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# PRONIOSOMAL GEL- AN EFFECTIVE TOOL FOR THE ENHANCED TOPICAL DELIVERY OF ECONAZOLE NITRATE

Chandhana Krishnan and Sujith S. Nair *

Department of Pharmaceutics, Crescent College of Pharmaceutical Sciences, Payangadi P O, Kannur - 670358, Kerala, India.

**Keywords:**

Econazole, Antifungal activity, Optimization, Proniosome

**Correspondence to Author:**
**Sujith S. Nair**

Professor,
Department of Pharmaceutics,
Crescent College of Pharmaceutical Sciences, Payangadi P O, Kannur - 670358, Kerala, India.

**E-mail:** sujiths@ccops.edu.in

**ABSTRACT:** The use of topical drug delivery systems is becoming increasingly popular due to their convenience and effectiveness. However, the potential of proniosomal gel for delivering econazole nitrate topically has not been widely studied. This study focuses on designing and optimizing a proniosomal gel formulation of econazole nitrate to improve antifungal therapy. The proniosomal gel was prepared using the coacervation phase separation method, incorporating Span 60, cholesterol, and other ingredients. The ratio of non-ionic surfactants to cholesterol significantly affects drug entrapment efficiency and release characteristics. The formulated proniosomes were evaluated for parameters such as entrapment efficiency, vesicle size, and in vitro drug release. Optimization using a central composite design examined the impact of varying Span 60 and cholesterol ratios on these properties. The optimized formulation showed a sustained drug release of 12 hours and a high entrapment efficiency of 95.41% at an optimal Span 60-to-cholesterol ratio of 6.65:1. The vesicles were found to be discrete and spherical. Additionally, the optimized formulation demonstrated superior antifungal activity, showing a larger zone of inhibition compared to a marketed preparation. With sustained drug release and high entrapment efficiency, econazole nitrate proniosomal gel appears to be a promising option for enhanced skin absorption, improved patient compliance, and better therapeutic outcomes. This study supports the potential of econazole nitrate proniosomal gel in antifungal treatment.

**INTRODUCTION:** The most challenging issue encountered in the advancement of topical drug delivery system is to overcome the physical, biochemical and immunological barriers of the skin. The rate of topical drug transport is mostly restricted by the stratum corneum, the outer skin layer. Several physical as well as chemical strategies have been determined to advance the topical permeation such as ultrasound, electroporation, heat, drug delivery carriers like liposomes, ethosomes, niosomes etc [1].

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The application of drug delivery vesicle could notably modify the physicochemical properties of the entrapped compound and thus facilitate in percutaneous transfer of large hydrophilic or electrically neutral molecules. Topical drug delivery system can maintain consistent plasma levels for an extended period of time after a single dose. To enhance the percutaneous transfer of econazole nitrate, several formulation strategies, including liposomes, niosomes, proniosomes, microemulsion has been explored.

During the last few decades, the transdermal permeation of various drugs employing niosomes have been assessed and established as an excellent transdermal nanocarrier. Proniosomes are dry, free flowing pro-vesicles with a liquid crystalline consistency upon hydration readily forms niosomes [2]. The components present in proniosomes namely

phospholipids and non-ionic surfactants have the potentiality to diffuse into the stratum corneum, interrupting the fluidity of the lipid bilayers causing defective permeablity barrier function to act as penetration enhancers [1]. Non-ionic surfactant and cholesterol ratio could influenceon entrapment efficiency and on release characteristics of the incorporated drug [2]. Proniosomal gel when applied to skin under occlusive condition get hydrated with the skin moisture and converted to niosome [3]. Proniosomal gel offer great potency to reduce the side effects of drugs and increase the therapeutic effectiveness of topical drug delivery [4]. Proniosomes are presumed to prevent numerous formulation related issues associated with liposomes, like physical and chemical instabilities, difficulties faced in sterilization, purity related issues of phospholipids and large-scale production process. Proniosomal gel are becoming more beneficial in the area of semisolid dosage forms due to its advancement in application and better percutaneous absorption [4]. Econazole Nitrate belongs to the class of imidazole broad spectrum antifungal agent categorised under BCS class II [5]. It has a terminal half life of about 4 hours [6]. The plasma protein binding is about 98% and the absorption is very poor when administered topically. It is commonly given by topical route for the controlling of superficial candidiasis, dermatophytosis, ptyriasis versicolor and skin contagions [7]. It interacts with 14α demethylase, a cytochrome p-450 enzyme required to convert lanosterol to ergosterol. Econazole inhibits the synthesis of ergosterol which is an essential component of fungal cell membrane, increasing the cellular permeability resulting in leakage of cellular contents, causing fungal cell death [8]. The present study aims at developing a new topical formulation for econazole nitrate defined by safety and high therapeutic efficacy, through designing an optimum proniosomal gel formulation with a subsequent enhancement in patient compliance.

## METHODOLOGY:

**Solubility of Drug:** For the purpose of solubility, beyond saturation additional amount of drug is added in the solvent (either aqueous or non-aqueous) at room temperature and kept for 24 hours with rare shaking. The supernatant was taken and evaluated by using UV double beam spectrophotometer. Solubility of econazole nitrate was tested in different solvents such as distilled water, phosphate buffer pH 7.4, ethanol (95% v/v) and in methanol [5].

