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Formulation and Evaluation of Eberconazole Hydrogel

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ABSTRACT: The aim of this project was to formulate and evaluate eberconazole hydrogel. Eberconazole (EBZ) is a BCS class II drug that has poor solubility and high permeability.It is a broad-spectrum imidazole derivative, which acts as a both fungicidal and fungistatic drug.Eberconazole hydrogelwas formulated to treat topical fungal infections and was achieved by incorporating drug into the gel matrix for effective delivery of drugs, increased local action in pain management and skin diseases.Hydrogels were prepared using different polymers like carbopol 934, HPMC, guar gum, xanthan gum and sodium CMC at different concentrations.These formulations were evaluated for pH, spread ability, viscosity, extrudability, drug content, invitro drug release. The results shows that formulations have passed all the evaluation tests and theinvitro studies showed higher drug release for formulation F3(of 93.24% in complete 5hrs)containing carbopol934, guar gum, propylene glycol as permeation enhancer and F5(of 96.52% in complete 5hrs)containing carbopol934, sodium CMC, propylene glycol as permeation enhancerandhence were selected for antifungal studies. Antifungal activity was performedcomparing these formulations (F3 & F5) to the standard by measuring the ZOI against the microbial agent Candida albicans. Formulation F5 exhibited higher zone of inhibition compared to F3 and standard.

KEYWORDS: Eberconazole nitrate, hydrogel, Candida albicans.

I. INTRODUCTION

Eberconazole nitrate is an imidazolederivative, which is a fungistatic or antifungal drug. Mostly used topically as 1% cream for the treatment of candidiasis, dermatophytosis, Tinea corporis, Tinea cruris and any other fungal infections.Hydrogels are three dimensional network structures. They have good ability to absorb and carry sufficient quantity of water in their porous structure. Hydrogels are flexible due to high water content. Hydrogels are smart enough to respond to fluctuations in environmental stimuli like ionic strength, temperature pH, presence of enzyme, electric field. They are soft rubbery and highly biocompatible.Eberconazole hydrogel was formulated using polymers, glycerin as humectant, methylparaben and propyl paraben as preservatives and propylene glycol as permeation enhancer.Eberconazole hydrogels were formulated for topical useinboth cosmetics and in treatment of dermatological disordersand for localized and systemic effect on skin surface.Eberconazole hydrogels were formulated to show effective delivery of drugs, increased local action in pain management and intreating skin diseases. In

II. MATERIALS AND METHODS

2.1 MATERIALS

Eberconazole wasa kind gift sample from Dr.Reddy's laboratories, Hyderabad. Methanol, Carbopol 934, HPMC, Guar gum, Xanthan gum, Sodium CMC, Methyl paraben, Propyl paraben, triethanolamine were purchased from S.D. Fine Chem, Mumbai. Propylene glycol and Glycerin were procured from SISCO research laboratories, Mumbai.

2.2PRELIMINARY STUDIES

1.Determination of absorption maxima (λmax) of Eberconazole Nitrate:

10µg/ml of the drug solution was scanned in UV-Visible spectrophotometer in the range of 400-200nm and absorption maxima was obtained.

2.Determination of standard graph (calibration curve) of Eberconazole nitrate:

Standard graph of eberconazole nitrate was determinedin both methanol and pH 7.4 phosphate buffer saline.Standard dilutions were madefrom 6-30µg/ml and scanned in UV-Visible spectrophotometer at 232nm.

3.Determination of drug-excipient compatibility studies:

Drug-excipient compatibility studies were performed to find out whether there were any interactions between drug and polymer**.**Thesamples of drug and drug-polymer physical mixtures were mixed with potassium bromide and grounded

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thoroughly to form a KBr film disc. The KBr disc were compressed by applying pressure of 5 tones for 5mins in a hydraulic press and the discs were scanned using FTIR spectrophotometer (Fourier Transfer Infrared spectrophotometer) over a wave number range 4000-400cm.

2.3 Methodfor Preparation Of Eberconazole Hydrogel

Variousdispersions of polymers like carbopol 934, HPMC, guar gum, xanthan gum and sodium CMC were made in water with the aid of magnetic stirring. The polymeric dispersions were soaked for 24hrs for complete swelling. Drug solution was added with aid of magnetic stirring to the above dispersions. To the above mixture, glycerin(humectant), methyl paraben, propyl paraben(preservatives) and propylene glycol (permeation enhancer) were added with continuous stirring. The formulation was left for 24hrs in dark to obtain a homogeneous mixture. Triethanolamine was used to adjust the pH.

