FORMULATION AND EVALUATION STUDIES ON TRANSDERMAL DOSAGE FORMS OF DICLOFENAC SODIUM

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ABSTRACT
The aim of the present study was to prepare and evaluate matrix type transdermal patches of Diclofenac sodium by using Hydroxy propyl methyl cellulose K15 (HPMCK15) and different grades of Eudragit (RL100, RS100, RLPO, RSPO) as polymers to minimize adverse effects associated with oral administration. Transdermal patches of Diclofenac sodium were prepared by solvent evaporation method by varying the blend ratios of HPMCK15 and Eudragit. The drug polymer interaction studies were carried out by FT-IR studies. The prepared patches were evaluated for their thickness, weight variation, folding endurance, percentage moisture absorption, percentage moisture loss and drug content. In vitro drug release was determined by using Franz diffusion cell in phosphate buffer (pH 7.4). The release data was studied for various kinetic parameters to understand the mechanism of drug release from the developed formulations. IR studies revealed that the drug, polymer and excipients were compatible with each other. Thin, flexible, smooth and uniform films were obtained with Eudragit and HPMC using dibutyl phthalate as plasticizer. Thickness, weights and drug contents of all the formulations remained almost uniform with low SD values. The formulations F7, F8 showed good release of drug than marketed formulation. Formulations contain Eudragit RLPO and HPMC K15, Eudragit RL100 and HPMC K15 showed good release when compared to the formulations contain Eudragit RSPO and HPMC K15. Studies have shown promising results and there is a scope for further pharmacokinetic evaluation.

Keywords: Diclofenac sodium, Hydroxy propyl methyl cellulose K15, Eudragit RL100, RS100, RLPO, RSPO, Release Kinetics.
INTRODUCTION

Transdermal therapeutic systems (TTS) are defined as self-contained discrete dosage forms when applied to the intact skin, deliver the drugs through skin at a controlled rate to the systemic circulation. Thus it is anticipated that transdermal drug delivery systems (TDDS) can be designed to input drugs at appropriate rates to maintain suitable plasma drug levels for therapeutic efficacy by using skin as the port \cite{1,2}.

Drug administration in conventional dosage forms like tablets, capsules, injectables or ointments cause fluctuations in drug concentrations in blood stream and tissues may lead undesirable toxicity and efficiency. The successful development of TTS depends on a pondered choice of drug, which should be non-irritant and cross the skin in adequate amounts to produce the therapeutic effect. Drugs produce these effects in small amounts with molecular weight range of 100-800 Da are ideal candidates for TDDS\cite{3}.

Transdermal route offers several advantages over other routes for the delivery of drugs with systemic activity. It provides a continuous mode of administration at rates approaching zero-order similar to that provided by an I.V Infusion and the delivery is non-invasive, no hospitalization is required. Additionally, the transdermal route as compared with the oral route reduces drug degradation at the site of administration due to its lower metabolic activity. Once the drug is absorbed, the hepatic circulation is by-passed, thus avoiding another major site of potential drug inactivation \cite{4,5}.

With the concept of delivering drug into the skin for both local effects in dermatology and through the integument for the systemic treatment of disease states can be achieved. This later process has been brought into sharp focus in recent years by the efforts of pharmaceutical field to develop transdermal delivery devices to treat motion sickness, angina, hormone deficiency and hypertension \cite{6,7}.

“Transdermal drug delivery systems are adhesive, drug containing devices of defined surface area that deliver a pre-determined amount of drug to the surface of intact skin at a pre-programmed rate. These systems provide drug systemically at a predictable rate and maintain the rate for extended periods of time.”

The skin site for transdermal drug administration: \cite{8-10}

The skin is one of the most extensive and readily accessible organ with a thickness of 2.97 ±
0.28 mm. It separates the underlying blood circulation network and viable organs from the outside environment. It serves as a barrier against physical and chemical attacks and shields the body from invasion by microorganisms. Microscopically the skin is a multilayered organ composed of anatomically many histological layers, but it is generally described in terms of three tissue layers; the epidermis, dermis and subcutaneous tissue.

Fig 1: Anatomy of the Skin

Fig 2: Permeation pathways of skin
REVIEW OF LITERATURE

Patel RP et al., [11] developed a matrix-type transdermal therapeutic system containing drug Aceclofenac with different ratios of hydrophilic (hydroxypropyl cellulose) and hydrophobic (ethyl cellulose) polymeric systems using 15 % w/w of dibutyl phthalate as plasticizer. Different concentrations of oleic acid and isopropyl myristate were used to enhance the transdermal permeation of drug. Formulation prepared with hydrophilic polymer containing permeation enhancer showed best in vitro skin permeation through albino rat skin as compared to all other formulations. These results indicated that the formulation containing 15 % of oleic acid with 10 % Isopropyl myristate give better penetration through rat skin.

