mangostin (prevent amyloidogenesis)	DSPE, PEG-2000	Transferrin (covalent binding)	Receptor-mediated endocytosis	Thin film hydration	SD rats, bEND3 cell line	• Particle size around 196.3 nm • PDI: 0.211 • Surface charge: -22.23mV • Entrapment efficiency: >88% • Coupling efficiency: 54.85% • 98% of the drug was released up to 36 h in a sustained manner	• Improves cellular uptake in time-dependent manner • Improves the pharmacokinetic behaviour (AUC: 2.8 µg/g.h, C_{max}: 50 µg/ml, T_{max}: 0.77 h, $t_{1/2}$: 0.82 h) hence increases the bioavailability. • Reduces cardiac toxicity	[227]
Stealth liposome (iv)	Rhodamine B (dye/metal ion detector, used as model drug)	DPPC, cholesterol, PEG-3400	Methoxy-XO4	Perivascular transfer or receptor-mediated transcytosis	Extrusion	APP/PS EN1 transgenic mice, Synthetic Aβ fibrils	• Size ranging from 150-170 nm	• Effectively binds to the Aβ plaque throughout the brain	[228]
Transferrin modified liposome	NGF (neuronal growth factor)	PC, DPPC, cholesterol, DSPE-PEG-2000	Cereport (RMP 7) & transferrin	Receptor mediated transcytosis (B_2 bradykinin & transferrin receptor)	Solvent evaporation method	HBMECs	• Size range from 152.3-189.1 nm • PDI: 0.13-0.19 • Surface charge range from -4.5 to -8.5 mV • Entrapment efficiency: 31.2 %	• Increased Transferrin and RMP7 conc. Increases the cellular uptake • Reduces cytotoxicity produced by SK-N-MC cells • Reduces neurotoxicity due to SK-N-MC cell	[229]
Lactoferrin modified liposome	NGF (neuronal growth factor)	Cholesterol, DPPC, PEG-2000, DPSE-PEG-2000	Lactoferrin	Receptor-mediated transcytosis	Solvent evaporation method	HBMECs, HAs & SK-N-MC cell	• Size ranging 100 – 150 nm • Surface charge: -3 to -11 mV • Entrapment efficiency: 28% • Increased lactoferrin concentration reduces the	• Improves the cell permeability • Increases HBMECS viability after 48 treatment with LF/NGF liposome and reduces the viability of SK-N-MC cell • Improves cell viability, enhance drug permeability, protect neurons from degenerative effect of plaque	[230]

							loading efficiency • Initial burst release followed by sustained and controlled release up to 90% for 48 h		
Dual targeting liposome	NGF (neuronal growth factor)	Soyabean phosphatidyl choline, PA, cardiolipin, PEG	ApoE, APMP	Carrier-mediated transcytosis or receptor-Mediated transcytosis (ldlr & glut 1 receptor)	Solvent evaporation method	Mice model, HBMECs, HAs & SK-N-MC cell	• Size: 129.7 nm • Surface charge: -4.1 to -9.8 mV • Entrapment efficiency: 35%	• Reduces rapid elimination, improve half-life • Enhance NGF permeability • Nontoxic to neuronal cells • Reduces toxic effect of amyloid plaque, enhance cell viability	[231]
Lactoferrin modified procationic liposome	Caumarin 6 (fluorescent probe/dye, model drug)	CHETA	Bovine Lactoferrin	Receptor and absorption mediated transcytosis (Conc. And time dependent)	Thin film solvent evaporation method	Kunming mice and new born Sprague – Dawley rats, BCECS and AC culture	• Size below 130nm • PDI: 0.175 • Surface charge: -32.3 to -4.3 mV • Entrapment efficiency: 77%	• Significantly improves AUC (1041.7μg/L·h),drug concentration (160.8 μg/L), half-life (20.6 h) and T_{max} (0.5 h). • Improve cell uptake • Reduced cytotoxicity • Improves brain targeting ability, significantly delivers drug to brain	[232]
Lactoferrin modified polymerosome	S14G-Humanin (neuroprotective agent)	PEG-PLGA	Lactoferrin	Receptor-mediated transcytosis	Self-assembly method	Kunming mice, BALB/c mice, Sprague-Dawley rats	• Particle size ranging from 90 -120 nm • Surface charge: -4 mV • Entrapment efficiency: 21.78 % • Loading efficiency: 0.77% • In vitro release: 70%	• Improves drug concentration and AUC in brain and so increases the bioavailability • Improves the tissue uptake of drug (3.32 folds improvement), enhance membrane permeability • Shows neuroprotective behavior, improves the function of cholinergic neurons	[233]
Glucose modified liposome	Coumarin 6 (fluorescent probe/dye, model drug)	Soyabean phospholipid, cholesterol (2:1) (lipid phase) & PEG with	Glucose	Carrier-mediated transcytosis (through glucose transporter)	Thin-film dispersion ultrasound	Mice model	• Size range from 80 to 105 nm • PDI: 0.15 to 0.30 • Surface charge: -20 to -30 mV	• Promotes drug transport through BBB in time-dependent manner • Enhance brain distribution, improved brain targeting ability	[234]

