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Research Article

# FORMULATION AND INVITRO EVALUATION OF INDOMETHACIN TRANSDERMAL PATCHES USING POLYMERS HPMC E5 AND ETHYL CELLULOSE

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**ABSTRACT**

The purpose of this research work was to develop and evaluate matrix-type Transdermal drug delivery system containing Indomethacin with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. The physicochemical compatibility of the drug and the polymers were studied by infrared spectroscopy. The results suggested no physicochemical incompatibility between the drug and the polymers. Transdermal patch formulations consists of Hydroxypropyl methylcellulose E5 and Ethyl cellulose in the ratios of 10:0, 0:10, 1:9, 2:8,3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 respectively were prepared. All formulations carried 20% v/w of dimethyl sulfoxide as penetration enhancer and 20 % v/w of dibutyl phthalate as plasticizer in chloroform and methanol (1:1) as solvent system. The prepared Transdermal patches were evaluated for *in vitro* release, moisture absorption, moisture loss and mechanical properties. The diffusion studies were performed by using Franz diffusion cells. The formulation, F8 with combination of polymers (3:2) showed maximum release of 75.28% in 24 h. Hence, it can be reasonably concluded that Indomethacin can be formulated into the Transdermal matrix type patches to sustain its release characteristics.

**Keywords**: Transdermal Patches, Indomethacin, HPMC E5 and Ethyl Cellulose

## INTRODUCTION

Conventional systems of medication which require multi dose therapy have numerous problems and complications. The design of conventional dosage form, whether a tablet, an injection or a patch, to deliver the right amount of medicine at the right target site becomes complicated if each medication were to be delivered in an optimal and preferred manner to the individual patient. The impetus for the development of novel drug delivery systems, apart from therapeutic efficacy is cost. Redesigning the modules and means to transport medicine into the body is less demanding and more lucrative task. To address these problems, controlled release drug delivery system, a novel drug delivery approach evolves, which facilitates the drug release into systemic circulation at a pre-determined rate[1, 2]. Controlled drug release can be achieved by Transdermal drug delivery systems which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time [3, 4, 5]. Transdermal drug delivery systems has gained a lot of interest during the last decade as it offers many advantages over the conventional dosage forms and oral controlled release delivery systems notably avoidance of hepatic first pass metabolism, less frequency of administration, reduction in gastrointestinal side effects and improves patient compliance[6]. For Transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin[7].

## MATERIALS AND METHODS

### Material

Indomethacin was received as gift from Micro Lab, Bangalore, India. Ethyl cellulose, Hydroxypropyl methylcellulose E5, Dimethyl sulfoxide and Dibutyl phthalate were received from Themis laboratory, Mumbai. All the other solvents and chemicals were of analytical grade.

### Preparation of Transdermal films

Matrix type Transdermal films containing Indomethacin were prepared by using different ratio of hydroxyl propyl methyl cellulose E5 and ethyl cellulose (10 cps). The polymers were weight in requisite ratio and dissolved in methanol: dichloromethane (1:1).Dibutyl phthalate 20% use as a Plasticizer and Dimethyl sulfoxide as penetration enhancer. Indomethacin was added to polymeric solution, homogeneous dispersion was formed by slow stirring with magnetic stirrer. The uniform dispersion was then poured into glass ring of 7.44 $cm^2$ area (2.88cm diameter) placed on mercury kept in petri dish. The solvent was allowed to evaporate under ambient condition (temperature: $32^0$ C, RH: 45%) by keeping inverted funnel over the petri dish. The prepared films were stored in desiccators

### Evaluation of Transdermal Patches

### Physical appearance

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.

### Thickness

The thickness of films was measured by digital Vernier calipers with least count 0.001mm. The thickness uniformity was measured at five different sites and average of three readings was taken with standard deviation[8, 9].

### 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[10].

### Drug content determination

The patches at 3.14 $cm^2$ were cut and added to a beaker containing 100ml of Phosphate buffered solution of pH 7.4. The medium was stirred with a Teflon coated magnetic bead for 24 hrs. The solution was later filtered and analyzed for drug content with proper dilution at 320nm spectrophotometrically[11].

### Folding endurance

The folding endurance was measured manually for the prepared films. A strip of film (2 x2cm) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance[12].