**Drug- excipient Compatibility:** FTIR spectroscopy method was used to carry out drug-excipients compatibility study. FTIR spectra of pure drug, span 60, cholesterol, lecithin and their physical mixture were taken by KBr pellet technique between 400- 4000cm$^{-1}$. Once spectra were recorded, the peaks of pure drug, polymer and physical mixtures of polymers and drug were compared for incompatibility [9].

**Determination of Melting point of Pure Drug:** Determined by using capillary method. Drug is filled into capillary tube up to the height of 3mm by sealing its one end. The capillary tube is introduced into the digital melting point apparatus and the point at which the drug starts melting note that point until the entire sample get melted [5].

**Method of Preparation Proniosomal Gel of Econazole Nitrate:** Econazole nitrate proniosomal gel was made using the coacervation phase separation method.

A clean glass beaker was used to mix the drug, surfactant, lecithin, and cholesterol. A specific amount of ethanol was added to dissolve all the components. The beaker was covered to prevent the ethanol from evaporating.

It was then placed in a water bath heated to 60-70°C for about five minutes until the surfactants fully dissolved. Next, phosphate buffer with a pH of 7.4 was added, and the mixture was warmed in the water bath until a clear solution formed. The beaker was then left in a dark place to cool at room temperature until the mixture turned into proniosomal gel [10].

**TABLE 1: FORMULATION DESIGN OF PRONIOSOMAL GEL OF ECONAZOLE NITRATE**

| Formulation code | Drug (mg) | Span 60 (mg) | Cholesterol (mg) | Lecithin (mg) | Ethanol (ml) | Phosphate buffer pH7.4 (ml) |
|---|---|---|---|---|---|---|
| F1 | 50 | 3000 | 300 | 1250 | 5 | 5 |
| F2 | 50 | 2000 | 300 | 1250 | 5 | 5 |

| | | | | | | |
|---|---|---|---|---|---|---|
| F3 | 50 | 1000 | 100 | 1250 | 5 | 5 |
| F4 | 50 | 1000 | 300 | 1250 | 5 | 5 |
| F5 | 50 | 2000 | 100 | 1250 | 5 | 5 |
| F6 | 50 | 3000 | 100 | 1250 | 5 | 5 |
| F7 | 50 | 2000 | 300 | 1250 | 5 | 5 |
| F8 | 50 | 2000 | 300 | 1250 | 5 | 5 |
| F9 | 50 | 2000 | 500 | 1250 | 5 | 5 |
| F10 | 50 | 2000 | 300 | 1250 | 5 | 5 |
| F11 | 50 | 1000 | 500 | 1250 | 5 | 5 |
| F12 | 50 | 3000 | 500 | 1250 | 5 | 5 |
| F13 | 50 | 2000 | 300 | 1250 | 5 | 5 |

**Evaluation Studies:**

**Entrapment Efficiency:** The entrapment efficiency was measured using a centrifugation method. A small glass tube containing 0.2 g of proniosomal gel was mixed with 10 ml of phosphate buffer (pH 7.4). The mixture was then sonicated for 30 minutes. To separate the niosomes containing econazole nitrate from the unentrapped drug, the solution was centrifuged at 9000 rpm and 4°C for 45 minutes. The supernatant was filtered, diluted with phosphate buffer, and analyzed using UV spectroscopy. The percentage of drug encapsulation (%EE) was then calculated by

$$\% EE = [(C_t - C_f) / C_t] \times 100$$

Where $C_t$ = total concentration of drug, $C_f$ = concentration of free drug [11].

**Vesicle size Analysis:** A small quantity of proniosomal gel was added in a 10ml of phosphate buffer (pH 7.4). The dispersion of proniosome was manually shaken for few seconds so that lumps of proniosome are disintegrated in to individual proniosomes. A drop of dispersion was placed on to the slide and examined under the microscope at 100x magnification, circular vesicles bodies were observed with uniform small size [12].

***In-vitro* Drug Release Studies:** The release of the proniosomal gel was tested using a locally made Franz-diffusion cell. The receptor compartment held 15 ml of phosphate buffer (pH 7.4) mixed with 10% methanol. A dialysis membrane was placed between the donor and receptor compartments. In the donor compartment, 10 mg of proniosomal gel was evenly spread on the membrane.

The receptor phase was kept at 37.5±0.5°C using a water jacket and was continuously stirred with a magnetic stirrer. Over 12 hours, 1 ml samples were taken at intervals and replaced with fresh buffer to maintain consistent conditions. The samples were analyzed using a spectrophotometer at 272 nm [13].

**Optimization by Design Expert Stat Ease Software:** Statistical design of experiment, a computer aided optimization technique, was used to recognize critical factors, their interactions and ideal process conditions that accomplish the targeted response.

The best formulation were established using Design Expert State Ease Software (version 13). Central composite design was employed for the optimization. In this study span 60, cholesterol was chosen as the two factors and percentage entrapment efficiency, mean vesicle size and *in-vitro* drug release were assessed as the responses. Hence, thirteen experimental trials were conducted. Contour plots were drawn and optimum formulation based on optimization criteria was selected [14].

