Formulation and Characterization of Diclofenac Potassium Transdermal Patches Prepared with *Ficus auriculata* Fruit Mucilage and Hydroxypropyl Methyl Cellulose K4M

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Introduction: The delivery of the drug at a predetermined controlled rate and its systemic effect is utmost important. Topically administered medicaments in the form of patches is being popular for its effectiveness. The main objective of this research was to formulate matrix-moderated transdermal patch of diclofenac potassium and to evaluate them concerning various *in-vitro* parameters.

Materials and Methods: Transdermal systems were formulated using diclofenac potassium and various proportions of *F. auriculata* fruit mucilage (5%, 10%, 15%, 20% and 25% of total polymer) and HPMC K4M as matrix polymers along with polyethylene glycol-400 as plasticizer and tween-80 as penetration enhancer via solvent evaporation method. Formulated patches of diclofenac potassium were tested for various physicochemical parameters. Also, *in-vitro* drug permeation and *in-vitro* release mechanisms were assessed using locally fabricated Franz-diffusion cell and dissolution apparatus respectively.

Results: The prepared patches possessed satisfactory physicochemical characteristics with p>0.05. The *in-vitro* permeation studies were performed using a locally fabricated Franz-diffusion cell. And it showed desired drug permeation through the dialysis membrane from the patches which were formulated using both *Ficus auriculata* fruit mucilage along with HPMC K4M (F4, F5 and F6). Which was better than the permeation data of standard patch (F1) formulated by using HPMC K4M only. The *in-vitro* release study was best explained by Korsmeyer-Peppas which showed that formulations containing more amount of *Eaauriculata* fruit mucilage (F4, F5 and F6) have n-value above 0.89, indicating controlled release diffusion and showed good result as compared to standard patch.

Conclusion: Higher the concentration of *F. auriculate* fruit mucilage in combination with HPMC K4M, better the permeation and controlled release of drug. The matrix forming mucilage (i.e. dried *F. auriculate* mucilage) thus can be used as promising polymer for formulating such patches as transdermal drug delivery system.

Keywords: Diclofenac potassium, *Ficus auriculata*, HPMC K4M, In-vitro permeation, In-vitro release. Transdermal Drug Delivery System.

List of abbreviations: API: Active Pharmaceutical Ingredient; Pvt.: Private; Ltd.: Limited; HCl: Hydrochloric Acid; HPMC: Hydroxyl Propyl Methyl Cellulose; pH: Potential of Hydrogen; Log: Logarithm; PEG: Poly Ethylene Glycol; R²: Regression Coefficient; n: Diffusion or release exponent; RPM: Revolution per Minute; SD: Standard Deviation; TDDS: Transdermal Drug Delivery System; UV: Ultraviolet

Abstract

Introduction: The self-discrete and self-contained dosage form which when applied to the intact skin, delivers the contained medicament at a controlled rate to the systemic circulation is known as Transdermal delivery system (TDDS) [1-13]. Basic components of TDDS are API, polymer, penetration enhancer and surfactant. In this system, the patch is loaded with drug relatively with high dosage, which is worn on the skin for an extended time. And the Fick’s law of diffusion applies i.e., the drug enters the bloodstream via diffusion directly through the skin. Since there is a high concentration on the patch and low concentration within the blood, the drug will keep diffusing into the blood for an extended period of time, maintaining the constant concentration of a drug in the blood flow [3].
TDDS has many merits over other conventional dosage forms. Like, it bypasses liver first-pass metabolism of drug which enhances bioavailability, therapy can be terminate with ease, decreases frequency of administration of drug and it is convenience to patients [5]. Many researchers suggested the transdermal route is an alternative route for lipophilic drugs into the blood circulation [9]. Diclofenac is a lipophilic Non-steroidal anti-inflammatory drug and is used to relieve pain, swelling (inflammation), and joint stiffness caused by arthritis. Its salt version (i.e. Diclofenac potassium) increases its hydrophilicity, which is required to penetrate drug through the skin layers. It has a melting point of 156-158 °C and partition coefficient 1.90 (Octanol Water System) with molecular size of 334.24 Dalton [14,15]. These characteristics of Diclofenac potassium meets all the criteria of the drug that can be formulated in TDDS [6].

