JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2023/32329
RESEARCH ARTICLE

Formulation and Evaluation of Herbal Excipients-Based Ketoconazole Cream for Fungal Infection

Janki B. Patel*, Mansi Gajera, Zalak Shah, Pinkal Patel, Kinjal Parmar, Vaishali Patel, Hetvi Patel, Disha Patel and Kanupriya Rathore

Faculty of Pharmacy, Department of Pharmaceutics, Parul Institute of Pharmacy and Research, Parul University, Vadodara – 391760, Gujarat, India; janki0410pharma@gmail.com

Abstract

The goals of the current studies were to create herbal excipients-based ketoconazole cream to enhance the efficacy against chronic mucocutaneous candidiasis. Ketoconazole, coconut oil and other herbal excipients namely shea butter, bees wax, Lanolin and Rose oil were used for the formulation. Each formulation was prepared with various concentrations of coconut oil. Every prepared formulations were evaluated successfully. Among all the formulations F4 was the best that exhibiting a higher *in vitro* diffusion rate 59.6 ± 0.10 % CDR within 480 min with maximum antifungal efficacy, compared with the marketed formulation. We might therefore say that herbal excipients-based cream improved patient compliance and is a superior alternative to oral preparation, easier administration, local bioavailability, and better results for individuals with persistent mucocutaneous candidiasis who are afflicted with fungi.

Keywords: Anti-Fungal Activity, Cream Formulation, Coconut Oil, Herbal Excipients, Ketoconazole, Shea Butter

1. Introduction

Chronic Mucocutaneous Candidiasis (CMC) is a condition with a wide range of symptoms and has been linked to several immunologic and hormonal disorders. Autosomal or acquisitive factors may predispose the host to CMC infection. The sickness frequently strikes children while they are young.

Candida species are common microorganisms that are found in the mucosal microflora of humans can elude mucosal tissue and cause candidiasis in the presence of defects in the cellular and immunological system that are built in the body, even during long-term antibiotic therapy, so has been identified as the most common cause of these lesions.

CMC is a heterogeneous set of disorders characterized by repeated and chronic skin lesions on the mucosal tissues, nails, and skin of the face, neck, and trunk. CMC is thought to be the phenotypic manifestation of immunologic, endocrinologic, and autoimmune illnesses. Almost CMC patients have a T-cell deficit, which can be hereditary or acquired[1,2].

Ketoconazole is an antifungal imidazole used to prevent and treat infection caused by fungus. It is inhibiting the production of ergosterol by fungus, it is equivalent to cholesterol, which enhances membrane fluidity and stop fungus to grow. In 1981, FDA initially authorized ketoconazole in the form of oral formulation for systemic use. At that time, it was considered a significant improvement over the earlier antifungal agents miconazole and clotrimazole because of its broad spectrum and good absorption. Anyway, ketoconazole found to frequently cause dose-dependent hepatitis and gastrointestinal side effects[3,4].

Coconut oil has long been utilized as a fungus cure. The first is that it has antifungal qualities and can be applied topically to treat minor or superficial infections. Coconut oil contain a chain of fatty acid, lauric acid and antimicrobial lipids which provide these benefits. Studies indicated that coconut oil was successful in treating

*Author for correspondence

Article Received on: 07.01.2023 Revised on: 07.04.2023 Accepted on: 08.05.2023

drug-resistant Candida species[5]. Coconut oil is also used to help wounds heal faster, a reliable source of anti-inflammatory, antioxidant, and moisturizing properties can help to eviate skin irritation and flakiness by lubricating the skin and speeding up the healing process. This can also help to reduce infection redness and other apparent symptoms.

In the current research, the herbal cream of ketoconazole based on herbal oil and excipients was looked for topical fungal infections. Herbal cream of ketoconazole for fungal infections was made with the use of coconut oil, shea butter, lanolin, beeswax and rose oil.

It was hypothesised that herbal excipients based ketoconazole containing cream would give synergistic antifungal activity. It may overcome the side effect and toxicity of the current therapy.

2. Materials and Methods

Ketoconazole, Coconut oil, Shea butter, Bees wax, Lanolin, and Rose oil were used in the development of herbal excipient base ketoconazole cream.

2.1 Preformulation Studies

Preformulation studies include spectroscopic drug identification by UV, and compatibility determination by Fourier-transformed infrared (FTIR/IR) spectroscopy[8].

2.2 UV Spectroscopic Characterization of Ketoconazole

The absorption maxima (λ_{max}) of ketoconazole was identified by examining the standard drug concentration in 7.4 pH phosphate buffer at 200-400 nm.

2.3 The Stock Solution's Preparation

100 mg of ketoconazole was dissolved in 100 ml of 7.4 pH phosphate buffer to get a concentration of 1 mg/ml. Afterwards, 10 ml solution was taken from that and make up to 100 ml using 7.4 pH phosphate buffer to reach a 100 µg/ml solution. This stock solution was scanned for maximum absorbance by a dual beam UV-visible spectrophotometer. λ_{max} of ketoconazole was found to be 226 nm.