**TABLE 2: FACTOR COMBINATION BY CCD FOR THE FORMULATION OF PRONIOSOMAL GEL**

| Formulation code | Point type | Coded factor level | |
|---|---|---|---|
| | | X1 | X2 |
| F1 | Axial | 1 | 0 |
| F2 | Center | 0 | 0 |
| F3 | Factorial | -1 | -1 |
| F4 | Axial | -1 | 0 |
| F5 | Axial | 0 | -1 |
| F6 | Factorial | 1 | -1 |
| F7 | Center | 0 | 0 |
| F8 | Center | 0 | 0 |

| | | | |
|---|---|---|---|
| F9 | Axial | 0 | 1 |
| F10 | Center | 0 | 0 |
| F11 | Factorial | -1 | 1 |
| F12 | Factorial | 1 | 1 |
| F13 | Center | 0 | 0 |

$X_1$- Span 60, $X_2$- Cholesterol

**Scanning Electron Microscopy (SEM):** The surface morphology and size distribution of the proniosomes were analyzed using SEM. A drop of proniosomal suspension was placed on a specimen stub coated with carbon and then with gold vapor using a Hitachi vacuum evaporator. The samples were examined under a scanning electron microscope to observe the vesicular shape and were then photographed [15].

**Drug Release Kinetics:** The exact mechanism of drug release from the dosage form, was understood from the study of drug release kinetics the data of in-vitro dissolution study of optimized formulation was integrated into various kinetics equations (zero order, first order, Higuchi model and Korsmeyer Peppa's model) [16, 17].

***In-vitro* Anti antifungal Activity:** In a 500 ml of conical flask require amount of saboured dextrose agar was taken and 250 ml of purified water is added. Heat is applied to dissolve the saboured dextrose agar completely. Sterilized for 15 minutes at 121°C at 15lb pressure in autoclave for about 20 minutes.

Then cooled it at room temperature and the fungal strain(Candida albicans) was dispersed in the medium and then the medium and then the medium was poured into the required petridish and allowed it to cool until it get solidified at room temperature and then the cups are bord in agar plate by using cork borer having 6mm diameter and calculated concentration of the optimized proniosomal gel, and marketed preparation were placed in the bores and incubated the petri plates for 72 hours at 28°C in incubator. The zone of inhibition was measured and the radius of the zone of inhibition was calculated [18].

**Stability Studies:** Stability study was carried out at temperature and humidity conditions as per ICH guidelines and the test were carried out in a stability chamber. The ability of vesicle to retain drug was assessed by keeping the proniosomal gel at three different temperature conditions, that is, Refrigeration temperature 5ºC±3ºC, Room temperature 25±2°C at 60%±5% RH and oven temperature 40±2°C at 75% ±5% RH.

Throughout the study the, proniosomal formulation were stored in aluminium foil-sealed glass vials. The sample were withdrawn at different time intervals over a period of 3 months and evaluated for entrapment efficiency, vesicle size and drug release [19].

## RESULT AND DISCUSSION:

**Solubility Profile:** Solubility studies were carried out in different solvent and it was found that Econazole nitrate is very slightly soluble in distilled water, sparingly soluble in phosphate buffer pH 7.4, slightly soluble in ethanol and freely soluble in methanol. The result complies with the pharmacopoeia specification.

**Identification of Compatibility by FTIR Studies:** FTIR studies were conducted in pure Econzole Nitrate, span 60, cholestrol, lecithin and physical mixture of drug with lecithin, span60, and cholesterol.

The FTIR spectra is shown below. Drug identification is done by performing FTIR studies. During FTIR studies, the peaks of Diacerein was obtained at 3105$cm^{-1}$ (C-H stretching aromatic), 1545$cm^{-1}$ (C=C stretching), 3668 $cm^{-1}$ (O-Hstretching), 1584$cm^{-1}$ (O=N=O stretching), 632$cm^{-1}$ (C-Cl stretching) etc.

There is no significant changes in the peak of the pure drug in the FTIR spectrum of physical mixture of pure drug with the polymesie, the span 60, cholesterol and lecithin.

It indicates that there is no chemical interaction between the drug and the polymers. This shows that econazole nitrate was compatible with another excipient.

