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Research Article

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Development of Novel Ketoconazole Emulgel Formulations for Enhancing Penetration

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ABSTRACT

Aim: This study aimed to develop and evaluate a novel emulgel formulation of ketoconazole to overcome its poor solubility and limited skin permeability, thereby enhancing its topical delivery and antifungal efficacy. Methodology: Ketoconazole was incorporated into an oil-in-water emulsion, which was then combined with a suitable gelling agent to form the emulgel. Various oils, emulsifiers, and gelling agents were optimized to achieve better drug release and skin permeation. The formulations were evaluated for physical appearance, pH, spreadability, viscosity, and drug content uniformity. In vitro skin permeation studies were conducted using excised rat skin to compare the permeation profile of the emulgel with a conventional ketoconazole cream. Ex vivo antifungal efficacy was assessed against Candida albicans to determine the therapeutic potential of the emulgel.

Results: The optimized ketoconazole emulgel exhibited ideal physicochemical properties, including an appropriate pH, superior spreadability, and viscosity suitable for topical application. In vitro permeation studies revealed a 3-fold increase in skin penetration compared to the conventional cream. Ex vivo antifungal studies demonstrated enhanced antifungal activity, with the emulgel showing significantly higher efficacy against Candida albicans than the conventional cream.

Conclusion: The development of a ketoconazole emulgel offers a promising strategy for improved topical delivery and antifungal efficacy. By enhancing skin penetration and providing sustained drug release, this emulgel system addresses the limitations of traditional formulations. Further clinical studies are recommended to explore its potential for treating superficial fungal infections.

Keywords: Ketoconazole, Emulgel, Skin Penetration, Antifungal Efficacy, Topical Drug Delivery, *Candida albicans*

INTRODUCTION

The pharmaceutical product containing an active molecule is applied to the diseased surface of the skin to treat local cutaneous disorders or the cutaneous manifestations of general diseases. Its goal is to confine the pharmacological or therapeutic effects of the drug to the skin's surface or within the skin, a method known as the topical drug delivery system. Topical formulations are designed to provide localized effects by being applied to the mucosal surface or penetrating the underlying layers of skin or mucous membranes for systemic effects.[1,2]

Gels are transparent or translucent semisolid formulations containing a high ratio of solvent to gelling agent. A gel is defined as a semi-rigid system in which the movement of the dispersing medium is restricted by a three-dimensional network of solvated macromolecules. The USP describes gels as semisolid systems comprising dispersions made up of either small inorganic particles or large organic molecules interpenetrated by a liquid. Gels exhibit viscoelastic properties, thinning under pressure for easy application and adhering to the skin due to their solid-like matrix when the application is completed. Most topical gels are prepared using organic polymers, such as carbomers, which provide an aesthetically pleasing, clear appearance and can be easily washed off the skin.[3]

The choice of base in a topical dermatological product significantly affects its effectiveness. Bases with high oleaginous content offer an emollient effect to dry, irritated skin. An emulgel is a formulation where an emulsion containing oil and an aqueous phase is entrapped in a gel base. The emulgel preparation begins with the formation of a primary emulsion, which is subsequently incorporated into a gel phase. Emulgel formulations consist of aqueous phases, oils, gelling agents, penetration enhancers, and emulsifiers.[4] Emulgels serve as vehicles for delivering hydrophobic

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drugs more efficiently through the skin, overcoming the limitations of conventional topical formulations, such as greasiness and low spreading coefficients. Conventional formulations often require rubbing for application, which may be unpleasant. The gel formulation, being a highly wet and rigid structure immobilized by surface tension, addresses these shortcomings.[5]

Fungal infections, or mycoses, are diseases caused by fungi, such as yeasts or molds, and commonly affect the skin or nails. However, they can also infect the mouth, throat, lungs, urinary tract, and other body parts. Fungi are organisms classified separately from plants or animals, capable of spreading through spore release. While most fungi naturally exist in the body (e.g., on the skin, in the mouth, or the gastrointestinal tract), certain conditions can lead to their overgrowth. Fungal infections can appear red, swollen, or bumpy on the skin, while infections in nails may cause discoloration, thickening, or cracking. Superficial or mucocutaneous infections affect the skin, nails, or mucous membranes, while subcutaneous infections penetrate beneath the skin. Deep fungal infections, which affect organs like the lungs or brain, often occur in individuals with weakened immune systems.[6]

MATERIALS AND METHODS

Preformulation study of ketoconazole

Organoleptic properties

The pure ketoconazole sample was studied for their organoleptic properties like color, odor, taste and crystallinity and pH.[7]

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. [8]

Determination of λmax By UV spectrophotometer

Standard stock solution was prepared by dissolving 10 mg of ketoconazole in 40 ml 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 1 ml of the solution was pipetted out and transferred into a 10 ml volumetric flask and diluted up to the mark with methanol to form 10µg/ml that was scanned in the range of 200-400 nm using UV-visible Spectrophotometer (Model: Jasco, Japan model V- 630).[9]

