



## A Novel Mucilage from *Ficus glomerata* Fruits for Transdermal Patches: Taking Indomethacin as a Model Drug

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### Abstract

The present study was performed to explore the matrix property of *Ficus glomerata* fruit mucilage for making transdermal patches. The mucilage was evaluated for its physicochemical properties. Various transdermal patches of indomethacin were prepared by solvent evaporation technique using different proportions of *F. glomerata* fruit mucilage. The compatibility studies between indomethacin and *F. glomerata* fruit mucilage revealed that there were no negative interactions between indomethacin and the mucilage. The formulated patches were evaluated for physical properties, pre-formulary, post-formulary and skin irritation characteristics and they were found satisfactory. The experimental results shows that the drug release from the patches delayed in controlled manner as the proportion of *F. glomerata* fruit mucilage increased. The accelerated stability studies proved that the formulated patches were stable at stressed storage conditions. It was concluded that *F. glomerata* fruit mucilage can be used as polymer for making transdermal patches.

*Keywords:* *Ficus glomerata*; Indomethacin; Transdermal patches.

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### 1. Introduction

Transdermal delivery has many advantages over conventional modes of drug administration as it avoids hepatic first pass metabolism and improves patient compliance. Intensive research has shown that transdermal route is a potential route of delivery of lipophilic drugs to the systemic circulation [1].

Indomethacin is an arylacetic acid derivative,

which has excellent anti-inflammatory, analgesic and antipyretic efficacy. Indomethacin has been widely used for treating conditions such as chronic rheumatoid arthritis, osteoarthritis, spondylosis deformans, acute gout, peri-arthritis and humeroscapularis [2]. The drug has a biological half-life of about 5 to 10 h and a plasma clearance of 1 to 2.5 ml/kg/min which make it a suitable candidate for administration by transdermal route [3].

Various experimental reports indicated that indomethacin is a suitable drug in controlled

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release formulations. In this study, *Ficus glomerata* fruit mucilage was used as a matrix forming polymer for controlling the release of indomethacin.

## 2. Materials and methods

### 2.1. Materials

Indomethacin was obtained as a gift sample from Waksman Selman Pvt. Ltd, Anantapur, India. *F. glomerata* fruits were obtained from the main market of Anantapur and were authenticated by the Botany department of Sri Krishnadevaraya University, Anantapur. Glycerin, propylene glycol, span-80, methyl paraben and propyl paraben were procured from S.D Fine chemicals, Mumbai. All of the reagents used were of AR grade. Indomethacin sample was characterized by its solubility, pH and UV spectrophotometric method for its authentication.

### 2.2. Extraction of the mucilage

The fruits of *F. glomerata* were thoroughly washed with water to remove dirt and debris then cut it into two pieces. The seeds which were present inside the fruit were removed. The pulps of the fruits were crushed and

soaked in water for 5-6 h, boiled for 30 min and left to stand for 1 h to allow complete release of the mucilage into the water. The mucilage was extracted using a multi layer muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of filtrate) was added to precipitate the mucilage. Then the mucilage was separated, dried in an oven at 40 °C, collected, ground, passed through a #80 sieve and stored in desiccator at 30 °C and 45% relative humidity before use [4].

### 2.3. Purification of the mucilage

The crude mucilage (1%) was homogenized (Potter homogenizer) with cold dilute trichloro acetic acid solution (5%). The solution was centrifuged (3500 rpm for 20 min), neutralized with sodium hydroxide by drop wise addition and then dialyzed for 30 h against distilled water. The mucilage was precipitated with ethanol (in the quantities of three times the volumes) and washed successively with ethanol, acetone and diethyl ether [4].

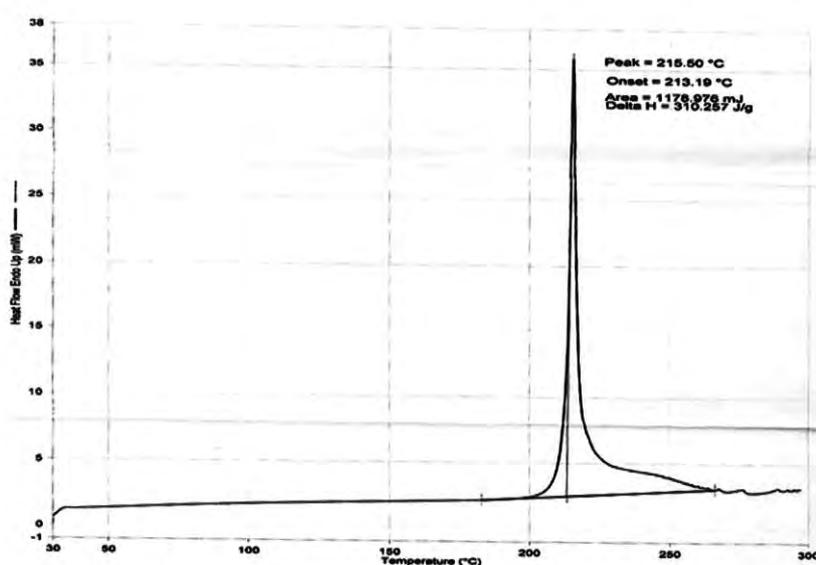


Figure 1. DSC thermo gram of Indomethacin pure drug.

