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Development and characterization of Ketaconazole transdermal patches for Pharmaceuticals

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Abstract

The present study aims to formulate and evaluate ketoprofen transdermal patches containing different polymer components. We formulated four formulas for the transdermal matrix patches of ketoprofen, using polyethylene glycol 400, HPMC, and ethyl cellulose as the polymers. These patches were evaluated for various physicochemical characteristics and drug content. In this study, ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC) were used as polymers to create matrix-type transdermal drug delivery systems (TDDS) for the drugs of interest. Five formulations were prepared using different concentrations of the polymers, either alone or in combination. The in-vitro permeation profiles and physicochemical properties suggest that the films from batch F1, prepared with HPMC, showed better release, with 76.56% of ketoconazole permeated across the skin at the end of 12 hours. In contrast, batch F2, prepared with EC, exhibited better-controlled release, with 45.11% permeated at the end of 12 hours.

KEY WORDS: antifungal, ketoconazole, transdermal patches, topical, drug delivery, and polymers etc.

1. INTRODUCTION

Drug distribution via the skin devices was developed lately to meet the goal of systemic therapy by topical treatment. “The transdermal method of drug delivery is getting popular since it can administer a wide number of medications to treat a variety of ailments. External application is meant for both topical and transdermal products[1]. Topical dermatological medications, on the other hand, are meant for local action, while systemic drug delivery is accomplished by the use of a transdermal drug delivery system. Because it offers several benefits over traditional drug administration, many rate-controlled transdermal drug delivery systems have been commercially developed. The fundamental goal of a transdermal medication delivery system is to deliver medications into systemic circulation via the skin at a predefined pace with little fluctuation between and within patients. Transdermal delivery is now one of the most promising medication delivery modalities. It lessens the strain on the digestive system and liver that comes with taking pills orally[2,3]. It improves patient compliance and reduces adverse side effects of a treatment caused by a momentary overdose, as well as providing convenience with transdermal medications that only need to be applied once. This results in improved bioavailability, more uniform plasma levels, and a longer duration of action, resulting in lower dosing frequency, fewer side effects, and better therapy due to the maintenance of plasma levels until the end of the dosing interval, as opposed to a decline in plasma levels with traditional oral dosage forms. Transdermal delivery allows for continuous input of medications with short biological half-lives and prevents pulsed entrance into systemic circulation, which may produce unwanted side effects[4,5].

Ketoconazole is included in Class II of the Biopharmaceutical Classification System, which includes a class of Biopharmaceutical Classification System means, including a class of drug is of this drug is of concern to pharmaceutical researchers[2]. The absorption of ketoconazole orally is not maximal due to the solubility and the side effects it causes; to overcome the deficiencies of this conventional system, a new drug delivery system is required. Topical ketoconazole available on the market today, such as cream, has side effects such as rash, itching, irritation, pain, and redness; therefore, to overcome this problem requires a new drug delivery system such as nanoemulsion.

Nanoemulsion has been widely used as a vehicle in topical medicine and is an alternative to insoluble, topical, or oral drugs[3-6].

2. Material and method

2.1 Material

All the chemicals used in this research were of standard pharmaceutical grade. Ketoconazole was procured as a gift sample from NANZ Pharmaceutical Paonta Shahib. Ethylcellulose PEG-400, Methanol, and chloroform were purchased from Grey scientific Ambala. All the chemical used were of analytical grade.

2.2 Preparation of matrix type of transdermal systems

HPMC and EC patches were made using the solvent evaporation technique, and HPMC and EC transdermal systems were made using the equations in Table 1. A magnetic stirrer was used to mix the liquids for 20 minutes.

For HPMC and EC patches, propylene glycol was employed as a plasticizer, and oleic acid was employed as a permeation enhancer. A certain amount of medicine was dissolved in a 1:1 solvent combination of chloroform and methanol, then added to the appropriate polymer solutions, mixed, and put onto a glass Petri dish. “Inverting the cut funnel over the Petri plate regulated the rate of solvent evaporation." The dried patches were removed after 24 hours and kept in a desiccator.