The choice and use of polymers play a vital role for a successful formulation of solid, liquid and semisolid dosage forms and are specifically important in the design of modified release drug delivery systems. Both artificial and natural polymers have been investigated substantially for this purpose, but the use of natural polymers for dosage forms formulation and other pharmaceutical applications is attractive because they are cheap, readily available, non-toxic, and capable of chemical modifications, potentially biodegradable and with few exceptions, also biocompatible [16,17]. Currently, researchers had formulated transdermal patches of Tramadol hydrochloride using fruit mucilage of F. caria and polyvinyl pyrrolidone via solvent evaporation technique. The formulations were evaluated for patch physicochemical properties, which showed the uniform drug release in a controlled fashion and concluded that F. carica fruit mucilage can be used as a matrix polymer with no signs of potential skin irritations [2].

Another use of natural mucilage can be seen in the formulation of buccal patches of Atenolol, formulated using fenugreek seed mucilage with HPMC which concluded that the developed Atenolol releasing buccal patches can be beneficial over conventional drug delivery systems by decreasing the dosing frequency and enhance patient compliance [1].

In early 2008, sustained release tablet of Diclofenac sodium was formulated using mucilage of Hibiscus rosa-sinensis Linn as rate controlling matrix. Matrix tablet containing dried mucilage and diciofenac sodium were prepared using direct compression technique and were evaluated for hardness, friability, weight variation along with in-vitro drug release. The result was acceptable and drug release kinetics from those formulations corresponded to zero-order kinetics. It was concluded that mucilage can be used as release-retarding agent for 12 hours and hence dried mucilage of Hibiscus rosa-sinensis was most suitable for sustained release of diclofenac sodium [10].

Ficus auriculata is a deciduous tree, which grows in tropical and subtropical regions and is commonly known as fig in English and newaro in Nepali. Traditionally, its fruit and root were used to treat digestive disorders, diabetes and jaundice. Its fruit contain natural latex and fibers which are the main source of mucilage. Earlier chemical examination of this plant has shown the presence of betulinic acid, lupeol, stigmasterol, bergapten, scopeletin, beta sitosterol-3-O-Beta-D-glucopyranoside, myricetin and quercetin-3-O-BetaD-glucopyranoside [4].

In this study, Ficus auriculate fruit mucilage and HPMC K4M were used as a matrix polymer for controlling the release of Diclofenac potassium in transdermal patches which was the main objective of this research. Promising result of this research can open a source of natural polymer for the design and manufacture of sustained release dosage forms. This can eventually alleviate the expenditure of synthetic polymers and the retail price of final dosage form.

Materials and Methods

Materials

Experimental drug and polymer diclofenac potassium and HPMC K4M respectively were generous gift from Asian Pharmaceutical Pvt. Ltd. Bhairahawa, Nepal. F. auriculate fruits were collected from Lekhnath-Khudi, Kaski-Nepal and authenticated by the National Herbarium and Plant Laboratory, Godawari, Lalitpur-Nepal. The other reagent used such as glycerin, propylene glycol-400, tween-80, methyl paraben, propyl paraben, methanol, ethanol and buffer chemicals (disodium hydrogen phosphate and potassium dihydrogen phosphate) were of analytical grade purchased from Merck KGaA, Germany. Dialysis membrane (AB-253a-visking-tube-22mmx2meter-semi-permiable-membrane-abron) was received from the laboratory of Pokhara University.
Methods

Extraction of the Mucilage

Fresh ripen fruits of *F. auriculata* were taken from the local community (Lekhnath, Khudi). *F. auriculata* fruits were washed to remove dirt's/debris with distilled water and cut into pieces. Seeds were also removed from the fruits. Pulps of the fruits were meshed and drenched in water for 5-6 hours and were boiled for 30 minutes. It was kept stand by for 1 hour for the complete release of mucilage. Then the mixture was filtered using muslin cloth by folding it eight times. Acetone (3:1) was added to the filtrate to precipitate the mucilage. After that the mucilage was taken out and dried at 40 °C in a hot air oven. Dried mucilage was milled in mortar and pestle, sieved through a #80 sieve and was preserved in a desiccator at room temperature until its use [2].
Preparation of Transdermal Patches

Excipients like Glycerol, Polyethylene glycol 400, Tween 80, Methyl and Propyl paraben were taken in a beaker at fixed proportion (Table 1). Diclofenac potassium of 100mg along with 10ml methanol was added. HPMC K4M was added slowly with continuous stirring in magnetic stirrer along with *Ficus auriculata* fruit mucilage (as matrix-polymer) for 15 minutes at 500rpm and 40ml water was added. The above solution was homogenized using a homogenizer for 15 minutes at 3000rpm. Obtained solution was left for 24 hours for complete de-airing and poured onto clean petri-dish of 7.5cm radius. Then it was kept at room temperature for 30 minutes to settle down and was heated in a hot air oven at 40±2 °C for 48 hours to remove the solvent completely using inverted funnel technique. The formulated patch was covered with aluminum foil and was stored in desiccator until its use [2,15].

