# Nanosponge Gel: A Promising Carrier for Enhanced Topical Delivery of Miconazole Nitrate

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**Abstract:** Miconazole nitrate (MN) nanosponges were prepared using the emulsion solvent diffusion method with ethyl cellulose as the polymer and polyvinyl alcohol as stabilizer. Preformulation studies confirmed the linearity in calibration curve (2–10 µg/ml, λ max 272 nm), and melting point (175–185°C). The nanosponges were formulated using Central Composite Design and the independent factor were ethyl cellulose and dichloromethane. Evaluated parameters include particle sizes of 263–991 nm, zeta potential -7.9 to -31.9 mV, entrapment efficiency 73.2–91.8%, in-vitro drug release 63.1–84.6% at 6 h, and yield 48.5–69%. The optimized formulation was subjected to SEM, and incorporated into a gel and evaluated for pH, suitable viscosity, spreadability, uniform drug content, and stability.
In-vitro diffusion study of gel showed 97.14% drug release over 13 hours, comparable to marketed cream (99.65%). Antifungal studies against *Aspergillus Niger* indicated effective activity, with nanosponges enhancing local penetration and sustained release. The formulation offers prolonged antifungal action, reduces dosing frequency, improves patient compliance, and provides a safe, convenient topical therapy. Overall, MN-N-Gel is a promising carrier for controlled topical delivery of Miconazole nitrate.

**Keywords:** Nanosponge: miconazole nitrate, ethyl cellulose, dichloromethane, polyvinyl alcohol, glutaraldehyde, dimethylsulphoxide.

## Introduction

Nanosponges are minuscule mesh-like formations that can encapsulate a wide range of substances. They are known for their spherical colloidal characteristics and have been shown to possess a significantly high capacity for solubilizing poorly soluble drugs through both their inclusion and non-inclusion behaviors[1]

Nanosponges consist of tiny particles featuring cavities that are only a few nanometres wide, allowing for the encapsulation of a diverse range of substances. These particles are capable of transporting both lipophilic and hydrophilic compounds, thus enhancing the solubility of molecules that are poorly soluble in water. Research in this area indicates that these minuscule mesh-like structures, known as nanosponges, have the potential to transform the treatment of various diseases.[2]

Fungal skin infections are among the more challenging dermatological conditions to treat. Topical therapy is considered a promising approach as it minimizes systemic side effects while directly targeting the affected area. Many antifungal drugs fall under the Biopharmaceutics Classification System Class II, characterized by low solubility and limited bioavailability. Incorporating them into nanosponge drug delivery system has been shown to enhance their solubility and improve bioavailability, making treatment more effective.[3]

## Materials and methods

**Materials:** Miconazole nitrate(Yarrow chem, Mumbai), Ethyl cellulose (SD fine chemicals, Mumbai), Polyvinyl alcohol (Essel fine chem, Mumbai), Dichloromethane(Karnataka Fine Chem, Bangaluru), Ethanol (Karnataka Chemicals), Carbopol 934(Central Drug House (P) Ltd. New Delhi), Triethanolamine(T.V Industrial estate, Mumbai), Propylene glycol(Nice chemicals (P) Ltd, Mumbai), Sodium hydroxide (SD fine chemicals, Mumbai) and Potassium dihydrogen ortho phosphate (SD fine chemicals, Mumbai).

## Methods

**Pre-formulation studies:** Preformulation testing is the initial stage in developing a drug dosage form. It involves studying the physical and chemical properties of the drug alone and in combination with excipients. The main aim is to obtain data that assist in designing a stable and easily scalable formulation.

**Identification of pure drug:**

Miconazole nitrate was identified using FT-IR spectrophotometry. The drug was mixed with IR-grade KBr (1:10 ratio) and compressed under 10-ton pressure to form a transparent pellet, which was scanned in the 4000–400 $cm^{-1}$ range.

**Determination of melting point:**

The melting point of Miconazole nitrate, an indicator of drug purity, was determined by the capillary method. The powdered sample was placed in a sealed capillary tube attached to a thermometer and heated in liquid paraffin until melting was observed. (n=3)[4]

**Calibration curve of Miconazole nitrate:**

**Determination of wavelength of maximum absorption (λ max):**

A 10µg/ml solution of Miconazole nitrate in 30% ethanol and pH 5.8 phosphate buffer solution was scanned for λ max.

**Preparation of Miconazole nitrate calibration curve:**

**Stock-1 solution:**

25mg of Miconazole nitrate drug was weighed accurately and dissolved in 5 ml of methanol in a 25ml volumetric flask. Then the volume was made up to 25 ml using methanol and shaken well to get a 1000 µg/ml solution.

**Stock-2 solution:**

From the primary stock solution, 1 mL was transferred into a 10 mL volumetric flask and diluted to volume with a phosphate buffer (pH 5.8) and 30% ethanol mixture to obtain a 100 µg/mL secondary stock solution. Aliquots of 0.2, 0.4, 0.6, 0.8, and 1 mL of this solution were each diluted to 10 mL with the same buffer mixture to prepare concentrations of 2, 4, 6, 8, and 10 µg/mL, respectively. The absorbance of each solution was recorded at 272 nm using a UV-Visible spectrophotometer. The procedure was repeated three times (n=3), and a standard calibration curve was plotted with concentration on the X-axis and mean absorbance on the Y-axis.

