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Formulation And Evaluation Of Antifungal Ketoconazole Emulgel: Controlled Drug Delivery System.

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ABSTRACT: The idea of this research is to develop a Ketoconazole emulgel that will allow the drug to penetrate deeper into the skin than currently available preparations. Ketoconazole is an antifungal medicine made up of imidazole that is used to treat a variety of fungal infections. Tinea, cutaneous candidiasis, pityriasis versicolor, dandruff, and seborrheic dermatitis are all fungal skin infections. When taken by mouth, this medication has a low absorption rate. To counter this, topical drug delivery is favored, as it prevents the drug's first-pass metabolism. The gelling ingredient carbopol 934 is used in the formulation of ketoconazole emulgel. In addition, for oil phase preparation light liquid paraffin as oil, span 20 as emulsifier is used and for aqueous phase propylene glycol as co-surfactant, tween 20 as emulsifier, methyl paraben & propyl paraben as preservative is used. The pH of emulgel was adjusted to 6- 6.5 using tri ethanolamine (TEA).Ketoconazole acts by inhibiting the fungus from producing ergosterol, the fungal equivalent of cholesterol, which increases membrane fluidity and inhibits fungus growth. The prepared emulgel were evaluated for their physical appearance, pH determination, viscosity, spreadability, in-vitro drug release and drug content. Physical characteristics of all the prepared emulgels were acceptable. When compared to all other formulations, the formulation batch F9 shows better drug release.

KEYWORDS: Emulgel, Topical formulation, ketoconazole, controlled drug delivery system.

I. INTRODUCTION:

"Topical drug delivery is described as the administration of a formulation to a specific area of the body, such as the ocular, rectal, nasal, vaginal, or skin, in order to increase bioavailability and reduce side effects".[1] Topical drug delivery refers to the localized treatment of dermatological conditions where the medication is not intended for systemic distribution; examples include the topical treatment of dermatological conditions such as eczema or psoriasis. Corticosteroids, antifungals, antivirals, antibiotics, antiseptics, local anesthetics, and antineoplastics are examples of medications given topically.

The purpose for preparation of topical preparations may be used for

i) Surface effects: remove dirt and germs, enhancement of appearance, prevent moisture loss, sunscreen, reduce infection.

ii) Stratum cornea effects: protective from sunscreens that penetrate this layer and moisturizing, catalytic a sloughing of the skin, useful in the treatment of psoriasis.

iii) Viable epidermal and dermal effects: various types of drugs may penetrate to these layers (anti-inflammatory, anesthetic, antipruritic, antihistamine).

iv) Systemic effects: some drugs such as scopolamine, nitroglycerin, clonidine, and estradiol has formulated in such a manner to gain systemic effects.

v) Appendage effects: various class of drugs are intended to exert their action in these portions of the skin (depilatory, exfoliate, antimicrobial, and antiperspirant)

PHYSIOLOGICAL FACTORS

1. Skin thickness: Varies from epidermis to subcutaneous layer. Epidermis has high thickness about 100–150 μm. Skin on the sole and palm has a high rate of diffusion.

2. Lipid content: It is an effective water barrier; percutaneous penetration increases when lipid weight in stratum corneum is low.

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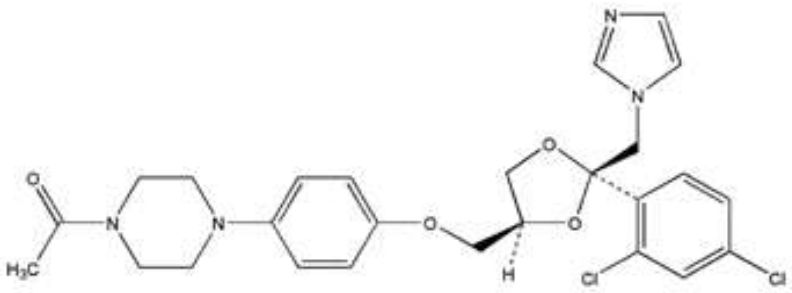
3. The density of hair follicles: Hair follicle infundibulum has a large storage capacity about 10 times more than the stratum corneum.
4. Skin pH: Sweat and fatty acid secreted from sebum influence the pH of the skin surface.
5. Blood flow.
6. Hydration of skin: Can enhance permeation of drug.
7. Inflammation of skin: That disrupts the continuity of stratum corneum increases permeability.
8. Skin temperature: Increase in temperature gives rise to increase in the rate of skin permeation

PHYSICOCHEMICAL FACTORS

1. Partition coefficient: More the value of log p more easily will be the percutaneous absorption of the drug.
2. The molecular weight (<400 Dalton).
3. The degree of ionization (only unionized drugs gets absorbed well).
4. Effect of vehicles:

Hydroalcoholic gel provides the most efficient absorption through the skin
"Ketoconazole {1-[4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan4-yl] methoxide] phenyl] piperazin-1-yl] Ethen one} is an antiandrogen and antifungal medication used to treat a number of fungal infections".[2]Applied to the skin it is used for fungal skin infections such as tinea, cutaneouscandidiasis, pityriasis versicolor, dandruff,and seborrheic dermatitis. When administered by oral route this drugs shows, poor absorption. To overcome this, topical drug delivery is preferred by which, the first pass metabolism of drug is by-passed. There by delivering the drug at predetermine rate and improve patients' compliance. Taken by mouth it is a less preferred option and only recommended for severe infections when other agents cannot be used. Common side effects when applied to the skin include redness. Common side effects when taken by mouth include nausea, headache, and liver problems.



ketoconazole

"Several antifungal medicines are available as topical formulations in the market (e.g., creams, ointments, and powders for the purpose of local dermatological therapy). Ketoconazole, which has antifungal and antibacterial effects, is one of these antifungal agents. It is used to treat dermatophytes and other skin infections that are mild and uncomplicated." [3]

Emulsion is a controlled release technique in which medication particles trapped in the internal phase travel through the external phase to the skin and are absorbed slowly. Internal phases operate as a drug reservoir, slowly releasing the medication through the external phase to the skin.

Gels are a newer type of dosage form that is created by trapping considerable amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles that can be natural or synthetic. Its bio adhesive property extends the time that medication is in contact with the skin. Emulgel acts as a dual control release mechanism since it has the properties of both an emulsion and a gel. Despite their advantages, gels have a significant limitation in the delivery of hydrophobic medicines. To get over this restriction, emulgel has been produced.

"Emulgel has been employed to overcome the issue of stability in cosmetics and pharmaceutical preparations. Emulgel has a

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number of beneficial features in dermatology, such as being thixotropic, greaseless, easily spreadable, efficiently removable, emollient, non-staining, water-disposable, longer time span of usability, bio-friendly, uncomplicated, and gratifying appearance".[4]Emulgel are better choice for the BCS class II drug that has poor solubility and high permeability. Several factors such as gelling agent, oil, emulsifiers influence the stability and efficacy of emulgel.Emulgel having many advantages like Incorporation of hydrophobic drugs, better loading capacity, Production feasibility and low preparation cost, better stability, Controlled release etc

RATIONALE

"Many typically used topical treatments including ointment, cream, and lotion have a number of drawbacks. When applied, they are extremely sticky, causing the patient discomfort. They also have a lower spreading coefficient and must be applied by rubbing. Furthermore, they have an issue with stability. The usage of translucent gels in cosmetics and medicinal preparations has increased as a result of all of these factors within the major group of semisolid preparations." [5]

II. MATERIALS AND METHODS

MATERIALS:

Ketoconazole IP was received as a gift sample from Aarti Drugs Limited, Mumbai (India). Carbopol 934, light liquid paraffin, propylene glycol, span 20, tween 20, methyl paraben, propyl paraben, methanol and triethanolamine were obtained from Research-lab fine chem industries, Mumbai. All the solvents were of analytical grade.

METHODS:

The incorporation process is used to make emulgel

STEP 1:preparation of gel using gelling agent

The gel in the formulations was made by dispersing a carbapol 934 (gelling agent) in purified water q.s with constant stirring at a moderate speed using mechanical stirrer, then the pH was adjusted to 6- 6.5 using tri ethanolamine (TEA).

STEP 2: preparation of emulsion

1. **Oil phase preparation:** oil phase of emulsion is prepared by dispersing the span 20 in light liquid paraffin.
2. **Aqueous phase preparation:** Aqueous phase of emulsion is prepared by dispersing tween 20 into purified water. Ketoconazole is dissolved in methanol in separate beaker. Simultaneously, in another beaker methyl paraben and propyl paraben are added in propylene glycol. Add these two solutions in aqueous phase by continuous stirring.
3. **Mixing of phases:** Both the oily and aqueous phases were separately heated at 70°C-80°C, then the oily phase was added to the aqueous phase with continuous stirring until it was cooled to room temperature. The emulsion was obtained, which is stored in well closed air tight container.

STEP 3:Incorporation of emulsion into gel base

The prepared emulsion is incorporated into gel base (1:1) in a dropwise manner with continuous stirring.