**Table 1.** Physicochemical characterization of *Ficus glomerata* mucilage.

Properties	<i>Ficus glomerata</i>
% yield (g /kg)	125±10.567
Solubility	Soluble and forms colloidal solution, in Luke warm water. Practically insoluble in ethanol, acetone, ether and chloroform
Odour	Characteristic
Appearance	Lustrous
<b>Identification</b>	
Mounted in 96% ethanol	Transparent angular masses
Mounted in ruthenium red	Particles stained red
Mounted in Iodine solution	Particles stained blue
Average particle size (µm)	212.58±20.515
Weight loss on drying (%)	6.33±5.210
Acid insoluble ash (%)	1
Swelling Index	85±11.246
pH	7.0
Test for Carbohydrate (Mollish test)	+
Test for Tannins (Ferric chloride test)	-
Test for chloride (Silver-nitrate test)	-
Test for Sulphate (Barium chloride test)	-
Uronic acid test	+
Test for foreign matter (%)	NMT 0.1
Test for heavy metal (lead)	20-25 ppm
Test for Arsenic	<1 ppm
Solubility	Soluble in lukewarm water, Practically insoluble in ethanol, acetone, ether and
Chloroform	
Charring (°C)	Decomposes above 200
Density of liquid (0.5% w/v)	1.368±0.099
Microbial count (cfu/g)	Bacteria:15; Fungi: 7
<b>Flow Properties</b>	
Angle of repose (θ°)	27.83±1.84
Loose Bulk density (g/cm <sup>3</sup> )	0.58±0.04
Tapped bulk density(g/cm <sup>3</sup> )	0.79±0.05
Carr's Index	26.58±1.29
Hausner's ratio	1.25±0.06

Cfu= Colony forming units; NMT= Not more than

#### 2.4. Characterization of the mucilage

The collected mucilage was evaluated for physicochemical characteristics viz., morphological characteristics, identification by chemical tests, solubility, melting range, pH, swelling index, ash values, presence of foreign organic matter, test for lead and arsenic, loss on drying, density, compressibility index and angle of repose etc.[5]. The values are shown in Table 1.

#### 2.5. Preparation of transdermal patches

Various proportions of *F. glomerata* mucilage was taken in a beaker add propylene

glycol as plasticizer, span-80 as penetration enhancer, propyl paraben and methyl paraben as preservatives, water as solvent and finally Indomethacin (100 mg) was added with continuous stirring in magnetic stirrer for 30 min at 500 rpm. The above mixture was poured within the glass bangles (6.1 cm diameter) placed on mercury surface in a petri dish. The rate of evaporation was controlled by inverting a funnel over the petri dish. The patches were dried at 40±2 °C for 24 h after the dried patches were taken out and stored in desiccator till use [6]. The formulae of various transdermal patches are shown in Table 2.



Figure 2. DSC thermo gram of *Ficus glomerata* fruit mucilage.

### 2.6. Differential scanning calorimetry studies

Differential Scanning Calorimetry (DSC) curves were obtained by a differential scanning calorimeter (Schimadzu DSC-50, Tokyo, Japan) at a heating rate of 10 °C/min from 25-250 °C in nitrogen atmosphere (20 ml/min) with a sample weight of 3 mg. The DSC thermo grams were shown in Figures 1 to 3.

### 2.7. Fourier transform infra-red (FT-IR) spectral analysis

Fourier Transformed Infrared (FT-IR) spectrums of indomethacin with *F. glomerata* fruit mucilage were obtained individually and in combinations on a Fourier-Transform Infrared (FT-IR) spectrophotometer (Perkin Elmer, spectrum-100, Japan) using the KBr disk method (5.2510 mg sample in 300.2502

