Formulation and evaluation of topical anti-fungal gel containing Itraconazole

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ABSTRACT

Introduction: Topical delivery was selected to enhance localized drug concentration at the site of infection while minimizing systemic side effects. Itraconazole makes the fungal cell membrane weak, leading to leakage of cell contents and ultimately fungal cell death. The present study focused on the formulation and evaluation of a topical antifungal gel containing itraconazole for the effective treatment of superficial fungal infections. **Methods:** The gel was prepared using suitable gelling agents such as Carbopol 940 and HPMC K4M, with Dimethyl Sulfoxide as a solvent and propylene glycol as a co-solvent. The formulation was optimized based on parameters including pH, spreadability, drug content and in vitro drug release. Antifungal efficacy was assessed using the agar well diffusion method against Candida albicans. The optimized formulation showed desirable physiochemical properties, sustained release, and significant antifungal activity, suggesting its potential as an effective topical treatment for fungal skin infections. **Results:** The results showed that the F7 formulation was found to be optimal, showing a skin-compatible pH of 6.43±0.025, good spreadability (10.84±0.1035), high drug content, and a sustained drug release profile reaching up to 93.07% over 240 minutes. **Conclusions:** The study successfully developed an optimized Itraconazole topical gel using Carbopol 940 and HPMC K4M. Among the formulations, F7 exhibited the best physicochemical properties and in vitro drug diffusion. These results confirmed23 that the developed gel is an effective delivery system for treating and preventing fungal infections.

Keywords: Carbopol, HPMC, Itraconazole, topical drug delivery.

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INTRODUCTION

Skin fungal infections are among the most common dermatological conditions. Treatment options available to doctors are numerous and include liquid dosage formulations, semisolid dosage forms and solid dosages. Gels are an intermediate state of matter containing both liquid and solid components. A gel is a two-component, cross-linked three-dimensional system consisting of an infinite rigid network structure that effectively immobilizes a proportionally large amount of a liquid continuous phase. This structural framework can be architected from either inorganic particles or organic macromolecules, predominantly polymers.[1] Clear, transparent gels are among the topical formulations that are most commonly used in cosmetics and pharmaceuticals.[2] Topical gels are semisolid homogenous preparation used to cure and treat topical diseases.[3] Similarly, the topical approach eliminates the gastrointestinal discomfort that occurs during the first pass, the metabolic deterioration that occur when medications are administered orally and the easier removal from the skin. Topical medication delivery methods using gel formulations have been suggested as a way around this drawbacks.[4] The spectrums of activity and modes of action of topical antifungal drugs vary, and there are few side effects or medication interactions.[5] Itraconazole is one of the triazole antifungal

drugs that prevent the creation of ergosterol by inhibiting an enzyme that is dependent on cytochrome P-450. Aspergillosis, blastomycosis, cryptococcal meningitis, and histoplasmosis have all been treated with it. It is a BCS class II medication with a high permeability and low solubility. Itraconazole has a poor oral bioavailability of 55% due to its exceedingly low solubility.[2] Triazole drugs target the development of membrane lipids that is unique to fungi. 5-fluorocytosine inhibits the replication of DNA unique to fungi.[6] The azole ring of itraconazole has three nitrogen atoms, which may enhance tissue penetration, extend half-life, and increase selectivity against fungal infection.[7]

Topical gels provide rapid drug release regardless of solubility and offer superior biocompatibility with minimal irritation. Their thixotropic, non-greasy and water-miscible nature ensures easy application and patient compliance.[8] The present study focused on the formulation and evaluation of a topical antifungal gel containing itraconazole for the effective treatment of superficial fungal infections.

METHODS

This study was conducted from October 2024 to April 2025 at the Universal College of Medical Sciences, Bhairahawa, Nepal, within the department of pharmacy and microbiology. Ethical clearance for this study was obtained from the Institutional Review committee of Universal College of Medical Sciences (Ref. No. UCMS/IRC/106/24).

The study was conducted in two distinct laboratory environments, a dry lab for computational analysis, mathematical modeling, and hypothesis generation using equipment such as an analytical balance and hot air oven and a wet lab for experimental procedures involving biological samples and chemical reactions. While the dry lab focused on risk-free digital simulations, the wet lab required stringent safety protocols and controlled environmental conditions to perform tasks using a magnetic stirrer, UV spectrophotometer, water bath, and pH meter.

