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Formulation and Evaluation of Ketoconazole Loaded Proniosomal Gel for Treatment of Fungal Infections

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ABSTRACT
Vesicular drug delivery system have gained wide attention in the field of nanotechnology. Among different of vesicles , Proniosomes became the superior over the other vesicular carriers. Proniosomes are dry formulation of water soluble non-ionic surfactant coated carrier system which immediately forms niosomes upon hydration. These 'Proniosomes' minimize problems of niosome physical stability such as aggregation, fusion and leaking, and provide additional convenience in transportation, distribution, storage, and dosing. Both hydrophilic and lipophilic drugs can be incorporated into these proniosomes. They have the potential to deliver drugs effectively through different routes at specific site of action to achieve controlled release action and reduce toxic effects associated with drugs. Proniosomal gels are translucent gels and liquid lamellar crystals of vesicular bilayers which can be formed by the addition of small quantity of gelling agent or water to the dry proniosomes (mixture of non-ionic surfactant, lecithin and cholesterol). Proniosomal gels offer better resistance towards stress caused by skin flexion, muco-ciliary movement and better percutaneous absorption due to the non-ionic surfactants used. Because of their high stability, ease of application and better percutaneous absorption they are widely used for various category of drugs such as Antifungals, NSAIDS, Anti psychotics, Anti-hypertensives etc.
Keywords: Proniosomes , Hydrophilic & Lipophilic drugs , Niosomes , Transdermal delivery ,Nonionic surfactants.

I INTRODUCTION

PRONIOSOMES

Proniosomes are dry product which could be hydrated easily immediately before use would avoid many of the problems. These dry formulations of surfactant coated carrier can be measured as needed and rehydrated by brief agitation in hot water to form niosomal dispersion. These are considered superior drug delivery system because of their lower cost, greater stability, non-toxic , biocompatible, biodegradable and non-immunogenic in nature.

ADVANTAGES

- Avoid physical stability issues a fusion, aggregation, sedimentation &leakage on storage.
- Avoid chemical stability like hydrolysis of encapsulated drug which limit shelf life of dispersion.
- Ease of storage and handling.
- No difficulty in sterilization , transportation , distribution.
- Improves bioavailability and minimize side effects.
- Enhance drug permeation through skin.

FORMATION OF NIOSOMES FROM PRONIOSOMES

The niosomes are prepared from the proniosomes by adding the aqueous phase with the drugto the proniosomes with brief agitation at temperature greater than the mean transition phase temperature of the surfactant.
T>Tm Where, T=Temperature
Tm=Mean Phase Transition Temperature

MECHANISM OF ACTION

The exact mechanism of penetration of drug in the vesicles through the skin are not yet explored, but the penetration will depends on the nature and type of the drug used, vesicle formed and hydration temperature for the conversion of proniosomes to niosomes. The lipid used in the preparation, act as carrier that will form depot at the site of action and hence sustains the action. The rate limiting stepin the penetration of drug through the transdermal drug delivery is the lipid (ceramides) part of stratum corneum which packed tightly as bilayer by hydrogen bonding.
The hydrogen bonding will strengthen and stabilize the lipid bilayer and as a result will impart the barrier property of stratum corneum.

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Proniosomes will hydrate to niosomes when applied to skin surface, the niosomes formed adsorbs, fuses and loosens the ceramides by competitively breaking the hydrogen bond network leading to thermodynamic activity at the surface. That will increase by the concentration gradient and hence increases the diffusion pressure for the driving of drug throught the stratum corneum.

II. MATERIALS AND METHODS

MATERIALS: Ketoconazole , Polaxomer , Tween 80 , soya lecithin , Carbapol , triethanolamine, methanol

METHOD:

1. PREFORMULATION STUDIES:

1. Physical Appearance

The drug (ketoconazole) powder was examined for its organoleptic properties like colour and odour.

2. Solubility Estimation

The sample was qualitatively tested for its solubility in various solvents. It was determined by taking 10 mg of drug sample in 10 ml of solvent excess drug in test tubes and well solubilized by shaking, according to IP.

3. Melting Point Determination

The Melting point was determined by the capillary method using Digital Meltingpoint apparatus.

4. Determination of Wavelength of Maximum Absorbance (λmax)

10 mg of drug(ketoconazole) was weighed accurately and transferred to 10ml of volumetric flask. Then 0.1 N HCl was added to dissolve the drug completely. The volumewas made up to 10 ml with solvent. The prepared sample was 1000 µg/ml. 1ml of above solution was then transferred to another 10 ml volumetric flask and diluted it up to the 10ml of solvent. The prepared sample was 100 µg/ml. Another 1ml of this solution was taken and diluted upto 10 ml . The concentration of this solution is 10 µg/ml. Now the absorbance is notes between 200 –400 nm in U.V. Spectrophotometer.

A) **Preparation of Calibration Curve of Ketoconazole:** The calibration curve was plotted between the concentration and absorbance.

B) Standard Curve of 0.1N HCl : The standard curves of ketoconazole were prepared in 0.1N HCl solution, at λmax 221 nm. The data were regressed to obtain the straight line.

