International Journal of Multidisciplinary Research and Growth Evaluation.

Development and *in vitro* Evaluation of Isavuconazole Transdermal Patch for Sustained Antifungal Activity

Nansri Saha [1*], K Bhuvaneshwari [2], A Saritha [3]

[1] Associate Professor, Department of Pharmaceutics, SSJ College of Pharmacy, Vattinagulapally, Gandipet, Rangareddy District, Telangana, India

[2] Student, Department of Pharmaceutics, SSJ College of Pharmacy, Vattinagulapally, Gandipet, Rangareddy District, Telangana, India

[3] Professor and Head of the Department, Department of Pharmaceutics, SSJ College of Pharmacy, Vattinagulapally, Gandipet, Rangareddy District, Telangana, India

* Corresponding Author: **Nansri Saha**

Article Info

ISSN (Online): 2582-7138
Volume: 07
Issue: 06
Received: 20-08-2026
Accepted: 22-09-2026
Published: 24-10-2026
Page No: 288-295

Abstract

The present study was aimed at the formulation and evaluation of Isavuconazole transdermal patches for sustained drug delivery using the solvent casting method. Isavuconazole, a broad-spectrum triazole antifungal agent, was selected to overcome the limitations associated with conventional oral therapy and to provide prolonged therapeutic action through transdermal administration. FTIR studies confirmed the absence of any significant interaction between the drug and selected excipients. Eight formulations (F1–F8) were prepared using varying concentrations of Ethyl Cellulose and HPMC K15M as matrix-forming polymers, PEG 400 as a plasticizer, and DMSO as a permeation enhancer. The prepared patches were evaluated for physicochemical properties such as physical appearance, thickness, weight uniformity, folding endurance, drug content, moisture loss, and moisture absorption. All formulations exhibited satisfactory physicochemical characteristics with good flexibility and uniform drug distribution. *in vitro* drug release studies were performed using a Franz diffusion cell apparatus with phosphate buffer pH 7.4 as the receptor medium. The cumulative drug release after 12 hours ranged from 92.36% to 99.84%. Among all formulations, formulation F8 exhibited the highest drug content (98.25%) and maximum cumulative drug release (99.84%). Drug release kinetic analysis revealed that the optimized formulation followed Zero-order kinetics, indicating controlled and sustained drug release. Stability studies conducted under accelerated conditions (40 ± 2°C and 75 ± 5% RH) for three months demonstrated that the optimized formulation remained stable without significant changes in its physicochemical properties or drug release profile. The results of the study suggest that the developed Isavuconazole transdermal patch is a promising drug delivery system capable of providing sustained antifungal therapy, improved patient compliance, and enhanced therapeutic efficacy.

Keywords: Isavuconazole, Transdermal Patch, Solvent Casting Method, HPMC K15M, Ethyl Cellulose, Franz Diffusion Cell, Drug Release Kinetics, Stability Studies

Introduction

Isavuconazole is a broad-spectrum triazole antifungal agent used primarily for the treatment of invasive fungal infections, including invasive aspergillosis and mucormycosis.[1] Transdermal drug delivery is an attractive approach for achieving prolonged drug release and maintaining relatively consistent drug concentrations over an extended period. [2] Transdermal patches can bypass gastrointestinal degradation and hepatic first-pass metabolism, potentially improve bioavailability, reduce

dosing frequency, and enhance patient compliance. [3] The incorporation of suitable polymers and permeation-enhancing agents into a matrix-type transdermal patch may improve drug partitioning into the skin and regulate its diffusion from the formulation. [4] Hydrophilic and hydrophobic polymers can be combined in appropriate ratios to form a stable polymeric matrix, while plasticizers can improve flexibility and mechanical properties of the patch. [5] The present study was consequently undertaken to develop and evaluate isavuconazole-loaded transdermal patches using suitable polymers and formulation components, with emphasis on their physicochemical characteristics, drug-release behavior, and suitability for sustained antifungal drug delivery. [6]

Materials

Isavuconazole was procured from Hetero Labs, HYD. HPMC and Ethyl cellulose were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