## FORMULATION STUDIES

**Preparation of Miconazole Nitrate Loaded Nanosponge**

Miconazole nitrate nanosponges were formulated using the emulsion solvent diffusion method, which involves both organic and aqueous phases. In the organic phase, the drug was dissolved in ethanol, and the polymer was dissolved in dichloromethane both the solution was mixed. The aqueous phase was prepared by dissolving polyvinyl alcohol in water. The organic phase was then added gradually to the aqueous phase under magnetic stirring. The mixture was stirred at 1000 rpm for 2 hours, after which the product was filtered and dried in an oven at 40°C for 24 hours.[5]

Statistical optimization was performed using Design Expert software (v13.0.5.0) with a Central Composite Design (CCD) under Response Surface Methodology (RSM). Ethyl Cellulose (X1) and Dichloromethane (X2) were chosen as independent variables at three levels (low, medium, high) based on preliminary studies. The dependent variables—particle size (Y1), entrapment efficiency (Y2), drug release at 6 h (Y3), and yield (Y4)—were analysed to evaluate the optimized nanosponge formulations.

**Table No 1: Formulations of Miconazole nitrate Nanosponges Prepared by Emulsion solvent diffusion Method.**

| Formulation code | Ingredients | | | | | |
|---|---|---|---|---|---|---|
| | Drug (mg) | EC (mg) | DCM (ml) | PVA (mg) | Ethanol (ml) | Water (ml) |
| F1 | 100 | 100 | 10 | 300 | 15 | 75 |
| F2 | 100 | 200 | 10 | 300 | 15 | 75 |
| F3 | 100 | 300 | 10 | 300 | 15 | 75 |
| F4 | 100 | 100 | 20 | 300 | 15 | 75 |
| F5 | 100 | 200 | 20 | 300 | 15 | 75 |
| F6 | 100 | 300 | 20 | 300 | 15 | 75 |
| F7 | 100 | 100 | 30 | 300 | 15 | 75 |
| F8 | 100 | 200 | 30 | 300 | 15 | 75 |
| F9 | 100 | 300 | 30 | 300 | 15 | 75 |

Formulation of MN nanosponges were conducted using the emulsion solvent diffusion method. Nine formulations were prepared by varying the concentration of EC and DCM. For EC, the lowest concentration is 100mg, while the highest concentration is 300 mg. For DCM, the lowest volume is 10 ml and the highest volume is 30ml. Drug, PVA, Ethanol and water were kept constant.

**Table No.2: Test Factors for Optimization of Process Parameters**

| Factors | name | Units | Low (level-1) | Medium (level0) | High (level+1) |
|---|---|---|---|---|---|
| A(X1) | Ethyl cellulose | mg | 100 | 200 | 300 |
| B(X2) | DCM | ml | 10 | 20 | 30 |

**Evaluation of Nanosponges**

**Particle size :**

The particle size of the prepared nanosponges was measured by a dynamic light scattering particle size analyzer. The 1 ml of prepared formulation was diluted with 10mL of distilled water and sonicated for 10 minutes with an ultra-sound probe before measurement and analyzed in the particle size analyzer. Horiba scientific china.(n=3)[6]

**Zeta potential:**

The surface charge of nanosponges was measured using a Horiba Scientific SZ-100 zeta sizer to assess stability. 1 mL of nanosponge dispersion was diluted in 10 mL of double-distilled water, sonicated for 15 minutes, and tested in an electrode-equipped cuvette.[7]

**Entrapment efficiency:**

Entrapment efficiency of the nanosponges was determined by the indirect centrifugation method. Two milliliters of nanosponge dispersion were centrifuged at 15,000 rpm for 30 minutes, and the drug content in the supernatant was measured at 272 nm using a UV-Visible spectrophotometer. Entrapment efficiency (%) was calculated using the standard formula (n = 3). [8]

$$EE\% = (\text{Total drug} - \text{Free drug}) \div \text{Total drug} \times 100$$

**Drug content:**

Miconazole nitrate content in nanosponges was measured by UV spectrophotometry. Nanosponges equivalent to 10 mg of drug were dissolved in 10 mL of ethanol, diluted with 30% ethanol and pH 5.8 phosphate buffer, and absorbance was measured at 272 nm to calculate drug content.

***In vitro* drug release study:**

In vitro drug release of nanosponges was performed using a USP Type-I (basket) dissolution apparatus with 200ml of 7:3 phosphate buffer (pH 5.8) and ethanol medium. The dissolution media was added in 200ml of beaker which was placed in dissolution jar. Nanosponges equivalent to 100 mg of drug were placed in a 5 µm stainless-steel basket, rotated at 50 rpm, and maintained at 37 ± 0.5 °C. Samples (5 ml) were withdrawn at intervals, replaced with fresh medium, and analyzed at 272 nm using a UV spectrophotometer. The %CDR was calculated, and tests were conducted in triplicate (n = 3)[9–11].

**Percentage yield:**

The percentage yield of the nanosponges was determined by accurately calculating the initial weight of the raw materials and the final weight of the nanosponges obtained. [12]

Percentage yield= (Practical mass of nanosponges / Theoretical mass) ×100

**Numerical optimization:**

Based on the criteria like, minimized particle size, maximized entrapment efficiency, and enhanced yield and drug release, the best formulation is selected by using Design Expert Software version 13. The recommended best formulation is further subjected to the surface morphology studies(SEM) and the same incorporated into gel.

