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Formulation and development of posaconazole topical gel: impact of polymer variability on antifungal efficacy

Harshit Gautam*, Abhishek Nagar

School of Health & Allied Science, Career Point University, Kota, Rajasthan, India

Corresponding author: Harshit Gautam, ✉ hrsht.gautam@gmail.com, **Orcid Id**: https://orcid.org/0009000557256044

School of Health & Allied Science, Career Point University, Kota, Rajasthan, India

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ABSTRACT

Superficial fungal infections represent a significant global health burden, affecting approximately 40 million individuals worldwide, particularly in developing nations. Posaconazole, a potent broad-spectrum triazole antifungal agent, exhibits poor aqueous solubility (0.02 mg/mL) and limited permeability, presenting formulation challenges for topical delivery. The present investigation aimed to formulate and evaluate Posaconazole topical gels using different polymers and study the effect of polymer variation on physicochemical properties, drug release behaviour, and antifungal efficacy. Five gel formulations (F1–F5) were prepared using gelling agents such as Carbopol 934P (1% w/w), Carbopol 940 (1% w/w), HPMC K4M (2% w/w), HPMC K15M (2% w/w) and Poloxamer 407 (20% w/w). Organoleptic characterization, determination of melting point, solubility profile, FTIR spectroscopy, DSC analysis and development of a UV spectrophotometric method were carried out as preformulation studies. The formulations were evaluated for: pH, viscosity, spreadability, extrudability, drug content uniformity, in vitro drug release, release kinetics, antifungal activity and stability. Preformulation studies showed the identity and purity of Posaconazole (melting point 168-172°C) and maximum solubility in DMSO (25.76 ± 0.32 mg/mL). The drug-excipient compatibility was demonstrated by FTIR and DSC. All the formulae showed acceptable physicochemical properties. The formulation F4 (HPMC K15M) showed the best properties: pH 6.72, viscosity 34,760 cP, spreadability 24.38 g·cm/sec, extrudability 95.74% and drug content 99.58%. In-vitro drug release by Higuchi kinetics (R2 = 0.992) was found, with 12 hours cumulative release of 97.84% in F4. The formulation was confirmed to be effective against the antifungal activity of Candida albicans, Aspergillus niger and Trichophyton rubrum. No significant changes were observed in the stability studies carried out under accelerated conditions (40 ± 2°C / 75 ± 5% RH) for three months. The HPMC K15M-based posaconazole gel is a promising topical formulation with desirable physicochemical properties, sustained drug release and excellent stability for effective treatment of superficial fungal infections.

Keywords: Posaconazole, Topical gel, Antifungal activity, Polymer variability, Drug release kinetics.

INTRODUCTION

The skin, as the largest and most accessible organ of the human body, serves as a critical barrier between the internal physiological environment and the external non-physiological world. With a surface area of approximately 2 m², the skin receives about one-third of the circulating blood volume and performs essential functions including protection against mechanical, thermal, and microbial insults, prevention of moisture loss, thermoregulation, and immune surveillance. The stratum corneum, the outermost layer of the epidermis, constitutes the primary physical barrier comprising 15-25 layers of flattened, keratinised hexagonal cells arranged in a "bricks and mortar" structure.

Fungal infections are an important worldwide health problem, and superficial mycoses affect approximately 40 million people across the world, especially in developing countries. Common diseases like tinea corporis, tinea pedis and tinea cruris are caused by dermatophyte fungi of the genera Trichophyton, Microsporum and Epidermophyton. Mucocutaneous infections are caused by Candida

species, especially by Candida albicans. Aspergillus species and other filamentous fungi cause more serious infections in immunocompromised patients. The rising incidence of fungal infections and the emergence of antifungal resistance to current drugs necessitate the development of new formulations with better efficacy and safety [1].

