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Unveiling the effects of nanoparticles-based antiepileptic drugs: Systematic review of *in vivo* studies

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Abstract

Background: Resistance and side effects of antiepileptic drugs (AEDs) pose a challenge in epilepsy therapy due to the limited drug bioavailability in penetrating the Blood-Brain Barrier (BBB). Nanoparticles can be one solution by encapsulating AEDs to enhance drug distribution to target cells. This study systematically assesses 1) the characteristics of nanoparticles, and 2) the potential of nanoparticle AEDs in managing seizures in experimental animal models.

Methods: This systematic literature review is limited to studies published between 2013 and July 2023 in the PubMed, ScienceDirect, ProQuest, MEDLINE, and Scopus databases. Inclusion criteria encompass studies involving animal models of epilepsy, that exploring nanoparticle-based of AEDs. These studies compare the characteristics of nanoparticles and their antiepileptic efficacy with non-nanoparticle groups. Review articles, publications in non-English languages, and ongoing studies without published results are excluded.

Result and Discussion: Fourteen studies met the inclusion criteria for this research. All studies utilized nanoparticles (n = 14). Lipid nanoparticles have a more compact size than any other nanoparticle, while the combination preparation method has an optimal nanoparticle formation in both lipid and polymeric nanoparticles. In animal model results indicated that nanoparticle-based drugs were beneficial in reducing seizure scores, improving seizure onset latency, and providing neuroprotective effects.

Conclusion: The characteristics of nanoparticle drug delivery varied, influenced by formulation factors and preparation methods. Nanoparticle-based AEDs exhibit higher efficacy compared to conventional AEDs. All studies included present an opportunity for the development of epilepsy therapies, although future studies are needed to confirm these findings.

Keywords: Nanoparticles; Antiepileptic Drug; Epilepsy; Seizure

1. Introduction

Epilepsy is one of the most common chronic diseases of the brain, characterized by recurrent and unpredictable seizures, leading to significant physical and psychosocial challenges for affected individuals. The health-related quality of life for epilepsy patients is profoundly impacted [1]. Conventional pharmacological therapy with Antiepileptic Drugs (AEDs) remains the standard approach, aiming to suppress abnormal neuronal activity and enhance inhibitory neurotransmitter functions to control seizures [2]. Despite the wide range of AEDs available, approximately 36.3% of epilepsy patients experience uncontrolled seizures, classified as drug-resistant epilepsy (DRE) [3]. Moreover, a

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substantial number of patients encounter adverse effects (e.g. impaired cognitive function, mood, and coordination), leading to treatment non-compliance and compromised quality of life [4].

A significant challenge in epilepsy treatment lies in the limited bioavailability of certain AEDs, resulting in reduced drug concentrations reaching the brain tissue. This limitation is attributed to the blood-brain barrier (BBB), which hinders the penetration of drugs into specific brain areas affected by epilepsy [5]. These limitations are compounded by other resistance mechanisms, including the overexpression of efflux multidrug transporters or modifications in the structure of excitability networks [6–8]. Consequently, some AEDs may not achieve their intended therapeutic effect, necessitating higher doses that may exacerbate side effects, which cannot simply adjusted [5, 9].

The emerging field of nanotechnology offers promising solutions for enhancing drug delivery and improving the efficacy of antiepileptic treatments. Nanoparticles, with their unique physicochemical properties, have shown potential in addressing the challenges posed by conventional AEDs. These nanocarriers can encapsulate antiepileptic medications, facilitating sustained drug release and targeted delivery to specific brain regions. Moreover, nanoparticles can enhance drug solubility, reduce toxicity, and improve the oral absorption of AEDs, thereby opening new avenues for epilepsy treatment [10].

2. Method

2.1. Search Strategy

This systematic review focuses on publications reporting outcomes of nanoparticle-based AEDs in the treatment of epilepsy. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, an extensive literature search was conducted using multiple databases, including PubMed, ScienceDirect, ProQuest, MEDLINE, and Scopus [11]. The study is limited to English-language publications between 2013 and July 2023. The search strategy utilized keywords ("epilepsy" OR "seizure") AND ("treatment" OR "therapy") AND ("nanoparticle") AND ("antiepileptic" OR "antiseizure" OR "anticonvulsant"). Titles and abstracts retrieved from the databases were screened based on eligibility criteria.

2.2. Eligibility Criteria and Data Extraction

This systematic review employs a methodical selection process to identify studies that meet well-defined inclusion and exclusion criteria. Inclusion criteria encompass animal studies utilizing experimental in vivo epilepsy models, specifically focusing on nanoparticle-based AED formulations. Included studies must compare the effectiveness of nanoparticle formulations with non-nanoparticle formulations. Exclusion criteria for this study are review articles, meta-analyses, systematic reviews, observational studies, case reports, case series, ongoing studies without published results, and publications not in the English language. Data extracted from selected studies include author information, animal populations, interventions with nanoparticle-based antiepileptic drugs, comparisons with non-nanoparticle drugs, and relevant outcomes. These outcomes encompass nanoparticle characteristics, seizure characteristics, pharmacokinetics, behavioral and neurological responses, electrophysiology, and cellular/molecular markers.

2.3. Study Objectives

The primary objective of this systematic review was to evaluate the potential of nanoparticle formulations of AEDs in mitigating seizures within animal models of epilepsy and compare them with conventional approaches by analyzing the pharmacokinetics profile related to drug release analysis and efficacy profile of in vivo study concerning seizure characteristics, behavioral responses, electrophysiological changes, cellular and molecular markers, and biochemical pathways.

2.4. Bias Risk Assessment

Study quality was assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Risk of Bias tool for Experimental in vivo studies [12]. The review process was distributed equally among the reviewers, ensuring each contributed equally. Any inconsistencies or differences in opinion were carefully addressed and resolved through discussion, resulting in a mutual consensus.

