iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 13 **Issue:** XII **Month of publication:** December 2025

DOI: https://doi.org/10.22214/ijraset.2025.76689

www.ijraset.com

Call: 08813907089 | E-mail ID: ijraset@gmail.com

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 13 Issue XII Dec 2025- Available at www.ijraset.com

Molecular Drug Delivery Vehicle for Crossing Blood Brain Barrier

Prateek Suthar[1], Shivraj Singh Rathore[2], Satveer Singh Shekhawat[3], Jaypal Prajapat[4], Mr. Aditya Pant[5]
[1, 2, 3, 4]*B. Pharm Students (BNCP),* [5]*Asst. Professor (Department of Pharmacology BNCP)*

Abstract: ***This article enlightens the challenges and vehicles for delivery the drug to brain. The blood-brain barrier is a major obstacle when it comes to delivering drugs into the brain because it's selective in nature. The restricted capacity of most pharmaceutical compounds to attain therapeutic concentrations within the brain poses a substantial obstacle in addressing neurological conditions. To overcome this, researchers have developed innovative drug delivery systems, including those utilizing lipids, polymers, inorganic materials, and biomolecules. These systems facilitate brain targeting through mechanisms such as receptor-mediated transcytosis, adsorptive transport, and triggered release. Even though there's been a lot of progress in labs in respective fields, we still have issues with safety, making these systems on a large scale, making bioavailability at brain sites and getting them into actual clinics. Which creates a need to keep coming up with new drug carrier designs to get better results for brain-related diseases.***

I. INTRODUCTION

The blood-brain barrier (BBB) is a selective barrier that protects the central nervous system (CNS) from harmful chemicals, molecules and keeps it balanced. Delivering drugs into the brain is important to treat CNS disorders, but the BBB makes it typical for drug delivery. Getting past the BBB is the main problem for beneficial brain drug delivery, with less than 1% of all CNS drug development efforts focusing on delivery systems. Modern drug discovery often creates compounds that cannot cross membranes well, which prevents them from getting through the BBB. While the BBB protects the brain, it impedes over 98% of small-molecule drugs and all macromolecular therapeutics, necessitating advanced delivery strategies. Nanocarrier technologies, surface modifications, and focused ultrasound are explored as methods to enhance drug transport across the BBB. While advancements in targeted drug delivery offer promise, challenges related to system stability, safety evaluation, and clinical translation require further research. Emerging strategies aim to carefully control permeability of the blood–brain barrier is so that medicines can enter the brain more easily and safely. Therefore, we have some methods which allows drugs carry through the barrier cells themselves (transcytosis), using nose-to-brain delivery with intranasal sprays, and using special triggers like sound, light, or chemicals to briefly and reversibly loosen the barrier so drugs can pass through, then allowing it to seal up again. (1–4)

The BBB is a real challenge for delivering drugs to the brain for conditions like epilepsy, stroke, brain cancer, and head injuries. Its arrangement, with endothelial cells, astrocytes, and tight junctions, is super specific about what enters, and those efflux transporters make it even harder for drugs to remain around. Enzymatic activity and efflux transporters like P-glycoprotein (Pgp) and breast cancer-resistant protein (BCRP) also limit amount of drug gets into the brain by breaking it down or actively eliminating it out. When someone has a stroke, we're racing against the clock because brain cells die super-fast, and there's not enough blood getting to the affected areas. In epilepsy, drug resistance is a huge problem, possibly related to BBB issues, too many drug-metabolizing enzymes and efflux transporters, and complicated neural networks, making treatment difficult.(5–7)

Glioblastoma is an aggressive brain tumor with a bad prognosis, mostly because it's tough to treat with available measures and the blood-brain barrier and tumor microenvironment make it even harder. The usual treatments, like surgery, radiation, and chemo such as temozolomide, don't really help people live much longer, and even newer drugs like bevacizumab haven't made a difference in overall survival. Even with all the progress, only two upon written drugs got approved in the last 25 years, and the bevacizumab didn't even help people live longer. New ways to get drugs across the BBB are emerging, like new drug designs such as nanoparticles and antibody-drug conjugates, plus creative delivery methods like convection-enhanced delivery and focused ultrasound. Future treatments will focus on combo therapies, early strategies, and flexible trial designs to fight Glioblastoma by getting drugs where they need to transport, boosting the immune system, and making treatments work efficiently. Even with all the progress in delivering drugs across the BBB, we still have issues with how stable the system is, how to test the drugs, their long-term safety, and getting them into actual use, so advance research is needed.(8–10)

This review looks at the molecular drug delivery methods made to cross the blood-brain barrier. It includes current strategies like lipid-based carriers, polymeric and inorganic nanoparticles, receptor-mediated transport systems, and non-invasive delivery approaches that aim to get more drugs into the brain. We'll give special attention to physical and chemical properties, surface changes, and targeting molecules affect how well drugs get through the BBB and produce effect. Also, we'll discuss the main challenges in getting these treatments to patients, like safety, how stable they are, and if they can be used in clinics. The main goal here is to pull together all the latest research to show what's working, what's not, and what's next for getting drugs to the brain and treating the brain disorders.(8,11,12)

II. BLOOD-BRAIN BARRIER: STRUCTURE AND TRANSPORT MECHANISM

For the brain cells to work efficiently, there's special system called the blood-brain barrier that keeps the brain's fluid separate from the rest of the body's blood. Brain capillaries are tough to get through the other capillaries because of how they're built and how they control blood flow to the brain. Because the blood-brain barrier has these unique cells called cerebral microvascular endothelial cells, and they're the first defense between the blood and the brain, lining those brain capillaries.(13–15)