Posaconazole is a broad-spectrum, second-generation triazole antifungal agent active against yeasts, moulds, and dermatophytes. The mechanism of action is inhibition of the fungal cytochrome P450-dependent enzyme lanosterol 14-alpha-demethylase, resulting in disruption of ergosterol synthesis, a critical component of fungal cell membranes [2-4].

The destruction of membrane integrity and fluidity leads to the death of the fungal cell. Posaconazole shows a potent antifungal activity but is practically insoluble in water, which, combined with its poor permeability, presents significant formulation challenges for topical delivery.

Topical delivery has many advantages for the treatment of superficial fungal infections, such as direct application of the drug to the site of infection, reduction in systemic exposure and toxicity, improved patient compliance and avoidance of first-pass metabolism. However, stratum corneum impermeability limits drug(s) penetration, which requires the use of appropriate formulation strategies to improve drug(s) delivery across the skin layers. Gels are semi-solid formulations that have become popular as topical vehicles because of ease of application, non-greasy feeling, good spreadability and ability to provide controlled drug release.

The choice of gelling agent has significant influence on gel properties, drug release profile and therapeutic efficacy. Various types of polymers have been used in the formulation of topical gels such as Carbopol (cross-linked polyacrylic acid derivatives), Hydroxypropyl Methylcellulose (HPMC) (cellulose ethers) and Poloxamers (triblock copolymers). Carbopol polymers form clear, elegant gels with excellent viscosity and mucoadhesive properties, and HPMC offers good biocompatibility and controlled release characteristics. Poloxamer 407 is a thermo-responsive polymer that changes from a sol to a gel at body temperature.

The objectives of the present study were:

Preformulation studies for evaluation of drug-excipient compatibility.

Formulation of Posaconazole topical gels using different polymers at different concentrations.

Evaluation of formulations for physicochemical parameters such as pH, viscosity, spreadability, extrudability, and drug content.

Study of the effect of polymer variability on drug release behaviour and release kinetics.

Antifungal activity against pathogenic fungal strains.

Stability studies of optimized formulation as per ICH guidelines.

Recently, different novel delivery systems have been explored for topical delivery of Posaconazole. Posaconazole and clobetasol propionate loaded transdermal nanosponge hydrogel was formulated by Kunde and Jagtap. The formulations exhibited high drug entrapment efficiency (>96%), sustained release and enhanced skin permeation (>98%) in 12 h. Posaconazole nanoemulgel was developed by Sarvan et al. using natural oils with droplet sizes <100 nm and improved antifungal activity over marketed formulations. Kuppala and co-workers prepared Posaconazole microsponges into a hydrogel. It showed a rapid initial release followed by sustained release for 12 h. Patil and Ahmad developed a posaconazole microemulsion-based gel with 86 nm globule size, 102.69% drug content and 87.27% drug permeation [5]. Cyclodextrin-based nanosponge gels were developed by Pasha et al., which showed significantly higher skin penetration (41.64-54.12 μg/cm²) compared to the control (5.68 μg/cm²). Nijhawan et al. prepared posaconazole gels using Carbopol 934, sodium alginate and HPMC and the maximum drug release of 82.93% in 360 minutes was seen in the Carbopol-based formulation (F1).

However, the systematic study of polymer variability on Posaconazole gel properties, release pattern and antifungal activity has not been addressed thoroughly. The present study attempts to bridge this knowledge gap by formulating and evaluating Posaconazole gels with different polymers and investigating the relationship between polymer type and formulation performance [6, 7].

MATERIALS AND METHODS

Materials

Posaconazole was obtained as a gift sample from a pharmaceutical company. Carbopol 934P, Carbopol 940, Hydroxypropyl Methylcellulose (HPMC K4M and HPMC K15M), Poloxamer 407, propylene glycol, polyethene glycol 400, Tween 80, triethanolamine, methanol and other analytical-grade reagents were obtained from commercial sources.

Preformulation studies

Organoleptic properties and melting point

Visual observation was carried out for organoleptic properties such as colour, odour, appearance and texture. The melting point of Posaconazole was determined using the capillary melting point apparatus (Veego, India) and compared with the reported values.

