Review Paper

ISSN: 3139-3683

JOURNAL OF HEALTH SYNAPSE (JHS)

Peer Reviewed Refereed Open Access International Multidisciplinary Journal

Publisher: *Scientistic Era Private Limited*
Journal Hompage: *https://healthsynapse.org*

Design and Characterization of Voriconazole-Loaded Topical Gel for Localized Antifungal Delivery

Mangal Singh Lodhi [a*], **Ankit Agrawal** [b], **Mahendra Chouhan** [c], **Arun Kumar Gupta** [d]

[a,b,c.d]*Department of Pharmacy, CDGI, Indore*

***Corresponding author:** mangalrajpoot86@gmail.com
ORCID: [a]*0009-0003-2603-3038,* [b]*0000-0003-4042-262X,* [c]*0009-0009-6976-3480,* [d]*0000-0002-1818-3963*

ARTICLE INFO

KEYWORDS:
Voriconazole; topical gel; Carbopol 971P; Candida albicans; Franz diffusion cell; antifungal delivery; stability

ARTICLE HISTORY
Received Date: 05 August 2026
Revised Date: 15 August 2026
Accepted Date: 30 August 2026
Published Date: 09 September 2026

CITATION
Lodhi, M. S., 2026 Design and Characterization of Voriconazole-Loaded Topical Gel for Localized Antifungal Delivery. *Journal of Health Synapse (JHS), 1(3), 67-73. https://doi.org/10.67529/jhs.v1i3.7*

A B S T R A C T

Voriconazole is a broad-spectrum triazole antifungal with limited aqueous solubility. The present study was designed to formulate and evaluate a voriconazole-loaded topical gel using Carbopol 971P for localized antifungal delivery. Five formulations (F1-F5) were prepared with increasing concentrations of Carbopol 971P and evaluated by preformulation studies, physicochemical testing, in vitro drug release, antifungal activity against Candida albicans, and short-term stability testing. Voriconazole showed solubility values of 0.75 mg/mL in water and 1.27 mg/mL in phosphate-buffered saline pH 6.4, with substantially higher solubility in chloroform, acetone, and ethanol. The melting point was 128°C and the UV absorption maximum was 255 nm. The calibration curve over 0-50 µg/mL was linear (R^2 = 0.9988). Drug content of the gels ranged from 97.0% to 98.0%, pH from 6.8 to 7.1, reported spreadability from 10.25 to 11.75, and viscosity from 46,685 to 48,942 cP. Increasing Carbopol 971P concentration increased viscosity and reduced spreadability. At 270 min, F1 showed the highest tabulated cumulative drug release (98.846%), followed by F2 (95.741%), F3 (94.11%), F5 (89.439%), and F4 (88.96%). F1 was selected as the optimized formulation and showed a reported antifungal inhibition value of 6.6 against C. albicans, compared with 7.6 for the standard drug and 0 for placebo. After one month, F1 retained 96.5% drug content at 30 ± 2°C/65 ± 5% RH, whereas drug content decreased to 75% at 40 ± 2°C/75 ± 5% RH. The study demonstrates that Carbopol 971P concentration strongly affects the rheological and release characteristics of voriconazole gels, with F1 providing the most favorable overall profile among the formulations tested.

I. Introduction

Voriconazole is a second-generation triazole antifungal with broad activity against clinically important yeasts and molds. Its antifungal effect results from inhibition of fungal cytochrome P450-dependent 14-alpha-sterol demethylation, which disrupts ergosterol synthesis and membrane function [1,2]. Although voriconazole is well established for systemic treatment of serious fungal infections, systemic exposure is associated with variable pharmacokinetics, drug-drug interactions, and adverse effects, providing a rationale for localized delivery when treatment at the skin surface or within superficial tissues is desired [1,2].

Topical delivery of voriconazole has been investigated using several formulation approaches. Microemulsions have been evaluated as vehicles for topical voriconazole and have shown improved antifungal activity and altered skin delivery behavior [3]. Carbopol-based nanostructured lipid carrier hydrogels have demonstrated enhanced skin delivery [4], while ethosomal preparations, nanostructured lipid carrier gels, electrospun nanofibers, topical creams, and transethosomal gels have also been studied as topical or dermal delivery systems [5-9]. These reports support the feasibility of developing voriconazole as a locally applied antifungal dosage form.

