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A REVIEW ON ANALYTICAL METHODS FOR ESTIMATION OF DIVALPROEX SODIUM IN PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

Anti epileptics are used in the adequate and impressive control and management of CNS disorders essentially characterized by recurrent attacks of disturbed brain function which ultimately give rise to motor, sensory, and psychic sequence of events. Divalproex Sodium (DS) is a fatty acid with anticonvulsant properties used in the treatment of epilepsy of bipolar disorder and depression. This agent binds to and inhibits gamma-aminobutyric acid (GABA) transaminase and its anticonvulsant activity may be exerted by increasing brain concentration of GABA and by inhibiting enzymes that catabolize GABA or block the reuptake of GABA into glia and nerve endings. On literature survey, it was found that not much work has been done on this particular drug for its determination in bulk and pharmaceutical dosage forms using chromatographic techniques.This review covers most recent analytical methods such as various chromatographic methods and other methods for determination of Divalproex Sodium in various pharmaceutical dosage forms were reported.

Keywords: Divalproex Sodium; Analytical Methods; Anti epileptic drug

INTRODUCTION

Divalproex sodium (DS) is the stable, coordinated compound comprised of sodium valproate and valproic acid in a 2:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Its

characteristic broad spectrum anticonvulsive activity and divalproex sodium is used in the treatment of a wide range of seizure disorders such as myoclonic epilepsy syndromes, absence epilepsy, generalized convulsions, partial seizures, and status epilepticus **[1]**. It is the treatment of the manic episodes of bipolar disorder. In rare cases, it is also used as a treatment for major depressive disorder, and increasingly taken long-term for prevention of both manic and depressive phases of bipolar disorder, especially the rapid-cycling variant. Its use has significantly increased over the past decades as a mood stabilizer as well as replacing lithium **[2]**. However, a retrospective cohort study of patients with bipolar found that patients treated with lithium had a lower risk of suicide attempt and suicide death than when treated with divalproex sodium **[3-4]**.

Divalproex Sodium is designated as sodium hydrogen bis (2propylpentanoate). Divalproex sodium has the following structure **(Figure 1)**.

Drug profile [4, 5] (Table 1, 2)

Mechanism of action of Divalproex Sodium (DS):

Divalproex Sodium is a fatty acid with anticonvulsant properties used in the treatment of epilepsy. Typically supplied in the sodium salt form. Divalproex dissociates to the valproate ion in the gastrointestinal tract. This agent binds to and inhibits gamma-aminobutyric acid (GABA) transaminase and its anticonvulsant activity may be exerted by increasing brain concentration of GABA and by inhibiting enzymes that catabolize GABA or block the reuptake of GABA into glia and nerve endings. Divalproex may also work by suppressing repetitive neuronal firing through inhibition of voltage-sensitive sodium channels. Valproic Acid is also a histone deacetylase inhibitor and is under investigation for treatment of HIV and various cancers **[6-7]**.

Marketed formulations of Divalproex Sodium (Table 3)

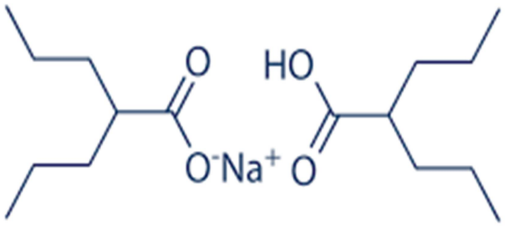

Figure 1: Chemical structure of DS

Table 1: Chemical Profile of DS.

Sr. No.	Parameters	Divalproex Sodium
1.	Molecular weight	310.4g/mol
2.	Molecular formula	$C_{16}H_{31}NaO_4$
3.	Melting point	222^0c
4.	pKa (Strongest Acidic)	5.14
5.	Solubility	Soluble in ethanol, DMSO, and dimethyl formamide
6.	Storage	Stored at room temperature, well maintained area.
7.	Color	white powder
8.	Odar	Characteristic odor

Table 2: Pharmacokinetic Profile of DS

Sr. No.	parameters	Divalproex Sodium
1.	Absorption	Orally absorbed
2.	Metabolism	Metabolized almost entirely by the liver
3.	Bioavailability	1%
4.	Half life	9-16 hrs
6.	Plasma protein binding	≈18.5%

Table 3: Marketed formulation of Divalproex Sodium

Sr. No.	Brand name	Company name	Formulation	Dose (mg)
1	Valprol-CR	Intas LTD	Tablet	500

Analytical Methods

This all are the methods which are used for the determination of Divalproex Sodium in marketed formulation. This all analytical methods are reported which are seen during the literature survey. Various HPLC, GC and other analytical methods for simultaneous determination of Divalproex Sodium and its combination with aripiprazole plus have been reported. Below describes the various methods with the method description and condition which are reported on review literature.