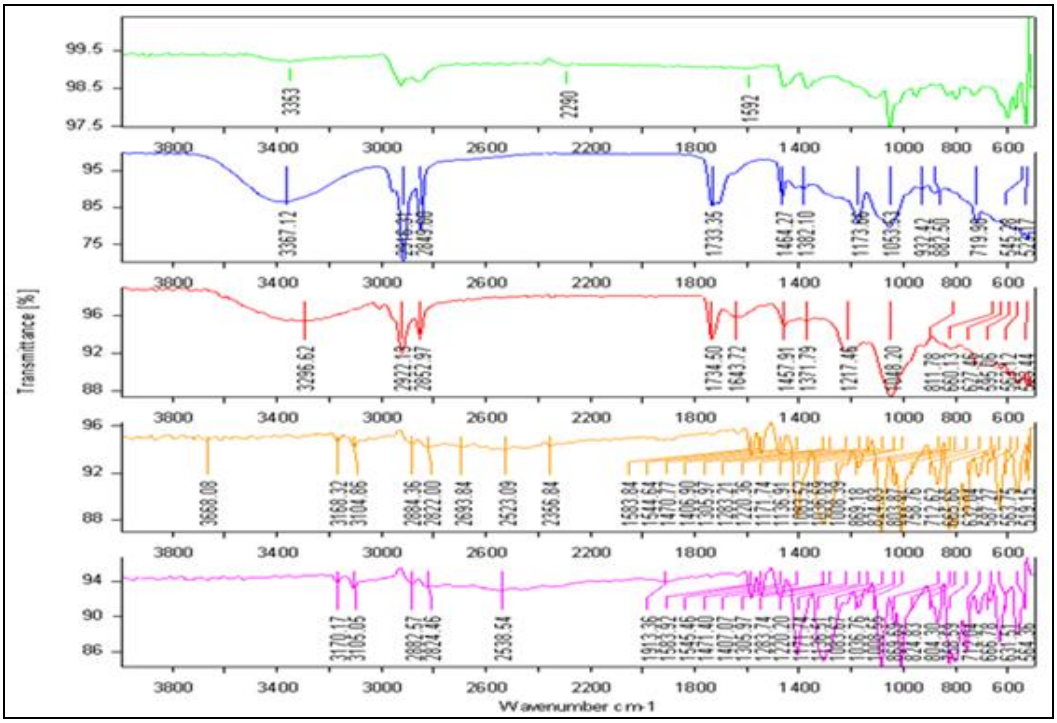


**FIG. 1: FTIR SPECTRUM OF ECONAZOLE NITRATE, SPAN 60, CHOLESTEROL, LECITHIN, PHYSICAL MIXTURE (ECONAZOLE NITRATE+SPAN 60+CHOLESTROL+LECITHIN)**

**Melting Point Determination:** Melting point of econazole nitrate was found to be 220°c (n=3).

**Percentage Entrapment Efficiency:** The entrapment efficiency of econazole nitrate in various proniosomal gels is summarized in **Table 3.** The percentage entrapment efficiency of the vesicles was primarily influenced by the fundamental properties of the surfactant, such as its HLB (hydrophilic-lipophilic balance), phase transition temperature, structural orientation, and critical packing parameter. Proniosomes prepared using Span 60 showed moderately higher entrapment efficiency compared to those made with other non-ionic surfactants. This can be attributed to Span 60's higher phase transition temperature (Tc, 53°C) and longer saturated alkyl chain (C16). Entrapment efficiency is a crucial parameter that reflects the stability of the vesicles and depends on the amounts of surfactant and cholesterol used. When the concentration of Span 60 was varied from 1000 mg to 3000 mg, the maximum and minimum entrapment efficiencies were observed. Increasing the concentration of Span 60 from 1000 mg to 2000 mg significantly improved entrapment efficiency, but further increasing it to 3000 mg resulted in a decrease. To prevent the formation of leaky and permeable proniosomes, cholesterol was added as a stabilizing agent. However, raising the cholesterol concentration beyond a certain level can disrupt the linear vesicular membrane structure, preventing the drug from being retained within the bilayers. The entrapment efficiency increased significantly when the cholesterol amount was raised from 100 mg to 300 mg, but further increases in cholesterol led to a decrease in entrapment efficiency.

**TABLE 3: PERCENTAGE ENTRAPMENT EFFICIENCY OF FORMULATIONS F1 - F13**

| Formulation code | Percentage entrapment efficiency (%) |
|---|---|
| F1 | 86.87±1.321 |
| F2 | 95.41±0.653 |
| F3 | 63.32.±0.341 |
| F4 | 60.16±0.359 |
| F5 | 84.34.±0.873 |
| F6 | 90.41±0.528 |
| F7 | 95.41±0.653 |
| F8 | 95.41±0.653 |
| F9 | 82.05±1.711 |
| F10 | 95.41±0.653 |
| F11 | 54.87±1.101 |
| F12 | 69.26±0.493 |
| F13 | 95.41±0.553 |

All value expressed as mean of ± SD, n = 3.

**Vesicle size Analysis:** All prepared proniosome formulations displayed vesicle size ranging from 5.20µm-10.37µm. The proniosomes were found as discrete round shaped vesicles without any

aggregation. Small vesicle size diameter is beneficial since it minimizes irritation and improves the transdermal permeation of the vesicles. High surfactant/lipid ratio showed vesicles with large diameter because of rise in the overall field of hydrophilicity. Both span 60 and cholesterol had predominant effect on vesicle size and was related to the increase in the overall degree of hydrophilicity. Raising cholesterol content diminished vesicle size since it caused a reduction in the hydrophilicity of bilayers, thus restricting the entry of water to the core of the vesicles.

**TABLE 4: MEAN VESICLE SIZE OF FORMULATION F1 -F13**

| Formulation code | Mean vesicle size(µm) |
|---|---|
| F1 | 7.41±0.54 |
| F2 | 5.20±0.18 |
| F3 | 5.83±0.47 |
| F4 | 7.84±0.71 |
| F5 | 9.62±0.35 |
| F6 | 10.37±0.72 |
| F7 | 5.20±0.18 |
| F8 | 5.20±0.18 |
| F9 | 6.15±0.74 |
| F10 | 5.20±0.18 |
| F11 | 8.34±0.63 |
| F12 | 6.74±0.44 |
| F13 | 5.20±0.18 |

All values expressed as mean of ± SD, n = 3.

***In-vitro* Drug Release:** The percentage of econazole nitrate released from various proniosomal gel formulations is presented in **Fig. 2**. All the formulation was found to have a linear release and most of the formulations were found to provide approximately 90% release with in a period of 12 hrs. Among all the formulations, F2 showed significant prolonged *in-vitro* drug release (96.78±0.44) for a period of 12 hrs.