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Potassium (mg)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>HPMC K4M %</td>
<td>100</td>
<td>95</td>
<td>90</td>
<td>85</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td><em>Ficus auriculata</em> fruit mucilage %</td>
<td>-</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>PEG 400 (gm)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Glycerol (gm)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Tween 80 (gm)</td>
<td>0.0036</td>
<td>0</td>
<td>0.0036</td>
<td>0.0036</td>
<td>0.0036</td>
<td>0.0036</td>
</tr>
<tr>
<td>Propyl paraben (gm)</td>
<td>0.0150</td>
<td>0.0150</td>
<td>0.0150</td>
<td>0.0150</td>
<td>0.0150</td>
<td>0.0150</td>
</tr>
<tr>
<td>Methyl paraben (gm)</td>
<td>0.0250</td>
<td>0.0250</td>
<td>0.0250</td>
<td>0.0250</td>
<td>0.0250</td>
<td>0.0250</td>
</tr>
<tr>
<td>Water: Methanol (4:1) (ml)</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Weight of HPMC K4M and *Ficus auriculata* fruit mucilage used were represented in percentage (%) of total polymer used.

Table 1: Different formulae of transdermal patches

Evaluation of Prepared Patches

Organoleptic characteristics: Prepared patches were inspected for its appearance, color, clarity, flexibility and smoothness [12].

Photo 2: Locally fabricated Franz-diffusion cell; Two side open ended test tube as donor compartment in which lower opening consist of dialysis membrane as semi-permeable membrane tightened by cotton thread. Receptor compartment was filled with 60 ml phosphate buffer of pH 6.8 placed on magnetic stirrer hot plate with temperature of 37±2 °C with the 100-rpm magnetic stirrer.
Drug content: The patch size of 4 cm² was taken and dissolved in 100ml of phosphate buffer of pH 6.8. The conical flasks containing patch solution were shaken for 2 hr. on water bath shaker to get complete solubility of a drug at 37±2 °C and 100rpm. The obtained solution was filtered and estimated spectrophotometrically at 273.5.0 nm using phosphate buffer (pH 6.8) as blank after suitable dilution [17].

Thickness: The thickness of the formulated patches was measured at 5 different points of each patch using a digital Vernier caliper and the average thickness was calculated [11].

Weight Uniformity: Three randomly selected patches were weighed individually and their average weight was calculated. The standard deviation for each film weight was noted to check the uniformity of weight [7].

Folding Endurance: The patch (2×2 cm size) was taken and folded repeatedly until it broke. The number of times the formulated patch could be folded without breaking was the folding endurance of the patch [18].

Moisture Content: The formulated patches were individually pre weighed and kept in a desiccator at room temperature for 12 hours (containing activated silica). The patches were individually reweighed until a constant weight was obtained. Then, the percentage of moisture content was calculated using the below formula [18].

\[
\text{%Moisture content} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100\%
\]

In-vitro permeation studies: In-vitro permeation study was carried out using a dialysis membrane as a permeation membrane as it has pore size between 10k-100k Dalton. The membrane was tied on one side of two-sided open-end cylinder to create a flat surface to place the transdermal patch. The side where transdermal patch reside was considered as a donor compartment. The entire surface of the membrane was in contact with the receptor compartment containing 60ml of Phosphate buffer with pH 6.8 which was maintained at a temperature of 37±2 °C. The content of the receptor compartment was agitated by a magnetic stirrer at a constant speed of 100 rpm. The 2ml of the sample was withdrawn from the receptor compartment every hour up to 8 hours and was replaced by an equal volume of fresh receptor medium to maintain a same volume in the receptor compartment. The concentration of the drug permeated was determined using an UV visible spectrophotometer at 273.5 nm after suitable dilution using Phosphate buffer pH 6.8 as blank. The same process was performed in triplicate for all formulations [17].

In-vitro Release Test: The locally fabricated apparatus was employed for assessment for the release of the drug from the prepared patches. With the help of patch cutter dry films were cut into the size of 4 cm². Then it was kept in a vial containing 100ml of phosphate buffer (pH 6.8) which was fitted with an IV tube to draw a sample. The apparatus was equilibrated at room temperature. 10ml of a sample was drawn
every hour up to 8 hours from the vial. With every withdrawal, an equal volume of fresh medium was replaced along with single agitation to maintain the same volume in the vial. Then the sample was filtered, analyzed using an UV spectrophotometer at 273.5 nm after suitable dilution. The experiment was performed in triplicate and the mean value was calculated [19].