3. Result

3.1. Literature search

Through the systematic literature review, 857 records were initially identified (**Figure 1**). Following the elimination of duplicate records (n=109) and articles deemed irrelevant (n=610), 14 studies met the inclusion criteria for qualitative analysis. Most studies were excluded due to their focus on non-epileptic conditions, absence of antiepileptic drugs, lack of comparison between nanoparticle and non-nanoparticle formulations, and non-experimental study design. Fourteen eligible studies were evaluated in detail for their quality and risk of bias. In this screening, the overall bias risk of each study was low; therefore, these studies were included in the review process. Details of risk assessment are mentioned in supplementary data.

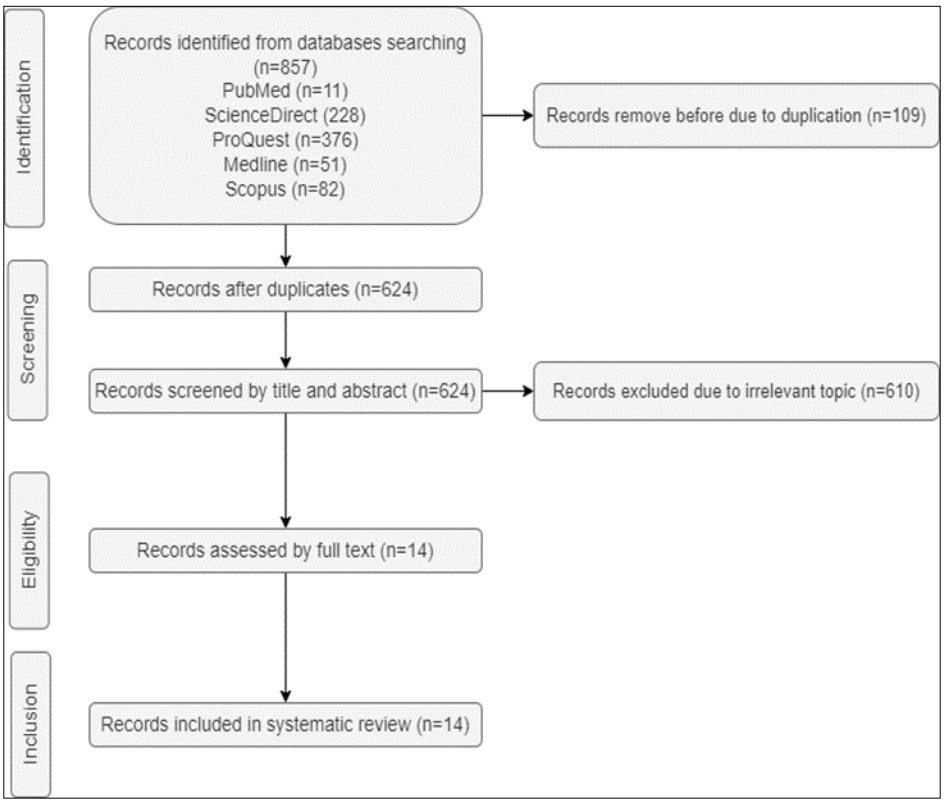

Figure 1 Study Selection Flowcharts

3.2. Characteristics of included studies

The characteristics of the fourteen studies included in the analysis are presented in **Table 1** for nanoparticle-based drug formulations and **Table 2** for the analysis of antiepileptic drug studies. In all conducted investigations, nanoparticles were employed. In the context of antiepileptic medications, a diverse array of drugs was used as part of the experimental protocols across the studies. Carbamazepine was engaged in multiple studies, including those conducted by Qushawy et al. [13], Kandilli et al. [14], and Zybina et al. [15]. Lamotrigine was administered in the research conducted by Hou et al. [16] and Shah et al. [17], while phenytoin was the selected antiepileptic medication in the studies conducted by Fang et al. [18], Wang et al. [19], de Oliveira et al. [20], and Rosillo-de la Torre et al. [21]. Gabapentin was the antiepileptic agent of choice in the investigation conducted by Wilson et al. [22], and lacosamide was employed in a study conducted by Temizyürek et al. [23]. Sodium valproate was administered in the research undertaken by Meenu et al. [24], and clonazepam was the selected antiepileptic medication in the study conducted by Leyva-Gómez et al. [25]. Additionally, oxcarbazepine was employed in the investigation by Musumeci et al. [26]. These antiepileptic medications were chosen to assess their efficacy and impact within the specific contexts of the respective studies' objectives.

Table 1 Characteristics of Nanoparticle-based Drugs and In Vitro Release Studies

No	Author	Nanoparticle Type	Chemical Compound	Preparation Method	Formulation						Characterization				Drug Release Study
					Polymer	Solvent	Oil Phase	Surfactant	Co-Surfactant	Other Materials	EE (%)	Size (nm)	ZP (mV)	PDI	
1	Zybina, et al., 2018	Polymeric Nanoparticle	CBZ	High pressure homogenization followed by solvent evaporation	PLGA	Dichloromethane, polyvinyl alcohol	-	Poloxamer 188	-	-	65-70	130-150	-0.3	0.2	The nanoparticles exhibited a release of approximately 90% of CBZ
2	Kandilli, et al., 2020	Polymeric Nanoparticle	CBZ and LEV	Modified nanoprecipitation	PLGA	Acetone	-	Pluronic F127	-	-	CBZ: 51.00 ± 5.944 LEV: 2.05 ± 0.367	180.62 ± 6.260	-27.08 ± 3.110	0.107 ± 0.030	CBZ release from the nanoparticles (NPs) reached 40% within 3 hours and 90% after 2 days. In contrast, LEV release from the NPs reached 80% within 30 minutes and 100% within 3 hours.
3	Shah, *et al*., 2021	Polymeric Nanoparticle	LTG	Emulsification-solvent evaporation	PLGA	Acetone	-	Poloxamer 407	-	-	71.3 ± 2.0	170.0 ± 2.8	-16.60 ± 2.96	0.191 ± 0.035	LTG solution had incomplete release (42%) after 24 hours due to poor solubility, while LTG-PNPs achieved complete release (94.5%).
4	Hou, et al. 2022	Polymeric Nanoparticle	LTG	Microfluidic chip	PLGA	Dimethylformamide + trifluoroethanol	DPPC + Cholesterol + DSPE-PEG2k-D-T7 / DSPE-	-	-	-	85.85	68.93 ± 0.59	-15.17 ± 0.63	0.26 ± 0.053	The formulation D-T7/Tet1-lipids@PL (2 : 1) demonstrated a cumulative drug release rate exceeding 50% over a 72-hour period, indicating a

