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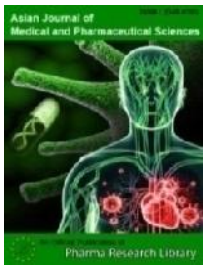

R E S E A R C H A R T I C L E

Pharmacokinetic Evaluation of Transdermal Drug Delivery of Diclofenac Potassium in Human Volunteers

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A B S T R A C T

Transdermal therapeutic systems are defined as self-contained discrete dosage forms which when applied to the intact skin, deliver the drugs through the skin, at a controlled rate to the systemic circulation. To any drug moiety to elicit its pharmacological action, it has to reach the systemic circulation without change. The object of the present study was to formulate a transdermal drug delivery system using a natural polymer. Badam gum was selected as the polymer owing to its ideal film forming properties. Dicolfenac potassium was used as model drug. The gum was subjected to preformulation tests such as pH, swelling index, ash values and microbial load. All the results were within acceptable limits. Compatibility studies were also conducted using FTIR studies, which showed that the drug and polymer were compatible. The gum gave good films starting from a concentration of 2% w/w. Films were prepared using various concentrations of the polymer such as 2, 2.25, 2.5, 2.75 and 3% w/w. The prepared films were subjected to dissolution studies and based on the release profile, 2.5% was selected to be the ideal concentration. The bioavailability of the drug from ideal batch of the formulated films (containing 2.5% w/w of badam gum with 15% DMSO as penetration enhancer) was determined in healthy human volunteers and comparison was made with that of orally administered marketed tablets of diclofenac potassium. The retention time of diclofenac potassium was found to be 11.983 min for standard solution. The retention time for sample was found to be 11.900 minutes.

Keywords: Transdermal delivery, pharmacokinetics, badam gum, Diclofenac sodium.

A R T I C L E I N F O

A U T H O R D E T A I L S

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C O N T E N T S

1. Introduction

Continuous intravenous infusion at a programmed rate has been recognized as a superior mode of drug delivery not only to bypass the hepatic first pass elimination but also to maintain a constant, prolonged and therapeutically effective drug level in the body. A closely monitored intravenous infusion can provide both the advantages of direct entry of the drug into the systemic circulation and control of circulating drug level [1]. However, such a mode of drug delivery entails certain risks and therefore necessitates hospitalization of patient and close medical supervision of medication. Recently, there has been an increasing awareness that the benefit of intravenous drug infusion can be closely duplicated, without its potential hazards, by continuous transdermal drug administration through an intact skin. In response to this new idea several transdermal drug delivery systems have been recently developed, aiming to achieve the objective of systemic medication through tropical application to the intact skin surface. Transdermal therapeutic systems are defined as self-contained discrete dosage forms which when applied to the intact skin, deliver the drugs through the skin, at a controlled rate to the systemic circulation [2]. These can sustain the duration of therapeutic activity. Transdermal delivery of drug has been subject of research interest since the introduction of the first transdermal product for delivery of Scopolamine in 1979. Prunus amygdalus is belonging to the family Rosaceae, The tree exudes a gum, which has been employed in place of tragacanth. It is obtained mostly from the trunk. Almond oil acts as demulcent, nutritive and slightly laxative and has action similar to olive oil. Useful in the preparation of nourishing creams, skin creams and cold creams 3. Diclofenac potassium have half-life is 1-2 hours 4. Diclofenac is metabolized in the liver by a cytochrome P450 siozyme of the CYP2C subfamily to 4-hydroxy diclofenac, the principal metabolite and other hydroxylated forms, after glucuronidation and sulfation, the metabolites are excreted in the urine (65%) and bile (35%).

2. Materials and Methods

Prunus amygdalus was obtained as a gift sample local market, Ooty. Acetone was obtained Merk, Tween 40 was obtained from sigma, and propylene glycol was obtained from new India enterprises. Sodium alginate, glycerol, sodium alginate was obtained from SD fine chem.

