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Permeation studies of Diclofenac sodium From Ficus carica fruit mucilage matrices for transdermal delivery

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ABSTRACT: The main objective of the present study was to develop matrix-moderated transdermal systems of Diclofenac sodium and to evaluate them with respect to various *in vitro* parameters. The matrix-type transdermal systems were prepared using Diclofenac sodium with *Ficus carica* fruit mucilage by the solvent evaporation technique. The drug (Diclofenac sodium) and polymer (*Ficus carica* fruit mucilage) interaction studies were performed. The transdermal patches were subjected to various physicochemical parameters viz. mechanical properties, permeation studies and skin irritation studies. The prepared patches possessed satisfactory pre formulary and formulary characteristics. *In vitro* permeation studies were performed using a Keshary-Chien diffusion cell across hairless Albino rat skin. The non-ionic surfactants Span 80 was used as permeability enhancer. The patches were seemingly free of potentially hazardous skin irritation. Hence, it can be concluded that Diclofenac sodium can be developed as a transdermal delivery system with *Ficus carica* fruit mucilage that is an alternative to intravenous administration and has minimal adverse effects.

KEY WORDS: Diclofenac sodium, *Ficus carica* fruit mucilage, transdermal delivery.

INTRODUCTION

Diclofenac sodium, an effective anti-diabetic drug that requires controlled release owing to its short biological half-life of 3.4 ± 0.7 h[1], was used as the core in transdermal matrix patches. The transdermal patches were evaluated in vitro and in vivo methods for controlled release. Various experimental reports indicated that Diclofenac sodium as a good candidate for controlled release formulation[2]. In this study, *Ficus carica* fruit mucilage was used as a matrix polymer for controlling release of Diclofenac sodium.

MATERIALS AND METHODS

Materials

Diclofenac sodium was obtained as a gift sample from Dr. Reddy's laboratories, Hyderabad. *Ficus carica* fruits were obtained from the main market of Anantapur and authenticated by the Botany department of Sri Krishnadevaraya University, Anantapur. Glycerin, Propylene glycol Methyl paraben, Propyl paraben, Span-80 procured from S.D. Fine chemicals Mumbai. All the reagents used were of AR grade. The drug samples were characterized by means of UV spectrophotometric method along with determination of solubility and pH for their authentication.

Methods

Extraction of mucilage[3]

The fresh ripen fruits of *Ficus carica* were obtained from main market of Anantapur town. The fruits were thoroughly washed with water to remove dirt and

debris and cut 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 minutes and left to stand for 1 hour 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. 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.

Preparation of transdermal films

Various proportions of *Ficus carica* mucilage was taken in a beaker add Propylene glycol (plasticizer), Span-80 (penetration enhancer) Propyl paraben, Methyl paraben (preservatives) and Diclofenac sodium (30 mg) were added with continuous stirring using teflon-coated magnetic bead placed in magnetic stirrer for 30 minutes 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. After 24 h the dried films were taken out and stored in desiccator. The quantities in the formulae were showed in **table 1.**

Evaluation of Transdermal Films

The films were evaluated for the following physicochemical properties:

Thickness: The thickness of the patch was determined using Digital caliper **(**BAKER-EC 10, Hyderabad, India**).**The mean thickness was measured at five different points of the film.

Moisture content[7]: The strips were then weighed individually and kept in a dessicator containing activated silica at 30°C for 12 h. The films were reweighed individually until a constant weight was obtained. Percentage of moisture content was then calculated based on the change in the weight with respect to the initial weight of the film. The prepared patches were cut into 20 × 50 mm strips. The film was weighed and kept in a desiccator containing calcium chloride at 30°C and dried for at least 12 h. The film was weighed until it showed a constant weight. The moisture content was the difference between the constant weight taken and the initial weight.

