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Research article

FORMULATION DEVELOPMENT AND CHARACTERIZATION OF KETOCONAZOLE ANTIFUNGAL CREAM

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Abstract

Objective: Aim of the present work was to develop and characterize an antifungal cream formulation for topical delivery of Ketoconazole in seborrheic dermatitis. Ketoconazole is a potent antifungal drug belongs to BCS-II showing high permeability and low solubility that can be delivered topically via skin if formulated in a cream formulation with improved physicochemical characteristics, drug release behaviour, and antifungal efficacy.

Methods: Preformulation studies including solubility, melting point, and drug–excipient compatibility studies were carried out to check suitability of ketoconazole for formulation development. Then six batches (K1–K6) were formulated using the emulsification method and optimized by characterization of their physicochemical characteristics i.e., pH, spreadability, extrudability, rheological profile, content uniformity, and physical appearance. The optimized formulation was further compared for invitro drug release profile with marketed cream formulation and evaluated for antifungal efficacy study and stability study for one month according to ICH.

Results and Discussion: The solubility studies revealed higher solubility of ketoconazole in organic solvents such as methanol and ethanol compared to aqueous media, while FT-IR analysis showing no significant interactions. All the formulations batches exhibited acceptable characteristics with skin-compatible pH and good homogeneity. Optimized batch K4 found to demonstrate with suitable viscosity, excellent spreadability and extrudability, and the highest drug content (93.50 ± 1.5%). The in-vitro drug release study indicated that optimized formulation (K4) showed 97.4% drug release within 5 hours, which was comparable to the marketed ketoconazole cream. Furthermore, antifungal efficacy testing against *Candida albicans* demonstrated a zone of inhibition of 12 ± 0.5 mm, slightly higher than the marketed formulation (11 ± 0.5 mm). Stability studies confirmed that the optimized formulation remained stable without significant changes in physicochemical parameters during storage.

Conclusion: The optimized ketoconazole cream formulation showed satisfactory physicochemical properties and *in vitro* drug release profile with promising antifungal activity and long-term storage stability making it suitable for effective topical anti-fungal preparations comparable with marketed conventional formulations.

Keywords: Ketoconazole, antifungal, topical formulation, cream, antifungal activity

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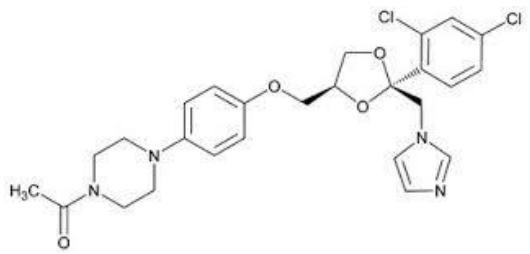
1. Introduction

Ketoconazole is a potent antifungal drug, categorized as class II under BCS system of classification exhibiting very low aqueous solubility and high permeability making the drug poorly bioavailable at the site of action. Ketoconazole cream is mainly designed for various fungal infection of skin and is widely used as topical antifungal treatment [1]. Chemical Structure of Ketoconazole; a 1,3-dioxolane substituted with a 2,4-dichlorophenyl group and an imidazol-1-ylmethyl group (Fig. 1). It also includes a phenylpiperazine moiety with an acetyl group. It is a broad-spectrum azole antifungal which is used in various skin infection such as ringworm, athlete's foot and seborrheic dermatitis, this condition occurs when fungi grow excessively on the surface of the skin, which leads to redness, itching and discomfort [2, 3]. Topical preparation for antifungal therapy not only helps in releasing the drug directly to the affected area and to stop fungal growth and promote healing [4].

Formulation of ketoconazole as a topical preparation provides several pharmaceutical advantages, including localized drug action which improves patient compliance and ease of application [5]. The use of excipients and the method of preparation, which ensures the uniform distribution of drug, optimal drug release and physical stability [6].

Therefore, understanding the formulation, principles and preparation process of ketoconazole cream is essential for producing a safe, stable and effective topical delivery system. This article presents the standardized method for the preparation of ketoconazole cream for topical antifungal delivery. [7].

