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PREPARATION AND EVALUATION OF ECONAZOLE NITRATE CONTAINING FILM-FORMING GEL

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ABSTRACT

Objective- The aim of present study is to develop a film-forming gel (FIFOGE) formulation of Econazole nitrate with hydroxypropyl methyl cellulose (HPMC) as a gelling agent, Eudragit RS PO as a film forming polymer and Triethyl citrate as a plasticizer. Tenia pedis is fungal infection of skin occurs in athlete's foot. Econazole nitrate is broad spectrum antifungal drug used in treatment of tenia pedis having high resistance towards fungal infection. For the treatment of fungal infection of skin, antifungal drug requires to be present for longer duration of action in contact with the skin. Therefore, the formulation having prolonged drug release is required. Method- Film-forming gel forms a thin, transparent film like layer on the skin and provides a prolonged release of Econazole nitrate. So, such formulation reduces duration of therapy and improves patient's compliance. To optimize this formulation, we applied the Response Surface Analysis technique and evaluated it. In the chosen design (Box-Behnken statistical screening design), 3 factors were evaluated, each at 3 levels and all 13 possible combinations were performed in the experimental trials. The Drug concentration, Eudragit RS (PO) and concentrationof Triethyl citrate were chosen as independent variables. Drug content was selected as dependent variables. Result- The optimized film-forming gel obtained was formulated and evaluated for all parameters.

Conclusion- Optimized formulation showed % Drug diffusion of 98.19% at 12 hour.

KEYWORDS: Film-forming gel (FIFOGE), Econazole nitrate, Eudragit RS PO, Teniapedis.

INTRODUCTION

In topical drug delivery systems, the main benefit is to bypass first-pass metabolism. The other advantages of topical formulations are avoidance of risk and difficulty caused by intravenous treatment and various drug absorption conditions such as changes in pH, enzymes presence, and gastric emptying time. This method of delivery of medicine applies a wide variety of preparations to their healthy or diseased skin, both dermatological and cosmetic. Dermatological preparations range from liquid to powder in formulation, but most approved products are semi-solid formulations [1-3]. In the last decades for transdermal drug delivery system (TDDS) film forming gel (FIFOGE) has studied intensively [4]. As the water soluble pharmaceutical carrier

gel was added, it adhered to the skin surface and formed a film providing protection and drug delivery at the application site [5]. Dermal application of film forming polymer is well known to provide the skin with a protective coating and also to monitor the release of drugs from dermal dosage forms [6].

To make antifungal local delivery effectual which is used on the surface of skin, the agents have to be separated from the carrier firstly into the stratum corneum, and after that separated to the local tissue includes viable epidermis, dermis, subcutaneous tissue and appendages. It creates problems when antifungal compound in general is hydrophobic and a mean is required to carry out the separation to give active agents therapeutic efficient concentration in situ. By dermal routes effective drug delivery from the film forming gel, can reduce gastrointestinal absorption unnecessarily, efforts have been taken to provide chemical enhancers for the drug penetration such as DMSO and azones. These materials are not suitable due to toxicity and also cause irritation; therefore, there is a requirement for enhanced formulation of antifungal which could diminish the therapeutic agent's systemic exposure. The multiple application requirements in a day are often allied with poor patient compliance. Thus, increasing active substance contact time to the skin and thereby decreasing the application frequency is object to thorough research. Drug delivery system prolonged release with feature of semisolid formulations and patches both may be employed here. The conception of film forming preparation is very latest. The formed film is significant for the prolonged release of drug to the skin. Some preparations of film forming gel examples have been reported in literature. Recently studies have been done on a lidocaine transdermal film [7], abio-adhesive film of oxybutynin [8], and a transdermal film of tramadol [9]. Bee GentleTM and GELNIQUE formulations are commercially available film- forming gel. Film is the prerequisite for the extended release of drug, differentiates it from another topical dermal gels.

The gels of drugs, with or without permeability enhancer, solvent or vehicle which are volatile in nature are typically applied onto the skin which forms the film insitu after solvent evaporation. Because of the fact, the formulations which include film forming agent, the films disappear shortly after application with the solvent evaporation technique, leaving a drug contains residue or recrystallized drug [10, 11].