		varying chain length (Linker)			method				
G-Technology: (Glutathione conjugated PEGylated liposome)	Amyloid β antibody (VHH)	DMPC, EYPC (lipid), PEG(Linker)	Glutathione	Carrier-mediated transcytosis	Post insertion method	APP/PS1 transgenic mice model & WT littermates	• Size: 108 nm • PDI: 0.061 • Entrapment efficiency: 40.8%	• Increases AUC, drug retention time and reduces clearance • Significantly increases drug bioavailability in brain, promising carrier for drug delivery to brain	[235]
G-Technology: (Glutathione conjugated PEGylated liposome)	DAMGO (opioid peptide)	Cholesterol, EYPC, mPEG-DSPE	Glutathione	Receptor-mediated transport	-	-	• Size: 127 nm • PDI: 0.024	• Improves drug conc. (120000 ng/ml) in the brain, half-life (6.9 h), drug retention time, reduces clearance, increases brain distribution two times • Significantly improves brain delivery of opioid peptide by two folds, prolongs the drug delivery to brain	[236]
G-Technology: (Glutathione conjugated PEGylated liposome) (Intraperitoneal injection)	Carboxyfluorescein (fluorescent dye, model drug)	HSPC, DSPE-mPEG-2000, cholesterol, 5(6)-carboxyfurescein	Glutathione	Carrier-mediated transcytosis	Ethanol injection method	Male Wistar rat	• Size: 105 to 108 nm • PDI: 0.049 to 0.065	• Improves brain distribution, drug concentration (5 folds), reduces drug clearance • 1.8 folds improvement • Enhance brain drug delivery	[237]
mApoE-PA bifunctional liposome	Rhodamine B (dye/metal ion detector, used as model drug)	Cholesterol, Bovine brain sphingomyelin	mApoE, PA	Receptor mediated transcytosis	Extrusion	BALB/c mice, APP-PS1 transgenic mice	• Size: 110 to 120 nm • PDI: 0.15 • Surface charge: -25 to -15 mV	• Enhance drug concentration in all vital organs • Reduction in amyloid β plaque by generating sink effect, memory improvement	[238]
DPS-PEG2000-	Curcumin (reduce Aβ	DPS, cholesterol,	DPS, curcumin,	Receptor-mediated	Thin film	Post-mortem	• Size: 116 to 159 nm • PDI: 0.195-0.206	• Reduction in amyloid β plaque	[239]

