Preparation and Evaluation of Transdermal Patches of An Anti-Inflammatory Drug

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ABSTRACT

Objective: The objective of the present study was to compare the release effect of Etodolac from different polymeric (hydrophilic and lipophilic) patches prepared by varying concentrations. The best polymeric combination was selected based on the release of the drug from the patches.

Methods: Polymers such as HPMC, MC, EC, PVA, Eudragit L-100, and Glycerin was used as a plasticizer. Permeation Enhancers used is Dimethyl Sulfoxide. Transdermal patches were prepared by using the solvent casting technique. FTIR was studied to estimate the incompatibility. Patches were evaluated for physicochemical Characteristics like thickness, weight variation, folding endurance, moisture loss, moisture absorption, water vapor transition, drug content, and In-vitro diffusion studies.

Results: The results obtained showed no physical-chemical incompatibility between the drug and the polymers. MC: EC was found to be a suitable polymer compared to other prepared polymeric combinations in the preparation of transdermal patches. From the evaluation of patches F6 containing (1:3) % of MC: EC was considered the best formulation for the transdermal delivery of Etodolac.

Conclusion: Transdermal patches were successfully prepared for Etodolac and their evaluation studies of each dosage form revealed that topically applied Etodolac patches possess immense potential to control the release rate of medicament to improve the bioavailability as well as patient compliance.

Keywords: ET-Etodolac, MC-Methyl cellulose, HPMC-Hydroxy propyl methyl cellulose, EC-Ethyl cellulose, PVA-Poly vinyl alcohol, EUD-Eudragit, Transdermal drug delivery.

INTRODUCTION

Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms that, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation. The transdermal route of administration is recognized as one of the potential routes for the local and systemic delivery of drugs. In comparison to conventional pharmaceutical dosage forms, offers many advantages, such as the elimination of first-pass metabolism, sustained drug delivery, reduced frequency of administration, reduced side effects, and improved patient compliance.

The Transdermal patch is medicated adhesive patch. These are prepared and deliver a therapeutically effective amount of drugs across the skin. The patches provide a controlled release of the medication into the patient. It acts as a carrier for a drug which holds it until the point of application. At this point, the adhesive secures the patch to the skin. It allows the drug access to the skin, it helps the permeation process. It delivers the drugs topically. A transdermal patch containing a high dose of drug into the skin which is retained for a prolonged period gets entered the blood flow through the diffusion process.

Advantages.

1. Self-medication is possible
2. Unwanted side effects get minimized
3. First-pass metabolisms of drugs get avoided.

Disadvantages.

1. Larger molecules size of the drug creates difficulty in absorption
2. Chances of allergic reactions at the site of applications such as itching, rashes, etc.

Transdermal drug administration generally refers to the topical application that is intact in the skin and simultaneously minimizes the retention and also metabolism of the drug in the skin. TDDS systems are useful for skin disorders, pains, angina pectoris, neurological disorders, etc. TDD systems are considered the new drug delivery systems which involve the demonstration of clinical safety and effectiveness of the drug. In novel techniques, drug delivery has been investigated in human medicine in recent years. Among the new drug delivery systems, there are mostly used for transdermal applications.

Limitations of TDD systems.

1. It cannot administer drugs that require high blood levels
2. Drug formulation may cause irritation or sensitization. Infection Tissue injury Tissue stress and malfunction Host defence against infection Tissue repair response Adaption to stress and restoration of a homeostatic state.
Etodolac is a non-steroidal anti-inflammatory (NSAID) with anti-inflammatory, analgesic, and antipyretic properties. Its therapeutic effects are due to its ability to inhibit prostaglandin synthesis. It is indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis. For acute and long-term management of signs and symptoms of osteoarthritis and rheumatoid arthritis, as well as for the management of pain. Etodolac is an anti-inflammatory agent with analgesic and antipyretic properties. It is used to treat osteoarthritis and rheumatoid arthritis and control acute pain. The therapeutic effects of etodolac are achieved via the inhibition of the synthesis of prostaglandins involved in fever, pain, swelling, and inflammation. The anti-inflammatory effects of etodolac result from inhibition of the enzyme cyclooxygenase (COX). This decreases the synthesis of peripheral prostaglandins involved in mediating inflammation. Etodolac binds to the upper portion of the COX enzyme active site and prevents its substrate, arachidonic acid, from entering the active site. Etodolac was previously thought to be a non-selective COX inhibitor, but it is now known to be 5-50 times more selective for COX-2 than COX-1. Etodolac belongs to BCS class II. Hazards of etodolac through the oral route are GI toxicity including bleeding, ulceration, perforation, and rectal injury, including renal papillary necrosis. As it possesses low solubility and high permeability the drug can easily penetrate the skin via transdermal drug delivery and reaches systemic circulation. TDDS increases patient compliance and reduces the drug load as compared to the oral route.