2.4 Preparation of Working Standard

The above stock solution was further diluted with 7.4 pH phosphate buffer to get different dilutions prepared in the range of 10–60 µg/ml. Keeping 7.4 pH phosphate buffer as a blank, each solution absorbance was measured using a UV visible spectrophotometer. The calibration curve was created by plotting Absorbance vs Concentration (µg/ml).

2.5 IR Study of Ketoconazole[6]

The IR band of pure drug was analyzed by using the Potassium bromide (KBr) compression method and observed. The pure drug was mixed with KBr powder [1:100] and then pressed under high pressure in a special transparent disc mould. Afterwards, the disc was placed into IR and record the band. Analyze the band of pure drug for identification. In this work, IR bands of pure drug and drug with excipients used in the formulation were analyzed for the interaction.

2.6 Formulation of Cream

Weigh all the ingredients in the required quantities. Take Beeswax and Shea butter in a China dish and melt the mixture at a temperature of 70 °C on a hot plate. After 2-3 minutes, add lanolin and coconut oil to it. Once the mixture is melted completely, add Ketoconazole to it and allow it to dissolve completely in the mixture. Then take it off from the hotplate. Add rose oil to it followed by the required quantity of warm water. Keep stirring it and let it cool to room temperature. Mix with a mechanical stirrer until a semi-solid cream is formed.

2.7 Evaluation of Creams

2.7.1 Physical Appearance[7,8]

The prepared topical cream was visually inspected for homogeneity, colour, odour, state, consistency, and texture.

2.7.2 pH of Creams[7,8]

For pH determination, 5 gm of the formulated cream was mixed in 50 ml distilled water and measured by using pH meter at 27 °C.

2.7.3 Viscosity

The Labman digital viscometer was used for the viscosity determination of the formulated creams. According to the standard operating procedure of the viscometer, the adaptor of the viscometer was filled with the formulated cream, and spindle no 2 was rotated at 6rpm, for viscosity determination.

2.7.4 Greasiness[9]

The cream formulation was applied on the skin surface as a thin smear and checked their greasiness.

2.7.5 Tube Extrudability[6]

For extrudability determination, % the quantity of the cream extruded from the tube upon applying finger pressure was evaluated. Better extrudability results from higher extruded quantities from the tube. The prepared cream formulations were filled in 5 gm clean, collapsible aluminium tube having 5 mm opening of the nasal tip. The tube was held between the thumb and index finger, pressure was applied on the tube for 1 second. The amount of extruded cream from the tube upon application of the pressure was evaluated for the determination of tube extrudability.

2.7.6 Irritancy[10,11]

The allergic reactions, if any, of the formulated creams were investigated by the skin irritancy test. On the left-hand dorsal surface, make a [1 cm^2] mark. The cream was then administered to the affected area, and the time was recorded. Then, for an interval of up to 24 hours, it is evaluated for irritancy, erythema, and edema, if any, and a report is made.

2.7.7 Spreadability[12,13]

For the spreadability determination wooden block with a pully at one end consisting of apparatus was used.

On the ground slide, 2 g of the formulated cream was placed. Another slide which has dimension, provided with the hook was placed on the fixed ground slide.1kg weight was poured on the two slides to create a consistent film of cream. Afterwards, a 30 gm pull was applied to the top slide. The top slide's time (measured in seconds) to travel 7.5 cm was calculated with the aid of a thread fastened to the hook. Better spreadability is indicated by a shorter interval.

The equation used for calculating Spreadability was:

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

Where, M = Weight (gm) taken, L = Length of the slide, T = Time (s) taken.

2.7.8 Acid Value[15]

Ether and alcohol solvent mixture was used for the acid value determination. 7gm of the formulated cream in 25ml methanol and ether was refluxed until the cream dissolved. 0.1N NaOH was used to titrate the sample solution using phenolphthalein as an indicator. The solution was titrated until pink colour appeared; it was the end point. Noted, in titration, 0.1N NaOH was used. The acid value was calculated:

$$\text{Acid value} = v^{*}5.6/w$$

Where, v = 0.1N NaOH used in titration

w = weight of formulated cream

2.7.9 Determination of the Type of Emulsion[14]

This test was used to determine the type of emulsion in two ways. first thing, formulated cream was taken in small quantities. One half was diluted with water, while the other was diluted with olive oil. Repeated independently for each cream.

2.7.10 Stability Test[16]

At 3 different temperature conditions, pH and Spreadability of the prepared cream were checked to determine the stability, i.e. by placing the cream formulations in the oven at 40 °C, in a refrigerator less than 10 °C and at ambient conditions. The values were compared at time 0 min and after a week.

2.7.11 Drug Content

In a 250ml volumetric flask, add 0.1 gram of the formulated cream and 20ml 7.4pH phosphate buffer, and stir for 30min. Using 7.4 pH buffer, the final volume up to 100ml was made, stirred and filtered, and measured the absorbance at 226nm. The drug content was calculated according to beer lambert's law.

