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Research Article

Evaluation of Transdermal Patches of Valproic Acid

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A B S T R A C T

Conventional System of Medication that requires multi dose therapy are having many problems. The controlled drug delivery is a newer approach is to deliver drug into systemic circulation. As Valproic Acid is a drug to control the manic disorder so it is necessary to maintain the concentration of drug in systemic circulation continuously. So a new approach known as transdermal drug delivery system is adopted to avoid the various drawbacks of oral and other conventional dosage form.

Keywords: Preformulation Transdermal Patches, Skin Valproic Acid,

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INTRODUCTION:

Valproic Acid is an organic weak acid and conjugate base is valproate. The sodium salt of the acid is sodium valproate and the complex of two is known as valproate semisodium. 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, myoclonic seizures and as second line treatment for partial seizures and infantile spasms.

Preformulation Studies:

Preformulation studies are the first step in the development of dosage form of any drug substance. The objective of preformulation studies are to develop a portfolio of information about the drug substance so that this information if useful to develop formulation. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture and pharmacokinetic- biopharmaceutical properties of the resulting products.

Materials:

Table: 1 List of Equipments

Name of Ingredients	Name of Manufacturer
Valproic Acid	Mirambika Pigment, Gandhinagar, Gujrat
Ethylcellulose	SD Fine Chem Ltd., Mumbai, India
Polyvinylpyrrolidone (PVP K-30)	SD Fine Chem Ltd., Mumbai, India
Di-n-butylpthalate	SD Fine Chem Ltd., Mumbai, India
Dimethyl sulphoxide	SD Fine Chem Ltd., Mumbai, India
Tween-80	SD Fine Chem Ltd., Mumbai, India
Eucalyptus oil	Central Drug House, New Delhi, India
Olive oil	Central Drug House, New Delhi, India
Chloroform	SD Fine Chem Ltd., Mumbai, India
n-Octanol	Central Drug House, New Delhi, India

Methanol	Sisco Research Laboratory, Mumbai, India
Monobasic potassium dihydrogen orthophosphate	Himedia Laboratories, Mumbai, India
Sodium hydroxide	Central Drug House, New Delhi, India
Dialysis membrane	Himedia Laboratories, Mumbai, India
Anesthetic ether	TKM Pharm Ltd. Hyderabad, India
Adhesive tape	Johnson & Johnson, India
Faxtin	Ind-Swift Ltd., Chandigarh, India
Calcium chloride	Central Drug House, New Delhi, India
Sodium chloride	Central Drug House, New Delhi, India
Aluminum foil	Gujarat foils Ltd. Indore, India
Carboxy methylcellulose	Central Drug House, New Delhi, India
Isopropyl alcohol	Central Drug House, New Delhi, India

EQUIPMENT USED:

Table: 2 List of Equipments

Name of Equipments	**Name of Manufacturer**
UV- Spectrophotometer	Model-1700, Shimadzu, Japan
Melting point apparatus	Gupta Scientific Industry, Ambala, India
FTIR (1800) spectrophotometer	Model-8400 S, Shimadzu, Japan
Electronic weight balance	Citizen Scales, Pvt. Ltd., Mumbai, India
Digital pH meter	Hanna Instruments, Romania
Hot air oven (Labline)	Bharat Emporium, Roorke, India
Deep freezer (Cold Cel)	Voltas Ltd., Mumbai, India
Vacuum desiccators (Hicon)	Grover Enterprises, Delhi, India
Magnetic stirrer	Remi Sales & Engineering Ltd., Mumbai, India
Sonicator	H. L. Scientific Industries, Ambala, India
Dissolution (Disso 2000) rate test	Labindia Instruments Pvt. Ltd. Thane, India
Micropipette	Genetix Biotech Asia Pvt. Ltd., Delhi, India
Thickness gauge	Muttato, Japan
Modified Franz diffusion cell	Fabricated Locally, Jhansi, India
Refrigerator (GL-195RLGE4)	LG Electronics India Pvt. Ltd., Noida, India
Shaking incubator (Sonar)	Associate Scientific Technologie, New Delhi, India
Scanning electron microscopy	Carl Zeiss AG, Germany
Humidity cabinet (Hicon)	Grover Enterprises, Delhi, India

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 ± 1^0c.

