Designing and characterizing of tramadol hydrochloride transdermal patches prepared with *Ficus carica* fruit mucilage and povidone

Hindustan Abdul Ahad*, Beludari Mohammed Ishaq, Muneer Shaik and Faheem Bandagisa
Department of Pharmaceutics, Balaji College of pharmacy, Anantapur, Andhra Pradesh, India

Abstract: The purpose of this investigation was to prepare matrix type transdermal patches of Tramadol HCl using various ratios of *Ficus carica* fruit mucilage and Povidone. The matrix type transdermal patches were prepared using Tramadol HCl with *Ficus carica* fruit mucilage and Povidone. The interactions between Tramadol HCl with *F. carica* fruit mucilage and Povidone were performed by Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared spectroscopy (FTIR). The prepared patches were examined for physicochemical characterization and *in vitro* drug permeation studies (using a Keshary-Chien diffusion cell across hairless Albino rat skin), skin irritation studies and accelerated stability studies. The drug was found to be free from negligible interactions with the polymers used. The formulated patches possessed satisfactory physicochemical properties, *in vitro* drug permeation and devoid of serious skin irritation. The selected formulation (F-5) was retains the characteristics even after the accelerated environmental conditions. The study concludes that *F. carica* fruit mucilage with Povidone is a good combination for preparing transdermal patches.

Keywords: Tramadol HCl, *Ficus carica* fruit mucilage, Povidone, transdermal patches, *in vitro* permeation.

INTRODUCTION

Transdermal delivery has many merits over normal dosage forms as it bypasses liver first pass metabolism, termination of therapy with ease and convenient to patients (Chien, 1992). Many researchers suggested transdermal route is an attractive route for lipophilic drugs in to blood circulation (Jain, 1997). Tramadol HCl is prescribed for the treatment of pain, inflammation and arthritis (McNaman *et al.,* 1996). It has a melting point of 179-180°C and partition coefficient 1.35 (Octanol water system) at pH 7. These characteristics make this drug to administer through this route (Finnin, 2003). In this study, *F. carica* fruit mucilage and Povidone were used as a matrix polymer for controlling release of Tramadol HCl in transdermal patches.

MATERIALS AND METHODS

Materials

Tramadol HCl was gifted from Unichem laboratories, Mumbai. *Ficus carica* fruits were obtained from the main market of Anantapur and authenticated by the department of Pharmacognosy, Balaji College of Pharmacy, Anantapur. Glycerin, Propylene glycol, Povidone, Span-80, Methyl paraben and Propyl paraben were received from S.D. Fine chemicals Mumbai. The reagents employed in this study were of Analytical Reagent grade. The drug samples were characterized and authenticated by solubility, melting point, pH and UV spectro-photometric methods.

**Corresponding author:* e-mail: abdulhindustan@rediffmail.com

Extraction of the mucilage

The fresh ripen fruits of *F. carica* were obtained from main market of Anantapur, India. The *F. carica* fruits were washed (to remove dirt/debris) with water then cut it into pieces. The seeds inside the *F. carica* fruits were separated. The pulps of the *F. carica* fruits were mashed and drenched in water for 5-6h, boiled for 30 min and abandon physically to stand for 1 h for complete release of mucilage into water. The mucilage was draw out using a multi-layer muslin cloth bag to remove the marc. Acetone was added (3 times the volume of filtrate) to precipitate the mucilage. Then the mucilage was divided, dried at 40°C in Hot Air Oven. The dried mucilage was compiled, milled, passed through a # 80 sieve and preserved at 30°C and 45% RH in a desiccator till its use (Mark *et al.,* 1917).

Purification of the mucilage

The crude mucilage (1%) was homogenized (Potter homogenizer) with cold dilute tri chloro 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 (Khandelwal, 2004).

Characterization of the mucilage

The collected mucilage was evaluated for physicochemical characteristics viz., morphological characteristics, chemical identification tests, solubility, pH, melting range, Ash values, foreign organic matter,

heavy metals, Density, Loss on drying, flow properties, compressibility index and swelling index as per Indian Pharmacopoeia (Indian pharmacopoeia, 1996).