**MATERIALS AND METHODS**

Preformulation studies

Before the formulation of a drug substance into a dosage form, it must be chemically and physically characterized. Pre-formulation studies give the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

Identification Studies

Organoleptic properties of Drug

The drug sample (Etodolac) was noted for its Organoleptic properties such as Color, odor, Taste, and appearance.

**Determination of melting point**

The melting point of the sample was determined by the open capillary tube small amount of powdered drug was filled inside the thin capillary tube and sealed from one side by melting. The capillary was placed into the melting point apparatus. After some time at a specific temperature drugs were melted was the melting point of the drug.

**Determination of solubility**

About 5mg of Etodolac was added to 10 ml of various solvents and sonicated for 10 minutes and inspected visually for solubility and compared with standard.

**Determination of Wave Length (λ max)**

Wavelength maxima (λ max) of Etodolac were determined as follows.

**Preparation of stock solution:**

The stock solution was prepared by dissolving 100mg etodolac in 100ml of phosphate buffer pH 7.4 in a volumetric flask by shaking manually for 10 min. The volume was adjusted with the same up to the mark to give the final strength, i.e. 100mg/ml.

**Selection of analytical wavelength (λ max):**

Appropriate volume 1ml of standard stock solution of Etodolac was transferred into a 50ml volumetric flask, diluted to a mark with phosphate buffer pH 7.4 to give a concentration of 20μg/ml. The resulting solution was scanned in the UV range (200-400nm).

**Preparation of dilution samples:**

Different aliquots of Etodolac in the range 2-20 μg/ml were transferred into a series of 10ml volumetric flasks, and the volume was made up to the mark with distilled water to get concentrations 2, 6, 10, 14, and 20μg/ml, respectively.

**Preparation of Calibration curve of Etodolac**

The solution which was prepared at the concentration of 2, 6, 10, 14, and 20μg/ml respectively, were scanned on a spectrophotometer in the UV range of 200-400 nm. The spectrum was recorded at 280 nm. The calibration curve was plotted as concentration vs. absorbance.

**Fourier transforms infrared (FTIR) spectroscopy**

Compatibility studies of the drug and the polymers were carried out using an FTIR spectrometer. 1 part of the sample is mixed thoroughly with 3 parts of dried potassium bromide and it was compressed into thin pellets. The pellets are then scanned under the IR region from 4000 cm⁻¹ to 400 cm⁻¹.

**Preparation of Transdermal patches:**

- Transdermal patches were prepared by using the solvent casting method. Different ratios of polymers are accurately weighed and dissolved in ethanol: water (1:1) solution and kept aside to form a clear solution. The Drug was dissolved and mixed until a clear solution was obtained.
- To this solution Glycerine (20% v/v of polymer composition) and Permeation enhancers (DMSO) of different concentration was added and stirred.
- The 10ml of the prepared solution was cast on a Petri dish.
- A funnel of suitable size was inverted over the Petri dish.
- Casting solvent was then allowed to evaporate for 24h to obtain dry patches.
• After 24 hrs, the dried patches are taken out, wrapped in aluminium foil, packed in self-sealing covers, and stored in desiccators for further studies (evaluation).

**Steps toward formulation development:**

**Calculation of flux and drug loading**

Potts and Guy showed to formulate an empirical relationship between Kp and two simple characteristics of the permeant; the octanol-water partition coefficient (Koct) and the molecular weight (MW).

\[
\log Kp \text{ (cm/hour)} = -2.72 + 0.71 \log Koct - 0.0061 \text{MW} \quad \ldots \quad (1)
\]

It must be realized that it is not the permeability coefficient alone that determines the efficiency of topical and transdermal delivery. It is the flux across the skin, which is the product of the permeability coefficient and the drug concentration in the vehicle. The maximum achievable flux is, therefore, Kp multiplied by the aqueous solubility (Sw).

\[
\text{Flux} = \log Kp \times Sw \quad \ldots \quad (2)
\]

**Calculation of Etodolac transdermal dose:**

From equation (1),

The permeability coefficient was computed to be 3.5911, the determined flux was determined to be 0.14077mg/cm²/hour, and finally, the dose was fixed to be 16.90mg/10 cm².