PREFORMULATION STUDY OF KETOCONAZOLE

1. **Organoleptic properties-**"The pure ketoconazole sample was studied for their organoleptic properties like color, odor, taste and crystallinity and pH". [6]
2. **Determination of Melting Point-** Melting point of ketoconazole sample was determined by using melting point apparatus. "Ketoconazole was filled in one end open capillary tube. The capillary was placed in melting point apparatus and gradually temperature rises when drug was melted the melting point of ketoconazole powder was recorded".[6]
3. **Determination of λmax By UV spectrophotometer-** Standard stock solution was prepared by dissolving 10 mg of ketoconazole in 40ml of methanol in a 100 ml volumetric flask. The solution was sonicated for 15 minutes to get a clear solution. Volume was mark up with methanol to get the final concentration of stock solution 100 µg/ml. From this 1ml of the solution was pipetted out and transferred into a 10ml volumetric flask and diluted up to the mark with methanol to form 10µg/ml that was scanned in the range of 200-400nm using UV-visible Spectrophotometer (Jasco, Japan model V-630).
4. **Preparation of the Calibration Curve:** From stock solution 1, 2, 3, 4, and 5 ml solution was transferred into a series of calibrated 10 ml

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volumetric flasks and the final volume was made up using methanol. Observed absorption maxima, λmax 204nm was used for further analysis of absorption for concentration ranging from 10 to 50µg/ml. The linear plot was constructed and correlation coefficient value was determined.

5. **Solubility Analysis-** The solubility of ketoconazole was determined by simply dissolving it in various solvents such as Dichloromethane, chloroform, ethanol, methanol, ether, distilled water. In this each solvent was taken into a separate test tube and excess amount of ketoconazole was added to each solvent and stirred manually.

6. **FTIR spectroscopy-** FTIR analysis for ketoconazole was done by FTIR spectrometerShimadzu (Model: FTIR-8400S). Each sample was mixed with potassium bromide in 1:100 and compressed to observed at the range from 4000 to 400cm-1

OPTIMIZATION OF EMULGEL: Nine Ketoconazole emulgel formulations (Table 3) were prepared according to a 3^2 factorial design employing the qualitative factors and levels show in table 1 and table 2.

Table 1: Factor and Level for the 3^2 Factorial Design

Independent Variables	Levels		
	Low (-)	Medium (0)	High (+)
X1=Gelling agent	0.5	0.75	1
X2=Liquid paraffin	2.5	3	3.5

Table 2: formulations of Ketoconazole Emulgel Formulation

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9
X1	-	-	-	0	0	0	+	+	+
X2	-	0	+	-	0	+	-	0	+

Table 3: Composition of different formulation batches (%w/w).

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ketoconazole	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Carbapol 934	0.5	0.5	0.5	0.75	0.75	0.75	1	1	1
Light liquid paraffin	2.5	3	3.5	2.5	3	3.5	2.5	3	3.5
Tween 20	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Span 20	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Propylene glycol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Methanol	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Methyl paraben	0.01	0.01	0,01	0.01	0.01	0.01	0.01	0.01	0.01
Propyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Purified water (q.s)	50	50	50	50	50	50	50	50	50

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Fig. 1. Preparation of Emulgel

EVALUATION OF EMULGEL KETOCONAZOLE

1. **Physical appearance**: The prepared Emulgel is checked visually for their color, homogeneity, consistency and phase separation. The color of formulation was checked against white and black background. The consistency of emulgel was checked by applying on skin.

2. **pH Evaluation:** pH evaluation is the important criteria especially for the topical formulation. The pH of emulgel should be between 5.8 – 6 to mimic the skin condition. If the pH of the prepared emulgel is acidic or basic, it may cause irritation to the patient. pH of the prepared emulgel was measured using digital pH meter by dipping the glass electrode into an emulgel. The measurement of pH of each formulation was done in triplicate and average values were calculated.

3. **Viscosity:** "Brookfield Viscometer was used to determine viscosity of prepared Emulgel formulation. For the determination of viscosity, prepared Emulgel formulation was added to the beaker and settled it for 30 minutes at 25-30 °C. Adjust the spindal in that way that spindal does not touch the bottom of the jar and rotate at a moderate speed 100 RPM for 10 minutes. The viscosity reading was noted". [7]

4. **Spreadability:** Spreadability is determined by apparatus which is suitably modified in the laboratory and used for the study. Spreadability was measured by two glass slides and a wooden block, which was provided by a pulley at one end on the basis of Slip and Drag characteristics of gels. A ground glass slide was fixed on this block. "A 1 gm of gel of different formulations were placed on the ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide. Excess of the gel was scrapped off from the edges. The top plate was subjected to pull of 50gms. If time taken for the separation of two slides is less then better the spreadability".[8] Spreadability is calculated by using the following formula:

$S = M \times L/T$

Where, S is the spreadability,

M is the weight in the pan (weight tied to the upper slide),

L = is the length moved by the glass slide

T = time taken to separate the slide completely from each

5. **Drug Content Determination:** Emulgel is mixed in a suitable solvent. Filter it to obtain clear solution. Determine its absorbance using UV spectrophotometer. From the standard equation by putting the absorbance value concentration and drug content can be obtained. Drug content was calculated using the slope and the intercept obtained by linear regression analysis of standard calibration curve.

