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FORMULATION AND CHARACTERIZATION OF ANTI-EPILEPTIC DRUG TRANSDERMAL PATCH FOR ENHANCE SKIN PERMEATION

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ABSTRACT
The present work was prepared and evaluates the transdermal patch for transdermal delivery of ethosuximide. The ethosuximide is an antiepileptic drug. Patch formulation was optimized by the different concentration of patch polymers (HPMC, PVP, and Ethyl cellulose, PEG400, Tween 80 and Methanol) include in preparation of patches by solvent casting method. The transdermal patch formulation to sustain release of ethosuximide, improve the bioavalibility of drug and patient compliance. In solvent casting method of TDDS (Transdermal drug delivery system) of ethosuximide transdermal patch was fully planned and urbanized by studies. The FTIR (Fourier transform infrared) revealed that no any type of chemical reaction between drug and polymer that are used in the formulation of transdermal patch. The transdermal patches prepare look like a thin, flexible and effortlessly emergence and there physico-chemical properties are observed. All type of preparations is showed better physico-chemical properties such as thinness, weight variation, drug substance and the flop endurance. The In-vitro % drug release from the patch has precious by the type and concentration of the polymer that showed data of % drug release." From the records the optimize formulation were screened. In those over and above formulation T4 was to be initiated with admiration. The gain In-vitro % drug release rate is 94.26% at the last of 24 hours. In T4 formulation that include methanol and polyethylene glycol to enhance the skin penetration at show maximum drug permeation.

KEYWORDS: Ethosuximide, drug In-Adhesive, matrix type, transdermal patches, Epilepsy.

INTRODUCTION
The design and development of latest approach of novel drug delivery systems assemble the drug molecules has been updated. This novel drug delivery system can also be improve the drug efficacy and improve patient compliance and therapeutic benefits. The design and development of particular drug dosage form can associate with different conventional method of delivery of drug[1]. A transdermal patch of transdermal drug delivery system administered to specific dose of drug through skin membrane and blood stream. Transdermal drug delivery system (TDDS) provided controlled release of the drug into the patient blood level profile, develop in reduction in side effects and, sometime, improve efficacy of dosage forms, avoid hepatic first pass metabolism, improve patient compliance, increase bioavalibility. In case of orally administration of ethosuximide (ETX) is 250-500 mg daily dose. This drug is used to treatment of epilepsy or more extensively used in "petit mal" seizures. The ethosuximide is much better to reduce the effect of low-threshold ca^{2+} in thalamic neurons and it's also role on neurotransmitter – related mechanism in corticothalamocortical seizures. Ethosuximide is look like a crystalline powder form. It is freely soluble in water, ethanol, benzene, chloroform and ether etc. The peak plasma concentration can achieve after oral drug administration and first pass metabolism of drug is about (60%) and the bioavalibility of oral dose of drug is upto (80%). Thus, the transdermal drug delivery system is a principle drug aspirant.

MATERIALS AND METHODS
Ethosuximide was received and purchase from Sigma Aldrich. Hydroxypropyl methyl cellulose was obtained from yarrow- Chem. products, Mumbai. Ethyl cellulose was purchase from SD fine chemicals, Mumbai and polyvinyl alcohol was purchase from Himedia, Mumbai. PEG400, Methanol, Tween 80 provide by the institute (Advance institute of biotech and paramedical sciences). All compounds and chemicals are used in this study were analytical grade.

Prepration of Transdermal Patch
Transdermal patch formulation of Ethosuximide was

prepared by the using of solvent casting method. The optimization of ethosuximide drug make transdermal patch was done by preparation of the 7 different formulations in which vary amount of concentration. The efficiency of drug amount of drug and polymer was studied by the absorbance of drug, excipients compatibility of drug, percentage drug release of drug, drug permeation study. Weight the accurately amount of ethosuximide was dispersed in a permeation enhancer solution in 500 ml of beaker. Then "Add adhesive solution in drug to enhancer mixture and mixed properly by using stirrer or sonicated then make a homogenous mixture. All the above mixer was sonicated for few minute to make solution is clear. The patches was prepared by cast the mixture on silicon coated polyester film and allows to dry at room temperature for over-night, dried out patches are plastic- coated and slice into 9.5 cm^2 area then store in polyethylene bag at 400 ^{0C}/ 75 % R.H, then further evaluated".

