# NANOPARTICLE-BASED DRUG DELIVERY FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS

## Abstract

Disorders of the (CNS) central nervous system, especially disorders of neurodegenerative, lead a severe threat to people's health and must be thoroughly studied by researchers to protect individuals. Over the last few decades, numerous therapy approaches have been used, but their therapeutic success has only partially alleviated the symptoms. Both the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BSCFB) protect the central nervous system (CNS) from harmful substances and present significant obstacles to the delivery of drugs into the CNS for the treatment of CNS complications like brain tumors, autism spectrum disorder, Parkinson's disease, Huntington's disease, Alzheimer's disease, etc. Using nanotechnology to treat neurological illnesses has emerged as an exciting and promising new method that has the potential to solve challenges linked with old-style treatment modalities. Nanoengineered molecules can traverse the blood-brain barrier, target precise cells or signaling pathways, respond to endogenous cues, operate as a vehicle for the transport of genes, assist nerve regeneration, and support cell survival, among other specialized duties.

**Keywords:** Nanotechnology, Blood-brain barrier BBB, drug delivery, Central Nervous System, Nanomedicine, Nanocarrier.

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# I.  INTRODUCTION

The brain is the most intricate organ in the body. It plays a role in controlling emotional, behavioral, and cognitive processes. The organ is also a target for various illnesses, from Cancer to trauma to neurodegenerative diseases. Injury, infection, tumors, and neurological abnormalities are just a few of the many health issues affecting the brain that are referred to as brain illnesses and disorders. According to the definition, "brain diseases" refers to a collection of medical conditions stereotypicallycontagious and regularlycarried on by outside factors, such as viruses, bacteria, and so forth [1]. In contrast, "brain disorders" refer to non-transmittable but frequently medical conditions which are inheritable brought on by disruptions of the normal body structure and functioning due to congenital disabilities or genetic malfunctions. From 1990 to 2013, India experienced a burden of mental, neurological, and drug use disorders that was 44% higher than that of several other Asian nations. The medical community should be alarmed by the predicted 23% additional growth of this burden in India by 2025.

With 276 million and 11.6% of the world's disability-adjusted life years (DALYs), neurological illnesses are the most significant reasonfor disability, accounting for 9 million fatalities and 16.5% of all deaths worldwide [2]. Brain disorders include ailments like multiple sclerosis (MS), autism spectrum disorder (ASD), and Alzheimer's disease (AD). Like most medications, the electrical, chemical, and physical barriers stop substances from entering the brain [3]. In the past, prospective medications were dissolved in ethanol, polysorbate 80 (PS-80), and dimethyl sulfoxide in an attempt to improve their diffusion and compassion across the blood-brain barrier (BBB) [4]. Nanoparticle (NP)-based therapeutics have lately emerged as a prospective therapy for brain disorders because of their straightforward transportability through the BBB and distinctive qualities likebiodegradability,  selectivity, tiny size, low toxicity, and solubility [5].

The primary causes of death and disability are syndromes of the central nervous system (CNS), which are of great concern to humanity and hence of interest to researchers all over the world. Globally, neurological illnesses were the second-largest cause of death in 2016 [9 million (8.8-9.4)] and the top source of disability-adjusted life years (DALYs) [276 million (95% UI 247-308)]. The burden of sickness in the world is increasing as a result of CNS disorders [6]. Current neurological disorders that are challenging to identify and treat contain Parkinson's disease, Huntington's disease, Alzheimer's disease, brain tumors, autism spectrum disorder, etc. [7]. Although several potential medications have been investigated to treat various neurological disorders, their efficacy is still constrained owing to a number of problems. Getting substances across peripheral barriers like the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB), particularly the BBB, is one of the most frequent challenges [8]. These materials include medications, nucleic acids, proteins, imaging agents, and other macromolecules [9].

This overview discusses the different kinds of nanoparticles (NPs) and how they help medications reach the central nervous system. Additionally, we have covered the BBB and problems with its permeability, drug delivery methods that cross the BBB, and NPs' targeting mechanisms.

## II. NANOPARTICLES

The term "nanotechnology" describes manipulation that occurs at a scale of 1–100 nm. The science and engineering behind designing, synthesizing, characterizing, and using materials and devices with a minimal functional organization in at least one dimension is known as nanotechnology [10]. In nanotechnology, a particle is a tiny unit that performs as a whole in terms of its properties and transport. It may be separated into fine and ultrafine particles based on size. While ultrafine particles have a diameter of 1 to 100 nanometers, fine particles range in size from 100 to 2500 nanometers. Nanoparticles, like ultrafine particles, range in size from 1 to 100 nanometers. Recently, there has been a lot of interest in the chemical and biological properties of inorganic nanoparticles with diameters between 10 and 1000 nm. There are several advantages of using nanoparticles for drug delivery over traditional methods, including their high drug-carrying capacity, high stability, controlled release, high specificity, and capacity to transport both hydrophilic and hydrophobic compounds [11]. Drug-loaded nanoparticles may reach the target area by diffusion, deterioration, erosion, or the application of outside energy. Ceramic nanoparticles and proteins are most often used in targeted medication delivery [12]. Accessible functionalization characteristics and high biocompatibility of changed molecules serve as the primary criterion for selecting an effective approach to produce nanoparticles of different sizes.

A growing corpus of research has been done recently on the use of nanoparticles for drug delivery in the treatment of illnesses of the central nervous system (CNS). A study offers insightful information about the state of nanomedicine at the moment and underlines the difficulties and possibilities for nano-therapeutics. The authors of the review talk about the potential of nanoparticles to revolutionize cancer treatment through targeted drug delivery and stress the significance of nanoparticle-based strategies in overcoming challenges like restricted drug solubility, subpar bioavailability, and non-specific distribution. It also emphasizes the promising role that nanoparticles can play in boosting treatment effectiveness while reducing off-target effects. In-depth descriptions of numerous metallic and non-metallic nanoscale drug delivery devices are included in the review. For effective drug loading and controlled release, it describes their production processes, surface changes, and encapsulating strategies. The article also discusses difficulties with medication delivery based on nanoparticles, including toxicity issues, immunogenicity, and regulatory issues.

