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REVIEW ARTICLE

Review on Nanoparticle drug delivery in Blood brain barrier

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ABSTRACT

Central nervous system is one of the most sensitive environment in human body. It was protected by blood brain barrier, it maintains homeostasis by regulating the transport of chemicals at the brain interface. BBB is highly complex structure that tightly regulates the movement of ions of a limited number of small molecules and of an even more restricted number molecules from the blood to the brain, protecting it from injuries and diseases. However, this protection mechanism is also a major obstacle during disease state since it dramatically hinders the drug delivery. In recent years, various tactics have been applied to assist drugs to cross the BBB including osmotic disruption of the BBB and chemical modification of prodrugs. Nanoparticle mediated drug delivery is one of the advance and effective system to treat CNS disorders. The present review describes that structure and functions of BBB. And also focused on preparation methods and evaluation methods for nanoparticles, emerging methods for the nanoparticle drug delivery in blood brain barrier (BBB).

Keywords: Blood brain barrier (BBB), Nanoparticles Central nervous system, Brain, Prodrugs.

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CONTENTS

1. Introduction

At the beginning of the third millennium, due to prolonged ageing, neurological disorders are growing, with a consequent high social impact due to the irprevalence and/or high morbidity and mortality. For the purpose of calculation of estimates of the global burden of disease, the neurological disorders are included in two categories: neurological disorders within the neuropsychiatric category and neurological disorders from other categories. Neurological disorders within the neuropsychiatric category include epilepsy, Alzheimer and other dementias, Parkinson's disease, multiple sclerosis, and migraine.

Neurological disorders from other categories include diseases and injuries which have neurological sequels such a scerebro vascular disease, neuro infections, and neurologicalinjuries[1]. The number of people with CNS disorders will be approximately 1.9 billion by 2020, unless concerted action is undertaken. Overcome to this problem, nanotechnology gives the Nano medicine and it's also being better effect to improve the CNS disorder. Nano medicine, the application of nanotechnology to health care, holds great promise for revolutionizing medical treatments, imaging, faster diagnosis, drug delivery, and tissue degeneration. Nano particle systems in CNS targeted drug therapy provide better penetration of therapeutic and diagnostic agents, and a reduced risk in comparison to conventional treatments. By using nanotechnology it is possible to deliver the drug to the targeted tissue across the BBB, release the drug at a controlled rate, and avoids degradation processes. These drugs provide challenges to delivering them orally or parentally, however these compounds can have significant benefits when formulated through nanoparticle technology[2,3].

2. Pathology of Blood brain barrier (BBB)

The mature blood–brain barrier (BBB) is composed of capillary endothelial cells (ECs) tightly connected with tight junctions (TJs) and adherens juntions (AJs) that prevent paracellular transport and have a low pinocytotic activity, although limited transcellular transport does occur. In addition, the BBB is influenced by closely associated perivascular astrocytic end-feet, pericytes, and microglia. These different cell types play essential roles in BBB induction and maintenance by regulating the proliferation, migration, and vascular branching of the brain endothelial cells. Additionally, the basement membrane provides structural support around the pericytes and endothelial cells. The basal lamina is contiguous with the plasma membranes of the astrocyte end-feet. The BBB provides strong resistance to movement of ions, with transendothelial electrical resistance (TEER) around 1500 X cm2, 100 times higher than that for peripheral micro vessels[4,5].

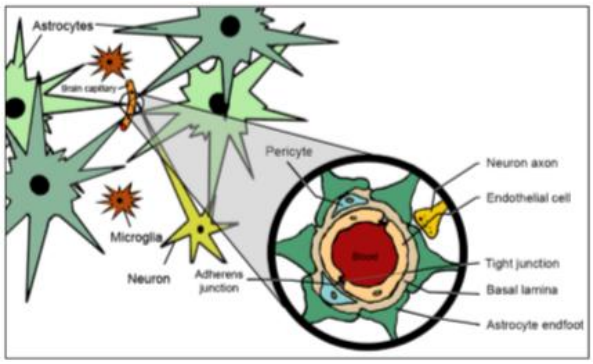

Fig 1: Anatomy of the Blood brain barrier

Endothelial Cells:

Compared to peripheral vasculature, BBB ECs are characterized by increased mitochondrial content, exhibit minimal pinocytotic activity, and lack fenestrations. The restricted paracellular permeability of the capillary EC layer is warranted by two intercellular molecular binding systems: the AJs and the TJs. TJs are dynamic complexes of multiple protein constituents including junctional adhesion molecules (JAMs), occludin, claudins (i.e., claudin-1, -3, and -5), and membrane-associated guanylatekinase (MAGUK)-like proteins (i.e., ZO-1,-2and-3). AJsarecomposedo fmultipleprotein components including vascular endothelium (VE) cadherin, actin, nectin, and catenin. Both on the basolateral and on apical surfaces of ECs there are different types of transporter proteins expressed.