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 pipette 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).

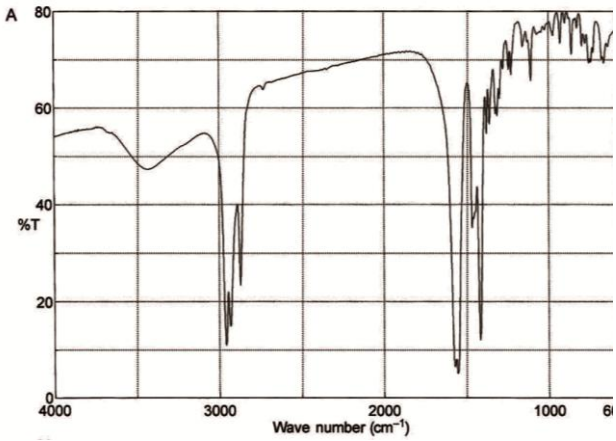

Figure: 2 (A) The infrared absorption spectrum of sodium valproate obtained in a KBr pellet.

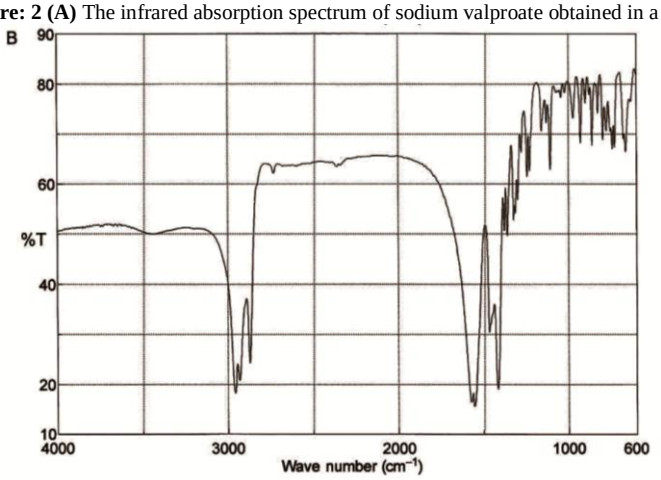

Figure: 3 (B) The infrared absorption absorption spectrum of valproate obtained in a KBr pellet

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: 4 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
++++= Soluble 10-30 parts
++= Slightly Soluble 100-1000 parts
+++++ = Free soluble 1-10 parts
+++ =Sparingly soluble 30-100 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: 5 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

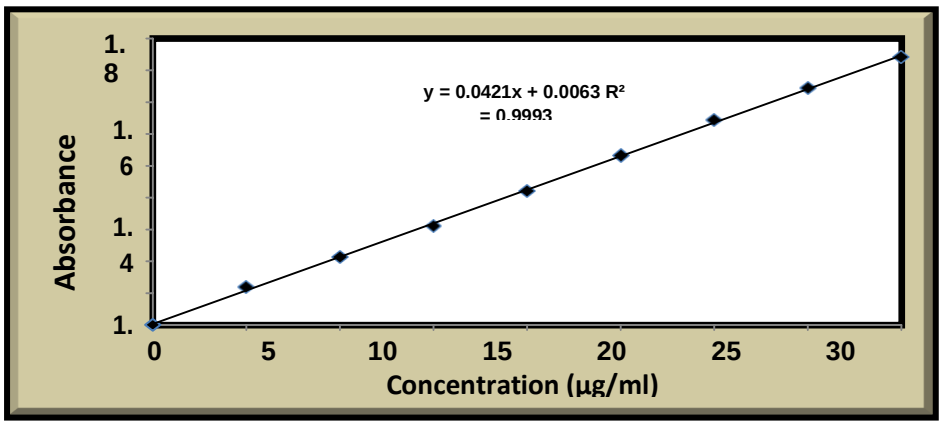

Figure: 3 Absorbance values of Valproic acid in chloroform at 212 nm

Table: 6 Absorbance values of valproic acid in 20% methanol in PBS pH 7.2 at 212nm

