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POLYMERIC NANOPARTICLES IN TREATMENT OF ALZHEIMER'S DISEASE: AN OVERVIEW

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ABSTRACT

Neurodegenerative diseases are the disorders that causes complete disabilities or death by damaging the neuron cells and affecting the motor and cognitive function of the brain. Alzheimer's is one such disease which is a type of dementia characterized by memory loss, neuronal death, cognitive decline that ultimately leads to patient's death. Polymeric nanoparticles are sub-micron sized, solid colloidal particles synthesized from naturalor synthetic polymers. The drug is either loaded inside or conjugated on the surface. As the usage of most of the drugs in treatment of Alzheimer's is restricted, nanoparticles having smaller size and larger surface area are preferred. Ideal properties of polymeric nanoparticles for drug delivery to the brain is discussed. Special mentions are given about the recent trends and applications of nanoparticles. Further conclusive work needs to be done in treatment of Alzheimer's disease using polymeric nanoparticles as it makes its way into the mainstream clinical practice.

KEYWORDS

Nanoparticles, Neurodegenerative disorders, Alzheimer's disease and Blood brain barrier.

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INTRODUCTION

Nanoparticles (NPs) are defined as solid colloidal particles which consist of macromolecular materials in the sizes ranging from 1-1000nm and are used therapeutically as drug carriers. The most common material used for the composition of nanoparticles are polymers[1]. Recent advances in nanomedicine resulted in the design of several controlled drug delivery systems of which the most used one is polymeric nanoparticles[2].

Polymeric nanoparticles (PNPs) are submicron sized solid colloidal particles in which the drug is loaded inside or is conjugated on the surface and are synthesized from natural or synthetic polymers.

These polymeric nanoparticles can carry medications directly to the central nervous system (CNS). Polymeric coating has number of advantages, including lowering the toxicity of medications with a high therapeutic ratio, increasing the solubility of hydrophobic pharmaceuticals, and giving extracellular stability[3].

Neurodegenerative diseases (NDDs) are the disorders that damage the neuron cells and affect the motor and cognitive functions which ultimately leads to complete disabilities or death[4]. Alzheimer's disease, multiple sclerosis, dementia, epilepsy, schizophrenia, traumatic brain injury, Parkinson's disease are the different types of NDDs[5]. Pathogenesis of NDDs include neuroinflammation, aging, oxidative stress, mitochondrial dysfunction, or metabolic disorders[6].Alzheimer's disease (AD) is an age-related disorder in which deposition of plaques takes place extracellularly around the cerebral vessel walls and in the parenchyma of the brain[7].

Most chemicals cannot enter the brain at therapeutically relevant concentrations, making therapy and diagnosis of disorders like Alzheimer's difficult. Nanocarriers appear to be a promising notion for enhancing therapeutic delivery to the CNS. Systemically administered nanocarriers that target the brain must bypass the mononuclear phagocytic system (MPS) and penetrate the blood–brain barrier (BBB), a highly selective structure. When nanoparticles cross the BBB, they are usually absorbed by endothelial cells before undergoing exocytosis into the brain (Figure No.1). Furthermore, once within the brain, the nanocarriers must travel to various brain locations in order to provide efficient therapeutics. Understanding and modifying the properties of nanocarriers is critical for obtaining systems with the best results.

Figure No.1 the brain capillaries are made up of specialised endothelial cells, pericytes, and astrocytes, and they irrigate the brain parenchyma. Endothelial cells have apical–basal polarity, and the polarised membranes are separated by tight junctions. NPs must interact with the apical membrane, be internalised by the endothelium, and undergo vesicular trafficking and exocytosis to reach the brain[8].

Polymeric nanoparticles come in a wide range of compositions, including single polymers, copolymers, protein-based, lipid–polymer hybrids, metal–polymer hybrids, and so on. Each of these systems can be improved to produce particles of various sizes, release and degradation profiles, functionalization options, and a variety of other characteristics. The design of particle characteristics in drug delivery allows for more control over particle interactions in biological settings, which affect biodistribution, clearance, transit across barriers, uptake and ultimately, therapeutic effect. Size, surface charge and targeted ligand coupling are all known to affect particle interaction with cells and tissue accumulation, including the brain[8].

