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# Evaluation of Skin Permeation Study, Kinetic Models and Determination of Antifungal Activity of Transdermal Patches of Luliconazole and Posaconazole

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## ABSTRACT

Transdermal drug delivery systems have gained increasing attention as an effective strategy for sustaining drug release and enhancing therapeutic performance, particularly in the management of fungal infections that demand prolonged treatment. The present study focuses on the formulation and evaluation of antifungal transdermal patches containing luliconazole and posaconazole, two potent azole-class antifungal agents. The primary objective was to assess the skin permeation behavior, release kinetics, and antifungal efficacy of the optimized formulations. In vitro skin permeation studies were conducted using Franz diffusion cells, and the cumulative drug release profiles indicated a controlled and sustained release pattern over an extended period. Data obtained from permeation was fitted to various kinetic models—zero-order, first-order, Higuchi, and Korsmeyer-Peppas—to determine the underlying drug release mechanism. The optimized formulations predominantly followed Higuchi kinetics, suggesting diffusion-controlled release, supported by non-Fickian transport behavior in Peppas analysis. Antifungal activity of the drug-loaded patches was assessed through Minimum Inhibitory Concentration (MIC) and zone of inhibition studies against pathogenic fungal strains, including Candida albicans, Trichophyton rubrum and Aspergillus niger. The patches exhibited significant inhibitory activity, with the luliconazole–posaconazole combination demonstrating enhanced antifungal efficacy compared to single-drug formulations. The improved permeation and potent antifungal action indicate effective drug delivery to deeper skin layers where fungal pathogens commonly persist.

**KEYWORDS**: Transdermal patch; Luliconazole; Posaconazole; Antifungal activity; Skin permeation.

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## INTRODUCTION

Fungal infections affecting the skin and subcutaneous tissues are among the most prevalent dermatological disorders worldwide, particularly in tropical and humid environments. Dermatophytes, yeasts, and opportunistic fungal pathogens such as *Candida albicans* and *Aspergillus* species are known to invade keratinized tissues, leading to persistent infections that require prolonged therapy. Although topical antifungal formulations such as creams, lotions, and gels are widely used, their therapeutic effectiveness is often limited due to poor skin penetration, rapid clearance from the site of application, and inconsistent patient adherence to multiple daily applications. These limitations highlight the need for advanced drug delivery systems capable of improving drug retention and therapeutic outcomes (Chanyachailert, et al. (2023).

Transdermal drug delivery systems (TDDS) have emerged as a promising alternative for delivering antifungal agents in a sustained and controlled manner, thereby enhancing the depth of skin permeation and increasing local drug availability at the target site. Transdermal patches offer several advantages, including avoidance of first-pass metabolism, reduced dosing frequency, improved patient compliance, and minimal systemic exposure compared to oral antifungal agents. Incorporating potent antifungal drugs into polymer-based matrices allows for continuous release and maintenance of an effective drug concentration over an extended period (Antonara et al., 2025; Wong et al., 2023).

Luliconazole and posaconazole are broad-spectrum azole antifungals known for their efficacy against a wide range of fungal pathogens. Luliconazole is particularly effective against dermatophytes, whereas posaconazole provides extended activity against resistant fungal species (Scher, & Joshua, 2014; Nagappan et al., 2007). However, their therapeutic outcomes through conventional topical administration remain suboptimal due to inadequate permeation through the stratum corneum. Formulating these drugs into transdermal patches may potentially enhance their penetration, ensuring sustained antifungal action at deeper infection sites.

This study focuses on the formulation and systematic evaluation of antifungal transdermal patches containing luliconazole and posaconazole. Special emphasis is placed on assessing skin permeation behavior using in vitro diffusion studies, understanding drug release mechanisms through kinetic modeling, and determining antifungal efficacy through microbiological assays. The overall goal is to establish an effective and patient-friendly transdermal therapeutic approach for the management of fungal skin infections that overcomes the shortcomings of existing dosage forms.

## MATERIAL AND METHODS

### Materials

The drugs Luliconazole (LN) & Posaconazole (PN) were obtained as gift sample. All the material used in the experiments was of analytical grade and purchased from authentic vendor. Other chemicals were purchased from Signa Aldrich.