Econazole nitrate is an imidazole antifungal that works by preventing the growth of fungus. Econazole nitrate is a Class II member of the Biopharmaceutical Classification System (BCS), characterized by high permeability and low solubility. This is a major factor responsible for successful fungal treatment. However, oral administration, including gastrointestinal irritation, is followed by side effects. Since econazole nitrate is normally offered as long-term therapy to a patient, attempts have been made to reduce its side effect. Antifungal patches, one of the methods have proven to be promising. As a vehicle they have been recently used to deliver various drugs to the skin. Against mould, dermatophytes, yeast, Econazole nitrate acts as a broad spectrum antifungal and it's quite active against some bacteria of the actinomycets, and it's also highly active against some gram positive bacilli and cocci. Econazole nitrate were progressively more administered by topical route may increase the bioavailability. It is very slightly soluble in water so because of its hydrophobicity, film forming gel can formulate.

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Film forming gel is having excellent release rate with good absorption property along with greaseless, easily spreadable, easily removable, non-staining. The objective of the current research was to formulate a film-forming gel (combination of gel and film) formulation of econazole nitrate by using hpmc as a gelling agent. Film forming gel has dual release mechanism due to gel and film.

MATERIALS AND METHOD

Materials:

Econazole nitrate gift sample from FDC limited Mumbai, India, Eudragit RS PO was purchased from M/S Balaji Drug Surat, Hydroxy Propyl Methyl Cellulose (HPMC) was purchased from Central Drug House (CDH) Delhi, Triethyl Citrate was obtained from Central Drug House (CDH) Delhi, and Methanol was purchased from Rankem, Mumbai, India.

Method of Preparation of FIFOGE:

The Eudragit RS PO and Hydroxy propyl methyl cellulose polymer solution were developed in methanol by means of dispersion method. Eudragit RS PO was dispersed in 20 ml of methanol containing Triethyl citrate. Hydroxy propyl methyl cellulose was dispersed in 15ml of aqueous methanol separately. Both solutions were allowed to swell for 24 hours to produce clear solutions. The polymeric solutions were mixed properly with continuous stirring at 50 rpm for 30min. Accurately weighed quantity (10mg) of the Econazole nitrate was dissolved in 15 ml methanol. The drug solution and polymeric dispersion were mixed properly with continuous stirring at 50 rpm for 30 min.

Experimental design

It is possible to model curvature with response surface methodologies, such as Box–Behnken and Central Composite Design (CCD). Because Box–Behnken requires fewer runs than CCD in cases of three or four variables, we chose it in our study. In this study, a 13-run, 3-factor (Drug, Eudragit RS-PO, Triethyl citrate), 3-level Box–Behnken statistical screening design was used and shown in **Table 1** to statistically optimize the formulation factors and evaluate the main effects, interaction effects and quadratic effects on skin permeation rates. Statistical analysis was performed using Expert-Design software (Version 11, Stat-EASE INC., Minneapolis, MN, USA). In the chosen design, 3 factors were tested, each at 3 levels and all 13 possible combinations were performed in the experimental trials. The Drug concentration, Eudragit RS (PO) and concentration of Triethyl citrate were chosen as independent variables. Drug content was selected as dependent variables.

		Factor1	Factor 2	Factor 3
Formula	Run	A:Drug	B:Eudragit:HPMC	C:TEC
		mg		ml
F1	1	10	1.5:1	0.8
F2	2	50	1:1	0.55
F3	3	50	1.5:1	0.3
F4	4	30	1:1	0.3

F5	5	50	1.5:1	0.8
F6	6	50	2:1	0.55
F7	7	30	2:1	0.3
F8	8	30	1:1	0.8
F9	9	10	1.5:1	0.3
F10	10	30	1.5:1	0.55
F11	11	10	2:1	0.55
F12	12	10	1:1	0.55
F13	13	30	2:1	0.8

Table 1: Matrix of a 3^3 factorial design for formulation of econazole nitrate based film forming gel.

Analytical Profile

The sample of Econazole nitrate procured for study was identified by Infrared spectrum is shown in **fig. 1**.

