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# FLUCONAZOLE LOADED NIOSOMAL GEL FOR TOPICAL APPLICATION

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**Abstract**

The barrier qualities of the skin are currently the subject of extensive investigation. Despite extensive investigate and progress exertions in this system and the advantages of these technologies, low stratum corneum permeability limits the efficacy of topical drug distribution.. In order to treat systemic and superficial fungal infections, fluconazole, a broad range imidazole derivative, is used. In contrast, the conventional formulation requires a high dose, which may result in serious allergic reactions and irregular heartbeat. Fluconazole niosomes were therefore formulated in an effort to increase lessen the side effects of topical treatment due to the poor skin penetration. The non-ionic surfactants Span 60, Tween 60, and Span 40 were combined with cholesterol in a variety of proportions to formulate fluconazole niosomes through thin film hydration and ether injection. The size, shape, entrapment effectiveness, and in-vitro drug release of the produced niosomal formulations were assessed. The niosomes had a spherical appearance, and their sizes ranged from 3.24 0.11 to 7.38 3.64 m. At the conclusion of 24 hours, it was discovered that the entrapment efficiency ranged from 50.420.51 to 78.630.91% and the in-vitro drug release ranged from 48.540.89 to 76.432.89%. Fluconazole niosomes produced with Span 60 and cholesterol in a ratio of 1:0.2 were the most effective and were added to 1% carbopol gel. The developed gel aimed at a number of physicochemical characteristics, including viscosity, appearance, pH, drug content, and antifungal efficacy. The in-vitro drug release research, which conducted using phosphate buffered saline pH 7.4, revealed a 28.201.73% concentration after 12 hours. This study discovered that the best topical antifungal formulation is fluconazole loaded in niosomes and blended with gel as opposed to generic medication gel.

**Keywords:** Niosomes; Fluconazole; Skin permeation; Carbopol gel; In-vitro drug release.

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## Introduction:

Localised drug distribution through the skin, vagina, rectal, and ocular cavities is known as topical drug administration. For local dermatological therapy, the market offers a range of topical medications including antifungal agents, including creams, ointments, and powders. One of the antifungal drugs is the imidazole derivative fluconazole, which has broad-spectrum antimycotic action. It is sold as creams,gels, and pills and works by preventing the manufacture of sterol ergosterol, a vital part of fungal cell membranes[1]. Localized oropharyngeal candidiasis, vaginal yeast infections, and fungal skin diseases like jock itch, ring worm, and athlete's foot are all commonly treated with fluconazole. Fluconazole side effects frequently include blisters, irritation, pain, or redness. Slight scorching at the submission spot, severe allergic responses (rash, stinging, and swelling of the mouth, face, lips, ortongue), and other adverse effects are also frequent. blisters, and blister-like lesions it was hypothesised that fluconazole would be incorporated into niosomes. It was also anticipated that the drug's toxicity and cost would decrease as the dose and frequency of its topical applications decreased. Fluconazole is encapsulated in niosomes, prolonging drug delivery, reducing side effects that are frequently experienced, and preventing significant drug accumulation[2].

Due to the vital need for innovative therapy options to treat skin diseases, dermatologic research is currently expanding. Skin conditions will nonetheless make patients' conditions more difficult. During topical application, the skin acts as a natural barrier to prevent particle penetration. Additionally, it offers a potential way to deliver drugs, particularly to skin that is injured and through the openings of hair follicles. Recent developments in dermatological treatment can be achieved by enhancing the dermal localization of bioactive into the injured skin region using cutting-edge nanocarriers that deliver the drugs directly to the target cells.[3].

An developing type of drug delivery devices called nanocarriers can be easily customised to carry medications to different regions of the body, including the skin. A local response is what is intended when most therapeutic substances are applied to human skin. Nanocarriers might serve as practical means for administering medicinal substances to the skin. When opposed to adding dermatologically active therapeutics directly to conventional multiphase semi-solid vehicles, loading them in nanoparticles may have a number of advantages. [4].

