

# Formulation and evaluation of transdermal drug delivery of topiramate

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## Abstract

**Background:** Transdermal drug delivery system (TDDS) was designed to sustain the release and improve the bioavailability of drug and patient compliance. Among the various types of transdermal patches, matrix dispersion type systems disperse the drug in the solvent along with the polymers and solvent is allowed to evaporate forming a homogeneous drug-polymer matrix. The objective of the present study was to design and formulate TDDS of topiramate (TPM) and to evaluate their extended release *in vitro* and *ex vivo*.

**Materials and Methods:** In the present study, an attempt has been made to develop a matrix-type transdermal therapeutic system comprising TPM with different ratios of hydrophilic and hydrophobic polymeric combinations using solvent casting technique.

**Results:** The physicochemical compatibility of the drug and the polymers was studied by Fourier transform infrared spectroscopy. The results obtained showed no physical-chemical incompatibility between the drug and the polymers. The patches were further subjected to various physical evaluations along with the *ex vivo* permeation studies using pig ear skin.

**Conclusions:** On the basis of results obtained from the physical evaluation and *ex vivo* studies the patches containing the polymers, that is, Eudragit L 100 and polyvinylpyrrolidone, with oleic acid as the penetration enhancer were considered as the best formulations for the transdermal delivery of TPM.

**Keywords:** Eudragit L 100, matrix dispersion system, oleic acid, penetration enhancers, permeation studies, polyvinylpyrrolidone

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## INTRODUCTION

Transdermal drug delivery system (TDDS) is a widely accepted means of drug delivery, and transdermal patches are devised to treat various diseases.<sup>[1]</sup> TDDS are extended release dosage forms that can offer a stable systemic drug concentration and avoid first pass metabolism. They can

even avoid gastrointestinal problems associated with drugs and low absorption.<sup>[2]</sup> These therapeutic advantages reflect the higher marketing potential of TDDS.<sup>[3]</sup> Most of the drug molecules penetrate through the skin through intercellular micro route and therefore the role of permeation or penetration enhancers in TDDS is vital

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as they reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells.<sup>[4]</sup> Chemical penetration enhancers act as accelerators or sorption promoters and can enhance drug flux. Sulfoxides-dimethyl sulfoxide,<sup>[5]</sup> azone,<sup>[6]</sup> pyrrolidines-N-methyl-2-pyrrolidone,<sup>[7]</sup> fatty acids lauric acid, capric acid, myristic acid, oleic acid,<sup>[8]</sup> terpenes and essential oils-menthol, eugenol,<sup>[9]</sup> oxazolidinones-4-decyloxazolidin-2-one,<sup>[10]</sup> surfactants - tween 80, span 20<sup>[11]</sup> are the various classes of penetration enhancers used in TDDS.

Nicotine patches were the first transdermal success raising the market value of TDDS in medicine to newer heights. Estradiol, fentanyl, testosterone, lidocaine, and some other drug combinations are the TDDS available in the present pharma market.<sup>[12]</sup> Methotrexate,<sup>[13]</sup> repaglinide,<sup>[14]</sup> diclofenac,<sup>[15]</sup> and aceclofenac<sup>[16]</sup> are the few drugs for which TDDS have been reported. Combination drugs such as theophylline-salbutamol sulfate,<sup>[17]</sup> and ketoprofen fumarate-salbutamol sulfate<sup>[18]</sup> TDDS were also formulated and evaluated *in vitro*.

Topiramate (TPM) is a novel antiepileptic drug derived from the naturally occurring monosaccharide D-fructose. It is not structurally related to other antiepileptic drugs and was originally synthesized as the part of a search for fructose-related compounds with hypoglycemic activity.<sup>[19]</sup> It has multiple mechanisms of action such as sodium and calcium channel blockade; potassium channel activation; glutamate receptor antagonism; gamma-aminobutyric acid potentiation; and carbonic anhydrase inhibition.<sup>[20]</sup> The objective of this study was to design and formulate TDDS of TPM and to evaluate their extended release *in vitro* and *ex vivo*.

