Review Article

Therapeutic Approaches of Nanotechnology for Epileptic Seizures: A Comprehensive Review of Current Knowledge

Aman Shrivastava[1,*], Jeetendra K Gupta[1], Manoj K Goyal[2]

[1]Department of Pharmacology, Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, INDIA.
[2]Jai Institute of Pharmaceutical Sciences and Research, Gwalior, Madhya Pradesh, INDIA.

ABSTRACT

Epilepsy is a chronic neurological condition in which several neurotransmitters act like neuromodulators. The symptoms of epilepsy are caused by abnormal electrical discharges in a group of neurons in the hippocampus region of the brain. This can also affect electrical impulse generation, either in the focal area or in the hippocampus region of the brain. This review aimed to develop a better understanding of the transportation of nanoparticles across the blood-brain barrier and how to enhance the delivery of the drug in epileptic conditions by the utilization of nanomaterials. A few clinical studies have reported that antiepileptic drugs are generally used for the treatment of epilepsy by decreasing the frequency and intensity of seizures or preventing tissue damage in the brain. In long-term therapy, antiepileptic drugs are primarily administered via the oral route, but they are not always beneficial. Therefore, intravenous routes are especially used in serious epileptic conditions. In this review, we discussed the drug delivery study of antiepileptic drugs that are used in the form of nanoparticles that can easily be transported across the blood-brain barrier. Besides, the nanoparticles can easily cross the blood-brain barrier and increase the uptake into the target cells. Drug absorption into the brain is substantially limited by some factors, especially in the blood-brain barrier, which affects the potency of antiepileptic drugs to reach and remain inside the brain. Novel drug delivery systems have already been studied in many clinical trials to enhance the therapeutic efficacy of antiepileptic drugs in epileptic conditions.

Keywords: Epilepsy, Nanotechnology, Drug delivery, Movement of nanoparticle, Neurodegenerative disorder.

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Correspondence:
Mr. Aman Shrivastava
Research Scholar,
Department of Pharmacology,
Institute of Pharmaceutical Research, GLA University,
17 Km Stone, NH-2,
Post Chaumuhan,
Mathura-281406,
Uttar Pradesh, INDIA.
E-mail: amanipsgwl@gmail.com

INTRODUCTION

Epilepsy is the fourth most common neurodegenerative and severe neurological condition causing migraines and stroke.[1] An epileptic condition is described by unusual electrical signal discharges in a group of neurons inside the brain, which can also lead to either partial or generalized seizures.[2] The sudden attack of epileptic seizures mainly affects the hemisphere region of the brain. When two or more unjustified seizures occur, the person can also be identified with epilepsy.[3] Epilepsy etiology is often identified after diagnosis, but in a few conditions where it is difficult to identify the preliminary triggers. Treatment depends on the state of epilepsy in which other conditions also develop, including the age of the patient, therapeutic efficacy of epileptogenic drugs as well as the presence of adverse effects in the patient.[3] Epilepsy is not a specific condition with a wide range of neurodegenerative disorders that can also trigger different types of other problems like (depressed mood, anxiety, learning difficulties, attention problems, Impaired impulse control, learning disabilities, and schizophrenia).[4] The Parenteral route of administration is also used in the case of an emergency condition or even during chronic care of a patient.[5] Future applications of biochips, immune nanoparticles (NPs), bioreactors, biodegradable polymers, neural