Determination of Analytical Wavelength

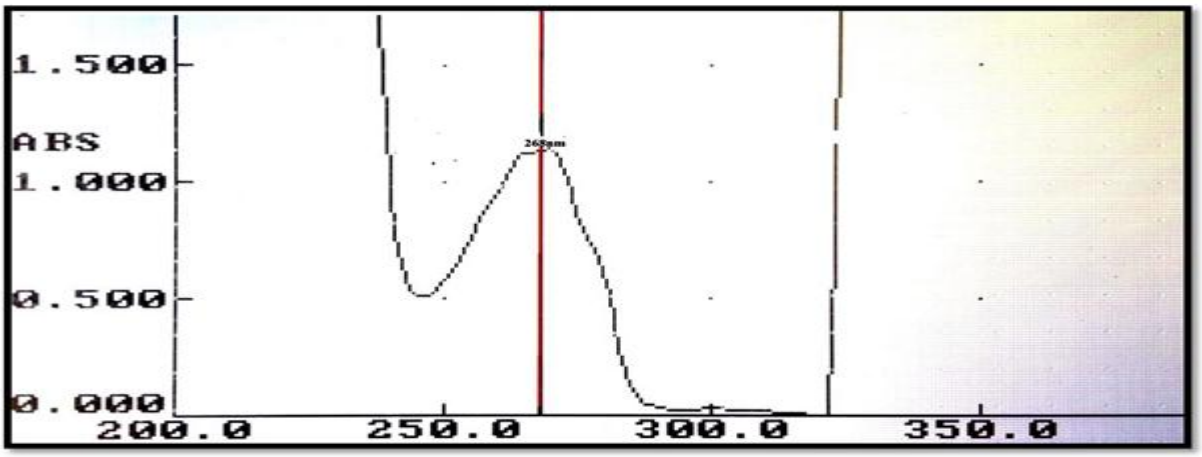

fig. 1:-UV Spectrum of Econazole nitrate

Calibration curve of Econazole nitrate

The standard calibration curve of Econazole nitrate was obtained by plotting Absorbance against Concentration. Econazole nitrate absorbance values are shown in **Table 2**. The standard curve is given in **fig. 2**. Correlation coefficient of 0.999 was found by the standard calibration curve
In the concentration range of 0-10 µg/ml (beer range) at 268 nm, a linear curve was observed. The calculations of drug content, in vitro dissolution study were based on this calibration curve.

S. No.	Concentration(µg/ml)	Absorbance
1	0	0
2	2	0.093
3	4	0.175
4	6	0.256
5	8	0.338
6	10	0.422

Table 2: Analytical data for calibration curve of econazole nitrate

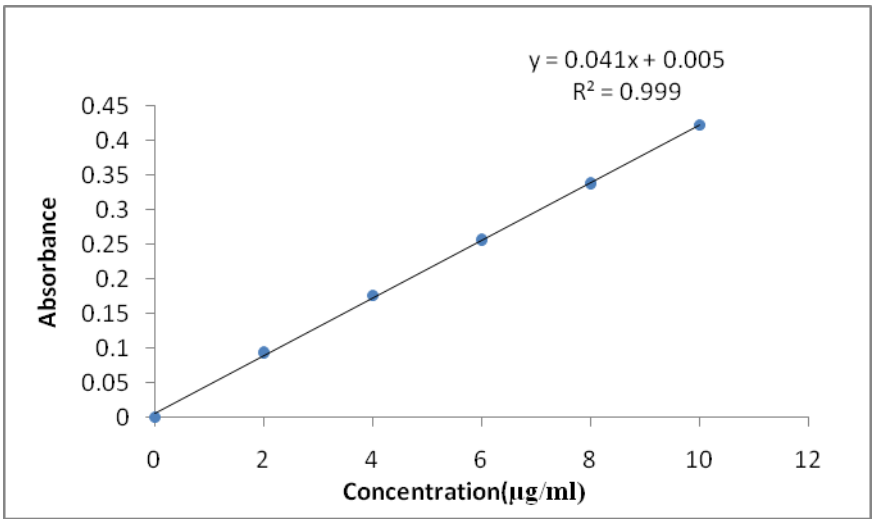

fig.2:- Calibration curve of Econazole nitrate in methanol

Compatability studies

From the pure drug spectrum shown in **fig. 3,** excipients spectrum shown in **fig. 4, 5** and drug combinations with excipients shown in **fig. 6**, the complete characteristic peak present was observed in the combination spectrum, thus implies compatibility between drug and excipients. The compatibility of the pure drug is seen on the basis of IR spectra in conjunction with the excipients.

