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REVIEW ON NANOTECHNOLOGY BASED DRUG DELIVERY SYSTEM FOR TREATMENT OF CNS DISORDER

Mr. Shrikant P. Gavhale*[1], Priyanka K. Sabale [2]

Department of Pharmacology, Shantiniketan College of Pharmacy, Dhotre (Bk.), Ahmednagar

ABSTRACT: Nanotechnologies are the materials and devices that have a functional organization in at least one dimension on nanometre (one billionth a meter) scale, ranging from a few to about 100 nanometres. Nanocarriers have facilitated the targeted delivery of chemotherapeutic resulting in the efficient inhibition of disease progression in malignant brain tumors. The BBB protects and isolates CNS structure (brain and spinal cord) from the rest of the body, and creates a unique biochemical and immunological environment. Due to the nano size, nanoparticles are able to pass through the BBB and are an effective alternative to drug administration and other approaches. Due to the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier, which prevent drug transport, treating illnesses of the central nervous system (CNS) is particularly difficult. Due to the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier, which prevent drug transport, treating illnesses of the central nervous system (CNS) is particularly difficult. Nanotechnology-based drug delivery systems are one of the emerging approaches to getting around these restrictions and effectively delivering medications to the CNS. Platform provides a viable therapeutic strategy for the management of some prevalent neurological disorders such as Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and Alzheimer's disease. This review sought to highlight developments in the study of the creation of nano-based therapies in light of how they may be used to treat CNS diseases. The difficulties encountered in clinical translation are also discussed in nanomedicine from the lab to the bedside.

KEYWORDS: Nanoparticles, Polymeric micelle, Dendrimers, Nanotechnology, Endocytosis, Endosomes, Alzheimer’s disease.

INTRODUCTION: The engineering of materials at the nanoscale, with a functional organization of less than 100 nm in at least one dimension, is referred to as "nanotechnology." In certain pathological conditions, such as strokes, Alzheimer's disease (AD), diabetes, Parkinson's disease (PD), seizures, and amyotrophic lateral sclerosis (ALS), the blood-brain barrier (BBB) is disrupted. Over the next 20 years, there will need to be a significant increase in global drug development aimed at brain diseases due to the growing number of elderly people and adolescents with central nervous system disorders [1]. The phrase "neurodegenerative disease" (NDD) refers to a group of disorders that primarily impact individual neurons within the neural network. The fundamental component of the nervous system, which mainly guards the spinal cord, is a network of neurons. The body cannot repair neurons because they normally do not reproduce or renew on their own; as a result, when neurons are damaged, they die [2,3]. Drug diffusion across the blood-brain barrier is the primary therapeutic pathway for brain disorders. Achieving optimal therapeutic outcomes against neurological diseases requires the safe, appropriate, and targeted delivery of drug compounds to the central nervous system (CNS)[4,5]. The most delicate and complex organ system, the brain, is shielded from harm by the blood-brain barrier.

Although it guards against potentially harmful and destructive substances in the bloodstream, it poses a significant barrier to the delivery of medications into the central nervous system [6]. Numerous potential medications have been researched to treat various neurological disorders, but a number of obstacles have limited their therapeutic success [7]. One of the biggest obstacles to medication delivery into the CNS microenvironment is the BBB. Tight junctions (TJs) and other specialized cells present in the barrier pose a high electrical resistance, which retards the paracellular flux of intended therapeutic molecules (Fig. 1) [7]

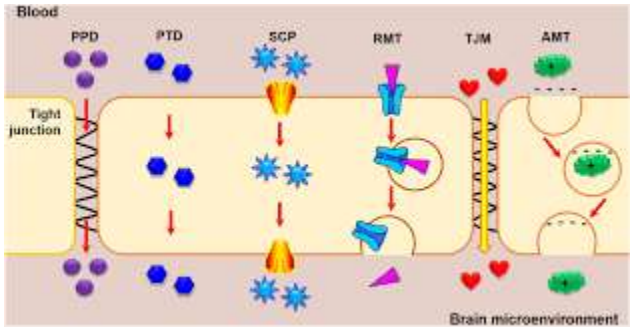

Fig. 1. Transport of solutes from blood to brain across the blood–brain barrier. PPD, passive paracellular diffusion; PTS, passive transcellular diffusion; SCP, solute carrier protein influx; RMT, receptor-mediated transcytosis; AMT, adsorptive-mediated transcytosis, and TJM, tight junction modulation.