Results

The mucilage characteristics were found acceptable. The results of physicochemical characteristics and drug contents of all formulations were shown in Tables 2 and 3 respectively. The value of all the physicochemical parameters was found to be in limit as p value was found to be greater than 0.05. The amount of Diclofenac potassium in the formulation was in a decent amount as needed. It proves that no more amount of drug was wasted during the research procedure.

IBM SPSS Statistics Version 25 was used to carried out ANOVA for Table 1 and Table 2. The result was not significant (p>0.05). It was shown in Table 5 and Table 6 respectively.

Table 2: Characterization data of formulated transdermal patches

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Thickness (mm)</th>
<th>Weight uniformity(gm)</th>
<th>Folding endurance (times)</th>
<th>Moisture content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.28± 0.225</td>
<td>2.53± 0.199</td>
<td>101±2</td>
<td>8.33± 3.936</td>
</tr>
<tr>
<td>F2</td>
<td>0.31± 0.230</td>
<td>2.50± 0.860</td>
<td>102±2</td>
<td>1.33± 0.711</td>
</tr>
<tr>
<td>F3</td>
<td>0.30± 0.063</td>
<td>2.45± 0.117</td>
<td>103±2</td>
<td>4.36± 0.633</td>
</tr>
<tr>
<td>F4</td>
<td>0.31± 0.190</td>
<td>2.48± 0.023</td>
<td>103±2</td>
<td>6.06± 1.279</td>
</tr>
<tr>
<td>F5</td>
<td>0.30± 0.190</td>
<td>2.38± 0.090</td>
<td>104±3</td>
<td>6.63± 1.829</td>
</tr>
<tr>
<td>F6</td>
<td>0.25± 0.196</td>
<td>2.43± 0.136</td>
<td>106±1</td>
<td>2.24± 2.552</td>
</tr>
</tbody>
</table>

Data of thickness, weight uniformity, folding endurance and moisture content were represented with their mean value ± Standard deviation (SD); Number of trials (n) = 5.

Table 3: Drug content evaluation data of formulated transdermal patches

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>101.82 ± 0.007</td>
</tr>
<tr>
<td>F2</td>
<td>99.38 ± 0.122</td>
</tr>
<tr>
<td>F3</td>
<td>98.79 ± 0.023</td>
</tr>
<tr>
<td>F4</td>
<td>98.86 ± 0.024</td>
</tr>
<tr>
<td>F5</td>
<td>97.40 ± 0.164</td>
</tr>
<tr>
<td>F6</td>
<td>99.60 ± 0.007</td>
</tr>
</tbody>
</table>

All the values mentioned as mean ± Standard deviation (SD); Numbers of trials (n) = 5

IBM SPSS Statistics Version 25 was used to evaluate p-value of each column and was found p>0.05. Numerator degree of freedom was 5 and Denominator degree of freedom was 25, F-statistics was found to be equal to 2.5336 of Table 2 and Table 3.

Standard curve of diclofenac potassium was represented in Figure 1. It was plotted using the data of concentration of drug along with its absorbance in maximum wavelength i.e. 273.5nm.

Figure 1: Calibration curve of absorbance vs. concentration (mcg/ml) for diclofenac potassium at 273.5 nm. The equation for the trendline is y = 0.0355x + 0.0149; R² = 0.9824
The kinetic plots for *in-vitro* drug permeation and drug release were shown in Figure 2 and Figure 3 respectively. All the evaluated parameters were within limits and found satisfactory. *In-vitro* permeation graph shows that formulated patch (F1) shows rapid permeation whereas formulations (F3, F4, F5 and F6) reveals drug permeation in the controlled fashion. In the absence of permeation enhancer (F2) could not meet the normal range of drug permeation.

![Figure 2: In-vitro permeation kinetics curves of concentration (mcg/ml) vs. time (hrs.) of all formulations (F1-F6) at 273.5 nm up to 8 hours; F2 did not contain tween 80 as permeation enhancer, so its line is deviated as compared to others](image1)

![Figure 3: In-vitro release kinetics curves of concentration (mcg/ml) vs. time (hrs.) of all formulations (F1-F6) at 273.5 up to 8 hrs; According to this data zero order, first order, higuchi release and korsmeyer's peppa's kinetic curves were plotted](image2)

![Figure 4: Zero-order kinetics curve of percentage (%) release vs. time (hrs.) of all formulations (F1-F6) at 273.5 nm up to 8 hours](image3)
Data obtained from drug release study were used to plot the graph to evaluate zero-order, first-order, Higuchi and Korsmeyer-Peppas release kinetics as shown in Figures 4, 5, 6 and 7 respectively. The curve obtained showed similar drug release rate in both standard patch and patch formulated using mucilage.
The main important data to explain the drug release pattern was defined by the R-value obtained from the graph of zero-order, first-order, Higuchi and Korsmeyer–Peppas release kinetics which are shown in Table 4. Formulations (F4, F5 and F6) containing more fruit mucilage possess control release of drug as compared with the standard formulation i.e. F1.