POLYMERIC NANOPARTICLES

PNPs are nanoparticles made of polymers including poly (butyl cyanoacrylate), poly (lactic acid) and poly (lactic-co-glycolic acid), as well as natural components like albumin and chitosan. These chemicals have an advantage over other types of nanoparticles as they are easier to biodegrade and so have less toxicity. They can also make nanocapsules (spherical structures with a liquid cavity enclosed in a solid shell) and nanospheres (spherical solid particles). Surface changes (such as PEGylation) are also possible with these NPs, which would boost circulation lifespan and BBB penetration. PNPs can be loaded with solid or liquid drugs, with the loaded drug remaining non-covalently absorbed or chemically bound to the NP surface[9].

Figure No.2 Physical characteristics such as composition and concentration, as well as size, shape, surface properties, crystallinity, and dispersion state, can all affect PNPs. These features are frequently evaluated using a variety of methodologies in order to fully characterise the NPs. Electron microscopy, dynamic light scattering (DLS) or photon correlation spectroscopy (PCS), near-infrared spectroscopy, electrophoresis, and chromatography are only a handful. Characterization of polymeric NPs is critical not only for their applicability, but also for determining concerns such as nanotoxicology and workplace exposure evaluation, which are necessary for assessing health

and safety risks and controlling manufacturing processes[10].

Nanoparticles are made of a variety of materials, including natural and manmade polymers, lipids, and metals. Because nanoparticles are more efficiently taken up by cells than bigger macromolecules, they are a good medium for distribution[11]. Nanoprecipitation, spontaneous emulsification or solvent diffusion, polymer polymerization, ionic gelation or coacervation, spray drying, emulsion solvent evaporation, supercritical fluid technology, and particle replication in non-wetting templates (PRINT) have all been used to produce NPs[12].

The use of nanoparticles in drug delivery allows for either active or passive administration of the conjugate (nanoparticle - drug) into specific cells. Antibodies and low molecular weight compounds like folic acid or peptides are commonly used in active transport because they have a molecule on the conjugate's surface that recognises the target location. Physical cues, such as temperature and pH of the surroundings, can also be used to achieve active transport. Passive transport, on the other hand, takes advantage of increased vascular permeability and tissue retention of small and big molecules. The release of the drug from the conjugate can be triggered by physiological changes in the environment, such as temperature, pH, or osmolality, or by enzymatic action, depending on the mechanisms used and the nanoparticle design[13].

For brain drug delivery, ideal nanoparticle features include:

Nontoxic, biodegradable, and biocompatible nanoparticles, such as polylactide homopolymers and polylactide-co-glycolide polymer nanoparticles.

Longer blood circulation time, with only PEGylated nanoparticles having a lower absorption and longer circulation time.

Cost-effectiveness studies should be conducted to assess the possibility for nanomedicine to be used in clinical settings. The number of patients who can benefit from those treatments will be limited as treatment costs rise.

It is vital to maintain physical stability and prevent aggregation in the blood, as certain types of nanoparticles have been deemed harmful due to physical rather than chemical surface features.

Non-invasive gene-targeting brain delivery, such as PEGylated immunoliposomes that enter their content into brain tissues via receptor-mediated transcytosis without damaging the BBB.

Nanoparticle size should be less than 100nm, because the rate of clearance increases as particle size grows beyond 100nm, affecting both biodistribution and bioavailability.

Targeted brain administration without the need of active reflux or a carrier-mediated route, to improve medication bioavailability and efficacy while lowering the therapeutic dose and its efficacy[14].

ALZHEIMER'S DISEASE TREATMENT WITH POLYMERIC NANOPARTICLES

Alzheimer's disease is marked by neuronal death, cognitive decline, memory loss, and, eventually, a breakdown of basic skills such as walking or swallowing, which leads to the patient's death. It is the most common type of dementia in the world, accounting for 60-80 percent of all dementia cases[15].

Even though the drugs based on the neurotransmitters were used to treat the cognitive impairments of the brain in AD several failures in the therapy were reported due to brain toxicity, less absorption in neuronal cell membranes, and other pharmacodynamic and pharmacokinetic parameters. The problems that occur during the treatment of AD was solved using nanoparticles which not only has unique physicochemical properties but can also cross the blood-brain barrier (BBB) such that these NPs deliver the drugs to the brain by enhancing the pharmacokinetic and pharmacodynamic properties of the drug and reducing its toxicity[16].

Polyethylene glycol is one of the polymers that has been proven to be quite useful as a nanoparticle coating material in degenerative illnesses (PEG). Because of its targeting powers and ability to resist uptake by the reticuloendothelial system, it is either employed for encapsulation or surface modification. Polyethylene oxide-modified polyepsilon-caprolactone has been found to extend circulation time and improve tumour targeting in mice with MDA-MB231 tumours. Non-biodegradable

polymers such as PEG, polyvinyl alcohol (PVA), monomethoxy poly-(ethylene glycol) and biodegradable polymers such as chitosan and collagen (mPEG), and polysorbate, have been used in the development of blood compatible polymers[17].

