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REVIEW ON ALZHEIMER DISEASE AND THE IMPLEMENTED PHARMACEUTICAL APPROACHES

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ABSTRACT

Alzheimer's disease was considered a huge health burden for scientists for many generations and is one of the biggest health problems for humanity. Since its discovery in 1906 by Alosi Alzheimer, drug delivery have being the major obstacle. With the presence of a selective membrane barrier allowing certain molecules to enter and exit, delivering drugs to the brain was considered a challenge but now, new cutting edge technologies have been developed allowing scientists to construct nano sized particles from different materials to bypass the BBB. Nevertheless, peptides, ligands and coating materials were added for modification of the particle for better targeting abilities. The following review focuses on the nanotechnology used for targeting Alzheimer's disease and the pharmaceutical strategies for drug delivery to the brain as well as a few collections have been mentioned for the nano sized particle that has been used for drug delivery, eventually the future perspective will be discussed for better engaging the Alzheimer's disease.

1-INTRODUCTION

Alzheimer’s disease (AD), also referred to simply as Alzheimer’s, is one of the biggest health problems in current humanity and the most common cause of dementia and considered as a significant public health problem, generally it starts gradually and worsens over time in older adults.[1] Recent investigations concluded that AD is one of the most complex diseases ever studied. Many factors support such theory based on many challenges that faced those researchers. To begin with, the brain is an organ like no other in terms of accessibility; a

complex organ in its structure and function as well as being the most inaccessible organ in the body, protected by a high selective barrier in which the investigation of any disease is correspondingly complicated and a difficult task.[2] AD is characterized by a, language problems, decline in memory and problem-solving other cognitive skills that affects a person's ability to perform everyday activities. This decline occurs because nerve cells (neurons) in parts of the brain involved in cognitive function have been damaged and no longer function normally.[3,4] In Alzheimer's disease, neuronal damage eventually affects parts of the brain that enable a person to carry out basic bodily functions such as walking and swallowing. People in the final stages of the disease are bed-bound and require around-the-clock care. In its final stages, Alzheimer's disease is ultimately fatal.[5]

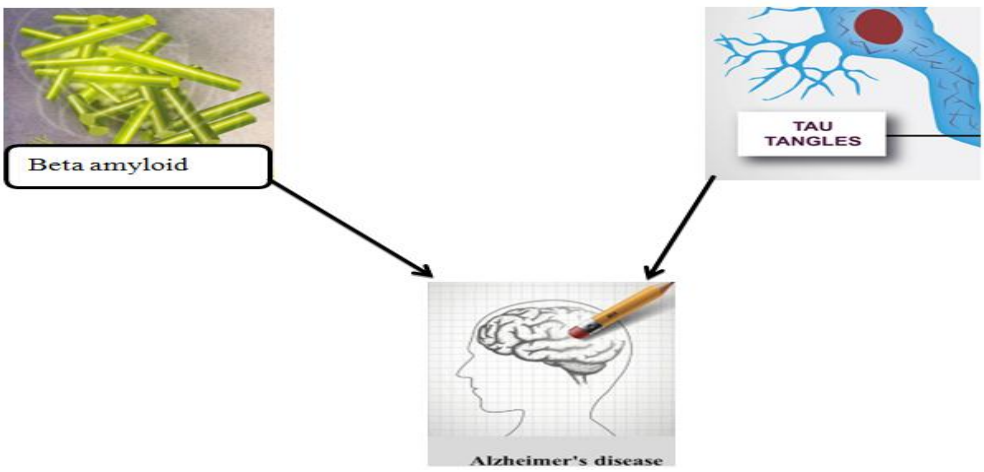
An essential extracellular hallmark for AD is the beta-amyloid which is considered chemically "sticky" and its accumulation will gradually be build up into soluble form and eventually into plaques. On the other hand neurofibllary tangles are considered as an essential intracellular hallmark, in which the main transport route for nutrients inside the neurons are destroyed.[6] Resulting in formation of tangles that blocks the nutrient transportation that will cause the death of the neuron. Tau is considered as major protein for the stability of the intracellular microtubules, its detachment is considered as the major reason behind the formation of neurofibllary tangles.[7] Other hallmarks such as Glutamate excitotoxicity and Acetylcholine deficiency are considered as extracellular hallmarks, focusing on receptors at the neurons. In which the overactive that happen at the glutamate receptors causes existoxicity.[8,9] The over stimulation of the neurons can lead to its death.[10] As for Acetylcholine which is considered as a crucial neurotransmitter responsible for transmitting signals between your brain cells and plays a major rule in memory, cognition, learning and other aspects of higher brain functions.[11,12]

The main obstacle faced by all the researchers for developing an ideal drug delivery method is the BBB, considered as homeostatic defense mechanism agaisnt pathogens that separate the major compartments of the central nervous system (CNS) as a primary objective and have the abilities to prevent entry and actively remove undesirable molecules from the brain.[13] It's identified anatomically as microvasculuture of the brain, intercellualer tight junctions of specially modified capillaries, veins and arterioles.[14,15] These tight junctions are formed by the "glued" endothelial cells together with multiple binding proteins (occludins, claudins and junctional adherin molecules) to form tight junctions (TJs) and adherin junctions (AJs).[16]

The barrier uptake essential nutrients, vitamins and hormons while enzymatically degrading many peptides and neurotransmitter through enzymatic and secratory functions of cells that comprises its role to BBB communication, homeostasis and nutrition. For cerebral drug targeting the BBB transport mechanism can be manipulated.[17] Naturally, the ideal drug should be small, lipophilic, hydrophobic and compact. In the peripheral circulation, systematic enzymatic attack and plasma protein opsonization can lead to drug metabloism before it reaches the brain.[18]

Nanotechnology exerts an increasing impact on the development of more effective tools for the diagnosis and treatment of human diseases. This applies in particular to central nervous system (CNS) disorders.[19] Development of therapeutics for CNS is, in fact, one of the most challenging areas in drug development, mainly due to the presence of the blood-brain barrier (BBB) which separates the blood from the cerebral parenchyma thus limiting the brain uptake of the vast majority of neurotherapeutic agents.[20] It's crucial to development various nanocarriers that possess both blood brain barrier permeability and ability of targeting one or multiple AD hallmarks simultaneously with sufficient bio-availability and biodegradability for optimal delivery, is of great importance for the intervention of AD.[21,22]

The following review article discuss the drug delivery method that have been developed to deliver various therapeutics targeting AD hallmarks, and the nature of the cargo including its synthesis method and the materials used for that. Nevertheless, the functionalization materials which can be used to modify the drug cargo and its ability to bind at the site of action as well as the different methods and materials used to enhance the BBB permeability. This review also discusses the future perspective in which the recent limitations facing many research works can be better engaged, for an ultimate drug delivery method.



