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FORMULATION AND EVALUATION OF ECONAZOLE LOADED TRANSDERMAL PATCH FOR ITS ANTIFUNGAL ACTIVITY AGAINST TINEA PEDIS

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ABSTRACT

The current work aims to create and define a transdermal patch loaded with Econazole for its antifungal action. The Biopharmaceutical classification system (BCS) Class II drug Econazole is a broad-spectrum imidazole antifungal. Econazole drug exhibits weak solubility causes it to be only partially absorbed after oral administration and bioavailability varies from person to person. Thus, a transdermal patch containing Econazole was developed, and more antifungal research was conducted on Tinea Pedis (Trichophyton interdigitale).Infrared spectroscopy research on the drug with the polymers suggested there was no incompatibility. The physical properties of developed transdermal patches, including thickness, weight variation, drug content, tensile strength, folding endurance, moisture content, and other critical characteristics were assessed. The present formulation study on Econazole is an effort to prepare transdermal patches and to evaluate the performance indicating that it can be used effectively to treat Tinea Pedis. This research was also designed to investigate the chance of manufacturing Econazole transdermal patches.

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INTRODUCTION

The motivation behind developing transdermal patches lies in the advantages they offer, including convenience, non-invasiveness, and reduced trauma compared to intravenous delivery. Patches are particularly suitable as a drug delivery system because they can effectively administer highly potent drugs with short half-lives, reducing the need for frequent administration. One of the best features of this delivery system is its easy application and the ability to keep it in place for a desired period, making it suitable for treating fungal infections like ringworm. Econazole, an imidazole antifungal with broad spectrum action falls under BCS class II due to its almost insolubility in water and inconsistent oral absorption, is often preferred to be used topically rather than orally for the treatment of cutaneous fungal infections.[15] Topical therapy is generally preferred for fungal infections as it helps maintain consistent levels of the drug in the bloodstream, reduces the frequency of dosage, improves patient compliance, and minimizes gastrointestinal effects. This approach ensures consistent levels of the medication in the bloodstream, reduces the frequency of dosage, improves patient compliance, and minimizes gastrointestinal side effects. The mechanism of action of Econazole involves interfering with the synthesis of ergosterol, a vital component of fungal cell membranes. It accomplishes this by obstructing the activity of the enzyme Cytochrome P-450. Consequently, the permeability of the fungal cell increases, leading to the leakage of cellular content and ultimately causing the death of the fungus.[1,2] Tinea Pedis, commonly known as athlete's foot, is a fungal infection that affects the feet, specifically the soles, spaces between toes, and nails. It is caused by a dermatophyte fungus called Trichophyton interdigitale, a clonal line within the sexual species T. mentagrophytes. This particular fungus is responsible for onychomycosis and Tinea Pedis in humans and has never been isolated from animals. The primary culprits of Tinea Pedis are Trichophyton rubrum and Trichophyton interdigitale, which together account for 70% of cases. [8]Tinea Pedis is among the most prevalent superficial fungal infections worldwide. It tends to be more common in communities like army barracks, boarding schools, and sports locker rooms, as well as among individuals who frequent swimming pools or wear nonporous shoes that can trap moisture. The incidence of this infection is higher in warm and humid climates that promote fungal growth but is less frequently observed in regions where shoes are not commonly worn. The objective of the present study is that Econazole has been widely utilized as an antifungal agent, which prompted the current study aimed at formulating and evaluating a transdermal patch formulation of Econazole for the treatment of athlete's foot. [3, 4]

METHODOLOGY

Materials:

Rajkot, Gujarat-based Chemdyes Corporation provided Econazole. Both Polyethylene Glycol 400 and Hydroxy Propyl Methyl Cellulose K-100 were purchased from Research Lab Fine Chem Industries in Mumbai. The chemical reagents utilized were all of analytical grade, and all additional substances were of pharmaceutical grade.