### Flatness

Longitudinal strips were cut out from the prepared medicated film the lengths of each strip were measured. Then variation in the length due to the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero

percent constriction was considered to be equal to a hundred percent flatness[13].

$$\text{Constriction (\%)} = \frac{L1 - L2}{L2} \times 100$$

Where, L1- initial length of strip

L2 - final length of strip

**Percentage moisture absorption**

The percent moisture absorption test was carried out to check the physical stability and integrity of the films at high humid conditions. In the present study the moisture absorption capacities of the films were determined in the following manner. The films were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of potassium chloride, which maintains80-90% RH. 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[14, 15]:

$$\text{\% Moisture absorption} = \frac{(\text{Final weight} - \text{Initial weight})}{\text{Initial weight}} \times 100$$

**Percentage moisture loss**

Percentage moisture loss was carried out to check the (physical stability) moisture sensitiveness during storage of patch. The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula[14, 15]:

$$\text{\% Moisture loss} = \frac{(\text{Final weight} - \text{Initial weight})}{\text{Initial weight}} \times 100$$

**Water vapors transmission rate**

Glass vials of 5 mL capacity were washed thoroughly and dried to a constant weight in an oven. About 1 g of fused calcium chloride was taken in the vials and the polymer films of 3.14 cm2 were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period until it show constant weight gain [7 days]. The vials were removed and weighed at 24 h time intervals to note down the weight gain[16].

$$\text{Transmission rate} = 100 \times \frac{(\text{Final weight} - \text{Initial weight})}{(\text{Area} \times \text{Time})}$$

**Tensile Strength**

The tensile strength was determined by the apparatus designed such that it had horizontal wooden platform with fixed scale and attachments for two clips that holds Transdermal patch under test. Out of the two clips one was fixed and other was movable. Weights were hanged to one end of pulley and the other end of pulley was attached with movable clip. The wooden platform was such fitted that it would not dislocate while the test is running. Three strips of patch were cut having 2cm length and 1cm breadth. The thickness and breadth of strips were noted at three sites and average value was taken for calculation. Weights were gradually added to the pan to increase the pulling force till the film was broken [17]. The tensile strength was calculated by using following formula.

$$\text{Tensile stress} = \frac{\text{Applied force}}{\text{Cross sectional area}} = \frac{m \times g}{b \times t}$$

Where,

m- Mass in kg

g- Acceleration due to gravity 9.8 $N/m^2$

b- Breath of specimen in mm

t – Thickness of specimen in mm.

**Percent elongation**

The percent elongation at break was measured by formula given below[17].

$$\text{Strain (E)} = \frac{\text{Total elongation}}{\text{Original length}} \times 100$$

Where,

L = length after force was applied

L0 = original length

**Diffusion studies**

The diffusion studies were done to get an idea of permeation of drug through barrier from the Transdermal system. In vitro studies are also done for TDDS development. Usually, two types of diffusion cells are used as horizontal and vertical. The Franz and Keshary Chien (K-C) type of diffusion cells are of horizontal type of cells. In this work, Franz type of diffusion cell was used. Diffusion cells generally comprise two compartments, one containing the active Compartment (donor compartment) and the other containing receptor solution (receptor compartment), separated by barrier i.e. rat abdominal skin. The cell consisted of sampling port and temperature maintaining jacket. The outlet and inlet was connected with latex tube so the jacket had stagnant water inside and heat was provided by hot plate. The taflon coated magnetic bead was used to stir the receptor solution using magnetic stirrer. The excised rat abdominal skin was placed on receptor compartment and both compartments held tight by clamps. Phosphate buffer pH 7.4 was used as receptor solution. The volume of diffusion cell was 50 ml and stirred with magnetic bead. The temperature was maintained at 37 ± 1°C with the help of hot plate. The diffusion was carried out for 24 hours and 0.5 ml sample was withdrawn at an interval of 1 hour. The same volume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions and the samples were analyzed at 320nm. Other designs of diffusion cells that are in existence include Valia-Chien (V-C) cell, Ghannam- Chien (G-C) cell, Jhawer-Lord (J-L) Rotating disc system[18, 19, 20, 21].

**Stability Studies of Indomethacin Transdermal patch**

In any rationale design and evaluation of dosage forms, the stability of the active component must be major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal conditions of temperature and humidity. However the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature. In the present study, stability Studies were carried out on selected formulation. The patches were stored at temp $40^0$C & RH 75 % for duration of three month. After an interval of three months sample was withdrawn and tested for drug diffusion[22].