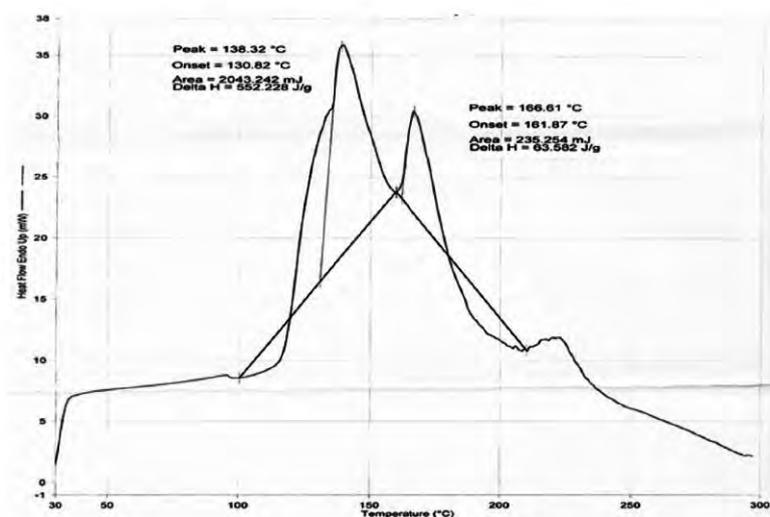


Figure 3. DSC thermogram of formulation blend F5.

**Table 2.** Different formulae of transdermal patches.

Ingredients	F1	F2	F3	F4	F5
Indomethacin (mg)	100.000	100.000	100.000	100.000	100.000
<i>Ficus glomerata</i> fruit mucilage (g)	1.000	2.000	3.000	4.000	5.000
Glycerin(ml)	0.300	0.3000	0.300	0.300	0.300
Propylene Glycol(ml)	0.180	0.180	0.180	0.180	0.180
Span-80 (ml)	0.060	0.060	0.060	0.060	0.060
Methyl paraben(g)	0.025	0.025	0.025	0.025	0.025
Propyl paraben(g)	0.015	0.015	0.015	0.015	0.015
Water up to (ml)	20.000	20.000	20.000	20.000	20.000

mg KBr). The scanning range was 400 to 4000  $\text{cm}^{-1}$  and the resolution was 1  $\text{cm}^{-1}$ . This spectral analysis was employed to check the compatibility of drugs with the polymers used. The FT-IR spectrums are shown in Figures 4 to 6.

## 2.8. Evaluation of physicochemical parameters

### 2.8.1. Thickness

The thickness of the formulated patches was determined using a digital caliper (BAKER-EC 10, Hyderabad, India). The mean thickness was measured at five different locations of the patch [7].

### 2.8.2. Tensile strength

Tensile strength of formulated patches was

determined by using computerized balance (Chiksan balance) with modifications. A  $1 \times 1 \text{ cm}$  patch was taken and subjected to studies [7].

### 2.8.3. Flatness and elongation breake

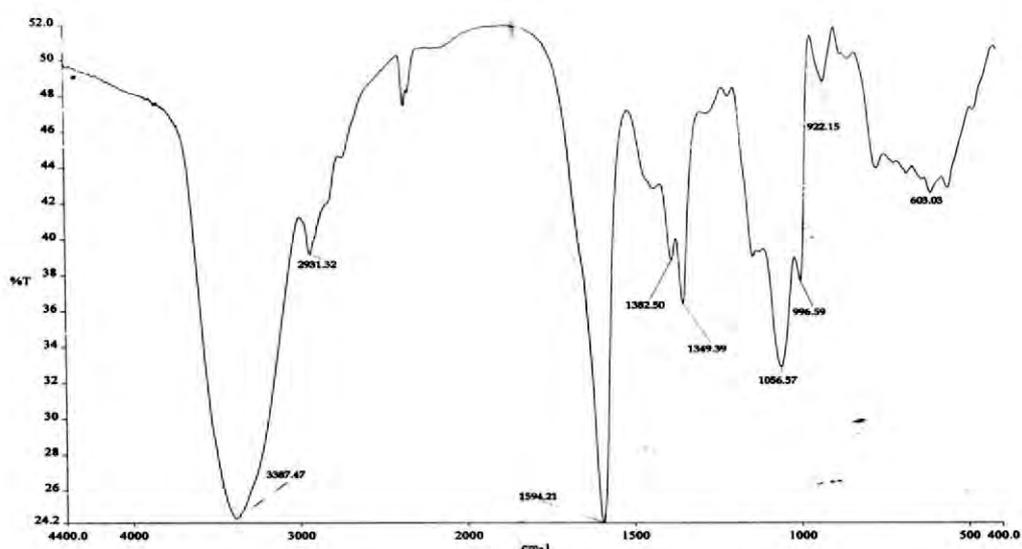
Longitudinal patches were cut out from the prepared transdermal patches. The flatness was determined at different by using vernier calipers [8]. The length before and after the breake point was considered in calculating the elongation breake [7]. Mathematically, it can be expressed in the eq.1.