A microscopic lamellar structure called niosomes (non-ionic surfactant vesicles) is formulated when cholesterol[5]. Because of their benefits in a number of areas, such as chemical constancy, high purity, content uniformity, low cost, straightforward non-ionic surfactant storage, and a large variety of surfactants accessible for niosome construction, niosomes are becoming more and more well-liked. A possible medicine delivery method is niosomes[6]. Niosome-encapsulated medicines have the potential to boost drug bioavailability and target the diseased area while reducing drug degradation and inactivation after administration[7]. Additionally, the use of niosomes as delivery mechanisms for oral vaccines, antitubercular, antileishmanial, anti-inflammatory, and other medications has been investigated[8].

As a result, in the recent learning, an effort will be complete to progress a gel of fluconazole niosomes. For the current investigation, fluconazole is chosen as an appropriate medicine to more successfully treat skin of the fungal infection.

## MATERIAL AND METHODS

### Materials:

Mumbai-based Cipla gave Fluconazole as a gift sample. We bought polymers from

SD Fine Chemicals Ltd.(Span 40 and 60, Tween 60)

**Niosome preparation procedure:**

**Thin film hydration method**

The thin film hydration method, as shown in Table 1, was utilised to formulated niosomes from the lipid combination of surfactant (span 40, span 60, and tween 60) and cholesterol, by various prescribed ratios. In 10 ml of chloroform, the surfactant, cholesterol, and drug were dissolved. At a temperature between 55 and 65 °C, the solvent was then evaporated using a flash evaporator(rotatory) while under reduced pressure. until a thin lipid film formed after being moved to a 100 ml round-bottom bottle from the lipid mixture. In order to hydrate the created film, 20 ml of PBS pH 7.4 were used. In the rotary evaporator the flask was rotated at 55 to 65 degrees for an additional hour while the hydration process continued. The hydrated niosomes were subjected to a 20-minute bath sonication procedure in order to produce niosomal dispersions with together allowed and tricked formulations of changing sizes.[9,10].

**Evaluation of Fluconazole niosomes:**

**Morphological characterization:**

The formulation of the vesicles was verified using optical microscopy at a 45 X magnification. The production of vesicles was monitored in the dry thin film of niosome suspension that had been spread done a glass slide and fixed by room-temperature drying. Digital photography was also used to capture a microphotograph of the niosome from the microscope[11] Figure 1. Using a scanning electron microscope, the chosen Minoxidil niosomes formulation's fine surface characteristics were examined.

**Fourier transform infrared spectroscopy study:**

The infrared spectra of fluconazole, excipients, and formulation (TNS4) were detected using the potassium bromide dispersion method.

**Entrapment efficiency:**

A rigorous dialysis approach was used to gauge the niosomes' level of entrapment efficacy. Niosomes were suspended in a dialysis tube that had a sigma dialysis membrane securely connected to one side of the tube. Using a magnetic stirrer and 100 ml of pH 7.4 PBS (0.2% T.80) while it was suspended, the unentrapped medication was then removed from the dialysis tube. The disruptive solution and the free drug were separated by a medium-thick, semipermeable barrier. At intervals of 60 minutes, 100 ml of the total medium was changed with new medium for about 7-9 hours, or until the absorbance levelled out. The calibration curve served as a guide to determine the drug concentration in the removed samples, which were then analysed for absorbance at 261.5 nm[12].

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

At a wavelength of 261.5 nm, the samples were examined13, 14. The membrane diffusion method was used to evaluate the release of fluconazole from niosomal preparations. The unentrapped drug was removed, leaving the residual niosomes dialyzed-interested in a 100 ml of PBS pH 7.4 including flask and methanol 10% v/v (to retain sink state), which functioned as the receptor compartment.. A magnetic stirrer was used to agitate the receptor medium as it was heated to 37 °C and 0.5% humidity. Aliquots of the 5 ml sample were periodically reserved, and the similar capacity of average was then added again. The composed models were examined[13,14], using a UV spectrophotometer calibrated at 261.5 nm. Three copies of each evaluation were made..