Calibration curve of Itraconazole using DMSO

A primary stock solution was prepared by dissolving 10 mg of accurately weighed itraconazole in Dimethyl Sulfoxide (DMSO) to a final volume of 100 ml. From this, aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1.0 ml and 1.2 mL were diluted to 10 ml with DMSO to obtain a series of standard solutions ranging from 2 to 12µg/ml. The absorbance of each solution was measured at 262 nm using a UV-spectrophotometer against a DMSO as blank and a calibration curve was constructed by plotting absorbance versus concentration.[9]

Preparation of Itraconazole topical gel

The topical antifungal gels were prepared by varying the polymer ratios of carbopol and HPMC. The polymers were allowed to swell in distilled water for 24 hours to obtain clear solutions, which were then mixed thoroughly under continuous stirring. Accurately weighed itraconazole was dispersed in a 10 ml solution of DMSO and Propylene Glycol and this drug dispersion was slowly integrated into the polymeric base with constant stirring until a uniform gel was formed. Polysorbate 80 was incorporated as a solubilizer, while triethanolamine and propylparaben were added as a neutralizing agent and preservative respectively. The final formulations were stored in airtight, light-resistant containers prior to further evaluation. The various formulations (F1–F7) were prepared by varying the concentrations of Carbopol and HPMC, while keeping the concentrations of the drug and other excipients constant.[10] Their detailed composition is presented in Table 1.

Table 1: Composition of different Itraconazole topical gel formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7
Itraconazole (gm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Carbopol 940(gm)	0.25	0.375	0.50	0.75	0.25	0.25	0.375
HPMC K4M(gm)	-	-	-	-	0.25	0.375	0.25
DMSO (ml)	5	5	5	5	5	5	5
Propylene glycol(ml)	5	5	5	5	5	5	5
Polysorbate 80 (ml)	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Propyl paraben(gm)	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Triethanolamine (ml)	QS	QS	QS	QS	QS	QS	QS
Distilled water(ml)	Upto 50 ml	Upto 50 ml	Upto 50 ml	Upto 50 ml	Upto 50 ml	Upto 50 ml	Upto 50 ml

Evaluation of topical gel

Physical evaluation

All itraconazole gel formulations were evaluated for their organoleptic characteristics, including color, clarity, odor, texture and consistency.[2]

Measurement of pH

The pH of the formulated gels was determined by dissolving 1 gm of the sample in 100 ml of distilled water. Measurements were performed in triplicate using a digital pH meter and the mean values were calculated.[11]

Spreadability

Spreadability was determined by placing 1 gram of the gel

formulation within a 1 cm diameter circle marked on a glass plate. A second glass plate was placed on top, and a 500 gm weight was placed on the upper plate for five minutes. The resulting increase in the diameter of the spread gel was measured. The average of three independent measurements was calculated.[12]

Drug content

To determine the drug content, 1 gm of the gel was accurately weighed and dissolved in minimum volume of DMSO, the diluted to 100 ml with pH 7.4 phosphate buffer. From the above stock solution, 1 ml was withdrawn and further diluted to 10ml with same buffer. The absorbance of final solution was measured at 262 nm using a UV spectrophotometer against a pH 7.4 phosphate buffer as a blank.[13]

In vitro diffusion study

The in-vitro diffusion study was conducted using a dissolution apparatus at a rotation speed of 50 rpm. One gram of the gel formulation was accurately weighed and placed at the bottom of the basket, which was pre-covered with filter paper and secured with rubber bands. The dissolution medium consisted of 900 ml of phosphate buffer (pH 7.4), maintained at a constant temperature of 37±0.5ºC. At predetermined time intervals, 5 ml samples were withdrawn and immediately replaced with an equal volume of fresh dissolution medium to maintain sink conditions. The collected samples were filtered and analyzed for drug content spectrophotometrically at 262 nm using a UV-Vis spectrophotometer.[14,15]

Anti-fungal effect

The antifungal activity of the gel formulations was evaluated using the agar well diffusion method against Candida albicans. A fungal suspension, standardized to 0.5 McFarland, was prepared and inoculated onto the surface of Mueller-Hinton Agar (MHA) supplemented with 2% glucose. The inoculation was performed by streaking a sterile swab three times over the entire surface, rotating the plate 60 degrees each time to ensure uniform distribution. After the surface was allowed to dry, 5 mm wells were created using a sterile borer.

Each drug-loaded gel, its corresponding blank (without drug) and a standard drug solution (at concentrations of 1000 µg/mL and 100 µg/mL) were introduced into the respective wells using a micropipette. The Petri dishes were then incubated at 35°C for 24 hours and the antifungal activity was assessed by measuring the resulting zones of inhibition.[16,17]

RESULTS

Calibration curve

The absorbance of itraconazole was measured for a concentration range of 2 to 12 µg/mL at 262 nm. The resulting calibration curve exhibited excellent linearity, with a regression coefficient (R^2) of 0.9988.

