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# DESIGN AND DEVELOPMENT OF NANOSPONGE LOADED TOPICAL GEL OF ITRACONAZOLE FOR ENHANCED ANTIFUNGAL ACTIVITY

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**ABSTRACT**

The objective of the present study was to develop nanosponge (NS) based topical gel of itraconazole that shows enhanced antifungal activity compared to pure drug. NS were fabricated with emulsion solvent diffusion technology composed of ethyl cellulose as polymer and beta-cyclodextrin (β-CD) as solubilizer. Factorial design ($2^3$) was constructed in a fully randomized manner to study all twenty possible experimental runs to find the optimum concentration of excipients in NS formulation. The NS were prepared by varying the content of drug (antifungal agent) (A), ethylcellulose (polymer) (B) and stirring time (C). The effect of these three independent variables on % of entrapment efficiency (R1) and *in vitro* % of drug release (R2) of prepared NS were evaluated. The optimized NS were used in topical gel formulation and evaluated for kinetic release pattern and finally antifungal activity was determined by agar diffusion technique. Total three formulations of NS were developed by conventional method and evaluated for entrapment efficiency (EE), solubility and % of drug release. F2 formulation that showed 72.34% of EE, 6.781mg/100 ml of solubility and 85.21% of drug release. Further statistical optimization, finally we achieved 86% of EE and 94% of *in-vitro* drug release with 200 mg ethyl cellulose, 258 mg of itraconazole and 2.2 hrs of stirring time. The same concentration of drug and polymer were used for preparation of NS and further confirmed by zeta-potential and SEM images. Topical gel that formulated with statistically optimized NS was follows the Higuchi and Korsmeyer kinetics for drug release. The antifungal activity of optimized nanogel formulation was tested against *Candida albicans* and showed enhanced antifungal activity compared to gel with pure drug. This study could be a promising step for enhancing the antifungal activity for other antibiotics via encapsulating the drug into NS formulation and loading them into a topical gel formulation which in turn contributes to the development of biomedical applications.

## INTRODUCTION

Topical drug administration depicts the simplest and easiest route of localized drug delivery system that takes place everywhere in the body through skin, rectum, vagina, eyes, ears and nose [1, 2]. Skin is the easiest reachable organ on human body for topical administration, thus, it represents main route of topical drug delivery system. Most topically applied pharmaceutical preparations probably have some localized actions and are formulated to

provide sustained local contact with minimal systemic effect. Topical delivery system shows valuable properties by bypassing first pass metabolism, avoidance of the risks and unsuitability of intravenous therapy, and of the different conditions of absorption like pH changes, presence of enzymes, gastric emptying time [3, 4]. Therefore, topical application of antimicrobial agents is considered an important alternative for oral or parenteral dosage form of various antifungal chemotherapeutic agents [5]. Controlled local release of antibiotics at infected sites is a new strategy to get beneficial treatment of chronic infections [6, 7]. Localized delivery systems, based on biodegradable polymers, are capable of slowing and controlling drug release for a certain period of time, with initial burst effect to circumvent the infection. Smart nanogels show pH-dependent drug release so antifungal agents can target and potentially treat polymicrobial infections associated with acidity [8].

Itraconazole is one of the triazole antifungal agents that inhibits cytocrome P-450 dependent enzyme resulting in impairment of ergosterol synthesis. It has been used against histoplasmosis, blastomycosis, cryptococcal meningitis and asperigillosis. It is a BCS class II drug having low solubility and high permeability. The extremely low solubility results into poor oral bioavailability (55%) of Itraconazole. Presently, it is available in the form of capsule (Sporanox R, Itaspore R, Canditral R) and solution dosage form (Sporanox oral solution). However, the marketed solution dosage form contains high amount of solubility-enhancing agents such as polyethylene glycol (PEG) 20000 and HP-β-cyclodextrin, which cause osmotic diarrhoea. It is also available in the form of oral solution at 10 mg/ml. Solutions, in general, are less stable and difficult to handle as compared to the solid dosage form [9]. In the preparation of NS, cyclodextrins (CDs) are most preferable polymer owing to their potential of solubilizing drug moieties which are water insoluble, and also they propose prolonged drug release. Moreover, bioavailability too can be increased by means of alterations in pharmacokinetic parameters. CDs belong to cyclic glucopyranose oligomers class. They are synthesized by enzymatic action on hydrolyzed starch [10, 11]. Compared to other available nanocarriers, CD NS offer maximum drug loading and has capacity to validate concerns associated to solubility, controlled release, bioavailability and stability of a range of therapeutic moieties [11, 12].

The objective of this work was enhancement of solubility of itraconazole by loading in nanosponges and further providing an efficient way of topical administration by formulating topical hydrogel containing itraconazole loaded nanosponges.