$$\text{Elongation (\%)} = \frac{L_1 - L_2}{L_2} \times 100 \quad \text{Eq1}$$

Where

L1=final length of each patch

L2=initial length of each patch

**Figure 4.** FTIR spectrum of indomethacin pure drug.

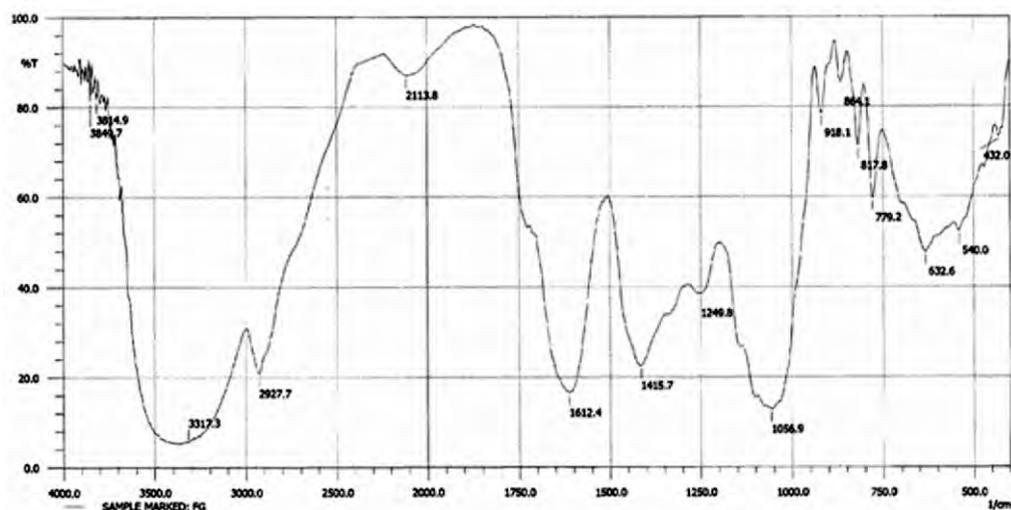


Figure 5. FTIR spectrum of *Ficus glomerata* fruit mucilage.

#### 2.8.4. Folding endurance

It can be determined by repeatedly folding a small piece of the patch (2×2 cm) at the same place till it breaks. The number of times the formulated patch can be folded without breaking was the folding endurance of the patch [7].

#### 2.8.5. Moisture content

The formulated patches were individually pre-weighed and kept in a desiccator containing activated silica at 30 °C for 12 h. The patches were individually reweighed until a constant weight was obtained. The

change in the weight from the initial gives the percent moisture content of the patch. The formulated patches were cut into 20×50 mm strips. The patch was weighed and kept in a desiccator (contained saturated solution of calcium chloride) at 30 °C and dried for at least 12 h till the patch shows constant weight. The moisture content value was the difference between the constant and the initial weight [9].

#### 2.8.6. Moisture uptake

The physicochemical studies like moisture content and moisture uptake provide the information regarding the stability of the

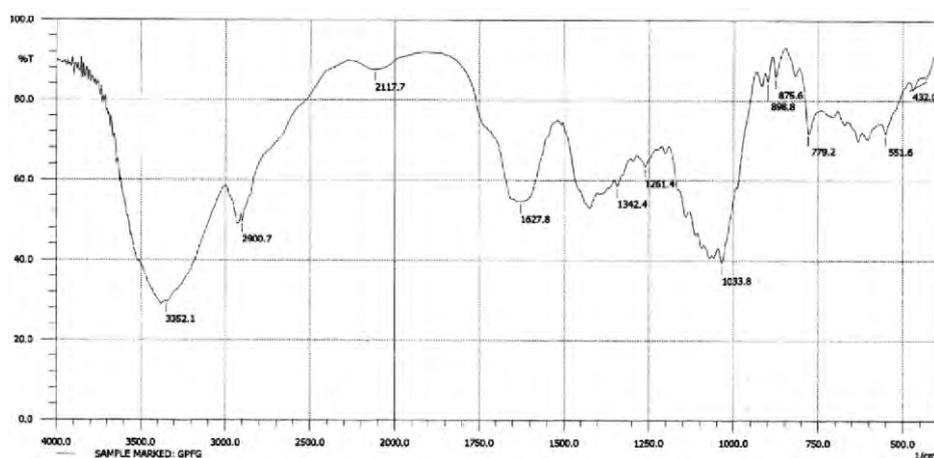


Figure 6. FTIR spectrum of formulation blend (F5).

