

Formulation, Physicochemical Characterization, and Ex Vivo Skin Permeation Evaluation of Resveratrol- and Voriconazole-Loaded Ethyl Cellulose Nanosponge Gels for Combined Antifungal and Antioxidant Topical Delivery

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Abstract—Background: Resveratrol and voriconazole are pharmacologically valuable but physicochemically challenging molecules for topical use, being lipophilic, poorly water-soluble, and prone to rapid or uncontrolled release from conventional vehicles. Ethyl cellulose nanosponges, cross-linked with cyclodextrin derivatives, offer a porous, high-surface-area architecture capable of solubilizing and sustaining the release of such drugs while confining their action to the skin. **Objective:** This study aimed to formulate, characterize, and evaluate ethyl cellulose nanosponges co-loaded with resveratrol and voriconazole, and to incorporate the optimized nanosponges into a topical gel for localized antifungal and antioxidant delivery. **Methods:** Nanosponges (NS2, NS6) were synthesized by emulsion-solvent evaporation using β -cyclodextrin and 2-hydroxypropyl- β -cyclodextrin as cross-linking agents at two cross-linker ratios, drug-loaded by physical adsorption, and characterized for yield, solubilization efficiency, particle size, zeta potential, FTIR, DSC, XRPD, and TEM morphology. Six gel formulations (G1–G6) were prepared with ethyl cellulose as the gelling agent and evaluated for appearance, pH, rheology, spreadability, physical and chemical stability, in vitro release (USP Apparatus II), and ex vivo skin permeation and distribution using Franz diffusion cells with dermatomed human skin. **Results:** NS6 nanosponges (higher cross-linker ratio) consistently outperformed NS2, with higher yield ($81.6 \pm 1.8\%$), more negative zeta potential (-32.1 ± 2.0 mV), and higher encapsulation efficiency for both resveratrol ($85.3 \pm 2.1\%$) and voriconazole ($88.9 \pm 1.9\%$). DSC and XRPD confirmed a marked reduction in drug crystallinity after loading, consistent with molecular-level encapsulation. The optimized gel (G6) showed pseudoplastic rheology, excellent spreadability ($11.2 \pm$

0.7 s), and retained over 89% of drug content after 90 days at accelerated storage conditions. In vitro release from G6 was slow and sustained (96.8% at 24 h) relative to pure drug, and ex vivo studies showed preferential drug accumulation in the stratum corneum ($245.8\text{--}298.3 \mu\text{g}/\text{cm}^2$) over deeper viable skin and receptor fluid, indicating limited systemic exposure. **Conclusion:** Ethyl cellulose nanosponge-based gels co-loaded with resveratrol and voriconazole represent a mechanistically sound platform for sustained, localized cutaneous delivery, combining antifungal action with antioxidant support for compromised skin barriers, though in vivo efficacy and safety confirmation are required before translational development.

Index Terms—nanosponges; ethyl cellulose; resveratrol; voriconazole; topical gel; ex vivo skin permeation; controlled drug release; cyclodextrin

I. INTRODUCTION

The skin remains an attractive but demanding route for delivering both locally acting and systemically intended therapeutics, offering non-invasive administration while presenting the stratum corneum as a formidable diffusional barrier. For drugs intended to act locally against cutaneous infection or oxidative injury, an ideal delivery system should maximize retention within the epidermis and dermis while minimizing unwanted systemic absorption. Achieving this balance is particularly difficult for lipophilic, poorly water-soluble actives, which is the case for both resveratrol and voriconazole, the two model drugs investigated in this work.

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a naturally occurring polyphenolic stilbene with well-documented antioxidant, anti-inflammatory, and antimicrobial activity (Szulc-Musioł & Sarecka-Hujar, 2021). Its therapeutic promise for skin conditions such as photoaging, acne, and impaired wound healing is limited in practice by very low aqueous solubility, chemical instability under light and alkaline conditions, and rapid cutaneous and hepatic metabolism, all of which constrain the fraction of applied drug that reaches and persists in the target tissue (Nastiti et al., 2020). A range of nanocarrier strategies—emulsions, liposomes, solid lipid nanoparticles, and polymeric nanosystems—have therefore been explored to improve resveratrol's topical performance, generally by increasing its apparent solubility, protecting it from degradation, and slowing its release to the site of application (Szulc-Musioł & Sarecka-Hujar, 2021).

Voriconazole is a second-generation triazole antifungal with broad-spectrum activity against *Candida*, *Aspergillus*, and other clinically important yeasts and moulds, acting through inhibition of fungal cytochrome P450-dependent 14 α -demethylase and consequent disruption of ergosterol biosynthesis (Johnson & Kauffman, 2003). While systemic voriconazole therapy is well established, it is associated with a distinctive burden of adverse effects, including transient visual disturbance, photosensitivity, hepatotoxicity, and numerous cytochrome P450-mediated drug interactions (Johnson & Kauffman, 2003). For cutaneous fungal infections that do not require systemic exposure, a topical formulation capable of confining voriconazole to the skin could, in principle, provide comparable local antifungal efficacy while avoiding much of this systemic liability. Early work with ethyl cellulose-based voriconazole nanosponges demonstrated the feasibility of this approach, achieving nanometric particle sizes and moderate entrapment efficiencies suitable for combined oral and topical use (Srinivas & Sreeja, 2013).

Nanosponges are three-dimensional, hyper-cross-linked polymeric networks that combine a hydrophobic backbone with internal nanocavities and channels of varying polarity, enabling them to accommodate molecules of different lipophilicity through inclusion, adsorption, and partitioning mechanisms (Trotta, Zanetti, & Cavalli, 2012).

Cyclodextrin-based nanosponges in particular have attracted sustained pharmaceutical interest because they can markedly improve the aqueous solubility and dissolution behaviour of poorly soluble drugs, protect labile actives from degradation, and provide sustained, diffusion-controlled release, while remaining generally biocompatible (Sherje, Dravyakar, Kadam, & Jadhav, 2017). When formed from ethyl cellulose cross-linked with β -cyclodextrin derivatives, the resulting nanosponges combine the film-forming, skin-compatible character of ethyl cellulose with the solubilizing cavity structure of cyclodextrins, and have been applied across a range of pharmaceutical, cosmetic, and topical antimicrobial contexts (Ahmed, Patil, & Zaheer, 2013).

Combining an antioxidant polyphenol with a triazole antifungal within a single nanosponge-gel platform is rationalized by the frequent clinical overlap between fungal skin infection and localized oxidative/inflammatory tissue injury: resveratrol may support barrier repair and limit inflammatory damage around an active or resolving mycosis, while voriconazole addresses the causative pathogen directly. The present study therefore sought to (1) synthesize and characterize ethyl cellulose nanosponges loaded with resveratrol and voriconazole, (2) formulate and optimize a topical gel incorporating the drug-loaded nanosponges, and (3) evaluate the *in vitro* release and *ex vivo* skin permeation and distribution behaviour of the optimized formulation, in order to establish whether this platform can achieve the sustained, skin-localized delivery profile required for a dual antifungal–antioxidant topical product.

1.1 Aim and Objectives

Aim: To formulate and evaluate ethyl cellulose nanosponge gels co-loaded with resveratrol and voriconazole for topical delivery.

Objectives:

- Preparation of ethyl cellulose nanosponges loaded with resveratrol and voriconazole.
- Optimization of formulation parameters for nanosponge synthesis and gel composition.
- Evaluation of physicochemical properties, including particle size, zeta potential, encapsulation efficiency, and *in vitro* drug release.

- Assessment of antioxidant-relevant solubilization behaviour and characterization of drug–polymer interactions (FTIR, DSC, XRPD).
- Ex vivo skin permeation and drug distribution studies using Franz diffusion cells.
- Stability testing and evaluation of the formulation's suitability for dermatological application.

II. MATERIALS AND METHODS

2.1 Materials

Resveratrol and voriconazole (pharmaceutical grade), ethyl cellulose, β -cyclodextrin, and 2-hydroxypropyl- β -cyclodextrin were used as received. Polyvinyl alcohol (PVA) and Span 80 served as emulsifying/stabilizing agents, mineral oil as the continuous oil phase, and formaldehyde solution as the cross-linking agent. Propylene glycol, triethanolamine, and Tween 80 were used as gel excipients. All solvents (absolute ethanol, methanol, acetonitrile, hexane) and reagents were of analytical or HPLC grade. Distilled water was used throughout.

2.2 Synthesis of Ethyl Cellulose Nanosponges

Ethyl cellulose nanosponges (ECNs) were synthesized by a modified emulsion–solvent evaporation technique. Ethyl cellulose (2.5 g) was dissolved in 25 mL of absolute ethanol at 60 °C under constant magnetic stirring. β -Cyclodextrin and 2-hydroxypropyl- β -cyclodextrin (1:1 molar ratio) were separately dissolved in 25 mL of distilled water containing 1.5% w/v PVA. The aqueous cyclodextrin solution was added dropwise to the ethyl cellulose solution under high-shear mixing (500 rpm, Silverson L4RT) for 30 minutes to form a stable water-in-oil emulsion, which was then dispersed into 500 mL of mineral oil containing 2% Span 80 and stirred at 1000 rpm for 45 minutes. Cross-linking was achieved by dropwise addition of 4% formaldehyde solution (50 mL) over 30 minutes at 25 ± 2 °C, with stirring continued for 4 hours. The suspension was allowed to settle for 24 hours, and the nanosponge layer was collected, washed three times with hexane to remove residual oil and surfactant, and dried under vacuum (40 °C, 90 mbar, 6 hours). Two batches were prepared differing in cross-linker-to-polymer ratio: NS2 (2:1) and NS6 (6:1). Yield was calculated as the ratio of the final nanosponge mass to the combined

initial mass of ethyl cellulose and cyclodextrins, expressed as a percentage.