Study of solubility

Solubility of Posaconazole in distilled water, ethanol, methanol, propylene glycol, PEG 400, DMSO and phosphate buffer pH 6.8 was determined. Excess quantities of drug were added to 5 mL of each solvent in sealed vials and shaken at room temperature for 24 hours. Samples were filtered through 0.45 μm membrane filters and spectrophotometrically analyzed at 262 nm.

FTIR analysis

FTIR spectra of pure Posaconazole and physical mixtures of Posaconazole with excipients were recorded on an FTIR spectrophotometer (Bruker, Germany) in the wavenumber range of 4000-400cm-1 using KBr pellet technique. The spectra were examined for characteristic functional groups and drug-excipient interactions.

DSC (differential scanning calorimetry)

Differential Scanning Calorimetry (DSC) analysis was performed with a Differential Scanning Calorimeter (Mettler Toledo, Switzerland). Samples (5-10 mg) were hermetically sealed in aluminium pans and heated at 10°C/min from 30 to 250 °C under a nitrogen atmosphere. The thermograms were analyzed for the melting endotherm and drug-excipient interaction.

Development of UV spectrophotometric method

Posaconazole standard stock solution (100 µg/mL) was prepared using methanol. To obtain the concentrations of 2, 4, 6, 8, 10, 12 and 14 µg/mL, serial dilutions were prepared. The absorbance was measured at 262 nm using a UV-Visible spectrophotometer (Shimadzu, Japan) using methanol as the blank. The calibration curve was made by plotting absorbance vs concentration.

Preparation of topical gel of posaconazole

Five gel formulations (F1-F5) were prepared using different polymers as described in Table 1. The procedure consisted of dispersing the polymer in distilled water with continuous stirring. For Carbopol-based formulations, the dispersion was allowed to hydrate for 24 hours. Posaconazole was dissolved in propylene glycol and PEG 400 and added to the polymer dispersion under constant stirring. Tween 80 was added to improve drug solubilization. Triethanolamine was added dropwise until a clear gel was obtained, and the pH was adjusted to 6.5-7.0 (for the Carbopol formulations). The final weight was set to 2. Formulations were kept in tightly closed containers at room temperature.

Table 1: Composition of posaconazole topical gel formulations

Ingredients (% w/w)	F1	F2	F3	F4	F5
Posaconazole	1.0	1.0	1.0	1.0	1.0
Carbopol 934P	1.0	--	--	--	--
Carbopol 940	--	1.0	--	--	--
HPMC K4M	--	--	2.0	--	--
HPMC K15M	--	--	--	2.0	--
Poloxamer 407	--	--	--	--	20.0
Propylene Glycol	10.0	10.0	10.0	10.0	10.0
PEG 400	5.0	5.0	5.0	5.0	5.0
Tween 80	1.0	1.0	1.0	1.0	1.0
Triethanolamine	q. s.	q. s.	q. s.	q. s.	q. s.
Distilled Water	q. s. to 100	q. s. to 100	q. s. to 100	q. s. to 100	q. s. to 100

Evaluation of posaconazole gel

Physical appearance and pH

Formulations were visually inspected for color, homogeneity, consistency, and grittiness. pH was measured using a digital pH meter (Eutech, India) after dispersing 1 g of gel in 10 mL distilled water and allowing it to stand for 2 hours.

Viscosity determination

Viscosity was measured using a Brookfield Viscometer (Brookfield, USA) with a suitable spindle at 25°C. The spindle was immersed in the gel, and readings were recorded after achieving equilibrium. The average of three determinations was reported.

Spreadability

Spreadability was determined using the glass slide method. One gram of gel was placed between two glass slides. A standardized weight of 125 g was placed on the upper plate for one minute.

The diameter of the spread gel was measured and the spreadability was calculated by:

Spreadability = (m x l)/t m = weight applied l = length t = time.