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1) **IR Spectra of Econazole nitrate (Plain drug)**

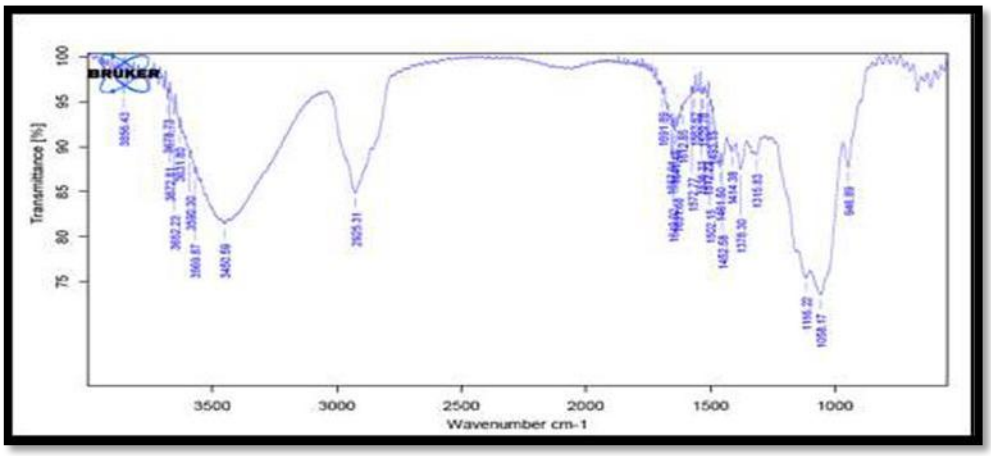


fig.3 (a): IR Spectrum of 1[2[(4chlorophenyl)methoxy]2(2,4dichlorophenyl)ethyl]imidazole ;nitric acid

2) **IR spectra of Eudragit RS PO (Excipient)**

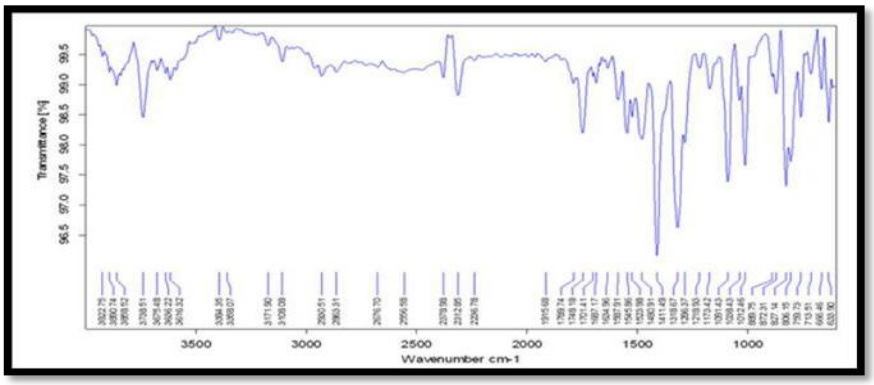


fig. 4:- IR spectrum of ExcipientEudragit RS PO

3) **IR spectra of HPMC (Excipient)**

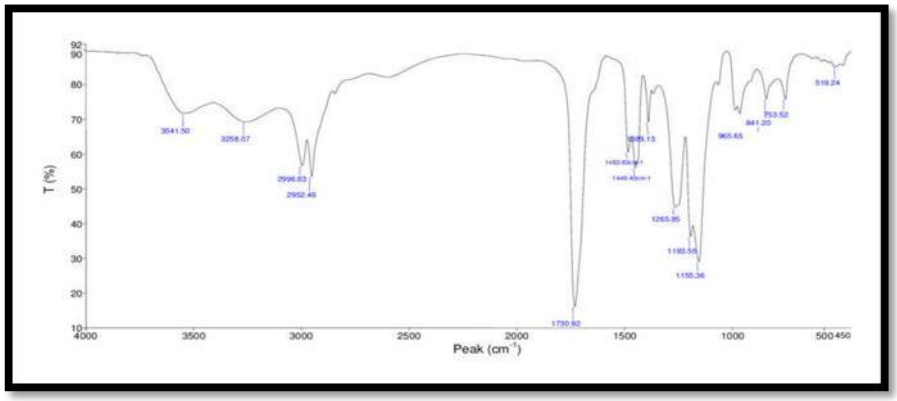


fig.5:-IR Spectrum of hydroxyl propyl methyl cellulose

4) IR spectra of Formulation (FIFOGE)

