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# Efficient delivery of Antiepileptic Drugs (AED's) and Nanomedicine for the treatment of epilepsy

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## Abstract

*A common brain disorder affecting people of all age groups is epilepsy. It is characterized by development of seizures. To control the frequency of seizures a broad group of AED's (Antiepileptic drugs) were given. Epilepsy is a neurological disorder. The limited solubility and accessibility of AEDs across the blood brain barrier (BBB) have limited their oral administration. Because of their long-term drug release, low toxicity, and biocompatibility, nanomaterials were employed to administer AEDs. This paper describes about different types of AED's and their structure, mechanism of action and treatment of epilepsy using nanocarrier via blood brain barrier. Nanomaterials crosses the BBB and used barrier for diagnosis of epilepsy. This paper describes about various AED's and nanomedicines for the treatment of epilepsy. Nanomaterial have been developed for efficient delivery of AED's as well as imaging agents into CNS. These nanomedicines easily cross BBB to diagnose epilepsy. Intranasal administration route is more efficient way to deliver nanoagents for diagnosis of epilepsy.*

**Keywords**: Epilepsy, Antiepileptic Drugs, Nanomaterial, Seizures, Nanomedicine, CNS, BBB.

## I. INTRODUCTION

Everyone, regardless of age, ethnicity, or location, can be affected by epilepsy, a persistent brain illness. It associated with dysfunction at different biological levels such as cellular, molecular as well as at circuit neurological levels. Forty to seventy million individuals throughout the globe are impacted by epilepsy [5]. Unexpected and aberrant electrical activity in the brain, known as seizures, is a hallmark of epilepsy. Instead of being a distinct illness, epilepsy is a collection of symptoms. According to ILAE (International League against Epilepsy) classified epilepsy under 3 different levels.

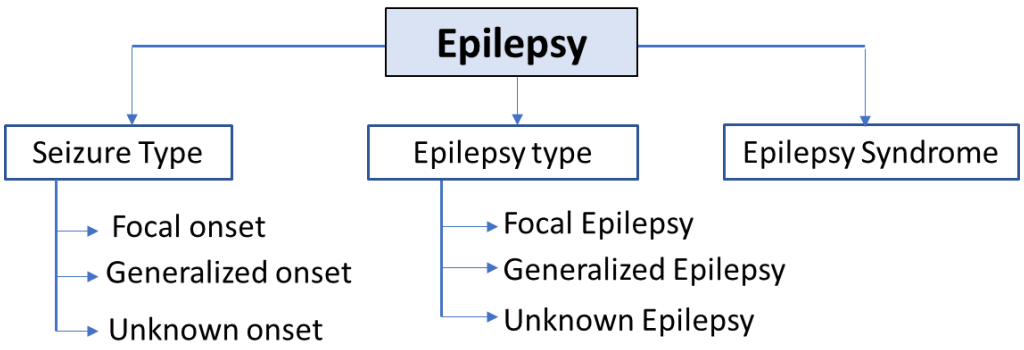



**Figure 1:** *Classification of Epilepsy with three different levels*

For Diagnosis of Epilepsy EEG (Electroencephalogram), MRI, Brain imaging results, Seizure triggers, age, prognosis [2] should be considered.

### 1.1. Antiepileptic Drugs:

Rapamycin, COX-2 inhibitors, TRK inhibitors, and JAK-STAT inhibitors are examples of targeted medications that can prevent the development of epilepsy. Epilepsy sufferers' first-line therapy for seizures is AEDs. General mechanism of AED's involves inhibiting neurotransmission excitation.

### 1.2. Structure of AED's (Antiepileptic drugs):

a) ***Phenobarbital***: It is a barbiturate widely used to treating seizures. Its action promotes the prolongation of the opening of the related chloride channel via binding to the GABA-A receptor.
b) ***Primidone***: It is used along with some other medicine to control seizures. It belongs to anticonvulsants. It works by modifying the transport mechanism of sodium and calcium channels and decreasing aberrant nerve firing.
c) ***Phenytoin***: It reduces the activity of P-450 enzyme system which involved in drug metabolism. Phenytoin suppresses aberrant brain activity.
d) ***Carbamazepine***: Its an anticonvulsant, reduces the nerve firing which causes seizures. It blocks sodium channels to prevent action potentials from firing repeatedly [9].
e) ***Oxcarbazepine (OXC)***: It is utilized in the treatment of patients suffering from both vital and complex forms of partial epilepsy. The action of this substance is to bind sodium channels, which in turn inhibits high-frequency repeated neuronal firing and the release of glutamate.
f) ***Valproate***: It is used to treat bipolar disorder, epilepsy and also migraine. The pharmacological action of this medicine involves the inhibition of voltage gated sodium channels and the augmentation of gamma-aminobutyric acid (GABA) levels within the central nervous system [8].
g) ***Lamotrigine***: This medicine is commonly used as a first treatment option for pregnant individuals. Its activity is by blocking Na-channel conductance and inhibit the release of glutamate [8].