Table 1: Composition of the hydrogel formulations

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
DRUG (mg)	50	50	50	50	50	50	50	50
CARBOPOL 934(gm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMC (gm)	-	0.5	-	-	-	-	-	0.5
GUAR GUM (gm)	-	-	0.5	-	-	-	-	-
XANTHAN GUM (gm)	-	-	-	0.5	-	-	-	-
SODIUM CMC (gm)	-	-	-	-	0.5	-	-	-
METHYL PARABEN(gm)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
PROPYL PARABEN (gm)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
GLYCERIN (ml)	5	5	5	5	5	5	5	5
PROPYLENE GLYCOL (ml)	2.5	2.5	2.5	2.5	2.5	5	10	10
TRIETHANOLAMINE (ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
WATER	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

2.4 EVALUATION STUDIES:

1.Visual examination:

The hydrogel formulations were examined for their physical propertiessuch as color, clarity, grittiness and homogeneity by visual inspection.

2. Determination of pH:

The pH of the hydrogel formulations were determined using pH meter. The pH meter was calibrated with standard buffer solutions (pH 4, 5 and 7). 1gm of the formulation was dispersed in distilled water and then the electrode was immersed

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into it for determination of pH. Measurements were done in triplicate.

3.Determination of viscosity:

The viscosity of the formulationswere measured using Brookfield viscometer. Spindle no.60 was used for the measurement at 100rpm at room temperature. 1gm of formulation was dispersed in distilled water. The spindle of the viscometer was immersed perpendicular in the center, making sure that spindle does not touch the bottom of the jar. Measurements were repeated 3 times to get concurrent results.

4.Determination of spread ability:

1gm of the sample was placed between two glass slides. A weight of 100gm was placed on the upper glass slide and allowed to rest for 1minute. The diameter of the gel was measured after a minute and calculated using formula:-

$$S = M \times L/T$$

5. Determination of extrudability:

The hydrogel formulations were filled in collapsible tubes. The tubes were pressed to extrude the material and the extrudability of the formulation was checked.

6. Determination of drug content:

The drug content of the formulations were determined by diluting 100mg of formulation in suitable amount of pH 7.4 phosphate buffer saline (100ml). Then suitable dilutions were made and scanned using UV-Visible spectrophotometer at 232nm.

2.5 In vitro drug release studies:

The In vitro drug release studies were performed using Franz diffusion cell. The diffusion cell consists of a receptor compartment and a donor compartment. In this study the dialysis membrane (from HIMedia Laboratories Pvt. Ltd) was soaked in pH 7.4 phosphate buffer saline for 24hours. Thedialysismembrane was then placed between the receptor compartment and donor compartment and clamped. The receptor compartment was filled with pH 7.4 phosphate buffer saline. About 1gm of the hydrogel formulation was placed on the dialysis membrane. About 2ml of aliquots was withdrawn periodically from the receptor compartment and fresh pH 7.4 phosphate buffer saline was simultaneously replaced. The samples were analyzed spectrophotometric ally at 232nm to determine the amount of drug dissolved.

2.6Antifungal study:

The antimicrobial activity was performed using Agar well diffusion method.The best selected formulations were compared with that of the standard (drug) against the microbial agent Candida albicans.

Agar well diffusion method:

Sabouraud dextrose agar was prepared and sterilized in autoclave, then allowed to solidify in petri plates. The petri plates were seeded with the microorganism using pour plate method. Wells of diameter 6mm-8mm were bored aseptically with a sterilized cork borer. Volume of about 20µl-100µl of the antimicrobial agent is introduced into the wells. The agar plates were incubated for 24hours at 45℃. The antimicrobial agent diffuses into the agar medium and inhibits the growth of the microbial strain. The diameter of zone of inhibition was measured.

III. RESULTS AND DISCUSSION

3.1 PRELIMINARY STUDIES

1. Determination of absorption maxima (λmax) of Eberconazole nitrate

A 10µg/ml standard solution of eberconazole in methanol was scanned in the range of 200-400nm using UV- Visible spectrophotometer and absorption maxima was found to be 232nm and graph is shown in figure 1.