Compendial method

Divalproex Sodium is official in United States pharmacopoeia (USP-2016) described chromatographic method.

Chromatographic methods

Various chromatographic methods for simultaneous determination of Divalproex Sodium and its combination with Aripiprazole plus have been reported.

Ramanjaneyulu S., *et al*. **[9]** specifies the RP-HPLC method for the analysis of Divalproex sodium in pharmaceutical formulation such as tablets was developed and validated as per ICH guidelines. The chromatographic method was standardized for Divalproex sodium using system employs isocratic elution using on Agilent SB C18, (150 x 4.6 mm, 5um) with Buffer and Acetonitrile were mixed in the ratio 60:40 v/v, as mobile phase set at flow rate 1.0 ml /min. The Percentage Assay values were calculated for both the drugs and found to be in between 98.0% - 102.0 %.

Rose MF., *et al.* **[10]** specifies the RP-HPLC method for simultaneous determination of divalproex sodium in Pharmaceutical Dosage form. The

chromatographic separation was achieved by using Agilent SB C18, 5 µm, 30^0c, (50 x 4.6 mm) analytical column with a mobile phase consisting 1-hexane sulphonic acid sodium salt anhydrous and Acetonitrile (50:50%v/v). The flow rate was set at a 1.0 ml/min, and detector wavelength of 210 nm using a PDA detector, the retention time (RT) was found to be 3.582min.

Ahmed Z., *et al.* **[11]** specifies the accurate and simple isocratic HPLC method was established and validated for the simultaneous quantification of aripiprazole and valproic acid in the FDC tablets. A reversed-phase C18 (250 × 4.6 mm) column in isocratic mode was used. The mobile phase consisted of acetonitrile and 0.32% KH_2PO_4 (60:40, v/v), flow rate was set at 1.0 mL/min and the detection was performed at 210 nm. Average percent recoveries of aripiprazole and valproic acid were 96.0 and 95.5%, respectively.

Israel DS., *et al.* **[12]** specifies the RP HPLC method for estimation of Divalproex in bulk and pharmaceutical dosage forms. Chromatographic separation was achieved on Agilent SB C18, (50 x 4.6 mm, 5 µm) using an isocratic mode with mobile phase composed of Buffer and Acetonotrile are taken in 60:40%v/v(P^H 4) The flow rate was 1.0ml/min, temperature is maintained at30^OC and detection was made at 210 nm. The run time was 8 min. The developed method was validated according to the ICH guide lines and different analytical parameters such as linearity, precision, accuracy, specificity, limit of detection, limit of quantitation were determined. The linearity of calibration curve for each analyte is in concentration range of 25 – 150ppm. There exists good correlation between peak area and analyte concentration. Relative standard deviation values for Divaprolex are 1.24. LOD for drug is 2.3 and LOQ is 9.4.

Yat P., *et al.* **[13]** specifies the method for the analysis of valproic acid in divalproex sodium formulations was developed and validated. Sample preparation was in methanol and 0.5% sodium dodecyl sulfate (1:9 v/v) and resolved on a C8 column with UV detection at 215 nm. The mobile phase consisted of acetonitrile and 25 mM sodium dihydrogen phosphate buffer, pH 3.5 (1:1 v/v) at a flow rate of 1.0 mL/min. The retention times were about 5 min.

Other methods

Subasranjan A., *et al.* **[14]** specifies the stability-indicating gas chromatography (GC) method has been developed and validated for the quantitative determination of divalproex sodium impurities in pharmaceutical preparation. A technique has been developed whereby the peak purity of a compound with poor UV

detection can be determined using a gas chromatograph coupled with a mass spectrometer. The drug products were subjected to hydrolysis, oxidation, photolysis, and heat to apply stress conditions. The stability-indicating nature of the method has been proven by establishing peak purity of all stressed samples. The chromatographic separation was performed on a fused silica capillary (Quadrex-FFAP, 30 meter, 0.32 mm and 1 µm film thickness) column. The method validation results indicate that the method is specific, accurate, linear, reproducible, rugged, and robust. The effectiveness of the technique was demonstrated with stability sample analysis of divalproex sodium in its pharmaceutical preparation.

