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# FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF TOLMETIN SODIUM

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## ABSTRACT
Transdermal films, employing Hydroxy Propyl Methylcellulose and Ethyl cellulose as film formers were developed for Tolmetin Sodium. The effect of HPMC K4M alone, binary mixture of HPMC K4M: EC and type of chemical penetration enhancers on physicochemical parameters including thickness, moisture content and moisture uptake was evaluated. Drug– Polymer Interaction studies were carried out using Fourier Transfer Infrared spectroscopy method. In-vitro permeation study was conducted using cellophane membrane as penetration barrier in modified Keshary-Chein diffusion cell. The drug content was high and uniformly distributed in films. Moisture uptakes were found to increase with increasing concentration of hydrophilic polymer (HPMC K4M). During *in-vitro* skin permeation studies, it was found that, HPMC K4M: EC showed highest flux, and EO has more enhancing effect compared to DMSO on permeation of Tolmetin Sodium across cellophane membrane. Analysis of release kinetics and mechanism of drug release, revealed that all the formulations follow apparent zero order release kinetics and drug release in HPMC K4M : EC binary mixture followed non-Fickian diffusion (n>0.5). Based on the above observations, it can be reasonably concluded that HPMC K4M: EC combination and penetration enhancer, EO are better suited for the development of TDDS of Tolmetin Sodium.

**KEYWORDS:** Transdermal Films, Tolmetin Sodium; Ethyl Cellulose, Hydroxy Propyl Methyl Cellulose, *In-vitro* Permeation.

## INTRODUCTION
Administration of drug in conventional dosage form requires- large dose, frequent administration and lacks extended duration, with chances of toxicity. While in controlled drug delivery devices there is efficient utilization of drug, desired extended duration, with very low chances of toxicity, facilitating enhanced patient compliance leading to better management of therapeutics. Transdermal drug delivery system is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through skin in a predetermined and controlled rate.[1] Transdermal therapeutic system are defined as self-contained, discrete dosage form which when applied to the intact skin deliver the drug(s) through the skin at a controlled and predetermined rate into the systemic circulation. Actually, transdermal delivery is a transport process of drugs through a multi-laminar structure, e.g. from the patch to stratum corneum then to the viable epidermis, and finally penetrating into the blood.[2]

## MATERIALS AND METHOD
### Materials
Tolmetin Sodium was a gift sample from Mylan Laboratories Ltd (Hyderabad, India), Hydroxy propyl methyl cellulose K4M from Fisher inorganics and Aromatics Ltd (Madras, India), Ethyl Cellulose obtained from Loba Chemie Pvt. Ltd (Mumbai, India) and Dichloromethane obtained from Molychem (Mumbai, India). Eucalyptus, DMSO and Glycerine from Finar chemicals Ltd (Ahmedabad, India)

### Method
**Preparation of Transdermal Patches of Tolmetin Sodium by Solvent Evaporation Techinique**
Matrix type transdermal patches containing the drug were prepared by solvent evaporation technique. The polymers were dissolved in suitable solvent system respectively. Drug and plasticizer were added to the polymer solution. The resultant homogeneous solution was poured into glass ring placed on mercury. Controlled solvent evaporation was achieved by inverting a funnel over the mercury for 24 hr. The dry film was wrapped in aluminium foil and kept in desiccator until used.[3]

**Evaluation of Transdermal Patches**

**Physical Appearance:** All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.[4]

**Thickness Uniformity:** The thickness of the formulated film was measured at 3 different points using a vernier caliper and average thickness of three reading was calculated.[5]

**Weight Uniformity:** For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated.[6]

**Folding Endurance:** Folding endurance involves determining the folding capacity of the films (2×2cm) subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break.[7]

**Percentage Moisture Absorption:** The films were weighed accurately and placed in the desiccators containing 10 ml of saturated solution of potassium chloride, which maintains 80-90% RH.[8] After 3 days, the films were taken out and weighed. The study was performed at room temperature. The percentage moisture absorption was calculated using the formula:

$$\% \text{ moisture absorption} = \frac{\text{Final weight-Initial weight} \times 100}{\text{Initial weight}}$$

**Percentage Moisture Loss:** The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride.[9] After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula:

$$\% \text{ moisture loss} = \frac{\text{Initial weight- Final weight} \times 100}{\text{Initial weight}}$$

**Drug Content Uniformity:** The patches (1 $cm^2$) were cut and added to a beaker containing 100 ml of distilled water and kept aside until it get dissolved. The medium was then stirred with magnetic bead. The contents were filtered using whatmann filter paper and the filterate was examined for the drug content at 325nm spectrophotometrically**.**

***In-vitro* Drug Release Studies:** *In-vitro* permeation studies were performed by using a modified Franz diffusion cell. The synthetic filter membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into size of 1 $cm^2$ and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer $P^H$ 6.8. The whole assemble was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 100 rpm, the temperature was maintained at 37±0.5$^0$C. The samples of 5 ml were withdrawn at regular time intervals with a time period gap of half an hour and analyzed for drug content spectrophotometrically at 325 nm. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time.

