Review article

Crossing the Barrier: Advanced Drug Delivery Strategies for Neurodegenerative Disorders

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Abstract -

A class of illnesses known as neurological ailments mainly impact the central nervous system (CNS) and can impair the blood-brain barrier's (BBB) structural and functional integrity, increase permeability and possibly cause damage to the CNS. The stability and homeostasis of the central nervous system depend on the BBB. It acts as a selective barrier to keep infections and dangerous chemicals out of the brain. Astrocytes, pericytes, microglial cells, tight junctions, and endothelial cells are the primary constituents of the blood-brain barrier. Therapeutic chemicals are transported across the blood-brain barrier using nanocarriers to treat neurological illnesses. These include cutting-edge drug delivery technologies that improve therapeutic targeting and lessen adverse effects, including liposomes and solid lipid particles (SLPs). However, getting medications over the BBB is still quite difficult because due of its selectiveness. To get around this obstacle, tactics like receptor-mediated transport (RMT), carrier-mediated transport (CMT), and passive diffusion are being investigated. The several methods for treating neurodegenerative illnesses with drug delivery systems that can penetrate the blood-brain barrier are the main topic of this review.

Keywords *- Blood-Brain Barrier, Neurodegenerative Diseases, Targeted Drug Delivery, Nanoparticle-based Delivery Systems, Liposomes, Intranasal Drug Delivery*

1. Introduction

Multiple sclerosis and other neurological disorders like Alzheimer's and Parkinson's disease have afflicted a sizable portion of the world's population in recent decades. The challenge of administering therapeutic chemicals across the central nervous system (CNS) poses a substantial obstacle to the treatment of various disorders [1]. In order to get past this, scientists have created a number of methods for breaking through the blood-brain barrier (BBB), which is selectively permeable and guards against dangerous substances while controlling the admission of necessary molecules [2,3]. Comprising astrocytes, pericytes, endothelial cells, and a basement membrane [5], the blood-brain barrier (BBB) is a highly regulated system that restricts the flow of chemicals into the brain [4]. Notwithstanding this protective role, the barrier poses a significant challenge for medication delivery. Restricting the brain's capacity to receive multiple medicines and achieve positive results [6]. In order to overcome this, nanotechnology delivery systems have been developed that can pass through the blood-brain barrier and deliver their payloads to specific locations in the brain, resulting in improved therapeutic effectiveness and fewer adverse effects [7]. Both organic and inorganic materials are used to create these nanocarriers, which are designed to have low toxicity, a long circulation time, and good biocompatibility. Additionally, a number of mechanisms have been investigated to enhance drug transport into the brain, including passive diffusion, receptor-mediated transport, carrier-mediated transport, and adsorptive-mediated transcytosis. Because of the way the blood-brain barrier (BBB) is structured, targeted drug delivery requires a carefully thought-out strategy [8]. The focus of this review is on treatment approaches for treating particular disorders of the brain [9]. Levodopa administration has been investigated using a variety of modalities, including inhalation, sublingual routes, transdermal systems, and sophisticated gene therapy approaches, especially for the treatment of Parkinson's disease [10]. An examination of the mechanisms underlying drug transport as well as the variables affecting their efficacy and constraints in crossing the blood-brain barrier are also included in the debate [11]. Additionally, this study aims to highlight several therapeutic approaches and provide an overview of the routes, difficulties, and limitations involved in drug delivery across the blood-brain barrier.