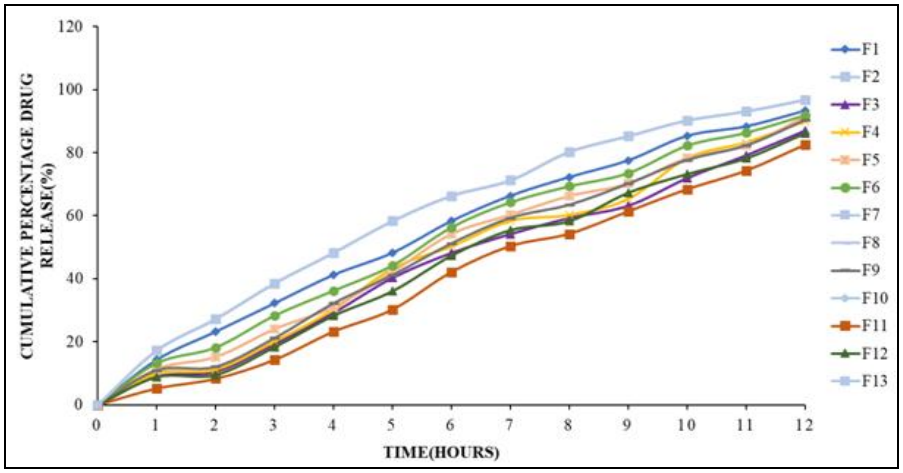


**FIG. 2: *IN-VITRO* DRUG RELEASE STUDIES OF FORMULATIONS F1-F13**

**Optimization by Design Expert Software:** Optimization was done by Design Expert Stat Ease Software version 13.0.7.0. Two factors were selected for optimizing the formulation. The factor selected were span 60 and cholesterol. Central composite design was used for optimization. To determine the best formulation, 3 responses that is vesicle size, entrapment efficiency and drug release were considered. 13 formulation were suggested by the software. The average values were submitted to multiple regression analysis using Design Expert Software. Polynomial models were generated for all responses The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the coefficient variation (CV), the multiple correlation coefficient (adjusted $R^2$) and predicted residual sum of square **Table 5.**

**TABLE 5: NUMERICAL TEST RESULTS OF MODEL ADEQUACY CHECKING FOR INFLUENCE OF INDEPENDENT VARIABLES ON RESPONSE VARIABLES**

| Response | Model | Sequential P value | $R^2$ | Adjusted $R^2$ | Predicted $R^2$ | Adequate precision | %CV |
|---|---|---|---|---|---|---|---|
| Y1 | Quadratic | <0.0001 | 0.9767 | 0.9601 | 0.9302 | 40.3416 | 1.52 |
| Y2 | Quadratic | <0.0581 | 0.8196 | 0.7346 | 0.6907 | 8.1732 | 1.78 |
| Y3 | Quadratic | <0.0001 | 0.9806 | 0.9668 | 0.9417 | 33.4014 | 1.15 |

Y1: Percentage Entrapment Efficiency, Y2: Mean vesicle size, Y3: *In-vitro* Drug Release.

The fit of the model was evaluated using the$R^2$ values. As observed from the **Table 8** predicted $R^2$ value was in reasonable agreement with the adjusted $R^2$ value (the difference is less than 0.2), indicating reliability of the models. Based on the fit summary quadratic model was chosen as best fit for percentage entrapment efficiency, mean vesicle size and *in-vitro* drug release as suggested by software. Adequate precision (which measures signal to noise ratio) was greater for all responses showing that the proposed models can be used to navigate the space.

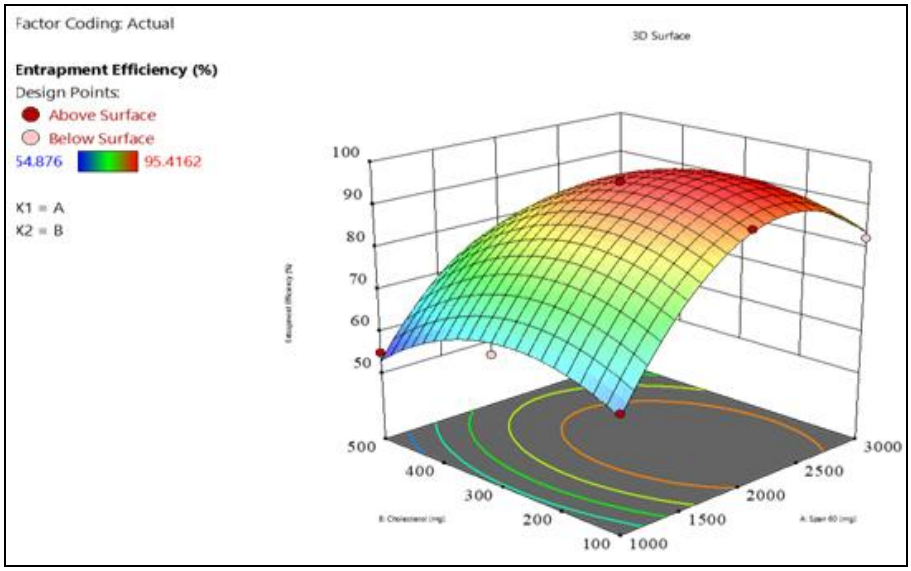


**FIG. 3: 3-D RESPONSE SURFACE PLOT SHOWING THE EFFECT OF AMOUNT OF SPAN 60 CHOLESTEROL FOR PERCENTAGE ENTRAPMENT EFFICIENCY (%)**