The selection of dose for oral dosage form was based on the following:

• **STEP 1: Calculation of permeability coefficient**

\[
\log Kp \text{ (cm/hour)} = -2.72 + 0.71 \log Koct - 0.0061 \text{MW}
\]

\[
\log Kp \text{ (cm/hour)} = -2.72 + (0.71 \times 11.4) - (0.0061 \times 287.359)
\]

\[
\log Kp = 3.5911
\]

• **STEP 2: Calculation of flux**

\[
\text{Flux} = \log Kp \times SW = 3.5911 \times 0.0392 = 0.14077 \text{mg/cm}^2/\text{hour}
\]

• **STEP 3: Calculation of dose for 10 cm²/12 hour**

\[
\text{Dose} = \text{flux} \times 10 \times 12 = 16.90 \text{mg/10 cm}^2/\text{12 hours.}
\]

The patches were prepared on Petri Plates.

The formula was calculated for the total area of patch spread on the Petri plates:

\[
\text{Radius}^2 \text{ of taken Petri plate was 4.5cm,}
\]

\[
\text{Area of film spread = 63.58 cm}^2
\]

\[
\text{Dose calculated = 16.90mg/10 cm}^2
\]

\[
\text{Drug load = 63.58/10 \times 16.90 = 107.45 mg/63.58 cm}^2
\]

**Evaluation of Transdermal patches:**

**Physical appearance:**

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

**Thickness:**

The thickness uniformity of the transdermal patch was recorded at three different places using a screw gauge and the average thickness was determined. (std value:- 0.12mm to 0.20mm)

**FORMULA DESIGN:**

<table>
<thead>
<tr>
<th>FR Code</th>
<th>Drug (mg)</th>
<th>Polymer ratio</th>
<th>Ethanol (ml)</th>
<th>Water (ml)</th>
<th>DMSO (%)</th>
<th>Glycerine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107.45</td>
<td>1:1</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>107.45</td>
<td>1:2</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>107.45</td>
<td>1:3</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>107.45</td>
<td>1:1</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>107.45</td>
<td>1:2</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>107.45</td>
<td>1:3</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>107.45</td>
<td>1:1</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>107.45</td>
<td>1:2</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
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<td>1:3</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>107.45</td>
<td>1:1</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>11</td>
<td>107.45</td>
<td>1:2</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>107.45</td>
<td>1:3</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

**Table 1:** Formulation table of ETODOLAC transdermal patches.
Weight Uniformity.\textsuperscript{28}

For each formulation, three randomly selected patches were used. For the weight variation test, 3 patches from each batch were weighed individually and the average weight was calculated.

Folding Endurance.\textsuperscript{29,30}

Evaluation of folding endurance involves determining the folding capacity of the patch subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the patch of a specific area (2×2 cm) at the same place until breaks. The number of times the films could be folded at the same place without breaking is the folding endurance value.

Percentage moisture absorption.\textsuperscript{31}

The percent moisture absorption test was carried out to check the physical stability and integrity of the patch in highly humid conditions. In the present study, the moisture absorption capacities of the patches are determined in the following manner. The patches were placed in the desiccators containing 200ml saturated solution of potassium chloride, to get the humidity inside the desiccators at 84%RH. After 3 days patches were taken and weighed the percentage moisture absorption of the patch was found.

\text{Percentage moisture absorbed} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100

Percentage moisture loss.\textsuperscript{32}

The patches were weighed accurately and kept in a desiccator containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The moisture loss was calculated using the formula.