5. Drug–Excipient Compatibility Study

Drug – Excipient compatibility study done by FT-IR spectroscopy. The presence of characteristic peaks associated with specific structural characteristics of the drug molecule was noted.

Fourier-Transform Infrared spectroscopy (FTIR) Study:

In FTIR study ,KBr pellets is used to determine the interaction of drug and excipient in solid sample . The IR spectrum of drug substance was authenticated using IR spectroscopy. The presence of characteristic peaks associated with specific structural characteristics of the drug molecule was noted.

2. METHOD OF PREPARATION OF PRONIOSOMES

1. Slurry method
2. Coacervation phase separation method
3. Slow spray coating method

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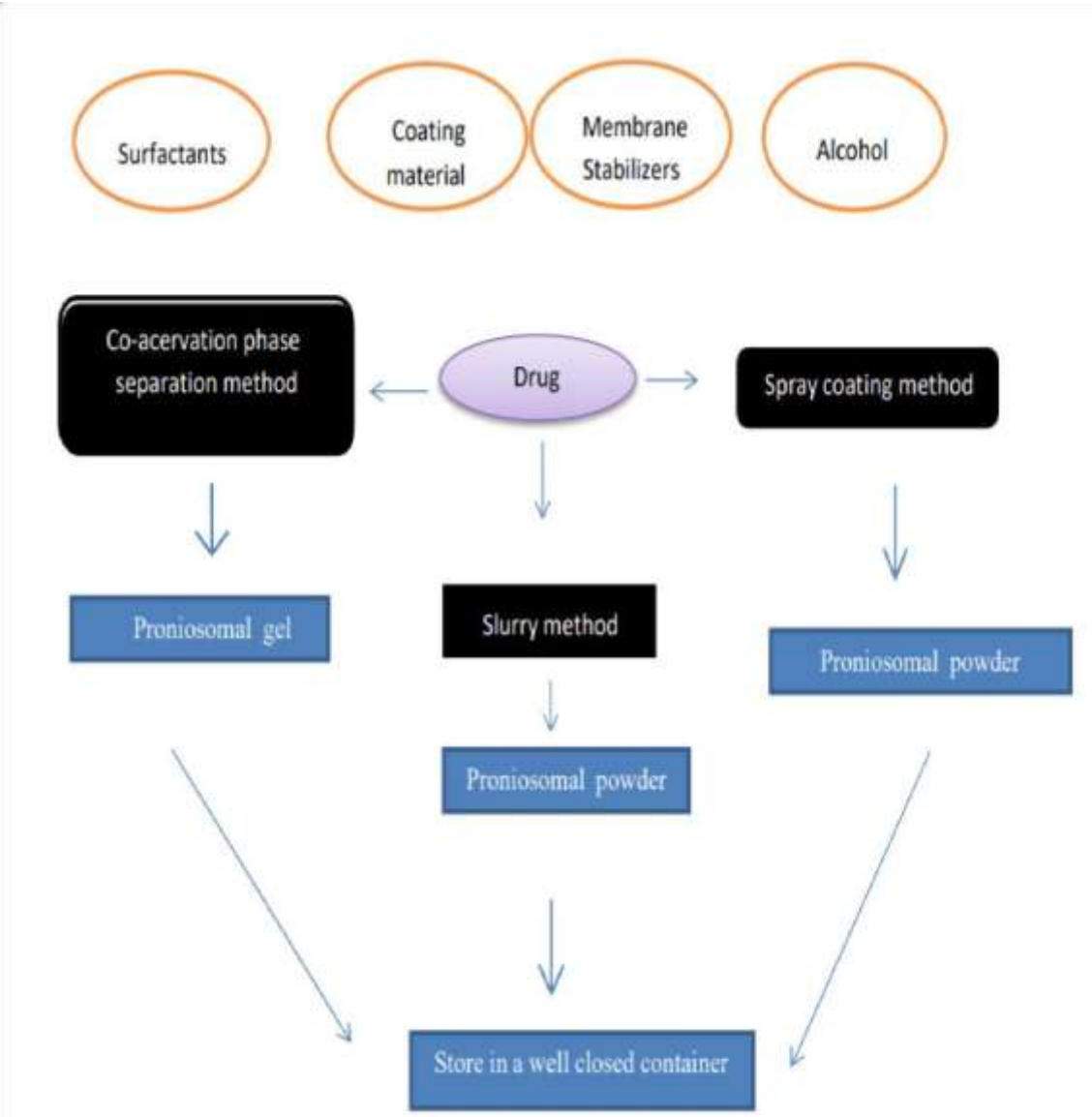

Fig.2.1. Diagrammatic Representation of Formulation Methods

Slurry method:

Maltodextrin as a carrier is added into 250ml round bottom flask and the entire volume of surfactant solution was added directly to the flask to form slurry. If the surfactant solution is less, then additional amount of organic solvent can be added to get slurry. The flask was attached to the rotary evaporator and vaccum was applied until the powder appeared to be dry and free flowing. The flask was removed from the evaporator and kept under vaccum overnight. Proniosomal powder was stored in sealed container at 4ºC. The time required to produce proniosomes is independent of the ratio of surfactant solution to the carrier material and appears to be scalable.

Advantages

- Maltodextrin is easily soluble in water and used as carrier material in the formulation; they were easily coated by simply adding surfactant in an organic solvent to dry Maltodextrin.
- Due to the uniform coating, it protects the active ingredient and the surfactants from hydrolysis and oxidation.
- The higher surface area results in thinner surfactant coating that makes the rehydration process efficient.

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Disadvantages

- The method is time-consuming and involves specialized equipment with vacuum and nitrogen gas.
- The thin-film approach allows only for a predetermined lot sizes. So material often wasted, so small quantities and small dose batch can be atedious one.

Coacervation phase separation method

Coacervation is usually defined as the spontaneous formation of a dense liquid phase from a macromolecular solution of poor solvent affinity. In coacervation the loss of salvation arises from the interaction of complementary macromolecular species. Coacervation is a phenomenon in which a macromolecular aqueous solution separates into two immiscible liquid phases. The denser phase, which is relatively concentrated in macromolecules is called coacervate and is in equilibrium with the relatively dilute macromolecular liquid phase. Liquid-solid separation is known as precipitation also it meanscoacervation.

Sequential events of coacervation process

- Individual (non interacting) polymer or colloids
- Primary (intra-polymer)
- Soluble aggregates
- Coaservates

Advantages

- Method is simple and without required any specialized equipment.
- Small quantities or small doses can be prepared on lab scale.

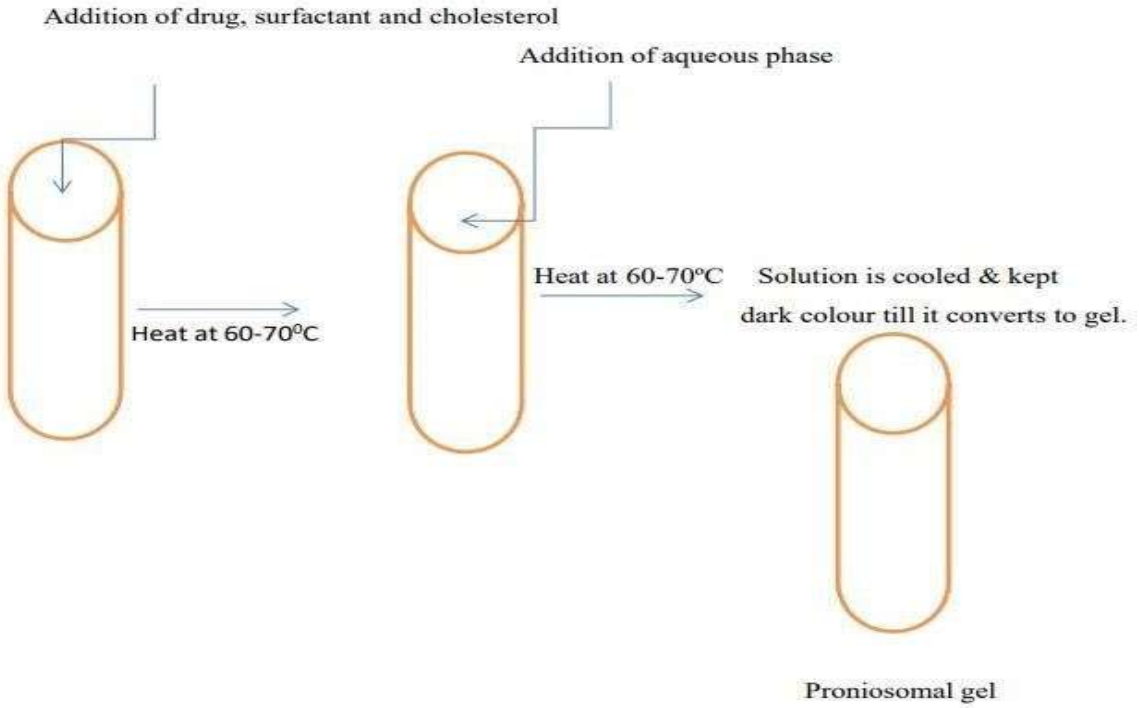

Fig.2.2. Diagramatic representation of Coacervation phase separation method

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Slow spray coating method

This method involves preparation of proniosomes by spraying surfactant in organic solvent onto sorbitol powder and then evaporation of the solvent. Because the sorbitol carrieris soluble in organic solvent, it is necessary to repeat the process until the desiredsurfactant loading has been achieved. The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles form as the carrier dissolves. The resulting niosomes are very similar to those produced by conventional methods and the size distribution is more uniform. It is suggested that this formulatinghydrophobic drug in a lipid suspension without concern stability of the suspension or susceptibility of the active ingredients hydrolysis.

Advantages

- Simple method and suitable for hydrophobic drug without concerns of instability oral susceptibility of active pharmaceutical ingredient tohydrolysis

Disadvantages

- Tedious method
- If the coating of surfactant solution was applied too quickly.
- The sorbitol particles would degrade and sample becomes viscous slurry.
- Sorbitol is found to interfere with encapsulation efficiency of the drug.

III. FORMULATION DEVELOPMENT COACERVATION PHASE SEPARATION METHOD

Proniosomal gel was prepared by coacervation phase separation method. Precisely weighed amounts of surfactant, lecithin, cholesterol and drug were taken in a clean and dry wide mouthed glass vial 5.0 ml capacity and alcohol (2.5ml) was added to it. The open end of the glass bottle was covered with a lid to prevent the loss of solvent from it and warmed over water bath at 60-70℃ for about 5 min until the surfactant mixture dissolved completely. Then the aqueous phase (0.1% glycerol solution) was added and warmed on a water bath till a clear solution was formed which was convertedinto proniosomal gel on cooling. The gel so obtained was preserved in the same glass bottle in dark conditions for characterization.

PREPARATION OF GEL BASE

In distilled water, a solution of Carbopol 934 (2% w/v) was allowed to swell for 34hr .The prepared proniosomal suspension was added into Carbopol 934 and mixed with mechanical stirring. Triethanolamine was added to adjust pH and was sonicated for 15 min and kept overnight to remove air bubbles.

Table.3.1. Formulation Chart for Ketoconazole Loaded Proniosomal Gel

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
DRUG (%)	2	2	2	2	2	2	2	2
CHOLESTROL (g)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
SOYA LECITHIN (g)	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
TWEEN 80 (ml)	-	-	-	-	0.7	0.8	0.9	1

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POLAXOMER 188 (g)	0.01	0.02	0.03	0.04	-	-	-	-
ORGANIC PHASE (ml)	5	5	5	5	5	5	5	5
AQUEOUS PHASE (ml)	5	5	5	5	5	5	5	5

IV. CHARACTERIZATION OF PRONIOSOMAL GEL

Physical Appearance

The physical appearance of the prepared gels was tested by visual observations after the gel had been set in the container. They were analysed for their appearance and the existence of any aggregates.

Homogenicity

All formulated gels were tested for homogeneity by visual inspection after the gels have been set in the container.

Colour Assesment and Transperancy

All the proniosomal gel formulations had pale yellow to vibrant yellow colour, were transparent in appearance, free from presence of particles.

Viscosity

The viscosity of the prepared gel was measured by using Brookfield Viscometer. The gel was rotated at 20 and 30 rpm using spindle no.64 the corresponding reading wasnoted.

Spreadability

The spreadability of the gel was determined using the following technique: 0.5g gel was placed within a circle of 1 cm diameter pre marked on a glass plate over which a second glass plate was placed. A weight of 500 g was allowed to rest on the upper glass plate for 5min. The increase in the diameter due to spreading of the gels was noted.

pH Determination

Digital pH meter was used to determine the pH of proniosomal gel. The pH meterwas calibrated before use with buffered solution pH 4.0, 7.40, 10.0. One gram of gel wasdissolved in 25 mL of distilled water and the electrode was then immersed into the above solution for 30 minutes until the constant reading was obtained.

Entrappment Efficiency

The proniosomal suspension (0.3g) was taken in a test tube and add 10ml of Isotonic phosphate buffer of pH 7.4. This aqueous solution was sonicated in a sonicator bath. The drug containing niosomes were separated from the dispersion by centrifugation at 3000 rpm for 30 min at 20 °C. The supernatant (1 ml) was taken and diluted with phosphate buffer (in 10 ml volumetric flask). And again, from stock solution, 1 ml was withdrawn and transferred to a 10 ml volumetric flask and made up to the mark with buffer. The drug concentration in the resulting solution was assayed by UV-visible spectroscopy method. The percentage of drug encapsulation was calculated by the following formula

Entrapment Efficiency = [(Ct – Cr) / Ct] × 100
Where,
EE= Entrapment Efficiency,

C_t = Concentration of total drug,
C_r = Concentration of unentrapped drug

Drug Content

Weigh 2 g of gel containing and add 1 ml of ethanol or methanol and 4 ml of phosphate buffer to a 10 ml volumetric flask and sonicate until dissolved. Make up the final volume with the buffer. The resulting solution was filtered using Whatman filter paper, and 1 ml of filtered solution was taken and transferred into a volumetric flask containing 10 ml of phosphate buffer pH 7.4 and the volume was made up to the mark with phosphate buffer pH 7.4 and absorbance was

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measured at 221nm.

In vitro Drug release Study

An in vitro drug release study was performed by using Franz diffusion cell assembly. It consists of two compartments, one of the receptor chambers containing a Phosphate Buffer Saline (PBS) of pH 7.4 and another donor compartment containing proniosomal gel . A egg membrane was previously soaked for 24h. The egg membrane was placed in contact with PBS filled in the receptor compartment to avoid disruption inthe ongoing process; it was ensured that no air bubbles were seen between the egg membrane and the liquid surface of PBS. The temperature was maintained at 37 °C at 50 rpm using a magnetic stirrer. 1 ml of the sample was withdrawn from the receptor chamber side tube at the time interval of 1h, 2h, 3h, 4h, 5h, 6h, 8h equilibrated with a new or fresh dissolution medium to maintain a sink state. Suitable dilution was carried out and was spectroscopically analyzed at 221 nm using UV-visible spectroscopy.

Anti-fungal studies

Mould is obtained from the retared bread. Agar (SDA) was added to 40 ml of distilled water in conical flask and stoppered with a cotton plug and autoclaved for 15 min at 15 lbs of pressure. After cooling it at room temperature, pour 20 ml into two sterilepetri plates between two flames, swirl the plates to remove air bubbles, and let it solidify at room temperature near the sterile area. Addition of Mould through a cotton swab and streaked in all directions into the solidified agar, bore four wells from the sterile borer to add the proniosomal gel formulation. Incubate at 25-30 °C for 72h for inhibition of fungi and observe the Zone of Inhibition and measure the diameter in mm; the greater the zone of inhibition, the more susceptible is the formulation.

Scanning Electron Microscopy (SEM)

The surface morphology of proniosomes was studied by Scanning Electron Microscopy (SEM). The shape of the formulation and the sizes of the vesicles were determined by SEM. A drop of proniosomal suspension was placed on the specimen stub which was coated with carbon and then with gold vapour appeared using a vacuum evaporator. The samples were examined under a scanning electron microscope for vesicular shape and then photographed.

Determination of zeta potential

The zeta potential of the proniosomal formulation was analyzed at 25°C using Zeta sizer. Proniosomal suspension was diluted 100 times with doubled-distilledwater and voltage was set at 1.4 V and electrodes were placed in dispersion for the measurement of zeta potential. Each sample was run 3 times and analysis was continued at 25 °C with a scattering angle of 173 °C.

Stability studies

The optimized proniosomal gel were kept at room temperature. After 30 days entrapment efficiency , drug content were noted.

V. RESULTS AND DISCUSSION

Fig.5.1. OPTIMIZED FORMULATION (F3)

DRUG CONTENT

Drug content is one of the important evaluation parameter for any type of dosage form which is determined by UV spectrophotometer.

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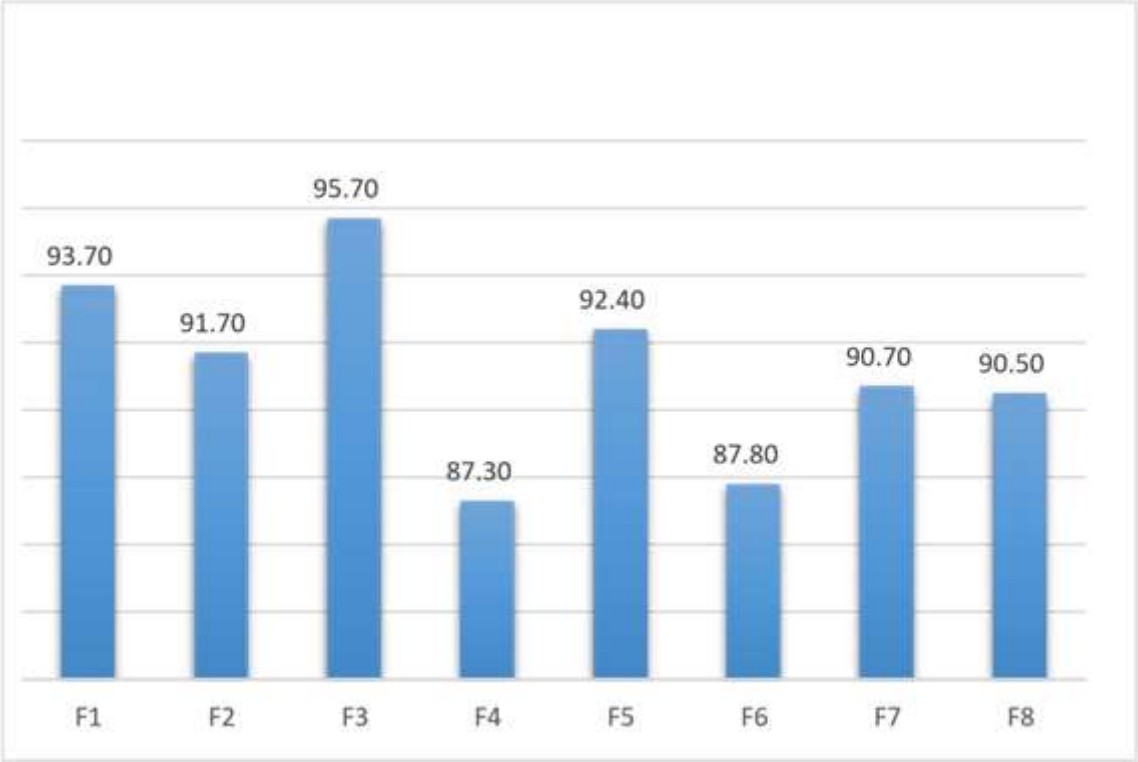

Fig.5.2. Graph of Drug Content

Inference

The % drug content of all formulations was in the range of **87.30-95.7%** indicating uniform distribution of drugs in all formulations.

IN-VITRO DRUG RELEASE

An in-vitro drug release study was performed using Franz diffusion cellassembly.

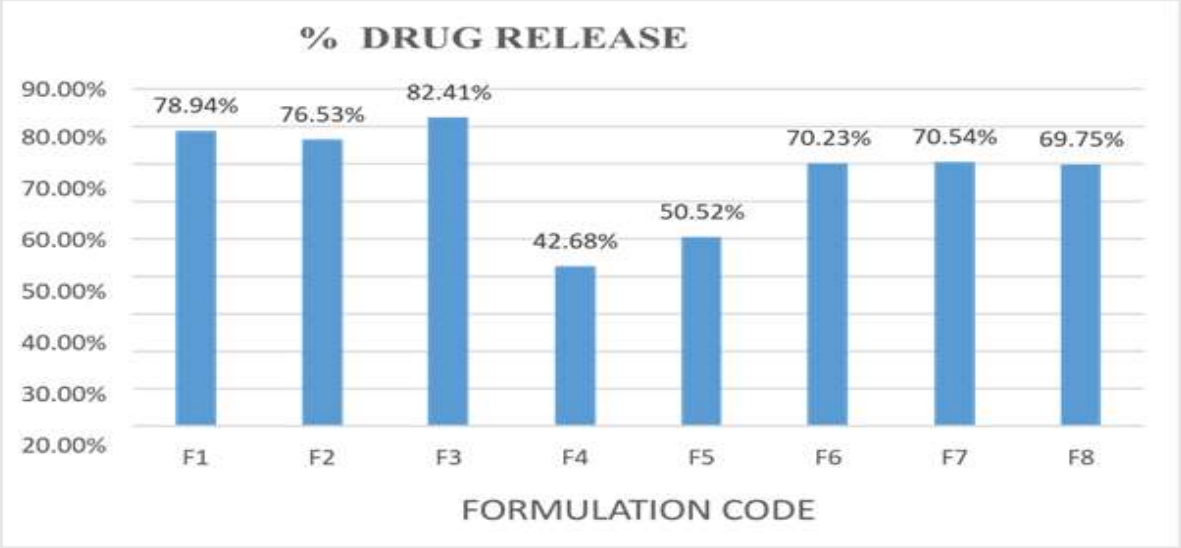

Fig.5.3. Graph for % Drug release

Inference

The optimized proniosomal formulation showed sustained drug release.

The cumulative % drug release at 8hrs for

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optimized formulation wasfound to be **82.41 %**

ENTRAPMENT EFFICIENCY

Entrapment Efficiency was proceeded using centrifuge and analysed using UV-Spectrophotometer.

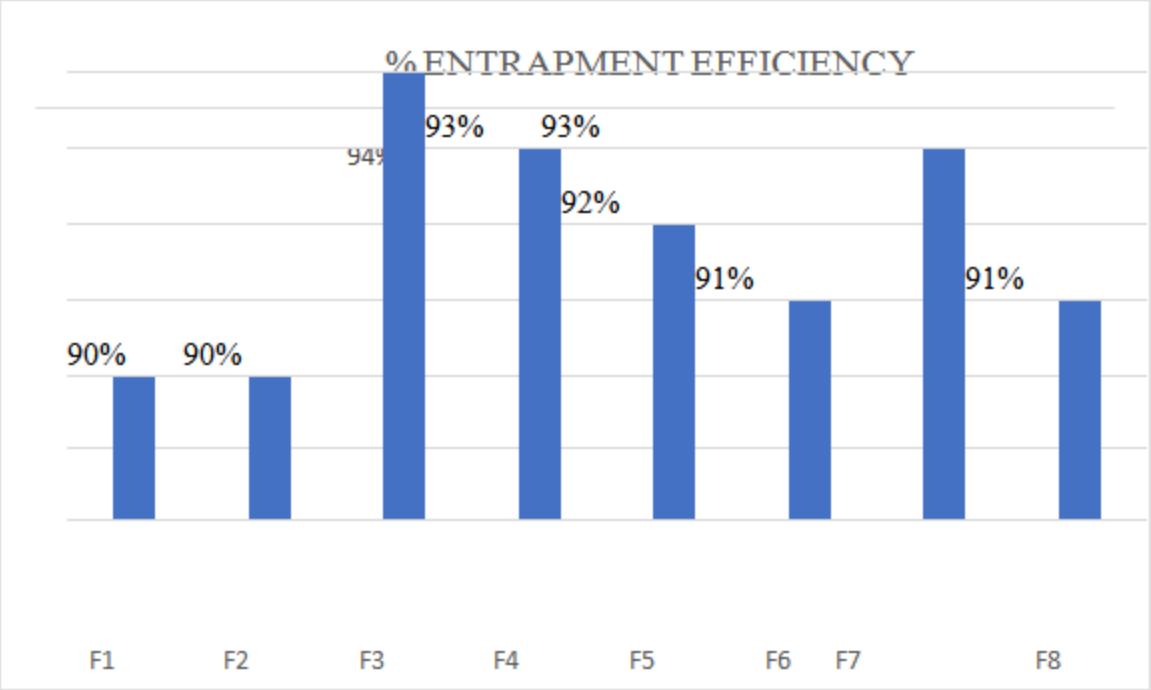

Fig.5.4. Graph of Entrapment Efficiency

Inference

The % Entrapment Efficiency was found to be in the range of **87.30 to 95.70%.** Increase in concentration of surfactant increases the entrapment efficiency of proniosomes due to high fluidity of the vesicles.

ANTI-FUNGAL STUDIES FOR OPTIMIZED FORMULATION

The micro-organism used for antifungal studies is MOULD which is taken from theretard bread.

Zone of inhibition for optimized proniosomal gel after 24hours is 2.5cm.

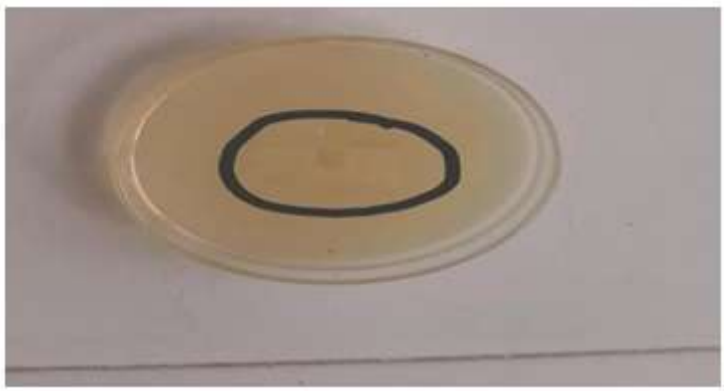

Fig.5.5. Image 1 Antifungal study of 2% ketoconazole

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Inference

Fig.5.6. Image 2 Antifungal study of 2% ketoconazole

The optimized formulation shows a good Antifungal Activity.

SCANNING ELECTRON MICROSCOPY OF OPTIMIZED FORMULATION

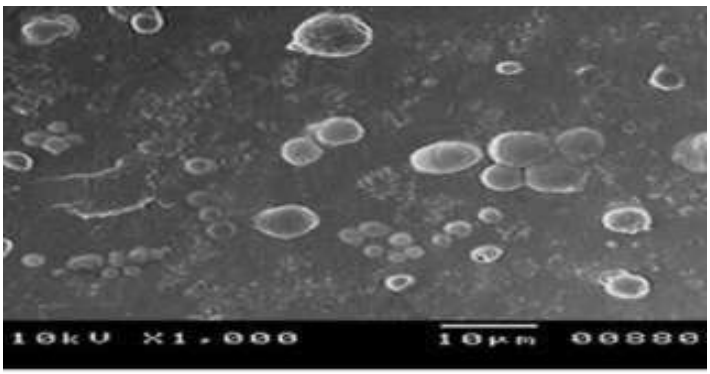

Fig.5.6.SEM IMAGE1 of ketoconazole proniosome

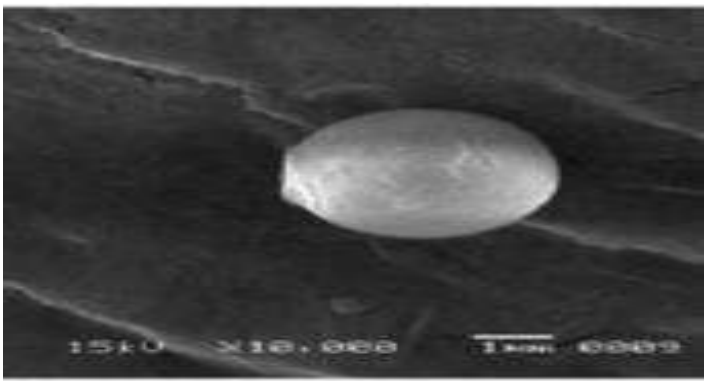

Fig.5.7. SEM IMAGE 2 of Ketoconazole proniosomes

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Inference
The results shows that the Ketoconazole loaded Proniosomes have spherical shape with smooth surface and discrete without any aggregration or agglomeration.

DETERMINATION OF ZETA POTENTIAL OF OPTIMIZED FORMULATION

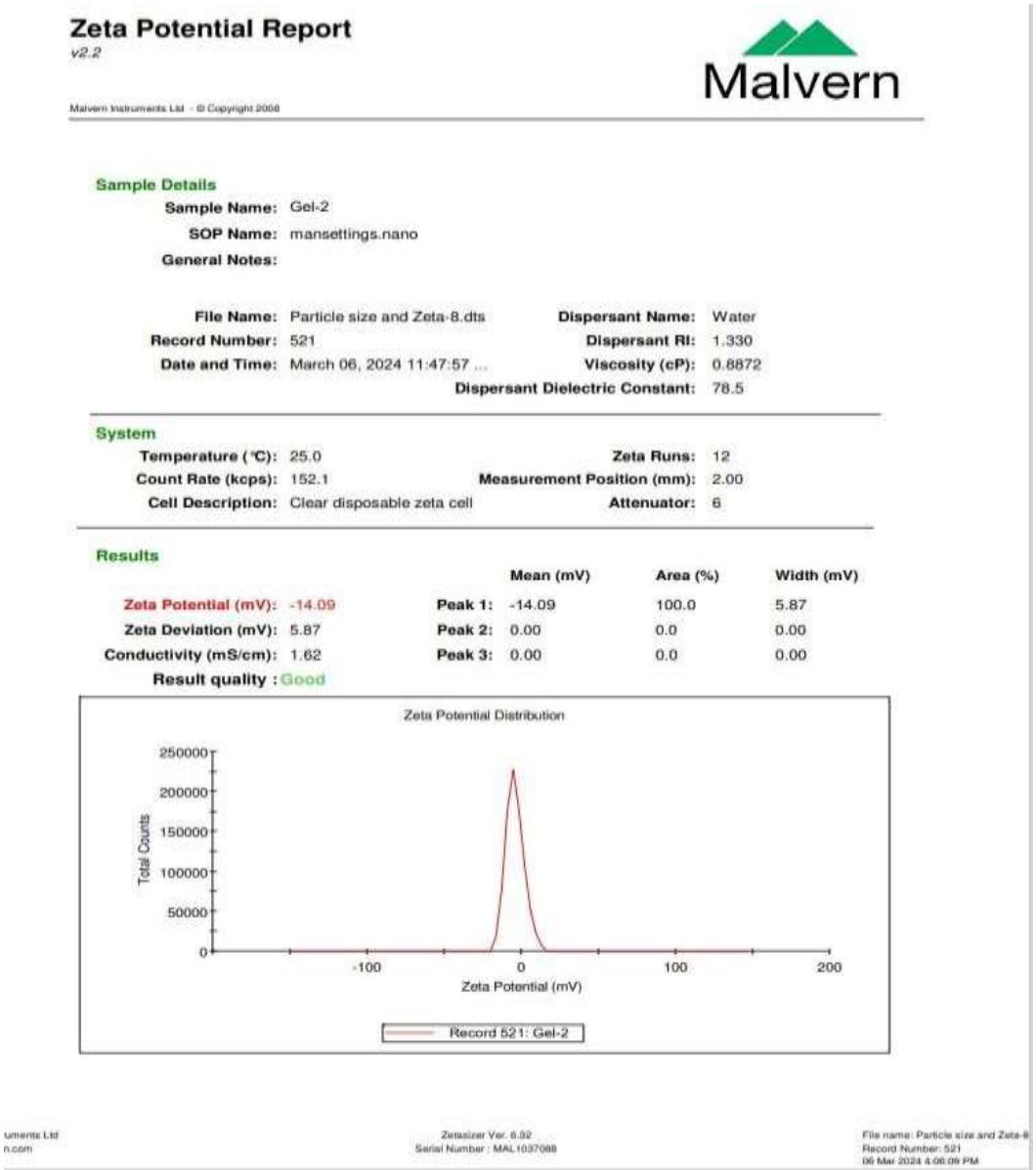

Fig.5.8. Zeta Potential of Ketoconazole proniosomes

Inference
The Zeta potential for the optimized formulation F3 was found to be
--14.09Mvand shows that the formulation is stable.

STABILITY STUDIES OF OPTIMIZED FORMULATION
The optimized proniosomal gel were kept at room temperature and it wassubjected to stability studies as per ICH guidelines.

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Fig.5.1. Datas for stability studies

Parameter	**Condition: At room Temperature**	
	Initial	**After 1 Month**
Entrapment Efficiency(%)	94%	93.7%
Drug Content (%)	95.7%	95%

Inference
No significant changes in Entrapment Efficiency, drug content when observed at room temperature.

VI. CONCLUSION

The purpose of this research was to prepare ketoconazole loaded proniosomes for sustained release of drug and incorporate it into topical gel delivery system to reduce the side effects by site specific targeting.

- The Physical compatibility of ketoconazole with excipients was studied. The drug and excipients were physically compatible with each other.
- The Chemical compatibility study of Ketoconazole with excipients was carried out using FTIR Spectrometer. It revealed no interaction between the drug and excipients.
- Among all these eight formulation, **Formulation (F3)** which is prepared using **polaxomer 188** exhibits high **viscosity (8048) , pH (6.8) , spreadability (5.12), % entrapment efficiency (93.7%) , drug content (95 %) and better In-vitro drug release (82.41%).**

Taking into consideration the high efficiency in systemic circulation delivery together with lack of physical and chemical instability and excellent safety profile, **Polaxomer 188** could be considered as very promising candidates as absorption and penetration enhancer for ketoconazole transdermally.

REFRENCE

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