Methodology

Formulation Design

Table 1: Formulation Design of Isavuconazole Transdermal Patches

F.no	Drug (mg)	Ethyl cellulose (mg)	HPMC k15M (mg)	PEG 400 (ml)	DMSO (ml)
F1	200	100	-	1	0.1
F2	200	200	-	1	0.1
F3	200	300	-	1	0.1
F4	200	400	-	1	0.1
F5	200	-	100	1	0.1
F6	200	-	200	1	0.1
F7	200	-	300	1	0.1
F8	200	-	400	1	0.1

Preparation of Transdermal Patches: Solvent Casting Method

Accurately weighed quantities of Ethyl Cellulose or HPMC K15M according to the formulation design (F1–F8) were dissolved separately in a suitable solvent system under continuous magnetic stirring until a clear polymeric solution was obtained. To this solution, PEG 400 (1 mL) was added as a plasticizer and mixed thoroughly to obtain a homogeneous dispersion. A weighed quantity of Isavuconazole (200 mg) was dissolved in a small volume of the solvent system and added slowly to the polymer solution under continuous stirring. Subsequently, DMSO (0.1 mL) was incorporated as a permeation enhancer and the mixture was stirred for 30 minutes to ensure uniform distribution of all components. The resulting solution was kept undisturbed for 15–20 minutes to remove entrapped air bubbles. The homogeneous casting solution was then poured into a glass Petri dish of known area lined with aluminum foil and allowed to dry at room temperature for 24 hours to facilitate complete solvent evaporation. After drying, the formed film was carefully removed from the Petri dish and cut into patches of the desired size. The prepared patches were wrapped in aluminum foil and stored in a desiccator containing anhydrous calcium chloride until further evaluation. [7]

Evaluation of Transdermal formulation [8-12]

Physico- Chemical Evaluation:

Physical Appearance

The prepared transdermal patches are visually inspected for their physical characteristics, including color, transparency, smoothness, flexibility, and uniformity. The patches are examined against a black and white background for the presence of air bubbles, cracks, crystal growth, or surface imperfections. The observations are recorded using descriptive terminology. A good-quality patch should be smooth, flexible, uniform, and free from visible defects.

Folding Endurance

Folding endurance is determined to evaluate the flexibility and mechanical strength of the transdermal patch. A strip of the patch (approximately 2 cm × 2 cm) is repeatedly folded manually at the same place until it breaks or develops visible cracks. The number of times the patch can be folded without breaking is recorded as the folding endurance value. The test is performed in triplicate, and the average value is reported.

Thickness of the Patch

The thickness of the transdermal patch is measured using a digital micrometer screw gauge or vernier caliper. Measurements are taken at three different points on each patch, namely the center and two opposite edges, to ensure uniformity. The mean thickness and standard deviation are calculated and expressed in millimeters (mm). Uniform thickness is important for consistent drug distribution and release.

Weight Uniformity

To determine weight uniformity, patches of identical dimensions are cut from different areas of the cast film and individually weighed using an analytical balance. The average weight and standard deviation are calculated. Uniformity in patch weight indicates uniform distribution of polymers and drug throughout the formulation.

Drug Content

A patch of known area is accurately weighed and cut into small pieces. The pieces are transferred into a volumetric flask containing a suitable solvent such as methanol and

stirred continuously until the drug is completely extracted. The resulting solution is filtered through Whatman filter paper No. 1 and suitably diluted. The drug concentration is determined using a UV-Visible spectrophotometer at the predetermined λmax of Isavuconazole. Drug content is calculated from the calibration curve, and the test is performed in triplicate.

Calculation

Drug Content (%)=Theoretical Drug Content/Actual Drug Content ×100

Moisture Absorption Studies

Moisture absorption studies are performed to evaluate the hygroscopic nature of the transdermal patches. The patches are accurately weighed and placed in a desiccator containing a saturated solution of potassium chloride, which provides approximately 84% relative humidity, at room temperature. After 72 hours, the patches are removed and reweighed. The increase in weight due to moisture absorption is calculated and expressed as percentage moisture absorption.

