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Formulation And Evaluation Of Sustained Release Tablet Of Divalproex Sodium Salt

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Abstract: ***Epilepsy/Migraine is a brain disorder in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally. Neurons normally generate electrochemical impulses that act on other neurons, glands, and muscles to produce human thoughts, feelings, and actions. Researchers believe that some people with epilepsy have an abnormally high level of excitatory neurotransmitters that increase neuronal activity, while others have an abnormally low level of inhibitory neurotransmitters that decrease neuronal activity in the brain About 50 million people worldwide have epilepsy, and nearly two out of every three new cases are discovered in developing countries. Epilepsy becomes more common as people age. Onset of new cases occurs most frequently in infants and the elderly. As a consequence of brain surgery, epileptic seizures may occur in recovering patients. Divalproex sodium is front line anticonvulsant/antiepileptic agent for treatment of simple and complex absence seizures. Divalproex sodium is combination of equivalent ratio (1:1) of valproic acid and sodium valproate and has been used in combination because there are minor differences in pharmacokinetics parameters of both drug (i.e. acid and its salt form).***

Keywords: Epilepsy, neurotransmitters, pharmacokinetics.

I. PLAN OF WORK

PREFORMULATION STUDIES

- ✓ Identification of drug
  - I R
  - HPLC
  - Melting point
- ✓ Solubility analysis
- ✓ Drug polymer interaction study

FORMULATION DEVELOPMENT

- ✓ Selection of drug
- ✓ Selection of polymers
- ✓ Optimization of drug polymer ratio
- ✓ Preparation of tablet

CHARACTERIZATION OF TABLET

- ✓ Physical appearance
- ✓ Diameter and Thickness measurement
- ✓ Hardness determination
- ✓ Friability study
- ✓ Uniformity of weight
- ✓ Disintegration time study
- ✓ Dissolution study

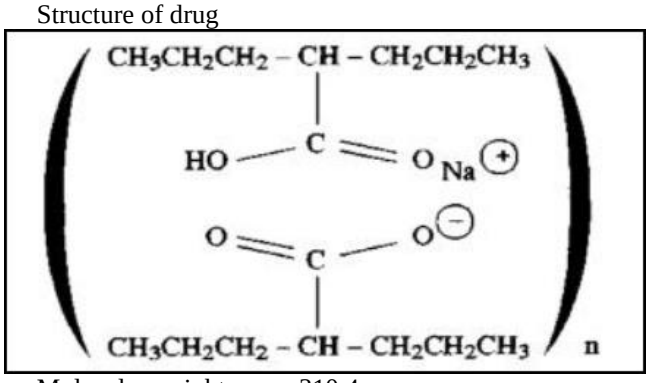
Comparison of formulated tablets with innovator tablet

STABILITY STUDIES: As per ICH guidelines

II. DRUG PROFILE

Name : Divalproex Sodium
IUPAC Name: Sodium 2-propylpentanoate 2-propylpentanoic acid

Structure of drug



Molecular weight 310.4
Molecular formula C16H31O4Na

PHYSICAL PROPERTIES

S. No.	Parameters	Properties
1.	Physical State	Amorphous Solid (An off powder) and Hygroscopic in nature
2.	Melting Point	222 ℃
3.	Solubility	Slightly water soluble Very soluble in Chloroform Freely soluble in methanol and ethyl ether Soluble in acetone
4.	Log P	2.549
5.	Log pKa	4.8

Table 1

DESCRIPTION

Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5M equivalent of sodium hydroxide

PHARMACOKINETICS/PHARMACODYNAMIC

PARAMETERS	SPECIFICATION
T_{max}	8-14 hrs
The plasma t ½	9 -16 hrs
Bioavailability	Approximately 80 to 90%
Site of absorption	Rapidly absorbed from the GIT
Absorption	Approximately 80 to 90%
Plasma protein binding	80-90%
Route of metabolism	Hepatic Metabolism (Mitochondrial ß-oxidation)
Volume of distribution	11.2 L/1.73 m2 [total valproate], 92 L/1.73 m2[freevalproate]

Table 3

MECHANISM OF DRUG ACTION

Divalproex binds to and inhibits GABA transaminase. The drug's anticonvulsant activity may be related to increased brain concentrations of gamma-amino butyric acid (GABA), an inhibitory neurotransmitter in the CNS, by inhibiting enzymes that catabolise 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.