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stem cells, and convection-enhanced drug delivery are being investigated for the diagnosis and treatment of diseases.[6] Scientists have recently achieved various therapeutic effects of antiepileptic drugs (AEDs) and increased their potency in epileptic patients.[7,8] Neurology has obtained a great interest in the study of nanostructured materials interacting with the central nervous system, and high-resolution imaging techniques for early detection. Besides, the nanomaterial has advanced features such as high biological and chemical stability, the feasibility of incorporating into both hydrophilic and hydrophobic molecules that can be delivered through a variety of outlets, including oral, parenteral, and inhalation routes.[9] The nanoparticles (NPs) are easily transported across the blood-brain barrier (BBB), where drug delivery systems have improved. This academic review is designed to look at the role of nanotechnology in the treatment of serious health problems, including epileptic conditions, cancer, infections, metabolic disorders, autoimmune disorders, and inflammatory conditions.[10] The therapeutic efficacy of drugs also depends on the delivery of NPs to the particular site of the central nervous system (CNS).[5] The mechanism of drug delivery can be achieved by the use of nanotechnology, which can enhance the pharmacological effect of the medicine.[11] Generally, drugs bind to a particular receptor, then show their therapeutic effect, but sometimes the drug molecules do not bind to the receptor properly. As a result, NPs is a biocompatible material that aids in drug delivery to the site of action or improves the pharmacodynamic effect.[12] The development of the carrier's system also helps to improve the therapeutic efficacy of a drug. Sometimes the drug molecule is not able to stabilize at the site.[4] The NPs help to influence the slow release of drug metabolism and their therapeutic efficacy. In below, (Figure 1) is represented nanoparticle molecule with BBB. The biocompatible material used in nanotechnology can also improve patient compliance for those who are suffering from epilepsy.[13] In epileptic conditions, the

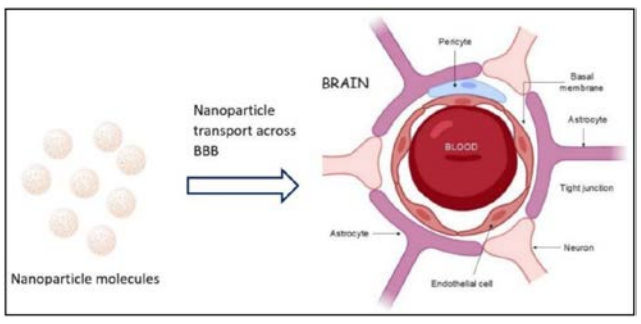

Figure 1: Nanoparticle and Blood-brain barrier.[15]

hemisphere of the brain produces abnormal electrical impulses in which stimulation and suppression of some neurotransmitters are also responsible for causing epilepsy. Barriers protect the nervous system from toxins and metabolic disturbances, among which the BBB plays a crucial activity in the regulation of homeostasis.[14]

Epidemiology

According to the World Health Organization, more than 50 million people around the world suffer from epilepsy, with over 80% of people living in low-and middle-income nations. But adequately diagnosed and treated, an estimated 70% of people with epilepsy could be seizure-free.[15] Various therapeutic strategies that are helpful for the regulation of epileptic conditions have already been developed. The treatment of epilepsy by the use of nanomaterials can help to recover more patients from seizures or significantly improve their quality of life.[9] The purpose of Nano-medicine is to reduce the therapeutic limitations of its application, improve understanding of the neurodegenerative disorder or basis of the disease, and provide more advanced diagnostic tools to create more effective therapies and defensive properties.[14,15] The Nano-medicine field of science and technology is primarily used to improve the diagnosis, treatment, and prevention of neurological diseases associated with major trauma conditions, as well as to maintain human health through the use of standardized nanoscale materials, biotechnology, and gene therapy.[15,16]

Pathophysiology of epilepsy

Epilepsy is a progressive chronic condition of the CNS in which the activity of nerve cells in the brain is affected by an excitatory neurotransmitter.[13] Recurrent seizures and episodic seizures with irregular behavior and sometimes lack of understanding are the highest occurrences in both males and females.[17] Anti-epileptic drug delivery in systemic circulation indicates that 90% of the active substances can be ineffective after the administration and distribution of AEDs to the brain.[18] There can also be significant potential side effects. Each neurotransmitter has the essential properties of changing neuronal activity in the hippocampal region of the brain and neurotransmitters also have the prime priorities for the analysis of the causes and treatment of epilepsy.[7] Neurotransmitters caused by ion-induced changes in the neuronal membrane cause a cell that is less excitable due to inhibition of post-synaptic potentials (IPSPs) or even more excitable due to excitatory postsynaptic potentials (EPSPs).[13] Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter that plays a major