Extrudability

The collapsibility of aluminium tubes was measured by filling them with gel and applying manual pressure.

The amount of gel extruded was expressed as a percentage:

Extrudability (%) = (Weight of extruded gel / Total weight of gel) × 100

Drug content uniformity

Accurately weighed 1 g of gel from each batch was transferred to a 100 mL volumetric flask containing 20 mL methanol. The mixture was stirred for 30 minutes to extract the drug completely. The volume was adjusted to 100 mL with methanol and filtered through Whatman filter paper. Suitable dilutions were prepared and analyzed spectrophotometrically at 262 nm.

***In Vitro* drug release study**

The in vitro drug release study was performed using a Franz diffusion cell (Orchid Scientifics, India). A dialysis membrane (MWCO 12,000-14,000 Da) was mounted between the donor and receptor compartments. Approximately 1 g of gel formulation was applied uniformly onto the membrane in the donor compartment. The receptor compartment was filled with phosphate buffer pH 6.8 (30 mL) maintained at 37 ± 1°C, and stirred continuously at 100 rpm.

Aliquots of 5 mL were withdrawn at predetermined time intervals (1, 2, 4, 6, 8, 10 and 12 hours) and replaced by an equal volume of fresh buffer to maintain sink conditions. The withdrawn samples were analyzed spectrophotometrically at 262 nm, and cumulative percentage drug release was calculated.

Release kinetics

The in vitro drug release data of the optimized formulation were fitted into various kinetic models:

Zero-order: $Q = k_0 t$

First-order: $\log Q = \log Q_0 - k_1 t/2.303$

Higuchi: $Q = kH\ t^{1/2}$

Korsmeyer-Peppas: $\log Q = \log k + n \log t$

where Q is the amount of drug released, k is the rate constant, t is time, and n is the release exponent indicating the release mechanism.

Antimycotic action

Antifungal Sensitivity Study: Sabouraud Dextrose Agar (SDA) medium was used to perform the antifungal sensitivity study against fungal strains Candida albicans (ATCC 10231), Aspergillus niger (ATCC 16404) and Trichophyton rubrum (clinical isolate). Fungal inoculum (1 × 10 6 CFU/mL) was spread on SDA plates. Wells of 6 mm diameter were prepared, and 100 mg of gel formulations were placed in the wells. Plates were incubated at 37°C for 24-48 hour and the diameter of the zone of inhibition was measured.

Stability studies

The optimised formulation (F4) was subjected to accelerated stability studies as per ICH guidelines.

Samples were stored at 40 ± 2°C / 75 ± 5% RH and 25 ± 2°C / 60 ± 5% RH for three months. Samples were withdrawn at 1, 2, and 3 months and evaluated for physical appearance, pH, viscosity, spreadability, drug content, and in vitro drug release.

Statistical analysis

All experiments were performed in triplicate. Data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using GraphPad Prism 8.0. Comparison between groups was done using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Significance was set at $p < 0.05$. [8, 9].

RESULT AND DISCUSSION

Preformulation studies

The organoleptic characteristics of Posaconazole matched reported values, appearing as a white to off-white, odourless, crystalline powder with fine texture. The melting point was found to be 168-172°C, which is in agreement with the reported range of 170-172°C, indicating drug purity.

Solubility studies showed the hydrophobic property of Posaconazole, practically insoluble in distilled water (0.02 ± 0.01 mg/mL). The drug showed the highest solubility in DMSO (25.76 ± 0.32 mg/mL), followed by methanol (8.45 ± 0.21 mg/mL), propylene glycol (6.84 ± 0.18 mg/mL) and PEG 400 (5.97 ± 0.14 mg/mL). In phosphate buffer pH 6.8 (0.38 ± 0.02 mg/mL) poor solubility was observed, which is in accordance with the BCS Class II classification of Posaconazole (low solubility, high permeability) [9-11]. The results showed that the formulation required co-solvents (propylene glycol and PEG 400) and surfactant (Tween 80) to increase drug solubilization.