Compatibility Studies:

10 mg of the drug and the polymer were mixed with 400 mg of potassium bromide individually and 100 mg of each mixture was taken and compressed into a pellet using a hydraulic press at 10 tones pressure. The pellet was scanned from 2000-400 cm^{-1} in an FTIR spectrophotometer [5]. Similarly, a pellet containing physical mixture of 1:1 drug and polymer was prepared and the characteristic spectrum was taken. These spectra were compared with the original spectra to determine any possible appearance or disappearance of peaks.

Formulation of transdermal patches

In the present study, matrix type transdermal patches of diclofenac potassium were prepared by moulding technique [6]. A mould of 8 cm length and 8 cm width and 0.5 cm height with a total area of 64 cm^2 was fabricated for this purpose.

Preparation of 2% Sodium Alginate Solution:

Two grams of sodium alginate was dissolved in 100 ml of water by heating and the solution was left to stand until all the air bubbles disappeared [7].

Preparation of Drug-loaded Transdermal Patches:

The Different concentrations of badam gum was accurately weighed and dissolved in 30 ml of distilled water. Badam gum was added in different proportions in order to prepare films of different concentrations ranging from 2-3%. The solution was stirred using a magnetic stirrer for one hour. Then, it was allowed to stand until all the air bubbles disappeared [8]. Appropriate quantities of penetration enhancers were added to study their effect on the release of drug. Then, the solution was poured into the moulds and dried at 58°C for 4 hours. Then, 10 ml of 2% solution of sodium alginate was added and the film was dried again for one hour. After drying, the patches were removed and packed in self-sealing covers.

Study on effect of formulation variables: The effect of formulation variables such as different concentrations of the polymer, different penetration enhancers on the weight variation, thickness, moisture content, drug content and *in vitro* drug release were studied [9].

Effect of Different Concentrations of Polymer:

Polymers used in transdermal therapeutic systems act as rate controlling membranes and by changing the polymer concentration, different release rates can be obtained. So, in the present study, five different batches of films, with 2, 2.25, 2.5, 2.75 and 3% of badam gum were formulated [10].

Dissolution Test for Transdermal Patches Prepared Using Different Concentrations of Polymer:

To select the ideal concentration of the polymer, dissolution test was performed on the transdermal patches prepared with different concentrations. The FDA paddle method (USP Apparatus II) was modified for this purpose. The transdermal patch was affixed to a watch glass which was placed at the bottom of the dissolution flask. The patch was held in position by sandwiching it between the watch glass and an aluminium wire mesh [11]. A distance of 24-26 mm between the paddle blade and the mesh was maintained throughout the experiment. The temperature was maintained at 31.5-32.8°C. Phosphate buffer of pH 7.4 was used as dissolution medium and the experiment was performed for a period of 6 hours at 50 rpm.

Effect of Different Penetration Enhancers: To reduce the resistance of the stratum corneum and its biological variability, penetration enhancers are incorporated in the transdermal preparations. An ideal penetration enhancer can be defined as a chemical with a unique property in relation

to the skin that reversibly reduces the barrier resistance of the horny layer without damaging any viable cells [12]. In the present study, penetration enhancers such as propylene glycol (40% w/w of polymer), combination of PEG-400 and propylene glycol (40% w/w of polymer), tween-40 (1% w/w of polymer) and DMSO (15% w/w of the polymer) were used to study the effect of permeation enhancement of the drug. This study was conducted using 2.5% w/w polymer concentration, which was selected as ideal.