For a conventional gel system, polymer concentration is a critical formulation variable because it influences viscosity, spreadability, extrusion, and drug diffusion from the gel matrix. The present study therefore formulated voriconazole topical gels using Carbopol 971P at five concentrations. The objectives were to characterize voriconazole, evaluate drug-excipient compatibility, prepare and characterize the gel formulations, compare in vitro drug release, assess antifungal activity of the optimized formulation against Candida albicans, and examine short-term stability under two storage conditions.

2. Materials and Methods

2.1 Materials

Voriconazole was obtained from Yarrow Chem Products. Carbopol 971P, methyl paraben, and propyl paraben were laboratory-grade materials. Triethanolamine, glycerol, purified water, phosphate buffer pH 6.4, and the required solvents and analytical reagents were used during formulation and evaluation.

Table 1. Materials used in the study

S. No.	Material	Manufacturer/Source
1	Voriconazole	Yarrow Chem Products
2	Carbopol 971P	Laboratory grade
3	Propyl paraben	Laboratory grade
4	Methyl paraben	Laboratory grade

2.2 Instruments

The principal instruments employed were a Shimadzu electronic analytical balance, Shimadzu UV-1900 UV-visible spectrophotometer, Bruker Tensor 27 FTIR spectroscope, Remi 2-ML magnetic stirrer, Sci. Works Franz diffusion cell, and a Sonics and Materials ultrasonicator.

2.3 Preformulation Studies

2.3.1 Solubility study

An excess quantity of voriconazole was added to each aqueous or organic solvent system and maintained at 37 ± 2°C for 72 h to attain equilibrium. Samples were centrifuged at 3000 rpm for 15 min, the supernatant was filtered through a 0.45 µm membrane filter, and dissolved drug was analyzed by UV-visible spectrophotometry at 255 nm.

2.3.2 Melting point

The melting point of voriconazole was determined in triplicate by the capillary method. The sample was heated gradually, and the temperature at which complete melting occurred was recorded.

2.3.3 Determination of λmax and calibration curve

Voriconazole was dissolved in phosphate buffer pH 6.4, filtered through a 0.45 µm membrane, and scanned over 200-800 nm using a UV-visible spectrophotometer. The maximum absorbance wavelength was recorded. For the calibration curve, standard solutions were prepared over 0-50 µg/mL and absorbance was measured at 255 nm. Concentration was plotted against absorbance and evaluated by linear regression.

2.3.4 FTIR spectroscopy

FTIR spectroscopy was used to identify characteristic functional groups of voriconazole and assess possible drug-excipient interactions. Spectra of pure drug and physical mixtures were recorded using the KBr pellet method at a resolution of 2 cm^{-1} over 4000-400 cm^{-1} and compared for retention or shifting of characteristic peaks.

2.4 Preparation of Gel Base

Carbopol 971P was dispersed in purified water and allowed to hydrate for 24 h. Voriconazole was dispersed separately in water and added to the hydrated polymer dispersion. The gel base was neutralized with a sufficient quantity of triethanolamine. Glycerol was incorporated as a moistening agent, and methyl paraben and propyl paraben were added as preservatives. The contents were stirred gently and continuously until a homogeneous gel was obtained.

Table 2. Composition of voriconazole gel formulations

S. No.	Ingredient	Function	F1	F2	F3	F4	F5
1	Voriconazole	Antifungal agent	2	2	2	2	2
2	Carbopol 971P	Polymer	0.5	1.0	1.5	2.0	2.5
3	Methyl paraben	Preservative	0.2	0.2	0.2	0.2	0.2
4	Propyl paraben	Preservative	0.5	0.5	0.5	0.5	0.5

S. No.	Ingredient	Function	F1	F2	F3	F4	F5
5	Triethanolamine	Neutralizing agent	q.s.	q.s.	q.s.	q.s.	q.s.
6	Glycerol	Solvent/moistening agent	0.03	0.03	0.03	0.03	0.03
7	Water	Vehicle	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL

Note: Numerical ingredient quantities are reproduced from the thesis formulation table; no unreported concentration units have been introduced.

2.5 Characterization of Topical Gels

The prepared gels were evaluated for pH, drug content, spreadability, viscosity, extrudability, in vitro drug release, antifungal activity, and stability. For pH determination, 1 g of gel was dispersed in 100 mL distilled water, allowed to stand for 2 h, and measured in triplicate. Drug content was determined by dissolving 1 g of gel in 100 mL phosphate buffer pH 6.4, filtering and diluting the sample, and measuring absorbance at 255 nm. Spreadability was evaluated between glass slides under a definite load by recording the time required for the upper slide to slip over the lower slide. Viscosity was measured using a Brookfield viscometer at 0.3, 0.6, and 1.5 rpm. Extrudability was defined as the weight required to extrude a 0.5 cm ribbon of gel within 10 s.