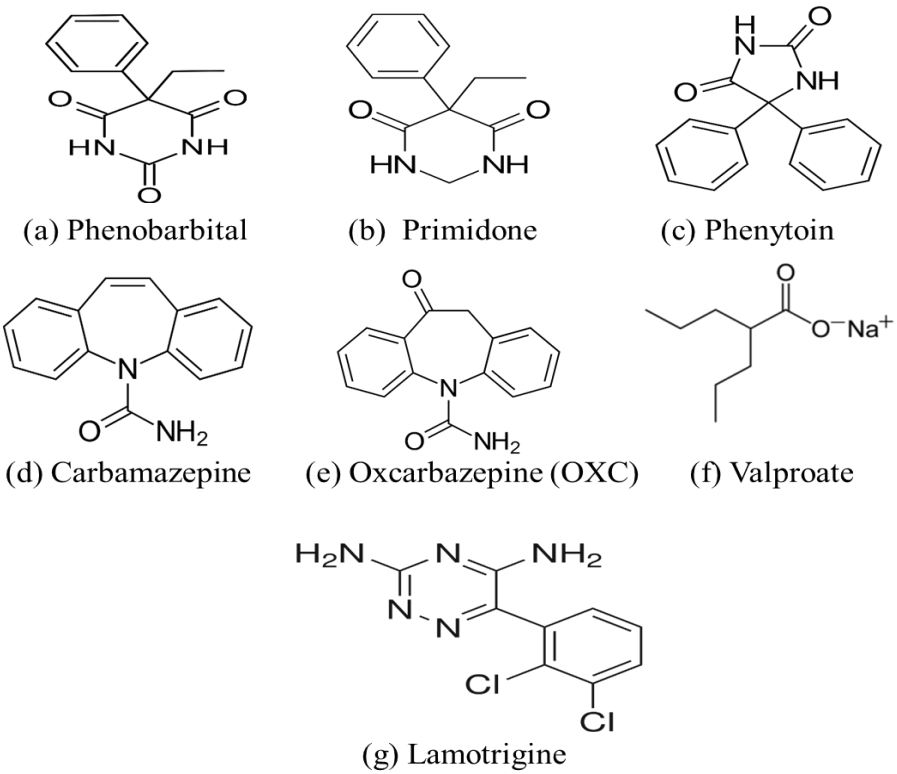



**Figure 2:** ***Structure of different types of AED's (Antiepileptic drugs)***

In most of AED's there is a presence of benzene ring. Few more AED's showed in below Table 1

**Table 1:** ***List of AED's in which benzene ring present***

| **Narrow Spectrum AED's (Effective against focal onset seizures)** | **Broad Spectrum AED's (Effective against both focal and generalized onset seizures)** |
|---|---|
| Cenobamate<br>Eslicarbazepine<br>Ethosuximide<br>Gabapentin<br>Lacosamide | Clobazam<br>Levetiracetam<br>Perampanel<br>Topiramate<br>Zonisamide |

## II. DRUG TESTING METHOD

HPLC (High Performance Liquid Chromatography), Gas Chromatography-Flame ionization and micro extraction methods, LC (Liquid chromatography) were used to determine antiepileptic drugs in biofluids. This assay helps to provide quantification of antiepileptic drugs in patient plasma sample. Drugs reduces the risk of epilepsy. According to WHO, quarter of all epilepsies are preventable because of easy identification of epilepsy patients.

