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Review article

NANOTECHNOLOGY-BASED NEURO-THERAPEUTICS FOR THE TREATMENT OF EPILEPSY

Santa Sarma*

Department of Pharmaceutical Sciences, Faculty of Science and Engineering, Dibrugarh University, Dibrugarh 786004, Assam, India

Abstract

Epilepsy, characterized by abnormal brain electrical activity, manifests as generalized or partial seizures originating from widespread or localized cerebral involvement, respectively. Treatment primarily involves administering antiepileptic drugs (AEDs) to control seizure frequency and severity while minimizing adverse effects. However, drug resistance and systemic toxicity remain significant challenges, necessitating innovative delivery systems. Nanotechnology-based approaches offer promising solutions by enabling targeted drug delivery across the blood-brain barrier (BBB), thereby enhancing drug efficacy and reducing peripheral toxicity. Various nanoparticle carriers, such as polymeric nanoparticles, liposomes, polymeric micelles, dendrimers, carbon nanotubes, nano-emulsions, solid lipid nanoparticles, and magnetic nanoparticles, have been explored for their ability to encapsulate and deliver AEDs to specific brain regions. Factors such as nanoparticle size, surface charge, and drug release mechanisms influence their efficacy in crossing the BBB and achieving sustained drug release. These advancements underscore nanotechnology's potential in revolutionizing epilepsy treatment through improved drug delivery systems that enhance therapeutic outcomes while minimizing systemic side effects.

Keywords: Epilepsy, Blood-brain barrier, Antiepileptic drug, Nanotechnology, Nanocarrier

Introduction

Epilepsy is characterized by abnormal electrical activity within the brain, which can result in either generalized or partial seizures. Generalized seizures are characterized by extensive involvement of both cerebral hemispheres. In contrast, partial seizures originate from a localized focus and are confined to specific regions of the brain. The presence of a focal lesion can occasionally be identified through electroencephalographic (EEG) readings and functional magnetic resonance imaging (fMRI), enabling the potential for targeted treatment to the affected region. In both generalized and partial seizures, the objective is to administer antiepileptic drugs (AEDs) to the brain in sufficient amounts to decrease the frequency and severity of seizures while minimizing adverse effects [1,2]. The current approach to seizure drug therapy involves achieving high levels of antiepileptic drugs (AEDs) in the blood, either through oral administration of pills or intravenous injections. Despite advancements in epilepsy treatment, the quality of life for patients with this disorder remains suboptimal. A significant challenge is drug resistance and the recurrence of epilepsy following the reduction of medication. Most antiepileptic drugs (AEDs) are administered either orally or intravenously [2]. Up to 40% of patients develop drug resistance during later stages of treatment, leading to uncontrolled seizures, an elevated risk of brain damage, and increased mortality rates [5]. Patients exhibit emotional and behavioral alterations, seizures, convulsions, muscular spasms, depressive symptoms, and, in certain instances, loss of consciousness [6]. Drug-resistant epilepsy presents a significant health challenge. Epilepsy

*Correspondence: Santa Sarma [E-Mail: sarma.santa99@gmail.com]

medications often have poor bioavailability and tend to become ineffective over time due to the development of drug resistance. Treating epilepsy is often complicated by the inability of available antiepileptic drugs (AEDs) to cross the blood-brain barrier (BBB). This challenge could be addressed through the development of appropriate drug delivery systems. The ideal system would enable localized and controlled release of antiepileptic drugs (AEDs) to targeted sites in the brain, reducing drug-associated toxicities and enhancing the drugs' efficacy. Numerous strategies for the effective delivery of antiepileptic drugs (AEDs) have been documented in the scientific literature. Nanotechnology-based systems appear to be a promising and innovative development in this field. Recently, several nanostructure drug delivery carriers have been reported as effective central nervous system (CNS) delivery systems. These carriers address the issue of antiepileptic drug (AED) elimination at the blood-brain barrier (BBB), resulting in increased drug persistence **[7]**.

Nanotechnology-based medicine (nano-medicine) involves the characterization and design of nano-carriers' surface properties for various medicinal strategies. Therapeutic agents are incorporated into or coated onto nano-carriers, which are small colloidal or compact structural platforms ranging in size from 1 to 1000 nanometers [8,9]. These nano-platforms (NPs) easily interact with the cellular environment at the molecular level, eliciting the desired physiological response. Nanotechnology-based antiepileptic drugs (AEDs) have recently garnered attention due to their ability to cross the blood-brain barrier (BBB), improved selectivity, and potential for sustained drug delivery to the brain. The effectiveness of nanoparticles (NPs) is influenced significantly by factors such as size, molecular weight, copolymer ratio, erosion mechanism, and surface charge. For instance, nanoparticle (NP) size significantly determines its efficiency in crossing the blood-brain barrier (BBB); NPs ranging from 35 to 64 nm can readily access most neural tissues [10,11]. Synthesis of size-specific nanoparticles (NPs) can be achieved through various preparation methods. Reducing the size of nanoparticles (NPs) results in a nano-carrier system with a large surface area capable of carrying high drug dosages, effectively reducing peripheral drug toxicity, and facilitating targeted drug delivery [10]. The surface charge of nanoparticles (NPs) is also critical in determining their efficiency in targeting the brain. Literature reports indicate that neutral and mildly negatively charged nanoparticles (NPs) are more effective than positively charged NPs. However, positively charged nanoparticles (NPs) can induce immediate changes in the blood-brain barrier (BBB) albeit for shorter durations, and subsequently, they are cleared by the reticuloendothelial system (RES) [12,13]. Various strategies have been employed in developing nano-carriers for delivering anti-epileptic drugs (AEDs) to specific sites within the brain. Evidence suggests that patients with epilepsy exhibit pathological changes in the permeability of the blood-brain barrier (BBB).