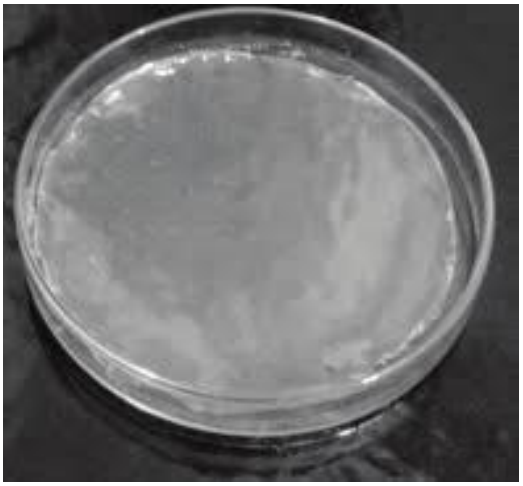


Fig.1: Transdermal patch.

Calibration Curve of Ethosuximide

The UV method was performed on Shimadzu (Model: UV-1800) double beam spectrophotometer with UV-probe software version 2.31. The absorption spectra of all solution were carried out in the range of 200-400 nanometers. The preparation of standard solution (1000 µg/ml) was further diluted with the buffer pH 7.4. The diluted solution are vortexed and then used for further analysis. The calibration curve was plot between the concentrations and absorbance. Filtrate was collected and further diluted with pH 7.4 phosphate buffer to get the final concentrations of drug in the work range. The absorbance of final diluted solution was observed at 223 nm. A plot of concentration of drug versus absorbance was plotted and that showed linear regression was applied.

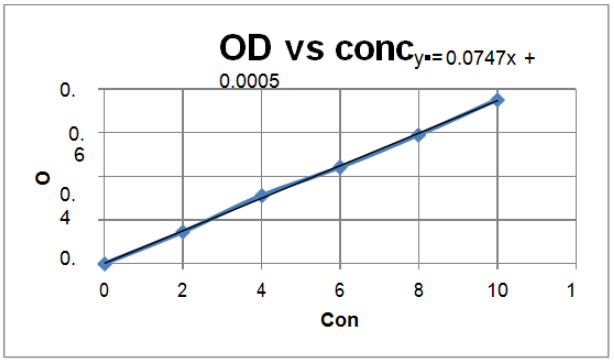


Fig.2: A Standard Curve of Ethosuximide phosphate buffer pH-7.4.

Study of Drug, Excipients Intraction

This compatibility study involving the interaction between drug and excipients are analyzed by the FTIR technique. Then, the FTIR spectra of ethosuximide, HPMC, PVA, Ethyl cellulose was recorded on FTIR-1700 (Shimadzu, Kyoto, Japan).

Evaluation of Transdermal Patch

The evaluation of prepared ethosuximide transdermal patches were physicochemical characteristics for instance thickness, wt. variation, drug content, folding endurance, content uniformity, tensile strength, moisture content, swelling index, % elongation etc.

Thickness of Patches[8]

The thickness of the Transdermal patches we "measure with a digital micrometer and thickness standard and std variation is resolute to make sure the thickness of prepare patches" at different point. The patch thickness is to determined by travelling microscope dial gauge, screw gauge.

Weight Variation[9]

A specific region of "patch is cut into the different areas. Then it is weighted in the digital balance. The average value and standard deviation to calculated from an individual weights. The prepared patches are properly dried at 60^0C for 4hrs before testing."

Drug Content[10,11]

A take specified area of patch is to dissolve in "appropriate solvent in exact volume. Then the solution is filtered, through a filter medium is evaluate the drug contain with suitable method (UV or HPLC technique). Each value represents average of 3 dissimilar samples".

