Review Article

Nano Emulsion: The targeted drug delivery in the therapy of Epilepsy

ABSTRACT

Around the world, 50 million people suffer with epilepsy; it significantly burdens society in terms of finances, society, and health. Our comprehension of the pathophysiological processes causing the illness and the factors affecting its prognosis has significantly advanced during the last ten years. Around a third of patients are still resistive to medical intervention, despite the fact that the number of antiepileptic drugs has expanded dramatically over the past 20 years. The ability of nanotech-based anti-epileptic drug (AED) administration methods to cross the blood brain barrier, increase specificity, and have the capacity for extended brain administration of drugs have lately attracted interest. Nanotechnology appears to be a promising and innovative development in this area. Nano emulsions have a mean droplet size of 20 to 200 nm and remain kinetically stable dispersions of two incompatible liquids with the assistance of an emulsifier or emulsifiers. The effectiveness of NEs as a delivery system for Central Nervous System-active medications used in effective regimens against difficult-to-treat CNS conditions.

Keywords: Epilepsy, Types of seizures, Antiepileptic drugs, Nanoemulsions.

1. INTRODUCTION

Epi is a Greek prefix, which means " onto," & labein, a Greek verb, which means "to take, grasp, or seize," are the roots of the word "epilepsy" [1]. One can experience epilepsy at any stage in their life, which is a serious worldwide health crisis [2]. It ranks the third most third-most prevalent severe neurological ailment and it is a long-lasting, non-communicable illness of the brain. The stereotyped behavioural abnormalities that characterise epileptic seizures, recurrent paroxysmal instances, which represent the disease's underlying neurological mechanisms [3]. Approximately 50 million people, or One percent of the world's population, suffer from epilepsy, a brain illness that shortens life. Although epilepsy is widespread, 80 percent of patients are found in nations with middle or low incomes. [4]. One percent of people have epilepsy in India [5]. The International League against Epilepsy (ILAE) describes a seizure of epilepsy as "a brief episode of signs or symptoms brought on by abnormally excessive or synchronous brain neuronal activity." The idea of epilepsy is described as ‘’a persistent propensity for epileptic seizures in the brain that has negative effects on neurobiology, cognition, psychology, and society’’ [6].

The pathogenesis of epileptic seizures is frequently attributed to an imbalance caused by the activation of glutamatergic neurotransmission and the inhibition of GABA-mediated neurotransmission in the brain, specifically in the hippocampal, neocortical, corticothalamic, and basal ganglia network [7].

A transient alteration in behaviour caused by extremely aberrant or synchronised neural activity in the brain is known as an epileptic seizure. Both observable symptoms and psychological signs, such as loss of consciousness, jerking, feeling rising from the abdomen towards the chest area, a burnt rubber smell, or a feeling of déjà vu can be present. The start of a seizure could have an unknown onset, be focal, or be generalised. Almost any injury that disturbs brain function can result in seizures, even though the origin of epilepsy in many people is unknown. There are numerous causes of these injuries, including acquired causes (such as those following a stroke, brain tumour, or brain trauma), infectious circumstances (including meningitis, encephalitis, and also neurocysticercosis), genetic changes, Immune system disorders, and occasionally disrupted levels of substances like sodium or sugar [8].

In addition to significantly higher morbidity and death, it is accompanied by depression and anxiety [4].

1.1 Types of Seizures

The commencement of a seizure can be focal (may initiate in a single region of the brain), generalised (occurring simultaneously in both regions), or undetermined. Based on degree of awareness-measure of consciousness is unharmed or damaged, focal seizures are categorised. nonmotor and motor seizures are further separated into focal and generalised forms [9].

Table 1: Seizure classification

Focal onset	Generalized onset	Focal onset
Aware or impaired awareness	Motor • Tonic-clonic • Other motor	Motor • Tonic-clonic • Other motor
Motor onset or nonmotor onset	Nonmotor	Nonmotor
Focal to bilateral tonic-clonic		Unclassified

1.1.1 Status epilepticus is characterised by seizures lasting less than 30 minutes or by episodes with no remission in between.

1.1.2 Sudden unexpected death in epilepsy (SUDEP) is described as a sudden, unexpected, nontraumatic, and nondrowning death in epileptic patients, regardless of the indication of a seizure, apart from reported SE, in which a toxicologic or physical source of death is not identified after postmortem examination. SUDEP is frequently brought on by seizures and seizure-induced alterations in cardiorespiratory performance are a tenable theory [9].