Flatness and elongation brake[8]: Longitudinal strips were cut out from the prepared transdermal patches. The flatness was determined at various points by using vernier calipers calculated. The percentage elongation brake was determined by noting the length just before the break point and substituted in the following formula

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

Where L_1 = final length of each strip; and L_2 = initial length of each strip.

Moisture uptake[9]: The water absorption capacities of various films were determined at 75% and 93% relative humidity (RH). Films were cut into 25 × 60 mm strips. A strip was weighed and kept in a dessicator at 40°C for 24 h, removed and exposed to RH conditions of 75% (containing saturated solution of sodium chloride) and 93% (containing saturated solution of ammonium hydrogen phosphate) in different desiccators at room temperature. Then the films were measured periodically to constant weights. The water absorption capacity of the films (in weight %) was calculated in terms of percentage increase in the weight of film over the initial weight of the specimen.

Determination of tensile strength[10]: Tensile strength was determined by using computerized Precisa bottom-loading balance, with necessary modifications. A 1 x 1cm patch was taken and subjected to studies.

Drug content determination of film

Four pieces of 1 cm^2 each (1 x 1 cm) were cut from different parts of the prepared trans dermal patch. Each was taken in separate stoppered conical flasks containing 100 mL of suitable dissolution medium (0.1-N HCL: CH_3OH mixture) and stirred vigorously for 6 h using magnetic stirrer. The above solutions were filtered and suitable dilutions were made. Absorbances were observed using UV-Visible spectrophotometer (Systronics 117) at their respective wavelengths, against a blank solution which was prepared by the same protocol but not containing drug.

Evaluation of skin irritation potential of polymeric matrices [11, 12, 13]

The primary skin irritation studies were carried out using modified Draize test. The hair of rabbits were removed by shaving from the dorsal area on both sides 24 h before test, one side of the back of each rabbit i.e. untreated skin area serves as the control for the test. Medicated patch was secured on experimental side using adhesive tape and the non-medicated patch was adhered on the control side of six rabbits. These patches were covered with occlusive covering to approximate the condition of use. The medicated patches were changed after 48 h and the fresh patches were secured at the same site. However the patches on the control side were not changed. The patches were secured on the back for seven days. After removal of patch after a week each of the areas were examined for any sign of erythema or oedema.

***In vitro* skin permeation studies with polymeric matrices[14, 15]:** The transdermal patches were subjected to in vitro evaluation across rat dorsal skin. After removal of epidermal hair, skin was cleaned and any

adhering subcutaneous tissue and blood vessels were removed. The skin was mounted overnight (12 h) on receptor phase to remove any water-soluble (UV absorbing) material. The in vitro skin permeation of Diclofenac sodium from various transdermal patches was studied using locally fabricated Keshary-Chien type of diffusion cell. The diffusion cell consists of two parts; the upper part i.e. the donor compartment and contains the active ingredient and the carrier adhesive/patch; the bottom part contains the receptor solution, the water jacket for temperature control and the sampling port. The effective permeation area of the diffusion cell and receptor cell volume was 1.0 cm^2 and 17.5 ml, respectively. The temperature was maintained at 37±2°C. The receptor compartment contained 17.5 ml of phosphate buffer saline (PBS) IP (pH 7.4) stirred by magnetic stirrer. The permeability studies were carried out across both rat and cadaver skin. Samples (1.0 ml) were withdrawn and replaced with the same volume of fresh receptor solution, through the sampling port of the diffusion cell at predetermined time intervals till 48 h. Absorbances of the withdrawn samples were measured at 276 nm. The experiments were done in triplicates, simultaneously blanks were also run and the average values reported. The matrices showing promising results from rat skin were evaluated across cadaver skin to determine actual permeation across human skin. Full thickness human chest skin samples were obtained after autopsy. Underlying fatty tissue was removed. Epidermal membranes were prepared using heat separation method. In this method, the full thickness skin samples were immersed in water at 60° for 45 seconds.