SYNTHETIC POLYMERIC NANOPARTICLES

Synthetic polymeric nanoparticles can be made from synthetic or natural polymers that degrade or not. Polyurethanes, polyesters, polyamides and polyanhydrides are among the synthetic polymers employed. Some polymers, such as the polyester poly (lactic acid), degrade hydrolytically, whereas others, such as the vinyl polymer polystyrene, degrade only enzymatically or not at all, such as the methacrylate ester poly (lactic acid) (methyl methacrylate).

Nanoparticles manufactured from organically derived polymers are more biocompatible and often degradable than synthetic nanoparticles. Chitosan, which is generated from the shells of crustaceans, is frequently utilised in antibacterial and drug delivery applications. Alginate, a substance derived from algae, has also been employed in drug delivery and hydrogels. Natural polymers are frequently degraded by hydrolysis or enzymatic processes.

POLY (LACTIC-CO-GLYCOLIC ACID)

Poly (lactic-co-glycolic acid) (PLGA) is a well-studied polymer that has been employed in a variety of biomaterials. PLGA is a polyester formed of lactic and glycolic acids, which are metabolised by the organism through the Kreb's cycle and excreted through the lungs, the kidneys can also create glycolic acid. The glass transition temperature of PLGA is higher than 37°C, giving it a rigid chain structure and high mechanical strength. In the presence of tin or aluminium-based catalysts, it is polymerized via random ring-opening copolymerization of glycolic and lactic acid cyclic dimers[18]. Direct polycondensation of lactic and glycolic acids, ideally in the melt state, can also produce PLGA, and tin can be utilised as a catalyst. Lewis acids, organometallic compounds, and zinc catalyst can all be used to achieve high molecular weights[19].

The hydrolytic de-esterification of the PLGA copolymers is followed by the clearing of their monomeric anions, glycolate and lactate, making them non-toxic and biodegradable[20]. Changing the lactic acid to glycolic acid ratio can alter the pace of degradation, mechanical strength, degree of crystallinity and thus drug loading and release kinetics. Poly (lactic acid) (PLA) is a crystalline hydrophobic polymer with poor mechanical strength, whereas poly (glycolic acid) (PGA) is a stiff and hydrophilic polymer with low mechanical strength due to its methyl sidechains. As a result, PLGA copolymers with a higher PLA: PGA ratio are more hydrophobic, which means they degrade and release drugs at a slower rate[21].

The polycondensation process, ring opening polymerization, and Segmer assembly polymerization are all methods for making PLGA. PLGA nanoparticles can be made from PLGA copolymer utilising processes like emulsion, nanoprecipitation, solvent co-evaporation, and spray-drying. Soft lithography can also be used to create non-spherical nanoparticles (e.g., cylindrical shapes). The terminal carboxylic acid groups can be used to introduce surface changes[22].

Chemotherapeutics, antibiotics, anti-inflammatory medicines, and proteins are among the drug compounds that have been incorporated into PLGA nanoparticles[23]. For bridging the BBB, a variety of PLGA formulations have been investigated. In transgenic mice, for example, PLGA nanoparticles loaded with Aβ generation inhibitor peptide and curcumin and coated with a cyclic transferrin-targeting peptide increased spatial memory and recognition[24]. In addition, two non-CNS targeting PLGA formulations have been authorised in clinical trials.

POLY (ALKYL CYANOACRYLATES)

Superglues or poly (alkyl cyanoacrylates) has long been used as a suture material[25]. Couvreur *et al*. were the first to develop PACA nanoparticles in 1972. They have a low toxicity and are destroyed in the intestinal tract by pancreatic juice esterases (orally) or serum esterases in the blood[26]. The alkyl side chain length can be changed to alter the degradation

time, which is measured in hours. PACAs can be made using a variety of polymerization methods, including free radical, anionic, and zwitterionic polymerization[27] and PACA nanoparticles can be made using either aqueous acidic phase polymerization or interfacial emulsion polymerization[25].