## III. FEATURES OF NANOPARTICLE

When used to deliver CNS medicine, nanoparticles should have the following promising properties:

- They must be biodegradable, non-toxic, and compatible with living things.
- They should have easily manipulable physical characteristics, depending on the delivery method.
- Various nanoparticles with modified chemical characteristics should make drug distribution to specific organs or cells possible [13].
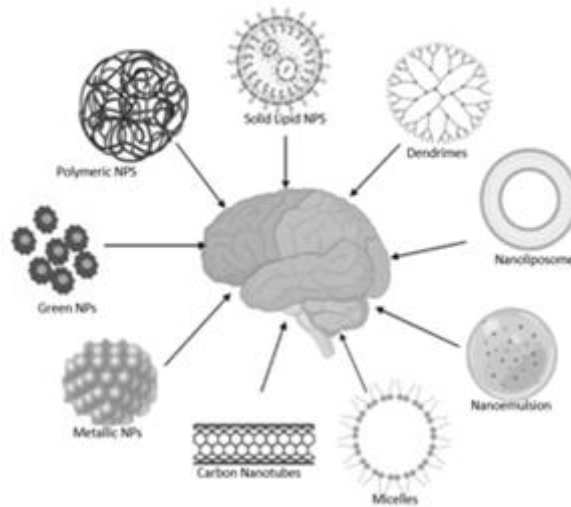- The formulation needs to be economical.

**Figure 1:** Drug delivery methods based on nanotechnology are used to treat central nervous system disorders. [biorender.com]

## IV. TYPES OF NANOPARTICLE

1. **Polymeric Nanoparticle**: Polymeric nanoparticles are a particulate dispersion of biodegradable and biocompatible polymers, with sizes ranging from 10 to 1000 nm. The core-shell structure of PNP is impacted by the presence of hydrophilic and hydrophobic blocks in the polymer chain [14]. In the center of these PNPs, a hydrophobic drug is enclosed in a thick polymer matrix, while the corona, made of hydrophilic polymers, provides the nanoparticles with steric stability and stealth properties. The drug-to-polymer ratio influences drug release levels, molecular weight, and polymer makeup. There are several different types of polymers, including poly(alkyl cyanoacrylate) and poly(butyl) cyanoacrylate, polyethylene glycol (PEG), poly-L-glutamic acid (PLGA), and others. Due to their biological inertness, these Nano polymers are the most often used.

   Polymeric nanoparticles loaded with quinoline derivatives and doxorubicin are utilized to treat Alzheimer's disease (AD) and glioblastoma respectively. Similarly, nanosuspensions—a combination of crystalline drugs and non-ionic surfactants—and nano gels (a crosslinked polymer) have depicted superior pharmacokinetic control in CNS disorders [15].

2. **Solid Lipid Nanoparticle:** Solid-lipid nanoparticles (SLNs), which have a nanometric range of 50–1000 nm, are thought of as colloidal nano drug carriers that are made by homogenizing melting lipids under high pressure and dispersing the resultant mixture in water at 70 °C [16]. Because they are simple to make and have great physical stability, SLNs are at the forefront of the fast-evolving nano-delivery system and are now gaining a lot of interest as cutting-edge drug carriers [12]. The top of the nanoparticle is filled with the drugs that are to be delivered [17]. The importance of lipid nanoparticles in the development of nucleic acid vaccines has recently been demonstrated by self-amplifying RNA in SLN nanoparticles [18]. Human African trypanosomiasis (HAT) and AD are both

treated with diminazene aceturate- and quercetin-loaded SLN particles, respectively [19]. Neurological issues are treated using a related substance called 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine (DO-FUdR), which is included in SLN [20].

SLNs are preferable to use as a brain drug delivery system due to a number of advantages, including as low intrinsic cytotoxicity, physical stability, protection of labile pharmaceuticals against degradation, and controlled release.

3. **Dendrimers**: Emerging polymeric structures known as dendrimers have a central core, repetitive building blocks in interior layers, and periphery-located functional components [21]. Dendrimers' usability and potency are influenced by the monomer used, the desired polymer structure, as well as the synthesis procedures. The Dendrimers have other characteristics that make them a valuable therapeutic tool in biomedical and pharmaceutical research, including high density, high penetration capacity, low dispersity, and peripheral functional group reactivity. For both hydrophobic and hydrophilic medicinal compounds, polyamidoamine (PAMAM), polypropylene imine (PPI), and polylysine are the most often used dendrimer drug carriers. Drugs can physically entrap dendrimers or form covalent bonds with peripherally functionalized dendrimer molecules to create dendrimer-drug conjugates [22].

More than 200 distinct dendrimers have been created and classified into several families based on their structural characteristics, including poly(propylene imine) (PPI), poly(amidoamine) (PAMAM), poly(carbosilane),poly(L-lysine) and dendrimers containing phosphorus. The PAMAM family of dendrimers is one of the most widely used nanomedicines due to its hydrophilic profile and biocompatible properties, and it is used in Alzheimer's disease to avoid A-induced toxicity [23].

4. **Nanoliposome:** These lipid nanoparticles are the utmost researched bilayer vehicles [24]. Since "liposome" covers a wide range of vesicles with typical sizes up to several micrometers, nanoliposomes are also known as "nanoscale bilayer lipid vesicles." To maintain their size within nanometric scales, nanoliposomes provide a larger surface area and an adequate stability profile [25]. Liposomes with neurotrophic compounds are utilized to treat brain diseases [26].

