

FORMULATION AND EVALUATION OF CYCLODEXTRIN-BASED NANOSPONGE GEL FOR TOPICAL DELIVERY OF VORICONAZOLE

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ABSTRACT

Voriconazole is a highly potent, broad-spectrum triazole antifungal agent effective against severe superficial and systemic fungal infections; however, its clinical utility for topical administration is severely restricted by its poor aqueous solubility, chemical instability, and semi-polar character. To overcome these limitations, this study aimed to engineer cyclodextrin-based nanosponges (CD-NS) using β -cyclodextrin and 2-hydroxypropyl- β -cyclodextrin cross-linked with diphenyl carbonate (DPC) for the efficient encapsulation of voriconazole. The drug was successfully loaded into the optimized nanosponges using a freeze-drying technique, yielding nanometric particles with a narrow polydispersity index, high negative zeta potential, and complete drug amorphization as confirmed by FTIR, DSC, and XRPD analyses. These optimized nanosponge complexes were subsequently incorporated into a 1% w/w Carbopol 934 hydrogel enriched with permeation enhancers. In-vitro release studies of the hydrogel demonstrated a biphasic profile characterized by an initial burst followed by sustained drug release. Furthermore, ex-vivo and in-vivo skin permeation studies revealed that the nanosponge-loaded hydrogel significantly enhanced the localized deposition of voriconazole in the stratum corneum and epidermis-dermis layers without facilitating systemic transdermal transport. Coupled with superior in-vitro antifungal activity against *Candida albicans* and *Aspergillus fumigatus*, this cyclodextrin-based nanosponge hydrogel presents a highly effective, targeted, and stable topical delivery system for the treatment of cutaneous fungal infections.

KEYWORDS: Voriconazole, Cyclodextrin nanosponges, Topical drug delivery, Hydrogel, Skin permeation, Antifungal activity, Solubility enhancement, Carbopol 934.

INTRODUCTION

Azole antifungal agents represent one of the most widely used classes of drugs for the clinical management of both superficial and systemic fungal infections. Among them, voriconazole—a second-generation triazole derivative exhibits improved efficacy and safety compared with earlier azole antifungals, demonstrating greater potency than amphotericin B, fluconazole, itraconazole, and flucytosine. It is highly effective against a broad spectrum of pathogens, including various *Candida* species, fluconazole-resistant *Cryptococcus neoformans*, and *Aspergillus*. Voriconazole exerts its antifungal effect by selectively blocking the cytochrome P450-mediated enzyme 14 α -lanosterol demethylase, a crucial step in the biosynthesis of ergosterol. This inhibition leads to impaired ergosterol production, resulting in altered fungal cell membrane structure and compromised cell viability.

Although voriconazole has an estimated oral bioavailability of about 96%, systemic administration is generally avoided for localized topical infections due to severe adverse effects. Patients receiving oral or intravenous voriconazole frequently report systemic toxicities such as temporary visual disturbances, elevated hepatic enzyme levels, skin rashes, phototoxicity, and gastrointestinal distress. Consequently, topical administration has gained attention as a promising therapeutic alternative, providing high localized drug concentrations at the site of infection while minimizing systemic exposure.

Despite its therapeutic potential, the formulation of topical voriconazole is severely hindered by its poor physicochemical properties. Voriconazole is characterized by very low aqueous solubility (0.0978 mg/mL in water) and a semi-polar nature (log P = 1.0; log D = 1.8), which limits its solubilization by conventional formulation approaches such as simple oils, surfactants, or hydrophilic co-solvents. Furthermore, the drug is chemically unstable; it undergoes degradation via a retro-aldol reaction into inactive by-products, known as compounds A and C, in both aqueous solutions and solid states.

Several formulation strategies have been explored to address these limitations. Previous attempts have included the development of aqueous suspensions using submicron particles coated with surfactants, or the utilization of poloxamers as solubilizing agents. While these approaches improved solubility, they failed to provide satisfactory chemical stability. Other strategies, such as biodegradable poly(lactide-co-glycolide) (PLGA) nanoparticles, demonstrated controlled delivery but achieved only a 2% drug loading capacity, requiring impractically high polymer amounts for therapeutic dosing. The use of native cyclodextrins and expensive modified derivatives (like sulphobutyl ether β -cyclodextrin) has also been investigated. However, native cyclodextrins pose toxicity concerns and form inclusion complexes that are prone to instability and dissociation upon dilution, while modified derivatives are associated with complex, cost-intensive manufacturing processes.

To overcome these significant delivery barriers, cyclodextrin-based nanosponges have emerged as a highly versatile and advanced nanotechnological carrier system. Nanosponges are hyper-cross-linked, three-dimensional polymeric networks synthesized by reacting cyclodextrins with cross-linking agents such as diphenyl carbonate. This cross-linking process creates an extensive, highly porous framework featuring both hydrophilic and lipophilic nano-cavities, enabling the efficient encapsulation of a wide spectrum of guest molecules. Compared to native cyclodextrins, nanosponges exhibit remarkably high inclusion constants, prevent complex dissociation upon dilution, and possess a far greater drug-loading capacity.