2.7.12 In vitro Diffusion Study[17,18]

For the *in-vitro* diffusion study, the Franz Diffusion Cell was used; the base of the cell was covered with

overnight wetted cellophane membrane. The 5gm of cream is transferred into the Franz Diffusion Cell. This cream-containing cell is tied on a stand and dipped into the 1000ml 7.4 pH Phosphate buffer and that solution is continuously stirred using a magnetic stirrer. The moment the stirrer is started 5ml of sample is withdrawn which is further replaced by adding 5ml of fresh 7.4 pH Phosphate buffer to the solution. The withdrawn sample's absorbance is measured at λmax 226nm and recorded as zero mins absorbance. The process is repeated after each 5mins interval and absorbance is taken by using a UV spectrophotometer. The marketed formulation was used for comparative studies with the prepared formulations.

2.7.13 Antifungal Study[8]

In-vitro antifungal activity of the prepared cream formulation was determined by cup-plate method/ agar well diffusion assay against *Candida albicans*. Stock culture of fungi was maintained at 4 °C on the slant of sabouraud dextrose agar. A loop of cells from the stock culture was transferred to a test tube containing nutritional broth for fungus, where they were cultured for 24 hours at 37°C to create the active culture for the experiment. The antifungal activity was performed by agar diffusion technique. The required quantity sabouraud dextrose agar dissolve in 100ml of distilled water with continuous heating and agitation, maintaining the pH 5.5. Autoclaved the prepared media at a temperature of 121°C and 15 lbs pressure for 15 min. The sterile media was then poured into the sterile glass petridish aseptically. Allow the media to solidify. When the media solidified, it was inoculated with the fungi species by streaking on the surface of the media. Prepare cavity on the surface of the agar plate using a sterile cork borer of 8mm diameter. The prepared cavity was then filled with the prepared cream formulation. Then after the petri dish was rested for at least 30mins and incubated for 24hrs to 48hrs at a temperature of 25 ± 1 °C. After incubation, the most uniform outer diameter of the zone of inhibition was recorded in millimetres. The prepared cream formulations were compared with ketoconazole and the marketed formulation of ketoconazole for its efficacy.

3. Results and Discussions

3.1 Preformulation Studies

Evaluation of the physicochemical properties and compatibility testing of the ketoconazole with other formulation ingredients, the pre-formulation studies for pure ketoconazole were carried out.

3.2 Characterization of Ketoconazole by UV Spectroscopy

The λ_{max} of ketoconazole was found to be 226 nm.

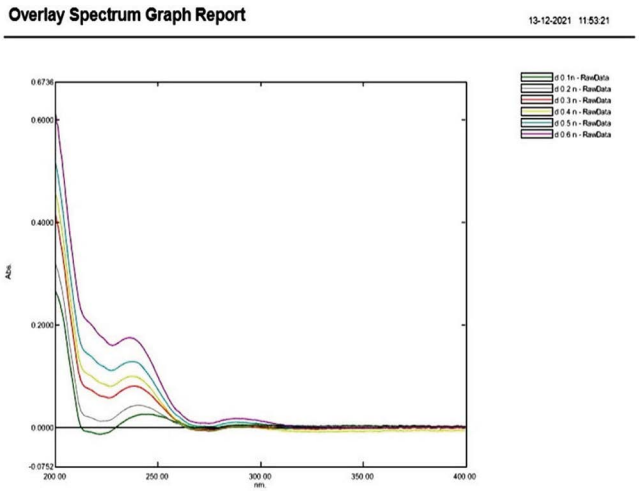

Figure 1. Absorption maximum of ketoconazole.

3.3 Standardization of Ketoconazole

The calibration curve of ketoconazole is shown in Figure 2

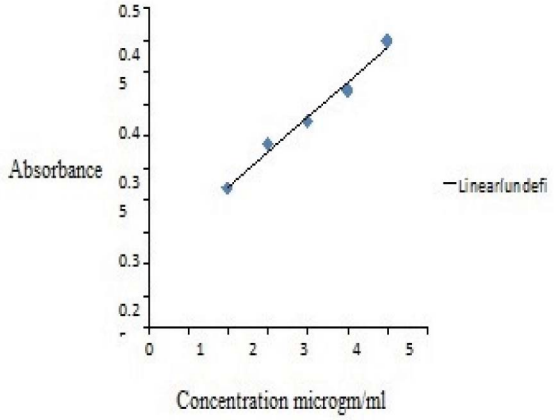

Figure 2. Calibration curve of ketoconazole.

3.4 IR study of Ketoconazole

IR band of ketoconazole estimated the existence of a peak at 867.52 cm^{-1} due to C-Cl stretching, then a peak at 1511.13 cm^{-1} due to aromatic C=C and C=N stretching. A peek at 1645.58cm^{-1} due to C=O while peaks at 1106.10cm^{-1} due to C-O and peak at 1077.52 cm^{-1} due to C-N. As per the literature, the reported peaks support the purity of the drug Figure 3. When the IR spectra of pure ketoconazole were compared with the physical mixture of ketoconazole with all excipients of cream Figure 4, the same characteristic peaks of ketoconazole were observed in the spectra. So from Figure 3 and Figure 4, it was concluded that all the ingredients of cream were compatible with ketoconazole Table 1.