Patel KN et al., [12] developed a matrix transdermal therapeutic system containing drug Diclofenac sodium with different concentrations of oleic acid, labrasol, triacetin as transdermal permeation enhancers. Formulation containing 5% drug, 85% adhesive solution, 10% triacetin found to be best formation which showed best release of Diclofenac sodium.

Hemanth B et al., [13] done study on effect of Diclofenac sodium patches with respect to oral dosage forms on human volunteers. Twenty young pre-orthodontic patients requiring bilateral maxillary and mandibular first premolar extractions were selected for the study. From this study observed that gradual increase in the pain relief scores and gradual decrease in the pain intensity score with both oral dosage forms as well as transdermal patches. But patient compliance was increased with transdermal patches formulations.

Sanjay D et al., [14] developed matrix type transdermal patches of carvedilol by using hydroxy propyl methyl cellulose (HPMC) and eudragit RS100 as polymers with different ratios and dibutyl phthalate and propylene glycol as plasticizer and permeation enhancer respectively. In vitro release studies indicate that patches containing hydroxyl propyl methyl cellulose, eudragit RS100 in the ratio of 1:4 showed best release. The formulation containing 30% w/w propylene glycol has exhibited better enhancement for the permeation of carvedilol.

Hamang K et al., [15] has developed controlled release transdermal patches of sertaconazole nitrate by using Ethyl cellulose (EC) and poly vinyl pyrrolidone (PVPK-30) with different ratios and dibutylphthalate as plasticizer. In vitro diffusion studies were performed by using cellulose nitrate membrane in modified Franz diffusion cell in buffer pH 7.4. Permeation
studies illustrated that the ratio of poly vinyl pyrrolidine and ethyl cellulose 1:5 showed good controlled release.

**Gudapa RR et al.,** [16] formulated matrix transdermal patches of an antihypertensive drug candesartan cilexetil using blends of two different polymeric combinations HPMCK100 and eudragit RL100, prepared formulations were subjected to various physicochemical evaluations and *in vitro* release study by using commercial semi permeable membrane. All the formulations exhibited good physicochemical characteristics. *In vitro* release showed that the formulation containing 400 mg HPMCK100 and 100 mg Eudragit RL100 showed faster release when compared to other formulations.

**Madhulatha A et al.,** [17] developed sustained release transdermal patches containing Ibuprofen with different ratios of chitosan and hydroxyl propyl methyl cellulose (HPMC) and combination of chitosan- HPMC by solvent evaporation technique. Prepared films were evaluated for physicochemical characteristics like thickness, weight variation, moisture content, moisture loss, drug content, and *in vitro* drug permeation study. The *in vitro* permeation studies using rat skin the formulation contain 0.2% plain chitosan and HPMC showed 86% drug release in 24 h.

**Updesh BL et al.,** [18] developed transdermal patches of budenoside by using different polymers with like eudragit RL100, eudragit RS100, ethyl cellulose and PVP with different ratios and PEG-400, urea and dimethyl sulfoxide (DMSO) as plasticizer and permeation enhancers respectively. Prepared films were evaluated for different characteristics like thickness, weight uniformity, moisture uptake, water vapor transmission study, moisture loss, drug content, and *in vitro* drug permeation study. Based on these studies patches containing PVA and Eudragit RL 100 patches provide best resistance to water vapor which provided better drug permeation.

**Ting Li et al.,** [19] formulated transdermal patches of indomethacin, Mascos 10 (poly acrylic acid type) pressure sensitive adhesive was used to prepare a drug-in-adhesive type patch containing a variety of permeation enhancers like azone, L-methanol, 2-isopropyl-5-methylcylohexyl heptanoate (M-HEP), isopropyl myristate (IPM), tween-80 and oleic acid. It was noted that patches containing Azone and L-ethanol showed increased indomethacin permeation than patches containing IPM, oleic acid and tween-80.
MATERIALS AND METHODS

Diclofenac sodium and Eudragit (RL100, RS100, RLPO, RSPO) were procured as gift samples from Corpuscle research solutions (Visakhapatnam), Poly vinyl alchohol (PVA) from Rolex Chemical Industries (Mumbai), Hydroxyl propyl methyl cellulose K15(HPMC-K15) was supplied by Supra Laboratories (Hyderabad), Di butyl phthalate and Oleic acid from Qualigens Fine Chemicals (Mumbai), Chloroform and Glycerin from S.D. Fine Chemicals (Mumbai). All the materials used in the formulations, evaluations used were of analytical and laboratory grade.

Analytical Method development studies:[20]

Phosphate buffer (pH 7.4) solution: Fifty ml of 0.2M potassium dihydrogen phosphate was taken in 200 ml volumetric flask, to which 39.1 ml of 0.2 M sodium hydroxide solution was added and the volume was made up to the mark with distilled water.