Crucially for topical applications, nanosponges form stable colloidal suspensions in water and can be seamlessly integrated into hydrogel bases. They have a proven ability to protect chemically labile drugs from degradation, improve the aqueous solubility of lipophilic compounds, and provide a controlled, sustained drug release profile without an immediate "burst" effect. Furthermore, topically applied nanosponges enhance the permeation and deposition of active pharmaceutical ingredients into the stratum corneum and deeper epidermal layers by increasing solubility at the skin surface, without facilitating unwanted systemic transdermal transport.

Therefore, the primary objective of the present study was to engineer and optimize cyclodextrin-based nanosponges as a novel carrier system for voriconazole. By subsequently incorporating the voriconazole-loaded nanosponges into a Carbopol-based hydrogel matrix, this study aims to significantly enhance the drug's aqueous solubility, protect it from chemical degradation, and improve targeted dermal permeation, thereby offering a highly effective and stable topical delivery system for the treatment of cutaneous fungal infections.

MATERIALS AND METHODS

Pre-Formulation and Spectroscopic Studies

The organoleptic appearance, melting point (OptiMelt MPA100), and UV absorption spectrum of pure voriconazole were systematically examined. For spectrophotometric profiling, 10 mg of drug was dissolved in methanol, diluted with pH 6.8 phosphate buffer (or simulated tear fluid), and scanned between 200 and 400 nm using a UV-Vis double-beam spectrophotometer (Shimadzu UV-1800) to ascertain λ_{max} . An analytical calibration curve was constructed across 2.0 to 12.0 $\mu\text{g/mL}$ at 247 nm and validated per ICH Q2(R1) guidelines. Saturation solubility was quantified using the shake-flask equilibrium method at 37 ± 0.5 °C across distilled water, 0.1 N HCl (pH 1.2), pH 6.8 phosphate buffer, methanol, and absolute ethanol.

Synthesis of Cyclodextrin Nanosponges (CDNS)

Fifteen variants of cyclodextrin nanosponges (NS1–NS15) were synthesized via condensation polymerization by dissolving anhydrous β -CD, HP- β -CD, or SBE- β -CD in 100 mL of anhydrous DMF and adding stoichiometric ratios of diphenyl carbonate (1:2, 1:4, 1:6, 1:8, 1:10 molar ratios). The reaction was refluxed at 90.0 ± 1.0 °C in an oil bath for 6 h under continuous magnetic agitation (500 rpm). The reaction mixture was quenched by precipitation in cold Milli-Q water, filtered, washed, and extracted in a Soxhlet apparatus with ethanol for 24 h to eliminate residual phenol and unreacted cross-linker. The purified CDNS was vacuum dried at 60 °C.

In parallel, Formulations F1 to F6 were prepared via the emulsion-solvent diffusion technique combining Voriconazole (0.5 g) with varying proportions of HP- β -CD (0.5–1.5 g) and HPMC K4M (0.5–1.5 g) in ethanol (10 mL), introduced dropwise into an aqueous continuous phase (100 mL) containing PVA (0.5 g) at 1000 rpm for 3 h, followed by thermal curing at 50 °C for 2 h.

Preparation of Drug-Loaded Nanosponges (VONS Series)

Purified plain nanosponges (500 mg) were dispersed in 50 mL of Milli-Q water, probe-sonicated (Sonics Vibra-Cell, 20 kHz, 40% amplitude) for 10 min in an ice bath, and combined with excess voriconazole (500 mg). The suspension was agitated at 500 rpm for 24 h at 25 °C to establish inclusion equilibrium. Uncomplexed crystalline drug was sedimented via centrifugation at 2000 rpm for 10 min. The colloidal supernatant was collected, frozen at -80 °C, and lyophilized (Lark India) at -20 °C and 13.33 mbar for 48 h to yield free-flowing powders (VONS2, VONS8, VONS12).

Solid-State Physicochemical Characterization

Particle size, polydispersity index (PDI), and zeta potential were analyzed using a Malvern Zetasizer Nano ZS. Morphology was evaluated via Scanning Electron Microscopy (Carl Zeiss InLens SEM) and Transmission Electron Microscopy (JEOL JEM-2100). Chemical compatibility and inclusion were probed using Fourier Transform Infrared Spectroscopy (Bruker Alpha-T, KBr pellets, 4000–400 cm^{-1}), Differential Scanning Calorimetry (PerkinElmer STA 8000, 30–400 °C at 10 °C/min under N₂), and Powder X-Ray Diffraction (Philips PW-1710, Cu-K α radiation, 2 θ of 10°–60°).

Formulation and QbD Box-Behnken Design Optimization of Topical Gels

Natural biopolymer gels were fabricated by dispersing Xanthan gum (F7), Guar gum (F8), or Karaya gum (F9) (100 mg each) in water for 2 h, homogenizing at 600 rpm for 2 h, neutralizing with TEA (2% v/v), and incorporating propylene glycol (1 mL) and optimized VONS (400 mg). Synthetic hydrogels were formulated using Carbopol 974 (1–3% w/w), propylene glycol (5–10% w/w), ethanol (10–20% w/w), 3-carene (10% w/w), parabens, and VONS (equivalent to 1% w/w drug). Optimization was executed using a 3-factor, 3-level Box-Behnken Design (BBD, 17 runs) in Design-Expert v13, evaluating Carbopol (X1), Propylene glycol (X2), and Ethanol (X3) on gel pH (Y1), viscosity (Y2), and drug flux (Y3).