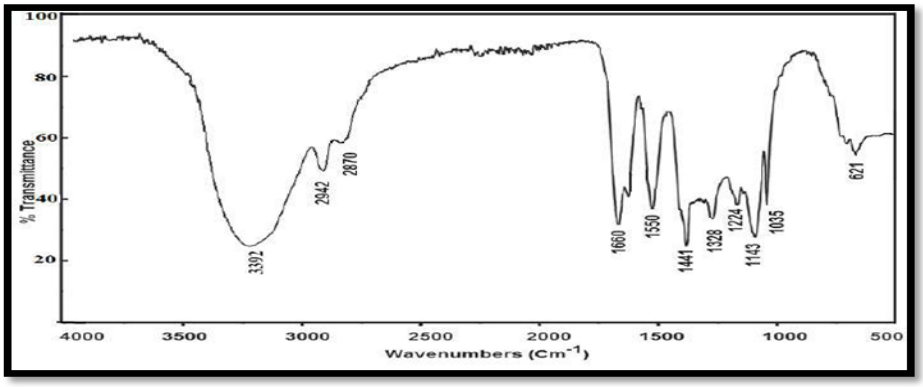


fig. 6:-IR Spectrum of Econazole nitrate with Polymer

Evaluation of Film forming gel

Characterization of gels

The film-forming gels were slightly opaque and yellowish in color. The thickness of film was 0.543 ± 0.025 mm when applied to skin. Within 3-6 min the gel forms a thin layer, and also the substance was not easily removed by clothing. The prepared gels are shown in **fig. 7** and the formed film was also shown in **fig. 8**.

fig. 7:- The prepared gel

fig. 8:- The formed film was shown and the whole area applied the gel and represented the separate part of the film from the skin.

pH determination [12]

The pH of the gel was discovered using automated pH meter. Standardized by using buffer solution (pH 7) before use. The pH measurement of each of the formulation was done in triplicate form and mean values were calculated.

Viscosity[13]

Viscosities of the gels were measured by a viscometer (Brookfield DV-II). The spindle (S 64) was rotated at 10 rpm. Before the measurements were determined, formulated gel samples were allowed to settle for 30 min. The mean value was taken from the three samples.

Drying time

Drying time of the formulated gel was evaluated by placing the gel on the glass slide. One

additional glass slide was put on top of it after 2 minutes without applying any pressure. On removing the glass slide, if no liquid remains on the slide, the film was said to be dry and if the liquid remains on the slide, the experiment was repeated until the applied formulation was found to be dry.

Drug content

For all the formulations, drug content was measured by dissolving 100 mg of gel in approximately 10 ml of phosphate buffer solution (pH 7.4). The solution was filtered. 1.0 ml of solution was taken from this and diluted up to 10.0 ml and lastly the absorbance of the prepared solution was finally measured at λ max of 268 nm by using UV visible spectrophotometer [14] is shown in **Table 3**.

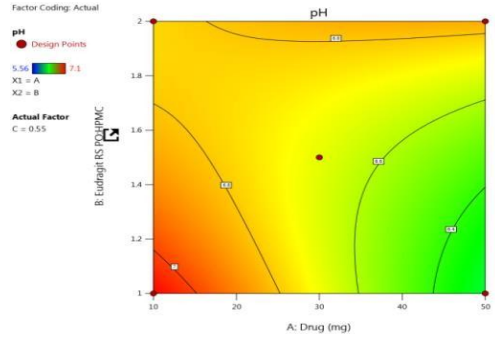
Formulation Code	pH±SD	Viscosity±SD (cps)	Drying time	Drug Content±SD (%)	% Yield
F1	6.41±0.03	900.00±100.00	3min±55sec	64.15±1.79	79.25
F2	6.70±0.01	1300.00±56.00	5min±12sec	52.17±1.23	97.50
F3	5.68±0.06	1060.00±208.00	4min±51sec	70.83±1.14	77.50
F4	5.75±0.02	1120.00±106.00	3min±56sec	99.15±1.78	90.57
F5	5.76±0.11	1180.00±152.00	5min±19sec	53.17±0.69	73.64
F6	6.82±0.07	1240.00±115.00	5min±65sec	46.29±1.37	80.00
F7	5.58±0.06	1020.00±152.00	7min±44sec	53.46±1.69	82.54
F8	5.75±0.01	1220.00±102.00	3min±56sec	40.12±1.48	86.41
F9	5.81±0.24	1280.00±136.00	4min±55sec	42.19±1.02	82.14
F10	6.68±0.06	1400.00±60.27	4min±34sec	62.52±0.93	91.57

