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FORMULATION AND EVALUATION OF ITRACONAZOLE LOADED NANOSPONGES

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ABSTRACT

Nanosponges are a novel class of hyper cross-linked polymer-based colloidal structures made of sub-microscopic particles with cavities a few nanometers wide.[1,6,11] This study aimed to formulate and evaluate itraconazole-loaded nanosponges and systemic fungal infections.[2] Nanosponges were prepared using the emulsion solvent diffusion method, incorporating different ratios of polymer and cross-linker.[1,5,12] Particle size, entrapment efficiency, drug loading, and in vitro drug release were all evaluated for the resultant nanosponges. Nanosponges are effective drug carriers for compounds with low solubility and high permeability.[11] Hydrogels, being three-dimensional porous structures, are commonly used in drug delivery systems. Recent advances have resolved many pharmacological limitations of hydrogels by synthesizing them using hydrophobic polymers cross-linked with water-soluble polymers.[7,25] Nanosponges, often synthesized from carbon-containing polymers, are porous (1–2 nm pores) and can absorb and release small molecules in a controlled manner.[10,17] These findings suggest that itraconazole-loaded nanosponges are a promising approach for enhancing the delivery and therapeutic efficacy of itraconazole.[12,21]

KEYWORDS: Nanosponges, Hydrogel, Antifungal activity, Drug deilivery system.

INTRODUCTION

The term nanosponge refers to a new class of nanoparticulate drug delivery systems characterized by their unique porous, sponge-like structure. These sub-micron particles, typically ranging in size from 200 to 500 nm, are composed of biodegradable polymers that

form a network of cavities capable of encapsulating various types of therapeutic agents.[1,6] Nanosponges possess a highly porous architecture with tunable pore sizes, often between 1 and 2 nanometers, making them particularly advantageous for the controlled release and solubility enhancement of drugs with poor aqueous solubility.[10,17] The concept of nanosponges emerged in the 1990s, initially as a solution to overcome the limitations associated with native cyclodextrins, particularly their inability to encapsulate large or charged molecules effectively due to their low water solubility and limited complexation capacity.[7] Since then, nanosponges have evolved into versatile carriers for both hydrophilic and lipophilic drugs, offering benefits such as enhanced stability, improved bioavailability, site-specific delivery, and sustained drug release.[11,16] Their surface can also be functionalized for targeted therapy, thus expanding their applications in pharmaceutical, cosmetic, and diagnostic fields. Itraconazole, a synthetic triazole antifungal agent, has demonstrated broad-spectrum activity against various fungal pathogens, including *Candida*, *Aspergillus*, and *Dermatophytes*. It acts by inhibiting lanosterol 14α-demethylase, a cytochrome P450 enzyme critical for ergosterol synthesis, which is essential for fungal cell membrane integrity.[2,3] Despite its clinical efficacy, itraconazole suffers from low water solubility and erratic bioavailability, especially when administered via conventional dosage forms.[2,12] These limitations often result in suboptimal therapeutic levels, frequent dosing, and potential systemic side effects. To address these challenges, nanosponge-based delivery systems offer a promising approach. By encapsulating itraconazole within the porous matrix of nanosponges, it is possible to enhance the drug's solubility, stability, and retention time at the site of action.[12,13] Moreover, incorporating these nanosponges into a topical hydrogel facilitates localized therapy, minimizes systemic exposure, and improves patient compliance.[21,25]

Topical drug delivery via hydrogel systems provides several advantages, including ease of application, non-invasiveness, and controlled drug release. Hydrogels are three-dimensional, hydrophilic polymer networks capable of holding large amounts of water while maintaining their structure. When combined with nanosponges, these systems can effectively deliver poorly water-soluble drugs like itraconazole in a sustained manner.[6,25] The present study focuses on the formulation and characterization of itraconazole-loaded nanosponges using the emulsion solvent diffusion method. These nanosponges were further incorporated into a hydrogel for topical application. The aim was to improve the solubility, stability, and antifungal efficacy of itraconazole while offering a sustained release profile. Key evaluations

included drug-excipient compatibility, drug loading, particle size, spreadability, in vitro drug release, and antifungal activity against *Candida albicans*. Through this work, we aim to demonstrate that nanosponge-based topical systems could serve as an effective alternative for treating superficial fungal infections, thereby overcoming the pharmacokinetic and therapeutic limitations associated with conventional formulations of itraconazole.

