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# A Synopsis of Nano-Technological Approaches Toward Anti-Epilepsy Therapy: Present and Future Research Implications

Nasimudeen R. Jabir[1], Shams Tabrez[1], C. K. Firoz[1], Syed Kashif Zaidi[2], Saleh S. Baeesa[3], Siew Hua Gan[4], Shazi Shakil[5], Mohammad Amjad Kamal[1,6*]

*[1]King Fahd Medical Research Center; [2]Center of Excellence in Genomic Medicine Research; [3]Division of Neurosurgery, College of Medicine [King Abdulaziz University, Jeddah, Saudi Arabia]; [4]Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia; [5]Department of Bio-Engineering, Integral University, Lucknow, 226026, India; [6]Enzymoic, 7 Peterlee Place, Hebersham, NSW 2770, Australia*

**Abstract:** Epilepsy is a non-communicable central nervous system disorder that affects over 60 million people worldwide. The existing developments in epilepsy treatment face major hurdles due to drug resistance and disease recurrence after reduction of medication. Nanotechnological anti-epileptic drug (AED) delivery systems have recently garnered attention due to their ability to cross the blood brain barrier, improved selectivity and potential for sustained drug delivery to the brain. This review focuses on several nano-based AED delivery systems, including liposomes, nano-emulsions, polymeric nanoparticles, solid-lipid nanoparticles and magnetic nanoparticles. Their limitations and future prospects in terms of AED delivery to the brain are also highlighted. It is hoped that the present communication is helpful in the identification of potential AED delivery systems based on their advantages and disadvantages.

**Keywords:** Epilepsy, liposomes, nano-emulsions, polymeric nanoparticles, solid-lipid nanoparticles, magnetic nanoparticles, therapy

## INTRODUCTION

Epilepsy is a non-communicable central nervous system (CNS) disorder in which an enormous increase in electrical impulses occurs in one focal locus of the brain and/or the entire brain, leading to partial or generalized seizures. Abnormal and drastic neuronal excitation may lead to physical and mental benign ailments and serious co-morbidities. Over 60 million people worldwide are affected with epilepsy [1]. Despite developments in epilepsy treatment, the quality of life of patients suffering from this disorder remains poor. A major hurdle is drug resistance and epilepsy recurrence after reduction of medication [2]. Most anti-epileptic drugs (AED) are administered orally or intravenously. Up to 40% of patients develop drug resistance at later stages of treatment [3, 4], resulting in uncontrolled seizures, a higher risk of brain damage and increased mortality rates [5]. Patients experience emotional and behavioral changes, seizures, convulsions, muscular spasms, depression and, in some cases, unconsciousness [6].

Drug-resistant epilepsy is a formidable health issue. Drugs for epilepsy suffer from poor bioavailability and eventually become ineffective over the course of treatment due to drug resistance [7]. Epilepsy treatment is often complicated due to the inability of available AEDs to cross the adjunctive blood brain barrier (BBB), which could be overcome through appropriate drug delivery systems. The ideal system would provide localized and controlled release of AEDs to targeted sites in the brain to help reduce drug-associated toxicities and enhance the efficacy of the drugs. Several strategies for the effective delivery of AEDs have been reported in the scientific literature. Nanotechnology-based systems appear to be a promising and innovative development. Several nanostructure drug delivery carriers have recently been reported as an effective CNS delivery systems to overcome the problem of AED elimination at the BBB and result in increased persistence of drugs [7].

Nanotechnology-based medicine (nano-medicine) refers to the surface property characterization and design of nano-carriers for various medicinal strategies [8, 9]. Therapeutic agents are embedded into or coated onto nano-carriers, small colloidal or compact structural platforms ranging in size from a 1 to 1000 nm [2, 10]. These nano-platforms (NPs) readily interact with the cellular environment at the molecular level to produce the desired physiological response. Nanotechnology-based AEDs have recently garnered attention because of their ability to cross the BBB, improved selectivity and potential for sustained drug delivery to the brain [11]. The size, molecular weight, co-polymer ratio, mechanism of erosion and surface charge are important factors when considering the effectiveness of NPs. For example, the size of the NPs is a very important determinant for its efficiency in crossing the BBB; NPs ranging from 35 to 64 nm easily access most neural tissues [12]. Size-specific NPs synthesis could be achieved through different preparation methods. As a result of the reduction in the sizes of NPs, the nano-carrier system presents a large surface area that can carry large dosages of drugs, efficiently decrease the peripheral toxicity of drugs, and provide adequate delivery of drugs to their targets [7]. The surface charge of NPs is also an important factor in determining their efficiency in brain targeting. It has been reported in the literature that neutral and mildly negatively charged NPs are more effective than positively charged NPs. On the other hand, positively charged NPs are able to make immediate alterations in the BBB (albeit for shorter durations) and are later eliminated by the reticulo-endothelial system (RES) [13, 14].