Potassium dihydrogen phosphate (0.2 M) solution: Potassium dihydrogen phosphate (27.218 g) was added to 1000 ml volumetric flask containing distilled water and the volume was made up to the mark with distilled water.

Sodium hydroxide (0.2 M) solution: Eight gram of sodium hydroxide was taken in 1000 ml volumetric flask containing distilled water and volume was made up to the mark with distilled water.

Determination of λ max of Diclofenac sodium in phosphate buffer (pH 7.4):[20]

Preparation of Diclofenac sodium standard stock solution (1000 µg/ml) in Phosphate buffer (pH 7.4) Standard stock solution of Diclofenac sodium was prepared by dissolving accurately weighed 100 mg of Diclofenac sodium in the little quantity of phosphate buffer (pH 7.4) in 100 ml volumetric flask. The volume was then made up to 100 ml by using phosphate buffer (pH 7.4) to obtain the solution of 1000 µg/ml. From the standard stock solution, 1 ml was diluted to 100 ml with phosphate buffer solution (pH 7.4). The resulting solution containing 10µg/ml was scanned between 200 to 400 nm.

Calibration curve of Diclofenac sodium in phosphate buffer solution (pH 7.4): [21] From the Diclofenac sodium standard stock solution (1000 µg/ml), 10 ml solution was diluted to 100 ml using 7.4 pH phosphate buffer solutions (100 µg/ml). From this 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1 ml of solutions were taken into different volumetric flasks and made up to 10ml with
phosphate buffer solution (pH 7.4) so as to get the concentrations of 2 µg, 4 µg, 6 µg, 8 µg, and 10 µg respectively. The absorbances of these solutions were measured at λ max 274 nm.

**PREFORMULATION STUDIES**

**Determination of melting point:** [22] Melting point of the drug was determined by taking small amount of drug in a capillary tube closed at one end. The capillary tube was placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed thrice and average value was noted.

**Determination of solubility:** [23] The solubility of Diclofenac sodium was determined by adding excess amount of drug to measured volume of distilled water in a glass vial to get a saturated solution. The solution was sonicated and kept at room temperature for the attainment of equilibrium. The concentration of Diclofenac sodium was determined spectrophotometrically by measuring at 274 nm after 24 h.

**Determination of pH:** [24] The pH of Diclofenac sodium was determined using potentiometer for freshly prepared 1% aqueous solution of Diclofenac sodium.

**Determination of partition coefficient:** [25] The known quantity of Diclofenac sodium was added into 5 ml of 1-octanol and it was mixed with 5 ml of water in a separating funnel. Then two phases were allowed to equilibrate at 37°C for 24 h with intermittent shaking. The concentration of the drug in the aqueous phase and organic phase was determined by UV spectroscopic method after necessary dilution. The apparent partition coefficient (Kp) was calculated as the ratio of drug concentration in each phase by the following equation.

\[
\text{Partition coefficient of the drug (Kp)} = \frac{\text{Concentration of the drug in organic phase}}{\text{Concentration of the drug in aqueous phase}}
\]

**Drug excipient compatibility (FTIR) study:** [26,27] Pure drug Diclofenac sodium and polymers were subjected for FTIR spectroscopic analysis for compatibility studies and to ascertain whether there was any chemical interaction between the drug and the polymers used. The FT-IR spectra of Diclofenac sodium pure drug and Diclofenac sodium with polymers are studied for absence of drug polymer interaction.

**Preparation of transdermal patches of Diclofenac sodium:** [28] Transdermal patches of Diclofenac sodium were prepared by solvent evaporation technique. Required quantities of
Diclofenac sodium and HPMC-K15 and Eudragit (RS100, RL100, RSPO, RLPO) and DBP etc. were weighed as per formulations shown in table 5. To these mixtures required quantity of solvent chloroform was added. This solution poured in moulds containing dried PVA laminates which were prepared by dissolving PVA in water with continuous stirring and heating. Then this drug polymer mixture solution allowed to air dry for 24 h at room temperature. After drying the patches were peeled from mould and wrapped in aluminum foil and stored in desiccator for further studies.

**Evaluation of transdermal patches of Diclofenac sodium** [29, 30, 31, 32]

**Physical appearance:** The prepared patches were physically examined for colour, clarity and surface texture.

**Thickness uniformity:** The thickness of patches was measured by using electronic caliper, with a least count of 0.01mm. Thickness was measured at three different points on the film and average readings were taken.

**Uniformity of weight:** The patch of size 1x1 cm$^2$ was cut and weight of each patch was taken individually, the average weight of the patch was calculated.

