In the present study an attempt was made to design the matrix type transdermal patch of Mefenamic Acid (NSAIDs) with HPMC E-5 and ethyl cellulose polymer in various concentrations. Transdermal patch were formulated by solvent casting technique with different polymer proportions using Polyethylene Glycol-400 as plasticizer. The physicochemical compatibility of the drug and the polymers was carried out by Infra Red spectroscopy (FTIR). The results suggested no physicochemical incompatibility between the drug and the polymers. Blank films were prepared and evaluated for characteristics like smoothness and flexible. Further drug loaded patches were evaluated for their thickness, weight uniformity, folding endurance, percent moisture content, percent moisture uptake, surface pH, tensile strength, drug content, and in-vitro release study. The release profiles were found to be varied with various concentrations of HPMCE-5 and Ethylcellulose Polymer. The in-vitro release profile showed highest drug release 98.21% in 8 hours from F-1 and minimum 64.82% in 12 hours from F-2 cannot be considered as ideal formulation. The F-5 showed the release of 91.04% in 12 hours considered as ideal formulation.

**Key words:** NSAIDs, HPMC, Solvent Casting Technique, Plasticizer.

**Introduction**

Transdermal patch generally refers to topical application delivers agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. Transdermal Patch offers many advantages over the conventional dosage forms or controlled release oral systems. Transdermal patch provides constant blood levels,
avoids first pass metabolism, increased patient compliance, and avoids dose dumping.\(^1\) The application of transdermal delivery to a wider range of drugs is limited due to the significant barrier to penetration across the skin which is allied primarily with the outermost stratum corneum layer of the epidermis.\(^2\) Formulation on skin can be classified into two categories according to the target site of the action. One has systemic action after drug uptake from the cutaneous micro vascular network and other exhibits local effects in the skin.\(^3\) Transdermal drug delivery can closely mimics the slow intravenous infusion without its potential hazards and also offer another most important advantage in allowing the patient to terminate the drug therapy by simply removing the patch at desired time if toxicity develops.\(^4\)

NSAID (Non-steroidal anti-inflammatory drugs) are mostly used for the preparation of transdermal patches for the treatment of inflammation or pain. The NSAID patches are safer and convenient then its oral form. Patient with rheumatism received different NSAID tablets. The side effects like stomach bleeding, increased acidity, ulcers are avoided by using transdermal patches of NSAID. The analgesic patch of NSAID may be used on the site of bruise, sprain or strain.\(^5\) These patch when applied topically in the form of transdermal patch, without reaching higher plasma drug concentrations the drug penetrate the skin, subcutaneous fatty tissue, and muscle in amounts sufficient to exert local therapeutic effects. Hence NSAIDs offer the advantage of local, enhanced drug delivery to affected tissues with a reduced incidence of systemic adverse events. In Rheumatoid Arthritis patients are advised to take the NSAIDs for prolong period but the side effects related to systemic toxicity and GIT irritation are the main drawbacks of NSAIDs drugs.

Mefenamic Acid is NSAIDs drug that inhibits the prostaglandin synthesis and act as agent to control pain and inflammation condition. The half-life of Mefenamic Acid is 1-2 hours and need to be administered 3 to 4 times a day. Because of its short biological half-life and frequent administration, it is considered as a suitable candidate to formulate it into a sustained release matrix type transdermal patch system.

Main objective of study is to develop transdermal patch of Mefenamic Acid to achieve more patient compliance, to reduce the dosing frequency, to enhance the release rate of drug for quick onset of action, to avoid the oral administration of drug to omit the GIT related bioavailability problems and to improve local availability of drug to site of action in arthritis.

**Material and Methods**

Mefenamic Acid, HPMC E 5, Ethyl Cellulose, PEG-400, Dichloromethane, and Methanol were purchased from Chemdyes corporation ltd Rajkot, Gujrat.

**Method**

HPMC E-5, Ethyl Cellulose, was used for the formulation of Transdermal Patch. Polyethylene glycol (PEG 400) was used as a plasticizer. The polymers were dissolved in Dichloromethane: Methanol (4:1) solvent. The drug was dispersed uniformly in the viscous solution with continuous stirring. The resulting mass was poured into Petri disc. The petri disc was left undisturbed at room temperature for one day. The patch was obtained intact by slowly lifting from the petri disc and transdermal patches were cut into radius of 2 cm\(^2\).