Compatibility studies

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 30°-300°C in nitrogen atmosphere (20 ml/min) with a sample weight of 3.0012mg. The DSC thermo grams were shown in fig. 1.

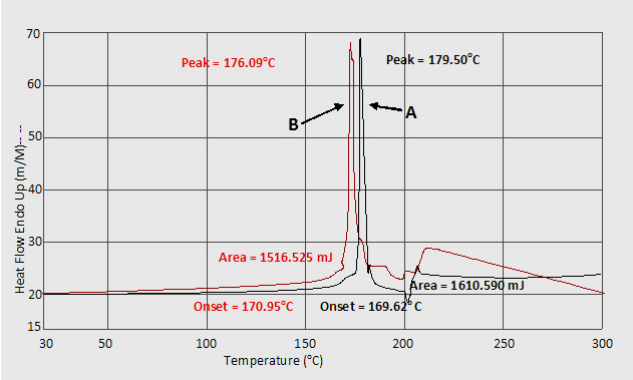

Fig. 1: DSC spectrums of A) Pure drug; B) Formulation blend (F-5)

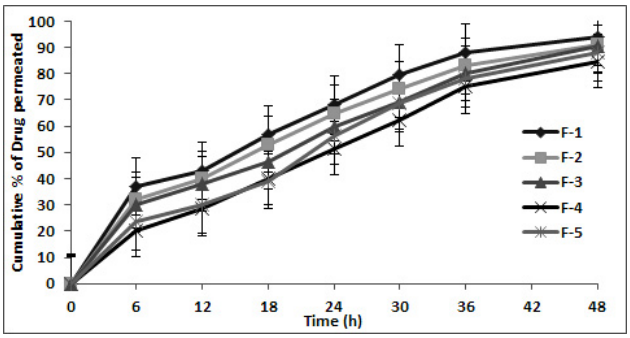

Fig. 2: Zero order plots of transdermal patches

Fourier transform infra-red (FTIR) spectral analysis

FTIR spectrums of Tramadol HCl with *F. carica* fruit mucilage were obtained individually and in combinations on a Fourier Transform Infrared spectrophotometer (Perkin Elmer, spectrum-100, Japan) with KBr disk technique (4.9914mg sample in 299.0025mg KBr). The sample was scanned from 400 to 4000cm^{-1} at a resolution of 1 cm^{-1}. The FTIR spectrums were shown in fig. 2.

Preparation of transdermal patches

Transdermal patches were prepared by the solvent evaporation technique. Various proportions of *F. carica* 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 Tramadol HCl (100mg) was added with continuous stirring in magnetic stirrer for 30min at 500rpm. The obtained homogeneous solution was spread onto a silicone-coated release liner (Shivam Trading Company, Mumbai, India) on which a glass bangles of 6.1cm diameter and placed on mercury surface in a Petri dish and a funnel was inverted on it. After it was settled at the room temperature for 10 min. The formed patches were heated in an oven at 40±2°C for 24h to completely remove the solvent. By this a release layer of drug was prepared. Finally, the patches were covered with a fabric backing film (Rustx - Hi Tech International, Raigad, India). Later stored in desiccator till use (Williams and Barry, 1990; Davis and Illum, 1998; Geeta and Sanju, 2009; Hindustan, 2010). The formulae of various transdermal patches were shown in table 2.