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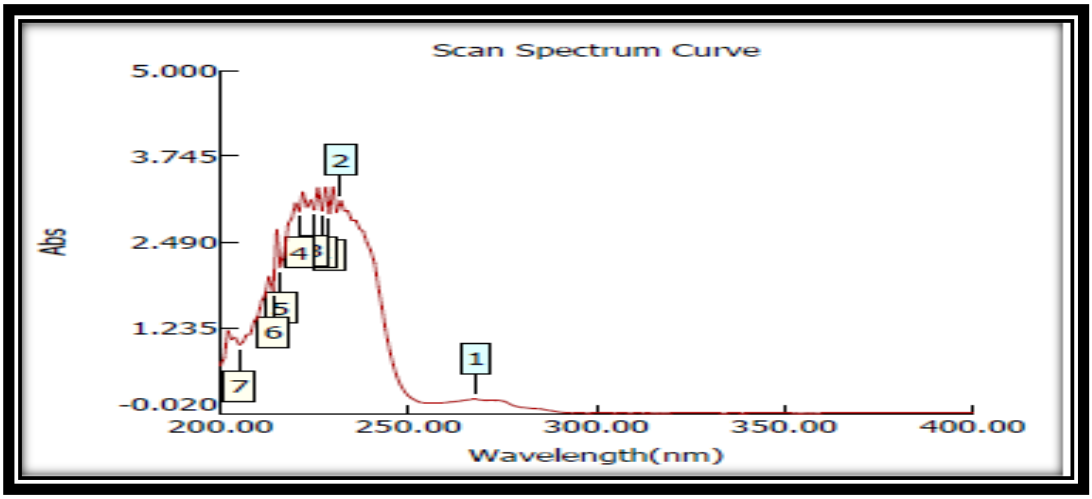

Figure 1: Absorption maxima (λmax) of Eberconazole nitrate in methanol

2. Determination of standard graph (calibration curve) of Eberconazole nitrate

Thestandard dilutions of eberconazole nitrate were made in the range of 6-30µg/ml with pH 7.4 phosphate buffer saline and scanned using UV-Visible spectrophotometer at 232nm.The equation for was found to be y = 0.038x - 0.1736 and R^2 = 0.9947. The slope values were further used in analytical study. The graph is shown in figure 2.

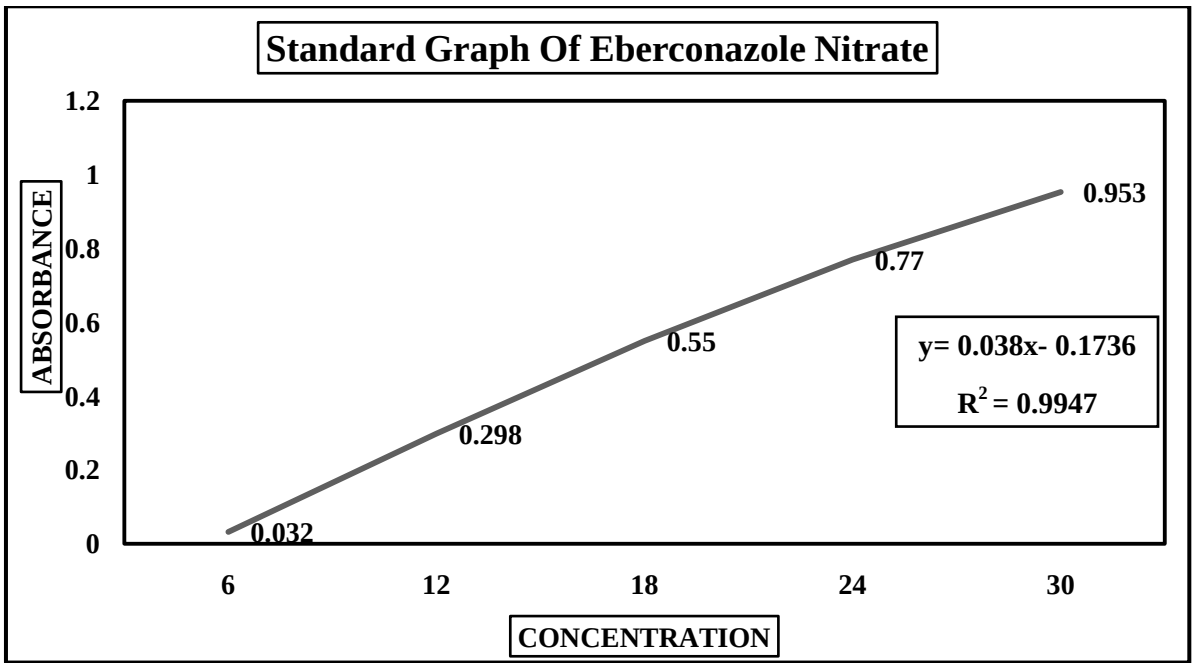

Figure 2: Standard graph (calibration curve) of Eberconazole nitrate in pH 7.4 phosphate buffer saline. The graph was observed to be linear in the range of 6-30µg/ml

