DESIGN, PREPARE AND CHARACTERIZATION OF ECONAZOLE ETHOSOMAL GEL

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ABSTRACT :

The aim of the present work was formulation and evaluation of the ethosomal gel of Econazole for topical delivery. The drug release from Ethosomes depends on many factors including the composition of Ethosomes, the type of drug encapsulated and nature of the cell. Once it is released a drug that normally crosses the membrane of a cell will enter the cell, other drugs will not enter. This study aimed at developing and optimizing ethosomal gel formulation of Econazole in order to improve its bioavailability. In evaluation study the effect of the varying composition of lipids on the properties such as encapsulation efficiency, particle size and drug release were studied. Moreover, the release of the drug was also modified and extended over a period of 8 hr in all formulations. F3 emerged as the most satisfactory formulation in so far as its properties were concerned. Further, release of the drug from the most satisfactory formulation (F3) was evaluated through dialysis membrane to get the idea of drug release. Drug release from ethosomal formulation was found in very sustained and controlled manner. It was concluded that prepared gel containing econazole loaded ethosomal formulation was optimized and successfully formulated in the gel form can be of use for topical preparation for its affect.

Keywords: Ethosomal gel, Econazole, bioavailability, Cold method technique, in vitro drug release studies.

I.INTRODUCTION

The Pharmaceutical Industry worldwide caters to the specific health needs of the patients suffering from various diseases by designing and supplying suitable dosage forms which are popularly called as Formulations in the parlance of the Pharmacists.[1] An urge for preparing specialized drug delivery systems as emanated in order to enhance Bioavailability and deliver the drugs at the desired specific sites of the human body. Ethosomes are ethanolic liposomes". Ethosomes can be defined as noninvasive delivery carriers that enable drugs to reach deep into the skin layers and/or the systemic circulation.[2]These are soft, malleable vesicles tailored for enhanced delivery of active agents. The vesicles have been well known for their importance in cellular communication and particle transportation for many years. Vesicles would also allow controlling the release rate of drug over an extended time, keeping the drug shielded from immune response or other removal systems and thus be able to release just the right amount of drug and keep that concentration constant for longer periods of time.[3] Ethosomes are composed mainly of phospholipids, (phosphatidylcholine, phosph-atidylserine, phosphatitidic acid), high concentration of ethanol and water. The nonaqueous phase range between 22 % to 70 %. The alcohol may be ethanol or isopropyl alcohol. To formulate and optimized binary ethosomal gel encapsulated with econazole.[4] Ethosomal vesicles used for delivery of drugs to reach the deep skin layers and/ or the systemic circulation and are the advanced forms of liposomes that are high in ethanol content. They can incorporate hydrophilic and hydrophobic drugs to enhance the accumulation of drug.[5] Econazole is used to treat a variety of fungal skin infections such as athlete's foot, jock itch, and ringworm. This medication is also used to treat a skin condition known as pityriasis (tinea versicolor), a fungal infection that causes a lightening or darkening of the skin of the neck, chest, arms, or legs.[6]

II.MATERIALS AND METHODS

Econazole was collected as a gift sample from Hetero labs, Hyderabad and various excipients like, Propylene glycol , Soya lecithin, Ethanol and Carbopol 934were purchased from AR chemicals, Hyderabed.

METHODOLOGY

Fourier transform infrared spectroscopy:[7]

Fourier transform IR spectra were obtained on Shimadzu FT-IR spectrometer. Samples were prepared in KBr disks (2mg sample in 200mg KBr). The scanning range was 450-4000 cm^{-1} and the resolution was 4 cm^{-1}.

Method of Preparation:

Cold Method

This is the most common method utilized for the preparation of ethosomal formulation. In this method phospholipid, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer. Propylene glycol or other polyol is added during stirring. This mixture is heated to 30°C in a water bath. The water heated to 30° C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to desire extend using sonication or extrusion method. Finally, the formulation is stored under refrigeration.[8]

Table - :1 composition of lipids for preparation of liposome

Ingredients	F1	F2	F3	F4
Phosphatidylcholine	10	20	30	40
Solvent(Methanol)	10	20	30	40
Propylene glycol	5	5	5	5
econazole	10	10	10	10

GEL PREPARATION:

1gm of carbapol 934 is taken in a beaker and to this add 2ml of distilled water with continuous stirring, to this add 2ml of propylene glycol,0.5ml of triethanolamine, required amount of ph 7.4 buffer under a homogenizer. The ethosomes chosen was mixed with the gel to obtain ethosomal gel.[9]

Evaluation of Ethosomes:

Entrapment efficiency:

Entrapment efficiency (%EE) of VLT ethosomal vesicles was determined by the centrifugation method. The vesicles were separated in a centrifuge at 15000 rpm for 60 min . The sediment and supernatant liquids were separated; amount of drug in the sediment was determined by analyzing the vesicles using ethanol. The vesicles were broken to release the drug, which were then estimated for the drug content. The absorbance of the drug was noted at 232 nm. From this, the entrapment efficiency was determined by the following equation.[10]

$$\%\ \text{Entrapment efficiency} = \frac{\text{entrapped drug}}{\text{total drug added}} \times 100$$

- **Vesicle physical analysis:**

The shape, surface characteristics, and size of the Ethosomes were observed by scanning electron microscopy.

- ***In vitro* drug Release Study:**

In vitro release studies were carried out using unjacketed vertical franz diffusion cells with a diffusional surface area of 6.154 cm^2 and 20 mL of receptor cell volume. Prior to the study, the dialysis membrane was soaked in phosphate buffer pH 6.8 Formulation equivalent to 10 mg of econazole was placed in the donor compartment. The receptor compartment consisting of PB pH 6.8 was maintained at 37±2°C under constant stirring upto 24 hrs. The donor chamber and the sampling port were covered with lid to prevent evaporation during the study. Aliquots of 5 mL were withdrawn periodically at different time intervals and replaced with equal volume to maintain constant receptor phase volume. At the end of the study, the samples were suitably diluted and the amount of drug was determined spectrophotometrically.[11]

Kinetics of drug release[12,13]:

To study kinetices data obtained from invitro releasae were plotted in various kinetic models.

- **Zero-order equation :**

$$\%\ R = Kt$$

This model represents an ideal release profile in order to achieve the pharmacological prolonged action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets with low soluble drugs.

- **First order equation:**

$$\text{Log \% unreleased} = Kt / 2.303$$

This model is applicable to study hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

- **Higuchi equation :**

$$\%\ R = Kt^{0.5}$$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

- **Korsmeyer-Peppas equation :**

$$\%R=Kt^{n}$$

This model is widely used, when the release phenomenon could be involved.

Stability Studies:

The success of an effective formulation can be evaluated only through stability studies. The prepared Econazole ethosomal gel placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 3 months[14].

3.RESULTS AND DISCUSSIONS

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected lipid and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug, lipid and other chemicals.

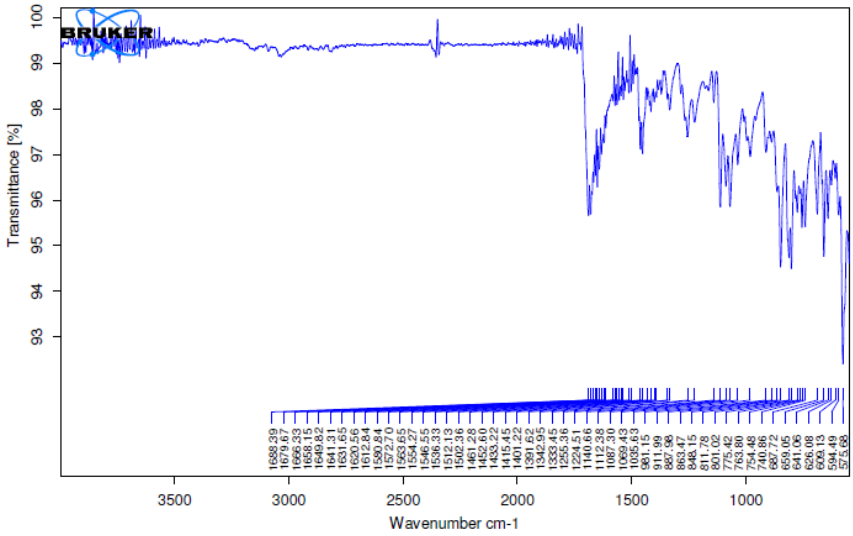

Fig- :1 FTIR Studies of Pure Drug

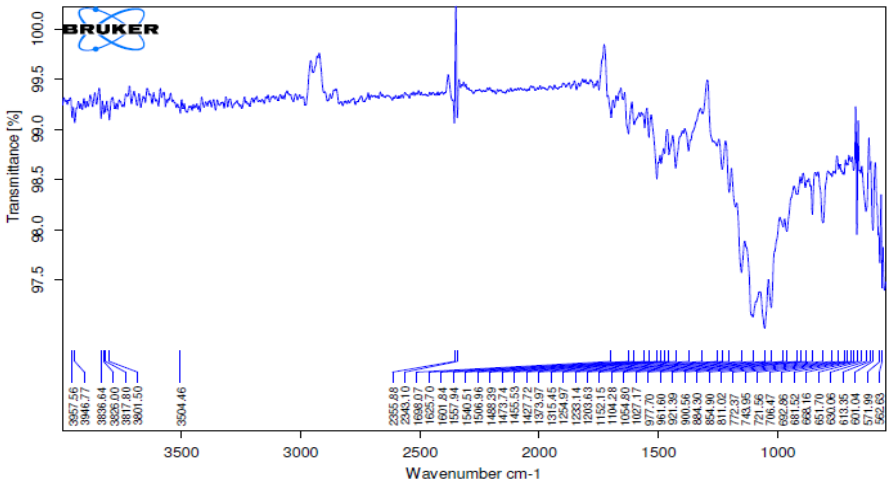

Fig -:2 FTIR Studies of Optimization

Particle size

Vesicle shape: Vesicle shape of the prepared formulation was found to be spherical from the SEM(scanning electron microscope analysis at 15.00kV

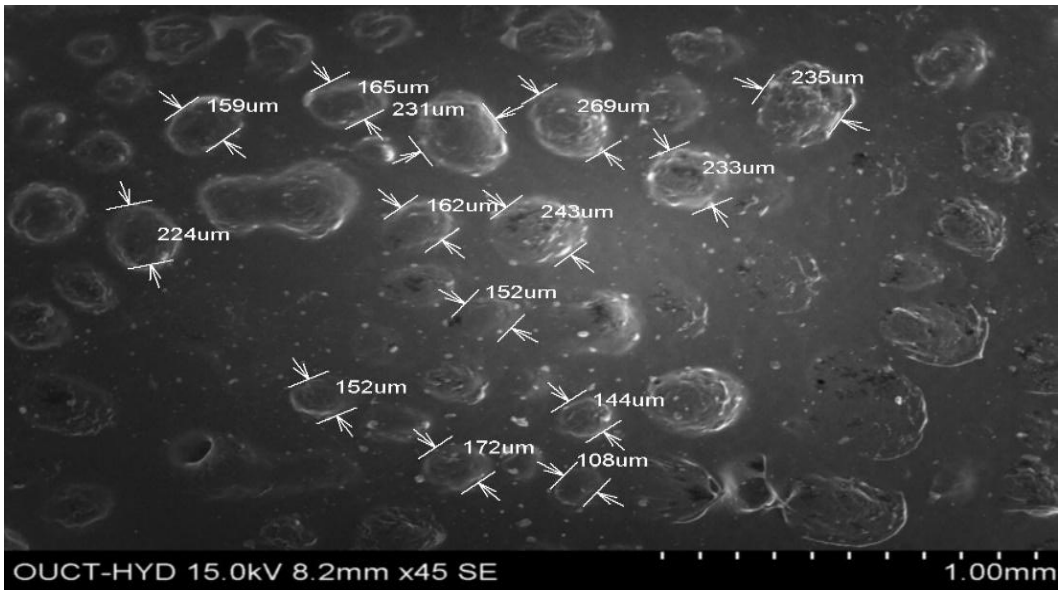

Fig-: 3 Particle size of optimization formulation

Table: 2 Mean particle size (mps) of different formulation of ethosomal gel

Sr. No	Formulation No.	Particle size(µm)
1	F1	221
2	F2	213
3	F3	218
4	F4	210

Drug entrapment efficiency

Table-:3 Different batches of ethosomal gel made by using different ratio of lipids

Sr. No	Formulation no.	PDE
1	F1	83.98
2	F2	72.45
3	F3	92.74
4	F4	69.22

Drug release studies

Table-: 4 Cumulative percentage drug release from various formulation of ethosomal gel

Time	Batch code			
	F1	F2	F3	F4
0	0	0	0	0
1	14.25	17.25	18.95	16.50

2	27.10	20.18	22.65	21.18
3	32.21	31.12	37.21	38.30
4	45.17	42.28	45.31	44.35
5	53.24	51.63	61.52	59.24
6	65.42	63.28	74.32	71.60
7	73.28	72.32	86.21	83.28
8	89.75	88.75	93.28	91.10

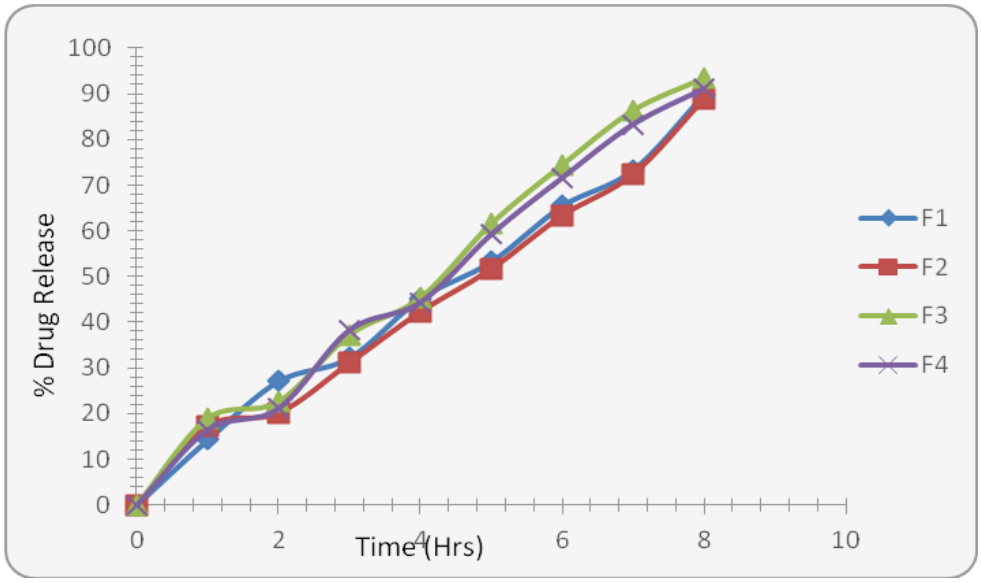

Fig- : 4 *In vitro* drug release of various formulations

All the formulation F3 were found to release the drug in 8 h. The cumulative percentage release was found to be 93.28 %.

ZERO ORDER KINETICS

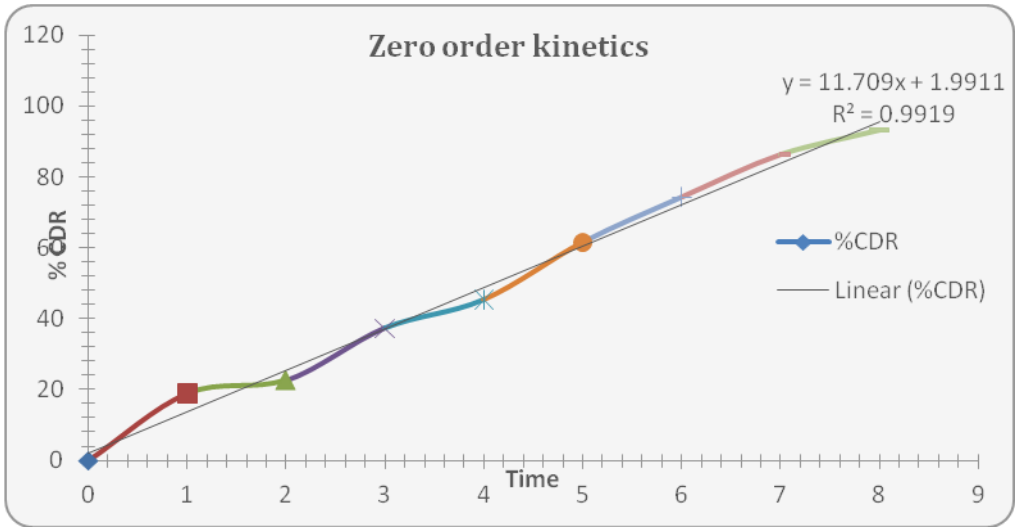

Fig-: 5 Zero order kinetics

FIRST ORDER KINETICS

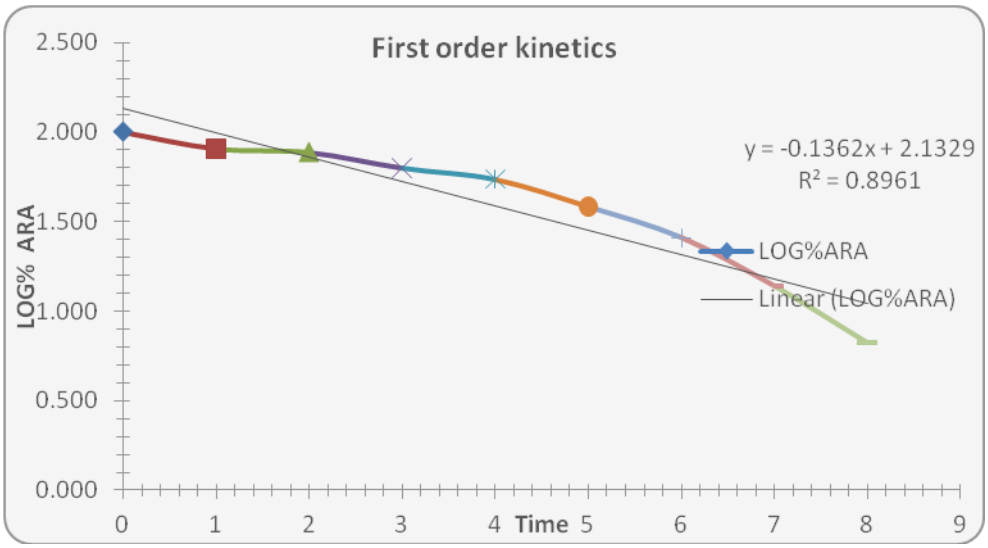

Fig-:6 First order kinetics

HIGUCHI MODEL

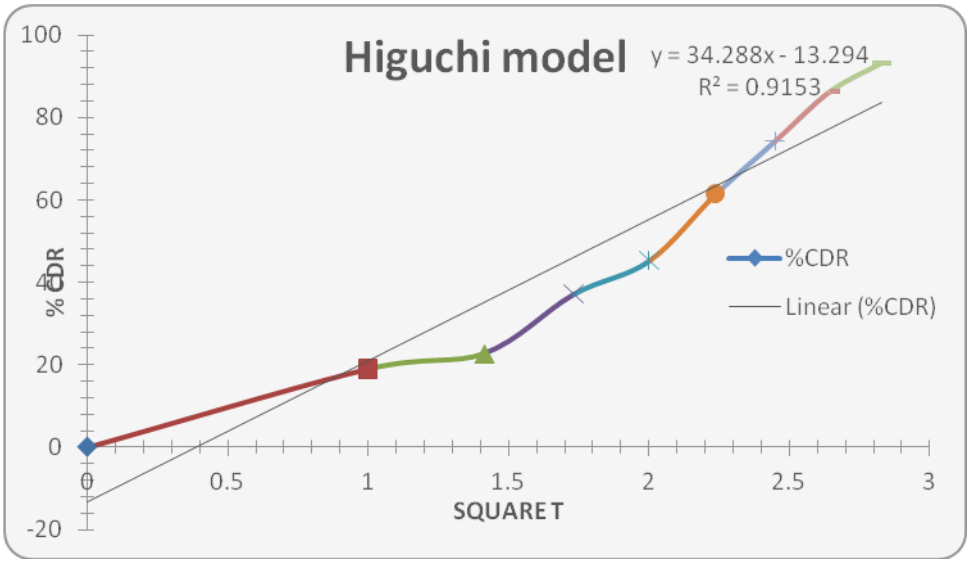

Fig-: 7 Higuchi model

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi and Peppas. Regression values are higher with Zero order release kinetics.

Table-:5 Regression equations of optimized formulation

F. No	In vitro release in phosphate buffer P^H 7.4 Regression values			
	Zero order	First order	Higuchi Plot	Kross mayerpeppas
F_3	0.991	0.896	0.915	0.699

The table indicates that r^2 values are higher for Zero order release kinetics. compared for all the formulations. Hence release from all the ethosomes followed diffusion rate controlled mechanism.

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-3 after 3 months. Parameters quantified at various time intervals were shown;

Table- : 6 Results of stability studies of optimized formulation F-3

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications

F-3	**25^0C/60%RH % Release**	93.28	93.20	93.17	93.11	**Not less than 85 %**
F-3	**30^0C/75% RH % Release**	93. 28	93.21	93.18	93.12	**Not less than 85 %**
F-3	**40^0C/75% RH % Release**	93. 28	93.18	93.11	93.08	**Not less than 85 %**

IV.CONCLUSION

To this day the most common form of delivery of drugs is the oral route. Even though this has the notable advantages of easy administration, it also has significant draw backs namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high or frequent dosing which are not only cost prohibitive and inconvenient but also unsafe. In order to surmount these lacunae these is an urgent need for the development of Novel drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific) spatial and temporal placement within the body, thereby reducing both the size and number of doses. The increasing demand for efficient administration and delivery of Pharmaceutical dosage forms possessing the attributes namely minimum side effects, improved patient compliance has resulted in the formulation of novel drug delivery system. The revolutionary technology of drug delivery is off late being focused on the transdermal route in contrast to the conventional oral route. More over the bioavailability is poor and the onset of action is slow for most of the drugs which are sparingly suitable in water.

Therefore there is a dire and urgent need to modify the route of administration. The most suitable route of administration is definitely the transdermal route. Recent technological trends have been established to enhance the permeation by reducing the carrier size and making more malleable lipid layer in the form of novel medicament carrier as Ethosomes. Ethosomes are very effective since they enhance the penetration of drugs via skin to several times whose compound to the simple creams, elixirs and liposomal carriers. Hence there is an absolute necessity to formulate econazole as Ethosomes in order to increase the penetration of the drug through the skin.

The present work also focuses on making the formulation more pharmaceutically acceptable. The prepared ethosomal gel formulations were characterized for vesical shape, vesicle size, physical appearance, and percentage drug entrapment. In-vitro drug release profiles of prepared ethosomal gels were established. Based on in-vitro drug release profile it was found that release of medicament from formulated ethosomal gels followed zero order kinetics.

The present study involves formulation and characterization of ethosomal containing econazole used to treat fungal skin infections. The present work also focuses on making the formulation more pharmaceutically acceptable. The prepared ethosomal formulations were characterized for vesical shape, vesicle size, physical appearance, and percentage drug entrapment. In-vitro drug release profiles of prepared ethosomoes were established. Ethosomal system is a highly efficient drug delivery system. The maximum entrapment efficiency of ethosomal vesicles as determined by ultracentrifugation was 92.74 % for ethosomal formulation containing ethanol (F3). Econazole ethosomal gel has specific vesicular size and shape confirmed by SEM. Stability studies was carried out for a period of 3 months and showed no significance changes in the characteristics of ethosomes. From the above observations it was concluded that ethosomes formulation F3 was found to be the best formulation among all the formulation of ethosomes .

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