Different approaches have been used in the pursuit of potential nano-carriers for AED delivery towards brain-specific sites. Evidence indicates that there are pathological alterations in the permeability of the BBB in patients with epilepsy. Various nano-carriers may be able to easily access targeted brain sites by manipulating the

*Address correspondence tothis author at the King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia; Tel: 02-98644812; Fax: + 15016368847;
E-mail: meu.fabg@hotmail.com

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permeability of the BBB. Modification of NPs with surface ligands facilitates the crossing of the BBB by nano-carriers. Due to the presence of transport molecules, such as growth factors, insulin and transferrin, in the BBB, NPs are desirable drug carriers in the mapping strategies of epilepsy diagnosis and treatment [15].

To the best of our knowledge, no single article reviewing multiple nano-technological AED delivery systems has been published. In the present communication, we focus on several nano-technological delivery systems that could be used as AED brain delivery systems in the future, after completing the appropriate clinical trials. It is hoped that the present communication will be helpful in the identification of potential AED delivery systems based on the advantages and disadvantages of each available system.

## THE BLOOD BRAIN BARRIER (BBB): A MAJOR CHALLENGE IN DEVELOPING THERAPIES FOR EPILEPSY

The blood brain barrier acts as a neuroprotective barrier that prevents the entry of harmful substances into the brain while supplying essential nutrients to the tissues [8]. The BBB consists of a network of brain capillaries (micro-vessels) that are the smallest vessels of the vascular system, with a diameter of 3-7 μm. To ensure an efficient nutrient and oxygen supply, approximately 100 billion of these micro-capillaries are tightly packed and are separated by a distance of only 40 μm. The transport of compounds in and out of the brain, leukocyte migration and maintenance of homeostasis of the brain micro-environment are regulated by the micro-vascular endothelial cells of the BBB [8]. The adjacent endothelial cells of the brain capillaries contain tight junctions [16, 17] with multi-protein cell-cell interactions and a few perforations and pinocytotic vesicles [18-21]. As a result, only drugs with a molecular mass of < 400-500 daltons can pass through the BBB [15]. However, before drugs are able to reach the CNS, macrophages tend to phagocytose them within the RES, and astrocytes further limit drug accumulation in the brain [22, 23]. Macrophages, mast cells and local microglial cells contribute to the CNS immune system [24]. Lymphatic drainage and the absence of major histocompatibility complex molecules also afford considerable protection to the CNS [25]. The blood-cerebrospinal fluid formed by the epithelial cells of the choroid plexus is another barrier in the CNS and regulates the exchange of molecules between blood and cerebrospinal fluids through facilitated diffusion and active transport mechanisms [26, 27]. In summary, tight barriers to the CNS prevent conventional pharmacological drugs or chemotherapeutic agents from reaching targeted locations within the brain.

Epilepsy treatments are currently confined to controlling brain seizures by exposing brain tissues to sufficient dosages of AEDs via the oral, parenteral and rectal routes. However, these approaches unnecessarily increase the threshold of total body drug and tend to increase resistance to AEDs in epileptic patients. Among the different drug delivery systems targeting the brain, the molecular and nano-carrier approaches are the two main approaches [28]. In the molecular approach, drugs target brain cells due to their lipophilic potential, size, receptor mediation or site-specific enzymes that help to convert inactive drugs to their active forms. However, the scope of this approach is rather limited because knowledge of the potential drug candidates and associated metabolic pathways is still being developed through ongoing research. In the nano-carrier approach, different classes of compounds in use or under development are administered intravenously, orally, intrathecally or as implanted devices. The major AED-nanomaterial formulations reported to date include liposomes, polymeric nanoparticles, nano-emulsions, solid lipids and magnetic nanoparticles. A pictorial representation of epilepsy brain treatment by the use of several nano-carriers is provided in (Fig. **1**).