Table 1. Interpretation of FTIR spectra of ketoconazole and Physical mixture of ketoconazole and excipients of cream

Bond	D 2 ketoconazole cm^{-1}	D1 mixture cm^{-1}
C-Cl	867.52	867.38
C=N	1511.13	1510.70
C-N	1077.52	1079.70
C=O	1645.58	1644.10
C-O	1106.10	1105.27
C-H	1460.14	1464.09

3.5 Formulation of Creams

Table 2 optimized formula for cream formulation.

Table 2. Optimized formula for cream formulation

Name of the material	Quantity used			
Formulation code	F1	F2	F3	F4
Ketoconazole	2g	2g	2g	2g
Shea butter	30g	30g	30g	30g
Beeswax	20g	20g	20g	20g
Lanoline	14g	14g	14g	14g
Coconut oil	25ml	45ml	49ml	55ml
Rose oil	2ml	2ml	2ml	2ml
Water	qs	qs	qs	qs

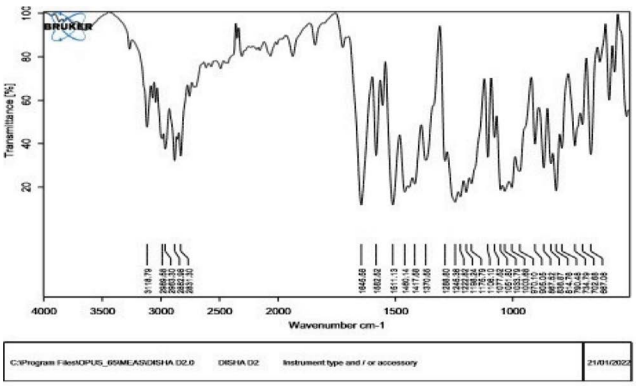

Figure 3. FTIR spectra of ketoconazole.

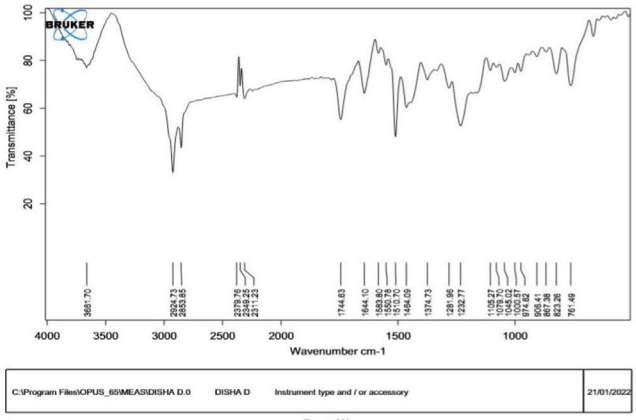

Figure 4. IR spectra of a mixture of Ketoconazole and other excipients of cream.

3.6 Physical Appearance

In this evaluation homogeneity, colour, odour, state, consistency and texture of the four formulations were checked Table 3.

3.7 pH of Creams

The pH of the cream is a crucial parameter to consider. The cream's pH should be appropriate for the skin. The prepared cream formulations were found to have pH ranging 6.2 – 6.7. Hence suitable for the skin. Results are shown in Table 4, Figure 5.

3.8 Viscosity

The viscosity of cream was measured with a Labman digital viscometer at 22.9 °C and 6 rpm using spindle no. 2. The results indicated that all four formulations had appropriate viscosity in Table 5.

Table 3. Results of physical appearance of homogeneity, color, odor, state, consistency and texture

TEST	F1	F2	F3	F4
Homogeneity	Homogenous	Homogenous	Homogenous	Homogenous
Colour	Creamy white	Creamy white	Creamy white	Creamy white
Odour	Characteristic	Characteristic	Characteristic	Characteristic
State	Semisolid	Semisolid	Semisolid	Semisolid
Consistency	Acceptable	Acceptable	Acceptable	Acceptable
Touch	Even	Even	Even	Even

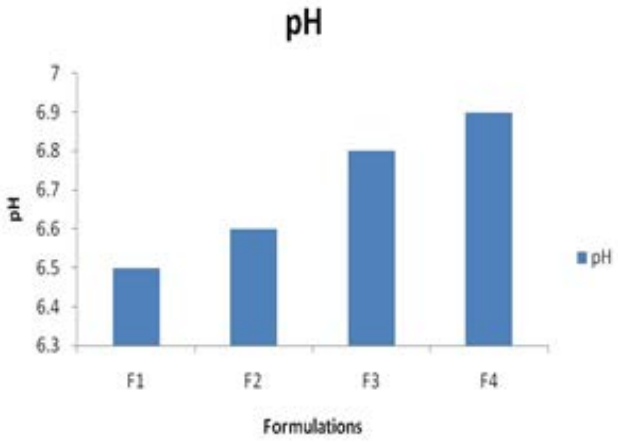

Figure 5. pH of prepared cream formulations.