F11	6.65±0.02	1040.00±146.00	5min±39sec	50.61±1.17	88.37
F12	7.20±0.01	1260.00±152.00	4min±52sec	75.00±1.19	88.16
F13	6.81±0.07	1150.00±118.00	7min±44sec	57.48±1.23	77.88

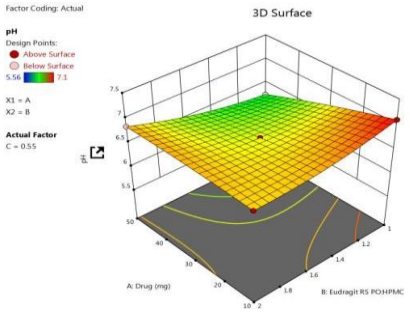
Table3:- Evaluation parameters of different formulation(F1-F13)

Optimization of Econazole nitrate film forming gel formulation

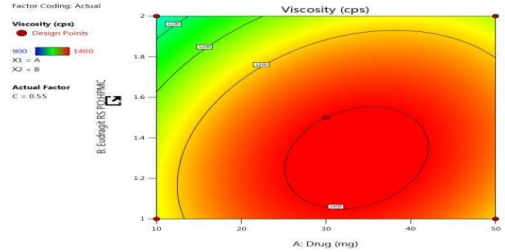
To determine the optimized formulation response surface designs were used in this study with Design-Expert software. A useful approach for selecting pharmaceutical formulations, computer optimization technique is used based on response surface methodology [15]. 3-dimensional response surface plots and 2-dimensional contour plots are shown in **fig.9**. Thirteen experimental film forming gel formulations were prepared using HPMC, Eudragit RS PO and Triethyl citrate. The optimized formulation of econazole nitrate film forming gel was determined and shown in **Table 4** and optimized formulation was selected for pharmacokinetic studies by evaluating it for various evaluation parameters and shown in **Table 5**.



(i)



(ii)



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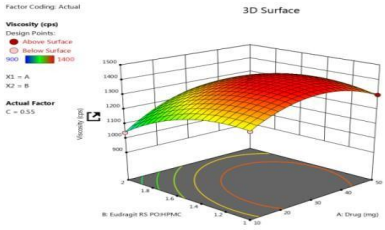

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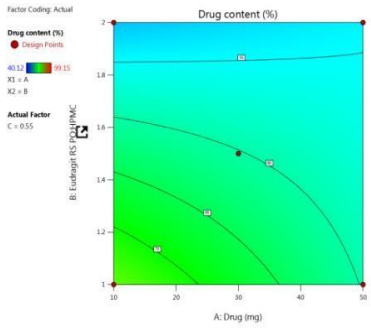
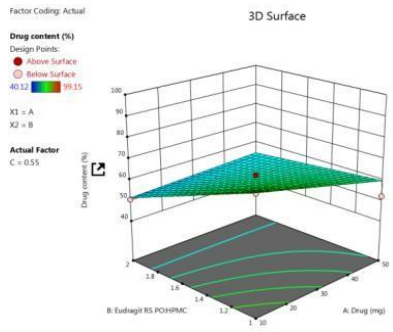
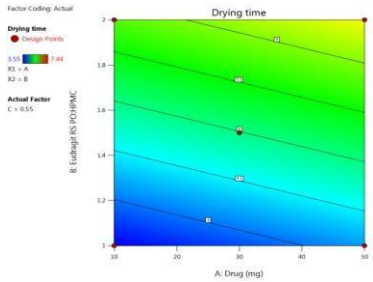
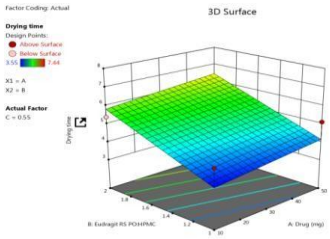


