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Formulation and Evaluation of Ointment of Valproic Acid

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A B S T R A C T

The objective of proposed study are as to the developed low dose maintenance therapy so reduce the risk of potential side-effects and improve patient compliance. The present study is focused on the development of transdermal drug delivery system (Patches) for sustain delivery of Valproic Acid.

Keywords:- Transdermal patch, Valproic acid, sustain drug delivery system.

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INTRODUCTION

Valproic acid is a mood stabilizer anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. Adverse effects are rare and hepatoxicity is severe is younger less than 2 years. Valproic acid inhibit enzyme gamma transmenase, which blocks the conversion of GABA **(Gamma Amino Butyric Acid)** to succinic semi aldehyde and more of GABA is available in the CNS. Valproic Acid is an organic weal acid and conjugate base is valproate. The sodium salt of the acid is sodium valproate and the complex of two is known as valproate samisodium. It is used to treat epilepsy and bipolar disorder and to prevent migraine headaches. Valproate has a broad spectrum anticonvulsant activity. Primarily it is used as a first line treatment for tonic clonic seizures, myocolnic seizures and as second line reatment for partial seizures and infactile spasms.

Preformulation Studies:-

Preformulation investigations are designed to identify those physiochemical properties and excipients that may influence the formulation design, method of manufacturer and pharmacokinetics, biopharmaceutical properties of the resulting products.Preformulation studies includes description of the substance, taste, colour, odour, melting point, incompatibility with other ingredients.

MATERIAL

Valproic acid, wool fat liquid paraffin, Cetostearyl alcohol was obtained as a gift sample from Mirambika pigment 155/1 Dhannot, Chhatral, Kadi Road District Gandhi Nagar.

Identification of Drug:

Physical Appearance:

The drug sample (Valproic Acid Batch No. 132102) was purchased from Mirambika Pigment Distt. Gandhi Nagar Gujrat India. The supplied powder of drug sample (Valproic Acid) was a colorless to pale yellow, have characteristic odour.

Determination of Melting Point:

Melting point of valproic acid was determined using digital melting point apparatus by capillary fusion method. A capillary was taken and its one end sealed with the help of burner. The open end of the capillary tube was pushed into a small plug of the powder and tube was tapped gently, so that collected material settled down. The process was repeated several times. Then the capillary tube was placed in the melting point apparatus.Valproic acid does not melt, decomposed at 120 ± 1^{0}c.

Determination of Uv Absorption Maxima:

To determination of absorption maxima (λ_{max}), the accurately weighed quantity 10 mg of valproic acid drug sample was dissolved in methanol and volume make upto 100 ml with methanol in a 100 ml volumetric flask to obtain a stock solution 100 µg/ml. Then 1 ml of this stock solution was pipetted out in a 10 ml volumetric flask and volume was made upto the mark with methanol to obtained the concentration 10 µg/ml. The resulting solution was then scanned between 200-400 nm using UV-visible spectrophotometer (Model-1700, Shimadzu, Japan). The UV spectrum sample (valproic acid) was recorded and obtained λmax=212 was matched with the UV spectrum as reported in official monograph.

Fourier Transform Infrared (FT-IR) Spectroscopy:

The infrared spectroscopy of the pure drug sample was carried out to identity the drug. A pellet of drug was prepared by compressing of the drug with IR grade potassium bromide by applying of 5.5 metric ton of pressure in KBr press. The pellet was mounted in IR compartment and scanned between wave number 4000-450 cm^{-1} using FT IR spectrophotometer (Model-8400 S, Shimadzu, Japan). The observed peaks corresponding to various functional groups were compared with the reference (B.P, 2009).