**Surface morphology studies:**

SEM analysis was done on the optimized nanosponges exterior morphology. The powders were imaged by a scanning electron microscope (SEM) run at an accelerating voltage of 10 kV using ZEISS EVO 18 SEM. The powder in a few µg was fixed onto the stub by a double-sided sticky carbon tape and subjected to sputter coating then kept inside the SEM chamber and analysed at different magnifications to obtain better clarity on the particle morphology/topology.

**PREPARATION OF MICONAZOLE NITRATE TOPICAL GEL**

In this, gel-forming Carbopol 934 was soaked overnight in a sufficient quantity of water to get good dispersion. After 24 hours soaking, Polyethylene glycol, which acts as a penetration enhancer and methylparaben, which acts as a preservative, were added. All this is kept on the magnetic stirrer to get good dispersion using magnetic agitation. To the above, triethanolamine was added drop by drop to adjust the pH of the formulation, and to this, nanosponges equivalent to 2% drug was added.[13]

**Table No 3: Formulation of miconazole nitrate topical gel.**

| sl.no | Ingredients (%) | Gel A | Gel B | Gel C |
|---|---|---|---|---|
| 1 | Carbopol 934 | 0.25 | 0.5 | 0.75 |
| 2 | Purified water | 25±5 | 25±5 | 25±5 |
| 3 | Methyl Paraben | 0.02 | 0.02 | 0.02 |
| 4 | 2% drug equivalent of nanosponges containing Miconazole nitrate | 500 mg | 500 mg | 500 mg |
| 5 | Gel texture | Low viscous gel | Soft gel with good texture | Hard gel |

**Evaluation of Nanosponge Topical Gel:**

**Physical Appearance**: The prepared gel was examined for clarity, color, homogeneity and presence of foreign particles.

**pH:** The pH of dispersion was measured using a digital pH meter.[14]

**Rheological Study by Viscosity Measurement: Viscosity** was determined by a Brookfield programmable DV-E viscometer. In the present study, we selected spindle no. cP 63 with an optimum speed of 10 rpm was used to measure the viscosity of the preparation.

**Spreadability:** Spreadability was measured by the parallel-plate method, a simple and economical technique. One gram of the sample (prepared 48 h prior) was placed between two glass plates, and a 100 g weight was applied for 1 minute. The resulting diameter was measured to determine spreadability. In these cases, spreadability is determined by the formula:

$A=\boldsymbol{\pi r 2}$ Or Si = $(\mathbf{d\ 2} \times \boldsymbol{\pi}\ /\mathbf{4})$

Where,

Si- spreading area($mm^2$) depending on mass,

d- spreading area diameter(mm)

**Content Uniformity:** Drug content was determined by dissolving 1 g of gel in 10 ml of phosphate buffer (pH 5.8) with 30% ethanol, filtering through Whatman No. 41, and diluting appropriately. Absorbance was measured at 272 nm using a Shimadzu UV-Vis spectrophotometer, and drug content was calculated from the calibration curve of miconazole nitrate. Tests were performed in triplicate (n = 3).

**In-vitro Drug Diffusion Study:**

In-vitro diffusion studies were conducted using the dialysis sac method with a 2.4 nm pore membrane hign media molecular weight cut off 12,000. The diffusion of drug from the prepared nanosponge formulation was compared with commercial miconazole nitrate cream. The detail of marketed sample is as follows. The formulation equivalent to 100 mg of drug was placed in dialysis sac and immersed in a USP Type-I basket. The basket was made to rotate in a beaker containing 200ml of 7:3 ratio of phosphate buffer (pH 5.8) and ethanol. This modification will enable the basket to completely get immersed in dissolution media. The setup was maintained at 37 ± 0.5 °C with a rotation speed of 50 rpm. Samples (5 ml) were withdrawn at intervals, replaced with fresh medium, and analyzed at 272 nm using a UV spectrophotometer to calculate %CDR (n = 3).[15]
Marketed product information:

| | |
|---|---|
| Generic name | Miconazole Nitrate Cream IP 2% w/w |
| Brand name | Micogel |
| Net wt | 15g |
| Mfg date | Sep 23 |
| Exp date | Aug 26 |
| Mfg by | Cipla pvt ltd |

**Drug Release Kinetic Data Analysis:**

Drug release kinetics were analyzed using four common models: Zero-order (cumulative % drug released vs. time), First-order (log % drug remaining vs. time), Higuchi (cumulative % drug released vs. √time), and Korsmeyer-Peppas (log cumulative % drug released vs. log time) to evaluate release rate and mechanism.[16,17]

**Antifungal activity:**

The antifungal activity against *Aspergillus Niger* was assessed by comparing MCN-N-gel, marketed MCN cream, pure drug solution, and a DMSO control. Potato dextrose agar (19.5 g in 500 ml water) was sterilized, poured into Petri dishes, and allowed to solidify, after which the test organism was spread on the surface. Wells were created, and the samples were added. The plates were incubated at 37 °C for 48 hours, and the zones of inhibition were measured in millimetres.

**Stability study:** The stability of MN-N-Gel was evaluated by storing the formulation in a glass container at room temperature for one month. Changes in pH, drug content, and drug release were monitored after 15 and 30 days of storage.

## RESULTS AND DISCUSSION

The drug was identified using various methods, including the melting point method, UV spectroscopy, and FTIR spectroscopy. All parameters were found to be within acceptable limits and complied with the requirements of the official compendia.