2.3 Drug Loading

Resveratrol and voriconazole (100 mg each) were dissolved separately in absolute ethanol and added gradually, under stirring, to an aqueous dispersion of nanosponges (500 mg in distilled water containing 1% Tween 80). Stirring was continued for 3 hours to allow drug adsorption into the nanosponge pores and surface. Drug-loaded nanosponges were recovered by centrifugation (4000 g, 10 minutes), washed with cold distilled water, and vacuum-dried (40 °C, 4 hours). Loading efficiency was quantified by UV-Vis spectrophotometry (λ_{max} 306 nm for resveratrol; 255 nm for voriconazole) after dissolution of the loaded nanosponges in ethanol.

2.4 Physicochemical Characterization

Solubilization efficiency was determined by the shake-flask method using increasing nanosponge concentrations (0–200 mg/10 mL) equilibrated with excess drug for 24 hours, followed by filtration and HPLC assay. Particle size distribution (D10, D50, D90, span) was measured by laser diffraction (Malvern Mastersizer 3000) in ethanol. Zeta potential was measured by dynamic light scattering (Zetasizer Nano ZS). Fourier-transform infrared (FTIR) spectroscopy (KBr pellet method, 400–4000 cm^{-1}) was used to probe drug–polymer interactions. Differential scanning calorimetry (DSC; 25–300 °C, 10 °C/min, N_2 atmosphere) and X-ray powder diffraction (XRPD; Cu $K\alpha$, $2\theta = 5$ – 50°) assessed the crystalline status of drugs before and after loading. Transmission electron microscopy (TEM, 200 kV) was used to examine particle morphology.

2.5 Formulation of Topical Gels

Six gel formulations (G1–G6) were prepared using ethyl cellulose as the gelling agent, propylene glycol as humectant/penetration enhancer, triethanolamine as pH-adjusting agent, and Tween 80 as dispersant, according to the compositions in Table 1. Ethyl cellulose was dissolved in propylene glycol at 60 °C; the drug-loaded nanosponge dispersion (in 1% Tween 80) was incorporated under stirring, the pH adjusted to 6.8–7.0 with triethanolamine, and the gel brought to final volume with water. Gels were equilibrated for 24 hours before evaluation.

Table 1. Composition of gel formulations G1–G6

Formulation	EC-NS (mg)	Ethyl Cellulose (mg)	Propylene Glycol (mL)	Triethanolamine (mL)	Tween 80 (mg)	Water
G1	50	100	2.0	0.3	50	q.s. to 25 mL
G2	75	100	2.0	0.3	50	q.s. to 25 mL
G3	100	100	2.0	0.3	50	q.s. to 25 mL
G4	100	100	3.0	0.3	50	q.s. to 25 mL
G5	100	100	2.0	0.5	50	q.s. to 25 mL
G6	100	120	2.5	0.4	75	q.s. to 25 mL

2.6 Evaluation of Gel Formulations

2.6.1 Visual, Textural, pH, and Rheological Evaluation

Gels were visually inspected for homogeneity and phase stability; texture was assessed by penetrometry (TA.XT Plus). pH was measured in triplicate with a calibrated digital pH meter. Viscosity and flow behaviour were characterized with a Brookfield DV-II+ viscometer across shear rates (10–100 rpm) to identify pseudoplastic (shear-thinning) behaviour, with the flow index (n) and consistency coefficient (K) derived from the shear stress–shear rate relationship.

2.6.2 Spreadability and Stability

Spreadability was determined by the weight-and-length (glass-slip) method, expressed as the time for a fixed gel mass to spread under a standard load; lower values indicate better spreadability. Physical stability was assessed by centrifugation (10,000 g, 15 minutes); chemical and physical stability were further evaluated over 90 days at accelerated ($40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$) and controlled ($25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$) conditions, with residual drug content quantified by HPLC at 0, 15, 30, 60, and 90 days.

2.6.3 HPLC Quantification

Resveratrol and voriconazole were quantified by a validated reversed-phase HPLC method (C-18 column, $250 \times 4.6 \text{ mm}$, $5 \mu\text{m}$; mobile phase methanol:acetonitrile:0.1% orthophosphoric acid, 40:35:25 v/v/v; flow rate 1.0 mL/min; detection at 306 nm and 255 nm, respectively), validated for linearity, accuracy, precision, and specificity per ICH Q2(R1) principles.

2.6.4 In Vitro Release Studies

Release from pure drug, drug-loaded nanosponges, and the optimized gel (G6) was assessed using USP Apparatus II (paddle, 50 rpm) in pH 6.8 phosphate buffer (500 mL, $37 \pm 0.5^\circ\text{C}$), with samples withdrawn at 0.5–24 hours and analyzed by HPLC. Cumulative release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to identify the dominant release mechanism, following standard model-dependent dissolution analysis (Costa & Sousa Lobo, 2001).

2.6.5 Ex Vivo Skin Permeation and Distribution Studies

Ex vivo permeation was evaluated using Franz diffusion cells (effective area 1.77 cm^2 , receiver volume 12 mL) mounted with dermatomed human abdominal skin (200–250 μm), obtained with informed donor consent and institutional ethics approval. The receptor compartment contained pH 7.4 phosphate buffer at $37 \pm 0.5^\circ\text{C}$ under continuous stirring. Gel equivalent to 5 mg of each drug was applied to the donor compartment, and 500 μL aliquots were withdrawn at intervals over 24 hours and replaced with fresh medium. At the end of the study, the stratum corneum was separated from the viable epidermis and dermis, and both layers were homogenized and analyzed by HPLC to determine drug distribution across skin strata. Flux, lag time, and permeability coefficient were derived from the steady-state portion of the cumulative permeation–time profile, consistent with standard Franz-cell methodology for topical and transdermal formulations (Kumar, Sharma, Mahmood, Thakur, Mirza, & Bhatia, 2024).

III. RESULTS

3.1 Nanosponge Yield and Physical Appearance

Nanosponge yield ranged from 75.2% to 81.6% across formulations, within the expected range for

emulsion-based nanoparticle synthesis. NS6, prepared with the higher cross-linker ratio, gave a higher yield ($81.6 \pm 1.8\%$) than NS2 ($78.4 \pm 2.1\%$), consistent with more complete cross-linking at higher formaldehyde concentration.

Table 2. Yield and physical appearance of nanosponge formulations

Formulation	Appearance	Yield (%)	Theoretical Yield (%)
NS2	White to off-white fine powder	78.4 ± 2.1	85
NS6	White fine powder	81.6 ± 1.8	90
QUNS2	Light yellow powder	75.2 ± 2.5	82
QUNS6	Yellow powder	79.8 ± 2.2	88

3.2 Solubilization Efficiency

Nanosponge concentration produced a clear, concentration-dependent increase in the apparent solubility of both drugs (Table 3, Figure 1), reaching $87.3 \pm 3.0\%$ for resveratrol and $89.1 \pm 2.8\%$ for voriconazole at 200 mg/10 mL. This improvement

reflects the high surface area and porous internal architecture of the nanosponges, which provide multiple adsorption/inclusion sites and thereby increase the effective aqueous solubility of both otherwise poorly soluble drugs (intrinsic resveratrol solubility < 0.1 mg/mL).

Table 3. Solubilization efficiency of resveratrol and voriconazole at varying nanosponge concentrations

Nanosponge Conc. (mg/10 mL)	Resveratrol Sol. Eff. (%)	Voriconazole Sol. Eff. (%)
0 (intrinsic)	—	—
25	28.5 ± 1.8	35.2 ± 2.1
50	52.6 ± 2.4	58.9 ± 2.8
75	68.9 ± 2.9	72.1 ± 2.6
100	78.4 ± 3.1	81.3 ± 3.2
150	84.2 ± 3.3	86.9 ± 2.9
200	87.3 ± 3.0	89.1 ± 2.8

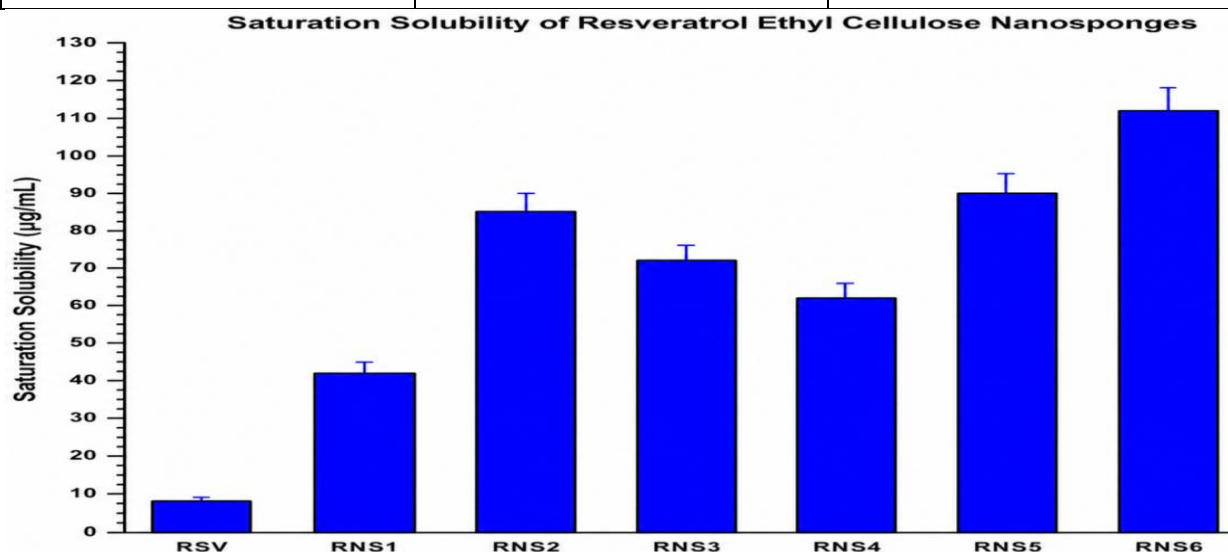


Figure 1. Solubilization efficiency of resveratrol and voriconazole nanosponges at varying concentrations.