3.Determination of Drug-Excipients compatibility studies

Purity of drug and drug-excipients compatibility studies were performed using FT-IR analysis.The FT-IR studies were performed for drug (Eberconazole nitrate) and the physical mixtures. The studies are shown infigures 3&4 and tables 2&3.

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FUNCTIONAL GROUP	REPORTED FREQUENCY	OBSERVED FREQUENCY
NH	3500-3100	3020.58cm^{-1}
C-H	3300-3000	2572.27cm^{-1}
C=H	2200-2050	1565.80cm^{-1}
C=C	2100-1800	1034.05cm^{-1}
C-Cl	1050-650	893.55cm^{-1}

Table 2: Drug-Excipient Compatibility Studies of Eberconazole

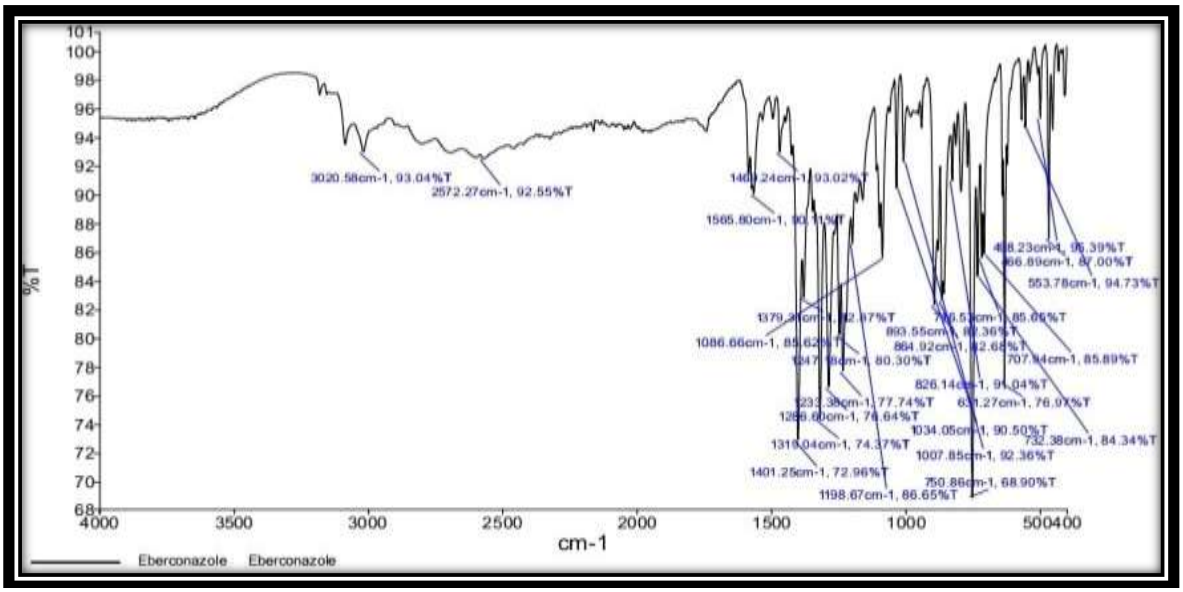

Figure 3: Drug-Excipient Compatibility Studies of Eberconazole

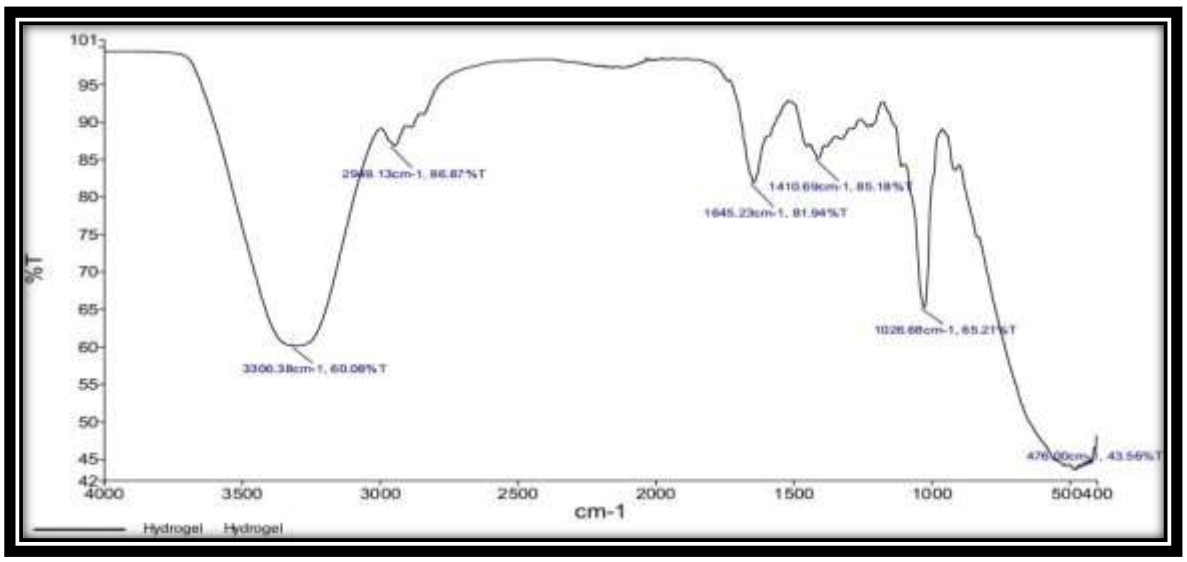

Figure 4: Drug-Excipient Compatibility Studies of Selected Formulation

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Table 3: Drug-excipient compatibility studies of Selected Formulation

FUNCTIONAL GROUP	REPORTED FREQUENCY	OBSERVED FREQUENCY
NH	3500-3100	3306.38cm^{-1}
C-H	3300-3000	2949.13cm^{-1}
C=H	2200-2050	1645.23cm^{-1}
C=C	2100-1800	1410.69cm^{-1}
C-Cl	1050-650	1026.68cm^{-1}

TheIR spectra of physical blend of the polymers and thedrug with the polymers showed neither shift nor disappearance of characteristic peaks suggesting that there was no interaction between drug and polymers and they are very much in conformity with the standard reference spectra.

3.2 EVALUATION OF EBERCONAZOLE HYDROGEL

1.Visual examination: The prepared hydrogel formulations were inspected visually for their color, clarity, grittiness and homogeneity. It was observed that all formulations were white and smooth. All formulations also showed good homogeneity with absence of grittiness. The physical appearances of the formulations are given in the table 4.