## MATERIALS AND METHODS

TPM was procured from MSN Organics Pvt. Ltd., Hyderabad as a gift sample. Polyvinyl alcohol was purchased from Himedia, Mumbai. Ethyl cellulose, oleic acid, propylene glycol (PG) were purchased from SD – Fine chemicals, Mumbai. Eudragit-L 100 and hydroxypropyl methyl cellulose K-15 M were purchased from Yarrow-Chem products, Mumbai. Polyvinylpyrrolidone, cellulose acetate phthalate (CAP), carbopol 940, tween 80, chloroform, dichloromethane were purchased from Accord labs, Secunderabad. All chemicals and reagents used in the present study were of analytical reagent grade (AR grade).

### Preformulation studies

Before formulating the drug substance into a transdermal patch (dosage form), preformulation studies were carried

out to establish the physicochemical characteristics of a drug (TPM) and its compatibility with different excipients.

Compatibility study of drug with the excipients was determined by Fourier transform infrared (FTIR) spectroscopy (Shimadzu 1800).

### Calibration curve of topiramate

Wavelength maximum of TPM was found to be 263.5 nm using ultraviolet (UV)-visible spectroscopy (Elico SL159, Hyderabad). Standard solution (10 µg/ml) was prepared from stock solution (1 mg/ml) with phosphate buffer (pH 7.4). Aliquots of standard drug solution ranging from 1 to 8 ml were transferred into 10 ml volumetric flask and were diluted up to the mark with phosphate buffer pH 7.4. Thus, the final concentration ranges from 1-8 µg/ml. The absorbance of each solution was measured at 263.5 nm against phosphate buffer (pH 7.4). A plot of concentrations of the drug versus absorbance was plotted. The linear regression analysis was applied.

### Formulation of transdermal patch

In the present study, drug loaded matrix type transdermal patches of TPM were prepared by solvent casting method<sup>[21]</sup> using different ratios of hydroxyl propyl methyl cellulose (HPMC), ethyl cellulose, polyvinylpyrrolidone (PVP), eudragit L100, Cellulose acetate phthalate (CAP), carbopol and polyvinyl alcohol (PVA). A weighed amount of PVA (2.5% w/v) was added to a requisite volume of warm distilled water and a homogenous solution was made by constant stirring and intermittent heating at 60°C for a few seconds and poured into glass molds already wrapped with aluminium foil around open ends and were kept for drying at 60°C for 6 h, forming a smooth, uniform, and transparent backing membrane. Backing membrane was used as a support for drug-polymer matrix. The polymers in different ratios as given in Table 1 were dissolved in the respective solvents. Then, the drug was added slowly in the polymeric solution and stirred with the help of magnetic stirrer to obtain a uniform solution. Propylene glycol (PG) was used as a plasticizer. Oleic acid and tween 80 were used as the penetration enhancer. Then the solution was poured on the glass molds of 5 cm × 5 cm and dried at the room temperature. Then the patches were cut into 1 cm × 1 cm patches and preserved in the polyethylene bag at 40°C and 75% relative humidity for further evaluation.<sup>[22]</sup>

### Preliminary screening

#### Evaluation of transdermal patches

All the prepared formulations were subjected for preliminary screening to check the effect of various polymer combinations.

**Table 1: Composition of different formulations of transdermal patches of topiramate**

Polymer	Matrix forming polymer	Formulation and ratio	Drug (TPM), mg	Solvent system
HPMC	Eudragit L 100	F1 (2:0.1)	625	Methanol:dichloromethane (1:1)
		F2 (2:0.25)		
		F3 (2:0.50)		
		F4 (2:0.75)		
		F5 (2:1)		
HPMC	PVP	F6 (2:0.1)	625	Alcohol:water (1:1)
		F7 (2:0.25)		
		F8 (2:0.50)		
		F9 (2:0.75)		
		F10 (2:1)		
HPMC	Ethyl cellulose	F11 (2:0.1)	625	Chloroform:methanol (1:1)
		F12 (2:0.25)		
		F13 (2:0.50)		
		F14 (2:0.75)		
		F15 (2:1)		
HPMC	CAP	F16 (2:0.1)	625	Chloroform:methanol (1:1)
		F17 (2:0.25)		
		F18 (2:0.50)		
		F19 (2:0.75)		
		F20 (2:1)		
HPMC	Carbopol	F21 (2:0.75)	625	Methanol:dichloromethane (1:1)
		F22 (2:1)		
		F23 (2:2)		
		F24 (2:3)		
		F25 (2:4)		

TPM: Topiramate, HPMC: Hydroxyl propyl methyl cellulose, PVP: Poly vinyl pyrrolidone, CAP: Cellulose acetate phthalate

#### *Microscopic pictures of transdermal patches*

Microscopic pictures of all the formulations were observed using an electronic microscope with digital camera to determine the surface of the films formed and uniform dispersion of drug and polymer.