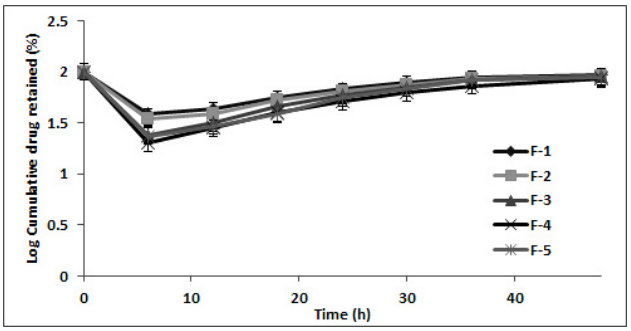

Fig. 3: First order plots of transdermal patches

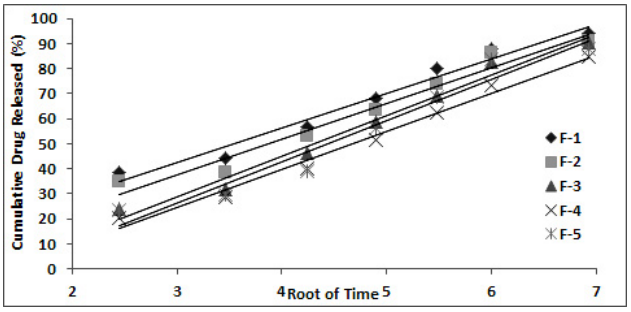

Fig. 4: Higuchi's plots of transdermal patches

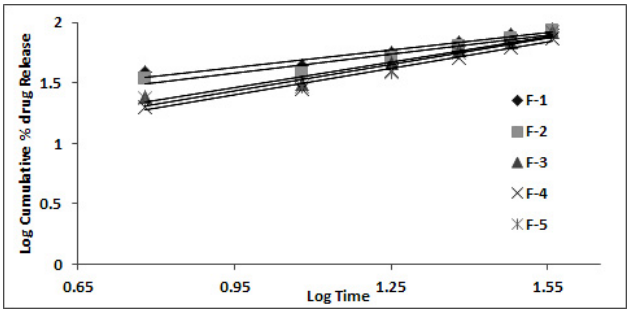

Fig. 5: Korsmeyer Peppa's plots of transdermal patches

Evaluation of physicochemical parameters

Thickness

The thickness of the formulated patches was determined using Digital caliper (BAKER-EC 10, Hyderabad, India). The thickness was measured at five different locations and average was calculated.

Tensile strength

Tensile strength of formulated patches was estimated by using computerized balance (Chiksan bottom-loading balance) with few alterations. Tensile strength of a 1x1cm transdermal patch was studied.

Flatness and elongation brake

The prepared transdermal patches were cut longitudinally. The flatness was determined at different by using Vernier calipers (COLUMBUS, Mumbai, India). The length before and after the brake point was determined and it is expressed as follows (Prashant *et al.*, 2005).

Elongation (%) = $L_1 - L_2$ X 100/ L_2

Where, L_1=final length of each patch; L_2=initial length of each patch

Folding endurance

It can be determined by repeatedly folding a small piece of the patch (2 x 2cm size) at the same point till it breaks. The number of times the formulated patch can be folded without breaking was the folding endurance of the patch (Tanwar, 2005).

Moisture content

The formulated patches were individually pre weighed and kept in a desiccator at 30°C for 12h (containing activated silica). 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 patches were cut into 20×50mm size. The patch was weighed and kept in a desiccator

Table 1: Different formulae of transdermal patches

Ingredients	F-1	F-2	F-3	F-4	F-5
Tramadol HCl (mg)	100	100	100	100	100
Ficus carica fruit mucilage (%)	5	10	15	20	25
Povidone (mg)	2.5	5	7.5	10	12.5
Glycerin (ml)	0.18	0.18	0.18	0.18	0.18
Propylene Glycol (ml)	0.24	0.24	0.24	0.24	0.24
Span-80 (ml)	0.06	0.06	0.06	0.06	0.06
Methyl paraben (g)	0.025	0.025	0.025	0.025	0.025
Propyl paraben (g)	0.025	0.025	0.025	0.025	0.025
Water (vehicle) up to (ml)	20	20	20	20	20

Table 2: Result of mechanical properties of formulated transdermal patches

Formulation	Thickness (µm)	Tensile strength (N/mm^2)	Elongation (%)	Folding endurance
F-1	695±2.28	0.312±0.07	16.15±2.36	76±7.0
F-2	698±5.93	0.315±0.05	17.55±1.85	80±4.0
F-3	685±3.69	0.318±0.02	18.85±1.98	82±6.0
F-4	680±5.15	0.325±0.04	19.52±2.33	88±2.0
F-5	682±2.26	0.333±0.01	21.38±0.04	95±1.0

Table 3: Result of mean weights, moisture content, moisture uptake and dug content of formulated transdermal patches