Astrocytes:

Astrocytes are glial cells that help, support and protect neurons by controlling neurotransmitter and ion concentrations to maintain the homeostatic balance of the neural microenvironment, by modulating synaptic transmission and by regulating immune reactions and by interacting with endothelial cells through their endfeet projections that encircle the basolateral side of cerebral capillaries.

Pericytes:

Pericytes regulate BBB integrity, i.e., tight or adherens junctions and transcytosis across the BBB; angiogenesis, i.e., micro vascular remodeling, stability, and architecture; phagocytosis, i.e., clearance of toxic metabolites from the central nervous system; cerebral blood flow, capillary diameter; neuro inflammation, i.e., leukocyte trafficking into the brain; and multi potent stem cell activity.

Microglia:

Microglia, the primary immune cells of the brain, are ubiquitously distributed in the CNS and are activated in response to systemic inflammation, trauma, and several CNS pathophysiology's. Microglial activation in response to pathophysiological stress or scantrigger changes in cell morphology, which include reduced complexity of cellular processes and transition from a ramified morphology to an amoeboid appearance.

Functions:

- The main function of the Blood Brain Barrier is to protect the brain and keep it isolated from harmful toxins that are potentially in the blood stream.
- The blood– brain barrier allows the passage of water, some gases, and lipid soluble molecules by passive diffusion.
- The blood–brain barrier acts very effectively to protect the brain from many common bacterial infections. Thus, infections of the brain are very rare. However, since antibodies are too large to cross the blood-brain barrier, infections of the brain which do occur are often very serious and difficult to treat. Viruses easily bypass the blood-brain barrier, however, attaching themselves to circulating immune cells.
- BBB expresses certain enzymes like peptidases along with several cytosolic enzymes and efflux pglycoprotein system that helps effluxing drugs from the endothelial cells back into the blood which helps in its further protecting action towards the brain microenvironment. Thus the BBB is often the

ratelimiting factor in determining permeation of therapeutic drugs into the brain.

- BBB work as a dynamic biological entity, in which active metabolism and carrier-mediated transports occur.
- The delivery of drugs to CNS via the cardiovascular system is often precluded by formidable barriers viz. The BBB and the Blood Cerebro Spinal Fluid Barrier (BCB).

Nano particle drug delivery for Brain

When applying nanoparticles for brain drug delivery, the first question that has to be answered is whether nanoparticles, by themselves, could cross the BBB. Nanoparticles in general have the advantages on multi functionalization, ability to carry drug payloads, control of drug release and modification of the pharmacokinetics of the drug. Moreover, nanoparticles, because of their nano size (< 200 nm), could penetrate into 'leaky' tumor tissue to facilitate drug delivery according to the enhanced permeability and retention (EPR) effect[6]. However, for brain drug delivery, observing increased drug concentration in the brain using nanoparticles doesnot necessarily imply that the small size of the nanoparticles makes them cross the healthy BBB. Nanoparticles could increase the drug concentration at the surface of BBB cells, or nanoparticles could provide more opportunities to the drug to cross the BBB by increasing their circulation time in the blood compared to conventional formulations[7].

Nanoparticle targeted to the brain in following steps:

- Nanoparticle drug concentration increasing the inside, or at the luminal surface of BBB cells, establishing a local high concentration gradient between blood and brain, higher than that obtainable after systemic administration of the free drug. The gradient should then favour the enhanced passive diffusion of the drug. As for example, this task could be realized by synthesizing NPs functionalized to target brain capillary endothelial cells. This feature can be followed or not by their subsequent uptake from targeted cells.
- By moving themselves into the CNS, together with their drug cargo. As for example, this task can be realized enabling NPs targeting of brain capillary endothelial cells and their subsequent transcellular passage across the BBB.