2.6 In Vitro Drug Release Study

In vitro drug release was studied using a Franz diffusion cell at 37°C with phosphate buffer pH 6.4 as receptor medium [10,11]. Five milliliters of voriconazole gel was placed on a dialysis membrane positioned in contact with the receptor medium. The receptor phase was stirred at 100 rpm. Samples of 1 mL were withdrawn at predetermined intervals and replaced with an equal volume of fresh phosphate buffer to maintain sink conditions. Voriconazole release was quantified spectrophotometrically at 255 nm.

2.7 In Vitro Antifungal Activity

Antifungal activity of the optimized voriconazole gel was evaluated against Candida albicans using the agar cup-plate method. A spore suspension was prepared in sterile water and adjusted to approximately 1×10^6 spores/mL. One milliliter of suspension was mixed with molten Sabouraud agar and poured into sterile Petri dishes. After solidification, wells of 1 cm diameter were prepared with a sterile borer. Approximately 0.5 g of medicated gel, placebo gel, or standard drug was placed into the wells. Plates were incubated at 25 ± 1°C for 3 days, and the inhibition response was recorded as the mean of three determinations.

2.8 Stability Studies

The optimized formulation F1 was stored for one month at 30 ± 2°C/65 ± 5% RH and 40 ± 2°C/75 ± 5% RH. After storage, drug content and the in vitro release profile were reassessed.

3. Results and Discussion

3.1 Preformulation Studies

Voriconazole exhibited limited solubility in aqueous media and substantially greater solubility in the tested organic solvents. Solubility was 0.75 mg/mL in water, 1.27 mg/mL in phosphate-buffered saline pH 6.4, 1.70 mg/mL in dichloromethane, 23.00 mg/mL in chloroform, 21.00 mg/mL in acetone, and 22.00 mg/mL in ethanol. The solubility profile is consistent with the formulation challenge of incorporating a poorly water-soluble drug into an aqueous gel system.

Table 3. Solubility of voriconazole in different solvents

S. No.	Solvent	Solubility (mg/mL)
1	Water	0.75
2	Dichloromethane	1.70
3	Phosphate-buffered saline (pH 6.4)	1.27
4	Chloroform	23.00
5	Acetone	21.00
6	Ethanol	22.00

The melting point of voriconazole was 128°C, within the range reported in the thesis for the drug. The UV absorption maximum in phosphate buffer pH 6.4 was observed at 255 nm and was used for subsequent analytical

measurements. The calibration data showed a strong linear relationship between concentration and absorbance over 0-50 µg/mL, with the regression equation y = 0.01993x + 0.01748 and R^2 = 0.9988.

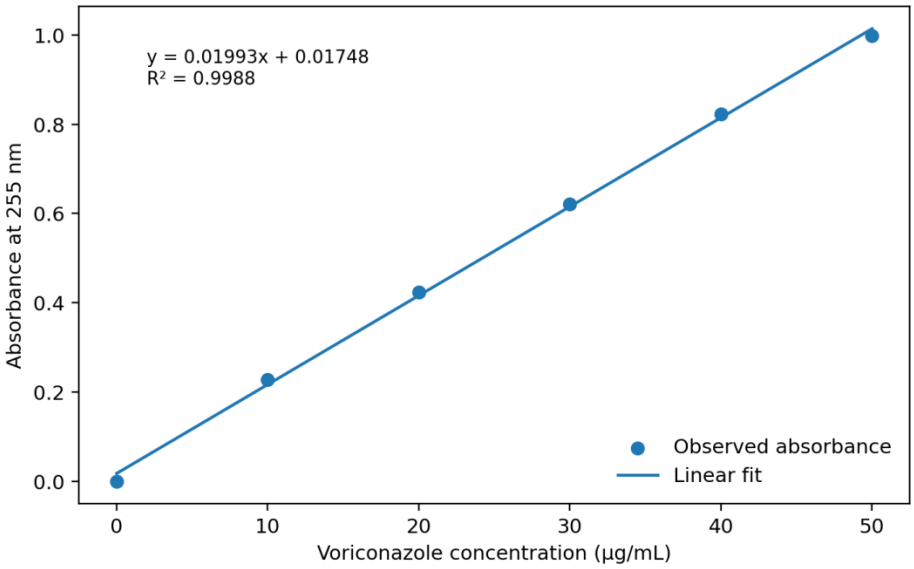

Figure 1. Calibration curve of voriconazole in phosphate buffer pH 6.4 at 255 nm.