### Pre-formulation Studies:

Pre-formulation studies represent the initial step in drug dosage form development, involving the investigation of the physical and chemical properties of the drug alone and in combination with excipients. The primary objective is to provide essential information for developing stable, bioavailable, and scalable formulations.

### Identification of the Pure Drug:

The IR spectrum of the pure drug was found to be consistent with the standard spectrum of miconazole nitrate. The spectrum of miconazole nitrate exhibited the functional groups corresponding to the reference peaks, as shown in Figure 1.

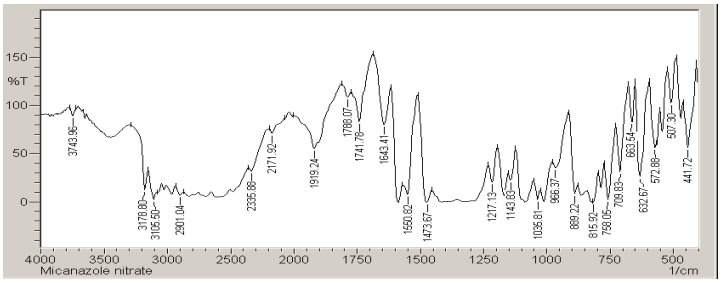


**Figure No 1: IR Spectrum of Miconazole Nitrate**

### Determination of Melting Point:

The melting point of drug sample was found to be $175^0$C. this was lying within the reported range of 175-$185^0$C. It is indicating the purity of the drug.[4]

### Calibration curve of miconazole nitrate:

**Determination of wavelength of maximum absorption (λ max):** Standard solution of miconazole nitrate was scanned in UV spectrometer with wavelength range of 200-400nm. The absorption maxima were found to be 272nm.

**Preparation of Miconazole nitrate calibration curve:** Miconazole nitrate showed linearity in the range of 2-10µg/ml and the absorbance are shown in figure no.

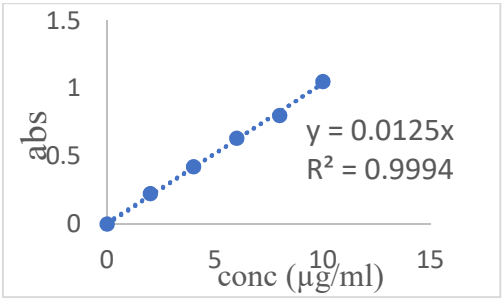


**Figure No 2: Calibration Curve of miconazole nitrate in pH 5.8 phosphate buffer**

## FORMULATION STUDIES

### Preparation of Miconazole Nitrate-Loaded Nanosponges

Miconazole nitrate-loaded nanosponges were formulated using the emulsion solvent diffusion method. Dichloromethane (DCM) and ethyl cellulose (EC) were selected as independent variables in the design of experiments (DOE) due to their significant impact on particle size and entrapment efficiency. A Central Composite Design (CCD), implemented under Response Surface Methodology (RSM), was employed to optimize these formulation variables and obtain nanosponges with desirable physicochemical and drug delivery characteristics. The optimized formulations were subsequently evaluated based on critical quality attributes.

### Design of Experiment

### Optimization of Nanosponge Parameters Using Central Composite Design:

The formulation parameters were optimized using a $3^2$full factorial design approach within the CCD framework. The experimental results and corresponding responses are summarized in Table No 4.

**Table No 4: Effect of Various Parameters on Characteristics of Nanosponges:**

| Formulation code | Factor 1 EC (mg) | Factor 2 DCM (ml) | Particle size (nm) | Zeta potential (mV) | Entrapment efficiency (%) | Drug content (%) | $6^{th}$ hr drug release (%) | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| F1 | 100 | 10 | 299 | -9.5 | 73.2 | 75 | 63.12 | 42 |
| F2 | 200 | 10 | 630 | -7.9 | 78.7 | 82 | 78.18 | 59.3 |
| F3 | 300 | 10 | 990.9 | -10.3 | 81.6 | 83.2 | 81.7 | 60.2 |
| F4 | 100 | 20 | 263 | -14.5 | 83.8 | 85.6 | 76.412 | 61 |
| F5 | 200 | 20 | 367.3 | -22.4 | 84 | 89.2 | 79.51 | 72 |
| F6 | 300 | 20 | 764.4 | -26.9 | 85.7 | 86 | 82.36 | 72.8 |
| F7 | 100 | 30 | 282 | -19.9 | 88 | 89.1 | 77.29 | 65.2 |
| F8 | 200 | 30 | 442.1 | -26 | 88 | 87.8 | 80.17 | 72.1 |
| F9 | 300 | 30 | 794 | -31.9 | 89.8 | 90.2 | 84.6 | 73 |

### Evaluation of Nanosponges by DOE:

### Particle size:

The ANOVA results for the linear model of particle size showed that the model was significant (F = 27.70, $p$ = 0.0009), indicating a strong influence of formulation variables. The concentration of Ethyl Cellulose ($p$ = 0.0004) significantly affected particle size, while Dichloromethane volume ($p$ = 0.1387) showed less significant effect.