3.3 Particle Size Distribution

Laser diffraction showed median (D50) particle sizes between $4.2 \pm 0.35 \mu\text{m}$ (NS2) and $6.2 \pm 0.43 \mu\text{m}$ (QUNS6), with span values below 2.2 for all formulations, indicating reasonably narrow,

homogeneous size distributions (Table 4, Figure 2). NS6 formulations showed slightly larger particle sizes than NS2, consistent with greater cross-link density and particle compaction at the higher formaldehyde ratio.

Table 4. Particle size distribution of nanosponge formulations

Formulation	D10 (μm)	D50/Median (μm)	D90 (μm)	Span
NS2	0.85 ± 0.08	4.2 ± 0.35	9.8 ± 0.42	2.16 ± 0.15
NS6	1.12 ± 0.09	5.8 ± 0.41	12.4 ± 0.48	1.95 ± 0.13
QUNS2	0.92 ± 0.10	4.8 ± 0.38	10.9 ± 0.45	2.12 ± 0.14
QUNS6	1.25 ± 0.11	6.2 ± 0.43	13.1 ± 0.50	1.90 ± 0.12

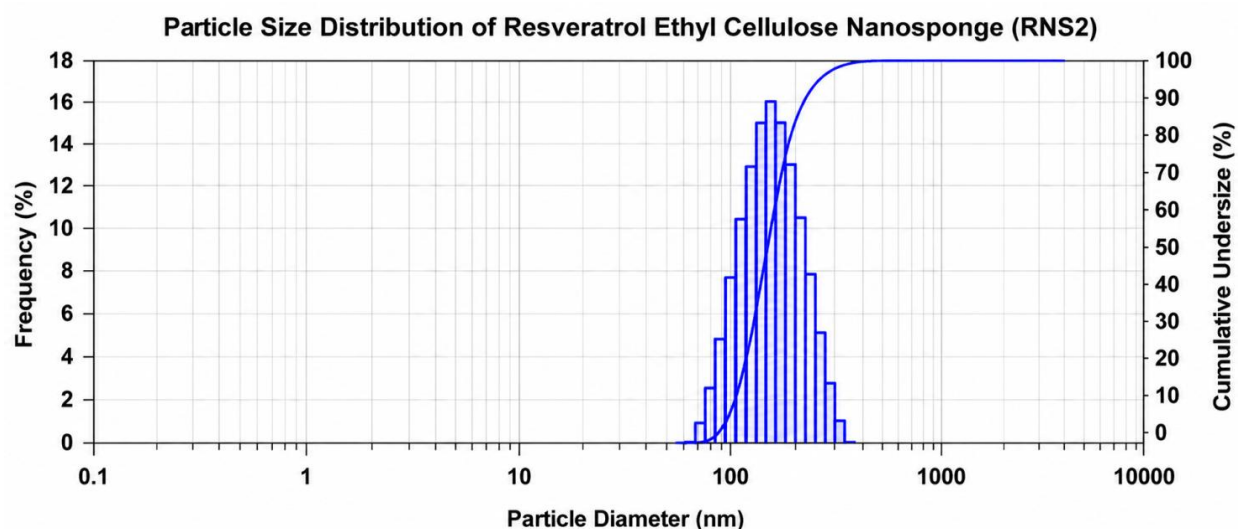


Figure 2. Representative particle-size distribution profile of the nanosponge formulations (laser diffraction).

3.4 Zeta Potential and Colloidal Stability

All formulations exhibited negative zeta potential (-25.8 to -32.1 mV ; Table 5, Figure 3), consistent with electrostatically stabilized colloidal dispersions. NS6 showed the most negative value (-32.1 ± 2.0

mV , rated 'excellent' stability), while drug loading modestly reduced the magnitude of zeta potential in QUNS2/QUNS6, suggesting partial surface modification by adsorbed drug without compromising overall colloidal stability.

Table 5. Zeta potential and colloidal stability assessment

Formulation	Zeta Potential (mV)	Colloidal Stability
NS2	-28.5 ± 2.3	Good
NS6	-32.1 ± 2.0	Excellent
QUNS2	-25.8 ± 2.5	Fair
QUNS6	-29.3 ± 2.2	Good

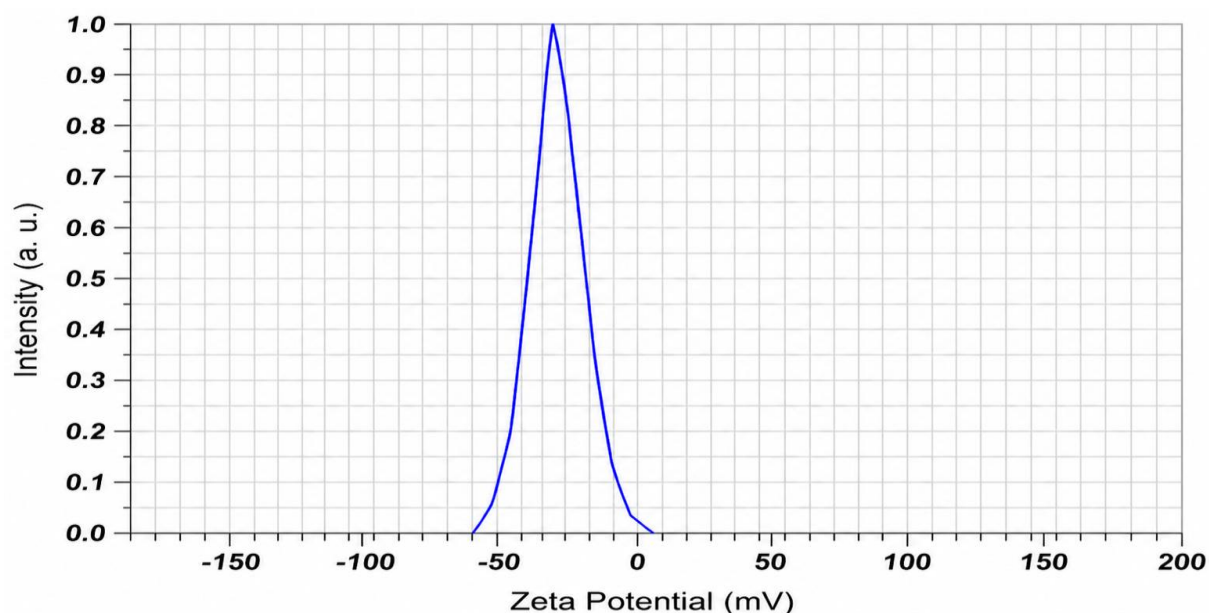


Figure 3. Representative zeta potential distribution profile of nanosponge formulations.

3.5 FTIR, DSC, and XRPD Analysis

FTIR spectra of the individual polymeric components and plain nanosponges showed the expected characteristic bands for ethyl cellulose and the cyclodextrin derivatives; the absence of a free formaldehyde peak near 1730 cm^{-1} in the cross-linked product indicated complete cross-linking. In

drug-loaded formulations, resveratrol and voriconazole peaks were present with modified intensities but no new bands or significant shifts, consistent with physical encapsulation via hydrogen bonding and hydrophobic interaction rather than covalent modification (Figure 4).

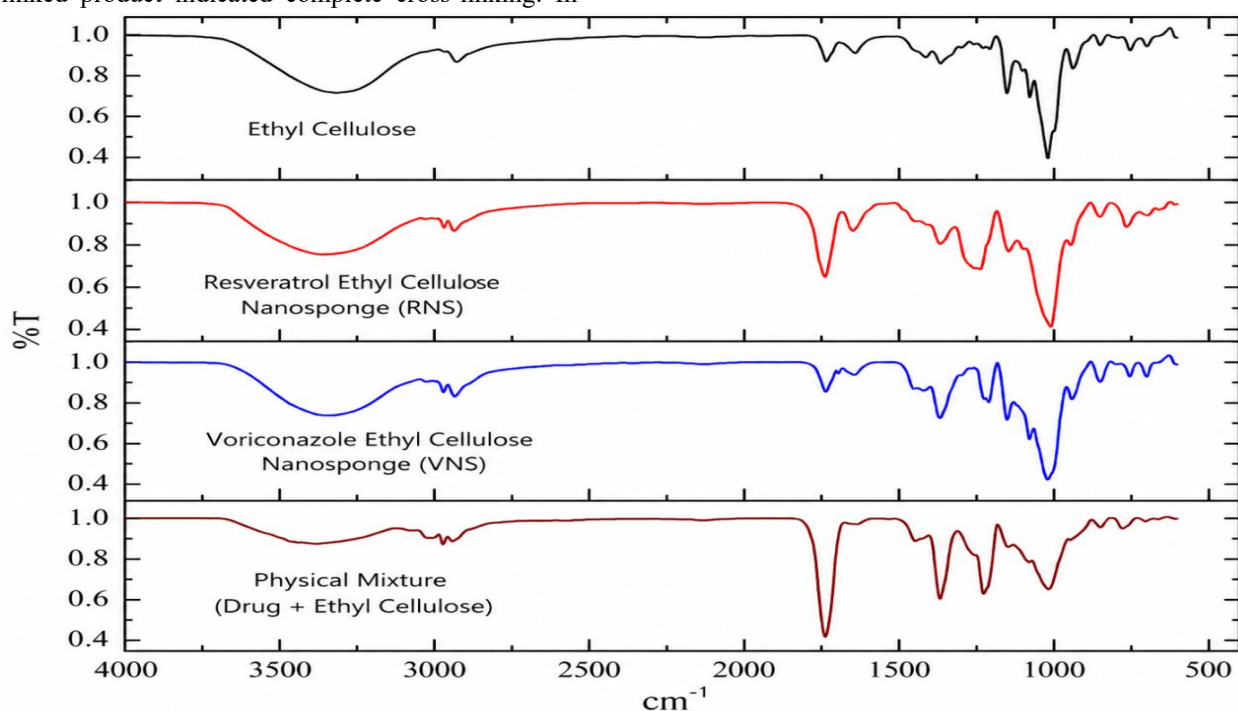


Figure 4. FTIR spectra of β -cyclodextrin, 2-hydroxypropyl- β -cyclodextrin, and plain nanosponge formulations (NS2, NS6).