FTIR spectrum of pure Posaconazole showed characteristic absorption peaks at 3400-3200 cm-1 (O-H stretching), 3100-3000 cm-1 (Aromatic C-H stretching), 2950-2850 cm-1 (Aliphatic C-H stretching), 1600-1500 cm-1 (C=N stretching of triazole ring), 1500-1450 cm-1 (Aromatic C=C stretching), 1250-1050 cm-1 (C-O stretching) and 1200-1000 cm-1 (C-F stretching). The FTIR spectra of physical mixtures with the polymers showed all characteristic peaks without significant shifts, disappearance or appearance of new peaks, confirming the absence of chemical interactions between Posaconazole and the excipients.

The DSC thermogram of pure Posaconazole showed a sharp endothermic peak at 170.5°C, which was related to the melting point of Posaconazole, confirming the crystalline nature of Posaconazole. The optimized formulation showed the drug peak at 168.9 °C with little intensity reduction and minor broadening, probably due to drug dispersion in the polymeric matrix. No other peaks or major changes were observed, confirming thermal compatibility between Posaconazole and formulation components.

UV-Visible spectrophotometric scan exhibited a prominent absorption maximum (λmax) at 262 nm in methanol.

The calibration curve was linear in the concentration range 2-14 µg/mL, with the regression equation y = 0.053x - 0.003 and correlation coefficient R2 = 0.999, which shows that the method obeys Beer-Lambert's law and is validated for quantitative estimation.

Posaconazole gel formulation evaluation

Physical characteristics and pH

All formulations (F1-F5) were smooth, homogeneous and translucent without particulate matter or phase separation. Carbopol-based formulations (F1 and F2) were white in color whereas HPMC-based formulations (F3 and F4) were off-white in color. Poloxamer-based formulation (F5) was white in appearance. Formulation F4 was found to be excellent in homogeneity and consistency.

The pH values of the formulations were in the range of 6.21-6.72 (Table 2), which is in the acceptable physiological range for topical application (5.0-7.0). The optimum pH was found to be closest to the normal skin pH, which was the pH of formulation F4 (6.72). The product should be compatible with skin pH to prevent irritation and maintain normal skin barrier function.

These results are consistent with previously published studies of Posaconazole topical gels.

Table 2: Physicochemical characterization of posaconazole gel formulations

Parameter	F1	F2	F3	F4	F5
pH	6.21	6.34	6.48	6.72	6.58
Viscosity (cP)	24,850	27,430	30,280	34,760	31,920
Spreadability (g·cm/sec)	18.42	19.67	21.15	24.38	20.84
Extrudability (%)	86.12	88.45	91.38	95.74	89.26
Drug Content (%)	96.24	97.86	98.74	99.58	97.42

Viscosity

The viscosity values ranged from 24,850 cP (F1) to 34,760 cP (F4) (Table 2). Formulation F4 showed the highest viscosity, indicating better gel structure and retention on the skin. The formulation based on HPMC K15M exhibited better viscosity than other polymers due to the higher molecular weight of HPMC K15M and its capacity to generate more robust hydrogen bonding networks

with water molecules. Carbopol-based formulations exhibited moderate viscosity, while the Poloxamer-based formulation exhibited acceptable viscosity. The observed differences in viscosity are consistent with the rheological properties of the polymers. HPMC K15M has a higher molecular weight (~ 80,000-100,000 Da), so solutions are more viscous than HPMC K4M. Carbopol polymers (934P and 940) are cross-linked polyacrylic acids that gel upon neutralisation.

Carbopol 940 generally has a higher viscosity than 934P due to its higher molecular weight. Poloxamer 407 is a thermoreversible gelation-forming gel at physiological temperatures.

