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PERMEATION STUDIES OF PIOGLITAZONE HCL FROM *FICUS CARICA* FRUIT MUCILAGE MATRIX TRANSDERMAL PATCHES

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ABSTRACT

The main purpose of the present study was to develop matrix moderated transdermal patches of Pioglitazone HCl using various ratios of *Ficus carica fruit mucilage*. Physical parameters such as moisture content, moisture uptake, tensile strength, elongation and folding endurance were evaluated. The matrix type transdermal patches were prepared using Pioglitazone HCl with *Ficus carica fruit mucilage* by the solvent evaporation technique. The interactions between Pioglitazone Hcl and *Ficus carica* fruit mucilage and Pioglitazone HCl were performed. The transdermal patches were subjected to various physicochemical parameters like mechanical properties, permeation studies and skin irritation studies were performed. The prepared patches possessed satisfactory preformulary and formulary characteristics. *In vitro* permeation studies were performed using a Keshary-Chien diffusion cell across hairless Albino rat skin. The nonionic surfactants Span 80, Glycerin, Propylene glycol in the formulation played a key role as permeability enhancers. The patches were found to seemingly free of potentially hazardous skin irritation. The experimental result shows that the release of drug from the patch was delayed in controlled manner as the proportion of *Ficus carica* fruit mucilage increased. It was concluded that Pioglitazone HCl can be developed as a transdermal patches with *Ficus carica* fruit mucilage.

INTRODUCTION: Transdermal drug delivery system (TDDS) is one of the novel drug delivery systems. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal drug delivery systems are polymeric formulations which to applied to skin deliver the drug at a predetermined rate through dermis to exhibit systemic effects.

Pioglitazone Hcl is commonly prescribed drug for the treatment of patient with type II diabetes mellitus. It modulates the transcription of the insulin-sensitive genes which involved in the control metabolism of glucose and lipid in the lipidic, muscular tissues and in the liver. The mean serum half-life of Pioglitazone Hcl and total Pioglitazone Hcl ranges from 3 to 7 hr and 16 to 24 hr, respectively. Pioglitazone Hcl has an apparent clearance, calculated to be 5 to 7 L/hr and hence was used as core in transdermal matrix patches for controlled release of drug.

The transdermal patches were evaluated *in vitro* and for controlled release. Various experimental reports indicate that Pioglitazone Hcl as a good candidate for controlled release formulation. Ficus carica fruit mucilage has gelling property when air cooled [3, 4].

MATERIALS AND METHODS: Pioglitazone Hcl was obtained as a gift sample from Concept Pharmaceuticals, Aurangabad. *Ficus carica fruit* were obtained from the main market of Sangamner town and authenticated by the Department of pharmaceutics, AVCOP, Sangamner. Glycerin, Propylene glycol, Methyl paraben, Propyl paraben, Span-80 procured from S.D. Fine chemicals Mumbai. All the reagents used were of Analytical Reagent grade. The drug samples were characterized and authenticated by means of UV spectrophotometric method. Determination of solubility and pH is also determined.

Extraction of mucilage: The fresh fruits of *Ficus carica* were obtained from main market of Sangamner town. The fruits 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. Crushed pulp soaked in water for 5–6 hours then boiled for 30 minutes. Allow to stand for 1 hour to complete release of the mucilage into the water. The mucilage was extracted using muslin cloth bag to remove the marc from the solution. To the filtrate added Acetone (in the quantities of three times the volume of filtrate). The precipitated mucilage was separated, dried in oven at 40°C, collected, ground, passed through a sieve no. 80. Dried mucilage is stored in a desiccator at 30°C and 45% relative humidity till use.