Evaluation of transdermal films: The prepared films containing 2.5% w/w polymer and different permeation enhancers were evaluated for the following parameters:

a. Uniformity of weight
b. Uniformity of patch thickness
c. Folding endurance
d. Moisture content
e. Drug content
f. In vitro drug diffusion study

a. Uniformity of Weight:

This is physical evaluation for the transdermal films of specific size, which should give the uniform weight. This will indirectly reflect the uniform thickness and the uniform content for the active ingredients [13]. This was done by weighing three different patches of the individual batch taking the uniform size at random and the average weight was calculated. The individual weight should not deviate significantly from the average weight of the three. The tests were performed on films, which were dried at 60°C for 4 hours prior to testing.

b. Uniformity of Patch Thickness:

The uniformity of the thickness of the transdermal film is an important parameter to find out the drug release characteristics from the same [14]. Therefore, uniform thickness is the ideal characteristic for constant or uniform drug diffusion from the transdermal patches. In the present study, the thickness of the films was measured at different points. The average of 5 readings was calculated.

c. Folding Endurance:

The folding endurance of the film was determined by repeatedly folding a small strip measuring 2 x 2 cm size at the same place till it was broken [15].

d. Moisture Content:

Moisture content can influence the mechanical strength and the drug release of transdermal system and therefore, in the present study, determination of the moisture of the formulated patch was carried out [16]. The moisture content of the films was determined by keeping the pre-weighed films in a desiccator for 48 hours and weight was taken again.

$$\text{Moisture Content (\%)} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

e. Drug Content:

A formulated patch having 1 cm^2 area was cut into small pieces and transferred into a graduated glass-stopper flask, which contained 25 ml of phosphate buffer. It was closed and shaken vigorously for 12 hours period in a shaker. The solution was filtered and suitable dilutions were made [17]. The absorbance was measured using UV-Visible spectrophotometer at 276 nm against a blank solution which was prepared following the same procedure using dummy patch.

In vitro Drug Diffusion Study:

The vertical type skin permeation system developed by Franz is widely used for studying the kinetics of percutaneous absorption. The Franz diffusion cell has a receptor compartment with an effective volume of approximately 10-12 ml and an effective surface area for permeation varying from 1.57 to 4.71 cm^2. The solution in the receptor compartment is stirred using a rod shaped magnet [18]. The stirring magnet rotates at a speed of 600 rpm. The temperature in the bulk of the solution can be maintained at a constant level by circulating thermo stated water through water jacket surrounding the receptor compartment.

Formulation development

Effect of Polymer Concentration:

To study the effect of polymer concentration on drug release, five different batches of films were prepared using 2, 2.25, 2.5, 2.75 and 3% w/w of the polymer [19]. Based on the results, polymer concentration of 2.5% was selected as the ideal batch.

Pharmacokinetic study design and data handling

Study design:

This was a single dose, randomized; complete two ways, two periods cross over study with a washout period of 07 days between the two treatment sessions[20]. In eachdosing session, volunteers receivedeither the Reference or the test formulation of diclofenac Potassium as a single dose, only on the study day, as per the randomization code at a fixed time.

Evalution of pharmacokinetic parameters

Plasma concentrations and time points, Subject, period, sequence, treatment, AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, and $t_{½\ inter}$ subject, intra subject, and/or total variability.

Rounding off of confidence interval values:

Confidence interval (CI) values should not be rounded off therefore, to pass a CI limit of 80-125, the value should be at least 80.00 and not more than 125.00.

Bioavailability study:

Bioavailability is usually determined by comparing the rate and extent of absorption of the drug from the formulation under evaluation, to the data obtained following the administration of a reference standard [21]. The following parameters should be assessed in a bioavailability study involving oral administration of single doses of matrix tablet formulation.

a. The peak height concentration (C_{max})
b. The time of the peak concentration (T_{max})
c. The area under the plasma concentration-time curve (AUC)
d. Half-life ($t_{1/2}$)

Formulation Development of Transdermal Films

Preformulation studies: Preformulation studies was carried out for the possible interactions with various inert ingredients intended for use in the final dosage form and the results showed that there is chemical interaction between the selected ingredients.

Compatibility Studies:

One of the requirements for the selection of suitable excipient or carrier for pharmaceutical formulation is its compatibility. Therefore, in the present work, a study was carried out using FTIR spectrophotometer to confirm the absence of any possible chemical interaction between diclofenac potassium and badam gum.