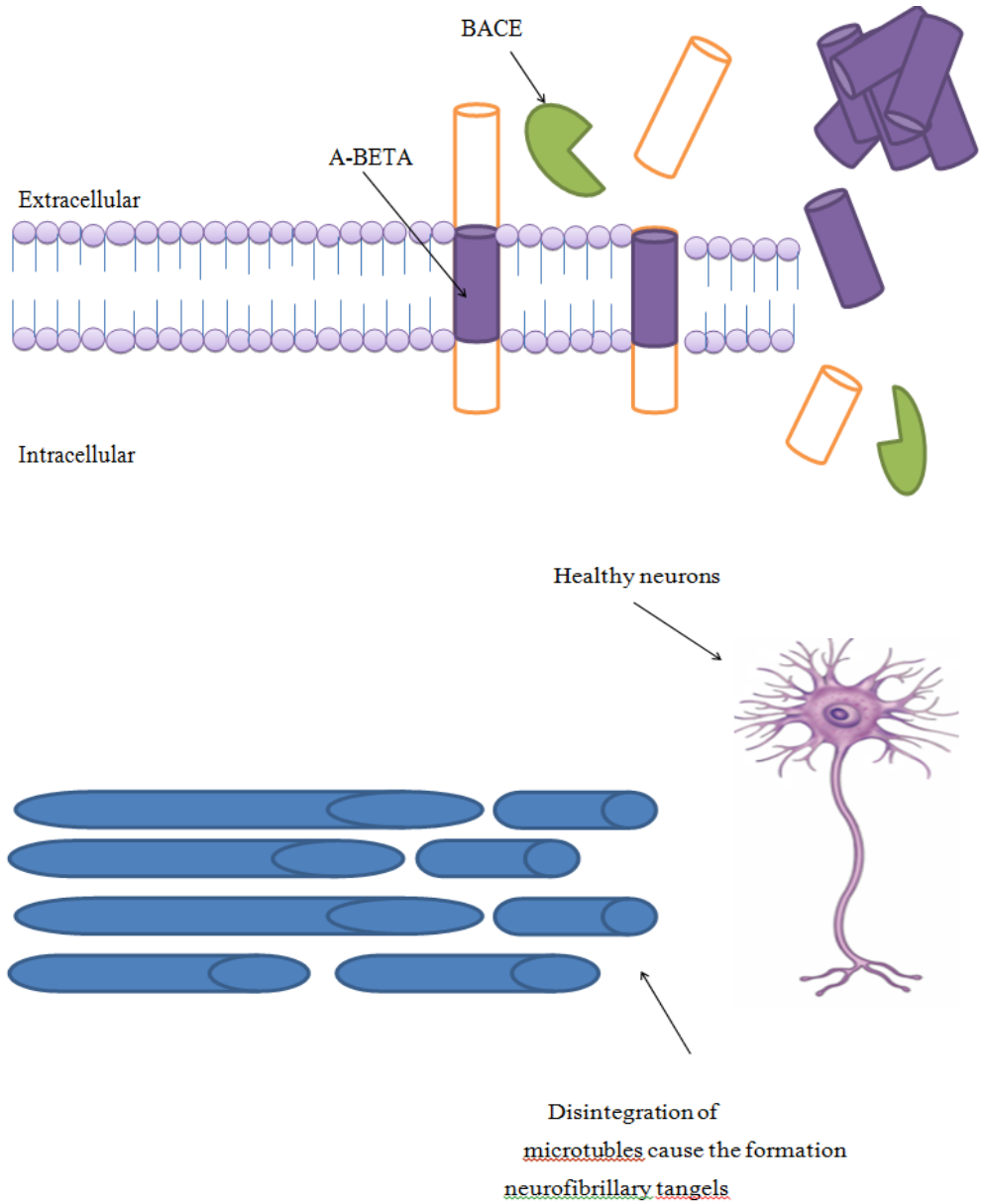


Figure 1.

2-Nano-technology

Advanced technology is needed for better approach and understanding of the disease to overcome the problems and limitations caused by previous drug delivery methods.[23] The most recent technology for such purpose is the nano-sized particles, with small size and high drug loading ability of various therapeutics, as well as its ability to be modified with different materials which can be used for its protection and highly specific for site targeting, nano-sized particles are considered as cutting edge technology for its ability to delivery therapeutics.[24,25] Such technology has offered the scientist with many advantages, such as its ability to maintain drug levels in a desirable range for therapeutic purpose, as well as it can

increase the permeability across the BBB and extending the half-life as well as the solubility and stability.[26] Nevertheless, nanotechnology can be designed to serve the disease as required, for example the system can be designed to release the drug in a controlled manner or trigged manner depending on the desired release way. For designing a nano-sized particle 2 aspects should be taken in consideration, which are the carrier (nano-sized particle), and the other is a therapeutic agent (cargo).[27] Depending on the specific properties of either component of the system, the drug is adsorbed or conjugated to the surface of the nanoparticle, or encapsulated and protected inside the core.