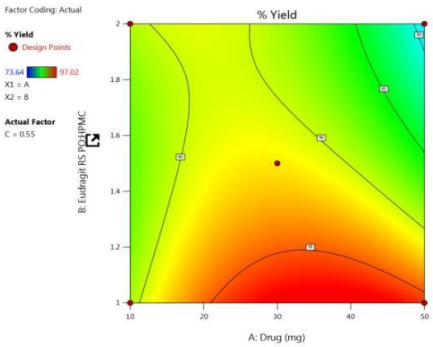


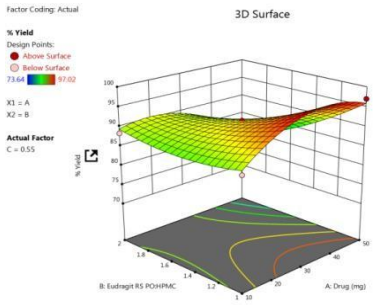
(v) **(vi)**





(vii) **(viii)**





(ix) **(x)**

fig. 9:-a) Contour plot presentation shows the effect of Eudragit RS PO:HPMC and Drug on i)pH iii)Viscosity v)Drug Content vii)Drying time ix)Percentage Yield b) Surface response plot presentation shows the effect of Eudragit RS PO:HPMC and Drug on ii)pH iv)Viscosity vi)Drug Content vii)Drying time x)Percentage Yield

Ingredients	Quantity
Econazole nitrate(mg)	37.7 mg
Eudragit RS PO:HPMC	2:1
Triethyl citrate(ml)	0.63 ml
Methanol	q.s to 50 ml

Table 4:- Optimized formula obtained from design

Parameters	Result
pH±SD	**6.92±0.23**
Viscosity±cps	**1240cps±30.55**
Drug Content±SD(%)	**65.22%±2.46**
Drying Time	**5min±9sec**
% Yield	**88.71%**

Table 5:- Evaluation parameters of optimized formulation

In-vitro Drug Diffusion study

The diffusion of in-vitro drugs of optimized formulation was examined by means of Franz-type modified diffusion cell. The cell consists of two chambers with a diffusion membrane (rat skin) between the donor and the receptor compartment which has a diameter of 1.5cm [16,17]. Phosphate buffer saline (PBS, pH7.4) of 100ml was used as the receptor medium, which was thermoregulated at 37±0.5°C with water bath and stirred at constant rate by magnetic stirrer during the experiment. The film-forming gel containing drug placed over the drug release membrane in the donor compartment which was separated by the diffusion membrane from the receptor compartment that was previously soaked for 24 hrs in PBS. Samples (2ml) were collected at 0.5,1,2,3 upto 12 hrs and analyzed spectrophotometrically at λ max against blank and the percent of drug released was calculated [18] and shown in **Table 6** and graph was also plotted to show the drug diffusion and was presented in **fig. 10**. Subsequently, the receptor compartment was replenished with an equal volume of PBS at every time of sample withdrawal.

Time(hr)	% Drug diffusion±SD
0.5	**7.96±0.108**

1	**13.42±0.135**
2	**18.27±0.589**
3	**23.79±1.139**
4	**30.81±0.983**
5	**38.77±0.409**
6	**47.39±1.032**
7	**58.53±0.592**
8	**66.59±0.318**
9	**77.54±0.503**
10	**84.09±0.103**
11	**91.96±0.567**
12	**98.19±0.215**

Table 6:- Percentage drug diffusion of optimized formulation

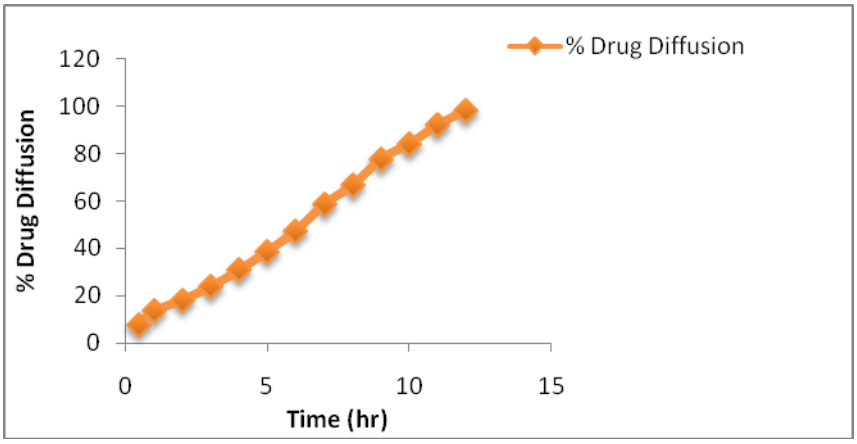


Fig:10 in-vitro drug diffusion of optimized formula

RESULT AND DISCUSSION

The pH of the formulations was increasing with the conc. of Eudragit RS PO:HPMC ratio as per the response surface curve. As well, the viscosity of the formulations was decreasing with the concentration of Eudragit RS PO:HPMC as shown in surface response curve and their contour plot. There are very minute changes are shown in the drug content with the comparison of Eudragit RS PO:HPMC and drug ratio, higher the ratio of X1 & X2 getting more drying time and percent yield of formulations are higher when the ratio of X1 & X2 are almost high at their range.