							PEG2k-Tet1								suitable drug release profile.
5	Meenu, et al., 2019	Polymeric Nanoparticle	Sodium valproate	Double emulsion-solvent evaporation technique	PLGA	Acetonitrile	Water-in-oil emulsion	Polysorbate 80	Span 20	-	30	220 ± 78	−32.9	-	The nanoparticles showed sustained drug release kinetics. The release pattern was more than 85% of the loaded drug being released from the nanoparticles by the end of the 6th day.
6	Musumeci, et al., 2018	Polymeric Nanoparticle	Oxcarbazepine	The solvent displacement method followed by polymer deposition	PLGA	Acetone	-	Tween 80	-	-	85.1 ± 2.1	256.16 ± 2.94	−15.12 ± 0.36	0.144 ± 0.024	N/A
7	Wilson, et al., 2014	Polymeric Nanoparticle	Gabapentin	pH-coacervation method	Bovine serum albumin	Sodium chloride, ethanol	-	Polysorbate 80	-	Glutaraldehyde	-	141.9	-30.3 ± 2.4	-	Displayed a biphasic pattern: in the fast phase, an initial burst effect occurred, releasing 5-12% of gabapentin rapidly within 15 minutes, followed by a slow and sustained release of the drug over time. The cumulative percentage of drug released over 24 hours ranged from 35% to 49.5%, depending on the drug-polymer concentration.

8	Fang, et al., 2016	Polymeric Nanoparticle	PHT	Interfacial polymerization	Dextran 70, alpha-BCA monomer	ultrapure water, acetone	Triolein	Pluronic P85	-	-	96.63 ± 5.53	268.00 ± 2.54	-36.60 ± 0.45	0.09 ± 0.01	The P85-PHT-PBCA-NPs exhibited controlled release of PHT, with an initial release of 55.25±2.65% within the initial 4 hours and an accumulated release of 89.79±0.78% over a 72-hour period
9	Qushawy, et al., 2019	Lipid Nanoparticle	CBZ	Modified hot high-shear homogenization ultra-sonication	-	Water	Glyceryl Monostearate	Poloxamer 188	-	-	71.91 ± 1.20	45.11 ± 6.72	−33.3 ± 1.45	0.277 ± 0.03	The release rate of CBZ from the NP was significantly slower compared to its release from the free CBZ suspension, which was sustained for 12 h and the cumulative CBZ concentration was 70.23 ± 1.48%
10	Leyva-Gómez, et al., 2014	Lipid Nanoparticle	CLZ	Emulsification-diffusion technique	Compritol 888 ATO	2-butanone, water	-	Poloxamer 407	-	-	0.11	332 ± 9.8	-20.8 ± 1.7 mV	-	Increased drug permeability across the in vitro BBB in NP group. The Pst-Psf ratio, which represents the permeability of CLZ, was higher for CLZ-SLN compared to CLZ alone, indicating an improvement in CLZ permeability with the SLN formulation.
11	de Oliveira, et al., 2020	Hybrid Nanoparticle	PHT	Interfacial deposition of the preform	Chitosan	Acetone	Grape seed oil	Polysorbate 80	Soybean lecithin	-	70.5 ± 1.5	174.3 ± 0.9	(+16.3 ± 1.32)	0.16 ± 0.01	A higher percentage of drug release (62%) after 72 hours compared to non-NP group, which only reached 39% of drug

				ed polymer											release after the same time. The dissolution efficiency of NP group was also significantly higher (58%) than non-NP group (37%).
12	Wang, et al., 2016	Hybrid Nanoparticle	PHT	Soap-free emulsion copolymerization	2-dimethylaminoethyl methacrylate, styrene, and sodium 4-vinylbenzene sulfonate (NaSS)	Water	-	-	-	Potassium persulfate, sodium pyrosulfite - Acrylate-poly (ethylene glycol)-N-hydroxy succinimadyl-ester - ANG	-	Original Size: 90.8 ± 8.9 Under Electrical Field: 209.0 ± 21.0	-	-	A significant increase in the release of accumulated PHT (phenytoin) when exposed to an external electric field with a current of 100 μA, showing an increased by nearly 100% under this condition. The particle size also increased dramatically, as the current increased, and the concentration of NaSS in the formulation positively correlated with the diameter of nanoparticle under electrical field.
13	Rosillo-de la Torre, et al., 2015	Hybrid Nanoparticle	PHT	Co-precipitation	-	Liquid water	A mixture of $FeSO_4 \cdot 7H_2O$ and $FeCl_3 \cdot 6H_2O$	NH_4OH	-	-	-	24.3 ± 9.93	-	-	The results show an initial burst release of 250.366 ± 10.94 μg (94%) of the loaded drug during the first 4 hours. After that, a sustained release of 2 μg for each sample collected was observed during the rest of the experimental time (48 hours). At the end of

															the experiment, a total of 264.68 ± 8.77 µg of PHT loaded in the nanoparticles was released.
14	Temizyürek, et al., 2022	Inorganic Nanoparticle	Lacosamide	NaBH4 reduction method	PEG-COOH	Distilled water, methanol, phosphate buffer	-	-	-	Chloroauric Acid, Sodium Tetrahydridoborate, Thiol (-SH) end group ligands, Glu-TetraAc, GSH	-	1.7	-	0.252	N/A

Note. – BBB= Blood Brain Barrier; CBZ = Carbamazepine; CLZ= Clonazepam; EE= Entrapment Efficiency; LEV=Levetiracetam; LTG= Lamotrigine; N/A= Not Available; NP= Nanoparticle; PDI= Polydispersity Index; PHT= Phenytoin; PLGA= Poly (lactic-co-glycolic acid); PNP= Polymeric Nanoparticle; SLN= Solid Lipid Nanoparticle; ZP= Zeta Potential.