In addition to microscopic study, transdermal patches were evaluated for their physicochemical characteristics.

#### *Thickness*

The thickness of the prepared transdermal films was measured by screw gauge with least count at five different sites, and the average was calculated with an SD.<sup>[23]</sup>

#### *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.<sup>[24]</sup>

#### *Weight variation*

The patches were subjected to weight variation by individually weighing ten selected patches randomly and the average was calculated.<sup>[25]</sup>

#### *Drug content uniformity*

Each patch from different formulations (patch size of 1 cm<sup>2</sup>, equivalent to 25 mg of drug) was dissolved in phosphate

buffer (pH 7.4) and shaken continuously for the 24 h using a magnetic stirrer to extract the drug from the patch. After filtration and dilution with phosphate buffer, % drug content was measured spectrophotometrically at a wavelength of 264 nm.<sup>[26]</sup>

#### *In vitro drug release studies*

*In vitro* drug release studies were carried out using the paddle over disc method.<sup>[27]</sup> Dry films of known thickness were cut into circular shape, weighed, and fixed over a glass plate with an adhesive. The plate was then placed in a 500 mL phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32°C ± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm, and samples (5 mL aliquots) were withdrawn at appropriate time intervals up to 12 h and analyzed for drug content at 264 nm using double beam UV-visible spectrophotometer (Elico SL159, Hyderabad). The experiment was performed in triplicate, and the mean value was calculated.

Based on physicochemical characterization and drug release patterns, F17, F9, and F5 formulations were selected to which permeation enhancers like oleic acid and tween 80 were incorporated, and resultant new formulations with permeation enhancers were labeled from F26 to F31 and details were given in Table 2. For all six formulations, *ex vivo* diffusion studies were performed using pig ear skin.

**Table 2: Composition of formulations of transdermal patches of topiramate with permeation enhancers**

Polymer	Matrix forming polymer	Formulation and ratio	Drug (TPM), mg	Penetration enhancer (mL)	Solvent system
HPMC	CAP	F26 (2:0.25)	625	Oleic acid, (1)	Methanol:dichloromethane (1:1)
HPMC	PVP	F27 (2:0.75)	625	Oleic acid, (1)	Chloroform:methanol (1:1)
HPMC	Eudragit L 100	F28 (2:1)	625	Oleic acid, (1)	Chloroform:methanol (1:1)
HPMC	CAP	F29 (2:0.25)	625	Tween 80 (0.25)	Methanol:dichloromethane (1:1)
HPMC	PVP	F30 (2:0.75)	625	Tween 80 (0.25)	Chloroform:methanol (1:1)

TPM: Topiramate, HPMC: Hydroxyl propyl methyl cellulose, PVP: Poly vinyl pyrrolidone, CAP: Cellulose acetate phthalate

### Ex vivo skin permeation study

An *in vitro* permeation study was carried out by using Franz diffusion cell.<sup>[28]</sup> The skin samples were obtained from the back of pig ear and using a depilatory preparation hair was removed. The skin samples were washed with phosphate buffer (pH 7.4). The prepared skin was mounted between donor and recipient compartments of diffusion cell. Then the formulated patches were positioned over the skin by placing the patch on the stratum corneum side of the skin toward the donor compartment, and dermis side was facing toward receptor compartment. The receptor compartment of the diffusion cell was filled with phosphate buffer (pH 7.4) and every 1 h, 5 ml of sample was taken and replaced the same with receptor fluid, and the sample was analyzed for drug content at 264 nm using double beam UV-visible spectrophotometer (Elico SL159, Hyderabad).

### Kinetic modeling of dissolution data

Drug release kinetics were analyzed by various mathematical models such as a zero-order and first-order kinetic models; Higuchi and Korsmeyer–Peppas models to ascertain the kinetics of drug release.