Unlike other endothelial cells in the body, these brain cells don't involve in large amount of pinocytosis, and they're super tightly sealed by these attachments called tight junctions (TJs). This special feature enables closing any gaps between the cells, preventing harmful chemicals and molecules from getting through the spaces between them. Tight junctions are intricate structures made of a bunch of proteins, like claudins, occludin, and JAMs. These proteins connect to the cell's internal structure through other proteins like ZO-1 and ZO-2, creating a seal that stops ions and water-loving molecules from getting through the barriers. The neurovascular unit (NVU) comprised of endothelial cells, pericytes, and astrocyte end feet, plays a critical role in maintaining the integrity of the blood-brain barrier (BBB).Pericytes managing the endothelial cells work, and astrocytes keep the barrier strong with their signaling molecules, all working together to protect and stabilize the brain. (2,13,15)

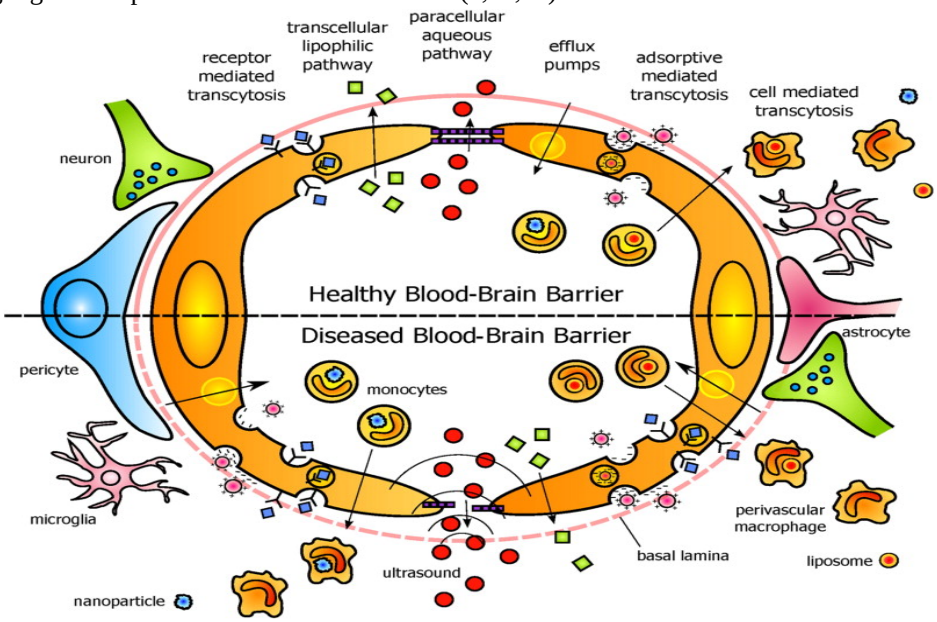


Fig no. 1 (16)

The blood-brain barrier is strictly regulated, but important chemicals and molecules still enter the brain with help of special transport systems. Small, fatty molecules like oxygen, CO2, and some drugs can just slip through the endothelial membranes with passive diffusion, following the concentration gradient. But tight junctions block out large, water-loving molecules. The BBB uses CMT and RMT to get essential polar nutrients where they need to be provided. CMT makes sure nutrients get at desired sites effectively and selectively, using proteins like GLUT-1 for energy and different transporters for amino acids.RMT helps large molecules like insulin and transferrin cross the BBB by latching onto receptors and using vesicular transport. Additionally, there are these efflux transporters from the ATP-binding cassette family, like P-glycoprotein, BCRP, and MRPs, that actively pump foreign substances and many drugs back into the bloodstream. This protects the brain, but it also makes it difficult to get drugs into the central nervous system.(1,4,17,18)

ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 13 Issue XII Dec 2025- Available at www.ijraset.com

III. DESIGN PRINCIPLES FOR BBB- CROSSING DELIVERY VEHICLES

According to the design of drug delivery vehicles that can cross the blood-brain barrier (BBB) is a balancing act. It need eligibility to enter brain to be therapeutically useful, while keeping systemic exposure, immunogenicity, and toxicity low. Most successful systems combine tuned physicochemical properties, active targeting via BBB transport pathways, and the stability & safety of engineering across the entire "blood → BBB → brain parenchyma" journey. The physicochemical requirements include size, surface charge, lipophilicity, surface coating, shape and ligand density. Size willaffectduration of molecules circulation, how cells take them up, and efficiency they get through the BBB. Most eligible and better BBB nanocarriers are around 10-100 nm – small enough to avoid the spleen and interact with endothelial cells, but big enough to not get cleared rapidly by the kidneys like particles under 5-6 nm. On the otherhand, particles over 200 nm usually can't cross the BBB well and get taken up more by the MPS. So, it's important to check their size in serum because protein adsorption can make them seemlarger than their actual size.(19–24)

IV. MOLECULAR DRUG DELIVERY VEHICLE

Having efficient molecular drug delivery systems is key to getting around the blood-brain barrier (BBB). The TGs, efflux transporters, and enzyme barriers frequently prevent conventional small-molecule medications from entering the brain efficiently. Therefore, sophisticated delivery systems are designed to use the BBB's own transport mechanisms, such as receptor-mediated and adsorptive-mediated transcytosis, to keep drugs safe and improve their effectiveness in the body. The most widely described of these are lipid-based systems, polymeric carriers, inorganic and hybrid nanocarriers, and biomolecule-based platforms. (10,12,25–27)

A. Lipid-Based Systems (Liposomes and Lipid Nanoparticles)-

Some of the earliest and most researched nanocarriers for delivering medications to the brain are lipid-based systems. This is because they are biocompatible and resemble to human's biological membranes. Lipid-based systems are some of the first and most studied and described nanocarriers for delivering drugs to the brain. That's because they're a lot like own biological membranes and they're biocompatible. Liposomes are basically little spheres with one or more phospholipid layers around a watery center. That means they can carry both water-loving and fat-loving drugs. Their dual nature lets us design them in lots of ways and change their surface to help them get past the blood-brain barrier.(10,12,28)