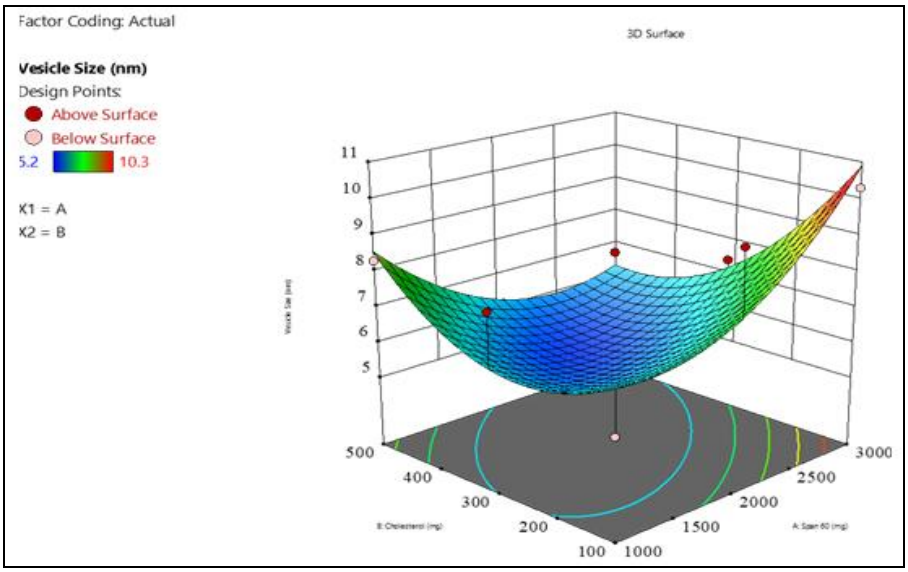


**FIG. 4: 3-D RESPONSE SURFACE PLOT SHOWING THE EFFECT OF AMOUNT OF SPAN 60 CHOLESTEROL FOR VESICLE SIZE (µM)**

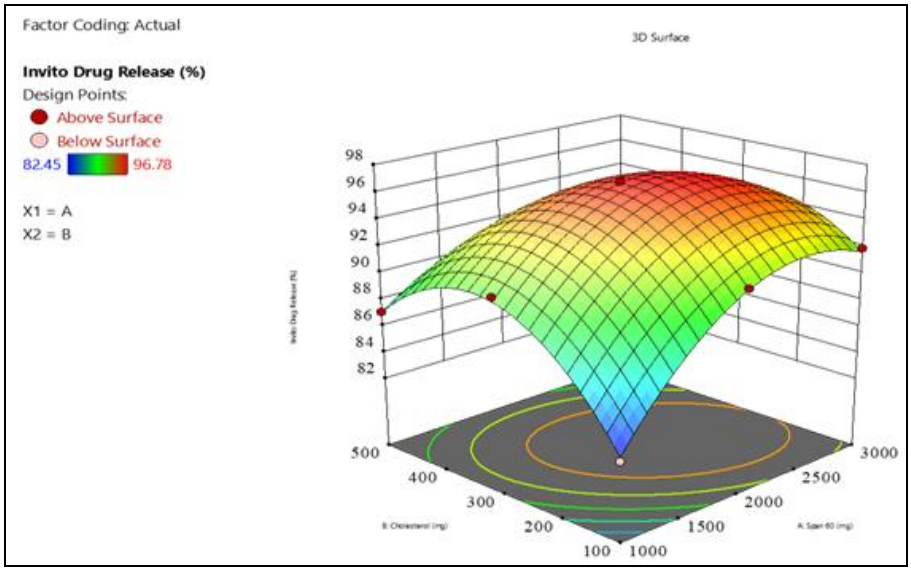


**FIG. 5: 3-D RESPONSE SURFACE PLOT SHOWING THE EFFECT OF AMOUNT OF SPAN 60 CHOLESTEROL FOR *IN-VITRO* DRUG RELEASE (%)**

The desirability function approach is one of the most widely used method for optimization of multiple responses. Overall desirability function is a measure of how well the combined goals for all responses are satisfied. Desirability function ranges from 0-1, with value closer to 1 inhdicating a higher satisfaction of response goal. The numerical optimization tool provides 3 set of optimum solution **Table 6** among which 2083.165 mg of span 60 and 312.989 mg of cholesterol were selected by the software as optimized concentration with desirability of 0.976. The area of optimized formulation was also ratified using overlay plot as shown in figure6 in which yellow region represents the area satisfying the imposed criteria.

**TABLE 6: DESIRABILITY TABLE**

| Sl. no. | Span 60(mg) | Cholesterol (mg) | Y1 | Y2 | Y3 | Desirability | |
|---|---|---|---|---|---|---|---|
| 1 | 2083.165 | 312.989 | 95.416 | 5.538 | 96.713 | 0.976 | **Selected** |
| 2 | 2071.549 | 311.289 | 95.409 | 5.534 | 96.710 | 0.974 | |
| 3 | 2065.328 | 309.356 | 95.401 | 5.531 | 96.708 | 0.971 | |

Y1: Percentage entrapment efficiency, Y2: Mean vesicle size, Y3: *In-vitro* drug release.