Drug Content = (Concentration × Dilution Factor × Volume taken) × Conversion Factor.

6. **In-vitro drug diffusion study:**Release of ketoconazole from emulgel formulation was measured through dialysis membrane by using Franz diffusion cell. Dialysis membrane was

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soaked in diffusion media for overnight and then placed on support screen of diffusion cell assembly. Phosphate buffer at pH 5.5 was used as the receptor medium and 1g of gel was placed on the donor side. At predetermined time interval, 2ml of sample was withdrawn from the receptor compartment and replaced with same volume of phosphate buffer at pH 5.5. The aliquots were analyzed by UV spectrophotometer at 226nm.

7. **Stability study:**"Emulgel was packed in aluminium collapsible tubes (5gm) and subjected to stability study at 5°C, 25°C/60% RH, 30°C/65%RH for 1 month. Samples are withdrawn at each 10days as per ICH guidelines and analyzed for their physical appearance, pH, drug content, drug release profile etc.".[9]

III. RESULTS AND DISCUSSIONS:

Preformulation Studies of Drug:

Organoleptic properties-

1. **Organoleptic properties:**The drug was studied for their organoleptic properties like color, odor, taste, crystallinity and pH observation was recorded in table 4.

Table 4: Organoleptic properties of ketoconazole.

Parameters	Result
Colour	White
Odour	Odourless
Appearance	Crystalline powder

2. **Melting point-** Melting point of drug was determined by capillary method was found to be 148.6℃(Table 5). The observed value was found to be in between the range of reported value i.e., 148 ℃ to 152℃. The observed melting point confirmed the drug as ketoconazole.

Table 5: Melting point of ketoconazole.

Drug	Observed	Reference
ketoconazole	149±2	148.0 ℃ to 152.0 ℃
Ketoconazole	148±2	-
ketoconazole	149±2	-

3. **Determination of λmax by UV-** Identification of drug was also carried out using UV Visible Spectrophotometer. Methanol was used as the medium and observed absorption maxima were compared with the reported value. The wavelength of maximum absorbance acts as a characteristic value for a compound. Observed value for the obtained sample of pure ketoconazole was 204nm found to be identical to the reported value that confirmed the obtained sample as ketoconazole.

Media	λ max Observed
Methanol	204 nm

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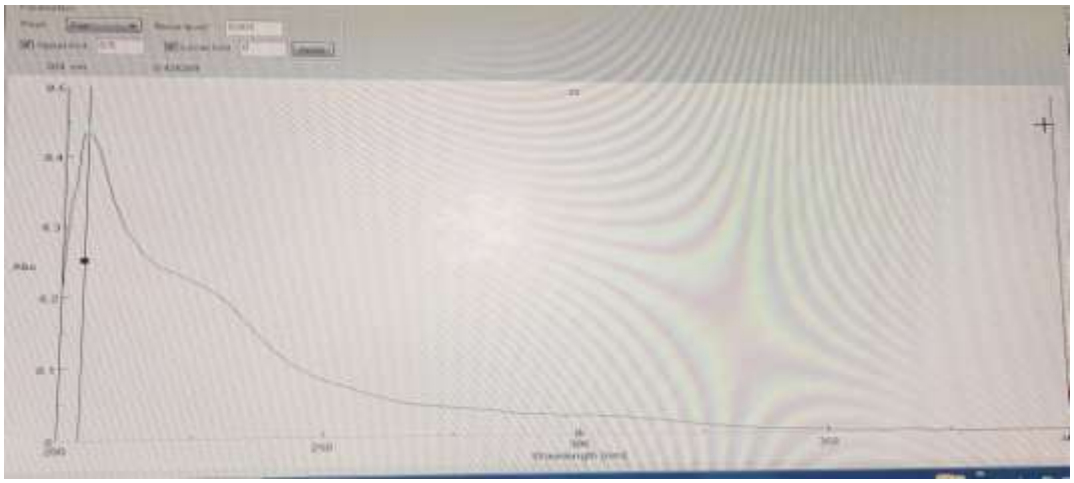

Fig. 2: λmax of ketoconazole is 204nm.