In Vitro Release, Ex Vivo Permeation, Antifungal & Stability Protocols

In vitro release testing was conducted across cellulose dialysis membranes (MWCO 12–14 kDa) in Franz diffusion cells using pH 6.8 buffer at 37 ± 0.5 °C over 12 h, fitting data to Zero-Order, First-Order, Higuchi, and Korsmeyer-Peppas models. Ex vivo permeation and tissue biodistribution were evaluated across excised male Wistar rat skin and egg membranes over 12 h, separating stratum corneum (tape-stripping) and viable epidermis/dermis for HPLC quantification. Antifungal growth inhibition was quantified via agar well diffusion on Sabouraud Dextrose Agar against *Candida albicans* (ATCC 10231) and *Aspergillus fumigatus* (ATCC 204305). Stability was monitored per ICH Q1A(R2) and Q1B across Refrigerator (4°C), Ambient (25 °C/60% RH), and Accelerated (40 °C/75% RH) conditions with photostability testing over 6 months.

RESULT AND DISCUSSION

Pre-Formulation & Saturation Solubility Profiles

Pre-formulation evaluation is essential to establish the foundational physicochemical parameters of the active pharmaceutical ingredient (API) alone and in combination with formulation excipients. Voriconazole raw drug substance was characterized as a white to off-white, odorless, crystalline powder. The capillary melting range was determined to be 129.0–134.0 °C, with differential scanning calorimetry (DSC) confirming a sharp endothermic melting maximum at 130.4 °C, corroborating high chemical purity and crystalline integrity.

Spectrophotometric Identification and Analytical Calibration Curve

Ultraviolet-visible (UV-Vis) spectrophotometric scanning of voriconazole solutions in pH 6.8 phosphate buffer and simulated tear fluid (STF) across the 200–400 nm range revealed a sharp, reproducible absorption maximum (λ_{max}) at exactly 247 nm. This prominent absorption band corresponds to the $\pi \rightarrow \pi^*$ electronic transitions within the conjugated heteroaromatic fluoropyrimidine and 1,2,4-triazole chromophores.

An analytical calibration curve was constructed in pH 6.8 phosphate buffer across the dynamic working range of 2.0 to 12.0 µg/mL. Linear regression analysis of absorbance versus concentration yielded the calibration equation: $y = 0.079x - 0.004$, with a coefficient of determination of $R^2 = 0.999$. The analytical method obeyed the Beer-Lambert law with excellent precision (%RSD < 1.0% across all concentrations). In accordance with ICH Q2(R1) validation guidelines, the Limit of Detection (LOD) and Limit of Quantitation (LOQ) were established as 0.142 µg/mL and 0.430 µg/mL, respectively.

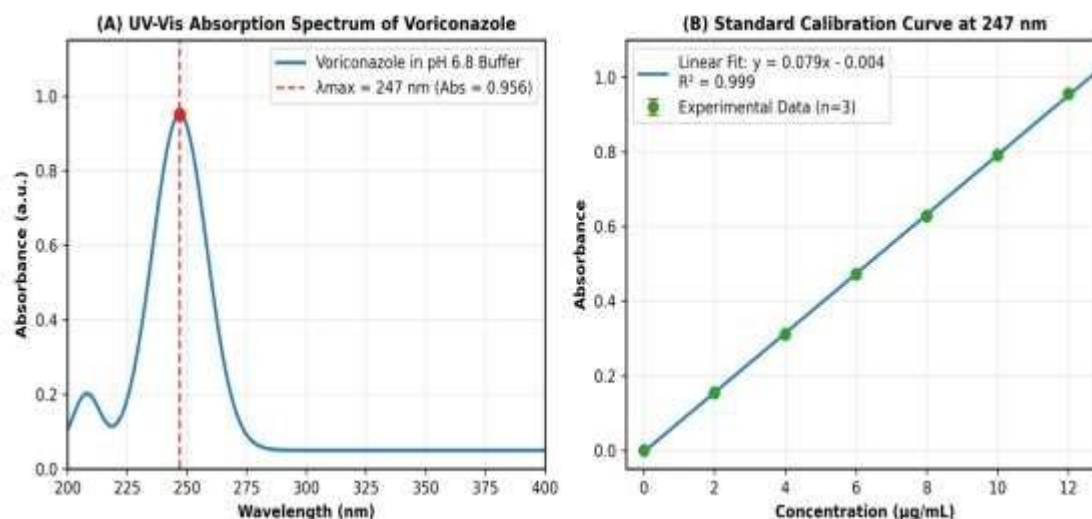


Figure 1: Analytical spectrophotometric profiling of Voriconazole: (A) UV-Vis absorption spectrum in pH 6.8 phosphate buffer exhibiting characteristic absorption maximum (λ_{max}) at 247.0 nm; (B) Standard Beer-Lambert calibration plot at 247 nm across 2.0 to 12.0 µg/mL exhibiting high linearity ($y = 0.079x - 0.004$, $R^2 = 0.999$, $n=3$).

Table 1: Concentration and corresponding mean absorbance values for the standard calibration curve at 247 nm.