**RESULTS AND DISCUSSION**

In this work an attempt was made to formulate and evaluate TDDS for sustained release Indomethacin by solvent casting method. Low molecular weight, good permeability and shorter half-life of Indomethacin made it a suitable drug candidate e for the

development of transdermal patches. The main objective of formulating the transdermal system was to prolong the drug release time, reduce the frequency of administration and to improve patient compliance. The Standard Calibration Curve of Indomethacin at pH 7.4 shown in table and figure 1 and FTIR Spectrum figure 2. The compatibility parameters characterization was done by FTIR method shown in figure 2, 3, 4, and 5. Seven formulations were prepared using different polymers in different ratios and combinations, along with plasticizers and penetration enhancer. Mercury was used as a substrate for pouring the polymeric solution shown in table 2. The films were evaluated for uniformity of thickness, weight variation, drug content, folding endurance, tensile strength, % elongation, % flatness, % moisture absorption , Moisture vapor transmittance rate shown in table 3 and 4. In vitro diffusion studies using Franz diffusion cell. Cellophane membrane was used for the diffusion study table 5 and figure 6. Stability studies for drug diffusion of optimized batch F8 at 40°C and 75% RH for 90 days table no.6 and figure no. 7

The weight variation was found in the range of 474-483 mg. Thickness of transdermal patch was measured by micrometer screw gauge. The thickness of the films varies between 247.81 ± 6.89 to 259.15 ± 5.93. The tensile strength of the films was found vary with the nature of the polymer. It was found to vary between 3.93 ± 0.15 to 5.94 ± 0.17 N/mm$^2$. Flatness of all prepared patches was found to be 100%. Folding endurance of the transdermal patches was measured and it was varied between 69.23 ± 7.29 to 120.87± 5.86. The drug content uniformity was determined for all the seven formulations by spectrophotometric method and found in between 97.91 ± 0.27 to 100.41 ± 0.31 %. The % moisture absorption at 75% RH for all the formulations was in the range of 2.47 ± 0.21 to 4.54 ± 0.19 %. The % moisture absorption at 84% RH for all the formulations was in the range of 3.12 ± 0.31 to 4.98 ± 0.20 %. Moisture vapour transmission rate for all formulation was in the range of 1.58 ± 0.21 to 3.87 ± 0.32%. % Elongation for all formulation was in the range of 40.46 ± 5.32 to 72.43 ± 4.23%. The In vitro diffusion study was carried out in phosphate buffer pH 7.4 for 24hours. It was considered that the drug is dispersed uniformly throughout the film. The fabricated transdermal patches of Indomethacin were subjected to in-vitro permeation study across excised rat skin using modified Franz diffusion cell having a receptor volume of 50 ml and an effective surface area of 3.14 cm2. This study was carried out for 24 hours and cumulative percent permeated was calculated based on the amount of drug originally present in the patch. The batch F8 was optimised batch of Indomethacin transdermal patches prepared by using HPMC E5: EC (6:4) Showed good physical properties and ideal release kinetics. The formulation F8 showed the maximum diffusion through the membrane for 24 hours. It showed the diffusion of 75.28 %.

**Table 1: Standard Calibration Curve of Indomethacin at pH 7.4**

| Sr. No | Concentration of drug in ug/ml | Absorbance |
|---|---|---|
| 1 | 0 | 0.0 |
| 2 | 5 | 0.092 |
| 3 | 10 | 0.192 |
| 4 | 15 | 0.237 |
| 5 | 20 | 0.362 |
| 6 | 25 | 0.458 |
| 7 | 30 | 0.544 |
| 8 | 35 | 0.650 |
| 9 | 40 | 0.710 |
| 10 | 45 | 0.776 |