PACA nanoparticles can be functionalized by esterifying cyanoacetic acid with PEG-amine, folic acid, or pharmaceuticals to produce cyanoacetate esters, which can subsequently be polymerized. Encapsulation or adsorption has been used to load a range of medications, including hydrophilic or poorly soluble compounds, peptides, proteins, and nucleic acids[28]. PACA nanoparticles have been treated with PEG to avoid macrophage absorption or polysorbate 80 to boost their ability to permeate the BBB for brain delivery[29]. A considerable rise in Aβ level was identified in the plasma when PACA nanoparticles were decorated with anti-Aβ1-42 antibody in another investigation, leading to memory recovery in an Alzheimer's disease animal model (Figure No.3)[30].

Clinical trials for several PACA-formulated nanoparticles have been conducted, but not for CNS disorders. PACA nanoparticles containing doxorubicin or mitoxantrone, for example, have been evaluated in patients with resistant solid tumours and hepatocellular carcinoma[31]. A phase II experiment was halted due to significant acute respiratory distress episodes[32]; however, this problem was remedied by switching the delivery method from intra-hepatic arterial to intravenous slow infusion. Unfortunately, when compared to the best standard of care, a phase III trial found no additional survival advantage for patients[26]. Variability in drug entrapment rate and release characteristics has been suggested as one of the causes for the lack of clinical translation[33].

NATURAL POLYMERIC NANOPARTICLES

Synthetic polymer's usage is sometimes limited due to their high cost, purity, and unfavourable toxicity characteristics. Because of their low toxicity, sustainability, low cost, and unique physicochemical features, such as biodegradability, nanoparticles based on naturally occurring polymers have also been investigated as an alternate technique in brain medication delivery[34].

Alginate

Alginate, an anionic linear unbranched polymer, is extracted from brown seaweed (phaeophyceae). It's a random copolymer that connects β-d-mannuronic acid and α-l-guluronic acid via 1, 4-glycosidic linkages. Alginate is a nonimmunogenic chemical licenced by the FDA for use in wound healing, drug delivery, and tissue engineering. Alginate has hydroxyl and carboxylic acid functional groups, which can be used to add highly reactive functional groups (e.g., aldehyde groups) or chemical (e.g., phosphate or sulphate) or biological (e.g., amino acids) groups to improve bio-integration and bio-affinity[35]. Complexation (with cationic chemicals or divalent cations like Ca^{2+}) is used to make alginate nanocapsules and nanoaggregates[36]. A water/oil emulsion approach with gelation is used to make alginate nanospheres[37]. Mixing alginate nanoparticles with other polymers, such as poly[(2-dimethylamino)ethyl methacrylate], or using disulfide cross-links, can produce responsive alginate nanoparticles (pH or redox)[38]. It was recently discovered that alginate-formulated nanoparticles can be used to transport drugs to the brain. For example, lactoferrin-coated alginate-cholesterol micelles have been shown to transport a neuroprotective steroid to the brain[39] and alginate nanoparticles cross-linked with chitosan have been shown to increase anti-depressant delivery to the brain[40]. Doxorubicin-alginate nanocomplexes with chitosan matrices also exhibited improved absorption into rabbit brains[41].

ALGINATE AND CHITOSAN

Due to its low cost, biodegradability, and availability across a wide variety of molecular weights, chitosan is one of the most often utilised natural polymer-based nanoparticles for drug administration[42]. It also has special biological features like anti-cancer, antibacterial, and antioxidant capabilities. Chitosan includes three different types of functional groups (amine, primary, and secondary hydroxyl) that can be used to make a variety of chemical changes

(FigureNo.4). Its biodegradability is influenced by its molecular weight, degree of deacetylation and chemical alterations[43].

Chitosan is created by deacetylating chitin, a natural polymer found in crustaceans and fungus, and consists of randomly dispersed β-(1, 4)-linked D-glucosamine and N-acetyl-D-glucosamine units[44]. Chemical cross-linking, ionic gelation, and microfluidic synthesis are all ways that can be used to make chitosan nanoparticles[45]. Because of their positive charge, which increased cell absorption and made them appropriate for loading with negatively charged medicines, these natural nanoparticles have showed promise in brain delivery[46].

Antibody-modified PEG-chitosan nanoparticles, for example, demonstrated a high brain absorption, which was attributed to the antibody's synergy with the positive chitosan charge[47]. Despite this, chitosan nanoparticles have drawbacks, including inadequate drug loading effectiveness on hydrophobic substrates[48]and poor molecular weight control. Chemical changes, such as grafting palmitic acid, have been proven to improve drug loading efficiency.

RECENT ADVANCES

Recent advancements have focused on the use of natural antioxidants in conjunction with nanotechnology to aid in targeting while also improving bioavailability and stability, as well as reducing negative effects.