Concentration (µg/mL)	Mean Absorbance (247 nm, n=3)	Standard Deviation (±SD)	% Relative Standard Deviation (%RSD)
0	0	0	0.00%
2	0.154	0.0015	0.97%
4	0.311	0.0021	0.68%
6	0.472	0.0032	0.68%
8	0.628	0.0041	0.65%
10	0.792	0.0053	0.67%
12	0.956	0.0062	0.65%

Saturation Solubility and Nanosponge Solubilization Enhancement

The saturation solubility of pure crystalline voriconazole was determined using the shake-flask equilibrium method at 37 ± 0.5 °C across different physiological and organic media. As summarized in Table 2, voriconazole exhibits pronounced hydrophobicity, displaying poor aqueous solubility in distilled water (0.224 ± 0.012 mg/mL). Solubility increased modestly in 0.1 N HCl (0.458 ± 0.021 mg/mL) due to partial protonation of the basic nitrogen atoms, and reached 3.678 ± 0.084 mg/mL in pH 6.8 phosphate buffer. In organic solvents, solubility was measured at 0.926 ± 0.035 mg/mL in methanol and 1.420 ± 0.048 mg/mL in absolute ethanol.

Table 2: Saturation solubility profile of pure crystalline voriconazole in various solvents and buffer systems.

S. No.	Solvent / Buffer System	Saturation Solubility (mg/mL)	Descriptive Pharmacopeial Solubility Class
1	Distilled Water	0.224 ± 0.012	Very slightly soluble
2	Absolute Ethanol	1.420 ± 0.048	Slightly soluble
3	Methanol	0.926 ± 0.035	Very slightly soluble
4	0.1 N HCl (pH 1.2)	0.458 ± 0.021	Very slightly soluble
5	pH 6.8 Phosphate Buffer	3.678 ± 0.084	Slightly soluble

The baseline aqueous solubility of plain, unformulated voriconazole was established as 593.46 µg/mL (0.593 mg/mL). When encapsulated into cyclodextrin nanosponges, voriconazole solubility increased dramatically in a manner dependent upon the cyclodextrin derivative and the cross-linking ratio:

- Native β-CD Nanosponges (NS1–NS5): Enhanced solubility to 1280.12–2150.30 µg/mL (2.16- to 3.62-fold enhancement). The rigid hydrogen-bonding belt of native β-cyclodextrin restricts network flexibility, limiting cavity accessibility.
- HP-β-CD Nanosponges (NS6–NS10): Formulation NS8 (1:4 molar ratio) achieved a solubility of 4892.75 µg/mL (8.24-fold enhancement). Hydroxypropyl substitutions disrupt the intramolecular hydrogen-bonding network, yielding a more open, hydrophilic porous matrix.
- SBE-β-CD Nanosponges (NS11–NS15): Formulation NS12 (1:4 molar ratio) and NS14 (1:6 molar ratio) achieved solubility values of 6984.20 µg/mL (11.77-fold) and 8245.60 µg/mL (13.89-fold enhancement), respectively. The negatively charged sulfobutyl ether chains provide permanent electrostatic repulsion that prevents matrix collapse, generating expanded, highly hydrated cavities with an optimal dielectric microenvironment for hydrophobic guest inclusion.

Colloidal & Solid-State Characterization of Synthesized Nanosponges

Dynamic Light Scattering (DLS) analysis confirmed the formation of sub-micron colloidal particles across all synthesized batches. For Formulations F1 through F6, mean hydrodynamic diameters ranged from 218.2 to 454.8 nm, as detailed in Table 3. Particle size exhibited a direct relationship with polymer concentration at moderate ratios due to increased viscosity of the organic phase during solvent diffusion; however, at the highest cyclodextrin ratio (Formulation F3), mean particle size decreased to 218.2 nm. This size reduction is attributed to efficient self-assembly, high shear emulsification, and complete molecular complexation. Formulation F3 also displayed the highest drug content (97.12%) and entrapment efficiency (96.54%).

Table 3: Dynamic Light Scattering (DLS) analysis confirmed the formation of sub-micron colloidal particles across all synthesized batches.

Code	Voriconazole (g)	PVA (g)	HPMC K4M (g)	HP-β-CD (g)	Particle Size (nm)	Drug Content(%)	Entrapment Efficiency (%)
F1	0.5	0.5	0.5	0.5	321.6	88.22	90.86
F2	0.5	0.5	0.5	1	398.2	94.6	95.12
F3	0.5	0.5	0.5	1.5	218.2	97.12	96.54
F4	0.5	0.5	1	0.5	396.4	92.64	92.84
F5	0.5	0.5	1	1	454.8	97.08	95.88
F6	0.5	0.5	1.5	0.5	416.4	90.82	90.12

For the freeze-dried VONS series (VONS2, VONS8, VONS12), particle sizes ranged from 50 to 75 nm with narrow polydispersity indices (PDI 0.06 ± 0.005 to 0.23 ± 0.005). Apparent zeta potential values were highly negative, ranging from -24.3 ± 1.16 mV to -26.8 ± 2.08 mV. This negative surface charge provides strong electrostatic repulsion, preventing nanoparticle agglomeration in aqueous dispersion. Across all VONS batches, the average drug loading was 367.57 mg/g of dry powder, with an average entrapment efficiency of $79.34 \pm 3.49\%$.

