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Research Article

Formulation and evaluation of transdermal patch of stiripentol for treatment of seizures

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ABSTRACT

Dravet syndrome is identified as sever myoclonic epilepsy in infancy. It is characterized as behavioural deterioration or regression together with the cognitive decline due to epileptogenic activity during maturation period. The primary treatment for the Dravet syndrome is generally valproic acid and clobazam. Stiripentol is a drug which acts in the both directly by inhibiting $GABA_A$ receptor and indirectly by inhibiting Valproic acid and clobazam metabolism to control the seizures in Dravet syndrome. As it is insoluble in water results into the poor bioavailability and therefore coming up with the transdermal patch as a sustainable dosage form is necessary. It is bit of a hustle to feed the babies with the regimen. So, formulation of transdermal patch results into better bioavailability and avoid the hustle of feeding the babies with better seizure management. Here we have used HPMC and PVP as the matrix forming polymers to facilitate the sustained release and the evaluations were done.

Keywords: Dravet Syndrome, stiripentol, HPMC, PVP, Transdermal patch

INTRODUCTION

Transdermal route of administration has become more valuable in recent time because it avoids hepatic first pass metabolism and maintains plasma concentration throughout the treatment, thereby decreasing the dosing frequency and reducing gastrointestinal irritation resulting in improved patient compliance. Transdermal patch of Stiripentol is prepared using solid dispersion method. Easy removal of patch at any time from the target site will terminates the treatment preventing the chances of overdose and under dose [1-3]. The Stiripentol is the orphan drug which is practically insoluble and having high permeability. The transdermal patch was prepared by solvent casting method [4].

Stiripentol is a structurally unique anticonvulsant that has been introduced as adjuvant therapy of Dravet syndrome, a rare form of severe childhood epilepsy. Stiripentol is an antiepileptic drug used in the treatment of epilepsy as an adjunct therapy along with clobazam and valproate. Food and Drug Administration approval of this drug was granted on August 20, 2018; Unrelated to other anticonvulsants. STP belongs to the group of aromatic allylic alcohols and may potentiate the effect of other antiepileptic drugs (AEDs) due to pharmacokinetic interactions. It elevates the levels

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of Gamma- Aminobutyric Acid (GABA), a major inhibitory neurotransmitter that regulates electrical activity in the central nervous system [5].

DRAVET SYNDROME (DS)

Dravet Syndrome was earlier described as severe myoclonic epilepsy of infancy by Charlotte Dravet in 1978 and later renamed as Dravet Syndrome in 1989. It is very rare type of early-onset genetic epilepsy syndrome which is manifests as intractable epilepsy and neurodevelopmental delays. Dravet Syndrome was a part of eight epileptic encephalopathy syndromes, which was reported by the International League against Epilepsy task force [6]. 'Epileptic encephalopathy' is described as behavioural deterioration or regression together with cognitive decline due to epileptogenic activity during the brain maturation period [7].

Dravet syndrome is a severe form of epilepsy by:

i. Frequent, prolonged seizures often provoke by high body temperature.
ii. Sleep disturbances.
iii. Hypotonia.
iv. Ataxia.
v. Speech impairment.
vi. Developmental delay.

Dravet Syndrome:

Dravet Syndrome is the severe end of a spectrum of disorders related to mutations in genes for the sodium ion channel. The sodium ion channel is a gated pore-like structure in the cell membrane that regulates the movement of sodium ions In and Out of the cell, helping to generate electrical signals along with neurons. A sodium ion channel is a critical component of any tissue requiring electrical signals including the brain and heart. More than 80% of patients with Dravet syndrome have a mutation in the *SCN1A* gene, but not all *SCN1A* mutations lead to Dravet syndrome. These genes are situated on the long arm (q) of chromosome 2 at position 24.3 and code for the alpha subunit of the transmembrane sodium channel protein. A mutation in any of those 2 genes will cause an individual to develop dysfunctional sodium channels, which are significant pathway for sending chemical signals in the brain, produced the phenotypic show the myoclonic epilepsy from the individual. A properly functioning channel would respond to a voltage difference across the membrane and form a pore through in which only sodium ions can pass. The influx of sodium influences the generation of action potential by temporarily changing the charge of the cell. When the gene is mutated, eventually translated protein improperly folds its pore segment within the cell membrane because it has different amino acid chemistry, which shows the channel inactive. It is also possible for a mutation to reduce the number of channels prepared by an individual, which causes to the development of Dravet syndrome [8].