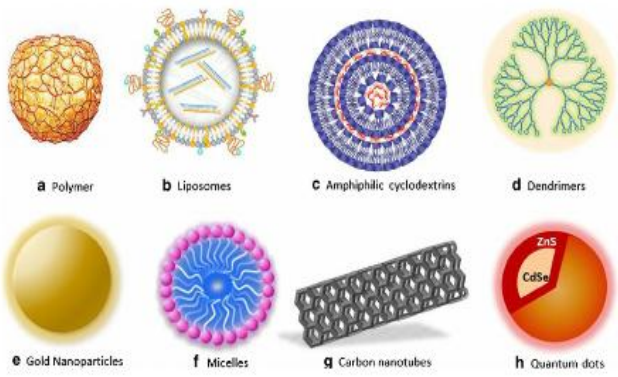

Fig 2: Different types of Nanoparticles

3. Types of Nanoparticles

The following nanoparticles are most commonly used to treatment of CNS disorders. The commonly utilized nanoparticles are lipid based nanoparticles, solid lipid nanoparticles and polymer based nanoparticles[8].

Lipid based nanoparticles

Liposomes:

Liposomes, first described in 1965 are established drug and gene delivery carriers with clinical evidence of efficacy and several commercially available approved clinical formulations. Liposomes are small artificial vesicles of spherical shape that can be created from cholesterol and natural nontoxic phospholipids. Due to their size and hydrophobic and hydrophilic character (besides biocompatibility), liposomes are promising systems for drug delivery. Liposomes are the first generation of nanoparticulate drug delivery systems and are constituted by one or more vesicular bilayers (lamellae) composed of amphiphilic lipids, delimiting an internal aqueous compartment. Liposomes have been largely utilized for brain drug delivery, for the treatment of cerebral ischemia, for delivery of opioid peptides and brain tumours. Liposomes can trap both hydrophobic and hydrophilic compounds, avoid decomposition of the entrapped combinations, and release the entrapped at designated targets. Because of their biocompatibility, biodegradability, low toxicity, and aptitude to trap both hydrophilic and lipophilic drugs and simplify site-specific drug delivery to tumour tissues[9,10].

Cationic liposomes:

Cationic liposomes containing positively charged lipids have been developed and initially used as transfection vehicles, to deliver genetic material (e.g., DNA) into the cell, avoiding the lysosomal digestion.Cationic LPs are ideal for delivering drugs and genetic material due to their positively charged surface, which facilitates interaction with the cell membrane and enhances uptake. Their advantage is also their disadvantage: due to the cationic properties, peripheral tissues and serum proteins bind and block them from being able to pass the BBB[11]. Song and coworkers have constructed an ApoE-containing high density lipoprotein(HDL)inspired nano carrier, which is BBB permeable and has high Aβ-binding affinity, for the treatment of Alzheimer's disease (AD).

Solid Lipid Nanoparticles (SLNs):

Solid lipid nanoparticles (SLNs) are a stable lipid based nanocarrier with a solid hydrophobic lipid core, in which the drug can be dissolved or dispersed. They are made with biocompatible lipids such as triglycerides, fatty acids, or waxes[12]. They are generally of small size allowing them to cross tight endothelial cells of the BBB and escape from the reticulo endothelial system (RES). High-pressure homogenization or micro-emulsification can be used for manufacturing of nanoparticles. In addition, functionalizing the surface of solid lipid nanoparticles with polyethylene glycol (PEG) can result in increased BBB permeability. The advantages of SLNs are controlled released of the incorporated drug can be achieved up to several weeks. There is also a scope for drug targeting by coating or

attaching with the legends. In their small particle size they have cross the liver and spleen easily[13].

Polymer-Based Nanoparticles

Polymeric Nanoparticles:

Over the last decade polymeric nanoparticles have attracted researchers in targeting drug molecules to brain. Polymeric Nanoparticles are nanosized carriers (1 – 1000 nm), made of natural or synthetic polymers, in which the drug can be loaded in the solid state or in solution, or adsorbed or chemically linked to the surface. Now days, the use of polymeric Nanoparticle is one of the most promising approaches for CNS drug delivery. As name only suggest polymeric nanoparticles are nanoparticles which are prepared from polymers. Most popular ones are polylactides (PLA), polyglycolides (PGA). Poly(lactide-co-glycolides)(PLGA), polyanhydrides, polycyanoacrylates, and polycaprolactone. In spite of development of various synthetic and semi-synthetic polymers, also natural polymers such as chitosan can be utilized. Nanoparticles can be synthesized from preformed polymers or from a monomer during its polymerization, as in the case of alkyl cyanoacrylates. As such, Nano spheres or Nano capsules can be synthesized, with their resultant structures that are dependent upon the technology employed in the manufacture[14].

