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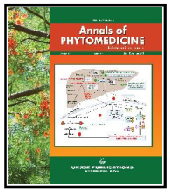

Review Article : Open Access

A comprehensive review of an analytical method for the estimation of sodium valproate with valproic acid

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Abstract

This comprehensive review delves into the advancements in liquid chromatography with high-performance (HPLC) techniques valproic acid in and sodium valproate analysis. The paper scrutinizes the evolution of analytical techniques, focusing on their efficacy, sensitivity, and specificity in determining these compounds. Various methodologies, including column selection, mobile phase compositions, and detection strategies, are assessed in detail. Additionally, the review explores the challenges encountered and the prospects for refining analytical approaches for these crucial pharmaceutical components.

1. Introduction

An anticonvulsant called for the treatment of seizures, valproic acid (2-propylpentanoic acid) is utilized. Its composition differs from that of the majority of other antiepileptic medication structures. A frequent neurological encephalopathy, epilepsy is more than ten times more common in children than in adults (Dongli Zhang *et al.,* 2020). Brain dysfunction disease known as pediatric epilepsy causes significant harm to cranial nerves and places a heavy physical and psychological load on sufferers and their families. Because children's development is incomplete and their ability to metabolize drugs is not as strong as that of adults, there are few treatment choices available for juvenile epilepsy due to safety concerns (Roger and Kathleen, 2015). The brands of sodium valproate with valproic acid that are most frequently used are byzantine, epilim chromosphere, and epilim chrono. They are most frequently used to treat bipolar disorder manic episodes and epilepsy. For the treatment of complex partial seizures, commonly known as psychomotor seizures, altered consciousness, and automatism-associated forms of focal epilepsy, the FDA approved valproic acid use in 1983 (Akella Anuradha *et al.,* 2023). Single or combined with sodium valproate acid numerous dose forms for valproate are available, including liquid, enteric-coated tablet, pill, injectable, supranational, sprinkle, and formulations with controlled release. Gas chromatography technique described in monographs for valproic acid dissolving and assay (Vimal Raj and Sumithra, 2023). Valproic acid is also estimated using a variety of other techniques, such as capillary electrophoresis, isotope dilution mass spectrometry, using MS in high-performance liquid chromatography (HPLC) detection, and elevated throughput LC-MS, as well as high-performance HPLC with fluorescence detection. According to a survey of the literature, no such simple RP-HPLC approach has been published for a valproic acid estimate in formulation-specific dissolving investigations, such as pharmacophores (Subhamalar *et al.,* 2023; Sivakumar *et al.,* 2022).

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2. Drug profile

A medication known as an anticonvulsant (or antiepileptic) is valproic acid. The exact manner in which this medication for bipolar illness treatment is unknown. Nonetheless, valproic acid is believed to increase gamma-aminobutyric acid (GABA) concentrations in the brain to decrease or eliminate manic episodes (Chateauvieux *et al.,* 2014). Many common types of seizures in children can be effectively treated with valproic acid: absence seizures (one of the best medications for these fleeting moments of fixation) and myoclonic seizures.

Seizures that are both tonic and clonic, like those seen in lennox-gas taut syndrome (Marlene *et al.,* 1998). A pentatonic acid stem with a propyl substituent is what makes valproic acid, a branched-chain saturated fatty acid. It functions as an anticonvulsant, a GABA agent, a teratogenic agent, a psychotropic agent, an inhibitor of histone deacetylase, and an antimanic drug. The molecular formula of valproic acid $C_8H_{16}O_2$ (Luyu Gong *et al.,* 2020).

The density of valproic acid at 25°C is 0.9 g/ml, molecular weight-144.211 g/mol. Brand names: convulse, syon ell, byzantine, belvo, and depakote. The acid's sodium salt is known as sodium valproate, and the coordination complex between the two is called di-valproex sodium (DVP). A therapeutic range of 50-100 mcg/ml is recommended for total VPA serum concentration when measured clinically. The IUPAC name for sodium valproate is 2-propylpentanoic acid.