3. Results and Discussion

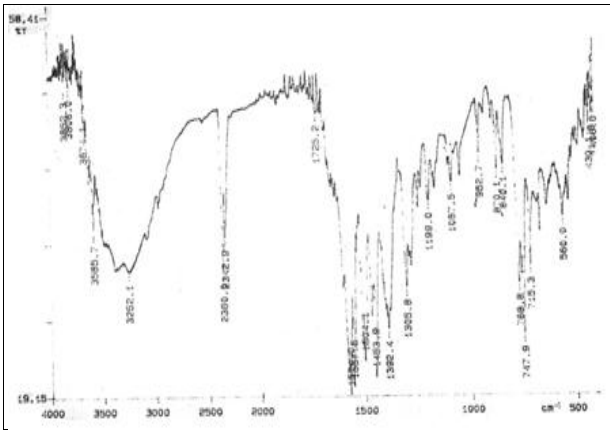

Fig 1:FTIR spectrum of pure diclofenac potassium

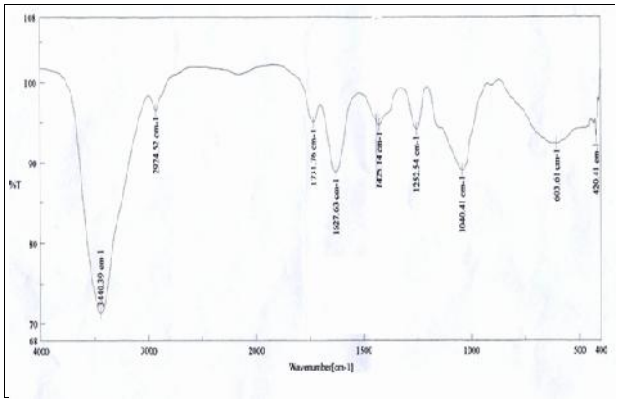

Fig 2:FTIR spectrum of pure badam gum

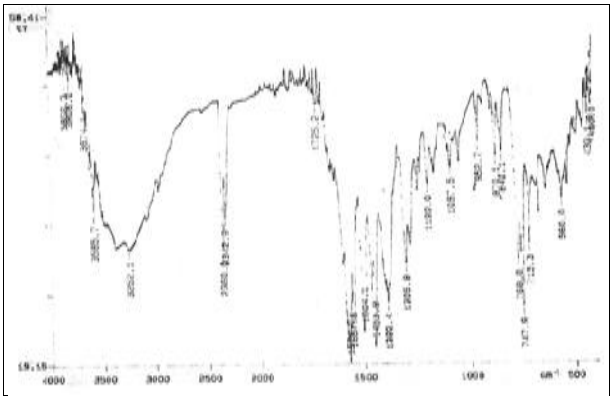

Fig 3: FTIR spectrum of diclofenac potassium and badam gum mixture

Effect of Different Concentrations of Polymer:

To study the effect of polymer concentration on drug release, five different batches of films were prepared using 2, 2.25, 2.5, 2.75 and 3% w/w of the polymer. The results are shown in Table 4. Based on the results, polymer concentration of 2.5% was selected as the ideal batch.

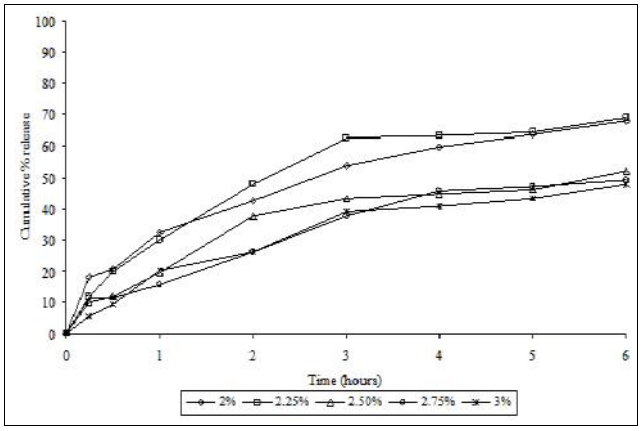

Fig 4: Dissolution profiles of transdermal films prepared using different concentrations of badam gum

Effect of Penetration Enhancers:

Different penetration enhancers like propylene glycol (40% w/w of polymer), combination of PEG-400 and propylene glycol (40% w/w of polymer), tween-40 (1% v/v of polymer solution) and DMSO (15% w/w of polymer) were used. The selected ideal concentration of badam gum was used in this study.

