*International Journal of Universal Pharmacy and Bio Sciences 9(4): July-August 2020*

***INTERNATIONAL JOURNAL OF UNIVERSAL PHARMACY AND BIO SCIENCES***

***IMPACT FACTOR 4.018****

***ICV 6.16****

**Pharmaceutical Sciences** **Research Article……!!!**

# PREPARATION AND EVALUATION OF PRONIOSOMAL GEL LOADED WITH SERTACONAZOLE

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**KEYWORDS:**

Sertaconazole, antifungal agent, Topical.

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## ABSTRACT

Sertaconazole, a lipophilic drug with a large molecular weight of 437.77 g/mol and has a limiting aqueous solubility is expected to show a poor transport across the skin. The present work describes the novel, surfactant based provesicular drug carrier system (proniosomes),for enhanced skin delivery. Different proniosomal gels were prepared with non-ionic surfactants (spans), cholesterol, soya lecithin and carbopol by co-acervation phase separation method. The prepared formulations were characterized for optical microscopy, particle size analysis, drug entrapment, drug content, rheological studies, in-vitro diffusion and stability studies. The result revealed that Sertaconazole in all formulations was successfully entrapped with uniform drug content. FT-IR studies showed the compatibility of drug with excipients. The optimized proniosomal gel formulation containing of span 60 (F6) showed higher permeation and drug retention as compared to other formulations and marketed formulation (Onabet). No significant changes in physical appearance, pH, vesicle size, entrapment efficiency, drug content and % cumulative drug release was recorded after stability studies. Thus, proniosomes can be used to enhance the topical delivery of poorly water-soluble drug Sertaconazole for athlete's foot treatment.

## INTRODUCTION:

The NDDS should ideally deliver the drug at a rate as needed by the body over the period of treatment and it should channel the active entity to the site of action. Conventional dosage forms including prolonged release dosage forms are unable to meet none of these. At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery. Approaches are being adapted to achieve this goal, by paying considerable attention either to control the distribution of drug by incorporating it in a carrier system, or by altering the structure of the drug at the molecular level, or to control the input of the drug into the bio environment to ensure an appropriate profile of distribution[1].

Novel drug delivery system aims at providing some control, whether this is of temporal or spatial nature or both release of drug in the body. Novel drug delivery attempts to either sustain drug action at a predetermined rate or by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects. It can also localize drug action by spatial placement of controlled release systems adjacent to or in the diseased tissue or organ or target drug action by using carriers or chemical derivatization to deliver drug to particular target cell type[2].

Sertaconazole is commonly used in topical formulations to treat various skin disorders like athlete's foot, tineapedis. It is an imidazole derivative, which acts as a fungistatic, fungicidal, antibacterial, anti-inflammatory, antitrichomonal, and antipruritic. It inhibits 14 a-demethylase, which blocks ergosterol synthesis resulting in the prevention of fungal cell multiplication and hyphae growth.The selected model drug is hydrophobic in nature and oral bioavailability is very poor and negligible and undergo more than 99 % protein binding.In this study we are going to prepare Sertaconazole proniosomal gel by co-acervation phase separation method for the treatment of fungal infection.

## MATERIALS AND METHODS:

### MATERIALS:

Sertaconazole from Arya Pharma Lab Pvt. Ltd, Nepal, Soya lecithin from Sipro Biotech Limited, Ahmedabad. All other reagents and solvents were of analytical grade.

### METHODS:

#### Drug and excipients compatibility studies by FT- IR Spectroscopy

The compatibility between pure drug and surfactants, cholesterol, lecithin was detected by FTIR spectra obtained on Perkin Elmer 1600 series USA. The potassium bromide pellets were prepared on KBr press. To prepare the pellets the solid powder sample were ground together in a mortar with 100 times quantity of KBr. The finely grounded powder was introduced into a stainless steel die. The powder was pressed in the die between polished steel anvils at a pressure of about $10t/in^2$. For liquid samples thin

film of sample liquid is made on pellet. The spectra's were recorded over the wave number of 8000 cm-I to 500 cm –l shown inFIGURE:1-4.

**Preparation of Proniosomes of Sertaconazole**

Co-acervation phase separation method is the most common method utilized for the preparation of proniosomal formulation. In this method, drug along with surfactant, lecithin and cholesterol was mixed in wide-mouth glass tube with absolute ethanol. Then the open end of the glass tube was covered with a lid and the tube was warmed in a water bath at 65±3$^0$C for 5 min. Then 1.6 ml of phosphate buffer pH 7.4 was added and the mixture was further warmed in water bath for about 2 min, so that a clear solution was obtained and then was allowed to cool at room temperature. Formulation chart shown in TABLE:1.

**TABLE:1 Formulation of proniosomes of sertaconazole**

| Ingredients | Formulations | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Sertaconazole(mg) | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |
| Span 20 (mg) | 250 | 500 | 750 | - | - | - | - | - | - |
| Span 60 (mg) | - | - | - | 250 | 500 | 750 | - | - | - |
| Span 80 (mg) | - | - | - | - | - | - | 250 | 500 | 750 |
| Cholesterol (mg) | 750 | 500 | 250 | 750 | 500 | 250 | 750 | 500 | 250 |
| Soya lecithin (mg) | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| Ethanol (ml) | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |

**Preparation of Proniosomal gel**

Required quantity of Carbopol-934P was weighed and soaked in a required quantity of distilled water for 3 hours, the mixture was transferred to mechanical stirrer at 100 rpm to form homogenous viscous solution. The mixture was neutralized by drop wise addition of triethanolamine. Other excipients (0.2% methyl paraben and 0.02% propyl paraben) was added on it. Mixing was continued until a formation of a transparent gel. The prepared proniosomes were mixed with carbopol gel, such that the prepared gelhave 2% w/w Sertaconazole concentration (300 mg drug per 15gm of gel), shown in TABLE:2.

**TABLE: 2 Formulation of proniosomal gel containing sertaconazole**

| Ingredients | Formulations |
|---|---|
| Sertaconazole (%w/w) | 2 |
| Carbopol (%w/w) | 1.0 |
| Methyl paraben (%w/w) | 0.2 |
| Propyl paraben (%w/w) | 0.02 |
| Triethanol amine (%w/w) | |

**EVALUATION OF PROMOSOMAL GEL CONTAININGSERTACONAZOLE**

**Physical examination**

The prepared gel formulations were inspected visually for their color, odour, homogeneity, consistency, grittiness and spreadability.

**Determination of pH**

The pH of gels was determined using a calibrated pH meter. The readings were taken for average of 3 samples.

**Rheological studies**

Rheological study was carried out by Brookfield viscometer by selecting suitable spindle and at 10 rpm. Preparation was kept in 30 ml beaker which was set up to spindle groove was dipped avoiding trapping of air bubbles. Start the motor after entering the spindle number. Floating point display is used for the viscosity. Spindle was selected by trial and error method.

**Spreadability Coefficient Studies**

The spreadability of the gel formulation was determined 48h after preparation. The two glass slides are taken. At the lower slide sufficient amount of gel was placed and covered by upper slide. Upper slide was pressed by uniform weight of 20 g for 2 hrs.Time taken for second slide to slip out from other was measured.

Spreadability = Weight tied on upper slide (g) x Length of glass slide (cm) / time

**Microphotography**

The niosomes were mounted on glass slides and viewed under a microscope with magnification of 1200X for morphological observation after suitable dilution. The photomicrograph of the preparation also obtained from the microscope by using a digital SLR camera.

**Vesicle size analysis**

Hydration of proniosomal gel (100mg) was done by adding saline solution (0.9% solution) in a small glass vial with occasional shaking for 10 min. The dispersion was observed under optical microscope at IOOX magnification. The sizes of vesicles were measured using a calibrated ocular and stage micrometer fitted in the optical microscope .samples were then assayed spectrophotometrically using UV-Visible spectrophotometer at 260 nm.

**Drug entrapment efficiency**

Proniosomal gel (0.1 g) was reconstituted with 10 ml of pH 7.4 phosphate buffer in a glass tube. The aqueous suspension was sonicated in a sonicator bath for 30 min. The sertaconazole containing niosomes were separated from untrapped drug by centrifuging at 10,000 rpm at $4^0$C for 30 min. The supernatant was taken and diluted with pH 7.4 phosphate buffer and the concentration in the resulting

solution was assayed by spectrophotometrically using UV-Visible spectrophotometer at 260 nms[2].The percentage of drug encapsulation was calculated by the following equation.

EE [(Ct- Cf)/Ct] x100

Where,

Ct is the concentration of total drug,

Cf is the concentration of free drug.

**Drug content analysis**

Proniosomes equivalent to 20 mg drug were taken into a standard volumetric flask. They were lysed with 25 ml of methanol by shaking for 15 min. The clear solution was diluted to 100 ml with methanol. Then 10 ml of this solution was diluted to 100 ml with saline phosphate buffer 7.4. Aliquots were withdrawn and the absorbance was measured at 260 nm and drug content was calculated from the calibration curve.

**In-vitro diffusion studies**

In-vitro diffusion studies of proniosomal gel were carried out using egg membrane. Proniosomal gel equivalent 20 mg drug was taken. The membrane was mounted on a vertical Franz diffusion cell facing the receptor compartment. The donor side was charged with 20 mg equivalent drug formulation. The membrane surface area available for diffusion is 2.54 $cm^2$. The receptor compartment was filled with phosphate buffer pH 7.4. Temperature was maintained at 37 ± 0.5°C. The receptor compartment was constantly stirred at 100 rpm. Samples from the receptor fluid (1ml) were withdrawn at various time intervals and replaced immediately by fresh buffer solution. The samples were then assayed spectrophotometrically using UV-Visible spectrophotometer at 260 nm.

**Kinetic Analysis of in-vitro release rates**

The results of in-vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero- order Kinetic model — Cumulative % drug released versus Time.
2. First- order Kinetic model — Log cumulative % drug remaining versus Time.
3. Higuchi's model- Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / peppa's model- Log cumulative percent drug released versus log time.

**Stability studies**

The optimized proniosomal formulae F6 was sealed in 5 ml clear glass vials and stored at 40 ± 2°c and 75 ± 5% RH. After 60 days, hydration step was carried out and the entrapment efficiency as well as the mean particle size of each sample was determined and compared to the freshly prepared proniosomes-derived niosomes.

## RESULTS AND DISCUSSION

### PREFORMULATION STUDIES

**TABLE: 3 Solubility analysis**

| Solvent | Solubility (mg/ml) at 25°±1°C | Solubility |
|---|---|---|
| Water | 0.05±0.01 | Practically Insoluble |
| Ethanol | 25±1.000 | Sparingly soluble |
| Methanol | 82±1.000 | Soluble |
| Phosphate buffer pH 7.4 | 95±1.000 | Soluble |

**TABLE: 4 Melting point determination**

| Sample | Melting point of sample in literature | Melting point of sample experimented determine* |
|---|---|---|
| Sertaconazole | 164 - 166°C | 164°C ± 1°C |

**Drug and excipients compatibility studies by FT-IR spectroscopy**

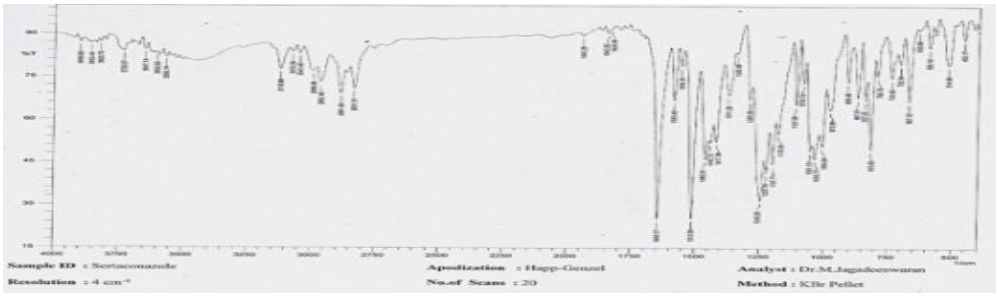

**FIGURE: 1 FT-IR Spectrum of pure drug Sertaconazole**

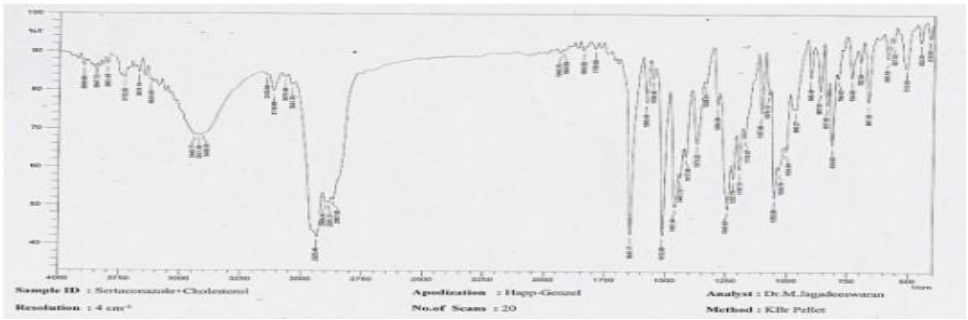

**FIGURE:2 FT-IR Spectrum of Sertaconazole+Cholesterol**

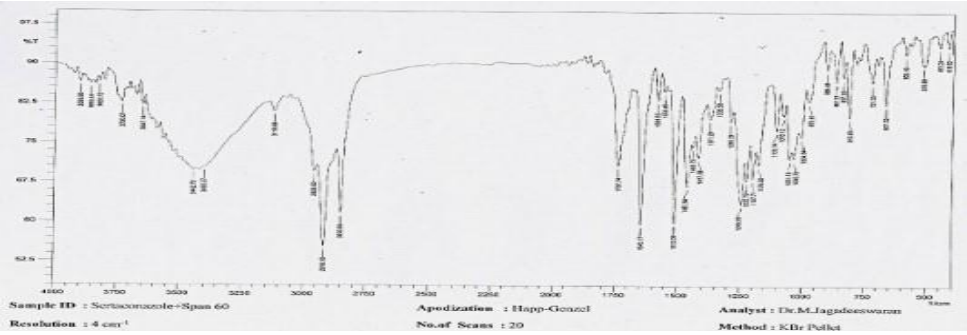

**FIGURE: 3 FT-IR Spectrum ofSertaconazole+Span 60**

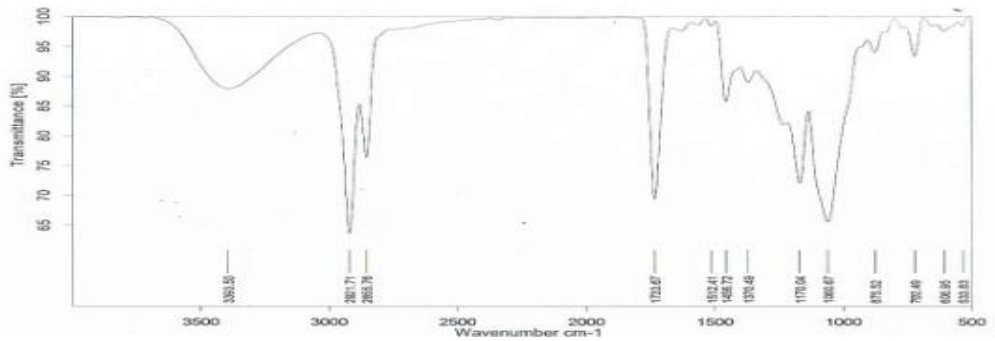


**FIGURE: 4 FT-IR Spectrum of Sertaconazole+Span 20**

**EVALUATION OF PROMOSOMAL GEL**

**TABLE: 5Physical examination**

| Test | Spreadability | Washability | Homogenicity | Colour | Odour | Phase separation |
|---|---|---|---|---|---|---|
| F1 | Easy | Washable | Yes | Opaque | Aromatic | No |
| F2 | Easy | Washable | Yes | Opaque | Aromatic | No |
| F3 | Easy | Washable | Yes | Opaque | Aromatic | No |
| F4 | Easy | Washable | Yes | Opaque | Aromatic | No |
| F5 | Easy | Washable | Yes | Opaque | Aromatic | No |
| F6 | Easy | Washable | Yes | Opaque | Aromatic | No |
| F7 | Easy | Washable | Yes | Opaque | Aromatic | No |
| F8 | Easy | Washable | Yes | Opaque | Aromatic | No |
| F9 | Easy | Washable | Yes | Opaque | Aromatic | No |

**i) Determination of pH**

The pH of Proniosomal gel was determined by using a calibrated pH meter. Thereadings were taken for average of three samples. The pH values exhibited by gels are found in range of 6.73±0.057 to 7.21±0.173 at 25°C.

**ii) Rheological studies**

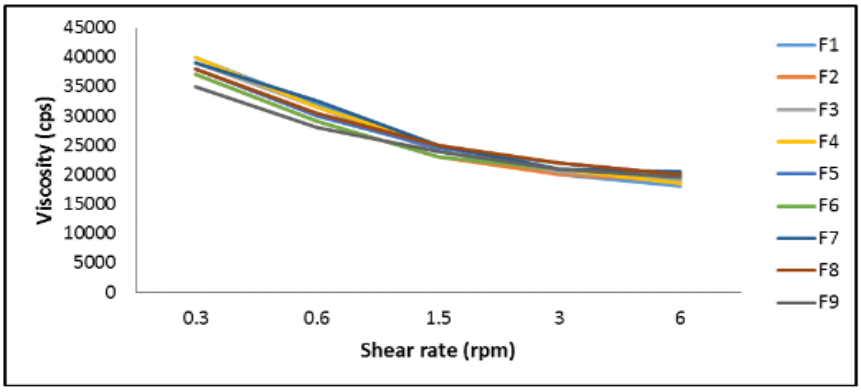


**FIGURE: 5 Rheological profile of Sertaconazole gel formulations**

**Spreadability Coefficient Studies**

**TABLE: 6 Spreadibility of Sertaconazole gels**

| Formulations | Time | Spreadability (gcm/sec) ± SD |
|---|---|---|
| F1 | 4.9 | 30.61 ± 0.03 |
| F2 | 5.1 | 29.41 ± 0.32 |
| F3 | 5.3 | 28.30 ± 0.15 |
| F4 | 4.6 | 32.60±0.08 |
| F5 | 5.7 | 26.31 ± 0.28 |
| F6 | 5.5 | 27.27 ± 0.42 |
| F7 | 5.9 | 25.42 ± 0.21 |
| F8 | 5.8 | 25.86 ± 0.55 |
| F9 | 5.4 | 27.77 0.06 |

*All readings are average of three determinations( n=3)

**Vesicle size analysis**

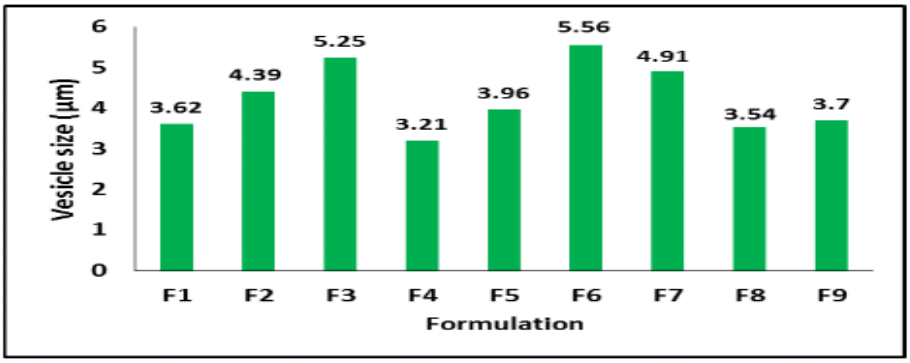


**FIGURE: 6 Comparison of vesicle size of proniosomal formulations**

**Drug entrapment efficiency**

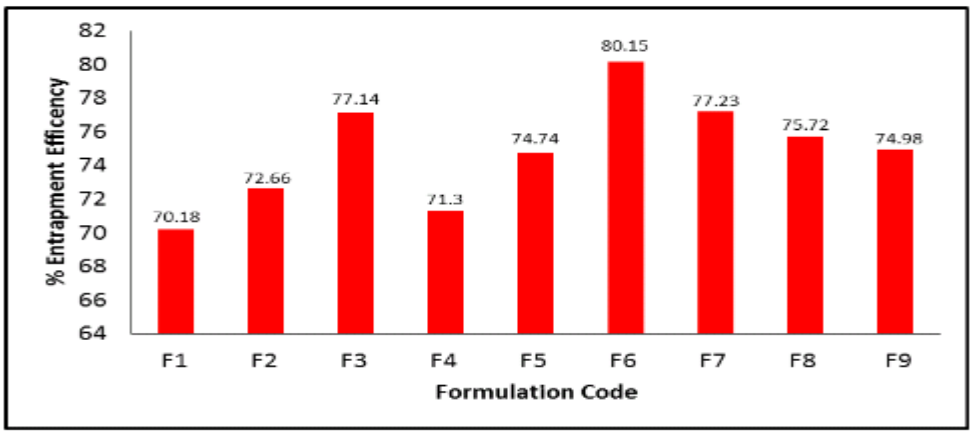


**FIGURE: 7Comparison of entrapment efficiency of proniosomal formulation.**

**Drug Content Analysis**

The drug content estimation was done and the absorbances were measured by UV spectrophotometer (Shimadzu UV-1800).Drug content of all the formulations were found between 92.51±0.005 to98.80 ± 0.012%.

**Microphotography( Optical photomicrograph)**

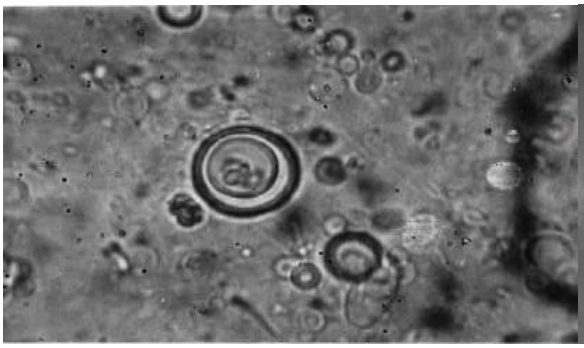

**FIGURE: 8Proniosomalformulation F3**

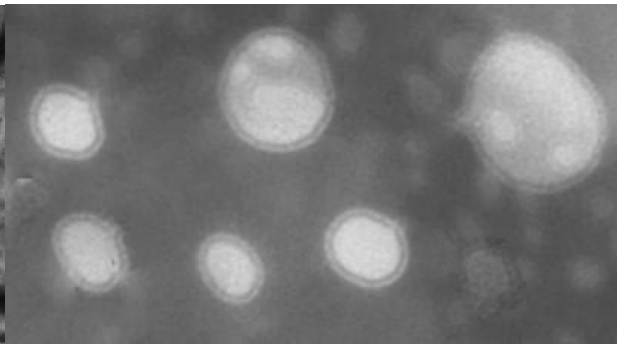

**FIGURE: 9Proniosomal formulation F6**

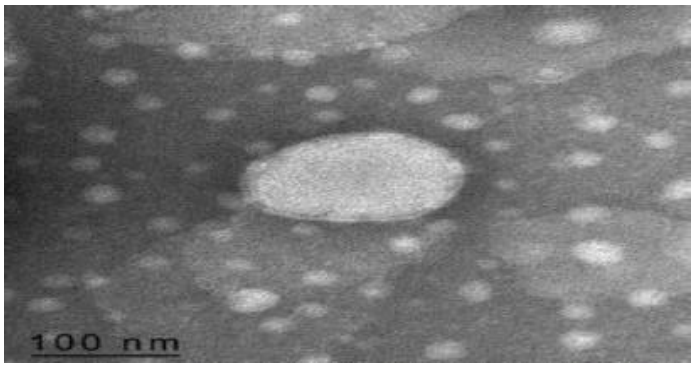


**FIGURE: 10Proniosomal formulation F7**

**In-vitro diffusion studies**:

The in-vitro diffusion profile of Sertaconazole from the gel containing different concentrations of cholesterol and surfactant was carried out for 12 hrs. Among all the formulations F6 released more 76.19±0.053 of the drug in 12 hrs.

IN VITRO DRUG RELEASE STUDIES OF SERTACONAZOLE GELS

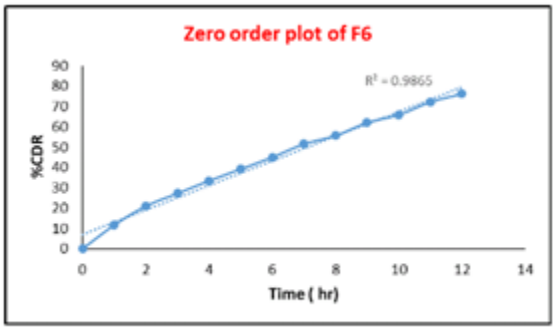


Figure 11 Zero order plot of F6 formulation.

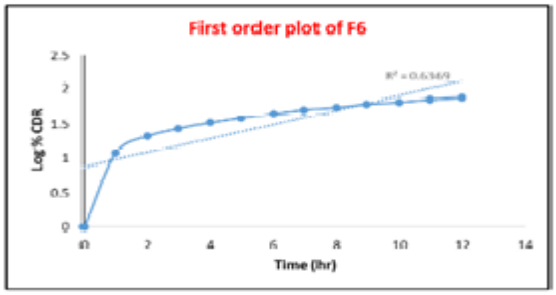


Figure 12 First order plot of F6 formulation.

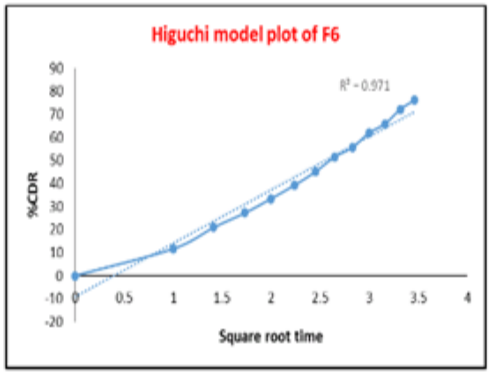


Figure 13 Higuchi's plot of F6 formulation.

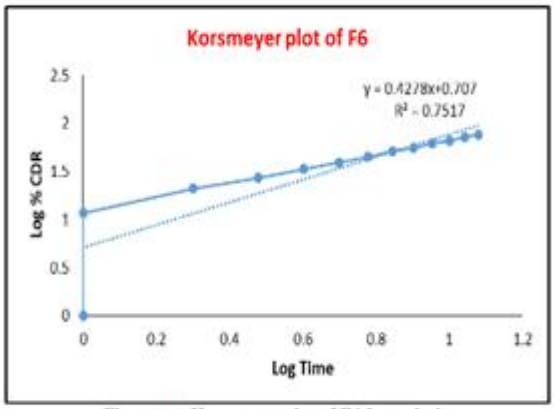


Figure 14: Korsmeyer plot of F6 formulation.

The in vitro drug release showed highest regression value for the zero order kineticsand release data was best fit with Higuchi model kinetics because the value of 1-2 was greater in this model. The formulation follows the diffusion controlled mechanism for drug release. The 'n' value was found to be 0.42, indicating that the drug release mechanism was diffusion and fickian release.

**TABLE: 6Drug Release Kinetics:**

| Formulation | Drug Release Kinetics | | | | |
|---|---|---|---|---|---|
| | Zero Order | First Order | Higuchi | Korsemeyerpeppas | |
| | Correlation coefficient($r^2$) | Correlation coefficient($r^2$) | Correlation coefficient($r^2$) | Correlation coefficient($r^2$) | N value |
| F6 | 0.9865 | 0.6369 | 0.9710 | 0.7517 | 0.42 |

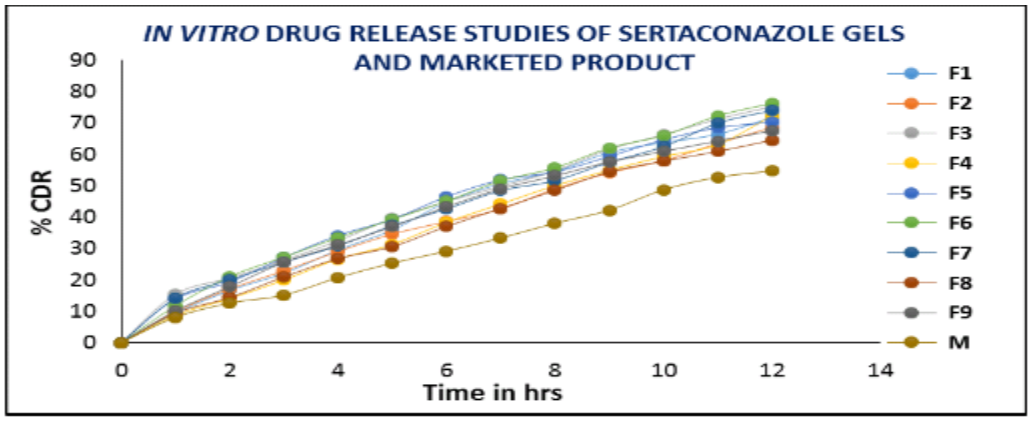


**FIGURE: 15 Comparative drug release profile of the proniosomal formulations and marketed product**

**Stability studies:**

The stability studies were carried out for prepared Sertaconazole gels for 90 days in $40^0C \pm 2^0C$ and RH- Formulation F6 were analyzed for visual appearance, pH, vesicle size, entrapment efficiency, drug content and in-vitro diffusion studies. Around 12 weeks of stability studies revealed that there was no change in visual appearance. Formulation F6 has shown slight changes in pH which was in acceptable limits (±0.5). Study of the drug content, in-vitro diffusion studies, and pH revealed that there were no definite changes observed that justify drug degradation

**TABLE: 6Stability data of selected F6 formulation stored at 40°C ± 20°C and 75% ± 5% RH**

| No of days | Physical Appearance | pH | Vesicle Size(gm) | % Drug Entrapment | % Drug Content | % CDR |
|---|---|---|---|---|---|---|
| 0 | No change | 6.89±0.068 | 5.56±0.07 | 80.15±0.88 | 96.10±0.010 | 76.19±0.053 |
| 30 | No change | 6.66±0.215 | 5.45±0.05 | 80.10±0.91 | 95.73±0.003 | 76.07±0.039 |
| 60 | No change | 6.78±0.337 | 5.23±0.09 | 80.03±1.01 | 95.49±0.014 | 75.89±0.045 |
| 90 | No change | 7.31±0.145 | 5.03±0.16 | 79.98±0.86 | 95.23±0.008 | 75.56±0.031 |

**CONCLUSION:**

The present work is an attempt to develop transdermal delivery of Sertaconazole as proniosomal gel using different concentrations of cholesterol, surfactant and soya lecithin by co-acervation phase separation method. The prepared 9 formulations were characterized for optical microscopy, particle size analysis, drug entrapment, drug content, rheological studies, in-vitro diffusion and stability studies. Vesicle size, entrapment efficiency and in-vitro diffusion studies were dependent on surfactant:cholesterol ratio and quantity of ethanol used. Proniosomal gel system prepared with span 60 (F6) shows larger size of vesicles as compared to other formulations and Sertaconazole was

successfully entrapped within the lipid bilayer of the vesicles with high efficiency. Formulated proniosomal gel (F6) has shown better controlled drug release compared to other concentrations and marketed formulation (Onabet).

So, from overall study we can conclude that better transdermal delivery of drug like Sertaconazole can be formulated as proniosomal gel using span 60 which improves bioavailability. Proniosomal gel formulated with span 60 could be considered as very promising candidates absorption and penetration enhancer for delivering Sertaconazole transdermally. This type of drug delivery system can serve as a novel approach for treating diseases with better patient compliance.

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