Various nanoparticle carriers can potentially access specific brain sites by modulating blood-brain barrier (BBB) permeability. Surface ligand modification enhances nanoparticle transport across the BBB. Nanoparticles (NPs) are advantageous drug carriers in epilepsy diagnosis and treatment mapping strategies due to the presence of transport molecules like growth factors, insulin, and transferrin in the blood-brain barrier (BBB) [14]. In addition to these methods, several novel approaches are being developed to enhance the penetration and retention of anti-epileptic drugs (AEDs) in the brain. Furthermore, gene and cell therapies for epilepsy treatment are currently under development [15].

Epilepsy and its causes

The term "epilepsy" originates from the Greek word, which signifies to seize, be seized, or attacked. Epilepsy is a neurological disorder distinguished by aberrant electrical activity in brain neurons. The occurrence of recurrent seizures is indicative of cerebral neuronal dysfunction associated with the disorder. It represents a lifelong predisposition, with seizures potentially initiating at any point in life and manifesting sporadically or with increased frequency [3].

Epilepsy can arise following a specific identifiable event (e.g., asphyxia, head injury, meningitis), termed "symptomatic epilepsy," or it can develop without any identifiable cause or event, known as "idiopathic epilepsy" [4,5]. A seizure occurs due to excessive neuronal discharges in the brain, presenting as a sudden abnormal bodily function that may include loss of consciousness, increased or decreased muscular activity, or abnormal sensations [5,6]. Excessive neuronal discharges or excitation can persist in a localized area of the brain (a focal lesion or focus), leading to partial (focal) seizures. Alternatively, they may initiate simultaneously throughout the entire brain and spinal cord, resulting in generalized seizures [4]. Epilepsy can impact individuals of any age, race, sex, or background. It may develop shortly after birth due to complications or during childhood, as seen in cases of febrile convulsions and other childhood illnesses. The onset of epilepsy can also coincide with hormonal changes, such as those occurring during puberty, pregnancy, and menopause. In elderly individuals, epilepsy is often a consequence of neurodegenerative conditions, such as Alzheimer's disease. Additionally, epilepsy can occur across multiple generations within the same family [3].

In the majority of cases, the cause of epilepsy is unknown and is classified as idiopathic. However, several recognized factors can increase the risk of developing epilepsy. The various causes of epilepsy include:

Metabolic factors: Hypoglycemia, hyperglycemia, electrolyte imbalance, hypomagnesemia, hyperbilirubinemia, pyridoxine deficiency/dependency, uremia, phenylketonuria, and porphyria.

Infections: Meningitis, encephalitis, AIDS, rabies, cerebral malaria, toxoplasmosis, tetanus, and pertussis.

Birth trauma: Cold injury in newborns, hypothermia, and head injury in later life.

Anoxia: Birth asphyxia and anoxic conditions later in life.

Toxic factors: Alcohol use and withdrawal, carbon monoxide poisoning, certain drugs (e.g., high-dose intravenous penicillin, strychnine), and lead poisoning.

Space-occupying lesions: Hemorrhage, abscess, tumor, tuberculoma, toxoplasmosis, cerebrovascular accidents (strokes), sickle cell crisis, and vascular anomalies.

Degenerative diseases: Dementia, cerebrovascular degeneration, and Niemann-Pick disease.

If an acute disturbance, such as hypocalcemia, an infection like meningitis, poisoning, or any of the other causes, is promptly recognized and adequately treated, the development of epilepsy can be prevented [2,3]. However, if the disturbance is too severe or not treated correctly, convulsions may become prolonged and continuous, leading to brain anoxia due to the lack of oxygen and subsequent brain damage, which can result in epilepsy [6].

According to current research, serious head injury, brain tumors, and specific cerebrovascular diseases are considered primary causes of epilepsy. However, in 60-70% of cases, epilepsy is classified as idiopathic, meaning no specific cause is identified. In addition to recognized factors, certain causes contribute directly or indirectly to epilepsy. These factors include genetic predisposition, effects of brain maturation, exposure to flashing lights, hyperventilation, decreased alertness, inadequate sleep or disruptions in sleep patterns, emotional stress, sensitivity to specific sensory stimuli like smells, sounds, or touch, alcohol consumption, hormonal fluctuations (such as during menstruation), high fever, and overhydration.

Conventional treatment and their limitations

The conventional treatment of epilepsy involves a comprehensive approach that includes patient history, physical examination, diagnostic investigations, and drug therapy. After obtaining a detailed patient history, including information about seizures, family history, and previous seizure management, several examinations are conducted. These include observation, measurements, physical examination, and neurological assessments. Following the initial examinations, further investigations are conducted, which typically include laboratory tests, skull X-ray examinations, electroencephalography (EEG), computer-assisted tomography (CT) scans, and magnetic resonance imaging (MRI) [17]. After completing the initial diagnosis and examinations, epilepsy treatment typically begins with drug therapy. It is recommended to initiate treatment with a single medication. The selection of the drug ideally depends on the specific type of epilepsy and the nature of the seizures [3, 17]. Since determining the exact type of epilepsy can be challenging initially, treatment typically commences based on the presenting seizure type. Generalized tonic-clonic seizures (GTCS) are the most common type of seizures. The main four antiepileptic drugs (AEDs) - phenobarbitone, phenytoin, carbamazepine, and valproate are nearly equally effective in treating these seizures [17]. If distinguishing between primary and secondary generalized tonic-clonic seizures is possible, phenobarbitone or valproate is typically preferred for primary GTCS, while phenytoin or carbamazepine may be chosen for secondary GTCS. However, all four medications are effective and can be individually considered as alternatives if needed [17].