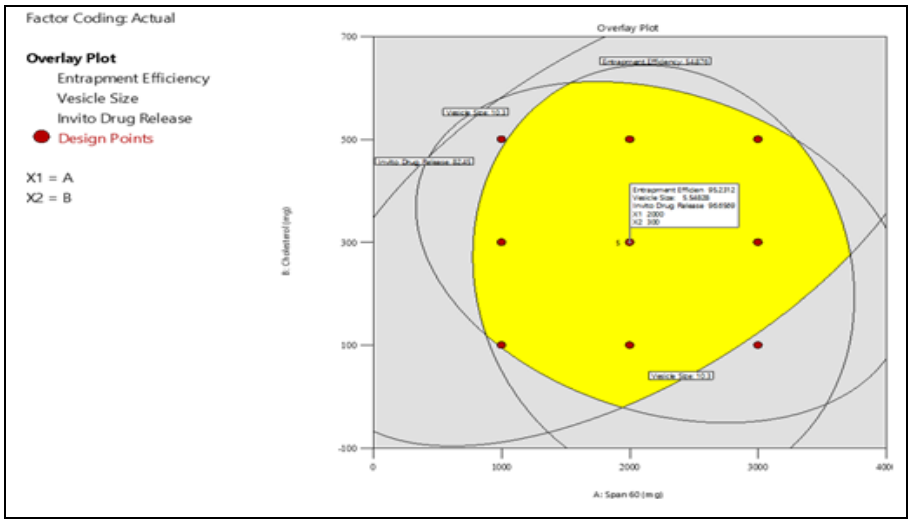


**FIG. 6: OVERLAY PLOT OF OPTIMIZED FORMULATION ECONAL NITRATE PRONIOSOMAL GEL**

The experiment was carried out in triplicate at the selected optimum concentrations (2083.165mg of span 60 and 312.989mg of cholesterol) and the resulting proniosomal gel were evaluated for entrapment efficiency, vesicle size and drug release. The result are shown in **Table 7.**

**TABLE 7: RESPONSE VALUES OF PREDICTED, EXPERIMENTAL AND PERCENTAGE ERROR OBTAINED AT OPTIMAL LEVELS OF THE FACTORS**

| Response | Predicted value | Observed value | % error |
|---|---|---|---|
| YI | 95.23 | 95.41 | 0.001 |
| Y2 | 5.54 | 5.20 | -1.06 |
| Y3 | 96.65 | 96.78 | 0.001 |

Y1: Percentage entrapment efficiency, Y2: Mean vesicle size, Y3: *In-vitro* drug release.

**FIG. 7: PHOTOGRAPH OF OPTIMIZED FORMULATION**

**Scanning Electron Microscopy Examination:** The fig shows the SEM image of the proniosomal gel. It has nearly spherical shape with a smooth surface showing that encapsulated drug vesicles are in nano-size range with no sign of aggregation, signifying the homogeneity of the produced proniosomal gel.

**Drug Release Kinetics:** In the optimized formulation, the correlation coefficient for zero-order kinetics was 0.9397, for first-order release kinetics it was 0.9821, and for the Higuchi plot, it was 0.9065. This indicates that the formulation follows first-order kinetics. To understand the exact mechanism of drug release from the proniosomal gel, the data was analyzed using the Korsmeyer-Peppas plot.

The slope of the plot, represented by 'n', explains the release mechanism: if n = 1, the release is time-independent (zero-order); if n = 0.5, it follows Fickian diffusion; if n is between 0.5 and 1, it shows non-Fickian diffusion; and if n > 1, it indicates super case transport. The 'n' value for the best batch was 0.7951, suggesting non-Fickian diffusion.

**TABLE 11: KINETIC STUDIES OF THE OPTIMIZED FORMULATION**

| Zero order | First order | Higuchi | Korsmeyer-Peppas |
|---|---|---|---|
| $R^2$ | $R^2$ | $R^2$ | $R^2$ |
| 0.9397 | 0.9821 | 0.9065 | 0.9618 |