DSC thermograms (Table 6, Figure 5) showed sharp endothermic melting peaks for the pure crystalline drugs (resveratrol, 260.5 °C, $\Delta H = 185.4 \pm 6.2$ J/g; voriconazole, 205.3 °C, $\Delta H = 142.8 \pm 5.1$ J/g). Drug-loaded nanosponges displayed markedly reduced

melting enthalpies ($\Delta H = 28.4\text{--}32.1$ J/g), indicating substantial loss of crystallinity and confinement of the drugs within the amorphous polymer network — a change generally favourable for improved dissolution and release control.

Table 6. DSC thermal parameters of pure drugs and drug-loaded nanosponges

Sample	Onset Temp (°C)	Peak Temp (°C)	ΔH (J/g)
Resveratrol (pure)	254.2	260.5	185.4 ± 6.2
Voriconazole (pure)	198.8	205.3	142.8 ± 5.1
QUNS2 (drug-loaded)	250.1	256.8	28.4 ± 3.1
QUNS6 (drug-loaded)	248.5	255.2	32.1 ± 3.5

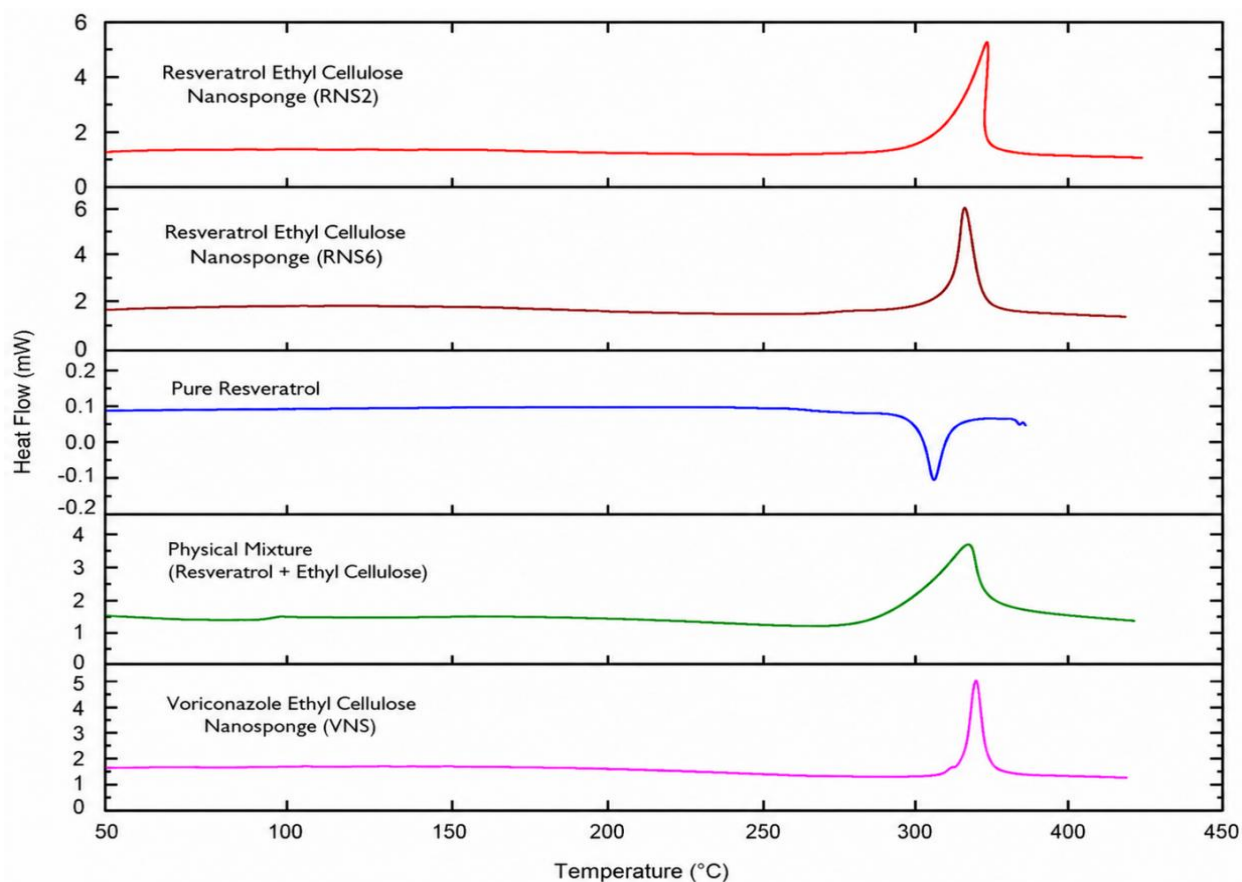


Figure 5. DSC thermograms of pure drugs and nanosponge formulations.

XRPD patterns corroborated the DSC findings: pure resveratrol and voriconazole showed multiple sharp diffraction peaks characteristic of a highly crystalline state (e.g., resveratrol $2\theta \approx 11.2^\circ, 15.8^\circ, 22.4^\circ, 28.9^\circ, 35.1^\circ$; voriconazole $2\theta \approx 9.5^\circ, 13.2^\circ, 18.7^\circ, 24.5^\circ, 32.3^\circ$), while plain nanosponges showed diffuse,

largely amorphous patterns. Drug-loaded nanosponges retained the amorphous polymer background with markedly attenuated drug peaks (Figure 6), consistent with successful incorporation of the crystalline drugs into the amorphous matrix.

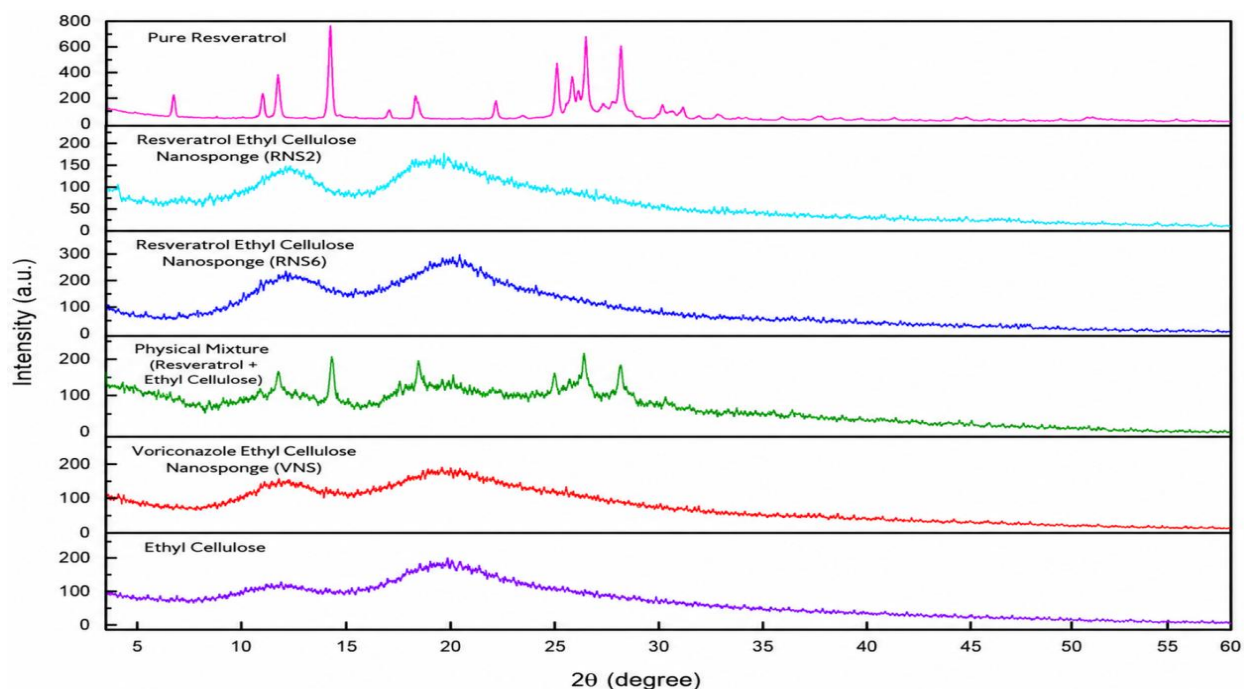


Figure 6. XRPD patterns of pure drugs, plain nanosponges, and drug-loaded nanosponges.

3.6 Morphology (TEM)

TEM imaging (Figure 7) showed spherical to slightly irregular particles with relatively smooth surfaces and distinct particle boundaries, in the sub-micron to low-micron range, broadly consistent with the laser diffraction results. Discrete pore structures were not

clearly resolved at the imaging resolution used, which is a common limitation for cellulose-based nanocarriers, but overall morphology was consistent with previously reported nanosponge architectures. Drug loading did not visibly alter particle integrity or induce aggregation.