Doxorubicin and (3H)-prednisolone-loaded pegylated liposomes are used to treat autoimmune encephalitis and brain tumors, respectively. (3H) Daunomycin, an antineoplastic agent mediated by the OX26 monoclonal antibody, is conjugated with a liposome and exhibits drug transport to the brain. To treat strokes, heat shock protein (HSP)-encapsulated liposomes are used [27].

5. **Nanoemulsions:** Nanoemulsions, which have a size range of 100–500 nm, are colloidal particle systems that are either oil–in–water (O/W) or water–in–oil (W/O) based on edible oils, surface–active agents (surfactants), and water [28]. They have lately been marketed as a drug delivery technique to solve a number of problems with conventional delivery systems, such as insufficient bioavailability, poor targetability, and BBB penetration. The various oils and surface enhancers used in preparation are the key elements impacting nanoemulsions' adaptability [28].

For instance, making nanoemulsions from oils rich in omega-3 polyunsaturated fatty acids (PUFA) enables nanocarriers to pass through biological barriers, such as the BBB, and facilitates the rapid delivery of medications to remote regions, including the brain. The oral bioavailability of paclitaxel was dramatically enhanced by the nanoemulsion system using pine nut oil [29].

6. **Micelles:** Micelles are 80–100nm-thick monolayered spherical lipid nanostructures with hydrophobic ends facing inside and hydrophilic ends facing outward. Due to their tiny size, micelles have a shorter body circulation time than liposomes, making them more quickly transportable substances [12]. Polymeric micelles are thought to be more stable, long-lasting, and biodistributed than conventional micelles. These modified micelles demonstrate improved target penetration because of their nanoscale size, ease of transport to the target area, and low critical association concentration (CMC) [30].

There have been several attempts to alter the micelles such that a loaded medicine with a greater concentration can easily cross the BBB. One such modification includes using polyclonal antibodies to a brain-specific antigen, 2-glycoprotein, or insulin to target the receptor on the luminal side of the BBB. These modified micelles were injected intravenously into mice and filled with either a fluorescent dye or the neuroleptic drug haloperidol. This significantly amplified the neuroleptic effect of the medication and increased the transfer of the light dye to the brain [31].

7. **Carbon Nanotubes and Fullerenes:** CNT possesses exceptional physical, mechanical, and aspect ratio properties at nanoscale sizes less than 100nm [32]. High solubility and biocompatibility of functionalized CNTs are generally influenced by the size, shape, and surface properties of the charged molecules. These variables have a big influence on how cells absorb medicinal substances. Following oxidation, the carboxyl group can be linked, and the sidewall or tip of the CNT can be given an organic group as a method of functionalization. Additionally, the biocompatibility, solubility, and aggregation of CNTs connected to polymers and dendrimers have all been enhanced. Although acetylcholine-loaded SWCNT (single-wall carbon nanotube) has been investigated for the treatment of AD and stem cell therapy combined with CNT has been used for the treatment of stroke, relatively few studies of the CNT for the treatment of the CNS have been recorded. Less aggregation, good solubility with lower toxicity, and antifungal efficacy were seen when amphotericin B was administered alone compared to amphotericin B-loaded CNT [33].

Modifying carbon nanohorns and nanodiamonds was said to improve the use of nanotechnology in the biosciences and pharmaceutical sectors [12]. The therapeutic use of diamond nanoparticles in the treatment of tumor patches and wound healing is essential. Fullerene is a specific kind of carbon allotrope that is made up of 60 linked carbon atoms, 60 vertices, and 32 faces. The utility of nanosized C60 in drug delivery has been established through significant studies. They were more promising than any other type of nanomaterial due to their antioxidant and radical oxygen-quenching properties [34]. Hydrated C60 fullerene enhances cognitive performance by reducing oxidative stress-induced damage to astrocytes and glial fibrillary acidic proteins (GFAP) [35].

8. **Metallic and Non-Metallic Nanoparticle:** Both metallic and non-metallic nanoparticles have drawn a lot of interest in the realm of clinical diagnostics and treatments. A possible

drug delivery system (DDS) has emerged for non-metallic nanoparticles like zinc oxide (ZnO) and iron oxide ($Fe_2O_3$/$Fe_3O_4$) as a result of their growing usage. In order to increase the anticancer efficiency of pharmaceuticals, these nanoparticles have undergone substantial research as efficient transporters.

In particular, maghemite nanoparticles (-$Fe_2O_3$-NPs) and magnetite nanoparticles ($Fe_3O_4$-NPs) have demonstrated significant benefits in therapeutic outcomes, drug administration, and imaging of integrins on tumor cells [36]. These metallic nanoparticles have proven to be particularly beneficial in achieving desired therapeutic results and the destined delivery of drugs.

There are several benefits to using metallic nanoparticles as drug delivery vehicles, including enhanced stability and half-life of the drug carriers in circulation, accurate biodistribution, and passive or active targeting to the intended target location. A further potential field in bionanotechnology is the green production of metallic nanoparticles, which has commercial and environmentally friendly advantages over biological and physical approaches.

When pH, incubation time, mixing ratio, and temperature are perfectly regulated, green synthesis, which uses plant extracts to create metallic nanoparticles, ensures stability and monodispersibility. The production of gold nanoparticles has been successfully carried out using a variety of plant extracts, including curry, mango, neem, turmeric, and guava. Plant extracts with high levels of polyphenols, which help break down organic matter [37], have the capacity to lower metal ions in tissues and organs as well as on their surface. Because of this quality, they are fantastic candidates for the creation of non-metallic nanoparticles. Non-metallic nanoparticles may be created by using the reducing abilities of plant extracts, providing a safe and affordable method for medication delivery systems.

9. **Green Nanoparticle:** The greatest option for manufacturing and using nanotechnology to lessen its risks is now green nanotechnology. To enhance the quality of the nanoparticles and make them application-specific with a continuous process of production, it became important to synthesise the nanoparticles using a green approach while keeping in mind the 12 principles of green chemistry [38]. Green synthesis employs simple, inexpensive, ecologically friendly, and easily accessible raw materials with fewer procedures and no harmful chemicals or byproducts.