4. Calibration curve of ketoconazole:

The wavelength of maximum absorbance, λ max for ketoconazole in methanol was determined with the help of UVVisible Spectrophotometer.Prepared solution of concentration 40µg/ml was scanned in the range of 200-400nm. The λmax observed was 204nm. Observed absorption maxima, λmax 204nm was used for further analysis of absorption for concentration ranging from 10to 50µg/ml. The linear plot was obtained and concentration range 10to 50µg/ml and correlation coefficient (r^2) value were found to be 0.9956. The results were plotted as in Fig 3

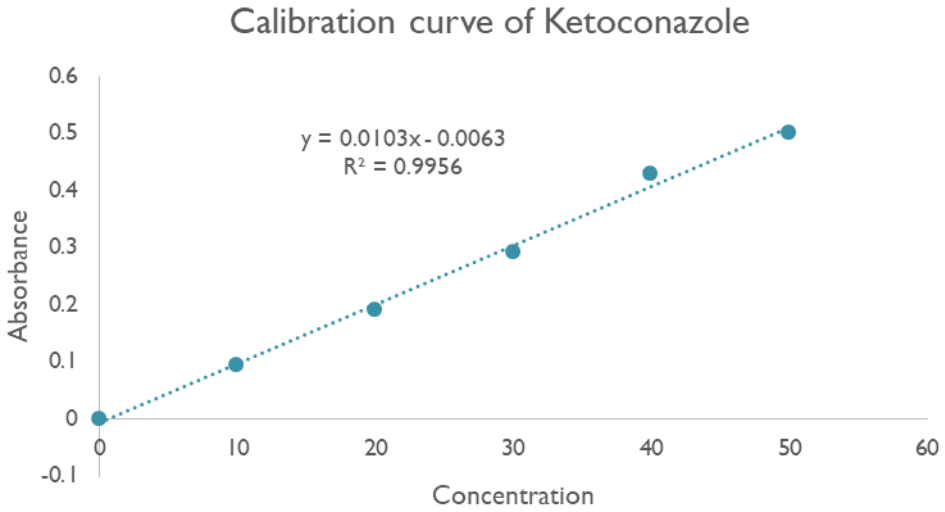

Fig 3: Calibration curve of ketoconazole.

Table 6: Absorbance data of ketoconazole for preparation of calibration curve at 204 nm.

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.095
3	20	0.192

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4	30	0.293
5	40	0.430
6	50	0.502

5. Solubility Analysis- The solubility of ketoconazole in various medium was studied and the results of study were shown in table 7

Table 7: Solubility Determination in Solvents

Solvents	Solubility
Distilled Water	Practically insoluble
Dichloromethane	Freely soluble
Chloroform	Soluble
Methanol	Soluble
Ethanol	Sparingly soluble
Ether	Practically insoluble

6. FTIR- FTIR Spectrum of ketoconazole was obtained by scanning the drug in the range of 4000 to 400cm [10]. Observed FTIR spectra and standard value were as mentioned in table 8. The observed value was within the range or very close to the characteristic peaks of standard value confirming drug as ketoconazole.

Table 8: IR ranges(functional groups) of ketoconazole.

Sr. No.	Functional Group	Observed Ranges (cm^{-1})	Standard Ranges (cm^{-1})
1	C=O	1643.41cm^{-1}	1680-1630cm^{-1}
2	C-N	1033.88cm^{-1}	1230-1020cm^{-1}
3	C=C(Aromatic)	1512.24cm^{-1}	1600cm^{-1} and 1475cm^{-1}
4	C-Cl (Stretch)	817.85cm^{-1}	850-550cm^{-1}