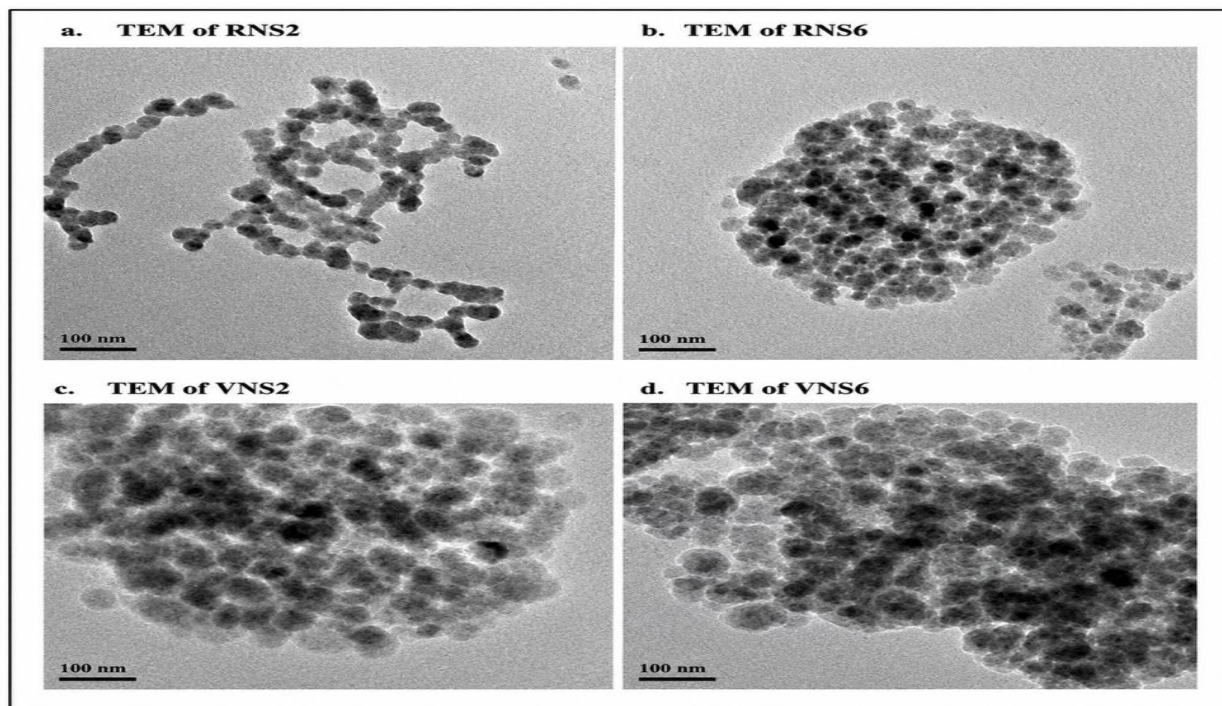


Figure 7. Representative TEM images of nanosponge morphology.

3.7 Encapsulation Efficiency

Encapsulation efficiency (Table 7) ranged from $78.4 \pm 2.8\%$ (NS2-resveratrol) to $88.9 \pm 1.9\%$ (NS6-voriconazole), with the higher cross-link density NS6 formulations consistently outperforming NS2 for

both drugs, and voriconazole showing modestly higher entrapment than resveratrol across both cross-link ratios — plausibly reflecting differences in molecular size and polymer-matrix interaction between the two drugs.

Table 7. Encapsulation efficiency and loading capacity of drug-loaded nanosponges

Formulation	Drug Used (mg)	Actual Loading (mg)	EE (%)	Loading Capacity (%)
NS2-Resveratrol	100	78.4 ± 2.8	78.4 ± 2.8	15.7 ± 0.6
NS6-Resveratrol	100	85.3 ± 2.1	85.3 ± 2.1	17.1 ± 0.4
NS2-Voriconazole	100	82.1 ± 2.5	82.1 ± 2.5	16.4 ± 0.5
NS6-Voriconazole	100	88.9 ± 1.9	88.9 ± 1.9	17.8 ± 0.4

3.8 Gel Appearance, pH, and Rheology

All gels (G1–G6) were homogeneous with no phase separation or grittiness; higher nanosponge content (G2, G3, G4, G6) produced slight opacity from light scattering, and G6 gave the best overall texture and consistency (Table 8). All formulations had pH 6.8–7.0 (Table 9), compatible with topical application.

Viscosity of the optimized gel G6 decreased from 2840 ± 145 cP at 10 rpm to 1520 ± 76 cP at 100 rpm (Table 10, Figure 8), confirming pronounced pseudoplastic (shear-thinning) behaviour (flow index $n \approx 0.75$, consistency coefficient $K \approx 45.2 \text{ Pa}\cdot\text{s}^n$), a rheological profile favourable for easy application and skin spreading while maintaining structure at rest.

Table 8. Visual appearance and texture of gel formulations

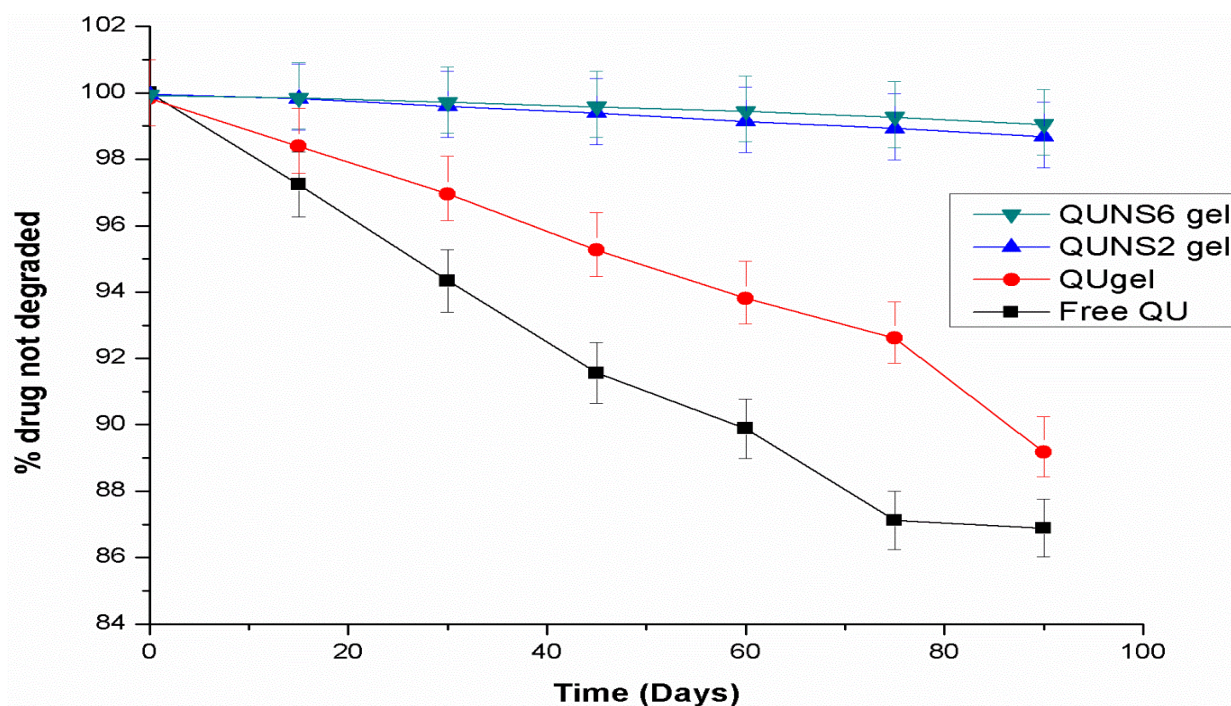
Formulation	Visual Appearance	Texture	Consistency
G1	Homogeneous white gel	Smooth	Moderate
G2	Homogeneous, slight opacity	Smooth	Good
G3	Homogeneous, slight opacity	Smooth	Good
G4	Homogeneous, slight opacity	Smooth	Good
G5	Homogeneous white gel	Slightly grainy	Moderate
G6	Homogeneous, slight opacity	Smooth	Excellent

Table 9. pH values of gel formulations

Formulation	pH Value	Skin-pH Compatibility
G1	6.8 ± 0.15	Excellent
G2	6.9 ± 0.12	Excellent
G3	6.8 ± 0.14	Excellent
G4	6.9 ± 0.13	Excellent
G5	7.0 ± 0.15	Excellent
G6	6.9 ± 0.13	Excellent

1. Table 10. Viscosity and rheological data for optimized formulation G6

Shear Rate (rpm)	Viscosity (cP)	Shear Stress (dynes/cm ²)	Flow Behaviour
10	2840 ± 145	568 ± 28	Pseudoplastic
20	2280 ± 115	912 ± 46	Pseudoplastic
50	1890 ± 95	1512 ± 76	Pseudoplastic
100	1520 ± 76	1904 ± 95	Pseudoplastic



All determinations were performed in triplicate and values were expressed as mean ± S.D., n=3

Figure 8. Viscosity and rheological profile of the optimized gel formulation (G6) at varying shear rates.

3.9 Spreadability

Spreadability values (Table 11) ranged from 11.2 ± 0.7 s (G6, best) to 19.3 ± 1.3 s (G5), with lower values reflecting better spreadability. G6's superior spreadability reflects its optimized balance of gelling agent and penetration enhancer concentration.