Nano spheres are the dense polymeric matrices in which drug are dispersed, where as Nano capsules present a liquid core surrounded by a polymeric shell. Most techniques involving the polymerization of monomers include the addition of the monomer into the dispersed phase of an emulsion, an inverse micro emulsion or dissolved into a non-solvent of the polymer. Finally, two main approaches have been proposed for the preparation of nanoparticles by synthetic polymers. The theory of the first scheme follows the emulsification of a water-immiscible organic solution of the polymer, in a surfactant-containing aqueous phase, and followed by solvent evaporation. The second approach follows the precipitation of a polymer after the addition of a non-solvent of the polymer[15].

Various mechanisms for nanoparticle mediated drug uptake by the brain. These include:

1. Enhanced retention in the brain–blood capillaries, with an adsorption on to the capillary walls, resulting in a high concentration gradient across the BBB.
2. Opening of tight junctions due to the presence of nanoparticles.
3. Transcytosis of nanoparticles through the endothelium.

Advantages of polymeric nanoparticles are Increases the stability of any volatile pharmaceutical agents, easily and cheaply fabricated in large quantities by a multitude of methods, Delivers a higher concentration of pharmaceutical agent to a desired location.

Polymeric Micelles:

Polymeric micelles are nano sized water dispersible clusters of polymeric molecules and thus are excellent nanocarriers for PDT (Photodynamic therapy) drugs. Along with photosensitizing agents, iron oxide nanoparticles were encapsulated inside the nanocarrier, which allowed them to respond to externally applied magnetic field. This magnetically guided drug delivery would allow for the use of lower concentration of drug to deliver a therapeutic dose, significantly reducing the amount of PDT drugs that accumulate in normal tissue. Photodynamic therapy (PDT) is a novel therapy technique, used for treating the superficial tumors. In this therapy, photosensitizing agents are used for photochemical irradiation of malignant cells[16]. Stability can be improved by cross linking between the shell and the core chains. Additional tenable features of polymeric micelles are the possibility to render them responsive to external stimuli (pH, light, temperature, ultrasound, etc.).

Dendrimers:

Dendrimers are branched polymers, reminding the structure of a tree. A dendrimer typically symmetric around the core, and when sufficiently extended it often adopts a spheroidal three-dimensional morphology in water. Dendrimers exhibit a highly branched, 3D architecture and comprise an initiator core, several interior layers composed of repeating units, and multiple active surface terminal groups. The branches and surface groups of dendrimers increase exponentially in number with the generation (G) of the dendrimers, whereas the diameter of dendrimers increases by about 1 nm with the generation[17].

Magnetic Nanoparticles: Magnetic NPs (MNP) are nanoparticles with a metal core (mostly iron-oxide) that has an unpaired electron, therefore, has magnetic property. Ironist he most popular core material due to its low toxicity and easy elimination through the endogenous iron metabolic pathway and is usually used in oxide form because it is a more stable state. Multiple coating is used to enhance drug delivery, such as polysaccharides (dextrin), polyethylene-glycol (PEG), phospholipids, peptides, for protection of the metal corefromthe body, improve pharmaco kinetics, lower toxicity. Fluorophores/ radionuclides are used for basic research and for diagnostic purposes. Iron-oxide MNPs can also be used as a contrast agents for magnetic resonance image (MRI), and therapy via magnetic fluid hyperthermia (MFH).

Gold Nano particles:

Gold NPs (Au NP) are also a popular form of metallic core NPs. Au NPs are mostly coated covalently with an organic layer to improve biocompability, biophysical properties, and targeting. They are available in a wide variety of optical and electric features and structures, such as Nano spheres and nanorods. Au NPs have low toxicity and also easily cross the BBB. For example, a wheat germ agglutinin horse radish peroxidase (WGA-HRP) conjugated Au NPs has been shown to be able to cross the BBB through intramuscular injection in the diaphragm of rats. They are also used for imaging as X-ray contrast agents for computer tomography (CT)[18].