Table 2 *In Vivo* Studies

No	Author	Population	Seizure Model	Induced Seizure Method	Intervention (Administration/ Dosage)	Comparison (Administration/ Dosage)	Outcome
1	Qushawy, et al., 2019	Albino mice (male; 25–28 g; 8-10 weeks)	Acute	PTZ at 70 mg/kg; i.p.	CBZ-SLN at 50 mg/kg; p.o	CBZ at 50 mg/kg; p.o	- Extended survival time (prolonged the time to death after lethal dose administration)
			Kindling	PTZ at 35 mg/kg; i.p. for 15 repetitive injections			- Higher percentage reduction in the final seizure score - Histopathological examination revealed that there is higher reduction in degenerative cell percentage and higher percentage of surviving cells in the CBZ-SLN group
2	Hou, et al. 2022	C57BL/6 mice	Acute	KA, at 0.3 mg/mL, 550 nL, injected	D-T7/Tet1-lipids@PL (2 : 1) at	Lamotrigine at 2 mg/kg, i.p	- Reduce the intensity of epileptic convulsions and delay their onset. - Show good results in treating

		(male/female, 6-8 weeks)		into right dorsal hippocampus	5 mg/kg or 2 mg/kg, i.p		epilepsy through behavioral observation and electrophysiological signal monitoring. -In the chronic epilepsy model, the tissues of the mice treated with D-T7/Tet1-lipids@PL (2:1) did not exhibit any significant pathological alterations when stained with hematoxylin and eosin (H&E).
				Pilocarpine at 320 mg/kg, i.p	D-T7/Tet1-lipids@PL (2 : 1) at 2 mg/kg, i.p	Lamotrigine at 2 mg/kg, i.p	- Delay the onset of epilepsy and lessen the severity of epileptic seizures - Behavioral observation and electrophysiological signal monitoring demonstrated excellent efficacy in treating epilepsy - The blood analysis of the mice revealed normal ranges for hematological markers and biochemical parameters.
			Chronic	KA, at 0.3 mg/mL, 550 nL, injected into right dorsal hippocampus, for 6 weeks	D-T7/Tet1-lipids@PL (2 : 1) at 5 mg/kg or 2 mg/kg, i.p	Lamotrigine at 2 mg/kg, i.p	- A relatively normal EEG condition, whereas the LFP power within the group was notably lower in comparison to the other groups - Intact hippocampal structure - The biochemical and hematological parameters found in the blood of the mice were within normal limits.
3	Fang, et al., 2016	Sprague-Dawley rats (Female, 160 - 180 g, 6-8 weeks)	Status-Epilepticus (PHT-resistant)	Lithium chloride at 127 mg/kg; i.p. After 16-24 h, methyl scopolamine (1 mg/kg) injected i.p, 30 min before pilocarpine administration. Max. 5 pilocaripine injections at dose 15 mg/kg every 30 min, until the onset of SE). First dose was at 30 mg/kg	P85-PHT-PBCA-NPs at 35 mg/kg. twice daily i.p	Phenytoin loading dose at 75 mg/kg, followed by twice daily at 50 mg/kg i.p	- An increase in the brain/plasma PHT concentrations' AUC ratio in comparison to the control group - After P85-PHT-PBCA-NP therapy, PHT concentrations in the liver/plasma and kidney/plasma were significantly lower than in the control group. -When compared to the conventional group, the nanoparticle medication groups demonstrated a higher percentage decrease in the frequency of spontaneous recurring seizures (SRS).

4	Wang, et al., 2016	Sprague-Dawley rats (male; 260-300 g)	Electrical Stimulation	Maximal electroshock at 50 Hz, 150 mA, for 0.2 s through ear clips using rodent shocker	Angiopep-2 and phenytoin sodium-loaded electroresponsive hydrogel nanoparticles at 50 mg/kg; i.p	Phenytoin solution at 50 mg/kg; i.p	ANG-PHT-ERHNP exhibits a stronger antiepileptic impact than standard therapeutic doses, even at lower effective therapeutic doses.
			Acute	PTZ at 80 mg/kg; i.p			Decreased the severity of seizures, lowered the incidence of generalized seizure, and increased the latency of generalized seizure
				Pilocarpine at 30 mg/kg, i.p			Enhanced the latency of generalized seizures and status epilepticus and also decreased the fatality rate
5	Wilson, et al., 2014	Adult Wistar rats (male; 180–220 g)	Electrical Stimulation	Maximal electroshock, at 50 mV for 0.2 s, using electroconvulsiometer	Gabapentine bound with albumin nanoparticle coated with polysorbate 80 at 50 mg/kg; i.p	Gabapentin free drug 50 mg/kg; i.p	- Increased the concentration of gabapentin in the brain (by approximately threefold) - Reductions in the duration of all convulsion phases and a decrease in the average duration of seizure phases - There were no death occured in the group that received polysorbate 80-coated nanoparticles (extended survival time)
			Acute	PTZ at 70 mg/kg; i.p			- Decreased the duration of all seizure phases - There were no death occured in the group that received polysorbate 80-coated nanoparticles (extended survival time)
6	Temizyürek, et al., 2022	WAG/Rij rats (male and female; 250-280 g, 5 months)	Genetic (absence seizure model)	-	LCM-GNP at 35 µg LCM + 0.5 g GNP/mL; i.v	Lacosamide at 35 µg/mL; i.v	-Diminished SWD-like discharges in electrophysiography test in terms of both frequency and amplitude -Reduced expression of GFAP, Glut-1, and P-gp, mostly in the cerebral cortex, which suggests that neuronal activity is being modulated.
7	Meenu, et al., 2019	Wistar rats (male; 150–200 g)	Acute	PTZ at 60 mg/kg; i.p	Nano sodium valproate at 300 mg/kg; i.p	Standard sodium valproate at 300 mg/kg; i.p	- Prevention against seizures in the group receiving therapy with nano sodium valproate - Enhanced plus maze testing and decreased behavioral impairment in passive avoidance when using nano sodium valproate