All areas of chemistry are included in "green chemistry," but there is a particular emphasis on chemical compound synthesis and chemical engineering techniques used in industrial settings using natural resources. On the other hand, laboratory investigations are also impacted by the fundamental principles of green chemistry, creating a safer environment. According to sustainable chemistry, or "green chemistry," the use and production of hazardous compounds are reduced during reaction and synthesis. Green chemistry also involves processes for creating renewable materials. Green chemistry's key objectives are building the most efficient responses, using renewable resources for materials and energy, using safe solvents or reactants, and avoiding waste formation.

**Table 1: Different types of nanoparticles and their examples**

| TYPE | SIZE(nm) | EXAMPLE | |
|---|---|---|---|
| | | DRUG | DISEASE |
| Polymeric Nanoparticle | 10- 1000 | Chitosan-coated erythropoietin | Brain targeting |
| | | PLGA encapsulated NMDA-NRI vaccine | Alzheimer's disease [15] |
| Solid Lipid Nanoparticle | 50- 1000 | LDL- cholesterol conjugates | Parkinson's disease, Alzheimer's disease |
| | | LDL nanoparticles | Epilepsy, stroke, Trauma, Alzheimer's disease [19] |
| Dendrimers | Diameter range 1.5- 13.5 | Anxiolytic and antipsychotic agents | Psychotic disorder [23] |
| Nanoliposome | Less than 100 | Glutathione encapsulated liposomes | Myoclonus |
| | | Tempamine loaded liposome | Multiple sclerosis and Parkinson's disease [27] |
| Nanoemulsion | 100-500 | Doxorubicin and W198 | Breast cancer cells [29] |
| Micelles | 80- 100 | Doxorubicin | Cancer |
| | | Paclitaxel-loaded copolymer micelle | Lung cancer [31] |
| Carbon Nanotubes | Diameter of 3.5- 70 nm | Streptavidin-HRP-bounded SWCNT-annexin conjugates | Breast cancer |
| | | Stem cell-loaded CNT | Parkinson's disease, Alzheimer's disease, and ischemia [35] |
| Metallic and Non Metallic Nanoparticles | 1 nm to a few hundred nm | Silica gold nanoshells, Maghemite nanoparticles | Brain tumor, Cancer |
| | | | Tumor [37] |
| Green Nanoparticles | 1 to 100 nm | Murraya koenigii Stabilized silver nanoparticles | Alzheimer's disease, Parkinson's disease, Cancer, etc. [40] |

The term "green nanotechnology" has been used to describe the process of creating new nanomaterials using the 12 principles of green chemistry to positively impact the economy, society, health, and environment.

For instance, the extract of Corallina officinalis includes proteins with carbonyl groups and polyphenols that may aid in forming and stabilizing gold nanoparticles [39]. Murraya koenigii leaf extract created and stabilized silver and gold nanoparticles [40].

## V. ROLE BBB AND ITS INFLUENCE ON THERAPY FEASIBILITY

The BBB is a protective layer that surrounds the human brain, the most fragile and complex organ in the body. The BBB is a physical barrier made by endothelial cells (ECs) whose major purpose is to maintain and regulate the flow of nutrients and other essential substances to the brain while maintaining its integrity. ECs are present on both the outer and inner surfaces of the densely packed tight junctions that make contact with the outer EC membranes and prevent easy material ingress. The BBB has a number of important activities, including regulating the flow of chemicals into and out of the brain, preserving ionic balance, and preventing the diffusion of circulating agents, neurotransmitters, xenobiotics, and other substances that may jeopardize the health of the brain [41].

According to studies, high electrical and chemical [P-glycoprotein (Pgp)], resistance is highly correlated with poor permeability of molecules across the blood-brain barrier (BBB). Cyclic adenosine monophosphate and astrocytes are two critical regulators of tight junction activity that have been discovered. The BBB is severely damaged in brain illnesses and disorders, which results in uncontrolled molecule diffusion and additional brain damage. Most prospective drugs do not enter because they do not fulfill the needed parameters since the BBB blocks the admission of materials based on their size and solubility [42]. Focused ultrasound temporal disruption is a frequently employed method to enhance drug transportation across the barrier, although the mechanism at play and the technique's impact on a disturbed barrier have yet to be fully understood. Nanoparticlesneighboringhave recently shown themselves to be effective in this capacity, and as a result, the hunt for a non-disruptive method for medication delivery to the brain has also been given significant emphasis.

## VI. NORMAL DRUG DELIVERY TO CNS AND THEIR CHALLENGES

For traditional therapy to be effective, the medicine must be fat-soluble and have a low molecular weight (400-600 Daltons). Invasive, non-invasive, and other techniques can be used to transfer this material, however BBB only allows for a little amount of medicine penetration. The main reasons for treatment failures in the brain include slow drug action, association or conversion of the drug into non-transporting forms, and decreased neuronal absorption [43]. Some catalytic reactions in the neurological system also degrade medications that have a broad impact or stay inactive in the brain.
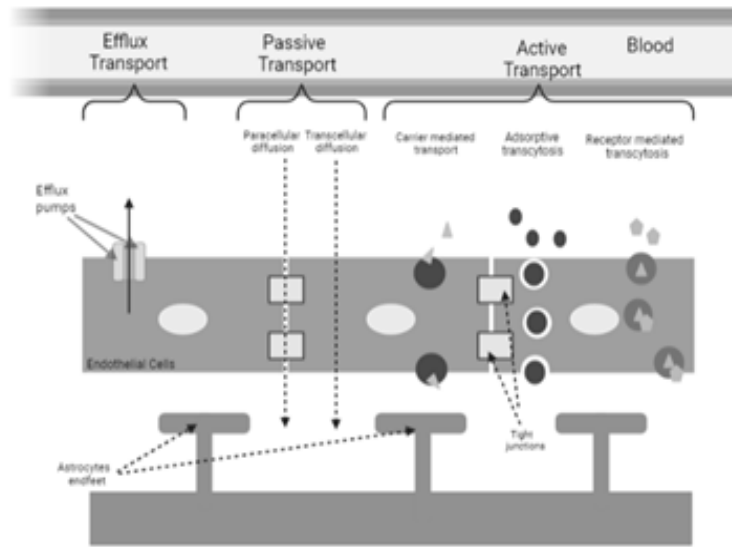
**Figure 2:** Transport mechanisms that traverse the blood-brain barrier [biorender.com]