In a recent study, Cano *et al*. created a nanovehicle of epigallocatechin-3-gallate (EGCG), the tea plant's major polyphenol, which has generated interest as a potential treatment for a variety of illnesses. The PNP system used in this study is made up of a PEGylated PLGA polymeric matrix that was created in an antioxidant environment that included ascorbic acid (AA). Both nanoencapsulation and AA safeguard EGCG's chemical composition and protect it from in vivo clearance, increasing its bioavailability and potency. This nanosystem is able to traverse the BBB, according to the findings. Furthermore, it greatly lowers astrogliosis and Aβ plaque load in a transgenic mouse model of AD, while also improving synapsis expression, spatial learning, and memory functions, suggesting pharmaceutical efficacy[49].

Ahlschwede *et al*. recently developed a curcumin loaded PLGA nanocarrier with a multi-functionalized covering of chitosan, antibodies, and the penetrating peptide K16ApoE, which takes drug penetration across the BBB one step further. K16ApoE-targeted NPs efficiently cross the BBB, implying active targeting and increased uptake into the brain, as well as providing specific MRI contrast to detect Aβ plaques[50].

In addition to other chemicals, such as selenium, which may have various preventive functions in the course of AD, curcumin has been explored for potential biomedical therapy. In this regard, Huo *et al*. created a curcumin/selenium combination carrier with the goal of inhibiting Aβ aggregation[51].

Sun *et al*. quercetin (QT), a flavonoid found in many fruits and vegetables, was encapsulated in PLGA matrix and its effects on Aβ42 fibril inhibition and disintegration were investigated. These NPs increase the survival of neuronal cells and improve cognitive and memory deficiencies in mice without causing any side effects in other organs[52].

Other chemical components have been added to AD-targeting nanoparticles. Efforts to raise Zinc levels in the brain are noteworthy. For more effective targeting, Vilella et al. created a zinc-loaded polymeric nanocarrier with a BBB penetration peptide coating. This study indicates that zinc loaded PLGA NPs can considerably lower neuroinflammatory cytokines and Aβ plaque burden in transgenic AD mice without having any deleterious behavioural consequences[53].

Alzheimer's disease is worsened by neuroinflammation. The presence of hazardous substances like Aβ peptide and τ neurofibrillary tangles activates microglia, which are macrophage-like resident immune cells in the brain. This activation can result in the synthesis of a variety of neurotoxic chemicals, including glutamate, reactive oxygen species, and inflammatory cytokines, all of which can cause neurotoxicity in different ways. Microglia activation leads to molecular neurotoxicity in AD, especially in advanced stages, and neuroinflammation has been targeted as a therapeutic

target in the disease. Sanchez-Lopez et al. employed a dexibuprofen-loaded PEGylated polymeric nanosystem (DXI, the active enantiomer of ibuprofen)[54]. In a well-established mouse model of AD, DXI in the nanocarrier exhibited superior efficacy than DXI in its free form in terms of memory impairment and cognitive decline, as well as lowering microglia activation and Aβ plaque area. Microglia, on the other hand, may play a protective role in the development of Alzheimer's disease, according to other research, implying that they don't just cause neuroinflammation during the disease[55].

Peptides are used in NPs for a variety of reasons, including improving BBB targeting and delivering direct medicinal compounds. Zhang and colleagues investigated the prospect of treating Alzheimer's disease with the H102 peptide, which is a β-sheet breaker peptide encapsulated in polymeric NPs, in a 2014 study. Two different nanocarriers with either a TGN or QHS surface coating were employed to transport the peptide. Both nanocarriers enhanced H102 brain penetration, as well as spatial learning and memory processes in AD mice, according to the findings. The same researchers published a follow-up work three years later that combined the two surface coatings in the same nanovehicle, resulting in even greater H102 peptide delivery[56].

Overall, the nanosystem's ability to reduce Aβ plaques and τ protein phosphorylation, preserve synapses, boost Aβ-degrading enzymes, in transgenic AD mice, spatial learning and memory have improved. These results highlight the critical role of coating techniques in improving the therapeutic effectiveness of nanomedicine in Alzheimer's disease. Nanomedical applications for Alzheimer's disease are also generating a lot of interest in the delivery of endogenous proteins and peptides as a treatment approach. Seong *et al*. developed vitamin D-binding protein (DBP) PLGA NPs as a result. DBP has the potential to reduce Aβ aggregation and accumulation, however it is quickly metabolised after being administered *in vivo*. As a result of these findings, DBP-PLGA NPs strongly suppress Aβ aggregation in an *in vitro* model and can dramatically reduce neuroinflammation, Aβ accumulation, neuronal death, and cognitive impairment *in vivo*.