Method of Preparation of Transdermal Patch:

A transdermal patch containing Econazole was created using the solvent casting method. This involved using film-forming polymers such as Polyvinyl Pyrrolidione K-30(PVP K-30) in combination with Hydroxy Propyl Methyl Cellulose K-100(HPMC K-100). A mixture of water and methanol in a 1:1 ratio was prepared, and HPMC K-100 and PVP K-30 were added while continuously stirring.[14] Econazole was dispersed in the polymeric solution, and Propylene Glycol was added as a plasticizer and penetration enhancer. Additionally, Polyethylene Glycol 400(PEG 400) was included in the mixture. The entire solution was then poured into a glass petri dish, taking care to prevent sudden evaporation by placing an inverted funnel over the dish. The solution was left to dry at room temperature for 24 hours. Finally, the resulting film was separated and stored within desiccators until evaluation tests could be conducted. [5, 6] In Table 1 the detailed composition of Econazole transdermal patch is given.

Table 1 Composition of Transdermal Patch of Econazole.

INGREDIENTS	FORMULATIONS								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Propylene Glycol (ml)	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
HPMC K-100 (gms)	0.5	1	1.5	0.5	1	1.5	0.5	1	1.5
PVP K-30 (gms)	0.5	0.5	0.5	1	1	1	1.5	1.5	1.5
PEG 400 (ml)	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Econazole (mg)	20	20	20	20	20	20	20	20	20
Methanol (ml)	5	5	5	5	5	5	5	5	5
Distilled Water (ml)	5	5	5	5	5	5	5	5	5

EVALUATION PARAMETERS:

Analytical Characterization of Drug through UV Spectroscopy Identification of Drug and Preparation of Standard Calibration Curve by UV Spectroscopy:

Econazole weighing 100 mg was accurately measured the volume was then brought up to 100 ml using methanol, resulting in a stock solution with a concentration of 100µg/ml. To prepare a standard calibration curve, different volumes of the stock solution were pipetted into 10 ml volumetric flasks. Methanol was added to each flask to make a final volume of 10 ml, resulting in concentrations of 2, 4, 6, 8, 10, and 12µg/ml. The absorbance of these solutions was measured using a UV spectrophotometer. [7]

FTIR Analysis:

For evaluating the compatibility of the drug with other excipients, both the drug alone and in combination with other excipients was scanned using FTIR. Each sample was scanned using a 400–4000 cm^{-1}wavelength range. For the compatibility study, the potassium bromide pellet method was used to collect the FTIR spectra of the pure medication and the excipients. [9]

Thickness:

To measure the thickness of a drug-loaded patch at various points on a film, microscope was used. [10]

Uniformity of Weight:

A sample of 10 randomly chosen patches were individually weighted and subjected to mass fluctuation. Then, the average weight of the patches was noted. Each formulation batch underwent such a determination. [11]

Moisture content:

The patches (n = 3) were individually weighed and maintained in a calcium chloride-filled desiccator at 37°C for 24 hours. When the weight of each individual patch remained unchanged, the final weight was recorded. The difference between the starting and final weights relative to the final weight was used to compute the percentage of moisture content. [11]

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

Determination of Tensile Strength and Percentage Elongation Break Test:

The pulley system is used to determine the tensile strength of the transdermal patch. With the help of two small catchers the patch was pulled in the opposite direction by gradually increasing the force until the patch was broken. The tensile strength was noted in kg/cm^2.[12]The percentage elongation break was determined by noting the length just before the break point, the percentage elongation was determined from the below mentioned formula.

$$\text{Elongation percentage} = \frac{(L1 - L2)}{L2} \times 100$$

Where, L1 is the final length of each strip, and L2 is the initial length of each strip. [13]

Folding Endurance:

This was assessed by repeatedly folding one film at the same location on a 2 cm× 2 cm (4 cm^2) strip until it broke. The value of folding endurance was determined by how many times the film could be folded in the same location without breaking. [11]

Drug Content Determination:

To ascertain the quantity of the drug, patches measuring 2 cm×2 cm (4 cm^2) were excised and placed into a beaker containing 100 ml of a phosphate buffered solution with a pH of 7.4. The mixture was continuously stirred using a magnetic stirrer for duration of two hours. Following this, the solution was filtered using Whatman filter paper with a pore size of 0.45µm. Subsequently, the filtered solution was suitably diluted and the absorbance of the resulting solution at a wavelength of 271 nm was then determined, using a placebo patch as a reference. [11]

Antifungal Activity:

The microorganism's inoculum was created from bacterial cultures. Clean and sterilized Petri plates were filled with 15ml of Saubroad agar (Hi media) medium, which was then allowed to cool and solidify. A 100µl volume of fungal strain broth was extracted using a pipette and evenly spread over the medium until it dried completely using a spreading rod. Using a sterile cork borer, wells with a diameter of 6mm were created. Solutions of the compounds (100µl/ml) were prepared in DMSO and 100µl of the test solutions and standard were added to the wells. The petri plates were then incubated at 37°C for 24 hours. Miconazole (1mg/ml) was prepared as a positive control, while DMSO served as the negative control. The antibacterial activity was assessed by measuring the diameters of the zones of inhibition (ZI). All experiments were conducted in triplicate.

RESULTS

Physical Characterization:

The physical characteristics of drug and patch were studied by visual examination characterization are shown in Table 2.

Table 2 Physical Description of Econazole.

Characterization	Description	
	Drug Sample	Patch
Colour	White	White
Appearance	White or Almost White Powder	Smooth and Opaque
Odor	Odourless	Odourless

Analytical Characterization of Drug through UV Spectroscopy:

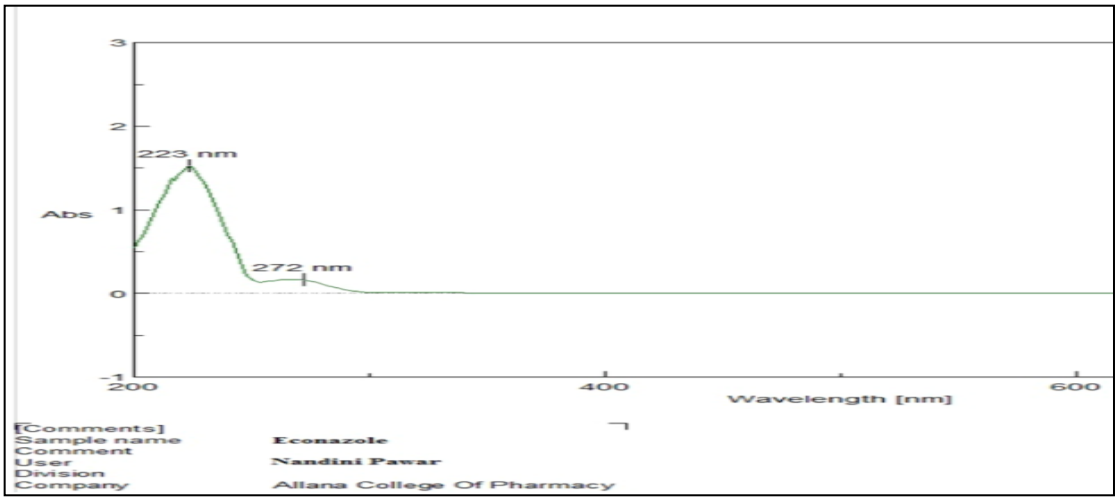

Figure 1 λ max of Econazole

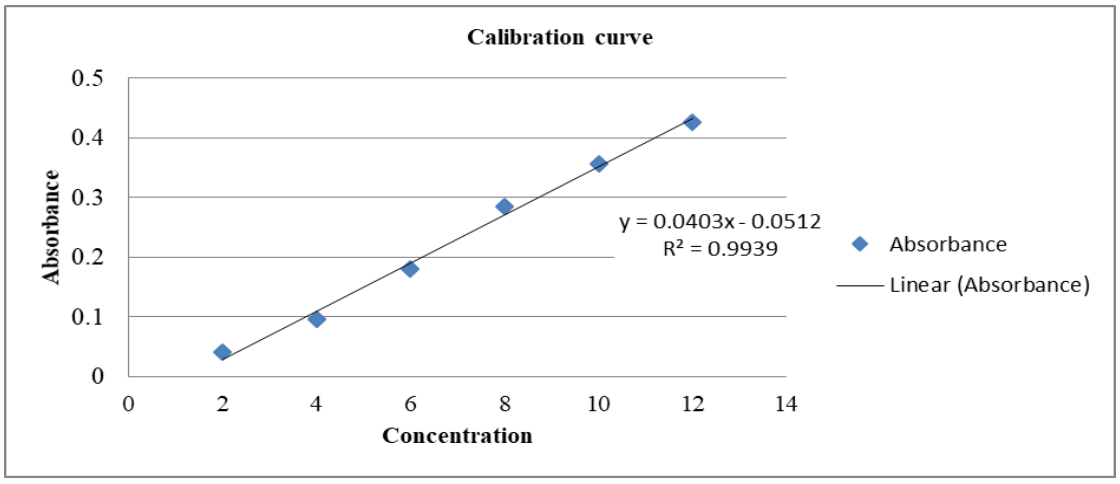

Figure 2 Calibration Curve of Econazole

FTIR Analysis:

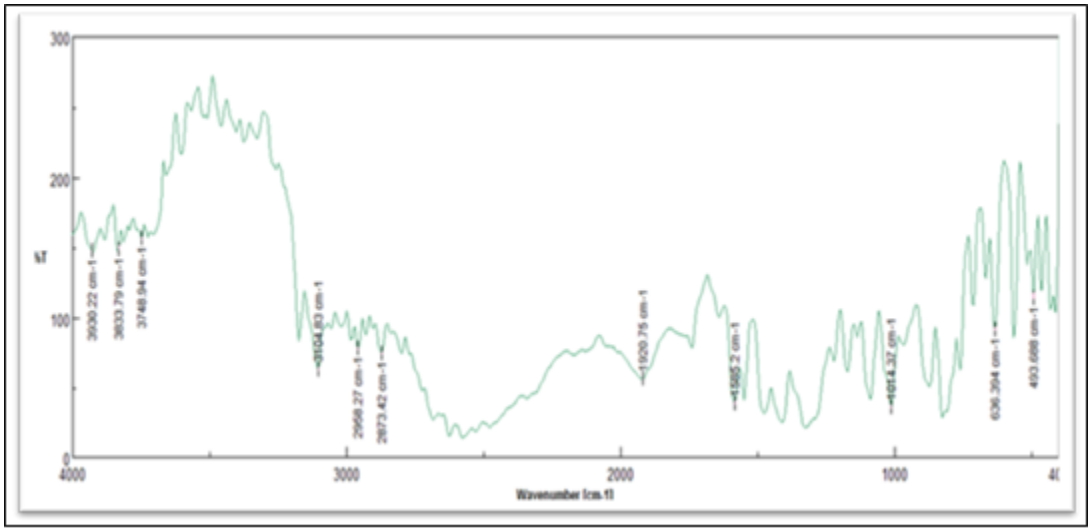

Figure 3 FTIR of Econazole

Table 3 Identified functional groups through FTIR.