Normally, liposomes don't form in sufficient amount in the brain because our bodies eliminate them out swiftly with anefficient system called the mononuclear phagocyte system (MPS). To overcome this, we've started adding molecules like PEG to their surface. This helps them remain in circulation longer and avoids them getting targeted by our immune system. These "stealth liposomes" are more stable and have a better chance of interacting with the cells that make up the blood-brain barrier.(19,29,30)

Targeted liposomes get even better at crossing the BBB when they add molecules like transferrin, lactoferrin, apolipoprotein E, or antibodies that fight against BBB receptors. These modifications help the liposomes use a special pathway to get across the BBB and drop off drugs right into the brain. Lots of studies before human trials have shown that these tweaked liposomes deliver anticancer drugs, brain-protecting meds, and genetic material much better.(28,31,32)

Lipid nanoparticles (LNPs) are like the next generation of lipid-based carriers and are the major topic of discussion about them because they're eligible at delivering genetic material. LNPs are usually made of ionizable lipids, cholesterol, phospholipids, and PEG-lipids, which form a solid or semi-solid center. They are ideal for passing through the entire body and targeting the BBB because they are incredibly small (typically a wavelength of less than 100) and it can alter their surface charge.(6,31)

Ionizable lipids stay neutral at normal body pH, which means less toxicity, but they get a positive charge in acidic endosomes, helping them escape and release drugs inside cells. This is very helpful for getting compounds like siRNA, mRNA, and gene-editing molecules into the brain. Even with all these benefits, researchers are still working on making them more brain-specific, less likely to cause immune reactions with repeated doses, and safe for the long haul for large duration of administration.(33–35)

B. Polymeric Carriers (Nanoparticles, Micelles, and Dendrimers)-

Polymeric carriers are very versatile because there are so many biodegradable and biocompatible polymers which can be used to make carriers. We usually make polymeric nanoparticles from molecules like poly(lactic-co-glycolic acid) (PLGA), polycaprolactone, chitosan, and polyethylene glycol derivatives. These systems are great because they release drugs in a controlled and sustained way, make them more stable, and protect delicate drugs from breaking down.(36–38)

They can design polymeric nanoparticles with precise control over their size, surface charge, and instead of their hydrophobic nature, and all that affects their way of interaction with and get across the BBB.

If modification occurs on their surface with targeting ligands or surfactants like polysorbate 80, it's been shown to help them get into the brain better by picking up apolipoproteins from blood plasma, kind of like natural lipoproteins work . These biomimetic methods have really boosted how well antiepileptic, anticancer, and anti-Alzheimer's drugs get delivered in animal studies. (31,39,40)

These small, self-assembling particles are called polymeric micelles, and they are composed of amphiphilic block copolymers.They have their water-hating core that can dissolve drugs that donot mix well with water, and a water-loving shell that keeps them stable in watery places. Their small size (usually 10–80 nm) is great for getting into the brain and not getting eliminated out swiftly.(8,41,42)

Micelles are very handy for delivering hydrophobic neurotherapeutics that donot get absorbed easily. Additionally , there are these smart micelles that release their chemicals when they sense changes in pH, redox conditions, or enzymes, which helps them deliver drugs right where they're needed in the brain . But, keeping micelles stable when they get diluted in the blood is still a challenge that must be overcome.(33,36,43)

Dendrimers are super branched, uniform macromolecules with a clear 3D shape. Their many surface groups let them carry large number of drugs, change their surface precisely, and interact with BBB receptors in multiple ways. Poly(amidoamine) (PAMAM) dendrimers are some of the most studied for getting molecules to the brain.(14,28,37)

Dendrimers look promising for getting small molecules, proteins, and nucleic acids across the BBB, especially in brain inflammation and neurodegenerative diseases. But we need to be careful about them being toxic, especially the higher-generation cationic ones, so we must really optimize their surface chemistry and how much it takes.(37,44)

C. Inorganic and Hybrid Nanocarriers-

Inorganic nanocarriers like gold nanoparticles, silica nanoparticles, iron oxide nanoparticles, and quantum dots have some great physical and chemical properties that make them stand out from organic systems. They're very stable, so they can tweak their size and shape, and they can even do double duty for imaging and therapy (they call that theragnostic).(7,45)

Gold nanoparticles are especially neat because they're easy to make, allow them to manipulate with their surface, and they're very biocompatible. Allow to attach drugs, peptides, or nucleic acids to their surfaces, and if addition of the right molecule, they can even help target the blood-brain barrier . Plus, their optical properties let us track where they reach in the body and amountof thementer the brain in real-time.(23,40)

Mesoporous silica nanoparticles have a big surface area and pore volume, so they can hold large number of drugs and release them slowly. If we change their surface with polymers or targeting ligands, they can get into the brain better and not be as toxic. But researchers still need to investigate how well they break down over time and if they build up in the brain.(46)

Scientists have also viewed at iron oxide nanoparticles for delivering drugs to the brain with magnets.Additionally, they can aid in diagnosis and treatment by acting as contrast substances in MRIs.To achieve the best for each world, hybrid nanocarriers combine inorganic and organic materials. Consider lipid-polymer hybrid nanoparticles and metal nanoparticles coated with polymers. Compared to single-component systems, these have greater stability, release medications more effectively, in addition target more precisely. However, despite their potential, they are difficult to manufacture and get approved due to their complexity.(10,23,30,40,45)

D. Biomolecule-Based Systems (Peptides, Antibodies, and Exosomes)-

Biomolecule-based delivery systems use natural biological pathways to get across the BBB, which means they're very specific and do not create complexity within our body as much. Peptide-based carriers are made to interact with BBB transporters or cell membranes, helping them get into the brain. Researchers viewed l a lot at cell-penetrating peptides and receptor-targeting peptides for getting small and large molecules where they need to be provided.(12,38,44,47)