curcumin bifunctional nanoliposome	plaque formation)	PEG-2000	Anti-transferrin monoclonal antibody	transcytosis	hydration	human brain, hCMEC/D3 human brain endothelial cells	• Surface charge: -7.43 to -2.01		
PA-peptide bifunctionalized liposome	-	Sphingomyelin, cholesterol	PA & mApoE	Endocytosis (receptor mediated)	-	BALB/c mice, hCMEC/D3 cells	• Size: 123 nm • PDI: <0.1 • Surface charge: -15.2 mV	• Increases BBB permeability up to 5 folds • Inhibit amyloid plaque formation, and cause disaggregation of already formed aggregates in a dose-dependent manner	[18]
Multifunctional nanoparticle/ Liposome	--	sphingomyelin, cholesterol	mApoE, PA	Receptor mediated transcytosis	Extrusion	Transgenic APP/PS1 mice model	• Particle size around 140nm • PDI: 0.143 • Surface charge (-18.32mV) assures the stability of the formulation	• Enhances the efflux of Aβ oligomer from brain using transwell cellular model • Reduces brain Aβ level • Enhances brain permeation	[149]
Liposome	Calcein (Fluorescent dye)	Sphingomyelin, cholesterol	PA, cardiolipin,	-	Repeated extrusion method	APP/PS1 transgenic mice, hCMEC/D3 and human neuro-blastoma SH-SY5Y cells	• Size: 105 nm • PDI: 0.01 • Surface charge: -25.06 mV	• Improves BBB permeability • Reduces amyloid concentration in brain thus reduces the severity of AD	[240]
Liposome	Rivastigmine (AChE and BuChE inhibitor)	Egg yolk-Phosphotidyl-choline, Dihexadecyl phosphate, Cholesterol	-	Receptor-mediated transport	Lipid hydration and heating	Male albino rats	• Particle size range from 67.5-186.3 nm • PDI: 0.612 -0.755 • Surface charge: -24.6 to -6.6 mV • Entrapment efficiency: 75.8 -97.4 % • fast release in the first 3h followed by slow release	• Increases half-life • Decreases the toxicity • Improves memory and neurological deficits	[147]

							for next 24h up to 89 % • Release kinetic: zero order kinetic, Higuchi diffusion model		
Liposome	H102 peptide (β sheet breaker)	Cholesterol, EPC, DMPC-PEG-2000	-	-	Thin film hydration	Male SD rats, Calu-3 cell line	• Size: 112 nm • PDI: 0.185 • Surface charge: -2.96 • Entrapment efficiency: 71.35% • Initial burst release followed by Sustained release for 12 h up to 97% • Follow first order release kinetic	• 2.7 fold improves the AUC, increased drug conc. • Increases overall bioavailability • Significantly increases cellular uptake • Reduces toxicity • Improves cholinergic functioning, memory improvement	[241]
Flexible liposome	Galantamine hydrobromide (AChE inhibitor)	PEG	-	-	Thin film homogenization	SD rat, PC-2 cell line	• Size: 112 nm • Surface charge: -49.2 mV • Entrapment efficiency: 83.6%	• Improves all pharmacokinetic parameters (AUC: 55.4 μg·h/ml C_{max}: 13.98 μg/ml, T_{max}: 0.75 h) hence bioavailability • Improves cell permeability • Less toxicity • Improved drug efficacy	[242]
CPP-modified liposome	Rivastigmine (AChE and BuChE inhibitor)	DSPE, EPC, cholesterol & PEG	CPP	Endocytosis & transcytosis	Ammonium sulphate gradient the loading method	Male SD rat, BMVECs	• Size: 178.9 nm • PDI: 0.333 • Surface charge: -8.5 • Entrapment efficiency: 30.5 % • Prolong drug release for 6-7 h up to 85% drug released	• Significantly improves cell permeability • Less cytotoxic effect • Improves brain drug delivery, enhance pharmacokinetics, reduces hepatic first-pass metabolism and GI side effects	[243]