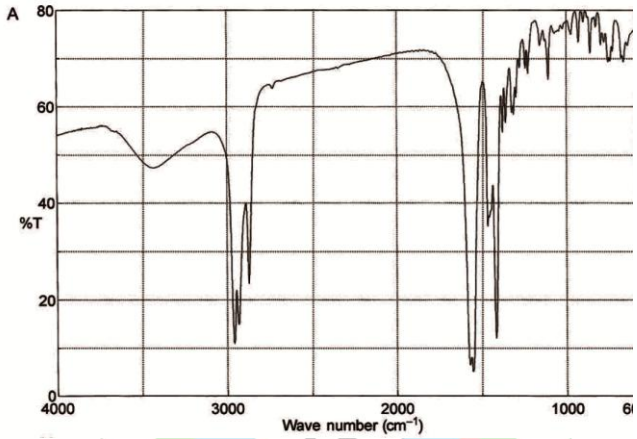

Figure: 2 (A) The infrared absorption spectrum of sodium valproate obtained in a KBr pellet.

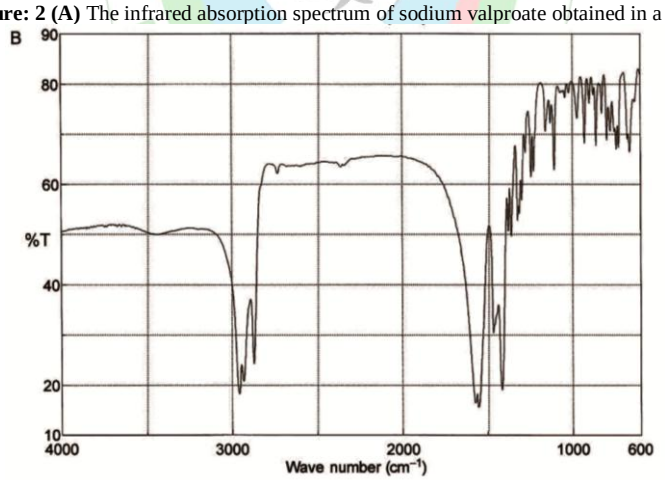

Figure: 3 (B) The infrared absorption absorption spectrum of valproate obtained in a KBr pellet

Table: 3 Valproic acid sodium Valproic comprehensive Profile.

A. Assignments for the infrared absorption bands of sodium valproate	
Frequency (cm^{-1})	Assignments
2960	Aliphatic C-H stretch
2930	
2870	
1565	Antisymmetrical and symmetrical stretching
1555	virbration of COO^- group
1465	

1415	
B. Assignments for the infrared absorption bands of sodium valproate	
Frequency (cm^{-1})	Assignments
3435	O-H stretching vibration of carboxylic acid
2965	Aliphatic C-H stretch
2875	
1705	C=O stretch
1080	O-H bending vibration

DETERMINATION OF SOLUBILITY:

The dissolution and diffusion fluid for drug release and permeation studies respectively was selected based on solubility data of valproic acid in various fluids. The solubility of drug sample was determined by adding 100 mg of drug sample in successively increasing amount in various fluids like methanol, chloroform, phosphate buffer solution pH 7.2 and buffer containing 5%, 10% and 20% (v/v) of methanol as co-solvent. The volume of solvent required to dissolve the drug was recorded (Prasanthi and Lakshmi, 2012). Slightly soluble in water, freely in acetone, alcohol, ether, chloroform.

Table: 2 Solubility of Valproic acid in different solvents.

Sr No.	Solvent	Solubility
1.	Methanol	+++++
2.	Chloroform	++++
3.	Methanol : PBS pH 7.2 (05:95)	++
4.	Methanol : PBS pH7.2 (10:90)	+++
5.	PBS pH 7.2	+

+++++ =Very Soluble < part +++++ = Free soluble 1-10 parts

++++= Soluble 10-30 parts +++ =Sparingly soluble 30-100 parts

++= Slightly Soluble 100-1000 parts + = Very slightly soluble 1000-10000 parts

Determination of Partition Coefficient:

The partition coefficient of drug was determined in n-Octanol as a non-aqueous phase and phosphate buffer solution pH 7.2 (PBS pH 7.2) as an aqueous phase. These two phases were mixed in equal quantities and kept for saturation with each other in separating funnel. After mixing the system remain undisturbed for 30 minutes. The partition coefficient was determined by taking 10 mg of drug in separating funnels containing 10 ml portion of each of n-Octanol and PBS pH 7.2. The separating funnels were shaken on mechanical shaker for 24 h. Two phases were separated and aqueous phase was filtered through Whatman filter paper and the amount of the drug in aqueous phase was determined, after appropriate dilution by spectrophotometrically at λ_{max} 212 nm by using phosphate buffer solution pH 7.2 as a blank.