2.1-Pharmaceutical Strategies for delivery of AD drugs

Suitable drug carriers that can transport therapeutics across BBB for the treatment of Alzheimer's disease can be enhanced using nanoparticles.[28] Other approaches also involve the use of different biochemicals to modify the drug nano-carriers or the therapeutic material and methods of local delivery. Recent research shows the use of focused ultrasound and bilized microbubbles that can enhance transport or bypass the BBB by causing disruptions in the tight junction of the brain endothelial.[29] The improved delivery of drugs across the BBB has been shown over the use of many different systems and established using a wide collection of methodologies, in vitro and in vivo.[30] All of these investigations seem promising; nevertheless the absence of consistent approaches has made challenging to track down any one best technique for a given disorder.[28,31] As many of the recent clinical trials fails because of the poor investigation concerning the BBB penetration, the BBB remain as the main obstacle for this investigations.[32] As the BBB interference or the administration of the drug straight into the brain is not a route due to toxic effects and low diffusion of the therapeutic molecule in the brain parenchyma. A promising approach for drug systemic delivery to the central nervous system is the use of nano-sized carriers.[29,33]

2.2-The use of Nanotechnology for AD therapy

Recently, a wide range of nano-carriers, such as polymers, emulsions, lipo-carriers, solid lipid carriers, carbon nanotubes, metal based carriers and many others have been adapted to develop successful therapeutics with sustained release and improved efficacy.[34] The use of Nano-carriers is a fast developing field for medical application, nanoparticles or nanostructures are highly expected for the ability to delivery drug through the BBB.[35,36] They are characterised as colloidal structures comprising of natural or synthetic polymers ranging in size from 1 to 1000nm.[37] The application of this nanotechnology in drug delivery

systems has developed the kinetic profile of drugs in biological systems as well as its bioavailability.[21] The development of nanotechnology aid in directing drugs to specific molecular targets and safely delivers drugs to specific sites of action.[37] The sustained release of nano-drug delivery systems enhances the controlled release profile of loaded drugs, thereby minimizing the dosage-regimen. Thus, the overall effectiveness of drug candidates can be enhanced by adapting nano-drug delivery.[38] At present NPs are found to play a significant advantage over the other methods of available drug delivery systems to deliver the drug across the BBB.[39,40] Due to their size and functionalization, nanoparticles are able to penetrate and facilitate the drug delivery through the barrier, including number of mechanisms and strategies found to be involved in this process, which are based on the type of nano-materials used and its combination with therapeutic agents, such materials include polymeric nanoparticles non-viral vectors of nano-sizes for CNS gene therapy and liposomes etc.[21,41,42] In which the therapeutic molecule (Ex:protein or peptide) is incorporated internally either encased by the polymer matrix or distributed throughout, and can have external additions such as PEG and ligands to increase stability and specificity of targeting, respectively.[41] They are mainly produced by emulsion/solvent evaporation or precipitation solvent diffusion from a variety of polymers such as dextran, starch etc. As an advanced technology, nanoparticles are expected to reduce the need for invasive procedures for delivery of therapeutics to the CNS as various number of drug delivery systems have been used such as liposomes, nano-gels and nano-biocapsules microspheres and nanoparticles to improve the bioavailability of the drug in the brain, but microchips and biodegradable polymeric nano-particulate careers are found to be more effective therapeutically in treating brain tumor.[43] Many limitations minimize the effect for nanotechnology such as the presence of the blood–brain barrier (BBB), which highly regulates drug permeation, lack of unique target biomarkers for the diseased cells and the presence of highly selective barriers, and cell types which strongly influence the interaction with nanoparticles by the presence of lipid composition, surface receptor and interaction of nanoparticles with biological components after administration and physical factors that also contribute to the overall limitations and the concentration of the nanoparticles in the brain blood vessel, blood circulation, accumulation in non-target organs and elimination.[44,45] Recently, a wide range of nano-carriers, with different modifications such as polymers, emulsions, lipo-carriers, solid lipid carriers, carbon nanotubes, metal based carriers etc., have been adapted to develop successful therapeutics with sustained release and improved efficacy by facing all the limitations caused by the brain.[46]

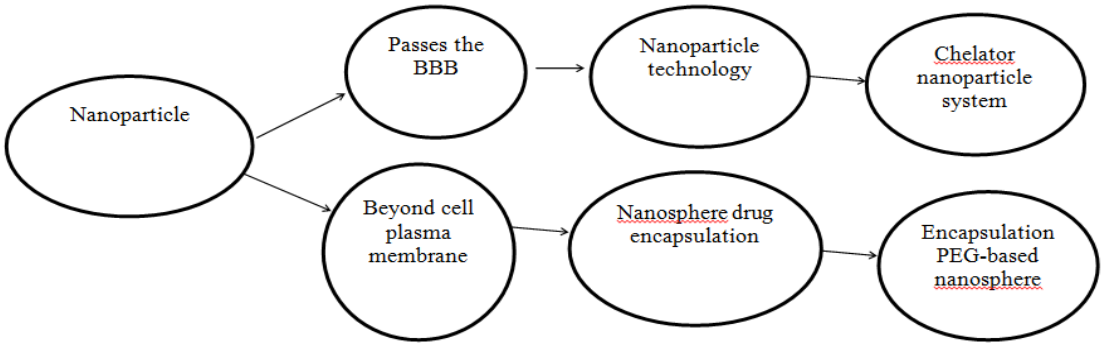


Figure 3: The following figure shows how nanotechnology is applied for Alzheimer disease treatment.