Phenytoin, is considered a first-line antiepileptic drug, although its use is less frequent due to its higher incidence of side effects [17]. Phenytoin is also highly effective as an anticonvulsant for partial seizures, generalized tonic-clonic seizures (GTCS), and seizures occurring during sleep. The primary issue with phenytoin is its narrow therapeutic index, where a small margin exists between the therapeutic level and the point at which the metabolizing enzyme becomes saturated, causing serum levels to rise sharply and potentially reach toxic levels. Increases in phenytoin dosage should not exceed 50 mg increments to mitigate the risk of toxic side effects [18]. The side effects of phenytoin include drowsiness, gum hypertrophy, and hirsutism, while higher dosages can lead to ataxia and nystagmus. Prolonged use at high doses may also potentially cause reversible cerebellar signs, and there is concern that chronic therapy could result in permanent cerebellar syndrome [3,17]. Mild sub-clinical neuropathy is common after prolonged phenytoin therapy, though it may also occur with other medications. If signs of toxicity appear, the dosage should be skipped for one day and then resumed at a lower level. If feasible, switching to another anticonvulsant may be considered to avoid further complications [17].

Phenobarbitone, if it is the only available drug in a dispensary or health center, then all patients with epilepsy might be started with phenobarbitone treatment [4]. This medication is no longer recommended in the developed world, but it remains a useful, effective, and cost-effective anticonvulsant [3]. However, if there is no improvement or if the condition worsens, the dosage should not exceed 120 mg daily. In such cases, the patient should be referred to a clinic or hospital where other anticonvulsants are available [17]. The primary side effects of phenobarbitone include drowsiness, particularly noticeable during the initial week of treatment. This effect typically diminishes over time but may recur if the dosage is increased excessively. In some children, phenobarbitone treatment may lead to reduced scholastic performance or changes in behavior, such as hyperactivity and occasional aggressiveness [17].

Carbamazepine, introduced to the market after 1960, is primarily indicated for complex partial seizures [51]. It is also effective against other types of partial seizures and generalized tonic-clonic seizures (GTCS), but not for generalized absences and myoclonic seizures. Initial treatment with carbamazepine may cause drowsiness and dizziness, which can recur with high dosages. Additional potential side

effects include double vision and ataxia. Due to its short half-life, carbamazepine requires twice-daily dosing, and when used in combination with other drugs, it may need to be administered three times daily [2,17,18].

Valproate has been available on the market since 1966 [3]. The primary indications for valproate are generalized absences, myoclonic seizures, and drop attacks. It is also used for generalized tonic-clonic seizures (GTCS) that occur after awakening. If necessary, valproate might be used for all other types of seizures as well [17]. When phenobarbitone cannot be used for febrile convulsion prophylaxis, valproate may serve as an alternative [19]. Despite its short half-life, its pharmacodynamic effects in the central nervous system persist longer than its serum presence, necessitating three-times-daily dosing to avoid high peak concentrations [6]. Specific side effects include weight gain, hair loss, and gastric irritation. Of greater concern is its teratogenic effect, with an increased risk of spina bifida in fetuses. This risk can be mitigated by supplementing folate in all women at risk of pregnancy [18].

Ethosuximide is specifically used for absence seizures [17]. If other types of seizures are also present in the same patient, additional medications must be added to manage those seizure types. In epileptic syndromes where absence seizures, myoclonic seizures, drop attacks, or generalized tonic-clonic seizures (GTCS) occur together, valproate is often preferred because it can effectively treat all these different seizure types simultaneously [17].

Clonazepam is rarely used as monotherapy. It is typically added when seizures are not adequately controlled, particularly in children experiencing drop attacks and myoclonic seizures [3].

Diazepam is employed for treating status epilepticus or febrile convulsion status [18]. It is also used to halt a febrile convulsion and prevent it from becoming prolonged. Administration is typically intravenous; however, if vein access is difficult, the same solution can be administered rectally [6].

In addition to these commonly used drugs, newer antiepileptic medications are now being utilized for various types of seizures. These newer drugs include topiramate, levetiracetam, tiagabine, lamotrigine, and gabapentin, among others [19].

Table 1: Available drug therapy for epilepsy treatment

Type of seizure	**First choice drugs**	**Second choice drugs**	**Alternative drugs**
Generalized tonic-clonic/ simple partial with or without Generalization	Carbamazepine, Phenytoin	Valproate, Phenobarbitone	Lamotrigine, Gabapentin, Topiramate, Primodone, Levetiracetam
Complex partial with without Generalization	Carbamazepine, Phenytoin, Valproate	Gabapentin, Levetiracetam, Lamotrigine	Clobazam, Topiramate, Zonisamide
Absence	Valproate	Lamotrigene, Ethosuximide	Clobazam, Clonazepam
Myoclonic	Valproate	Lamotrigine	Topiramate
Atonic	Valproate	Clobazam, clonazepam	Lamotrigine
Febrile seizures	Valproate	-	-
Status Epilepticus	Lorazepam, Diazepam	Fosphenytoin, phenobarbitone	General anesthetics

Limitations of conventional drug therapy

While antiepileptic drugs are widely used today, they come with several drawbacks. In addition to the mentioned side effects, these medications can have toxic effects on the brain and other tissues [20,21]**.** The current approach to drug therapy for seizures focuses on achieving therapeutic levels of antiepileptic drugs in the bloodstream, typically through oral pills or intravenous injections [17].In both pill and intravenous forms, drugs must enter the brain by crossing from the bloodstream into brain tissue [8]. This route seems plausible due to the brain's high vascularity, with approximately 100 billion capillaries separated by a distance of about 40 micrometers, forming an intricate network capable of distributing drugs throughout the brain [22]. However, these methods face significant challenges, primarily due to the blood-brain barrier (BBB) [23]. The structural characteristics of brain capillaries tightly regulate molecular transport into the brain interstitial fluid: these include the absence of fenestrae in endothelial cells, tight junctions between endothelial cells, a reduced number of pinocytotic vesicles, and direct communication between endothelial cells and astrocytes [24,25]. Consequently, only low molecular weight (under 1000 Daltons) lipid-soluble molecules can freely cross the BBB. Furthermore, molecular efflux pumps actively transport drugs that manage to cross the BBB back into the bloodstream, limiting their accumulation in the brain [7,26]. Before drugs can even reach the brain, factors such as systemic toxicity and macrophage phagocytosis within the reticuloendothelial system also hinder their success through the trans vascular route [5,27]. To overcome these challenges, several new approaches are being developed to enhance the entry and duration of antiepileptic drugs (AEDs) in the brain. These include drug delivery systems, prodrugs, inhibition of efflux pumps, hyperosmolar BBB opening, and methods to bypass the BBB by directly delivering drugs to the ventricles and cortex. Additionally, gene and cell therapies are emerging as potential avenues for treating epilepsy [4,15].