Spreadability and extrudability

The values of spreadability ranged from 18.42 g.cm/sec (F1) to 24.38 g.cm/sec (F4) (Table 2). The formulation F4 showed the best spreadability, which indicated easy application and uniform distribution on the skin. Good spreadability is essential to make sure uniform application of the drug over the affected area for better therapeutic efficacy.

The extrudability values ranged from 86.12% (F1) to 95.74% (F4) (Table 2). Formulation F4 showed the highest extrudability with an excellent ease of removal from the tube. The higher extrudability of F4 is attributed to the best gel consistency obtained with HPMC K15M, which allows smooth extrusion under manual pressure.

Uniformity of drug content

All the prepared formulations exhibited good uniformity of drug content ranging from 96.24% to 99.58% (Table 2). The formulation F4 showed the highest drug content (99.58%), which points toward the uniform distribution of Posaconazole in the gel matrix. The acceptable values of drug content show the reproducibility of the preparation method and no loss of drug during processing. These results are in agreement with previously reported Posaconazole gel formulations.

***In Vitro* drug release study**

The in vitro drug release profiles of Posaconazole formulations (F1–F5) over 12 h are presented in Table 3 and Figure 1. All formulations exhibited a sustained release profile of the drug, with cumulative release of 81.48% (F1) to 97.84% (F4) at 12 hours.

Table 3: Cumulative percentage of posaconazole formulations released

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
1	12.42	13.58	15.24	18.36	14.12
2	21.84	24.17	27.56	32.74	25.63
4	38.26	41.73	46.92	54.38	43.75
6	52.18	56.84	62.47	70.15	58.42
8	64.92	69.38	74.56	82.73	70.18
10	73.64	78.15	83.41	91.26	79.34
12	81.48	85.72	89.65	97.84	86.93

The formulation F4 (HPMC K15M-based) showed a significantly higher ($p < 0.05$) cumulative drug release (97.84%) at 12 h compared to other formulations. The improved release from F4 can be due to the ideal gel structure and hydration characteristics of HPMC K15M. HPMC K15M is a hydrophilic polymer that rapidly hydrates in aqueous media and forms a gel layer, which helps in drug diffusion. The higher molecular weight of HPMC K15M compared to HPMC K4M provides a more stable gel matrix with controlled release properties.

The Carbopol-based formulations (F1 and F2) exhibited moderate release of drug (81.48 % and 85.72%, respectively). The Carbopol polymers, having a cross-linked network, limit the diffusion of the drug to some degree, resulting in a slower release as compared to the HPMC formulations. The poloxamer-based formulation (F5) showed the cumulative release of 86.93% at 12 hours, indicating its sustained release capability.

The sequential pattern of release of the formulations (F4 > F5 > F3 > F2 > F1) indicates that the type and concentration of the polymer significantly impact the drug release behaviour. These results are in agreement with other antifungal drug studies where HPMC-based formulations showed better release characteristics (10).

Kinetics of release

The in vitro drug release data of the optimized formulation (F4) were fitted to various kinetic models to explore the release mechanism (Table 4).

Table 4: Release kinetics parameters of optimized formulation (F4)

Kinetic model	Regression equation	R^2 value
Zero-order	y = 8.142x + 10.254	0.964
First-order	y = -0.081x + 2.012	0.978
Higuchi	y = 28.364x½ + 2.416	0.992
Korsmeyer-Peppas	y = 0.621x + 1.742	0.986

The highest correlation coefficient ($R^2 = 0.992$) was found for the Higuchi model of the optimized formulation, indicating that the drug release was mainly diffusion-controlled. The release exponent (n = 0.621) from the Korsmeyer-Peppas model indicated non-Fickian (anomalous) diffusion by diffusion and polymer relaxation mechanisms.

Higuchi kinetics is a square-root-of-time dependence, and it describes the drug release from a matrix system in which the rate of release is controlled by diffusion through the polymer matrix. The non-Fickian diffusion (n between 0.5 and 1.0) indicates that drug release is controlled by a combination of Fickian diffusion and polymer chain relaxation, a mechanism typical of hydrophilic polymer matrices.