Figure 1: Chemical Structure of Ketoconazole



2. Materials:

All the materials received in the lab were of analytical grade. Ketoconazole was gifted from xylopia, Ahmedabad, Other materials were used available from the Institute and were used as received. Dissolution apparatus, Brookfield viscometer, Digital pH meter, UV-visible spectrophotometer, Franz diffusion cell etc were used from the Institute. Other analyses were carried outside.

3. Methods:

3.1 Solubility study of Ketoconazole

The standard shake flask method was used for solubility study of ketoconazole wherein an excess amount of ketoconazole (i.e., 50mg to 1 g) was weighed and added in a specific quantity around 10-25 mL of solvents like 0.1N HCl, Phosphate buffer 6.8, propylene glycol, ethanol and polyethylene glycol, 1,4-dioxane+water etc. flasks were kept at 37C and 100 rpm for 1 hr. Aliquots were taken at the end of experiments, centrifuged at 10000*30 min and supernatant were taken for determination of concentration of ketoconazole using UV-visible spectrophotometer in triplicate.

3.2 Melting point study:

The melting point study was performed by capillary method wherein a small quantity of ketoconazole was taken in a capillary tube which was sealed at one end and then placed in inverted position in an apparatus and the temperature was recorded when the drug started melting.

3.3 Drug-excipient compatibility study using FT-IR:

FT-IR spectrum of Ketoconazole drug and the mixture of drug with excipients were analysed between 4000-400 cm^{-1} IR range for any probable interactions in various ratios of drug and excipients. The peaks obtained in the spectra were compared with that of standard IR or pure drug [13].

3.4 Formulation of Ketoconazole Cream[8]:

Chemicals used: Ketoconazole(0.2g), propylene glycol (2-3.5 mL), cetyl alcohol (1-1.5), stearyl alcohol (0.4-1g), cyclomethicone (0.4–0.6 g), sorbitan monostearate (0.4–0.6 mL), Tween 80 (0.8-1 mL), disodium EDTA (0.01 g) and purified water (quantity sufficient to about 12.2-14.5 mL).

Melting method: Cetyl alcohol, stearyl alcohol, cyclomethicone and sorbitan monostearate were taken together and heated at about 60-70°C until they melt and form a uniform oily phase. In another container propylene glycol, Tween 80, disodium EDTA were taken in required amount of water and heated at about 60-70°C.

Method: The cream base is prepared by emulsifying the melted oil phase with the aqueous phase at same temperature with continuous stirring, Water soluble ingredients were dissolved into aqueous phase and heated at 60-70°C while Ketoconazole was dissolved into the oily phase, and heated at 60-70°C. Oily phase and aqueous phase were mixed together with constant stirring at same temperature. Stirring was continued until cooling, so a smooth and uniform cream was formed.

Table 1: Composition of ketoconazole cream formulation batches

Ingredients		Batches (20g)					
Batch Code	Percent (%w/v)	K1	K2	K3	K4	K5	K6
Ketoconazole	2	0.4	0.4	0.4	0.4	0.4	0.4
Propylene Glycol	10	2	3	3.5	3.3	3.5	3.5
Cetyl alcohol	5	1	1	1.5	1.5	1.3	1.3
Stearyl alcohol and	2	0.4	0.4	0.8	1	0.8	0.6
Cyclomethicone	2	0.4	0.4	0.4	0.4	0.6	0.6
Sorbitan Monostearate	2	0.4	0.4	0.4	0.4	0.6	0.6
Tween 80	2	0.8	0.8	0.8	1	1	1
Disodium EDTA	0.05	0.01	0.01	0.01	0.01	0.01	0.01
Water QS to 20 g	100	14.8	13.8	12.6	12.4	12.2	12.2

3.5 Preparation of Standard Curve of Ketoconazole:

First, the wavelength was determined where do we get the maximum peak of ketoconazole in UV-visible spectrophotometer in the concentration range taken for the preparation of formulation under study. Then standard curve was taken by accurately weighing 10mg of ketoconazole by dissolving into 100 mL volumetric flask containing methanol. The Final volume was adjusted to get final stock solution of 100 µg/mL. Various dilutions were prepared using methanol to make 0 to 20 µg/mL concentration range and absorbance were taken for each concentrations at λ_{max} 224 nm using a double beam UV-Visible spectrophotometer containing quartz cell[14].