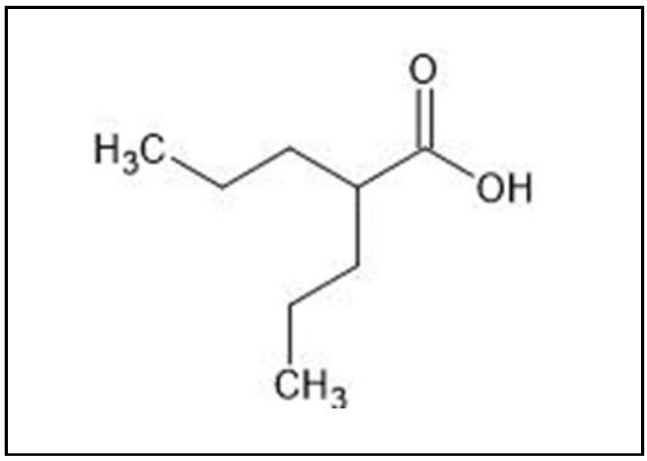

Figure 1: Sodium valporate with valporic acid.

2.1 Drug-drug interactions

Antipsychotic medications are prescribed along with antiepileptic medications and interactions can impact toxicity as well as efficacy. This article has reviewed the clinical information regarding notable interactions between the antipsychotic drugs carbamazepine, valproic acid (sodium valproate) vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine, levetiracetam, pregabalin, felbamate, zonisamide, phenobarbital, and phenytoin and risperidone, olanzapine, quetiapine, clozapine, amisulpride, sulpiride, ziprasidone, aripiprazole, haloperidol, and chlorpromazine and carbamazepine. Additionally provided was scant data regarding interactions between pimozide, zuclopenthixol, periciazine, fluphenazine, and flupentixol and antiepileptic drugs (Besag and Berry, 2006).

2.2 Mechanism of action

VPA is a drug with several different as of yet unidentified modes of action. Among the proposed VPA modes of action are: Inhibition of voltage-gated sodium channels, VPA blocks sodium ions from entering neurons, which reduces the excitability and firing rate of the neurons. In addition to being widely used in the treatment of generalized and partial epilepsies, valproate, a prominent antiepileptic medication has been approved for use in the treatment of pain caused by nerves, bipolar disorders, prevention of migraines (Pinder *et al.,* 1997; Divya and Sanjeev *et al.,* 2021). The various mechanisms of action that reflect this broad range of activities are covered in this review. Special attention is paid to how VPA affects the GABAergic system and how enzymes connected to brain metabolism and the tricarboxylic acid cycle (TCA cycle) such as α-ketoglutarate dehydrogenase, GABA transaminase and succinate semialdehyde dehydrogenase (SSA-DH) (GABA-T). *In vitro* studies have shown that VPA is a strong SSA-DH inhibitor. Significant inhibition of GABA is observed in brain homogenates. In addition to its effect on the GABA shunt, VPA has the potential to block the TCA cycle at the α-ketoglutarate dehydrogenase step. Mood-stabilizing impact and the way that VPA treats migraines are believed to be attributed to its effects on excitatory membranes and excitatory neurotransmission. Neuropathic pain may involve GABA-mediated responses. However, there are still a lot of unanswered questions regarding the VPA's methods of action.

2.3 Synthesis

Once rectified and purified, the unrefined item quantitative neutralization of an aqueous sodium hydroxide solution is added by valproic acid. Additionally, it causes sodium valproate dehydration crystallization, adds toluene band water refluxing, and passes through rear filtration with chloroform washing and dry end product. Dipropyl cyanoacetic ester is produced by alkylating cyanoacetic ester with two moles of propyl bromide (Mohan Kumar *et al.,* 2015).

3. Sodium valproate with valproic acid method development and optimization

Mugdha Karde *et al.* (2012) have developed a 4.6 × 150 mm, 5 µm zorbax eclipse XBD-C18 column utilized for their quantification. The mobile phase was made up of acetonitrile: 50:50 v/v, citric acid buffer (pH 3) at 1.5 ml/min, and UV detection at 210 nm. The suggested method's linearity was examined between 50 and 400 µg/ml (r^2 = 0.9997). In the triplicate recovery trials, three concentration levels 80%, 100%, and 120% of the test concentration were employed. Valproic acid recovery was observed to range from 96.63 to 101.88%. A relative standard deviation of less than 2.0% was discovered. A percentage RSD number less than one suggested that the method's precision was good. It was discovered that the verified HPLC process was accurate, linear, and exact.

Jouyban and Maryam Abbaspour (2018) valproate was extracted, preconcentrated, and determined from human plasma and urine samples were achieved by the development of quick, incredibly effective, and dependable microextraction of liquid-liquid (LLME) techniques, which were subsequently followed by gas chromatography-flame ionization detection. The 0.05-0.22 µg/ml and 0.1-0.5 µg/ml ranges were found to be the limits of quantification and lower detection limits for valproate, respectively. For plasma and urine, 0.5-500 and 0.1 – 200 µg/ml were the linear ranges, respectively, ($r^2 \geq 0.9995$), the preconcentration factors ranged from 7 to 44 and the recoveries for the spiked samples ranged from 55-86%.