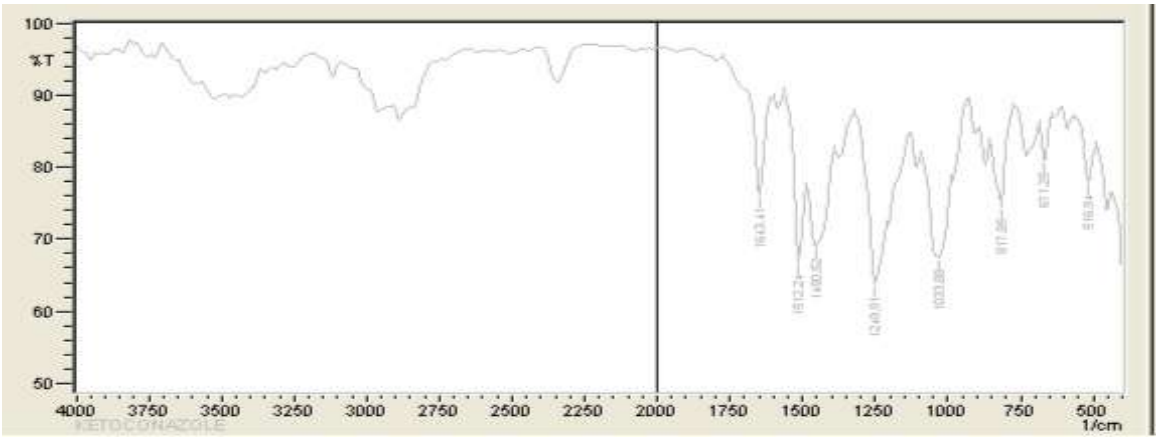

Fig 4: FTIR spectra of ketoconazole.

7. Drug excipients compatibility study: An FTIR spectrum of formulation shows significant peaks of ketoconazole indicating no interaction between ketoconazole and carbapol 934

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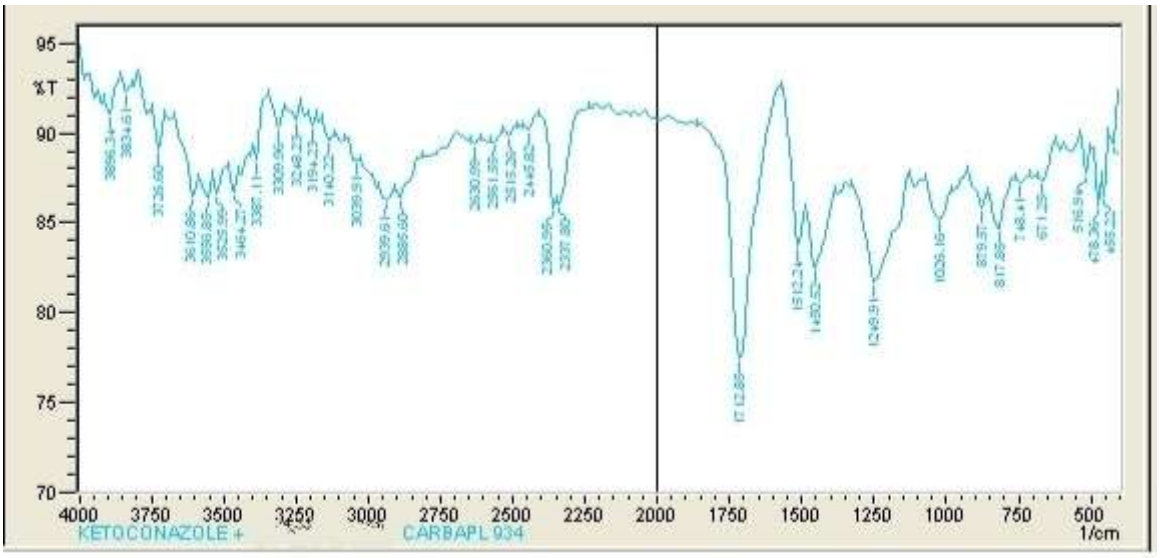

Fig 5: FTIR spectra of ketoconazole + carbapol 934**.**

Table 9: IR ranges (functional groups) of ketoconazole.

Sr. No.	Functional Groups	Observed Ranges (cm^{-1})	Standard Ranges (cm^{-1})
1	C=O	1712.85cm^{-1}	1680-1630cm^{-1}
2	C-N	1026.16cm^{-1}	1230-1020cm^{-1}
3	C=C(Aromatic)	1512.24cm^{-1}	1600cm^{-1} and 1475cm^{-1}
4	C-Cl (Stretch)	817.85cm^{-1}	850-550cm^{-1}

EVALUATION OF EMULGEL:

1. Physical appearance- Emulgel formulations were viscous creamy preparations with a smooth homogeneous texture and glossy appearance. The color of formulation was checked against white and black background. The consistency of emulgel was checked by applying on skin. Results have been discussed in Table 9.

Table 10: Physical parameter of formulation batches

Batch code	Color	Phase separation	Homogeneity	Consistency
F1	Light orange	No	Homogenous	Excellent
F2	Light orange	No	Homogenous	Excellent
F3	Light orange	No	Homogenous	Excellent
F4	Light orange	No	Homogenous	Excellent
F5	Light orange	No	Homogenous	Excellent
F6	Light orange	No	Homogenous	Excellent
F7	Light orange	No	Homogenous	Excellent
F8	Light orange	No	Homogenous	Excellent
F9	Light orange	No	Homogenous	Excellent

2. pH determination- pH of prepared emulgel was measured by using pH meter. The pH of the all emulgel formulations was in the range of 5.7-6.3 which considered acceptable to avoid the risk of skin irritation upon application to skin.