2.3-BBB and Brain receptors

BBB or Blood Brain Barrier can be considered as nutrient provider for the brain as it supply it with the necessary alimentary for the brain to operates in a healthy manner. However, it restricts the movement of ions and fluid to ensure an optimal environment for brain function as well as prevents the introduction of harmful substances to the brain. To a certain extend that can beneficial, yet BBB was always considered as an immense obstacle for many systemic delivery of neurotherapeutics.[47] After decades sicentist were able to find a window of opportunity for certain molecules with specific size, mainly the lipid-soluble with size 400-600 Da or less, making it the difficult accessible organ by numerous molecules. On the other hand, the BBB efflux transport systems was another milestone that researchers had to encounter, in which the drugs that meet the criteria are exported from the brain. Nonetheless, other organs have tight junctions that helps nutrients to reach them by slipping between blood vessel endothelial cells, but when it comes to brain the its entirely different, tight junctions present at the brain are consist from protein structures that button up the membranes of neighboring endothelial cells near their blood-facing, or luminal, ends. Thus, the brain vasculature restrict the flow of molecules from the blood to the CNS.[49] Receptors that promote the transfer of various macro-molecule are present on the BBB, which is accessible for drug transport (~20 m2) that is more than adequate for treating the whole brain volume, the barrier properties of the BBB continue to limit brain drug delivery via the bloodstream.[50] Other necessary nutrients that is needed for the brain to function such as proteins, amino acids and water-soluble compound such as ions and vitamins possess specific transport systems enclosed in the plasma membranes of the BBB to permit brain entry. There are two primary classes of transport systems function at the BBB. The first, carrier-mediated transport, relies on molecular carriers present at both the apical (blood) and basolateral (brain)

membranes of the BBB. These carriers tend to be highly stereospecific and function in the selective transport of small molecules such as ions, energy sources and amino acids. Using carrier-mediated transport systems for noninvasive drug delivery by conjugating therapeutics to the natural substratese. One factor to take into consideration is that since carrier-mediated transport systems are typically small, stereospecific pores, they are not particularly amenable to the transport of large-molecule therapeutics. While the other is the Receptor-mediated transport mechanisms are also present at the BBB, and these involve the vesicular trafficking system of the brain endothelium). Brain influx of nutrients such as iron, insulin, and leptin occurs by a transcellular, receptor-mediated transport mechanism known as transcytosis.

Table 1.

Receptor-Mediated transport (RMT)	Carrier-mediated transport (CMT)
Transferrin receptor (TFR)	Glucose transporter 1 (GLUT1)
Insulin receptor (IR)	Organic anion transporting polypeptide (OATP)
Lipoprotein receptor (LPR)	Large neutral amino acid transporter (LAT)
Diphtheria Toxin receptor (DPTR)	

Receptors expressed on blood brain barrier are located on both luminal side (blood) and abluminal, in which the following receptors possess the ability to regulate trafficking of different molecules, including essential nutrient and drug molecules.

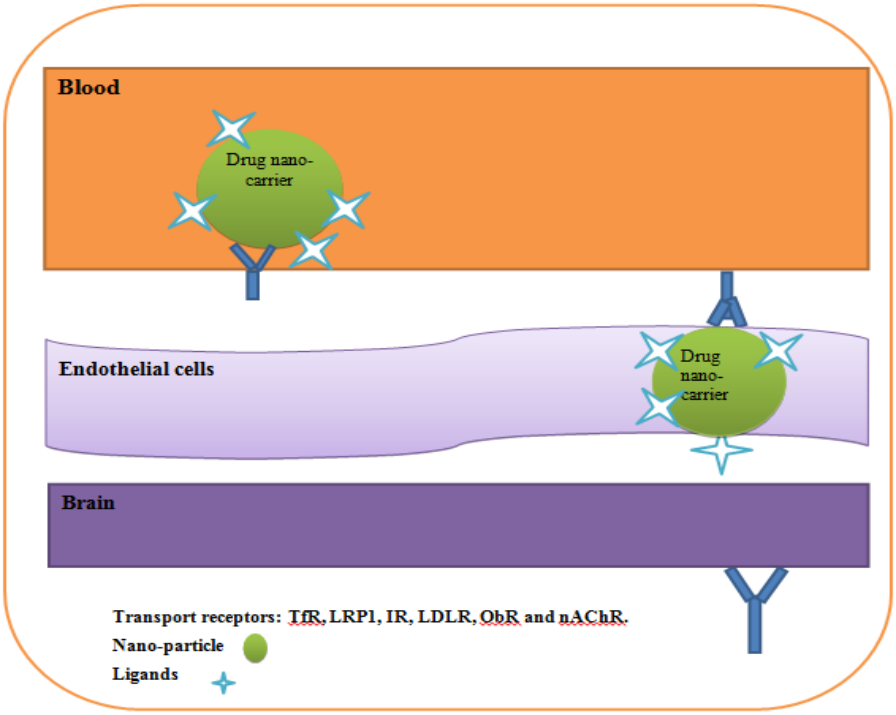


Figure 2: Nano-particles are modified with peptide ligands that bind with various receptors at the brain endothelial promoting transcytosis. The targeting to endocytic

cell-surface receptors present on brain endothelial cells allows for binding and transport across the cell trough vesicular transcytosis. Receptor-mediated transport receptors include TfR, LRP1, IR, LDLR, ObR and nAChR.

3-NANOPARTICLE USED FOR AD MEDICAL APPLICATION

3.1-HDL-like nanoparticles

Known as the good cholesterol, High density lipoproteins are considered as natural nano-carriers with different shapes as well as protein and lipid composition. They are well recognized for their biological role and are highly suitable as a nano-platform for medical diagnostics and therapeutics. In human, lipoprotein metabolism consist of two interrelated pathway, in the first pathway, the apolipoprotein B which delivery lipids consist mainly of cholesterol and triglycerides from intestine and liver to other tissues.[51,52] Another pathway is the use of HDL to remove the excess cholesterol from the blood vessels and transport it to the liver in a process known as revers cholesterol transport.[53] When compared with other lipoproteins, HDL is quite dense and considered as small lipoproteins due to the availabili ty of apolipoprotein. Now day's scientist has developed the synthetic form of HDL, with many advantages and modification to its structure and constituent. Recent investigation for the different uses of synthetic HDL has shown its effectiveness in atherosclerotic arteries, by removing the excess cholesterol after that its deliver it to the liver for elimination.[54,55] Yet many limitations face the synthetic form of HDL, such as the short half-life as well as the narrow therapeutic index, and here where comes the use of different modification materials which can be attached to the surface of the sHDL or to the component used for its synthesis.[56] Its natural role is the reverse cholesterol transport, and that's how the excess cholesterol is removed from the periphery and delivered to the liver for excretion. Beside that natural HDL have other vasoprotective roles including its reduce the endothelium inflammation, regulate the vascular tone by increasing nitric oxide and induction of endothelium repair.[57]

HDL structure

Many strategies have been developed to increase the level of HDL and improving its role for targeted therapy. For example the synthetic HDL has been used to target the acute coronary syndrome (ACS), in which it was used to successfully reduce the platelet aggregation.[58] The synthetic form of HDL have been constantly developed to resemble the natural HDL, specially the components used for the establishing the sHDL surface. The natural HDL

synthesis begins in the liver and small intestine where ApoA-1 the crucial protein which make 70% of the protein composition of the HDL, which its main source, Thus forming the first structure of HDL which is the lipid free.[59, 60]

Table 2: Examples of the structural diversity of HDL-like NPs for drug delivery.