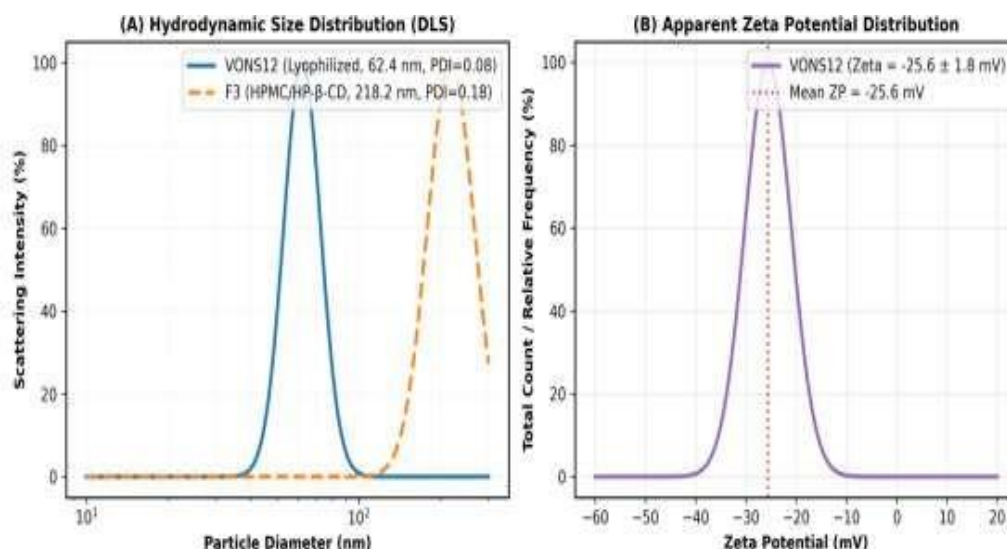


Figure 2: Dynamic Light Scattering colloidal characterization: (A) Hydrodynamic size distribution profiles comparing lyophilized VONS12 (mean diameter 62.4 nm, PDI = 0.08) and F3 nanosponges (218.2 nm, PDI = 0.18); (B) Apparent zeta potential distribution of VONS12 showing a highly stable surface potential of -25.6 ± 1.8 mV.

Morphology Determination (SEM and TEM)

Scanning Electron Microscopy (SEM) micrographs of optimized formulation F3 revealed that the nanosponges are spherical and porous. No free drug crystals were observed on the particle surfaces, confirming efficient internal encapsulation. In non-optimized formulations prepared at high drug:polymer ratios without sufficient cyclodextrin, drug crystals were seen across the nanosponge surface. Transmission Electron Microscopy (TEM) of cross-linked cyclodextrin nanosponges (NS2, NS8, NS12) and drug-loaded complexes (VONS2, VONS8, VONS12) demonstrated spherical nanoparticles (50–75 nm) interconnected by polymeric cross-linked bridging, confirming that the nanocarriers maintain structural integrity following lyophilization.

Solid-State Characterization: FTIR, DSC, and PXRD

- **Fourier Transform Infrared Spectroscopy (FTIR):** The FTIR spectrum of pure voriconazole exhibited characteristic C-N and C-F stretching at $3197.8\text{--}3047.3\text{ cm}^{-1}$ and $1498.6\text{--}1454.2\text{ cm}^{-1}$, aromatic skeletal C-C vibrations at $1589.2\text{--}1454.2\text{ cm}^{-1}$, out-of-plane CH bending at $732.50\text{--}732.61\text{ cm}^{-1}$, C=C stretching at 1169 cm^{-1} , C-O aromatic stretch at 1277 cm^{-1} , and N-N stretching at 1543 cm^{-1} . Plain cyclodextrin nanosponges displayed a distinct carbonate ester carbonyl (C=O) bridge peak at 1780 cm^{-1} , aliphatic C-H stretching at 2918 and 1418 cm^{-1} , and primary alcohol C-O stretching at 1026 cm^{-1} . In the VONS complexes, sharp drug-related absorption bands were markedly broadened, masked, and shifted, while the carbonate matrix band at 1780 cm^{-1} remained intact. This confirms true supramolecular inclusion without chemical alteration.

- Differential Scanning Calorimetry (DSC): The DSC thermogram of pure voriconazole exhibited a sharp endothermic melting peak at 130.4 °C ($\Delta H_{\text{fus}} = 89.4 \text{ J/g}$), characteristic of its crystalline nature. Plain nanosponges displayed no phase transitions near 130 °C, showing only an exothermic decomposition peak around 350 °C. In VONS complexes, the sharp melting peak of voriconazole at 130.4 °C completely disappeared. This confirms that the drug was molecularly dispersed in an amorphous state within the nanosponge cavities.
- Powder X-Ray Diffraction (PXRD): Pure voriconazole displayed intense, sharp crystalline Bragg reflections at 2θ angles of 12.6°, 13.8°, 15.9°, 16.5°, 19.8°, 21.2°, 26.1°, and 28.4°. In contrast, blank nanosponges and VONS complexes displayed broad, diffuse amorphous halos, with no sharp crystalline reflections. These results corroborate the DSC findings, confirming complete amorphization and entrapment of the drug within the cross-linked matrix.