## LIPOSOMES

Liposomes refers to unilamellar or multilamellar phospholipid vesicles that enclose a central aqueous compartment [29]. Liposomes are the most investigated AED delivery system because

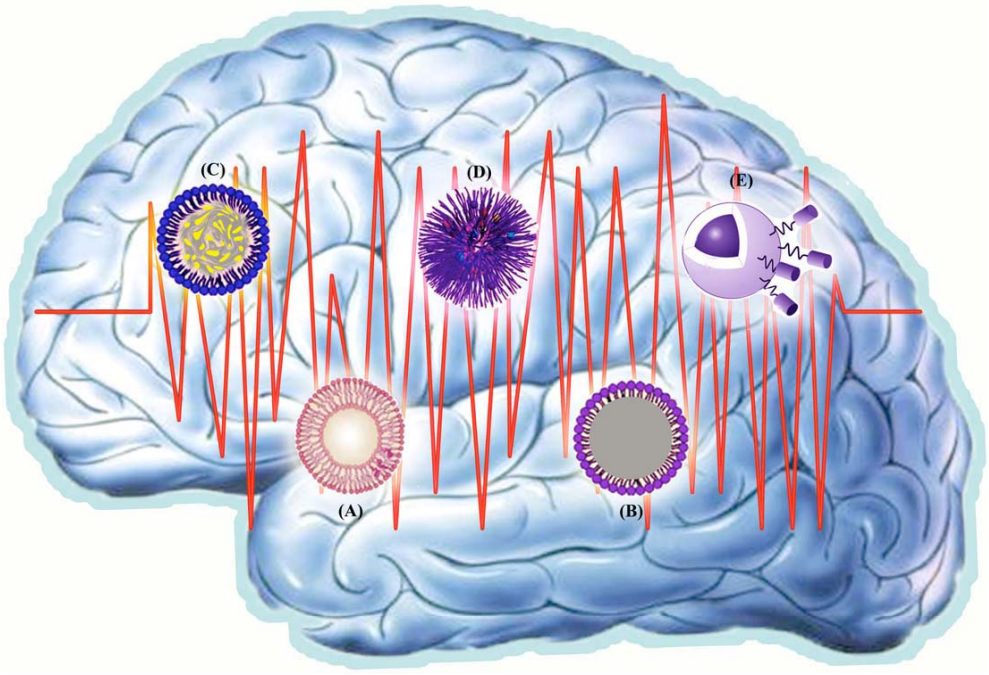


**Fig. (1).** Pictorial representation of epileptic brain treatment with various carriers. (**A**) Liposomal nanoparticle; (**B**) Solid lipid nanoparticle; (**C**); Nanoemulsion; (**D**); Polymeric nanoparticle; (**E**) Magnetic nanoparticle.

of their biocompatibility, biodegradability and ability to encapsulate drugs with diverse lipophilicities and molecular weights [30]. The ease of altering their dimensions, membrane fluidity and surface characteristics make them ideal nano-carriers. There have been reports about the enhanced bioavailability of drugs across cellular membranes and minimization of enzymatic degradation through the use of liposomal carriers [31]. Liposome half-lives can be improved through vesicle size reduction, enhanced surface hydrophilicity or the use of glycolipids and polyethylene glycol [32, 33]. Hydrophilic moieties form a peri-liposomal layer adjacent to the liposome surface and prevent opsonins from accessing the liposome surface, which hides these nano-carriers from immediate RES-mediated clearance [2].

For the purpose of stimulus-dependent release of drugs from liposomes, a pH- and temperature-sensitive liposome has been developed, which discharges its drug contents in response to an acidic environment and enhanced temperature (41°C-42°C) applied to the target site [34]. In an early study, Loeb *et al.* (1982 and 1986) reported that liposome-entrapped gamma-aminobutyric acid (GABA) inhibits penicillin and isoniazid-induced epileptogenic activity in rodents [35, 36]. In one study, a thyrotropin-releasing hormone liposome formulation resulted in an extended anticonvulsant effect and suppressed seizures in amygdaloid-kindled rats [37]. In another study, the same research group reported successful prevention of seizures in response to certain threshold concentrations of liposomal GABA in amygdaloid-kindled rats. Mori *et al.* (1995) used liposome-entrapped phenytoin (PHT-L) to investigate status epilepticus in a rat model. They reported suppression of total seizures and stable cortical spiking activity in response to PHT-L [38].