Calculation

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture Loss Studies

Moisture loss studies are carried out to determine the amount of moisture lost from the transdermal patches under dry conditions and to assess their stability during storage. Accurately weighed transdermal patches are placed individually in a desiccator containing a suitable desiccant such as anhydrous calcium chloride. The desiccator is maintained at room temperature for a period of 72 hours. After the specified storage period, the patches are removed from the desiccator and reweighed using an analytical balance. The difference between the initial and final weights represents the amount of moisture lost from the patch. The test is performed in triplicate, and the average percentage moisture loss is calculated.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

***In-vitro* Drug Release Studies**

The *in vitro* drug release study of the formulated transdermal patches was carried out using a Franz diffusion cell apparatus. A dialysis membrane (or cellulose acetate membrane) was selected as the diffusion barrier and was soaked overnight in phosphate buffer pH 7.4 to ensure proper hydration before use. The hydrated membrane was carefully mounted between the donor and receptor compartments of the Franz diffusion cell, ensuring that no air bubbles were entrapped beneath the membrane. The receptor compartment was filled with phosphate buffer pH 7.4, which served as the diffusion medium. The temperature of the receptor medium was maintained at 37 ± 0.5°C throughout the study using a thermostatically controlled water bath to simulate physiological conditions. The diffusion medium was continuously stirred with a magnetic stirrer at a constant speed of approximately 50–100 rpm to maintain uniform drug distribution. A transdermal patch of known dimensions was placed on the surface of the membrane in the donor compartment, with the drug-loaded side facing the membrane. The donor and receptor compartments were then securely clamped together to prevent leakage during the experiment. The diffusion area and receptor volume were noted for subsequent calculations. At predetermined time intervals (0.5, 1, 2, 4, 6, 8, 10, 12hours), a fixed volume of sample (1 mL) was withdrawn from the receptor compartment and immediately replaced with an equal volume of fresh phosphate buffer pH 7.4 maintained at the same temperature. This replacement ensured sink conditions throughout the study and maintained a constant volume in the receptor compartment. The withdrawn samples were analyzed using a UV-Visible spectrophotometer at the predetermined wavelength maximum (λmax) of the drug. The concentration of drug released into the receptor medium was determined from the previously constructed calibration curve. The cumulative amount of drug released at each sampling interval was calculated and expressed as cumulative percentage drug release.

Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{\text{Da}}{\text{Dt}} \times 100$$

Where, Dt = Total amount of the drug in the patch
Da = The amount of drug released

***In-Vitro* Drug Release Kinetics**

The in-vitro drug release data obtained from the diffusion studies were analyzed using various kinetic models to determine the mechanism of drug release from the formulated transdermal patches. The cumulative percentage drug release data were fitted into different mathematical models, namely Zero-order, First-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models. The correlation coefficient (R^2) values obtained from each model were compared, and the model showing the highest R^2 value was considered to best describe the drug release mechanism. The release exponent (n) value obtained from the Korsmeyer-Peppas equation was used to identify the nature of drug release, such as Fickian diffusion, non-Fickian transport, or Case-II transport. The kinetic analysis provided information regarding the rate and mechanism of drug release from the transdermal patches.

Stability Studies

Stability studies of the optimized transdermal patch formulation were carried out according to the International Council for Harmonisation (ICH) guidelines to evaluate the physical and chemical stability of the formulation during storage. The formulated patches were individually wrapped in aluminum foil and packed in suitable containers to protect them from environmental conditions. The samples were stored in a stability chamber maintained at 40 ± 2°C temperature and 75 ± 5% relative humidity (RH) for a period of three months. At predetermined intervals of 0, 30, 60, and 90 days, samples were withdrawn and evaluated for various parameters such as physical appearance, color, flexibility, folding endurance, thickness, drug content, and in-vitro drug release. Any changes in the appearance of the patches,

including discoloration, brittleness, or deformation, were carefully observed and recorded. Drug content analysis was performed using a UV-Visible spectrophotometer, and the in-vitro drug release study was conducted using the Franz diffusion cell method.

The results obtained at different storage intervals were compared with the initial values to assess the stability of the formulation. The formulation was considered stable if no significant changes were observed in its physical characteristics, drug content, and drug release profile throughout the storage period. The stability study confirmed the ability of the optimized transdermal patch formulation to maintain its quality, efficacy, and performance under accelerated storage conditions.