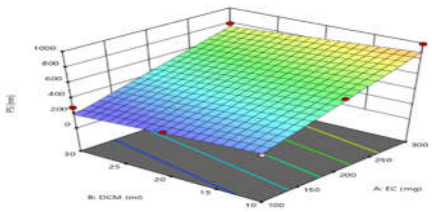

**Figure No 3: 3-D graph of Particle Size.**

### Final Equation in Terms of Coded Factors

Particle size= +536.97+284.22A*-66.97B*

The particle size of miconazole nitrate-loaded nanosponges was measured using a Nano Particle Analyzer (SZ-100), with values ranging from 263 nm to 990.9 nm. The observed increase in particle

size with rising EC concentration is attributed to the greater availability of polymer, which promotes the formation of larger particles. Conversely, higher levels of DCM enhance solvent diffusion and dispersion, leading to the formation of smaller particles. All formulations exhibited particle sizes below 1 µm, confirming the successful formation of nanosponges.[7,18–21]

**Zeta potential**:

Zeta potential analysis was performed to evaluate the colloidal properties and stability of the prepared nanosponge formulations. Zeta potential values are typically expressed in millivolts (mV), with values greater than +30 mV or less than −30 mV generally indicating good colloidal stability due to sufficient electrostatic repulsion among particles. The zeta potential of the nanosponges ranged from −7.9 mV to −31.9 mV. These results suggest that some formulations possess moderate to good stability, with values near or below −30 mV indicating strong repulsive forces and reduced aggregation tendencies.[19]

**Entrapment Efficiency:**

The ANOVA for the linear model of entrapment efficiency showed that the model was significant (F = 30.29, $p$ = 0.0007), indicating a strong influence of formulation variables. Both Ethyl Cellulose concentration ($p$ = 0.0342) and Dichloromethane volume ($p$ = 0.0003) significantly affected entrapment efficiency, with DCM showing a more dominant effect.

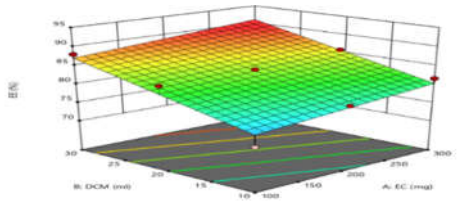

**Figure No 4: 3-D graph of Entrapment Efficiency.**

**Final Equation in Terms of Coded Factors**

Entrapment efficiency=+83.64+2.02A*+5.38B*

The entrapment efficiency of miconazole nitrate nanosponges ranged from 73.2% to 91.8%. EE increased with both DCM and EC concentrations, with DCM having a more significant impact due to its role in drug solubilization and uniform co-precipitation. Smaller particle sizes were associated with lower EE, and DCM was identified as the dominant factor influencing entrapment.[21–23]

**Drug content:**

Drug content, determined by UV spectroscopy in ethanol, ranged from 75.0% to 90.2%, indicating effective drug loading across all formulations.

**Drug release:**

The ANOVA results for the linear model of 6th-hour drug release indicated that the model was significant (F = 8.88, $p$ = 0.0161), suggesting that the formulation variables affected drug release. Ethyl Cellulose concentration ($p$ = 0.011) had a significant effect, whereas Dichloromethane volume ($p$ = 0.0752) exhibited a comparatively lesser influence.

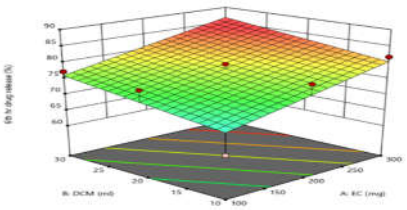

**Figure No 5: 3-D graph of 6$^{th}$ hr drug release.**

**Final Equation in Terms of Coded Factors**

$6^{th}$ hr drug release: +78.14+5.33A*+3.16B*

Ethyl cellulose (EC) and dichloromethane (DCM) both positively influence drug release at the 6th hour, as shown by their positive coefficients in the equation. EC has a stronger effect than DCM, likely because EC controls the polymer matrix density and diffusion pathway, while DCM mainly impacts early particle formation with less effect on later drug release.[24,25]

**Table No 5: *In-vitro* drug release data of Miconazole nitrate Nanosponges Prepared by Emulsion solvent diffusion Method.**

| Cumulative Percentage Drug Release | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Time (hrs)** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| **1** | 3.32± 0.0004 | 9.964± 0.0032 | 7.9744± 0.0041 | 5.960± 0.0285 | 10.86± 0.0135 | 8.625± 0.0183 | 6.439± 0.021 | 9.964± 0.0032 | 8.415± 0.0041 |
| **2** | 15.069± 0.0038 | 16.16± 0.0004 | 15.040± 0.028 | 13.04± 0.0319 | 17.25± 0.0372 | 15.22± 0.0878 | 12.83± 0.022 | 17.03± 0.0257 | 14.36± 0.0460 |
| **3** | 16.61± 0.0009 | 29.65± 0.0374 | 29.221± 0.0157 | 29.60± 0.4267 | 30.11± 0.0134 | 29.93± 0.0247 | 30.54± 0.031 | 30.10± 0.0102 | 30.78± 0.0037 |
| **4** | 41.41±0 | 54.91± 0.0136 | 52.246± 0.0330 | 52.71± 0.0013 | 57.34± 0.0346 | 54.91± 0.0136 | 53.56± 0.047 | 52.70± 0.0056 | 52.48± 0.1594 |
| **5** | 52.041± 0.0004 | 64.00± 0.0042 | 64.647± 0.0338 | 66.22± 0.0029 | 65.54± 0.0283 | 66.01± 0.0136 | 66.85± 0.041 | 64.00± 0.0041 | 65.35± 0.0134 |
| **6** | 63.129± 0.0042 | 78.18± 0.0021 | 81.713± 0.009 | 76.41± 0.0035 | 79.51± 0.0090 | 82.33± 0.0291 | 77.29± 0.004 | 80.15± 0.0365 | 84.60± 0.0735 |
| **7** | 71.98± .0038 | 88.15± 0.0024 | 86.154± 0.0033 | 88.13± 0.0189 | 88.13± 0.0275 | 89.23± 0.0278 | 89.45± 0.037 | 89.91± 0.0127 | 91.91± 1.8830 |
| **8** | 86.82± 0.0004 | 92.50± 0.0047 | 91.009± 0.0140 | 90.83± 0.0405 | 97.32± 0.0047 | 95.93± 0.0348 | 90.34± 0.030 | 93.43± 0.0471 | 95.68±0 |