Liposome formulations are used in the treatment of several malignant conditions in which secondary epilepsy is a characteristic feature. Neoplasms in the brain are often major etiological factors for epileptic seizures. Immunoliposomes are a successful strategy for optimal drug delivery to the brain. They are formulated by the conjugation of polyethylene glycol (PEG)-stabilized liposomes with monoclonal antibodies to the rat transferrin receptor. Immunoliposomes have been reported to deliver drugs at concentrations four times higher than PEG-liposomes [39]. Some studies of PEGylated immunoliposomes combined with anti-neoplastic drugs have yielded encouraging results with respect to delivery of drugs to targets [40, 41]. In one study, Yang *et al.* (2012) reported improved remission in mouse model glioma in response to guided chemotherapy using PEGylated liposomal doxorubicin in combination with repeated pulsed high-intensity focused ultrasound [42]. In another study, Anders *et al*. (2013) reported the improved pharmacokinetics and efficacy of PEGylated liposomal doxorubicin compared to non-liposomal doxorubicin in a mice model [43].

In another study, Bickel *et al.* (2001) used a monoclonal antibody associated with a liposome. The monoclonal antibody could attach an AED encapsulated liposome to a transferrin receptor that transports iron across the BBB via receptor-mediated transcytosis and enhances the entry of the linked liposome into the brain tissue [44]. Kohane *et al.* (2002) reported seizure suppression and minimal histological alterations in animals that received liposomal muscimol (a natural GABA agonist in brain histology that shows anticonvulsant activity) in focal seizures in rats [45]. Atif *et al.* (2007) reported the higher anticonvulsant potential of liposome-entrapped amiloride compared to free amiloride and minimization of hyperkalemia in a mice model [46]. Alam *et al.* (2008) reported an optimal liposomal combination of amiloride hydrochloride having encapsulation potential. The formulation led to an increased seizure threshold in mice, which clearly indicated a higher uptake old in mice, which clearly indicated a higher uptake of liposomal amiloride hydrochloride by the brain cells compared to the free form [47].

Reactive oxygen species (ROS) are well known etiological agents in different forms of neurodegenerative diseases, including epilepsy [48, 49]. Hidekatsu *et al.* (1992) prolonged the anticonvulsant effect in amygdaloid-kindled rats using certain concentrations of a superoxide dismutase-liposomal formulation [50]. Kizelsztein *et al.* (2009) reported the use of controlled release tempamine (a potential antioxidant) via PEGylated liposomes containing tempamine in an animal model [51]. Curcumin is a natural compound known for several pharmacological activities including an anticonvulsant effect, but the bioavailability of this polyphenol limits its uses in several diseases [52]. Recently, Agarwal *et al.* (2013) reported that administration of a liposomal curcumin formulation led to significant increase in the seizure threshold current and latency to myoclonic and generalized seizures in a mice model [53].

The reported general limitations of these liposomal formulations include rapid immune-mediated clearance from the blood stream by RES, low stability after extended storage, fast metabolic degradation of phospholipids and failure to supply a continuous release of drugs compared with other nano-carriers [54]. Newer generations of liposomal-AED formulations have overcome some of these drawbacks, such as shelf life and stability, in comparison with the preceding generations of liposomal-AED formulations [55]. Moreover, liposomal formulations of several pharmacologically active AEDs in the pre-clinical stage of development, including valproic acid, superoxide dismutase, GABA and amiloride, are expected to open new opportunities regarding drug delivery to the brain [56].

## POLYMERIC NANOPARTICLES

Most polymeric nanoparticles are biodegradable and biocompatible, and have sizes between 10 to 1000 nm; they can be utilized for different methods of nanomaterial drug delivery. Polymeric nanoparticle formulations include poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid), poly(alkylcyanoacrylates), poly(e-caprolactone), poly(methylidenemalonate) and poly(lactic-co-glycolic acid) [PLGA]. Due to their safety and biocompatibility, the U.S. Food and Drug Administration (USFDA) approved the use of PLGA-based nano-carriers in humans. The potential degradation of PLGA inside the body can also be utilized to make them effective nano-carriers and can be achieved by changing the copolymer ratio [57].

Drugs loaded on polymeric NPs are released at the targeted sites through a combination of different mechanisms of diffusion and polymeric degradation. The drug unloading efficiency, which can vary from hours to months, depends on the drug-polymer ratio and molecular weight and chemical composition of the polymers [56]. β-Carotene is an antioxidant used for the treatment of epileptic convulsions at a dose of 200 mg/kg. According to Mohammad *et al.* (2012), the bioavailability and stability of polysorbate-80-coated β-carotene nanoparticles (P-80-BCNP) for epileptic convulsions in mice models is higher than that of unmodified β-carotene [58].