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 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 50 µg/ml. The linear plot was constructed and correlation coefficient value was determined.[10]

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.[11]

FTIR spectroscopy

FTIR analysis for ketoconazole was done by FTIR spectrometer (Model: Shimadzu FTIR-8400S). Each sample was mixed with potassium bromide in 1:100 and compressed to observed at the range from 4000 to 400cm^{-1}.[12]

Optimization of Emulgel

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**.[13]

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

Independent variables	Levels		
	Low(-)	Medium(+)	High(+)
X1 = Gelling Agent	0.5	0.75	1
X2 = Gelling Agent	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	+	+	+
X@	_	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
Purified water (q.s)	50	50	50	50	50	50	50	50	50

Figure 1. Preparation of Emulgel.

Evaluation of Emulgel

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.[14]

pH Evaluation

Evaluating pH is a critical parameter, particularly for topical formulations. The pH of an emulgel should ideally range between 5.8 and 6 to align with the skin's natural pH and prevent irritation. If the pH deviates significantly toward acidic or basic levels, it may lead to discomfort or irritation for the user. The pH of the prepared emulgel was assessed using a digital pH meter by immersing the glass electrode directly into the formulation. Each formulation's pH was measured three times, and the average value was calculated to ensure accuracy.[15]

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.[16]

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 was 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 50 g.[17] If time taken for the separation of two slides is less then better the spreadability". Spreadability is calculated by using the following formula:

$S = M \frac{L}{T}$ 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

Drug Content Determination

1 g of gel was placed on the donor side. At predetermined time interval, 2 ml 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 226 nm. The emulgel is dissolved in an appropriate solvent and filtered to achieve a clear solution. The absorbance of the resulting solution is measured using a UV spectrophotometer. By substituting the absorbance value into the standard calibration equation, the concentration and drug content of the emulgel can be determined. Drug content was calculated using the slope and the intercept obtained by linear regression analysis of standard calibration curve.[18]

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

In-vitro drug diffusion study

Release of ketoconazole from emulgel formulation was measured through dialysis membrane by using Franz

diffusion cell. Dialysis membrane was 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 Emulgel was packed in aluminum collapsible tubes (5 g) and subjected to stability study at 5°C, 25°C/60% RH, and 30°C/65% RH for 1 month. Samples are withdrawn at each 10 days as per ICH guidelines and analyzed for their physical appearance, pH, drug content, drug release profile etc.[19]

RESULT & DISCUSSION

Preformulation Studies of Drug: Organoleptic properties-

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

Melting point

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

Table 5: Melting point of Ketoconazole.

Drug	Observed	Reference
Ketoconazole	149±2	
Ketoconazole	148±2	148.0 to 152.0 C
Ketoconazole	149±2	

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 204 nm found to be identical to the reported value that confirmed the obtained sample as Ketoconazole.

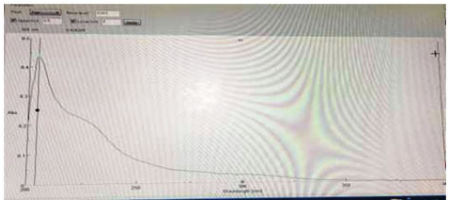

Figure 2: λmax of ketoconazole is 204 nm.

Calibration curve of Ketoconazole

The wavelength of maximum absorbance, λmax for ketoconazole in methanol was determined with the help of UV Visible Spectrophotometer. The λmax observed was 204 nm. Observed absorption maxima, λmax 204 nm was used for further analysis of absorption for concentration ranging from 10 µg/ml to 50 µg/ml. The linear plot was obtained and concentration range 10 µg/ml to 50 µg/ml and correlation coefficient (r^2) value were found to be 0.9956 (**Figure 3**).

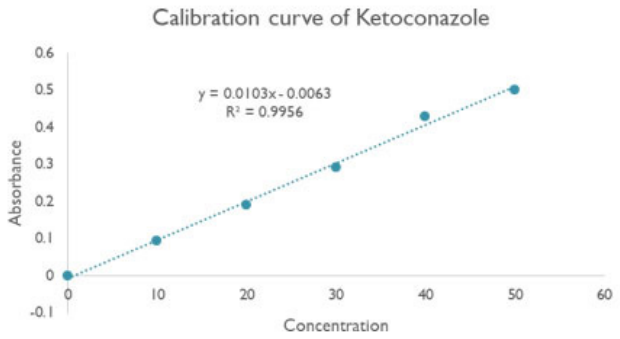

Figure 3: Calibration curve of Ketoconazole.

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

S. No. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.095
3	20	0.192
4	30	0.293
5	40	0.430
6	50	0.502

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

FTIR

FTIR Spectrum of ketoconazole was obtained by scanning the drug in the range of 4000 to 400 cm^{-1}. 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: FTIR ranges (functional groups) of Ketoconazole.