Reddy SR., *et al.* **[15]** specific GC method has been developed, optimized and validated for the determination of seven related substances namely N,N-dimethyl valpronamide, valeric acid, 2-methyl valeric acid, 2-ethyl valeric acid, 2-isopropyl valeric acid, 2-n-butyl valeric acid and 2-propyl-2-pentenoic acid in divalproex sodium (DPS) drug substance ,Chromatographic separations were achieved on DB-FFAP column (30m × 0.53 mm, 1.0 µm), The analysis was carried on gas chromatograph systems (Agilent 6890N model/Shimadzu GC-2010 model) equipped with an AOC- 5000 combipal auto sampler and a data handling system with HPCHEM station/Empower-2/GC solutions. Agilent J&W DBFFAP (30m × 0.53 mm, 1.0 µm) column that consists of nitroterephthalic acid modified polyethylene glycol material was used as stationary phase. Helium was used as the carrier gas with a constant pressure of 90 kPa. The initial column oven temperature of 130°C is maintained for 28 min and then increased to 230°C at a rate of 6°C/min, followed by holding at 230°C for 5.4min. The run time was fixed as 50min. The injection volume is 1.0 µL with a split ratio set at 3:1. The injector temperature and detector temperature were 230°C and 240°C, respectively. For the ignition of FID, highpurity gases were used in the volumes of 50mL/min (Hydrogen), 500 mL/min (Zero air) and 40 mL/min Nitrogen.were in the ranges of 4–5 and 12–15 µgmL−1, respectively.

Kumar UA., *et al.* **[16]** specifies the RP-UPLC method has been developed and validated for the Quantitative determination of Divalproex sodium (DPX) in tablets. An isocratic method for analysis of Divalproex sodium was achieved on Waters Acquity UPLC column with BEH C8, (100x2.1 mm, 1.7µm). Mobile phase A consisted of 10 mM monobasic sodium phosphate adjusted to pH 3.5 with ortho phosphoric acid. Mobile phase B was acetonitrile. The mobile phase used was prepared by mixing

mobile phase A and mobile phase B in the ratio, 50:50 (A:B), at a flow rate of 0.4 mL/min. The variable wavelength ultraviolet spectrophotometric detector was set at 215 nm. The assay linearity was good (typically r2= 0.9992) and the standard curves were linear in the detection range 50-150 µg/mL.

Roy B., *et al.* **[17]** specifies the LC–MS method for the determination of Valproate semisodium in human plasma was developed and validated. Sample preparation involved the protein precipitation method. Chromatographic separation was performed on Sunfire C18 5µm (150 X 4.6) mm column with the mobile phase consisting of Acetonitrile: 10 mM ammonium acetate buffer 80:20 v/v. The method was validated over the concentration range of 1.012 µg/mL. to 120.399 µg/mL. and the Lower limit of quantitation (LLOQ) was 1.012 µg/mL. The intra- and inter-day precision of the method at four concentrations was 2.26-10.67% and 3.58-10.49 %.

T Hassib SO., *et al.* **[18]** specifies the method depends on using RESTEK C18 column (5 µm, 250 mm × 4.6 mm) and a mobile phase composed of acetonitrile:water (55: 45, v/v), pH = 3.3 adjusted with phosphoric acid. The method was conducted in an isocratic mode with a flow rate of 1ml/min and ultraviolet detection at 210 nm. The linearity range was 2–40 µg/ml for RUF and DIA, 0.5–40 µg/ml for LAM and CLO, and 36–180 µg/ml for VAL.

DISCUSSION

The presented review highlights on various analytical methods reported for estimation of Divalproex sodium in alone or in combination with aripiprazole plus used methods. These methods are found to be rapid, accurate, sensitive, economical and reproducible for determination of Divalproex sodium in various marketed formulations.

CONCLUSION

So, from all above information it should be concluded that various chromatographic methods and other methods were used for determination of Divalproex sodium alone or in combination which has been successfully used on a routine basis and allows the quantification of the drug in various pharmaceutical dosage form and in short analytical time.

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