## VII. DIFFERENT MODES OF TRANSPORT ACROSS THE BLOOD-BRAIN BARRIER (BBB)

Because there are fewer "windows" between neighbouring endothelial cells in brain capillaries than in other organs, where a variety of molecular transport channels might pass across endothelial or epithelial barriers, the endothelium is considerably more permeable there. The solute stream via the BBB is more controlled than it is in the case of generic capillaries because more large molecules are stopped from crossing the barrier and are instead transported into and out of the brain tissue without being recognised by specific proteins [44]. Depending on the solutes' physical and chemical properties as well as the biological structures present in the blood vessel wall, different solute molecules penetrate the barrier in different ways. Molecules are transferred across the BBB through both passive and active transport [45].

The following non-energetic transport techniques are referred to as passive transport, sometimes known as passive diffusion:

- **Paracellular diffusion**, which allows hydrophilic compounds to travel between endothelial cells; and
- By passing via endothelial cells, **transcellular diffusion** enables small lipophilic substances to penetrate the brain parenchyma.

The system can achieve its inherent entropy through passive transport by accounting for the gradients that occur naturally in biology.

Several intrinsic variables, including pharmacokinetics, hydrogen bonds, and charge, influence a substance's capacity for passive diffusion. The octanol/water partition coefficient may be used to assess this procedure; for effective passive transport, it should have a value between 10:1 and 100:1. Steroids and diphenhydramine are two examples of commercially available medications that enter the brain via this mechanism [46].

The molecules entering the brain are influenced in part by the paracellular route. This is often true for compounds with extended half-lives, restricted distribution, and potent CNS effects. Examples include erythropoietin and antibodies [47].

The transcellular pathway frequently involves the passive diffusion of gases (e.g., $O_2$, $CO_2$), water, and liposoluble compounds. However, a molecule's ability to pass across membranes cannot just be controlled by lipophilicity. Despite being lipophilic, molecules need to be between 400 and 500 Da in order to traverse the BBB. In contrast to other lipophilic substances, such as immunosuppressants (such as cyclosporine A), it has been found that certain tranquilizers, such as benzodiazepines, may cross the BBB more readily [48].

Including nutrients, ions, and endogenous compounds, active transport enables the energy-dependent transfer of substances into the brain along with their gradient [49]. There are three types of transport that fall under this category: (i) receptor-mediated transcytosis; (ii) absorptive-mediated transcytosis for positively charged peptides; and (iii) carrier-mediated transcytosis, which is suitable for relatively small molecules.

The primary mode of transport for endogenous peptides, including insulin, transferrin, insulin-like growth factor, and the nicotinic acetylcholine receptor, is receptor-mediated transcytosis. By selectively attaching to the right ligands, these receptors can start internalization into cells. In a unique approach, the receptor is processed back to the luminal membrane while macromolecules are removed from the luminal side of the brain endothelial cells and delivered to the brain [50].

Transcytosis mediated by absorptive mechanisms does not include plasma membrane receptors. The plasma membrane and polycationic molecules can interact electrostatically to initiate this transit mode, which has a negative charge. Specific interactions between the negatively charged endothelium surface and positively charged blood proteins result in a non-selective transport route via the BBB [51].

Carrier-mediated transport uses the luminal and abluminal membranes of capillary endothelial cells to deliver nutrients to the brain. The extracellular fluid of the brain is related to the abluminal membrane, whereas the luminal membrane of endothelial cells is connected to the blood component. The BBB is traversed by specialized transporters that allow the movement of amino acids. For instance, the brain may absorb glucose more easily thanks to the glucose transporter (GLUT-1). [52] The System-L transporter carries the energy-dependent amino acids valine, histidine, methionine, and tyrosine.

In the BBB, efflux mechanisms are also present. The P-glycoprotein (Pgp) mechanism is the most well-known and is prone to pumping out unwanted compounds like antibiotics and anticancer medications [53].
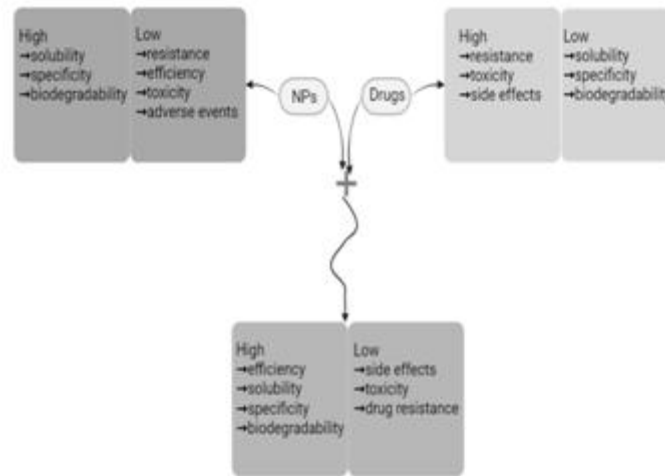
**Figure 3:** The benefit of drug loading over different treatments for NPs. Potential medications can be advantageously included in NPs' and pharmaceuticals' properties to deliver high efficacy and efficiency. NPs are Nanoparticles. [biorender.com]

## VIII. NANOPARTICLES IN BRAIN DISORDER TREATMENT

1. **Nanoparticles can more easily penetrate the BBB due to their small size**: The blood-brain barrier (BBB) and the blood-cerebrospinal fluid (CSF) barrier have been the two biggest barriers to treating brain diseases and disorders. P-gp carefully controls material efflux through the BBB; as a result, its downregulation is associated with the development of tumours and neurological disorders [54]. Inhibiting P glycoprotein enhances the BBB-crossing ability of medicines and the effects that result. Rats' P-gp-mediated phenytoin resistance is suppressed by nanoparticles of PBCA (poly (butyl cyanoacrylate)) [55]. Furthermore, SL nanoparticle-encased andrographolide, a neuroprotective drug, is more permeable to the BBB than free andrographolide, according to a recent study. The results demonstrate that nanoparticles can enhance the target ability and diffusion of potential treatments by regulating p-gp.