## METHODS

### Pre-formulation studies

Ultraviolet Visible (UV-Visible) Spectroscopy

The standard solutions of Itraconazole (10 µg/mL) were separately scanned in 200 to 800 nm range using methanol as blank. Maximum absorbance wavelengths were determined. Further, serial dilutions of drug were prepared and their absorbance's were recorded and calibration curve was plotted.

Fourier Transform Infra-Red (FTIR) Spectroscopy

FT-IR spectrum of itraconazole, excipient mixture was recorded over the range of 4000 to 400 $cm^{-1}$ by KBr pellet method using a FTIR spectrophotometer (Bruker, FTIR Spectrometer).

### Synthesis of β-CD NS

Various synthetic methods are available for synthesizing NS, we have adopted classical emulsion solvent diffusion technology' in the present study. Using β-CD as a solubilizer and ethyl cellulose as polymer in different ratios, three types of NS formulations was prepared (Table 1). β-CD was dissolved in hot water. Then, dispersion phase was prepared by taking required amount of di-chloromethane (DCM), ethyl cellulose (EC) and therapeutic active drug i.e., Itraconazole (ICZ). This mixture was undergone sonication in the sonicator for 10

min. This reaction mixture was added to the continuous phase containing beta-cyclodextrin with continuous stirring using a magnetic stirrer for about 2 hrs (Whirlmatic Spectra Lab, Mumbai, India). The continuous phase (β-CD) was allowed to react for 2 hrs so as to ensure completion of crosslinking reaction amongst them; resulting in formation of NS. Later, the mixture was allowed for filtration. The obtained solid mass was then dried at a temperature of 50ºC and then NS were stored at 25 ℃ until further use [13, 14].

**Evaluation of NS** [12, 13, 15]

**Entrapment efficiency (%)**

Powder equal to 10 mg of the drug was accurately weighed and dissolved in methanol or DMSO and volume is made upto 100 ml in volumetric flask. Further dilutions were done and absorbance was observed at wavelength 260 nm against blank under UV Spectrophotometer and results were observed in triplicate.

Entrapment efficiency= Actual drug content / Theoretical drug content x 100

**Saturated solubility studies for nanosponges**

Saturated solubility studies of all the prepared nanosponges were done by taking 10 ml of water and excess amount of nanosponges were added. The saturated solutions were placed in orbital shaker for 48 hrs at room temperature, and then the samples were filtered by using 0.4µ Whatman filter paper. The amount of dissolved drug was detected by UV spectrophotometer and solubility was measured in triplicate.

***In-vitro* dissolution testing of nanosponges**

Plain ICZ 10 mg and Nanosponges of ICZ which were equivalent to 10 mg of pure drug was taken & conducted in-vitro drug release. In vitro release tests were carried out by dialysis sac method using dialysis membrane with a molecular weight cut-off (LA653) of 12 to 14 kDa (Hi media Lab, Mumbai). Dialysis membrane was washed with deionized water to remove excess glycerin and then soaked overnight in phosphate buffer pH 7.4. Accurately, 10 mg of plain ICZ and equivalent amount of ICZ–NS were dispersed in phosphate buffer pH 7.4 into dialysis sacs with both ends closed by clamps. Dialysis sac was placed in the dissolution vessel of USP Dissolution apparatus (8 stage) (LAB INDIA PVT LTD, Mumbai, India) containing 500 ml of phosphate buffer pH 7.4 at 100 ±2 rpm and 37 ±0.5 °C. At predetermined time intervals. The temperature kept at 37±0.5℃, at 50 rpm. 5ml of the dissolution medium was withdrawn and 5ml of buffer was replaced to maintain sink conditions. It was done for 30min and the results are recorded and done in triplicate. If necessary, dilutions were made. The UV nanometers set to 260 nm were the drug was detected.

After conventional formulation the concentration of drug and excipients were further optimized by full factorial design.

**Experimental design for optimization of excipients for formulation of NS**

In the present work a 3-factor and 2-level full factorial design ($2^3$FFD) was implied to obtain statistically significant and optimized formulation ingredients. Design Expert® software, version 13.0 (Stat-Ease Inc., Minneapolis, MN, USA) was used to create design. The three independent variables viz. amount of itraconazole (A), amount of polymer (B) and stirring time were optimized using Design of Experiment (DoE) at two levels: low (−1), and high (+1) (Table 2). % of entrapment efficiency (R1) and *in vitro* drug release at 30 min (R2) were selected as response variables. On a scale of diverse parameters, prepared NS formulations were evaluated and characterized.

**Zeta potential and poly dispersity index (PDI)**

Zeta potential of statistically optimized nanosponges was measured by zeta potential analyzer (Zeta sizer Ver 6.20 with serial number: MAL1004428) by placing sample in zeta dip cell to check the size distribution in nanosponge formulation. Zeta potential of optimized formulation was measured and it was stable among other formulations. Poly dispersity index was measured for optimized formulation by using zeta sizer and placing the sample in disposable sizing cuvette, at temperature 25˚C.