DS seems during the first year of life in healthy infant, usually with a generalized tonic clonic seizure which is often extend less than 5 minutes. Status epilepticus is a seizure having more than 5 minutes and sometimes it more than 30 minutes, which is common, specially in the early development years. Seizures vary with age. Most of the patients are seizure free up to the age of five months and first seizure seem between the age of five to eight months due to any kind of provoke like fever, vaccination, bathing and sometimes in absence of the provoke [9]. First seizure is generally focal or generalized tonic-clonic activity. If electroencephalogram (EEG) is performed during the first seizure activity, it may be either normal for age or may show abnormal theta activity between 4-5 Hz over the vertex [10]

NEED: -

- Sever myoclonic epilepsy of infancy i.e., Dravet syndrome caused by loss of functional mutation in one copy of SCN1A (haploinsufficiency), and also decrease function of sodium channel in GABAergic inhibitory neuron.
- Dravet syndrome affects the children from 1 year old to 10-year-old age.
- It is bit of a hustle to administer oral dosage forms to children of that age. So, for the easy administration and to increase bioavailability. Considering such issues, the appropriate dosage form is to be formulated.
- Stiripentol indicated in the treatment of Dravet syndrome in patients of age 2 to older. It also helps in inhibiting metabolism of the clobazam and valproic acid resulting into increase in the effectiveness.
- STP's bioavailability is low so coming up with the sustainable dosage form is necessary.
- Transdermal patches are formulated as it is having several advantages like sustainable release; prolong onset of action, dose frequency reduction, lesser side effects, and elimination of pre-systemic metabolism as the drug directly enters into the blood.

OBJECTIVE: -

- To decrease hustle to feed the dosage form to children.
- To develop and evaluate transdermal patch of Stiripentol for the treatment of Dravet syndrome.

MATERIALS AND METHOD

Materials: - Materials used in this experiment were as follows

- Stiripentol was produced by Atos chemicals, Surat, Gujrat.
- Hydroxy propyl methyl cellulose E5 premium grade research lab fine chem, Mumbai.
- Polyvinyl pyrrolidone was procured from research lab fine chem, Mumbai.
- Propylene glycol was procured from alpha chemika, Mumbai, Maharashtra.
- Oleic acid and methanol were being available by the college laboratory.

Method of preparation:
Formation of the patch: The HPMC E5 in methanol: water (1:1) was mixed and heated in a porcelain dish. The PVP is mixed on magnetic stirrer with solvent. Then add the HPMC solution to the PVP solution and then let it stir on magnetic stirrer for 40 mins. Spread the solution on patch former with the help of spreader. And as soon as it dries off the patch is peeled of as a film.

Formulation table: -

Table 1: Formulation table of transdermal patch for Stiripentol.

Sr. No	Ingredients	F 1 %	F 2 %	F 3 %	F 4 %	F 5 %	F 6 %	F 7 %	F 8 %	F 9 %
1	HPMC (gm)	1.5	1.75	1.75	2	1.39	2.10	1.5	2	1.75
2	PVP (gm)	0.75	0.44	0.625	0.5	0.625	0.625	0.5	0.75	0.80
3	Propylene glycol (ml)	1	1	1	1	1	1	1	1	1
4	Oleic acid (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
5	Methanol: Water (1:1)	q. s	q. s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Evaluations of the transdermal patch of Stiripentol:

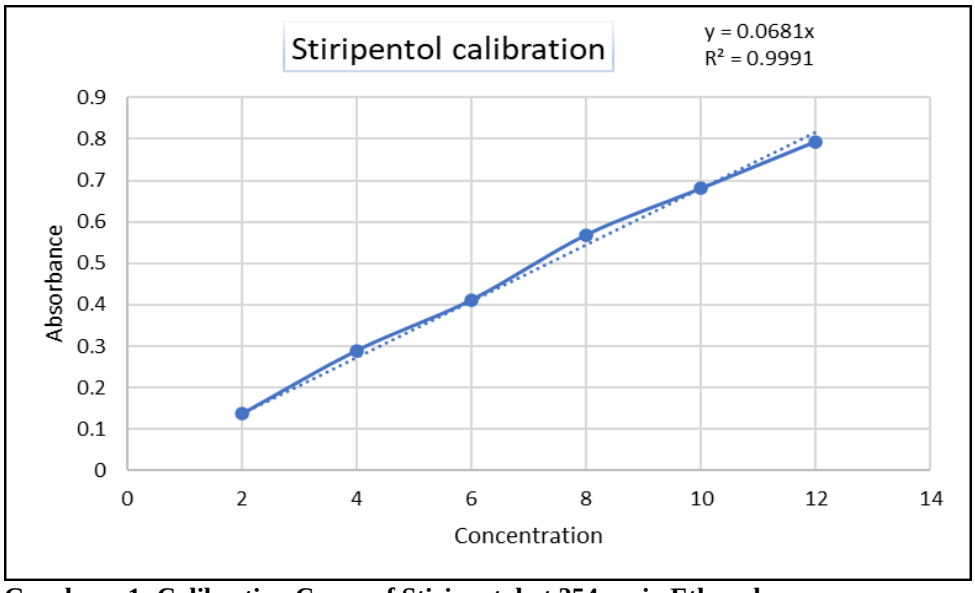
IR spectrum of individual drug: The drug and potassium bromide disk were prepared manually and separately for each drug by press method. Potassium bromide was used as a blank while running spectrum.

Drug - Excipients compatibility study: The physical mixture of both drugs [Stiripentol] with excipient was prepared in 1:1 ratio. The sample was kept at 38^0C for 45 days and was analyzed for any interaction of drugs and excipients.

A) Calibration curve of Stiripentol:

Preparation stock solution of Stiripentol (In Methanol): 10mg pure Stiripentol was dissolved in 100 ml solvent (Methanol) to get a 100ug/ml stock solution. Prepare concentration of 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml and 10µg/ml respectively. Then measure absorbance of prepared dilutions at the respective wavelength (254nm)

Development and standard curve of using UV-spectrophotometer (In Methanol AR): The standard curve of Stiripentol in methanol using UV-spectrophotometer (Shimadzu UV 1900) was estimated. The absorbance show at 254nm is noted down as show in table no.2. The standard plot of absorbance against concentration plotted as show graph no. 1.



Graph no. 1: Calibration Curve of Stiripentol at 254nm in Ethanol.

Evaluation

1) Physical Appearance: Physical parameters such as appearance and colour were checked.

2) Weight Variation: Weight variation was studied by individually weighing 10 randomly selected patches and average weight was calculated. The individual weight should not deviate significantly from the average weight. (11)

3) Thickness: Patch thickness was measured using digital micrometer screw gauge at three different places, and the mean value was calculated. (11)

4) Percentage moisture content: The weighed films were kept in desiccators at room temperature for 24 h containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 h, the films were reweighed and determine the percentage moisture uptake