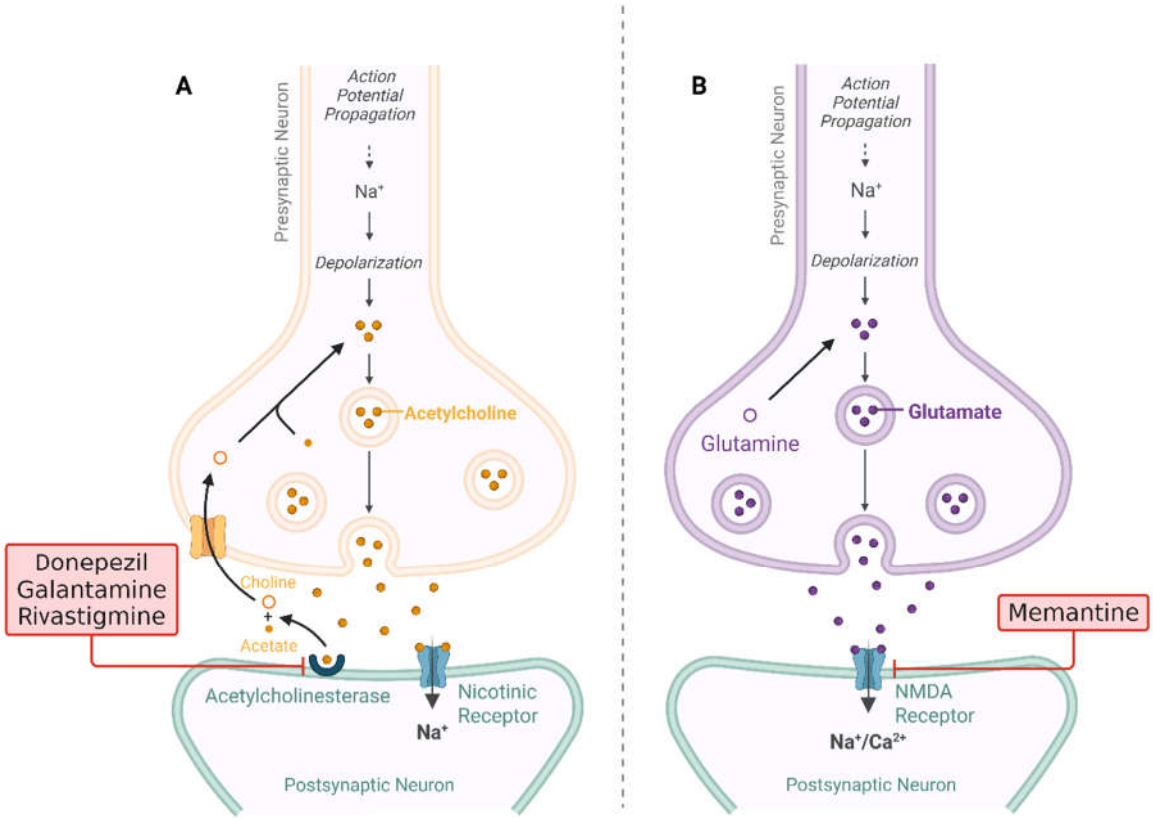

Figure 1: Alzheimer's Disease (AD) - Current Treatments

2. Mechanism of drug delivery across BBB

Facilitating the supply of vital nutrients, preserving ionic equilibrium, and offering defense against neurotoxins and infections are the core functions of the blood-brain barrier (BBB) [12]. The BBB is a key regulatory mechanism in the brain because the central nervous system alters the permeability of cerebral capillaries to stop certain macromolecules and the permeability of cerebral capillaries to stop certain macromolecules and poisons from entering the brain [13]. The brain's architectural structure, which includes the blood-brain barrier (BBB), blood-cerebrospinal fluid (CSF) barrier, and blood-spinal cord barrier, has changed over time to show different levels of permeability. The blood-brain barrier is the most extensive and important of these systems [14,15]. It is made up of layers of astrocytes and pericytes, as well as endothelial cells that are closely linked to brain tissue in what is referred to as the Neurovascular Unit (NVU) [16]. The transfer of water and salts from the circulation into the extracellular fluid is facilitated by this arrangement [18]. Damage or infection impairs the brain tissue's ability to filter salts and water, which raises intracranial pressure and causes edema [17]. The BBB works in these situations to stop fluid from leaking in from different body parts, which could lead to health issues. Passive diffusion, receptor-mediated transport, efflux pumps, carrier-mediated transport, and adsorptive-mediated transport systems are the five ways that chemicals can cross the blood-brain barrier [4,12].

a) Passive diffusion

Non-ionic diffusion, or the movement of substances without the use of energy (ATP), is what defines it. These proteins serve as solute transporters. The cell membrane has a large number of ligand-gated channels that react to hormones or neurotransmitters. This process, which is also known as paracellular transport, shows that the drug can enter the systemic circulation through gastrointestinal epithelial cells by largely passing through tight junctions as a water-soluble substance [67,75]. Osmosis, passive transport, and active transport are some of the ways that materials move across biological membranes [24]. Rather than through changes in membrane voltage, these channels are activated by the binding of particular molecules. They exhibit selectivity, saturation, and competition with similar substrates in their transport kinetics. This includes both persorption and penetration via the epithelial cells' tight connections. Notably, more than 90% of medications follow the passive diffusion method of absorption. In order to improve solute diffusion across the membrane, several membrane proteins form an alternate pathway with the solutes [22]. Diffusion and lipid dissolution, ligand-gated channels, voltage-gated channels, facilitated diffusion, pore-forming ionophores, and diffusion-mediated ionophores are among the mechanisms of passive transport that have been described. The electrochemical gradient, also known as the concentration gradient, is the main force behind this process. In order to balance their distribution, substances travel from regions of higher concentration to regions of lower concentration, as determined by osmosis; this movement requires no energy, making the process passive [23].

b) Transcellular diffusion

Another name for it is intracellular transport. Substances pass through the gastrointestinal (GI) epithelial barrier during this procedure. The mechanism can be divided into three successive phases: the transit through the intracellular milieu; the subsequent permeation of the lateral membrane; and the permeation of the GI epithelial cell membrane, which functions as a lipoidal barrier. Transcellular transport is essential for maintaining physiological balance and for the secretion and absorption of ions, nutrients, and other biomolecules in a variety of tissues. There are several ways that the transport process can take place, including transcytosis, active transport, assisted diffusion, and passive diffusion. While active transport requires the use of energy to move molecules against concentration gradients, passive and facilitated diffusion allow substances to move in line with their gradients. Transcytosis is a specialized mode of transport that moves macromolecules, such proteins, between in epithelial tissues, such as those in the kidneys, intestines, and blood-brain barrier, where the selective translocation of chemicals is crucial, this transport mechanism is especially important. Understanding transcellular transport is crucial for developing effective drug delivery methods in the clinical and pharmaceutical fields, especially when it comes to oral medications and treatments targeted at the brain or other isolated organs. [21].

c) Carrier-mediated transcytosis

Given that it indicates a primary process, it is also known as protein-assisted diffusion. The interspecies variability in the neurovascular transport system, which is characterized by differences in substrate specificity, transporter expression profiles, and regulatory mechanisms, is a significant factor that contributes to the low efficacy rates in the formulation of neuroaxis and acne pharmacotherapeutics. This makes it more difficult to directly extrapolate results from animal models to human subjects. The carrier, which represents a membrane constituent, can interact

with solute molecules for transportation via non-covalent bonding [22,67]. Through immunohistochemistry analyses performed on human brain tissue slices and cultured neurovascular lining cells, the expression of transport proteins was thoroughly investigated; nevertheless, these studies provide important information, depending on the selectivity of each antibody used. Antibody specificity requires careful consideration. Anti-PGP antibodies, for example, may attach to muscle proteins, such as MyHC protein, in a non-specific manner. Furthermore, factors including clinical circumstances and tissue fixation techniques may affect the cellular distribution of transport proteins as well as the specificity of antibody binding in cadaveric samples [26]. The role of the carrier protein at the human cellular interface has been partially revealed by tissue-level immunoanalytical and transcriptomic analysis; however, functional evidence is still necessary to fully clarify the distinct roles of the corresponding carrier protein in cerebral endothelial barrier transport. More detailed assessment of protein-facilitated translocation across the brain vascular interface in humans has been made possible by recent developments in positron emission tomography (PET) tracers and visualization techniques. Higher plasma concentrations are correlated with an improved pharmacological response in the carrier group. Together, they make up the vitamin and intrinsic factor complex. Free vitamins can be released in the lumen by the process that happens after membrane transfer, namely the complex's dissociation. Vitamins B1 and B2 are absorbed in the intestines, and excess glucose is converted into blood erythrocytes as an example of such transport mechanisms [27].