**Scanning electron microscopy (SEM)**

SEM analysis significant for determination of surface morphology and size of the particle. SEM was used at an acceleration voltage of 15kV, 30KV at work distances (WD) 14mm, 41mm at different magnifications. Based on evaluation parameters, NS formulation was selected and they were used in the gel formulation.

**Formulation of Itraconazole loaded nanosponge gel** [16, 17]

The nanogel was formulated using the optimized ratio of polymer containing ICZ equivalent to 50 mg was incorporated into the gel base composed of Carbopol 934 (1%), Glycerol (15%), Triethanolamine (q.s.) and distilled water up to 1g (Table 3).

**Evaluation of nanogel:** The prepared nanogel was evaluated for physical appearance, pH, rheological parameters and content uniformity etc.

***In-vitro* drug diffusion study**

*In- vitro* drug diffusion study was studied using dialysis bag. The NS gel equivalent to 50 mg of the drug was placed in a Dialysis Bag having 8 cm length and 3 cm breadth; both the sides are tied with thread. This acted as the donor compartment. Then the bag was placed in a beaker containing 100 ml phosphate buffered methanol pH 7.4, which acted as receptor compartment. The temperature of the receptor medium was maintained at 37°±2°C and the medium was stirred at a speed of 100 rpm using a magnetic stirrer. 5 ml of the samples were collected at a predetermined time and replenished immediately with the same volume of fresh buffer PB mixture pH 7.4. The sink condition was maintained throughout the experiment.

The collected samples were analyzed spectrophotometrically at 260 nm using UV-Visible spectrophotometer.

**Kinetics of drug release** [18]

To analyze the drug release mechanism, *in-vitro* releases were fitted into a zero-order, first order, Higuchi and Korsmeyer- peppas model.

**Microbiological study**

Antifungal activity for the prepared Nanosponge gel was carried out. *Candida albicans* was grown in Malt Extract Agar, (MAE) with medium composition: malt extracts 17 g/L and agar 20g/L. The assay was done using the agar well diffusion method. Sterile agar plates were prepared by pouring the sterilized media in sterile Petri dishes under aseptic conditions. 0.1 ml of the test organism (*Candida albicans*) was spread on agar plates. Using a sterile tube with a diameter of 6mm, the wells were made according to the number of samples. The wells were inoculated with 80µL of sample. The antimicrobial activity was interpreted based on the size of inhibition zone (IZ) diameter, which was measured in mm from observation of clear zones surrounding the wells [19].

**Table 1: Composition of ICZ nanosponges**

| Formulation | F1 | F2 | F3 |
|---|---|---|---|
| ICZ (mg) | 250 | 250 | 250 |
| EC (mg) | 100 | 200 | 300 |
| β-cyclodextrin (mg) | 200 | 200 | 200 |
| DCM (ml) | 10 | 10 | 10 |
| Distilled water (ml) | 10 | 10 | 10 |

**ICZ-Itraconazole; EC-Ethyl cellulose; DCM -Dichloro methane**

**Table 2: Selected variables at two different levels**

| Variables | Low Level (-1) | High Level (+1) |
|---|---|---|
| Ethyl cellulose | 150 | 250 |
| Itraconazole | 100 | 500 |
| Stirring time (Hrs) | 1.0 | 2.0 |

**Table 3: Preparation of Gel**

| Gel base ingredients | Concentration |
|---|---|
| Carbapol 934 | 1 % |
| Glycerol | 15 % |
| Triethanolamine | Q.S |
| Distilled water | Upto 1g |

## RESULTS AND DISCUSSION

From the spectral study (Fig 1& 2), there was no change in the peaks of drug and excipients in formulation-2 (ICZ-NS, Glycerol, Triethanolamine). Therefore, it can be inferred that there was no interaction seen among the drug and the excipient.