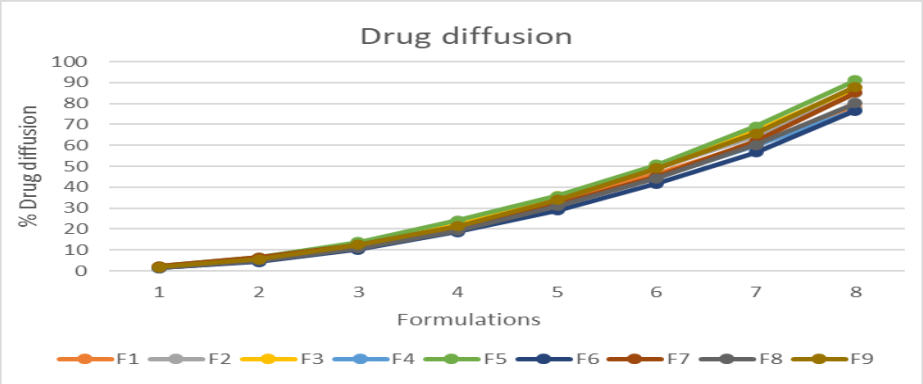
5) Folding endurance: The folding endurance of patches was determined by repeatedly folding a strip of film at the same place till it tends to break. It is determined as the number of times the film is folded at the same place either to break the film or to develop visible cracks. (11)

6) In-Vitro Permeation Studies: Permeation studies are carried out in order to determine transition of drug from patch to skin microcirculation. In this study, synthetic membrane like cellulose nitrate was placed between the donor and receptor compartment of Franz diffusion cell. Receptor compartment was filled with phosphate buffer of pH 5.4. Transdermal patch was placed upon the cellulose nitrate membrane facing towards the donor compartment. The other side of cellulose nitrate membrane was towards the receptor compartment having phosphate buffer. The receiver compartment was maintained at room temperature and was continuously stirred with the help of magnetic stirrer. Samples were withdrawn at specific time interval and equal amount of phosphate buffer was replaced each time to maintain volume of receptor compartment at a constant level. Samples withdrawn were then analyzed for their absorbance and concentration was then calculated. Graph was then plotted between % drug release and time interval which compares % drug release from different batches. (12)

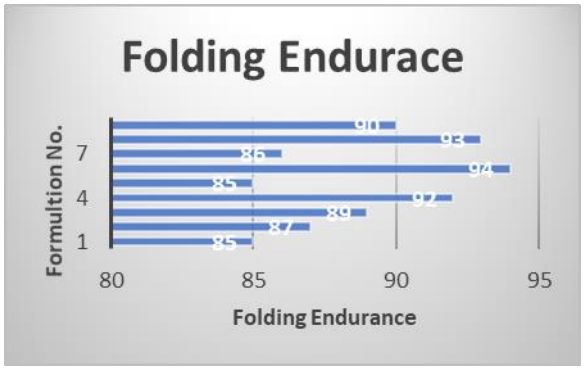
RESULTS AND DISCUSSION

Table 2: Thickness, Folding endurance, % drug diffusion, % Flatness, Moisture content of transdermal patch of Stiripentol.

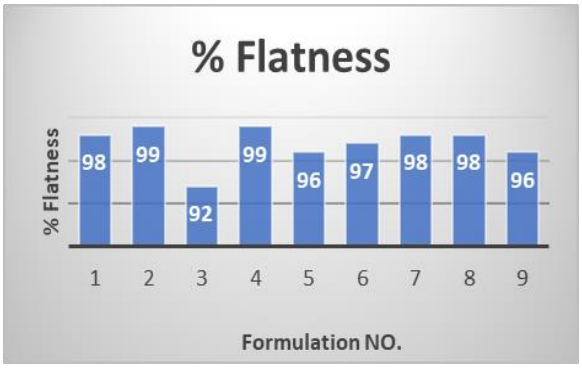
formulations	thickness	folding endurance	% drug diffusion	%flatness	moisture content
F1	0.700 ± 0.001	85	77.96	98±1	1.6 ± 0
F2	0.708± 0.000	87	84.88	99 ± 0	1.2 ± 0
F3	0.699± 0001	89	87.4	92 ± 2	1.5 ± 0
F4	0.706 ± 0.001	92	76.8	99± 0	1.2 ± 0
F5	0.712 ± 0.001	85	91	96 ± 2	1.8 ± 0
F6	0.713 ± 0.001	94	76.6	97± 0	1.6 ± 0
F7	0.714 ± 0.001	86	85.25	98 ± 1	1.7 ± 0
F8	0.716 ± 0.001	93	80.06	98 ± 0	2.0 ± 0
F9	0.715 ± 0.001	90	87.92	96 ± 0	1.9 ± 0