RESULTS AND DISCUSSION

The mechanical properties viz. thickness, tensile strength, elongation and folding endurance of formulated transdermal patches (table 2) were within the limits and were represented in table 2. The mean weights, moisture content, moisture uptake (at RH 75% and RH 93%) and dug content of formulated transdermal patches were within the limits(table 3). The results of skin irritation studies showed negligible erythema with prepared films when compared with control (table 4). The absence of edema indicates that the polymeric patches are compatible with the skin and hence can be used for transdermal application. The dissolution data was interpreted with the pharmacokinetic calculations viz. zero order, first order, Higuchi, Peppa's and Hixon Crowell's plots which proves that dried *Ficus carica* fruit mucilage can be used as a matrix former in transdermal delivery systems.

CONCLUSIONS

This investigation revealed that *Ficus carica* 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 In vitro permeation data revealed that dried *Ficus carica* fruit mucilage can be used as a matrix former in transdermal delivery systems.

Table-1: Different formulae of Diclofenac sodium with *Ficus carica* mucilage

INGREDIENTS	DFC-1	DFC-2	DFC-3	DFC-4	DFC-5
Diclofenac sodium(mg)	100	100	100	100	100
Ficus carica fruit mucilage (%)	04	08	12	16	20
Glycerin(ml)	0.3	0.3	0.3	0.3	0.3
Propylene Glycol(ml)	0.18	0.18	0.18	0.18	0.18
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)	0.015	0.015	0.015	0.015	0.015
Water up to (ml)	20	20	20	20	20

Table 2: Mechanical properties of Diclofenac sodium transdermal patches

Parameter	Thickness (µm)	Tensile strength (N/mm^2)	Elongation (%)	Folding endurance
DFC-1	755±12.6	0.393±0.06	21.45±0.55	99±1.0
DFC-2	765±58.7	0.296± 0.06	29.65±0.10	102±0.8
DFC-3	745±56.5	0.325± 0.11	34.54±0.15	112±1.2
DFC-4	775±48.3	0.347± 0.10	38.56±0.58	100±0.8
DFC-5	750±28.5	0.317± 0.09	41.11±0.33	119±0.5

Number of trials (n) = 3

Table 3: 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%	
DFC-1	1.672±0.12	2.958±0.26	4.102±0.45	7.159±0.02	99.3±0.25
DFC-2	1.666±0.15	3.125±0.23	5.016±0.88	5.368±0.24	98.9±0.24
DFC-3	1.675±0.06	2.989±0.25	4.578±0.15	4.892±0.68	90.5±0.68
DFC-4	1.689±0.15	3.124±0.34	3.451±0.16	5.208±0.65	101.7±0.12
DFC-5	1.669±0.17	3.054±0.51	4.354±0.87	8.180±0.61	91.9±0.61

Number of trials (n) = 3

Table 4: Results of skin irritation test.

Formulation	Visual observation	
	Erythema	Edema
Normal	0.00±0.00	0.00±0.00
Adhesive tape(USP)	1.45±0.21	1.60±0.25
DFC-5 (Diclofenac patch)	1.62±0.35	1.24±0.17
Blank	1.51±0.14	1.18±0.42
Formalin (0.8% v/v)	3.85±0.18	3.49±0.36

Visual observation values are expressed as Mean ±SEM, n=6; * significant compared to formalin ($p<0.05$); DFC-5=Diclofenac *Ficus carica* fruit mucilage patch; Blank= without drug;

