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Review Article

Design, Optimization, and In-Vitro Evaluation of Ethyl Cellulose Nanosponge Gel for Enhanced Cutaneous Delivery of Itraconazole

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A B S T R A C T

Itraconazole (ITZ) is a potent BCS Class II triazole antifungal agent characterised by exceptionally low aqueous solubility, which limits its topical bioavailability and therapeutic efficacy. The present study aimed to design, optimise, and evaluate ethyl cellulose-based nanosponge hydrogels of itraconazole prepared via the emulsion solvent diffusion technique for enhanced controlled cutaneous release. Ten formulations (F1–F10) were prepared by varying drug-to-polymer and surfactant ratios. Particle size and polydispersity index (PDI) analysis revealed nanometric dimensions ranging from 205.6 nm to 882.7 nm. Scanning Electron Microscopy (SEM) confirmed the porous, spherical, and spongy morphology of the synthesised nanosponges. Formulation F6 exhibited the highest drug entrapment efficiency (70.6%) with an optimal particle size of 205.6 nm and PDI of 0.585. The optimised nanosponges were successfully incorporated into a Carbopol 934 hydrogel matrix containing permeation enhancers. In vitro release kinetics followed a zero-order transport mechanism with a high correlation coefficient (R^2 = 0.9958), fitting best into the Korsmeyer-Peppas model (n = 1.1581, indicating a Super Case II transport mechanism), achieving up to 88.6% cumulative drug release. The developed nanosponge gel system presents a promising platform for enhancing the solubility, stability, and controlled topical release of Itraconazole.

Keywords: Itraconazole, Nanosponges, Ethyl Cellulose, Polyvinyl Alcohol, Emulsion Solvent Diffusion, Topical Hydrogel, Drug Delivery

Introduction

Nanosponges are novel spherical colloidal drug delivery platforms consisting of tiny mesh like porous structures capable of encapsulating a wide range of active pharmaceutical ingredients (APIs). Their unique structural topology features hydrophobic internal cavities and hydrophilic external branching, enabling the simultaneous loading of both lipophilic and hydrophilic molecules.[1-3] Synthesised by cross-linking polymers (such as cyclodextrins, ethyl cellulose, or polystyrenes) with multi-functional reagents, nanosponges form three-dimensional scaffold networks that dramatically enhance the solubilisation capacity of poorly water-soluble drugs.[4-7] Compared to conventional nanoparticles, nanosponges offer superior drug loading efficiency; prolonged drug release profiles; enhanced stability across wide pH (1–11) and temperature ranges (up to 130°C); and reduced local skin irritation.[8-12] For topical drug delivery, nanosponges act as reservoir systems that steadily release the active

agent into the stratum corneum, avoiding peak-valley concentration fluctuations and systemic toxicity.[13-17] Itraconazole (ITZ) is a broad-spectrum triazole antifungal agent widely indicated for cutaneous and systemic fungal infections.[18] It acts primarily by inhibiting fungal cytochrome P-450-dependent 14-α-demethylase, thereby blocking the conversion of lanosterol to ergosterol and destroying fungal cell membrane integrity.[19] However, ITZ belongs to Biopharmaceutics Classification System (BCS) Class II, possessing extreme lipophilicity and poor aqueous solubility (<10 µg/mL), which hampers its dissolution rate and skin permeation.[20] Incorporating ITZ into a porous polymeric nanosponge hydrogel system provides an ideal strategy to bypass solubility limitations, enhance cutaneous retention, and prolong antifungal activity.

Materials and Methodology

Materials

Itraconazole (pure API) was generously provided by Dr Reddy's Laboratories Ltd. Ethyl Cellulose (EC) was procured from S. D. Fine Chemicals Ltd, Mumbai. Polyvinyl alcohol (PVA) and dichloromethane (DCM) were obtained from C.D.H. Laboratories, New Delhi. Carbopol 934, propylene glycol, and triethanolamine were of analytical grade.

Preformulation and Analytical Methods

Organoleptic Characterisation & Melting Point: Physical characteristics (colour, odour, state) were evaluated visually. The melting point of ITZ was determined using the capillary fusion method. UV Spectrophotometric Analysis: A standard stock solution of ITZ was prepared in phosphate buffer (pH 7.4). Absorbance was measured at λmax = 230 nm using a UV-Visible spectrophotometer (Shimadzu UV-1700E). A linear calibration curve was constructed in the

Concentration range of 1-5 µg/mL ($R^2 \approx 0.999$). Drug-Excipient Compatibility: Fourier Transform Infrared (FTIR) spectroscopy (KBr pellet method) was performed to rule out chemical interactions between ITZ, ethyl cellulose, and PVA.

Formulation of Itraconazole-Loaded Nanosponges

Nanosponges were fabricated using the emulsion solvent diffusion method. The dispersed phase was prepared by dissolving a specified amount of itraconazole (0.5 g) and ethyl cellulose (0.5 g to 5.0 g) in 20 mL of dichloromethane. The aqueous continuous phase was prepared by dissolving polyvinyl alcohol (0.5% to 3.0% w/v) in 50 mL of purified water under mild warming. The organic phase was added dropwise into the aqueous phase under continuous high-speed magnetic stirring at 1000 rpm for 3 hours. Upon diffusion of DCM, polymeric micro/nano-droplets solidified into discrete porous nanosponges. The resulting nanosponges were filtered (Whatman filter paper), washed with distilled water, dried at 40°C for 24 hours, and stored in a vacuum desiccator.