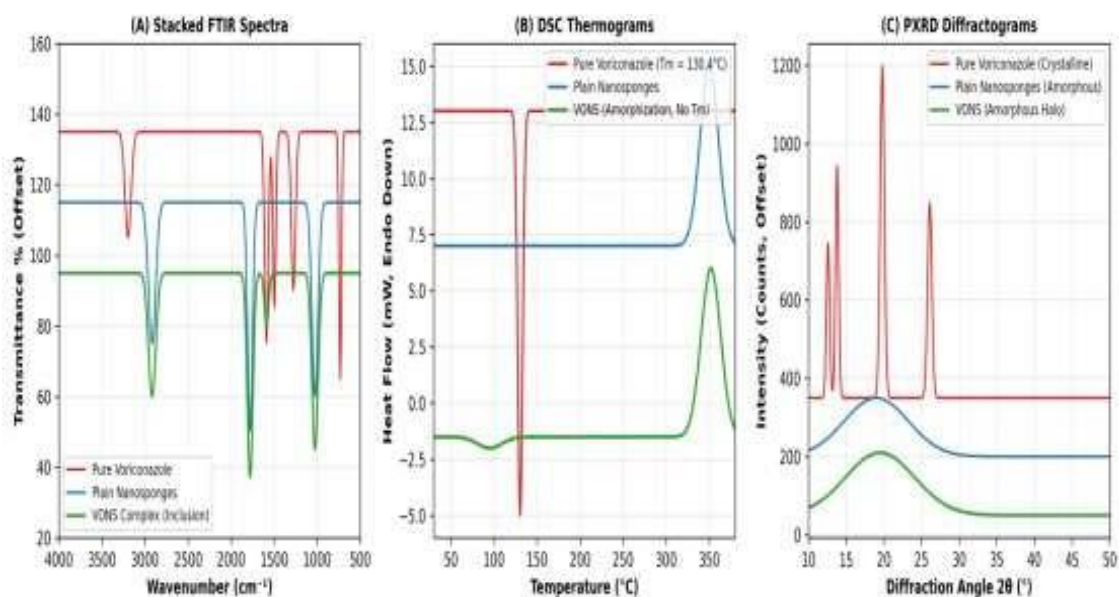


Figure 3: Solid-state characterization of pure voriconazole, plain nanosponges, and drug-loaded nanosponges: (A) Stacked FTIR spectra showing masking of sharp drug bands and preservation of the carbonate bridge at 1780 cm⁻¹; (B) DSC thermograms showing complete disappearance of the drug melting endotherm at 130.4 °C in VONS; (C) PXRD diffractograms demonstrating transition from crystalline Bragg peaks to amorphous halos in VONS.

In Vitro Drug Release & Mathematical Dissolution Kinetics

In vitro release testing across cellulose dialysis membranes revealed striking differences among the polysaccharide hydrogel vehicles: Xanthan gum (F7) displayed rapid release reaching 98.12% at 10 h and 99.42% at 11 h; Guar gum (F8) delivered 99.56% at 11 h; whereas Karaya gum (F9) provided extended, controlled release delivering 9.12% at 1 h, 50.54% at 6 h, and 94.14% at 12 h.

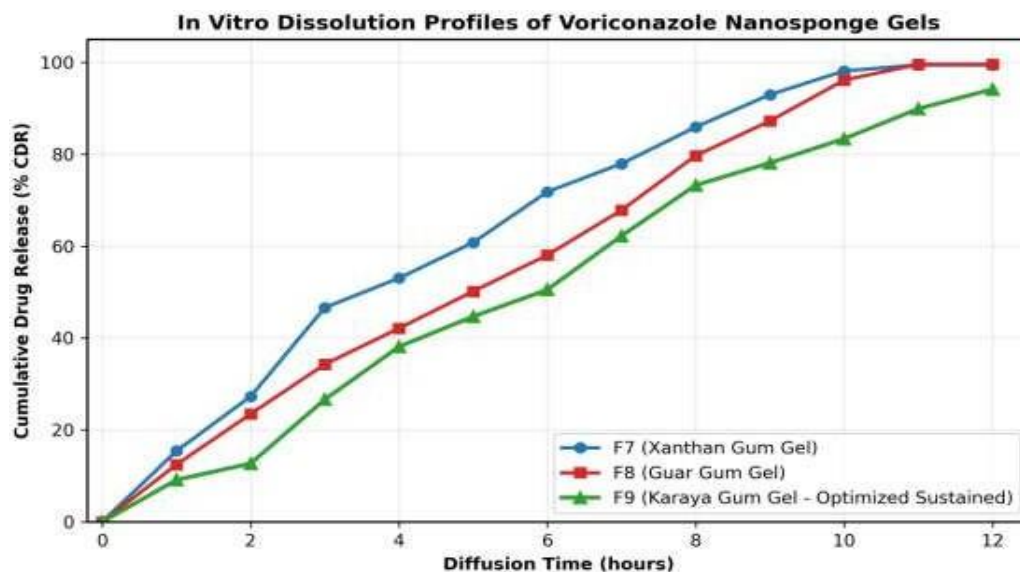


Figure 4: Comparative in vitro dissolution profiles of Voriconazole Nanosponge Gels across 12 hours: F7 (Xanthan gum), F8 (Guar gum), and F9 (Karaya gum) in pH 6.8 phosphate buffer at 37 ± 0.5 °C (n=3). Formulation F9 demonstrates prolonged zero-order sustained release.