Structural feature	Examples
Particle core form	Cholesterol esters Inorganic scaffolds (Au)
Shape	Discoidal Spherical
Protein associated with particle	Full-length apoA-I ApoA-I-mimetic peptide ApoE
Phospholipids	Phosphatidylcholine 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) 1,2-dimyris-toyl-sn-glycero-3-phosphocholine (DMPC) 1,2-dioleoyl-sn-gly- cero-3-((N(5-amino-1-carboxypentyl)iminodiacetic acid) succinyl)(- nickel salt) (NiLipid) 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[folate(polyethylene glycol)-2000] (DSPE-PEG2000-folate) (PF) 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-[3-(2-pyridyldithio)propionate] (PDP PE) [Dipalmitoylphosphatidylcholine (DPPC) Pyropheo-phorbide conjugated to the glycerol backbone of lysophospholipids
Lipid layer surrounding the particle	Monolayer Bilayer
Mechanism of drug loading	Covalent attachment Encapsulation Integration in lipid layer

Lipid-free apoA-I has garnered significant interest of late because the absence of lipid appears to be a requirement for the interaction of apoA-I with the ABCA1 transporter, a key reaction for the maintenance of plasma HDL levels. As for the ApoA-1 consist of both polar ad non-polar surface, it gives the lipid free ApoA-1 ability to possess negative and positive charges and is highly solvent exposed. Lipids play a key role to determine its shape, giving the lipid free ApoA-1a structure of amphipathic alpha-helices.[61,62]

The second structure is the lipid poor –HDL, which have the structure of a disc shape, consist of two rings of ApoA-1 one at the top and the other is at the bottom wrapping with its main component the ApoA-1 with the ability to solubilize the phospholipids around phospholipids bilayer in a double belt model.[63] Which are generated by exposure of lipid-free apoA-I to the cholesterol/phospholipid transfer activity ABCA1.

The lipid rich HDL particle is the dominant form of HDL in the human plasma. That has a spherical structure in which the amphipathic helices of ApoA-1 situated on the surface of the molecule and contains a neutral lipid core composed of cholesteryl ester and triglyceride.

Reconstituted HDL nanoparticle has the ability to carry different types of drugs.

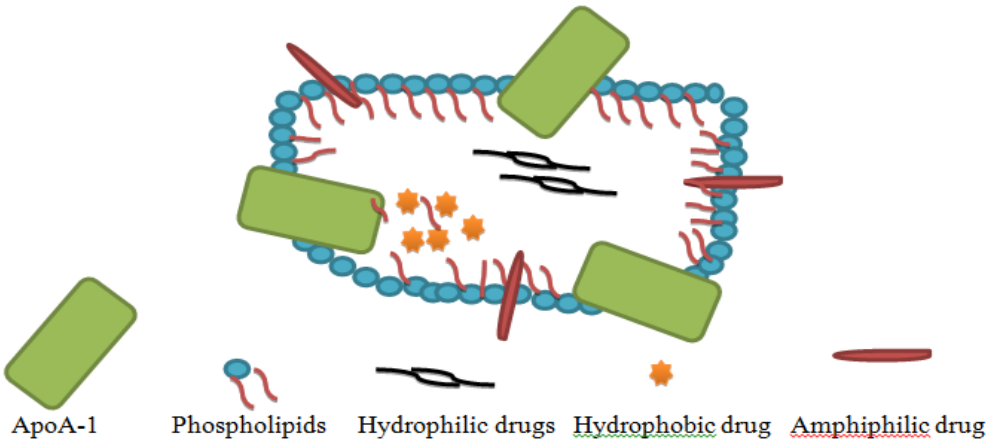


Figure 4.

3.2-Polymeric-Nano-carriers

Natural and plant-based polymers could be used for control release of drugs and also helps in targeting drug to the site of action, Polymeric NPs are solid colloidal carriers composed of synthetic, semi-synthetic or natural polymers with size ranging from 10 to 1000nm.[64] In which they are categorized as either nano-spheres or nano-capsules. In nano-spheres, drug is isolated in polymeric matrix however nano-capsules are reservoir system in which drug is limited within a polymeric shell.[65] Both polymeric nano-spheres and nano-capsules have been discovered for the delivery of peptide and protein therapeutics. Many aspects affect the properties of polymeric nanoparticles such as the nature of the polymer synthetic or natural as well as the preparation process involved. Polymeric nanoparticles considered as an innovative strategy for enhanced delivery method for non-invasive drug delivery routes such as nasal, pulmonary transdermal, and oral.[66] Therapeutic molecules can be adsorbed, encapsulated or chemically linked to the surface of polymeric NPs. Several techniques can be used for the incorporation of proteins and peptide in polymeric NPs.[67] Natural polymers are usually more likely to be sensitive to processing conditions. Hence, NPs with natural polymers are generated using mild techniques including ionic gelation, coacervation and polyelectrolyte. Recently polymeric NPs helps to with the problems related with synthetic and metallic polymer based NPs.[68] To overcome for the preparation of NPs polysaccharides of natural origin have been used as polymers to overcome the problems associated with metallic and

synthetic polymer-based NPs.[69] To avoid the use of toxic chemicals, high-cost and to prevent toxic effect of by-products of synthetic polymers, plant-based polymers that are abundantly available in nature may be evaluated for their composition, structure and toxicity.[70]