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

Water Vapour transmission rate (WVTR).\textsuperscript{34}

The water vapor transmission rate (WVTR) of the film was measured by the modified ASTM E96 method. The film was sealed on the top of a glass vial (4 ml) containing 2.5 ml of distilled water (100%RH; 3169 Pa vapor pressure at 25°C), which was placed in a desiccator at 25°C and 0% RH containing fused calcium chloride (0 Pa water vapor pressure). The vials are weighed every 24 hrs for 1 week. The amount of water vapor permeated through the films detainted from the weight loss. WVTR and water vapor permeability (WVP) were calculated using the formula.

\begin{align*}
\text{WVTR} &= \frac{\Delta W}{\Delta t} \times A \\
\text{WVP} &= \frac{\text{WVTR}}{\Delta P} \times L
\end{align*}

where WVTR is in g/h m\textsuperscript{2}, \(\Delta W/\Delta t\) is the rate of water gain in g/h, \(A\) is the exposed area of the film in m\textsuperscript{2}, \(L\) is the mean thickness of film specimens in m, and \(\Delta P\) is the difference in partial water vapor pressure between the two sides of film specimens in Pa. The water vapor pressure on the high-stream side of the film was 3.169 kPa (i.e., saturated water vapor pressure at 25°C), while the low-stream side is assumed to be zero. Three replicates of the determinations were done.

Drug content.\textsuperscript{35}

The prepared drug contained patches specified surface area of 2cm\textsuperscript{2} and was cut and transferred into a graduated glass stopper flask containing 100ml of phosphate buffer 7.4. The flask was shaken for 4hrs on a mechanical shaker. Then the solution was filtered through 42 number Whatman filter paper and 1ml was diluted to 10ml with phosphate buffer the absorbance was measured at 280nm using a placebo patch solution as blank and the drug content was calculated.

\% Drug content = \frac{\text{Actual weight of drug}}{\text{Theoretical weight of drug}} \times 100

In vitro diffusion studies.\textsuperscript{36}

In vitro, skin permeation studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 20ml. The egg membrane was mounted between the donor and receptor compartments of the diffusion cell. The formulated patches were cut into sizes 2cm\textsuperscript{2} and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50rpm; the temperature was maintained at 37±0.5°C. The samples of 1ml have withdrawn at
intervals of 30mins, 1, 2, 3, 4, 5, 6, 7, 8, and 24 hrs and, were analyzed for drug content spectrophotometrically at 276nm against blank. 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 centimeter patches were plotted against time.

Kinetics/release pattern of selected formulation F6. For analyzing the mechanism of drug release kinetics of patch F6, the data obtained were fitted to various kinetic equations of zero order, first order, Higuchi model and, Korsmeyer-Peppas model. The regression coefficient was calculated. Graphs of kinetic models were plotted with suitable data.

RESULTS AND DISCUSSION

RESULTS:

Preformulation studies

Preformulation studies of Etodolac was carried out based on the following parameters

Organoleptic properties of the Drug

The drug was identified on based organoleptic properties. Etodolac is a white crystalline-colored powder; it is odorless, bitter in taste, and appeared as a Fluffy powder.

The melting point of Drugs

The normal range of the melting point of Etodolac is 146°C, which shows that the melting point of the drug was lying within the range(145-148°C). The melting point indicates the purity of the drug.

Solubility of Drug

Etodolac was freely soluble in DMSO, soluble in anhydrous ethanol, methanol, and chloroforms, very slightly soluble in water which shows it is lipophilic in nature.

Determination of λ max of Etodolac

The λ max of the Etodolac was found to be 276.6nm in phosphate buffer 7.4.

Calibration curve of Etodolac.

<table>
<thead>
<tr>
<th>SL NO</th>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0.1748±0.0005</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0.3992±0.0003</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>0.6618±0.0006</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>0.865±0.0003</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>1.2294±0.0003</td>
</tr>
</tbody>
</table>

Fourier transform infrared (FTIR) interaction Studies

![Figure 3: FTIR Spectra of Etodolac.](image)

![Figure 4: FTIR Spectra of comparison.](image)
Table 3: Physicochemical evaluation data of Etodolac transdermal patches