#### Zero order kinetics

$$Q_t = Q_0 + K_0 t$$

Where  $Q$  is the amount of the drug dissolved in time  $t$ ,  $Q_0$  is the initial amount of drug in the solution (most times,  $Q_{50}$ ) and  $K$  is the zero order release constant.<sup>[29]</sup>

#### First order kinetics

$$\ln Q_t = \ln Q_0 - K_1 t$$

Where  $Q_t$  is the amount of drug released in time  $t$ ,  $Q_0$  is the initial amount of drug in the solution and  $K$  is the first order release constant.<sup>[30]</sup>

#### Higuchi model

$$Q_t = K_H t_{1/2}$$

Where  $Q_t$  is the amount of drug released in time  $t$ ,  $K_H$  is release rate constants.<sup>[31]</sup>

#### Korsmeyer–Peppas model

$$Q_t/Q_\infty = at^n$$

Where  $n$  is the release exponent and the function of  $t$  is  $Q_t/Q_\infty$  (fractional release of the drug).<sup>[32]</sup>

### Statistical comparison of dissolution profiles

The model independent mathematical approach proposed by Moore and Flanner for calculating a similarity factor  $f_2$  was used as a basis for comparison between dissolution profiles of different samples. The release profiles are considered to be similar when  $f_2$  is between 50 and 100. The release profile of products was compared using an  $f_2$  which is calculated from following formula.<sup>[33]</sup>

$$f_2 = 50 \times \log \left\{ \left[ 1 + \left( \frac{1}{n} \right) \sum_{t=1}^n W_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Where  $n$  is the release time and  $R_t$  and  $T_t$  are the reference and test value at time  $t$ .

## RESULTS

Transdermal patches of TPM were prepared by matrix type solvent casting method to achieve a controlled release, improved bioavailability of the therapeutic drug and to reduce the toxicity. This is the first report on transdermal drug delivery of TPM and found to be effective compared to previously reported dosage forms of TPM.<sup>[34]</sup>

### Preformulation studies

Preformulation studies, that is, FTIR studies revealed the compatibility of excipients and polymers with TPM. Calibration curve of TPM was constructed and found to be linear and microscopic pictures of formulations with different polymers were compared.

### Evaluation of transdermal patches

The prepared formulations were evaluated for different physicochemical characteristics such as thickness, folding endurance, weight variation and % drug content and the results were shown in Table 3.

However, above-mentioned parameters were also studied for optimized formulations with permeation enhancers, but no significant change was found in these parameters with permeation enhancers.

**Table 3: Evaluation of physicochemical characteristics of topiramate transdermal patches**

Formulation	Polymer	Evaluation parameters			
		Thickness	Percentage of weight variation	Folding endurance	Percentage of drug content
F1	Eudragit L 100	0.230±0.1303	0.054±0.0114	298±1.23	82.45±0.003
F2		0.294±0.0101	0.078±0.01	304±2.45	95.21±0.0034
F3		0.326±0.0230	0.120±0.02	315±2.11	76.04±0.0064
F4		0.548±0.0516	0.138±0.014	322±0.14	89.71±0.0076
F5		0.648±0.0083	0.146±0.020	312±3.23	87.32±0.0032
F6	PVP	0.388±0.0286	0.052±0.023	224±5.67	87.16±0.0042
F7		0.414±0.0541	0.067±0.0534	264±2.45	84.25±0.0053
F8		0.454±0.0610	0.068±0.078	236±5.34	89.70±0.0023
F9		0.506±0.0403	0.099±0.0678	244±2.78	82.82±0.0043
F10		0.614±0.0054	0.123±0.0786	246±3.54	85.91±0.0076
F11	Ethylcellulose	0.584±0.0409	0.075±0.0102	209±6.27	87.71±0.0063
F12		0.632±0.0249	0.097±0.0234	213±6.39	89.96±0.0086
F13		0.742±0.0496	0.123±0.0308	210±6.3	77.87±0.0054
F14		0.746±0.0114	0.137±0.0143	234±7.02	92.62±0.0078
F15		0.834±0.0403	0.144±0.0102	245±7.35	92.53±0.0045
F16	CAP	0.276±0.0207	0.054±0.034	154±4.67	85.34±0.0032
F17		0.324±0.0371	0.064±0.0234	176±5.67	88.67±0.0027
F18		0.448±0.0238	0.098±0.01023	165±3.8	81.68±0.0028
F19		0.696±0.0313	0.134±0.0342	157±5.98	84.84±0.0054
F20		0.820±0.011	0.146±0.0123	174±4.76	84.52±0.0054
F21	Carbopol	0.213±0.0456	0.0643±0.023	158±8.52	83.64±0.0075
F22		0.225±0.01201	0.0754±0.010	172±10.58	90.12±0.0083
F23		0.231±0.0342	0.0986±0.010	170±10.25	85.84±0.0032
F24		0.239±0.2045	0.112±0.023	168±9.56	82.63±0.0808
F25		0.254±0.431	0.122±0.034	152±13.23	92.01±0.0432