role in epilepsy. In certain situations, the presynaptic potential activity of neuronal cells may decrease the postsynaptic potential in the cell by the release of GABA neurotransmitters.[19] The discharge intensity of the transmitters depends on the depolarization of the presynaptic terminals by which excitability can affect synaptic activation. In anticonvulsant activity, three main categories of pathways are already known: Ion channel regulation, which enhances the activity of inhibitory and excitatory neurotransmission Ca^+ and Na^+ channels have the most impact on ion channels.[20] This involvement increases the concentration of GABA in the CNS and focuses primarily on the reduction of glutamate and the neurotransmission of aspartate.[1,2] Anticonvulsant drugs are divided into three generations. Between 1857 and 1958, the first-generation entry into the market contained potassium bromide, phenobarbital (PB), and several other primarily derivative improvements that occurred in the composition of barbiturates, such as ethosuximide, phenytoin, and trimethadione. In 1960 and 1975, the second generation of AEDs involved valproate, benzodiazepine, carbamazepine, and some other barbiturates. The Tiagabine drug is designed to target the mechanism considered relevant by the third generation of AEDs for the prevention of epileptic seizures.[2,7]

Limitation of AEDs for the treatment of epilepsy

- Treatment of acute and chronic seizure disorders requires the use of AEDs by various routes.[6]
- Various categories of drugs have epileptogenic potential. These drugs may influence the epileptogenesis process in the brain and may be responsible for the causing of epilepsy.[1]
- The parenteral route is used when the response is not seen by the oral administration after that rapid clinical response is required for improving the patient's condition.[21]

MOVEMENT OF NANOPARTICLES ACROSS THE BLOOD-BRAIN BARRIERS (BBB)

Controlled drug delivery of nanoparticles to improve therapeutic efficacy via the BBB as well as drug bioavailability in the hippocampus region of the brain. The proper drug delivery system also helps to improve the treatment of epilepsy in patients.[20] In general, BBB has a significant role in preserving homeostasis. It consists of four basic cellular elements: endothelial cells, astrocytes, pericytes, and the base membrane.[22] Various approaches have been studied for the delivery of anticonvulsant drugs directly into the central nervous system for the treatment of epileptic seizures.[9] Many other direct drug delivery systems require a specific technique that is used to prevent the distribution of seizures in specific or other hemisphere regions of the brain. The BBB acts as a protective barrier in the brain against a neurotoxic agent.[10] The BBB is a metabolic barrier while regulating the transfer of drug molecules according to their physiological properties between both the peripheral systemic circulation as well as within the whole brain. It is useful to distinguish a variety of enzymes that reduce metabolite concentration in the membrane of capillary endothelial cells of the brain associated with a large number of transporter proteins that primarily regulate the efflux and influx movement of molecules.[21] Although there are other barriers that play an important role in nanoparticle delivery, such as the CSF brain barrier (CBB), blood-brain barrier (BBB), the surface of the BBB is larger than the surface of the CBB. Therefore, it is known to be the primary site for crossing endogenous substances into the CNS.[23] Diffusion allows the movement of substances from CSF to the brain parenchyma. The passage of endogenous substances across the BBB is mediated by several mechanisms.[5] The brain has a high demand for nutrients and energy for molecule transportation. They also provide a beneficial framework for the analysis of drug delivery approaches. Substances can potentially pass through the BBB under physiological conditions, receptor-mediated transport, carrier-mediated transport, and adsorption ability through transcytosis.[2] Most substances are transported into the brain through carrier-mediated transport and receptor-mediated transport in Figure 2. In this case, the molecule structure has a high affinity for specific carriers or receptors.[9]

ROLE OF NANOPARTICLES AND LIPOSOMES (LPS)

Liposomes are also referred to as nanoparticles in Figure 4. They may be different in their structure or stability. The size of a liposome may be between a few nanometers to even up to 10 micrometers.[24] Generally, NPs are made up of solid materials, where the encapsulation system, like nanosomes, acts as a liposome that possesses only a single lipid monolayer.[6] Commonly, nanosomes are used in cosmetics. The size of the dense particles ranges from 1 to 1000 nm. NPs are made up of different types of polymers and encapsulating substances during the preparation phase. They are selected according to the polymers and the product to be delivered.[25] It is commonly defined that both structural and morphological parameters of the materials (surface load, size, shape) and the polymers