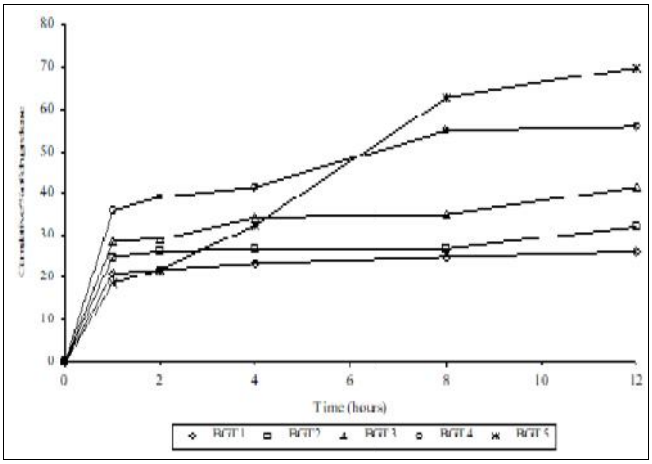

Fig 5: In vitro drug diffusion from different batches of transdermal films

Based on the above results, DMSO was selected as ideal penetration enhancer at 15% concentration since it was found to enhance the permeation of the drug to maximum extent.

Pharmacokinetic study design and data handling:

Each 50µl standard solutions were injected and the chromatograms were recorded. The retention time of diclofenac potassium was found to be 11.983 min for standard solution. This was followed by injection of sample solution obtained from the plasma samples. The retention time for sample was found to be 11.900 minutes. The peak response factors obtained from the sample chromatograms

were compared and the plasma concentration of diclofenac potassium at different time intervals was calculated. The pharmacokinetic such as C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{½}$ and elimination rate constant (K_{el}) were calculated.

Discussion

The object of the present study was to formulate a transdermal drug delivery system using a natural polymer. Badam gum was selected as the polymer owing to its ideal film forming properties. Dicolfenac potassium was used as model drug. The gum was subjected to preformulation tests such as pH, swelling index, ash values and microbial load. All the results were within acceptable limits. Compatibility studies were also conducted using FTIR studies, which showed that the drug and polymer were compatible. The gum gave good films starting from a concentration of 2% w/w. Films were prepared using various concentrations of the polymer such as 2, 2.25, 2.5, 2.75 and 3% w/w. The prepared films were subjected to dissolution studies and based on the release profile, 2.5% was selected to be the ideal concentration. The effect of various penetration enhancers on the release profile was evaluated. Penetration enhancers such as propylene glycol (40% w/w of polymer), tween-40 (1% w/v of the polymer solution), PEG-400 and propylene glycol (40% w/w of polymer), dimethyl sulfoxide (DMSO, 15% w/w of polymer) were the penetration enhancers used. In vitro diffusion studies were carried out using Franz diffusion cell and mouse skin was used as membrane. Phosphate buffer of pH 7.4 was selected as diffusion medium. The films having DMSO (15% w/w of the polymer) as penetration enhancer, showed a maximum release of 69.71% after 12 hours. The prepared films were also evaluated for various physical parameters such as uniformity of weight, uniformity of film thickness, folding endurance, moisture content and content uniformity. Ideal batch of film was also subjected to skin irritation study. It was found that the films did not produce any skin irritation. The bioavailability of the drug from ideal batch of the formulated films (containing 2.5% w/w of badam gum with 15% DMSO as penetration enhancer) was determined in healthy human volunteers and comparison was made with that of orally administered marketed tablets of diclofenac potassium. From the results of this study, it was found that absorption was delayed from the transdermal system through human skin. The absorption and bioavailability of the drug from the transdermal therapeutic system was poor when compared to that of conventional tablet due to skin and climatic condition. But the transdermal system exhibited a delayed release pattern. So we concluded that the transdermal system may be better for therapy compared with conventional dosage form. However, it needs to be subjected to study in more number of human volunteers, with a wide range of penetration enhancers to increase the skin permeability, which may be helpful in achieving the therapeutic window.