**Folding endurance:** The folding endurance was measured manually for the prepared patches. A strip of patch (2 x 2 cm$^2$) was cut and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

**Percentage moisture loss:** The patches were weighed individually and kept in a desiccators containing calcium chloride. The final weight was noted when there was no change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

**Percentage moisture uptake:** The patches were weighed accurately and placed in a desiccators where a humidity condition of 80-90% RH was maintained by using saturated solution of potassium chloride. The patches were kept until uniform weight is obtained, then taken out and weighed. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.
**Drug content uniformity:** The patches were tested for the content uniformity. The patches of size 1 cm² was cut and placed in a 100 ml volumetric flask. The contents were stirred using a magnetic bead for 24 h to dissolve the patches. Subsequent dilutions were made with phosphate buffer (pH 7.4). The absorbance of the solution was measured against the corresponding blank solution at 274 nm using UV-visible spectrophotometer. The experiment was repeated three more time to validate the result.

**In vitro release studies:** [33, 34] The fabricated patch were cut into 1 cm² and placed on the commercial semi permeable membrane (cellophane membrane) and attached to the diffusion cell such that the cell’s drug releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH 7.4 at 37±1°C. The elution medium was stirred magnetically. The aliquots (2 ml) was withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analyzed for drug content using UV spectrophotometer at 274nm.

**Kinetics of drug release** [34]

In membrane controlled systems, first the drug will partition from reservoir into polymer matrix that comprises the rate controlling membrane. In the membrane, diffusion will occur down the concentration gradient at a rate, which will be controlled by the diffusion coefficient of the drug in the polymer. Once the drug has diffused through the rate controlling membrane, it will partition into skin. Diffusion occurs down the concentration gradient at a rate that is controlled by diffusion of drug in the polymer.

The rate of permeation dQ/dt across various layers of skin can be expressed by the following equation.

\[
d\frac{Q}{dt} = P_s(C_d–C_r) \quad \text{(1)}
\]

Where,

\[C_d = \text{concentration of drug in donor compartment.}\]
\[C_r = \text{concentration of drug in receptor compartment.}\]
\[P_s = \text{overall permeability coefficient.}\]

Whereas \(P_s\) can be defined as follows

\[
P_s = \frac{K_{sd}Dss}{H_s} \quad \text{(2)}
\]
Where,

\[ K_{sd} = \text{partition coefficient of penetrant molecule from system on to the stratum corneum.} \]

\[ D_{ss} = \text{apparent diffusivity for steady state diffusion of penetrant molecule through skin tissue.} \]

\[ H_s = \text{thickness of the skin tissue.} \]

\( P_s \) can be considered as a constant, if \( K_{sd}, D_{ss} \) and \( H_s \) terms in the above equation are constant under a given set of conditions. Equation (1) suggests that to achieve a constant rate of drug permeation, one needs to maintain a condition in which the drug concentration of the surface of stratum corneum \( (C_d) \) is consistently and substantially greater than the drug concentration in the receptor side \( (C_r) \); i.e., \( C_d >> C_r \) under such condition equation (1) can be reduced to,

\[
dQ/dt = P_s C_d \quad \text{---------------- (3)}
\]

The rate of skin permeation \( dQ/dt \) should be constant, if magnitude of \( C_d \) value remains fairly constant throughout the course of skin permeation. To maintain \( C_d \) at a constant value, it is necessary to deliver the drug at a rate \( R_d \) that is either constant or always greater than the rate of skin absorption \( R_a \); i.e., \( R_d >> R_a \). By making \( R_d \) greater than \( R_a \) the drug concentration on the skin surface \( C_d \), is maintained at a level equal to or greater than equilibrium (or saturation) solubility of drug in stratum corneum \( C_s^e \); i.e. \( C_d \geq C_s^e \).

A maximum rate of skin permeation \( (dQ/dt)_m \) was expressed by the following equation.

\[
(dQ/dt)_m = P_s C_s^e \quad \text{---------------- (4)}
\]

Apparently the magnitude of \( (dQ/dt)_m \) is determined by permeability coefficient \( P_s \) of the skin to the drug and equilibrium solubility of the drug in the stratum corneum \( C_s^e \).

**Table 1: Composition of various transdermal patches of Diclofenac sodium**

<table>
<thead>
<tr>
<th>Formulations (mg/ml)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
<th>F11</th>
<th>F12</th>
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</thead>
<tbody>
<tr>
<td>Diclofenac sodium</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<td>50</td>
<td>50</td>
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<td>50</td>
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<td>50</td>
</tr>
<tr>
<td>Eudragit RL 100</td>
<td>100</td>
<td>200</td>
<td>300</td>
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<tr>
<td>Eudragit RS PO</td>
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<td>--</td>
<td>100</td>
<td>200</td>
<td>300</td>
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<tr>
<td>Eudragit RL PO</td>
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<td>--</td>
<td>100</td>
<td>200</td>
<td>300</td>
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<tr>
<td>Eudragit RS 100</td>
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<td>--</td>
<td>--</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>--</td>
</tr>
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<td>HPMC K15</td>
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<td>400</td>
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<td>500</td>
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<td>300</td>
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<td>DBP</td>
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<td>0.25</td>
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<td>0.25</td>
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<tr>
<td>Oleic acid</td>
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<td>0.1</td>
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<tr>
<td>Chloroform</td>
<td>15</td>
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<td>15</td>
<td>15</td>
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<td>15</td>
<td>15</td>
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</tr>
</tbody>
</table>