2. TREATMENT

Epilepsy is currently treated with monotherapy with contemporary antiepileptic medicines, while some cases call for polypharmacy, or the use of two or more anticonvulsants. Regulation of Cl- channel-mediated GABA inhibition of neurotransmitters that are excitatory and irrational neuronal firing are

examples of therapeutic approaches. These therapeutic approaches, however, have a wide range of negative side effects [10].

2.1 Antiepileptic Medications (AEDs): The main goal of AEDs is to stop epileptic episodes. They are also helpful for a variety of non-epileptic disorders and are frequently used as a treatment mental illness, neuropathic pain, and migraine. AEDs can also be helpful therapy of phobias, anxiousness, and syndrome of restless legs, essential tremor, schizophrenia, myotonia, dystonia, essential tremor, myotonia, Chronic stress disorder after trauma, and withdrawal from alcohol and alcoholism [11].

Table 2: Classification of AEDs

Type of Seizures	Drugs
Focal seizures and most Generalised seizure types	Benzodiazepines, Phenobarbital, Levetiracetam, Lamotrigine, Topiramate, Felbamate, primidone and Valproic acid,
Focal seizures, with or without Secondary generalisation:	phenytoin, Gabapentin, Carbamazepine, tiagabine, Lacosamide, pregabalin, Vigabatrin.
Absence seizures	Ethosuximide

AEDs prevent the spread of aberrant firing, that is required for the manifestation of behavioural seizure activity to distant regions. The extraordinary property of the medications is their ability help control seizures while maintaining normal neurological function. AEDs suppress seizure-related firing without affecting non-epileptic activity via specifically modifying the excitability of neurons by means of a range of molecular targets. This is mostly accomplished via influencing sodium and calcium-voltage-gated channels, or by promoting inhibition through GABAA (gamma-aminobutyric acid, type A) receptors [11].

Although there are many antiepileptic medications in the market, their effectiveness has been restricted because of adverse effects, poor gastrointestinal absorption, drug resistance, BBB penetration, and plasma protein binding [12].

2.2 Other treatments include: Drug-resistant epilepsy, Emergency treatments, Surgical procedure, Medical intervention, Neurostimulation [6].

3. NANOEMULSION

About 20 and 40% of epileptic individuals still experience medically intractable epilepsy, despite major advancements in recent decades. About 70% of AEDs are successful, yet there are still a lot of problems that require to be fixed counting inadequate bioavailability, solubility, blood-brain barrier (BBB) permeability, high cost, unavailability, and unpleasant effects [13]. Since traditional medicines have a low bioavailability and eventually lose their effectiveness as therapy goes on owing to drug resistance, managing epilepsy with them can be difficult. Appropriate drug delivery methods can alleviate the difficulties in treating epilepsy caused by the current AEDs' inability to traverse the nearby

BBB. Systems built on nanotechnology appear to be an innovative and promising improvement in this area. Using customised nanocarriers to target drug molecules to the brain is a new method of selectively delivering medications to the brain [5].

Nanoemulsions are created delivery devices for biologically active substances for controlled release and drug delivery [14]. Due to their ability to improve solubility of lipid soluble medicines, penetration through biological membranes, and efficacy in therapy because of their predictable shape distribution, high loading of drugs, and endurance in biological systems, Due to the nanometre-sized droplet width of NE, these formulations have attracted a lot of attention as drug delivery systems for lipophilic medications. [15].

NE are thermally stable and isotropic, homogeneous system of water, oil and surfactants/co-surfactants. NE droplet sizes (o/w and w/o) range from 20 to 200 nm [16]. Over traditional formulations, the NE system has a number of advantages. One of the best methods for making lipophilic medications more water soluble is NE, which also improves the drug's bioavailability in the bloodstream [17]. Drug distribution (targeted and sustained) depends heavily on the transport characteristics of the drug, which are affected by the nanoscale droplets' larger interfacial areas [15].

Water in oil NE, droplets of water scattered over a phase of continuous oil and bi-continuous NE are the three forms of NE that can form [14]. When oil is spread in the continuous aqueous phase, oil in water NE occurs. To create NE, many methods include, ultrasonication, phase inversion temperature, high pressure homogenization, emulsion inversion point, and more newly found methods like the bubble bursting method are employed [18].