Table 4: Visual examination of Eberconazole Hydrogel Formulations

FORMULATION	**PHYSICAL APPEARANCE**			
	Color	**Clarity**	**Grittiness**	**Homogeneity**
F1	White	Smooth	Absent	Good
F2	White	Smooth	Absent	Good
F3	Yellowish	Smooth	Absent	Good
F4	Off-white	Smooth	Absent	Good
F5	Off-white	Smooth	Absent	Good
F6	White	Smooth	Absent	Good
F7	White	Smooth	Absent	Good
F8	White	Smooth	Absent	Good

2. Determination of pH of eberconazole hydrogel

The pH of the prepared formulations were measured using pH meter. The pH values of all formulations were in the range of 7.05-7.84 which were neutral and hence are acceptable for topical application. The pH of all formulations are given in table 5.

3. Determination of viscosity of eberconazole hydrogel

The viscosity of the hydrogel formulations were measured using Brookfield viscometer. The viscosity of the formulations changes as concentration of polymer changes. It is seen that among all the formulations F5 showed higher viscosity and hence skin retention time and permeability is high and adheres to the skin more compared to the other formulations. The values of

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viscosity were ranging from 8478-9344cps. The viscosity of the formulations are given in table 5.

4. Determination of spread ability of eberconazole hydrogel

The spread ability of the hydrogel formulations were measured and the diameter of the formulations were ranging from 5.30-7.52cms. High spread ability was seen in F5. The results of the spread ability studies of all the formulations are given in the table 5.