Formulation	Weights (g)	Moisture content (%)	Moisture uptake (%)		Drug Content (%)
			RH 75%	RH 93%	
F-1	1.563±0.19	2.46±0.26	4.20±0.49	4.19±0.43	99.92±0.59
F-2	1.556±0.18	2.50±0.26	4.10±0.46	4.51±0.04	99.66±0.25
F-3	1.551±0.25	2.29±0.13	3.16±0.59	4.25±0.44	100.80±0.18
F-4	1.560±0.35	2.28±0.30	2.18±0.09	4.21±0.08	99.35±0.19
F-5	1.562±0.04	2.22±0.01	2.15±0.01	3.28±0.02	100.23±0.39

All values mentioned as mean ±S.D; Number of trials (n) = 5

Table 4: Results of skin irritation test

Formulation	Visual observation	
	Erythema	Edema
Normal	0.00±0.00	0.00±0.00
Adhesive tape (USP)	1.36±0.01	1.66±0.05
F-5 (Tramadol HCl-patch)	1.59±0.01	1.26±0.09
Placebo	1.42±0.01	1.21±0.02
Formalin (0.8% v/v)	3.79±0.02	3.39±0.03

All observations were expressed as Mean ±SEM, Number of trials (n) =6; F-5=formulated transdermal patch

Table 5: Mean percent reduced blood glucose levels with F-5 transdermal patches vs. placebo in rabbits

Time (h)	Mean Reduced blood glucose levels (%)	
	Group-I (Control) Placebo	Group-II F-5
0	0.000±0.000	0.00±0.00**
4	0.006±0.001	12.3±0.02**
8	0.012±0.001	39.5±0.14**
12	0.007±0.001	37.6±0.91**
16	0.022±0.001	38.9±0.03**
22	0.019±0.001	39.8±0.05**
28	0.006±0.000	30.5±0.03**
36	0.001±0.000	32.8±0.04**
42	0.006±0.001	27.8±0.05**
48	0.005±0.001	26.5±0.01**

All values mentioned as mean ±S.D; Number of animals (n)=6 P**<0.01, highly significant when compared with normal control

Table 6: Accelerated stability study of selected F-5patches

Parameter	Before Stability studies	After Stability studies
Thickness (µm)	682±2.26	682±2.25
Elongation (%)	21.38±0.04	21.38±0.03
Folding endurance	95±1.0	95±1.0
Tensile strength (N/mm^2)	0.333±0.01	0.333±0.01
Moisture content (%)	2.22±0.01	2.22±0.01
Moisture uptake at RH 75% (%)	2.15± 0.01	2.14±0.01
Moisture uptake at RH 93% (%)	3.28±0.02	3.27±0.01
Drug content (%)	100.23±0.39	100.22±0.22

All values mentioned as mean ±S.D; Number of trials (n) = 3

(containing saturated solution of calcium chloride) at 30°C and dried for at least 12h till the patch shows constant weight. The moisture content was the difference between the constant weight taken and the initial weight (Tanwar, 2005).

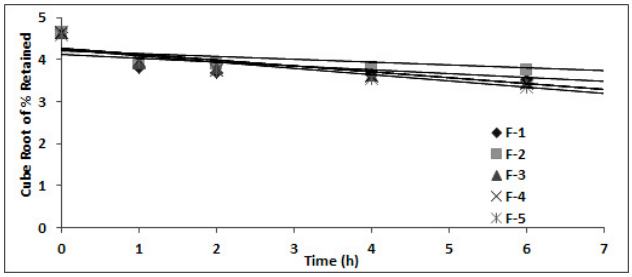

Fig. 6: Hixon Crowell's plots of transdermal patches.

Drug content of the patch

A 5x5cm transdermal film was cut into small pieces, kept in 100ml phosphate buffer of pH 7.4 and shaken continuously for 24h. The resulting solution was then ultra sonicated for 15min and filtered. The drug content was estimated spectrometrically using UV/Visible spectrophotometer (Elico SL 210, Mumbai, India) at wavelength of 272nm (Shinde *et al.*, 2008).