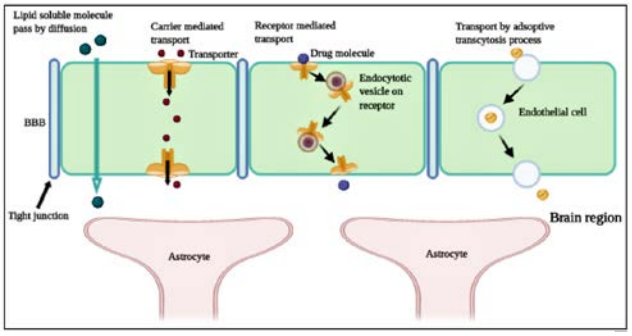

Figure 2: Transport processes across the blood-brain barrier. Drug molecules can cross BBB under physiological conditions through passive diffusion, carrier-mediated transport, receptor-mediated transport, and transport by transcytosis process.[2]

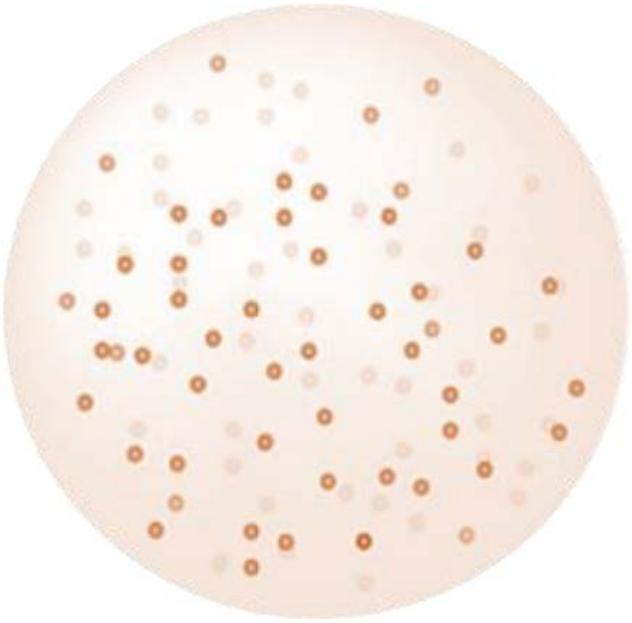

Figure 3: Polymeric NPs.[2]

used should be correlated with the toxicity study of Nanodevices that are already applied in various fields of medical research.[26] An overview of the first advanced successful treatment of complex pathologic diseases such as cancer, HIV, stroke, and many other diseases requiring selective therapy.[5] Besides, when LPs are injected into the bloodstream, removal and degradation are regulated, along with the shape and properties of phospholipids. A variety of techniques have been developed, such as the use of stabilizers or the shift in the initiation of interaction. Polymeric NPs also have a high capability to cross the phospholipid barrier of the cell.[21]

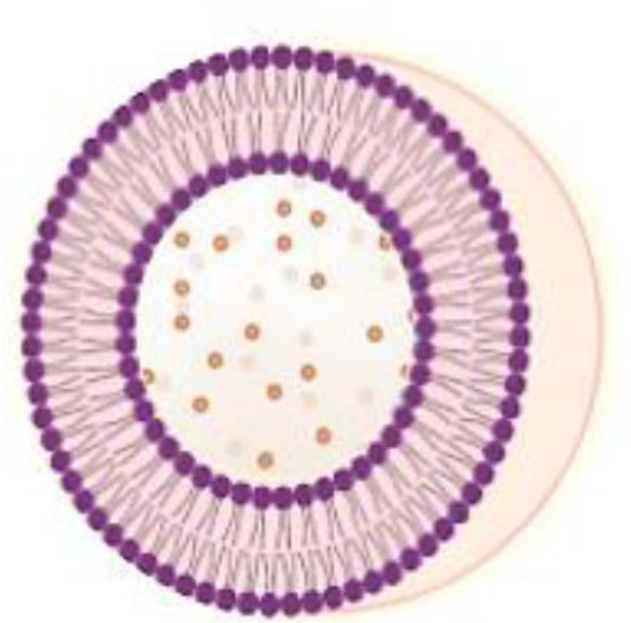

Figure 4: Liposomes LPs.[2]