S. No.	Concentration (µg/ml)	Mean Absorbance	± S.D.
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

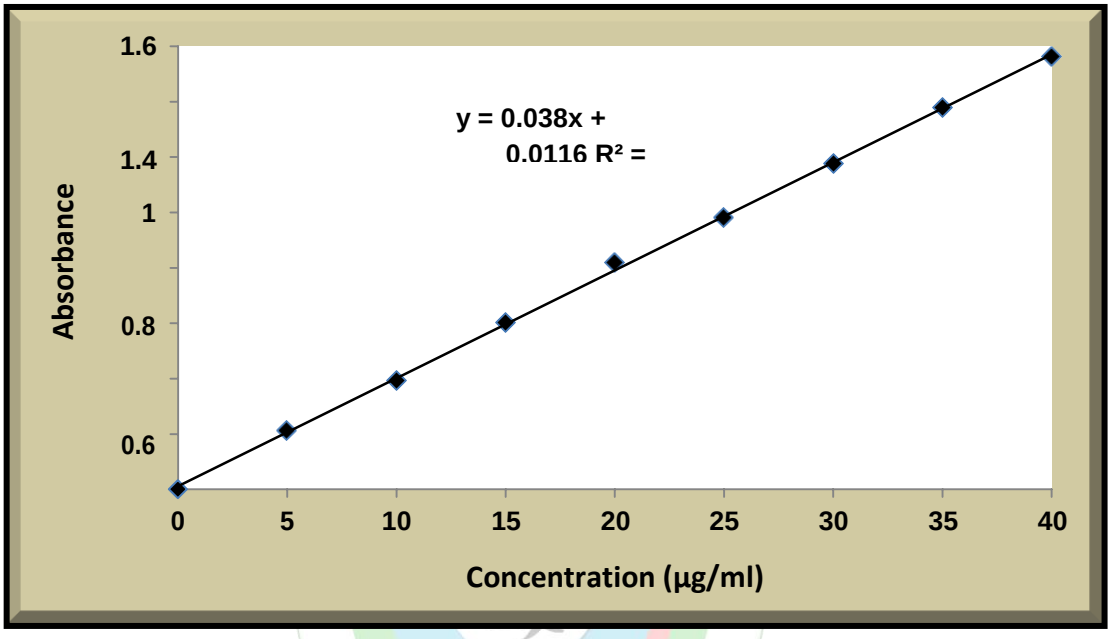

Figure: 5 U.V. Absorbance values of Valproic acid in 20% methanol in PBS pH 7.2 at 212 nm

FORMULATION OF VAPROIC ACID TRANSDERMAL PATCHES:

The transdermal patches were prepared by using ethylcellulose (EC) and polyvinylpyrrolidone K-30 (PVP) polymers in different composition. The EC and PVP are most commonly used polymers in transdermal drug delivery system because of their compatibility with drugs and sustained release properties (Kandavilli *et al.*, 2012). In preliminary studies, various formulations were prepared with or without plasticizer. The transdermal patches prepared without plasticizer were found to be brittle and hence di-n- butyl phthalate was used as plasticizer to reduce the brittleness of the transdermal patches. The studies indicated that addition of di-n-butyl phthalate at 30% w/w of total dry polymers weight produces smooth, uniform and flexible films. Hence, further formulations were prepared by using plasticizer at 30% w/w of polymers weight in all the patches. Hence, on the basis of preliminary formulation studies, the optimum polymer ratio was subjected with various penetration enhancers used in different concentration in order to enhance the *in vitro* permeability of drug molecule. The fabricated films were evaluated for various physiochemical parameters and the composition of formulations is given in Table. 1.8.