Carbon Nanotubes:

Carbon nanotubes (CNT) are made of graphene cylinders with open ends. The number of graphene layers can determine the flexibility of the carrier: fewer layers mean more flexibility. CNTs are used as a chemotherapy drug, RNA, and protein delivery agent and also as biosensors. As a CNS treatment possibility, a multi-walled carbon

nanotube was functionalized with an amine group (MWCNTs-NH3+) to effectively pass through the BBB via transcytosis in both in vitro and in vivo mouse models.

Nano particles how to cross the blood brain barrier

Many medicines are not able to reach the brain due to the lack of drug-specific transport systems through the BBB. The development of new strategies based on NPs to enhance the brain drug delivery is of great importance in the therapy and diagnosis of CNS diseases and it is based on the interactions between NPs and the BBB and on their intracellular traffic pathways[19].

Ultrasound and Microbubbles:

BBB can be disrupted with focused ultra sound (FUS), but for more locations pecific drug delivery is combined with intravenously injected micro bubbles (MBs), by widening interendothelial clefts and tight-junctions. This method, also called as sonoporation, relies on the mechanical action of the gas MBs in ultrasonic pressure waves. These MBs are about 1 to 10 um in diameter with a lipid or protein shell, containing heavy gasses, which can be excreted by exhalation and make MBs more stable[20].

These particles also can be used as a drug delivery system by itself, for example, molecules can be attached to theshell and they have also been used to deliver stem cells and viral vectors. Providing MBs with magnetic coating also can increase the effectivity of drug delivery by keeping them in the target area.

Intranasal Drug Delivery:

Intranasally administered drugs can infiltrate the CNS through the olfactory or trigeminal routes by intracellular and extracellular pathways. In the intracellular route, the drug is taken up by olfactory or trigeminal sensory neurons which transmit to the olfactory bulb or to the pons. The extracellular route is between the supporting cells, where the drug is passing through the TJs, Para cellular cleft, the lamina propria, perineural space, and then arrives at the subarachnoid space. Through the respiratory route, the drug molecules can reach the brainstem. Intranasally administered drugs are distributed mainly in the distal areas of the CNS, besides the olfactory bulb or in the brainstem.

Receptor-Mediated Opening:

Adenosine receptor (AR) substrates can modulate BBB permeability. They can be used for enhanced drug delivery intothebrainbyactivatingA2Areceptorsorrestrictingtheentryo fneurotoxic agents or inflammatory immune cells into the brain. This can occur in case of some diseases, such as stroke or sclerosis multiplex, by inhibiting AR activation. Glutamate receptors can also modify the permeability of the BBB; N-methyl-D-aspartate (NMDA) receptor antagonists decrease the permeability[21]. In addition, neuronal activation, using high-intensity magnetic stimulation, increases barrier permeability and facilitates drug delivery.

Exploring and targeting new receptors that could be utilized for receptor-dependent endocytosis are likely to provide more efficient systems of brain drug delivery, mainly because theseuptakemechanismsarerelativelyun affected by lysosomal degradation.

Lipoprotein Receptors: ApolipoproteinE (apoE) isa34kDa protein constituent of both very-low-density lipoprotein (VLDL) and high-density lipoprotein (HDL), which transports cholesterol and other lipids in the plasma and in the CNS. The lipoproteins complexes can be taken up in the brain through the recognition of apo E by specific receptors at the BBB, which include the low-density lipoprotein receptor (LDLR) and the LDLR-related protein(LRP).

Transferrin Receptor (TfR):

The transferrin receptor (TfR) is the most widely studied receptor for BBB targeting. TfR is a trans membrane glycoprotein, consisting of two linked 90-kDa subunits, each one binding a transferrin molecule. The receptor is highly expressed on immature erythroid cells, placental tissue, and rapidly dividing cells, both normal and malignant. Furthermore, it is expressed on hepato cytes and endothelial cells of the BBB. The role of the receptor is the regulation of cellular uptake of iron via transferrin, a plasma protein which transports iron in the circulation[22].Cellularuptakestartswiththebindingoftransferri n to the transferrin receptor followed by endocytosis.

Efflux Transporter Inhibition:

Inhibition of efflux transporters at the BBB can enhance the brain concentration of the substrate drugs which might lead to unwanted and serious CNS side effects from the compounds and also in other cases can provide a therapeutic advantage. However, the delivery of an anticonvulsant, encapsulated carbamazepine NPs was not affected by the inhibition of P-gp, because NPs circumvented the transporters of the BBB. The CNS protective effect of BBB makes it quite difficult to treat brain malignancies or brain metastases, whereas the peripheral diseases are well controlled. The CNS barrier can be partially overcome in the case of efflux transporter substrates by modulation of transporter proteins (e.g., P-gp or Mdr1)[23].