Peptides like angiopep-2 and TAT have shown they can get through the BBB well easily, either by attaching with receptors or by sticking to the cell surface and getting pulled in. They're small and easy to make, which is great, but they can get broken down by enzymes and clearup quickly, which might limit how useful they are in clinical uses.Antibody-based systems use monoclonal antibodies or antibody fragments that bind to BBB receptors like transferrin or insulin receptors. These antibodies act like tiny "shuttles," carrying attached drug cargos across the BBB. Antibody-drug conjugates and bispecific antibodies have looked really promising in preclinical models for brain tumors and lysosomal storage disorders.But, antibody-based delivery has related problems, like high production costs, immunogenicity, and not being able to carry a large number of drugs. Researchers are actively working on making smaller antibody fragments and making them bind better to get around these major issues.(17,25,46)

Exosomes are a new and exciting type of biomolecule-based nanocarriers. These natural extracellular vesicles are involved in cell-to-cell communication and can cross the BBB normally. Exosomes from stem cells or immune cells can be loaded with drugs, RNA, or proteins and tweaked to target specific areas better.Exosomes are promising for drug delivery since they come from our own bodies, making them compatible and less likely to cause immune problems and they also can naturally cross the blood-brain barrier, which is relevant for brain-related diseases and conditions. But before we can use them everywhere, we still need to figure them out to make them in large quantity, really understand them, and make sure they're always the same as the original eligible molecules to cross BBB.(44,48,49)

V. TARGETING AND TRANSPORT STRATEGIES

Delivering medicines to the brain is very hard because of that complex blood-brain barrier. So, to get around it, scientists have come up with some interesting ways to deliver the drugs in, like using the body's own transport systems or making drugs that react to the problems occur inside due to many reasons. The best mode right now are methods like receptor-mediated transcytosis, adsorptive-mediated transcytosis, and these "smart" delivery systems.(13,22)

Receptor-mediated transcytosis (RMT) is a very selective and natural way for molecules to get across the blood-brain barrier (BBB). Basically, drug molecules or tiny carriers get tricked out with special tags that hook onto specific receptors on the brain's blood vessel cells. We're talking about receptors like the ones for transferrin, insulin, low-density lipoprotein, and leptin. Once the tag latches on, the whole complex association gets binds into the cell in little bubbles, travels across the cell in those bubbles, and then bursts out on the brain's side.RMT is pretty good because it's specific, does not mess with our whole body as well as it is, and gets more of the good compounds into our brain. Scientists have looked into it for large duration of time for delivering molecules like peptides, proteins, nucleic acids, and nanoparticles. But there are some drawbacks, like the receptors getting fully occupied, other natural molecules competing for those receptors, and the receptors sometimes getting less active, which can create complexity with how well the mechanism get through. So, it's really important to get the right number of tags and use special antibodies or peptides that only target those specific receptors for RMT to work well.(1,18,21,34)

Adsorptive-mediated transcytosis (AMT) works by using electrostatic interactions instead of specific ligand-receptor binding. The inside surface of the brain's blood vessel cells has a negative charge because of molecules like glycocalyx and membrane phospholipids. So, any compounds with a positive charge, like molecules or tiny carriers, canbind to this surface without needing a specific cross matching, which then starts the process to get the molecules inside and move across.AMT is not as selective as receptor-mediated transcytosis (RMT), but it can move more compounds and doesnot have problems with receptors getting fully occupied. Scientists have studied this a lot with positively charged proteins, cell-penetrating peptides, and tiny charged nanoparticles. But, if something has too much positive charge, it can attract large numbersof plasma proteins, get eliminated out swiftly by our body's immune system, and even be toxic. So, systems based on AMT need to find a good balance between having enough positive charge to interact with our brain's blood vessels and being safe for our whole body as well.(12,14,38,44)

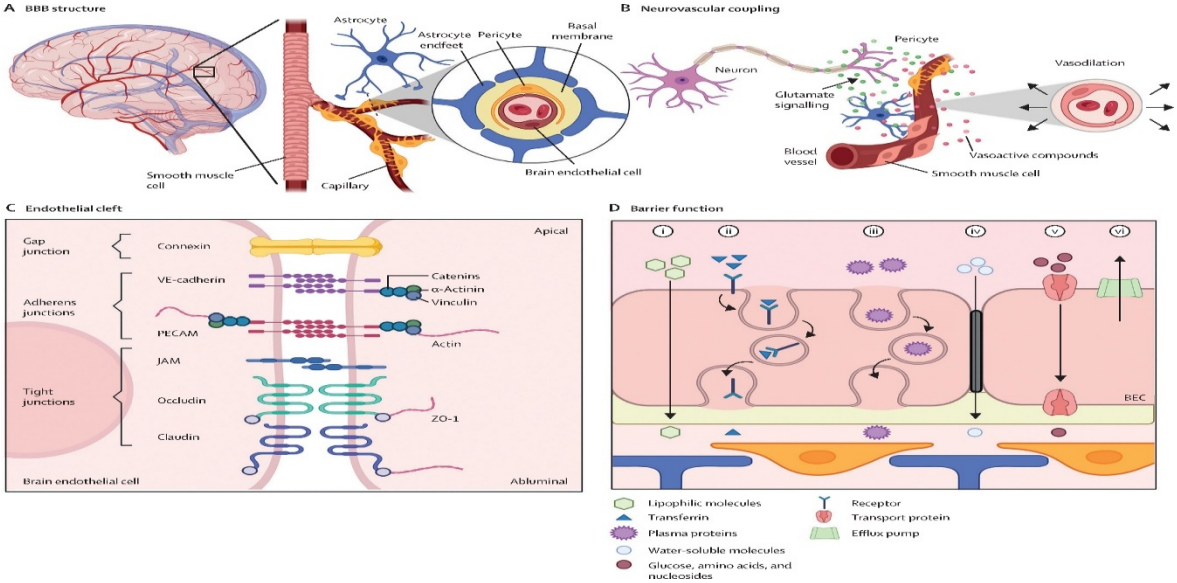


Fig no. 2 (32)