Nanotechnology for epilepsy treatment

Nanotechnology has been extensively utilized over the past two decades to enhance the delivery of therapeutics and imaging agents for various medical applications. It is widely employed across different fields. Numerous strategies for the effective delivery of antiepileptic drugs (AEDs) have been documented in the scientific literature. Nanotechnology-based systems represent a promising and innovative advancement. Recently, several nanostructured drug delivery carriers have been reported as effective systems for central nervous system (CNS) delivery, overcoming the challenges of AED elimination at the blood-brain barrier (BBB) and resulting in increased drug persistence [10,22,23].

Nanotechnology-based medicine, or nanomedicine, involves the characterization and design of nano-carriers for various medicinal strategies. Therapeutic agents are embedded in or coated onto nano-carriers, which are small colloidal or compact structural platforms ranging in size from 1 to 1000 nm [8,9]. These nanoparticles (NPs) readily interact with the cellular environment at the molecular level to produce the desired physiological response. Nanotechnology-based antiepileptic drugs (AEDs) have recently garnered attention due to their ability to cross the blood-brain barrier (BBB), improved selectivity, and potential for sustained drug delivery to the brain. The size, molecular weight, co-polymer ratio, mechanism of erosion, and surface charge are important factors in determining the effectiveness of nanoparticles. For example, the size of the nanoparticles should be small enough to travel through the physical restrictions of the brain interstitial space (50 nm) but large enough to allow for sufficient drug loading. Nanoparticles ranging from 35 to 64 nm can easily access most neural tissue [9]. Size-specific nanoparticle synthesis can be achieved through various preparation methods.

As nanoparticle sizes decrease, the nanocarrier system presents a large surface area that can carry a large dosage of drugs, efficiently reduce peripheral toxicity, and provide adequate delivery of drugs to their targets. The surface charge of NPs is also crucial in determining their efficiency in targeting the brain. Literature reports that neutral and mildly negatively charged NPs are more effective than

positively charged NPs. Positively charged NPs can cause immediate alterations in the BBB and are later eliminated by the reticuloendothelial system (RES) [12,13]. Once drugs are loaded into NPs, they are released through a combination of desorption, diffusion, and polymeric degradation and erosion. In vivo, variables such as the molecular weight of the polymer and the mechanism of erosion (bulk or surface) affect the speed of drug release, which can vary from a few hours to many months [8,13].

Different approaches have been employed to develop potential nano-carriers for delivering antiepileptic drugs (AEDs) to brain-specific sites. Evidence suggests that patients with epilepsy experience pathological alterations in the permeability of the blood-brain barrier (BBB) [14]. Various nano-carriers may effectively target brain sites by manipulating the BBB's permeability. Modifying nanoparticles (NPs) with surface ligands facilitates their crossing of the BBB. Due to the presence of transport molecules such as growth factors, insulin, and transferrin in the BBB, NPs are desirable drug carriers for mapping strategies in epilepsy diagnosis and treatment [14,15].

The different classes of nano-colloidal carriers used in drug delivery are as follows:

Polymeric nanoparticles: Polymeric nanoparticles (NPs) are typically made of biodegradable polymers and entrap drugs through encapsulation or polymer-drug conjugation. This method is one of the most widely used for targeting drugs to the brain in the treatment of epilepsy [28].

Liposomes: Liposomes are made up of phospholipids and contain an aqueous core surrounded by a lipid bilayer. Hydrophilic drugs can be incorporated into the core; hydrophobic and amphiphilic drugs can be integrated into the bilayer [12].

Polymeric micelles: Polymeric micelles are formed in an aqueous environment from the associations of block copolymers containing both hydrophilic and hydrophobic segments. The hydrophobic core can be loaded with lipophilic drugs, while the hydrophilic surface increases the stability of the micelles in aqueous solutions [28].

Dendrimers: Dendrimers consist of numerous polymeric monomers that create branched, tree-like structures, providing multiple arms to which drugs can be attached [5,24].

Carbon Nanotubes: Carbon nanotubes, composed of benzene rings, can carry drugs either inside the lumen of the tube or attached to their sides.

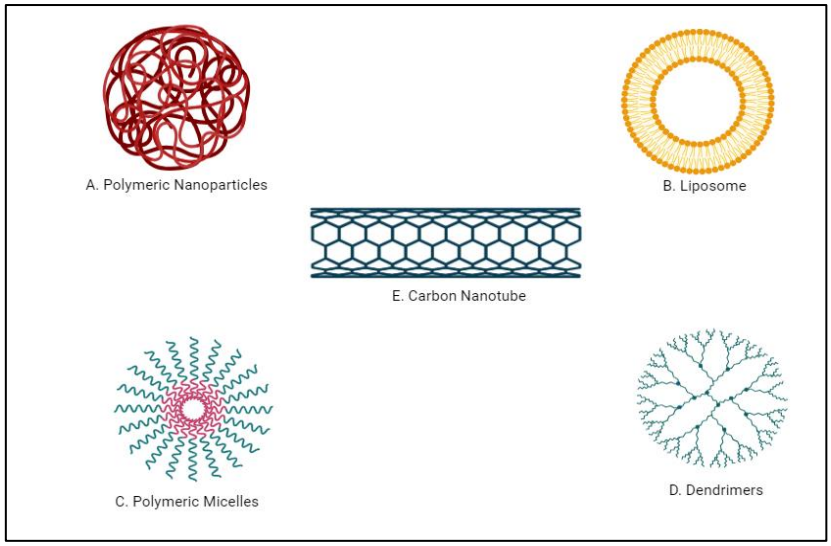

Fig.1: Different classes of nano colloidal carriers used in drug delivery

Nanoparticles used for drug loading and targeting to the brain for epilepsy treatment