Results and Discussion

Evaluation of Transdermal Formulation

Weight (Mg)

Table 2: Physicochemical evaluation of Isavuconazole patches

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (%)	% Moisture loss	% Moisture absorption
F1	149	0.21	185	92.31	4.90	5.79
F2	152	0.26	191	93.41	4.73	5.81
F3	153	0.24	205	89.56	4.32	5.50
F4	154	0.28	193	94.54	4.20	5.28
F5	158	0.25	215	95.75	3.95	5.07
F6	157	0.20	243	96.36	3.57	4.89
F7	159	0.27	249	97.82	3.53	4.73
F8	160	0.29	258	98.25	3.42	4.49

Weight Uniformity

The weight of the formulated Isavuconazole transdermal patches ranged from 149 mg to 160 mg. The increase in patch weight from F1 to F8 was mainly attributed to the increase in polymer concentration in the formulations. All patches exhibited uniform weight distribution, indicating proper mixing of the drug and excipients during the solvent casting process. The results demonstrated the reproducibility of the formulation method and uniform distribution of ingredients throughout the polymer matrix.

Thickness

The thickness of the patches varied between 0.20 mm and 0.29 mm. The increase in thickness observed in formulations containing higher polymer concentrations was expected due to the greater amount of polymer present in the casting solution. Uniform thickness among the patches suggests that the solvent casting technique produced films of consistent dimensions, which is important for achieving uniform drug release.

Folding Endurance

Folding endurance values ranged from 185 to 258, indicating good flexibility and mechanical strength of all formulations. Formulations containing higher concentrations of HPMC K15M (F5–F8) exhibited greater folding endurance than those containing Ethyl Cellulose (F1–F4). The highest value was observed for formulation F8 (258 folds), indicating excellent flexibility and resistance to breakage during handling and application.

Drug Content

The percentage drug content of the prepared patches ranged from 89.56% to 98.25%. All formulations showed satisfactory drug loading and uniform drug distribution within the polymer matrix. Formulation F8 exhibited the highest drug content (98.25%), indicating efficient incorporation of Isavuconazole into the polymeric film. The results confirmed that the solvent casting method was suitable for producing patches with uniform drug distribution.

Moisture Loss

The percentage moisture loss was found to be between 3.42% and 4.90%. Lower moisture loss values indicate better stability of the patches during storage. The decrease in moisture loss with increasing polymer concentration suggests improved water-retaining capacity of the polymer matrix. Formulation F8 exhibited the lowest moisture loss (3.42%), indicating superior stability compared to the other formulations.

Moisture Absorption

The moisture absorption values ranged from 4.49% to 5.81%. All formulations exhibited acceptable moisture uptake characteristics. The moderate moisture absorption observed in HPMC-containing formulations may be due to the hydrophilic nature of HPMC. However, the values remained within acceptable limits, indicating that the patches possess adequate resistance to environmental humidity. Formulation F8 showed the lowest moisture absorption (4.49%), suggesting better storage stability.

In vitro Release Study

Table 3: *in vitro* drug release profiles of Isavuconazole transdermal patch (F1-F8)

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	16.79	17.48	18.76	17.48	18.91	21.25	20.25	25.39
2	27.48	26.73	25.18	26.37	28.65	29.48	30.72	31.84
3	38.43	37.40	36.34	38.91	40.28	41.76	42.85	44.12
4	45.72	46.37	47.81	48.10	49.63	50.84	52.16	53.48
6	57.89	58.42	58.82	63.25	65.38	67.42	69.58	71.84
8	72.13	73.59	74.15	75.91	77.48	79.26	81.35	83.42
10	82.32	83.61	84.97	86.32	87.54	89.18	91.26	93.15
12	92.36	93.36	95.26	96.36	97.14	98.28	99.12	99.84

Discussion

The *in vitro* drug release study confirmed that all formulations provided sustained release of Isavuconazole over a period of 12 hours. Drug release increased progressively with increasing HPMC concentration. The optimized formulation F8 exhibited nearly complete drug release and superior physicochemical characteristics, making it a promising candidate for effective transdermal delivery of Isavuconazole.