The properties and applications of materials with mean size ranging from 0.1 to 100 nm aim to cross the BBB has been drawing attention due to their distinctive optical, thermal, magnetic, and physicochemical properties, such as small size, large specific surface area, strong adsorption capacity of macromolecules, and high chemical reactivity [8].

In this Review, we provide an overview of nanotechnologies that have been investigated in the context of neurological disease, discuss the evidence for efficacy and toxicity of nanomaterials in specific disorders of the CNS

NANOPARTICLES:Characteristics of NPs for drug delivery to the brain-Small and highly lipophilic molecules can passively diffuse across the blood-brain barrier. Lipophilicity and a compound's permeability and solubility are frequently closely associated [9]. Lipophilicity has two drawbacks, though. Lipophilicity has an impact on certain drug parameters. Compounds with a high lipophilicity may be formed that have a rapid metabolism, low solubility, and poor absorption [10]. Drug delivery using nanotechnology is an option in certain situations. To be used for drug delivery to the central nervous system, NPs and nanostructures need to meet specific requirements [11,12].

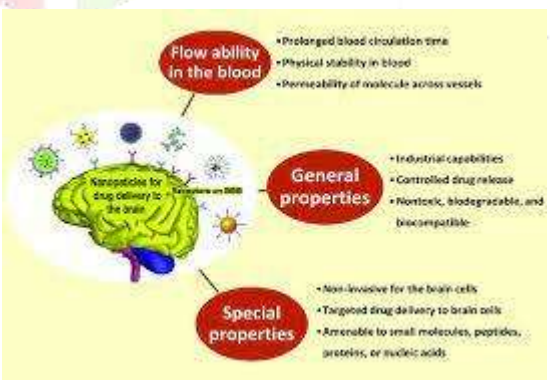

Fig. 2. Ideal characteristics of NPs for drug delivery to the brain [13,14,15]

TYPES OF NANOPARTICLES –

1.Lipid NPs-Müller and Gasco made the discovery of lipid NPs in 1961.Liposomes are tiny spherical, first-generation colloidal vesicles. They resemble the cell membrane because they are made of hydrophilic components with one or more lipid bilayers at their core. morphologically and have the potential to deliver drugs [16,17]. Solid lipid NPs (SLNs), liposomes, and nanostructured lipid carriers (NLCs) were among these NPs. Lipid nanoparticles can be employed by drug delivery systems [18,19]. Drugs encapsulated in lipid nanoparticles have a longer bloodstream half-life, fewer adverse effects, and greater therapeutic effects on central nervous system disorders. Lipid NPs are highly valuable for drug delivery to the CNS because of these properties [20]. They are typically divided into three groups based on the size and quantity of bilayers: multilamellar, which ranges from 20 to 100 nm, small unilamellar, which ranges from 10 to 50 nm, and large unilamellar, which ranges from 50 to 1000 nm [21].

2. Pharmaceutical NPs-In order to improve a drug's therapeutic efficacy, pharmaceutical NPs have been developed to regulate drug release and shield it from enzymatic or chemical degradation [22,23]. PNPs are biocompatible and biodegradable mixtures of colloidal polymers. The lipophilic medication that encloses the dense polymer matrix in the core gives the nanoparticles steric stabilization. For delivery, the medication can be encapsulated, engrossed, or chemically bonded to the surface [24]. Furthermore, PEG frequently modifies the NPs' surface in order to improve the colloidal solution's stability and extend the duration of its bodily maintenance [25,26].

3. Polymeric micelles-Amphiphilic polymers make up polymeric micelles, which are more stable than non-polymeric ones [27]. These micelles exhibit shell-core structures with hydrophobic block polymers (like L,D-lactine polycaprolactone) as the core and hydrophilic block polymers (usually PEGs) as the shell. They form spontaneously in amphiphilic copolymer solutions.[28] The temperature and concentration of the solution affect how micelles form [29]. The particle size of the polymeric micelles is reported to be between 10 and 100 nm [30]. The drug is shielded from interacting with serum proteins and non-target cells by the micelle shell. Once the loaded drug reaches the target cell, it releases through a diffusion mechanism [31].