ENHANCEMENT OF AEDS DELIVERY TO THE BRAIN

Antiepileptic medicinal products are normally administered by intravenous and oral routes.[22] Several biological factors significantly reduce the entry of drugs to the brain, especially the BBB, which disrupts the potency of the drug molecule to reach and remain inside the brain.[27] Advanced nanotechnology techniques are helping to improve the entry of nanomaterials into the brain, especially in the case of emergency conditions.[28] There are various nanomaterials or liposomal substances that can enhance drug delivery in the brain. New drug delivery techniques were also developed to enhance the efficacy of AEDs.[2] These approaches are divided into three categories: drug modification, drug transportation enhancement into the blood-brain barrier, and nanomaterial delivery enhancement.[26] The following techniques may increase drug penetration and efficacy across the BBB, increasing the drug's therapeutic potency in epileptic disorders.[14]

a) Modification of Drug

Another option is to bring AEDs into the brain that encapsulate desorption, immersion, and polymer degradation or oxidation that occurs within the delivery region of nanostructures.[29] Some factors also decrease the potency of the active constituent, such as the molecular weight and degradation phase of the particle that influence the release rate of the drug.[2] It can also occur within a few hours or days.[9] The drug products can be modified in the form of prodrugs, LPs, and polymeric NPs in Figure 3. Prodrugs are

important in the treatment of epilepsy because they help to improve the epileptic condition.[26] Prodrugs are made from a material bound to a separate compound that can be obtained *in vivo* by enzyme cleavage or hydrolysis. Prodrugs generally show their therapeutic effect by the release of the dosage form with the release of certain supplements or derivatives.[30] The attached enzymes can make the substance much more lipophilic, thus enhancing its ability to cross the BBB. Once the seizure begins, inappropriate activation of the prodrug is significantly decreased because the activity of the enzyme is reduced, while neuronal excitement can also occur.[28] Systemic toxicity is reduced by limiting prodrug efficacy or minimizing the seizure intensity in the brain.[2] In LPs, they are self-assembled structures with the physiological plasma membrane and its properties. The middle core of the aqueous membrane is surrounded by a singular or several bilayer phospholipids in Figure 5.[6] During the entry of liposomes into the cell or by the transfer of drug into the extracellular fluid, LPs have to deliver drugs to cells and subsequent delivery of the drugs via the plasma membrane. LPs range generally from approximately 50 nm to 1 nm in diameter.[8] The specific structure of aqueous and lipid components allows hydrophilic, amphiphilic, and hydrophobic drugs to be encapsulated within the properties of LPs.[17] Polymeric nanoparticles (NPs) function as a stealth polymer and play an important role in drug release.[1] Encapsulation of drugs into LPs or NPs prevents *in-vivo* degradation of drugs and reduces toxic effects, while normal NPs and LPs are eliminated from the plasma.[18]

b) Enhancement of the transportation of drugs into the blood-brain barrier

The proper transportation of NPs across the BBB enhances the therapeutic efficacy of the drug. In this state, the tight junction can inhibit or prevent the transportation of drugs.[26] The NPs have high permeability, allowing them to pass through the membrane. An alternative strategy for improving transport across barriers is the Efflux Pump.[8,10] The BBB is associated with the delivery of drugs with manipulations that initially alter the permeability of the barrier. These apical membranes of endothelial cells help ABC transporters hydrolyzed by the transfer of molecules into the circulation against their concentration gradients. Such transporters are also able to affect the efficiency of drug distribution within the CNS.[10] As a potential way of improving the efficacy of anticonvulsant therapy in such patients, the binding of ABC transporters in the specific region of the brain has already been reported.[23] Probenecid is injected intracranially into the cortex 30 min before phenytoin