Targeting is the incorporation of ligands into the nanocarrier system corresponding to the carrier molecule or endocytosis systems in the brain capillaries, which enhances transport across the BBB. The addition of targeting moieties to the nano-delivery systems also facilitates the uptake of particle delivery systems into the brain. In one study, poly(butylcyanoacrylate) NPs encapsulated with an anti-convulsant N-methyl-D-aspartate (NMDA) receptor

antagonist (probenecid) were coated with PEG-containing surfactant. Parenteral administration of probenecid with this nanocarrier system prolonged its anti-convulsive activity compared to the free drug [59].

Veronesi *et al*. (2009) reported on a nanoparticle formulation of thyrotropin-releasing hormone (TRH) with sustained release and neuroprotective features. In their study, D,L-polylactide NP containing TRH (TRH-NP) yielded positive results in both *in vitro* and *in vivo* models. In cultured rats, fetal hippocampal neurons treated with TRH-NP have been reported to possess neuroprotective potential against glutamate toxicity. Treatment with intranasal TRH-NP prior to kindling temporal epilepsy in a rat model increased the stimulus needed for kindling. TRH-NP also prolonged the clonus interval and reduced its duration in treated subjects, which accounts for the extended bioavailability of TRH [60]. In another study using the same nano-formulation, Kubek *et al*. (2009) reported similar findings and added that intranasal application of an unprotected TRH analog is dose dependent and can fully suppress a kindled seizure depending on its stage [61]. Zhuzhu *et al*. (2007) used poly(ε-caprolactone) [PCL] micro-carriers for the extended delivery of phenytoin. They reported sustained drug release from micro-carriers, which could be beneficial for the long-term treatment of AED-resistant patients [62].

Hsiao *et al*. (2012) reported on a novel formulation of ethosuximide incorporating nano-capsules of chitosan, glycerophosphate di-sodium salt and glycerol. The subcutaneous administration of this formulation resulted in suppression of the spike wave discharge in a rat model. These nanocapsules could be compressed as a depot drug delivery system for antiepileptic drugs in long-term use because of their stable release (no sudden spike concentrations) over time [63]. Several successful polymeric nano-formulations of major AED drugs have been reported in the scientific literature, including clonazepam [64-68], ethosuximide [69, 70], valproate [71], loperamaide [72], phenytoin [69, 73] and carbamazepine [69]. New generation AED-polymeric nanoparticle formulations are also being developed or are in preclinical testing for novel routes of drug administration via the intranasal (thyrotropin), oral (phenytoin, diazepam, and carbamazepine) and parenteral (ethosuximide) routes [56].

The major advantage of polymeric NPs over liposome-based models lies in their easy preparation, greater stability (*in vivo* and *in vitro*) and efficient storage potential. Another advantage of polymeric NPs over liposomes is their potential for continuous and controlled release of drugs over extended periods of time. The disadvantages associated with polymeric NPs and liposomes are their rapid clearance from the plasma due to opsonization and subsequent phagocytosis in the RES. Polymers such as PEG, polyvinyl alcohol, poly-acrylamide and polysaccharides have been incorporated into the surface of these nano-carriers to increase their circulation time. The conjugation of these polymer chains produces a stealth-like character because the particles are no longer recognized and opsonized by RES, which increases the circulation time from several minutes to many hours.

## SOLID-LIPID NANOPARTICLES (SLNS)

SLNs are physiological lipid-based delivery systems that offer physical stability, protection of labile drugs from degradation, ease of preparation and lower toxicity due to their unique properties, including their small size, large surface area, high drug loading and phase interaction at the interfaces; thus, they have the potential to improve the efficacy of pharmaceuticals, nutraceuticals and other materials [29]. SLNs have been developed as an alternative delivery system to the existing traditional carriers, such as liposomes and polymeric NPs. SLNs are new-generation lipid emulsions where the liquid-lipid has been substituted with a solid-lipid [29]. Recently, SLNs have made substantial progress in targeted drug-delivery against various disorders such as cancer and neurodegenerative diseases, including epilepsy [29, 74-76].

Several studies have reported on different SLN formulations that may be administered via different routes, including the parenteral, oral, rectal, ophthalmic and topical routes, which leads to controlled delivery and enhanced bioavailability of the entrapped drugs [74-79]. Several studies have also highlighted the advantages of SLNs over other nanoparticle formulations in brain targeting [80-83]. Restricted entry to the BBB and the reduced bioavailability of specific drugs are the major challenges in epilepsy treatment. A number of scientific studies on the use of different SLN formulations loaded with specific AEDs has suggested the high efficacy of these delivery systems for epilepsy treatment [84-89]. These studies have demonstrated high therapeutic potential and BBB-crossing ability by these AEDs.