Table 1: Drug content of transdermal patches prepared using different concentrations of badam gum

S. No.	Polymer concentration (%w/w)	Drug content (mg/cm^2)
1	2.00	0.715 (0.03)
2	2.25	0.724 (0.33)
3	2.50	0.710 (0.28)
4	2.75	0.731 (0.51)
5	3.00	0.708 (0.39)

Values in parenthesis represent SEM

Table 2: Dissolution profile of transdermal patches prepared using different concentrations of badam gum

S.No	Time (hours)	Cumulative % of drug release				
		2.00%	2.25%	2.50%	2.75%	3.00%
1	0.25	18.30	11.90	10.10	11.50	5.55
2	0.50	20.80	19.77	11.90	11.60	9.45
3	1.00	32.50	30.00	19.70	15.86	20.12
4	2.00	42.50	47.85	37.90	26.16	26.16
5	3.00	53.90	62.70	43.20	37.80	39.24
6	4.00	59.90	63.14	44.64	45.72	40.80
7	5.00	63.80	64.20	46.00	47.04	43.44
8	6.00	67.70	69.04	52.10	49.20	47.88

Table 3: Physicochemical properties of different batches of films

S.No	Property	BGT1	BGT2	BGT3	BGT4	BGT5
1	Uniformity of weight (average of 3 patches, mg)	21.5 (0.60)	35.1 (0.10)	26.6 (0.48)	37.5 (0.33)	32.4 (0.25)
2	Uniformity of thickness (μm)	500	150	250	375	200

3	Folding endurance	> 50	> 100	> 100	> 100	> 100
4	Moisture content (%)	10.8	13.7	12.8	14.6	11.2
5	Drug content (mg/cm^2)	0.715	0.659	0.724	0.730	0.744

Table 4: In vitro drug diffusion profiles from different batches of transdermal films

Time (hours)	Cumulative % of drug release				
	BGT1	BGT2	BGT3	BGT4	BGT5
1	21.02	24.90	28.7	35.81	18.51
2	21.95	26.25	29.3	38.95	21.92
4	23.46	26.76	34.22	41.65	32.40
8	25.06	26.83	35.0	54.86	62.54
12	26.26	32.07	41.5	55.77	69.71

Table 5: Mean plasma concentrations of diclofenac potassium at different time intervals

Time (h)	Plasma Concentration of drug (mg/ml)	
	Transdermal patch	Marketed tablet
0.0	0	0
0.5	0.003652	0.011419
1.0	0.014871	0.055709
1.5	0.040097	0.189347
2.0	0.05286	1.649565
3.0	0.099963	1.667468
4.0	0.130701	1.244996
6.0	0.237025	0.478056
8.0	0.170393	0.172247
12.0	0.003279	0.02388
24.0	0.00091	0.011388

4. Conclusion

As natural excipient, we selected the gum obtained from Prunus amygdalus for the preparation of films. From the above studies, it can be concluded that the gum obtained from the above source can be used for the preparation of transdermal therapeutic system, based on the following ideal characteristics.

- Low cost
- Sustained release profile over a prolonged time
- Good physical and microbiological stability

Obviously transdermal delivery of diclofenac potassium appears to be more desirable than the existing oral administration. The poor absorption of the drug from the transdermal system may be improved with wide range of chemical penetration enhancers and needs to be subjected to studies in more number of volunteers for achieving the best transdermal therapeutic systems by using badam gum as a natural polymer for human use.

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