**Kinetics and Mechanism of Drug Release**

The mechanism of Tolmetin sodium release from all formulations was determined by fitting the release data in the following mathematical model. The drug release kinetics was evaluated by using the linear regression method.[10-12]

**Korsmeyer -** Peppas (log cumulative % drug release vs log time)

The $r^2$ & n values are calculated for the linear curves obtained by regression analysis of the above plots. The release pattern of all formulations was concluded based on the $r^2$ & n values.

**Statistical Analysis**

Each formulation was prepared in duplicate, and each analysis was triplicate. Effect of formulation variables on Drug content and Drug permeation ($T_{50\%}$& $T_{80\%}$) were tested for significance by using analysis of variance (ANOVA: single factor) with the aid of Microsoft1 Excel 2002.[10-12] Difference was considered significant when $p < 0.05$.

## RESULTS AND DISCUSSION

**Identification by FTIR spectroscopy**

Figs: 1 - 4 shows IR spectrum of pure drug with characteristic absorption peaks of C-O stretch at wave number 1040 $cm^{-1}$, $COO^-$ at 1747 $cm^{-1}$, Aromatic C-H stretch at 3024 $cm^{-1}$. These results suggest that there was no interaction between the drug and EC: HPMC K4M used in the present study.

**Table 1: Composition of Transdermal Patches of Tolmetin Sodium.**

| Formulation | Drug (mg) | HPMC (mg) | Ethyl Cellulose (mg) | Penetration Enhancer (% 2 w/w polymer) | |
|---|---|---|---|---|---|
| | | | | DMSO | E.O |
| $H_1$ | 100 | 100 | --- | --- | --- |
| $H_2$ | 100 | 200 | --- | --- | --- |
| $H_3$ | 100 | 300 | --- | --- | --- |
| $F_1$ | 100 | 50 | 50 | --- | --- |
| $F_2$ | 100 | 100 | 100 | --- | --- |
| $F_3$ | 100 | 150 | 150 | --- | --- |
| $F_4$ | 100 | 150 | 150 | --- | --- |
| $F_5$ | 100 | 150 | 150 | --- | --- |
| $F_6$ | 100 | 150 | 150 | --- | --- |
| $F_7$ | 100 | 150 | 150 | --- | --- |
| $F_8$ | 100 | 150 | 150 | --- | --- |
| $F_9$ | 100 | 150 | 150 | --- | --- |

**Table 2: Physico-Chemical Evaluation of Formulated Patches of Tolmetin Sodium.**

| Formulation | Weight Variation (mg) (± S.D, n=3) | Thickness (mm) (± S.D, n=3) | Folding Endurance (± S.D, n=3) | % Moisture Absorption (± S.D, n=3) | % Moisture Loss (± S.D, n=3) | Drug Content (%) (± S. D, n=3) |
|---|---|---|---|---|---|---|
| $H_1$ | 253±2 | 0.089 ± 0.007 | 271±2.64 | 04.55 ± 0.04 | 03.23 ± 0.06 | 98.11 ± 0.12 |
| $H_2$ | 254±5.5 | 0.095 ± 0.002 | 280±1.56 | 06.85 ± 0.09 | 05.34 ± 0.02 | 99.54 ± 0.11 |
| $H_3$ | 324.3±3 | 0.104 ± 0.001 | 279.6±1.52 | 11.24 ± 0.01 | 08.10 ± 0.08 | 98.54 ± 0.23 |
| $F_1$ | 221.2±4 | 0.109 ± 0.032 | 282±2 | 05.10 ± 0.03 | 03.56 ± 0.03 | 99.32 ± 0.50 |
| $F_2$ | 241.3±3.7 | 0.111 ± 0.022 | 252±2.6 | 07.18 ± 0.23 | 06.65 ± 0.05 | 98.64 ± 0.42 |
| $F_3$ | 256.3±3.4 | 0.115 ± 0.021 | 278±2.6 | 11.98 ± 0.21 | 09.23 ± 0.04 | 99.15 ± 0.36 |
| $F_4$ | 274±1.7 | 0.112 ± 0.032 | 290±1.7 | 06.11 ± 0.28 | 04.54 ± 0.36 | 98.71 ± 0.28 |
| $F_5$ | 237.6±1.5 | 0.117 ± 0.023 | 273±1.73 | 08.21 ± 0.11 | 05.35 ± 0.07 | 99.01 ± 0.87 |
| $F_6$ | 224.3±4 | 0.110 ± 0.022 | 288.3±0.5 | 09.12 ± 0.23 | 06.32 ± 0.45 | 98.12 ± 0.24 |
| $F_7$ | 235.3±3.7 | 0.109 ± 0.031 | 263±1.7 | 04.21 ± 0.14 | 01.11 ± 0.06 | 99.11 ± 0.24 |
| $F_8$ | 232.3±2.7 | 0.105 ± 0.011 | 274.6±2.5 | 05.48 ± 0.45 | 03.78 ± 0.03 | 98.25 ± 0.95 |
| $F_9$ | 293.3±1.5 | 0.112 ± 0.021 | 282±2 | 07.12 ± 0.09 | 04.76 ± 0.01 | 99.42 ± 1.22 |