<table>
<thead>
<tr>
<th>FR code</th>
<th>Thickness (mm)*</th>
<th>Weight uniformity (gm)*</th>
<th>Folding Endurance*</th>
<th>%Moisture Absorption*</th>
<th>%Moisture Loss*</th>
<th>WVT (g/cm²)</th>
<th>Drug content*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.123±0.005</td>
<td>2.74±0.748</td>
<td>100±0.816</td>
<td>25±0.161</td>
<td>16.66±0.013</td>
<td>1.533*10^8</td>
<td>72.40±0.461</td>
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<tr>
<td>F2</td>
<td>0.156±0.005</td>
<td>3.95±1.076</td>
<td>100±1.247</td>
<td>24±0.135</td>
<td>16.66±0.020</td>
<td>2.265*10^8</td>
<td>67.18±0.372</td>
</tr>
<tr>
<td>F3</td>
<td>0.190±0.010</td>
<td>3.01±0.886</td>
<td>100±0.471</td>
<td>25±0.052</td>
<td>33.33±0.012</td>
<td>2.567*10^8</td>
<td>82.44±0.596</td>
</tr>
<tr>
<td>F4</td>
<td>0.120±0.010</td>
<td>2.74±0.748</td>
<td>100±0.471</td>
<td>33.33±0.227</td>
<td>33.33±0.016</td>
<td>1.135*10^8</td>
<td>82.06±0.037</td>
</tr>
<tr>
<td>F5</td>
<td>0.150±0.010</td>
<td>1.17±0.392</td>
<td>100±1.247</td>
<td>25±0.183</td>
<td>16.66±0.012</td>
<td>1.354*10^8</td>
<td>81.71±0.156</td>
</tr>
<tr>
<td>F6</td>
<td>0.173±0.005</td>
<td>1.66±0.454</td>
<td>100±1.247</td>
<td>14.28±0.025</td>
<td>10.11±0.012</td>
<td>2.437*10^8</td>
<td>98.32±0.824</td>
</tr>
<tr>
<td>F7</td>
<td>0.126±0.005</td>
<td>3.41±0.932</td>
<td>100±1.633</td>
<td>33.33±0.021</td>
<td>25±0.008</td>
<td>1.755*10^8</td>
<td>81.78±1.038</td>
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<tr>
<td>F8</td>
<td>0.150±0.010</td>
<td>1.97±0.538</td>
<td>100±2.867</td>
<td>24.61±0.013</td>
<td>25±0.020</td>
<td>1.192*10^8</td>
<td>80.51±0.954</td>
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<tr>
<td>F9</td>
<td>0.186±0.011</td>
<td>2.16±0.529</td>
<td>100±2.867</td>
<td>29.5±0.031</td>
<td>16.66±0.037</td>
<td>3.319*10^8</td>
<td>78.87±1.124</td>
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<tr>
<td>F10</td>
<td>0.123±0.005</td>
<td>3.13±0.855</td>
<td>100±2.449</td>
<td>34±0.045</td>
<td>33.33±0.021</td>
<td>1.597*10^8</td>
<td>74.27±0.738</td>
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<tr>
<td>F11</td>
<td>0.153±0.005</td>
<td>1.33±0.444</td>
<td>100±2.867</td>
<td>15.6±0.020</td>
<td>12.33±0.029</td>
<td>1.868*10^8</td>
<td>95.35±1.106</td>
</tr>
<tr>
<td>F12</td>
<td>0.186±0.005</td>
<td>1.65±0.450</td>
<td>100±2.449</td>
<td>20±0.024</td>
<td>25±0.021</td>
<td>1.626*10^8</td>
<td>85.26±1.441</td>
</tr>
</tbody>
</table>

Table 4: In vitro cumulative drug release of etodolac transdermal patches

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Time (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>F1</td>
<td>0.148</td>
</tr>
<tr>
<td>F2</td>
<td>0.242</td>
</tr>
<tr>
<td>F3</td>
<td>0.186</td>
</tr>
<tr>
<td>F4</td>
<td>0.116</td>
</tr>
<tr>
<td>F5</td>
<td>0.191</td>
</tr>
<tr>
<td>F6</td>
<td>0.228</td>
</tr>
<tr>
<td>F7</td>
<td>0.94</td>
</tr>
<tr>
<td>F8</td>
<td>0.96</td>
</tr>
<tr>
<td>F9</td>
<td>0.78</td>
</tr>
<tr>
<td>F10</td>
<td>0.65</td>
</tr>
<tr>
<td>F11</td>
<td>0.252</td>
</tr>
<tr>
<td>F12</td>
<td>0.111</td>
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</tbody>
</table>

Figure 5: %Cumulative drug release of Etodolac transdermal patches of different combination
Table 5: Data of regression coefficient of different kinetic models

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero order (R²)</th>
<th>The first order (R²)</th>
<th>Higuchi (R²)</th>
<th>Korsmeyer-Peppas (R²)</th>
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<tr>
<td>F6</td>
<td>0.9362</td>
<td>0.6254</td>
<td>0.9726</td>
<td>0.9846</td>
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</table>

Kinetics/release pattern of selected formulation F6.