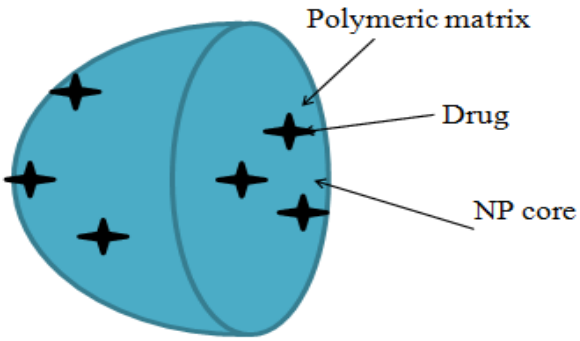


Figure 5.

In an investigation conducted by Liangfang zhang et al, who designed a self-assembled lipid-polymer hybrid nanoparticle as a potent drug delivery for its ability to combines both the merits of the polymeric NPs and liposomes.[71] Liangfang zhang et al, has used the nano-precipitation or double emulsion methods which are both considered simple to carry out and scalable methods for nano-system preparation. The system was consisted of a hydrophobic polymeric core and a hydrophilic polymeric shell and a lipid monolayer at the interface of the core and the shell. His nano-system was self-assembled via the PLGA (poly (D,L-lactic-co-glycolic acid) terminated with ester linkage as a model of hydrophobic polymer to form the polymeric core of the nano-system.[72] The polyethylene glycol (PEG) which can be used for coating the NP and prolong its circulation. It has been demonstrated that the hybrid NP has tunable size and surface charge, high drug loading yield, sustained drug release profile, favorable stability in serum, good cellular targeting ability and its simple synthesis process may be amenable to further scale-up if desired. All these positive attributes make the lipid-polymer hybrid NPs a promising drug delivery vehicle for further *in vivo* evaluation.[73] In another study, Zhang et al designed an advanced dual-functional NP drug delivery system which is consist of PEGylated poly(lactic acid) polymer containing two targeting peptides, TGN and QSH, conjugated to the surfaces of the NPs. TGN specifically targets ligands at the BBB, while QSH has good affinity for $A\beta_{1-42}$, which is the main component of amyloid plaques.[74] In this study, the optimal maleimide/peptide molar ratio was 3 for both TGN and QSH on the surface of the NPs. These NPs were delivered to amyloid plaques with enhanced and precisely targeted delivery in the brains of AD model mice.

3.3-Liposomes

Liposomes were discovered in the 1960s, since then they were under constant investigation, liposomes were valued for their technological and biological merits, and considered as very reliable and one of the most successful drug-carrier system up to date.[75] It consists of vesicular self-assembling colloidal structures composed of one (unilamellar) or more (multilamellar) lipid bilayers surrounding a core aqueous compartment. The aqueous core provides an environment in which hydrophilic drugs can be encapsulated, while lipophilic drugs can be incorporated into the lipid bilayer. Its first formulation was composed only of natural lipids, now day's man things can be added to it such as natural and or synthetic lipids and surfactants. Their structure is nearly spherical with size range from few nanometers to several micrometers, but as for the desirable size for therapeutic purpose it ranges from 50 to 450 nm. Liposomes have similar morphology of cell membrane giving it the ability to incorporate various therapeutic and functionalization material.[76] In a study conducted by KARTHIK ARUMUGAM et al, in which rivastigmine a class of acetyl-cholinesterase inhibitors for mild to moderate alzheimer patients, and liposomes as the drug vehicle by intranasal route. For the liposome formulation, lipid bilayer method hydration was used, by using cholesterol and soya lecithin as lipid components.[77,78] A rat model was used to check the amount of free drug administrated orally and intranasal as well as intranasal liposome rivastigmine. The samples were divided into 3 groups for the vivo study, all 3 groups received same amount of rivastigmine in which the 1st group was the free drug administrated orally, group 2nd was also a free drug but administrated intranasal and the 3rd sample was liposomes administrated through intranasal route.[79-81] The AUCs of these groups were compared, the intranasal liposome group had five-fold higher AUC (36.13 ± 1.87 mg min mL–1) when compared to orally administered free drug (6.58 ± 0.26 mg min mL–1) and an almost three-fold higher value compared free drug administrated intransally (12.99 ± 0.87 mg min mL–1). This concluded that intranasal liposome rivastigmine had longer half-life than the free drug intranasal and the oral administration.

In a study recently conducted from Mourtas et al, focusing on using liposome for targeting A-beta amyloids using azido-decorated liposomes functionalization with an alkyne-derivatized ligand by 1,3-dipolar Huisgen cycloaddition reaction (Also known as click chemistry reaction).[82] The research group found out by SPR experiments that the liposomes decorated with the planar curcumin had the highest affinity constant (in the 1–5 nM range) reported thus far for Aβ fibrils, whereas nonplanar curcumin-decorated liposomes did not show any

binding.[83,84] As for the polymer NPs, these systems could pave the way for the development of colloidal systems able to capture Aβ as one of the most occurring hallmarks for AD and to reduce its inherent toxicity.[85,86]

3.4-Solid lipid nano-carriers

The SLN are spherical in structure with size range from 10 to 1000m in diameter. In the late 19th century solid particles were established and had advantages over the liposomes and in terms of protection incorporated active compounds against chemical degradation and more flexibility in modulating release of the compound.[87] By gaining such conclusion about the solid nanoparticle, in the 1990s emulsions and liposomes were combined by the development of the 'solid lipid nanoparticles' (SLN). The SLN released by simply exchanging the liquid lipid (oil) emulsions by a solid lipid, which means lipids solid at room temperature but also at body temperature.[88] SLN is been rapidly developed for drug delivery and research work, due to their abilities and numerous nanocarriers which were based on solid lipid such as solid lipid nanoparticles, nanostructured lipid carriers, lipid drug conjugates.