4.Dendrimers-A densely branched, three-dimensional molecule called a dendrimer is made up of an initial core, multiple internal layers, repeating units, and multiple terminal active surface groups [32]. Dendrimers perform very well and have very little dispersion. Dendrimers have very low dispersion and high performance [33-36]. Dendrimers are used for hydrophobic and hydrophilic drug delivery [37]. When drugs are transported through cellular internalization or endocytosis in different cell membranes or biological barriers, dendrimers help to make this possible [38,39]. Drug delivery and imaging have made use of a variety of dendrimers, such as polyamidoamine (PAMAM) dendrimers, polyhydroxylamine, and polypropylene amine [40]. It has also been reported that PAMAM dendrimers conjugated with PEG can be used to deliver medication and lessen blood clotting in the treatment of ischemic stroke [41].

5.Nanogels-Networks of nanoscale polymers, such as polyethylene amine and PEG or polyacrylic acid and pluronics, can form ionic or non-ionic chains. These networks are known as nanogels [42]. Because the hydrogel NPs exhibit both hydrogelic and NPs properties at the same time, they are one of the unique drug delivery systems. These nanogels' primary benefit is their high loading capacity (40–60%), which is uncommon for other NPs [43].

MODE OF ACTION OF NANOPARTICLES -The ability of nanoparticles to penetrate brain endothelial tissue can be attributed to a variety of their physiochemical characteristics, including their small size, surface charge, hydrophilicity, and ability to target ligands with nanocarriers. The positive charge on the nanoparticle's surface interacts with the negative charge on the brain's endothelial cells due to electrostatic interactions between the carrier and cells. When the lipophilic nature of the nanomaterials combines with the compound's permeability and solubility, it improves the latter's characteristics and quickens the adsorption process [44-46].

The nanoparticles can enter the cell through macropinocytosis, a vesicle mediated endocytosis or by phagocytosis which can be carried out through the following two pathways (Figure 3):

(i) Clathrin-Mediated Endocytosis-All mammalian cells use this mechanism. By binding to a particular receptor on the plasma membrane, the nano-carrier induces the cytoplasmic protein clathrin-1 to polymerize, which forms an inward budding that eventually engulfs the cargo [47]. Dynamin's GTPase activity prevents inward budding, which leads to the creation of vesicles coated in clathrin. Actin facilitates the clathrin coat's shedding, which creates early endosomes. These endosomes then transfer their contents to late endosomes and, ultimately, lysosomes, where they are broken down. The pH gradually drops during the transition from late endosomes to lysosomes, which causes the drug to be released from the nano-vehicle and eventually released at the target site [48].

(ii) Caveolar Pathway for Delivery in the Brain-This pathway differs from the clathrin-mediated pathway in that it evades lysosomal delivery. Three isoforms of the caveolin protein—caveolin-1, caveolin-2, and caveolin-3—are found in mammalian cells and aid in the passage of caveolae, which are flask-shaped invaginations in the plasma membrane. Following their binding to the caveolar receptor, the nano carriers internalize to form the cavicle , a type of vesicle. The good cavicle is then propelled by actin-derived energy, eventually fusing with pH-neutral caveosomes. It then advances toward the endoplasmic reticulum, entering the cytosol and entering the nucleus via the nuclear pore complex [47].

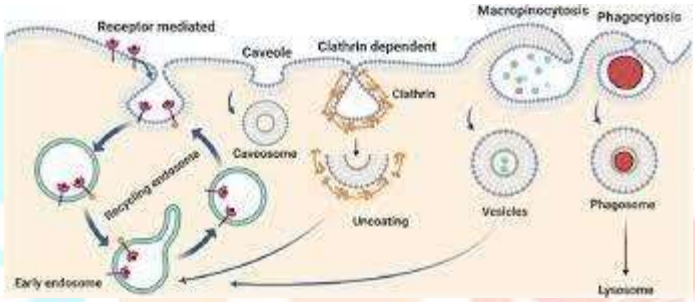

Figure 3: Macropinocytosis and phagocytosis pathways for drug delivery into brain. [49]