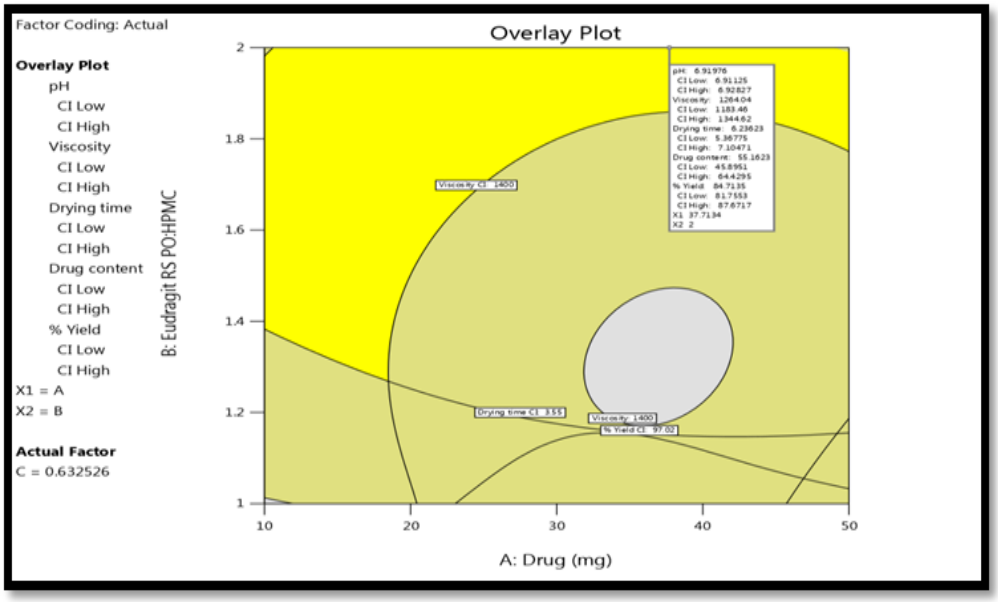


fig. 11:- Overlay Plot of optimized formulation

By using overlay plot shown in fig.11, the optimized formulation was chosen by graphical optimization methodology. For the graphical optimization of the formulation, the constraints applied were pH (6.92), viscosity (1264cps), drying time (6.2sec), drug content (55.16%) and percent yield (84.70%) as shown in their overlay plot fixed for the reason. Based upon the afore-listed criteria, the optimized formulation was selected. The optimized formulation contain exhibiting observed values of the formulation as 37.7 as X1 and 2 as X2, thus signifying high degree of predictive ability of design methodology. The % Drug diffusion was found to be 98.19%. Using the checkpoint obtained from experimental design tools, the optimised formulation was prepared. For all the above parameters, an optimised formulation was assessed.

CONCLUSION

For controlled and targeted drug delivery, a topical route is the most popular and successful route. The goal of this work is to develop econazole nitrate containing film-forming gel for prolonged release based on topical delivery and to treat skin fungal infection in a short duration of time. FIFOGE also proves to be an efficient dosage method for the topical delivery of antifungal. It also stays adhered to the affected portion for a longer time without being rubbed off. It offers prolonged effect than conventional gels, and also there is no need for regular re-application. The idea of FIFOGE will change the therapy of different diseases and provide young researchers and scientists with a broad platform in the field of film forming gel. The prepared topical drug delivery system of Econazole nitrate using HPMC:Eudragit RS PO and triethyl

citrate had shown strong positive outcomes for all the calculated parameters. In order to make the film forming gel ideally suited for the treatment of Tenia pedis and other fungal infections, the optimised batch displays all criteria within the specification. It has been concluded that moderate level of HPMC:Eudragit RS PO and triethyl citrate was useful for the formulation of prolonged release of topical film forming gel.

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CONFLICT OF INTERESTS

Declared none

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