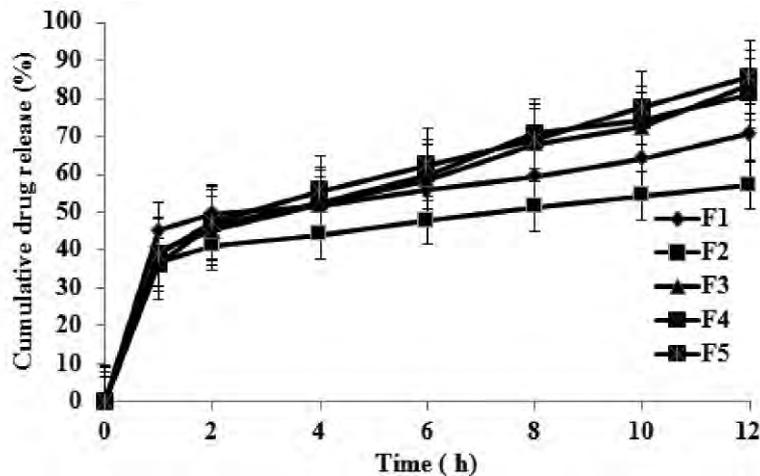


Figure 7. Zero order plots of prepared transdermal patches.

formulation. The moisture content was determined by keeping the drug matrix patches in a desiccator containing activated silica until they showed constant weight. The weight difference between relative weights to the final gives the percentage moisture content. The water absorption capacities of various patches were determined at 75% and 93% relative humidity (RH). Patches were cut into 25×60 mm strips. A patch was weighed and kept in a desiccator at 40 °C for 24 h. Then the patch was kept in a desiccator with RH of 75% (containing saturated solution of

sodium chloride) and 93% (containing saturated solution of ammonium hydrogen phosphate) at room temperature. Then the patches were measured periodically to constant weights and the water absorption capacity was calculated [9].

#### 2.8.7. Drug content of the patch

Four pieces each of 1×1 cm of prepared patches were cut and took in a stoppered conical flasks containing 100 ml of dissolution medium (0.1 NHCl:CH<sub>3</sub>OH) and stirred for 6 h, filtered and suitable dilutions were made.

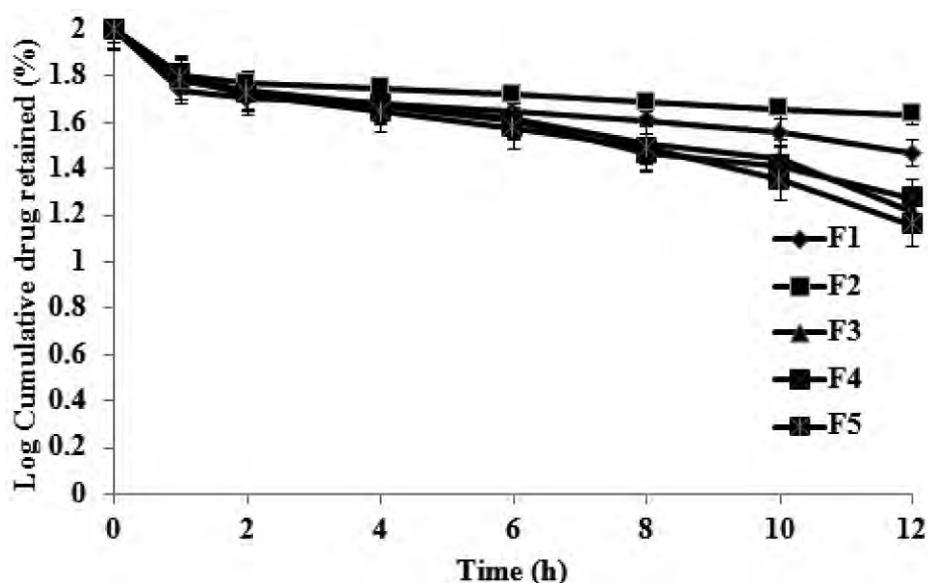


Figure 8. First order plots of prepared transdermal patches.

**Table3.** Result of mechanical properties of formulated transdermal patches.

Parameter	Thickness ( $\mu\text{m}$ )	Tensile strength ( $\text{N}/\text{mm}^2$ )	Elongation (%)	Folding endurance
F1	630 $\pm$ 35.6	0.294 $\pm$ 0.14	15.33 $\pm$ 0.89	98 $\pm$ 1.8
F2	650 $\pm$ 62.5	0.285 $\pm$ 0.25	18.22 $\pm$ 0.23	124 $\pm$ 0.9
F3	685 $\pm$ 55.8	0.311 $\pm$ 0.05	22.66 $\pm$ 0.36	115 $\pm$ 1.2
F4	690 $\pm$ 25.6	0.325 $\pm$ 0.12	24.95 $\pm$ 0.39	99 $\pm$ 1.5
F5	635 $\pm$ 29.6	0.326 $\pm$ 0.10	26.23 $\pm$ 0.84	119 $\pm$ 1.4

Number of trials (n)=3

Absorbance was observed using UV-Visible double beam spectrophotometer (Elico SL 210, Mumbai, India) at 238 nm against a blank [9].