**Formulation of niosomes entrapped Fluconazole:**

Fluconazole corresponding to 1% w/w in a chosen niosomal suspension (TNS4) was added to a gel base made up of carbopol

(1%), triethanolamine (qs), and enough distilled water. Evaluation of niosomal gel[15,16].

A. **Physical appearance:** Checks were made on the resulting gel's clarity, colour, homogeneity, and presence of extraneous elements.

B. **pH:** The gel was precisely measured at 2.5 grammes and dissolved in 25 ml of purified water. Using a digital pH metre, the pH of the dispersion was determined

**C. Rheological study:**

**Viscosity measurement:** By using the Brookfield programmed DV III ultra viscometer used to determine viscosity. For the purpose of measuring viscosity, we selected spindle number CP 52 at an optimal speed of 0.01 rpm.

**D. Content uniformity:**

The drug concentration of the final formulation measured by carefully combining 10 mg equivalent of niosomal gel with 20 ml of PBS pH 7.4 in a 100 ml volumetric bottle. The mixture was subsequently filtered using Whatmann filter paper No. 41. The aforementioned solution was diluted by adding 3 ml of PBS pH 7.4 to a 10 ml volumetric flask. With the aid of a Shimadzu UV-visible spectrophotometer and a blank as a reference, the concentration of fluconazole was determined at 261.5 nm. The outcomes are shown in Table 2.

**E. *In vitro* drug diffusion study:**

Following the addition of 20 ml of PBS pH 7.4 and thorough mixing, 10 mg equivalent of niosomal gel from a 100 ml volumetric flask was added. The volume of PBS was then added to the solution, and the pH was corrected to 7.4 by filtering it through Whatmann filter paper No. 41. The aforementioned solution was added to a 10 ml volumetric flask as needed, along with 3 ml of PBS pH 7.4. A Shimadzu-UV-visible spectrophotometer set at 261.5 nm and a blank were used to measure the fluconazole concentration. While the entire assembly was fixed, the medium in the compartment was stirred using a magnetic stirrer at a temperature of 37°C by softly touching the lower end of the cell-containing gel (1-2 mm deep) to the diffusion media. The receptor compartment was periodically emptied of aliquots (5 ml), and the same amount of new buffer was added in their place. At 261.5 nm, the material was assessed using a UV-visible spectrophotometer. Two separate experiments were conducted. [17,18].

**In vitro antifungal activity**

*Aspergillus niger* was used as the test organism in studies comparing the living movement of niosomal formulation to simple gel Fluconazole and commercial Fluconazole ointment. This is resolute by agar diffusion testing utilizing the "Cup plate" method. The trial microorganisms were added to a film of Sabouraud's dextrose agar media (20 ml) and allowed to set up in the petri plates. Cups were created on the firm agar layer using a sterile borer (5 mm). Niosomal gel solution (1 g of drug) is placed in 0.5 ml of one cup (i.e., hole) designated with a "F," and advertised gel solution (1 g of drug) is placed in 0.5 ml of the other cup (i.e., hole) marked with a "M." Comparable is a third. The petri dishes underwent a 24-hour incubation process at 37 C after being left at room temperature for an hour. We measured the reserve areas surrounding each cup.[19,20].

## RESULTS AND DISCUSSION

Thin film hydration was used in the present investigation to produce fluconazole niosomes from cholesterol and a range of non-ionic surfactants (Span 40, Span 60, and Tween 60) in various ratios (1:0.2, 1.5:0.3, and 2:0.4). The produced Fluconazole niosomes' particle size, shape, entrapment efficiency, and in vitro drug release were all evaluated. The ideal preparation for topical treatments was then added to the gel.as shown in Table 2.

**Vesicle formation:**

The equilibrium between the lypophilic and hydrophobic segments of non-ionic surfactants is essential for the production of niosome vesicles. To observe the vesicle production, the produced vesicles were examined at a magnification of 45 X. Niosomes were seen to be smooth-surfaced, spherical vesicles. When cholesterol is added, the size of these vesicular suspension's changes. The correlation between niosome size and cholesterol content is thought to be responsible for the shrinking of vesicles due to an increase in hydrophobicity and the beneficial interaction between medicines and niosomal environment. The produced niosomes were measured, and they ranged in diameter from 3.24 0.11 to 7.38 3.64 m. Future, the surface morphology examined using a scanning electron microscope. Figure-2.