d) Adsorptive-mediated transcytosis

Adsorptive-mediated transcytosis (AMT) is best suited for the blood-brain barrier (BBB). This procedure makes it possible for cationic substances to adhere to endothelial cells' luminal interface, which in turn causes their transcytosis and exocytosis at the albuminal interface. This process is supported by the presence of a transcytosis pathway as well as the distinct morphological and enzymatic characteristics of BBB endothelial cells. Furthermore, the necessary energy for the active transport of substances across the barrier is provided by the significant mitochondrial density in the cerebral endothelium cytoplasm. This mechanism includes both blood-brain barrier penetration and binding to the surface of endothelial cells. Because of their affinity for interacting with polycations, cationic compounds improve the penetration dynamics throughout the cerebral vasculature when they interact with proteins [19]. The blood-brain barrier is also crossed by cationized particles, which can be explained as positively charged proteins attaching to the negatively charged membrane surface and creating electrostatic interactions between them. Protamine, histones, and glycocalyx during their passage through the blood-brain barrier are notable examples. Pharmacological drugs and therapeutic compounds can be delivered across the blood-brain barrier more easily thanks to this transcytosis pathway [20]. The BBB's surface is the target of the glycocalyx and its negative charge. The cerebral extracellular space's (ECS) luminal surface exhibits an overall negative charge at normal pH. Early ultrastructural studies revealed that heparan sulphate proteoglycans and sialylated glycoconjugates, which are essential components of the glycocalyx, significantly contribute to this negatively charged barrier. Furthermore, anionic sites have been found on both the abluminal and luminal surfaces of the cerebral ECS [19,20].

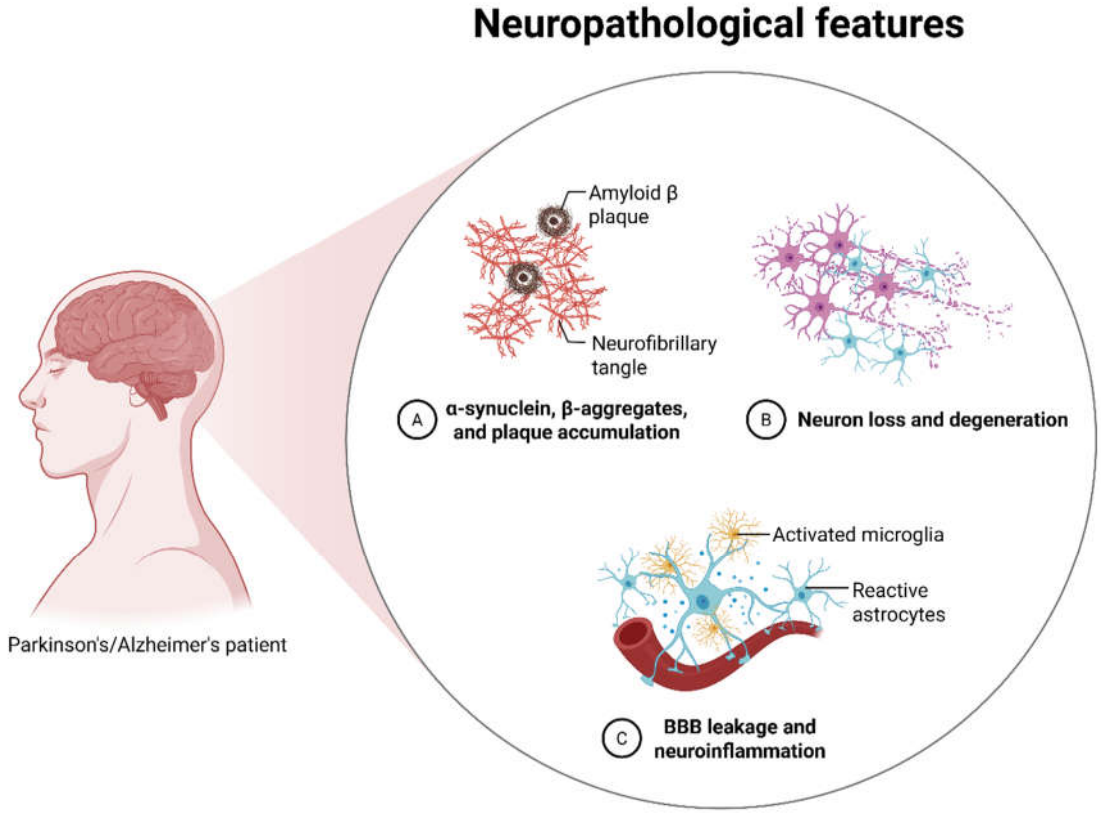

Figure 2: Histopathological Features of Parkinson's Disease and Alzheimer's Disease

e) Receptor-mediated transcytosis

Proteins classified as receptors are identified by their extracellular domains, which are capable of binding specific ligands and facilitating their transportation into intracellular spaces. Certain therapeutic drugs strategically use endothelial cell receptors in the field of pharmacological administration to increase their efficacy in reaching certain target locations. By reducing off-target toxicity, this methodological approach makes it easier for pharmacological substances to pass through cellular membranes. An exogenous ligand first binds with its corresponding receptor located on the cell surface in the receptor-mediated transcytosis (RMT) paradigm [67,69]. The ligand-receptor complex is absorbed into the cellular environment as a result of this contact, which starts the endocytosis process, which leads to the creation of an endosome. The endosome is then moved throughout the endothelial cell. Its encapsulated cargo is then exocytosis and released into the brain parenchyma. Numerous receptors are commonly used for the targeted administration of medicines to the nervous system and have been extensively studied for their critical role in RMT. Prominent instances include the glutathione transporter, insulin, lipoprotein, transferrin, and diphtheria toxin receptors [50]. For the translocation of macromolecules and heterogeneous agents—which can have a diameter of up to 80 nm or a molecular weight of about 80 kDa—across the blood-brain barrier, RMT is especially important. These channels make it easier for macromolecules to move through the body's many physiological barriers [21]. These mainly consist of transferrin (Tf), insulin (INS), low-density lipoproteins (LDLs), and insulin-like growth factors 1 and 2 Three separate stages can be distinguished in the RMT process: 1) Endocytosis: Certain substances, such proteins, have a tendency to attach to their

corresponding cellular surface receptors, which causes a ligand-receptor complex to develop. Numerous biochemical and immunological processes are crucially regulated by this process [28]. 2) Intracellular Trafficking: Endosomal sorting is another name for this stage. The receptor may return to the cellular surface when the previously formed ligand-receptor complex dissociates, but it will also be subject to cytosis and destruction [29]. 3) Exocytosis: In addition, the complex can separate into several vesicles that pass through the plasma membrane, allowing it to subsequently attach to the surface of nearby cells and ultimately cause chemicals to be released into the pericellular space [32].