5. Determination of extrudability:

The extrudability of the hydrogel formulations were studied using collapsible tubes. The study showedgood extrudability for all the formulations. The results of extrudability studies of the formulations are given in table 5.

6.Determination of drug content:

Thedrug content of the eberconazole hydrogel formulations were determined by dissolving the formulations in pH 7.4 phosphate buffer saline and measuring its absorbance at 232nm in UV-Visible spectrophotometer.Drug content of all formulations were in the range of 76.31-97.36%, in which F5 showed higher drug content. The drug content of the formulations are given in the table 5

Table 5: pH, viscosity, spreadability, extrudability and %drug content of the formulations

Formulations	pH	Viscosity (cps)	Spreadability (cm)	Extrudability	%Drug content
F1	7.52±0.03	8478	7.01	Good	76.31
F2	7.16±0.05	8629	5.30	Good	89.42
F3	7.55±0.02	8819	6.16	Good	94.73
F4	7.09±0.04	8850	6.30	Good	86.84
F5	7.84±0.09	9344	7.60	Good	97.36
F6	7.60±0.03	8980	6.90	Good	92.10
F7	7.43±0.08	9142	7.05	Good	96.84
F8	7.65±0.07	9236	7.52	Good	95.89

3.3Invitro diffusion studies of eberconazole hydrogel

Invitro diffusion studies were performed using Franz diffusion cell and it showedF3 and F5 exhibited higher drug release in complete 5 hours compared to other formulations. Cumulative percent drug release graph is given in figures 5 & 6.

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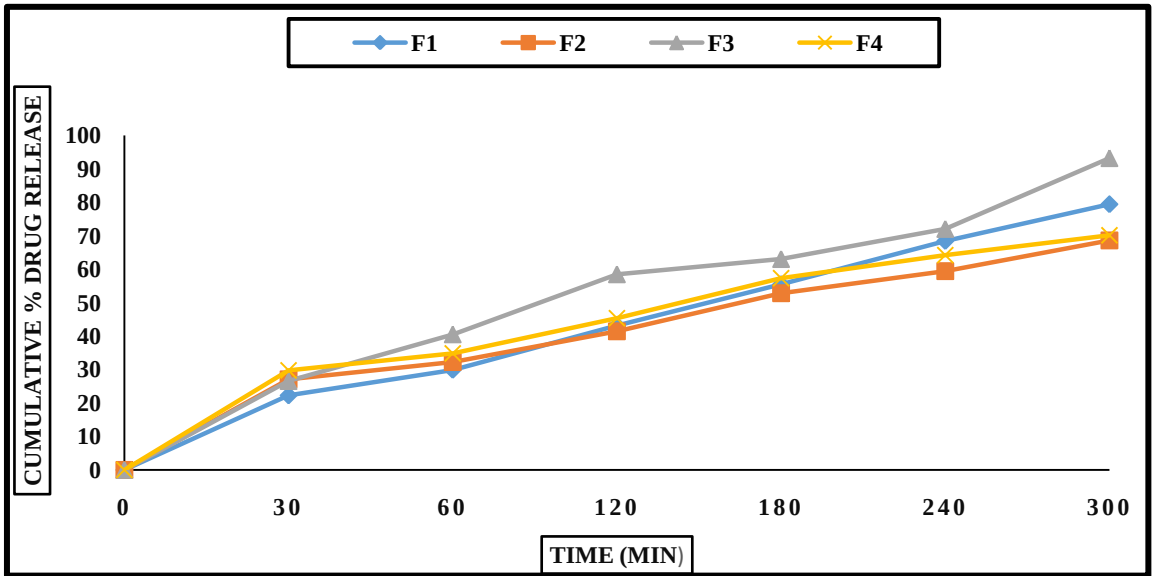

Figure 5: Cumulative percent drug release of eberconazole hydrogel Formulations from F1 to F4