**The effect of drug solubility on particle size and entrapment efficiency:**

It is common knowledge that niosomes prefer to uptake lipophilic medications over hydrophilic ones. This comparatively large drug loading was anticipated given the drug's lipophilicity, which led to the drug being preferentially partitioned to the lipid phase of the vesicles. When a drug is contained in nonionic surfactant vesicles, The growth in particle size is most likely the result of the drug's interaction with the head groups of the surfactant, which raises the vary and resiprocal repulsion of the surfactant bilayers. Since the hydrocarbon chains offer the drug molecules a favourable solubilizing environment, it is hypothesized that lipophilic drugs will be positioned amongst the fatty acyl side chains of the bilayer membrane.

**Sonication:**

One of the utmost widely utilized processes for producing a phospholipid vesicle of recognized size is sonication. It has been established that cavitation, or bubble formation, is the primary outcome of sonication and is what causes the majority of the physical belongings of sonography on lipid membranes. Niosome preparation was done after 20 minutes of sonication.

**Entrapment efficiency:**

To prepare niosomes, procedure variables including vacuum, hydration medium, hydration time, and flask rotation speed are crucial. If these settings are chosen incorrectly, brittle niosomes may form or drugs may leak from niosomes due to inappropriate hydration. The thickness and homogeneity of the lipid coating were clearly influenced by the flask's spinning speed. Hydration temperatures must be greater than the gel-to-liquid phase transition temperature of the system. The findings indicate how phase transition temperatures affect increased entrapment efficiency. Cholesterol (CHO) is required for the production of stable nonionic surfactant-based vesicles. Ion permeability, combination, the fusion procedure, resistance, size, and form are only a few of the features of membranes that are impacted by the presence of CHO. Biomembranes and lipid vesicles both almost always contain CHO. CHO can pass through the bilayer membrane because it is amphipathic, aligns its aliphatic chain with the hydrocarbon chains in the middle of the membrane, and points its hydrophilic head towards the aqueous surface. The effects of CHO on the nonpolar tail of nonionic surfactants and the chain order of liquid-state bilayers are well recognized. Increased levels of fluconazole entrapment are caused by a rise in cholesterol levels. The increase in drug level in niosomes is made possible by cholesterol's capacity to close the leaky area in the bilayer membranes, which is assumed to be the cause of the increase in entrapment efficiency. By an rise in surfactant concentration, entrapment efficiency rose, and maximum drug release took longer.The unentrapped medication was separated using dialysis to evaluate the entrapment

efficiency, which ranged from 51.640.32 to 78.630.91%. Table- 3.

***In vitro* release study:**

Drug is not soluble in water, a suitable medium must be created that can give the drug enough solubility to sustain the necessary sink state during diffusion trials. PBS pH 7.4 was initially chosen because it has improved the stability of minoxidil. For the diffusion experiment, it was thoughtthat a medium containing 10% methanol would be adequate. 100 ml of receptor medium were utilised. Lower drug elution from the vesicles is the result of the decreased membrane permeability caused by the increase in cholesterol content. At the conclusion of 24 hours, it was discovered that the formed niosomes' in vitro drug release ranged from 48.540.92 to 76.432.89% (Table 2). To characterise the release kinetics, the in-vitro drug release data were fitted to first order charts, higuchi diffusion plots, and peppas log-log plots. In the regression coefficient values for the full graph, both techniques demonstrated high linearity. Slope values for the Peppas log-log plot were also computed. The slope values of the Peppas plots, which were always between 0.62 and 0.80, showed the use of a non-fickian (anomalous) release mechanism, such as a combination of diffusion and erosion-controlled drug release. When compared to all other thin film hydration formulations, TNS1, TNS2, and TNS4 showed the maximum drug release. Compared to TNS1 and TNS2, TNS4 had the highest entrapment efficiency. Additionally, it demonstrated that TNS4's particle size is smaller than TNS1's. As a result, formulation TNS4 was determined to be the best after taking into account all of these factors. Its vesicle size was 3.55 0.35 m, its entrapment efficiency was 74.97 0.23 %, and its drug release was 76.43 2.89 % after 24 hours. The best ENS4 for the ether injection method had a vesicle size of 3.53 0.07 m, an entrapment efficiency of 67.36 0.39%, and a drug release of 71.44 2.20% after 24 hours. When compared to the ether injection method, the formulation made using thethin film hydration method demonstrated improved drug release. Finally, pellets from the best TNS4 formulation were obtained by centrifuging, and they were added to a 1% carbopol. as shown in Figure 5 and 6.