Stimuli-responsive or smart delivery systems are like the next level of brain-targeting strategies. They're built to change their physical and chemical properties or release drugs when they sense specific alterations inside or outside the body. Inside, that could be changes in pH, redox gradients, enzyme activity, or inflammation. Outside, it might be light, ultrasound, magnetic fields, or temperature.For instance, pH-sensitive nanoparticles can let them in your bloodstream but then released their drugs in the slightly acidic environment of sick brain tissue or inside cells. Redox-responsive systems use the higher glutathione levels inside cells to trigger drug release right where it's needed. Magnetic nanoparticles can even be guided across the blood-brain barrier with external magnets, helping them pile up in the desired site. These smart systems make treatments work better and help avoid side effects and toxicity throughout the body.(5,45,50)

VI. THERAPEUTIC APPLICATIONS AND TRANSLATIONAL PROGRESS

CNS disorders, like those neurodegenerative diseases and brain tumors, are some of the most challenging conditions in modern medicine. That's because they're very complex and the blood-brain barrier (BBB) makes it hard for drugs to get to the brain and to provide effect for cure. Old-school drug treatments mostly just help with symptoms, not actually fixing the disease itself. Lots of developments are really into new ways to deliver genes and RNA, hoping to fix diseases at their core and offer lasting relief. In diseases like Alzheimer's, Parkinson's, Huntington's, ALS, and SMA, there's growing proof that gene therapies and RNA-based methods can go straight for the bad genes or protein clumps. Gene therapy tools, like viral vectors (think AAVs) and non-viral molecules like lipid nanoparticles, have been tweaked to get past the BBB better and boost how much the brain takes in. Cool new CRISPR/Cas9 systems, ASOs, and microRNAs let us fine-tune gene expression, which means we might be able to fix disease-causing mutations and cut down on the toxic proteins linked to neurodegeneration. RNA therapies, like ASOs, siRNAs, and mRNA delivery, are looking very good for real-world use in its practical application. For instance, Spinraza (nusinersen) and Qalsody (tofersen) are already being used clinically for spinal muscular atrophy and ALS, showing that RNA molecules can totally work for brain and nerve problems. These treatments use the basic Watson-Crick pairing to shut down bad genes or boost good ones, which is great because regular small molecule drugs often can't get enough into the brain to perform their function. Gene and RNA therapies, like those using mRNA, lookvery good for brain tumors and other CNS cancers. They possess the capability to suppress oncogenic agents or stimulate the body's intrinsic defense mechanisms. We're seeing some gradual progress with mRNA, where it can reprogram immune cells or drop tumor suppressor genes right into the cancer cells. Although, tiny nanoparticles help deliver these treatments better, right where they're needed, and releasing them slowly. Even tinier carriers like liposomes and exosomes are being used to get these therapeutic nucleic acids across the brain's protective barrier and keep them from breaking down. In animal studies, these treatments have shown a lot of promises, cutting down on bad proteins and making the vehicles work better. But getting these new treatments out to everyone who needs them is still tough. We're encountering snags such as immune reactions to the delivery mechanisms, unintended side effects, and production scalability. Researchers are exploring innovative methods, like intranasal gene delivery to the brain, to bypass the blood-brain barrier without surgery. This could broaden accessibility and make treatments available to a larger population. A large number of clinical trials are happening right now, checking out gene and RNA therapies for brain disorders, which look good for getting them approved. Like, the AMT-130 gene therapy for Huntington's recently showed it could really slow down the disease in people who got it, which is a huge step forward. To get these therapies out there, we need to keep working on better delivery, sharper targeting, and a deeper dive into how our brains work.(5,8,27,29,33,34,41)

VII. SAFETY, CHALLENGES AND FUTURE PERSPECTIVES

Even though scientists made big strides in creating advanced drug delivery systems to get past the blood-brain barrier (BBB), safety and toxicity are still huge barriers for using them in clinical application. Nanocarriers – molecules like lipid nanoparticles, polymer systems, inorganic nanomaterials, and biomolecule-based vectors – can mess with biological systems in ways we don't always expect. Their size, how they're charged on the surface, what they're made of, and what they break down into all really affect where they go in the body, how cells take them up, and if they'll be toxic. If compounds that don’t break down build up in the brain or other organs, it could cause brain inflammation, oxidative stress, or long-term cell damage, which is a big worry for long-term treatments for brain diseases. Another huge issue is how they affect the immune system. Nanoparticles with modified surfaces, targeting molecules, or repeated doses can trigger immune responses, making them eliminate out of the blood faster or causing allergic reactions. Even natural carriers such as exosomes, typically well-tolerated by the body, may exhibit batch-to-batch variability and unforeseen biological effects contingent upon their origin. Also, strategies that temporarily affect with the BBB's integrity—like focused ultrasound or chemical permeabilizers—need to be very carefully tuned to keep toxins, pathogens, or inflammatory substances from getting into our brain.

From a regulatory angle, the rules for nanomedicines that target the BBB are still being figured out. The current toxicology guidelines are mostly for regular drugs and might not fully catch the risks specific to nanomaterials, like how they move through our body differently, protein corona forming, and where they end up long-term. Regulatory folks want tons of lab, animal, and human safety data, but the differences between animal BBB models and human ones make it difficult to assess risk. Manufacturing hurdles—like making enough, making it the same every time, keeping it sterile, and quality control—also slow down getting regulatory approval and using them in clinics. Super precise engineering and designs inspired by nature are totally changing how we get drugs across the blood-brain barrier. Intelligent nanocarriers, which respond to various stimulus, are garnering significant interest. They are engineered to precisely release their therapeutic payload in response to specific triggers such as pH fluctuations, enzymatic activity, redox potential, or external modalities like ultrasound and magnetic fields. These methodologies have the potential to substantially enhance therapeutic efficacy and mitigate adverse effects by enabling targeted and spatiotemporally controlled drug delivery.At the same time, scientists are getting constantly interested in delivery systems that mimic biology, especially compounds like membrane-coated nanoparticles and exosomes. These compounds use our body's own transport methods, which means they're better at being recognized by cells, avoiding our immune system, and getting through the blood-brain barrier. Although, new ways to tweak things genetically and chemically have led to delivery systems with special ligands that can specifically target pathways like those for insulin, transferrin, and low-density lipoprotein receptors. All these cool new ideas are really pushing us towards smarter, more effective ways to get drugs to the brain in a clinical setting. (5,9,27,28,42,51)