The release kinetics study revealed that the release of Posaconazole from the optimized gel formulation is mainly governed by diffusion through the hydrated polymeric matrix, with polymer relaxation contributing to the overall release process. The Higuchi fit

of the model (R2 = 0.992) is in agreement with the previous studies on Posaconazole transdermal patches, where the Higuchi kinetics showed a good correlation (R2 = 0.971).

Antifungal activity

Table 5: Antifungal activity of Posaconazole gel formulations against Candida albicans, Aspergillus niger and Trichophyton rubrum. All formulations exhibited significant zones of inhibition, indicating strong antifungal activity.

Table 5: Antifungal activity of posaconazole formulations

Formulation	Zone of Inhibition (mm)		
	C. albicans	A. niger	T. rubrum
F1	18.6 ± 0.8	17.4 ± 0.6	16.2 ± 0.7
F2	19.2 ± 0.7	18.1 ± 0.8	17.3 ± 0.6
F3	20.4 ± 0.9	19.2 ± 0.7	18.5 ± 0.8
F4	22.8 ± 0.6	21.6 ± 0.5	20.7 ± 0.7
F5	19.8 ± 0.7	18.7 ± 0.6	17.9 ± 0.8
Marketed Cream	20.1 ± 0.8	19.0 ± 0.7	18.2 ± 0.6

The formulation F4 showed the highest inhibition zones against C. albicans, A. niger and T. rubrum, with diameters of 22.8 ± 0.6 mm, 21.6 ± 0.5 mm and 20.7 ± 0.7 mm for all tested strains, respectively. The improved antifungal activity of F4 is attributed to the HPMC K15M gel matrix, which provides optimised drug release and skin permeation properties. The sustained and complete release of the drug (97.84% at 12 hr) from F4 ensures enough concentration of drug at the site of fungal infection, which results in enhanced antifungal efficacy.

The antifungal activity against all three strains tested confirms the broad-spectrum nature of Posaconazole. The diameters of the zone of inhibition were comparable to those previously observed for Posaconazole formulations. The transdermal patches (11) showed zones of 24.8 mm (C. albicans), 23.6 mm (A. niger) and 22.9 mm (T. rubrum).

Stability study

The optimized formulation (F4) was studied for stability for three months at accelerated (40 ± 2°C/75 ± 5% RH) and room temperature (25 ± 2°C/60 ± 5% RH) conditions according to ICH guidelines. The results are shown in Table 6.

Table 6: Stability data of optimized formulation (F4)

Parameter	Initial	1 Month	2 Months	3 Months
Physical Appearance	Smooth, homogeneous	No change	No change	No change
pH	6.72	6.70	6.68	6.66
Viscosity (cP)	34,760	34,520	34,310	34,080
Spreadability (g·cm/sec)	24.38	24.24	24.10	23.96
Drug Content (%)	99.58	99.24	98.93	98.61
Drug Release at 12 h (%)	97.84	97.52	97.16	96.88

No significant changes ($p > 0.05$) in physical appearance, pH, viscosity, spreadability, drug content and drug release profile were observed in the 3-month storage period in either condition. All the parameters evaluated were within acceptable limits which confirms the stability of the formulation.

The small decrease in viscosity (from 34,760 to 34,080 cP) over 3 months was within acceptable limits and was likely caused by polymer chain relaxation or slight dehydration. Drug content decreased slightly from 99.58% to 98.61%, and drug release at 12 hours decreased from 97.84% to 96.88%, showing excellent chemical stability and sustained release properties.

Stability data indicated that HPMC K15M-based Posaconazole gel was stable under accelerated conditions for three months without any change in physicochemical and performance characteristics. This is in accordance with ICH guidelines for accelerated stability testing of topical semisolids, recommending storage at 40 °C/75% RH with evaluation at 0, 1, 2 and 3 months.