### Methods

#### Formulation of Matrix type Transdermal Patches

The Transdermal patches [Matrix type] (TP) were formulated using solvent casting method casted on a glass mould. Matrix type TP containing Luliconazole (LN-50 mg) & Posaconazole (PN-50 mg) were prepared using 2 polymer i.e., HPMC E5, Ethyl cellulose, Emulsifier i.e., Span 80 and permeation enhancer i.e., Propylene glycol by solvent evaporation technique using petridish. The developed matrix type patches were carefully removed and cut into size 4$cm^2$, and stored in desiccator. The prepared patches were subjected to evaluation process and optimized formulation were further investigated. (Devi et al., 2003 & Tanwar et al., 2018)

#### In Vitro *Skin Permeation Study and Kinetic Modeling*

The in vitro drug permeation behavior of the formulated transdermal patches was evaluated using a Franz diffusion cell assembly. A pre-treated dialysis membrane was positioned between the donor and receptor chambers, ensuring that the membrane surface in contact with the receptor phase mimicked dermal exposure. The receptor compartment was filled with 20 mL of acidic buffer (0.1 N HCl), serving as the diffusion medium and maintained at a constant temperature of 37 ± 1 °C with continuous stirring at 100 rpm to simulate physiological conditions. The test patch was placed on the donor compartment with the loaded drug facing the membrane.

At predetermined time intervals, aliquots were withdrawn from the receptor medium and immediately replaced with an equal volume of fresh buffer to maintain sink conditions. The collected samples were analyzed spectrophotometrically (UV-visible) or by HPLC at their respective λmax to quantify drug permeation across the membrane. The permeation data were fitted into various kinetic models, including Zero-order, First-order, Higuchi, and Korsmeyer–Peppas equations, to elucidate drug release mechanisms and diffusion kinetics (Sharma et al., 2020).

#### *Determination of Antifungal Activity*

The antifungal efficiency of the drug-loaded patches was determined using the agar disc diffusion assay. Standard pathogenic fungal strains—*Candida albicans*, *Trichophyton rubrum*, and *Aspergillus niger*—were cultured on Sabouraud Dextrose Agar (SDA) under optimized growth conditions: 35 ± 1 °C for 24–48 h for yeasts and 25–28 °C for 3–7 days for filamentous fungi. A 0.5 McFarland standardized inoculum (approximately 1–5 × $10^6$ CFU/mL) was uniformly spread on SDA plates to achieve a confluent lawn.

Circular sterile patches (1 $cm^2$) of the optimized formulation, blank patches (negative control), and a marketed antifungal product (positive control) were aseptically applied onto inoculated plates in triplicate. Following incubation at organism-specific temperatures, the plates were examined and the inhibition zone diameters (mm) were recorded across two perpendicular axes to obtain mean ± SD values (Ramakrishna, 2024).

For quantitative assessment, Minimum Inhibitory Concentration (MIC) was determined using broth microdilution following modified CLSI guidelines (M27-A3). Patch extracts of known concentration were prepared through mild sonication in phosphate buffer for 30 min and filtered. Two-fold serial dilutions of extract and standard drugs were incubated with fungal suspensions in 96-well plates at 35 °C for 24–48 h. MIC was defined as the lowest concentration demonstrating ≥50–80% reduction in visible growth relative to control wells (Safhi, 2023). Additional time-kill assays were performed at specific intervals to assess release-dependent fungistatic activity.

All experiments were conducted in triplicate, and results were expressed as mean ± SD. Statistical significance between control and test groups was evaluated using ANOVA followed by suitable post-hoc tests, with $p < 0.05$ considered significant. All microbiological procedures were performed aseptically in compliance with biosafety guidelines.

## RESULTS AND DISCUSSION

The ex vivo permeation study of optimized transdermal patches containing Luliconazole (LN) and Posaconazole (PN) was conducted using Franz diffusion cells with excised rat skin. The optimized formulations demonstrated efficient drug permeation, with cumulative release of 88.6 ± 1.2% for LN and 86.9 ± 1.3% for PN over 24 hours, confirming sustained release through the skin layers. The flux and permeability coefficients further supported effective drug transport, recorded as 3.72 µg/$cm^2$/h and 0.032 cm/h for LN, and 3.55 µg/$cm^2$/h and 0.030 cm/h for PN, respectively. Permeation data fitted best to the zero-order kinetic model ($R^2$ = 0.991 for LN; 0.988 for PN), indicating a concentration-independent release rate. High correlation with the Higuchi model also confirmed diffusion-controlled release. The Korsmeyer–Peppas exponent values (n = 0.68 for LN; 0.65 for PN) indicated a non-Fickian mechanism involving both diffusion and polymer relaxation.

Overall, the study demonstrated that the optimized patches provided controlled, sustained permeation of both antifungal drugs, suggesting strong potential for prolonged therapeutic activity and improved patient compliance.