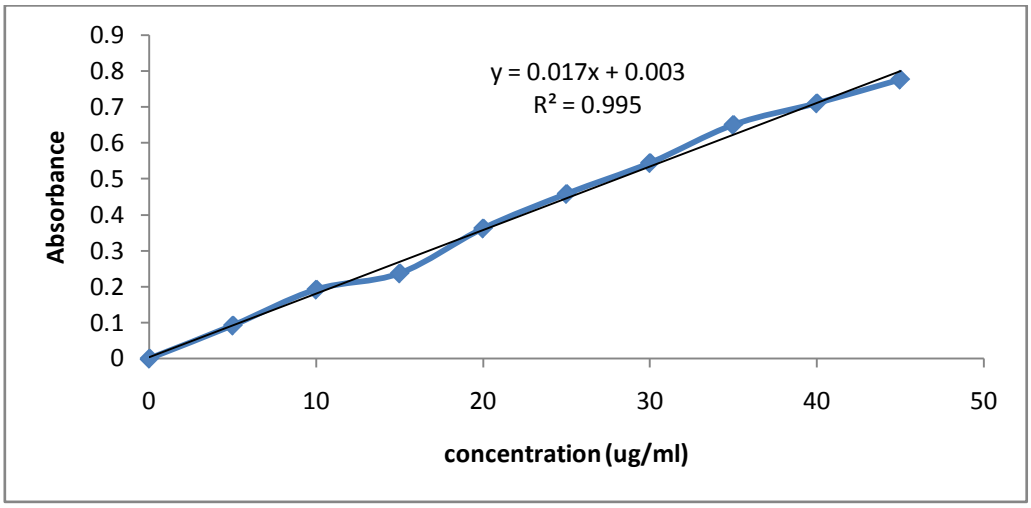


**Fig. 1: Standard Calibration Curve of Indomethacin at pH 7.4**

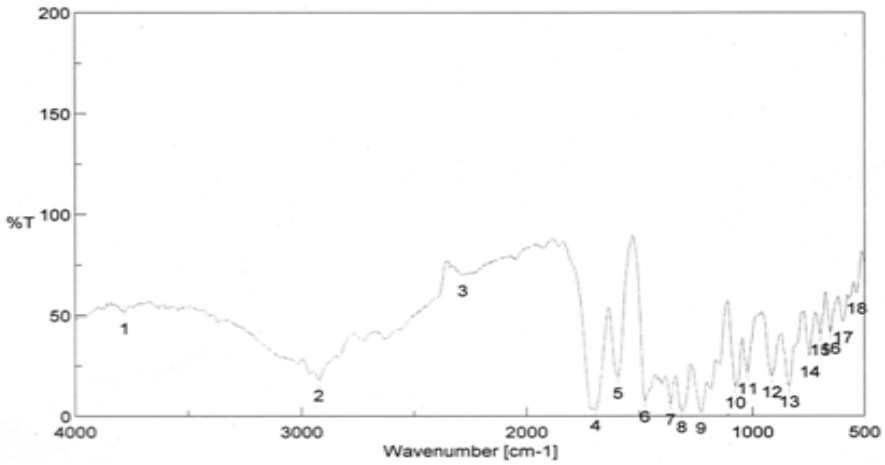


**Fig. 2: FTIR Spectra of Indomethacin**

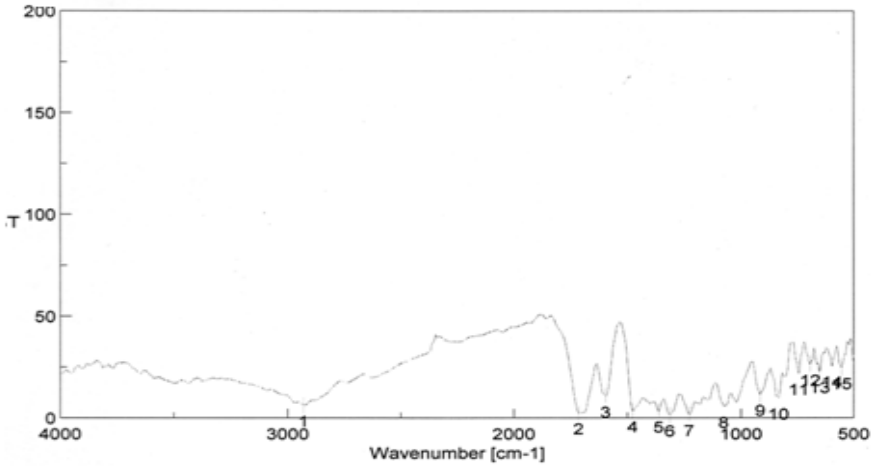


**Fig. 3: FTIR spectrum of mixture of Indomethacin and Ethyl cellulose**

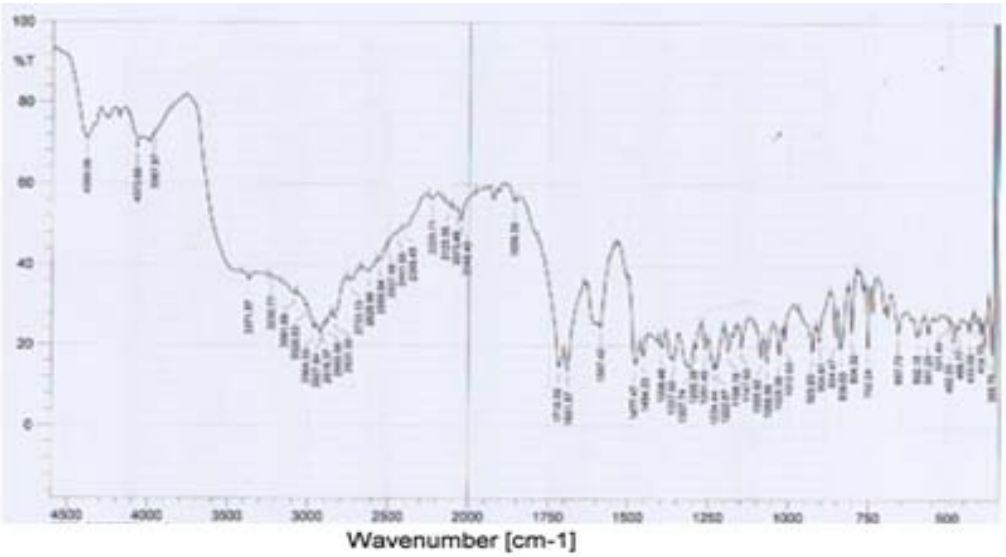


**Fig. 4: FTIR spectrum of mixture of Indomethacin and HPMC E5**

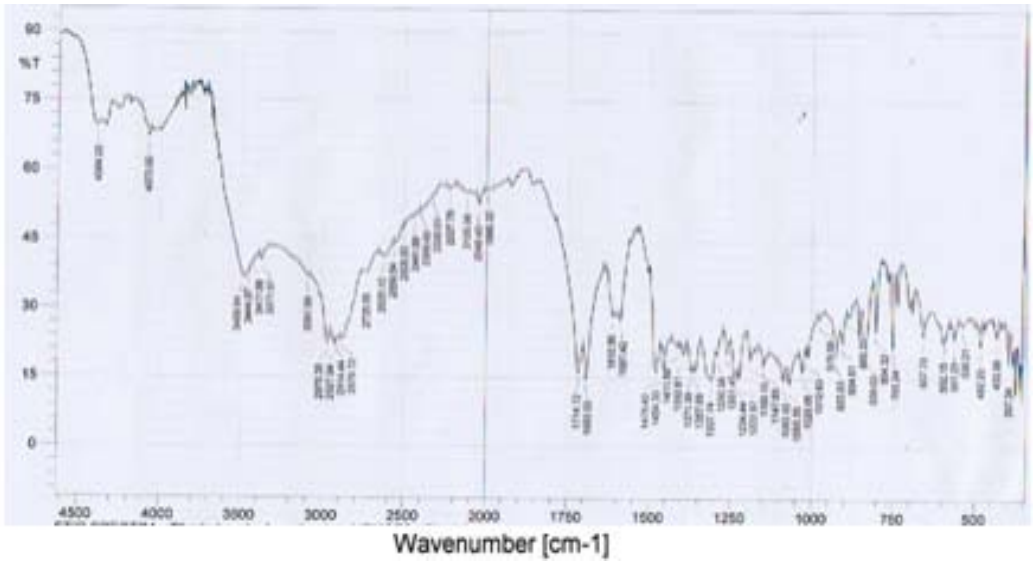


**Fig. 5: FTIR spectrum of mixture of Indomethacin, Ethyl cellulose and HPMC E5**

**Table 2: Formulation of Indomethacin Transdermal patches**

| Batch No. | Drug (mg) | Polymer weight (Mg) | | Plasticizer DBP (%) | Penetration enhancer DMSO (%) | Solvent (M:DCM) (1:1) (ml) |
|---|---|---|---|---|---|---|
| | | Ethyl cellulose | HPMC E5 | | | |
| F1 | 75 | 300 | 0 | 20 | 20 | 4 |
| F2 | 75 | 00 | 300 | 20 | 20 | 4 |
| F3 | 75 | 270 | 30 | 20 | 20 | 4 |
| F4 | 75 | 240 | 60 | 20 | 20 | 4 |
| F5 | 75 | 210 | 90 | 20 | 20 | 4 |
| F6 | 75 | 180 | 120 | 20 | 20 | 4 |
| F7 | 75 | 150 | 150 | 20 | 20 | 4 |
| F8 | 75 | 120 | 180 | 20 | 20 | 4 |
| F9 | 75 | 90 | 210 | 20 | 20 | 4 |
| F10 | 75 | 60 | 240 | 20 | 20 | 4 |
| F11 | 75 | 30 | 270 | 20 | 20 | 4 |

*HPMC E5: Hydroxypropyl methyl cellulose E5 *DBP: Dibutyl phthalate *DMSO: Dimethyl sulfoxide *M: Methanol *DCM: Dichloromethane *20 % w/w of DBP and DMSO to the polymeric weight.