2. **Nanoparticles have little toxicity and can be used to increase the toxicity of traditional medications in the cells they are intended to treat:** The therapeutic efficacy of most medicines is influenced by their cytotoxicity. In comparison to traditional treatments, nanoparticles drastically lessen brain toxicity. For instance, in a brain ischemia-reperfusion model, intranasal injection of PLGA nanoparticles is reported to be extremely effective in transporting the mitoNEET ligand inhibitor NL-1 with minimum toxicity. Additional research has shown that encapsulating cytotoxic drugs into nanoparticles (NPs) significantly enhances their solubility, bioavailability, and sustained release [56]. Examples include the antifungal drug amphotericin B, the antipsychotic drug thioridazine, and the anticancer drug sorafenib.

   Instead, nanoparticles may increase the cytotoxicity of conventional drugs in the area they are meant to treat, such as tumor cells. Recent research has shown that the anticancer medicine 3N-cyclopropylmethyl-7-phenyl-pyrrolo-quinolinone was more

hazardous when treated with polyethylene glycol (PEG)-modified silica (Si) nanoparticles than when the drug was free. Despite the promise that has been shown for nanoparticles, some of these materials, like Si nanoparticles, may potentially be harmful. It has been shown that porosity and particle size can influence how Si nanoparticles behave [57]. The addition of PEG, commonly recognized as PEGylation, is a technique that may be used to increase the effectiveness of nanoparticles in addition to using particle sizes and shapes that exhibit reduced toxicity.

In conclusion, the evidence suggests a significant decrease in drug toxicity when some nanoparticles are loaded with the drug instead of when the drug is administered freely. Even though encapsulation can occasionally increase cytotoxicity, the effect can be mitigated by PEGylation or by changing the particle size and porosity. A fresh idea called "green chemistry" has emerged using chemical processes that don't employ toxic or dangerous materials.

3. **NANOPARTICLESs Enhance the Bioavailability and Solubility of Traditional Drugs:** Solubility and bioavailability are crucial factors in determining a drug's effectiveness. The capacity of a medicine to dissolve is known as its solubility, whereas its bioavailability refers to how well it can travel to the systemic blood circulation and, ultimately, the intended location [58]. In contrast to solubility, drug- or body-related variables can influence drug bioavailability. Age, sex, intestinal pH, genetics, medication dose, and formulation are a few of them. Due to the significance of these characteristics, enhancing one might result in higher therapeutic effectiveness and, ultimately, better illness therapy. When silver (Ag) nanoparticles are utilized, methane and ethane are proven to be substantially more soluble in water, and this solubility has been shown to increase with nanoparticles mass loading. According to a recent study, putting carvedilol, a hydrophobic medicine, within CS-sodium tripolyphosphate (STPP) nanoparticles boosts the drug's bioavailability and encourages delayed, sustained release of the medication.

Similarly, adding curcumin (a polyphenol and turmeric compound) with PEGylated SL nanoparticles can increase oral bioavailability and solubility [59]. Numerous additional potential medications, including astaxanthin, astilbe, sorafenib, and apigenin, have also shown enhanced bioavailability and solubility after being encapsulated in nanoparticles. The studies mentioned above imply that nanoparticles may improve the solubility and bioavailability of less soluble medicines, enhancing their effectiveness.

4. **Nanoparticles improve the Specificity and Biocompatibility of Conventional Drugs:** The drug's biocompatibility and specificity guarantee efficient delivery to the intended spot. Drugs are included in nanoparticles to improve these properties significantly. Recent research demonstrates that chimeric antigen receptor T-cell membrane-encapsulated nanoparticles have excellent biocompatibility and safety in normal cells while having high specificity in targeting tumor cells by recognizing glycan-3 proteins, which are highly expressed in hepatocellular carcinoma cells. The outstanding biocompatibility and selectivity of the nanoparticles were further supported by the finding that biomimetic gold (Au) nanoparticles stabilized by seaweed extracts were fatal in breast cancer cells MDA-MB-231 at a dose of less than 45 µg/mL while having no

effects on human embryonic kidney cells at 150 μg/mL. Additionally, compared to ordinary antibody-conjugated magnetic micron beads, which only exhibit about 20% specificity and sensitivity, specific antibody-loaded iron oxide (IO) nanoparticles have high sensitivity and specificity, greater than 95 and 90%, respectively, in capturing amyloid (A) and Tau proteins in the serum and CSF-mimicking samples and about 80–90% in human whole blood samples, indicating the technique's potential as a biomarker for dementia [60]. Overall, the information suggests that nanoparticles are highly selective and biocompatible and may be utilized more to deliver medications to the desired areas.

## IX. USE OF NANOPARTICLES IN THE TREATMENT OF MANY CNS DISORDERS

Potential use of various nanomaterials and nanoparticles for the treatment of various CNS illnesses

1. **Alzheimer's Disease:** A frequent form of dementia known as AD is characterized by age-related, progressive neuronal degeneration that reduces cognitive function and other neuropathological characteristics. One of the pathogenic characteristics linked to the development of neurodegenerative illnesses, such as AD, is the buildup of Tau proteins [61]. According to a recent study, protein-capped cadmium sulfide and IO nanoparticles may efficiently prevent Tau proteins from polymerizing and fibrillating, with inhibition rates of 63 and 49%, respectively. The accumulation of Aβ, which causes a decrease in Aβ-binding ability and plaque development, is another pathogenic aspect of AD. A serine/threonine kinase known as GSK-3 has been linked to the development of Aβ, hyperphosphorylation of Tau proteins, and AD progression.