Table 1: Formulation design of transdermal systems

S.No.	Ingredients (mg/ml)	Formulations				
		F1	F2	F3	F4	F5
1.	Ketoconazole	40	40	40	40	40
2.	HPMC	120	-	60	80	40
3.	EC	-	120	60	40	80
4.	Propylene glycol	0.12	0.12	0.12	0.12	0.12
5.	Oleic acid	0.25	0.25	0.25	0.25	0.25
6.	Chloroform	7.5	7.5	7.5	7.5	7.5
7.	Methanol	7.5	7.5	7.5	7.5	7.5

Note: The above formulae gave total area of 19.63 sq.cm. each

2.3 Evaluation of Transdermal patches

“All of the transdermal patches that had been manufactured were tested for compliance with official and in-official standards”

(a). Thickness determination

The goal of this investigation was to see if the thickness of the produced films was uniform. The film's thickness was measured in five different places. A baker digital calliper was used to calculate the average of five measurements[2].

(b). Uniformity of weight

This was accomplished by weighing five distinct patches from each batch at random and calculating their average weight. The tests were carried out on films that had been dried at 60°C for four hours before being tested[3].

(c). Folding Endurance

The folding endurance was measured manually for prepared films. A strip of film was folded at the same place till it broke. The number of times the film can be folded at the same place without breaking was the folding endurance value[3].

(d). Moisture content

The film was weighed and dried for at least 24 hours in a desiccator with calcium chloride at 40°C. The film was then weighed many times until it showed a consistent weight[5,6].

(e). Moisture uptake

A weighted film was taken from a desiccator and exposed to two distinct relative humidities at room temperature: 75 percent RH (saturated sodium chloride) and 93 percent RH (saturated ammonium hydrogen phosphate), then the weights were measured periodically to maintain constant weights[7,8].

(f). Drug Content

“Four 1 cm2 (1 cm x 1 cm) pieces were cut from different parts of the film. Each was placed in a conical flask with 100 mL of suitable dissolving fluid” (phosphate buffer), which was aggressively agitated for 6 hours with a magnetic stirrer. Filters were used to filter the aforesaid solutions, and appropriate dilutions were created. Absorbance was measured at their respective wavelengths using a Shimadzu 160A UV visible recording spectrophotometer against a blank solution made using the same process but without the patch[9].

(g). *In-Vitro* Diffusion Study

A modified Franz diffusion cell was used to evaluate the in vitro release profile of the produced TDDS formulations. The elution medium was 17 mL of phosphate buffer with a pH of 7.4, and the barrier was the epidermis of freshly excised pig

skin. The drug-releasing surface of the film was facing the receptor compartment when it was placed between the donor and receptor compartments. A magnetic stirrer was used to fill the receptor compartment with the elution medium, and a small bar magnet was used to mix the elution medium at a speed of 60 rpm. A thermostatic setup was used to keep the temperature of the elution medium at 371oC. Diffusion tests lasted 24 hours, and an aliquot of the sample was taken. The aliquot's drug concentration was evaluated spectrophotometrically and estimated using a standard calibration curve.

2.4 Results

2.4.1 Evaluation of Transdermal patches

Table 2 evaluates various formulations (F1 to F5) of ketoconazole transdermal patches, focusing on physical appearance, weight, thickness, and drug content. All formulations share a consistent physical appearance, marked as "++." The weight of the patches varies, with F2 being the heaviest at 315.1 mg and F1 the lightest at 272.2 mg. Thickness measurements show minor differences, with formulations F1 and F5 having the greatest thickness at 0.167 mm. Drug content across the formulations is high and consistent, ranging from 97.2% (F4) to 98.9% (F3), indicating effective drug incorporation. The provided standard deviations highlight the precision of these measurements, with each value averaged over three samples (n=3), ensuring reliability. This comprehensive evaluation assists in identifying the most suitable formulation by balancing physical characteristics and drug content, which is crucial for consistent and effective transdermal drug delivery.

