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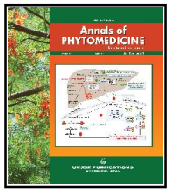

Review Article : Open Access

A review on analytical aspects of ethosuximide: An antiepileptic drug

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Abstract

One out of 50 individuals can have multiple epileptic convulsions during their life, necessitating the use of antiepileptic medication for treatment. One of the most common illnesses of the brain is epilepsy. Ethosuximide, also known as 2-ethyl-2-methylsuccinimide, is a commonly employed succinimide for the management of seizures known as "petit mal seizures." It is also a useful substance for research on absence seizures. When it comes to treating kids suffering from petit mal (generalized absence) epileptic seizures, this medication is the best option, whether used alone or in combination. Ethosuximide's main mode of action towards absence seizures is its inhibition of low-threshold T-type (Transient-type) calcium electrical currents within thalamic nerve cells. At the beginning of ethosuximide therapy, nausea, abdominal pain, vomiting, diarrhea, and anorexia are frequently experienced side effects. This article provides a complete review of the "antiepileptic drug ethosuximide" which will be helpful for the researchers for their research purposes.

1. Introduction

Ethosuximide, also known as 2-ethyl-2-methylsuccinimide, is a commonly employed succinimide for the management of seizures known as "petit mal seizures." It is also a useful substance for research on absence seizures (Zimmerman and Burgmeister, 1958; Mares *et al*., 1994). One out of 50 individuals can have multiple epileptic convulsions during their life, necessitating the use of antiepileptic medication for treatment, one of the most common illnesses of the brain is epilepsy (McCrea and Sarah, 2002). Partial and primary generalized convulsions are the two categories based on the kind and extent of aberrant electrical impulses in the brain (McCrea and Sarah, 2002). Interactions that are complicated between the brain's cerebral cortex and the region known as the thalamus cause typical absence seizures (Gören and Onat, 2007). In almost half of the patients, ethosuximide reduces the frequency of seizures, and nearly all of the patients absence seizures are controlled (Browne *et al*., 1975; Berkovic *et al*., 1987). The therapeutic profile of ethosuximide for the treatment of epilepsy is limited. When it comes to treating children with generalized absence (petit mal) epilepsy, this medication is the best option, whether used alone or in combination (Gören and Onat, 2007). One of the three succinimides that serve as anticonvulsants is ethosuximide (Edwardson and Dean, 1992; Zhang *et al*., 1996). N-2-dimethyl-2-phenylsuccinimide (methsuximide) and N-methyl-2-phenylsuccinimide (phensuximide) are the remaining pair (Browne, 1983).

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2. Discovery and further history

Ethosuximide was discovered in the 1950's. It was given FDA Approval in the year 1960. Ethosuximide is a medication that is categorized as an anticonvulsant. It works by reducing the inappropriate electrical discharge in the brain.

3. Drug profile

Table 1: Drug profile of ethosuximide

Brand name	*Zarontin*
Generic name	Ethosuximide
Type	Small molecule
Groups	Approved
Molecular weight	Average:141.1677 g/mol Monoisotopic:141.078978601 g/mol
Synonyms	Aethosuximide Atysmal Ethosuximid Ethosuximide Ethosuximide Ethosuximidum Etosuximida Thilopemal
Chemical formula	$C_7H_{11}NO_2$
IUPAC name	3-ethyl-3-methyl pyrrolidine-2,5-dione
Drug bank accession number	DB00593
External ids	CI-366 CN-10, 395 CN-10395 PM-671

3.1 Structure of ethosuximide

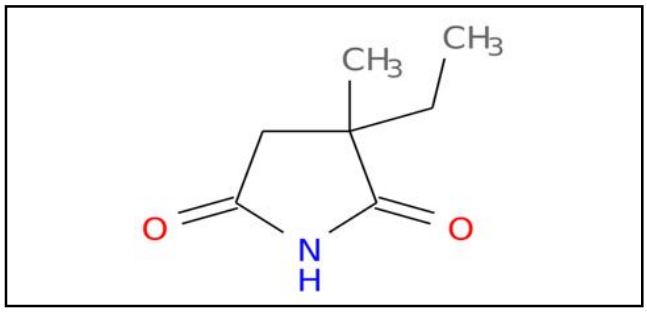

Figure 1: Structure of ethosuximide.