f) Efflux pumps

The homeostasis of the organism is maintained in large part by this system. The blood-brain barrier's (BBB) selective permeability is facilitated by the specialized P-glycoprotein (P-gp) transporter. The removal of harmful compounds from bacterial cells is one of its primary roles [30]. It also stops different hydrophobic substances from entering the brain. P-gp at the BBB is known to affect the systemic availability of substrates to the central nervous system (CNS), despite the fact that its exact mechanism is yet unknown. Additionally, the BBB actively transports a number of neuromodulators out of the brain. One such example is dehydroepiandrosterone sulphate (DHEAS), a norsteroidal that promotes learning, memory improvement, and neuroprotection by interacting with GABA and sigma receptors. while simultaneously protecting neurons from harm caused by excitatory amino acids [31]. The concentration of substrates in the extracellular fluid of the brain is first determined by this transporter system, which then analyses the substrates' capacity to bind to pharmacological receptors. ABCG2 (breast cancer resistance protein), ABCB1 (P-glycoprotein), and ABCCs (multidrug resistance-associated proteins, Mrps) are some of the key subgroups of the ATP-Binding Cassette (ABC) transporter family. These transporters, which are found on the blood-facing side of the barrier, limit the entry of different substrates into the brain in an energy-dependent manner [30].

g) Nanocarriers

For the delivery of medications to treat disorders of the central nervous system (CNS), nano delivery systems present a promising way to get beyond the blood-brain barrier's (BBB) restrictiveness [23]. Notwithstanding their potential, the physicochemical characteristics of nanocarriers—such as their optical properties, particle size, surface area, and volume ratio—present considerable obstacles in CNS therapy. These nanoparticles are usually between 1 and 100 nanometres in size [33]. Because of their many benefits, including enhanced stability, regulated drug release, high drug-loading capacity, prolonged bloodstream circulation time, and efficient targeting capabilities, nanomaterials are widely used in the development and delivery of therapeutic agents across the blood-brain barrier. Additionally, nanoparticles are used in regenerative medicine and tissue repair, which may improve clinical results and patients' quality of life [34]. The behaviour and distribution of nanomaterials within the body are largely determined by their size and hydrophilicity [24, 25]. Nanoparticles hold a lot of promise for treating neurological conditions because of their many functional characteristics [35]. As a component of nanocarrier systems intended to pass the blood-brain barrier, both organic and inorganic nanoparticles and exhibit lower toxicity [36]. Lipid-based systems, cationic liposomes, solid lipid nanoparticles, metallic nanoparticles, polymer-based nanoparticles, and nano emulsions are among the different kinds of nanocarriers that are engaged [37]. The

incorporation of biodegradable and biocompatible amphiphilic components, like fatty acids and phospholipids, in their formation further increases their benefits [38, 65].