PVP: Poly vinyl pyrrolidone, CAP: Cellulose acetate phthalate

**Table 4: Kinetic model fitting data for optimized formulations**

Formulations	Zero order	First order	Higuchi	Peppas	n
F17	0.93135	0.67937	0.85233	0.897091	0.88795
F9	0.93157	0.59613	0.77001	0.83638	1.06916
F5	0.9395	0.6091	0.78709	0.948879	1.36023

### Drug release studies

The release characteristics of all prepared formulations were studied *in vitro* and compared. The results were given in Figures 1-4. Based on these results, F17, F9, and F5 were taken as optimized formulations. The *in vitro* release data of F17, F9, and F5 formulations was fitted well into the zero order and first order equations. Korsmeyer-Peppas and highuchi models were also applied to test the release mechanism, and results are shown in Table 4.  $T_{50}$  and  $T_{90}$  of transdermal formulations of TPM without permeation enhancers were calculated from respective graphs.

### Ex vivo permeation studies through pig ear skin

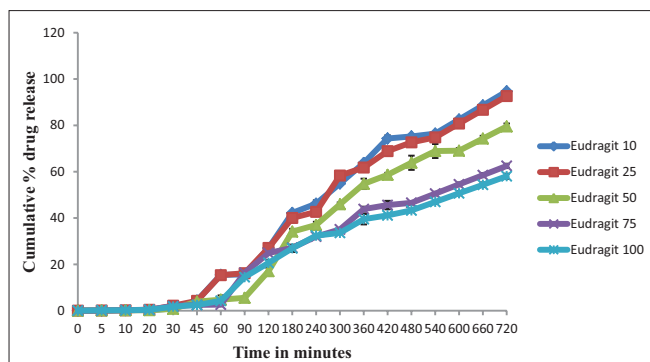
After carrying out the *in vitro* dissolution studies, optimized formulations (F17, F9, F5) with controlled drug release were subjected to the *ex vivo* drug permeation studies (Approval no 318/PO/ERC/S/01/CPCSEA). The results of drug permeation studies from optimized formulations with and without permeation enhancers using pig ear skin are depicted in Figures 5-7.  $T_{50}$  and  $T_{90}$  of transdermal formulations of TPM with permeation enhancers were calculated from respective graphs.

## DISCUSSION

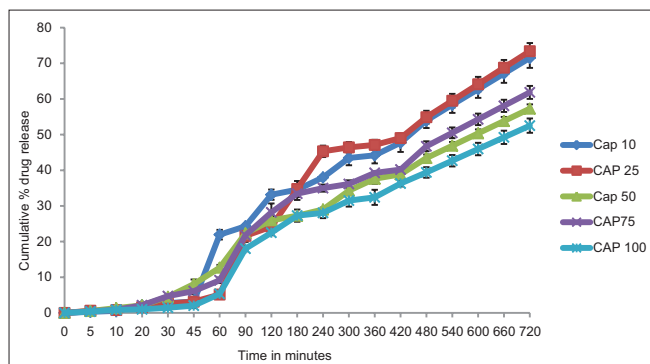
The microscopic pictures of TPM were revealed that the formulations prepared from ethylcellulose and carbopol were observed to be nonuniform in drug distribution. In microscopic pictures of formulations prepared from CAP, surface morphology was good in lower concentrations. Transdermal patches prepared from Eudragit L 100 and PVP were found to have the uniform surface morphology from lower to higher ratios of the polymer, indicating that the drug was uniformly distributed all over the patch.