3.2 Physicochemical properties

3.2.1 Description three-cycle-second line remove hyphens

Ethosuximide, also known as {R, S}-2-ethyl-2-methylsuccinimide ($C_7H_{11}NO_2$), is a crystalline white substance (Loscher and Schmidh, 1994).

3.2.2 Solubility

Ethosuximide dissolves easily in water and less easily in organic solvents (Löscher and Schmidh, 1994).

Table 2: Physicochemical properties of ethosuximide

Properties	Values
Melting point (°C)	64.5°C
Water solubility	101.0 mg/ml
LogP	0.38
Log S	-0.15
pKa (strongest acidic)	10.73
pKa (strongest basic)	-6.6
Refractivity	35.963 Mol^{-1}

3.3 Pharmacodynamics

Ethosuximide is employed for the management of seizures. This medication inhibits the three-cycle-per-second paroxysmal wave activity and spike linked to consciousness lapses, which are frequently observed in absence seizures (petit mal). The central nervous systems threshold for convulsive stimulation is raised and the motor cortex appears to be depressed, which decreases the incidence of epileptiform attacks.

3.4 Pharmacokinetic properties

3.4.1 BCS classification

Ethosuximide is classified as BCS class-I compounds (*i.e.,* compounds with high solubility and high permeability).

3.4.2 Absorption

After taking one oral dosage of ethosuximide (750 mg), the medication's peak plasma levels in healthy adult males reached 15 µg/ml, 3-5 h later and stayed there for 24 h (Hansen and Feldberg, 1974). Clinical efficacy of ethosuximide is observed at plasma concentrations between 40-100 mg/l or 300-700 µmol/l. But still, slow titration may be necessary to achieve levels as high as 150 mg/l (1000 mmol/l) in certain patients (Sherwin, 2002). Serum levels among nursing infants are kept within 15 and 40 mg/l. Ethosuximide's plasma concentrations rise in direct proportion with rising doses because of its linear kinetics (Patsalos, 2005). It takes seven to twelve days for ethosuximide levels in the body to reach a stable level (Browne *et al.*, 1975; Buchanan *et al.*, 1969). 93% of ethosuximide is bioavailable after oral administration.

3.4.3 Protein binding

The amounts of ethosuximide in saliva, tears, as well as brain fluid are the same as those in plasma because it has no connection to proteins in plasma (Buchanan *et al.*, 1969). Ethosuximide is dispersed uniformly in rat's medulla, pons, cerebellum, midbrain, and cerebral cortex (Patel *et al.*, 1977). It passes through the placenta and is similar to the mother's blood levels in newborns (Koup *et al.*, 1978).

3.4.4 Distribution

It was previously stated that the apparent amount of distribution of ethosuximide in kids or adults is 0.7 l/kg (Buchanan *et al.*, 1969; Buchanan *et al.*, 1973).

3.4.5 Metabolism

Hepatic metabolism accounts for roughly 80% of ethosuximide's metabolic processes, while it is carried out by cytochrome P450 enzymatic compounds, primarily CYP3A and, to a lesser extent, CYP2E as well as CYP2C/B (Millership *et al.*, 1993).

3.4.6 Elimination

Since ethosuximide is a mixture of about two different enantiomers, research was done on the enantiomer ratio and plasma levels in patients receiving long-term treatment (Nivetha *et al.*, 2023). The elimination amounts of both of the enantiomers and the metabolism of ethosuximide remained identical, and there appeared no stereoselectivity (Villen *et al.*, 1990). Ethosuximide elimination proceeds according to the first-order kinetics (Eadie *et al.*, 1977).

3.4.7 Half-life

For adults, the duration of half-life for ethosuximide removal was between 30-60 h, while for young babies or kids, it varied from 30 and 40 h (Buchanan *et al.*, 1969; Kuhnz *et al.*, 1984). The half-life of ethosuximide was found to be 53 h.

3.4.8 Clearance

Reduced concentrations of ethosuximide are the consequence of co-medicating epileptic patients with anticonvulsant medications that induce an enzyme, as this increases ethosuximide clearance (Giaccone *et al.*, 1996). Adults have a total body clearance of 0.010 -0.015 l/kg/h (Eadie *et al.*, 1977; Natchiappan *et al.*, 2021).

3.4.9 Excretion

The remaining portion of an ethosuximide dosage, or about 20% of it, passes unaltered in the urine. The primary metabolic product of ethosuximide is the hydroxyethyl derivatives, which remain inactive and excrete in the form of glucuronide through urine (Millership *et al.*, 1993).