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Table 11: pH of formulations F1-F9

Sr. No.	Formulation code	*pH value (±S.D.)
1	F1	6.2±0.10
2	F2	5.9±0.15
3	F3	6.3±0.35
4	F4	5.7±0.32
5	F5	6.3±0.26
6	F6	6.1±0.20
7	F7	5.8±0.26
8	F8	6.0±0.15
9	F9	6.3±0.30

*Data are represented as mean±standard deviation (SD), n=3

3. Rheological study-The measurement of viscosity of the prepared emulgel was done with Brookfield viscometer (Brookfield DV-E viscometer). Viscosity was found to 2346 cps. Viscosity was increased with increase in gelling agent concentration.

Table 12: Viscosity of formulationsF1-F9

Formulation code	*Viscosity (cps) (±S.D.)
F1	2161±9.01
F2	2168±4.58
F3	2190±6.50
F4	2272±7.54
F5	2287±7.93
F6	2295±5.29
F7	2325±5.03
F8	2341±6.50
F9	2345±2.08

*Data are represented as mean ± standard deviation (SD), n=3

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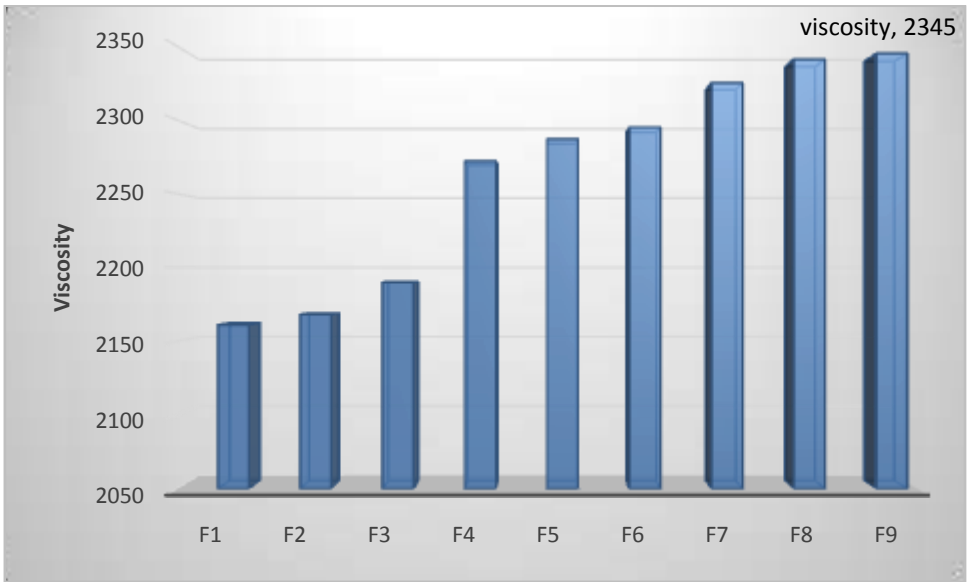

Fig.6: Viscosity of ketoconazole emulgel

It is clearly seen from the bar graph that as the concentration of Carbopol 934 increases the viscosity of the prepared emulgel get increases which is clear evidence from batch F1 and F9.

4. **Spredability-**A ground glass slide, measuring 20 cm in length, was fixed on the table. An excess of emulgel (about 1 g) was placed on this ground slide. A 500-gm weight was placed on the top of the two slides for 5 minutes, to expel air and to provide a uniform film of the emulgel between the slides. The top plate was then subjected to a pull with 50 g of weight tied on the upper slide, at a distance of 7 cm. Lesser the time taken by the slides to move the specified distance of 7 cm, the better the spreadability of the emulgel.

Table 13: Spreadability of formulations F1-F9

Sr.No.	formulations	Time(sec)	Length(cm)	Weight (gm)	Spredability S=M.L/T
1	F1	25	7	50	14
2	F2	23	7	50	15.21
3	F3	26	7	50	13.46
4	F4	21	7	50	16.66
5	F5	24	7	50	14.58
6	F6	23	7	50	15.21
7	F7	21	7	50	16.66
8	F8	22	7	50	15.90
9	F9	20	7	50	17.50