In a study conducted by Bondi et al. a developed ferulic acid-loaded SLN was established by using the microemulsion technique for AD therapy.[89] In the study, two SLN was tested for their effectiveness, the ferulic acid-loaded and the unloaded SLN. Both ferulic acid-loaded and the unloaded SLN was synthesized by using the oil in water micro-emulsion technique. The samples that were loaded with ferulic acid –SLN showed a fully drug release within 10 hours at a neutral pH of 7.4.On the other hand the unloaded SLN were able to penetrate the cell membrane with no cytotoxic effect on cell proliferation.[90] Based on his research, Bondi et al. proved that the loaded FA- SLN possessed higher protective activity in comparison with the unloaded SLN against oxidative stress induced in neurons concluding the SLN are excellent carries for transporting FA into the cells, which on the other hand can be considered as a potential drug delivery system for Alzheimer disease.[91]

The investigation and different methods was carried out for inhibiting the formation of β-amyloid. Girish Modi et le. Worked on the use of nanogels as an advanced nanotechnology for inhibiting the formation of β-amyloid, his nanogel was modified with polysaccharide pullulan backbones with hydrophobic cholesterol moieties (cholesterol-bearing pullulan, CHP) as artificial chaperones to inhibit the formation of β-amyloid (1–42) fibrils with marked amyloidgenic activity and cytotoxicity.[92] The nanogel was biocompatible and 20–30 nm in

diameter as well as its ability to prevent aggregation of proteins associated and inhibit amyloid fibers from forming.[93] Cholesterol-bearing pullulan, CHP-nanogel were able to incorporate up to 6-8 of β-amyloid (1–42) molecules per particle and prompt a change in the conformation of β-amyloid from a random coil to an alpha-helix- or β-sheet-rich structure. The nanogel showed high level of stability in 24hour period under 37 degrees, under such conditions the CHP-nanogel was able to inhibit the aggregation of β-amyloid. Nevertheless, Girish Modi et le order to release monomeric β-amyloid molecules, the nano-gel had to be dissociated by the addition of methyl-β-cyclodextrin.

In a study c+onducted by Jorge Palop et.al, a PhD candidate at Gladstone Institutes, working on a possible cell therapy for AD treatment, that the transplanting of genetically altered interneurons for improving cognitive function can possibly be effective against AD. The main theory of this method focuses on the damaging specific neurons which can alter brain wave and rhythms, and inhibiting interneurons that are especially important for managing brain rhythms. Interneurons control complex networks between neurons, by permitting signals to be sent to one another in a harmonized manner.[94,95] An imbalance between 2 type's neurons can create tension leading to multiple neurological and psychiatric disorders including autism, AD etc. Palop worked previously on inhibiting interneurons in mouse models with AD, resulting in poor effectiveness due to the disturbance of rhythms that organize the excitatory, causing an imbalance in the brain network and cells fail to function harmoniously, leading to poor memory formation and epileptic activity.[96] The researchers at Gladstone Institutes noticed that the functions of interneurons was in enhanced as well as it activity been genetically improved when adding a protein called Nav1.1.[95] Nevertheless, such discovery was concluded by overcoming the toxicity at the disease environment and restoring brain function.[97]

3.5-Virus like particles (VLPs)

On molecular level virus like particle resembles natural virus but since they lack viral genomes, making them absolutely noninfectious, nonetheless VLPs they can be naturally come about or synthesized through the individual expression of viral structural proteins. Many viral structural proteins have an intrinsic ability to self-assemble into virus-like particles (VLPs).[98] Virus particle consists of various parts including the genetic material (DNA or RNA), a protein coat that protects these genes, and in some cases an envelope of lipids that surrounds the protein coat when they are outside a cell. The size of viruses ranges

from a few tens to a few hundreds of nm, which is equal to 1/100 to 1/1000 of the cell (a few to a few tens of μm in size) of any other common living organism. V LPs make excellent vaccines against the virus from which they were derived.[99,100] VLP-based vaccines to prevent infection by two viruses, Hepatitis B Virus and Human Papillomavirus, have been approved for human use. Both of these vaccines safely and consistently induce high titer, durable antibody responses in humans.[101] In a study conducted by Bryce chackerian et.al, using VLP-based vaccines for immunoprophylaxis against an amount of other human virus infections are in clinical and preclinical development. VLPs make effective vaccines because their particulate nature and multivalent structure provoke strong immune responses.[99,102] VLP-based platforms have certain advantages for the develop-ment of vaccines for AD. They are highly immunogenic and can even overcome the effects of immune tolerance that may exist in AD patients. Their modular nature allows for the display of different A-beta derived peptides. They can serve as a source of linked T helper epitopes, meaning that T-cell responses need not be directed against A-beta. Indeed, VLP-based immunogens for AD have been tested in animal models and can induce high titer anti-body responses against A-beta without concomitant T-cell responses and can reduce A-beta-related pathology. The current CAD106 clinical trial will establish whether a VLP-based vaccine against A-beta can mitigate disease in humans.

4-NANOPARTICLE FUNCTIONALIZATION

4.1-Nanoparticle Functionalization

Different nano-carriers can be loaded with various functionalization materials for longer bioavailability, protection from interaction with blood protein serum, very specific for targeting receptors located at the BBB. Nevertheless, recently many functionalization materials are been constantly developed for targeting different receptors on the BBB with high affinity with different possible routes based on receptors and absorptive transocytosis. Materials used for the functionalization can be protein, peptide and other coating materials, attached to the nano-carriers with different methods based on their chemical and physical properties. The four most abundant receptors located on the BBB are Tfr, insulin and leptin yet targeting these receptors have been an overwhelming task for many years.[53] As the ligands used for targeting the receptors can vary in size and chemical composition causing difficulty for their attachment with the carrier and the possibility of interactions with blood protein serum before reaching their site of action. Proteins were the main materials used for functionalization, by time their production was expensive and high immunogenicity was a