							- Nano sodium valproate decreases oxidative stress in acute and chronic seizure situations by preventing lipid peroxidation and preserving brain GSH.
			Kindling	PTZ at 30 mg/kg; i.p	Nano sodium valproate at 75 mg/kg; i.p	Standard sodium valproate at 300 mg/kg; i.p	- Prevention against seizures at lower dosages for the Nano sodium valproate group - Enhanced plus maze testing and decreased behavioral impairment in passive avoidance when using nano sodium valproate - Decreased oxidative stress in seizure models, both acute and chronic, by preventing lipid peroxidation and preserving brain GSH.
8	Leyva-Gómez, et al., 2014	Swiss Webster mice (male; 25 –30 g)	Acute	PTZ at 80 mg/kg; i.p	CLZ-SLN at 0.01–3 mg/kg; i.p., and 0.01–1 mg/kg; p.o	Clonazepam at 0.01–3 mg/kg; i.p., and 0.01–1 mg/kg; p.o	- Delayed myoclonus onset and inhibited generalized seizures, complete protection against myoclonus. Prevention of tonic seizures and mortality - Delayed generalized seizures
		Wistar rats (male; 280 – 300 g)	Acute	PTZ at 40 mg/kg; i.p	CLZ-SLN at 0.3 mg/kg; i.p	Clonazepam at 0.3 mg/kg; i.p	- Higher latency to the onset of paroxystic activity - Decreased seizure score with most exhibiting minimal convulsive behavior, including motionless staring, indicating a marked reduction in seizure severity
9	Musumeci, et al., 2018	Wistar rats (male: 200-220 g)	Acute	PTZ at 50 mg/kg; i.p	Oxcarbazepine loaded nanoparticles at 0.5 mg/kg; i.n	Oxcarbazepine at 0.5 mg/kg; i.n	- After intranasal administration, Oxcarbazepine loaded nanoparticles showed no symptoms related to initial stage seizures. They led to delayed onset of PTZ-induced seizures, reduced seizure stage, and symptom duration, all of which were statistically significant - Preserve brain structure and enchanced neuroprotection by a progressive decrease in anti-GFAP levels in a dose-dependent fashion in the hippocampus and increased expression of neural markers (anti-NF and anti-TUB) in mature neurons
10	de Oliveira,	C57BL/6 mice (male and female;	Acute	Pilocarpine at 300 mg/kg,; i.p.	G(PHT-LNC PHT) at 3 mg/kg; p.o	PHT suspension at 3 mg/kg; p.o	- The application of lipid-core nanocapsules filled with phenytoin causes a delayed latency to

	et al., 2020	25–35 g, 30–90)					myoclonic and generalized seizures in a matter of seconds. - Phenytoin-loaded lipid-core nanocapsules result in a longer survival period, expressed in seconds. - Treatment with phenytoin-loaded lipid-core nanocapsules reduces the seizure stage.
11	Rosillo-de la Torre, et al., 2015	Wistar rats (male; 250 - 300 g)	Pharmaco resistant	3-mercaptopropionic acid (3MPA) at 7.5 mg/kg; i.p	PHT loaded in the silica core of iron oxide NPs at 75 mg/kg; i.p	PHT at 75 mg/kg; i.p	- The afterdischarge threshold value was higher (%) - The percentage of myoclonus, clonus, and tonic-clonic seizures were observed to be lower
12	Kandilli, et al., 2020	Albino wistar rats (male; 140-180 g)	Kindling	PTZ at 35 mg/kg; i.p	CBZ+LEV-PLGA-NPs at an equivalent to 30 mg/kg of CBZ and 1.2 mg/kg of LEV; i.p.	CBZ at 30 mg/kg; i.p. and LEV at 1.2 mg/kg; i.p. combination	On days 1 and 2, the CBZ+LEV-PLGA-NPs group exhibited a significant reduction in seizure scores relative to CBZ+LEV, with the largest reduction noted on day 3.
13	Shah, et al., 2021	Albino rats (male: 200-350 g)	Acute	PTZ at 100 mg/kg	LTG-PLGA NP at 0.833 mg/kg; i.n	LTG at 0.833 mg/kg; i.n and i.v	- Delayed onset of seizure after 15, 30, and 60 minutes administration
14	Zybina, et al., 2018	Wistar rats (male, 200 - 300 g)	Acute	INH at 300 mg/kg, i.p	CBZ-NP at 0.7; 1; 3 and 5 mg/kg. i.v	Carbamazepine at 15; 20; 25; and 30 mg/kg. i.p	- Enhance antiepileptic activity by a remarkable reduction in the minimum effective dose (from 30 mg/kg to 1 mg/kg). Demonstrated significant improvements in delaying seizure onset, reducing seizure duration, and diminishing seizure intensity compared to the control group. - Reduced paroxysm duration and increased paroxysm latency
					Pretreatement with Verapamil (40 mg/kg i.p), followed by CBZ-NP at 0.7 mg/kg. i.v	Pretreatment with Verapamil (40 mg/kg i.p), followed by Carbamazepine at 20 mg/kg i.p	- Verapamil significantly enhanced CBZ's anticonvulsant effect, reducing its effective dose by a minimum of 30% (from 30 mg/kg to 20 mg/kg).