**Table 2:** ***Novel AED's and their mechanism of action***

| **AED** | **Primary indication** | **Mechanism** |
|---|---|---|
| Lacosamide | Focal seizures | Inactivation of voltage gated sodium channels |
| Rafinamide | Lennox-Gastaut syndrome | Prolongation of inactivated stage of voltage-gated sodium channel. |
| Ezogabine | Focal seizures | Enhances trans membrane potassium currents mediated by KCNQ family of ion channels. |
| Perampanel | Focal seizures | Glutamate receptor antagonist. |

General side effects of AED's are dizziness fatigue, aggression, weight gain, hostility, anger, mood swing, hypersensitivity, headache, nausea, blurred vision etc.

### 2.1. Nanomedicine:

Nanomaterials are used for diagnosis of epilepsy and also other CNS disorders. AED's delivery by nanoparticle is more efficient compared to delivering free AED's to the brain. PNP's, Liposomes, micelles, dendimers, carbon nanotubes and emulsions are used for encapsulation of AED's. The major advantage of usage of NP's is then controlled and sustained release of drug over time [10].

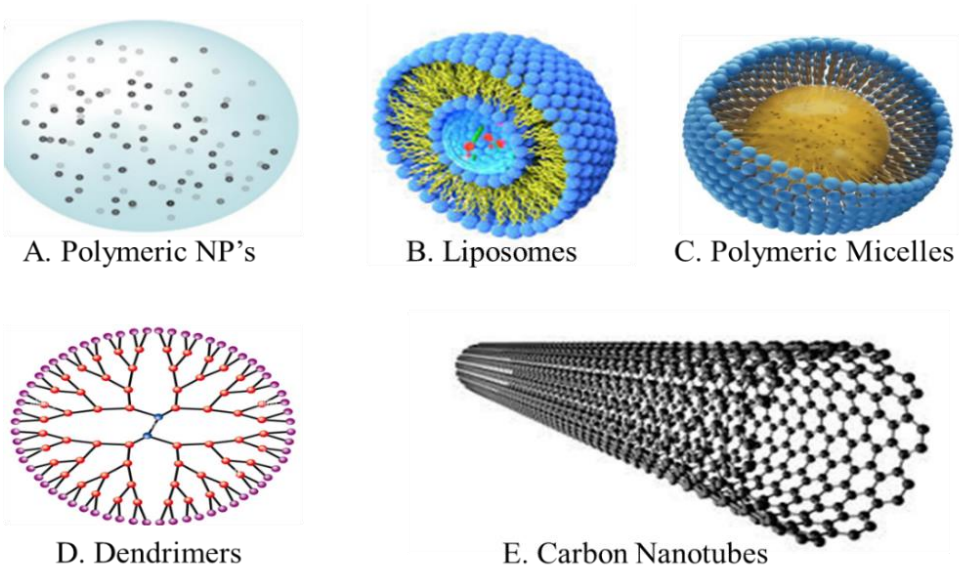



**Figure 3:** ***Some of the Nano colloidal carriers' classes for drug delivery.***

## III. BLOOD BRAIN BARRIER (BBB) STRUCTURE AND EFFECTIVE PATHWAYS TO THE BRAIN

AED's encapsulated nanomedicine has an ability to penetrate BBB and Nanomedicine is distinguished by its chemical, biological and physical properties [3, 6].

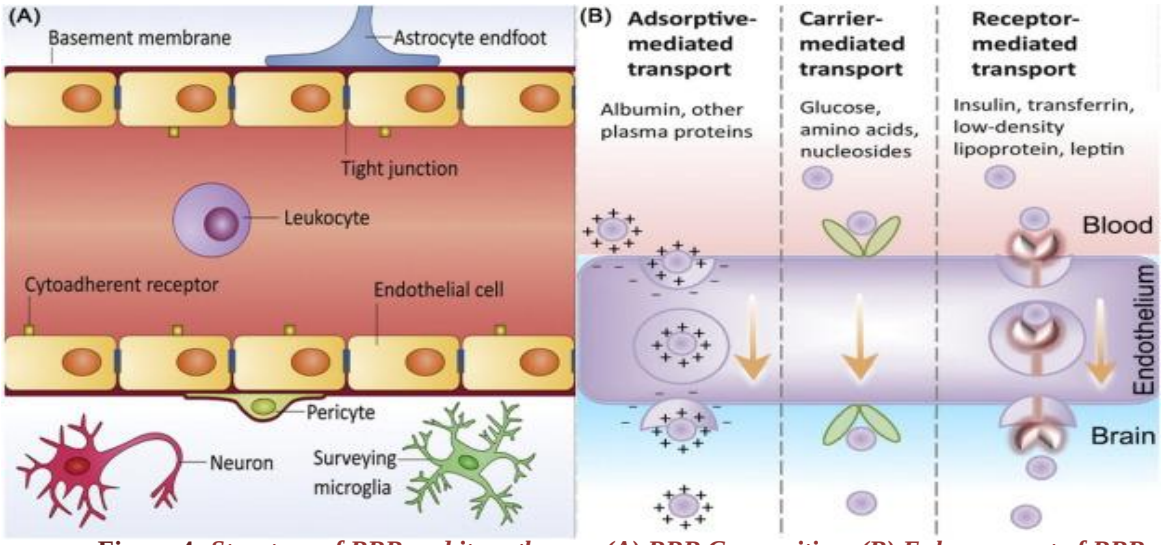
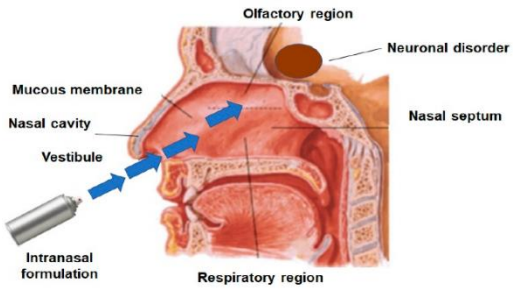