OBJECTIVES

- To formulate itraconazole-loaded nanosponges for enhancement of solubility.[12]
- To provide an efficient dosage form by formulating nanosponge-loaded gel for topical delivery.[21]
- To sustain the release of the drug through nanosponge-loaded gel.[22]

MATERIAL AND METHODS

MATERIAL

Formulation of Nanosponges was carried out using the emulsion solvent diffusion method as described in literature.[12,15,20] The aqueous phase consisted of polyvinyl alcohol, while the organic phase contained polyethylene glycol and dichloromethane with the drug. After two hours of stirring at 1000 rpm, the mixture was filtered and allowed to air dry.[12,20]

METHODOLOGY

Figure No 1: Itraconazole Drug.

Formulation table

Table No. 2: Formulation Of Nanosponges.

Name of ingredient	A	B	C	D	Role
Itraconazole	0.5 g	0.5 g	0.5 g	0.5 g	Active pharmaceutical

					ingredient
Polyethylene Glycol	0.5 g	1 g	1.5 g	2 g	polymer
Polyvinyl Alcohol	2 ml	2 ml	2 ml	2 ml	polymer
Dichloromethane	20 ml	20 ml	20 ml	20 ml	Organic solvent
Distilled water	100 ml	100 ml	100 ml	100 ml	vehicle

Formulation Table

Table No. 3:- Formulation of Nanosponges Loaded Hydrogel.

INGREDIENT	QUANTITY	ROLE
Formulated Nanosponges(D)	300 mg	Active ingredient
Carbopol	1 g	Gelling agent
Glycerine	5 ml	Moisturizing agent
Triethanolamine	q.s	neutralizer
Distilled water	100 ml	vehicle

Procedure

Formulation of Nanosponges

Nanosponges were formulated using the emulsion solvent diffusion technique. This process involved the preparation of two separate phases: an organic phase and an aqueous phase. The aqueous phase contained polyvinyl alcohol, while the organic phase included the drug and polymer, both dissolved in an appropriate organic solvent—dichloromethane. The organic phase was gradually added to the aqueous phase under continuous stirring at 1000 rpm for a duration of two hours. The resulting nanosponges were then collected through filtration and allowed to air-dry at room temperature. A total of four batches were prepared, each with varying polymer concentrations as detailed in Table 2.

Formulation of Nanosponge loaded hydrogel

To prepare the gel, the gelling agent Carbopol 940 was first soaked in water for 2 hours, then dispersed using a magnetic stirrer at 600 rpm to obtain a uniform mixture. After stirring, the dispersion was left undisturbed for 15 minutes to allow any trapped air to escape. In a separate beaker, the previously optimized nanosponge formulation (Batch D), containing Itraconazole equivalent to the required drug amount and dissolved in water, was gradually added to the Carbopol dispersion with continuous stirring. The gel was then formed by slowly adding a triethanolamine solution while stirring, which neutralized the mixture and initiated gel formation. The detailed composition of the nanosponge gel is provided in Table 3.

Evaluation parameters

Preformulation Studies

Drug-Exciepients Compatibility Study

The drug and excipients selected for the formulation were evaluated for physical and chemical compatibility studies.

Determination Of Melting Point

A capillary tube with a small quantity of medication was placed in a melting point apparatus, with one end of the tube sealed, and the temperature was recorded when drug melts.

Evaluation Of Optimized Nanosponges

Fourier Tranform Infrared Spectroscopy

FTIR analysis was performed to assess the potential formation of chemical bonds between the drug and the polymer. The samples were scanned over a spectral range of 400 to 4000 cm^{-1} using a carbon black reference (Model: Nicolet iS10 Mid). To enhance signal sensitivity and minimize moisture interference, the detector was thoroughly purged with clean, dry helium gas.

Scanning Electron Microscopy

SEM is a powerful imaging technique that provides high-resolution images by scanning the surface of a sample with a focused beam of electrons. The interaction of the electrons with the atoms on the sample surface generates signals that are used to form detailed images of the surface topography and composition.

Evaluation of Nanosponges Loaded Gel

Drug content

A precisely weighed gel formulation containing 10 milligrams of itraconazole was dissolved in 10 milliliters of methanol. This solution was diluted and absorbance of solutions measured spectrophotometrically at 260nm. Drug content was calculated**.**

Percentage Yield

After the empty container containing the gel formulation was weighed, the container containing the gel formulation was weighed once more. The practical yield is then obtained by subtracting the empty container's weight from the container containing the gel formulation. Then the percentage yield was calculated.

Spread ability

When no more spreading was anticipated, a sample of 0.5 g of each formula was placed between two slides that had been separated into squares with sides of 5 mm and left for around five minutes. Diameters of spreaded circles were measured in cm and were taken as comparative for spreadability. The results obtained are average of three determinations**.**

Antifungal Activity

The prepared emulgel formulations were tested against Candida albicans using the agar cup method. A certain volume of fungal suspension (C. albicans) was poured into sterilized PDA (Potato Dextrose Agar). About 20–25 mL of this media was poured aseptically into sterile Petri dishes. A sterile cork borer was used to create wells in the agar plate once the agar had set. The prepared emulgel was poured into each well. The plates were then incubated at 35°C–37°C for 48 hours. Antifungal activity was determined by measuring the zone of inhibition around the wells, indicating the effectiveness of the formulation against Candida albicans.