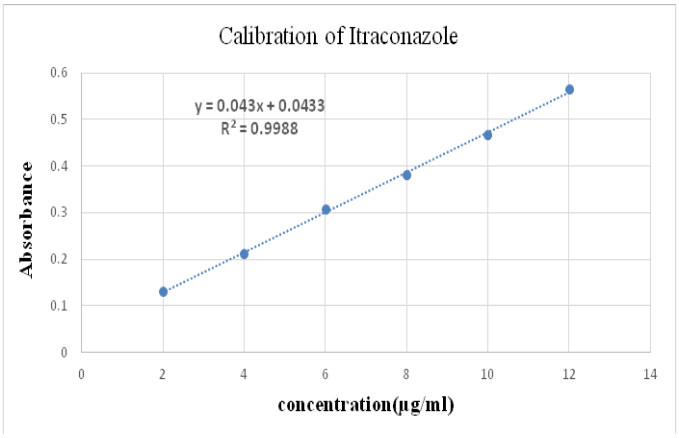

Figure 1: Calibration curve of Itraconazole

Physical evaluation

All the formulations exhibited smooth and uniform texture with absence of grittiness, lumps and air bubbles. All formulations were homogenous without any phase separations. All the formulations were white in appearance.

Measurement of pH

The pH value extends from 5.85±0.070 to 6.45±0.045 higher is in formulation F6 6.45±0.045 and least in F4 5.85±0.070.

Spreadability

The diameters of the gel spreadability in the circle ranged from 9.50±0.6806 to 11.50±0.1154. The highest spreadability observed in F1 prepared from Carbopol 0.25 and lowest spreadability observed in F4 prepared from 0.75 carbopol.

Drug content

The percentage drug content in all the prepared formulations was found to be consistent and within an acceptable range. Formulation F7 exhibited the highest drug content at 97.67±0.64%, while formulation F1 showed the lowest at 90.69±1.36%.

In -vitro drug release

The results of the dissolution studies for all the formulations were thoroughly evaluated. Formulation F7, which contained 0.375 gm of Carbopol940 and 0.25 gm of HPMC K4M showed an optimal and uniform drug release profile, reaching approximately 93.07% release at the end of 240 minutes. Formulation F1 containing 0.25 gm of Carbopol 940 showed lowest release within the same timeframe. The results visually represented in Figure 2.

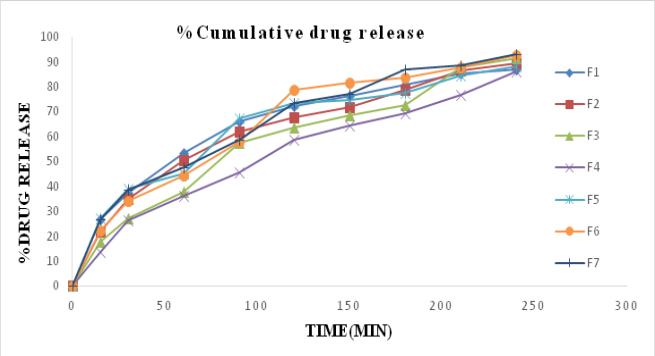

Figure 2: Cumulative % of drug release.

Antifungal effect

The microbiological study confirms that Itraconazole maintained its antifungal efficacy against Candida albicans when incorporated into the topical gel base. No significant difference was observed in the zones of inhibition across all formulations, as the concentration of the active drug remained constant throughout. These results, which demonstrate the sustained potency of the drug within the gel matrix, are summarized in Table 2 and visually represented in Figure 3.

Table 2: Zone of inhibition obtained antifungal susceptibility test.

	Zone of inhibition(mm)
Formulations	Candida albicans
F1	26±0.2055
F2	25±0.2646
F3	23±0.2645
F4	25±0.4025
F5	28±0.1733
F6	26±0.2646
F7	27±0.1022
Standard	26.58±0.2507
Negative control	18.57±0.9759

The values are expressed as mean ± SD (standard deviation)

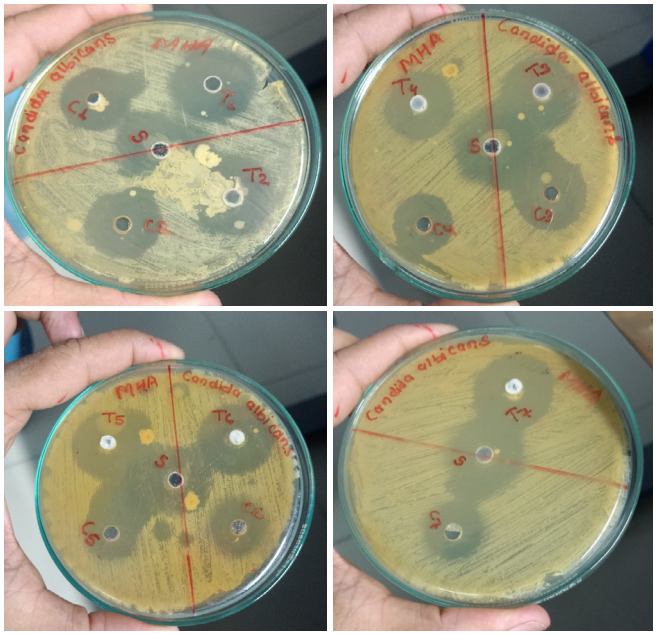

Figure 3: Zone of inhibition in Candida albicans antifungal susceptibility test.