*Values represented as mean ± SD(n=3)

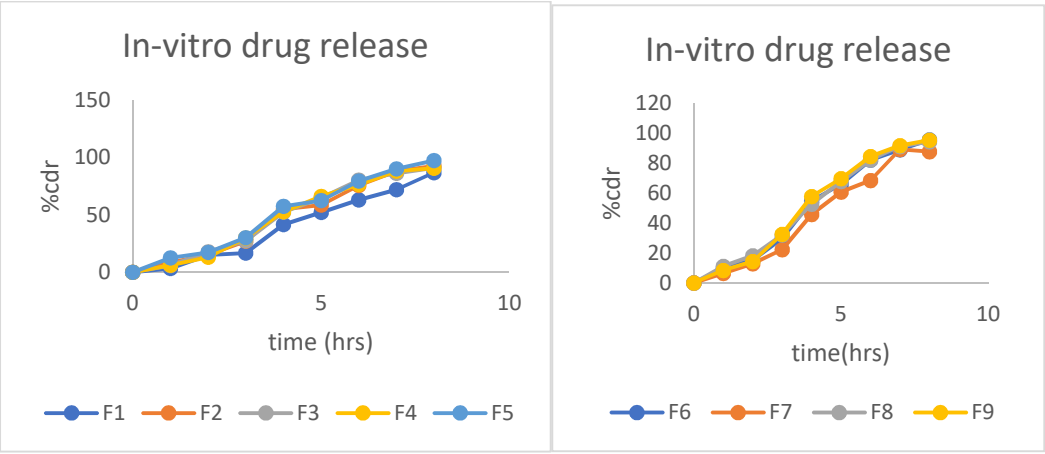


**Figure No 6: *In-vitro* drug release graph of Miconazole nitrate Nanosponges of F1-F10**

**Percentage yield:**

The ANOVA for the quadratic model of percentage yield showed high significance ($F = 51.66$, $p = 0.0041$), indicating strong dependence on formulation variables. Both EC concentration ($p = 0.0032$) and DCM volume ($p = 0.0015$) had significant effects. The interaction term (AB) showed a moderate effect ($p = 0.0607$), while the quadratic terms $A^2$ ($p = 0.0224$) and $B^2$ ($p = 0.0132$) were also significant, confirming curvature in the response. These results highlight the importance of both individual and interactive effects in optimizing yield.

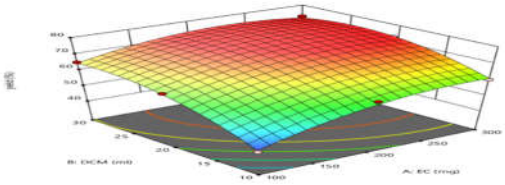

**Figure No 7: 3-D graph of yield.**

**Final Equation in Terms of Coded Factors**

Practical yield: $+72.24+6.30A^{*}+8.14B^{*}-2.60AB-5.45A^{2}-6.62B^{2}$.

The practical yield of nanosponges ranged from 48.5% to 69% and increased with higher concentrations of EC and PVA. Both EC and DCM showed a non-linear (curvilinear) effect. At low to moderate EC levels, yield improved due to better stabilization, but excessive EC increased viscosity, leading to aggregation and yield loss. Similarly, moderate DCM levels enhanced yield by aiding polymer and drug solubilization, while high DCM led to rapid evaporation and particle breakage. These results confirm the significant and complex influence of EC and DCM on yield.[26,27]

**Optimized Formulation:**

**Constraints**

The formulation variables Ethyl Cellulose (A) and Dichloromethane (B) were constrained within their respective ranges to maintain feasible experimental conditions. The responses were optimized with specific objectives: particle size (PS) was targeted to minimize, while entrapment efficiency (EE), 6th-hour drug release, and percentage yield were aimed to maximize. These goals ensured the development of nanosponges with small size, high drug loading, sustained release, and efficient production.