**Niosomal gel:**

Carbopol was used for the preparation of niosomal gel in this investigation because of its hydrophilic and bio adhesive characteristics, which may cause a drug to spend longer at the place of absorption by relating with the mucosa. After being incorporated into the gel base, niosome stability was improved, which may be attributable to the absence of niosome fusion.

Aesthetics, pH, viscosity, drug content, in-vitro drug release, and antifungal activity were assessed for promising formulation (TNS4). Whitish is the colour of the niosomal gel formulation. The gel had a pH of 5.56 0.05 and a viscosity of 8370 cps. It was discovered that the niosomal gel contained 96.420.60% of medication. The generated niosomal gel formulation is also put through an in-vitro releaseinvestigation, and the results are related with commercially available gel (Flucos) and plain FLZ gel. After 12 hours, the amounts of the medication produced by theniosomal gel formulation, FLZ plain gel, and commercialized gel varied: 28.201.73, 73.081.01, and 86.370.98%. To describe The data from the in-vitro drug release was fitted to first order plots, higuchi diffusion plots, and peppas log-log plots to determine the release kinetics. The values of the regression coefficients for the entire graph demonstrated good linearity. The Peppas log-log plot's slope values were computed. The niosomal gel release exponents, FLZ plain gel, and commercialized gel were all 0.6953, 0.7614, and 0.6975, respectively. This would indicate that several mechanisms are involved in controlling the release of the medication because it appears

to link the diffusion and erosion mechanisms, a phenomenon called anomalous diffusion.

**IR study:**

The pure drug IR spectra exhibitsdistinctive peaks at 3120, 1619, and 558 cm-1 caused, respectively, by N=H, -F, and O-H. The peaks of formulations TNS4, ENS4, and ENT7 also shared similarities. TNS4, ENS4, and ENT7, at 3346, 1635, and 558 cm-1, 3347, 1635, and 557 cm-1, respectively. This demonstrates that the drug's structure in the formulations is unaltered. There were no drug-excipient interactions as a result. Figures 3 and 4

In vitro Antifungal Activity

Depends on in-vitro characterization experiments, the FLZ niosomal gel formulation underwent additional cup-plate testing for antifungal efficacy. Zones of inhibition for FLZ niosomal gel formulation (F), FLZ plain gel (P), and commercial gel (M) were compared. F, P, and M results came in at 25.3 0.57, 19.6 1.52, and 23.3 3.78 mm, respectively. According to the outcomes, F (TNS4) reaches its peak antifungal activity after 24 hours.

## CONCLUSION

According to the study's findings, cholesterol content and the kind of surfactant had an impact on the effectiveness of drug entrapment and the rate at which it was released from niosomes. In a formulation with asurfactant to cholesterol ratio of 1:0.2, therewas more drug release. By seeing theseoutcomes we can decided FLZ-niosome- loaded gel formulations had longer durations of action than formulations that included FLZ in its non-niosomal form, andthat it is possible to successfully boost the antifungal activity.