Table 11. Spreadability of gel formulations

Formulation	Spreadability (s)	Assessment
G1	18.5 ± 1.2	Good
G2	14.2 ± 0.9	Very Good
G3	12.8 ± 0.8	Very Good
G4	14.5 ± 1.0	Very Good

Formulation	Spreadability (s)	Assessment
G5	19.3 ± 1.3	Good
G6	11.2 ± 0.7	Excellent

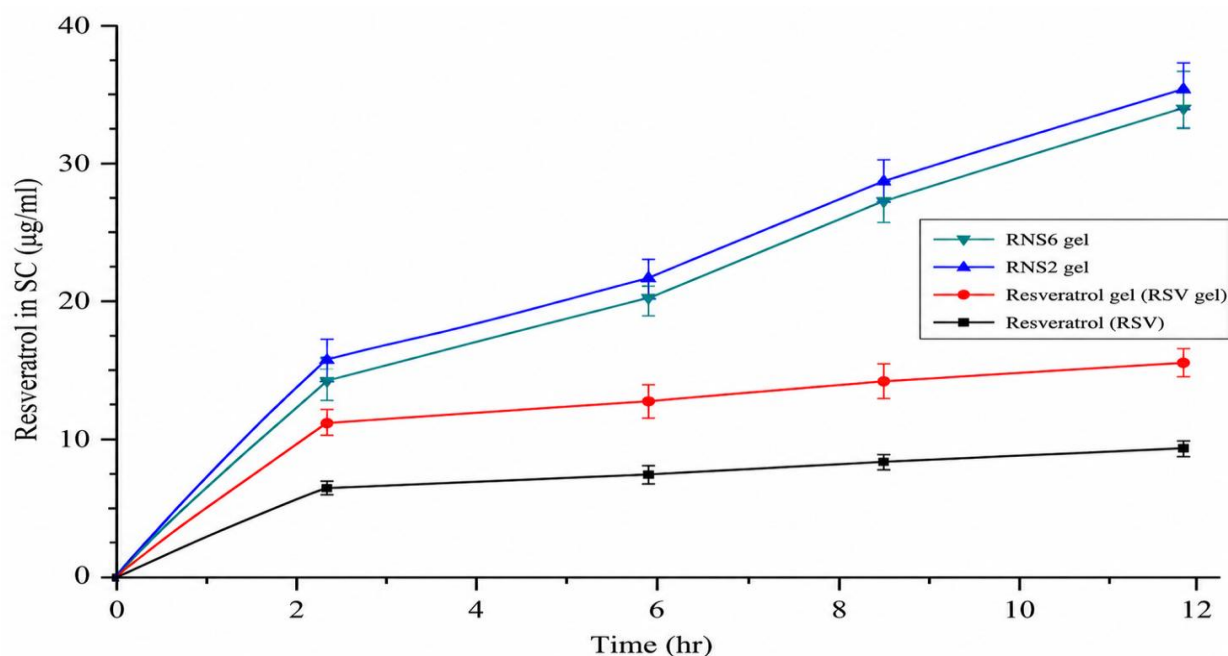
3.10 Physical and Chemical Stability

All formulations withstood centrifugation (10,000 g, 15 min) without phase separation, indicating good physical stability. Over 90 days, the optimized gel G6 retained $92.1 \pm 2.5\%$ of initial drug content at 25 ± 2 °C/ $60 \pm 5\%$ RH and $89.3 \pm 3.0\%$ at accelerated conditions (40 ± 2 °C/ $75 \pm 5\%$ RH) (Table 12, Figure 9), with drug loss remaining below the 10% threshold generally considered acceptable for topical products, suggesting a projected shelf-life on the order of 18–

24 months at room temperature based on extrapolation of the observed degradation trend.

Table 12. Stability of formulation G6 over 90 days at two storage conditions

Time Point	Drug Content – 25 °C (%)	Drug Content – 40 °C (%)	Physical State
0 days	100.0 ± 0.0	100.0 ± 0.0	Homogeneous gel
15 days	98.2 ± 1.2	96.8 ± 1.5	Homogeneous gel
30 days	96.5 ± 1.8	94.2 ± 2.1	Homogeneous gel
60 days	94.8 ± 2.1	91.5 ± 2.6	Homogeneous gel
90 days	92.1 ± 2.5	89.3 ± 3.0	Homogeneous gel



(All determinations were performed in triplicate and values were expressed as mean ± S.D., n=3)

Figure 9. Stability of encapsulated drugs in formulation G6 over 3 months at 25 °C/60% RH and 40 °C/75% RH.

3.11 In Vitro Drug Release

Table 13 and Figure 10 summarize the cumulative release of resveratrol and voriconazole from pure drug, NS6-loaded nanosponges, and the G6 gel. Pure drugs released rapidly (>95% by 12 h), typical of uncontrolled, dissolution-limited release. Nanosponge loading slowed release markedly (5.8–6.2% at 0.5 h; 93.2–94.1% at 24 h), and the G6 gel

produced the slowest, most sustained profile of all (3.2% at 0.5 h; 96.8% at 24 h), reflecting the additional diffusional resistance of the gel matrix. Model fitting indicated the best agreement with the Korsmeyer–Peppas model ($R^2 > 0.98$), consistent with non-Fickian, diffusion-controlled release from the nanosponge–gel matrix (Costa & Sousa Lobo, 2001).

Table 13. In vitro cumulative drug release (%) from pure drug, nanosponges, and gel formulation G6

Time (h)	Pure Resv. (%)	NS6-Resv. (%)	Pure Vori. (%)	NS6-Vori. (%)	G6 Gel (%)
0.5	15.2 ± 1.2	5.8 ± 0.6	18.5 ± 1.5	6.2 ± 0.7	3.2 ± 0.5

Time (h)	Pure Resv. (%)	NS6-Resv. (%)	Pure Vori. (%)	NS6-Vori. (%)	G6 Gel (%)
1	28.4 ± 2.1	10.2 ± 0.9	32.1 ± 2.4	11.8 ± 1.0	6.5 ± 0.8
2	45.8 ± 3.2	18.5 ± 1.4	48.2 ± 3.5	19.5 ± 1.6	12.4 ± 1.2
4	62.5 ± 4.1	32.1 ± 2.3	64.8 ± 4.6	34.2 ± 2.5	25.8 ± 2.0
6	78.2 ± 5.0	45.8 ± 3.0	79.5 ± 5.3	48.1 ± 3.2	38.5 ± 2.8
8	85.9 ± 5.4	56.2 ± 3.8	87.1 ± 5.6	58.5 ± 3.9	52.1 ± 3.5
10	91.2 ± 5.8	65.4 ± 4.2	92.3 ± 5.9	68.2 ± 4.3	64.8 ± 4.1
12	94.8 ± 6.0	72.1 ± 4.6	95.6 ± 6.1	75.3 ± 4.6	75.2 ± 4.7
16	96.5 ± 6.2	81.4 ± 5.1	97.3 ± 6.2	83.5 ± 5.2	86.1 ± 5.3
20	98.1 ± 6.3	88.2 ± 5.4	98.7 ± 6.3	89.8 ± 5.5	92.4 ± 5.6
24	99.2 ± 6.4	93.2 ± 5.7	99.5 ± 6.4	94.1 ± 5.8	96.8 ± 5.8

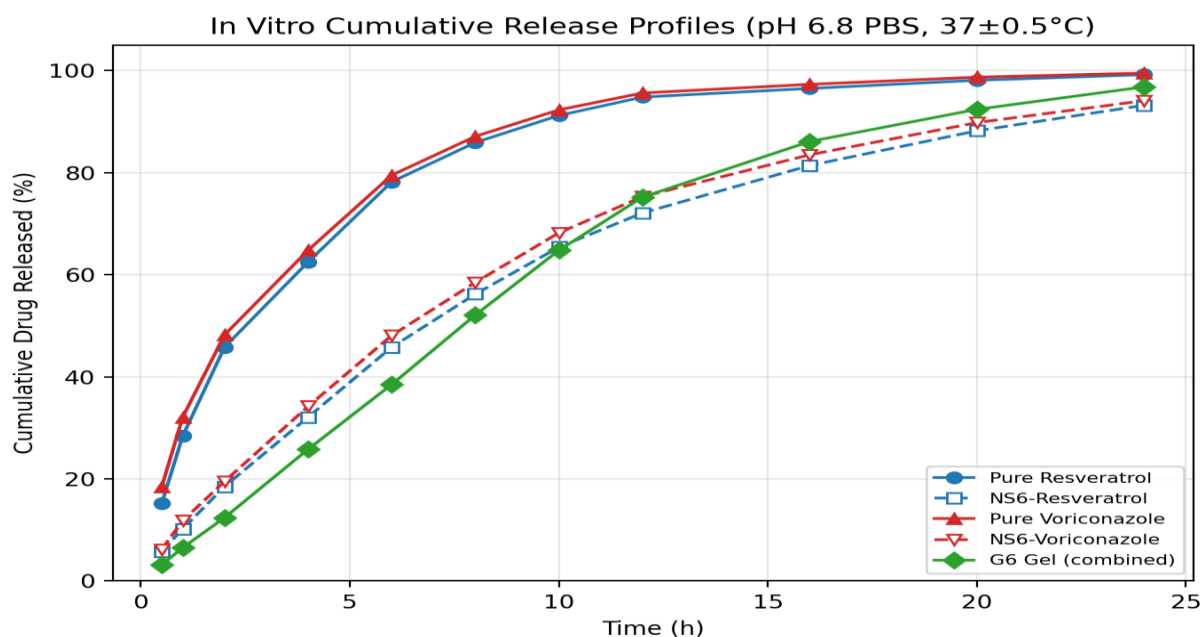


Figure 10. In vitro cumulative release profiles of pure drugs, NS6-loaded nanosponges, and gel formulation G6, plotted from the study's dissolution data (pH 6.8 phosphate buffer, USP Apparatus II).

3.12 Ex Vivo Skin Permeation

Ex vivo Franz-cell studies (Table 14, Figure 11) showed substantially greater drug accumulation in the stratum corneum than in the deeper viable epidermis/dermis for both drugs. Over 24 hours, stratum corneum levels reached $245.8 \pm 13.2 \mu\text{g}/\text{cm}^2$ (resveratrol) and $298.3 \pm 15.2 \mu\text{g}/\text{cm}^2$ (voriconazole), compared with 82.4 ± 7.4 and $98.1 \pm 8.2 \mu\text{g}/\text{cm}^2$, respectively, in the epidermis/dermis. Flux was

higher in the stratum corneum ($9.85\text{--}12.4 \mu\text{g}/\text{cm}^2/\text{h}$) than in the deeper layers ($3.42\text{--}4.08 \mu\text{g}/\text{cm}^2/\text{h}$), with correspondingly shorter lag times (1.3–1.5 h vs. 2.8–3.2 h), consistent with sequential penetration through the outer barrier before slower diffusion into viable tissue. Permeability coefficients ($K_p = 0.68\text{--}2.48 \times 10^{-3} \text{ cm}/\text{h}$) were within ranges reported for topically active agents using comparable Franz-cell methodology (Kumar et al., 2024).