**Table No 6: Comparision of DOE predictions of optimum formulation evaluation versus actual results**

| | EC | DCM | Particle Size (nm) | Entrapment Efficiency (%) | 6th hr drug release (%) | Yield (%) |
|---|---|---|---|---|---|---|
| **DOE Predicted** | **183.563** | **30** | **423.285** | **88.696** | **80.422** | **73** |
| Actual | 183.563 | 30 | 401 | 89.2 | 80.17 | 72.26 |

***In-vitro* drug release data of Optimized Miconazole nitrate Nanosponges Prepared by Emulsion solvent diffusion Method.**

**Table No 7: *In-vitro* drug release data of Optimized Miconazole nitrate Nanosponges Prepared by Emulsion solvent diffusion Method.**

| Time (hrs) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| %CDR±SD* | 8.63± 0.01547 | 15.27± 0.0053 | 29.89± 0.0197 | 54.92± 0.0123 | 66.00± 0.001 | 80.17± 0.008 | 91.9± 0.0065 | 95.6± 0.074 | 97.89± 0.041 |

***Values represented as mean ± SD (n=3)**

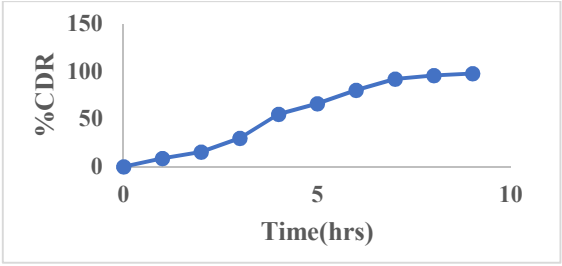


**Figure No 8: *In-vitro* drug release graph of Optimized Miconazole nitrate Nanosponges**

**Numerical optimization:**

As per the criteria's, the optimized Formulation shows minimized particle size (401±0.047), maximized entrapment efficiency (89.28±0.0033%) and 6$^{th}$ hr drug release (80.152±0.0368).

The selected optimized formulation is subjected to SEM

**Surface morphology studies by using scanning electron microscopy**

A surface characteristic of the optimized formulation was determined by SEM as shown in Fig No 9. It was observed to be smooth, spherical structure having porous surface and there was no drug crystals present on it.

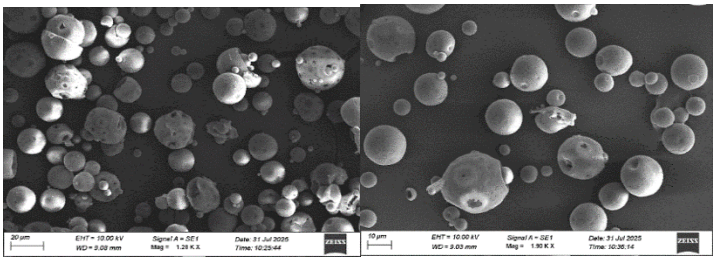

**Figure No 9: SEM Images of Miconazole nitrate Nanosponges Prepared by Emulsion solvent diffusion Method**

SEM analysis was done on the optimized miconazole nitrate loaded nanosponges exterior morphology. It provides detailed visualization of the shape, and surface characteristics of the nanosponges. The image confirms that nanosponges were almost spherical in shape, discrete particles without aggregation, as well as a porous surface with no drug crystal on the surface of nanosponges.

**Preparation of Miconazole nitrate loaded Nanosponges Topical Gel:**

Prepared Gel composed of 0.5% of Carbopol, Purified water and Methyl paraben added with Miconazole nitrate Nanosponges. Miconazole nitrate nanosponge gel was successfully prepared and exhibited favorable stability. The incorporation of nanosponges into the Carbopol gel matrix appears to have maintained the structural integrity while ensuring a uniform distribution within the gel. The choice of carbopol as the gelling agent is particularly advantageous due to its biocompatibility, non-toxicity, and ability to form a smooth, consistent gel, which is essential for topical applications.

**Evaluation of Miconazole nitrate loaded Nanosponges Gel:**

**Table No 8: Results of Various Evaluation Parameters of Miconazole nitrate loaded Nanoponges Gel.**

| **Parameter** | Appearance | Homogeneity | Spreadability | pH* | Drug content* | Viscosity* |
|---|---|---|---|---|---|---|
| **Results** | Off-white | Good | 10.17 $mm^2$ | 5.2 | 79.6 % | 2867 cP |

***Values represented as mean ± SD (n=3)**

**Physical appearance:** The prepared gel was slightly translucent white, likely due to dispersed miconazole nitrate and nanosponges. This off-white color indicates uniform nanosponge distribution and formulation stability.

**pH:** Miconazole nitrate is stable in slightly acidic to neutral conditions, and the observed pH of 5.4 falls within this optimal range, supporting its chemical stability in the gel. This pH is also compatible with skin (4.5–5.5), which is critical for maintaining the skin's barrier and natural defence. Topical preparations outside this range can cause irritation, dryness, and other adverse effects. In this study, we examined the importance of skin pH in topical formulations and strategies to optimize it for safety and efficacy.

**Rheological Study by Viscosity Measurement:** The gel's viscosity of 2867 cP indicates a medium-to-high consistency, ideal for topical use. It ensures the gel stays in place, has a smooth, stable texture at 50 rpm, and provides both easy application and adequate skin coverage.[28]

**Spreadability:** Spreadability of the nanosponge gel was found to be 10.17 $mm^2$(Table No 8). The value of spreadability indicates that the nanosponge gel is easily spreadable by small amount of shear.

**Content Uniformity:** The drug content of MN-loaded nanosponges gel was 79.6%, reflecting good uniformity and minimal drug loss during formulation and gel incorporation. This high encapsulation efficiency is significant given the complexity of forming stable nanosponges and ensuring even distribution within the gel, which is crucial for maximizing the therapeutic potential by delivering a substantial amount of active ingredient to the skin.