4.1 Physical Appearance of the formulation:

Developed ketoconazole cream formulations were observed for physical appearance like colour, odour, texture etc.

4.2 Determination of pH:

The pH of the formulation was measured using digital pH meter which was calibrated using standard buffer solutions at pH 4.0, 7.0 and 9.2. For measuring the pH of the ketoconazole cream formulation, one gram of the formulation sample was taken and dispersed in a 10 to 100 mL DW (distilled water) with continuous stirring for 30 min using a magnetic stirrer and allowed to stabilize for 10 min. The electrode was washed with demineralised water and then immersed in a dispersion at constant temperature and pH value was recorded once the reading stabilized[9,10].

4.3 Viscosity study of the cream formulation:

Prepared batches of ketoconazole cream formulations were subjected to viscosity study using Brookfield Viscometer at 20 and 30 rpm using spindle no 64. The corresponding dial reading was recorded which was used to calculate the viscosity of each formulations.

4.4 Spreadability of the formulation:

Spreadability of the formulation batches were performed by placing 1g of the developed cream formulation within the circular area having 1.0cm diameter, pre-marked between two glass slides and applying fixed weight to the top slide for 1 min. The increase in the diameter after the weight applied was calculated. The same procedure repeated thrice for each formulations and spreadability was determined as per following formula[11].

$$S = (M*L)/T$$

Where, M= Fixed weight in gm applied to the upper slide,

T= Time

L= increase in diameter due to cream formulation spreaded after weight applied

4.5 Extrudability study of the formulation:

All the formulation batches were subjected to extrudability evaluation. First the cream was filled in the aluminium collapsible tube using crimping machine and stored at room temperature for 24 hrs. Tubes were placed between two glass plates and approx. 500 g to 1 kg weigh was applied for 10 seconds and extruded cream was collected and weighed. The tubes were also weighed again and the extrudability was calculated using the following formula[12].

$$Extrudability\ (\%) = \left[\frac{\text{Weight of cream extruded (g)}}{\text{Total weight of cream in tube}}\right]* 100$$

4.6 Content Uniformity study:

20 mg equivalent quantity of cream formulation was weighed and transferred to a 100 mL volumetric flask containing 1mL of methanol to dissolve ketoconazole and adjusting the final volume with 7.4 pH phosphate buffer solution. The solution was then mixed thoroughly and then filtered through 0.45-µ membrane

filter. 1 mL of the filtrate was pipetted out and diluted to 10 mL using 7.4 pH phosphate buffer solution. The solution was mixed well, filtered if necessary and analysed for the absorbance at λ_{max}-224nm using UV-Visible spectrophotometer[15].

4.7 In-vitro drug release profile:

The *in-vitro* drug release profile was performed by using Franz diffusion cell which consists of two chambers or compartments, where, in one chamber (receiver) there was a phosphate buffer solution (pH 7.4, 37°C, 50 rpm), taken as release medium and in another chamber which was acting as donor chamber containing ketoconazole cream formulation separated by a diffusion membrane previously soaked in PBS for 24 hours. The membrane was placed in contact with PBS solution in receiver chamber, ensuring no air bubbles in the membrane and on the media surface. 1mL sample at specified time intervals were withdrawn from the receiver chamber and replenished with fresh PBS to maintain sink condition. The samples were again diluted using phosphate buffer solution pH 7.4, filtered and analysed by UV at 224 nm for the absorbance.