HOW TO TAKE

Take drug with or without meals.

SIDE EFFECTS

This drug may cause headache, fainting, abnormal dreams, amnesia, depression, poor coordination, hallucinations, sleepiness or difficulty sleeping, nervousness, numbness and tingling, personality changes, tremors, weakness, chest pain, rapid or irregular pulse, palpitations, heart block, heart failure, low blood pressure, vision problems, eye irritation, ringing in the ears, nosebleed, runny or stuffy nose, decreased appetite, constipation, diarrhea, dry mouth, nausea, vomiting, thirst, bad taste in mouth, frequent urination (especially at night), impotence, enlarged breasts, muscle cramps, joint pain, shortness of breath, difficulty breathing, increased skin sensitivity to sun or heat lamps, stiff neck, swelling, weight gain, and allergic reactions (including itching and rash).

Notify your prescriber of serious or bothersome symptoms.

INTERACTIONS

Divalproex sodium, valproate, or valproic acid may interact with carbamazepine, cimetidine, cyclosporine, drugs called beta blockers (such as propranolol), midazolam, rifampin, some anesthetics, triazolam and alcohol.

STORAGE

Store at 77 ℉ (25℃) away from moisture, Do not store in bathroom.

TOXICITY

Over dosage with Divalproex Sodium may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from divalproex levels as high as 2120 µg/mL.

III. METHODOLOGY PREFORMULATION STUDIES

Preformulation studies are described as the process of optimizing the delivery of drug through which determination of physico-chemical properties of the new compound that could affect drug performance and development of an

efficacious, stable and safe dosage form. Preformulation is the first step in the rational development of dosage form of a drug substance and it is defined as an investigation of physico-chemical properties of a drug substance alone and when combined with excipients.

IDENTIFICATION OF DRUG DIVALPROEX SODIUM

PHYSICAL PROPERTIES

For a drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug.

PHYSICAL APPEARANCE

It is white to off white crystalline powder.

MELTING POINT DETERMINATION

The melting point of compound is the temperature at which it changes from a solid to liquid. This is a physical property often used to identify compounds.

Generally two methods are used to determine melting point of drug substance.

MELTING POINT APPARATUS

PROCEDURE

- ✓ A cleaned capillary tube was taken.
- ✓ A small amount of compound (divalproex sodium) was placed on a clean surface. The compound was put into the capillary tube.

The capillary tube was placed in melting point apparatus (Macro Scientific Works) and the sample was observed continuously. Slow heating was done for most accurate results. The melting range was recorded which begins when the sample first starts to melt and ends when the sample melted completely.

CHROMATOGRAPHIC CONDITION

Flow Rate: 1.2 ml/ min
Wavelength: 210 nm
Injection Volume: 50 µl

PROCEDURE

Column was saturated with mobile phase. Then blank solution, reference solution (5 replicate) and test solution (2 replicate) was filled in vials and then vials are fitted in set box individually. Chromatographic parameters were adjusted and HPLC was run for 15 min.

Percentage drug release =

$$\frac{\text{Sample reading}}{\text{Standard reading}} \times \frac{\text{Wt. of Std (61.3)}}{100} \times \frac{900}{1} \times \frac{\text{Potency}}{100} \times \text{Factor} \times \frac{100}{\text{Claim}(500)}$$

Note: In this case factor was one and potency was 90.75

IV. RESULTS AND DISCUSSION

Formulation and evaluation of sustsined release tablet of divalproex sodiumwas carried out. The standard & sample solutions were prepared & the U.V spectrums were recorded. The present of individual drug found in formulation were calculated & presented in tables. The result of analysis shows that the amounts of drug were in good agreement with the label claim of the formulation.

V. CONCLUSION

Formulation and evaluation of sustsined release tablet of divalproex sodiumwas carried out. The fourmulation method may be used in.