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation Design Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mefenamic Acid (mg)</td>
<td>F-1  F-2  F-3  F-4  F-5  F-6  F-7</td>
</tr>
<tr>
<td>HPMC E-5 (mg)</td>
<td>380  380  380  380  380  380  380</td>
</tr>
<tr>
<td>Ethyl Cellulose (mg)</td>
<td>1000 200  850  750  650  450  350</td>
</tr>
<tr>
<td>PEG-400 (ml)</td>
<td>1.8  1.8  1.8  1.8  1.8  1.8  1.8</td>
</tr>
<tr>
<td>DCM: Methanol (4:1) (ml)</td>
<td>14  14  14  14  14  14  14</td>
</tr>
</tbody>
</table>
Result and Discussion

Spectral Analysis of Mefenamic Acid

The spectrum of UV was analysed by UV/Vis spectroscopy and λmax found to be 285 nm.

Drug Excipient Compatibility Study by FT-IR Spectroscopy

Figure 2. Comparative Drug Excipients compatibility study
As seen in the above figure all the characteristic peaks of Mefenamic Acid did not deviate significantly. So there was no major sign of incompatibilities seen in the interaction studies and thus all excipients can be used for the formulation.

Preparation of Standard Curve of Mefenamic Acid At pH 5.8

Table No.2. Standard Calibration Curve of Mefenamic Acid in Phosphate Buffer pH 5.8

<table>
<thead>
<tr>
<th>Concentration mcg/ml</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>0.0432</td>
</tr>
<tr>
<td>5</td>
<td>0.0760</td>
</tr>
<tr>
<td>10</td>
<td>0.1557</td>
</tr>
<tr>
<td>15</td>
<td>0.2260</td>
</tr>
<tr>
<td>20</td>
<td>0.3001</td>
</tr>
<tr>
<td>25</td>
<td>0.3728</td>
</tr>
<tr>
<td>30</td>
<td>0.4361</td>
</tr>
</tbody>
</table>

Figure.3. Standard Calibration Curve of Mefenamic Acid at pH 5.8

Evaluation of transdermal patch

Thickness of the patch
The thickness of each patch was measured by using screw gauge at five different positions of the patch and the average was calculated.  

Weight Uniformity
Patches sizes of 2 cm radius (4 cm diameter) was cut. The weights of five patches were taken and the weight variation was calculated.  

Folding Endurance
A patch of 2 cm radius (4 cm diameter) was cut evenly and repeatedly folded at the same place till it brakes. The numbers of times the film was folded at the same place without breaking give the value of the folding endurance.
**Tensile Strength**

The tensile strength is determined by apparatus designed in such a way that it contains a horizontal wooden platform with fixed scale and attachment of two clips that holds transdermal patch under test. Out of two clips one was fixed and other was movable. Weights were hanged to one end of pulley was attached with movable clip. Three strips of patch were cut of 2cm length and 2cm breadth. The breakage of patch was observed and total weights taken were used for calculation. The tensile strength was calculated by using following formula.\(^{10}\)

\[
\text{Tensile strength} = \frac{\text{Total Elongation}}{\text{Original Length}} = \frac{L - L_0}{L_0} \quad \text{eq.no.7}
\]

Where, \(L = \text{Length after force was applied}\)
\(L_0 = \text{Original Length}\)

**Percentage Moisture Content**

The prepared films were weighed individually and kept in a desiccator containing fused

\[
\text{Percentage moisture content} = \left[ \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \right] \times 100. \quad \text{eq.no.1}
\]

Calcium chloride at room temperature for 24h, After 24h, the films were reweighed and determined the percentage moisture content from the mentioned formula.\(^9\)\(^{11}\)

**Percentage Moisture Uptake**

The weighed films were kept in desiccators at room temperature for 24h containing saturated solution of potassium chloride in order to maintain 84% RH. After 24h, the films

\[
\text{Percentage moisture uptake} = \left[ \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \right] \times 100. \quad \text{eq.no.2}
\]

Were reweighed and determined the percentage moisture uptake from the below mentioned formula.\(^9\)\(^{11}\)

**Surface pH**

Transdermal Patch was left to swell for 1 h on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 5.8 under stirring and then poured the solution into the Petri dish allowed to stand till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch.

**Drug Content**

A specified area of patch was dissolved in a phosphate buffer solution. The contents was stirred to dissolve the film. The content was transferred to a volumetric flask. The absorbance of the solution was measured at wavelength 285nm and determine the drug content.\(^12\)

**In Vitro Drug Release Study**

In Vitro drug release study was performed by using a modified diffusion cell. The cellulose acetate membrane used for the determination of drug from the prepared transdermal matrix-type patches. The cellulose acetate membrane was mounted between the donor and receptor compartment of the diffusion cell. The prepared transdermal film was placed on the cellulose acetate membrane and cover with aluminum foil. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads, and the temperature was maintained at 32±0.5°C, because the normal skin temperature of human is 32°C. The samples was withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase should replenish with an equal volume of phosphate buffer at each sample withdrawal.\(^11\)
Comparison of Release Profile