Murad Abualhasan *et al.* (2020), the 2-hydroxyacetophenol reaction was used in the development of the HPLC process. Because of this specific reaction's superior separation, it was selected as the modified analytical method. Furthermore, the addition of valproic acid structure with benzoyl by this reagent results in a prolonged conjugation, which causes the parent drug's absorbance to shift into a more hyperchromic and bathochromic change. In contrast, the process employing only one phenol group was introduced by trichlorophenol. By introducing conjugation into this research effort, we were able to successfully establish an approach to sodium valproate analysis. To create an ester with the medication, valproic acid, and 2-hydroxyacetophenone were reacted to introduce the conjugation. The medication became more lipophilic with the addition of the benzoyl ring.

Lau Cam and Roos (2006), a straightforward, precise, and repeatable HPLC technique for the measurement of sodium salts of valproic acid in dose forms used in commerce. When phenacyl bromide and triethylamine were mixed with acetone to create the respective phenacyl ester derivatives, the internal standard and the analyte, sodium caproate, were found in the ultraviolet range. On the micros orb-MV C18 column, the ester derivatives were immediately analyzed using a mixture of methanol, acetonitrile, and water in the ratio of

50:20:30 and detected at 245 nm. Phenacyl caproate and phenacyl valproate eluted at a flow rate of 2 ml/min, approximately 4.5 and 8.5 min, respectively (Himanshu and Priyanka, 2020; Mounika and Hymavathi, 2021).

Peak height ratios and valproic acid concentrations were correlated linearly, or its equivalent in the 30-750 µg range (r^2 = 0.9997) in sodium valproate. For a set of replicate injections, the RSD was 1.10% (n=6) based on peak height ratios. From commercial dosage forms that had been spiked, recoveries of sodium or valproic acid ranged from 101.0-102.6% of added (n = 2). For valproic acid in USP 23, the assay results produced by the suggested HPLC method and the GC method agreed rather well.

Ibrahim Alsarra *et al.* (2005), the main topics of this chapter are sodium valproate and valproic acid. One kind of valproic acid is a transparent, colorless light-yellow liquid that is a little bit sticky has a distinct odor, and is only mildly soluble in water. It is mildly readily soluble in acetone, alcohol, chloroform, ether, benzene, n-heptane, and methyl alcohol but soluble in 0.1 N hydrochloric acid. Sodium valproate powder is crystalline, deliquescent, hygroscopic, and white or almost white. The chapter also includes descriptions of compendial and thermal methods of analysis. It is discovered that valproic acid is stable at room temperature. The overall content of valproic acid remains unchanged when a blood sample containing the medicine is refrigerated or frozen for seven days. The majority of methods for analyzing sodium valproate and its counterpart in biological liquids that have been described involve chromatography, particularly gas chromatography; however, there are some reports of high-performance liquid chromatography (HPLC). Additional techniques like potentiometry, capillary electrophoresis, fluorescence polarization, enzyme immunoassay, and flow injection analysis are also employed (Raghavi *et al.,* 2023; Dhritimoni and Sumithra, 2023).

4. Conclusion

In conclusion, the HPLC conditions optimization of all of the degradation products were separated from the VPA peaks by developing specific chromatographic settings. Combining two antiepileptic medications, the combination of valproic acid and sodium valproate is called valproic acid. Together, they lessen the abnormal and excessive firing of nerve cells in the brain responsible for controlling seizures or fits. Analytical methods for estimating sodium valproate and valproic acid often involve chromatography techniques like HPLC or GC as well as spectroscopic methods like UV-visible spectroscopy. These methods are utilized due to their accuracy, sensitivity, and ability to separate and quantify the compounds in various matrices. The outlook for these methods continues to evolve with advancements in technology, aiming for increased efficiency, sensitivity, and robustness in drug analysis.

Chromatographic methods like gas chromatography (GC) and high-performance liquid chromatography (HPLC) are commonly used in analytical procedures for quantifying sodium valproate with valproic acid. These techniques are frequently combined with mass spectrometry (MS) or ultraviolet (UV) detection. These methods offer accurate quantification by separating and detecting the compounds within a sample. They are widely used due to their sensitivity, specificity, and reliability in determining the concentration of both sodium valproate and valproic acid in various matrices, including biological samples and pharmaceutical formulations.

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Conflict of interest

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

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