Carradori *et al*. created a new surface modified PNP that contained a monoclonal antibody that targeted Aβ1-42. The goal of this work was to reduce brain Aβ by binding blood circulating Aβ peptides and eliminating them through traditional NPs removal routes. Animals with Alzheimer's disease who were administered this nanovehicle had decreased amounts of Aβ soluble peptide and its oligomer in their brains, a higher level of plasma Aβ, and a complete reversal of memory loss[57].

Finally, PNPs have been successful in delivering genetic modifiers. In this regard, a recent work by Liu *et al*, indicates that multifunctional NPs can efficiently deliver a therapeutic gene in an in vivo model of AD. These NPs were made up of: (i) RVG29 is a peptide that has been shown to bind n-acetylcholine receptors present in the BBB and brain parenchyma cells. (ii) plasmid DNA encoding BACE1-AS shRNA, which was delivered into the brain to inhibit BACE1, which is linked to Aβ plaque formation; and (iii) τ-fibril production has been found to be disrupted by D-peptide, an all-D amino-acid inhibitor. The combination of these cargos reduces memory loss and neurofibrillary tangles in NPs-treated transgenic mice, with a significant decrease in the key enzyme involved in Aβ plaque production[58].

APPLICATIONS OF POLYMER BASED NANOPARTICLES IN NDDS

Nanotechnology's application in a variety of fields, including medical, opens intriguing opportunities for maximising the benefits of nanoscale particles. This is owing to nanoparticle’s superior qualities when compared to their bulk counterparts. Nanomaterials have special features in drug delivery systems due to their enormous surface area to volume ratio at the nanoscale. Nanoparticle’s robust technology in medicine has opened new possibilities, such as building drug delivery systems in circumstances where larger molecules are unable to pass bodily barriers to reach injured areas. Overcoming brain barriers for the treatment of NDDs is one such application of NPs in medicine[59].

Antibiotics, antineoplastic agents, and several CNS-active medications all face a barrier in the CNS due to the BBB[60]. Surface modification has been used to improve the penetration of NPs and thus the drug concentration in the brain[61]. It has been established that lipophilic NPs with diameters of less than 100nm can pass through the BBB via diffusion[62]. NDDs therapies may experience side effects like as early breakdown in the gastrointestinal tract, resulting in rapid drug clearance. Furthermore, prolonged contact or activation of medication molecules at incorrect target sites results in the occurrence of a variety of undesirable consequences in the body[63]. Various intelligent functional carrier systems, such as polymers and their functionalized and modified forms, are then used to dramatically change the therapeutic potential of neurodegenerative medicine[64]. Nanoparticles composed of solid colloidal natural or synthetic polymers and lipids are used in these drug delivery systems and are usually delivered intravenously. Nanometre drug systems, with diameters ranging from 1 to 100 nm, are designed to interact with biological systems at the molecular level[65].

FUTURE PROSPECTS

In the coming years, more emphasis will be placed on identifying the complex aetiology of NDDs as well as the molecular mechanisms implicated in their pathogenesis. Similarly, a deeper knowledge of the BBB's physiology and molecular regulation will aid in overcoming the BBB's inherent barriers to effective CNS medication delivery. While polymeric nanocarriers are definitely one of the most effective strategies for overcoming CNS delivery issues, clinical translation of nanocarrier-based medicines remains a difficult and costly task for the pharmaceutical industry. As a result, nanotechnology has failed to make its way into mainstream clinical practise. To make the transition from the bench to the clinic, strict validation processes for *in vitro* and *in vivo* protocols are required. Similarly, large-scale production issues necessitate chemists and engineers innovating, as well as regulatory policies that ease access to trials and patients. Despite significant advances in basic and preclinical research, translating these nanovehicles into clinical practise remains one of the most difficult issues in the field, and will be a key focus of most nanomedicine studies in the coming decades[66].