**Table 3: Weight variation, thickness, drug content, flatness, % elongation of Indomethacin Transdermal patches**

| Batch No. | Weight variation (mg) | Thickness (um) | Drug Content (%) | Flatness | Elongation (%) |
|---|---|---|---|---|---|
| F1 | 475.20 ± 5.20 | 250.71 ± 3.21 | 98.57 ± 0.34 | 100% | 72.43 ± 4.23 |
| F2 | 477.32 ± 4.1 | 253.18 ± 5.32 | 99.11 ± 0.29 | 100% | 40.46 ± 5.32 |
| F3 | 479.13 ± 3.8 | 259.15 ± 5.93 | 99.24 ± 0.39 | 100% | 46.32 ± 3.96 |
| F4 | 478.13 ± 3.2 | 249.31 ± 7.31 | 98.95 ± 0.24 | 100% | 54.78 ± 4.65 |
| F5 | 474.32 ± 4.9 | 247.81 ± 6.89 | 97.91 ± 0.27 | 100% | 58.93 ± 5.20 |
| F6 | 478.43 ± 3.4 | 254.41 ± 5.92 | 100.41 ± 0.31 | 100% | 61.98 ± 3.85 |
| F7 | 474.13 ± 4.13 | 256.38± 5.85 | 97.94 ± 0.38 | 100% | 64.87 ± 6.24 |
| F8 | 473.50 ± 3.11 | 249.00 ± 4.76 | 97.64 ± 0.50 | 100% | 65.87 ±5.32 |
| F9 | 478.32 ± 4.51 | 251.00 ± 3.66 | 99.45 ± 0.48 | 100% | 67.15 ± 4.34 |
| F10 | 475.66 ± 3.48 | 256.33 ± 4.61 | 99.25 ± 0.38 | 100% | 69.19 ± 5.12 |
| F11 | 475.31 ± 4.23 | 253.45 ± 4.14 | 100.11 ± 0.21 | 100% | 71.43 ± 3.24 |

**Table 4: Tensile strength, folding endurance, MVRT, %moisture content and moisture absorption of Indomethacin transdermal patches**

| Batch No. | Tensile strength ($N/mm^2$) | Folding endurance | MVTR (%) | Moisture content (%) | Moisture Absorption (%) | |
|---|---|---|---|---|---|---|
| | | | | | 75%RH | 85%RH |
| F1 | 3.93 ± 0.15 | 120.87 ± 5.86 | 3.87± 0.32 | 4.32 ± 0.20 | 4.54 ± 0.19 | 5.98 ± 0.20 |
| F2 | 5.94 ± 0.17 | 69.23 ± 7.29 | 1.58 ± 0.21 | 2.27 ± 0.15 | 2.47 ± 0.21 | 3.12 ± 0.31 |
| F3 | 5.08 ± 0.13 | 85.56 ± 5.35 | 1.7 ± 0.19 | 2.41 ± 0.09 | 2.80 ± 0.29 | 3.47 ± 0.23 |
| F4 | 4.98 ± 0.19 | 87.23 ± 4.56 | 1.98 ± 0.32 | 2.53 ± 0.18 | 3.13 ± 0.24 | 3.80 ± 0.19 |
| F5 | 4.81 ± 0.21 | 94.53 ± 7.23 | 2.23 ± .024 | 2.87 ± 0.16 | 3.59 ± 0.23 | 4.03 ± 0.25 |
| F6 | 4.34 ± 0.22 | 105.23 ± 5.63 | 2.65 ± 0.26 | 3.21 ± 0.18 | 3.91 ± 0.12 | 4.20 ± 0.18 |
| F7 | 4.09 ± 0.16 | 109.51 ± 5.89 | 2.90 ± 0.24 | 3.51 ± 0.25 | 4.03 ± 0.17 | 4.78 ± 0.15 |
| F8 | 3.92± 0.19 | 110.21 ± 4.76 | 3.03 ± 0.18 | 3.67 ± 0.16 | 4.15 ± 0.12 | 4.92 ± 0.30 |

| | | | | | | |
|---|---|---|---|---|---|---|
| F9 | 3.56 ± 0.22 | 114.56 ± 3.66 | 3.12 ± 0.26 | 3.75 ± 0.24 | 4.27 ± 0.21 | 5.13 ± 0.15 |
| F10 | 3.32 ± 0.12 | 116.33 ± 4.61 | 3.27 ± 0.19 | 3.91 ± 0.18 | 4.34 ± 0.24 | 5.43 ± 0.21 |
| F11 | 3.09 ± 0.17 | 117.45 ± 4.14 | 3.49 ± 0.21 | 4.18 ± 0.09 | 4.51 ± 0.12 | 5.61 ± 0.25 |