Table 1.Composition of Itraconazole Nanosponge Batches (F1 – F10)

Batch	ITZ (g)	Ethyl Cellulose (g)	PVA (% w/v)	DCM (mL)	Purified Water (mL)
F1	0.5	3.0	2.0	20	50
F2	0.5	2.0	1.0	20	50
F3	0.5	3.0	3.0	20	50
F4	0.5	0.5	1.0	20	50
F5	0.5	1.0	0.5	20	50
F6	0.5	1.0	1.0	20	50
F7	0.5	1.0	2.0	20	50
F8	0.5	1.0	3.0	20	50
F9	0.5	2.0	2.0	20	50
F10	0.5	5.0	3.0	20	50

Preparation of Nanosponge-Loaded Hydrogel

Carbopol 934 (100 mg) was soaked in distilled water for 2–3 hours and homogenised at 600 rpm. Triethanolamine was added dropwise to adjust the pH to skin-compatible neutral conditions (6.8–7.0). Optimised ITZ nanosponges corresponding to 1% w/w drug concentration were incorporated along with propylene glycol (permeation enhancer) to form a smooth, homogenous hydrogel.

Characterisation and Evaluation

Particle Size & Polydispersity Index (PDI): Measured via Dynamic Light Scattering (DLS) using a Malvern Zetasizer (version 7.03) at 25°C. Scanning Electron Microscopy (SEM): Surface topography and internal porous morphology were examined using SEM at an accelerating voltage of 15 kV following gold-palladium sputter coating. Entrapment Efficiency (% (EE): Nanosponges (50 mg) were

dissolved in methanol, ultracentrifuged for 40 minutes, and the unentrapped drug in the supernatant was analysed at 259 nm.

Entrapment Efficiency (% (EE) = [(Total Drug − Free Drug) / Total Drug] × 100 In-Vitro Drug Release & Kinetics: Evaluation was conducted across a modified Franz diffusion cell using a synthetic cellophane membrane in phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C and stirred at 600 rpm. Aliquots were withdrawn over 10 hours and analysed spectrophotometrically at 259 nm. Data were fitted into zero-order, first-order, Higuchi, and Korsmeyer-Peppas mathematical models using BIT-SOFT software.

Results and Discussion

Preformulation Properties

Pure itraconazole was obtained as a white, crystalline, odourless powder with a melting point of 116–118°C. Solubility testing confirmed high solubility in ethanol/chloroform and poor solubility in water (<0.01 mg/mL). FTIR spectra showed characteristic absorption bands matching standard IP spectrums without any evidence of drug-polymer incompatibility.

Particle Size, PDI, and Entrapment Efficiency

As presented in Table 2, particle size ranged from 205.6 nm (F6) to 882.7 nm (F2). Polydispersity index values ranged between 0.403 and 0.777, indicating uniform size distribution. Increasing polymer concentration yielded slightly larger particle sizes due to higher organic phase viscosity during emulsification. Entrapment efficiency ranged from 25.9% to 70.6%. Formulation F6 (drug:polymer ratio 1:2 with 1% PVA) demonstrated superior drug loading (70.6%) and the smallest particle.

Surface Morphology (SEM)

Scanning electron microscopy images revealed that the fabricated nanosponges were highly spherical and non-aggregated and possessed a highly porous matrix surface. The micro-cavities within the polymer backbone confirmed successful sponge-like network formation essential for drug entrapping.

In-Vitro Drug Release and Release Kinetics

In vitro drug release profiles across 10 hours for formulations F1–F10 are summarised in Table 3. Formulations demonstrated controlled drug diffusion over time without initial burst effects. Formulation F10 achieved maximum release (88.6% at 10 h), while optimised batch F6 achieved 74.9% release.

Kinetic modelling of release data indicated that the release mechanisms followed zero-order kinetics over first-order or Higuchi models. Application of the Korsmeyer-Peppas equation yielded a correlation coefficient (R^2) of 0.9958 and a release exponent (n) value of 1.1581. An exponent n > 1.0 indicates a Super Case II transport mechanism, wherein drug release is governed by combined polymer relaxation, erosion, and matrix swelling.

Table 2.Particle Size, Polydispersity Index, and Drug Content (% EE) of Batches

Formulation Code	Particle Size (nm)	Polydispersity Index (PDI)	Drug Content (% EE)
F1	579.8	0.682	38.5%
F2	882.7	0.777	25.9%
F3	306.1	0.487	43.8%
F4	363.2	0.599	55.2%
F5	269.2	0.403	51.8%
F6 (Optimized)	205.6	0.585	70.6%
F7	-	-	60.4%
F8	-	-	58.9%
F9	-	-	65.7%
F10	-	-	69.3%

Table 3.Cumulative In Vitro Drug Release (%) of Itraconazole Nanosponge Formulations

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	8.1	1.7	2.8	0.9	0.8	0.4	1.3	9.0	2.7	3.6
2	17.1	8.1	11.6	11.3	9.0	11.6	13.8	12.7	11.4	13.0
4	29.8	15.3	21.6	32.3	23.4	24.3	24.0	26.2	30.7	32.3
6	34.4	19.8	34.4	42.3	36.8	42.7	33.5	44.4	51.7	51.8

8	45.4	36.8	53.6	51.5	45.2	50.2	40.4	56.2	61.3	60.6
10	65.6	70.4	69.8	79.6	83.1	74.9	69.6	80.4	70.0	88.6

Conclusion

In this study, itraconazole-loaded polymeric nanosponges were successfully formulated via the emulsion solvent diffusion technique using ethyl cellulose and PVA. Formulation F6 exhibited optimum nanosize (205.6 nm) and maximum drug entrapment efficiency (70.6%). Incorporation of nanosponges into Carbopol 934 hydrogel provided controlled release following zero-order kinetics and Super Case II transport mechanisms up to 10 hours. Overall, the developed nanosponge hydrogel represents a highly suitable and clinically viable carrier for the topical delivery of poorly water-soluble antifungal drugs like itraconazole.

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