**Table 3: Permeation, Flux, Enhancement Factor, Kinetics and Drug release mechanism of Tolmetin Sodium from HPMC K4M Alone and EC: HPMC K4M films through Cellophane Membrane.**

| Formulation | Drug Permeated (8hr) (µg/cm$^2$) (±sd, n=3) | Flux (µg cm$^2$ hr$^{-1}$) (±sd, n=3) | Enhancement Factor (E) | Zero Order | First Order | Higuchi | First Order | Korsmeyer Peppas |
|---|---|---|---|---|---|---|---|---|
| | | | | $R^2$ | $R^2$ | $R^2$ | $R^2$ | n |
| $H_1$ | 380.67 ± 3.0 | 14.814 ± 0.3 | 1 | 0.9323 | 0.9634 | 0.9524 | 0.9812 | 0.8954 |
| $H_2$ | 605.56 ± 2.1 | 27.345 ± 1.6 | 2.43 | 0.9754 | 0.9412 | 0.9280 | 0.9854 | 0.899 |
| $H_3$ | 820.67 ± 1.0 | 67.021 ± 0.3 | 3.41 | 0.9564 | 0.9852 | 0.9686 | 0.9393 | 0.82 |
| $F_1$ | 730.78 ± 1.2 | 37.241± 2.1 | 1.09 | 0.8745 | 0.8969 | 0.8778 | 0.8945 | 0.67 |
| $F_2$ | 505.78 ± 3.2 | 30.12 ± 0.6 | 2.11 | 0.8616 | 0.8285 | 0.8585 | 0.8927 | 0.59 |
| $F_3$ | 410.89 ± 3.0 | 19.63 ± 0.5 | 3.14 | 0.8449 | 0.8876 | 0.8459 | 0.8979 | 0.54 |
| $F_4$ | 780.67 ± 4.1 | 29.38 ± 0.4 | 3.29 | 0.8654 | 0.8139 | 0.9856 | 0.8668 | 0.61 |
| $F_5$ | 570.68 ± 2.5 | 24.57 ± 0.03 | 4.56 | 0.8773 | 0.8798 | 0.8811 | 0.8927 | 0.77 |
| $F_6$ | 380.89 ± 1.9 | 18.14 ± 0.20 | 7.36 | 0.8645 | 0.8867 | 0.8925 | 0.8881 | 0.64 |
| $F_7$ | 810.56 ± 3.2 | 34.18 ± 0.10 | 3.89 | 0.8363 | 0.8881 | 0.8247 | 0.8934 | 0.67 |
| $F_8$ | 610.09 ± 3.1 | 30.12 ± 0.30 | 5.98 | 0.8537 | 0.8436 | 0.9863 | 0.8948 | 0.61 |
| $F_9$ | 426.57 ± 2.2 | 27.25 ± 0.45 | 11.45 | 0.8227 | 0.8554 | 0.8585 | 0.8954 | 0.62 |