For analyzing the mechanism of drug release kinetics of the patch F6, the data obtained were fitted to various kinetic equations of zero order, first order, Higuchi model and Korsmeyer-Peppas model. The regression coefficient was calculated. Graphs of kinetic models that were plotted with suitable data are shown in the following Figure and regression coefficients.

Physical appearance:

All the patches were evaluated for their physical appearance, and they were found to be transparent, smooth, uniform, and flexible.

Thickness:

The thickness of the optimized patches was varied from 0.123±0.005mm to 0.190±0.005mm for MC: HPMC, 0.120±0.010mm to 0.173±0.005 for MC: EC, 0.126±0.005mm to 0.186±0.011mm for MC: PVA, 0.123±0.005mm to 0.186±0.005mm for MC: EUD L-100. 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 drugs from the patch. Low SD values in the patch ensure uniformity of the patches prepared by solvent casting technique.

Weight Uniformity:

The weights ranged between 2.74±0.748 gm to 3.01±0.886 gm for MC: HPMC patches, 2.74±0.748 gm to 1.66±0.454 gm for MC: EC patches and 3.41±0.932 gm to 2.16±0.529 gm for ME: PVA, 3.13±0.855 gm to 1.65±0.450 gm for MC: EUD L-100, which indicates that different batches patch weights, were relatively similar. Weights of hydrophilic: hydrophilic patches are more compared to weights of hydrophilic:hydrophobic. There were no significant differences (p>0.05) in the weights of the patches within and among the batches while this was also the case with the patch’s thickness within the batches but not among the batches.

Folding Endurance:

Folding endurance was measured manually; patches were folded 100 times maximum all patches pass the test. Folding endurance results indicated that the patches would not break and would maintain their integrity with general skin folding when applied. The folding endurance was found to be best in the all-prepared patches containing DMSO as a penetration enhancer.

Percentage moisture absorption:

Hydrophilic: Hydrophilic (MC: HPMC, MC: PVA) patches absorbed the highest amount of moisture (25±0.161-24±0.135, 33.3±0.021-24.6±0.013) and Hydrophilic: Hydrophobic (MC: EC, MC: EUD L-100) patches absorb the least amount of moisture (14.28±0.025-23.33±0.227, 15.6±0.200-24.0045). The moisture content is less in hydrophobic polymer used formulations. This could be due to the increased hydrophobic nature of the polymers.

DISCUSSION

Compatibility Studies by FTIR:

Compatibility studies of the drug and the polymers were carried out using Shimadzu–FTIR spectrometer. The Infrared (IR) spectra of Etodolac and physical mixtures with Etodolac, MC, HPMC, EC, PVA, and EUD L-100 were recorded by FTIR spectrometer as shown. The spectra of Etodolac were shown to exhibit the peak at 3340 cm⁻¹: N-H stretching; 2971 cm⁻¹; N-H stretching: CN stretching, 2359 cm⁻¹: C=O stretching, 1739 cm⁻¹ for C-H bending, 1411 cm⁻¹ vibrations. From the characteristic peak, it was observed that the chemical integrity of the drug was not disturbed in both physical mixtures and polymer. This proves that there is potential compatibility between drugs and excipients.

Evaluation of Transdermal patches:

A Total of 12 Etodolac formulations were prepared from different polymeric concentrations (hydrophilic-hydrophobic) and permeation enhancers (DMSO) as shown in table 5.3. The results of thickness, Weight uniformity, folding endurance, %Moisture absorption, %Moisture loss, WVT, and %Drug content are shown in Table 2. In-vitro drug release results are shown in Tables 3. Kinetic studies of the best formulation.
matrix which has less affinity for water which is resulted in decreased moisture absorption. Low moisture absorption protects the patch from microbial contamination and bulkiness of the patches. Which helps in the shelf life of the patches.42