Alzheimer's disease treatment with polymeric nanoparticles

S.No	Method	Polymer used	Drug loaded
1	Polymerization technique	Polymeric n-butyl-2-cyanoacrylate	Quinoline-derivatives
2	Emulsion polymerization method	Poly (n-butylcyano acrylate)	Rivastigmine
3	Emulsion polymerization method	Core-shell nanoparticles composed of a polystyrene core and a degradable poly (butyl-2-cyanoacrylate) shell	Thioflavin T
4	Nano-precipitation method	Trimethylated chitosan conjugated-PLGA	Coenzyme Q10(Co-Q10)
5	Anionic polymerization method	Poly(butyl) cyanoacrylate	Curcumin
6	Interfacial deposition	Eudragit S100	Melatonin
7	Emulsion/solvent evaporation technique	Poly (ethylene glycol)-poly(lactic acid) modified with wheat germ agglutinin	Vasoactive intestinal neuroprotective peptide
8	Chemical synthesis and activation	Polystyrene	Ion chelator- MAEHP

9	Spontaneous emulsification method	Chitosan	Tacrine
10	Ionic gelation with tripolyphosphate anions	Chitosan	Rivastigmine
11	Polymerization method	Polysorbate-80 coated poly(n-butylcyanoacrylate)	Tacrine
12	Emulsification and chemical crosslinking method	Chitosan	6-coumarin
13	Ionic gelation with triphosphate anions	Chitosan	Estradiol
14	Nanoprecipitation method	Eudragit S100	Melatonin
15	Single emulsion technique	Tween 80(T-80) coated polylactide-co-glycolide	Estradiol

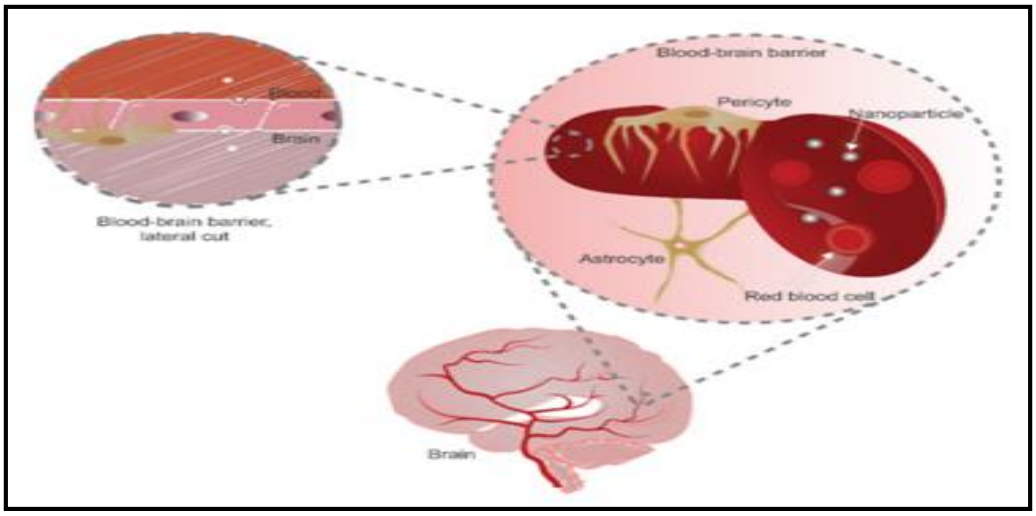

Figure No.1: Depicts the blood-brain barrier

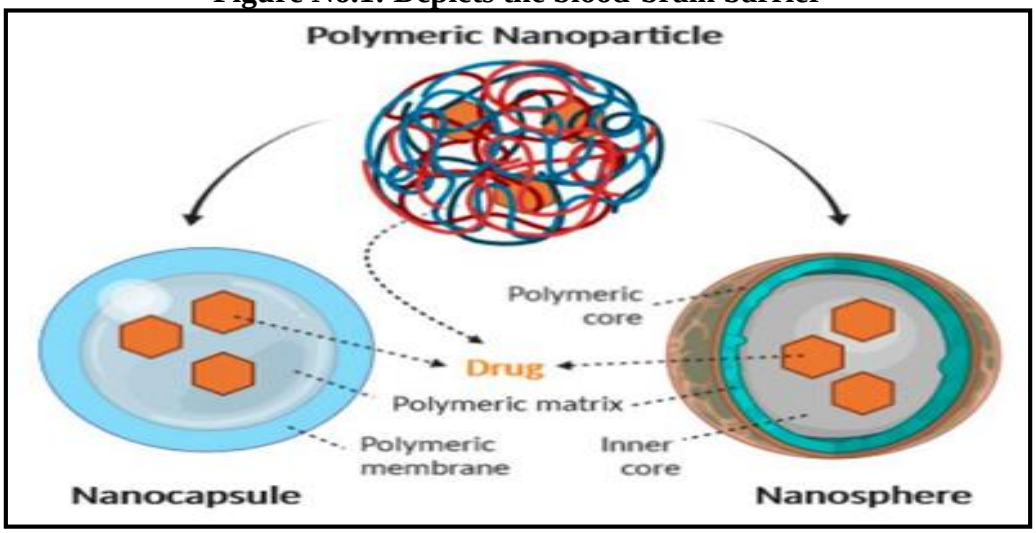

Figure No.2: The structure of nanocapsules and nanospheres is depicted schematically (arrow stands for the presence of drug or bioactive within the nanoparticles)