-- : No ingredient was added. HPMC: Hydroxy Propyl methyl cellulose. DBP: Dibutyl phthalate.
RESULTS

Fig 3: UV spectrum of Diclofenac sodium in pH 7.4 phosphate buffer solution

\[ y = 0.0356x + 0.0095 \]
\[ R^2 = 0.9993 \]

Fig 4: Standard graph of Diclofenac sodium in pH 7.4 phosphate buffer

\[ y = 0.0356x + 0.0095 \]
\[ R^2 = 0.9993 \]

Table 2: Preformulation studies of Diclofenac sodium

<table>
<thead>
<tr>
<th>S.no</th>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Melting point</td>
<td>282 ± 1.15°C</td>
</tr>
<tr>
<td>2</td>
<td>Solubility</td>
<td>35mg/ml</td>
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<tr>
<td>3</td>
<td>Partition coefficient</td>
<td>3.52</td>
</tr>
<tr>
<td>4</td>
<td>pH</td>
<td>3.47</td>
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</tbody>
</table>
Fig 5: IR spectrum of Diclofenac sodium pure drug

Fig 6: IR spectrum of F7 formulation

Fig 7: IR spectrum of F8 formulation
Table 3: Evaluation parameters data of F1 to F12 patch formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness Uniformity</th>
<th>Weight Uniformity</th>
<th>Folding endurance</th>
<th>% moisture absorption</th>
<th>% moisture loss</th>
<th>% DC</th>
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</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.25±0.007</td>
<td>757.96±4.0796</td>
<td>191.66±4.7258</td>
<td>7.656±1.342</td>
<td>5.83±0.0578</td>
<td>95.48±0.7795</td>
</tr>
<tr>
<td>F2</td>
<td>0.23±0.017</td>
<td>767.36±2.2233</td>
<td>132.33±6.1100</td>
<td>8.608±0.3474</td>
<td>6.1±1.0440</td>
<td>98.296±0.6450</td>
</tr>
<tr>
<td>F3</td>
<td>0.24±0.014</td>
<td>760.83±2.1385</td>
<td>150.33±9.6090</td>
<td>7.842±1.7008</td>
<td>2.46±0.3278</td>
<td>97.966±1.1968</td>
</tr>
<tr>
<td>F4</td>
<td>0.24±0.021</td>
<td>784.97±6.0740</td>
<td>82±6.0021</td>
<td>13.726±1.5230</td>
<td>2.14±0.1967</td>
<td>97.546±0.5783</td>
</tr>
<tr>
<td>F5</td>
<td>0.25±0.01</td>
<td>762.96±3.1895</td>
<td>122.33±8.3266</td>
<td>11.962±0.7187</td>
<td>3.19±0.2433</td>
<td>97.783±0.1950</td>
</tr>
<tr>
<td>F6</td>
<td>0.26±0.017</td>
<td>763.93±3.9068</td>
<td>157.66±7.5055</td>
<td>11.008±1.3344</td>
<td>2.03±0.5477</td>
<td>98.506±0.5368</td>
</tr>
<tr>
<td>F7</td>
<td>0.24±0.015</td>
<td>753.03±2.8254</td>
<td>187.66±9.8657</td>
<td>7.626±2.0954</td>
<td>1.76±0.5415</td>
<td>97.116±0.7553</td>
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<tr>
<td>F8</td>
<td>0.25±0.01</td>
<td>764.25±3.0298</td>
<td>132±4.5825</td>
<td>8.170±0.5700</td>
<td>2.40±0.2220</td>
<td>96.876±0.9899</td>
</tr>
<tr>
<td>F9</td>
<td>0.24±0.01</td>
<td>764.14±4.8294</td>
<td>149.33±8.1445</td>
<td>8.292±0.1516</td>
<td>5.4±0.5291</td>
<td>98.59±0.3119</td>
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<tr>
<td>F10</td>
<td>0.27±0.01</td>
<td>769.1±1.3527</td>
<td>84±7.00121</td>
<td>10.870±0.0491</td>
<td>3.84±0.8912</td>
<td>95.503±0.5506</td>
</tr>
<tr>
<td>F11</td>
<td>0.25±0.007</td>
<td>779.13±5.9433</td>
<td>121.66±7.6376</td>
<td>11.04±1.0396</td>
<td>2.07±0.7162</td>
<td>95.803±1.8855</td>
</tr>
<tr>
<td>F12</td>
<td>0.26±0.007</td>
<td>774.26±4.550</td>
<td>157.66±6.1101</td>
<td>11.185±0.5807</td>
<td>3.08±0.6656</td>
<td>91.496±2.8457</td>
</tr>
</tbody>
</table>

± S.D * : Standard deviation of three determinations.