Wavenumber	Group Identified	Standard Range
2873.42cm^{-1} , 2958.27 cm^{-1}	Alkanes CH (stretch)	3000 – 2850cm^{-1}
636.394cm^{-1}	Chloride	785 – 540cm^{-1}
1014.37cm^{-1}	C-O	1300-1000 cm^{-1}

Compatibility studies:

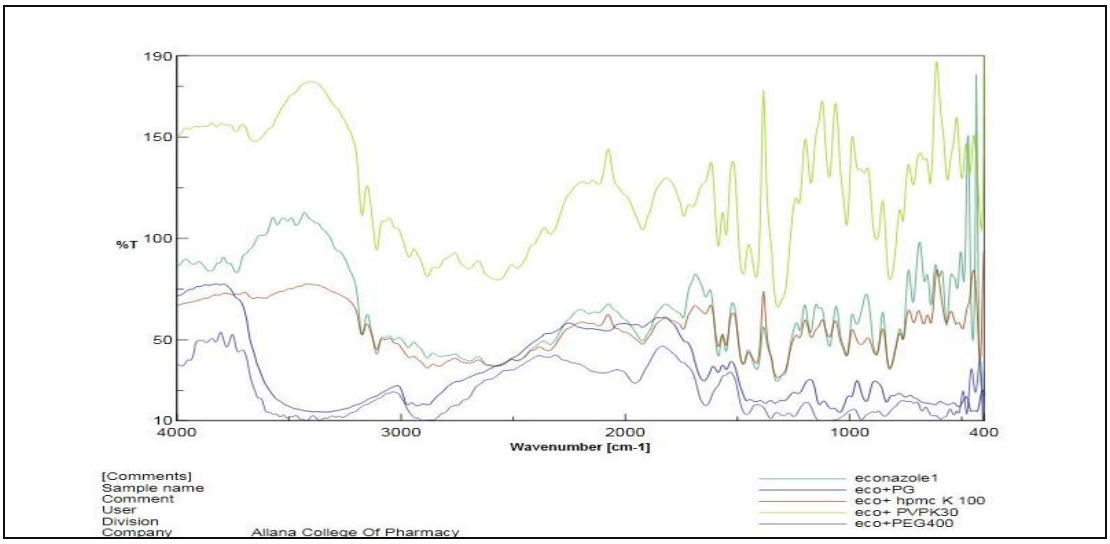

Figure 1 Compatibility studies of drug with excipients

Physiochemical Properties:

For various physiochemical evaluation all the formulation were subjected. The result of the film thickness, weight variation, moisture content, tensile strength, percent elongation, folding endurance and drug content are shown as Table 4 and Table 5.

Table 4 Results of Physiochemical properties of Batch F1 to F5.

Evaluation	FORMULATIONS				
	F1	F2	F3	F4	F5
Thickness (µm)	0.6	0.56	0.4	0.4	0.3
*Weight variation (mg)	0.2554 ±0.0285	0.2755 ±0.0316	0.3139 ±0.0318	0.3585 ±0.1402	0.3233 ±0.0201
Moisture content (%)	4.0625	5.3232	6.2015	5.3639	2.2388
Tensile strength (kg/cm^2)	20	80	100	50	20
% elongation	9.09	13.04	16.67	6.54	4.76
Folding endurance	183	205	225	58	97
Drug content (%)	83.82	86.95	88.36	89.85	93.19

*n=3 Average of three determinations

Table 5 Results of Physiochemical properties of Batch F6 to F9.

Evaluation	FORMULATIONS			
	F6	F7	F8	F9
Thickness (µm)	0.3	0.6	0.4	0.4
*Weight variation (mg)	0.4172 ±0.0416	0.296 ±0.0078	0.2502 ±0.0077	0.3209 ±0.0136
Moisture content (%)	6.6137	5.0335	2.3529	5.7142
Tensile strength (kg/cm^2)	30	40	80	120
% elongation	5.66	9.50	13.04	10.31
Folding endurance	82	79	155	113
Drug content (%)	87.88	90.35	92.19	90.14

*n=3 Average of three determinations.

Antifungal Activity:

Table 6 Zone of Inhibition of Trichophyton Interdigitale.

Sr. No.	Samples	Zone in diameter (mm)
1	Control	0
2	Standard (Miconazole)	28
3	Econazole	19

Figure 5 Antifungal activity against Trichophyton Interdigitale.