Preparation of transdermal patches: Various ratios of *Ficus carica* mucilage were taken in a beaker, Propylene glycol (plasticizer) , Span-80 (penetration enhancer) Propyl paraben, Methyl paraben (preservatives) and Pioglitazone Hcl (10 mg) were added with continuous stirring for 30 min at 500 rpm. The above mixture was poured within the glass bangles with a diameter of 6.1 cm, placed on mercury surface of the Petri dish. The evaporation rate was controlled by inverting a funnel over the Petri dish. After 24 hours the patches are dried and stored in desiccator. The various formulae were showed in Table 1. [5, 6]

TABLE 1: DIFFERENT FORMULAE OF PIOGLITAZONE FICUS CARICA MUCILAGE TRANSDERMAL PATCHES

INGREDIENTS	F1	F2	F3	F4	F5
Pioglitazone	20	20	20	20	**20**
Ficus carica fruit mucilage (%)	2	4	6	8	**10**
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)	0.02	0.02	0.02	0.02	**0.02**
Propyl paraben (g)	0.01	0.01	0.01	0.01	**0.01**
Water up to (ml)	**20**	**20**	**20**	**20**	**20**

Pre formulation study: [7]

1. **Drug- Polymer Interaction studies:** Interaction studies were conducted on the medicated TDDS formulations by comparing them with the pure drug and placebo formulations on the basis of assay, UV and IR and DSC analyses.

2. **Assay:** The patches were dissolved in methanol and the drug content was determined by UV Spectrophotometry.

3. **UV Analysis:** The medicated and blank formulations were filtered through Whatman filter paper no. 42 and scanned spectrophotometerically at the range of 200–400 nm (Systronics-117, Mumbai).

4. **IR analysis:** The IR absorption spectra of the pure, medicated and blank formulations were taken in the range of 400–4000 cm–1 using the potassium bromide disc method (Hitachi-270-30 IR spectrophotometer, Japan).

5. **Differential Scanning Calorimeter (DSC):** The DSC of the pure drug and drug-polymer blend was studied at a scanning rate of 100C/ min between 50 to 3000C (Perkin Elmer, USA).

Evaluation of formulated Transdermal Films: [8]

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

2. **Determination of tensile strength:** Tensile strength of patch was determined by using computerized precise bottom- loading balance, with necessary modifications. A 1 X 1cm patch was taken and subjected to studies.

3. **Elongation brake:** Longitudinal strips of prepared transdermal patches cut and used. The percentage elongation brake was determined by observing the length just before the break point and substituted in the eq. 1.

Elongation (%) = L1 – L2 X 100/ L2 ---------- (1)

Where, L1 = final length of each strip; L2 = initial length of each strip.

4. **Folding endurance:** Folding endurance of patches was determined by repeatedly folding a small strip of film (2 X 2 cm) at same place till break down. The number folding at the same place without breaking was the folding endurance value.

5. **Moisture content:** The strips were weighed separately and kept in desiccator containing activated silica at 30°C for 12 hour. The films were reweighed individually until a constant weight was obtained. Percentage of moisture content was then calculated based on weight change with respect to the initial weight of the film. The prepared patches were cut into 20 × 50 mm strips.

6. **Moisture uptake:** The physicochemical properties like moisture content and moisture uptake provide the information regarding the stability of the formulation. The moisture content was determined by keeping the drug matrix patches in a desiccator containing activated silica until they showed constant weight. The percentage moisture content was calculated from the weight differences relative to the final weight.

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 desiccator 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. The films were measured periodically for constant weights. The water absorption capacity of the patches was calculated in terms of percentage increase in the weight of patch over the initial weight of the specimen.

7. **Determination Drug content in film:** Four pieces of 1 cm^2 each (1 X 1 cm) were cut from different parts of the prepared transdermal patch. Each piece was taken in separate stoppered conical flasks containing 100 mL of suitable medium (0.1-N HCl: CH_3OH mixture) and stirred continuously for 6 hour using magnetic stirrer. Obtained solutions were filtered and suitable dilutions were made. Absorbance observed using UV Visible spectro-photometer at their respective wavelengths, against a blank solution which was prepared by the same protocol but not containing drug [9, 10].