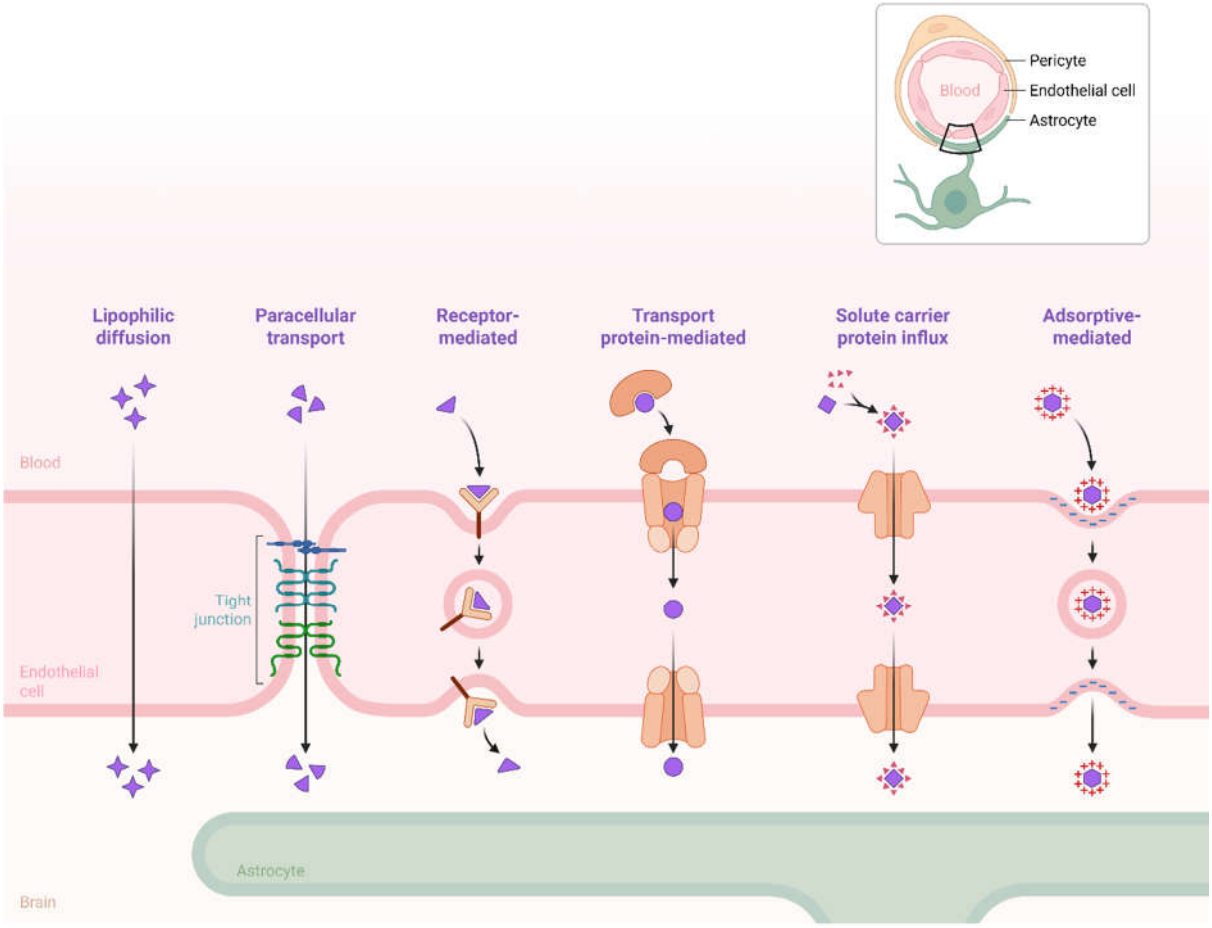

Figure 3: Solute Transfer Across Blood-Brain Barrier

h) Cationic liposomes

The ability of positively charged liposomes to interact with negatively charged elements on cell surfaces, including proteoglycans, and bind anionic nucleic acids to create lipoplex structures was originally shown by Phillip Felgner and his group. Nucleic acids are able to enter mammalian cells more easily thanks to this interaction. One type of nanoparticle employed in the administration of neuropharmaceuticals is cationic liposomes. These lipid-based compounds are physically stable and water-attractive due to their positive charge and hydrophilic head groups and hydrophobic tails [39]. In order to give medication for conditions connected to the brain, cationic liposomes—especially those designed for brain-targeted delivery—are being studied as potentially effective means of overcoming the neurovascular barrier [40]. The blood-central nervous system barrier acts as a barrier to prevent the passage of certain molecules. introducing big molecules, such enzymes, into brain tissue. One important aspect affecting the effectiveness of cationic liposome–nucleotide-based molecules in distribution applications is their structural arrangement into certain anisotropic fluid phases [41]. DOTAP (dioleoyl trimethylammonium propane) is a common example of a cationic lipid, whereas helper lipids like dioleoyl phosphatidylethanolamine aid in

membrane fusion [42]. PEG conjugation, which involves the conjugation of polyethylene glycol chains, has been used to increase the therapeutic delivery effectiveness of liposomes by extending their bloodstream residency time. [43].

i) Solid-lipid nanoparticles

By preventing therapeutic chemicals from degrading and enabling controlled, site-specific release, solid lipid colloidal carriers provide a flexible and focused drug transport mechanism. This method reduces possible side effects while also improving treatment efficacy. Fatty acids, waxes, and triglycerides are among the lipid-derived components used to create these nanoparticles [45]. Solid lipid nanoparticles (SLNs), which are known for their high surface area, steady zeta potential, and nanoscale dimension that usually falls between 50 and 500 nm, are considered to be promising carriers for improving drug bioavailability and attaining sustained drug release. Their ability to cross the neurovascular barrier is enhanced by their solid internal matrix, which is often coated with polyethylene glycol (PEG) and remains stable at physiological temperatures [44,65]. entails the use of triglycerides, fatty acids, and waxes; their solid structure allows for a steady and extended release of medication while also protecting it from chemical destruction. SLNs can be administered via a range of routes, including parenteral and oral delivery methods, due to their low toxicity profiles and biocompatibility [46]. SLNs can preferentially accumulate in sites of tissue injury, such as stroke-affected areas, thanks to passive targeting made possible by increased vascular permeability and the phenomena of nanoparticle retention. Increased vascular permeability and worse lymphatic circulation in these areas are the causes of this buildup, which encourages the long-term retention of lipid nanoparticles [46, 47]. By solubilizing poorly water-soluble medications (laden compounds), the hydrophobic core of SLNs helps to improve the specificity of targeted administration while resolving issues related to drug solubility and release. Many benefits are offered by SLNs, such as improved biocompatibility, medication stability, safety, economical manufacturing, scalability, as well as the flexibility to accommodate various treatment needs. However, they also have certain drawbacks, including a tendency to gel, irregular drug release profiles, difficulties crossing biological barriers, and limited drug encapsulation capacity, which could reduce their efficacy in particular therapeutic settings [67,68].

j) Metallic nanoparticle

Particularly when it comes to transporting therapeutic drugs to the brain, metal nanoparticles (MNPs) have shown great promise as drug carriers. Their potential to improve drug efficacy by targeted administration, raising the therapeutic index and tackling issues like multidrug resistance, has sparked a lot of interest in their use in medicine. In addition to medication administration, MNPs are used in a number of biomedical domains, such as nutraceutical formulations, the creation of biocompatible materials, and in vivo and in vitro diagnostics [48]. Metal nanoparticles are regarded as useful instruments in the treatment of various medication administration, MNPs are used in a number of biomedical domains, such as nutraceutical formulations, the creation of biocompatible materials, and in vivo and in vitro diagnostics [48]. Metal nanoparticles are regarded as useful instruments in the treatment of various disorders, especially those affecting the central nervous system (CNS), due to their special size and ability to regulate medication release. However, a significant obstacle to effective medication administration is the blood–brain barrier's (BBB) complexity. It has been demonstrated that properly designed nanoparticles with specific surface changes have the ability to successfully pass the blood-brain barrier and enter

the central nervous system. Because of their low physiological reactivity, gold, silver, and platinum are often utilized metals in drug delivery via nanoparticles [49]. Current clinical research continues to focus on these nanoparticles' possible neurotoxic effects and their capacity to cross the blood-brain barrier. The size, shape, surface properties, chemical makeup, and aggregation behaviour of nanoparticles all affect their toxicity and BBB permeability. Chemical reduction techniques can be used to create metal nanoparticles, which can then transcytoses across the blood-brain barrier. Peptide conjugation techniques have been used to boost nanoparticle transport across the BBB and increase CNS permeability. Attaching nanoparticles to endothelial cells' transferrin receptor is one efficient technique. By functioning as a ligand to carry medications, proteins, genes, and ions to particular target areas, transferrin, an iron-binding protein, is essential to receptor-mediated transport. Both therapeutic and diagnostic goals are supported by this approach. These conclusions are based on a bibliometric analysis of 583 pharmacology, toxicology, and pharmaceutics-related publications that were obtained from the Scopus database as of mid-September 2022 [51].