### Drug excipient compatibility studies

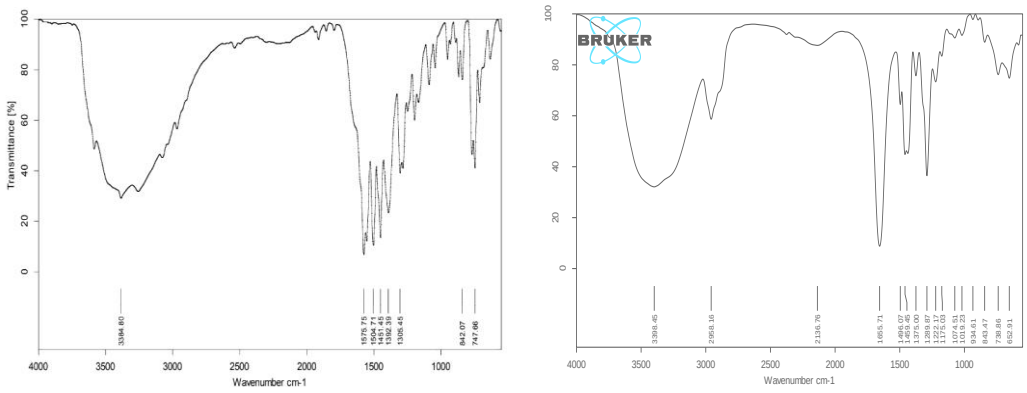


**Figure1. FTIR of Itraconazol Figure 2. FTIR of optimized formulation (F2)**

Among these F2 formulation has highest % of EE and saturation solubility show in Table 4. All the NS formulations released more than 78% of drug at the end of 30 min. As the concentration of ethyl cellulose increased in the formulations F1-F3 decreased the % of drug release from the nanosponge. The NS prepared with β cyclodextrin & optimum concentration of polymer released more amount of drug in F2. This may be due to cyclodextrin forms soluble complex with drug. Among all the 3 formulations F2 was selected as the optimized formulation based on solubility, entrapment efficiency, & *in-vitro* drug release.

### Experimental design for optimization of excipients for formulation of NS

The experimental design matrix and their results of central composite design (CCD) analysis were given in Table 5. The following regression equation was obtained.

Entrapment efficiency (%) =

$$86.7+14.11A+7.40B+5.09C-0.25AB+5.75AC-4.75BC-7.19A^2-6.48B^2+1.65C^2$$

The effect of process parameters were demonstrated by analysis of variance (ANOVA), regression coefficient, P and F values were shown in Table 6. The model F-value of 12.74 indicates that the proposed model is significant. There is only a 0.02% chance that an F-value this large could occur due to noise.

Three dimensional (3D) plots and two-dimensional (2D) contour plots shown in Figure 3a & 3b, 4a & 4b were used to study the interactions between the significant variables for high % of entrapment efficiency [20] because these were simple and easy to understand. Significant interaction was specified by elliptical shape and circular shape specifies the moderate and no interaction between the factors [21]. The shape of the counter plot was elliptical

that means interaction between the concentration of drug and ethyl cellulose has moderate effect on % of entrapment efficiency. The shape of the counter plot shown in below figures describes there was insignificant interaction between concentration of drug and stirring time, concentration of ethyl cellulose and stirring time on % of entrapment efficiency.

**Table 4: Evaluation of NS**

| Formulation | % of Entrapment efficiency | Solubility (gm/100ml) | % of drug release | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0 min | 5 min | 10 min | 15 min | 20 min | 25 min | 30 min |
| F1 | 62.62 | 1.452±0.18 | 0 | 23.6 | 30.4 | 45.6 | 58.6 | 67.8 | 78.2 |
| F2 | 72.34 | 5.453±0.34 | 0 | 32.6 | 42.8 | 57.6 | 69.3 | 77.5 | 85.2 |
| F3 | 58.92 | 6.781±0.78 | 0 | 30.2 | 37.4 | 50.8 | 61.4 | 73.5 | 80.8 |

**Table 5: CCD with 20 experimental and predicted values of independent variables**

| Factor 1 Ethyl cellulose (mg) | Factor 2 Itraconazole (mg) | Factor 3 Stirring time (Hrs) | Response 1 Entrapment Efficiency (%) | Response 2 Drug release (%) |
|---|---|---|---|---|
| 150 | 100 | 1 | 54 | 63 |
| 150 | 100 | 2 | 60 | 57 |
| 150 | 100 | 2 | 58 | 60 |
| 150 | 200 | 2 | 84 | 88 |
| 150 | 200 | 2 | 80 | 83 |
| 150 | 200 | 1 | 72 | 75 |
| 200 | 258.3012 | 2.2 | **86** | **94** |
| 100 | 350 | 1.5 | 42 | 51 |
| 200 | 350 | 2.8 | 78 | 84 |
| 200 | 350 | 2 | 70 | 77 |
| 150 | 100 | 2 | 79 | 81 |
| 150 | 150 | 0.5 | 48 | 56 |
| 65.9104 | 400.012 | 2 | 51 | 59 |
| 234.09 | 350 | 2 | 71 | 79 |
| 100 | 90.894 | 1 | 58 | 65 |
| 200 | 250 | 2 | 83 | 90 |
| 100 | 250 | 1 | 65 | 74 |
| 150 | 350 | 1.5 | 75 | 83 |
| 150 | 350 | 1.5 | 74 | 78 |
| 100 | 100 | 1 | 60 | 67 |

**P-values** less than 0.0500 indicate model terms are significant. In this case model terms A-Ethylcellulose, B-Itraconazole, C-Stirring time, AC, BC, $A^2$, $B^2$ are significant model terms. The model terms AB, $C^2$ that showed greater than 0.1000 indicate that these were not significant. The predicted $R^2$ 0.8669 was in reasonable agreement with the adjusted $R^2$ 0.8874 which depicted the adequacy of the model to predict response. The value of the coefficient of variation (CV% 9.08) revealed the precision and reliability of the model.