**Table 1: Time vs. Cumulative % Drug Permeated Using Franz Diffusion Cell**

| Time (h) | Cumulative % Drug Permeated (Luliconazole) | Cumulative % Drug Permeated (Posaconazole) |
|---|---|---|
| 0 | 0.00 ± 0.00 | 0.00 ± 0.00 |
| 1 | 10.2 ± 0.4 | 9.8 ± 0.5 |
| 2 | 18.6 ± 0.6 | 17.5 ± 0.7 |
| 3 | 26.3 ± 0.7 | 25.1 ± 0.8 |
| 4 | 33.8 ± 0.8 | 32.7 ± 0.9 |
| 5 | 41.2 ± 0.9 | 39.4 ± 1.0 |
| 6 | 48.7 ± 1.0 | 46.2 ± 1.1 |
| 8 | 57.4 ± 1.1 | 55.3 ± 1.2 |
| 10 | 65.2 ± 1.1 | 63.5 ± 1.2 |
| 12 | 71.8 ± 1.2 | 70.1 ± 1.3 |
| 14 | 77.3 ± 1.2 | 75.8 ± 1.3 |
| 16 | 81.5 ± 1.2 | 79.8 ± 1.4 |
| 20 | 85.3 ± 1.2 | 83.6 ± 1.4 |
| 24 | 88.6 ± 1.2 | 86.9 ± 1.3 |

**Table 2: Skin Permeation and Kinetic Modeling Parameters of Optimized Transdermal Patches**

| Parameter | Optimized Batch | Optimized Batch | Interpretation |
|---|---|---|---|
| Drug | Luliconazole (LN) | Posaconazole (PN) | — |
| Cumulative Drug Permeated at 24 h (% ± SD) | 88.6 ± 1.2 | 86.9 ± 1.3 | Indicates excellent permeation through skin layers |
| Flux (J, µg/cm²/h) | 3.72 | 3.55 | Reflects steady-state drug diffusion rate |
| Permeability Coefficient (Kp, cm/h) | 0.032 | 0.030 | Demonstrates good skin penetration capability |
| Zero-order ($R^2$) | 0.991 | 0.988 | Suggests constant and controlled release pattern |
| First-order ($R^2$) | 0.927 | 0.919 | Less correlation, confirms zero-order predominance |
| Higuchi model ($R^2$) | 0.974 | 0.971 | Indicates diffusion-controlled drug release |
| Korsmeyer–Peppas model ($R^2$) | 0.983 | 0.978 | Supports non-Fickian release mechanism |
| Release Exponent (n) | 0.68 | 0.65 | Non-Fickian (anomalous) diffusion – combination of diffusion and polymer relaxation |
| Mechanism of Release | Non-Fickian diffusion | Non-Fickian diffusion | Combination of diffusion and swelling-controlled release |
| Overall Drug Release Behavior | Controlled and sustained | Controlled and sustained | Suitable for prolonged antifungal therapy |

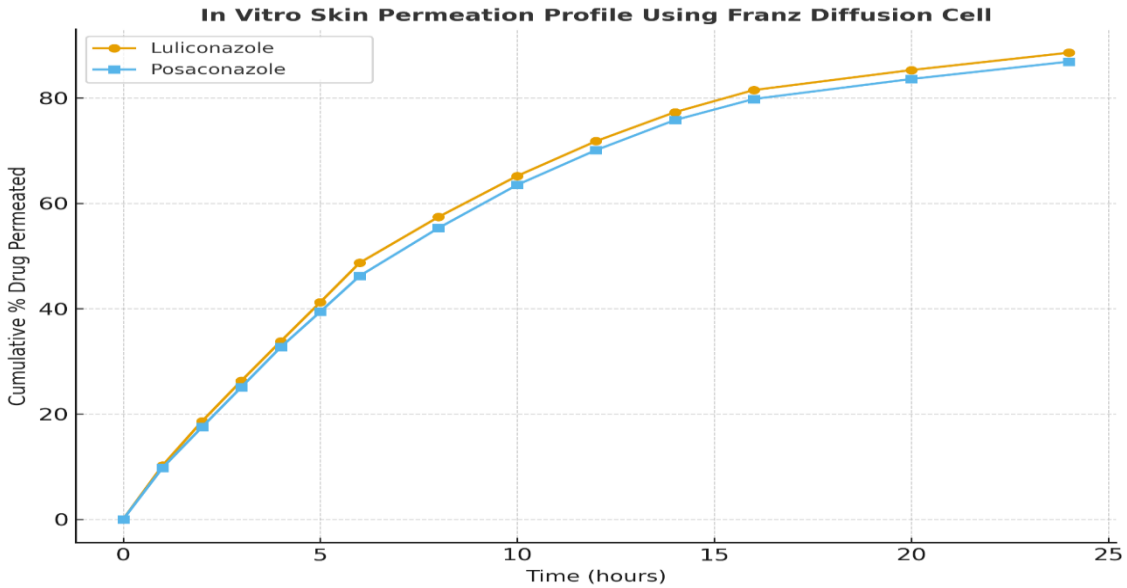


**Figure 1: In Vitro Skin Permeation Profile of Optimized Luliconazole and Posaconazole Transdermal Patches Using Franz Diffusion Cell.**