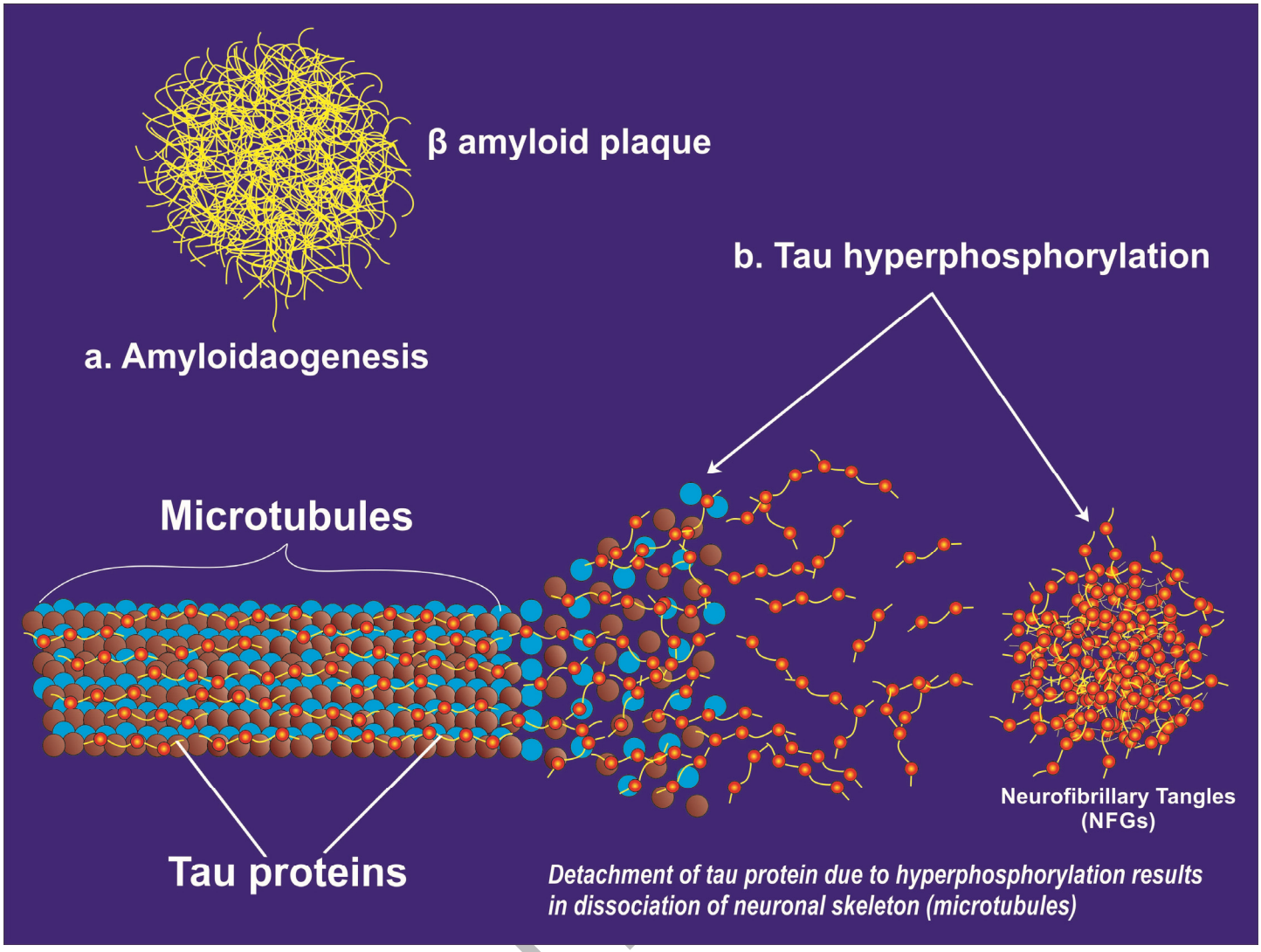


Figure 1

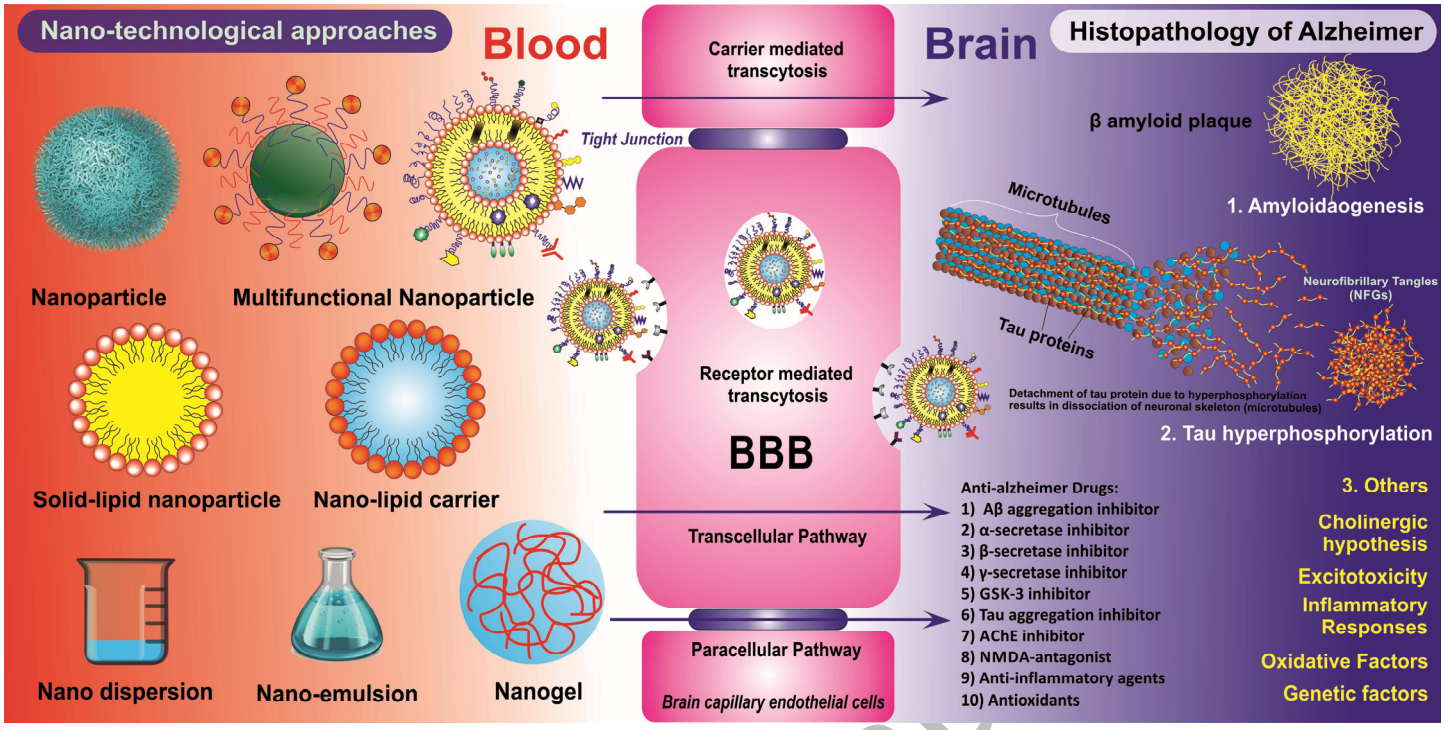