4.8 Anti-fungal efficacy study of Ketoconazole cream formulation:

Potato Dextrose Agar (with 150mL of water) medium was prepared, sterilized, and inoculated with *Candida albicans*. Inoculated medium was poured in devided petri dishes, allowed to solidify and make the two to four wells with the help of borer in both petri dishes to add the 2%w/v cream of optimized formulation batch of ketoconazole formulated and 2%w/v marketed ketoconazole cream formulation, The plates were then incubated for 36 to 72 hrs in an incubator at 25 to 27°C. The zone of inhibition was measured and recorded in mm.

4.9 Stability study:

Stability study of the optimized batch was carried out as per ICH guidelines at storage conditions (25ºC±2ºC/60 %±5% RH), and at accelerated temperature conditions (40±2°C /75%±5% RH) at specified time points after 30, 60, and 90 days interval the samples were withdrawn and evaluated for appearance, consistency, spreadability, extrudability, pH, drug content uniformity etc.

4. Results and Discussion:

4.1 Solubility profile of Ketoconazole:

Equilibrium solubility study done using shake flask method It shows higher solubility in Methanol > Ethanol> PEG 400 > Propylene glycol > Tween 80 > PBS pH 7.4 > Distilled water at 25°C as shown in following table 1.

Table 1: Solubility study of Ketoconazole in different solvents

Name of Solvent	Solubility (mg/mL)*
Distilled Water	0.018±0.005
Ethanol	25±2.0
PEG 400	20±1.5
Prolylene glycol + Water	18±1.5
Tween 80	13±1.5
Phosphate buffer pH 7.4	0.03±0.005
Methanol	35

*Values are presented as mean ± standard deviations (SD) where n=3

4.2 Melting point determination of ketoconazole:

Ketoconazole drug started melting at 149ºC which was within the range provided as per IP 2007 (148 to 152ºC).

4.4 Drug-excipients compatibility study using FT-IR:

Functional group peaks of Ketoconazole at 1711.40 cm^{-1}, C-N at 1026.80 cm^{-1} and C=C (Aromatic) peak at 1511 cm^{-1} and C-C1 (stretch) peak at 816.80 cm^{-1} (Fig. 3) were observed which confirms with the standard value peaks at 1680-1630 cm^{-1} of C=O, 1230-1020 cm^{-1} of C-N and 1600 cm^{-1} and 1475 cm^{-1} of C=C and 850-550 cm^{-1} of C-Cl. Thus, it was concluded that there was no any drug excipients compatibility issues found in the formulations under study.

Figure 2: UV Spectrum of (a) Ketoconazole in PBS 7.4 pH and (b) ethanol

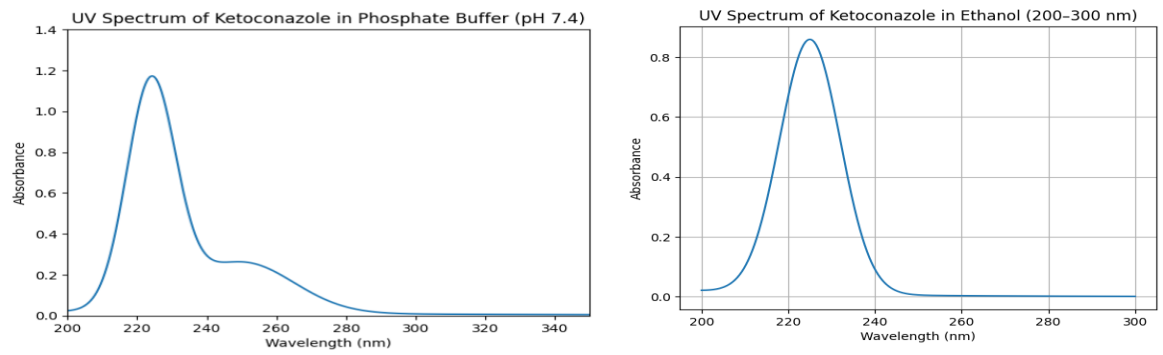
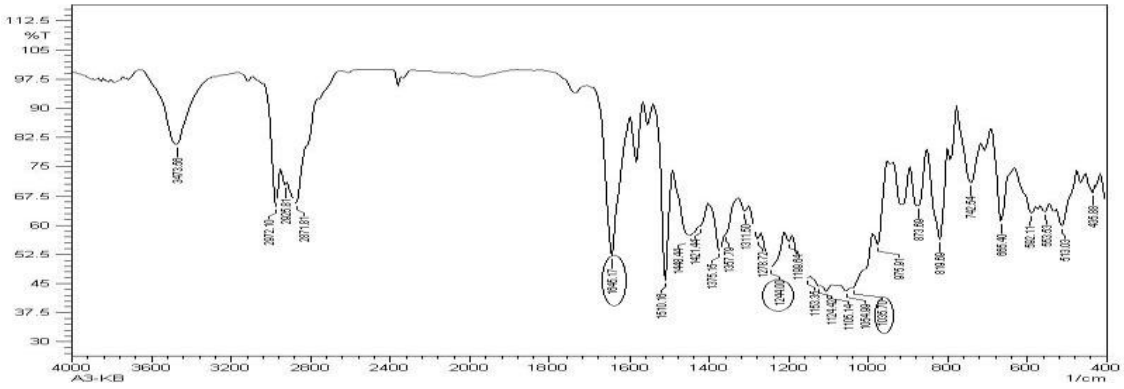