Epilepsy treatment currently focuses on controlling seizures by administering adequate doses of antiepileptic drugs (AEDs) via oral, parenteral, and rectal routes. However, these methods can lead to systemic drug exposure and contribute to drug resistance in epileptic patients. Among the various drug delivery systems targeting the brain, two primary approaches are prominent: the molecular approach and the nano approach [29]. In the molecular approach, drugs interact with brain cells based on their lipophilicity, size, receptor binding capabilities, or enzymatic conversion within specific brain regions. This method primarily utilizes the inherent biochemical pathways for drug action, which continue to evolve through ongoing research efforts [17].

Conversely, the nano approach involves administering different classes of compounds intravenously (IV), orally, intrathecally, or via implanted devices. This approach leverages nanotechnology to enhance drug delivery efficiency, targeting specificity, and therapeutic effectiveness. Notable formulations in this domain include liposomes, polymeric nanoparticles, nano-emulsions, solid-lipid nanoparticles, and magnetic nanoparticles, each designed to optimize drug pharmacokinetics and enhance therapeutic outcomes [29]. These advancements underscore ongoing efforts to refine epilepsy treatment strategies by integrating sophisticated drug delivery systems that promise improved efficacy and reduced systemic side effects [30,31].

Polymeric nanoparticles: Polymeric nanoparticles (NPs) are widely used in nanomaterial drug delivery due to their biodegradability, biocompatibility, and size range of 10 to 1000 nm. Formulations include poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid) (PLGA), poly(alkylcyanoacrylates),poly(e-caprolactone), and poly(methylidenemalonate). PLGA-based nano-carriers, approved by the U.S. Food and Drug Administration (USFDA), are safe and effective for human use. The degradation of PLGA within the body can be controlled by adjusting copolymer ratios, enhancing their efficacy as nano-carriers [43]. Drugs loaded onto polymeric NPs are released at targeted sites through diffusion and polymeric degradation mechanisms, with release efficiency varying from hours to months depending on drug-polymer ratios, molecular weights, and polymer compositions. For instance, beta-carotene nanoparticles coated with polysorbate-80 (P-80-BCNP) show higher bioavailability and stability in treating epileptic convulsions compared to unmodified beta-carotene [44]. Polymeric NPs offer advantages over liposome-based models due to their easier preparation, greater stability both in vivo and in vitro, and efficient storage capabilities. They also allow for continuous and controlled drug release over extended periods [44]. However, both polymeric NPs and liposomes face challenges such as rapid plasma clearance via opsonization and subsequent phagocytosis in the reticuloendothelial system (RES) [38]. Surface modification with polymers like PEG, polyvinyl alcohol, polyacrylamide, and polysaccharides extends circulation times by imparting a stealth-like character that prevents recognition and opsonization by the RES, thus increasing circulation times from minutes to hours [39,40].

Liposomes: Liposomes are unilamellar or multilamellar phospholipid vesicles that enclose a central aqueous compartment. They are the most extensively studied antiepileptic drug (AED) delivery system due to their biocompatibility, biodegradability, and ability to encapsulate drugs with diverse lipophilicities and molecular weights [32,33]. The ease of modifying their dimensions, membrane fluidity, and surface characteristics makes them ideal nano-carriers [34]. Liposomes enhance drug bioavailability across cellular membranes and minimize enzymatic degradation. Their half-lives can be extended by reducing vesicle size, enhancing surface hydrophilicity, or incorporating glycolipids and polyethylene glycol (PEG). Hydrophilic moieties form a peri-liposomal layer that prevents opsonins from accessing the liposome surface, thus hiding the nano-carriers from immediate reticuloendothelial system (RES)-mediated clearance. For stimulus-dependent drug release, pH- and temperature-sensitive

liposomes have been developed, discharging their drug contents in response to acidic environments and elevated temperatures (41°C-42°C) at the target site [35,36]. Liposome formulations are used in treating various malignant conditions where secondary epilepsy is a characteristic feature. Brain neoplasms, major etiological factors for epileptic seizures, are effectively targeted by immune liposomes. These are formulated by conjugating PEG-stabilized liposomes with monoclonal antibodies to the rat transferrin receptor, delivering drugs at concentrations four times higher than PEG-liposomes [37]. Studies combining PEG-related immune liposomes with antineoplastic drugs have shown promising results in targeting drug delivery [38,39]. Despite their advantages, liposomal formulations face limitations such as rapid immune-mediated clearance by the RES, low stability after extended storage, fast metabolic degradation of phospholipids, and failure to provide continuous drug release compared to other nano-carriers [40]. However, newer generations of liposomal-AED formulations have addressed some of these issues, improving shelf life and stability. Pre-clinical developments of liposomal formulations for AEDs like valproic acid, superoxide dismutase, GABA, and amiloride show promise for future advancements in brain-targeted drug delivery [41,42].

Nano-Emulsions (NE): Nano-emulsions (NEs) are easily prepared through spontaneous emulsification and offer improved stability and solubility for loaded drug molecules [89,45]. These heterogeneous drug delivery systems, composed of oil, water, and surfactants, typically have droplet sizes ranging from 10 to 100 nm [46]. Several studies have demonstrated that NEs provide increased absorption rates, rapid and efficient drug penetration, reduced toxicity and irritation, protection from hydrolysis and oxidation, and versatility in administration routes [89,45,46]. One significant advantage of AED-loaded NEs is their ability to cross the blood-brain barrier (BBB) even for drugs with reduced bioavailability. For example, a novel mucoadhesive NE formulation loaded with amiloride was found to be effective when administered via the intranasal route, offering a promising treatment for epilepsy [89]. An optimized olanzapine-loaded NE formulation showed better nose-to-brain delivery than an olanzapine solution in a rat model, and subsequent studies reported improved stability and non-toxicity towards nasal cilia for this NE formulation [90, 91]. Carbamazepine used as a NE for treating generalized tonic-clonic and partial seizures, demonstrated targeted drug delivery and higher bioavailability in a mice model when stabilized by 1-O-alkylglycerol/lecithin [92].