major issue. Eventually researchers turned their eyes to much smaller molecules, with huge amount of study focusing on their method of purification and production. Peptides were considered a very attractive candidate, their conjugation with the nano-carrier resulted in minimizing the undesirable side effects and achieves the therapeutic effect with a lower dose.[103] Both linear and cyclic peptides have been explored as trafficking moiety due to ease of synthesis, structural simplicity, and low probability of undesirable immunogenicity. These molecules combine the low cost of small drugs with the high specificity of biologics. As peptides are easy to modify, their attachment with the receptor should meet with certain requirements to ensure accurate binding with the targeted site. At first the peptide should bind with the receptor expressed on the targeted cell, and no other cells expressing the same receptor, as well as its stability during the systematic circulation to ensure effective concentration. Other crucial factors that plays a key role in designing an optimal drug delivery system is the drug release, which is the process by which the drug is released by diffusion or the release of drug by dissolution of the nano-carrier matrix is known as drug release.[104] It's a crucial step in the overall drug delivery system as it can help to determine the drug stability, formulation development and therapeutic site. The effectiveness of the drug is related to the drug component as well as the solubility and the diffusion. After the administration of the drug through a nano-carrier, other parameters are considered to check the effectiveness such as the particle size and release process.[105] For faster drug release the size of the particle is a key factor, in which the smaller particle size the larger the area to volume ratio, resulting in the drug being close to the surface of the particle in which the drug is released faster. An overall optimal drug release will depends on many factors, at first the design of the nano-carrier, and fully understanding the process by which the nano-carrier is affected by the inner environment of the systemic circulation eg:(pH and thermo-sensitivity), with full knowledge of the physiological factors as well as the time of release and site of therapeutic.

4.2-Safety issues concerning the use of nanotechnology for Alzheimer treatment

The evolvement of nanotechnology and its applications for Alzheimer disease treatment have promoted serious issues in relation to NP-mediated toxicity and adverse reactions.[106] Making it a huge concern for IV injected Alzheimer's nanoparticle loaded medicines, regardless to their uses whether for reaching the brain for diagnostic imaging or therapeutic purposes.[107] In particular, nanoparticles size, shape, and surface characteristics can modulate pharmacokinetics and biodistribution. Investigation in this area of research is still scant and

particularly in relation to the brain. However, from the therapeutic perspective the benefit-to-risk ratio is a crucial point that researchers should pay much attention to, depending on the nanoparticles dose and on the frequency of dosing.

5-CONCLUSION

Nanotechnology is able to provide potent agents to modify the course of specific pathological mechanisms involved in AD. Even though, translation of these strategies to actual modification of Alzheimer's disease course in human subjects lies largely not only on biocompatibility of these agents, all disease modifying strategies designed to slow or halt the Alzheimer's disease molecular pathogenesis have failed by phase-3 clinical trials. The chances of finding a cure for AD in the future are low, there is also no considerable research progress explaining the underlying mechanisms of AD. Establishing and validating relevant animal models used in preclinical studies, and methodologies used in drug design and discovery has no promising research future either. While toxic side effects remain the major concern regarding different nanoparticles. Methodological breakthrough in targeted particles is shown by their biochemical characteristics. The structural barrier (BBB) imposes boundaries and sets limits to the delivery of therapeutic drugs to the brain which makes treating patients suffering from tumors, virus generated neuronal infections, and neurodegenerative diseases a very demanding task. Therefore, several diverse techniques have been developed and put to use for both direct and indirect drugs delivery to the brain in order to achieve proper drug delivery to patients. In several case studies direct injections or convection-enhanced drug delivery or cerebrospinal fluid or intranasal delivery verified their unreliability by being problematic to the patient or fails. Nonetheless, biodegradable biomaterials should be used to minimize toxic effects in the brain in order to have a lower risk of nanoparticle generated cytotoxicity and invasiveness. Furthermore, Biomaterials for making nanoparticle should be biocompatible and should have a very short half-life. Therefore, biodegradable polymers like polylactic acid, polycaprolactone, poly (lactic-co-glycolic acid), the poly (fumaric-co-sebacic) anhydride chitosan, and modified chitosan, as well as solid lipids, should be used in the preparation of the nanoparticles. Other drug nano-carrier such as the reconstituted HDL services as an excellent therapeutics delivering vehicle and it unique size making the penetration of the BBB more likely with the right peptide ligands. According on that, A solid argument could be made stating that the field has a good understanding of at least the generalities of apoA-I organization in its lipid-free form and in simple discoi-dal particles. Although, more research needs to be done in order to understand

the importance of the more dynamic sequences within these structural frameworks for better application for Alzheimer disease. Moreover, active drug molecules can be coupled to a desired protein or peptide that increases its circulating life, solubility, stability and antigenicity. To wrap it up. Moreover, active drug molecules can be coupled to a desired protein or peptide that increases its circulating life, solubility, stability and antigenicity. To wrap it up, plenty of studies have focused on applications of various drug delivery system and their modifications, however, more research need to be conducted to better understand the materials used for constructing the drug carrier as well as the conjugates peptides. Researchers should have better understanding of the mechanisms underlying the beneficial biological properties of materials used for constructing the drug carrier as well as the conjugates peptides since they offer incredible opportunities which will in return promote more rational drug design.

6-ABBREVIATIONS

AD Alzheimer disease
BBB Blood Brain Barrier
TJs Tight junctions
AJs Adherin junctions
HDL High density lipoprotein
Aβ Amyloid beta
RMT Receptor-mediated transcytosis
SLN Solid lipid nanoparticle
NP Nanoparticle
PEG Polyethylene glycolated.
PLGA Poly(lactic-co-glycolic acid)
IV Intravenous
FA Ferulic acid
CHP Cholesterol-bearing pullulan
ACS Acute coronary syndrome
TfR Transferrin receptor
CNS Central nervous system
PAMAM Poly(amidoamine)
VLPs Virus like particles
SLN Solid lipid nano-particles

DNA Deoxyribonucleic acid

RNA Ribonucleic acid

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