Note. - CBZ = Carbamazepine; CLZ= Clonazepam; EEG= Electroencephalography; GFAP= glial fibrillary acidic protein; G(PHT-LNC PHT)= Granules containing Phenytoin (PHT) and PHT-loaded nanocapsules; INH= Isoniazid; i.p= Intra Peritoneal; i.v= Intra Venous; KA= Kainic Acid; LCM-GNP= Lacosamide-conjugated gold nanoparticles; LEV= Levetiracetam; LTG= Lamotrigine; NP= Nanoparticle; PHT= Phenytoin; PLGA= Poly (lactic-co-glycolic acid); p.o= Per Oral; PTZ= Pentylenetetrazole; SLN= Solid Lipid Nanoparticle.

4. Discussion

Nanoparticles have attracted significant nanotechnology attention due to their distinctive properties and extensive potential applications [27]. The extensive research into nanoparticles is primarily driven by their inherent attributes, including heightened stability, precise targeting capabilities, and controlled drug release mechanisms [27, 28]. These qualities make nanoparticles exceptionally well-suited for an ideal pharmacotherapeutic approach, particularly in disorders such as epilepsy, where the need for on-demand drug release and effective blood-brain barrier penetration is pronounced [29]. Furthermore, nanoparticles offer a versatile formulation approach, as they can be synthesized from diverse organic and inorganic materials, encompassing lipids, proteins, polymers, and metals [27, 30].

Maximizing the effectiveness and safety of nanoparticles in epilepsy treatment necessitates a holistic evaluation of critical properties. These properties encompass size, shape, surface attributes, core stability, biocompatibility, toxicity, release kinetics, and intricate targeting mechanisms [31, 32]. While a universal nanoparticle blueprint remains elusive, specific attributes have emerged as pivotal in aiding these agents to overcome the blood-brain barrier [33, 34]. Notably, nanoparticles with dimensions smaller than 200 nm, particularly in the 10 to 100 nm range, exhibit remarkable permeability and optimal performance [35, 36]. The sustained release of drugs plays a vital role in epilepsy management, ensuring therapeutic drug levels within the brain, reducing seizures, and minimizing the need for frequent medication administration [37–39]. Strategies like pH-responsive polymers and stimuli-responsive systems are employed for controlled and sustained drug release [40]. Additionally, surface modifications, such as attaching targeting ligands and implementing stealth coatings, enhance specificity, stability, and circulation longevity [16, 41]. An ideal surface charge for effective brain drug delivery is either positive or neutral, allowing nanoparticles to interact with the blood-brain barrier and cellular receptors [42–44]. However, despite extensive research and its significant potential, the availability of nanomedicines for therapeutic purposes remains limited. This limitation persists due to the many aspects yet to be explored, from human physiology's intricacies to nanoparticles' inherent characteristics [45].

4.1. In vitro release studies of nanoparticle-based drug delivery systems

A few vital reasons for the challenges in nanoparticle-based drug delivery systems are the physicochemical complexity and preparation method diversity of nanoformulations, which can influence the optimal drug effects. A study by Qushawy et al. [13] using lipid nanoparticles of Carbamazepine showed a more compact size than polymeric nanoparticles used by Zybina et al., [15]. This result is similar to the study by Akel *et al.,* [46], which compared PLGA nanoparticles and Solid Lipid nanoparticles (SLN) of Meloxicam; SLN has a lower Z-average because of particle deposition in the SLN surface. Moreover, the study that used the same interfacial polymerization method of Phenytoin with different polymer formulations showed that Phenytoin with Chitosan polymer has a smaller particle size than Dextran-70 Alpha n-butyl cyanoacrylate (BCA) Monomer [18, 20]. However, another study showed that Chitosan polymer nanoparticle size is higher than lipid and other polymer nanoparticles [47]. This difference may be attributed to the range of PLGA concentrations studied and the impact of PLGA copolymers, lactic acid, and glycolic acid on nanoparticle size and the molecular weight of the PLGA. Nonetheless, another study showed that the incorporation of a lower concentration of polymer within polymeric nanoparticles significantly reduces their size, thus allowing a more substantial amount of drug integration [48]. Chitosan-coated nanoparticles are a part of lipid-polymer hybrid nanoparticles, which exhibit increased particle size due to the Chitosan adsorption on the surface of the nanoparticles.This particle size is a crucial parameter that impacts various nanoparticle properties, including surface area and reactivity. When the nanoparticle size decreased, the surface-to-volume ratio would be increased, subsequently making the nanomaterial surface more reactive. In common, nanoparticle size can be responsible for its capability to impede biological systems [49, 50]. Most studies in this review have less than 200 nm of antiepileptic nanoparticles, whose preferred size is within 50 - 200 nm [51]. The zeta potential in hybrid nanoparticle also has a positive value due to the electrostatic interaction of chitosan coating, causing a charge shift of the nanoparticles. This positive charge leads to an improvement in the permeability of drugs [46, 47].

Another study that used the same poly(lactic-co-glycolic acid) (PLGA) polymer for Carbamazepine nanoformulations has a more compact particle size with high-pressure homogenization and solvent evaporation method than the modified nanoprecipitation method [14, 15]. The study by Qushawy *et al.* [13], also produced smaller carbamazepine lipid nanoparticles size by high shear homogenization ultrasonication method. This result is similar to Ghaderi *et al.,* [52], which showed that the average nanoparticle size is smaller in the emulsion solvent evaporation technique compared to the nanoprecipitation technique. In contrast, a study by Hernandez-Giottonini *et al.,* [53] displayed no significant effect on the diameter size of polymeric nanoparticles when prepared by emulsification techniques. In polymeric nanoparticle preparation method using solvent evaporation, nanoparticle characteristics are influenced by stirring speed, homogenizer type and polymer concentration. But in high pressure homogenization method, the final particle size depends on the pressure applied and fewer homogenizing rounds are required. Selection of polymeric and lipid

nanoparticle preparation method depends on drug solubility and stability, polymer or lipid type, route of administration, and intended drug application. In other way, a combination of both ultrasonication and high-speed homogenization can be used to achieve smaller particle sizes in lipid nanoparticle type. For optimal polymeric nanoparticle formation, use a high-speed homogenizer or ultrasonicator, with subsequent evaporation [54].