Pharmacokinetic studies in beagle dogs showed that the carbamazepine-loaded NE had similar profiles to a carbamazepine/hydroxypropyl-beta cyclodextrin complex solution [93]. This suggests that NE-loaded carbamazepine is a valuable formulation for emergencies requiring rapid CNS action. Additionally, clonazepam microemulsions have been used for rapid brain delivery to treat acute status epilepticus patients, highlighting the potential of NEs in emergency epilepsy management [93].

Solid lipid nanoparticles (SLNs): Solid lipid nanoparticles (SLNs) are physiological lipid-based delivery systems that offer physical stability, protection of labile drugs from degradation, ease of preparation, and lower toxicity. Their unique properties, such as small size, large surface area, high drug loading, and phase interaction at the interfaces, make them promising for improving the efficacy of pharmaceuticals, nutraceuticals, and other materials [32]. SLNs have emerged as an alternative to traditional carriers like liposomes and polymeric nanoparticles (NPs) [32]. These new-generation lipid emulsions substitute liquid lipids with solid lipids and have shown significant progress in targeted drug delivery for various disorders, including cancer and neurodegenerative diseases like epilepsy [47,48]. SLN formulations can be administered via various routes, including parenteral, oral, rectal, ophthalmic, and topical, allowing controlled delivery and enhanced bioavailability of entrapped drugs. Studies have highlighted SLNs' advantages over other nanoparticle formulations in brain targeting, particularly in overcoming the challenges of restricted blood-brain barrier (BBB) entry and reduced bioavailability of specific drugs [47,48]. Diazepam, a poorly water-soluble AED used since the 1970s for prolonged fits

or status epilepticus, has had its bioavailability to the CNS enhanced through various administration routes [51]. Temozolomide, known for reducing seizure frequency in intractable epilepsy patients, has been delivered to the brain using a transferrin-tailored SLN capable of crossing the BBB [53,54]. Carbamazepine, a lipophilic drug and clinical choice for treating complex partial seizures, acts by inactivating sodium channels [55]. An SLN formulation of carbamazepine containing the biopolymer chitosan has demonstrated prolonged controlled release and improved therapeutic efficacy for epilepsy treatment [96]. Similarly, riluzole-loaded SLNs offer higher drug loading, greater efficacy compared to free riluzole, improved brain drug delivery, and more selective bio-distribution [97].

Gabapentin, a GABA-analog AED effective for partial and generalized tonic-clonic seizures, has been incorporated into SLNs, showing drug release via diffusion from the matrix or matrix erosion due to lipid degradation [57]. The scientific literature suggests that SLNs are promising drug carriers for epilepsy treatment due to their advantages in toxicity, production feasibility, and scalability. Therefore, further investigation into SLNs as brain-targeted drug delivery systems for both newer and older neurotherapeutics is warranted. SLNs may offer an alternative drug delivery system for administering molecules to the brain with prolonged drug release profiles, resulting in improved therapeutic effects in seizure treatment [98].

Magnetic nanoparticles (MNPs): Magnetic nanoparticles (MNPs) are highly promising for targeted delivery of therapeutic agents due to their ability to be precisely controlled by an external magnetic field [58,59]. This capability enables controlled and sustained drug release and facilitates transportation across targeted tissues while minimizing toxicity to non-targeted areas [60]. MNPs, composed primarily of cobalt (Co), nickel (Ni), and iron (Fe), are utilized in various applications, particularly in tumor-targeted gene therapy. Surface modifications with biodegradable polymers or non-biodegradable materials like silica enhance their biocompatibility and stability, crucial for applications such as crossing the blood-brain barrier for brain tumor treatment. Despite decades of research, MNPs have yet to receive clinical approval, but advancements in gene delivery and magnetoreception suggest promising avenues for future cancer therapies.

Stealth polymers: Drugs encapsulated in liposomes or nanoparticles (NPs) are shielded from in vivo degradation and toxicity. However, upon intravenous injection, these conventional NPs and liposomes are rapidly cleared from the bloodstream within minutes due to opsonization and subsequent phagocytosis by the reticuloendothelial system cells [63]. To prolong circulation time, polymers like PEG, polysaccharides, poly(acrylamide), and poly(vinyl alcohol) are attached to NP and liposome surfaces. These polymer chains create a stealth effect, preventing opsonization and extending circulation from minutes to hours. PEG, known for its hydrophilic nature that resists plasma protein binding, is the most commonly used polymer. Its effectiveness depends on chain length and surface density, with denser and longer chains proving most effective in preventing plasma protein binding. PEG can be incorporated into colloidal carriers through covalent attachment, physical entrapment, adsorption, or as a copolymer [64,65].

Despite enhancing circulation time, PEG-modified NPs and liposomes do not guarantee blood-brain barrier (BBB) penetration [68]. Additional targeting agents are necessary alongside PEG to facilitate BBB penetration in nano-delivery systems [69,70].