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| Ingredients | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $TNS_1$ | $TNS_2$ | $TNS_3$ | $TNS_4$ | $TNS_5$ | $TNS_6$ | $TNT_7$ | $TNT_8$ | $TNT_9$ |
| Ratios (Drug: Surfactant: Cholesterol) | 1:1:0.2 | 1:1.5:0.3 | 1:2:0.4 | 1:1:0.2 | 1:1.5:0.3 | 1:2:0.4 | 1:1:0.2 | 1:1.5:0.3 | 1:2:0.4 |
| Fluconazole* | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Span 40* | 100 | 150 | 200 | -- | -- | -- | -- | -- | -- |
| Span 60* | -- | -- | -- | 100 | 150 | 200 | -- | -- | -- |
| Tween 60* | -- | -- | -- | -- | -- | -- | 100 | 150 | 200 |
| Cholesterol* | 20 | 30 | 40 | 20 | 30 | 40 | 20 | 30 | 40 |
| Chloroform# | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| PBS (pH 7.4)# | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |

Table-1: Formulations of Fluconazole Niosomes prepared by Thin Film Evaporation Method

***** mg, # ml

TNS: Formulation containing Span-40 and Span-60 as a Surfactant Prepared by Thin Film Evaporation Method TNT: Formulation containing Tween-60 as a Surfactant Prepared by Thin Film Evaporation Method

**Evaluation of Niosomal Gel:**

**Evaluation Parameters of Fluconazole Niosomal Gel ($TNS_4$)**

| Sl. No. | Parameter | Result |
|---|---|---|
| 1 | Appearance | Off-white |
| 2 | Homogeneity | Good |
| 3 | pH* | 5.56 ± 0.057 |
| 4 | Percent drug content* | 96.42 ± 0.606 |
| 5 | Viscosity* (cps) | 8370 |

| Sl. No. | Formulation code | Particle size ± SD (µm) | Percentage entrapment efficiency* | Cumulative percent drug released* (After 24 hrs) |
|---|---|---|---|---|
| 1 | $TNS_1$ | 4.213±0.12 | 51.643±0.32 | 74.324±1.647 |
| 2 | $TNS_2$ | 3.260±0.14 | 54.640±0.42 | 72.520±1.972 |
| 3 | $TNS_3$ | 4.106±0.05 | 56.230±0.40 | 62.194±0.923 |
| 4 | $TNS_4$ | 3.553±0.35 | 74.970±0.23 | 76.433±2.899 |
| 5 | $TNS_5$ | 3.953±0.16 | 70.563±0.61 | 65.468±0.574 |
| 6 | $TNS_6$ | 3.245±0.11 | 62.580±0.45 | 67.394±2.231 |
| 7 | $TNS_7$ | 7.38 ± 3.64 | 71.66 ± 0.69 | 57.909±1.734 |
| 8 | $TNS_8$ | 6.84 ± 2.93 | 76.36 ± 2.27 | 50.465±1.432 |
| 9 | $TNS_9$ | 6.3 ± 2.25 | 78.63 ± 0.91 | 48.547±0.954 |