Figure 2

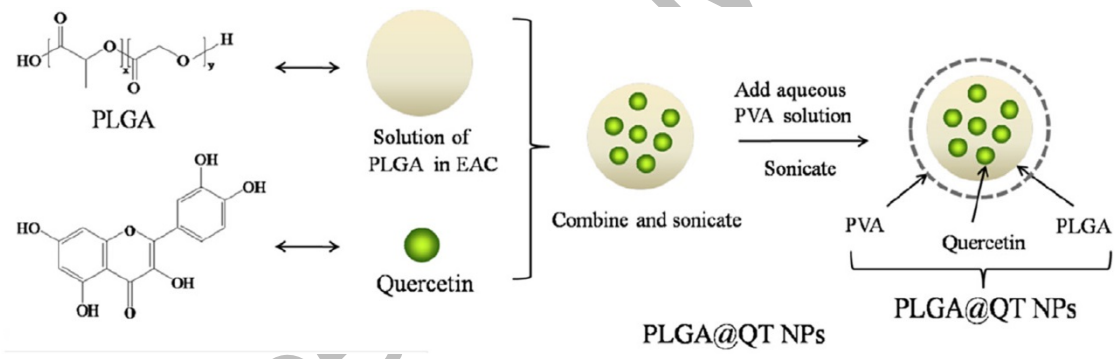


Figure 3