Table 2: Evaluation of Ketoconazole Transdermal Patch

S. No.	Formulation Codes	Physical appearance	* Weight (mg) ± SD	*Thickness (mm) ± SD	** Drug Content ± SD
1	F1	++	272.2 ± 0.49	0.167 ± 0.0067	98.5 ± 0.25
2	F2	++	315.1 ± 0.34	0.149 ± 0.0102	98.1 ± 0.36
3	F3	++	279.5 ± 0.35	0.149 ± 0.0102	98.9 ± 0.37
4	F4	++	291.7 ± 0.42	0.149 ± 0.0044	97.2 ± 0.27
5	F5	++	325 ± 0.44	0.167 ± 0.0067	97.8 ± 0.41

Table 3 evaluates the performance of different ketoconazole transdermal patch formulations (F1 to F5) by assessing their moisture uptake, tensile strength, folding endurance, and cumulative drug release. Moisture uptake varies, with F5 having the highest at 9% and F2 the lowest at 4.83%. Tensile strength, which measures the patch's resistance to breaking under tension, ranges from 2.830 ± 0.194 MPa in F1 to 1.673 ± 0.220 MPa in F3. Folding endurance, indicating the patch's flexibility and durability, is highest in F2 and F4 (157.66 ± 7.505) and lowest in F5 (82 ± 6). The percentage of cumulative drug release, a critical factor for therapeutic efficacy, is highest in F1 at 76.56% and lowest in F2 at 45.11%. These evaluations reveal the trade-offs among different formulations, helping to identify the optimal balance of moisture management, mechanical strength, durability, and drug release for effective transdermal delivery.

Table 3: Evaluation of ketoconazole Transdermal Patches

S.No.	Moisture uptake	Tensile strength	Folding endurance	% Cumulative release
F1	5.85	2.830 ± 0.194	98 ± 6.027	76.56
F2	4.83	2.460 ± 0.170	157.66 ±7.505	45.11
F3	5.65	1.673 ± 0.220	122.33 ± 8.326	59.67
F4	4.88	1.816 ± 0.216	157.66 ±7.505	65.87
F5	9	1.876 ± 0.209	82 ± 6	53.56

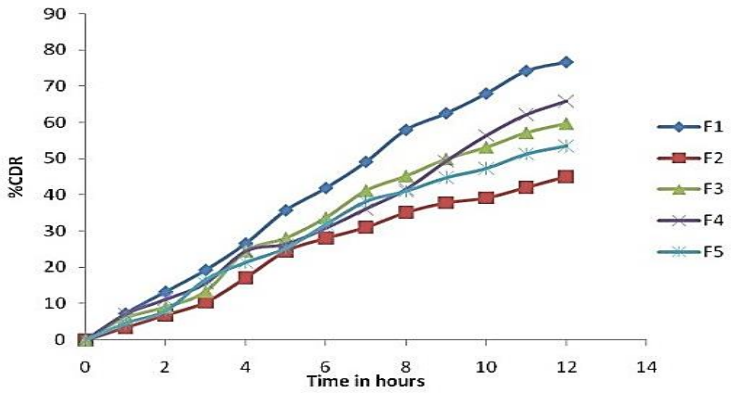

Figure 1: Cumulative release of Ketoconazole from patch

The diagram illustrates the percentage of cumulative drug release (%CDR) from five different ketoconazole transdermal patch formulations (F1 to F5) over a period of 12 hours. The x-axis represents time in hours, while the y-axis indicates the %CDR. Formulation F1 demonstrates the highest %CDR, consistently increasing and reaching approximately 80% by the 12-hour mark. F2 exhibits the lowest %CDR, with a gradual increase to around 45%. F3, F4, and F5 show intermediate release profiles, with F4 and F5 displaying similar trends, reaching around 60% and 55%, respectively. F3 shows a slightly higher release than F4 and F5, approaching 65%. This graph provides a clear comparison of the drug release rates of each formulation, highlighting F1 as the most effective in releasing ketoconazole over the observed period.

3. CONCLUSION

This study focuses on the formulation and evaluation of ketoprofen transdermal patches utilising different polymer components. The study aims to assess the physicochemical characteristics, drug content, and in vitro release profiles of the patches, comparing ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC) as polymers. Five formulations were prepared using varying concentrations of these polymers, either individually or in combination. The results indicated that patches formulated with HPMC demonstrated superior release properties, with 76.56% of ketoconazole permeating the skin over 12 hours. Conversely, patches prepared with EC showed better-controlled release, with 45.11% permeation over the same period. This suggests that HPMC-based patches may be more suitable for formulations requiring faster drug release, while EC-based patches are better suited for controlled-release applications.

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