**FTIR Spectroscopy**

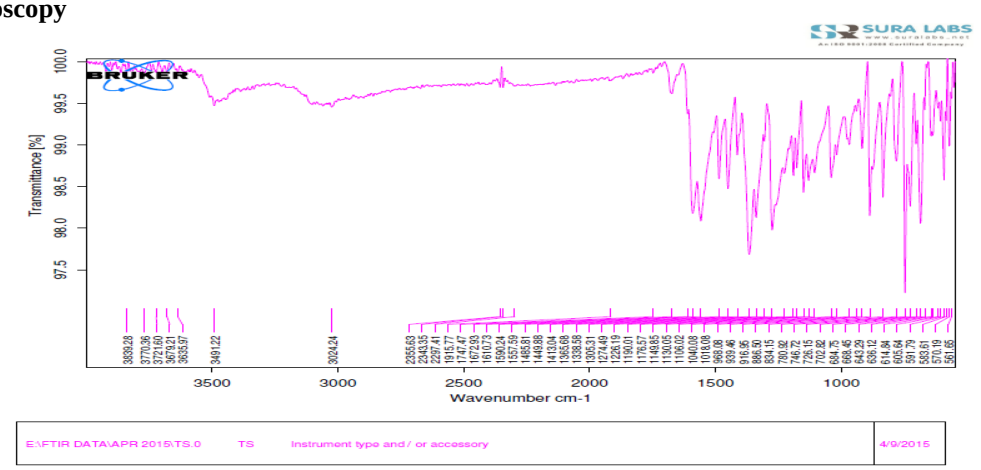


**Fig. 1: FTIR Spectra of Tolmetin Sodium.**

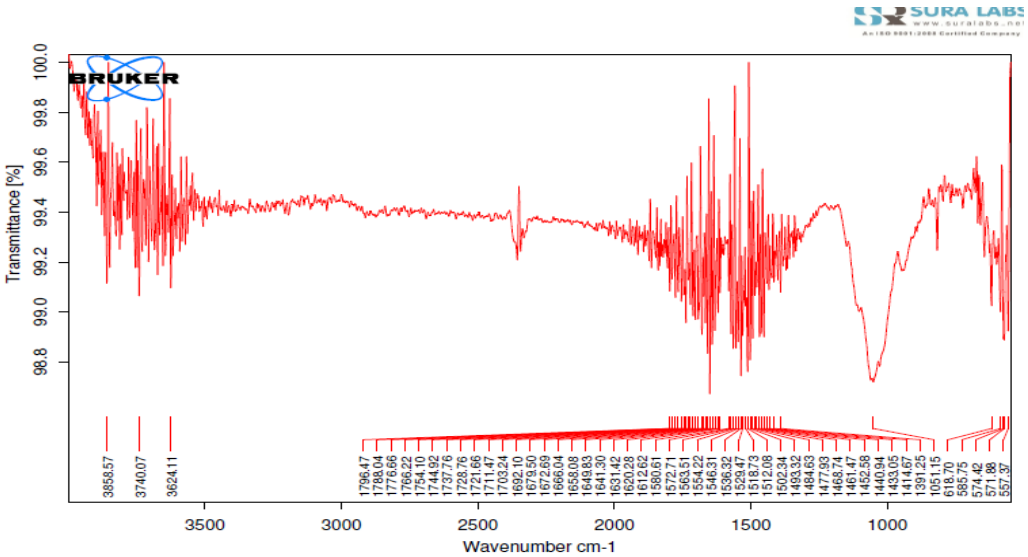


**Fig. 2: FTIR Spectra of HPMC.**

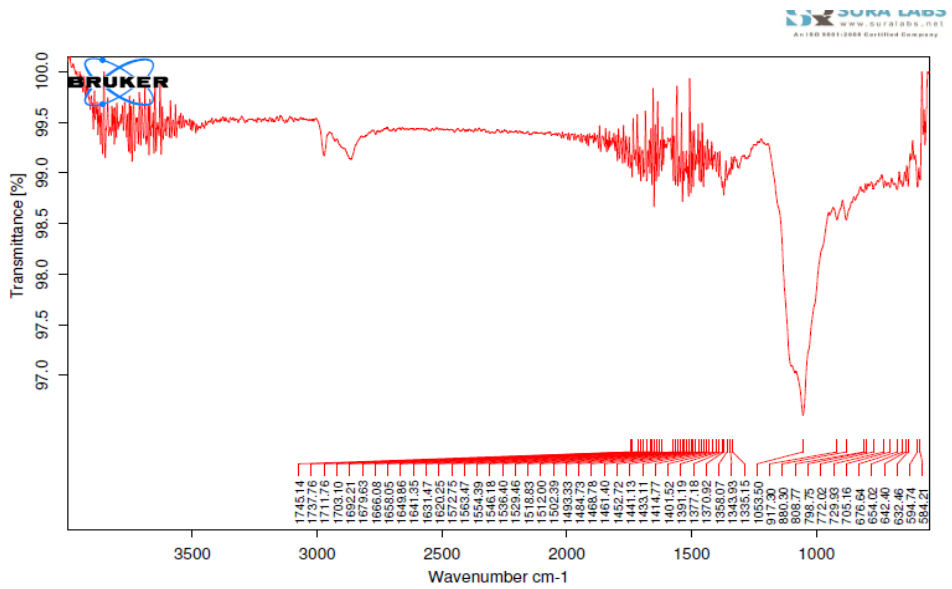


**Fig. 3: FTIR spectra of Ethyl Cellulose.**

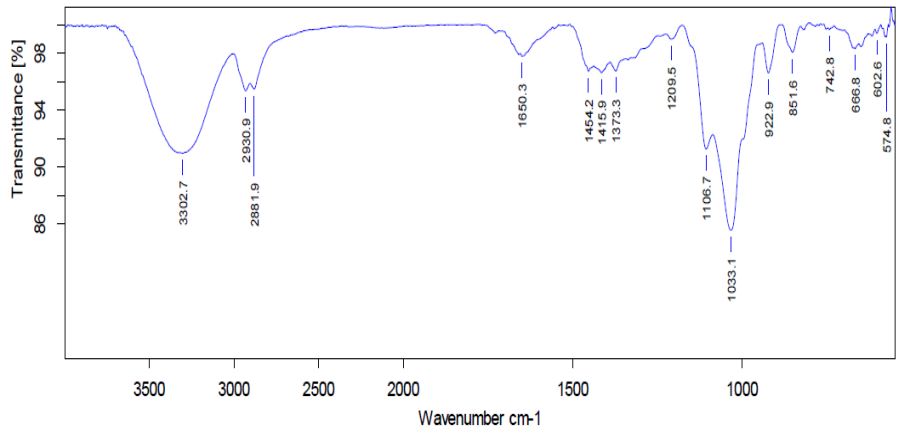


**Fig. 4: FTIR Spectra of Drug and Polymer ($F_6$).**

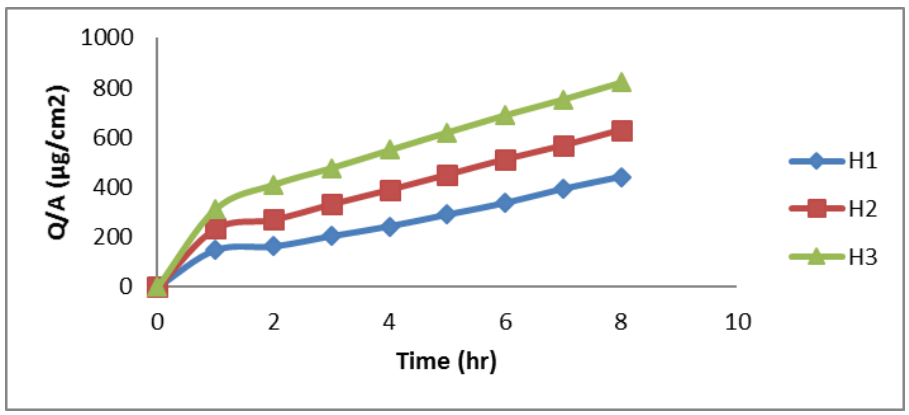


**Fig. 5: Effect of Concentration of HPMC K4M on Drug Release.**

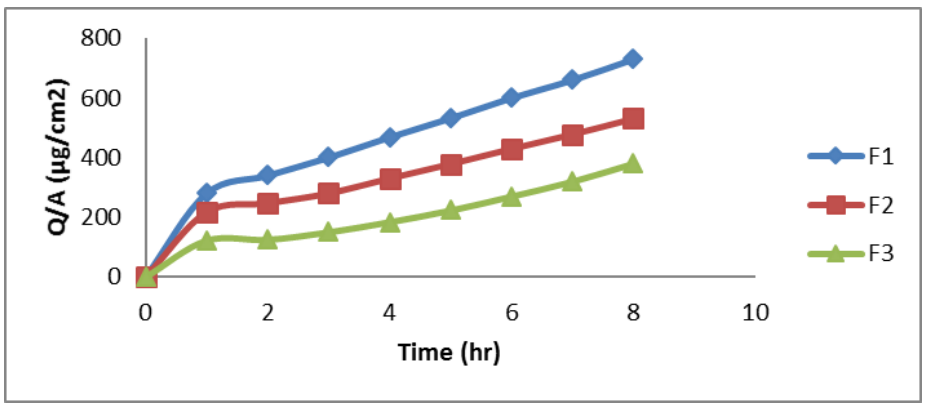


**Fig. 6: Effect on Drug Release from HPMC K4M:EC.**

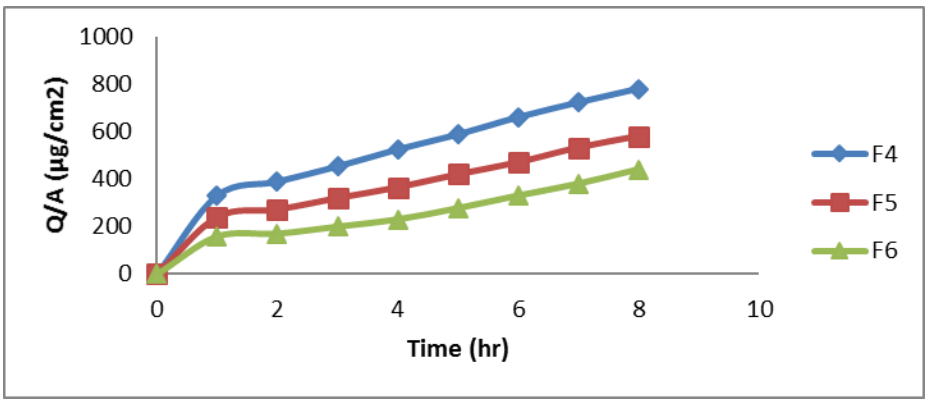


**Fig. 7: Effect on Drug Release from HPMC K4M: EC using Penetration Enhancer DMSO.**

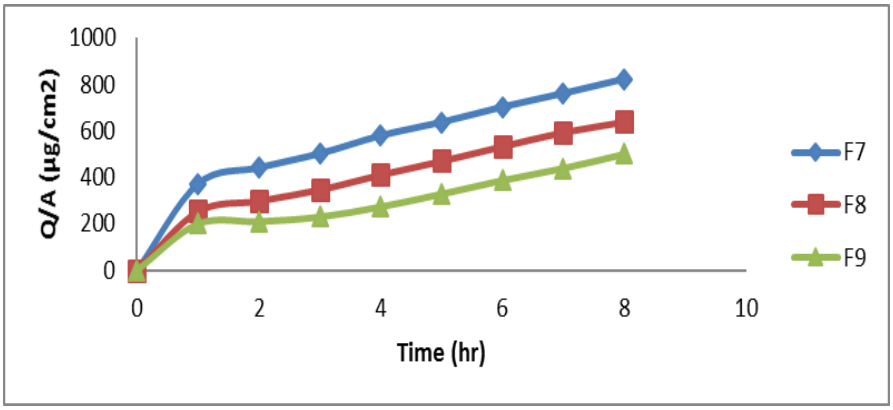


**Fig. 8: Effect on drug release from HPMC K4M: EC using penetration enhancer E.O.**

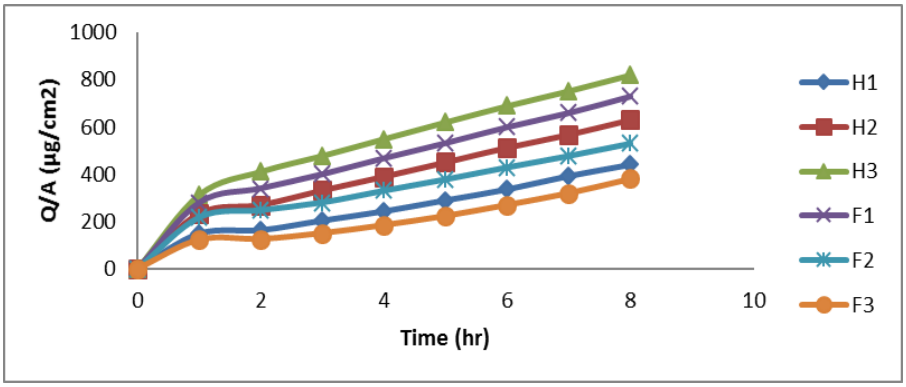


**Fig. 9: Comparative Permeation study of HPMC K 4M: EC with plain HPMCK4M.**

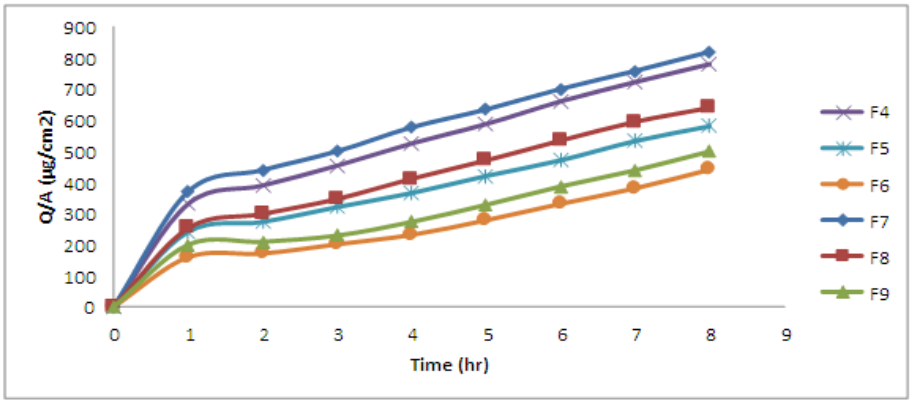


**Fig. 10: Comparision of Chemical Penetration Enhancer DMSO with Ecalyptus Oil.