VIII. CONCLUSIONS

The blood-brain barrier is a major obstacle when it comes to treating brain disorders, cause it's super selective and protective. While crucial for maintaining cerebral homeostasis, the BBB severely limits drug penetration, thereby necessitating the development of sophisticated delivery strategies. This review emphasizes how a deeper comprehension of the BBB's structural integrity, transport mechanisms, and molecular interactions has enabled the creation of delivery systems designed to overcome these biological obstacles.

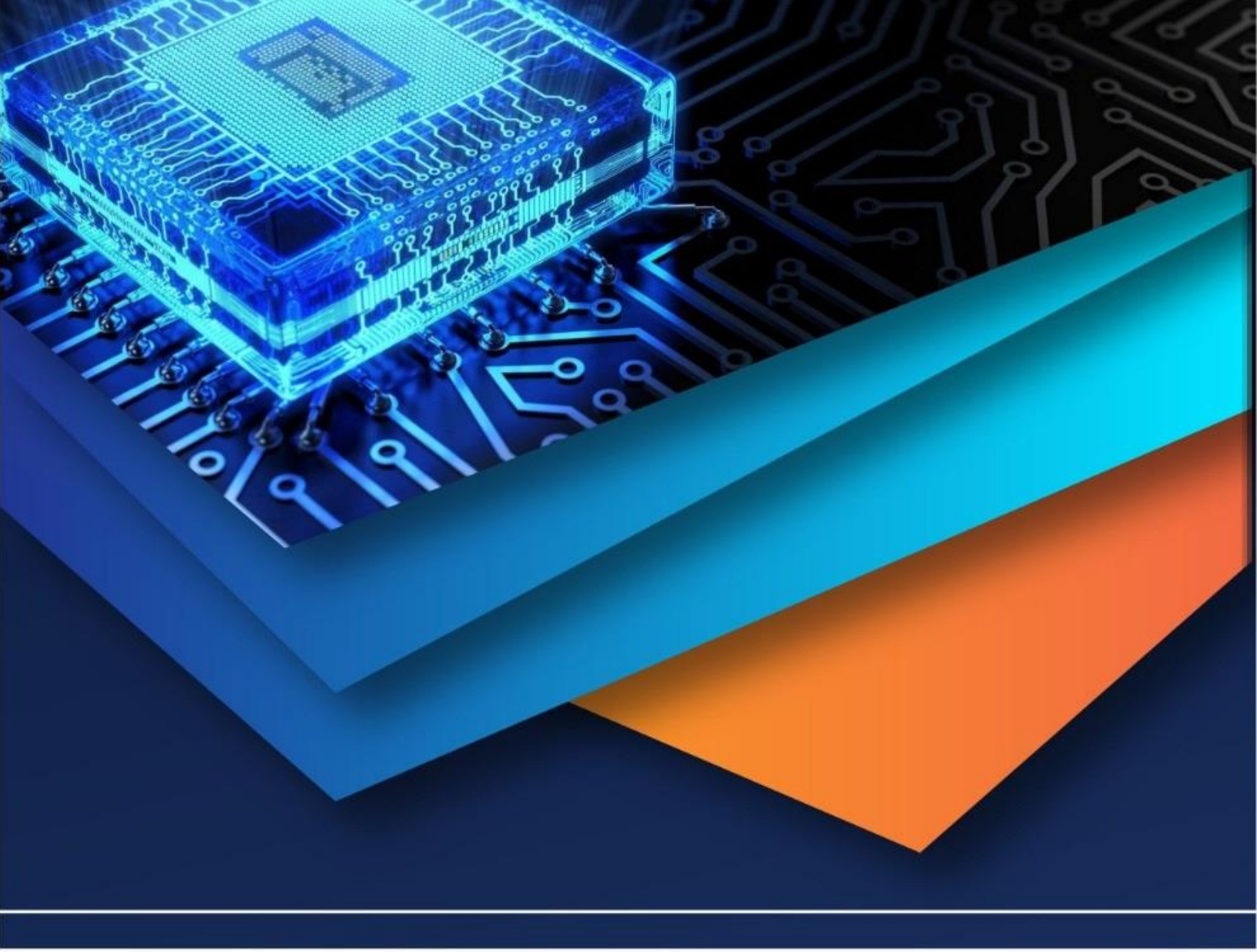
Recent advancements in molecular drug delivery, including lipid-based systems, polymeric carriers, inorganic nanocarriers, and biomolecule platforms, demonstrate considerable potential for transcending the BBB and enhancing therapeutic efficacy. A very new recent advancement in the research field for molecular vehicles to cross BBB is a peptide molecule with 4 amino acids which are discovered and are under trial procedure, if its outcomes are beneficial in relation to brain disorders, so it can be applicable for vast variety of disorders across the globe for everyone.