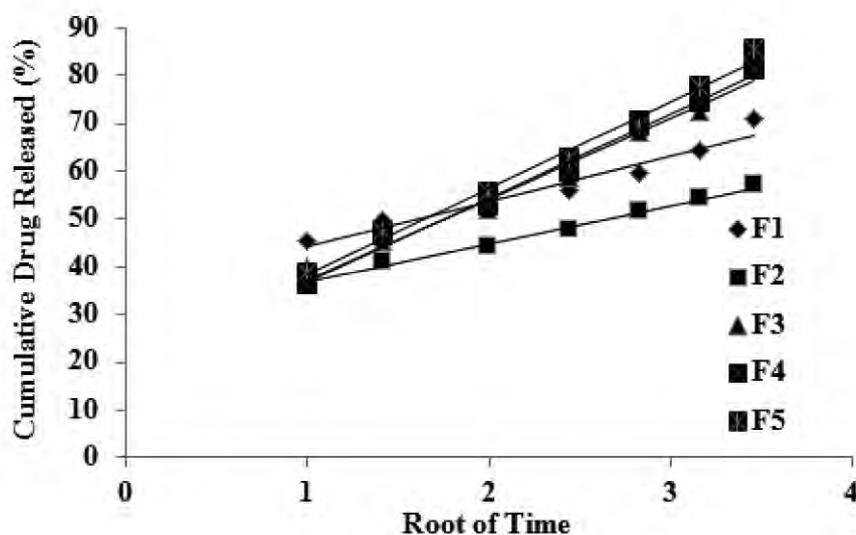
### 2.8.8. *In vitro* skin permeation studies

The epidermal hair of rabbit was removed and skin was cleaned from tissues and blood vessels. The skin was mounted overnight (12 h) on the receptor phase to remove any material (UV absorbing). The *in-vitro* skin permeation of indomethacin from various transdermal patches was studied using KC diffusion cell [10]. The KC diffusion cell consists of upper donor compartment which contains the formulated patch and the bottom receptor compartment which contains dissolution medium, the water jacket (for maintaining the temperature conditions) and a sampling port. The effective permeation area of the diffusion cell was 1.0 cm<sup>2</sup> and receptor cell volume was 17.5 ml. The receptor

compartment contained a phosphate buffer saline of pH 7.4 which was stirred by a magnetic stirrer. The temperature was maintained at 37 $\pm$ 2 °C. One ml samples were withdrawn through the sampling port of the KC diffusion cell for the period of 48 h. The withdrawn samples were checked for absorbance at 238 nm. Three trials were made and blanks were also run and the average values were noted [9]. The *in-vitro* skin permeation data was treated with kinetic modeling and the plots were shown in Figures 7 to 11.

### 2.8.9. *Skin irritation studies*

The skin irritation studies were carried out using modified Draize test [11]. Totally six rabbits were selected. The hairs at the dorsal area of rabbits were removed by shaving 24 h before test. One side of the rabbit's back (untreated skin area) serves as the control and other as experimental side. The formulated patch was applied on experimental side and the non-medicated patch on the

**Figure 9.** Higuchi's plots of prepared transdermal patches.

**Table 4.** Result of mean weights, moisture content, moisture uptake and drug content of formulated transdermal patches.

Formulation	Weights (g)	Moisture content (%)	Moisture uptake (%)		Drug Content (%)
			RH 75%	RH 93%	
F1	1.561±0.51	2.848±0.12	3.206±0.37	6.145±0.01	97.4±0.02
F2	1.584±0.12	2.851±0.23	4.125±0.52	5.249±0.12	98.3±0.19
F3	1.564±0.14	2.645±0.35	3.130±0.73	3.936±0.49	99.7±0.23
F4	1.566±0.34	2.758±0.35	2.210±0.96	5.219±0.20	100.2±0.22
F5	1.597±0.01	2.854±0.56	3.206±0.37	3.906±0.59	100.7±0.45

Number of trials (n)<sup>3</sup>

control side of the rabbits. The medicated patches (F5) were changed after 48 h and the fresh patches were adhered at the same site without changing the control side. The patches were secured on the back of the rabbit for seven days. After seven days, the patches were removed and examined for any sign of erythema or edema.

#### 2.8.10. Scanning electron microscopy (SEM) studies

The selected formulation's (F5) surface morphology was studied by using Scanning Electron Microscope (FE-SEM, Carl Zeiss, Germany). The SEM photographs are shown in Figure 12.