**

**Evaluation of Transdermal Patches**

Table – 2 shows thickness of various films that are varied from 0.089 ± 0.007 to 0.104 ± 0.001mm for HPMC K4M films and 0.109 ± 0.032 to 0.117 ± 0.023 mm for HPMC K4M: EC films. Low standard deviation values in the film thickness measurements ensures uniformity of the patches which indicates that the formulation variables did not produce any significant changes ($p>0.05$) on the thickness of film.

**Weight Uniformity**

Table – 2 shows weights of various films that are ranged between 253 ± 0.2 mg and 293.3 ± 0.3 mg. The results indicates that different patches weight were relatively similar.

**Folding Endurance**

Table – 2 shows folding endurance of transdermal films. The result was found to be ≥ 200 which indicates the films were sufficiently flexible.

**Moisture Loss and Moisture Absorption**

Moisture Loss and moisture uptake studies provide information regarding stability of the formulation. The results revealed that the moisture uptakes were found to increase with increasing concentration of hydrophilic polymer (HPMC). The presence of penetration enhancer Eucalyptus oil did not show any major changes in moisture Loss and moisture uptake values (table - 2). In case of DMSO, slight increment in these parameters was observed. This may be due to the more water affinity of

DMSO. The small moisture content in the formulation helps them to remain stable and from being a completely dried and brittle films. Physico chemical studies conducted on different polymeric films containing Tolmetin sodium favored the combination of these polymer and their blends for preparation of transdermal films.

**Drug Content Analysis**

Drug content of all formulations are shown in table - 2.The drug content for HPMC films was >98.11% whereas drug content for HPMC K4M: EC films was >98.12% with low standard deviation (1.22%). The result of drug content analysis of prepared formulation have shown that the method employed to prepare films in this study was capable of giving films with uniform drug distribution and insignificant batch variability ($p>0.001$).

***In-Vitro* drug diffusion Studies**

An *in-vitro* drug permeation study is predictive of *in-vivo* performance, and also, valuable and necessary for studying the rate and mechanisms of percutaneous absorption of drugs. In our work, the concentration of hydrophilic polymers and type of penetration enhancers were used as variable. In the present study, *in-vitro* permeation study was carried out using cellophane membrane as penetration barrier. The cumulative amount of drug permeated per $cm^2$ was plotted against time and the steady state permeation flux was calculated from slope of linear portion of the curve.

In first part of study, $H_1$, $H_2$ & $H_3$ containing Tolmetin Sodium in polymeric matrix of Hydroxy propyl Methyl Cellulose were prepared. It was observed that as the concentration of hydrophilic polymer HPMC increased in the formulations ($H_1$, $H_2$ and $H_3$), the mean cumulative amounts of drug permeated (380.67 ± 3.02, 605.56 ± 2.11, 820.67 ± 1.09 µg/$cm^2$ ((Fig - 5 & Table - 3) and flux (14.819±0.36, 27.345±1.67, 67.02±0.37µg/$Cm^2$hr) increased substantially. From the release studies it was observed that by increasing the proportion of HPMC, tend to increase cumulative amount of drug release. Increase in drug release may be attributed due to the fact the formation of gelaneous pores. The formation of such pores leads to decrease the mean diffusion path length of drug molecules to release into diffusion medium hence to cause in faster release. These results are in good agreement with Gannu *et al*, where they studied the release of anitrendipine and matrix film composed of ERL/HPMC and ERS/HPMC.