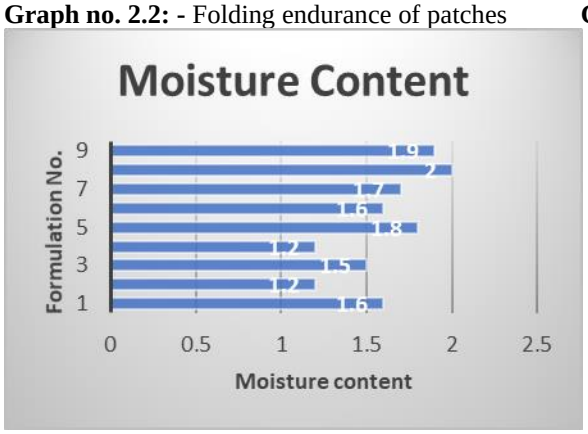
Graph no 2.1: - % Drug diffusion of stiripentol from transdermal patch



Graph no. 2.2: - Folding endurance of patches



Graph no.2.3: - % Flatness of patch



Graph no.2.4: - Moisture content of patch

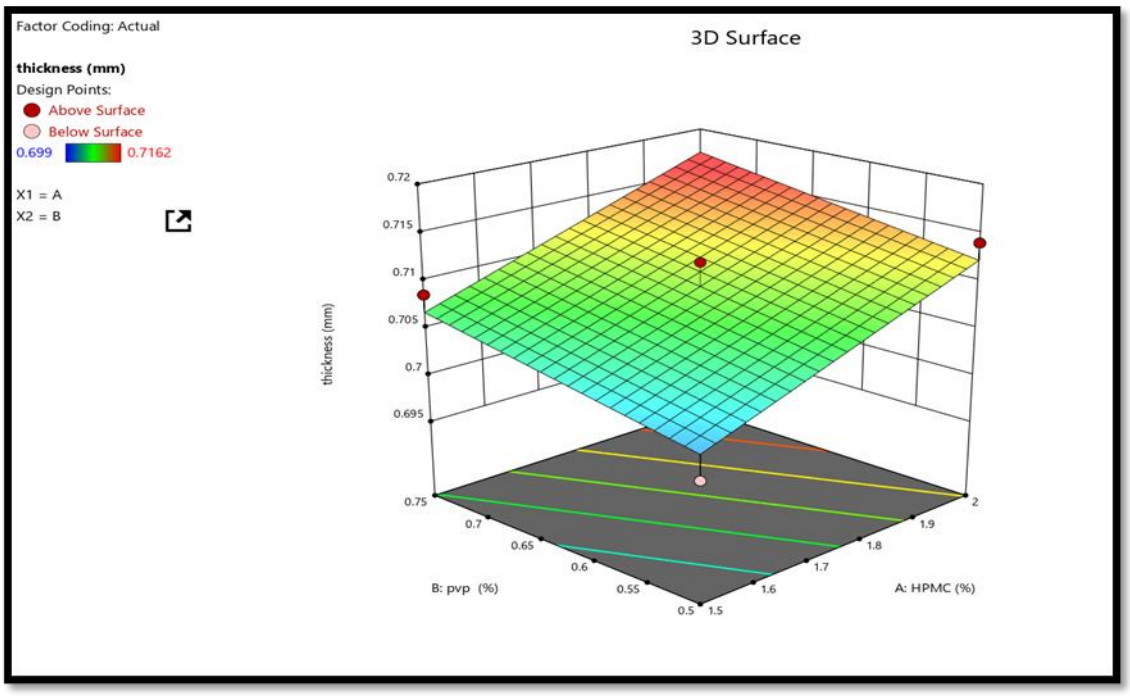


Fig no.1.1: - 3D plot for effect of concentration of PVP and HPMC on Thickness of transdermal patch of Stiripentol.