Preparation of Calibration Curve:

The calibration curve of Valproic acid was prepared in chloroform and 20% methanol in PBS pH 7.2. The absorbance values corresponding to each concentration was plotted on y-axis and concentration on x-axis. The regression was found to be 0.999 in both chloroform and 20% methanol in PBS pH 7.2. The calibration curve showed the linearity between the concentrations ranging from 5-40 µg/ml analyzed by using UV spectrophotometer at wavelength of 212 nm.

Table: 3 Absorbance values of Valproic acid in chloroform at 212 nm

Sr No.	Concentration (µg/ml)	Mean Absorbance	± S.D "(n=3)
1.	5	0.242	± 0.015
2.	10	0.422	± 0.024
3.	15	0.625	± 0.026
4.	20	0.838	± 0.032
5.	25	1.082	± 0.044

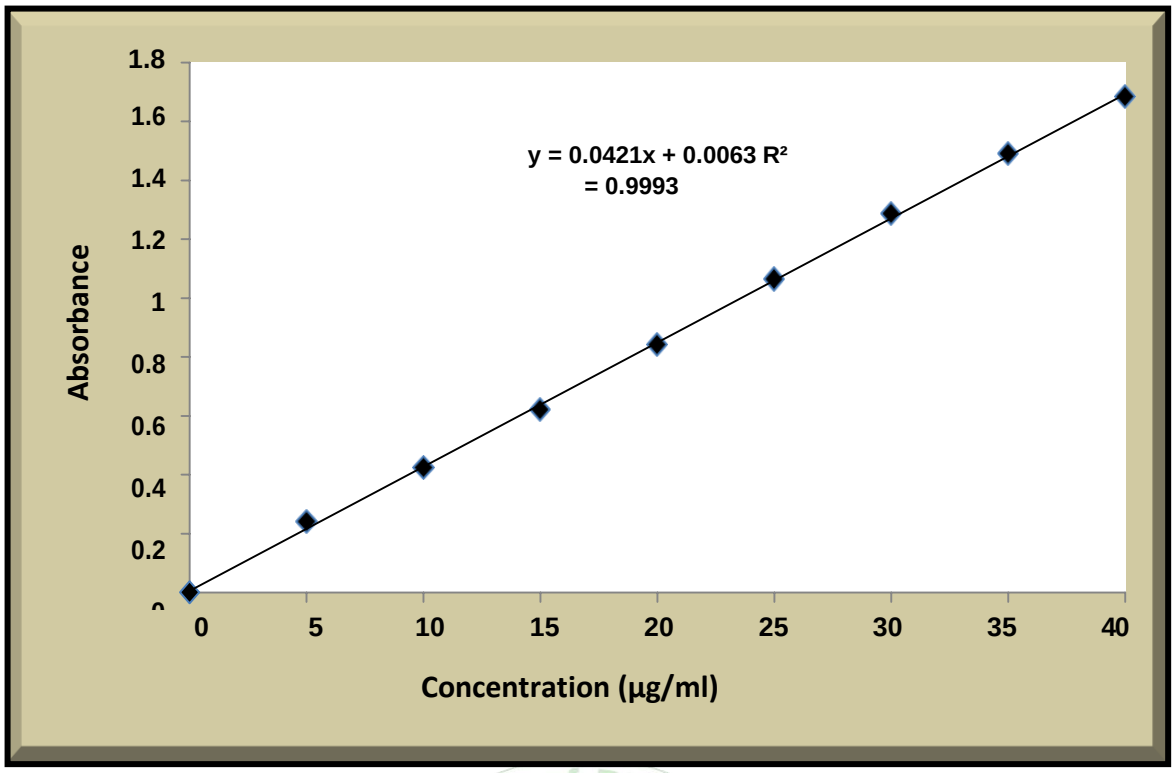

Figure: 3 Absorbance values of Valproic acid in chloroform at 212 nm

Table: 4 Absorbance values of valproic acid in 20% methanol in PBS pH 7.2 at 212nm