**Table 6: ANOVA results of the quadratic model for the response 1-% of entrapment efficiency**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| **Model** | 5615.41 | 9 | 623.93 | 17.65 | < 0.0001 | significant |
| A-Ethyl cellulose | 2717.2 | 1 | 2717.2 | 76.85 | < 0.0001 | |
| B-Itraconazole | 748.29 | 1 | 748.29 | 21.16 | 0.001 | |
| C-Time | 354.15 | 1 | 354.15 | 10.02 | 0.0101 | |
| AB | 0.5 | 1 | 0.5 | 0.0141 | 0.9077 | |
| AC | 264.5 | 1 | 264.5 | 7.48 | 0.021 | |
| BC | 180.5 | 1 | 180.5 | 5.1 | 0.0474 | |
| $A^2$ | 744.17 | 1 | 744.17 | 21.05 | 0.001 | |
| $B^2$ | 604.92 | 1 | 604.92 | 17.11 | 0.002 | |
| $C^2$ | 39.37 | 1 | 39.37 | 1.11 | 0.3162 | |
| **Residual** | 353.59 | 10 | 35.36 | | | |
| Lack of Fit | 46.26 | 5 | 9.25 | 0.1505 | 0.971 | not significant |
| Pure Error | 307.33 | 5 | 61.47 | | | |
| **Cor Total** | 5969 | 19 | | | | |

The **Model F-value** of 17.65 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

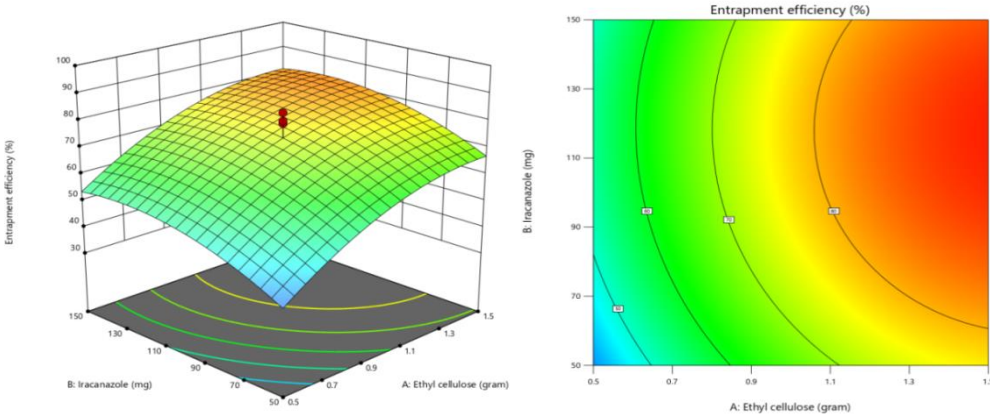


**Fig 3a& 3b: 3D surface plot and counter plot showing the effect of drug and ethyl cellulose concentration on % of EE.**

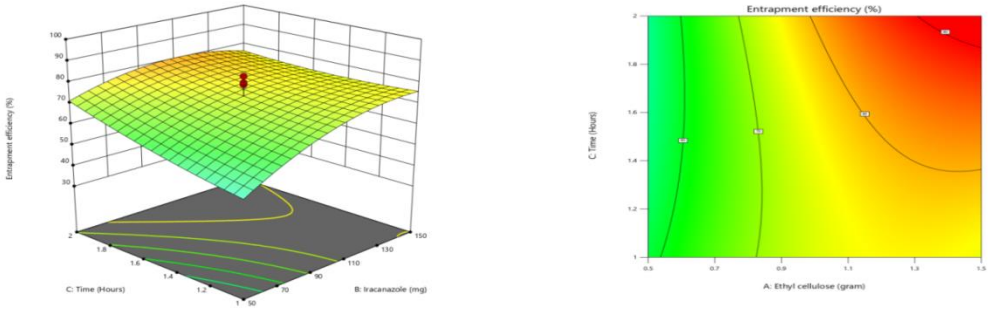


**Fig 4a & 4b: 3D surface plot and counter plot showing the effect of ethyl cellulose concentration and stirring time on % of EE**

On the other hand a probability plot (Fig 5a & 5b) was used to verify the absence of constant error. Distribution of the cluster of the points around the straight line which underlines the errors was distributed normally for all the responses and the assumption was satisfied. Therefore, the model was reliable to describe and adequate for their respective responses