*MVRT: Moisture vapour transmission rate *RH: Relative humidity

**Table 5: Invitro drug diffusion study of Transdermal patches of batches F1 to F11**

| Time hr | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 25.93 | 6.87 | 8.02 | 8.82 | 9.1 | 9.92 | 10.28 | 11.43 | 16.11 | 19.17 | 21.17 |
| 2 | 35.92 | 10.91 | 12.31 | 13.32 | 14.91 | 15.03 | 15.92 | 17.67 | 21.54 | 24.57 | 27.53 |
| 3 | 44.41 | 14.59 | 15.36 | 17.85 | 19.77 | 19.91 | 19.95 | 21.45 | 27.87 | 33.87 | 35.82 |
| 4 | 57.02 | 17.55 | 18.68 | 20.27 | 22.98 | 22.79 | 22.85 | 25.87 | 33.39 | 36.49 | 41.34 |
| 5 | 69.17 | 20.93 | 21.41 | 22.91 | 23.5 | 24.91 | 25.63 | 29.54 | 41.51 | 46.32 | 48.51 |
| 6 | 77.8 | 23.6 | 24.51 | 24.81 | 25.91 | 27.41 | 28.91 | 31.59 | 48.90 | 52.81 | 56.97 |
| 7 | 81.47 | 25.98 | 26.91 | 27.36 | 28.42 | 29.92 | 31.68 | 33.98 | 56.61 | 59.65 | 63.62 |
| 8 | 90.12 | 28.5 | 29.5 | 30.13 | 32.49 | 33.41 | 35.51 | 37.41 | 63.77 | 68.21 | 68.75 |
| 9 | 90.65 | 31.98 | 32.4 | 33.41 | 35.32 | 36.91 | 38.03 | 40.32 | 71.39 | 77.59 | 79.36 |
| 10 | 90.91 | 34.5 | 35.4 | 36.46 | 37.32 | 38.97 | 41.18 | 43.89 | 77.59 | 79.91 | 80.19 |
| 11 | 91.17 | 36.12 | 37.98 | 38.91 | 40.19 | 42.13 | 43.46 | 45.79 | 79.21 | 81.43 | 83.48 |
| 12 | 91.85 | 38.98 | 40.42 | 41.46 | 43.13 | 44.41 | 45.91 | 49.11 | 80.54 | 83.83 | 86.76 |
| 24 | 92.09 | 55.61 | 61.91 | 63.19 | 65.18 | 67.22 | 69.77 | 75.28 | 81.25 | 87.81 | 88.61 |