Table 4. pH of prepared cream formulations

SN	Formulation	pH
1	F1	6.5
2	F2	6.6
3	F3	6.8
4	F4	6.9

3.9 Greasiness

The cream was smeared on the skin surface, and the smear was examined to see if it was greasy or grease-like. It was concluded that all four formulations were non-greasy based on the results in Table 5.

3.10 Tube Extrudability

Table 6 shows the results of the tube extrudability test.

3.11 Irritancy

On the left-hand dorsal surface, make a 1 cm^2 mark. The cream was then administered to the affected area,

Table 5. Viscosity and Greasiness of the prepared cream

Formulation	Viscosity (cps)	Greasiness
F1	19959	Non-Greasy
F2	20000	Non-Greasy
F3	11228	Non-Greasy
F4	20918	Non-Greasy

Table 6. Tube extrudability of prepared formulations

SN	Formulation	Tube extrudability
1	F1	Good
2	F2	Good
3	F3	Excellent
4	F4	Good

and the time was recorded. Then, for up to 24 hours, it is evaluated for irritancy, erythema, and edema, if any, and reported. All four formulations, F1, F2, F3 and F4, showed no signs of irritancy, erythema, edema, according to the data.

3.12 Spreadability

The spreadability of the four formulations was tested, and it was found that for F4, the two slides separation time taken is less, therefore, as indicated in the evaluation test, F4 showed better spreadability Table 7, Figure 6.

3.13 Acid Value

The acid value was calculated by using this formula,

Acid value = v*5.6/w

Table 7, Figure 7.

Table 7. Spreadability and acid value of the prepared cream

Formulation	Spreadability	Acid value	Type of emulsion
F1	32.14	8	Oil/water
F2	22.5	6.4	Oil/water
F3	26.47	7.6	Oil/water
F4	15	6.4	Oil/water

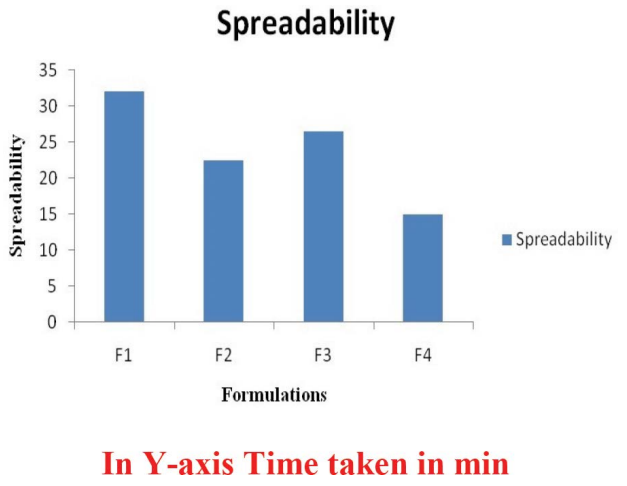

Figure 6. Spreadability of prepared cream formulations.

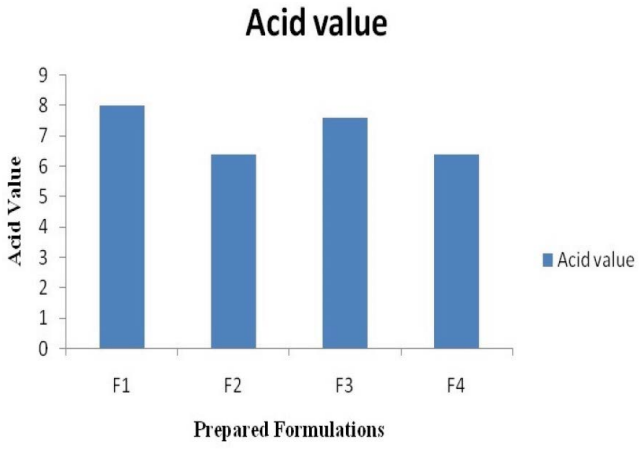

Figure 7. Acid value of prepared cream formulations.

3.14 Determination of the Type of Emulsion

Olive oil and water were used in the experiment. Prepared creams were not found homogeneous in olive oil, but they were diluted homogeneously in water and found stable in water**.** So for all formulations (F1, F2, F3 and F4), the type of emulsion was found to be O/W type (Table 7).

3.15 Stability

All the prepared cream formulations passed the test of homogeneity at different temperature ranges over a week. However, there was a slight variation in the pH Table 8, Figure 8, Figure 9.

3.16 Drug Content

Results are tabulated in Table 9.