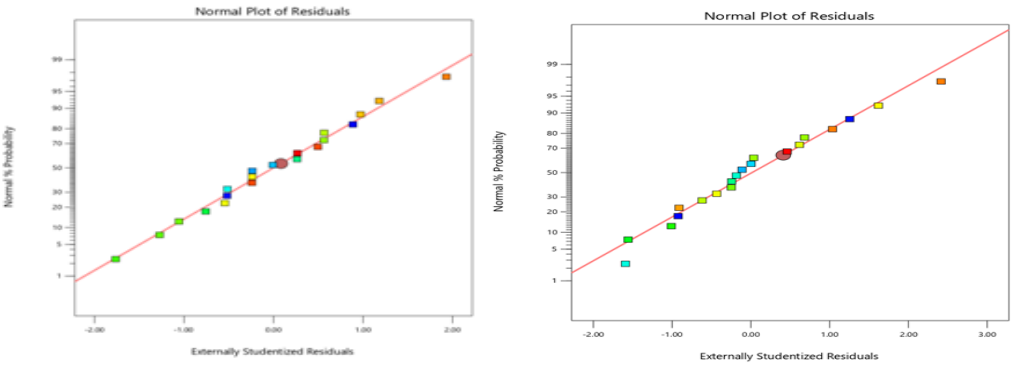


**Fig 5a & 5b: Probability plots for response 1 and response 2**

**Table 7: ANOVA results of the quadratic model for the response 2-% of Drug release**

| Source | Sum of Squares | Df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| **Model** | 4866.8 | 9 | 540.76 | 10.09 | 0.0006 | significant |
| A-Ethyl cellulose | 2613.07 | 1 | 2613.07 | 48.77 | < 0.0001 | |
| B-Iracanazole | 652.64 | 1 | 652.64 | 12.18 | 0.0058 | |
| C-Time | 313.27 | 1 | 313.27 | 5.85 | 0.0362 | |
| AB | 6.13 | 1 | 6.13 | 0.1143 | 0.7423 | |
| AC | 120.13 | 1 | 120.13 | 2.24 | 0.002 | |
| BC | 78.13 | 1 | 78.13 | 1.46 | 0.255 | |
| $A^2$ | 588.82 | 1 | 588.82 | 10.99 | 0.0078 | |
| $B^2$ | 382.91 | 1 | 382.91 | 7.15 | 0.0234 | |
| $C^2$ | 99.19 | 1 | 99.19 | 1.85 | 0.2035 | |
| **Residual** | 535.75 | 10 | 53.58 | | | |
| Lack of Fit | 198.42 | 5 | 39.68 | 0.5882 | 0.7128 | not significant |
| Pure Error | 337.33 | 5 | 67.47 | | | |
| **Cor Total** | 5402.55 | 19 | | | | |

The **Model F-value** of 10.09 implies the model is significant. There is only a 0.06% chance that an F-value this large could occur due to noise.**P-values** less than 0.0500 indicate model terms are significant. In this case A, B, C, $A^2$, $B^2$, AC were significant model terms. The interaction between concentration of ethyl cellulose and stirring time was significant that can influence the % of drug release. Interaction between concentration of ethyl cellulose and drug has no affect on % of drug release. Also interaction between concentration of drug and stirring time has no affect on % of drug release shown in Figure 6a & 6b; 7a & 7b; 8a & 8b. The Predicted $R^2$ of 0.6310 is in reasonable agreement with the adjusted $R^2$ of 0.8116; i.e. the difference is less than 0.2.

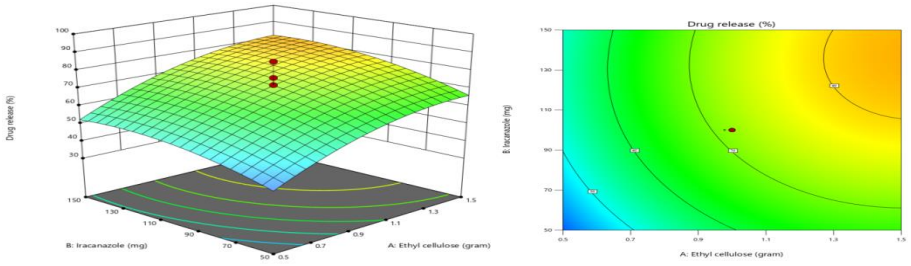


**Fig 6a & 6b: 3D surface plot and counter plot showing the effect of drug and ethyl cellulose concentration on % of drug release.**