S. No.	Concentration (µg/ml)	Mean Absorbance	± S.D. (n=3)
1.	5	0.212	± 0.011
2.	10	0.395	± 0.020
3.	15	0.605	± 0.029
4.	20	0.815	± 0.018
5.	25	0.982	± 0.021
6.	30	1.172	± 0.038
7.	35	1.380	± 0.042
8.	40	1.561	± 0.040

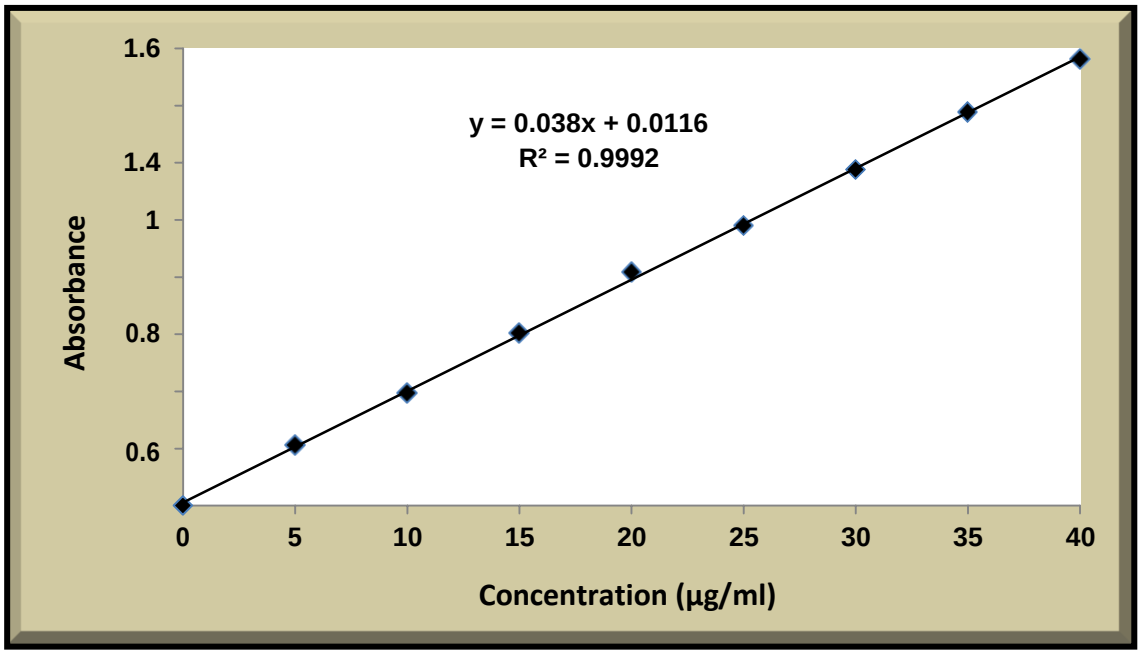

Figure: 4 U.V. Absorbance values of Valproic acid in 20% methanol in PBS pH 7.2 at 212 nm

METHODS: -

Table: 5 Formula Each 5 gram contain

Sr.No	**Ingredients**	Quantity given	Quantity Taken
1	Valproic Acid	5 Gram	500 mg
2	Cetostearyl Alcohol	10 Gram	1 gram
3	Wool fat	10 Gram	1 gram
4	Liquid Paraffin	20 Gram	2 gram
5	Purified water to	50 Gram	5 gram

Procedure - Melted Cetostearyal alcohol, Wool fat and liquid paraffin together. Dissolved Valproic Acid in warm water to about temperature to 60^0 C. Added the warmed aqueous liquid to the melted substances mixture and strred thoroughly until cold.