**Figure 4:** ***Structure of BBB and its pathways. (A) BBB Composition. (B) Enhancement of BBB Penetration through 3 methods for Nanomaterials.***

Blood brain barrier protect the brain from xenobiotics and helps to maintain stable microenvironment. It is highly semipermeable in nature. Functionalized solid lipid nanoparticles effectively blocked plasma membrane p-gp and inhibited its expression, shielding the medication from cell efflux [1, 7].

Nanoparticles are effectively penetrated through BBB because of its higher surface volume ratio, quantum properties and biodegradability property.

**a)**

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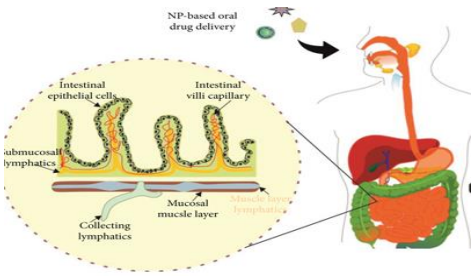


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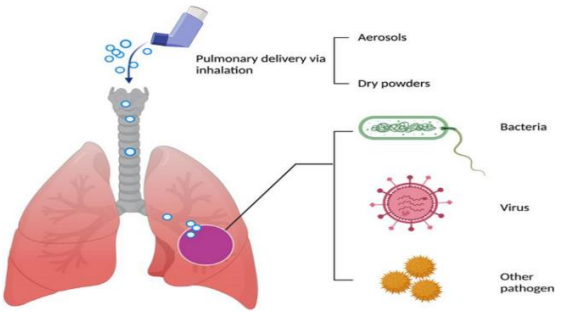


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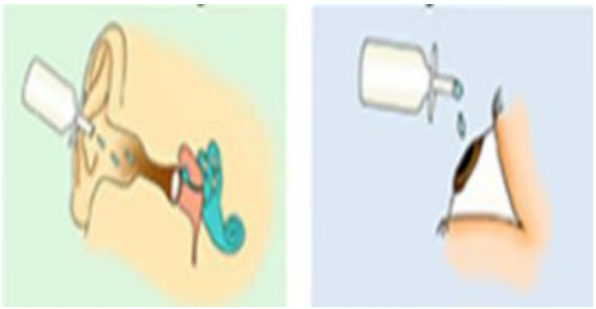

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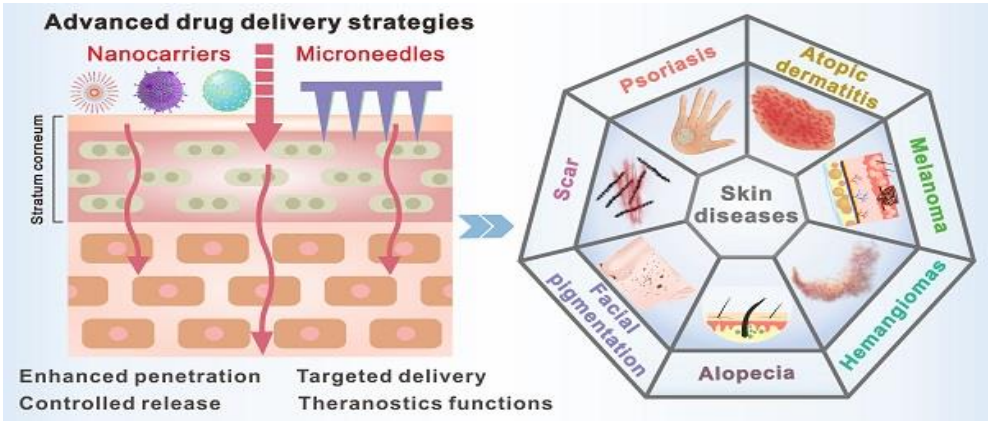