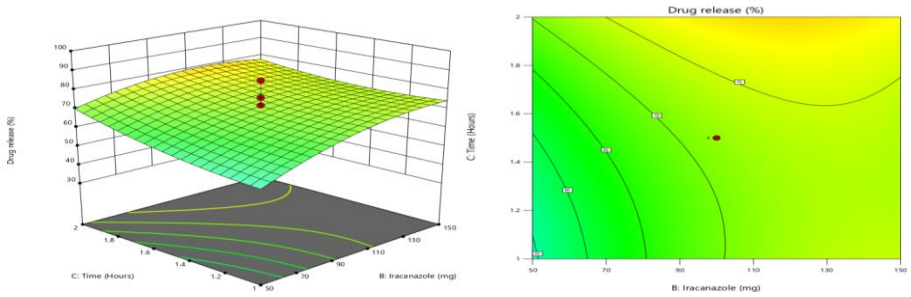


**Fig 7a & 7b: 3D surface plot and counter plot showing the effect of drug and stirring time on % of drug release.**

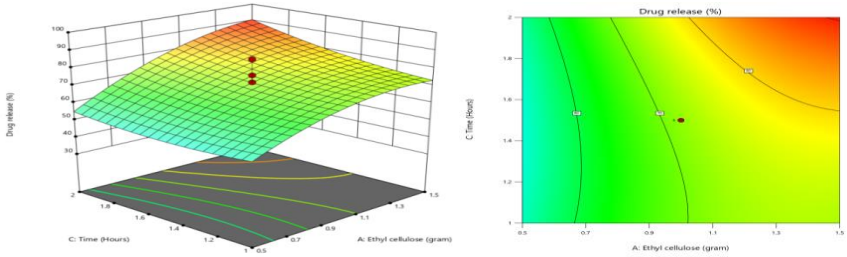


**Fig 8a & 8b: 3D surface plot and counter plot showing the effect of ethyl cellulose content and stirring time on % of drug release.**

**Zeta potential**

Zeta potential of optimized formulation was found to be -23.8 which indicate good stability of the formulation shown in Fig 9a & 9b. Poly dispersity index of optimized formulation having better PDI value with 0.260.

**Scanning electron microscopy (SEM)**

The morphology and surface texture, topography of NS2 was observed by scanning electron microscope (Fig 10). Optimized NS were finally loaded in gel formulation and all the evaluated parameters were in the acceptable range only

***In-vitro* drug diffusion studies:**

The percentage drug release for nanogel was 96.91% in 10 hrs as shown in Table 8. The results indicated that a sustained drug release was offered by formulation over extended period of time.

**Release Kinetics**

Various kinetic models were used to describe the release kinetics of itraconazole nanogel as shown in Figure 11 a, b, c, d. With respect to Higuchi kinetics, the plots were found to be fairly linear as indicated by their highest regression values. Higuchi equation is considered one of the widely used and the most well-known controlled release equation. Thus, this model was applied in the release profile of itraconazole (% drug release vs. Square root time) and evaluation was done in the graphical presentation.

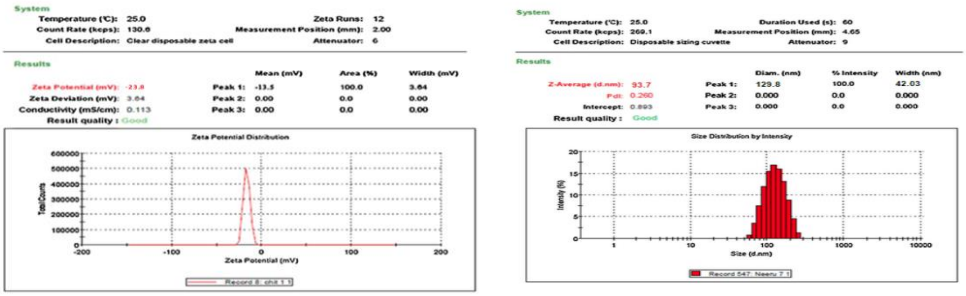

**Fig 9a & 9b: Zeta potential and Poly Dispersity Index of statistically optimized formulation**

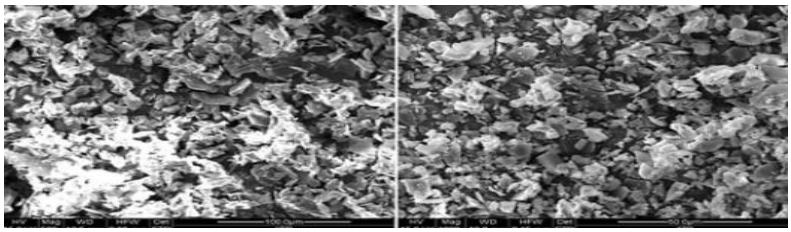

**Fig 10: SEM images of optimized NS**

**Table 8: % drug release of nanogel**

| Time (hrs) | 0 | 0.25 | 0.5 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| nanogel | 0 | 16.1 | 21.4 | 28.9 | 39.7 | 46.6 | 55.9 | 63.5 | 71.0 | 80.5 | 89.3 | 95.6 | 98.2 |