Several previously mentioned studies have low entrapment efficiency, high zeta potential, and high polydispersity index (PDI), paradoxically with decreased nanoparticle size [13, 15, 20]. This result is influenced by various physicochemical properties such as surfactant, co-surfactant, polymer type and concentration, aqueous and oil phase, and other materials involved [55]. Entrapment efficiency (EE%) refers to the amount of drug enclosed within the nanoparticle structure. High entrapment efficiency is desirable as it enhances the drug-loading capacity of nanoparticles [10, 51]. Low entrapment efficiency value in most studies might be due to the high solubility of drugs that correlated to additional substances to the nanoparticle formulation. It causes the drug to leak into the aqueous phase [14]. Previously obtained data shows that increasing polymer concentration would decrease the entrapment efficiency value [56]. Furthermore, zeta potential is used to measure the electrostatic charge on the surface of particles, which plays a significant role in nanoparticle suspension stability. Nanoparticles with a zeta potential around more negative than -30 mV and more positive than +30 mV have demonstrated good stability and drug loading capacity [51, 57]. All included studies have a negative zeta potential, except the study by de Oliviera *et al.* [20], which has a positive result. The zeta potential could be a positive or negative value, depending on the net charge of the polymer used to form the nanoparticles. Similar to the previous study, this positive zeta potential is due to the positive charge of the chitosan polymer [58, 59]. Additionally, the PDI measures the size distribution of nanoparticles. A low PDI indicates a narrow, uniform particle size distribution preferred for drug delivery applications [16]. All studies included have PDI values less than 0.3, considered tolerable, and demonstrate homogeneity samples as drug products [60].

4.2. Effectiveness of Nanoparticle-Based Antiepileptic Drugs

Nanoparticle-based antiepileptic drugs offer several distinct advantages compared to traditional antiepileptic medications. These advantages encompass improved drug delivery, enhanced efficacy, targeted drug delivery, and potentially reduced side effects. Firstly, nanoparticle antiepileptic drugs leverage nanotechnology to enhance drug delivery to the brain, allowing for precise targeting of specific regions within the brain. This innovative approach has great possibilities to improve the efficacy of drug therapy for epilepsy significantly [29, 61]. By utilizing nanoparticles, drug compounds can be efficiently transported to areas where they are most needed. Furthermore, the efficacy of nanoparticle antiepileptic drugs has demonstrated notable enhancements compared to conventional antiepileptic medications. These nanoparticles have shown promise in improving seizure management, ultimately providing better outcomes for individuals with epilepsy [34, 61, 62]. One of the most significant advantages of nanoparticle-based drug delivery is the ability to achieve targeted drug delivery to the brain. Nanoparticles can breach the blood-brain barrier, a critical obstacle in delivering medications to the brain. This targeted approach allows for increased drug concentration in specific brain regions, further boosting the effectiveness of epilepsy pharmacotherapy [29, 62]. While the side effects of nanoparticle antiepileptic drugs are an ongoing subject of study, there is the potential for these formulations to reduce adverse effects compared to traditional treatments [10, 34, 63, 64].

There are three studies by Qushawy et al. [13], Kandilli et al. [14], and Zybina et al. [15] that demonstrate the use of nanoparticles in drug delivery, particularly Carbamazepine (CBZ), can enhance anticonvulsant effects and neuroprotection. The study by Qushawy et al. [13] highlights the superiority of Solid Lipid Nanoparticles (SLN) loaded with CBZ in prolonging survival time, reducing seizure scores, and enhancing neuroprotection. Factors such as nano size and nanoparticle characteristics contribute to increased permeability through biological membranes, retention in brain capillaries, and surfactant effects that open tight junctions between brain endothelial cells [13]. Furthermore, the findings of Kandilli et al. [14] indicate that the use of Nanoparticles PLGA Carbamazepine and Levetiracetam (CBZ+LEV-PLGA-NPs) can result in a significant decrease in seizure scores, especially on days 1 to 3. The PLGA nanoparticle formulation proves successful in enhancing the anticonvulsant effects of the CBZ+LEV combination, with sustained release of the encapsulated active substance [14]. The study by Zybina et al. [15] emphasizes the effectiveness of nanoparticle-bound carbamazepine (CBZ-NP) in improving antiepileptic activity with a reduction in the minimum effective dose. The rapid release process of nanoparticles supports strong pharmacological effects with high drug concentrations around neuron membranes. Additionally, the combination with Verapamil has been proven to enhance the anticonvulsant effects of CBZ through various mechanisms, including Pgp inhibition, blocking calcium entry into neurons, and inhibiting CYP450 [15].

Research by Hou et al. [16] and Shah et al. [17] indicates that nanoparticles of Lamotrigine have the potential to delay seizure onset, reduce seizure-related brain activity, and maintain blood parameters and brain integrity. The study by Hou et al. [16] demonstrates that nanoparticles, especially lipida@PL NPs, have the potential to delay seizure onset,

reduce seizure-related brain activity, and maintain normal blood parameters. The treatment group shows preserved electroencephalography (EEG) activity and unaffected hippocampal structure, indicating the potential of nanoparticles in delaying seizures and preserving brain integrity. This study also suggests that a series of lipida@PL NPs exhibit good biocompatibility and the ability to inhibit both the initiation and spread of ictal release [16]. The research by Shah et al. [17] highlights the potential of intranasal administration of PLGA nanoparticles loaded with Lamotrigine (LTG-PNP) in delaying seizure onset. The use of nanoparticles intranasally enhances the efficacy of Lamotrigine, with a higher amount reaching the brain and demonstrating greater therapeutic action. The correlation between nanoparticle characteristics, such as nano size, increased surface area, and the ability of Poloxamer 407 to inhibit P-gp-mediated efflux, suggests that these characteristics contribute to better therapeutic outcomes [17].