Figure 1: Zero order plot of formulated transdermal patch

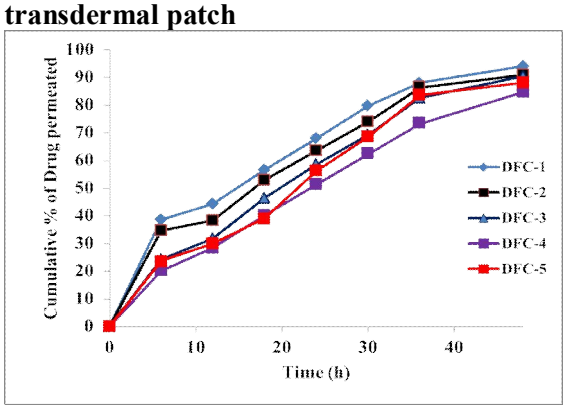


Figure 2: First order plot of formulated transdermal patch

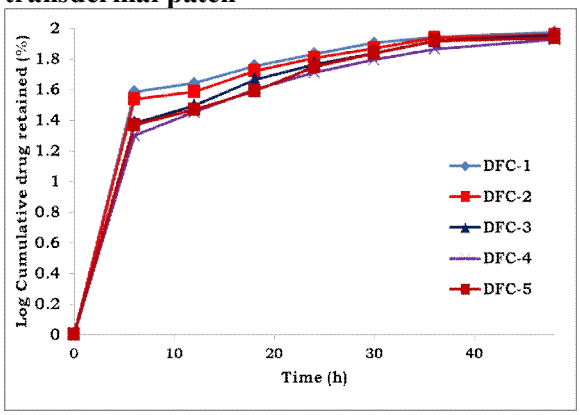


Figure 3: Higuchi's plots of formulated transdermal patch

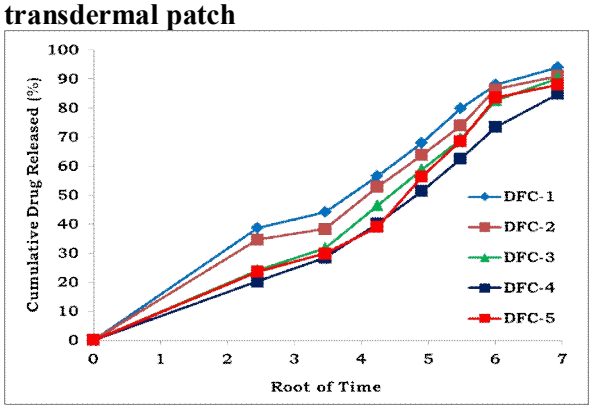


Figure 4: Peppa's plot of formulated transdermal patch

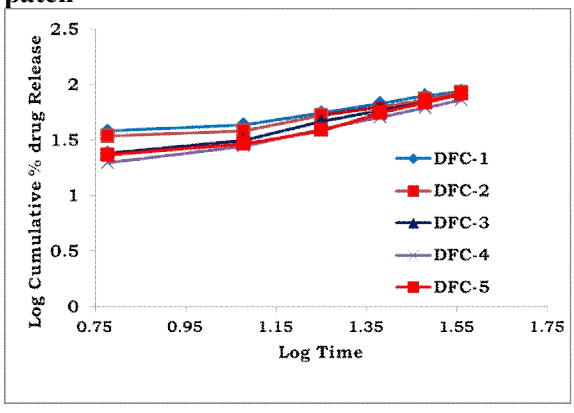
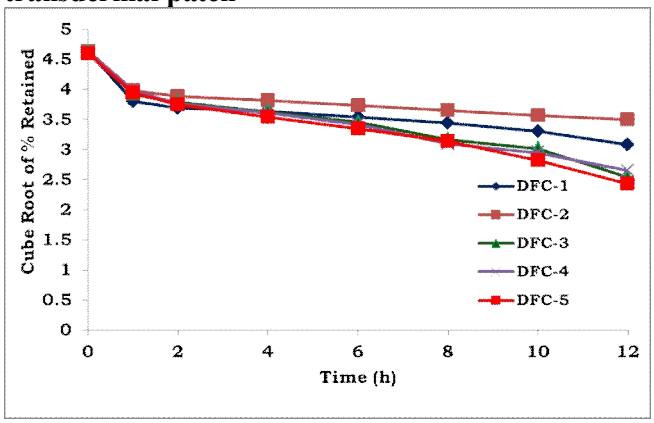


Figure 5: Hixson crowell's plot of formulated transdermal patch



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