#### 2.8.11. Accelerated stability studies

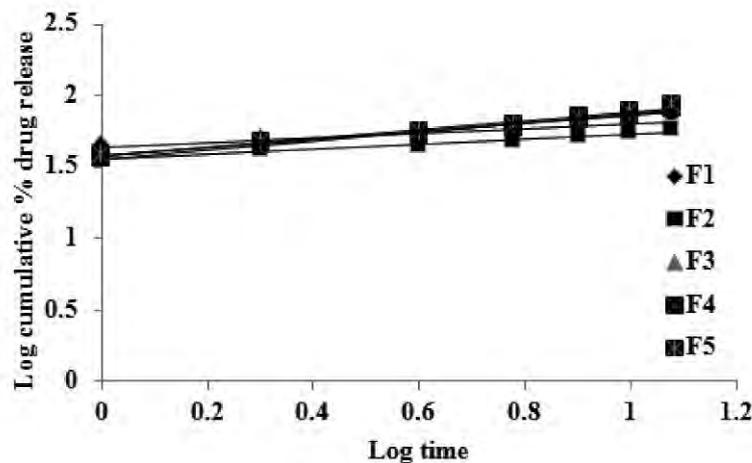
The optimized formulation (F5) was subjected to accelerated stability studies were conducted according to the International Conference on Harmonization (ICH) guidelines by storing the transdermal patches at 40±0.5 °C

and 75±5% RH for 3 months [12].

### 3. Results and discussion

#### 3.1. Pre formulation studies

The DSC scan of indomethacin showed a short endothermic peak at 215.50 °C. The thermogram of formulated transdermal patches showed an endothermic peak of drug at 215.07 °C and 215.68 °C, respectively, indicating a slight change in terms of shifting towards the lower temperature. This minor change in the melting endotherm in the drug could be due to the mixing of the drug and excipients which lower the purity of each component in the mixture and may not necessarily indicate potential incompatibility. The characteristic peaks in FTIR spectrum of indomethacin were also observed even in formulation blend, indicating that there is no incompatibility between the indomethacin and the excipients used.

**Figure 10.** KorsmeyerPeppas's plots prepared transdermal patches.

**Table 5.** Results of skin irritation test of formulated transdermal patches.

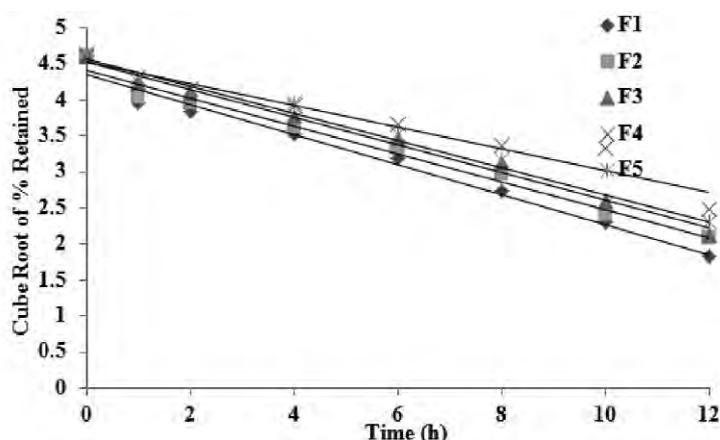
Formulation	Visual observation	
	Erythema	Edema
Normal	0.00±0.00	0.00±0.00
Adhesive tape (USP)	1.31±0.21	1.60±0.25
F5 (Indomethacin-patch)	1.52±0.35	1.24±0.17
Blank	1.51±0.14	1.18±0.42
Formalin (0.8% v/v)	3.75±0.18	3.39±0.36

Visual observation values are expressed as Mean ±SEM, n=6; \* Significant compared to formalin ( $p<0.05$ ); F-5=Indomethacin *Ficus glomerata* fruit mucilage patch; Blank=Patch without drug

### 3.2. Post formulation studies

The thicknesses of formulated matrix transdermal patches ( $630\pm35.6$  to  $690\pm25.6$   $\mu\text{m}$ ) showed uniformity in thickness. The tensile strength of formulated patches ( $0.285\pm0.25$  to  $0.326\pm0.10$   $\text{kg}/\text{cm}^2$ ) and the elongation of the patches ( $15.33\pm0.89$  to  $26.23\pm0.84$   $\text{N}/\text{mm}^2$ ) were within the limits. The prepared patches did not show any signs of cracking, which might be attributed to the addition of the plasticizer, propylene glycol. The folding endurance of the patches ( $98\pm1.8$  to  $124\pm0.9$ ) indicates that the formulated patches maintain their integrity without breaks up on the general usage of patch. All these values were shown in Table 3. The formulated patches showed uniformity in weight ( $1.561\pm0.51$  to  $1.597\pm0.01$  g). The moisture content ( $2.645\pm0.35$  to  $2.854\pm0.56\%$ ) in the formulated transdermal patches was low, which helps the patches to remain stable and from being a completely dried and reduce brittleness during storage. The patches showed uniformity in drug content ( $97.4\pm0.02$  to