DISCUSSION

Physical Characterization:

The films of Econazole obtained by the solvent casting method had acceptable characteristics. The prepared films were transparent and had a smooth surface without any interactions between the drug and polymer.

Analytical Characterization of Drug through UV Spectroscopy:

The identification of drug was done by UV spectroscopy and the peak was observed at 271nm. Further, the calibration curve was plotted for the same.

FTIR Analysis:

FTIR spectroscopy was used to identify chemical bonds and functional groups present in the sample, the obtained results are shown in Table 4. FTIR spectra obtained from the drug and excipient samples displayed similar absorption patterns and characteristic peaks. The presence of common absorption bands and the absence of significant differences in peak intensities and positions support the conclusion of compatibility.

Physiochemical properties:

The detailed results for the evaluation of physiochemical properties are shown in Table4 and Table 5. The discussion about the evaluation tests carried are discussed below.

Patch Thickness:

The thickness of the patches was observed to vary between 0.3 and 0.6 µm. This indicates that the patches have a consistent thickness throughout.

Folding Endurance:

The Durability of Folding of the patches ranged from 58 to 225. The patch formulation F3 exhibited the highest folding endurance (225), while F4 had the lowest (58).

Weight Variation:

The weight of all prepared patch found to be in the range between 0.2502 ±0.0077 to 0.4172 ±0.0416. This shows that they are relatively similar in weight.

Moisture Content:

For all the formulation the moisture content was found to be in the range of 2.2388 to 6.2015.

Tensile Strength:

For all the formulation the tensile strength was found to be in the range of 20 to 120 kg/cm2.

% Elongation:

For all the formulation the % elongation was found to be in the range of 4.76 to 16.67.

Drug Content:

The drug content of all prepared patch found to be in the range between 83.82 to 93.19. This shows a near uniform drug content was noted for the similarity in all prepared batches.

Antifungal Activity:

The anti-fungal profile of Econazole and standard compounds (Miconazole) was evaluated by measuring the zone of inhibition against fungal strain (Trichophyton Interdigitale ATCC-9533) via well diffusion method. The compounds Econazole exhibited good activity as compared to the standard Miconazole.

CONCLUSION

In conclusion, this research paper aimed to formulate and evaluate an Econazole-loaded transdermal patch for its antifungal activity against Tinea Pedis. The formulation process involved selecting appropriate polymers, plasticizers, and permeation enhancers to optimize the patch's physicochemical properties and enhance drug permeation through the skin. Various parameters such as thickness, weight variation, drug content uniformity were evaluated. The results of the evaluation tests indicated that the formulated transdermal patch exhibited desirable characteristics, including uniform drug content, satisfactory thickness, folding endurance and all the overall evaluations conducted. Furthermore, the antifungal activity of the Econazole-loaded transdermal patch was assessed against Tinea Pedis. The patch demonstrated potent antifungal effects, inhibiting the growth of Tinea Pedis effectively. These findings suggest that the transdermal patch could serve as an effective and convenient dosage form for treating Tinea Pedis. Overall, this research highlights the potential of the Econazole-loaded transdermal patch as a novel therapeutic approach for the management of Tinea Pedis. The formulation and evaluation processes have provided valuable insights into the development of transdermal patches for antifungal applications. The future prospects could be the modifications in transdermal patches used for development of foots liners for treatment of athlete's foot.

Conflict of Interest:

There are no conflicts of interest.

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ABBREVIATIONS:

BCS-	Biopharmaceutical Classification System
PVP K-30-	Polyvinyl Pyrrolidione K-30
HPMC K-100-	Hydroxy Propyl Methyl Cellulose K-100
PEG 400-	Polyethylene Glycol 400
DMSO-	Dimethyl sulfoxide
UV-	Ultraviolet
FTIR-	Fourier transform infrared
mg-	milligram
ml-	millilitre
µl-	microliter
µg-	microgram
µm-	micrometre
kg-	kilogram
cm-	centimetre
°C-	degree Celsius

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