Table 4: *In vitro* cumulative percentage drug release from F1 to F12 patches

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
<th>F11</th>
<th>F12</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>4.0</td>
<td>44.475</td>
<td>32.613</td>
<td>32.798</td>
<td>37.733</td>
<td>34.266</td>
<td>29.403</td>
<td>63.249</td>
<td>60.057</td>
<td>42.847</td>
<td>37.697</td>
<td>30.073</td>
<td>23.346</td>
</tr>
<tr>
<td>5.0</td>
<td>45.887</td>
<td>41.756</td>
<td>33.498</td>
<td>44.190</td>
<td>39.583</td>
<td>30.592</td>
<td>67.453</td>
<td>64.218</td>
<td>59.552</td>
<td>42.834</td>
<td>37.686</td>
<td>30.536</td>
</tr>
<tr>
<td>6.0</td>
<td>53.111</td>
<td>43.570</td>
<td>42.789</td>
<td>50.396</td>
<td>44.772</td>
<td>37.035</td>
<td>71.591</td>
<td>68.303</td>
<td>67.945</td>
<td>49.542</td>
<td>42.837</td>
<td>37.073</td>
</tr>
<tr>
<td>7.0</td>
<td>59.374</td>
<td>54.794</td>
<td>53.778</td>
<td>54.463</td>
<td>49.126</td>
<td>44.196</td>
<td>74.572</td>
<td>70.150</td>
<td>71.340</td>
<td>54.499</td>
<td>49.542</td>
<td>44.866</td>
</tr>
<tr>
<td>8.0</td>
<td>65.487</td>
<td>62.324</td>
<td>60.013</td>
<td>58.282</td>
<td>54.544</td>
<td>50.187</td>
<td>79.947</td>
<td>76.593</td>
<td>74.543</td>
<td>57.057</td>
<td>54.843</td>
<td>49.970</td>
</tr>
</tbody>
</table>

Fig 8: *In vitro* cumulative percentage drug release from F1 to F12 patches
Fig 9: *In vitro* drug release profiles of F7, F8 and Marketed formulation (Nupatch)

Table 5: Results of model fitting of Diclofenac sodium from F1 to F12 patches

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi matrix</th>
<th>Peppas</th>
<th>‘n’</th>
<th>Best fit</th>
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</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.9526</td>
<td>0.9847</td>
<td>0.9893</td>
<td>0.9861</td>
<td>0.5651</td>
<td>Higuchi</td>
</tr>
<tr>
<td>F2</td>
<td>0.9233</td>
<td>0.9362</td>
<td>0.9486</td>
<td>0.9177</td>
<td>0.5462</td>
<td>Higuchi</td>
</tr>
<tr>
<td>F3</td>
<td>0.9389</td>
<td>0.9348</td>
<td>0.9356</td>
<td>0.9283</td>
<td>0.5468</td>
<td>Zero order</td>
</tr>
<tr>
<td>F4</td>
<td>0.9696</td>
<td>0.9945</td>
<td>0.9871</td>
<td>0.9960</td>
<td>0.6172</td>
<td>Peppas</td>
</tr>
<tr>
<td>F5</td>
<td>0.9769</td>
<td>0.9946</td>
<td>0.9822</td>
<td>0.9928</td>
<td>0.6175</td>
<td>First order</td>
</tr>
<tr>
<td>F6</td>
<td>0.9579</td>
<td>0.9681</td>
<td>0.9702</td>
<td>0.9829</td>
<td>0.5584</td>
<td>Peppas</td>
</tr>
<tr>
<td>F7</td>
<td>0.8221</td>
<td>0.9362</td>
<td>0.9521</td>
<td>0.9307</td>
<td>0.5476</td>
<td>Higuchi</td>
</tr>
<tr>
<td>F8</td>
<td>0.8465</td>
<td>0.9462</td>
<td>0.9679</td>
<td>0.9518</td>
<td>0.5402</td>
<td>Higuchi</td>
</tr>
<tr>
<td>F9</td>
<td>0.9610</td>
<td>0.9782</td>
<td>0.9711</td>
<td>0.9732</td>
<td>0.5628</td>
<td>First order</td>
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<tr>
<td>F10</td>
<td>0.9760</td>
<td>0.9853</td>
<td>0.9452</td>
<td>0.9515</td>
<td>0.7036</td>
<td>First order</td>
</tr>
<tr>
<td>F11</td>
<td>0.9927</td>
<td>0.9911</td>
<td>0.9478</td>
<td>0.9515</td>
<td>0.7036</td>
<td>Zero order</td>
</tr>
<tr>
<td>F12</td>
<td>0.9770</td>
<td>0.9707</td>
<td>0.9401</td>
<td>0.9588</td>
<td>0.6263</td>
<td>Zero order</td>
</tr>
<tr>
<td>Marketed patch</td>
<td>0.8313</td>
<td>0.8918</td>
<td>0.9542</td>
<td>0.9274</td>
<td>0.6468</td>
<td>Higuchi</td>
</tr>
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</table>