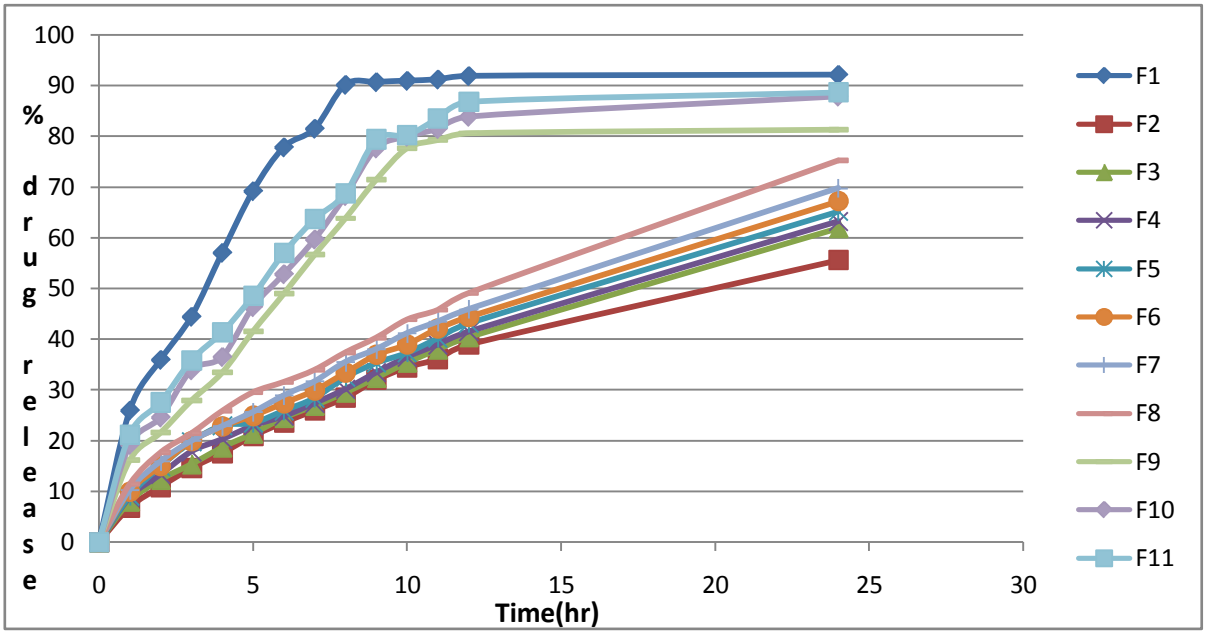


**Fig. 6*: Invitro* drug diffusion study of Transdermal patches of F1 to F11**

**Table 6: Comparative Stability studies for drug diffusion of optimized batch F8 at 40°C and 75% RH after 90 days.**

| Time (hr) | Cumulative % Drug diffused at 0 days | Cumulative % Drug diffused at 90$^{th}$days |
|---|---|---|
| 0 | 0 | 0 |
| 1 | 11.43 | 9.89 |
| 2 | 17.67 | 13.23 |
| 3 | 21.45 | 17.89 |
| 4 | 25.87 | 21.89 |
| 5 | 29.54 | 25.32 |
| 6 | 31.59 | 28.35 |
| 7 | 33.98 | 30.23 |
| 8 | 37.41 | 32.03 |
| 9 | 40.32 | 37.56 |
| 10 | 43.89 | 39.13 |
| 11 | 45.79 | 43.06 |
| 12 | 49.11 | 45.89 |
| 24 | 75.28 | 72.96 |

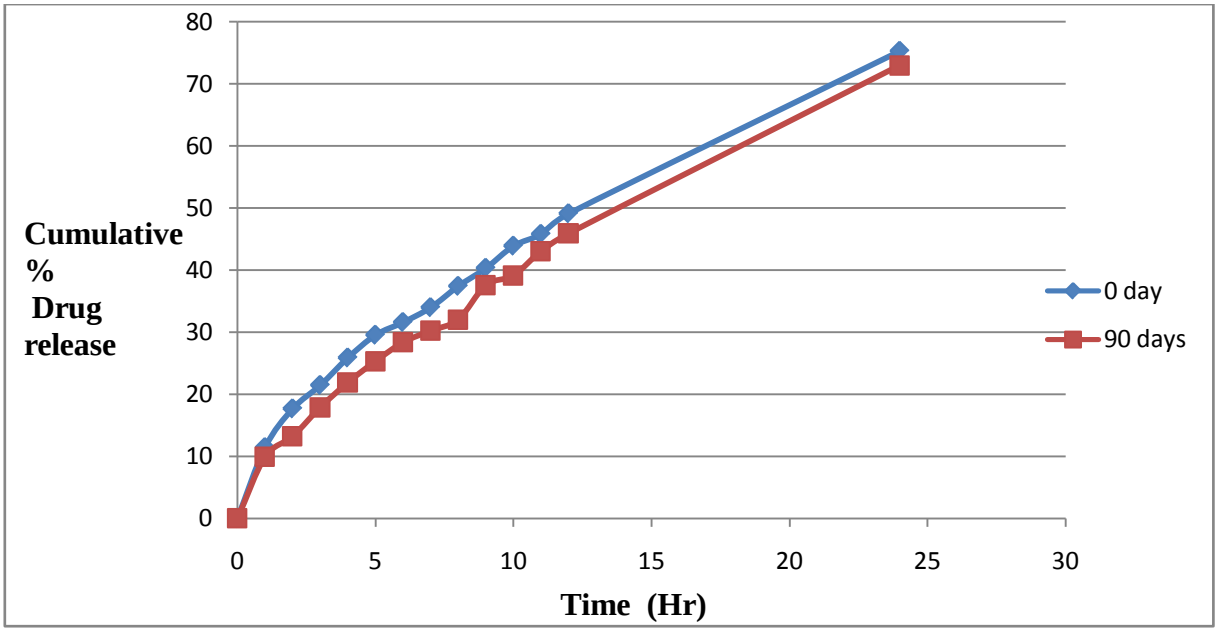


**Fig. 7: Comparative Stability studies for drug Diffusion of batch F8 at 40°C and 75% RH after 90 days**

## CONCLUSION

Finally, we conclude that the formulated transdermal patches of Indomethacin showed good thickness, drug content uniformity and tensile strength. The used polymer (Hydroxypropyl methylcellulose E5: Ethyl cellulose) can be used to develop transdermal patches in 6:4 proportions. As the concentration of hydrophilic polymer increases the folding endurance also increases, the increased folding endurance shows the good film consistency. In moisture uptake study the moisture uptake is going decreases as the concentration of ethyl cellulose were increases. From drug diffusion study, it is conclude that, as the concentration of ethyl cellulose increases the in-vitro drug diffusion rate decreases.

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