k) Nano-emulsion

Drugs intended to pass the blood–brain barrier (BBB) can be encapsulated in nano emulsions, which are extremely versatile delivery vehicles. By solubilizing medicinal compounds inside their dispersed phase, these emulsions can improve the bioavailability of drugs. Drugs that are hydrophobic and generally have trouble passing across the blood-brain barrier can be transported using oil-in-water (O/W) nano emulsions. However, hydrophilic chemicals are better delivered via water-in-oil (W/O) nano emulsions. Nano emulsions offer flexible methods for creating BBB-permeable treatments since they can be made by in situ polymerization or by adding pre-formed polymers, depending on the particular medication and delivery needs. Nano emulsions, particularly oil-in-water varieties, are a specific type of nanoscale drug delivery technology that falls under the larger category of nanoparticle delivery systems [52]. They can be manufactured in multiple dose forms, such as liquids, and provide a versatile platform for targeting the central nervous system (CNS). This allows them to be delivered via a variety of channels, such as intravenous, intranasal, and pulmonary paths. These pathways are particularly pertinent to treatments that target the brain. Nano emulsions are especially useful for delivering poorly soluble medications across the blood-brain barrier (BBB), improving therapeutic results due to their increased solubilization capacity and improved kinetic stability over traditional dispersions. In order to stabilize the emulsion, the formulation usually consists of water, appropriate surfactants, and nanocomposite oils, such as fatty acids and triglycerides [53]. Furthermore, nano emulsions have shown promise for efficient medication delivery to the brain because of their small particle size and capacity for surface modification. By interacting with the barrier's tight junctions, oils high in omega-3 fatty acids have also demonstrated potential in increasing BBB permeability [54].

l) Polymer-based nanoparticle

Different polymerization processes can be used to generate polymeric nanoparticles from a wide range of monomers, allowing their characteristics to be tailored for particular medical applications. The primary kinds of polymer-based nanoparticle systems used in brain-targeted medication delivery are highlighted in this section. These consist of hybrid systems, naturally occurring polymer nanoparticles, and manufactured polymer nanoparticles [55]. For every category, the synthesis techniques and physical properties—like particle size, surface chemistry, and drug loading capacity—are examined. The capacity of nanoparticles to pass through the blood–

brain barrier (BBB) is largely dependent on their size, shape, surface charge, and presence of surface ligands. By getting over the BBB's limitations, polymeric nanoparticles present a viable way to improve drug delivery to the brain [65]. Targeted drug delivery is made possible by their ability to target particular brain tissues or cells. These systems have the ability to release therapeutic substances at a regulated rate, guaranteeing ideal medication concentrations at the intended location and reducing side effects. PACA (polyalkyl cyanoacrylate) nanoparticles are one such instance, which have demonstrated promise in the delivery of drugs to the brain [56]. These PACA nanoparticles are frequently coated with polysorbate 80 and designed with cell-penetrating peptides or polyethylene glycol (PEG). This surface alteration improves their capacity to traverse the blood-brain barrier and helps them avoid being discovered by macrophages. By protecting medicinal substances from deterioration in the bloodstream, they also increase drug stability [57].

m) Synthetic polymeric nanoparticles

Although poly (alkyl cyanoacrylate) (PACA) is best known for its usage in surgical adhesives, it has also been widely used as a suture material. PACA nanoparticles have been recognized for their biocompatibility and ease of degradation since they were first introduced by Couvreur et al. in 1972 [75]. Enzymatic activity, primarily from pancreatic fluid esterases or serum esterases when given orally or intravenously, causes these nanoparticles to degrade in the digestive tract. The length of the polymer's alkyl side chains can be changed to alter the degradation time, which is typically a few hours. As demonstrated by poly (butyl cyanoacrylate) (PBCA), for instance, polymers with longer chains, such as octyl, breakdown more slowly than those with shorter chains, such as butyl. The toxicity of the polymer is also influenced by the structure of these side chains. A variety of polymerization techniques, such as anionic, radical, and interfacial processes, can be used to create PACAs. Usually, interfacial emulsion polymerization or an acidic aqueous environment are used to create the nanoparticles [56,57]. Furthermore, by esterifying cyanoacetic acid with different alcohols, their characteristics can be adjusted for certain uses.

- ### Study of neurological disorders

Among the most complex and incapacitating diseases, neurological disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, and brain tumors affect millions of individuals worldwide [58]. Effective treatment of many disorders remains challenging despite significant advancements in pharmacological research because of the blood-brain barrier (BBB) [59], a highly selective and protective membrane that prevents the majority of medications from entering the central nervous system (CNS) [60]. In order to get over this barrier, researchers have created novel drug delivery systems that minimize systemic side effects while facilitating the passage of therapeutic molecules across the blood-brain barrier [61]. These strategies include exosomes, dendrimers, peptide-based delivery systems, intranasal administration methods, and nanocarriers such liposomes, solid lipid nanoparticles, and polymeric nanoparticles [62]. Additionally, chemical tactics like prodrugs and receptor-mediated transport as well as physical methods like targeted ultrasound have been studied [63]. Even though these techniques have demonstrated potential in improving drug bioavailability, brain targeting, and controlled release, there are still obstacles to overcome, especially when it comes to large-scale production, guaranteeing biocompatibility, preventing immunological reactions, and implementing these technologies in clinical settings [64].Among the most common neurological conditions, Alzheimer's disease, Parkinson's disease,

stroke, epilepsy, and multiple sclerosis each have their own pathogenic mechanisms and clinical manifestations. Memory, reasoning skills, and behaviour are the main areas affected by Alzheimer's disease, a chronic and progressive brain ailment. It is intimately associated with the accumulation of neurofibrillary tangles and beta-amyloid plaques in the brain, which lead to a substantial loss of neurons, particularly in the cerebral cortex and hippocampus. This condition is the leading cause of dementia worldwide and primarily affects the elderly [33].