Figure 3: FTIR of Ketoconazole with excipients



4.3 Preparation of Standard Curve of Ketoconazole

4.3.1 Determination of wavelength of ketoconazole

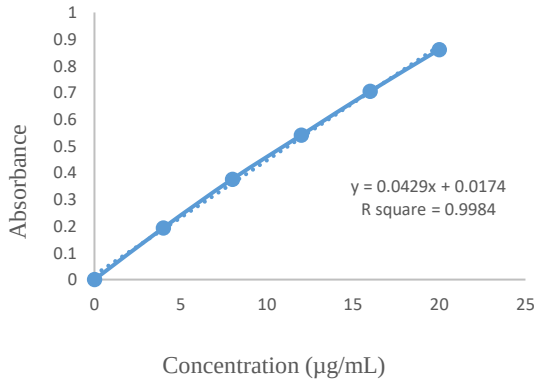
A specified quantity of pure Ketoconazole drug sample in a phosphate buffer solution (pH 7.4) were analysed using UV-visible spectrophotometer and scanned between the range of 200nm to 400nm The highest peak obtained was considered as λ_{max} of Ketoconazole. The Maxima was found at 224nm in PBS 7.4pH and 221nm in ethanol.

4.3.2 Preparation of Standard Curve

Table 2: Standard Curve of Ketoconazole

Concentration (µg/mL)	Absorbance
0	0
4	0.194
8	0.376
12	0.541
16	0.705
20	0.861

Figure 4: Standard Curve of Ketoconazole in PBS (pH-7.4)



4.5 Physical Appearance of the formulation:

All the prepared formulation batches were subjected to physical evaluation of colour, odour, consistency and homogeneity study (see table 3). All the formulations were found White, clear, homogenous with excellent consistency and odour.

Table 3: Physical parameters of the formulation batches

Batch code	Colour	Consistency	Homogeneity	Odour
K1	White	Excellent	Homogenous	Good
K2	White	Excellent	Homogenous	Good
K3	White	Excellent	Homogenous	Good
K4	White	Excellent	Homogenous	Good
K5	White	Excellent	Homogenous	Good
K6	White	Excellent	Homogenous	Good

4.6 pH, viscosity, spreadability and Extrudability and drug content uniformity study

The prepared ketoconazole cream formulations were evaluated for various parameters including pH, viscosity, spreadability, extrudability, and drug content to determine their suitability for topical administration. The results obtained are summarized in Table 4.

The pH of all the formulation batches K1 to K6 were found within the acceptable range (5.7±0.20 to 6.4±0.30) as physiological skin (pH -6.5) which proved that all the formulations were compatible with the skin and were non-irritant when applied to the skin. Amongst all the formulations prepared, batch K2 was found to exhibit lowest pH (5.7±0.20) and K6 exhibited highest pH value (6.4±0.30). However, the variation was minimum indicating skin-friendly formulations.