In second part of study, *in-vitro* permeation study revealed that the formulations ($F_1$ – $F_3$) containing Tolmetin Sodium in polymeric matrix of Hydroxy Propyl Methyl Cellulose and Ethyl Cellulose (HPMC K4M : EC) film showed the mean cumulative amounts of drug permeated (730.78 ± 1.25, 505.78 ± 3.21, 410.89 ± 3.09 µg/$cm^2$ (Fig - 6) and flux (37.241 ± 2.12, 30.12 ± 0.67, 19.63 ± 0.56µg $cm^{-2}$ $hr^{-1}$) decreased substantially in the 8hr respectively for cellophane membrane (Table - 3). It was observed that as the concentration of hydrophobic polymer (Ethyl Cellulose) increased in the formulation, the mean cumulative amounts of drug permeated (Figure - 6) and flux were decreased significantly ($P<0.05$). The decrease in drug release rate from films containing more lipophilic polymer combinations of HPMC K4M: EC in comparison to films containing more Hydrophilic polymer ($H_1$ to $H_3$) may be attributed to the relatively hydrophobic nature of polymer which have less affinity for water, this result in decrease in the thermodynamic activity of the drug in the film and decreased drug release. These results are in good agreement with results of Parasarathy *et al*, where they studied the release of Naproxen from matrix film composed of EC: HPMC K4M polymeric combination.

In further study, formulations $F_4$ to $F_6$ and $F_7$ to $F_9$ were selected to evaluate the effect of enhancers like DMSO and E.O on *in-vitro* permeation of drug through the cellophane membrane. Figs 7 & 8 show that addition of enhancers further significantly increased ($p<0.05$) the values of the amount of drug permeated and flux compared to their counterpart without enhancers (Table - 3). Among the penetration enhancers used, E.O has shown the highest amounts of drug permeated and flux. The enhancement factor for E.O was highest compared to DMSO (Table - 3) in the barrier and the relative order of the release rates for the enhancers was E.O > DMSO.

**Release Kinetics and Mechanism of Drug Release**

Different kinetic models (Zero-Order, First Order, Higuchi's Equation and Korsmeyer's equation) were applied to interpret the drug release kinetics and to know the mechanism of drug release from these matrix systems.

The formulations $H_1$, $H_2$ & $H_3$ showed strong linearity for both Higuchi and Korsmeyer models with higher $R^2$ values, and further more 'n' values of Korsmeryer model were <0.5. It indicates that diffusion is the mechanism of drug release from formulations $H_1$, $H_2$ & $H_3$ for cellophane membrane. When HPMC loaded formulations plotted with Korsmeyer et al.'s equation, irrespective of drug concentration showed high linearity ($R^2$ = 0.9393 to 0.9854) with a comparatively high slope(n) values ranging from 0.82 to 0.89 (Table - 3). It indicates drug release followed Fickian Diffusion. Presence of swellable polymer (HPMC) in the matrix might not be to controlled release as the concentration increases in the polymer matrix.

The liberation of the active drug from the TDDS is regulated by the physicochemical characteristics of the drug and delivery device as well as the physiological behavior of the biological surface. Various release kinetics of Tolmetin Sodium from HPMC alone formulations and also from various blends of the experimental polymeric combinations 'EC/HPMC' through the cellophane membrane which may help us to consider some assumption of behavioral changes of films

with respect to drug release due to the variation of polymeric composition in their blends. Diffusion of any molecule in a multi-polymeric matrix depends on structural and morphological parameters of the polymeric blend. Diffusion in polymers occurs through the amorphous polymeric region and diffusivity of drug molecule is related to the mobility of polymer chains and, thereby, to the free volume of the system. For larger pores with respect to the size of drug molecules, diffusion occurs by localized activated jumps from one pre-existing cavity to another. Smaller pre-existing cavities may be unable to accommodate the larger diffusing drug molecules. Therefore, many monomer segmental rearrangements by altering the mobility of polymer chains may be involved in allowing the drug molecules to diffuse. Thus, the matrix of various blends of EC/HPMC had definite influence on the diffusivity of Tolmetin Sodium, since the motion of a drug molecule is restricted by the variation of three-dimensional network of the polymer chains.

## CONCLUSION

It is concluded that among all formulations, formulation with Ecalyptus oil following almost zero order release which was determined by means of kinetics of drug release (Korsmeyer peppas equation). During storage the drug remained intact and stable in the TDDS with no significant chemical interaction between the drug and the excipient.

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