Folding Endurance[12]

In this study estimation involves determining the folding capability of the patches. "This resolute repetitive fold at same place till that breaks. The quantity of times the layer might be many folded at the same place without any infringement gives in the significance of the folding endurance."

Content Uniformity[13]

Ten "patches are selected and satisfied is determined for individual patches. If 9 out 10 patches have content between 85 % to110 % specified importance and one has satisfied not less than 75% to 125% of the individual value, then transdermal patches exceed the test of content uniformity. But if 3 patches have content in the series of 75% to 125%, then extra 20 patches are experienced for drug content. If these 20 patches have variety from 85% to 110%, then the patches exceed the analysis."

Tensile Strength[14]

Tensile Strength = F/a.b (l+L/l)

F is the required to break; a is thickness of layer; b is thickness of layer; L is length of film; l is elongation of layer at break point.

Moisture Content[14,15]

"The prepared layer is to weigh independently one by one and stain in a desiccators. Containing fused calcium chloride at room temperature for 24 hrs. And weighed after 24 hrs the layer and find out moisture fraction of content from the below formula".

% Moisture content = Initial weight – Final weight x 100 / Final weight

In vitro % drug release Studies[15]

"In these experiments the paddle over disk method (USP apparatus V) is employ for estimation of the drug release from the prepare batches .The drug for the prepared patches. Dry films of known as clear cut shape to the thickness and weigh, variable over a glass plate with a bonding agent. The 500ml of glass plate is placed on medium dissolution and phosphate buffer pH 7.4, at 32 ± 0.5^0C. The paddle is placed at 2.5 cm distance for the beaker plate and operates with the rate of 50 rotations per minute. The Sample (5ml aliquots) can be reserved at suitable time of intervals up to 24 hours and analyzed by UV spectrophotometer or HPLC. The test is to perform in 3 times and the indicate rate can considered."

In vitro % drug release skin penetration Studies[15]

"In-vitro % drug release skin penetration study may be passed out by means of diffusion cell. Abdominal skin thickness of the male rats weight 200 to 250 grams. Hair of abdominal region are to be removed suspiciously by using a electric clipper; the skin is dermal side is carefully cleaned with the help of distilled water to remove any type of adhere tissue or blood vessels in the skin, and then it equilibrated for an hour in dissolution medium or phosphate buffer $_p$H 7.4 before the initial testing and is placed on a magnetic stirrer with a small magnetic needle for uniform delivery of the diffuse. The temperature of the cell is maintained at 32 ± 0.5^0 C using a thermostatically illicit to heater. The isolated rat skin piece is to be mounting between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume is of definite quantity is to be detached from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Sample is the filtered with the filter medium and it analyzed spectrophotometrically or HPLC. The slop can resolute the directly curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hrs. The permeability coefficient was deduced by in-between the flux by the final drug load (mg cm-2)."

Stability study

The prepared transdermal patch were packed in polyethylene coated aluminum foils and kept at 25^0C/65% R.H. and 40^0C/75%R.H. for two months. The drug content of that patch was determined at different time interval in triplicate and patches was inspected for any physical changes brought about on storage.

RESULT AND DISCUSSION

Visual Appearance

The all of formulations are visually translucent slight and smooth. The some of the polymers are use to without help and some of them are used in the combinations .The films which are formed with good emergence and the smooth are used for additional evaluations.

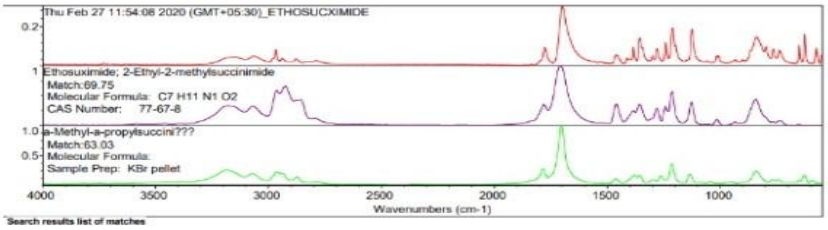
Table 1: Formulation chart of Ethosuximide transdermal patches.