FTIR comparison of pure voriconazole and the drug-excipient physical mixture showed retention of the characteristic drug peaks without significant positional shifting. This observation indicated no major drug-excipient incompatibility under the conditions used for the formulation study.

3.2 Evaluation of Gel Formulations

All five formulations showed drug content within a narrow range of 97.0-98.0%, indicating relatively uniform incorporation of voriconazole into the gel matrix. The measured pH values ranged from 6.8 to 7.1. These formulations were near neutral; because normal skin surface is typically mildly acidic, skin compatibility should be interpreted on the basis of direct tolerability testing rather than pH alone [12,13].

The reported spreadability values decreased progressively as Carbopol 971P concentration increased, whereas viscosity increased from 46,685 cP for F1 to 48,942 cP for F5. This inverse relationship is consistent with increasing gel-network density and resistance to flow as polymer concentration increases.

Table 4. Evaluation parameters of voriconazole gel formulations

Formulation	Drug content (%)	pH	Spreadability (reported unit)	Viscosity (cP)
F1	97 ± 0.027	6.8	11.75	46,685
F2	98 ± 0.027	7.1	11.08	47,835
F3	97.5 ± 0.017	6.9	10.75	48,278
F4	98 ± 0.012	6.8	10.70	48,879
F5	97 ± 0.018	7.0	10.25	48,942

Note: The spreadability values and source-reported unit are retained from the thesis because the described slide-separation method and reported unit are not fully aligned.

3.3 In Vitro Drug Release

All formulations showed increasing cumulative release over 270 min. F1 showed the highest tabulated terminal release (98.846%), followed by F2 (95.741%), F3 (94.11%), F5 (89.439%), and F4 (88.96%). Although F2 showed a slightly greater value at 30 min, F1 produced the highest cumulative release at later time points and at the end of the study. The overall pattern supports an inverse association between polymer concentration and release, consistent with greater diffusional resistance in more viscous polymer networks.

Table 5. In vitro cumulative drug release (%) of formulations F1-F5

Time (min)	F1	F2	F3	F4	F5
30	14.65	17.422	15.668	12.429	11.353

Time (min)	F1	F2	F3	F4	F5
60	37.964	33.072	30.697	30.711	21.283
90	46.892	41.544	40.588	40.375	35.755
120	56.719	56.324	57.437	52.048	53.137
150	64.7	62.701	63.107	59.402	63.688
180	73.533	71.859	68.934	66.21	71.121
210	78.619	78.923	75.815	71.71	74.502
240	88.318	87.266	86.127	81.739	80.149
270	98.846	95.741	94.11	88.96	89.439

Correction applied: the terminal F1 value is reported as 98.846% in the thesis table; this tabulated value is used consistently in the manuscript.