3.17 In vitro Diffusion Study

In vitro diffusion tests were performed on the final formulations. The combined percent drug release of F1 was 40.69±1.10 %, F2 was 45.23±1.10 %, F3 was 50.23±1.12 % and F4 was 59.6±1.10 % and for the marketed formulation was 55.6±1.11 % respectively. Therefore, from the data, F4 formulation exhibited improved outcomes when compared to the other

Table 8. pH of prepared formulations after a week at various temperatures

Difference temperature conditions at 0 time to 1 week	F1	F2	F3	F4
pH in time 0	6.5	6.6	6.8	6.9
At room temperature (1 week)	6.5	6.8	6.8	6.9
At 40 °C (1 week)	6.8	6.9	6.9	6.9
Below 10 °C (1 week)	6.7	6.8	6.8	6.9

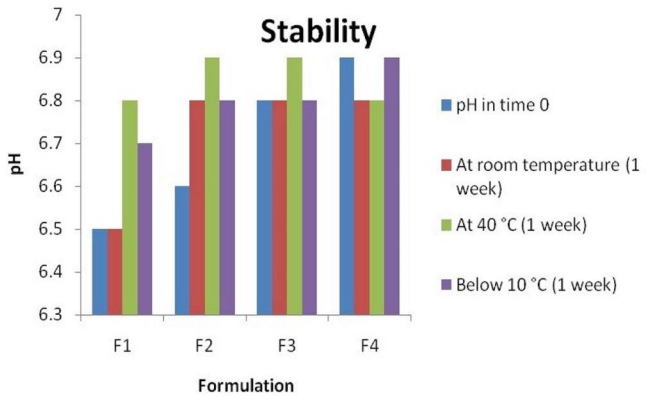

Figure 8. pH Comparison for stability at different temperature conditions.

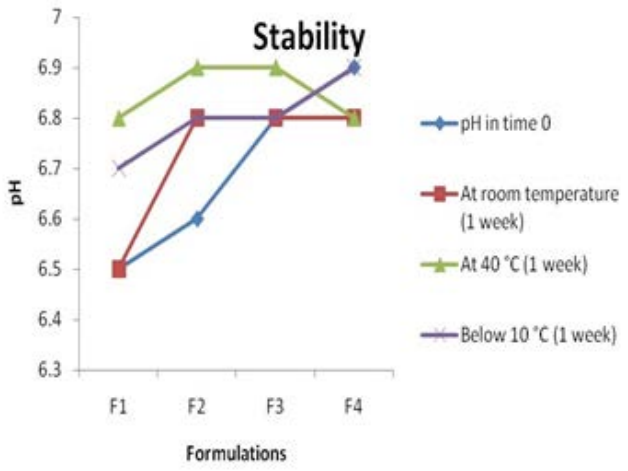

Figure 9. Graphical presentation of Stability results.

Table 9. % drug content of the prepared formulations

Formulation	% Drug content
F1	85.12±0.016
F2	89.23±0.004
F3	91.12±0.015
F4	92.32±0.014

formulations and the marketed formulation. The results were shown in Table 10, Figure 10.

3.18 Antifungal Study

After incubation, the most uniform outer diameter of the zone of inhibitions was recorded in millimetres. The F4 formulation showed a good antifungal effect compared to pure ketoconazole and the marketed formulation Figure 11, Table 11, Figure 12.

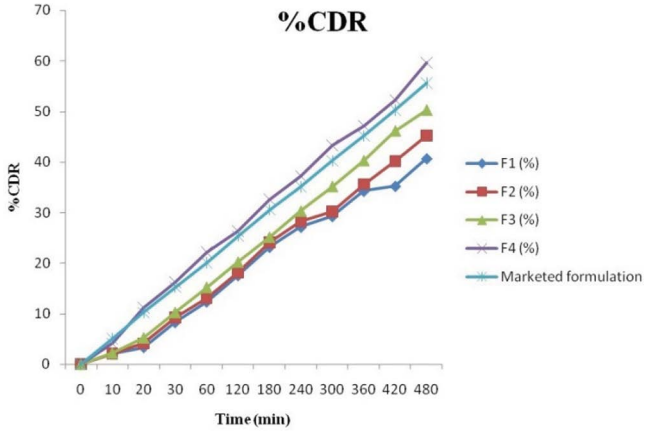

Figure 10. Comparison of drug release profile of prepared formulations (F1, F2, F3, F4) with marketed formulation.

Table 10. % drug diffusion

Time (in Minutes)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	Marketed formulation
0	0	0	0	0	0
10	2.1±1.12	2.11±1.17	2.23±1.10	4.1±1.14	5.1±1.15
20	3.33±1.10	4.12±1.15	5.21±1.14	11.21±1.10	10.21±1.12
30	8.26±1.09	9.25±1.06	10.23±1.12	16.23±1.14	15.23±1.12
60	12.33±1.13	13.12±1.12	15.21±1.15	22.12±1.12	20.12±1.10
120	17.55±1.12	18.17±1.10	20.19±1.06	26.32±1.10	25.32±1.08
180	23.15±1.09	24.12±1.12	25.11±1.08	32.52±1.12	30.52±1.10
240	27.12±1.10	28.23±1.14	30.25±1.10	37.11±1.12	35.11±1.14
300	29.25±1.12	30.21±1.13	35.12±1.12	43.23±1.14	40.23±1.16
360	34.25±1.14	35.63±1.08	40.23±1.14	47.12±1.08	45.12±1.08
420	35.23±1.08	40.12±1.10	46.12±1.10	52.21±1.16	50.21±1.15
480	40.69±1.10	45.23±1.10	50.23±1.12	59.6±1.10	55.6±1.11