RESULTS AND DISCUSSION

Drug -Excipients compatibility study

The optimization of a formulation can be done only after a trough investigation of physio chemical properties of the drug and excipients. the drug and the polymer must be compatible for a successful formulation.

Physical compatibility study

Chemical compatibility study

FTIR Of Itraconazole

The potential information regarding the drug-polymer interaction is provided by FTIR spectroscopy. Figure displays the itraconazole FTIR spectrum.

FTIR Of Nanosponges

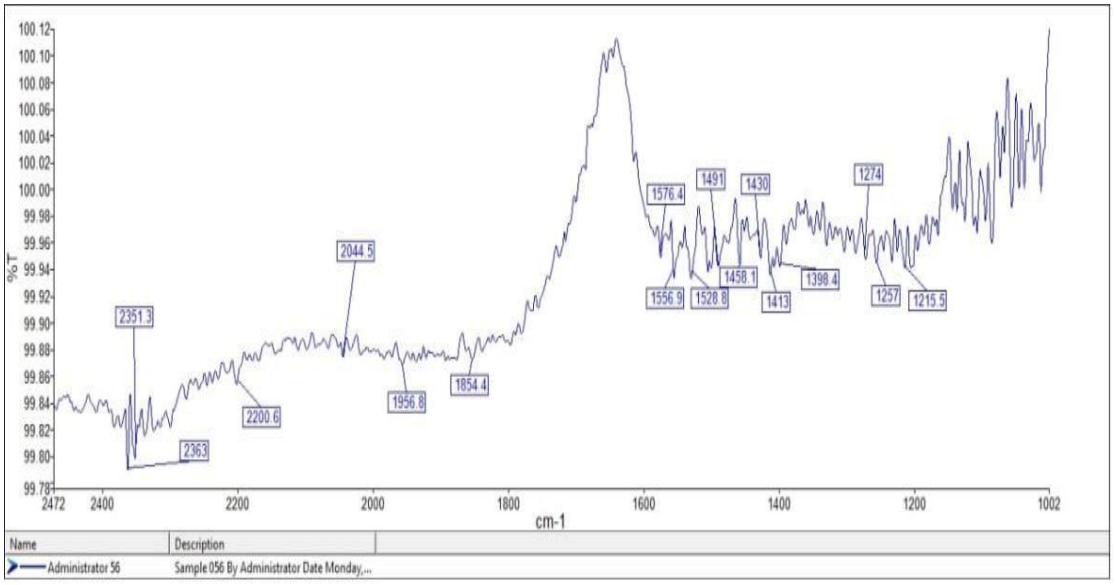

Figure No 2: FTIR Spectrum of Itraconazole.

The potential information regarding the drug-polymer interaction is provided by FTIR spectroscopy. Figure displays the itraconazole FTIR spectrum.

Table No. 4:-FTIR Spectral Interpretation of Itraconazole.

Wave number (cm)	Type of Vibration
2351.3	O-H Strteching
2200.6	C-H Strteching
1956.8	C=O Strteching
1576.4	N-O Strteching