Formulation	T1	T2	T3	T4	T5	T6	T7
suximide (mg)	100 mg	100 mg	100mg	100mg	100mg	100mg	100mg
HPMC (mg)	300	250	200	150	-	-	-
PVP (mg)	-	40	80	120	240	190	140
EC (mg)	-	-	-	-	100	150	200
PEG400 (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2
ween 80 (ml)	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Methanol (ml)	10	10	10	10	10	10	10

FTIR Studies

The Infrared spectrum of pure drug of Ethosuximide that showed peaks at 3700.15, 3595.76, 1559.90, 1030.99, 995.97 for O-H stretch, C-O stretch, N-O stretch, C-F stretch. UV spectrum studies: The UV absorption records at 223.5nm and the concentration estimate of pure ethosuximide that showed a good linearity (r^2-0.9964) over the concentration range of 1-10 µg/ml. Hence, the given sample of pure ethosuximide was found to obey the Beer-Lambert's law over this following range. The FTIR spectra of the drug and polymers, physical mixtures of the drug and the polymer and the transdermal formulations are displayed in Fig 3. Salient spectral data for the drug and the polymers are as follows:

Ethosuximide: IR (KBr: ν, cm−1): 1550.05 (N-O Streching), 1085.34 (C-O stretching), 3730.53 (O–H bond stretching). Hydroxypropyl methylcellulose (HPMC): IR (KBr: ν, cm−1): 3459.48 (O–H stretch), 2936.77 (C–H stretch, aliphatic), 1394.58 (C–O–C, stretching, dialkyl).The absorption bands of the characterization of the drug as well as a polymers are found to be present at the usual positions in the formulations. That indicates the absence of any drug–polymers interaction in the formulation suggestive of their reciprocal compatibility."



Functional Group	Absorption Location	Absorption Intensity
O-H stretching (alcohol)	3700-3584	medium, sharp
N-O stretching	1550-1500	strong
C-O stretching primary alcohol	1085-1050	strong
C-F Stretching fluoro compound	1400-1000	strong
C=C alkene	995-985 915-905	strong

Fig. 3. FTIR of pure drug and polymers.

Thickness of the film

The thickness of film will found in the range of 0.2 to 0.24 mm, and it means the uniform thickness patches was found in all the batches.

Folding endurance

The folding endurance of the all batches was found to be folding is less than 500 times. Do not show any cracks of films even after folding upto 500 times which showed a good patch flexibility.

Weight Variation

A Uniform patches weight is found to single polymer batches and that are also in combination of batches. And they founsd by weight valuation of batches and found by weight variation to the 46.6 to 73.5 mg weight was found.

Drug content

The result showing the drug content method that are prepared of employ on the patch of capability to produce patches with distribution of mostly uniform drug and % distribution were found in between 80 to 100%.

Tensile strength

The Tensile strength range from 2.5 to 6.0 dynes/cm^2, and increase the e polymer concentration is boost in tensile strength.

Table 2: A physicochemical Evaluation data's of transdermal patches T1-T7.

Formulation	Thickness	Weight variation	%drug content	Folding endurance	Tensile strength kg/mm^2
T1	0.2± 0.01	0.148±0.01	95.92±3.32	55±12.02	2.44±0.80
T2	0.17±0.02	0.149±0.005	94.59±3.14	36.4±20.10	2.77±0.79
T3	0.12±0.004	0.152±0.020	96.41±2.17	38±17.20	2.398±0.70
T4	0.15±0.008	0.162±0.011	98.12±2.24	58±20.32	3.80±1.79
T5	0.20±0.09	0.149±0.017	97.12±2.02	56±21.03	3.90±1.89
T6	0.22±0.003	0.153±0.014	95.90±1.40	55±10.40	2.80±1.89
T7	0.24±0.003	0.151±0.015	96.60±1.41	57±10.40	2.90±1.73

Table 3: A physicochemical Evaluation data's of transdermal patches T1-T7.