Evaluation of Ointment of Valproic Acid.

Penetration In It weighed quantities of ointments were rubbed over definite areas of skin for a given length of time and remaining quantities were collected and absorbed quantities are given in the table.

Table: 6 For absorbed quantities of ointment of valproic acid.

Sr. No.	Quantities applied	Time (Minutes)	Area	Quantity Collected	Quantity Absorbed
1.	4 80 mg	4 minute	3.75 Inch	4.20 Mg	60 mg
2.	500 mg	5 Minute	4.59 Inch	4.28 mg	72 mg
3.	520 mg	6 Minute	5.22 Inch	440 mg	80 mg
4.	540 mg	7 Minute	6.00 Inch	450 mg	90 mg

Rate of release of medicament- Small amount of ointment of Valproic Acid was placed on the surface of nutrient agar contained in a petri dish. Agar plate was previously seeded with a suitable organism like S. aureus after a suitable period of incubation , the zone of inhibition was measured and correlated with rate of release. The rate of release of Valproic acid was confirmed by incorporating an iron salt in the agar and measured the coloured zone around the sport where ointment of valproic acid was applied. Inhibition of coloured zone was found to be approximate 90% due to bactericidal nature of medicament and rate of release of drug was found to be optimum.

Irritant Effect – The prepared valproic acid ointment was applied on the skin and eyes of rabbits. Reactions are noted at intervals of 24, 48.72 and 96 hours. There was no lesions on cornea, iris, conjunctiva and after 2 weeks there was observed that no patches, rashes on the skin which showed that the drug did not have any irritant effect

Assay of Valproic Acid Ointment

Procedure- A portion of the ointment sample equivalent to about 80 mg of Valproic Acid was warmed with 30 ml of ethanol (90% V/V) to melt the base and extracted with the solvent. It was further extracted with two 30 ml aliquots of ethanol (96% V/V). The combined extracts were filtered and made up to 100 ml with ethanol. A 5ml aliquot of extract was diluted to 50 ml in volumetric flask with ethanol (96% V/V) and the absorbance measurements were carried out, at wavelength. The concentration of Valproic acid was determined by spectrophotometeric assay using built in software.

Determination of Valproic acid in commercial Valproic Acid Ointment

Table: 1 Analysis of Synthetic mixture of Valproic Acid.

VALPROIC ACID			
Added (Gram X 10^3)	Found (Gram X 10^3)	Recovery (%)	RSD (%)
12.00	11.92	99.3	1.1
9.60	9.58	99.8	0.5
6.00	6.07	101.2	0.9
4.80	4.78	99.6	0.3
3.00	2.97	99.0	

Table: 2 Assay Result of Valproic Acid.

Batch No	Valproic Acid (6% W/W)		
	% of label claim (gm)		
	Proposed Method	USP Method	E %
1	99.9± 0.6	100.5 ± 1.2	-0.6
2	100.4±1.0	101.6±1.7	-0.2
3	100.6±1.2	99.8±1.5	+0.8

E= Relative error in spectrophotometer Versus USP Method.

RESULT AND DISCUSSION:

The formulated ointment of Valproic acid was found to be clear, smooth, free form grittyness, Uniform, flexible in their physical appreance and free from entrapment of air bubble. Evaluation of prepared ointment is done to determine the quality of ointment which is responsible for good quality of semi solid preparation. Penetration rate of release of medicament, absorption of medicament into blood stream and irritant effect was observed and the result parameters shows good quality of ointment and values were found within the limits.

Valproic acid is a pale yellow anticonvulsant drug by which we prepared an ointment to make a transdermal patch to avoid the disorders of oral rout therapy and ointment packed in a patch which is used as transversal drug delivery system. This new system avoids the drawbacks and hazards of multiroutes therapy and also known as conventional or sustained route therapy in which the absoption of drug bypass the liver function and stomach activity mainly enzymes and HCL acid which causes acidity and many more other problems this is the main advantage of this conventional drug delivery system

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