3.5 Mechanism of working

Complex connections between the cerebral cortex and the thalamus cause typical absence seizures. Several distinct inhibiting and

stimulating systems that originate from the forebrain and brainstem govern this thalamocortical circuitry. The electroencephalographic signatures of absence seizures, known as spike-and-wave discharges, are thought to be produced by corticothalamic rhythms. T-type with a low threshold Ca^{2+} flows in the thalamus are engaged in the thalamocortical circuitry's autonomous pacemaker oscillating movement. It has been suggested that ethosuximide reduces those minimal threshold T-type Ca^{2+} flows in thalamic synapses (Gören and Onat, 2007). Ethosuximide's primary mode of action towards epileptic fits is the inhibition of minimal-threshold T-type (Transient-type) calcium flows within thalamus neurons, however effects at the cortex levels may also be important. The rate of ethosuximide metabolism is accelerated by concurrent treatment with antiepileptic medications that induce enzymes including barbiturates, phenytoin and carbamazepine (Glauser and Perucca, 2015; Sivakumar *et al.,* 2022). Ethosuximide binds to calcium channels with T-type voltage sensitivity. In addition to mediating the entry of calcium ions into excitable cells, numerous other calcium-dependent workflows, including gene expression, muscular contraction, hormones as well as the release of neurotransmitters, cell motility, division of cells, and the death of cells, are mediated by voltage-sensitive calcium channels (VSCC). The isoform alpha-1G is responsible for producing T-type calcium winds. The "low voltage-activated (LVA)" T-type calcium channels are potently blocked by mibefradil. This kind of channel is unique due to the fact it opens at relatively low potentials and inactivates in response to voltage. T-type channels facilitate calcium signaling in the secretory cells as well as vascular smooth muscle, and they play pace-making roles in cardiac nodal cells as well as central neurons.

3.6 Synthesis of ethosuximide

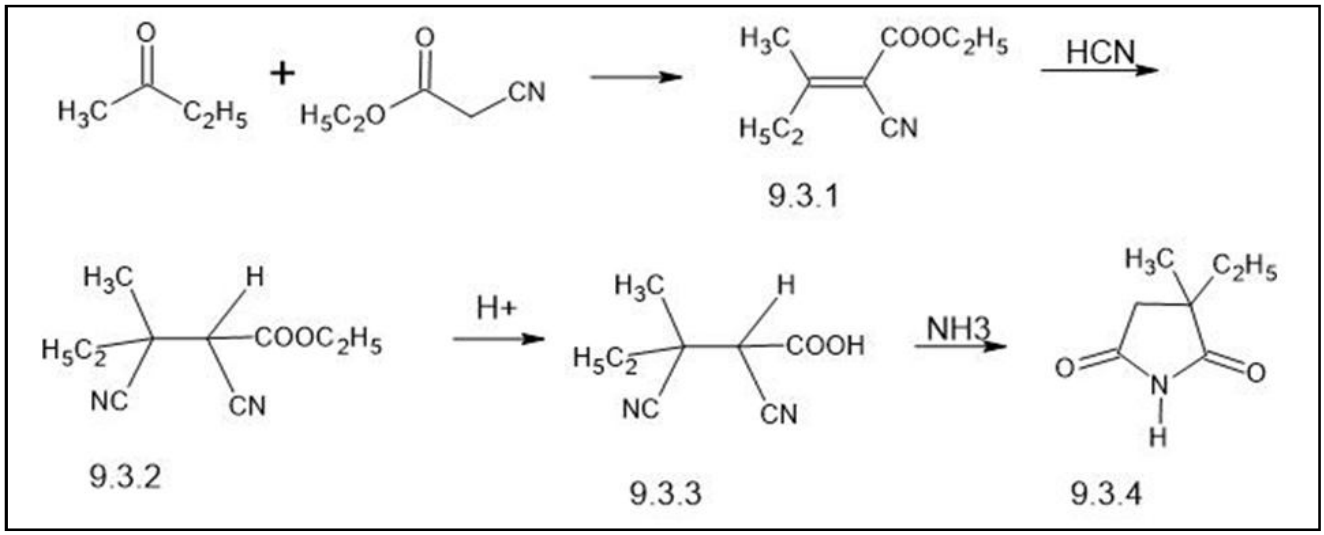

Figure 2: Synthesis of ethosuximide.