**Figure 5:** ***Common non-invasive/injection routes of administration based on Nanoparticle size.***

a) ***Nose to brain delivery***: This method is more advantageous because of its rapid onset of drug action, non-invasiveness and reduced toxicity. CNS disorders can be treated by this route of drug delivery. It reduced systemic side effects. Recent studies indicated nanoparticles equal or less than 100 nm cross BBB. NP's reach brain through either olfactory or respiratory pathway.
b) ***Oral delivery***: Easy way to deliver of drug is by oral administration because of its minimal invasiveness. Bioavailability of drug is reduced due to pH fluctuation and enzyme activity hence encapsulating drugs in nanoparticle of size 50-100 nm is a solution to protect the drug.
c) ***Pulmonary delivery***: It is the therapy of choice for illnesses that affect the respiratory system.
d) ***Topical ocular and otic delivery***: In order to treat glaucoma, this particular approach is often utilized.
e) ***Topical dermal and Transdermal delivery***: This method is used in acne treatment. NP's small than 10 nm potentially reach stratum corneum (outer most layer of epidermis).

### 3.1. Nanocarriers having AED's:

**Table 3:** ***List of Nanocarriers with Antiepileptic drugs***

| AED's | Nano system | Synthetic mode and route | Clinical outcome |
|---|---|---|---|
| Piperine | Cu-QDs/HA-PLGA | Emulsification solvent evaporation method N/A-route | Sustained and Effective drug delivery |
| Piperine | CS-STPP NP's | Ionic gelation method IP-route | Seizure behavioral sign inhibition |
| Carbamazepine and Levetiracetam | PLGA | Nano precipitation IP-route | Decrease side effect and drug dose, improvement in bioavailability, solubility |
| Oxcarbazepine | PLGA-PEG-PLGA | Ring opening polymerization IN-route | Less toxicity |

### 3.2. Nanomedicines in diagnosis of Epilepsy:

1] ***µPEA (micro pillar electrode array)***: It consists of recording sites. Neural recording is an area where it shows a lot of potential. Its signal to noise ratio was 234 µv and average noise is 22 µv.

2] ***Nanoscale imaging agents***:

- MNP (Magneto nanoparticle): MNP's was prepared by Akhtari et.al., Amt-MNP's (Alpha methyl Tryptophan) has an increased cellular uptake and permeability across BBB. Intracranial electroencephalogram (EEG) confirmation of bilateral or unilateral epileptogenic lesions served as their sites.[4]
- Multimodal nano agents for molecular imaging of p-gp was developed by Yu et.al.

## IV. CONCLUSION

Epilepsy is a CNS disorder characterized by recurring and spontaneous epileptic seizures which may be short or long period of vigorous shaking. Epilepsy is because of acquired and congenital factors. MRI, EEG, CT may display abnormal structural lesions. It can be cured by using AED's and when drug resistance occur operation has to be carried out depending upon condition of the patient. About 35-40% of epilepsy patients' shows refractory epilepsy not respond to AED's. In this time nanomedicines play an important role in monitoring epilepsy.

This paper describes about various AED's and nanomedicines for the treatment of epilepsy. Nanomaterial have been developed for efficient delivery of AED's as well as imaging agents into CNS. These nanomedicines easily cross BBB to diagnose epilepsy. Intranasal administration route is more efficient way to deliver nano agents for diagnosis of epilepsy. Novel platform to diagnose epilepsy is by nanomedicines. By altering nanocarriers with various functional groups, it is possible to enhance the effectiveness of medication delivery while simultaneously reducing the adverse effects that are associated with the central nervous system disease area.

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### Conflicts of Interest

The authors declare no conflict of interest.

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