Discussions

Mucilage Characteristics

The extracted mucilage was brownish-yellow with a sweet odor and soluble in water produces a yellowish viscous solution. It was found to be non-sticky and have minute particles. The average particle size of dried mucilage was found to be uniform.

Physicochemical Characteristics

The thickness of formulated matrix transdermal patches (0.28 ± 0.225 to 0.313 ± 0.230 mm) showed uniformity in thickness. The prepared patches did not show any signs of cracking, which might be because of the plasticizer (PEG 400). The formulated patches showed uniformity in weight (2.38 ± 0.090 to 2.534 ± 0.199 gram). The folding endurance was above 100, which indicates that the formulated patches maintain their integrity without breakup on the general usages of the patch. The folding endurance of the patches was increased as the proportion of F. ariculata fruit mucilage increased in the formulation. All these values were shown in Table 2.

The moisture content in the formulated patches was ranged from (1.33 ± 0.711 to 8.33 ± 3.936 %), which maintains suppleness, thus preventing drying, brittleness, bulkiness and microbial contamination. As shown in Table 2 [7].

ANOVA table of Table 1 and Table 2 showed p value more than 0.05. Which was found not to be significant in both cases. It reflected that the formulations were same and the formulations had same results for physicochemical parameters like thickness, weight uniformity, folding endurance, moisture content and drug content respectively.
The standard graph of diclofenac potassium was plotted as concentration (mcg/ml) versus absorbance at the maximum wavelength i.e. 273.5nm as shown in Figure 1. The standard graph showed good linearity with an R² value of 0.9824 which indicate that it obeys Beer-lambert's law.

The patches showed uniformity in drug content that was found between (97.40 ± 0.164 to 101.82 ± 0.007 %). It can also comply that there is compatibility between diclofenac potassium and F. auriculata fruit mucilage. All these values were shown in Table 3 and found to be in the limit [8].

The permeation result showed that diclofenac potassium permeates slowly when used with F. auriculata fruit mucilage and HPMC K4M in combination (F3, F4, F5 and F6) as compared with the standard (F1). Formulation (F2) have a minimum amount of drug concentration permeated through a dialysis membrane as it did not contain any permeation enhancer as shown in Figure 2. It reveals that F. auriculata fruit mucilage can be used as a matrix polymer in the formulation of a transdermal drug delivery system.

The obtained release kinetics data were introduced into the zero-order release model, first-order release model, Higuchi model and Korsmeyer-Peppas release model to establish the drug release mechanism and kinetics of drug release from the formulated patches as shown in Figure 4, 5, 6 and 7 respectively. The criteria for selecting the most appropriate model were based on the best goodness of fit indicated by the value of the regression coefficient. The result showed by formulations (F1, F4, F5 and F6) was best explained by the Korsmeyer-Peppas release model indicating controlled release diffusion as they have an R² value above 0.89. On the other hand, F2 and F3 tend to follow non-fickian diffusion release. All these values were shown in table 4.

Formulations F4, F5 and F6 showed desired drug permeation result and controlled release diffusion. These formulations were formulated using more amount of F. auriculata fruit mucilage (i.e. 15%, 20% and 25% of total polymer). Above mentioned information confirms that instead of using HPMC K4M only, use of more amount of F. auriculata fruit mucilage in transdermal drug delivery system provides better permeation and release rate. This may be due to high swelling and matrix-forming capacity of F. auriculata fruit mucilage.

The use of fruit mucilage of F. auriculata was found to be significant in the formulation of transdermal patches of diclofenac potassium. The findings of this experiment may bolster the use natural polymers instead of synthetics in near future by pharmaceutical industry.

Conclusion

The study explores that, increase in the ratio of polymers (i.e. Extracted F. auriculata fruit mucilage:HPMC K4M) in the formulations have better result as compared to that of standard formulation (i.e. use of HPMC K4M only). Formulated patches also showed considerable physicochemical properties. And the in-vitro permeation and release data of formulations (F4, F5 and F6) showed desired drug permeation result and controlled release diffusion respectively. It reflects that the F. auriculata fruit mucilage has good swelling and matrix forming properties. Thus, in combination with HPMC K4M it can be used in the formulation of diclofenac potassium transdermal patch.

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References