Step 1: Knoevenagel reaction conditions are used to condense methylethylketone and cyanoacetic ester to produce ethosuximide, which is known as 3-ethyl-3-methypyrrolidine-2,5-dione (9.3.4).

Step 2: Next, the resultant product is mixed with hydrogen cyanide (9.3.1).

Step 3: The synthesized dinitrile (9.3.2) is hydrolyzed acidically, and 2-methyl-2-ethylsuccinic acid (9.3.3) is the resultant output.

Step 4: This product (2-methyl-2-ethylsuccinic acid) reacts with ammonia to produce the diammonium salt, which then undergoes hetero-cyclization to produce ethosuximide (9.3.4) when heated further (Vardanyan *et al.,* 2006; Pradeep Singh *et al*., 2022).

3.7 Medicinal uses

The succinimide-based drug ethosuximide has a limited therapeutic range for the management of epilepsy. When it comes to treating children with generalized absence (petit mal) epilepsy, ethosuximide is the preferred medication (Posner *et al.,* 2005; Berkovic, 2005). Recent research on ethosuximide has revealed the novel therapeutic potential for the drug due to its potent analgesic effects in both humans and experimental models. In a variety of nociceptive models, the analgesic properties of ethosuximide were investigated (McGivern, 2006). Ethosuximide in combination with other antiepileptic medications may be helpful for individuals with peculiar absence epileptic seizures who furthermore show signs of drop attacks and seizures of tonic-clonic origin (Vimal Raj and Sumithra, 2023). Ethosuximide is thought to be equally as effective as valproate in treating childhood and juvenile absence epilepsy, even though (due to inadequate study design) there is not enough proof for a significant level of effectiveness of all epileptic medications during the initial individual treatment (Glauser *et al.,* 2006).

3.8 Adverse effects

Ethosuximide side effects that are frequently noticed in patients are associated with the central nervous system or gastrointestinal tract (Mattson, 1995; Rogvi-Hansen and Gram, 1995; Brodie and Dichter, 1997). At the beginning of ethosuximide therapy, nausea, abdominal pain, vomiting, diarrhea, and anorexia were frequently experienced. Effects on the central nervous system include headaches, drowsiness, hiccups, dizziness, exhaustion, insomnia, and psychotic behaviors (Posner *et al.,* 2005; Wallace, 1996). A wide range of unusual reactions, such as rash, allergic skin irritation, stevens-johnson disorder, serum sickness reaction, systemic lupus-like syndrome, agranulocytosis, and aplastic anemia, have also been linked to ethosuximide (Teoh

and Chen, 1975; Glauser, 2000). An agranulocytosis induced by ethosuximide was detected in a male child with down syndrome who was 16 months old at the time of diagnosis (Imai *et al.,* 2003; Subhamalar *et al.,* 2023; Indumathy *et al.,* 2023). Eosinophilia, leukopenia, pancytopenia, and agranulocytosis are a few of the side effects of hematopoietic effect (Posner *et al.,* 2005; Alka Rani and Wamik Azmi, 2021).

3.9 Treatment of overdose

The first step in overdose management consists primarily of monitoring, supportive care, and airway protection. If, the patient is male, consider AC-1 mg/kg (50 g maximum) within an hour of ingestion. It is not advised for individuals with a changed mental state to undergo gastric lavage (Akella Anuradha *et al.,* 2023). When a patient cannot protect their airway or has respiratory distress, consider intubation as a means of protecting their airway. Benzodiazepines are recommended for the treatment of seizures (Raghavi *et al.,* 2023). Exchange of plasma or compelled diuresis is ineffective. Hemodialysis should be taken into consideration in cases where ethosuximide toxicity is severe. Hemostasis with charcoal for mesuximide may be useful in eliminating N-desmethyl metabolite (Yadav and Juneja, 2019).