TABLE 2: RESULT OF MECHANICAL PROPERTIES OF FORMULATED TRANSDERMAL PATCHES

Formulations	Thickness (µm)	Tensile strength (N/mm^2)	Elongation (%)	Folding endurance
F1	**645**±45.8	0.311 ± 0.08	15.34±0.26	75± 1.2
F2	**655**±45.6	0.310± 0.10	16.34±0.34	81± 1.9
F3	**680**±45.8	0.314 ± 0.22	18.34±0.16	85± 0.9
F4	**685**±45.8	0.322 ± 0.05	19.34±0.24	91± 1.5
F5	**645**±35.5	0.334 ± 0.09	21.34±0.21	95± 1.4

Number of trials (n=3)

TABLE 3: RESULT OF MEAN WEIGHTS, MOISTURE CONTENT, MOISTURE UPTAKE AND DRUG CONTENT OF FORMULATED TRANSDERMAL PATCHES

Formulations	Weights(g)	Moisture content (%)	Moisture uptake (%)		Drug Content (%)
			RH 75%	RH 93%	
F1	1.565±0.19	2.455±0.16	5.206± 0.39	4.195 ± 0.23	97.5± 0.26
F2	1.569±0.20	2.552±0.14	4.116± 0.39	5.205 ± 0.23	98.4± 0.54
F3	1.555±0.34	2.215±0.36	3.126± 0.46	5.175 ± 0.23	99.9± 0.53
F4	1.555±0.25	2.535±0.18	3.210± 0.59	5.245 ± 0.23	98.8± 0.32
F5	1.585±0.16	2.255±0.24	3.189± 0.54	3.194 ± 0.23	99.9± 0.76

***In-vitro* skin permeation studies with Polymeric Matrices:** The transdermal patches were subjected to *in vitro* evolution across goat dorsal skin. Epidermal hairs are removed, skin was cleaned. Then any adhering subcutaneous tissue and blood vessels were removed. The skin was mounted overnight (12 hr) on receptor phase to remove any water soluble UV absorbing material. The *in vitro* skin permeation of Pioglitazone from various transdermal patches was studied using locally fabricated Franz type of diffusion cell. The diffusion cell consists of two parts upper part and lower part. Upper part called donor compartment which contains active ingredients and the carrier adhesive patch.

Lower part contains the receptor solution, the water jacket for temperature control and the sampling port. The temperature was maintained at 37±2°C. The receptor compartment contained 15 ml of phosphate buffer saline (PBS) IP (pH 7.4) stirred by magnetic stirrer. The permeability studies were carried out across both goat skins. 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. Absorbance of the withdrawn samples were measured at 225 nm.

The experiments were done in triplets, simultaneously blanks were also run and the average values reported [11, 12].