The viscosity of all the formulations was found in the range of 21600±100 cps to 29,700±150 cps which indicated good semisolid consistency and homogeneity of all the formulations. Amongst all the formulations

prepared batch K5 showed highest viscosity indicating thicker cream base matrix providing longer residence time on skin while batch K1 showed lowest viscosity indicating relatively softer formulation. But the viscosity values were within the desirable range for topical cream preparations ensuring proper stability and applicability.

The spreadability of all the prepared formulation batches were found between 15.46±0.5 to 17.66±0.5 g.cm/sec, indicating good spreading behaviour facilitating uniform application of cream formulation on skin surface. Batches K4 and K6 demonstrated highest spreadability as compared to other batches while batch K5 have lowest spreadability may be due to its comparatively higher viscosity.

The extrudability study of the cream exhibited ease of removal of the cream formulations from the collapsible tubes (varies from 62.5±0.5% to 85.5±0.5%). Higher the extrudability more easily the formulation can be removed from the tubes while administration. Batch K6 (85.5±0.5%) exhibited highest extrudability value followed closely by batches K5 (85.0±0.5%) and K4 (83.5±0.5%) and lowest for batch K1 indicating higher resistance during extrusion from the collapsible tube.
The percentage of drug content of all the formulations were found within the acceptable pharmacopoeial limits. The drug content of the formulations was found between 85.20±1.5% to 93.50±1.5% which indicated uniform drug incorporation and distribution within the cream base. Amongst all the batches prepared batch K4 was found to have 93.50±1.5% drug content.

Overall evaluation of the parameters suggested that amongst all the formulation batches prepared, batch K4 exhibited most favourable characteristics i.e., suitable pH, moderate viscosity, excellent spreadability and extrudability with highest drug content. Therefore, batch K4 was considered the optimized ketoconazole cream formulation batch amongst all prepared batches and were further evaluated for *in-vitro* drug release profile study, antifungal efficacy study and stability study.

4.7 In-vitro drug release study

In-vitro release study for optimized batch was performed to evaluate the release behaviour as compared with marketed formulation. Dissolution medium was PBS 7.4pH was taken to simulate physiological conditions. Aliquots were withdrawn at specified time intervals and analysed using UV-Visible spectrophotometer at 224nm by diluting the aliquots with specified concentration range with PBS 7.4 pH and the final amount of drug released was calculated.

The observed release profile indicated controlled release of ketoconazole from the optimized batch formulation. Amongst all batches batch K4 was found to provide 97.4% drug release at the end of 5 hours which showed similar release pattern compared with marketed formulation of ketoconazole formulation.

4.8 Anti-fungal efficacy study of Ketoconazole cream formulation

The ZOI (zone of inhibition) of the optimized batch was found 12mm as compared with Marketed formulation 11mm after 72 hours indicated that the optimized batch formulation was equally effective in exhibiting antifungal activity with marketed formulation.

Table 5: Zone of Inhibition of optimized ketoconazole vs marketed cream formulation

Formulation	ZOI in mm*
Optimized formulation	12±0.5
Marketed formulation	11±0.5

*Values are presented as mean ± standard deviations (SD) where n=3

Table 4: pH. Viscosity and Spreadability determination of formulation batches K1 to K6

Sr. No	Batch code	pH value*	*Viscosity (cps)	*Spreadability S=M.L/T	Extrudability	*Drug content %
1	K1	6.0±0.10	21600±100	15.90±0.5	62.5±0.5	86.40±1.5
2	K2	5.7±0.20	27200±150	16.21±0.5	68.0±0.5	85.90±1.5
3	K3	6.3±0.15	24400±100	16.50±0.5	76.5±0.5	85.20±1.5
4	K4	6.1±0.10	25800±150	17.66±0.5	83.5±0.5	93.50±1.5
5	K5	5.8±0.15	29700±150	15.46±0.5	85.0±0.5	91.50±1.5
6	K6	6.4±0.30	24900±100	17.50±0.5	85.5±0.5	89.75±1.5