4. Method development of ethosuximide

Mitesh Bhatt *et al.* (2010) quantified ethosuximide in the blood plasma through the creation and approval of an ultra performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method that is straight forward, quick, sensitive, and specific. Pravastatin served as the internal standard during the creation and approval of an ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) technique that is simple, fast, sensitive, and specific for the quantification of ethosuximide in human plasma. The analyte was separated by chromatography using isocratic separation with a flow rate of 0.250 ml/min on a hypersil gold C18 column (100 mm × 2.1 mm × 1.9 µm). With 0.25 ml of human plasma, a simple solid-phase extraction method is used in the assay. The procedure used was linear with the measured concentration ranging from 0.25-60.0 µg/ml. The 0.25 µg/ml was the lower limit of quantification (LLOQ). The precision and accuracy of the quality control samples both within and between days were both within 10.0%. For ethosuximide and pravastatin, the recovery was 95.1% and 94.4%, respectively. Every sample had an analysis period of 1.8 min. The procedure produced peaks with outstanding chromatographic properties and was very reproducible.

El-Shabrawy *et al.* (2018) for the first time studied the chemical stability of ethosuximide (ESX), an antiepileptic medication, within specific stress conditions suggested by the ICH. With a pH 3.5 mobile phase consisting of 0.05 M sodium dihydrogen phosphate and 90:10 v/v methanol, a stability-indicating HPLC method was used to separate ESX from possible products of decomposition using 210 nm ultraviolet (UV) detection. The column used was the promosil C18 column. The validity of the strategy was verified, exhibiting a linearity range of 2.0-30.0 µg/ml and a lower limit of detection of 0.14 µg/ml. The developed method's results were in good agreement with the USP official method. ESX was exposed to extreme acidic, alkaline, and oxidative conditions to study its stability. Under these circumstances, the medication was susceptible to breaking into components and producing particular breakdown products. The drug was effectively separated from all of the formed products of decomposition using the verified HPLC technique for stability indication, demonstrating its suitability for purity and stability testing.

Nabizadeh *et al.* (2023) developed for the very first instance ever, an affordable and effective electro-membrane (EME) technique that uses HPLC-UV to determine ethosuximide in a complicated biological framework. The factors influencing traditional EME were assessed. After immobilizing octanol in a polypropylene membrane, two platinum electrodes were subjected to a voltage of 35 V for 15 min. To ionize ETX, the pH of the phases of donors and acceptors was changed to 11 and 13, respectively. The ETX's range of linearity was 0.25 to 8.00 µg/ml and the enrichment factor was 21.02 with an acceptable R^2 e–0.9986 under ideal microextraction conditions. The recommended method's intra- and inter-day precision and accuracy were determined to have relative errors of less than 7.0% and RSD less than 9.5%, respectively. In the human blood plasma as well as specimens of saliva, the mean relative recovery of ethosuximide was 74.47% and 81.68%, correspondingly; the associated concentrations for quantification and detection limits were 0.25 and 0.08 µg/ml. Additionally, the EME-HPLC-UV method was used for successfully analyzing the blood plasma and saliva specimens of willing participants who had administered only one dosage of ethosuximide to assess the method's application.

Sghendo *et al.* (2002) developed a method for enantiomers of ethosuximide in plasma and urine which can be resolved and quantified using a chiral gas chromatographic (GC) approach that has been modified, made sensitive, and made repeatable. Diethyl ether was used to extract the samples *via* liquid-liquid extraction, and a gas chromatographic column which is chiral (25QC2/CYDEX-β 0.25) was used to separate and quantify the enantiomers. Using GC/MS equipment, the procedure employed ions with mass-to-charge ratios (m/z) exactly equal to 55 and 70 units, as well as the characteristics of the ethosuximide and α,α-dimethyl-β-methylsuccinimide, which served as the internal standard. An electron impact selective-ion monitoring method was implemented for collecting the data. The method's limit of quantitation of 2.5 µg/ml was found for the samples of urine as well as blood plasma that contained the two enantiomers. For urine samples, the method demonstrated linearity, precision, and reproducibility within the range of about 5-300 µg/ml for concentrations, and between 10-250 µg/ml for specimens of plasma.

Heipertz *et al.* (1977) presented a quick and easy gas chromatographic technique for the simultaneous measurement of the metabolite PEMA and anti-seizure medications ethosuximide, phenobarbital, primidone, diphenylhydantoin and carbamazepine in serum. This procedure involves extracting 1 milliliter of serum using ether both before and after the precipitation of proteins using ammonium sulfate. The extract is then injected into methanol without forming derivatives. The extremely polar corrosive phase (SP 1000, which is terephthalic acid-containing modified carbowax 20 M) is used for separation in gas chromatography. The instrument has a nitrogen-selective detector for detection, and peak areas are quantified automatically using a computerized integrating method about an internal standard mesantoin. The efficiency of different stationary phases and support materials is evaluated. This approach was found to be dependable and produce repeatable results in the analysis of more than 800 regular serum specimens including external and internal quality control specimens.