Table 2: Evaluation of Fluconazole niosome

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

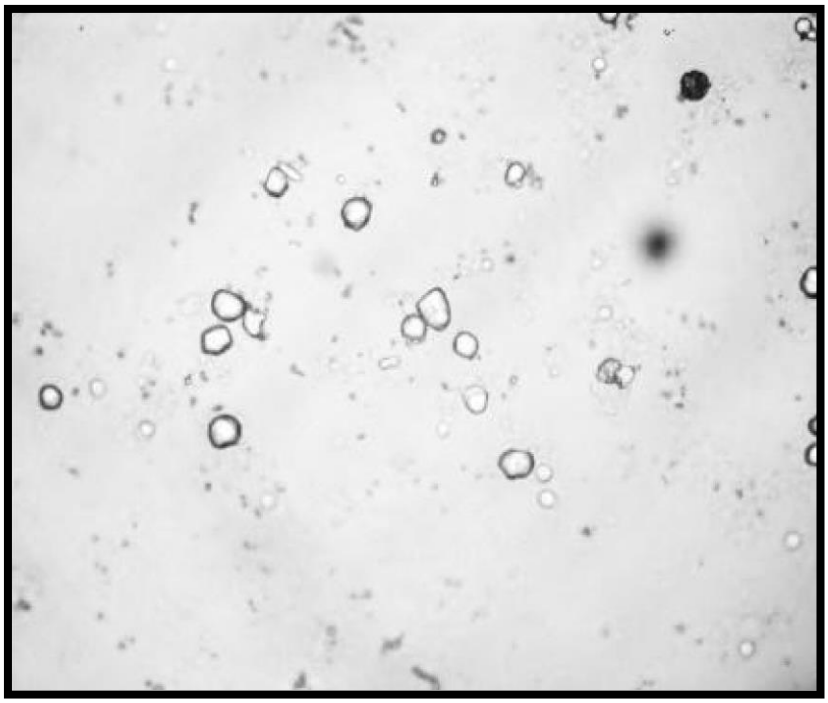

**Figure 1: Microphotograph of Niosome**

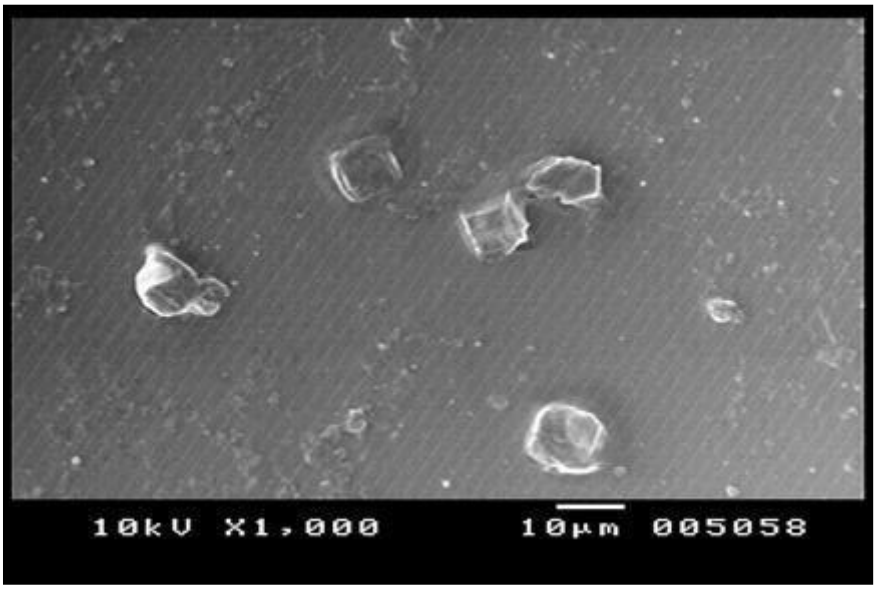


**Figure-2 SEM Image of Niosomes**

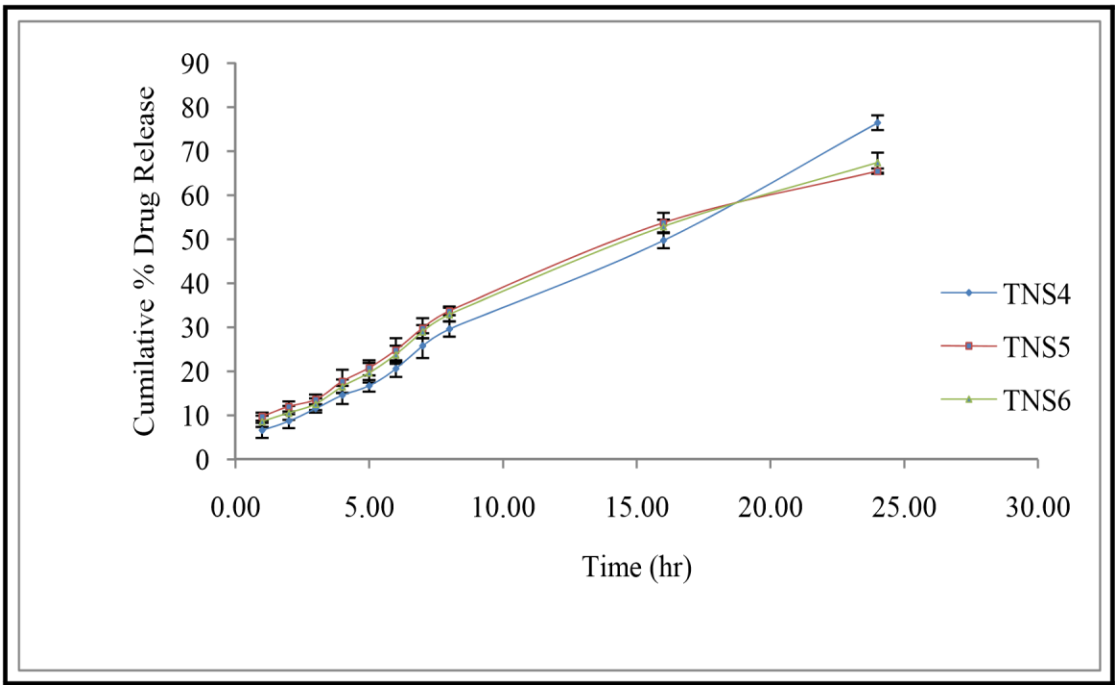


Figure 3 *In-vitro* Release Plot of Fluconazole Niosomes Prepared using Span 60 and Cholesterol

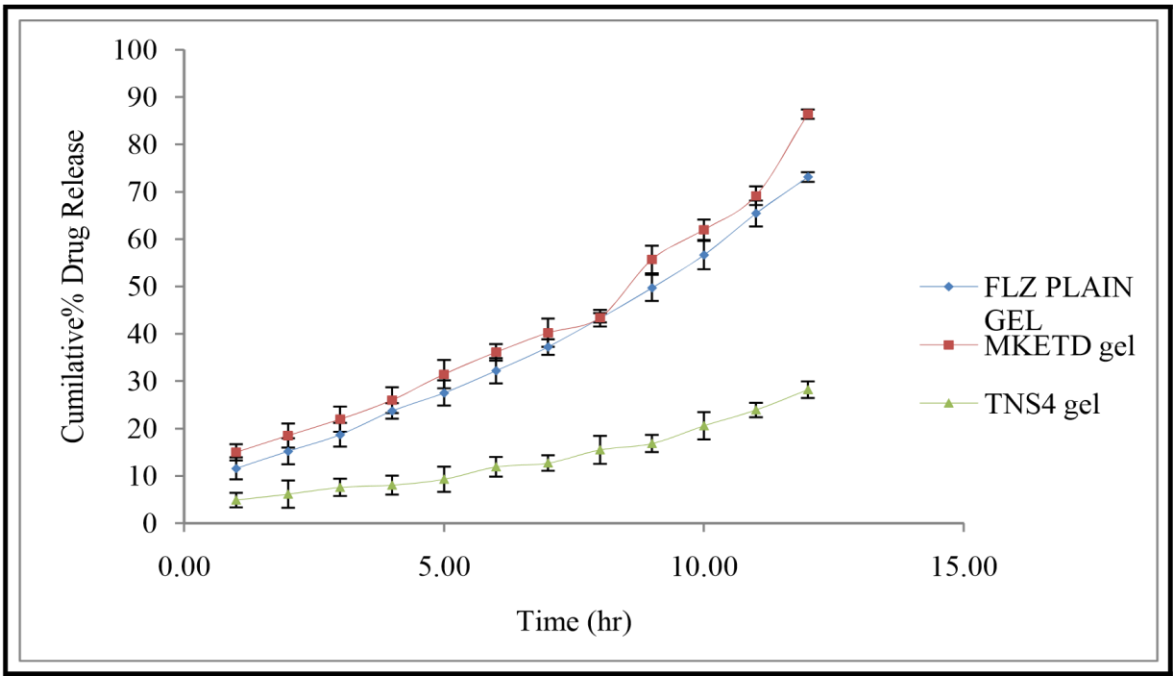


Figure 4: : *In-vitro* Release Plot of Fluconazole Plain Gel, Marketed Gel (Flucos) and Fluconazole Niosomal Gel ($TNS_4$)