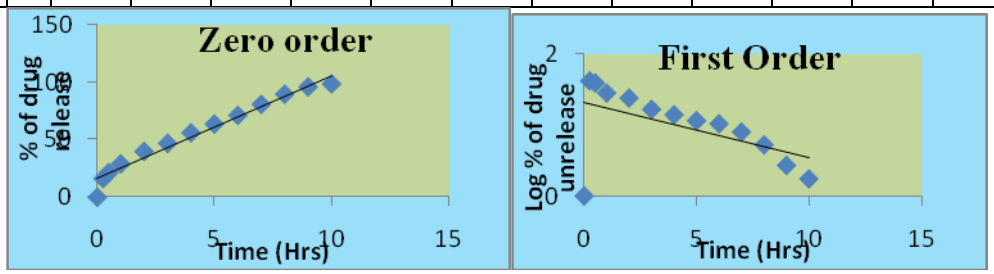


**Fig 11a & 11b: Zero order plot and first order plot**

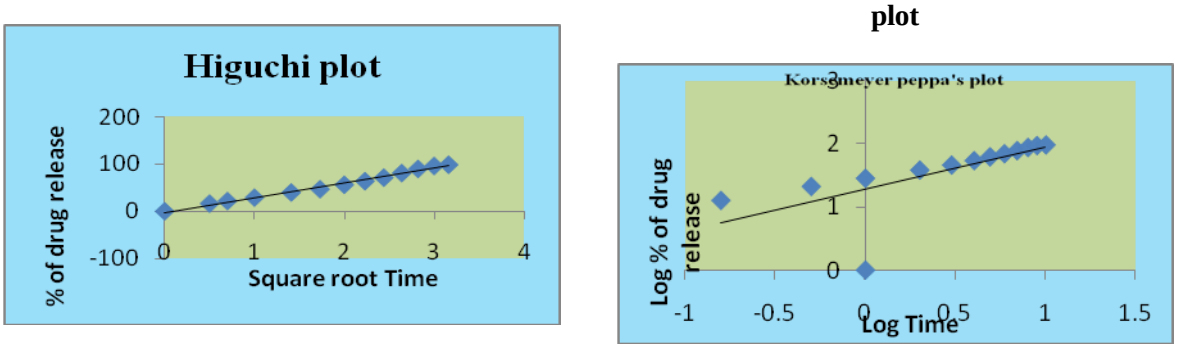


**Fig 11c & 11d: Higuchi plot and Korsemeyer peppas plot**

It can be observed in the figure that graphical representation of % of drug release against time represents that drug release of itraconazole from the hydrogel was perfectly following Higuchi drug release model as the drug release profile was very closest to trend line or regression line and the highest value of coefficient of correlation values ($r^2$) was 0.990 (Table 9) for nanogel formulation [22]. In Korsmeyer-Peppas release kinetics model which was considered the way of drug release from the gel across the membrane into the receptor media. To study release kinetics according to Korsmeyer Peppas model, a graph was plotted between log % drug release vs. log time. In general, it

can be perceived that the mechanism of drug release of the formulation follows anomalous diffusion coupled with erosion.

**Table 9: Drug release kinetics $r^2$ values**

| Nanogel | Zero Order | First Order | Higuchi | Peppas |
|---|---|---|---|---|
| | $r^2$ | $r^2$ | $r^2$ | $r^2$ |
| | 0.666 | 0.942 | 0.990 | 0.958 |

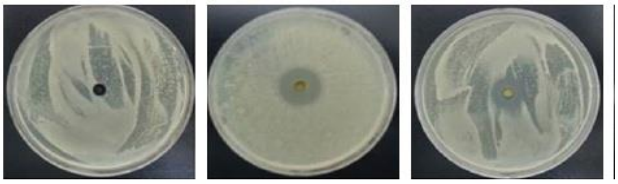

**Fig 12: Antifungal activity of control, Itraconazole nanogel & Itraconazole gel**

**Antifungal activity:** *In vitro* antifungal activity of itraconazole NS loaded carbopol gel formulation was assessed by well diffusion agar method for screening the antifungal potential against the *Candida albicans* and was expressed as diameter of the inhibition zones in millimeter (mm) as shown in Figure 12. It can be illustrated in the figure that at 72 hrs incubation time, the diameters of inhibition zones values were between 20 and 23 mm. It clearly explains that the drug-loaded nanogel showed relatively good inhibitory activities against the tested fungi when compared with the gel containing pure drug as seen in Figure 8.

## CONCLUSION

Itraconazole was successfully incorporated into the topical nanogel formulation. F2 NS showed good EE, solubility and % of drug release. Zeta-potential, PDI and SEM images confirmed the nanosize range of the statistically optimized NS formulation. PH value, viscosity and highest in vitro release profile after 10 hrs achieved the good nanogel formulation of itraconazole. Mathematical models played a vital role in the interpretation of mechanism of drug release from a dosage form to understand the drug release kinetics of a dosage form. The Higuchi kinetic was found to be fairly linear as indicated by their highest regression values. Also, the model Korsmeyer Peppas states the type of diffusion which was evaluated by value, n (release exponent) which is higher than 0.662 which implies that the drug release from the system follows Super case II transport. Therefore, it was concluded that our formula could be very promising topical alternative for the treatment of bacterial wound infection. However, further preclinical, clinical and long term stability studies should be performed.

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