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

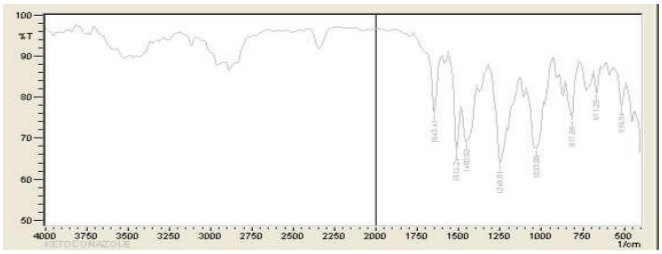

Figure 4: FTIR spectra of Ketoconazole.

Drug excipients compatibility study

An FTIR spectrum of formulation shows significant peaks of ketoconazole indicating no interaction between ketoconazole and carbapol 934.

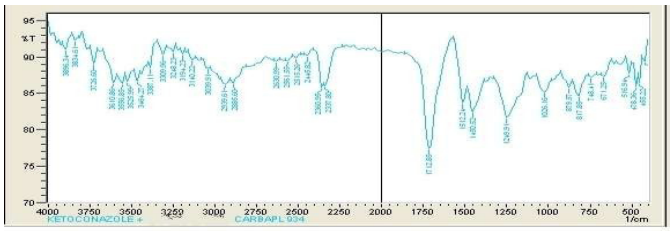

Figure 5: FTIR spectra of ketoconazole + Carbapol 934.

Table 9: FTIR 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

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. The 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

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.

Table 11: pH of formulations F1-F9.

S. 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

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 formulations (F1-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

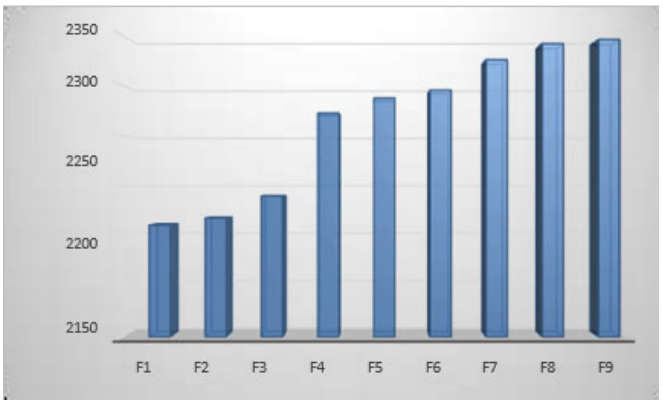

Figure 6: Viscosity of ketoconazole emulgel.

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.

Spreadability

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 g 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.

S. No.	Formulations	Time(sec)	Length(cm)	Weight (gm)	Spredability
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

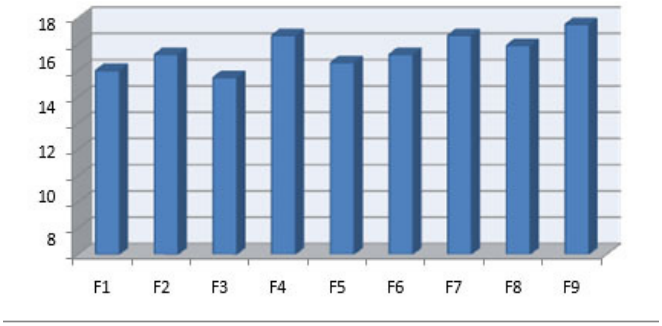

Figure 7: Spredability of ketoconazole emulgel.

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

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 226 nm. At the end of 4 hours the total amount of drug release from the F9 batch was found to 96.2 which 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
4	96.2

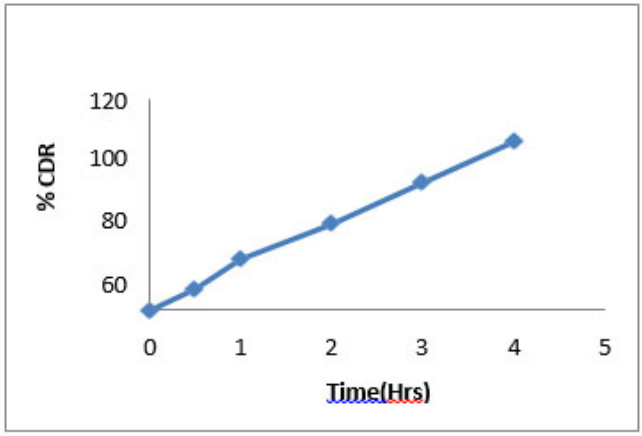

Figure 8: *In-vitro* drug diffusion study of emulgel (Batch F9).

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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CONFLICT OF INTEREST

No Conflict of interest declared.

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AUTHORS' CONTRIBUTION

Bhaskar Kumar Gupta: Analysis, Plagiarism correction, Revision

Eisha Ganju: Concept, Checking, Editing, Grammar correction

Susheel Deshmukh: Literature Review, Formatting, Writing manuscript

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