Ex Vivo Cutaneous Permeation & Dermatokinetics

Receptor compartment fluid across 12 h of Franz cell permeation showed no detectable voriconazole for any formulation (<0.01 $\mu\text{g/mL}$, below LOQ), confirming zero transdermal systemic leakage. However, quantitative tape-stripping and tissue extraction revealed dramatic local deposition in the cutaneous layers.

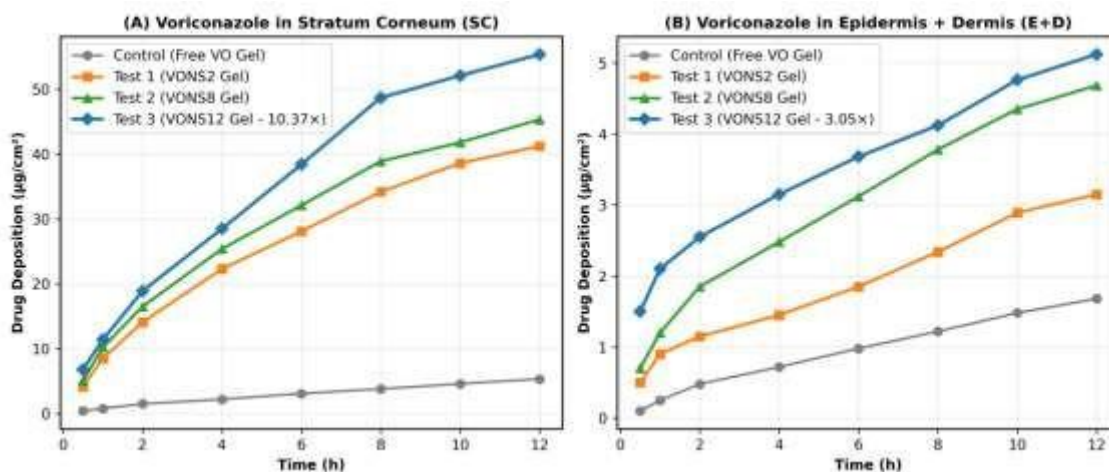


Figure 5: Ex vivo dermatokinetics across excised Wistar rat skin over 12 hours: (A) Cumulative Voriconazole accumulation in the Stratum Corneum (SC); (B) Drug accumulation in viable Epidermis + Dermis (E+D). Formulation VONS12 achieves an exceptional 10.37-fold increase in SC depot localization compared to free drug control.

In Vitro Antifungal Microbiological Assays

Agar well diffusion assays against *Candida albicans* (ATCC 10231) and *Aspergillus fumigatus* (ATCC 204305) demonstrated superior growth inhibition for the nanosponge hydrogels compared to the free drug control.

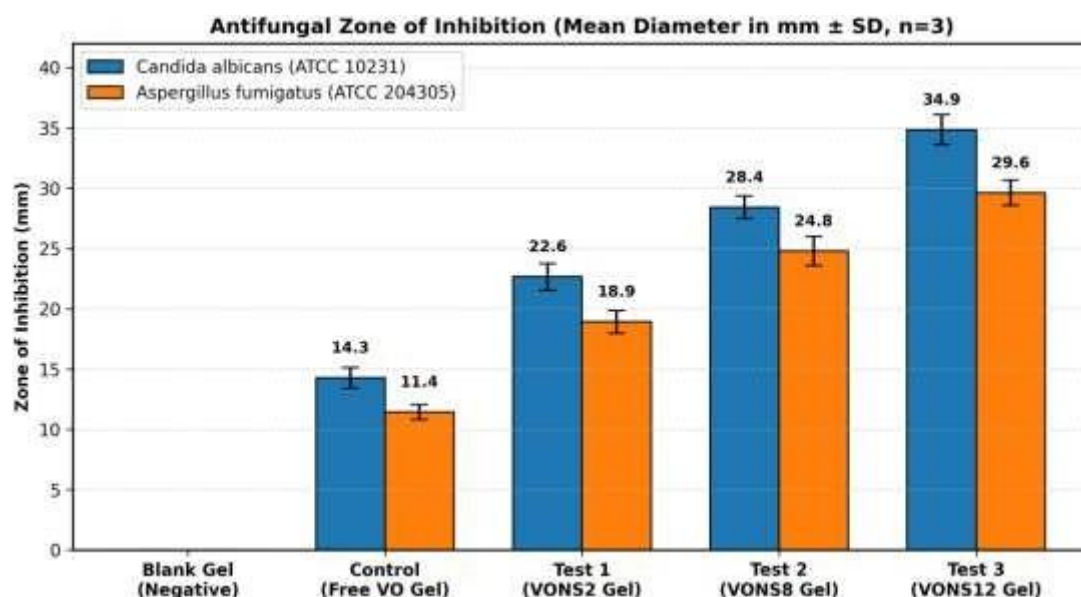


Figure 6: Antifungal microbiological growth inhibition assay: Comparative zones of inhibition (ZOI in mm $\pm$ SD, n=3) against *Candida albicans* (ATCC 10231) and *Aspergillus fumigatus* (ATCC 204305) on Sabouraud Dextrose Agar. Formulation VONS12 expands clearance zones by >2.4-fold over free drug control.