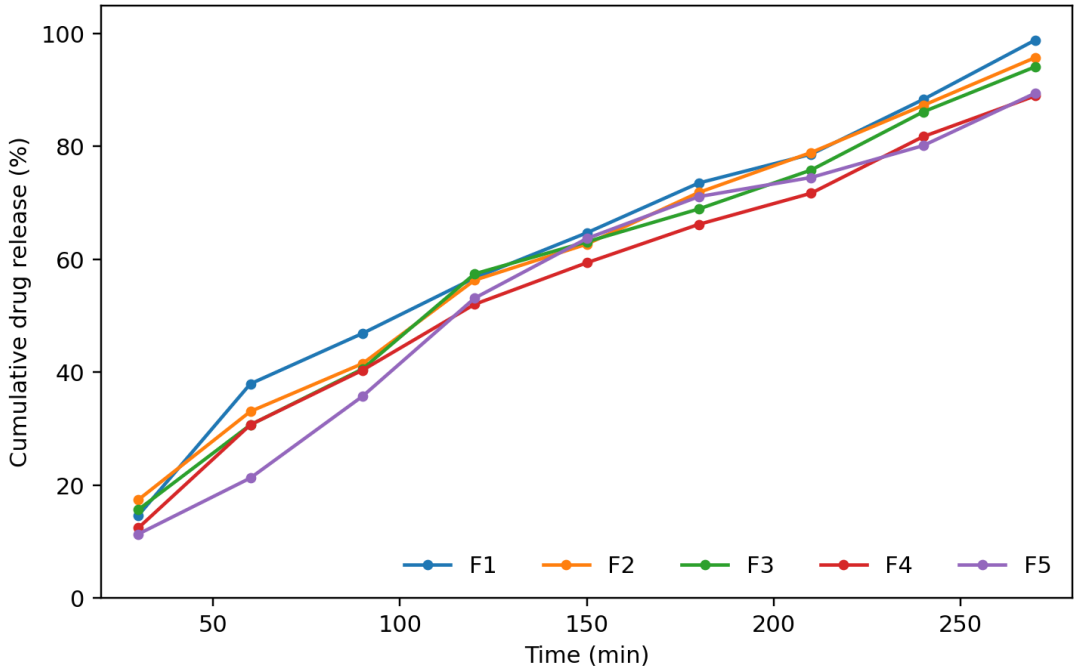

Figure 2. Comparative in vitro cumulative drug-release profiles of formulations F1-F5.

3.4 Antifungal Activity

Based on its in vitro release profile, F1 was selected for antifungal evaluation against Candida albicans. The placebo gel showed no inhibition response. F1 showed a reported inhibition value of 6.6, compared with 7.6 for the standard drug. The results indicate that voriconazole retained measurable antifungal activity after incorporation into the gel matrix.

Table 6. Antifungal activity of optimized formulation F1

Test sample	Zone of inhibition (reported value)
Standard drug	7.6
Placebo gel	0
F1	6.6

Note: The thesis table labels the unit as mm², whereas the method describes measurement of inhibition-zone diameter. The numerical values are retained unchanged and the unit is not re-assigned.

3.5 Stability Studies

After one month at 30 ± 2°C/65 ± 5% RH, F1 retained 96.5% drug content. Under 40 ± 2°C/75 ± 5% RH, drug content decreased to 75%. The corresponding terminal cumulative drug release values at 270 min were 97.81% and 92.60%, respectively. Thus, the formulation showed better retention of drug content and release performance under the lower-stress storage condition than under

accelerated conditions.

Table 7. Drug content and in vitro release of F1 after one month of storage

Parameter	30 ± 2°C / 65 ± 5% RH	40 ± 2°C / 75 ± 5% RH
Drug content (%)	96.5	75.0
30-min release (%)	22.00	14.49
60-min release (%)	44.00	34.85
90-min release (%)	51.88	48.55
120-min release (%)	58.46	52.85
150-min release (%)	64.20	58.55
180-min release (%)	73.25	64.36
210-min release (%)	78.60	74.04
240-min release (%)	86.59	82.10
270-min release (%)	97.81	92.60

3.6 Overall Discussion

The formulation series demonstrates the expected role of Carbopol concentration in controlling the physical behavior and release characteristics of a topical gel. F1, containing the lowest Carbopol 971P concentration, showed the greatest spreadability and the highest terminal drug release, while higher-polymer formulations showed greater viscosity and lower terminal release. Similar topical voriconazole research has emphasized the importance of vehicle structure, rheology, and skin-delivery behavior in determining formulation performance [3-9].

Within the scope of the present work, the antifungal assay supports retention of biological activity after formulation, because the medicated gel produced an inhibition response whereas the placebo did not. The stability findings, however, show a marked reduction in drug content under the higher-temperature and higher-humidity condition. Consequently, F1 can be considered the optimized formulation among the five tested batches, while the accelerated-condition result indicates that further formulation and stability work would be appropriate before longer-term product development.

4. Conclusion

Voriconazole-loaded topical gels were successfully prepared using Carbopol 971P as the gelling polymer. Preformulation studies established limited aqueous solubility, a melting point of 128°C, a UV absorption maximum at 255 nm, and a linear calibration relationship over the tested concentration range. The five formulations showed drug content of 97-98%, pH of 6.8-7.1, decreasing spreadability, and increasing viscosity with increasing Carbopol concentration. F1 showed the highest tabulated cumulative drug release at 270 min (98.846%) and measurable antifungal activity against Candida albicans, and was therefore selected as the optimized formulation. One-month stability testing showed better performance at 30 ± 2°C/65 ± 5% RH than at 40 ± 2°C/75 ± 5% RH. Overall, the findings support F1 as the most promising formulation among the batches evaluated for localized delivery of voriconazole.

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