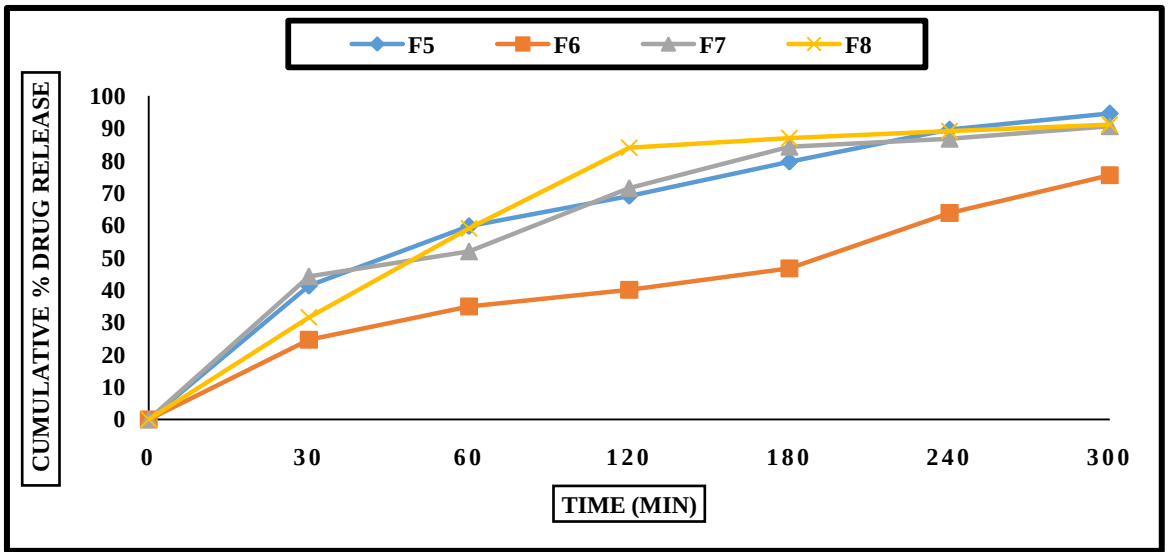

Figure 6: Cumulative percent drug release of eberconazole hydrogel Formulations from F5 to F8

3.4Antifungal activity:

The antifungal study was performed by measuring and comparing the diameter of zones of inhibition (ZOI) in mm for the selected hydrogel formulations. The zone of inhibition is the clear region around the well that contains an antimicrobial agent. It is stated that the larger the zone of inhibition, the more potent is the antimicrobial agent. Agar well diffusion method was used to determine the antifungal activity of the selected hydrogel formulations. The antifungal activity of the selected formulations was compared with that of the standard (drug) against Candida albicans.

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Table 6: ZOI of the selected hydrogel formulations and standard against Candida albicans

	FORMULATION-3	FORMULATION-5	STANDARD
ZOI	20mm	30mm	25mm

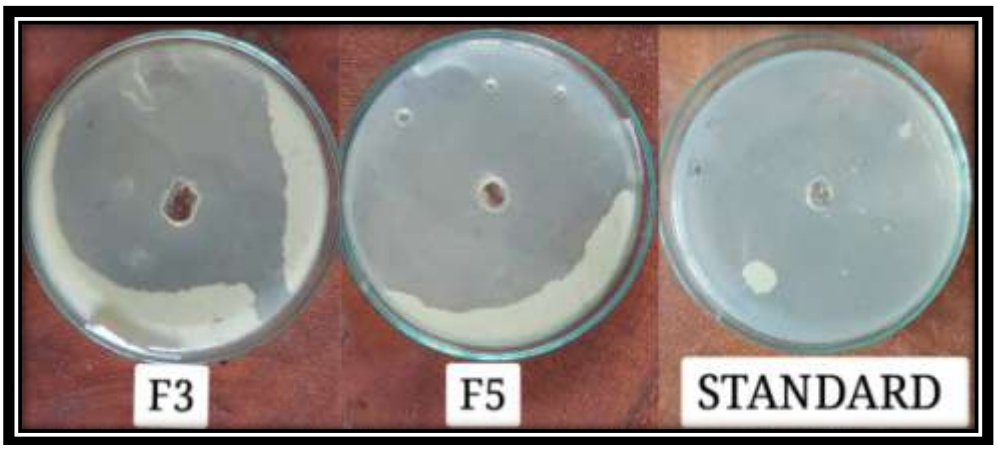

Figure 7: ZOI of formulation F3, F5 and standard (drug) against Candida albican

IV. SUMMARY & CONCLUSION

An attempt was made to formulate and evaluate Eberconazole hydrogel.The gels were formulated using various polymers. Formulation F5containing carbopol934, sodium CMC, propylene glycol exhibited higher drug release of 96.52% in5hrs and exhibited higher ZOI of 30mm against Candida albicans. Henceit may be concluded that eberconazole hydrogel formulation could be a promising topical alternative for the treatment of skin fungal infections.

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