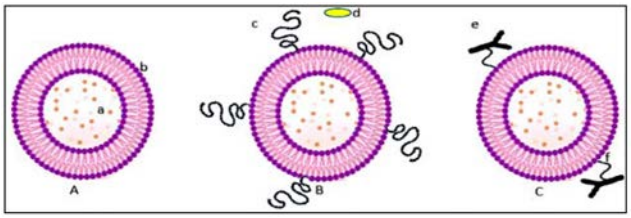

Figure 5: Structure of liposomes and modifications for improving the diffusion process of the BBB: A: Hydrophilic drugs (a) can be immersed inside the aqueous center of the LPs with lipophilic drugs, and (b) can be integrated into the bilayer of lipids or Polyethylene glycol (PEG).[2] B: Stealth Polymeric molecule, (c) the liposome surface can be conjugated with adsorption of protein and can prevent, (d) results in a rise in plasma blood circulation.[22] C: ligands may be added directly to the surface to directly control the liposome into and around the BBB.[9] (e) Along with the edge of the PEG chain, (f) the binding is desirable because it can cause direct surface conjugation.[29]

is injected intraperitoneally.[31] The concentration of phenytoin in extracellular fluid in the brain was significantly increased by Probenecid treatment.[14]

c) Improvement of direct drug delivery

Direct drug delivery can help to enhance the efficacy of drugs in a specific system. Besides, the delivery of AEDs via blood capillaries.[16] It is important to deliver them directly through the aorta to the brain parenchyma. Injections or implants are mainly used.[9] Adenosine was injected in the study of antiepileptic effects in which various methods are involved in drug delivery.[6] The average spike frequency develops but the strength is not reduced by intracerebroventricular injection of 100g adenosine approximately 20 min after administration, and the results have decreased with both frequency and amplitude of the molecule. In intranasal (IN) administration, the basic structural, physiological, and histological features of the nasal cavity give rise to involvement in the intranasal route for medicinal purposes.[31] In fact, with the use of the nasal cavity, several clinical applications can be achieved. The olfactory neuro-epithelium is the only brain region that has direct interaction with both the CNS and the external environment to improve its therapeutic ability.[6] The efficacy of the intranasal route has been reported in many clinical trials. Deferoxamine is an effective generic drug.[9] Prof. Frey and his colleagues discovered that the (IN) deferoxamine molecule bypasses, via iron-binding with drugs, the BBB and prevents brain damage during the study of animal models of Alzheimer's, Parkinson's, stroke, and some other neurodegenerative disorders.[5,6] In humans, a safe clinical assessment of deferoxamine was performed, and no serious other adverse effects were identified.[20,21]

CLINICAL APPLICATION OF NANOTECHNOLOGY

Clinical application of nanotechnology raises the therapeutic efficacy of the drug during clinical trials. Nanomaterials can deliver drugs across the BBB via nanoparticles.[32] In many other scientific and neuroscience fields, such as biomedical applications, DNA/genomic sensors are used. The additional advantages of nanotechnologies being used for the treatment of both CNS and peripheral conditions are major and can theoretically be distinguished from the emerging clinical opportunities for patients and health care staff.[16] It is useful that technical advances in scientific and surgical neuroscience have already been developed.[2] As a result, nanotechnology has a variety of potential applications in neurology and neurosurgery.[23,27] Recently, a study of animals has shown a progressive effect on both multiple sclerosis and autoimmune sclerosis resulting in encephalitis by Nano droplet administration made by pomegranate seed oil formulation.[15]

DISCUSSION

On the basis of the above discussion, it is clear that nanotechnology can be applied to things such as imaging, diagnosis, delivery of drugs, regenerative safety, and the prevention of multiple pathological conditions. Nanotechnology makes a major contribution specifically to drug delivery by increasing pharmacological outcomes, therapeutic efficacy, therapeutic activity, and improving the regulation of drug release rates as well as influencing drug penetration across the BBB. The adverse effects of some AEDs can develop neurotoxicity but occur only in rare cases. Modification of the BBB can also reduce systemic toxicity in the human body. The symptoms of epileptic seizures can also have a progressive harmful effect and these are treated well by the proper use of nanomaterials. Nanomaterials can easily be transported through various mechanisms, and receptors carry NPs and help to enhance the therapeutic efficacy of AEDs. A few clinical studies have already reported that NPs can progressively increase the permeability of drug molecules across the BBB and influence drug delivery in the central nervous system. AEDs are generally developed by nanotechnology in which patient compliance has also improved. LPs play a key role in the delivery of the drug to the brain. Further study is required to evaluate the particular mechanism of nanoparticle transport through the BBB. We can also investigate the neuroprotective effect of nanomaterials on the brain.