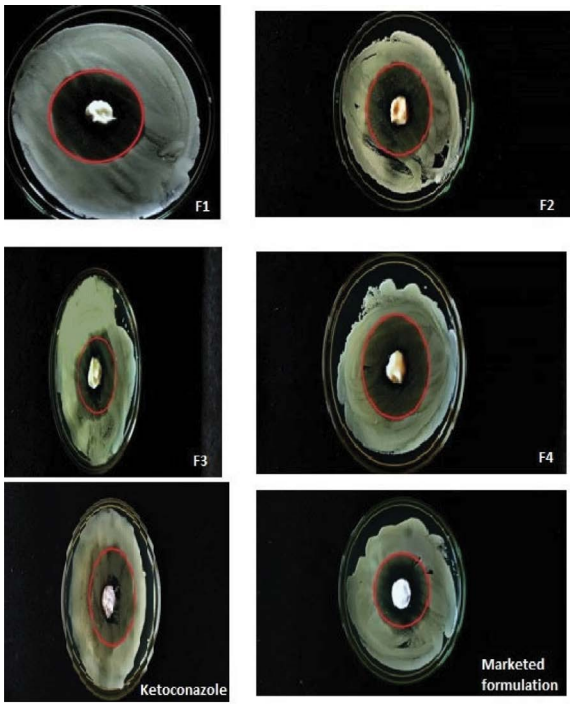

Figure 11. Antifungal activity of prepared formulations, ketoconazole and marketed formulation.

Table 11. Diameter of zone of inhibitions

Formulation	Inhibition of zone (mm)
F1	2.4
F2	2.3
F3	2.2
F4	3.2
Ketoconazole API	3.1
Marketed product	2.3

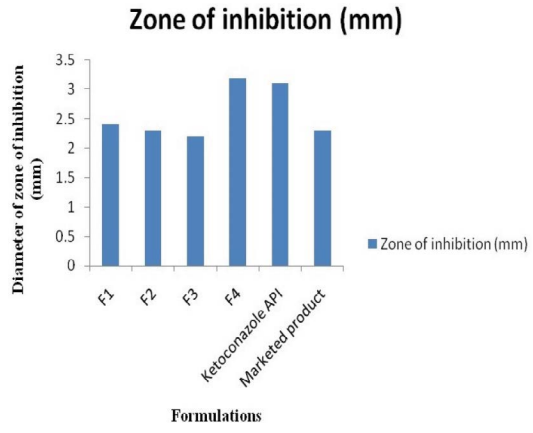

Figure 12. Zone of inhibitions of prepared formulations, Ketoconazole and Marketed formulation.

4. Conclusion

The herbal excipients and coconut oil containing ketoconazole cream were prepared by the trituration method. Herbal excipients, namely, Shea butter, Bees wax, Lanolin, Rose oil were used in the development of herbal excipient-based ketoconazole cream. A different ratio of coconut oil was used to formulate each cream. Data from the pre-formulation were within the predetermined bounds. The conclusion drawn from the entire discussion was that F4 was the best formulation available. The F4 formulation had the following characteristics that set it apart from the other formulations: a viscosity of 20918 cps, a drug content of 92.32±0.014 %, a spreadability of 15 cm, good tube extrudability, and a percent cumulative drug release of 59.6 ± 0.10 % within 480 minutes. The F4 formulation showed an excellent antifungal effect compared to pure ketoconazole and the marketed formulation, which proved about synergistic effect of ketoconazole and coconut oil. Hence, herbal excipient-based cream of ketoconazole with coconut oil enhances patient compliance, simple administration, and regional bioavailability, and is more compelling for patients with fungal infections suffering from chronic mucocutaneous candidiasis.

5. References

1. Khosravi AR, *et al.* Chronic mucocutaneous candidiasis, a case study and literature review. Journal de mycologiemedicale. 2018; 28(1):206-210. https://doi.org/10.1016/j.mycmed.2018.02.004
2. Humbert L, Cornu M, Emmanuelle PL, *et al.* Chronic Mucocutaneous Candidiasis in Autoimmune Polyendocrine Syndrome Type 1. Front. Immunol. 2018; 9-2570. https://doi.org/10.3389/fimmu.2018.02570
3. Maertens JA. History of the development of azole derivatives. Clin Microbiol Infect. 2004; 10(1):1-10. Available from: https://pubmed.ncbi.nlm.nih.gov/14748798/ https://doi.org/10.1111/j.1470-9465.2004.00841.x
4. Gupta AK, Lyons DC. The Rise and Fall of Oral Ketoconazole. J Cutan Med Surg. 2015; 19(4):352-7. Available from: https://pubmed.ncbi.nlm.nih.gov/25775613/ https://doi.org/10.1177/1203475415574970
5. Ogbolu DO, Oni AA, Daini OA, Oloko AP. *In Vitro* antimicrobial properties of coconut oil on Candida Species in Ibadan, Nigeria. J Med Food. 2007; 10(2):384-387. Available