- **Treatment of Neurodegenerative disorder**

Stroke (Ischemic and Hemorrhagic)

The most costly and chronic incapacitating illness impacting adults worldwide is stroke. The blood-brain barrier (BBB) briefly opens during an ischemic stroke (minutes to hours), then undergoes a refractory phase before reopening for an extended length of time (hours to days). Restoring blood flow, or reperfusion, is essential to reducing brain damage, but it can also exacerbate damage, a condition called reperfusion injury [65]. Specifically, it contributes to the BBB's eventual reopening, which is connected to endothelium activation and reactive oxygen species (ROS) generation. The loss and disruption of tight junctions is the main cause of the BBB dysfunction that happens during an ischemic stroke. Because of the activation of microglia and the influx of peripheral immune cells, the inflammatory response is mostly responsible for the breakdown of the blood-brain barrier (BBB) and subsequent cell death after a stroke [66]. Nitric oxide (NO), reactive oxygen species (ROS), pro-inflammatory cytokines like tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), as well as chemokines like macrophage inflammatory protein-1 alpha (MIP-1α/CCL3), monocyte chemoattractant protein-1 (MCP-1/CCL2), and chemokine ligand CXCL-1, are released when microglia, the brain's main immune defences, are activated. These signalling molecules activate the nuclear factor kappa B (NF-κB) pathway and excite the brain's endothelial cells. Peripheral leukocytes are drawn in and infiltrate the brain tissue as a result, escalating and maintaining the inflammatory response [67].

- **Alzheimer’s Disease**

The most noticeable sign of Alzheimer's disease (AD) is memory loss. Brain shrinkage, amyloid-beta (Aβ) peptide accumulation that forms senile plaques, hyperphosphorylated tau proteins that cause neurofibrillary tangles, and vascular alterations in the brain that cause cerebral amyloid angiopathy (CAA) are important pathogenic indicators. Amyloid-beta (Aβ) accumulation in brain tissue may be caused by impaired efflux transporter function on the apical side of blood-brain barrier (BBB) endothelial cells [68]. This theory is specifically supported by research that has demonstrated decreased expression of LRP and decreased activity of P-glycoprotein (P-gp) in both Alzheimer's patients and animal models. Furthermore, when activated, astrocytes and microglia can stimulate the formation of Aβ and play important roles in controlling its levels. In addition to being carriers of therapeutic chemicals, nanoparticles (NPs) can also be used as imaging tools or as a combination theragnostic agent [69]. These multipurpose systems frequently make use of nanoparticles—such as those composed of iron oxide, gold, silica, carbon nanotubes, or quantum dots—that naturally have imaging capabilities. Polymeric n-butyl-2-cyanoacrylate (BCA) nanoparticles loaded with radio-labelled ^{125}I-clioquinol are one example. Therapies for AD primarily try to prevent the development of tau tangles and amyloid-beta (Aβ) plaques, or to stop their buildup

surrounding neurons. However, by boosting neurotransmitter levels, the majority of approved drugs only reduce symptoms and halt the progression of the disease [70].

- **Parkinson's Disease**

A major neurodegenerative condition linked to aging, Parkinson's disease (PD) is typified by a progressive loss of voluntary motor function. It is increasingly common as people age and is often accompanied by symptoms such as sadness, cognitive decline, and sleep difficulties. The major clinical treatment for Parkinson's disease (PD) is still pharmacological therapy, which includes drugs like catechol-O-methyltransferase inhibitors, dopamine receptor agonists, and monoamine oxidase B inhibitors, among others. Reduced cerebral blood flow and vascular alterations in the striatum and substantia nigra (SN) associated with impaired blood-brain barrier (BBB) integrity have been noted in PD patients [68]. Vascular endothelial growth factor (VEGF) expression has been linked to an increased blood vessel density surrounding injured dopaminergic neurons in the SN of monkeys [92]. Furthermore, it has been demonstrated that injecting VEGF into rats' SN disrupts the blood-brain barrier, resulting in the death of dopaminergic neurons and severe inflammation. Neurotoxins administered locally or systemically are frequently used by researchers to simulate dopaminergic neurodegeneration [71]. Stereotactic injection of 6-hydroxydopamine (6-OHDA), which is unable to pass the blood-brain barrier, and systemic or localized MPTP delivery are common techniques. Although oxidative stress and fast neuronal death are caused by these toxins, they do not adequately represent the gradual character of the disease, non-motor symptoms, or protein misfolding processes. Additionally, the use of neurotoxins can directly cause neuroinflammation and harm different kinds of cells, making it more difficult to interpret the death of dopaminergic neurons. Research on Parkinson's disease is further aided by genetic models; for example, PD is known to be caused by duplications or triplications in the α-synuclein (SNCA) gene or autosomal dominant point mutations. These models are useful for examining the disease's course as well as its underlying mechanisms. By detecting contrast agent leakage, non-invasive imaging techniques like magnetic resonance imaging (MRI), especially dynamic contrast-enhanced (DCE) and dynamic susceptibility contrast (DSC) MRI, are useful for assessing the integrity of the blood-brain barrier (BBB). Positron emission tomography (PET), single-photon emission computed tomography (SPECT), transcranial were sonography (TCS), and thermal imaging are other diagnostic methods for Parkinson's disease that can also be used to evaluate dysfunction of the autonomic nervous system. Dopaminergic medicines, which target dopamine pathways, and nondopaminergic agents, such as cholinesterase inhibitors, which operate on other brain pathways, are the two primary types of medications used to treat Parkinson's disease [72].

MRI Analysis: White Matter Lesion (WML) in MRI Analysis Volume Estimation: The lesion segmentation toolkit in SPM8 was used to measure the white matter lesion volume, a known marker of small vessel disease. Both T2-weighted FLAIR and T1-weighted MRI scans were used in this investigation to estimate the volume of WMLs. Analysis using Dynamic Contrast-Enhanced (DCE): The "realignment" tool in SPM125 was used to correct motion in a set of 160 dynamic MRI images by aligning each image with the sequence's first frame. The sagittal sinus was located on the final motion-corrected picture using Micro in order to compute the vascular input function. From this area, about 50 voxels selected for examination.