CONCLUSION

In conclusion, epilepsy generally occurs due to continuous excessive electrical discharge in a group of neurons in the brain. AEDs are primarily administered via the oral route, but they are not always beneficial. Therefore, intravenous routes are especially used in serious epileptic conditions. NPs can easily cross the BBB and increase the permeability of the barrier. The BBB has a significant role in preserving homeostasis. It consists of four basic cellular elements: endothelial cells, astrocytes, pericytes, and the base membrane. The BBB protects the brain from neurotoxic agents by acting as a protective barrier. Diffusion allows the movement of substances from CSF to the brain parenchyma. The passage of endogenous substances across the BBB is facilitated by several mechanisms. The brain requires a high demand for nutrients and energy for the transportation of molecules. Advanced nanotechnology techniques are helping to improve the entry of nanomaterials into the brain, especially in the case of emergency conditions.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AEDs: Anti-epileptic drugs; **BBB:** Blood-brain barrier; **NPs:** Nanoparticles; **LPs:** Liposomes; **CNS:** Central nervous system; **GABA:** Gamma-aminobutyric acid; **PEG:** Polyethylene glycol; **IN:** Intranasal.

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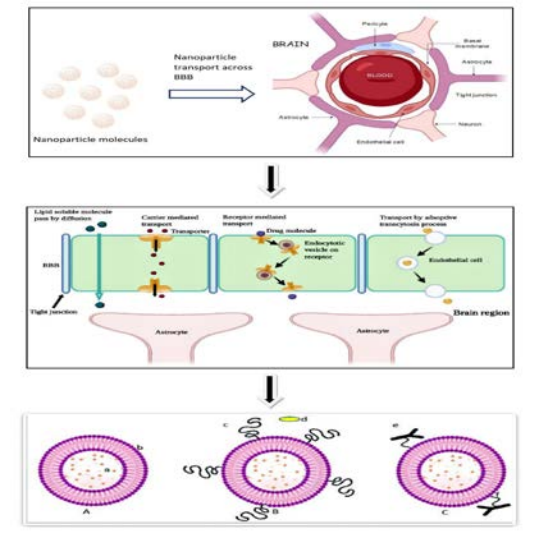
PICTORIAL ABSTRACT



SUMMARY

- The topics covered in this review article were summarized after extensive search on drug delivery studies of antiepileptic drugs that are used in the form of nanoparticles that can easily be transported across the blood-brain barrier.
- Drug absorption into the brain is substantially limited by some factors, especially in the blood-brain barrier, which affects the potency of antiepileptic drugs to reach and remain inside the brain.
- Nanomaterials can easily be transported through various mechanisms, and help to enhance the therapeutic efficacy of AEDs.
- The key role of this review article was to bring light over nanoparticles and their application in various epileptic conditions. This article may help researchers in their work on nanotechnology in epilepsy.

About Authors

Mr. Aman Shrivastava is an Assistant Professor at Institute of Professional Studies, College of Pharmacy, Gwalior, Madhya Pradesh, India, for the last 03 years. He is currently pursuing his Ph.D. from G.L.A University, Mathura, Uttar Pradesh, India. He is working in the areas of Pharmaceutical Sciences, neurological disorders, and pharmacology. He has 02 publications in Scopus and has been actively engaged in pharmacology and neurological research fields.

Dr. Jeetendra Kumar Gupta is currently Assistant Professor in Institute of Pharmaceutical Research, GLA University, Mathura, has been actively engaged in Pharmacology and Toxicology research and teaching for last 15 years. He has been eminent contributor of many review and research papers in journals of international repute.

Dr. Manoj Kumar Goyal is currently Principal in Jai Institute of Pharmaceutical Sciences and Research, Gwalior, Madhya Pradesh, India.

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