**DISCUSSION**

The pure sample of Diclofenac sodium was supplied by corpuscle research solutions, Visakhapatnam was used in the present investigation. In the first phase of our study the drug was subjected to various preformulation parameters namely purity, solubility, melting point, partition coefficient and permeability coefficient. The purity of the compound was 99%. The solubility studies indicated that Diclofenac sodium was freely soluble in water 35 mg/ml, phosphate buffer pH 7.4, ethanol, dimethyl sulfoxide, chloroform and methanol respectively. Melting point of Diclofenac sodium was found to be 282±1.15°C. Partition coefficient determination study of Diclofenac sodium was done with n-octanol and water. The partition coefficient value of Diclofenac sodium was found to be 3.52. This indicates that Diclofenac
sodium is lipophilic in nature. The pH of freshly prepared 1% aqueous solution of Diclofenac sodium was found to be 3.47. The $\lambda_{\text{max}}$ of the selected drug was found to be 274 nm and it was used throughout the study for the estimation of the drug in the formulations.

**Analytical studies:** The absorption maximum ($\lambda_{\text{max}}$) was obtained as 274 nm. This implies purity of the sample drug Diclofenac sodium. The $\lambda_{\text{max}}$ of Diclofenac sodium in pH 7.4 was found to be 274 nm which corroborates with literature. The calibration curve of Diclofenac sodium in pH 7.4 phosphate buffer solution shows linearity with $R^2$ of 0.9993.

**Preformulation studies:** Preformulation studies were carried out and the results was indicated to be within the range. The melting point, solubility, partition coefficient parameters were evaluated and the results obtained were corroborated to the existing ones.

**Drug excipient compatibility studies:** As described in the methodology section the Fourier transform infrared spectroscopy studies were carried out for pure drug and drug along with polymers taken respectively. The IR spectra of pure drug and formulations F7 and F8 are shown in Fig 5, 6 and 7 respectively. Due to replication of peaks in IR spectra of formulations as that of pure drug indicated the drug polymer compatibility. In the next step, a total of 12 formulations were prepared using various polymers such as Eudragit, HPMC alone and in combination as per formulae given in table 1.

**Evaluation of transdermal patches:** The transdermal patches of Diclofenac sodium were successfully prepared for the compositions given. The prepared patches were stored in aluminum pouch and preserved in desiccator for further studies. The prepared patches were evaluated for their physical parameters and they were found to be flexible and smooth in appearance. They were also found to be uniform in their weight and thickness.

**Physical appearance:** The patches formed were smooth with elegant appearance.

**Thickness:** With the help of digital calipers, the thickness of patches was measured and the average thickness was noted. The thickness results are found to be uniform. the results indicates that there was no much difference in the thickness within the formulations means the patches showed uniformity in their thickness.
Weight uniformity: Three different films of the individual batch were weighed and the average weight was calculated. The dried patches were weighed on digital balance and were found exhibit uniform weight. The data of the individual weights indicated to be within the limits and uniform. The patches exhibited uniform weight and there was no deviation in the weight of any formulation and the same was within the limits.

Folding endurance: The folding endurance was measured manually for the prepared patches. A strip of patch 2x2 cm was cut evenly and repeatedly folded at the same place till it broken. The number of times the patch could be folded at the same place without breaking gave the exact value of folding endurance. The result indicates as the HPMC concentration increases the folding endurance of the patches was increased.

Percentage moisture absorption: The recorded percent moisture absorption was of patches shown in table 3. The percentage moisture absorption of the prepared patches are in the following order F4<F5<F12<F11<F6<F10<F2<F9<F8<F3<F1<F7. The results show the moisture absorption of all the patches are within the acceptable limits.

Percentage moisture loss: The recorded percentage moisture loss of prepared patches was shown in table 3. The percentage moisture loss of patches are in the following order F2<F1<F9<F10<F5<F12<F3<F8<F4<F11<F6<F7. The results show that the moisture losses of all patches are within the acceptable limits.

Drug content uniformity: Drug content of the patch was carried out to ascertain that the drug is uniformly distributed into the formulation. The results obtained are represented in table 3. From the results obtained i.e., lowest S.D. values, it was clear that there was proper distribution of Diclofenac sodium in the film formulations. Hence it was concluded that drug was uniformly distributed in all the formulations. Delivery of drug through skin for systemic action is a promising route of administration.