Diazepam is a poorly water-soluble AED and has been used for the treatment of prolonged fits or status epilepticus since the 1970s [90]. To enhance the bioavailability of this particular drug to the CNS, several routes of administration have been tried [91]. In one study, Abdelbary and Fahmy (2009) studied SLN-based systems for the delivery of diazepam because of their higher entrapment efficiency and *in vitro* drug release [85]. Temozolomide has been reported in the scientific literature for its ability to reduce seizure frequency among patients with intractable epilepsy [92, 93]. In one study, Jain *et al*. (2013) reported a transferrin-tailored SLN that can cross the BBB for the site-specific delivery of temozolomide into the brain [94].

Carbamezapine is a lipophilic drug clinically considered the drug of choice for the treatment of complex partial seizures and acts through the inactivation of sodium channels [86, 95]. The anticonvulsant potential of carbamazepine is scientifically well documented, and its therapeutic efficacy is a promising development towards epilepsy treatment. Nair *et al*. (2012) reported that an SLN-carbamazepine formulation containing the biopolymer chitosan resulted in a prolonged controlled release and improved therapeutic efficacy for the treatment of epilepsy [86]. Riluzole, a pre- and postsynaptic modulator of glutamate transmission, has been identified as a potent neuroprotective drug with additional anticonvulsant, anxiolytic and anti-ischemic properties [96]. Bondì *et al*. (2010) demonstrated riluzole-loaded SLN delivery into the CNS with comparatively lower drug bio-distribution in different organs. Their study highlighted several advantages of riluzole-loaded SLN, such as higher drug loading, greater efficacy compared with free riluzole, the improved capability to carry the drug into the brain and more selective bio-distribution [87].

Gabapentin is a GABA-analog AED and is effective in the treatment of partial and generalized tonic-clonic seizures [97]. Dhana Lakshmi *et al*. (2012) reported on gabapentin- incorporated SLNs in which the release of the drug was either via diffusion from the matrix or via matrix erosion due to lipid degradation [88].

Carvedilol is a nonselective vasodilating beta-adrenoreceptor antagonist and is used clinically for the treatment of mild to severe chronic heart failure with systolic left ventricular dysfunction [98]. Goel *et al*. (2013) showed that carvedilol potentiates the anticonvulsive activity of gabapentin, which can be useful for the treatment

of epilepsy in patients with hypertension [99]. Recently, Shah and Lin (2013) reported that an anti-hypertensive carvedilol-loaded SLN drug has a synergetic effect with gabapentin [100].

Based on the available scientific literature, SLNs seem to be promising drug carriers for the treatment of epilepsy because of their advantages in terms of toxicity, production feasibility and scalability [80]. Therefore, the use of these carriers as brain-targeted drug delivery system for both newer or older neuro-therapeutics should be investigated further. SLN may be an alternative drug delivery system for administering molecules to the brain with prolonged drug release profiles, resulting in an improved therapeutic effect in the treatment of seizures [88].

## NANO-EMULSIONS (NE)

Nano-emulsions may be easily prepared through spontaneous emulsification and provide improved stability and solubility of the loaded drug molecules [94, 101]. Nano-emulsions are a heterogeneous drug delivery system composed of oil, water and surfactants with a droplet size typically in the range of 10 to 100 nm [102]. Several studies report that NE are an effective transport system providing an increased rate of absorption, rapid and efficient penetration of drug moieties, reduced toxicity and irritation, protection from hydrolysis and oxidation of the drug in the oil phase and the ability to be administered via multiple routes [94, 101-106].

The major advantage of AED-loaded NE is that they can pass through the BBB even with drugs that have reduced bioavailability. Jain *et al*. (2011) reported on a novel muco-adhesive NE formulation loaded with amiloride that could be administered via the intranasal route; this could be an effective treatment method for epilepsy [94]. Kumar *et al*. (2008) reported that an optimized olanzapine-loaded NE formulation gave better nose-to-brain delivery than an olanzapine solution in a rat model [107]. In a later study, the same group of researchers reported that an olanzapine NE formulation showed improved stability and was potentially non-toxic towards nasal cilia [108]. Recently, Shailaja *et al*. (2012) reported on a potentially stable olanzapine-loaded nano-formulation NE for improved delivery of olanzapine to the brain [109].