Formulation	% Elongation	% Moisture content	Swelling index	%Moisture up- take
T1	22.22±2.50	1.90±0.30	23.20±1.35	4.75±3.10
T2	23.09±2.11	2.2±0.70	24.80±0.70	3.4±3.5
T3	24.65±2.60	2.8±1.25	24.48±2.10	4.2±1.20

T4	25.70±4.10	3.0±1.78	22.35±0.72	3.5±0.80
T5	26.96±4.70	3.25±2.75	22.10±1.23	4.5±1.40
T6	25.02±4.18	3.10±0.95	23.19±1.35	4.2±1.05
T7	22.95±4.15	2.5±0.94	24.13±1.35	4.3±1.04

In- vitro % Drug release of medicated films

In Average cumulative present % drug release from (T1, T2, T3, T4, T5, T6, T7) containing mg of different polymer concentration was each other. They provide the 69.23%, 78.47%, 81.50%, 94.26%, 93.06%, 82.26%and 75.69% release. The Average increasing present % drug release from (T1, T2, T3, T4, T5, T6, T7) formulations of the Patches.

Table 4: In-vitro Drug release from transdermal patches by Dissolution method.

Time	T1	T2	T3	T4	T5	T6	T7
1	5.4	6.5	6.8	7.8	7.7	7.6	7.2
2	7.6	8	8.2	9	8.9	8.4	8
3	12.2	14.5	15.2	16.8	16.2	15.8	15.1
4	22.2	24.7	25.1	26.6	26	25.3	25
5	25.9	28.1	30.2	32.1	31.8	30.9	30.1
6	34.8	35.5	36.3	38.3	37.8	36.4	36
8	56.3	58.8	61.4	65.5	63.6	61.8	60.2
10	69.2	78.4	81.3	94.2	93	82.2	75.5

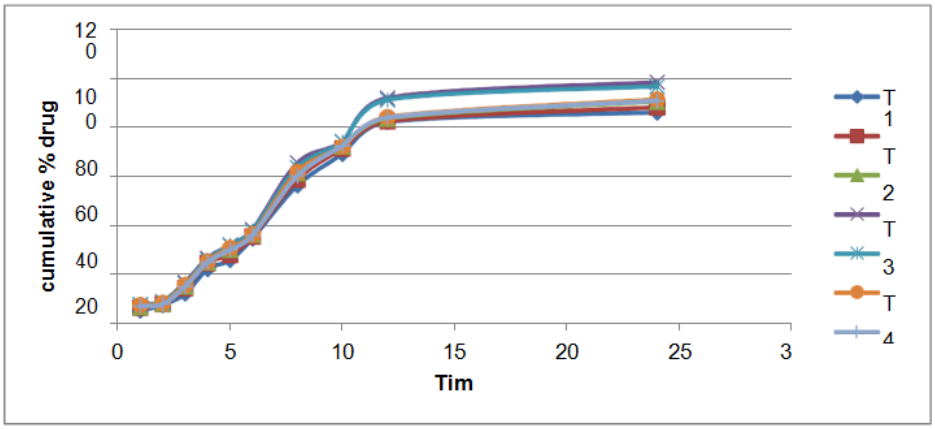


Fig. 4: In-vitro Drug release from transdermal patches by Dissolution method.

Stability study

The Stability study is performed on patches obtained with formulation for T4 at 2 months at different storages condition as per I.C.H guidelines. The result was found that no key alter in value of drug content and drug diffusion. It means that formulations are stable in dissimilar temperature. This patch stored at room temperature for 2 months; after 2 month, drug content of most satisfactory formulation was determined. Show in fig. in vitro diffusion of the most satisfactory formulation is T4 after stability studies.