Ou and Rognerud, (1984) developed a liquid chromatographic method in which under 10 min, phenytoin, ethosuximide, carbamazepine, phenobarbital, and primidone along with their bioactive by-products could all be measured at once *via* a straightforward, liquid-chromatographic technique. Acetone/acetonitrile/methanol/10 mmol/l phosphate buffer solution (10/8/21/61 in volume, pH calibrated to 7.95 using NaOH) as the mobile phase and a waters radial-NOVA PAK C18 reversed-phase column is used in this chromatographic system. Antiepileptic medications are taken out of 50 µl of the serum combined with 50 µl of ACN (acetonitrile) which has an internal standard of 10 50 ml of told barb per litre. Following the centrifugation, the leftover product is introduced into the column in 20 µl, allowed to flow out at ambient temperature using a mobile phase with 2.8 ml per minute as an average speed. At 200 nm, the column waste product is observed. The five antiepileptic medications can be identified through this method in quantities as minimal as 0.5 mg/l. The range of analytical restoration is 98-102%. The CV between runs varied from 4.7 to 7.1%, and the CV within runs from 2.9 to 5.8%. Pentobarbital, chloramphenicol and N-desmethyl-methsuximide were also able to be measured using this method.

Galan Valiente *et al.* (1989) created a straightforward, quick technique for a combined ethosuximide and phenobarbital assay in tissue from the brain, serum, and urine. Dichloromethane was used for obtaining specimens from brain tissues and serum at low pH levels while a surplus of ammonium sulfate was present. Dichloromethane was used for extracting the glucuronide conjugates from urine samples after β-glucuronidase was used to hydrolyze them enzymatically. A spherisorb 5 ODS column was used for the analysis of the resulting extracts and the eluent used was a combination of methanol, acetonitrile, and phosphate buffer (24:21:55 v/v). The procedure was accurate and repeatable, and there was no interference.

5. Marketed formulations

Table 3: Marketed formulations of ethosuximide

Name	Dosage	Strength	Route	Labeller
Ethosuximide	Capsule	250 mg/1	Oral	Greenstone LLC
Ethosuximide	Capsule	250 mg/1	Oral	Bryant ranch prepack
Ethosuximide	Solution	250 mg/5 ml	Oral	Greenstone LLC
Ethosuximide	Capsule, liquid filled	250 mg/1	Oral	Banner Life Sciences LLC.
Ethosuximide	Solution	250 mg/5 ml	Oral	Teva Pharmaceuticals USA, Inc.
Ethosuximide	Capsule	250 mg/1	Oral	Chartwell Rx, LLC
Zarontin	Solution	250 mg/5 ml	Oral	Parke-Davis Div of Pfizer Inc.
Ethosuximide	Capsule	250 mg/1	Oral	Heritage Pharmaceuticals Inc. d/b/a Avet Pharmaceuticals Inc.
Ethosuximide	Capsule	250 mg/1	Oral	Avera McKennan Hospital
Ethosuximide	Capsule	250 mg/1	Oral	Zydus Pharmaceuticals USA, Inc.

6. Conclusion

One of the most common illnesses of the brain is epilepsy. Ethosuximide, also known as 2-ethyl-2-methylsuccinimide, is a commonly employed succinimide for the management of seizures known as "petit mal seizures." It is also a useful substance for research on absence seizures. Recent research on ethosuximide has revealed a novel therapeutic potential for the drug due to its potent analgesic effects in both humans and experimental models. At the beginning of ethosuximide therapy, nausea, abdominal pain, vomiting, diarrhea, and anorexia were frequently experienced. Effects of the central nervous system (CNS) include headaches, tiredness, hiccups, giddiness, exhaustion, sleeplessness, and psychotic behaviors. Hemodialysis should be taken into consideration in cases where ethosuximide toxicity is severe. In the literature, many methods were not available for estimating ethosuximide through GC-MS. Therefore, a novel approach that can be developed in future research, validated, and compared with the available current method is crucial for the method development of ethosuximide.

This review offers a thorough knowledge of the drug and a current viewpoint on the analytical techniques of ethosuximide in any pharmaceutical dosage form.

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Conflicts of interest

The authors declare no conflicts of interest relevant to this article.

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