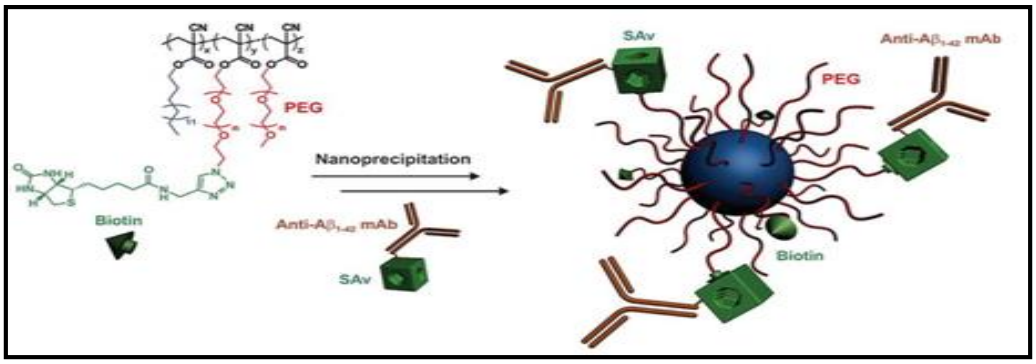

Figure No.3: PACA nanoparticles for BBB crossing were produced by nanoprecipitation of PEGylated PACA polymers functionalized with biotin, as shown in the diagram. After that, monoclonal anti-A1-42 antibody was used to functionalize the nanoparticles[30]

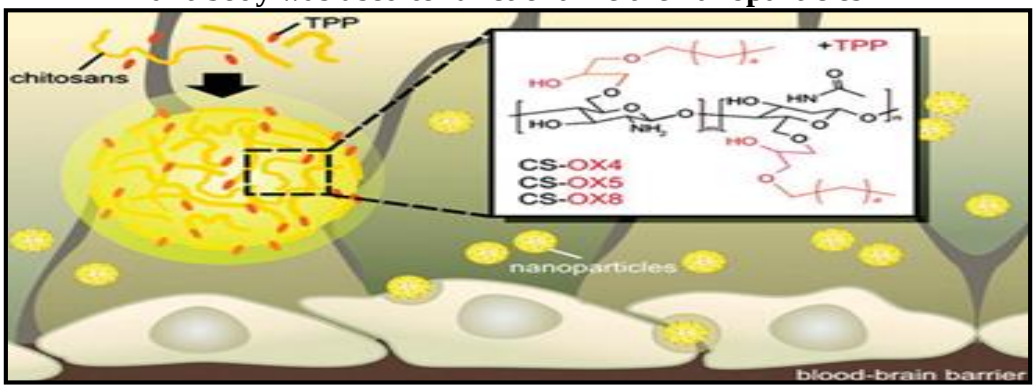

Figure No.4: Nanoparticle made of chitosan for BBB crossing. To improve BBB penetration, O-substituted alkyl-glyceryl chitosan nanoparticles were made with systematically varying alkyl chain lengths (butyl-OX4, pentyl-OX5, octyl-OX8) and sodium tripolyphosphate (TPP)[43]

CONCLUSION

To combat recent disorders nanoparticle carrier system has been a pioneer in one way or the other. The topic of neurodegenerative disorders like Alzheimer's is discussed. In Alzheimer's disease plaque deposits extracellularly around the cerebral vessel walls and in the parenchyma of the brain. In order to mitigate and treat this disorder polymeric nanoparticles have played a major role as discussed. As drug loading is quite high, and pharmaceuticals can enter the system without causing any chemical reactions it also limits the drug clearance and is site specific, hence it holds an edge over the other carrier systems. In the coming years, more emphasis will be placed on identifying the complex aetiology of NDDs as well as the molecular mechanisms implicated in their pathogenesis. Similarly, a deeper knowledge of the BBB's physiology and molecular regulation will aid in overcoming the BBB's inherent barriers to effective CNS medication delivery.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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