Kinetic Models

Zero Order Kinetics

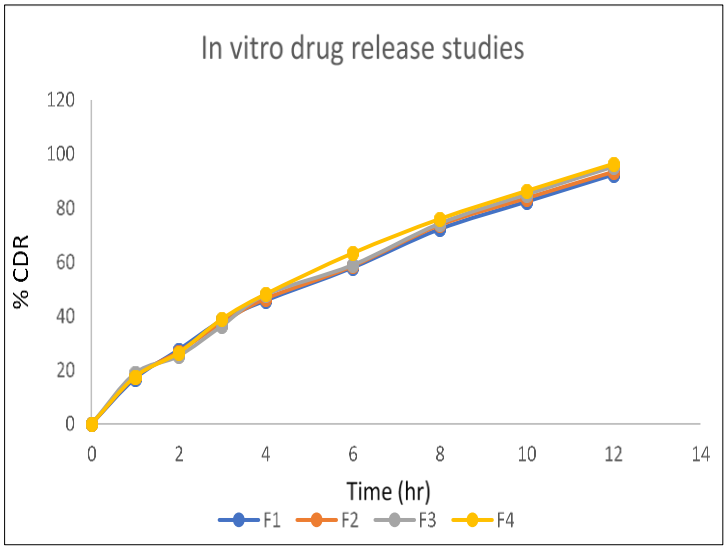


Fig 1: Drug release for (F1-F4) formulations

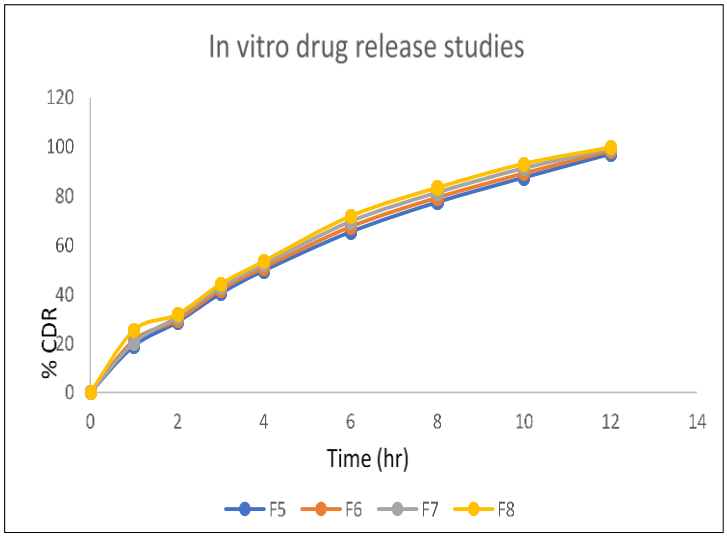


Fig 2: Drug release for (F5-F8) formulations

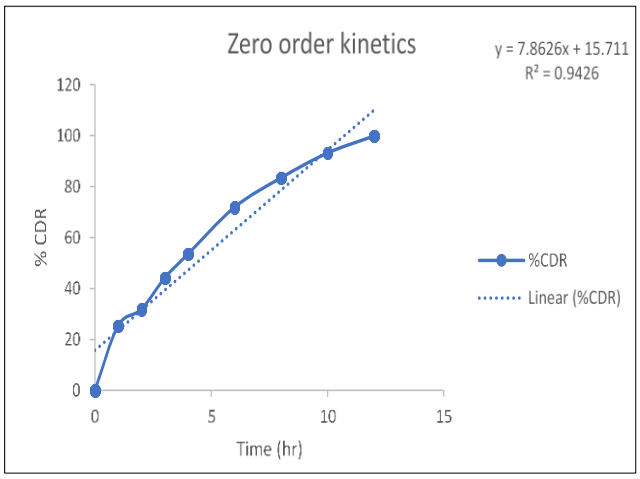


Fig 3: Zero order kinetics optimized formulation

First Order Kinetics

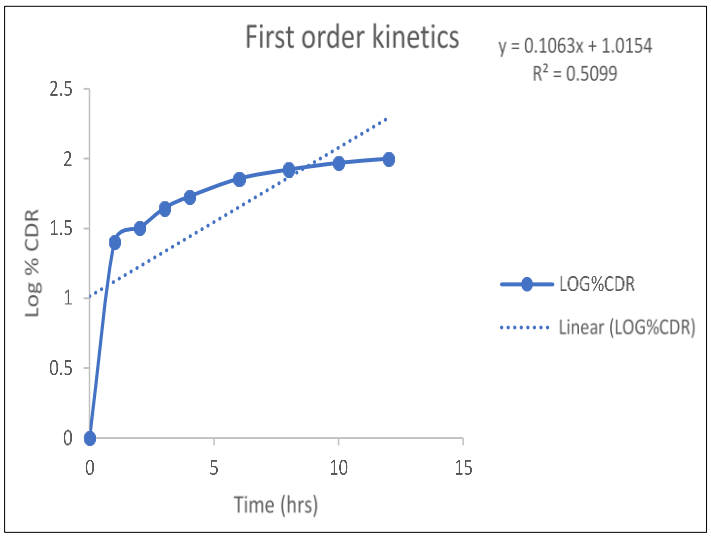


Fig 4: First order kinetics optimized formulation

Higuchi Model

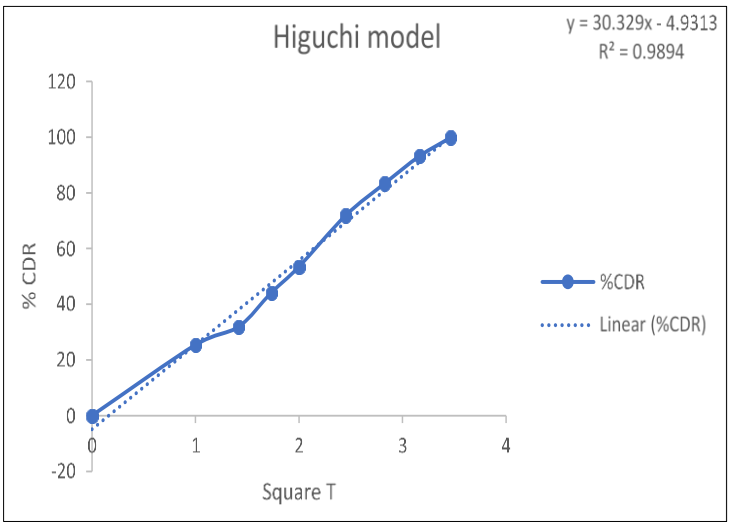


Fig 5: Higuchi model of optimized formulation

Korsmeyer Peppas

The values of *in vitro* release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix, Korsmeyer Peppas

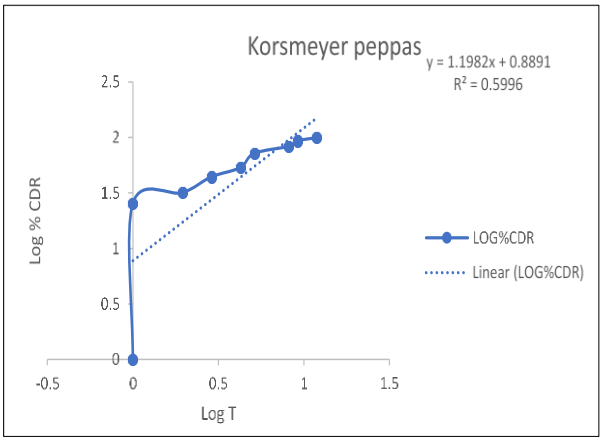


Fig 6: Korsmeyer peppas optimized formulation

Regression values are higher with Zero order release kinetics. Therefore, all the Isavuconazole patches follows Zero order release kinetics.

Stability Studies

Table 4: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Time in days	Drug content (%)	Folding endurance	Physical appearance	% Cumulative drug release
0	98.25	258	No change in color	99.84
90	97.36	257	Slight yellowish color	98.53

Conclusion

The study successfully developed and evaluated Isavuconazole transdermal patches using Ethyl Cellulose and HPMC K15M polymers by the solvent casting technique. The prepared formulations exhibited satisfactory physicochemical properties, good flexibility, uniform drug content, and acceptable moisture resistance. FTIR studies confirmed the compatibility of Isavuconazole with the selected excipients, indicating the suitability of the formulation components. Among all formulations, F8, containing the highest concentration of HPMC K15M, demonstrated superior performance with excellent mechanical properties, highest drug content (98.25%), and maximum cumulative drug release (99.84%) over 12 hours. The optimized formulation followed Zero-order release kinetics, indicating a controlled and sustained drug release profile suitable for transdermal drug delivery. Stability studies further confirmed that the optimized patch remained stable under accelerated storage conditions for three months. Therefore, the developed Isavuconazole transdermal patch can be considered a promising alternative to conventional dosage forms for the effective management of fungal infections, offering sustained drug release, improved patient compliance, and the potential to enhance therapeutic efficacy while minimizing dosing frequency.

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How to Cite This Article
Nansri S, Bhuvaneshwari K, Saritha A. Development and in vitro evaluation of isavuconazole transdermal patch for sustained antifungal activity. International Journal of Multidisciplinary Research and Growth Evaluation. 2026;7(6):288-295.

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