Adsorptive-Mediated Transcytosis:

The concept of adsorptive-mediated transcytosis through the BBB was originally suggested by the observation that cationic proteins can bind the endothelial cell surface but also cross the BBB. The mechanism, applied to NPs, is based on the proper functionalization of the irsurfaceallowingelectrostaticinteraction with the luminal surface of BBB. Given the presence of negative charges on endothelial cells this interaction can be promoted by conferring a positive charge to the NPs surface.

Crossing the BBB without Functionalization:

Although almost all nanomaterial's fall into the class of BBB impermeable, someexceptions have been reported in recent years. For instance, gold and silica NPs have been shown to reach the brain and accumulate in neurons even in the absence of any specific functionalization, with a mechanism that substantiallyisstillun known. Inthecase of silica the results indicated that NPs administered to rodents via intranasal instillation entered into the brain and especially deposited in the striatum. In the case of gold NPs precise particle distribution in the brain was studied ex vivo by X-ray microtomography, confocallaser and fluore scence microscopy. The authors found that the particles mainly accumulate in the hippocampus, thalamus, hypothalamus, and the cerebral cortex. The same holds true for Titanium

dioxide NPs that were found to cross the mice BBB particularly when smaller than 40nm[24].

Retrograde Transport: Tran synaptic retrograde transport could enable some types of nano carriers to travel from peripheral nerve terminals to neuronal cell bodies in the CNS. Studies in this regard have shown that NPs modified with PEI and other polyp lexes display active retrograde transport along neuritis but are unable to mediate efficient biological action suponreaching the neuronal body.

BBB Break down:

BBB breakdown occurs in neuro inflammatory diseases. NPs can transientlyandreversibly open the tight junctions located at the BBB and other sites, thus, increasing their Para cellular permeability. In particular, blood-brain barrier disruption therapy is an intensive, effective way of sending medication to brain tumors.

NPs Mimicking Activated Monocytes:

The therapeutic efficacy of drug-loaded NPs systemically administered depends on their ability to evade the immune system, to cross the biological barriers of the body, and to localize at target tissues. Nanoporous silicon particles can successfully perform all these actions when they are coated with cellular membranes purified from leukocytes, avoiding being cleared by the immune system. Furthermore, they can communicate with endothelial cells through receptor-ligand interactions and transport and release doxorubicin pay load across an inflamed endothelial barrier in vitro. Also the accumulation of coated NPs in mice inoculated with murine B16 melanoma was enhanced compared with that of non coated NPs. Particle coating using leukocyte membranes led to an approximately two fold increase in particle density inthetumor[25].

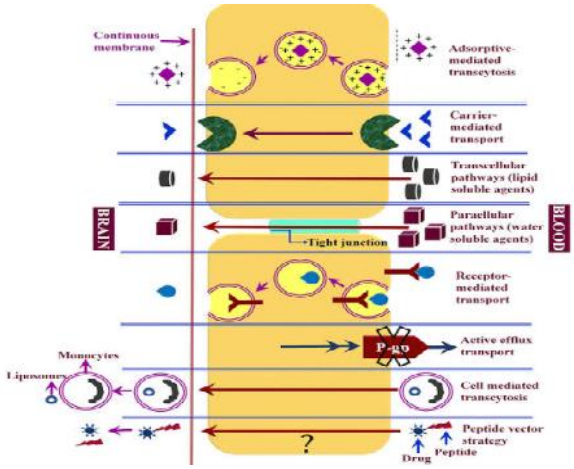

Fig 3: Nanoparticle drug delivery to the blood brain barrier

4. Conclusion

The present review concluded that the number of deaths due to neurological or neurodegenerative diseases is those of a world war, with connected huge socio economical problems and costs. The treatment of such diseases is hampered by the presence of BBB, insurmountable by most available and future potentially effective drugs. Therefore, the discovery and development of novel drug delivery systems for the treatment of such diseases is a major challenge for both the academic and pharmaceutical community. Nanotechnology represents an innovative and promising approach. NPs offer clinical advantages for drug delivery such as decreased drug dose, reduced side effects, increased drug half-life, and the possibility to enhance drug crossing across the BBB.

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