FTIR OF NANOSPONGES

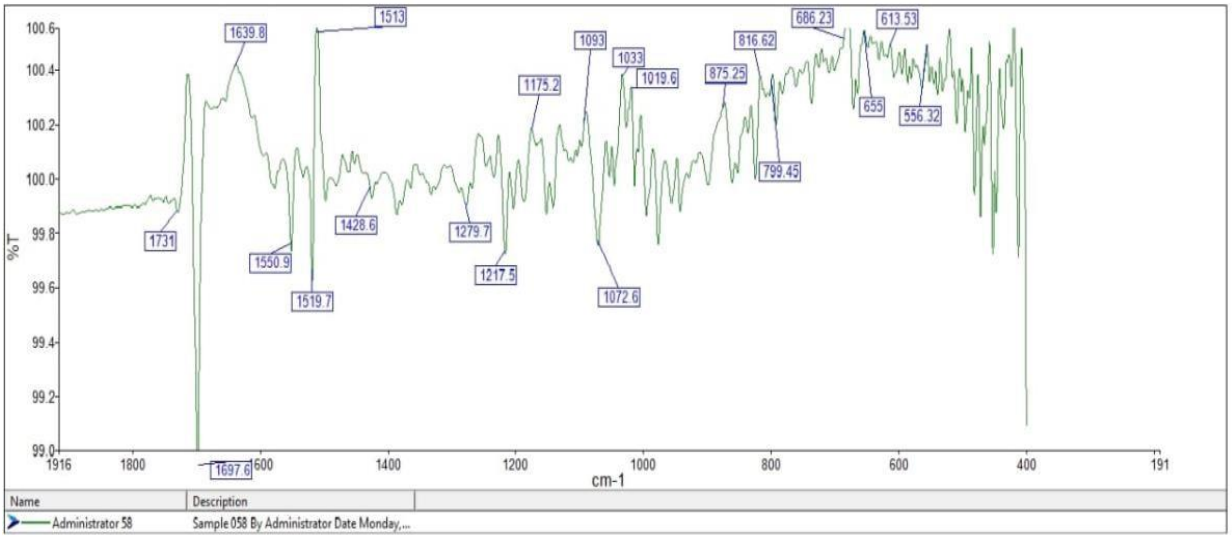

Figure No 3: FTIR Spectrum of Nanosponges.

Table 6:- FTIR Spectral Interpretation of Nanosponges.

WAVE NUMBER	TYPE OF VIBRATION
3085.88	O-H Strteching
2923.87	C-H Strteching
1743.52	C=O Strteching
3355.89	N-H Strteching

Scanning Electron Microscopy

The SEM shows two spherical particles with diameters of approximately 1.397 µm and 1.326 µm. The analysis was conducted at 15.00 kV with a magnification of 3.19x under high vacuum (1.06e-4 Pa).

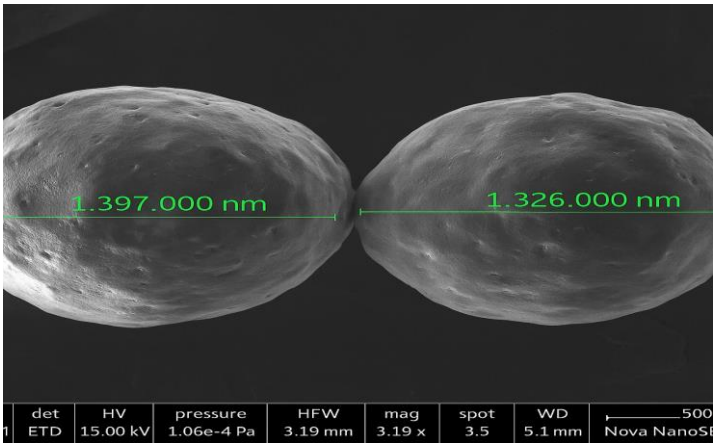

Figure No 3 Scanning Electron Microscopy.

Spreadability

The spreadability test shows a uniform spread of approximately 4.4 cm, indicating good consistency of the formulation. This suggests the sample has suitable rheological properties for topical application.

Figure No 4: Spreadability.

Antifungal Activity

The antifungal assay against *Candida albicans*, with a clear zone of inhibition around the test sample (T), indicating antifungal activity. The control (C) shows no inhibition zone, confirming the effect is due to the test compound.

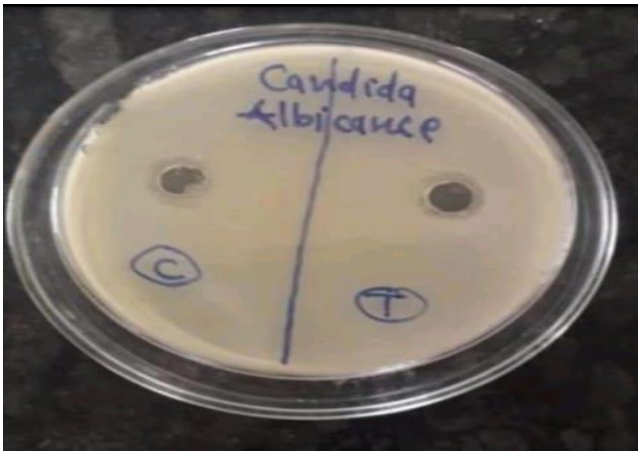

Figure No 5: Antifungal Activity.

CONCLUSION

This study demonstrated that itraconazole-loaded nanosponges can significantly improve drug solubility and allow for controlled release when incorporated into a topical gel formulation.[12,21,22] The results indicate promising antifungal efficacy with enhanced drug delivery performance. Future studies should explore in vivo evaluations and toxicity profiling.[22,23] This nanosponge delivery system shows significant potential for sustained drug release, making it a promising option for treating fungal infections (mycosis). Furthermore, advantages such as lower dosage requirements, reduced dosing frequency, enhanced bioavailability, and improved drug stability may be achieved. Future investigations should focus on establishing in-vitro/in-vivo correlation and conducting toxicity evaluations of the topical hydrogel formulation.

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