In contrast, treatment of 5XFAD mice with PLGA nanoparticles loaded with vitamin D-binding protein reduces cognitive deficits by preventing Aβ binding and accumulation. By encouraging anti-inflammatory responses and enhancing antioxidant status, Au nanoparticles have also been shown to generate cytoprotective benefits in rat models of AD. Additionally, it has been demonstrated that surface-coated Au nanoparticlescan decrease Aβ aggregation; however, the impact depends on the nanoparticles' diameter and surface chemistry. The Aβ fibrillization and related neurotoxicity in the AD model are reported to be considerably reduced by Au nanoparticles with negative surface potential. Additionally, a recent study indicates that smaller Au nanoparticles are more effective than bigger ones at suppressing Aβ fibrillization [62]. The information above suggests that nanoparticles can be utilized to more efficiently and effectively transport medications that target dysregulated peptides in AD, such as Aβ.

It delves into the potential of nanotechnology-based approaches for Alzheimer's disease treatment. It explores various nanoscale drug delivery systems, including polymeric nanoparticles, lipid-based nanoparticles, and inorganic nanoparticles, highlighting their advantages and challenges in targeting the pathology of Alzheimer's disease.

It commemorates the progress made in nanoparticle-mediated drug delivery for Alzheimer's disease over the past century. It specifically focuses on strategies to

overcome the blood-brain barrier, a major obstacle in drug delivery to the central nervous system, and discusses the potential of nanoparticles in improving drug penetration and efficacy [63]. Additionally, it was explored the use of iron oxide nanoparticles incorporated into mesenchymal stem cells as a potential therapeutic approach for Alzheimer's disease. The study investigates the effectiveness of this nanoparticle-based approach in enhancing stem cell therapy and neurodegeneration for Alzheimer's disease treatment [64].

2. **Parkinson's Disease:** One of the most prevalent forms of neurodegenerative disorders, PD, is very prevalent in people over 50. Motor and non-motor abnormalities are symptoms of the condition, defined by the loss of substantia nigra dopaminergic neurons and the development of Lewy bodies (LBs) [65]. Environmental and genetic variables are both significant in how the disease develops. By promoting neuronal loss and increased vulnerability to stressors, the LBs' synuclein aggregates help the illness proceed. Additionally, research demonstrates the efficacy of polymeric nanoparticles loaded with microRNA-124 in treating PD symptoms and correcting motor deficits. Treatment with iron (Fe) chelation nanoparticles modified with zwitterionic poly(2-methacryloyloxyethyl phosphorylcholine) and HIV-1-transactivating transcriptor to delay iron saturation in the blood and increase iron lifetime can reverse Parkinson's disease (PD) symptoms more successfully than individual treatments.

   Further research shows that administering Au nanoparticles to PD mice generated by alkaline reserpine can effectively restore behavioral deficits, enhance antioxidant status, and prolong neuronal life. In addition, compared to pure levodopa, the primary medication used to treat PD, treating PD-induced mice using nano dopamine medicines also improves motor deficits with low toxicity. Similar to this, metformin-loaded polydopamine nanoparticles (NPs) support anti-inflammatory, anti-apoptotic, and antioxidative properties linked to the proteolytic degradation of phosphorylated serine 129 of the synuclein protein induced by targeting a histone-lysine N-methyltransferase enzyme known as the enhancer of zest homolog 2 [65]. Selegiline CS nanoparticles, borneol and lactoferrin commodified nanoparticles, resveratrol nanoparticles, and Cerium nanoparticles are some morenanoparticlesand nano drugs that have been shown to offer substantial promise in the treatment of PD by controlling oxidative stress and inflammation. In conclusion, nanoparticles and nano drugs show tremendous promise in treating PD because of their role in controlling inflammation, oxidative stress, apoptosis, and -synuclein activities, and the downstream consequences in motor and non-motor dysfunctions.

   In this study, researchers investigated the use of nanoparticles as carriers for levodopa, a commonly prescribed medication for Parkinson's disease. By encapsulating levodopa within nanoparticles, the researchers aimed to improve drug stability, increase brain uptake, and minimize side effects. Levodopa-loaded delivery systems were created using a variety of nanoparticle types, including polymeric nanoparticles, lipid-based nanoparticles, and inorganic nanoparticles. These nanoparticles provide special benefits like improved stability, controlled release, and the capacity to pass the blood-brain barrier, enabling targeted drug delivery to the afflicted areas of the CNS. The study's results showed that when compared to traditional levodopa formulations, levodopa-loaded nanoparticles had superior drug release patterns, longer therapeutic impact, and

increased brain penetration. This customized drug delivery strategy shows promise for reducing motor fluctuations and improving treatment outcomes for Parkinson's disease sufferers. By utilizing nanoparticles as carriers for levodopa, researchers are exploring the potential of nanotechnology to overcome the challenges associated with drug delivery to the CNS in Parkinson's disease. These advancements in nanoparticle-based drug delivery systems hold significant implications for improving therapeutic efficacy and enhancing the quality of life for individuals with Parkinson's disease [66].

3. **Huntington's Disease (HD):** HD is a neurodegenerative illness that progressively worsens over time and has an autosomal dominant genetic basis. Genetically, the condition is caused by a mutation in the huntingtin gene, which can be seen by the expansion of polyglutamate repeats in exon-1 and the subsequent functional abnormalities in the downstream protein caused by posttranslational mechanisms [67]. Se, an essential metal with defenses against cytotoxicity and redox imbalance, is significantly reduced in the brain autopsies of HD patients. On the other hand, a recent study found that Se, iron, and chromium are three essential components that are noticeably higher in blood samples from HD patients when compared to healthy people. Se nanoparticles may help treat HD because, in Caenorhabditis worms, therapy with modest concentrations of the substance improves oxidative status and prevents the aggregation of huntingtin proteins, which reverses brain state.