Figure 5: % Drug Release of Ketoconazole from batch K4 and Marketed Formulation

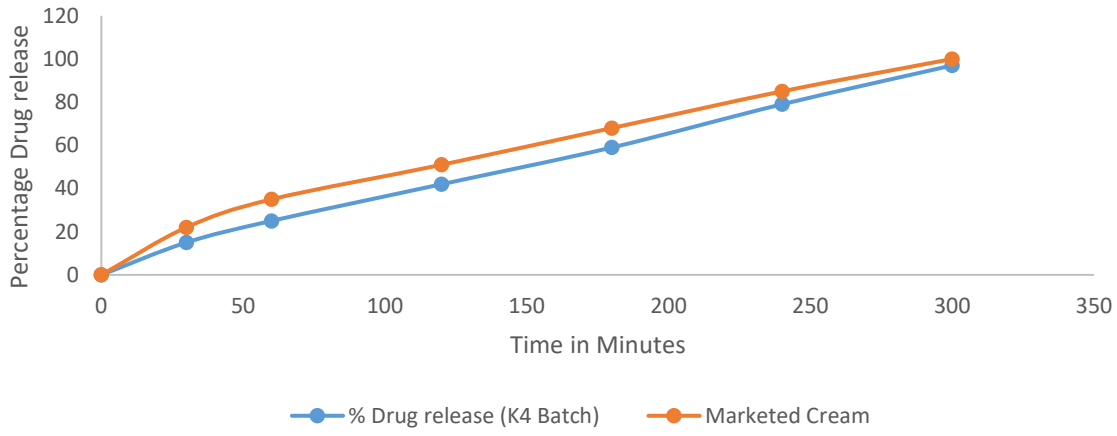
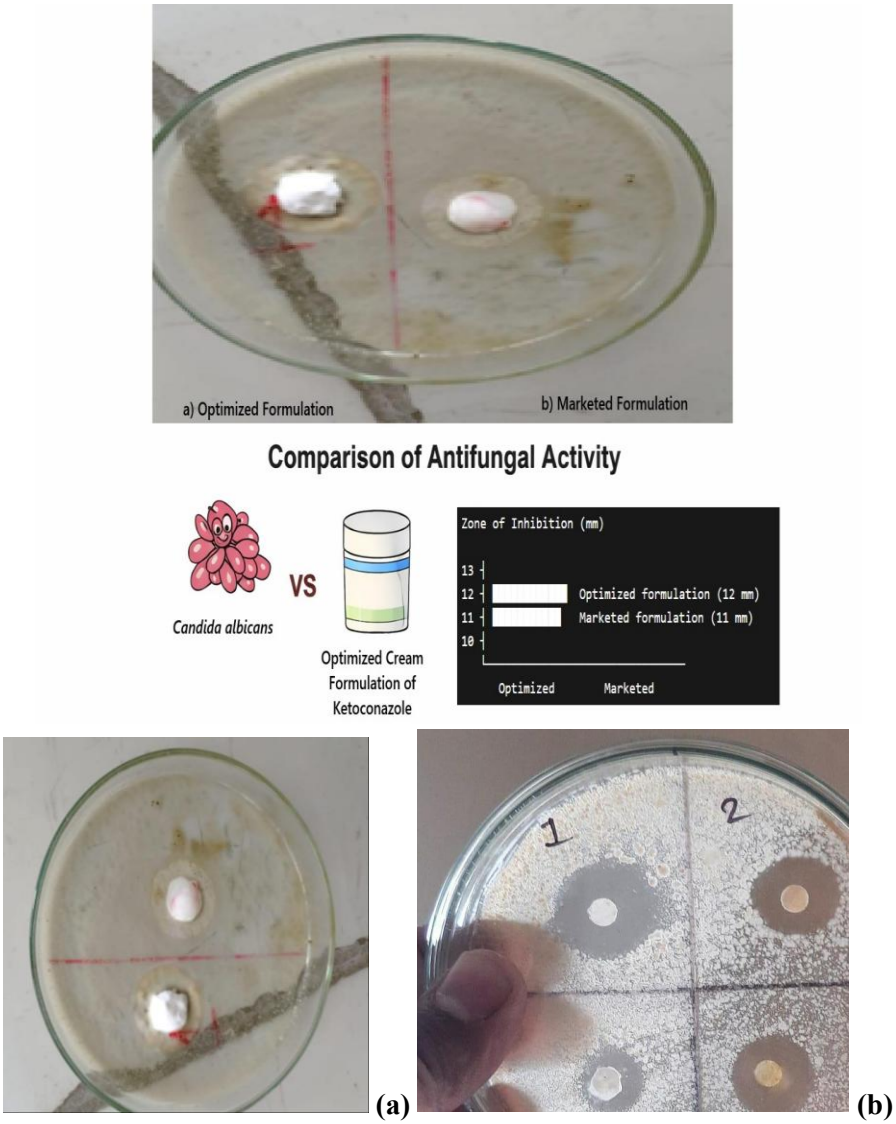