Advantages of several nano-carriers

Table 2: Advantages of several nano-carriers used in epilepsy treatment

Nano-carriers	Drugs used	Advantages
Liposomes • PEG Liposomes • Glycolipid conjugated • Immunoliposomes	Phenytoin, Thyrotropin	• Biocompatible • Size Diversity • Molecular weight and hydrophilicity aid in effective encapsulation and entry to neural tissues skipping body defense machinery.
Polymeric nanoparticles • PLGA • Poly (butyl cyanoacrylate) • D, L-polylactide • Poly (-caprolactone • Chitosan • Pullulan acetate-PEG • Poly (DL-lactide co-glycolide) Poly(glycolic acid)	Beta-Carotene Probenecid Thyrotropin Phenytoin Clonazepam Valproate Loperamide Carbamazepine Ethosuximide	• Biodegradable and biocompatible • Drug release could be achieved by choosing art polymer composition, ratio, and molecular weight. Preparation easiness and greater stability
Solid Lipid nanoparticles Chitosan	Diazepam Temozolomide Carbamazepine Riluzole Temozolomide Riluzole Carvedilol	• Greater physical stability • Lesser toxicity • Greater surface area improves both drug loading and its efficacy • Multiple routes of administration [94-100]
Nanoemulsion	Amiloride Olanzapine Carbamazepine Clonazepam Levetiracetam	• Stable preparation • Higher rate of absorption • Transmittable in multiple routes with less toxicity and irritation. • BBB permeable [89-93]
Magnetic nanoparticles	Carbamazepine Alpha-methyl Tryptophan Ethosuximide	• Precise modular control on transport and delivery to the targets • Minimum toxicity to other tissues. [58,101]

Targeting: Ligand-specific transport systems are crucial for delivering nutrients across the blood-brain barrier (BBB). Brain capillaries have carrier-mediated transport systems for monosaccharides, amino acids, peptides, choline, and organic cations, and receptor-mediated transcytosis systems for substances like lipoproteins, transferrin (Tf), insulin, insulin-like growth factor, and leptin. These systems are attractive for drug design because they move large quantities of molecules into the brain every minute. Small drugs and proteins, such as L-dopa for Parkinson's disease and antibodies, can utilize these carrier systems [72]. One approach to increase the brain uptake of particulate delivery systems involves

incorporating ligands that target these carriers or endocytosis systems, facilitating transport across the BBB [105]. These targeting ligands can be added directly or indirectly to colloidal carriers. Conjugating ligands to the ends of PEG chains (or other spacers) is most effective, as surface addition can be hindered by steric effects. A limitation of this technique is competition with natural substrates due to mimicking natural compounds [106]. Natural substances like mannose and choline have been attached to colloidal carriers to utilize carrier-mediated transport systems. Mannose derivatives on liposomes have shown mixed results; some studies show successful BBB crossing via glucose transporters, while others do not. Choline-coated nanoparticles showed enhanced BBB penetration in vitro, suggesting that the choline transporter on brain capillary endothelial cells may facilitate this, though the model's in vivo accuracy is uncertain [108,109]. In another study, MRZ 2/576, a noncompetitive NMDA receptor antagonist, was incorporated into poly(butyl cyanoacrylate) NPs coated with polysorbate 80 [110, 111]. This increased the drug's antiepileptic effects from 5-15 minutes to 210 minutes [112]. It is speculated that the polysorbate 80 coating binds to apolipoproteins B and E in the blood, forming a lipoprotein coat that mediates BBB transport via low-density lipoprotein receptors. Challenges include polysorbate 80 desorption, rapid NP degradation, and associated toxicity [113]. Receptor-mediated Tf transport can also enhance nano-system penetration across the BBB. Chitosan nanoparticles were produced using avidin-biotin conjugation to attach the monoclonal antibody OX26 to PEG chains on the particle surface [114]. OX26, which targets the Tf receptor (TfR), is more effective than Tf itself, as it binds to a different TfR domain, avoiding competition with physiological Tf levels [115]. Fluorescently labeled NPs with OX26 showed brain fluorescence in mice, indicating successful BBB crossing. Other studies with OX26-targeted immune liposomes have shown promising results [116].

Newer Drug Delivery Approach

Prodrugs: Prodrugs consist of a drug attached to a compound that is removed via enzymatic cleavage or hydrolysis in vivo. Initially inactive, the prodrug releases the active drug along with an additional compound or moiety, which can make the prodrug more lipophilic and increase its ability to cross the BBB. DP-VPA (DP16), a prodrug of valproic acid (VPA), links VPA with lecithin, ensuring the parent drug's inactivation in the systemic circulation [117]. At the seizure site, active VPA is released when lecithin is cleaved by A2 phospholipases, which are overactive at the target site, reducing systemic toxicity [118]. DP-VPA has shown greater efficacy than VPA in several epilepsy animal models, although not all [118].

Fosphenytoin, a prodrug of phenytoin with an attached phosphate ester, is inactivated and more water-soluble. When administered intramuscularly or intravenously, fosphenytoin is cleaved by alkaline phosphatases to yield active phenytoin, phosphate, and formaldehyde in non-toxic amounts [119]. It allows faster administration and less discomfort compared to phenytoin [120]. In a clinical study with 81 status epilepticus patients, fosphenytoin showed anticonvulsant effects in 76 patients [121]. XP13512, an isobutanoyloxyethoxy carbamate prodrug of gabapentin, is transported by monocarboxylate transporter type 1 and the sodium-dependent multivitamin transporter in the intestine. Cleaved by endogenous esterases, it releases active gabapentin. In monkeys, oral XP13512 showed significantly higher bioavailability than gabapentin (84% vs. 25%) [119].

BBB Modification

***Hyperosmolar BBB opening*:** One way to alter BBB functionality is by increasing the blood's osmolarity through brain capillaries. This can be done by injecting a 25% mannitol hyperosmolar solution intra-arterially. Mannitol reduces brain capillary endothelial cell size and widens tight junctions, increasing BBB permeability to drugs. This technique's advantage is its short, reversible effects; BBB permeability is enhanced for about 40 minutes and returns to normal within 8 hours.

Ideally, the BBB should remain open long enough to allow therapeutic drug levels into the brain but short enough to minimize edema and toxicity [122,123].