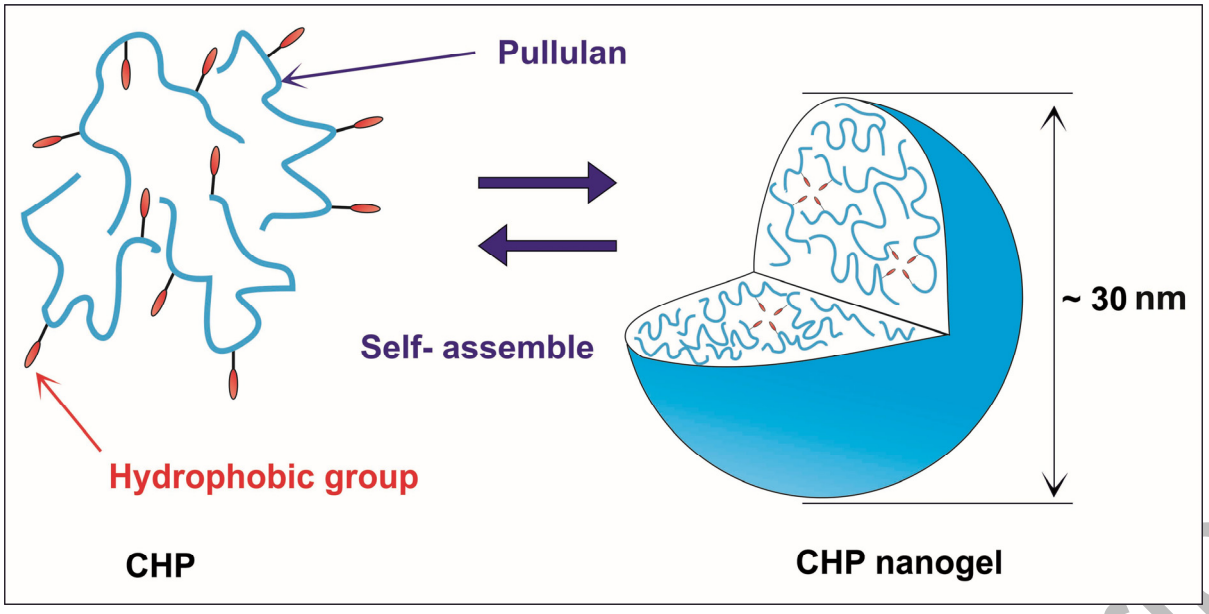


Figure 4

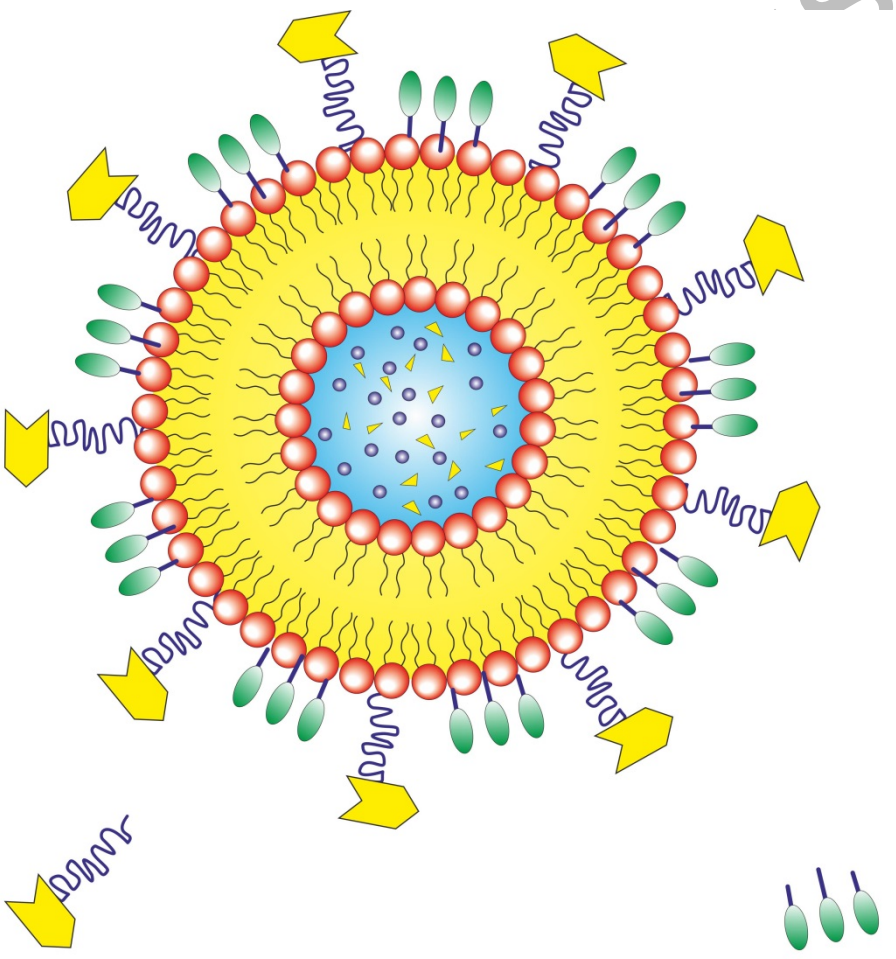


Figure 5