Percentage moisture loss:
The percentage of moisture loss was found more in MC: HPMC and MC: PVA patches ranging from 16.66±0.013% to 33.33±0.012% and 16.66±0.037% to 25±0.008, the lowest moisture loss was found in MC:EC and MC : EUD L-100 patches ranged from 10.11±0.012% to 23.33±0.016% and 12.33±0.029% to 25±0.021%. The moisture loss varied with different polymers. It was found that batches containing MC:EC were best in terms of moisture loss since they had a minimum water loss, due to hydrophobic polymeric concentration (1:3). The less moisture loss in the formulations helps the patch to remain stable, brittle, and free from complete drying.43

Water Vapour transmission rate (WVTR):
Water vapor transmission studies were carried out to determine the permeability characteristics of the transdermal patches. The water vapor transmission rates for the prepared patches ranged from 1.533*10^8 g/cm^2 to 2.567*10^8 g/cm^2 for MC:HPMC, 1.135*10^8 g/cm^2 to 2.437*10^8 g/cm^2 for MC:EC an d 1.192*10^8 g/cm^2 to 3.319*10^8 g/cm^2 for MC : PVA patches, 1.597*10^8 g/cm^2 to 1.868*10^8 g/cm^2 for MC: E UD L-100 patches, indicating that all the formulations were permeable to water vapor. M: EUD L-100 has less water vapor transmission rate compared to other prepared patches, showing Eudragit polymer shows low permeability than other polymers. The low water vapor transmission rates again emphasize the stability aspects of long-term storage.44,45

Drug Content:
The drug content ranged from 67.18±0.372% to 82.44±0.596% for MC: HPMC and for MC: PVA : 78.87±1.124 to 81.78±1.038. Percentage drug content was found to be highest for MC: HPMC patches when compared to MC: PVA patches. Good uniformity of drug content among the batches observed with the formulations of MC: EC patches ranged from, 81.7±10.156% to 98.32±0.824% and Drug content for MC:EUD L-100 patches were found to be 74.27±0.738% to 95.35±1.106%. The results indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability, which was determined using an ELICO spectrophotometer.36-49

In vitro diffusion studies:
The cumulative percentage release of Etdolac from prepared transdermal patches was investigated for 24h, shown in Table 6.3. In vitro drug release at the end of 24 h for MC: HPMC patches relationship can be established as F3>F2>F1, For MC: EC patches drug release from F4 to F6 was found to be F6>F5>F4, For MC: PVA patches drug release from F7 to F9 was found to be F7>F9>F8, For MC:EUD L-100 patches drug release from F10 to F12 was found to be F11>F10>F12. The in-vitro diffusion studies of various formulations were carried out to indicate the influence of various polymeric concentrations on the release of the drug. From the above results the best formulation was F6 the drug release was 97.70% at the end of 24Hrs. The cumulative amounts of drug released per square centimeter of patches were plotted against time were shown in Figure No 5.50

Kinetics/release pattern of selected formulation F6.
The Korsmeyer–Peppas model was applied to release profiles to determine the diffusion types. After the Korsmeyer–Peppas model application, the diffusion exponent, which is indicative of the release mechanism (n), was found for all samples. The n = 0.45 value indicates Fickian diffusion, while values between 0.45 and 1.00 suggest non-Fickian transport and values higher than 1.00 suggest case II transport of a drug which indicates the release of drug is independent on time.51

CONCLUSION
All the formulations showed good physicochemical properties such as thickness, weight uniformity, folding endurance, Water vapor transmission rate, moisture loss, moisture uptake, and drug content. The in vitro release data showed that drug release from the patch has been affected by the type and concentration of the polymer and it was concluded that MC: EC was the best polymer compared to other combinations. Among three formulations i.e., F4, F5, and F6 with different concentrations of MC: EC, formulation F6 shows more drug release and drug content. From this data, it was concluded that F6 is the optimized formulation.

The best formulation was found to be F6 containing (1:3) % of Methylcellulose and Ethyl cellulose showed an optimum drug release rate for 24h and extent of drug release was 97.70%, thickness (0.173mm), weight uniformity (0.166gm), folding endurance (100 times), %moisture absorbed (14.28%), %moisture loss (10.11%), WVTR (2.437*10^8 g/cm^2) and %drug content (98.32%).

Based on the observations, it can be concluded that the attempt at formulation and evaluation of Transdermal patches of an Anti-inflammatory drug was found to be successful in the release of the drug for an extended period of 24hrs

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