- ✓ Research Institution.
- ✓ Quality Control Department In Industries
- ✓ Approved Testing Laboratories
- ✓ Bio-pharmaceutics & Bio-equivalent Studies
- ✓ Clinical Pharmacokinetic Studies

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REFERENCES

[1] Ajay, V. Tirupa, M. and Yadav, A., 2011. Formulation and evaluation of Propanlol extended release tablet. *International Journal of Advances in Pharmaceutical Sciences*, Vol. 2, Issue 1, pp. 58-62.
[2] Asian guideline on stability study of drug product, 2005. 9th ACCQS-PPWG Meeting, Philippines, pp. 21-24.
[3] Aulton, M.E, 2002. *The Science of Dosage Form Design*. Livingstone, Churchill Publication, 2nd ed. pp. 413-416.
[4] Bacci, A. Sancini, G. Verderio, C. and Armano, C., 2002. Neurotransmitter Supply and Demand in Epilepsy. Current literature, Vol. 88, pp. 2302-2310.
[5] Banker, G.S. and Rhodes, C.T., 2005. *Modern Pharmaceutics.* New Delhi, CBS publishers and distributors, 4th ed., pp. 373-421.
[6] Bauden, C.L. Joseph R. and Patracia, J., 2006. A randmized placebo-contrlled multicenter study of Divalproex sodium extended release in treatment of Acute mania. *Journal of Clinical Psychiatry*, Vol. 67, pp. 1501-1510.
[7] Bhasker, C.M. and Gurudatta, J., 2000. Divalproex sodium extended-release tablets. *FDA Approved Labeling Text for NDA 21-168*, pp. 1-18.
[8] Crank, J., 1996. *The Mathematics of Diffusion*, Oxford, Oxford University Press.
[9] Dakkuri, A. Butler, L.D. and Deluca, P.P., 1978. Sustained release from inert matrixes III effect of

povidone on Tripelennamine Hydrochloride release. *Journal of Pharmaceutical Science*, Vol. 67, pp. 357–360.
[10] Dutta, K. Sandeep, J. and Ronald, C., 2004. Divalproex to Divalproex extended release conversion. *Journal of Controlled Release*, Vol. 24, Issue 9, pp. 495-508.
[11] Dutta, K. Sandeep, J. and Ronald, C., 2004. Divalproex to Divalproex Extended Release Conversion. *Journal of controlled release*, Vol. 24, Issue 9, pp 495-508.
[12] El-Zein, L. Riad, C. and Shied, A., 1998. Enhancement of carbamazepine dissolution: in vitro and in vivo evaluation. *International Journal of Pharmaceutics*, Vol. 168, pp. 209–220.
[13] El-Zion, H. and Glared, C., 2008. The use of hydroxyl propyl methyl cellulose in controlling the release of sparingly soluble drug from tablets prepared using polyethylene glycol. *Journal of Damascus University Health Science*, Vol. 25, Issue 1, pp. 575–590.
[14] *European Journal of Pharmaceutics and Biopharmaceutics*, Vol. 75, pp. 232–237.
[15] FDA Approved Labeling Text for NDA 21-168 of Depakote ER, 2000. Pp.1-18.
[16] FDA. *Guidelines for Submitting Documentations for the Stability of Human Drugs and Biologics*. Rockville (MD), 1987.
[17] FDA. 1987. *Guidelines for submitting documentations for the stability of human drugs and biologics*. Rockville (MD),
[18] Ganesh, G.N.K. kumar, S.R. Jawahar, N. Senthil, V. Nagasamy, D., 2010. Preparation and evaluation of sustained release matrix tablet of diclofenac sodium using natural polymer. *Journal of Pharmaceutical Science and Research*, Vol.2, Issue 6, pp. 360-368.
[19] George, A. and Burdock, N., 2007. Safety assessment of hydroxypropyl methylcellulose as a food ingredient. *Food and Chemical Toxicology*. Vol. 45, pp. 2341–2351.
[20] Ghosh, S. Saha, N.G. Subal D. and Kumar, G.N., 2010. Formulation and evaluation of sustained release dosage form of nifedipine hydrochloride using multi-unit chitosan treated alginate. *International Journal on Pharmaceutical and Biomedical Research*, Vol. 1, Issue 4, pp. 124-131.