APPLICATIONS OF NANOTECHNOLOGY IN CNS DISORDERS

Table No.1 -Applications of Nanotechnology in CNS disorders

Diseases	Nanocarrier used	Drug loaded	Animal models/cell line used	Outcomes/ Effects/ treatments	References
Alzheimer's diseases	Polysorbate 80-coated poly(N-butyl cyano Acrylate) Nanoparticles	Tacrine	Mice	Large amount of tacrine was found in the brain	50
	coated with polysorbate 80	Rivastigmine	Mice	Large amount of rivastigmine was able to pass through the BBB	51
	Fe_2o_3@CDs	Curcumin	PC12 cell lines	CURFe_3O_4@CDs have a strong a affinity toward Aβ and thus inhibit extracellular Aβ fibrillation. It also inhibits the Aβ-	52

				mediated production of ROS and neurtoxicity	
Parkinson's disease	SLNs	Rasagline	-	There were no changes in particulate matter, colloidal stability, and drug encapsulation effect	53
	Manganese oxide-based nanoparticles	Levodopa	Rat and pig	The analysis indicates that perhaps the nanoparticle production of Mn2+ induced a time-dependent alteration	54
	Chitosan coated nanoparticles	Levodopa	Rats	Endeavor to lessen the harmful effects of levodopa	55
Huntington disease	Nanoparticle loaded with siRNA —	-	-	Nanocarriers loaded with siRNA were administered from the nose directly to the brain to target the striatum and cerebral cortex	56
Ms	Fluorescent phosphorhydrazone dendrimers	-	HeLa (human epithelioid cervical carcinoma), HUVEC (human umbilical vein endothelial) cells, and HEK 293	The dendrimer worked as an anti-inflammatory agent and was suggested for treating MS	57
	LiF-Nano-formulations with PLGA		CD4	LiF-Nano-CD4 was successfully able to pass through BBB and also exhibited anti-inflammatory effects in frontal	58

				cortex	
Als	Carbon graphene nanoparticle	-	-	Graphene-based nanoparticles may help in delivering miRNA for the treatment of ALS	59

LIMITATIONS -Characterization and production of nanomaterials appear to be crucial for their use in medicine delivery in order to prevent unintentional toxicity to healthy cells. Future treatment development ought to be facilitated by these advancements, contingent on the degree of neurodegeneration a patient experience. A small number of nano formulations, such as organic or inorganic nanocarriers, are also being investigated in preclinical studies to see if they can prolong life and prevent the development of cancer [60,61] The vast majority of medications utilizing nanomedicine to treat central nervous system disorders have continuously investigated and prioritized pharmaceutical delivery methods based on nanotechnology. Furthermore, a number of nano-drugs are presently undergoing research trials; however, it is currently unknown how they will be transported and secured [62,63]. The characteristics and composition of nanoparticles can lead to BBB instability and oxidative stress. [64,65]. Numerous multifunctional nanomaterials have been the subject of research, and the results have shown remarkable challenges that need to be quickly overcome. For example, some of the micromaterials have properties like biological reasonableness, effectiveness, biocompatibility, and toxic effects in the living organism classifications [66].

CONCLUSION –Nanoparticles have been proven to be effective and strong carriers in comparison with the conventional therapy for addressing CNS disorders. Nanoparticles, such as lipo-somes, nanotubes, nanopharmaceuticals, micelles, andnanosensors, are in high demand as theranostics for neuroprotection. Currently, nano-based approaches for neuroprotection and regeneration are sought after to address neurological cells' physiology, biology, and pathology. Different kinds of nanoscalic approaches such as the reduction of reactive oxygen species and Aβ oligo-merization have been proven to be effective for treating neurological disorders. Nanoformulations of numerous drugs like edaravone, curcumin, and nerve growth factors 9 are generating great interest for neurological diseases; however, there are little data available on their adverse effects. Nanotechnology has a promising future in CNS disorder treatment due to the ability of nanoparticles to pass through the BBB, flexibility to be engineered according to the need, and targeted delivery. Nanotechnology could easily aid us to enhance our approaches for neurological disorder treatment.Although nanotechnology has tremendous potential to affect treatment options in clinical neuroscience, it is unlikely that use of nanotechnology alone will accomplish the complicated task of repairing the CNS. The most efficacious applications of nanomaterials in the treatment of CNS disease have combined the power of nanoscale interventions with growth factors or cells that enhance the overall effect of the nanoscale treatment, highlighting the importance of a combined approach to nanotherapeutics. Furthermore, the utility of nanotechnology applications in CNS disease can only be augmented by advances in our biological understanding of the processes involved in these disorders. The synergy between new understanding of the molecular basis of neurological diseases and the multifunctional capabilities of nanotechnology is the factor that stands to fundamentally change the practice of neurology.

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