In a study by Kelmann *et al*. (2007), carbamazepine as a NE was used in the treatment of generalized tonic clonic and partial seizures [110]. They reported that a formulation of carbamazepine-loaded NE, stabilized by 1-O-alkylglycerol/lecithin, showed targeted drug delivery and higher bioavailability in a mice model [111]. Kuminek *et al*. (2009) studied the pharmacokinetics of carbamazepine-loaded NE in beagle dogs and reported pharmacokinetic profiles similar to a carbamazepine/hydroxypropyl-beta-cyclodextrin complex solution [112]. They also suggested that NE-loaded carbamazepine is a valuable formulation in case of emergencies, when rapid action in the CNS is required. Clonazepam microemulsions have been used for rapid drug delivery to the brain for the treatment of acute status epileptic patients [113].

## MAGNETIC NANOPARTICLES (MNPS)

MNPs are potential candidates for the effective site-specific delivery of therapeutic agents. The biological and clinical application of MNPs has been suggested for more than three decades [29, 114]. MNPs gained significant attention in targeted medicinal therapy because their characteristic modulator-type control through an external magnetic field was able to give precise outputs, such as a controlled and sustained rate of drug release and transportation across desired tissues, thus minimizing toxicity to other tissues [115].

MNPs consist of three ferromagnetic elements: cobalt (Co), nickel (Ni) and iron (Fe). The applications of MNPs mainly depend upon the preparation processes [114]. Ni-based nano-materials as well as Co- and Cu-based nonviral carriers in gene therapy have already been reported for tumor targeting. We have also highlighted the significance of magnetically guided drug release and gene targeting via MNPs as a promising advance in cancer chemotherapy and gene therapy techniques [29]. Surface coating of MNPs with biodegradable (e.g., certain polymers) or non-biodegradable (e.g., silica) particles have further improved their biocompatibility, which is determined by particle surface characteristics, such as the hydrophilicity and surface charge [116]. These types of modifications often help to stabilize MNPs by preventing oxidation, increasing drug loading capacity and providing good dispersion [117].

Recently, exciting advancements in the application of MNPs have surmounted challenges in the treatment of brain diseases, such as permeability across the BBB [118]. Based on this approach, brain tumors, which may have deep intracranial locations, have been successfully targeted. For example, Akhtari *et al*. (2008) reported utilizing the potential of MNPs attached to non-radioactive alpha-methyl tryptophan in a rodent model of temporal lobe epilepsy and showed localized deposition of the drug in the epileptogenic tissues [119]. In their study, magnetic resonance imaging resulted in intra-parenchymal uptake of these MNPs for the delivery of AEDs; delivery of the AEDs was controlled by tuning the magnetic field. Huang *et al*. (2009) reported a novel flexible drug delivery chip-like device capable of fast and precise delivery, suggesting the potential use of this device for seizure prevention in patients suffering from epileptic disorders [120]. Recently, Liu *et al*. (2011) demonstrated that magnetic-field-sensitive alginate-chitosan hydrogel beads could be used as an effective epileptic drug carrier, due to their excellent super-paramagnetism and their potential for controlled drug release [121].

Even though binding drug particles to MNPs has been discussed for more than three decades, not one MNP has been approved for clinical practice as a delivery system. Nevertheless, progress has been made in MNP-mediated drug delivery, such as in gene delivery with magnetofection *in-vitro* cell lines, which could serve as a potential cancer treatment method [116]. The advantages and disadvantages related with the use of several nano-carriers in epilepsy treatment have been listed in Table **1**.

## CONCLUSION

Nanotechnology is a rapidly developing field that has given new hope for the treatment of various disorders, including CNS diseases. The ability to cross the BBB and the specificity of targeting seem to be the major hurdles for the success of AEDs in pharmacotherapy. Applications of nano-based drug delivery systems to epilepsy is a promising solution that may overcome these limitations. Various NP-based drug-delivery systems, such as liposomes, polymeric nanoparticles, NE, SLNs and MNPs, have been reported and suggested as AED delivery systems. Bearing in mind the different nano-based AEDs at various stages of clinical trials, the scientific community may discover new nano-based AEDs formulations in the near future for the treatment of epilepsy. SLNs and NE-based systems could become major delivery systems due to their potential to control toxicity and their high production feasibility and scalability. Nonetheless, the possibilities for toxicity associated with different nano-formulations should be considered before treatment using novel delivery systems for epilepsy is approved [8].