BIBLIOGRAPHY

[1] A Review of Blood-Brain Barrier Transport Techniques | Springer Nature Link (formerly SpringerLink) [Internet]. [cited 2025 Dec 29]. Available from: https://link.springer.com/protocol/10.1385/1-59259-419-0:193
[2] Pardridge WM. Blood–brain barrier delivery. Drug Discov Today. 2007 Jan 1;12(1):54–61.
[3] Mansor NI, Nordin N, Mohamed F, Ling KH, Rosli R, Hassan Z. Crossing the Blood-Brain Barrier: A Review on Drug Delivery Strategies for Treatment of the Central Nervous System Diseases. Curr Drug Deliv. 2019 Oct 1;16(8):698–711.
[4] Chen Y, Dalwadi G, Benson HAE. Drug Delivery Across the Blood-Brain Barrier. Curr Drug Deliv. 2004 Oct 1;1(4):361–76.
[5] de Boer AG, Gaillard PJ. Strategies to Improve Drug Delivery Across the Blood-Brain Barrier. Clin Pharmacokinet. 2007 July 1;46(7):553–76.
[6] Katz JS, Slika H, Sattari SA, Malla AP, Xia Y, Antar A, et al. Overcoming the Blood-Brain Barrier for Drug Delivery to the Brain. ACS Omega. 2025 Aug 5;10(30):32544–63.
[7] Silva GA. Nanotechnology approaches to crossing the blood-brain barrier and drug delivery to the CNS. BMC Neurosci. 2008 Dec 10;9(3):S4.
[8] Pardridge WM. Advanced Blood–Brain Barrier Drug Delivery. Pharmaceutics. 2023 Jan;15(1):93.
[9] Upadhyay RK. Drug Delivery Systems, CNS Protection, and the Blood Brain Barrier. BioMed Res Int. 2014;2014(1):869269.
[10] Li X, Tsibouklis J, Weng T, Zhang B, Yin G, Feng G, et al. Nano carriers for drug transport across the blood–brain barrier. J Drug Target. 2017 Jan 2;25(1):17–28.
[11] Dong X. Current Strategies for Brain Drug Delivery. Theranostics. 2018 Feb 5;8(6):1481–93.
[12] Novel delivery methods bypassing the blood-brain and blood-tumor barriers in: Neurosurgical Focus Volume 38 Issue 3 (2015) Journals [Internet]. [cited 2025 Dec 29]. Available from: https://thejns.org/configurable/content/journals$002fneurosurg-focus$002f38$002f3$002farticle-pE10.xml?t:ac=journals%24002fneurosurg-focus%24002f38%24002f3%24002farticle-pE10.xml&t:ac=journals%24002fneurosurg-focus%24002f38%24002f3%24002farticle-pE10.xml
[13] The blood-brain barrier. Transport across the cerebral endothelium. | Circulation Research [Internet]. [cited 2025 Dec 29]. Available from: https://www.ahajournals.org/doi/abs/10.1161/01.res.57.2.213
[14] Georgieva JV, Hoekstra D, Zuhorn IS. Smuggling Drugs into the Brain: An Overview of Ligands Targeting Transcytosis for Drug Delivery across the Blood–Brain Barrier. Pharmaceutics. 2014 Dec;6(4):557–83.