Table: 7 Composition of Valproic acid Transdermal patches

S. No.	Formulation Code	Valproic Acid (% w/w)	EC:PVP (Ratio)	Permeation Enhancer (% w/w)
1.	F1	20	4.5 : 0.5	-
2.	F2	20	4 : 1	-
3.	F3	20	2 : 1	-
4.	F4	20	3:2	-
5.	F5	20	2:3	-
6.	FD1	20	3:2	DMSO 2%
7.	FD2	20	3:2	DMSO 5%
8.	FD3	20	3:2	DMSO 10%

All formulations containing dibutyl phthalate (30% w/w of polymers weight) as plasticizer and chloroform as a solvent system.

EVALUVATION OF VAPROIC ACID PATCHES

Physiochemical Evaluation of Valproic Acid Patches:

The prepared transdermal patches were evaluated for their physiochemical characteristics like physical appearance, thickness, weight uniformity, drug contents, moisture contents, moisture uptake, flatness, folding endurance, tensile strength and pH. The results of physicochemical characteristics are given in Table 2.0.

The formulated patches were found to be clear, smooth, uniform, flexible in their physical appearance and free from entrapment of air bubble. The weight of transdermal patched varied from 165.42 to 170.88 mg which indicated that the prepared different batches of transdermal films were similar in weight. The thickness of different batches was found in range from 0.248 to 0.275 mm. A low standard deviation value in the film thickness measurement ensures the uniformity of formulated patches. No significant difference in drug content was observed in all the formulated patches which were found in range from 94.36 to 97.23%. The obtained results indicated that the method used for the preparation of transdermal patches was capable of possessing uniform drug content due to the homogenous dispersion of the drug.

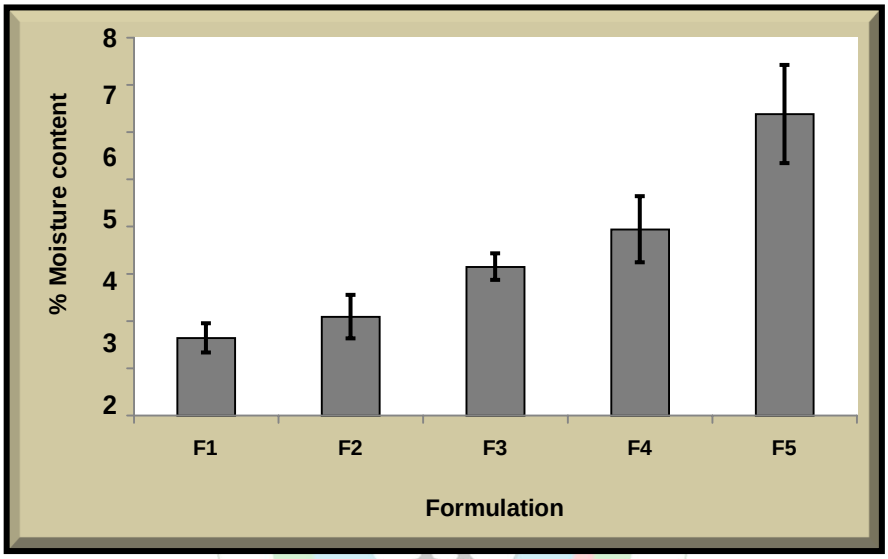

Figure: 6 Percentage of moisture content from Valproic acid transdermal patches containing different ratio of EC/PVP