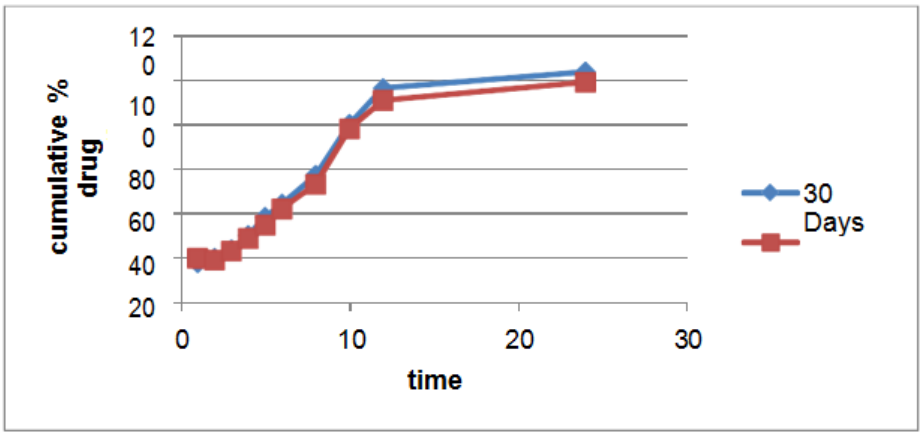


Fig. 5: In-vitro cumulative % of drug penetration stability shows of T4 formulation.

Comparative study of % drug release of T4 Formulation diffusion cell between rat skin

In case of comparative study, after the compression of skin permeation rate was of drug between rat skin and diffusion cells it is showed that the permeation rate was more rat skin. Shown in figure and table-5

Table 5: Comparative % cumulative drug release for T4 formulation in diffusion cell and rat skin.

S. No	Time	Rat skin	Diffusion cell
1	1	28.16	15.81
2	3	39.42	25.87
3	5	46.57	35.26
4	8	59.62	49.69
5	12	68.23	57.75
6	14	78.46	71.08
7	18	82.64	80.52
8	22	98.64	91.80
9	24	108.13	100.77

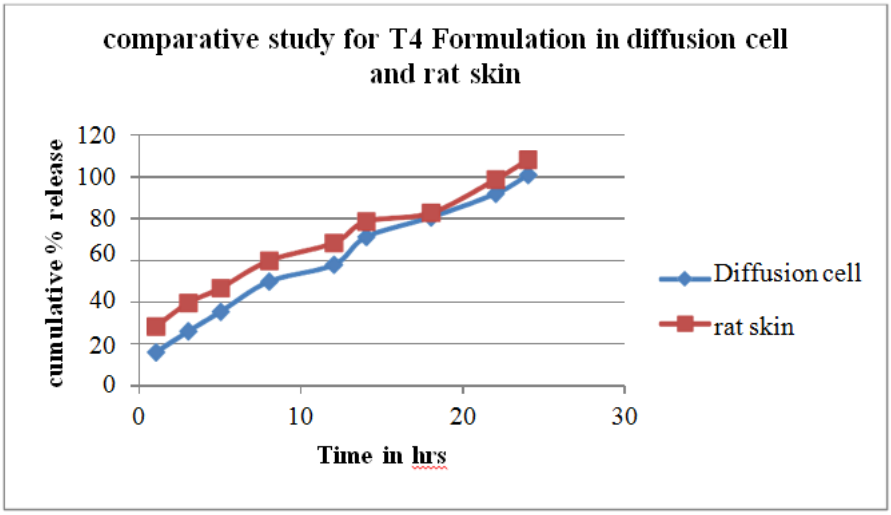


Fig. 6: A comparative cumulative % release of drug into T4 formulation in diffusion cell and rat skin.

CONCLUSION

Transdermal patch of ethosuximide was prepared efficiently by using special concentration of different polymers used in the patch formulation. The thin, flexible, smooth and transparent patch was obtained with HPMC, EC, and PVA. All formulation shows a good physicochemical property that is thickness, drug content, weight variation, folding endurance etc. ethyl cellulose are shows good release than PVA. All formulation gave a maximum drug permeation of T4 94.2% over 24 hour. The system is found to be stable at 37^0C and 45^0C. The discovery of this study exposed that the problem of ethosuximide with reported in oral formulation for child and adult with epilepsy defeat by applying ETX topical in form of transdermal patch and the main scope of the study to enhance pharmacokinetic activity and provide to patient compliance.

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