- **Multiple Sclerosis (MS)**

The myelin sheath that surrounds nerve fibers is the main target of MS, a chronic inflammatory and autoimmune illness that affects the central nervous system. The BBB regulates the flow of immune cells between the bloodstream and central nervous system (CNS) and is essential for controlling immunological activity in the brain. The possible significance of activated protein C in maintaining the integrity of the blood-brain barrier has not yet been thoroughly investigated, despite the fact that it is well-known for its anticoagulant qualities and has demonstrated advantages in lessening the severity of disease in MS models. Examining this protective effect could lead to a new therapeutic approach for delaying the course of MS [88]. Additionally, annexin A1 levels in cerebral microvascular endothelial cells and plasma are specifically decreased in MS patients. Increased BBB permeability is seen in mice models devoid of annexin A1. Through interactions with the cytoskeleton in cultured brain endothelial cells, the anti-inflammatory protein recombinant annexin A1 can decrease BBB permeability and restore barrier integrity, suggesting that it has potential as a therapeutic treatment [94]. Matrix metalloproteinases (MMPs) 1, 2, 3, 7, 9, and 12 have increased activity in the early stages of multiple sclerosis (MS) [89]. It is well recognized that these enzymes weaken the blood-brain barrier (BBB), allowing leukocytes to enter and aiding in the breakdown of myelin. There is evidence that angiogenic alterations are also well-established in multiple sclerosis (MS), suggesting a possible connection between angiogenesis, BBB disruption, and inflammation of brain endothelial cells (BECs), all of which may contribute to the advancement of the disease. Although it is clear that BBB failure contributes to the development of MS, it is unclear if this dysfunction causes or results from the disease. However, it can be claimed that BBB disruption may really be a causative component, given that MS is an autoimmune condition and that immune cell entry into the central nervous system (CNS) is a crucial phase in its development [90].

- **Epilepsy**

The most common method of diagnosing epilepsy involves a thorough review of the patient's medical history, including information about the type of seizures and the patient's health just before they occurred. A complete physical examination, with special attention to the nervous system, as well as a blood and other body fluid analysis are necessary [73]. A complete blood count, metabolic profiles, evaluations of thyroid and liver function, an electroencephalogram, and neuroimaging investigations should also be included in the diagnostic process [93]. The pharmacokinetic theory, the neural network hypothesis, the intrinsic severity hypothesis, the gene variant hypothesis, the target hypothesis, and finally the transporter hypothesis is some of the theories that have been put out in relation to refractory epilepsy [72]. Antiepileptic drugs must be administered via a variety of methods in order to treat both acute and chronic seizure disorders [74]. Antiepileptic medications are usually administered orally in the treatment of chronic epilepsy. When the oral route is impractical or a prompt clinical response is necessary, parenteral administration is used. Intranasal (IN), buccal, or sublingual methods can also be used to administer some drugs, especially for treatments that take place outside of a hospital. Oral formulations include extended-release medicines, tablets, capsules, suspensions, and solutions. Before entering the systemic circulation, drugs that are taken orally and absorbed through the gastrointestinal (GI) tract first pass through the liver, where first-pass metabolism may take place, resulting in decreased bioavailability [87].

Applications

Advanced Drug Delivery System Applications:
1. Breaking through the Blood-Brain Barrier (BBB): New drug delivery techniques allow drugs to pass through the BBB, which normally keeps the majority of therapeutic agents from reaching brain tissue [75].
2. Nanoparticle-Facilitated Delivery: Polymer-based systems, liposomes, and solid lipid nanoparticles are examples of carriers that reduce side effects, improve targeting in neurological illnesses like Alzheimer's, and protect medications from degradation [76].
3. Dendrimers and Micelle-Based Systems: By providing controlled drug release and enabling targeted distribution via receptor engagement, these structures can help cure diseases including glioblastoma and Parkinson's disease [77].
4. Intranasal (Nose-to-Brain) Delivery: This method uses the olfactory pathway to avoid the blood-brain barrier, enabling the efficient delivery of neuropeptides, insulin-like substances, and anticonvulsants for epilepsy and neurodegenerative diseases [95].

5. Hydrogel Delivery Platforms: These systems serve to lower the frequency of dose and minimize systemic adverse effects by delivering drugs directly into the central nervous system (for example, by intrathecal injection) in a sustained and site-specific manner [78].
6. Stimuli-Sensitive Systems: Perfect for treating inflammation or brain tumours, these clever delivery systems release drugs in reaction to particular stimuli like temperature, pH levels, or the presence of enzymes in diseased brain regions [79].
7. Improved Drug Effectiveness: By increasing the concentration of medications at the intended location, these systems enhance therapeutic results and enable the use of lower dosages [80].
8. Improved Patient Compliance: Patients are more comfortable and more likely to follow treatment plans when non-invasive or minimally invasive delivery modalities, including nasal sprays or implanted devices, are used [81].

9. Personalized Treatment Methods: Tailored therapies that adjust to the patient's condition and the course of neurological disease are supported by customizable delivery systems [96].

- ## Future prospects of drug delivery system across BBB

Future Prospects for Blood-Brain Barrier (BBB) Drug Delivery:
1. Exosome-Based Delivery: delivering therapeutic agents such as proteins, siRNA, or small chemicals straight to the brain by using exosomes, which are tiny, naturally occurring vesicles made by cells, as targeted carriers [82].
2. Focused Ultrasound with Microbubbles: This non-invasive technique uses microbubbles and ultrasound to briefly break down the blood-brain barrier, enabling targeted and accurate medication delivery to brain tissue [78].
3. Receptor-Targeted Nanoparticles: creating nanocarriers that mimic natural ligands, such insulin or transferrin, in order to use receptor-mediated mechanisms to pass the blood-brain barrier [75,71].
4. Intranasal Therapeutic administration: Using the olfactory and trigeminal nerve routes, nasal administration is being developed as a non-invasive method of accessing the central nervous system [83].

5. Biodegradable Polymer Carriers: Using degradable and biocompatible polymers to improve drug stability and decrease systemic exposure in extended-release medication formulations [84].
6. Peptide-Enhanced Nanocarriers: Adding brain-targeting peptides to nanoparticles or liposomes to enhance BBB penetration and accomplish site-specific medication delivery [85,].
7. Gene and RNA-Based Therapies: Using viral and non-viral delivery methods, gene-editing technologies such as CRISPR and RNA interference are being developed to treat genetic brain illnesses [91].
8. AI-Assisted Drug Development: Using machine learning and artificial intelligence to create medications with improved BBB penetration and optimal therapeutic qualities [86].

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