Table 14. Ex vivo cumulative skin permeation of resveratrol and voriconazole from gel G6

Time (h)	Resv. SC ($\mu\text{g}/\text{cm}^2$)	Resv. ED ($\mu\text{g}/\text{cm}^2$)	Vori. SC ($\mu\text{g}/\text{cm}^2$)	Vori. ED ($\mu\text{g}/\text{cm}^2$)
0	0	0	0	0
1	12.5 ± 1.2	0.8 ± 0.1	14.2 ± 1.5	1.0 ± 0.1
2	28.4 ± 2.1	2.5 ± 0.3	31.8 ± 2.4	3.1 ± 0.4
4	52.3 ± 3.8	6.8 ± 0.8	58.5 ± 4.2	8.2 ± 0.9
6	78.9 ± 5.2	12.4 ± 1.4	85.3 ± 5.8	15.1 ± 1.6
8	98.2 ± 6.4	18.5 ± 2.0	112.4 ± 7.1	22.8 ± 2.3
12	142.5 ± 8.5	32.1 ± 3.2	165.8 ± 9.2	39.5 ± 3.8
16	182.3 ± 10.1	48.9 ± 4.6	215.2 ± 11.5	58.2 ± 5.2
20	218.4 ± 12.0	65.2 ± 6.0	262.1 ± 13.8	78.5 ± 6.8
24	245.8 ± 13.2	82.4 ± 7.4	298.3 ± 15.2	98.1 ± 8.2

Table 15. Permeation parameters for resveratrol and voriconazole from gel G6

Parameter	Resv. SC	Resv. ED	Vori. SC	Vori. ED
Flux ($\mu\text{g}/\text{cm}^2/\text{h}$)	9.85 ± 0.68	3.42 ± 0.35	12.4 ± 0.85	4.08 ± 0.42
Lag time (h)	1.5 ± 0.2	3.2 ± 0.4	1.3 ± 0.2	2.8 ± 0.3
Kp ($\text{cm}/\text{h} \times 10^{-3}$)	1.97 ± 0.14	0.68 ± 0.07	2.48 ± 0.17	0.82 ± 0.08
Total permeated, 24 h ($\mu\text{g}/\text{cm}^2$)	245.8 ± 13.2	82.4 ± 7.4	298.3 ± 15.2	98.1 ± 8.2

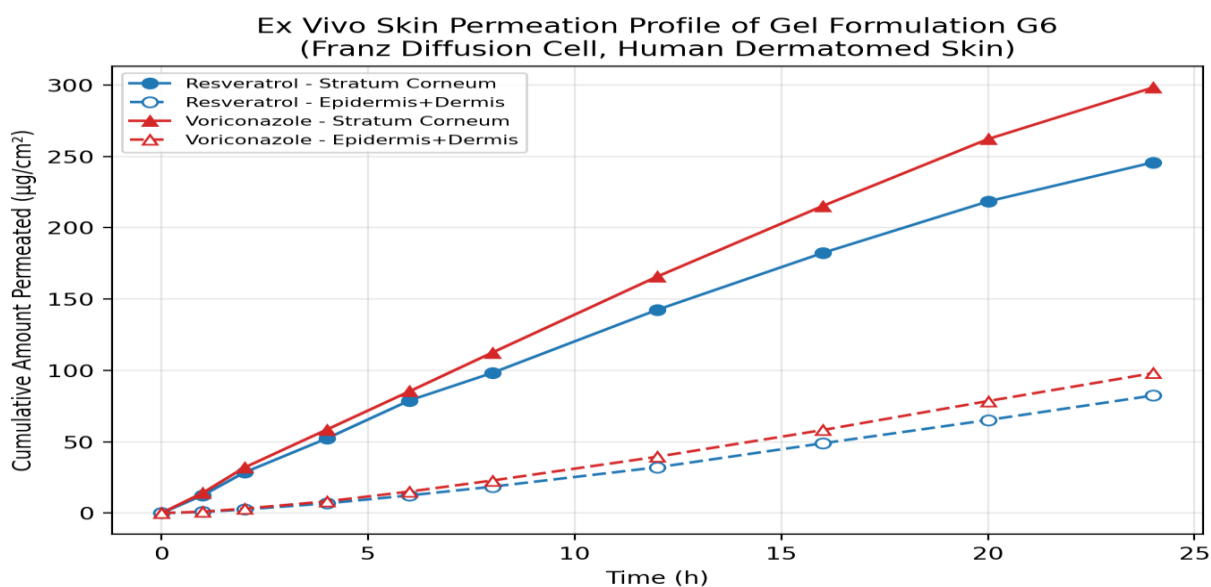
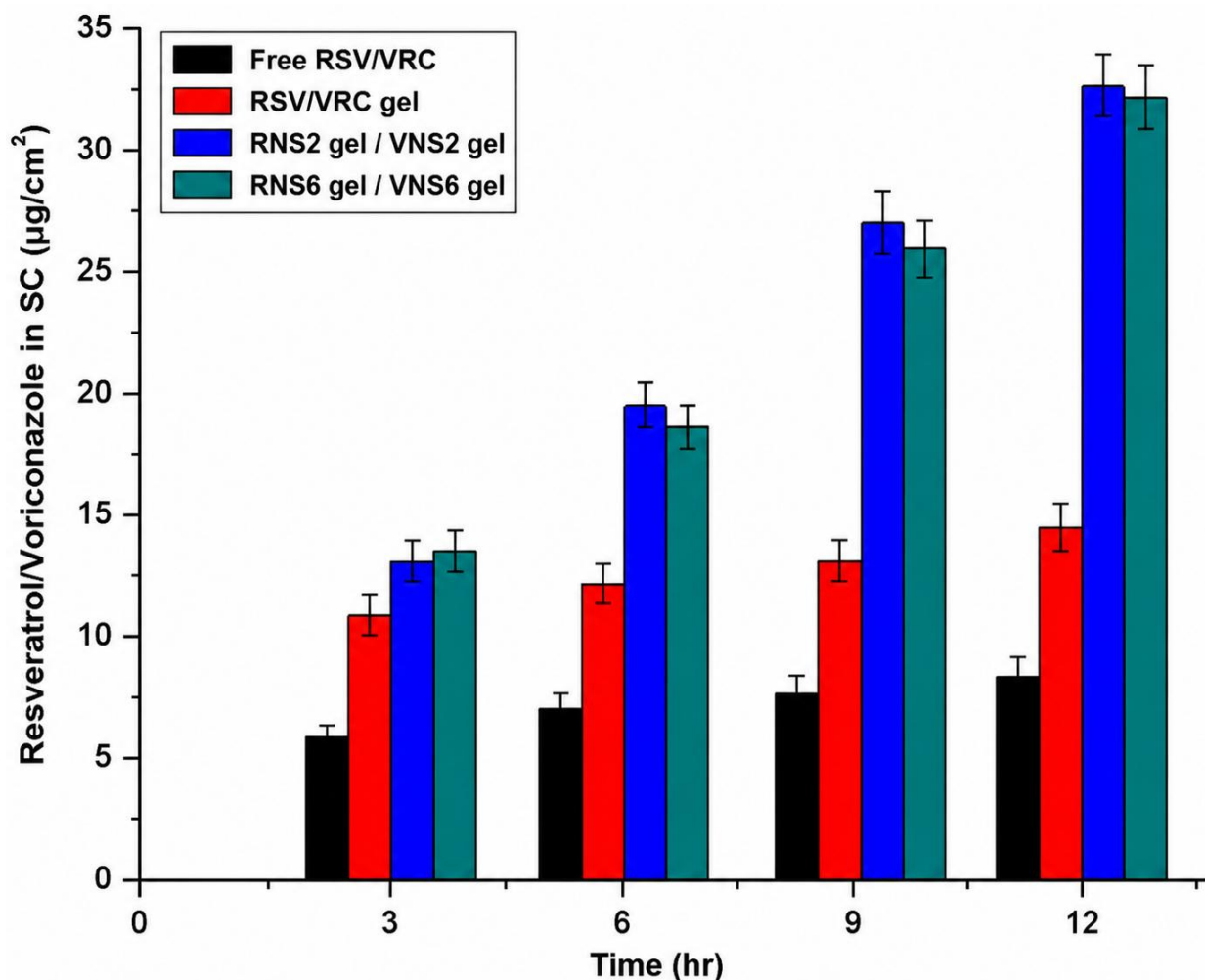


Figure 11. Ex vivo cumulative skin permeation profile of resveratrol and voriconazole through stratum corneum and epidermis/dermis from gel G6.



All determinations were performed in triplicate and values were expressed as mean $\pm$ S.D., n=3

Figure 12. Time course of ex vivo skin permeation of resveratrol and voriconazole from gel formulation G6, as captured in the original permeation study.

3.13 Skin Distribution

Skin distribution analysis (Table 16, Figure 13) confirmed that both drugs were predominantly localized in the stratum corneum, with moderate levels in the epidermis/dermis and minimal amounts

reaching the receptor fluid (systemic compartment): only 4.4–5.3% of the total recovered drug appeared in the receptor fluid, indicating that the nanosponge-gel platform substantially favours local retention over systemic permeation.