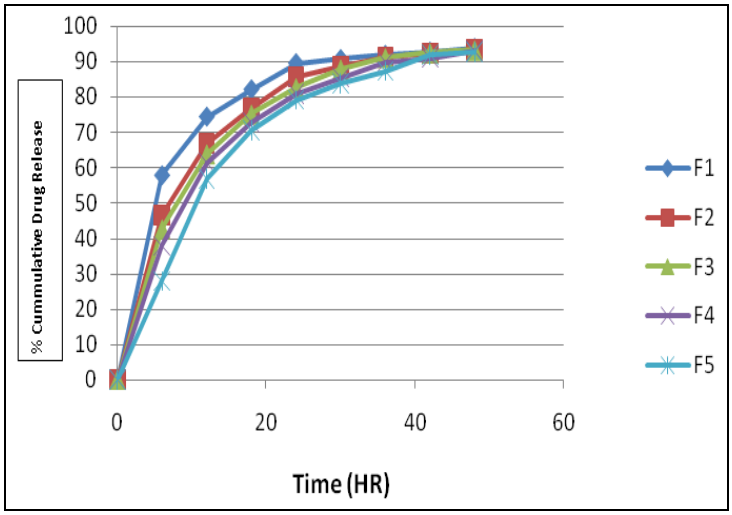

FIGURE 1: *IN VITRO* PERMEATION PROFILE OF FORMULATED TRANSDERMAL PATCHES

TABLE 4: PERMEATION PROFILE OF FORMULATED TRANSDERMAL PATCHES

Time/hr	F1	F2	F3	F4	F5
0	0	0	0	0	0
6	57.905	46.496	42.6466	37.953	27.9085
12	74.496	66.796	63.881	61.496	56.896
18	82.224	76.847	75.132	72.796	70.338
24	89.642	85.579	82.649	80.847	79.095
30	90.798	88.735	87.912	85.579	83.785
36	91.982	91.188	91.105	89.975	87.243
42	92.882	92.249	92.549	91.118	91.688
48	93.906	93.492	93.292	93.195	92.605

Evaluation of skin irritation potential of Patches: The primary skin irritation studies were carried out using modified Draize test. The hairs of rabbits were removed by shaving from the dorsal area on both sides before 24 hours of test. Untreated skin area serves as the control for the test. Medicated patch was applied 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 an occlusive till use. The medicated patches were altered after 48 hours and the fresh patches were applied at the same site. However the patches on the control side were unchanged. The patches were applied on the back for seven days. After removal of patch after 7 days each of the areas were examined for any sign of erythema or edema. [13, 14, 15]

TABLE 5: RESULTS OF SKIN IRRITATION TEST.

Formulation	Visual observation	
	Erythema	Edema
Normal	0.00±0.00	0.00±0.00
Adhesive tape(USP)	1.42±0.23	1.65±0.26
F-5 (Pioglitazone HCl-patch)	1.72±0.30	1.54±0.20
Blank	1.53±0.23	1.21±0.43
Formalin (0.8% v/v)	3.65±0.21	3.85±0.32

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

RESULTS AND DISCUSSION: The result of physicochemical evaluation of Ficus carica patches exhibits uniform drug content with minimum batch variation. The thickness of the patches varied from 645±45.8 to 685±45.8 µm. Tensile strength indicates the strength of film and explains risk of film cracking. But, no sign of cracking in prepared transdermal films was observed, which might be attributed to the addition of the plasticizer, Propylene glycol. The results of tensile strength were shown in Table 2.

Tensile strength of formulated patches was ranged from 0.310± 0.10 to 0.334 ± 0.09 N/mm^2. The elongations of formulated matrix transdermal patches were ranged from 15.34±0.26 to 21.34±0.21%. The folding endurance measures the capability of patch to withstand rupture. The folding endurance was measured manually and results indicated that the patches would not break and would maintain their integrity with general skin folding when used. The results of folding endurance were shown in Table 2. It was found that patches containing higher amount of the *Ficus carica* fruit mucilage was ranged from 75±1.2 to 95±1.4.

The weight of transdermal patches was within the Pharmacopoeial limits and ranged from 1.555±0.25 to 1.585±0.16 g. The results of the moisture content studies for different formulations are shown in Table 3. The moisture content was ranged from 2.215±0.36 to 2.552±0.14 %. The results of moisture uptake studies for different formulations are shown in Table 3. The moisture uptake of the transdermal patches was also low, which could protect the formulations from microbial contamination and also reduce bulkiness of films.

At RH 75% the moisture content was ranged from 3.126± 0.46 to 5.206± 0.39 % and at RH 93% it ranged from 3.194 ± 0.23 to 5.205 ± 0.23 %. The drug content in formulated films was ranged from 97.5± 0.26 to 99.9± 0.76%. The physical appearance of the patches and the effect on ageing indicated that the patches need to be stored in properly sealed air tight packing to keep them protected from extremes of moisture that may alter their appearance.

Thus, the properties were found to be within limits and satisfactory. The patches did not show any visible erythema or edema with the formulation or the base used.

CONCLUSION: The above study concludes that Ficus carica fruit mucilage can be used as a release retardant matrix forming material for making transdermal patches which retard the release in controlled pattern.

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