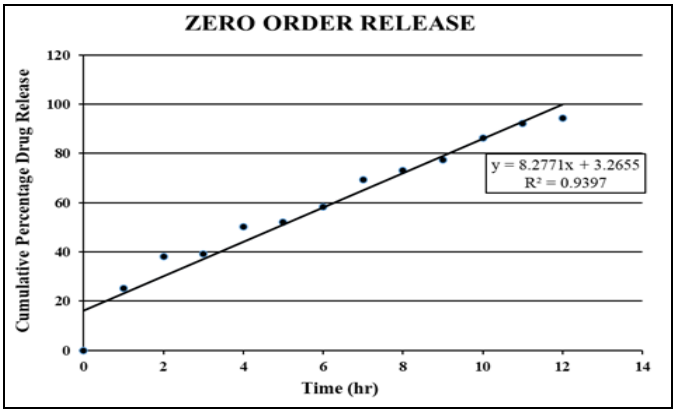


**FIG. 8: ZERO ORDER RELEASE KINETICS OF THE OPTIMIZED FORMULATION**

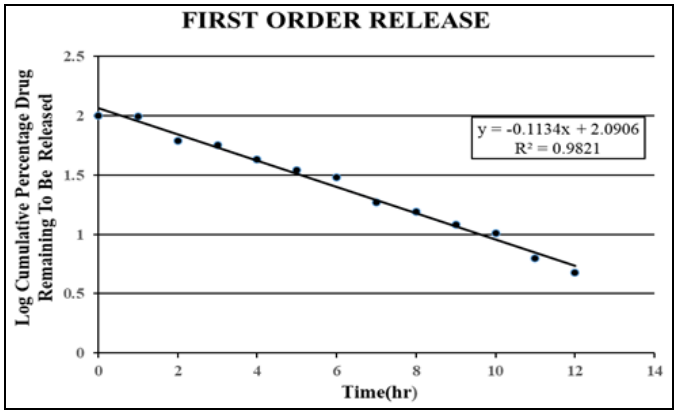


**FIG. 9: FIRST ORDER RELEASE KINETICS OF THE OPTIMIZED FORMULATION**

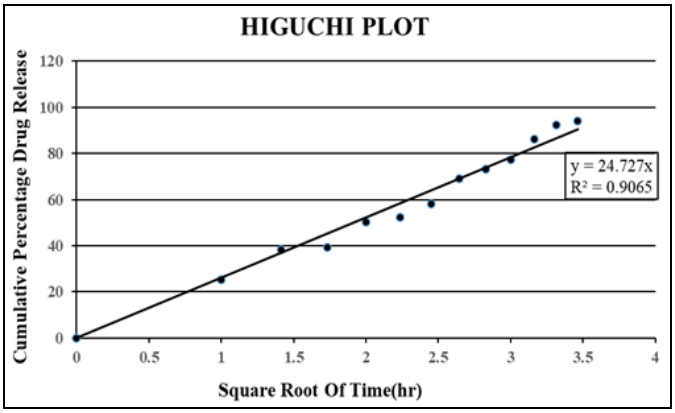


FIG. 10: HIGUCHI PLOT OF THE OPTIMIZED FORMULATION

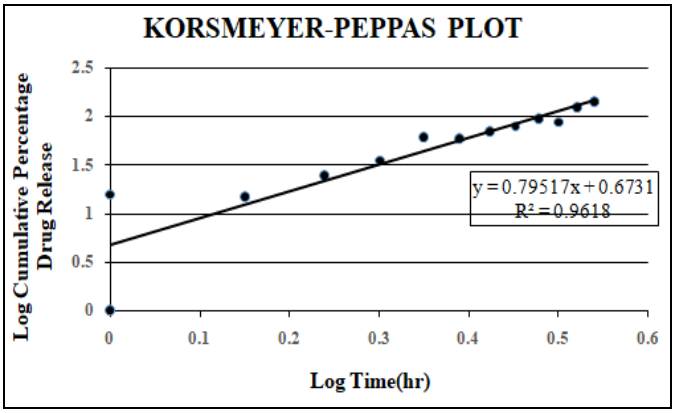


FIG. 11: KORSMEYER-PEPPAS PLOT OF THE OPTIMIZED FORMULATION

***In-vitro* Anti-fungal Study:** The optimized formulation showed greater antifungal efficacy against candida albicans at concentration 1%w/w compared to marketed preparation.

**TABLE 11: MEAN OF RADIUS OF ZONE OF INHIBITION (MM) OF OPTIMIZED FORMULATION IN DIFFERENT CONCENTRATIONS - (1): 0.5% W/W, (2): 0.75% W/W, (3): 1%W/W, (4): MARKETED PREPARATION AGAINST CANDIDA ALBICANS**

| Sl. no. | Formulation code | Mean of radius of zone of inhibition (mm) against candida albicans |
|---|---|---|
| 1 | Sample 1 | 9.05±0.21 |
| 2 | Sample 2 | 13.38±0.76 |
| 3 | Sample 3 | 17.05±0.38 |
| 4 | Sample 4 | 14.56±0.84 |

All values expressed as mean of ± SD, n = 3

**Stability Studies:** From prepared 13 formulation, the optimized formulation was used for stability studies as per the ICH guidelines for 3 months. It shows that prepared proniosomal gel pass stability studies without much significant changes in the percentage entrapment efficiency, mean vesicle size and in vitro drug release.

**TABLE 12: STABILITY STUDY OF OPTIMIZED FORMULATION**

| Storage condition | Sampling interval | Percentage entrapment efficiency (%) | Mean vesicle size(µm) | *In-vitro* drug release (%) |
|---|---|---|---|---|
| 40ºC ± 2ºC at | Initial study | 95.41±0.65 | 5.20±0.18 | 96.78±0.48 |
| 75% ± 5%RH | 30 days | 94.31±0.85 | 5.19±0.33 | 96.46±0.48 |
| | 90 days | 93.60±0.55 | 5.18±0.56 | 95.8±0.48 |
| 25ºC ± 2ºC at | Initial study | 95.41±0.15 | 5.20±0.11 | 96.78±0.48 |
| 60% ± 5% RH | 30 days | 95.15±0.63 | 5.19±0.74 | 96.55±0.48 |
| | 90 days | 94.83±0.79 | 5.19±0.09 | 95.62±0.48 |
| 5ºC ± 3ºC | Initial study | 95.41±0.43 | 5.20±0.12 | 96.78±0.48 |
| | 30 days | 95.32±0.63 | 5.19±0.22 | 96.29±0.48 |
| | 90 days | 94.65±0.81 | 5.18±0.44 | 95.57±0.48 |

**CONCLUSION:** This study successfully developed a proniosomal gel of econazole nitrate using the coacervation phase separation method with Span 60, cholesterol, and lecithin. The results demonstrate that this gel can be an effective option for sustained topical antifungal treatment. Optimization studies determined the best formulation, containing 2083.165 mg of Span 60 and 312.989 mg of cholesterol, which led to high drug entrapment, sustained release and well-formed spherical vesicles. The study also found that the number of non-ionic surfactants and cholesterol had a major impact on entrapment efficiency, vesicle size, and drug release. The optimized gel provided sustained drug release for over 12 hours and achieved an entrapment efficiency of 95.41%, improving skin retention and drug availability. The vesicles remained stable, discrete, and spherical, aiding in better skin absorption. The gel showed stronger antifungal activity than a commercially

available formulation, as indicated by a larger zone of inhibition in microbiological tests. This suggests that the formulation not only extends drug release but also enhances its therapeutic effect, making it a promising option for treating superficial fungal infections. In summary, econazole nitrate proniosomal gel shows great potential as an improved topical antifungal treatment. It offers better drug penetration, prolonged action, and higher effectiveness, which could lead to improved patient outcomes and greater treatment success.

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