**Table 1. Advantages and disadvantages of several nano-carriers used in epilepsy treatment**

| Nano-carriers | Drugs used | Reference studies | Advantages | Disadvantages |
|---|---|---|---|---|
| **Liposomes**<br>• PEG-Liposomes<br>• Glycolipid conjugated<br>• Immuno liposomes | GABA<br>Phenytoin<br>Thyrotropin | Loeb *et al.* [33,34]<br>Mori *et al*. [35,36]<br>Huwyler *et al.*[37]<br>Bickel *et al.* [42]<br>Kohane *et al.* [43]<br>Ali *et al* [44]<br>Alam *et al.*[45]<br>Yokoyama *et al.* [48]<br>Kizelsztein *et al.* [49]<br>Agarwal *et al.* [51] | • Biocompatible<br>• Size diversity<br>• Molecular weight and hydrophilicity aids into effective encapsulation and entry to neural tissues skipping body defense machineries | • Susceptibility to RES clearing is more than the other NPs<br>• Prone to phospholipid metabolic degradation leading short stay in the system<br>• In earlier generations, shelf life stability was quite low |
| **Polymeric nanoparticles**<br>• PLGA<br>• Poly(butylcyanoacrylate)<br>• D,L-polylactide<br>• Poly(ε-caprolactone)<br>• Chitosan<br>• Pullulan acetate-PEG<br>• Poly(DL-lactide-co-glycolide)<br>• Poly(glycolic acid) | β-Carotene<br>Probenecid<br>Thyrotropin<br>Phenytoin<br>Ethosuximide<br>Clonazepam<br>Valproate<br>Loperamide<br>Carbamazepine | Yusuf *et al.*[56]<br>Friese *et al.* [57]<br>Veronesi *et al.* [58]<br>Kubek *et al.*[59]<br>Zhuzhu *et al.*[60]<br>Hsiao *et al.*[61]<br>Jung *et al.*[62]<br>Nah *et al.*[65]<br>Ryu *et al.*[66]<br>Fresta *et al.* [67]<br>Kumar *et al.* [68]<br>Hamidi *et al.*[69]<br>Ueda *et al.* [70]<br>Thakur *et al.*[71] | • Biodegradable and biocompatible<br>• Programmed drug release could be achieved by choosing apt polymer composition, ratio and molecular weight<br>• Preparation easiness and greater stability | • Susceptibility to RES clearing and opsonization |
| **Solid lipid nanoparticles**<br>• Chitosan | Diazepam<br>Temozolomide<br>Carbamazepine<br>Riluzole<br>Temozolomide<br>Riluzole<br>Carvedilol | Sznitowska *et al.*[77]<br>Jain *et al.*[82]<br>Abdelbary *et al.*[83]<br>Nair *et al.*[84]<br>Bondì *et al.*[85]<br>Browne *et al.*[88]<br>Sherman *et al.*[90]<br>Ngo *et al.*[91]<br>Jain *et al.*[92]<br>Borowicz *et al.*[94]<br>Dhana *et al.*[86]<br>Goel *et al.*[97]<br>Shah *et al.*[98] | • Greater physical stability<br>• Lesser toxicity<br>• Greater surface area improve both drug loading and its efficacy<br>• Multiple routes of administration | |

**Table (1) contd…..**

| Nano-carriers | Drugs used | Reference studies | Advantages | Disadvantages |
|---|---|---|---|---|
| **Nano emulsion** | Amiloride<br>Olanzapine<br>Carbamazepine<br>Clonazepam<br>Levetiracetam | Jain *et al.*[92]<br>Kumar *et al.*[105,106]<br>Doheny *et al.*[93]<br>Shailaja *et al.*[107]<br>Kelmann *et al.*[108]<br>Madhusudhan *et al.* [109]<br>Kuminek *et al.*[110]<br>Vyas *et al.*[111] | • Stable preparations<br>• Higher rate of absorption<br>• Transmittable in multiple routes with less toxicity and irritation<br>• BBB permeable | |
| **Magnetic nanoparticles**<br>• Cobalt (Co) based<br>• Nickel (Ni) based<br>• Iron (Fe) based<br>• Alginate-chitosan | Carbamazepine<br>Alpha-methyl Tryptophan(diagnostic)<br>Ethosuximide | Akhtari *et al.*[117]<br>Wang *et al.*[113]<br>Jabir *et al.*[27]<br>Huang *et al.*[118]<br>Juan *et al.*[119] | • Precise modular control on transport and delivery to the targets<br>• Minimum toxicity to other tissues | |

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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