### Evaluation of transdermal patches

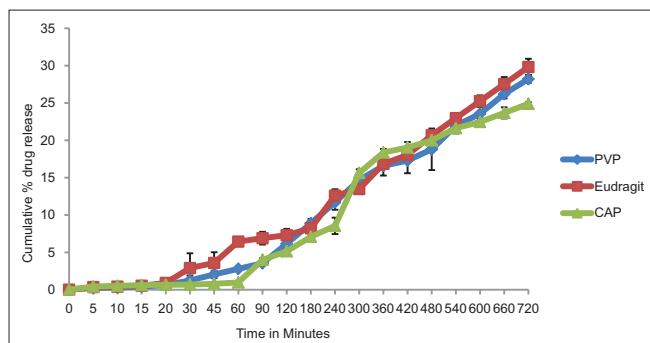
The prepared formulations with different polymer concentrations were smooth, opaque, flexible and uniform. The thickness of the films varied from 0.230 to 0.834 mm and highest thickness was of found to be 0.834 mm for F15, and lowest was of F1. From these values, it was observed that the thickness of the polymer depends on the solubility and concentration of the polymer. As the solubility decreases and concentration increases would increase the thickness of the patch. It infers that usage of the competent polymer is the prerequisite step to prepare a patch of optimum thickness, which can retard the release of drug from the patch. Weight variation of all the formulations varied from  $0.054 \pm 0.0114 - 0.146 \pm 0.020$ . Low SD values in the film ensure uniformity of the patches prepared by solvent casting technique. The folding endurance was



**Figure 1:** Comparative drug release profiles of transdermal drug delivery system with Eudragit L100

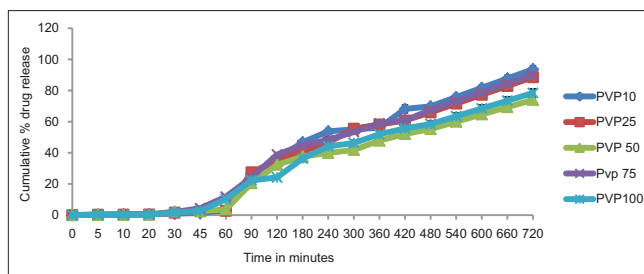


**Figure 3:** Comparative drug release profiles of transdermal drug delivery system with cellulose acetate phthalate

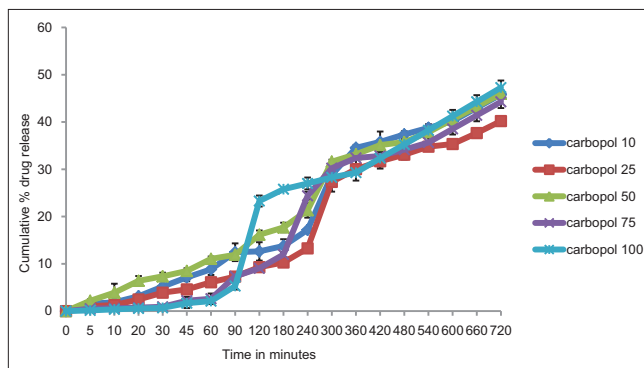


**Figure 5:** Comparative drug permeation profiles of transdermal drug delivery system without permeation enhancer

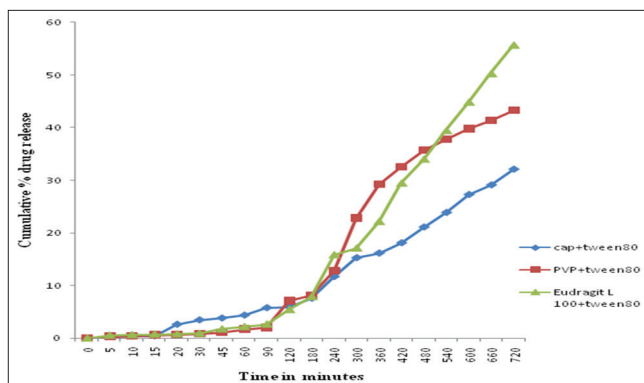
found to be >150 revealed that the prepared patches were having the capability to withstand the mechanical pressure along with good flexibility. The formulations prepared with Eudragit L100 was found to have the highest value of folding endurance and formulations made of CAP, PVP and carbopol respectively were found to have the lowest value of folding endurance. The drug content of all the formulations was in the range of  $76.04\% \pm 0.0564 - 95.21\% \pm 0.0134$  indicated that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability. All the results showed that the patches were uniform, as it



**Figure 2:** Comparative drug release profiles of transdermal drug delivery system with ethylcellulose



**Figure 4:** Comparative drug release profiles of transdermal drug delivery system with carbopol

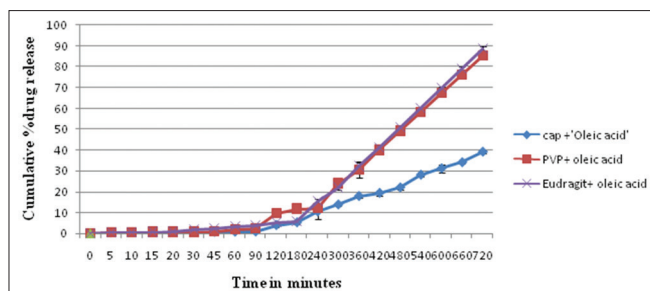


**Figure 6:** Comparative drug permeation profiles of transdermal drug delivery system with tween 80

was evidenced by SD value, which were  $<0.01$  for all the factorial design batches.