From the result of In-vitro study it is observed that as the concentration of hydrophilic polymer HPMC increases the drug release from the transdermal patch increases. The formulation F-1 showed maximum release of 98.21% in 8 hours. Hence the F-1 cannot be considered as ideal formulation because it fails to sustain the drug for 12 hours. The formulation F-2 showed maximum release of 64.82% in 12 hours. Hence the F-2 cannot be considered as ideal formulation because it fails to release the entire drug comprised within the transdermal patch. The formulation F-3 and F-4, F-6and F-7showed the maximum release of 96.82%, 97.93% in 9 and 11 hours respectively. The F-3 and F-4 cannot be considered as ideal formulation because it fails to sustain the drug for 12 hours. Formulation F-6 and F-7

![Figure 4. Comparative release profile of formulation F1-F7](image-url)
Showed the maximum release of 72.02% and 68.58% of Mefenamic Acid in 12 and 12 hours respectively. The formulation F-6 and F-7 also cannot be considered as ideal formulation because it fails to release the entire drug comprised within the transdermal patch. Formulation F-5 showed the maximum release of 91.04% of Mefenamic Acid in 12 hours. Hence the F-5 can be considered as ideal formulation it showed better release with sustained effect as compared to other formulations. This indicates that higher proportion of hydrophilic polymer can release the drug to greater extent but fails to sustain the release for long time and higher proportion of hydrophobic polymer can sustain the drug release for greater extent but fails to release entire drug comprised in transdermal patch. Formulation coded by F-5 was fulfilled the criteria for optimized formulation and released for 12 hrs. So, F-5 was considered as the optimized formulation.

Table No. 5. Curve fitting data of release profile for designed formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order $R^2$</th>
<th>First Order $R^2$</th>
<th>Higuchi Model $R^2$</th>
<th>Korsmeyer-Peppas Model $R^2$</th>
<th>$N$</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-1</td>
<td>0.9886</td>
<td>0.8364</td>
<td>0.9901</td>
<td>0.9908</td>
<td>0.7937</td>
</tr>
<tr>
<td>F-2</td>
<td>0.9800</td>
<td>0.8538</td>
<td>0.9947</td>
<td>0.9963</td>
<td>0.6450</td>
</tr>
<tr>
<td>F-3</td>
<td>0.9809</td>
<td>0.8234</td>
<td>0.9946</td>
<td>0.9907</td>
<td>0.7180</td>
</tr>
<tr>
<td>F-4</td>
<td>0.9681</td>
<td>0.7766</td>
<td>0.9970</td>
<td>0.9802</td>
<td>0.7141</td>
</tr>
<tr>
<td>F-5</td>
<td>0.9639</td>
<td>0.7559</td>
<td>0.9943</td>
<td>0.9755</td>
<td>0.7033</td>
</tr>
<tr>
<td>F-6</td>
<td>0.9881</td>
<td>0.8512</td>
<td>0.9930</td>
<td>0.9981</td>
<td>0.6903</td>
</tr>
<tr>
<td>F-7</td>
<td>0.9972</td>
<td>0.8967</td>
<td>0.9746</td>
<td>0.9919</td>
<td>0.6997</td>
</tr>
</tbody>
</table>

When the regression coefficient values of zero order and first order plots were compared, it was observed the ‘r’ value of zero order plots were in the range of 0.96 to 0.99 indicating drug release from most of the formulation was found to follow zero order kinetics. It is notable the ‘r’ values of the linear regression for Higuchi’s plot were found to be 0.997 indicating that the data fits the Higuchi’s model well and the drug release was found to be predominantly controlled by diffusion. When the In-Vitro release data was fitted to exponential model, the ‘r’ values were found to be in range of 0.97 to 0.99 in most of formulation, indicating the data fits the exponential model well. The slope ‘n’ values of exponential equation were found to be > 0.45 and < 0.89 indicating the drug release is governed by non-fickian diffusion mechanism.

Stability Study
Accelerated stability study was carried out for selected formulation F₅ for 1 month by keeping at 40°C/75 %RH and 30°C/65 %RH, the data showed no significant difference in the appearance, thickness, weight uniformity, folding endurance, % moisture content, % moisture uptake, tensile strength, and in-vitro release which confirms the stability of the product.

Conclusion
The matrix type transdermal patch of Mefenamic Acid was prepared successfully by using two different polymers and their combination by solvent casting method. From the in vitro drug release data it can be concluded that controlled release of Mefenamic Acid from the patch could be achieved for prolonged period.

Acknowledgment
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References