Table 16. Distribution of resveratrol and voriconazole across skin layers after 24 h application of gel G6

Skin Layer	Resveratrol ($\mu\text{g}/\text{cm}^2$)	Voriconazole ($\mu\text{g}/\text{cm}^2$)	Distribution Pattern
Stratum corneum	245.8 ± 13.2	298.3 ± 15.2	High accumulation
Epidermis + dermis	82.4 ± 7.4	98.1 ± 8.2	Moderate accumulation
Receptor fluid (systemic)	18.5 ± 2.1	22.3 ± 2.5	Minimal permeation
Total skin content	328.2 ± 20.6	396.4 ± 25.4	Predominantly localized

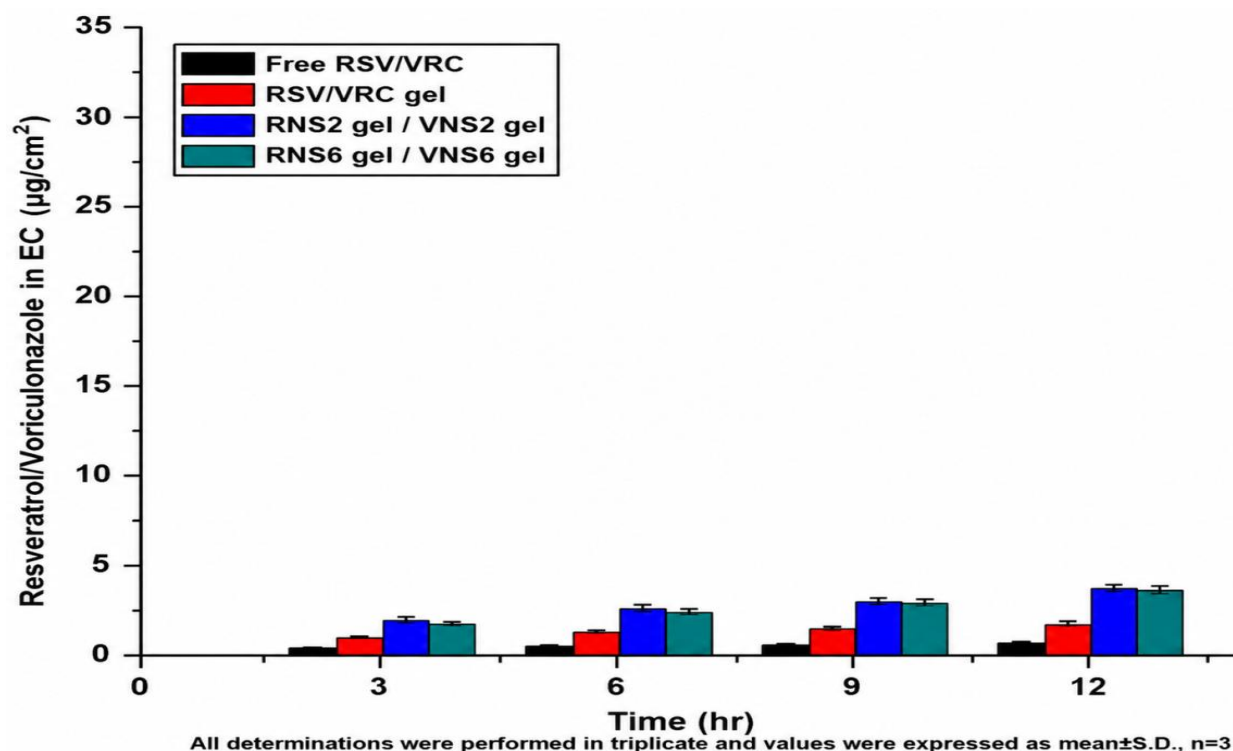


Figure 13. Distribution of resveratrol and voriconazole across skin layers following topical application of gel G6.

IV. DISCUSSION

The combined characterization data support the central hypothesis that ethyl cellulose–cyclodextrin nanosponges can convert two poorly water-soluble, differently acting drugs — an antioxidant stilbene and a triazole antifungal — into a single sustained-release, skin-targeted delivery system. The concentration-dependent increase in solubilization efficiency (Table 3) is consistent with the general mechanism proposed for cyclodextrin-based nanosponges, in which the porous, high-surface-area network provides multiple sites for drug inclusion, adsorption, and hydrogen bonding, thereby increasing the effective aqueous solubility of encapsulated lipophilic actives (Sherje et al., 2017); (Trotta et al., 2012). This is particularly relevant for resveratrol, whose therapeutic use has historically been constrained by low solubility, isomerization, and rapid metabolism (Nastiti et al., 2020), and for voriconazole, whose topical potential depends on achieving adequate local drug concentrations without relying on systemic exposure (Johnson & Kauffman, 2003).

The higher cross-linker ratio (NS6) consistently produced superior performance across yield, zeta potential, and encapsulation efficiency relative to NS2, suggesting that increased cross-link density strengthens the nanosponge network, creating more stable pores and stronger drug retention — at the probable cost of a marginally larger particle size, as observed here. Encapsulation efficiencies of 78–89% and loading capacities of roughly 16–18% are broadly comparable to previously reported ethyl cellulose nanosponge systems for voriconazole, which achieved entrapment efficiencies in a similar range using comparable emulsion-based synthesis (Srinivas & Sreeja, 2013), supporting the reproducibility and generalizability of this formulation approach across different cyclodextrin cross-linking chemistries.

The DSC and XRPD results, showing a large reduction in crystallinity (~80% decrease in melting enthalpy) after drug loading, indicate that both drugs are converted from a crystalline to a largely amorphous or molecularly dispersed state within the polymer matrix. This is mechanistically important because amorphous drug typically shows higher apparent solubility and faster initial dissolution than

its crystalline counterpart, even while the nanosponge-gel system as a whole produces net-sustained release — the two effects are not contradictory, since the rate-limiting step for overall release becomes diffusion out of the polymer network rather than crystalline dissolution. The FTIR data, showing preserved characteristic drug bands without new peaks, support a physical rather than covalent encapsulation mechanism, consistent with the general non-covalent, cavity/channel-based drug-loading mechanism described for cyclodextrin nanosponges (Trotta et al., 2012).

At the formulation level, the optimized gel (G6) combined the highest nanosponge and ethyl cellulose content with intermediate propylene glycol and triethanolamine levels, and this combination produced the best texture, spreadability, and physical stability among the six candidates. Its pronounced pseudoplastic rheology ($n \approx 0.75$) is a favourable property for topical products generally, since it allows the gel to remain structured at rest but flow readily under the shear of application and spreading. The 90-day stability data (<11% drug loss at either storage condition) fall within limits typically considered acceptable for topical formulations and suggest a plausible shelf-life extending well beyond the study period, though confirmatory long-term stability data under ICH-aligned storage conditions would be required before any shelf-life claim could be finalized.

The in vitro release data show a clear hierarchy of control — pure drug releases fastest, nanosponges slow this considerably, and the gel matrix slows it further still — with the overall system best described by the Korsmeyer–Peppas model, indicating a non-Fickian, diffusion-dominated release mechanism (Costa & Sousa Lobo, 2001). This layered control (nanosponge reservoir within a gel matrix) is consistent with the reservoir-type behaviour reported for other nanosponge-gel systems, in which the nanocarrier itself acts as the primary release-limiting compartment while the surrounding gel adds an additional diffusional barrier.

Ex vivo permeation and skin distribution data are arguably the most therapeutically relevant findings of this study. Both drugs accumulated preferentially in the stratum corneum, with markedly lower amounts reaching the epidermis/dermis and only a small fraction (4–5%) reaching the receptor fluid used as a

surrogate for systemic absorption. For a topical antifungal such as voriconazole, this distribution pattern is desirable: it concentrates the drug at and near the primary site of most dermatophyte and yeast infections while limiting the systemic exposure responsible for voriconazole's characteristic adverse-effect profile (Johnson & Kauffman, 2003). For resveratrol, stratum corneum and upper-epidermal accumulation is likewise consistent with its proposed role as a local antioxidant/anti-inflammatory support, rather than as a systemically absorbed agent (Szulc-Musioł & Sarecka-Hujar, 2021). The permeability coefficients obtained here are broadly consistent with values reported for other topically active drug-loaded systems evaluated using Franz-cell methodology (Kumar et al., 2024), supporting the internal validity of the ex vivo protocol used.

4.1 Limitations

Several limitations should be considered when interpreting these findings. First, all data derive from a single laboratory-scale synthesis and a single set of ex vivo experiments; inter-batch and inter-donor variability were not systematically assessed, and results should be treated as illustrative rather than definitive until replicated. Second, formaldehyde was used as the cross-linking agent; while unreacted formaldehyde was not detected by FTIR and washing steps were included to remove residual reagent, formaldehyde's known toxicity profile means that residual-monomer testing and, ideally, substitution with a non-toxic cross-linker (e.g., citric acid or carbonyldiimidazole-based chemistries commonly used in more recent nanosponge literature) would be necessary before any clinical translation. Third, ex vivo Franz-cell permeation, while a standard and informative surrogate, cannot fully capture the dynamic, immunologically active environment of infected or inflamed skin in vivo, nor confirm actual antifungal or antioxidant efficacy — the present study characterizes delivery, not pharmacodynamic outcome. Finally, no in vivo antifungal efficacy, antioxidant activity, or dermal irritation/sensitization data were generated in this work; such studies, together with a full stability programme under ICH-aligned conditions, represent the necessary next steps before further development.

4.2 Future Directions

Future work should prioritize (1) confirmation of in vivo antifungal efficacy against relevant dermatophyte and *Candida* models, (2) formal dermal irritation and sensitization testing, (3) replacement or reduction of formaldehyde cross-linker with a safer alternative, (4) extended real-time stability studies under ICH Q1A conditions, and (5) a head-to-head comparison against marketed topical antifungal and antioxidant products to establish comparative performance.

V. CONCLUSION

Ethyl cellulose nanosponges cross-linked with β -cyclodextrin derivatives were successfully synthesized and co-loaded with resveratrol and voriconazole, achieving encapsulation efficiencies of 78–89%, a substantial reduction in drug crystallinity, and negative zeta potentials consistent with good colloidal stability. Incorporation of the optimized nanosponge batch (NS6) into an ethyl cellulose gel (formulation G6) yielded a pseudoplastic, spreadable, physically and chemically stable topical product that sustained drug release over 24 hours and, in ex vivo human skin studies, preferentially localized both drugs within the stratum corneum while minimizing permeation into the systemic (receptor fluid) compartment. These findings support the mechanistic rationale for using nanosponge-gel platforms to deliver a combined antifungal–antioxidant regimen locally to the skin, while underscoring that in vivo efficacy, safety, and long-term stability studies remain necessary before this formulation could be considered for further pharmaceutical development.

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