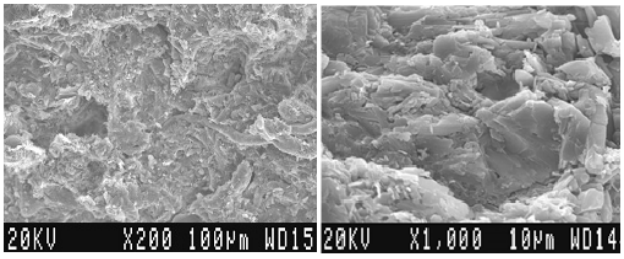

Fig. 7: SEM photographs of formulated patches (F-5) at 200 x and 1000x

Moisture uptake

Moisture uptake of the patches was determined by keeping the patches in a desiccator with activated silica until constant weight. The weight gained was determined. The water uptake capabilities of the various patches were determined at 75% RH and 93% RH. The patches were cut into 25×60 mm size, weighed and placed in a desiccator at 40°C for 24 h. Then the patch was placed in a desiccator at 75% RH (containing saturated solution of sodium chloride) and 93% RH (containing saturated solution of ammonium hydrogen phosphate) at room temperature. Later the patches were measured periodically to constant weights and the water absorption capacity was calculated (Satturwar *et al.*, 2005).

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 for 12h on receptor to remove any interfering UV absorbing material. The *in vitro* skin permeation of Tramadol HCl from various transdermal patches was studied using KC diffusion cell. 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 receptor cell volume was 17.5ml. The receptor compartment contained a phosphate buffer saline of pH 7.4, which was stirred by a magnetic stirrer. The temperature was maintained at 32±0.5°C (USP 2000; Andronis *et al.,* 1995; Bodde *et al.,* 2002; Rao *et al.,* 2003). 1 ml sample was withdrawn through the sampling port of the KC diffusion cell for the period of 48 h. The withdrawn samples were checked for absorbance at 272 nm. Three trials were made and blanks were also run simultaneously (Kurihara *et al.,* 1991; Jain *et al.,* 2008). The *in vitro* skin permeation data was treated with kinetic modeling and the plots were shown in figs. 2 to 6.

Skin irritation studies

Modified Draize test (Draize *et al.,* 1994) was adopted for skin irritation studies on selected six rabbits. The hairs at the dorsal area of rabbits were removed by shaving 24 h before test. The untreated skin area of the rabbit's back serves as the control and other as experimental side. The formulated patch was applied on experimental side and the non-medicated patch on the control side of the rabbits. The medicated patches (F-5) were changed after 48 h and replaced by 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 observed for any erythema or edema (Moghimi *et al.,* 1997; Satturwar *et al.,* 2005).

Scanning electron microscopy (SEM) studies

The selected formulation's (F-5) surface morphology was studied by using Scanning Electron Microscope (FE-SEM, Carl Zeiss, Germany). The SEM photographs were shown in fig. 7.

Accelerated stability studies

The optimized formulation (F5) was subjected to accelerated stability studies as per ICH guidelines by storing the transdermal patches at 40±0.5°C and 75±5% RH for 3 months (Remunan *et al.,* 1992) using programmable environmental test chamber (Remi, India). Physical parameters before and after accelerated stability study of optimized F-5 patches were observed.

RESULTS

The mucilage characteristics were found acceptable. Drug-excipient compatibility studies were shown in Fig.1. The results of physicochemical characteristics, skin irritation test, percent reduced blood glucose levels with F-5 transdermal patches vs. Placebo in Rabbits, accelerated stability study of selected F-5 patches were shown in table 3, 4, 5 and 6 respectively. The kinetic plots for *in vitro* drug permeation were shown in Fig.2 to 6 and SEM photographs of F-5 patches were shown in Fig.7. All the evaluation parameters were within limits and found satisfactory.