**In-vitro Drug Diffusion Study:**

**Table No 9: % Drug diffusion of Miconazole nitrate loaded Nanosponges Gel in comparison to the Marketed Miconazole nitrate Cream 2% W/W:**

| Time | Marketed MCN cream | MCN-N-Gel |
|---|---|---|
| 1 | 6.751±0.029 | 5.711±0.002 |
| 2 | 12.90±0.008 | 12.46±0.017 |
| 3 | 29.41±0.004 | 28.52±0.033 |
| 4 | 33.63±0.021 | 31.53±0.014 |
| 5 | 39.13±0.026 | 36.40±0.004 |
| 6 | 51.21±0.004 | 50.15±0.004 |
| 7 | 65.81±0.012 | 63.02±0.027 |
| 8 | 71.74±0.001 | 72.57±0.015 |
| 9 | 84.44±0.004 | 83.53±0.046 |
| 10 | 89.34±0.041 | 86.34±0.0188 |
| 11 | 93.33±0.008 | 91.21±0.001 |
| 12 | 95.01±0.013 | 93.55±0.007 |
| 13 | 99.65±0.040 | 97.14±0.046 |

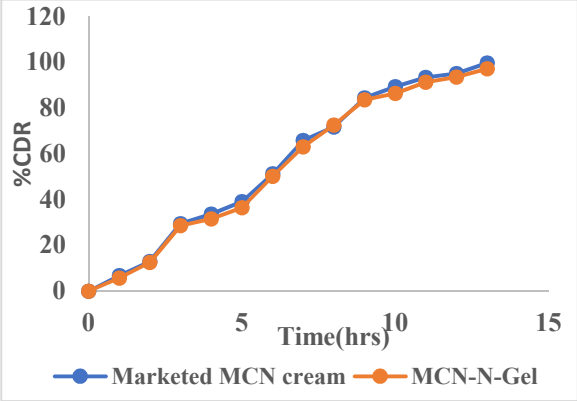


**Figure No 10: Graph showing In-vitro comparision study of MCN-N GEL and MKT MCN CREAM**

The % drug diffusion of MN-N-Gel (97.14±0.046%), which is comparable to the MKT MN cream (99.65±0.040%). Although the MKT MN cream showed slightly higher drug diffusion, the Nanosponges gel formulation demonstrated excellent diffusion characteristics. The high % drug diffusion of the Nanosponges system is effective in delivering the drug in a manner that is comparable with marketed cream.

**Drug Release Kinetic Data Analysis:**

**Table No 10: Regression Coefficient Values of Zero order, First Order Plots, Higuchi Diffusion Plots and intercept of Peppas Log-Log Plots and Slope of Peppas Log-Log Plots**

| Zero order | First order | Higuchi model | Korsmeyer Peppas model | | Kinetics of drug release | model | Mechanism of drug release |
|---|---|---|---|---|---|---|---|
| $R^2$ | $R^2$ | $R^2$ | $R^2$ | n | | | |
| 0.9895 | 0.9277 | 0.9453 | 0.9311 | 1.6802 | Zero order | Higuchi | Non fickian diffusion |

The data indicate the formulation follows zero-order kinetics with a non-Fickian diffusion release mechanism.

**Antifungal activity:**


**Figure No 11: Antifungal activity assessment of, MN-N- Gel (Miconazole nitrate Nanosponges Gel), MKT MN cream (Marketed Miconazole nitrate Cream), PDS (Pure Drug Solution) And Control (Dimethyl sulfoxide).**

**Table No 11: Antifungal activity against Aspergillus Niger Strains.**

| **Formulation** | MN-N-Gel | MKT MN cream | PDS | Control |
|---|---|---|---|---|
| **Zone of inhibition± SD** | 15.3±0.5 | 16.6±0.5 | 18.6±0.5 | 00 |

The antifungal activity against *Aspergillus niger* was evaluated for MN-N-gel, marketed MN cream, and pure drug solution, compared to DMSO control (Fig No11, Table No11). The pure drug solution showed a larger zone of inhibition due to rapid diffusion, while gel and cream bases limited drug release. Nanosponges enhanced penetration and local Miconazole concentration, improving drug uptake through the *A. Niger* cell membrane. These results confirm that nanosponges provide good antifungal activity against *A. Niger*.

**Stability study**

**Table No 12: stability study of MN-N-Gel**

| | **pH** | **Drug content** | **Drug release** |
|---|---|---|---|
| **Temp** | **R.M ($25^0$C)** | **R.M ($25^0$C)** | **R.M ($25^0$C)** |
| 1st day | 5.2±1.085 | 79.6±0.73% | 97.14±0.046% |
| 15 days | 5.2±1.085 | 79.5±0.73% | 97.14±0.046% |
| 30 days | 5.2±1.085 | 78.9±0.74% | 96.81±0.046% |

R.M= Room temperature

Stability studies of MN-N-Gel was carried out at room temperature storage conditions, as presented in Table No 12. The results showed no significant changes in pH, drug content and drug release indicating that the formulation remained stable, effective and preserved its physicochemical characteristics throughout the 30-days storage period.

**Conclusions**

With the help of central composite design, the optimized nanosponge formulation was developed for Miconazole nitrate. This was incorporated to gel formulation and subjected to comparison for invitro antifungal activity. The study evaluated the developed formulation was comparable antifungal activity to that of commercial formulation. These results highlight nanosponge-based gels as an effective approach for controlled topical delivery and enhanced bioavailability of poorly soluble drugs.

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