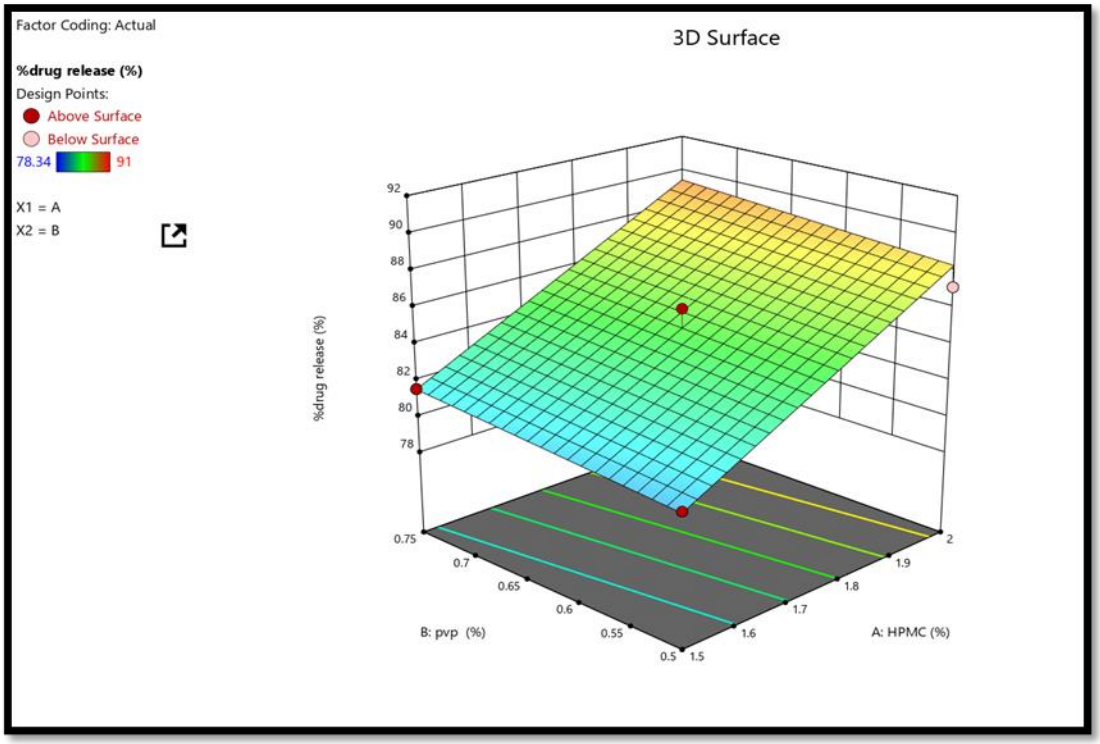


Fig no.1.2: - : 3D plot for effect of concentration of HPMC and PVP on drug release of Stiripentol from patch