DISCUSSION

Mucilage characteristics

The extracted mucilage was brownish yellow in colour with sweet odour and soluble in water produces yellowish viscous solution. The fruits gave 39±2.05% of yield. The Average particle size of dried mucilage was 132.06±2.26 µm. The Average particle size of dried mucilage was found to be uniform. The weight loss on drying was 2.85±0.06 and the percentage of swelling was 56.5±1.45%, which was found to be satisfactory. The dried mucilage was melted and charred at 162±2.5^{o}C. The density of 1.0% w/v solution was 1.006±0.01 and a pH of 7.2±0.1. All above trials were performed in triplicate. The mucilage has very negligible bio burden. The mucilage gave positive test for carbohydrates and uronic acid (common for all mucilages) and negative test for tannins, chlorides and sulphates. The amount of foreign matter was negligible. The heavy metal concentration was also found to be within the limits.

Compatibility studies

The DSC scan of Tramadol HCl showed a short endothermic peak at 179.50^{o}C. The thermo gram of formulated transdermal patches showed an endothermic peak at 176.09^{o}C indicating a slight change in terms of shifting towards the lower temperature. This minor change in the endotherm may be because of mixing of the drug with excipients used, which lowered the purity of each component. The characteristic peaks in FTIR spectrum of Tramadol HCl were also observed even in formulation blend, indicating that there is no incompatibility between the Tramadol HCl and the excipients used.

Physicochemical characteristics

The thicknesses of formulated matrix transdermal patches (680±5.15 to 698±5.93µm) showed uniformity in thickness. The Tensile strength of formulated patches (0.312±0.07 to 0.333±0.01 N/mm^2) and the elongation of the patches (16.15±2.36 to 21.38±0.04%) were within the limits, the percent elongation in formulations F-1, F-2, F-3 and F-4 were shown significantly deviated. The prepared patches did not show any signs of cracking, which might be because of the plasticizer (Propylene glycol). The folding endurance of the patches was increased as the proportion of *F. carica* fruit mucilage

increased in the formulation and it was range from 76±8.0 to 95±1.0 indicates that the formulated patches maintain their integrity without breaks up on the general usage of patch. All these values were shown in table 2.

The formulated patches showed uniformity in weight (1.551±0.25 to 1.563±0.19g). The moisture content in the formulated patches was ranged from 2.22±0.01 to 2.50±0.26 %. The moisture uptake of the prepared patches at 75% RH was ranged from 2.15±0.01 to 4.20± 0.49 and at 93% RH it was 3.28±0.02 to 4.51±0.04, which were minimal and helps the patches to remain stable and from getting dried completely and reduce brittleness during storage. The patches showed uniformity in drug content (99.35±0.19 to 100.80±0.18%). All these values were shown in table 3.

The drug permeation from prepared patches was sustained within the therapeutic range. The drug release mechanism from the formulated patches was Non-Fickian transport (fig. 2 to fig. 6). The patches did not show any visible erythema or edema with the formulation or the base used. The results of skin irritation studies were shown in table 4.The SEM photograph (fig. 7) indicates the uniform dispersion of polymeric solution with drug molecule and the *F. carica* fruit mucilage based patch shown porous surface, which may be suitable for the matrix system.

Formulation F-5 was selected for accelerated stability studies at 40±0.5°C and 75±5% RH for 3 months, because the percent elongation in formulations F-1, F-2, F-3 and F-4 were significantly varied. The folding endurance in formulations F-1, F-2 and F-3 were significantly varied. The weights of the formulations F-1, F-2, F-3 and F-4 were significantly varied. The percent moisture uptake at 75% RH for the formulations F-1, F-2 and F-3 were significantly varied and at 93% RH the formulations F-1 and F-3 were significantly varied. The values of physicochemical properties before and after accelerated stability studies were shown in table 5. The accelerated stability studies indicate that the formulation is quite stable at even at accelerated environmental conditions.

CONCLUSION

The study explores that *Ficus carica* fruit mucilage in combination with Povidone found to be suitable for use as a matrix forming polymers as the prepared patches gave satisfactory physical and mechanical properties. The prepared patches did not show any signs of potential skin irritation (no visible erythema/edema). This implies the prepared patches are found to compatible with the skin and hence can be used for preparing transdermal patches. The permeation of drug from the prepared patches was sustained within the therapeutic window. The accelerated stability studies indicate that the prepared patches are stable even at stressed storage conditions. The *in vitro* permeation data revealed that dried *F. carica* fruit mucilage with Povidone can be used as a matrix former for making transdermal patches.

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