The purpose of this study was to investigate the in vitro release profile of Diclofenac sodium from various patches containing different ratios of combination of polymers (HPMC and Eudragit).

In vitro release studies: In vitro release Diclofenac patches were carried out in diffusion cell using commercial available semi permeable membrane and phosphate buffer (pH 7.4) as diffusion medium. The release profile data of Diclofenac sodium were given in table 4 for
patches F1 to F12. From the diffusion studies it was observed that, at the end of 8 h drug diffusion from formulation F7 (79.947) was maximum than F1 (65.497), F2 (62.324), F3 (60.013), F8 (76.593), F9 (74.543), F10 (57.057), F11 (54.843), F12 (49.97) presented in table 25 and fig 12. The releases of prepared formulations are compared with the marketed Diclofenac patch Nupatch 100. The results shown that the formulations F7, F8 released (79.947, 76.593) drug little bit more than the marketed formulation (74.215). Whereas the formulation F9 has released (74.543) drug when compared with marketed formulation.

The kinetics of drug diffusion profiles was found out by plotting different graphical models. All the release profiles are calculated and the kinetic data is presented in respective table 5. The matrix diffusion controlled transdermal drug delivery system of Diclofenac sodium was studied for their in vitro drug diffusion to observe the kinetics of drug diffusion from formulations. From the above results, it was evident that the drug diffusion from the patches contain Eudragit RLPO and Eudragit RL100 is higher when compared to Eudragit RS100 and Eudragit RSPO. In these formulations the role of Eudragit (RL100, RLPO, RS 100, RSPO) is to control the release of the drug from the patches, the formulations containing Eudragit RL100 and Eudragit RLPO along with HPMC K15 showed higher release when compared to the other formulations having Eudragit RS100, Eudragit RSPO along with HPMC K15. The reason for this is the polymers Eudragit RL100 and Eudragit RLPO are more permeable when compared to Eudragit RS100 and RSPO.

In order to understand the mechanism of drug release, in vitro release data were treated to kinetic models and linearity was observed with respect to higuchi equation. As indicated by higher \( R^2 \) values, the drug release from all the formulations follows first order release and higuchi model. Since it was conformed as higuchi model and the mechanism was diffusion controlled. The peppa’s model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved. ‘n’ value could be used to characterize different release mechanisms.

Korsmeyer peppa’s equation is given as \( \% R = K t^n \) or \( \log \% R = \log K + \log t \) Where \( R = \) drug release; \( K = \) constant; \( n = \) slope; \( t = \) time.
Mechanism of drug release

<table>
<thead>
<tr>
<th>‘n’</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>0.5</td>
<td>Fickian diffusion</td>
</tr>
<tr>
<td>0.5 &lt; n &lt; 1</td>
<td>Non-fickian diffusion</td>
</tr>
<tr>
<td>1</td>
<td>Case II transport</td>
</tr>
</tbody>
</table>

The ‘n’ values obtained graphically from peppa’s plot were shown in table 5. The values obtained were more than 0.5, this indicates the release approximates non fickian diffusion from the formulations.

CONCLUSION

Diclofenac sodium a non-steroidal anti-inflammatory agent (NSAID) and have analgesic action which is selected for the preparation of transdermal delivery system as it as it complies with physicochemical properties required to permeate through skin. The preformulation studies involving description, melting point, solubility, partition coefficient of drug were found to be comparable with the standard. The patches were prepared by solvent evaporation method. The patches were subjected for following evaluation parameters such as physical appearance, weight variation, thickness, folding endurance, drug content, percent moisture absorption, percent moisture loss and diffusion studies. All the parameters were within the limits.

Based on these result the formulations F7 (79.94 %), F8 (76.59 %), F9 (74.54 %) showed best release in 8 h than other formulations. Formulations contain Eudragit RLPO and HPMC K15, Eudragit RL100 and HPMC K15 showed good release when compared to the formulations contain Eudragit RSPO and HPMC K15, Eudragit Rs100 and HPMC K15. Eudragit RLPO and Eudragit RL100 have highly permeable nature whereas Eudragit RS100, Eudragit RSPO have low permeable nature. So the formulations contain Eudragit RLPO and HPMC K15, Eudragit RL100 and HPMC K15 showed good release when compared to the formulations contain Eudragit RSPO and HPMC K15, Eudragit RS100 and HPMC K15.

The release of prepared patches was compared with the marketed Diclofenac Nupatch 100. The formulations F7, F8 showed good release of drug (79.94 %, 76.59 %), little bit more than marketed formulation (74.21 %). From the above studies, it is revealed that by the present work could improve patient compliance by the current transdermal patch.
ACKNOWLEDGEMENTS

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REFERENCES