Similarly, data suggest that TiO2 nanoparticles can accelerate the oxidation of methionine on the N-terminal domain of the mutant huntingtin protein, resulting in sulfoxide formation and preventing the protein from aggregating. Furthermore, research suggests that treating HD mice with polymeric nanoparticles modified with glycopeptides loaded with cholesterol can cure behavioral and cognitive deficits [68]. When the nose-to-brain transport is examined, it is shown that liposomal nanoparticles successfully deliver cholesterol through this pathway in HD mice models, demonstrating their promise for treating HD. By concentrating on important pathways that affect HD development, the data given above demonstrate the neuroprotective qualities of nanoparticles and their potential for treating HD [69].

The possibility of selenium nanoparticles in the treatment of Huntington's disease is explored. Insights into the special qualities of selenium nanoparticles, such as their antioxidant and neuroprotective activities, are provided in this news paper. It looks at how they can fight off oxidative stress, inflammation, and mitochondrial dysfunction—all of which have a role in the etiology of Huntington's disease. Selenium nanoparticles have a promising therapeutic potential for slowing the progression of Huntington's disease. Their capacity to improve neuronal survival, alter cellular signaling pathways, and control gene expression linked to neurodegeneration are all discussed in the paper. Furthermore, it sheds light on the challenges and future directions in the development of selenium nanoparticles as a viable therapeutic option for Huntington's disease [70].

4. **Brain Tumor:** Malignant and benign tumors that impacts the brain are called brain tumors. Because of the intricacy of the brain, benign tumor development, as well as metastatic disease, might result in adverse effects [71]. Cognitive impairment is linked to the disease's development. The disease's pathophysiology needs to be better understood, and it is currently unknown how to treat it. Nevertheless, several investigations have

documented the therapeutic benefit of nanoparticles in the delivery of promising anticancer medications. Growth and migration of glioblastoma cells can be significantly and specifically inhibited by using polymeric nanoparticles to deliver small interfering RNA to several genes, such as sodium-potassium (Na-K)-chloride cotransporter 1, yes-associated protein 1, roundabout homolog 1, and surviving glioblastoma cell growth and migration [72]. Ganciclovir and modified polymeric nanoparticles that have been loaded with herpes simplex virus type 1 thymidine kinase have been shown to drastically reduce the viability of glioma cells while boosting the survival of mice with tumours [73]. According to the aforementioned data, nanoparticles can be used to deliver medication to a specific brain tumour and to target it.

5. **Autism:** Leo Kanner, an American psychiatrist, first described autism as a neurodevelopmental disease with impaired communication and recurring stereotyped behaviors in 1943 [74]. The Diagnostic and Statistical Manual of Mental Disorders (DSM)-5's diagnostic criteria for ASD have recently undergone considerable revisions. Several diagnoses have been integrated into the one-dimensional diagnosis of ASD. Additionally, there are three ASD diagnostic criteria: (1) qualitative social interaction deficit, (2) in communication, and (3) confined repetitive, stereotyped, and repeating behavioral patterns, interests, and activities have been constructed two domains (1) Continuing issues with social engagement and communication (2) confined, recurrent patterns of action, passion, or interest.

   Since then, autism has been classified more broadly as an autism spectrum disorder (ASD), which encompasses a variety of symptoms, abilities, and levels of impairment. There is a need to create cutting-edge therapy alternatives for the illness despite the absence of worldwide data. ASD is a developmental disorder marked by issues with behavior and communication. Nanoparticles based on titanium dioxide are among the most widely manufactured and utilized nanoparticles (TiO2) [75]. Although TiO2 nanoparticles are often considered harmless and non-toxic, several studies have suggested that the rising use of nanoscale TiO2 particles may pose health risks [76]. Nanoparticle has been used in autism spectrum disorder, but little research has been done. This field of study has not been investigated.

   Only a small amount of study has revealed a negative side of the nanoparticle. Mice exposed to titanium dioxide (TiO2) nanoparticles showed behavioral impairment in their offspring similar to ASD; the substance has no physiological consequences [77]. The evidence above suggests that nanoparticles can deliver medications; however, further research is required to determine the nanoparticle effects to treat autism.

## X. CONCLUSION

   The World Health Organization and the Global Burden of Disease studies estimate that each year, neurological illnesses result in 9 million deaths and 276 million impairments worldwide. These instances are also anticipated to grow significantly shortly. It is difficult to treat and manage CNS diseases due to the BBB, a physiological interface that limits the entry of many therapeutic agents into the brain and is one of the most important issues in CNS sickness treatment. As a result, brain-targeted drug delivery systems are necessary to treat CNS illnesses. The nano-scaled drug delivery system has drawn researchers from many

sectors of biomedical science, notably neurology, because to its unique qualities, including its nanoscale size, high surface-to-volume ratio, selectivity, sensitivity, surface modification, charges, and stability.This is because traditional drugs cannot cross the BBB and are less effective than their nanoscale counterparts. The use of nanotechnology in the therapy and diagnosis of central nervous system conditions is a novel and exciting concept.

Only a few medications have received FDA approval or are undergoing different phases of clinical testing. Because the possible adverse effects of these methods on people are still primarily unclear, there are few clinical trials for nano-based treatments for central nervous system disorders. Rigid validation standards for both in vitro and in vivo protocols are needed from the bench to clinical trials since the area of nanomedicine is still relatively undeveloped and underexplored. Large-scale production necessitates innovation from engineers, chemists, and other experts in the industry. Similarly, regulatory laws must be adjusted to simplify access to trials and patients. More study is needed to comprehend nanoparticle safety issues and prove their therapeutic uses.

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