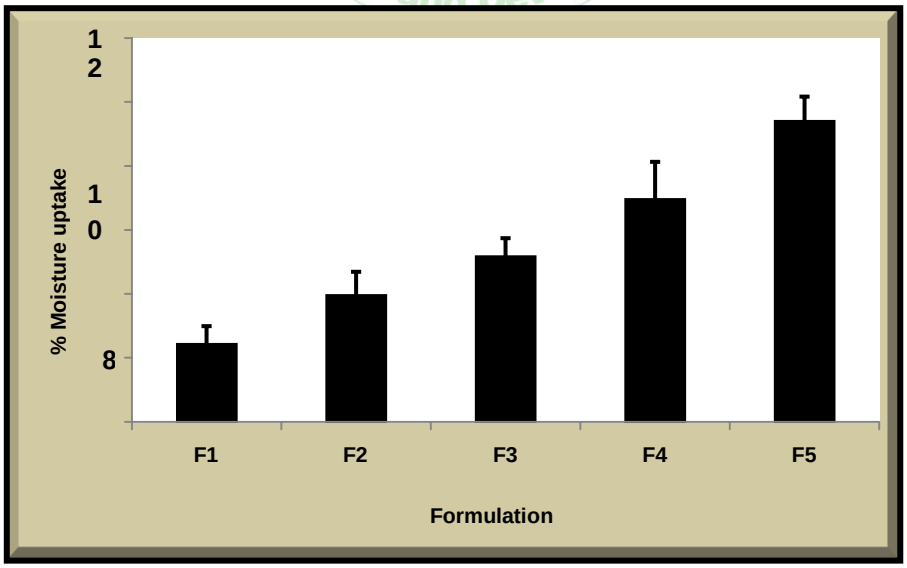

Figure: 7 Percentage of moisture uptake from valproic acid transdermal patches containing different ratio of EC/PVP.

Table: 8 physicochemical evaluation of Valproic Acid transdermal patches

F. Code	Thickness (mm)	Weight Variation (mg)	Drug Content (%)	Flatness	Folding Endurance	Tensile Strength (kg/mm^2)	pH
F1	0.273 ± 0.014	164.87 ± 2.08	96.25 ± 0.42	100	42 ± 4.08	0.417 ± 0.02	5.8
F2	0.254 ± 0.017	164.37 ± 1.48	97.26 ±1.42	100	48 ± 6.50	0.438 ± 0.04	5.8
F3	0.266 ± 0.008	167.19 ± 1.88	94.12 ± 0.74	100	44 ± 3.43	0.393 ± 0.01	5.8
F4	0.260 ± 0.012	165.20 ± 2.08	96.20 ± 1.11	100	39 ± 4.69	0.404 ± 0.03	5.7
F5	0.268 ± 0.011	166.49 ± 1.11	95.03 ± 1.56	100	34 ± 3.08	0.357 ± 0.06	5.7
FD1	0.265 ± 0.016	164.40 ± 1.89	96.78 ± 2.14	100	38 ± 5.37	0.370 ± 0.07	6.5
FD2	0.276 ± 0.010	166.72 ± 1.92	94.38 ± 0.92	100	36 ± 3.11	0.352 ± 0.03	6.6
FD3	0.269 ± 0.016	169.61 ± 2.33	96.20 ± 0.61	100	38 ± 4.15	0.346 ± 0.05	6.6
FT1	0.261 ± 0.022	165.20 ± 1.69	97.64 ± 1.04	100	37 ± 5.12	0.371 ± 0.02	6.3
FT2	0.256 ± 0.023	167.57 ± 2.12	95.68 ± 0.62	100	36 ± 3.91	0.397 ± 0.04	6.3
FT3	0.274 ± 0.013	168.97 ± 2.93	95.73 ± 1.80	100	40 ± 4.84	0.361 ± 0.02	6.4
FE1	0.246 ± 0.027	165.40 ± 2.18	98.23 ± 0.78	100	35 ± 4.32	0.394 ± 0.03	6.1
FE2	0.256 ± 0.014	167.60 ± 1.34	95.53 ± 1.21	100	38 ± 2.54	0.403 ± 0.04	6.5
FE3	0.267 ± 0.012	166.76± 2.76	97.19 ± 0.96	100	35 ± 3.63	0.372 ± 0.03	6.6
FO1	0.265 ± 0.016	168.56 ± 1.91	94.88 ± 1.13	100	36 ± 6.72	0.346 ± 0.02	5.7
FO2	0.273 ± 0.009	167.95 ± 4.32	94.58 ± 1.34	100	40 ± 3.91	0.363 ± 0.04	5.7
FO3	0.272 ± 0.014	172.01 ± 2.77	96.43 ± 0.69	100	43 ± 4.18	0.358 ± 0.05	5.7

APPLICATION OF KINETIC MODELS TO CHARACTERIZE THE IN VITRO DRUG RELEASE FROM VALPROIC ACID PATCHES:

In vitro drug release studies results were fitted in various kinetic models (Table 2.6) to study the release kinetics of data. Zero order as cumulative percent of drug released vs. time, first order as log cumulative percentage of drug remaining vs. time and Higuchi's model as cumulative percent drug released vs. square root of time (Prashar *et al.*, 2014). To determine the mechanism of drug release from formulations, the data were fitted into Korsmeyer Peppas equation as log cumulative percentage of drug released vs. log time. The value of n exponent was calculated from slope of the straight line. For matrix, if exponent n is 0.5, then diffusion mechanism is Fickian; if 0.5<n <1.0, mechanism is non- Fickian; if n is 1.0, mechanism is zero order and if n >1.0, then it is super case II transport (Dash *et al.*, 2010).

Table: 9 Release kinetic of Valproic Acid transdermal patches

F. Code	Zero order		First order		Higuchi Model		Korsmeyer Peppas Model
	r^2	K^0	r^2	K^1	r^2	K^H	(n)
F1	0.908	1.775	0.955	0.011	0.965	10.12	1.240
F2	0.912	2.077	0.946	0.013	0.981	12.72	1.086
F3	0.913	2.289	0.962	0.012	0.958	14.73	1.064
F4	0.915	2.567	0.972	0.015	0.971	16.82	1.282
F5	0.923	2.235	0.981	0.014	0.964	13.74	0.902
FD1	0.935	2.496	0.972	0.017	0.988	14.86	1.118
FD2	0.909	3.135	0.948	0.021	0.972	18.78	1.172
FD3	0.855	3.257	0.967	0.026	0.956	19.92	0.746

Where K^O = Zero order rate constant; K^1 = First order rate constant; K^H = Higuchi rate constant; n = Korsmeyer Peppas release exponent

On the basis of obtained results, it is clear that the release of drug from the transdermal patches is controlled by diffusion mechanism.

Assay:

Stability testing of Patches:- (i) Surface pH – patches were kept in contact with casting solvent for 30 minutes. Surface pH was measured by mean of a potentiometer (8). (ii) Visual Inspection- All the prepared patches were visually inspected for clarity, smoothness, homogeneity, stickiness, uniformity and flexibility found to be very correct. (iii) ATR Analysis- ATR Analysis of an optimized transdermal patch before initiation and after completion of the stability study was carried out to access the integrity and compatibility of the drug with the pressure sensitive adhesive component in the drug-in-adhesive matrix type transdermal patch. The sample was placed in the sample holder and spectral scanning was undertaken in the wave number region between 4000 cm-1 and 500 cm-1 at a resolution of 4cm-1 and scan speed of 2 mm /s.
As a result patches were found to be stable and durable.

RESULT AND DISCUSSION

The best optimized drugs in adhesive matrix type prophylactic transdermal patches of valproic acid were subjected to accelerated stability testing. The patches were stored at a temperature of 40 ± 2^0C and 75±5% RH for 180 days. The optimized formulation was found to be stable.

REFERENCES

1. Gururaj S and D. Reddy N, Design, development and evaluation of Sumatriptan succinate transdermal patches, International Journal of Pharmaceutical Science and Research, 2012, 3(6):1656-1662.
2. Naohiro N, Kazuhiro, T, Toshihiro S, Yoichi M. Development and evaluation of a monolithic drug-in-adhesive patch for valsartan, International Journal of Pharmaceutics, 2010, 402:103-109.
3. Parivesh S, Dqivedi S, Dwivedi A, Design, Evaluation Parameters and Marketed Produced of transdermal patches: A review, Journal of Pharmacy Research, 2010, 3(2):235-240.
4. Devi K and Paranjothi K, Development and Evaluation of Free Films and Transdermal Patches of Ketorolac Trimethamine using Polymers and Pressure Sensitive Adhesive, The Eastern Pharmacist, 1998,485:97-100.
5. Lee K, Uchida K, Kitagawa A, Gotu S: Effect of hydrophilic and lipophilic vehicles on skin permeation of tegafur, alclofenac and ibuprofen with or without permeation enharncers, Biologiacal and Pharmaceutical Bulletin, 1993, 16(12):1264-9.