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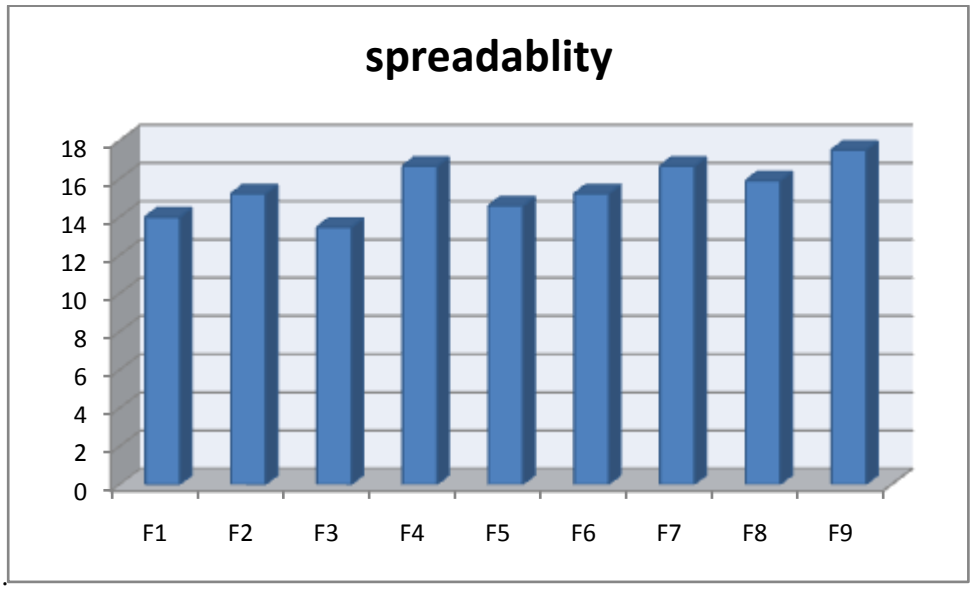

Fig 7: Spredability of ketoconazole emulgel.

5. Drug Content Determination- The drug content of different emulgel formulations was estimated by using UV spectrophotometer at 200-400 nm range.

Table 14: Drug content of Ketoconazole emulgel formulation.

Formulations	%Drug content
F1	37.37
F2	39.07
F3	47.33
F4	50
F5	54.61
F6	64.56
F7	71.35
F8	86.4
F9	88.59

6. In-vitro drug diffusion study: At predetermined time interval, 2ml of sample was withdrawn from the receptor compartment and replaced with same volume of phosphate buffer at pH 5.5. The aliquots were analyzed by UV spectrophotometer at 226nm.At the end of 4 hours the total amount of drug release from the F9 batch was found to 96.2which is the better %drug release as compare to other emulgel formulation.

Table 15: % Drug release of Batch F9

Time(hrs.)	%Drug release
0	0
0.5	12.16
1	29.32
2	49.14
3	72.93

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4	96.2

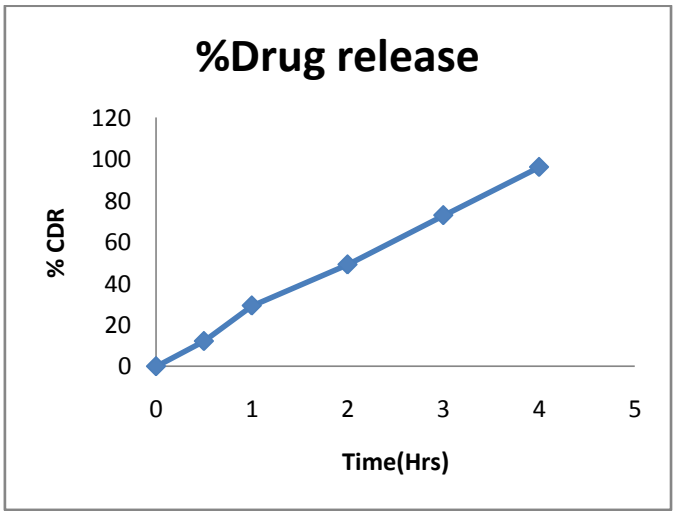

Fig 8: In-vitro drug diffusion study of emulgel (Batch F9)

IV. CONCLUSION:

Topical drug delivery will be extensively applied in the coming years to improve patient compliance. Emulgel has gained popularity due to its capacity to improve spreadability, adhesion, viscosity, and extrusion. Furthermore, they will be used to load hydrophobic medicines into water soluble gel bases for long-term stability.In a similar study, a ketoconazole topical emulgel was developed and subjected to physiochemical tests, including appearance, rheological investigations, spreadability, pH, Drug content and in vitro drug release. To investigate the rate and duration of drug release from emulgel, in vitro drug release and drug content of the test formulation was done. In vitro testing reveals a maximum release of 96.4 percent in 4 hours andthe drug content was found to be 88.59 in ideal (F9) formulations. Ketoconazole-containing emulgels had substantial antifungal efficacy. As a conclusion, an emulgel containing ketoconazole can be administered as a topical antifungal medication.

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