The use of nanoparticles for delivering Phenytoin (PHT) in the studies by Fang et al. [18], Wang et al. [19], De Oliveira et al. [20], and Rosillo-de la Torre et al. [21] demonstrates an enhancement in antiepileptic effectiveness by improving drug delivery to the brain and reducing seizure frequency. For instance, Fang et al. [18] showed that the use of P85-coated PBCA nanoparticles (P85-PHT-PBCA-NPs) enhances the delivery of Phenytoin to the brain, resulting in a twofold increase in the brain/plasma concentration ratio of PHT and a reduction in seizure frequency. This may be attributed to more effective brain targeting by the nanoparticles, leading to lower drug concentrations in the plasma compared to the PHT group [18]. Furthermore, Wang et al. [19] demonstrated that electro-responsive hydrogel nanoparticles with angiopep-2 (ANG) loading of PHT (ANG-PHT-ERHNP) exhibit strong antiepileptic effects, especially at low doses. The improved antiepileptic effect is due to a significant increase in the release of free PHT from ANG-PHT-ERHNP, correlating with the severity of epilepsy onset [19]. De Oliveira et al. [20] proposed the potential benefits of lipid-core nanocapsules loading Phenytoin in epilepsy management. The nano-capsule combination G(PHT-LNCPHT)3 showed the best mucoadhesive properties and enhanced dissolution efficiency, which can increase drug bioavailability, providing better in vivo anticonvulsant effects [20]. Lastly, Rosillo-de la Torre et al. [21] revealed that loading Phenytoin into iron oxide silica nanoparticle cores enhances its efficacy in reducing seizure-related activity. PHT in nanoparticle (NPs) form can reduce neuron excitation and epilepsy activity in animals with high P-gp expression, indicating a potential new strategy to address pharmacoresistant epilepsy by considering the key role of P-gp expression in the blood-brain barrier [21].

Research by Wilson et al. [22] demonstrates that albumin nanoparticles loaded with gabapentin and coated with polysorbate 80 can enhance drug delivery to the brain, reduce seizure duration, and ensure safety. Polysorbate 80-coated nanoparticles significantly reduce the duration of all seizure phases, indicating their ability to deliver gabapentin to the brain and enhance antiepileptic effects [22]. Temizyürek et al. [23] highlight the effectiveness of Gold Nanoparticle Conjugates (LCM-GNP) containing Lacosamide in reducing seizure activity, alleviating anxiety-like behavior, and influencing critical proteins in the cerebral cortex. A novel approach to efficient drug delivery to the brain through the blood-brain barrier, involving the conjugation of LCM to GNPs targeted to Glut-1 carriers on brain capillary endothelial cells, proves successful in achieving significant therapeutic efficiency [23]. Meenu et al. [24] study demonstrates the superiority of Nano Sodium Valproate in protecting against seizures and improving cognitive function, along with its antioxidant and neuroprotective properties. This superiority can be attributed to the slow and sustained release of the drug from nanoparticles effectively targeted to the brain, preventing phagocytosis and degradation in circulation. The progressive accumulation of nanoparticles, along with biodegradable, biocompatible, and functionalized properties, including surface modification like coating with polysorbate 80, results in prolonged efficacy of nano sodium valproate at lower doses [24].

Leyva-Gómez et al. [25] discovered that Solid Lipid Nanoparticles containing Clozapine (CLZ-SLN) effectively delay seizure onset and inhibit seizures more efficiently compared to conventional Clozapine (CLZ). The enhanced therapeutic effect is attributed to SLN's ability to cross the Blood-Brain Barrier (BBB) through two main mechanisms: adsorption to capillary walls and adhesion to endothelial cell membranes, facilitating drug release to the brain. The lipid proportion in the SLN formulation also plays a role in the anticonvulsant activity of CLZ by creating synergy. This study highlights the potential of CLZ-SLN in improving anticonvulsant efficacy through enhanced intestinal and BBB crossing [25]. Musumeci et al. [26] demonstrated that intranasal administration of nanoparticles loaded with Oxcarbazepine effectively delays and reduces Pentylenetetrazol (PTZ)-induced seizures with neuroprotective effects. Intranasal OXC-NP administration for three days once a day resulted in symptom-free rats in the first stage of seizures, indicating the potential of the olfactory route to reach the hippocampal region [26]. Collectively, these fourteen studies demonstrate that the use of nanoparticles in the delivery of antiepileptic drugs has great potential to enhance epilepsy management. Nanoparticles demonstrate better seizure control, increased neuroprotection, and significant antiepileptic activity, paving the way for the development of more effective and targeted therapies for epilepsy conditions [13–26].

5. Conclusion

Nanoparticle-based drug delivery systems, including nanoparticles, hold great promise for revolutionizing the treatment of epilepsy. According to this study, lipid nanoparticles have a more compact size than other types of nanoparticles. In contrast, the hybrid nanoparticle has a more positive charge, so that it will improve the permeability of drugs. The type or concentration of material involved determines the diverse physicochemical properties of nanoparticles. In the nanoparticle preparation method, a combination method can be used to achieve smaller particle sizes, both in lipid or polymeric nanoparticles. However, it should be noted that the choice of this preparation method depends on the type, route of administration and application of the drug. These approaches offer improved drug solubility, bioavailability, targeted delivery, stability, and controlled release. By overcoming the limitations imposed by the BBB and optimizing the characteristics of nanoparticles, the therapeutic efficacy of AEDs can be enhanced while minimizing systemic toxicity. Therapeutic efficacy observed in animal studies of nanoparticle-based AEDs, such as increased drug delivery to the brain, sustained release profile, delayed onset of seizures, lowered seizure frequency, reduced seizure severity, prolonged survival time, and improved cognitive function. The outcome of therapy using nanoparticle-based AEDs also preserved brain structure and enhanced neuroprotection. Further research and development in nanoparticle-based AEDs shows a potential transformation of epilepsy treatment and can improve the quality of life in patients with epilepsy.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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