3.1 Formulations of Nanoemulsion

3.1.1 Topiramate: A broad spectrum anti-epileptic medication called topiramate has been licenced in the treatment of both focal and tonic-clonic seizures. The brain bioavailability of topiramate is low following oral delivery during an epileptic seizure. The main dose-related adverse event with TPM use is severe weight loss. This study demonstrated that increasing brain bioavailability with intranasal administration of topiramate-containing NE is possible. The findings of this study provided a strong foundation for developing a TPM-containing NE formulation and putting it to use in clinical settings [19].

3.1.2 Letrozole (LET): To decrease the negative effects of LET on the peripheral nervous system, Iqbal and colleagues created a NE for letrozole to be delivered nose-to-brain. In mice with SE caused by kainic acid, the new formulation was contrasted with intraperitoneally administered free medication. Because of direct nose-to-brain transport, LET-NE treatment intraperitoneally increased absorption compared to the i.p. method. Only with LET-NE were additional neuroprotective effects seen. When given as an intranasal NE, LET was found to be present in higher concentrations in the mouse brain during gamma scintigraphy investigations. Histopathological studies and behavioural monitoring showed that LET-NE's anticonvulsant activity was greater to LET's. [20].

3.1.3 Amiloride to surge the brain's ability to absorb amiloride, an amiloride NE was created utilising a combination of the high energy ultrasonication method and aqueous micro titration method. It was found that formulation had a highly significant, targeting potential and efficiency, which means that amiloride is now more bioavailable in the brain. Assessment of in vivo data for biodistribution, pharmacokinetics, effectiveness of brain targeting, and transport were used to support this claim [21].

3.1.4 *Centella asiatica* (*C. asiatica*): The Ayurvedic medicine *C. asiatica* has been used to treat epilepsy. They created a NE that contained *C. asiatica* crude extract, and research has shown that it is a promising formulation that should be used in future studies for a pharmaceutical use, specifically for the management of epilepsy [22].

3.1.5 β-Caryophyllene: is a typical natural phenomenon cannabinoid receptor activator with possible anticonvulsant effects but low oral bioavailability. They used Pentylenetetrazole (PTZ)-induced seizure model to establish and define NE and its possible antiepileptic activity when administered intravenously to rats. By means of spontaneous emulsification, β-Caryophyllene-NE was created. A study conducted in vivo showed up *i.n.* NE treatment postponed the beginning of grand mal seizure. These outcomes showed that NE given through the *i.n.* pathway has the possibility to be anticonvulsant, demonstrating that the proposed approach provides effective intranasal BCP delivery [23].

3.1.6 Other Examples: Valproic acid loaded NE, Gabapentin loaded optimised NE, Phenytoin NE, Carbamazepine NE, Rutin NE, Cannabidiol NE. Herbal Formulations include *Centella asiatica* NE**,** NE of Safranol.

3.2 Advantages

1. By enhancing lipid solubility, it improves transport to the brain [24].
2. It increases the drug's bioavailability [25].
3. Non-irritating and not harmful.
4. NEs have small droplets with more surface area, which boosts absorption.
5. The huge NE interfacial area facilitates the delivery of the medicine or active component to the desired spot.
6. Effective at disguising flavour.
7. NEs can be used to produce both hydrophobic and hydrophilic medications [26].
8. Drugs that are prone to oxidation and hydrolysis may also be protected by NE [14].
9. Improve the profile of pharmacokinetics [27].

3.3 Disadvantages

1. Lack of stability is the biggest drawback of NE's [28].
2. Several debilitating processes, such as, including coalescence, ostwald ripening, flocculation, and creaming/sedimentation, cause NE to gradually divide into various phases over time 4].

4. CONCLUSION

Since neurological problems are becoming more common, there will eventually be a greater need for enhanced CNS therapies. With the help of epilepsy research, researchers have made incredible strides in understanding the risk factors and mechanisms behind epilepsies and comorbidities, as well as developing strategies and medications that will help us better manage seizures and any comorbid illnesses or side effects they may cause. However, there are still a lot of steps to be taken in order to provide efficient treatments that can enhance quality of life while preventing epilepsy and associated comorbidities. Approaches based on nanotechnology provide potentially efficient ways to enhance seizure identification and management. Particularly for the BBB, this poses a challenging obstacle to the transport of drugs to the brain, nanotherapeutics can be a potential vehicle. Effectiveness, safety, and enhanced bioavailability can all be attributed to NE formulation.

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