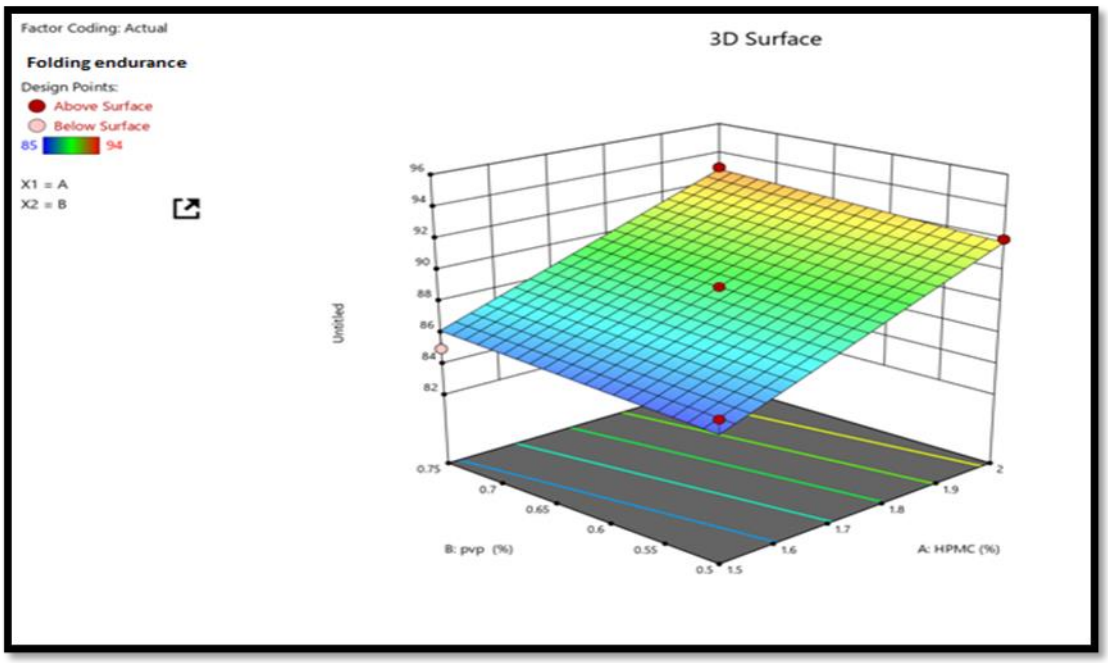


Fig no.1.3: - 3D graph of Folding endurance of patch

DISSCUSSION

The given experiment results in the following discussion for transdermal patch of the stiripentol
The weight variation was observed and it found to be in limits of uniformity. The mass ranges from 0.09 ±0.02 g for all of the formulations. The thickness of the patches for all formulations was found to be in the range of uniformity as 0.7 ± 0.01 mm. the concentration of polymers increases the thickness of the patch may get increased due to increase in viscosity of the given pouring solution.
Drug diffusion profile of various formulation prepared are shown in the table no 2. And the 3D plot of effect of HPMC and PVP on the drug diffusion from the patch is given in the fig: 1.2. The drug released from the patch was studied for the 6 hrs. The drug release from the transdermal

patch varied according to the various concentration of the polymer in the given formulation. The release of the stiripentol is guided by the amount of HPMC and PVP present in the patch. As the amount of matrix forming polymer increases the drug released also decreases. Therefore, the concentration of polymer is inversely proportional to the drug diffusion.

In this study, the above behavior was followed. Formulations containing lower amount of HPMC and PVP tends to release the drug immediately and at a faster rate in shorter amount of time. While the release slow down as the concentration of the polymer increases. This justifies the vital role of the matrix forming polymers in the drug release from transdermal patch.

Folding endurance is checked to determine integrity of the patch while it is applied to the body part. This gives the idea of the integrity of each formulation of transdermal patch. And found out as all the formulations shows the reasonable results and have goof folding endurance.

The % flatness of the patch and % moisture content of the patch is determined for every formulation. They all are in the limit and explains the effectiveness of texture and physical appearance of the given patch. Based on drug diffusion, folding endurance, thickness, % flatness, % moisture content etc. parameters the F4 formulation with HPMC 2gm and PVP 0.5gm was elected as an optimized formulation with the help of design expert software. It explains that the F4 formulation shows optimum results needed for the transdermal patch of the stiripentol. From the IR spectroscopy it was interpreted that there are no incompatibilities observed in the transdermal patch.

CONCLUSION

Development of the mucoadhesive buccal tablet of stiripentol is the one the alternative routes of the administration of the Dravet syndrome. It also provides sustained release and allows dose reduction with reduction of side effects. In present study the F4 formulation comprises of stiripentol shows the transdermal patch of stiripentol shows great diffusion and folding endurance and other parameters. The optimized batch shows good results at all of the evaluation parameters as well as satisfactory stability and comfortability. It also avoids the hustle to feed the children with the medication and it makes it easier for parents to feed their child with the appropriate treatment. Further work suggested is to perform pharmacodynamics and pharmacokinetic study in animals and human beings.

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