[15] Physiology of the Blood–Brain Barrier and Mechanisms of Transport Across the BBB. In: Nanotechnology-Based Targeted Drug Delivery Systems for Brain Tumors [Internet]. Academic Press; 2018 [cited 2025 Dec 29]. p. 49–74. Available from: https://www.sciencedirect.com/science/chapter/edited-volume/abs/pii/B9780128122181000038
[16] Blood–brain barrier dysfunction in multiple sclerosis: causes, consequences, and potential effects of therapies - The Lancet Neurology [Internet]. [cited 2025 Dec 29]. Available from: https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(23)00377-0/abstract
[17] Pardridge WM. Blood-Brain Barrier and Delivery of Protein and Gene Therapeutics to Brain. Front Aging Neurosci [Internet]. 2020 Jan 10 [cited 2025 Dec 29];11. Available from: https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2019.00373/full
[18] Scherrmann JM. Drug delivery to brain via the blood–brain barrier. Vascul Pharmacol. 2002 June 1;38(6):349–54.
[19] A Unique Carrier for Delivery of Therapeutic Compounds beyond the Blood-Brain Barrier | PLOS One [Internet]. [cited 2025 Dec 29]. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0002469
[20] Cornford EM, Hyman S. Blood–brain barrier permeability to small and large molecules. Adv Drug Deliv Rev. 1999 Apr 5;36(2):145–63.
[21] Tsuji A, Tamai I. Carrier-mediated or specialized transport of drugs across the blood–brain barrier. Adv Drug Deliv Rev. 1999 Apr 5;36(2):277–90.
[22] Characteristics of compounds that cross the blood-brain barrier | BMC Neurology [Internet]. [cited 2025 Dec 29]. Available from: https://link.springer.com/article/10.1186/1471-2377-9-S1-S3
[23] Design and Development of Nanomaterial-Based Drug Carriers to Overcome the Blood–Brain Barrier by Using Different Transport Mechanisms [Internet]. [cited 2025 Dec 29]. Available from: https://www.mdpi.com/1422-0067/22/18/10118
[24] Sugiyama Y, Kusuhara H, Suzuki H. Kinetic and biochemical analysis of carrier-mediated efflux of drugs through the blood–brain and blood–cerebrospinal fluid barriers: importance in the drug delivery to the brain. J Controlled Release. 1999 Nov 1;62(1):179–86.
[25] Molecular Determinants of blood–brain Barrier Permeation: Therapeutic Delivery: Vol 6, No 8 [Internet]. [cited 2025 Dec 29]. Available from: https://www.tandfonline.com/doi/abs/10.4155/tde.15.32
[26] Multifunctional Nanocarriers for diagnostics, drug delivery and targeted treatment across blood-brain barrier: perspectives on tracking and neuroimaging | Particle and Fibre Toxicology [Internet]. [cited 2025 Dec 29]. Available from: https://link.springer.com/article/10.1186/1743-8977-7-3
[27] Chen Y, Liu L. Modern methods for delivery of drugs across the blood–brain barrier. Adv Drug Deliv Rev. 2012 May 15;64(7):640–65.
[28] Nanoparticle- and Liposome-carried Drugs: New Strategies for Active Targeting and Drug Delivery Across Blood-brain Barrier | Bentham Science Publishers [Internet]. [cited 2025 Dec 29]. Available from: https://www.benthamdirect.com/content/journals/cdm/10.2174/1389200211314060001
[29] Zheng X, Yang J, Hou Y, Fang Y, Wu K, Song Y, et al. Current non-invasive strategies for brain drug delivery: overcoming blood–brain barrier transport. Mol Biol Rep. 2023 Dec 21;51(1):25.
[30] Full article: Nanoparticle-Based Combinational Strategies for Overcoming the Blood-Brain Barrier and Blood-Tumor Barrier [Internet]. [cited 2025 Dec 29]. Available from: https://www.tandfonline.com/doi/full/10.2147/IJN.S450853#d1e221
[31] Vieira DB, Gamarra LF. Getting into the brain: liposome-based strategies for effective drug delivery across the blood–brain barrier. Int J Nanomedicine. 2016 Oct 18;11:5381–414.
[32] Glia | Neurobiology Journal | Wiley Online Library [Internet]. [cited 2025 Dec 29]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/glia.22960
[33] Crossing the Blood–Brain Barrier: Recent Advances in Drug Delivery to the Brain | CNS Drugs [Internet]. [cited 2025 Dec 29]. Available from: https://link.springer.com/article/10.1007/s40263-016-0405-9
[34] Drug Delivery Challenges in Brain Disorders across the Blood–Brain Barrier: Novel Methods and Future Considerations for Improved Therapy [Internet]. [cited 2025 Dec 29]. Available from: https://www.mdpi.com/2227-9059/9/12/1834
[35] Drug Delivery to the Brain Via the blood–brain Barrier: a Review of the Literature and Some Recent Patent Disclosures: Therapeutic Delivery: Vol 2, No 3 [Internet]. [cited 2025 Dec 29]. Available from: https://www.tandfonline.com/doi/abs/10.4155/tde.11.3
[36] Mechanism of polymeric nanoparticle-based drug transport across the blood-brain barrier (BBB): Journal of Microencapsulation: Vol 30, No 1 [Internet]. [cited 2025 Dec 29]. Available from: https://www.tandfonline.com/doi/abs/10.3109/02652048.2012.692491
[37] Potential Use of Polymeric Nanoparticles for Drug Delivery Across...: Ingenta Connect [Internet]. [cited 2025 Dec 29]. Available from: https://www.ingentaconnect.com/content/ben/cmc/2013/00000020/00000017/art00006
[38] Hosoya K ichi, Ohtsuki S, Terasaki T. Recent advances in the brain-to-blood efflux transport across the blood–brain barrier. Int J Pharm. 2002 Nov 6;248(1):15–29.
[39] Drug Delivery Across the Blood–Brain Barrier: A New Strategy for the Treatment of Neurological Diseases [Internet]. [cited 2025 Dec 29]. Available from: https://www.mdpi.com/1999-4923/16/12/1611
[40] Emerging blood–brain-barrier-crossing nanotechnology for brain cancer theranostics - Chemical Society Reviews (RSC Publishing) [Internet]. [cited 2025 Dec 29]. Available from: https://pubs.rsc.org/en/content/articlelanding/2023/ea/c8cs00805a/unauth
[41] Gabathuler R. Approaches to transport therapeutic drugs across the blood–brain barrier to treat brain diseases. Neurobiol Dis. 2010 Jan 1;37(1):48–57.
[42] Pardridge WM. BLOOD-BRAIN BARRIER DRUG TARGETING: THE FUTURE OF BRAIN DRUG DEVELOPMENT. Mol Interv. 2003 Mar 1;3(2):90.
[43] Full article: Targeted Drug Delivery to the Brain Using Magnetic Nanoparticles [Internet]. [cited 2025 Dec 29]. Available from: https://www.tandfonline.com/doi/full/10.4155/tde.15.56
[44] Pulgar VM. Transcytosis to Cross the Blood Brain Barrier, New Advancements and Challenges. Front Neurosci [Internet]. 2019 Jan 11 [cited 2025 Dec 29];12. Available from: https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2018.01019/full
[45] Tosi G, Duskey JT, Kreuter J. Nanoparticles as carriers for drug delivery of macromolecules across the blood-brain barrier. Expert Opin Drug Deliv. 2020 Jan 2;17(1):23–32.
[46] Ahn SI, Sei YJ, Park HJ, Kim J, Ryu Y, Choi JJ, et al. Microengineered human blood–brain barrier platform for understanding nanoparticle transport mechanisms. Nat Commun. 2020 Jan 10;11(1):175.
[47] Welch KM. Primer on Cerebrovascular Diseases. Gulf Professional Publishing; 1997. 862 p.
[48] Khatami SH, Karami N, Taheri-Anganeh M, Taghvimi S, Tondro G, Khorsand M, et al. Exosomes: Promising Delivery Tools for Overcoming Blood-Brain Barrier and Glioblastoma Therapy. Mol Neurobiol. 2023 Aug 1;60(8):4659–78.

[49] Burdo JR, Antonetti DA, Wolpert EB, Connor JR. Mechanisms and regulation of transferrin and iron transport in a model blood–brain barrier system. Neuroscience. 2003 Nov 7;121(4):883–90.
[50] Fong CW. Permeability of the Blood–Brain Barrier: Molecular Mechanism of Transport of Drugs and Physiologically Important Compounds. J Membr Biol. 2015 Aug 1;248(4):651–69.
[51] Bors LA, Erdő F. Overcoming the Blood–Brain Barrier. Challenges and Tricks for CNS Drug Delivery. Sci Pharm. 2019 Mar;87(1):6.



10.22214/IJRASET

45.98

IMPACT FACTOR: 7.129

IMPACT FACTOR: 7.429

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY