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FORMULATION AND CHARACTERIZATION OF CARBOPOL GEL CONTAINING CLOTRIMAZOLE ETHOSOMES BY MECHANICAL DISPERSION METHOD

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ABSTRACT

The purpose of the present study was to develop a Clotrimazole Ethosomes entrapped gel using soya lecithin by using mechanical-dispersion method. This was employed to enhance the bioavailability and therapeutic efficacy of the drug. Optimization of formulation was done by studying entappment efficiency of prepared batches of ethosomes. Five formulations were prepared and formulation F5 possessed good entrapment efficiency. The formulation were also valuated for size, entrapment efficiency, viscosity, morphology and zeta potential, pH, Differential scanning calorimeter and vitro permeation studies. Results of this study revealed that the Clotrimazole Ethosomes entrapped gel can be a suitable drug delivery system.

KEYWORDS*:* In Vitro Penetration Test*,* Ethosomes*,* Carbopol, Clotrimazole*.*

INTRODUCTION

Development of novel drug delivery system has overcome some of the problem associated with the conventional drug delivery system and one of that system among nanosized drug carrier is Ehtosomes. This formulation has been intensively investigated and it provides better penetration of the drug in to the deep skin to treat invasive Fungal infection. [1]

Ethosomes comprising of phosphatidylen-thanolamine and it can be enhanced of about 5 to 26 fold in drug accumulation as compard to drug solution in normal. [2]

Ethosomes have been studied as a possible carrier for topical delivery of clotrimazole, an anti-fungal agent. The presence of ethanol in the aqueous compartment of the ethosomal vesicles favoured the encapsulation and enhanced its permeation via the skin because of the synergistic effect of ethanol vesicles and skin lipids. [3]

Ethosomes can provide effective intracellular delivery of hydrophilic, amphiphilic and lipophilic drug molecules. The size range of ethosomes varies from tens of nanometer to few microns. Ethosomal drug delivery system is a new novel tool for drug delivery with safety and efficacy. Ethosomes have become an area of research interest, because of its special characters such as enhanced skin permeation, improved drug delivery and increased drug entrapment efficiency. [4]

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It is like an elastic nanocarriers which offers advantages of ferrying the drug across membranes, sustaining drug release and protecting the encapsulated bio actives from external environment. The enhanced bioavailability and skin penetration of ethosomes is due to presence of ethanol in the bilayer arrangement of Ethosomes as compared to conventional vesicular delivery systems. Synthetic drug as well as phytomedicine can be delivered with this ultraformable nano structured vesicle system. [5]

Ethosome is a non-invasive vehicle, so it is safe to use it on the skin. [6-7] Ethosome can be formulated into a semi-solid dosage form, for instance, gel dosage forms. The water content in the gel has a function to moisturize the skin and is comfortable to be used. [8]

This drug delivery system not only helpful for the delivery of the drug but also increase the penetration and stability of Drug. [9] The purpose of the present study was to develop an Clotrimazole Ethosomes entrapped gel using soya lecithin by using mechanical dispersion method This was employed to enhance the bioavailability and therapeutic efficacy of the drug.

MATERIAL AND METHODS

Drug Cotrimazol obtained from Cipla Pvt Ltd Simour (H. P), Soya lecithin, carbopol 934 NF, Ethanol, Methanol, chloroform were purchased from central drug house, Delhi

METHOD OF PREPARATION

Ethosomes were prepared by mechanical - dispersion method as an briefly in a completely dried round bottom flask, Phospholipion in varying concentration was dissolved in a mixture of chloroform and methanol (3:1 v/v). A thin lipid film was then formed on the wall of the RBF using heating mental by maintain the temperature above the lipid transition temperature (55+2) and the organic solvent was completely evaporated, followed by hydration (6h) with hydro ethanolic mixture containing clotrimazole (1% w/v) the preparations were further subjected to sonication for 3 cycles of 5 min interval after sonication ethosomal formulation was stored in refrigerator.

VESICLE SIZE AND ZETA POTENTIAL MEASUREMENT

The vesicle size and zeta potential of clotrimazole ethososmes measure by Zetasizer. All vesicle size and zeta potential measurement were made on Zetasizer at 25°C. Sizing measurement were made on the neat ethosomes samples ,whereas the samples were diluted 1 in 10 with PBS for the Zeta potential measurments.

ENTRAPMENT EFFICIENCY

The entrapment of Clotrimazole ethosomes was determined by the centrifugation method. vesicular preparation containing 1% Clotrimazole were kept overnight at 4C and total volume of ethosomal suspension was measure 2 ml and diluted with Distilled water up to 5 ml and centrifuged in a centrifuge at 2000 rpm for 20 min. Clotrimazole was assayed both in the sediment and in the supernant. The entrapment capacity of Clotrimazole was calculated by taking the absorbance at 262 nm and calculated from the relationship [T-C/T] 100 where T is the total amount of Clotrimazole that is detected both in the supernant and sediment and c is the amount of clotrimazole detected only in the supernant.

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INCORPORATION INTO GEL

Carbopol 934NF 0. 95% w/v soaked in minimum amount of water for an hour. Ethosomal suspension 2 ml containing clotrimazole (1. 0%w/v) was added to the swollen polymer under continuous stirring at 700 rpm in closed vessel and maintained at temperature 30C until homogeneous ethosomal gels were achieved.

PH

The pH of gels was checked by using a digital Elico pH meter at room temperature initially ,the pH meter was calibrated using distilled water accurately 2. 5 gm of gel was weighed and dispersed in 25ml of purified water and then pH meter was dipped in the dispersion and the pH was noted

VISCOSITY OF GEL

Viscosity of Prepared gels were measured by Brookfield–DV-II+Pro Viscometer Apparent Viscosity measure at 25C and rotating the spindle at 25rpm.

IN VITRO PERMEATION STUDIES

The composition of ETH-5 was further used in which 1% Clotrimazole was added. The in vitro permeation of Clotrimazole from ethtosomes formulation was studied using locally fabricated diffusion cell. The in vitro diffusion of the drug through semipermeable membrane was performed. the semipermeable membrane soaked in 6. 4 pH buffer for 6-8 hours. It was clamped carefully to one end of the hollow glass tube, This acted as donor compartment. 900 ml of PBS 6. 4 was taken in a beaker which was used as a receptor compartment. The known quantity of ethosomal formulations was spread uniformly on the membrane. The donor compartment was kept in contact with the receptor compartment and the temperature was maintained at 37+0. 1 C. the solutions of the receptor side were stirred. At prederermined time intervals, sample was withdrawn from receptore compartment and replace by 5 ml of PBS. The drug concentration in the aliquot were determined at 238nm against appropriate blank and value was reported.

INTERACTION STUDY BY DSC

Transition temperature lipid system was determined by using Jade D,S,C Clotrimazole weight about 4. 200 mg and the transient temperature was measured in aluminium crucible at heating rate 10°c/min within temperature range from 30-300°C

Table 1.Coposition of Ethosomes

Composition in %w/v	**ET-1**	**ET-2**	**ET-3**	**ET-4**	**ET-5**
Soya Lecithin	0. 5	0. 5	1	1	1. 5
Chloroform	3	3	3	3	3
Methanol	1	1	1	1	1
Ethanol	10	20	10	20	30
Clotrimazole	1	1	1	1	1
Distilled water	qs	Qs	qs	Qs	qs
Carbopol 934NF	0. 95	0. 95	0. 95	0. 95	0. 95

Table 2.Entrapment Efficiency of Prepared formulations

S. no	Formulation code	Entrapment efficiency
1	ETH1	53. 8
2	ETH2	60. 1
3	ETH3	42. 8
4	ETH4	66. 5
5	ETH5	72. 4

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Table 3.pH of drug entrapped gel

FORMULATION	PH
ETH1	7. 1
ETH2	7. 4
ETH3	7. 2
ETH4	6. 5
ETH5	6. 9

Table 4.Viscosity of prepared gel

Formulation	Viscosity (CPS)
ETH5	3500+200

Table 5.Vesicle size and zeta potential

Formulation code	Zeta Potential (mv)	Size (nm)
ETH-1	-18. 8	377. 3
ETH-5	-42. 8	315. 0

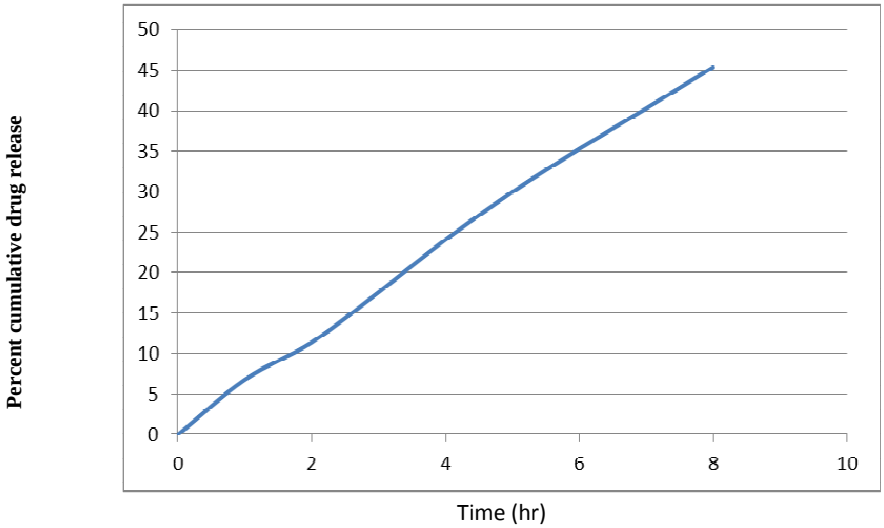

Figure 1.Percent cumulative drug release of the clotrimazole ethosomes entrapped gel.

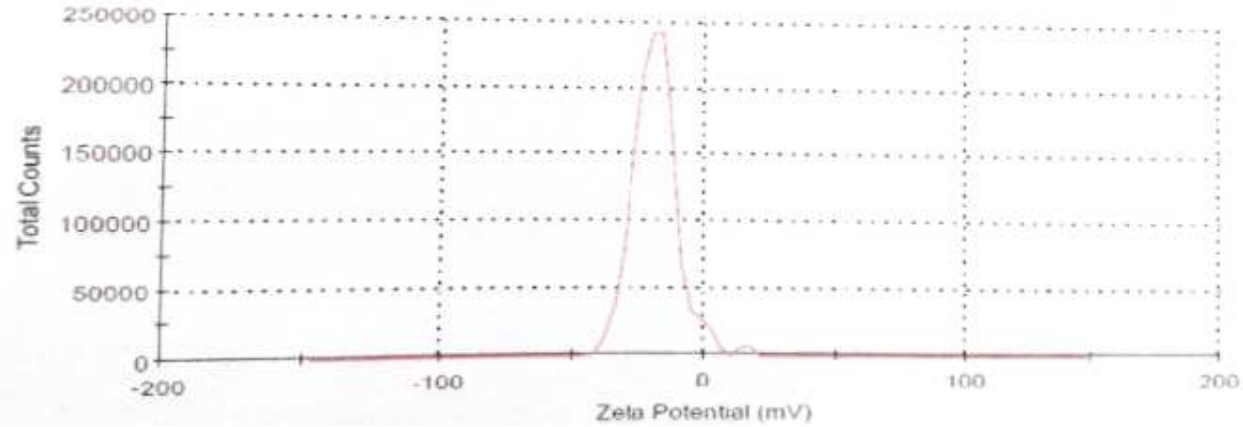

Figure 2.Zeta Potential of ETH1

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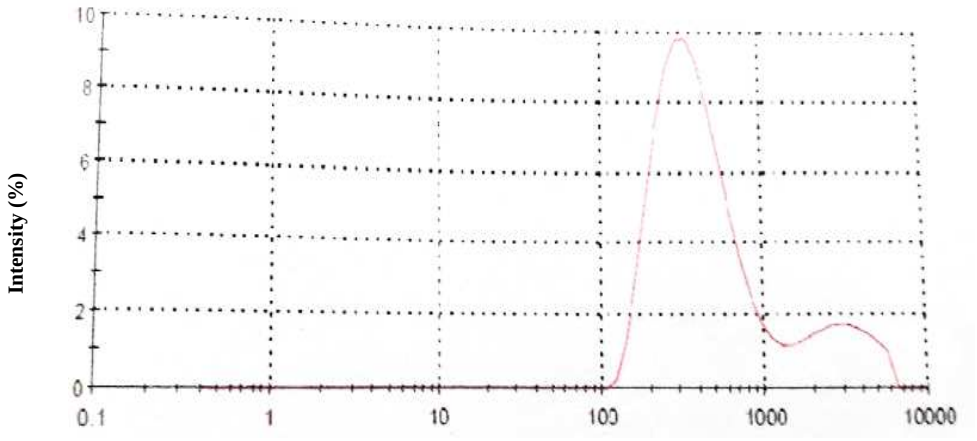

Figure 3.Size Distribution of ETH-1

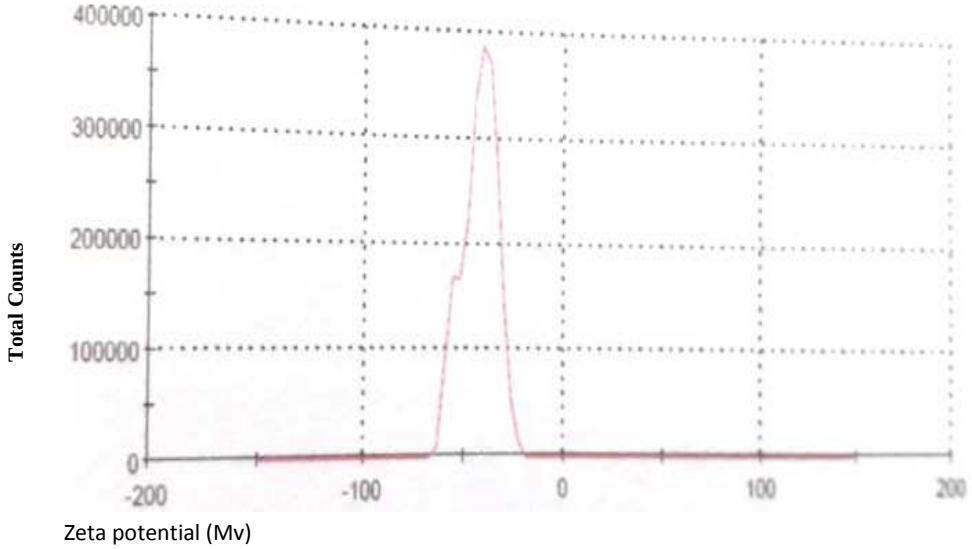

Figure 4.Zeta Potential of ETH5

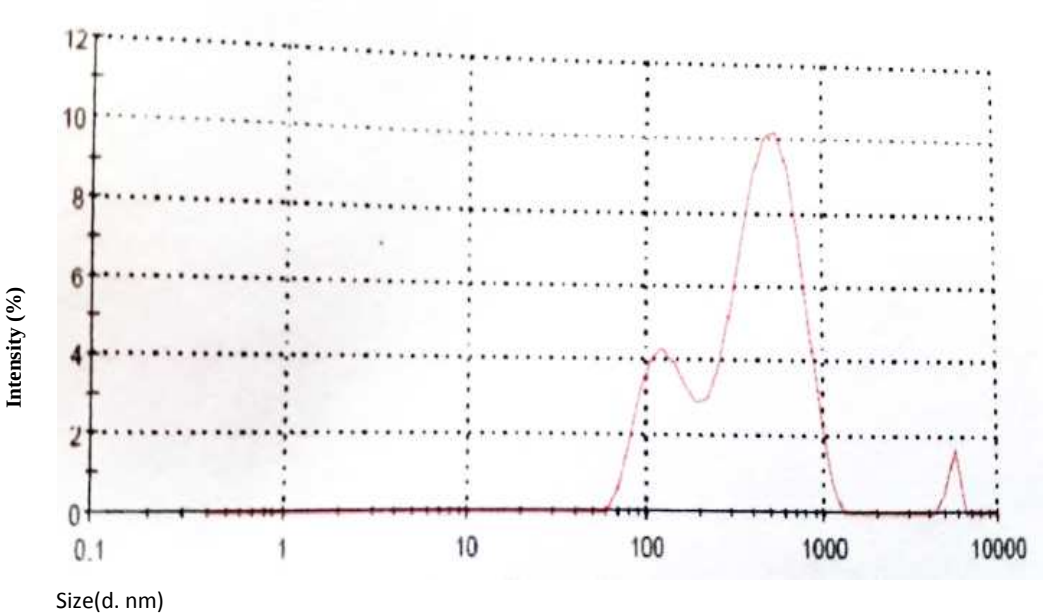

Figure 5.Size Distribution of ETH-5

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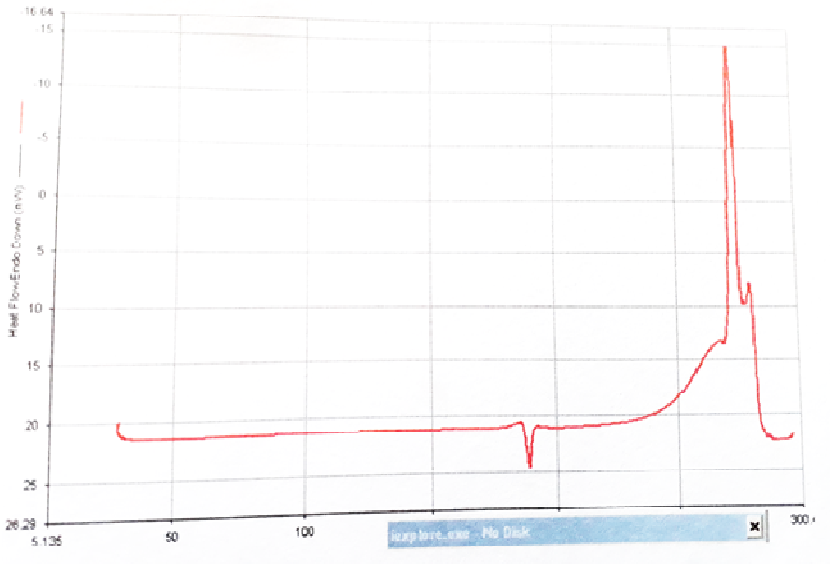

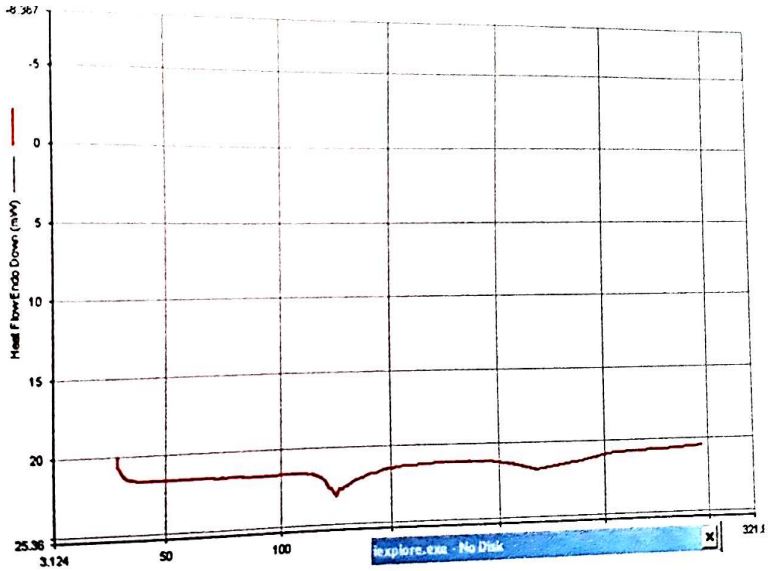

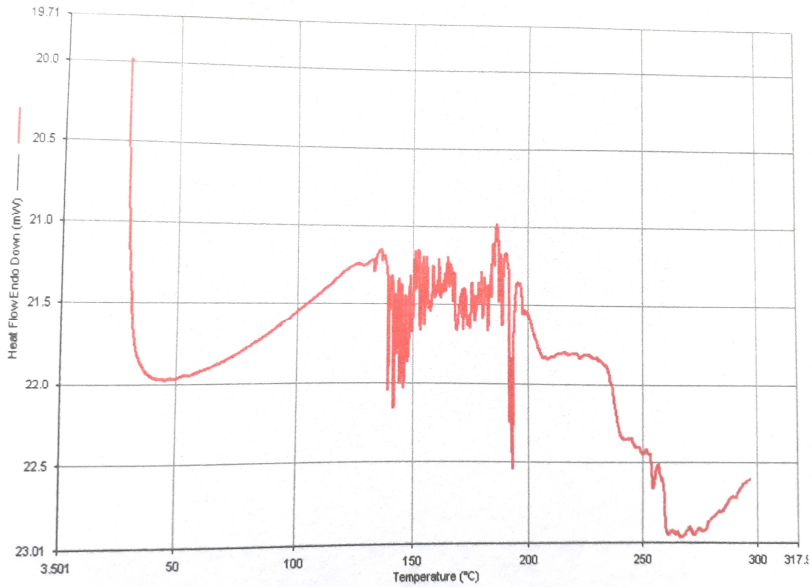

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Table 6.Vesicle size and zeta potential

Formulation code	Zeta Potential (mv)	Size (nm)
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ETH-5	-42. 8	315. 0

RESULT AND DISCUSSION

The entrapment efficiency of all the formulations was determined. Effect of ethanol concetration was observed on percentage entrapment of ethosomes. The entrapment efficiency was maximum for formulation ETH-5 (72. 4%) The entrapment was found to increase with increase ethanol concentration however perecent entrapment decreased when ethanol concentraion ecceed 40% solubility of Clotimazole also increased when ethanol was used in higher concentration. Therefore the drug also entrapped in the cire of the vesicles ,But as the concentraion of Ehtanol increased above 40% there was leakage of the drug from bilayer of the vesicles ,The entrapment efficiency increased with an increase in the concentration of lecithin but above 3% if lecithun concentration there was no increase in it. The size of batch ETH -5 formulation was in the range of 400 to 700nm and they were in High intesity in the formulation though the size range of some ethosomes formulation batch ETH-1 showed less than 100nm but their percent intensity was less and due to less entrapment efficiency they were not considered as best formulation bactch among all the prepared batch.

Viscosity of ETH-5 formulation entrapped carbopol gel was 3500 cps and the differential scanning theromogram showed the

DSC Differential scanning calorimetry of pure Clotrimazole exhibited a sharp melting endothermic peak at 170 °C though it was reported that the melting point of the drug is between 154-156 °C [Figure 2] it described t drug melting point. DSC of pure soya lecithin exhibited endothermic DSC thermogram of soya lecithin showed endotherm at 128. 93°C [Figure 3] DSC thermogram of Clotrimazole loaded ethosomes composed of soya lecithin and clotrimazole. The melting endotherm of soya lecithin was found to be shifted from 128. 93°C to 138. 28°C, [Fugure-4] signifying that all the lipid components interact with each other to a great extent while forming the lipid bilayer. Absence of the significant melting endotherm of Clotrimazole and shifting of the lipid bilayer components endotherm suggested significant interaction of Clotrimazole with bilayers, indicating the interaction of Clotrimazole with ethosome layer leading to enhanced entrapment of the drug and decreased rate of release. The DSC results of liposomes suggest enhanced entrapment efficiency of Clotrimazole in the ethsomal layer. [10] In vitro release

CONCLUSION

Though these vesicular systems offer a good potential for rational drug delivery, a thoughtfully designed process is required to optimize the process variables involved. Industrial scale production of efficacious, safe, cost effective and stable formulations of both these delivery systems appears to be a pre-requisite to ensure their utility as the trans-dermal vehicles.

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