***Efflux pumps*:** Enhancing BBB transport can be achieved by transiently modifying its permeability. P-glycoprotein (Pgp), multidrug resistance-associated proteins (MRP), and breast cancer resistance protein (BCRP) are ABC transporters on brain capillary endothelial cells. They hydrolyze ATP to move molecules against their concentration gradients into the systemic circulation, impacting drug localization within the CNS [124].

Direct Drug Delivery

***Intracerebroventricular administration*:** Instead of modifying drugs or the BBB, drugs can be delivered directly behind the BBB. In intracerebroventricular administration, the drug is introduced into the cerebrospinal fluid (CSF) via an outlet catheter from an implantable reservoir, like the Ommaya reservoir, or a pump. The pump approach is preferable because it maintains a continuous, high drug concentration in the CSF. This method reduces issues like systemic toxicity, drug metabolism in serum, and opsonization by serum proteins associated with intravenous delivery. However, drug penetration into brain parenchyma remains limited, with more localization at the ependymal cells lining the ventricles. Drugs move from CSF to brain parenchyma by slow diffusion, navigating through barriers of ependymal cells and astrocytes. The high tortuosity and restricted pore size of the extracellular space further slow drug movement. CSF cycles through the ventricular system in 4-5 hours, then exits the brain into the systemic circulation, causing potential drug loss before it accumulates in brain tissue. Continuous intracerebroventricular infusions can improve drug dispersion in the brain, reduce systemic spillover, and minimize toxicity compared to bolus injections [131]. However, all intracerebroventricular techniques are invasive, carrying risks of infection and increased intracranial pressure [132,133].

***Intracerebral administration*:** An alternative to delivering AEDs into the ventricles is direct delivery to the brain parenchyma via implant or injection. Adenosine was injected into the seizure focus or ventricles to study these delivery methods' antiepileptic effects after penicillin-induced seizures. A 100 microgram intracerebroventricular adenosine injection reduced spike frequency, though not amplitude, about 20 minutes post-administration. Conversely, local injection of the same adenosine amount significantly decreased both spike frequency and amplitude more effectively within 20 minutes, showing increasing antiepileptic effects up to 45 minutes post-administration. These findings indicate that locally injected adenosine offers superior anticonvulsant effects compared to intracerebroventricular injection [134].

Implants: Implants have been used to deliver AEDs. Polymeric matrices, with and without gamma-aminobutyric acid (GABA), were implanted near the substantia nigra in both hemispheres of rat brains to study effects in an amygdala-kindled epilepsy model [135]. Rats with GABA-releasing matrices experienced less severe seizures compared to control rats two days after implant introduction. However, by the seventh day, GABA levels dropped significantly, reducing the antiepileptic effects [135,136]. Polymeric matrices loaded with thyrotropin-releasing hormone (TRH) were implanted into the amygdala of kindled rats. TRH, not a traditional AED, showed temporary anticonvulsive effects in animal models. Rats receiving TRH implants showed hindered kindling progress, requiring more electrical stimulations and time to advance through kindling stages, with some antiepileptic effects persisting for 50 days [136]. Phenytoin was encapsulated in a nonbiodegradable, controlled-release polymer implanted 1-2 mm deep into the rat cortex [137]. Rats receiving phenytoin implants had significantly fewer spikes in electrocorticography when seizures were induced by cobalt chloride. The phenytoin implant was designed to release the drug for up to 3.5 years, similar to the Norplant system

for contraceptive steroids and small protein-loaded implants [138]. Recently, bioceramic materials have been investigated as implantable, sustained-release delivery vehicles for AEDs [139].

Convection-enhanced delivery: Convection-enhanced delivery (CED) was developed to improve drug distribution in the brain as an alternative to intraparenchymal injections [140]. In CED, a drug solution is gradually infused into a catheter placed in the brain interstitial space, using an external pressure source to cause convective and diffusive drug movement [141]. The typical CED apparatus consists of a small catheter connected to a pump, which creates pressure to drive fluid from the catheter into the brain interstitium. This method enlarges the drug distribution volume compared to intraparenchymal injection and implantation. Experimental work shows that smaller molecules travel farther than larger ones, and neutral or negatively charged molecules, or liposomes coated with PEG or bovine serum albumin, exhibit larger distribution volumes than positively charged agents of the same size [143]. CED can treat seizure foci locally, bypassing the blood-brain barrier and reducing systemic toxicity. However, it has drawbacks [144]. High pressures can cause fluid to flow back along the catheter's outside, leading to inefficient drug delivery. Poor catheter placement can cause tissue injury and air bubbles [145]. Traditional catheters with leading-edge outlets can create tissue plugs that block fluid flow. Recently, microfluidic devices with side outlets have been developed to reduce tissue damage and backflow [146].

Conclusion and Future Prospects

Nanotechnology is promptly advancing in the present era, specifically in the field of pharmaceutical and medicinal science. It is revolutionizing medicinal science by enabling the development of various innovative treatments and diagnostics at the molecular level, promising more effective, precise, and safer medical interventions. One of the biggest hurdles for facing AEDs in pharmacotherapy is overcoming the blood-brain barrier and guaranteeing targeted distribution. The use of nanotechnology and nano based medications for overcoming these constraints for epilepsy have been showing promising results. Various nanoparticle-based delivery systems, such as liposomes, polymeric nanoparticles, nanoemulsions (NE), solid lipid nanoparticles (SLNs), and magnetic nanoparticles (MNPs), have been suggested as AED delivery methods. However, different nano-based AEDs are still in infancy and in various clinical trial stages, new formulations may soon be available for epilepsy treatment. SLNs and NE-based systems are promising due to their potential to control toxicity and their feasibility for large-scale production. However, the potential toxicity of different nano-formulations should be carefully considered before approving novel delivery systems for epilepsy [147].

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Conflict of Interest

The author have no conflict of interest.

Availability of Data & Material

All the data were collected and accumulated from different research and review articles which are available on Google, Research Gate, Elsevier, and others.

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