Selection of optimised formula

On the basis of detailed evaluation of physicochemical parameters, in vitro drug release, release kinetics, antifungal activity and stability, the optimised formulation was selected as Formulation F4 (HPMC K15M-based gel) (Table 7).

Table 7: Characteristics of optimized formulation (F4)

Parameter	Value
Polymer	HPMC K15M
pH	6.72
Viscosity (cP)	34,760
Spreadability (g·cm/sec)	24.38
Extrudability (%)	95.74
Drug Content (%)	99.58
Drug Release at 12 h (%)	97.84
Release Kinetics	Higuchi (R^2 = 0.992)
Release Exponent (n)	0.621
Antifungal Activity (Zone, mm):	
- C. albicans	22.8
- A. niger	21.6
- T. rubrum	20.7
Stability (3 months)	Stable

The better performance of HPMC K15M as compared to other polymers may be due to the following unique properties:

High molecular weight, which provides good gel consistency.

Formation of a strong hydrogen-bonding network, which results in sustained drug release.

Biocompatible and non-irritating nature.

Good hydration properties, which facilitate drug diffusion.

Optimum viscosity for application and retention on skin.

HPMC K15M-based formulations have been shown in previous studies to benefit several antifungal drugs, allowing controlled release and better skin penetration. The release kinetics (Higuchi model) confirm the diffusion-controlled mechanism of drug release from this matrix system, which is desirable to maintain therapeutic drug concentrations over long periods [10-12].

CONCLUSION

In the present study, posaconazole topical gels were formulated and evaluated successfully using different polymers, such as Carbopol 934P, Carbopol 940, HPMC K4M, HPMC K15M and

Poloxamer 407. The effect of variation in polymer on formulation characteristics and antifungal activity was also studied.

The preformulation studies confirmed the identity and purity of Posaconazole with a melting point of 168-172°C and characteristic FTIR and DSC profiles. Poor aqueous solubility (0.02 mg/mL) required co-solvents (propylene glycol and PEG 400) for formulation. FTIR and DSC studies showed compatibility of the drug and excipients.

All five formulations showed acceptable physicochemical properties with pH values (6.21-6.72) within the physiological range. The HPMC K15M-based formulation (F4) showed excellent characteristics such as optimal pH (6.72), maximum viscosity (34,760 cP), good spreadability (24.38 g cm/sec), good extrudability (95.74%) and uniformity of drug content (99.58%). In vitro drug release studies showed sustained release over 12 h, with F4 showing the highest cumulative release (97.84 %). The kinetics of release followed the Higuchi model (R 2 =0.992), suggesting a diffusion-controlled release with non-Fickian (anomalous) diffusion as the mechanism of release (n=0.621).

The formulation was effective as an antifungal agent against Candida albicans, Aspergillus niger and Trichophyton rubrum, with the largest zones of inhibition observed with F4. Stability studies were done for a period of 3 months under accelerated conditions (40 ± 2°C / 75 ± 5% RH) and room temperature (25 ± 2°C / 60 ± 5% RH), which confirmed the stability of F4 with no significant changes in physicochemical parameters.

The posaconazole gel based on HPMC K15M is a promising topical formulation for the treatment of superficial fungal infections. Polymer variability correlation with formulation performance has been established, where HPMC K15M exhibited optimum characteristics for sustained drug release and improved antifungal efficacy. This formulation has advantages such as increased local delivery of the drug, decreased systemic absorption, better patient compliance and ease of application in the treatment of dermatophytosis and candidiasis.

Further studies can be done to study the pharmacokinetic and pharmacodynamic effects in animal models in vivo and clinical trials in humans. Alternate delivery systems like nanosponge-based hydrogels or microemulsion-based gels can be formulated for better penetration and efficacy of the drug. The principles developed herein can be extended to other poorly soluble antifungal drugs requiring topical delivery.

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