$100.7\pm0.45\%$ ). All these values are shown in Table 4. The patches did not show any visible erythema or edema with the formulation or the base used. The results of skin irritation studies are shown in Table 5. The drug permeation from prepared patches was sustained within the therapeutic range. The drug release mechanism from the formulated patches was non-Fickian transport (Figures 7 to 11). The SEM photograph (Figure 12 A, 12 B and 12 C) indicates the uniform dispersion of polymeric solution with drug molecule and the *Ficus glomerata* based patch shown porous surface, which may be suitable for the matrix system. In the present work accelerated stability studies were carried out for selected formulation (F5) at  $40\pm0.5$  °C and  $75\pm5\%$  RH for 3 months. The values of physicochemical properties before and after accelerated stability studies are shown in Table 5. The accelerated stability studies indicate that the formulation is quite stable at accelerated environmental conditions. Physical parameters before and after

**Figure 11.** Hixson Crowell's plots of prepared transdermal patches.

**Table 6.** Physical parameters before and after stability study of optimized F5 patches.

Parameter	Before stability studies	After stability studies (90 days)
Thickness ( $\mu\text{m}$ )	635 $\pm$ 29.60	634 $\pm$ 23.0
Elongation brake (%)	26.23 $\pm$ 0.84	25.18 $\pm$ 0.20
Folding endurance	119 $\pm$ 1.40	115 $\pm$ 2.30
Tensile strength (N/mm <sup>2</sup> )	0.326 $\pm$ 0.10	0.321 $\pm$ 0.19
Moisture content (%)	2.854 $\pm$ 0.56	2.828 $\pm$ 0.25
Moisture uptake at RH 75% (%)	3.206 $\pm$ 0.37	3.186 $\pm$ 0.65
Moisture uptake at RH 93% (%)	3.906 $\pm$ 0.59	3.907 $\pm$ 0.16
Drug content (%)	100.7 $\pm$ 0.45	100.5 $\pm$ 0.11

accelerated stability study of optimized F5 patches are shown in Table 6.

#### 4. Conclusion

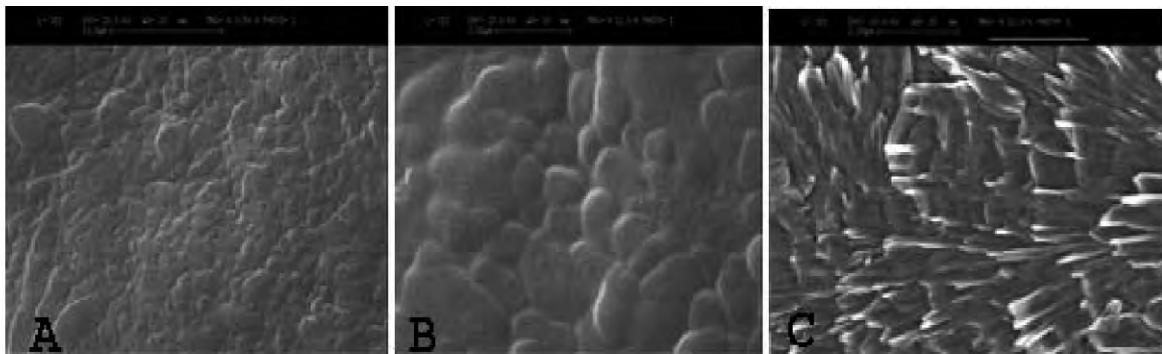
This investigation revealed that *F. glomerata* fruit mucilage appears to be suitable for use as a matrix former in the manufacturing of transdermal patches because of its satisfactory physical and mechanical properties. The formulated patches did not show any visible erythema or edema with the *F. glomerata* fruit mucilage, which indicates that the formulated patches are compatible with the skin and devoid of potential skin irritation and hence it can be used for transdermal application. The drug permeation from prepared patches was sustained within the therapeutic range. The accelerated stability studies indicate that the formulation is quite stable at accelerated storage conditions. The *in-vitro* permeation data revealed that dried *F. glomerata* fruit mucilage can be used as a matrix former in transdermal patches.

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**Figure 12.** SEM of formulated transdermal patches (A, B and C) at various magnifications.

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