from: https://pubmed.ncbi.nlm.nih.gov/17651080/ https://doi.org/10.1089/jmf.2006.1209
6. Purushotham Rao K, Khaliq K, Kharat SS, Sagare P, Patil SK. Preparation and evaluation of o/w cream for skin psoriasis. Int J Pharm Biol Sci. 2010; 1:3. Available from: https://www.semanticscholar.org/paper/Preparation-and-Evaluation-O%2FW-Cream-for-Skin-Rao-Khaliq/1a8107de854d50c891a4aae3b3f19f06dd5316b1?sort=relevance&page=2&citedPapersSort=relevance&citedPapersLimit=10&citedPapersOffset=10
7. Kumar I, Thakur B, Sharma A, Thakur R. Formulation and evaluation of herbal oil-based itraconazole cream for fungal infection. Asian J Pharm Clin Res. 2020; 13(11):76-81. Available from: https://www.researchgate.net/publication/345388044_FORMULATION_AND_EVALUATION_OF_HERBAL_OIL-BASED_ITRACONAZOLE_CREAM_FOR_FUNGAL_INFECTION https://doi.org/10.22159/ajpcr.2020.v13i11.39172
8. Veena S, Kaur S, Kulkarni G. Formulation and evaluation of antifungal cream of chlorphenesin. Int J Curr Pharm Res. 13(5): 76-81. Available from: https://innovareacademics.in/journals/index.php/ijcpr/article/view/43163
9. Navindgikar NN, Kamalapurkar KA, Chavan PS. Formulation and evaluation of multipurpose herbal cream. Int J Curr Pharm Res. 2020; 12(3):25-30. Available from: https://innovareacademics.in/journals/index.php/ijcpr/article/view/38300/22576 https://doi.org/10.22159/ijcpr.2020v12i3.38300
10. Uddandu Saheb SK, Reddy AP, Rajitha K, Sravani B, Vanitha B. Formulation and evaluation of cream from naturally containing plant extracts. World J Pharm Pharm Sci. 2018; 7:851-62. Available from: https://www.wjpps.com/Wjpps_controller/abstract_id/8925
11. Prajakta S, Shahu K. Formulation and evaluation of vanishing herbal cream of crude drugs. Asian J. Pharm. 2020; 8(3):66-69. https://doi.org/10.22270/ajprd.v8i3.725
12. Kasar MP, Kale K, Phadtare GD. Formulation and evaluation of topical antifungal gel containing itraconazole. Int J Curr Pharm Res. 2018; 10:71-4. Available from: https://innovareacademics.in/journals/index.php/ijcpr/article/view/28470/15266 https://doi.org/10.22159/ijcpr.2018v10i4.28470
13. Maru AD, Lahoti SR. Formulation and evaluation of moisturizing cream containing sunflower wax. Int J Pharm Pharm Sci. 2018; 10:54-9. Available from: https://innovareacademics.in/journals/index.php/ijpps/article/view/28645/16009 https://doi.org/10.22159/ijpps.2018v10i11.28645
14. Shriwas S, Dwivedi S. Development and evaluation of herbal cream containing hydro-alcoholic extract of Clitoria Ternatea Linn (roots) used for the treatment of vaginal infection. Int J Womens Health Gynecol. 2020; 2(1):115. Available from: https://www.pubtexto.com/journals/international-journal-of-womens-health-and-gynecology/fulltext/development-and-evaluation-of-herbal-cream-containing-hydroalcoholic-extract-of-clitoria-ternatea-linn-roots-used-for-the-treatmen
15. Sharma A, Vaidya D, Gupta A, Kaushal M. Formulation and evaluation of wild apricot kernel oil-based massage cream. J. Pharmacogn. Phytochem. 2019; 8(1):1017-1021. Available from: https://www.phytojournal.com/archives/2019/vol8issue1/PartQ/7-6-70-996.pdf
16. Parshad L, Gurunath KP, Chandrasekar SB, Umashankar C, Pawar AT. Formulation and evaluation of herbal formulations (ointment, cream, gel) containing Tridax procumbens and Areca catechu. Int J Sci Res Innov Std. 2017; 6(3):97-100. Available from: http://www.jsirjournal.com/Vol6_Issue3_02.pdf https://doi.org/10.31254/jsir.2017.6302
17. Sabale V, Kunjwani H, Sabale P. Formulation and *in vitro* evaluation of the topical antiageing preparation of the fruit of Benincasahispida. J Ayurveda Integr Med. 2011; 2:124-8. Available from: https://pubmed.ncbi.nlm.nih.gov/22022154/ https://doi.org/10.4103/0975-9476.85550
18. Debebe D, Gabriel T, Brhane Y, Temesgen A, Nigatu M, Marew T. Comparative in-vitro evaluation of brands of clotrimazole cream formulations marketed in Ethiopia. J. Drug Deliv Ther. 2018; 8:17-2. https://doi.org/10.22270/jddt.v8i1.1546