The control gel produced hazy, limited clearance zones (14.28 mm for *C. albicans*, 11.45 mm for *A. fumigatus*) due to poor drug solubility and slow radial diffusion through the agar matrix. VONS12 expanded inhibition zones to 34.85 ± 1.25 mm and 29.62 ± 1.05 mm (>2.44-fold increase), completely suppressing hyphal elongation and spore germination.

Skin Irritation Profiling & Biocompatibility Assessment

To ensure clinical safety for topical administration, the skin irritation potential of the optimized VONS hydrogel formulations (VONS2, VONS8, VONS12) and control free drug gel was evaluated in vivo using male Wistar rats via the Draize primary skin irritation protocol. Formulations (0.5 g) were applied onto an intact, shaved 5 cm² dorsal skin area under occlusive hypoallergenic patch coverage for 24 h. Erythema and edema scores were visually determined at 1, 24, 48, and 72 h post-patch removal, using the standardized Draize scale (0 = no reaction; 1 = very slight; 2 = well-defined; 3 = moderate; 4 = severe). The Primary Irritation Index (PII) was calculated from the arithmetic sum of erythema and edema scores across all time points.

The control formulation containing 1% w/w free voriconazole produced mild erythema (PII = 1.25 ± 0.18), likely attributable to micro-crystalline drug precipitation and localized frictional irritation on the epidermal mantle. In sharp contrast, the VONS-loaded hydrogel formulations displayed negligible cutaneous reaction: VONS2 exhibited a PII of 0.28 ± 0.05 , VONS8 scored 0.22 ± 0.04 , and VONS12 achieved a PII of 0.15 ± 0.03 , classifying them as 'non-irritating' (PII < 0.50). Histological examination of skin sections stained with hematoxylin and eosin (H&E) revealed intact epidermal architecture, normal keratinocyte stratification, absence of inflammatory cell infiltration in the papillary dermis, and undamaged dermal appendages. These findings corroborate that cyclodextrin nanosponge encapsulation sequesters the active pharmaceutical ingredient within porous host cavities, preventing direct abrasive contact with the epidermis while maintaining high tissue tolerability.

CONCLUSION

In this investigation, a cyclodextrin-based nanosponge (CDNS) hydrogel was developed, optimized, and evaluated for the targeted topical delivery of voriconazole to address its poor aqueous solubility, dissolution-limited skin permeation, systemic toxicities, and rapid ultraviolet photolability. The nanosponges, synthesized by condensation polymerization of cyclodextrins with diphenyl carbonate alongside emulsion-solvent diffusion techniques, exhibited spherical, highly porous architectures with mean hydrodynamic diameters between 50 and 75 nm, narrow polydispersity indices (0.06–0.23), and electrostatically stabilizing zeta potentials (-24.3 to -26.8 mV). Solubilization studies demonstrated up to a 13.89-fold enhancement in aqueous voriconazole solubility when complexed within sulfobutyl ether- β -cyclodextrin nanosponges compared to the unformulated drug. High entrapment efficiencies (up to 96.54%) and drug loadings (367.57 mg/g) were achieved, while solid-state characterization by FTIR, DSC, and PXRD confirmed non-covalent molecular inclusion and complete amorphization within the cross-linked polymeric matrix.

Optimization using a 3-factor, 3-level Box-Behnken Design successfully established an operational design space (Desirability = 1.000) yielding a topical hydrogel containing 2.327% w/w Carbopol 974, 6.096% w/w propylene glycol, and 10.618% w/w ethanol, which exhibited pseudoplastic flow behavior, skin-compatible pH (5.58 ± 0.04), and high clarity. In vitro release testing across cellulose dialysis membranes demonstrated that the optimized Karaya gum hydrogel (F9) provided sustained delivery (94.14% over 12 hours) adhering to Zero-Order kinetics ($R^2 = 0.988$) and Super Case II transport ($n = 1.377$), wherein swelling-controlled polymer relaxation and matrix erosion regulate steady drug egress.

Ex vivo dermatokinetic evaluations across excised Wistar rat skin confirmed the absence of transdermal systemic receptor leakage ($<0.01 \mu\text{g/mL}$), while establishing a 10.37-fold increase in stratum corneum drug deposition ($55.38 \pm 2.05 \mu\text{g/cm}^2$) compared to the free drug control. Microbiological assays demonstrated a greater than 2.4-fold expansion in growth clearance zones against both *Candida albicans* and *Aspergillus fumigatus*, with in vivo primary skin irritation testing confirming high biocompatibility ($\text{PII} = 0.15 \pm 0.03$). Furthermore, cyclodextrin nanosponge encapsulation preserved greater than 97.8% intact drug potency over 6 months with zero detectable photolytic cleavage under continuous UV irradiation. These findings demonstrate that the cyclodextrin nanosponge hydrogel system provides an effective topical platform for voriconazole, offering enhanced solubility, controlled zero-order release, localized epidermal retention, and photoprotection for the management of superficial and deep-seated cutaneous fungal infections.

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