Figure 6: In vitro antifungal activity efficacy study (a) and (b)



(a) **(b)**

The in-vitro antifungal efficacy study was performed on agar diffusion method using Candida albicans by measuring the zone of inhibition after 72 hours of incubation of the sample wells containing a) optimized batch formulation and b) marketed formulations as shown in fig. 6 (a & b) and summarized as per table 5.

The optimized formulation of ketoconazole cream exhibited higher zone of inhibition (approx. 12 mm) as compared to marketed cream formulation (11 mm). The difference between both the formulations was minimum however, optimized formulation batch produced marginally higher inhibition than marketed one suggesting enhanced antifungal activity. Thus, the results indicated that developed optimized formulation of ketoconazole cream formulation can be able to inhibit fungal growth with same therapeutic potential as marketed formulation.

4.9 Stability Study

The stability study of the prepared batches of the ketoconazole formulations was carried out as per ICH guidelines and periodically evaluating key physicochemical parameters like appearance, colour, odour, pH, viscosity, spreadability, extrudability, homogeneity and consistency etc. Stability studies are required to prove the formulation stability in terms of quality, safety and therapeutic efficacy throughout the shelf-life. Results of stability studies indicated no observable changes in viscosity, spreadability, extrudability, pH, colour, odour, drug content uniformity with 5 out of 5 formulation batches remained stable physically and chemically throughout the shelf life. No formulations under study showed any phase separation, drying or significant variation in parameters under study and retain the structural integrity during the storage. Overall, Ketoconazole cream formulation prepared exhibited promising stability characteristics.

5. Conclusion:

The study has successfully aimed at development and characterization of topical antifungal cream formulation of ketoconazole a broad-spectrum class -II antibiotic drug having poor aqueous solubility but can be effectively delivered via topical route by emulsifying in a cream formulation due to its high permeability. Preformulation studies confirmed identity and purity, solubility and compatibility of the Ketoconazole justifying its suitability with excipients selected in the formulation under development. Amongst all the formulation batches prepared batch K4 was found within the acceptable limits and exhibited good physical characteristics, homogeneity, pH, viscosity, spreadability, extrudability and the highest drug content (93.50%) indicating uniform content distribution throughout the cream base. The invitro drug release revealed that 97.4% drug release within 5 hours an efficient and comparable drug profile with conventional marketed cream formulation. The antifungal efficacy study against candida albicans showed 12 mm of zone of inhibition which was slightly higher than marketed formulation again confirmed the comparative potential of the optimized formulation in the therapy. Optimized formulation found stable after one month of stability study with no significant changes in appearance, pH, Viscosity, spreadability, extrudability and rug content uniformity confirming integrity of the formulation throughout the shelf life.

Thus, it can be concluded that the developed optimized formulation of ketoconazole exhibited satisfactory physicochemical properties with efficient drug release and significant antifungal efficacy and stability throughout the shelf life which was comparable with the marketed preparation. Further studies such as extended stability testing and invivo characterization of the formulation will be carried out to confirm its clinical efficacy and long -term stability.

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