DISCUSSION

Topical and transdermal drug delivery systems, including patches, gels, creams, and lotions, offer significant advantages over oral administration.[18] In this study, an itraconazole gel was formulated to overcome the systemic side effects associated with its oral dosage form. The physical evaluation confirmed that the gels were white, homogenous, and free from grittiness, with most formulations exhibiting excellent spreadability. The data obtained for pH, spreadability, drug content and anti-fungal activity were found to be consistent with results previously reported by Kasar PM et al. and Helal DA et al.[6,8] Among the seven developed formulations, F7 exhibited the most optimal physicochemical and biopharmaceutical characteristics. Its pH was found to be 6.43±0.025, which is well within the acceptable physiological range for topical applications, ensuring skin compatibility without irritation. The spreadability of F7 was recorded at 10.84±0.1035, reflecting excellent ease of application. Furthermore, a high drug content of 97.67±0.64% was achieved in F7, confirming a uniform distribution of Itraconazole and a validated formulation process. In terms of drug delivery, F7 demonstrated the highest cumulative release of 93.07%, indicating its superior efficiency in releasing the drug from the gel matrix. Consistent with the findings of Kasar et al.[6], who observed that increased polymer concentrations in Carbopol and HPMC gels lead to decreased drug release due to higher viscosity, this study also recorded a similar inverse relationship between polymer concentration and the rate of drug release. The antifungal efficacy of the formulated

Itraconazole gels was confirmed through the agar well diffusion method against Candida albicans. The results indicated that the drug successfully retained its therapeutic potency even after being incorporated into the gel matrix. Notably, there was no significant statistical difference in the Zone of Inhibition (ZOI) among all the formulations (F1–F7), as illustrated in Figure 3. This observation is attributed to the fact that the concentration of Itraconazole was kept constant across all batches. The consistent ZOI values across the formulations suggest that while the polymer ratios (Carbopol and HPMC) significantly influenced the drug's release rate and physical properties, they did not interfere with the drug's inherent antimicrobial activity. The findings from the antifungal susceptibility test (Table 2) validate that the developed topical system effectively delivers the active pharmaceutical ingredient (API) to inhibit fungal growth, making it a viable alternative to oral therapy for localized infections. Similar results were observed by Mousa AM,[19] who reported strong antifungal activity with broad zones of inhibition, a phenomenon credited to improved drug penetration and prolonged contact at the infection site. Conversely, Alyaha et al.[20] reported a significantly higher ZOI for ITS-TFS gels. This discrepancy can be explained by the higher degree of flexibility and deformability inherent in transferosomal systems, which facilitates superior penetration through the Candida albicans cell wall compared to conventional gel matrices.[19,20] The synergistic combination of Carbopol 940 and HPMC K4M in formulation F7 contributed to an optimal gel consistency and superior controlled-release profile. While carbopol enhanced the viscosity, HPMC acted as a structural matrix to ensure sustained drug delivery. Based on these comprehensive findings, formulation F7 was selected as the optimized formulation due to its physiological pH, excellent spreadability, high drug loading efficiency and efficient release kinetics. These attributes collectively indicate that F7 is a stable, effective and patient-compliant topical delivery system for Itraconazole.

CONCLUSIONS

In this study, topical gel of Itraconazole was prepared using different polymers like Carbopol 940, HPMC K4M in different concentration to obtain optimum drug release and evaluated to identify the most effective formulation based on physicochemical parameters such as drug content, pH, spreadabiility, in vitro drug diffusion. Among all, formulation F7 was found to be the most optimized and effective. The study showed that developed topical gel can treat and prevent fungal infections. Hence formulation F7 needs additional development for scaling up to commercial production.

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AUTHORS' CONTRIBUTIONS

RKM and GKY concept, designed the research. RKM, GKY, MK performed statistical analysis. RKM, GKY, PC, MK collected data. RKM prepared the first draft of the manuscript. RKM, GKY, PC, MK, SKG, VKM explained and interpreted the data and contributed to prepare the draft of the manuscript. RKM, MK, PC, SKG, VKM, AP contributed to revision and editing of the manuscript. All authors read and approved the final draft.

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