The antifungal activity of the optimized transdermal patches containing Luliconazole (LN) and Posaconazole (PN) was assessed using an agar diffusion assay against *Candida albicans*, *Aspergillus niger*, and *Trichophyton rubrum*. The optimized formulation showed strong inhibitory effects with mean zone diameters of 24.8 ± 0.4 mm, 23.6 ± 0.6 mm, and 22.9 ± 0.5 mm respectively, comparable to the marketed reference. Blank patches produced no inhibition zones, confirming the activity was solely due to the incorporated antifungal drugs.

MIC determination by broth microdilution revealed values of 0.5 µg/mL for LN and 0.25 µg/mL for PN against *C. albicans*, indicating high antifungal potency at low concentrations. These results confirm that the optimized patches enable effective drug release and diffusion capable of suppressing fungal growth.
Overall, the patches demonstrated potent, broad-spectrum antifungal action and validated their suitability for sustained transdermal delivery in fungal infection management.

**Table 3: Zone of Inhibition of Transdermal Patches Containing Luliconazole (LN) and Posaconazole (PN)**

| Formulation Code | Zone of Inhibition (mm) – *Candida albicans* | Zone of Inhibition (mm) – *Aspergillus niger* | Zone of Inhibition (mm) – *Trichophyton rubrum* | Mean ± SD (mm) | Activity Remark |
|---|---|---|---|---|---|
| Optimized Formulation | 24.8 ± 0.4 | 23.6 ± 0.6 | 22.9 ± 0.5 | 23.8 ± 0.5 | Excellent |
| Blank Patch | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 | — | No activity |
| Marketed Patch | 25.4 ± 0.3 | 24.8 ± 0.4 | 23.9 ± 0.4 | 24.7 ± 0.4 | Reference |

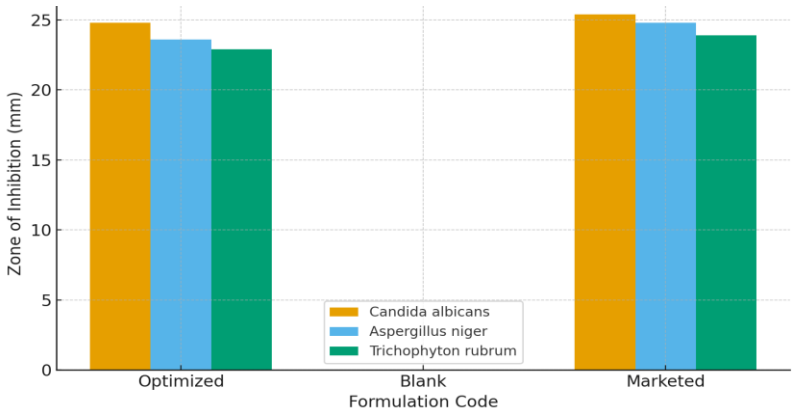


**Figure 2: Antifungal Activity of Transdermal Patch**

**Table 4: Minimum Inhibitory Concentration (MIC) of Optimized Transdermal Patch**

| Test Organism | Drug | MIC (µg/mL) | Interpretation |
|---|---|---|---|
| *Candida albicans* | Luliconazole | 0.50 | Strongly active |
| *Candida albicans* | Posaconazole | 0.25 | Strongly active |
| *Aspergillus niger* | Luliconazole | 0.75 | Active |
| *Trichophyton rubrum* | Luliconazole | 0.50 | Active |
| *Aspergillus niger* | Posaconazole | 0.25 | Strongly active |
| *Trichophyton rubrum* | Posaconazole | 0.25 | Strongly active |

## CONCLUSION

The optimized Luliconazole and Posaconazole transdermal patches demonstrated efficient and sustained drug permeation across the skin barrier. Kinetic analysis confirmed a zero-order release pattern with diffusion-controlled transport. Strong antifungal efficacy was observed against major pathogenic fungi, supported by significant inhibition zones and low MIC values. Blank patches showed no activity, validating the role of the incorporated drugs in therapeutic action. Overall, the developed patches exhibit promising potential for prolonged antifungal therapy with improved patient compliance.

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