### Drug release studies

Drug release studies are required for predicting the reproducibility of the rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance.<sup>[35]</sup> Drug release of F1–F25 formulations were varied between 40.19% and 97.03%. The order of *in vitro* drug release data was found to be highest for HPMC K15: Eudragit L 100 polymer and lowest for HPMC K15: Carbopol polymer.



**Figure 7:** Comparative drug permeation profiles of transdermal drug delivery system with oleic acid

The results indicated that the release of drug from patches increases with increasing concentration of HPMC K15 M. The cumulative percent of drug release in 12 h was noted. The drug release was found to increase with the increasing concentration of hydrophilic polymer in the polymer matrix. This is due to the fact that dissolution of an aqueous soluble fraction of the polymer matrix leads to the formation of gelataneous pores. The formulation of such pores leads to decreasing mean diffusion path length of drug molecules to release into the diffusion medium and hence, to cause higher release rate.

The *in vitro* release data of the formulations F5, F12, F14, F15, F18, F19, F21, F23 were best fitted into peppas model having the maximum  $r^2$  values of (0.952386), (0.854381), (0.874045), (0.758754), (0.90489), (0.892499), (0.966253), (0.992909), respectively than the other models. All the remaining formulations were following the zero order model as the best fit model. This indicates that as the concentration of the hydrophilic polymer in which 2% HPMC was used, was not sufficient for the formation of a matrix transdermal patch. Hence, zero order was found to be the best fit model for TPM release from formulations. From this, we can infer that concentration of the HPMC polymer plays a key role in drug release kinetics with a permeation enhancer.

#### Ex vivo permeation studies through pig ear skin

The results of *ex vivo* drug permeation studies were compared for optimized formulations with and without permeation enhancers. When compared with formulations without permeation enhancers the drug diffused from formulations with tween 80 was increased. The results indicated that drug penetration was increased with permeation enhancers and the percent drug permeated from F26 was found to be up to 32.57% and from F27 it was found to be 43.27%. In F28 the maximum drug permeated up to 55.7%. However, the formulations F30, F31 (HPMC: PVP; 2:0.75), (HPMC: Eudragit; 2:1) with oleic acid as a permeation enhancer shows optimum

permeation. Drug permeation from CAP was less when compared with that of PVP and eudragit because CAP is a cellulose derivative.  $T_{50}$  and  $T_{90}$  were calculated from the graph in which  $T_{90}$  was >12 h in all the formulations, but  $T_{50}$  was >12 h in F26, F27, F29.

## CONCLUSIONS

The transdermal patches of TPM prepared by solvent casting method using a combination of ethylcellulose, PVP, eudragit L 100, CAP, carbopol in various ratios using PG as plasticizers and oleic acid, Tween 80 as a permeation enhancers were studied. All the formulations showed good physicochemical properties such as thickness, weight variation, drug content, and folding endurance. The *in vitro* release data showed that drug release from the patch has been affected by the type and concentration of the polymer. From this data, optimized formulations were screened. Effect of penetration enhancers such as oleic acid and Tween 80 have been checked for optimized formulations using *ex vivo* permeation studies. These studies indicated that when compared with formulations without permeation enhancers the drug diffused from formulations with permeation enhancers was increased. Moreover, the formulations F30 (HPMC: PVP; 2:0.75), F31 (HPMC: Eudragit; 2:1) with oleic acid as permeation enhancer shows optimum permeation. The above formulations gave a maximum drug permeation of 88%, 85%, respectively over 12 h. These two formulations were considered as best formulations among the prepared patches. The findings of this study revealed that the problems of TPM with reported oral formulations for pediatrics with epilepsy can be overcome by applying TPM topically in the form of a transdermal patch.

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## Conflicts of interest

There are no conflicts of interest.

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