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TO DEVELOPED COMBINATION OF KETOCONAZOLE AND CURCUMIN TOPICAL DELIVERY LOTION FOR TREATMENT OF FUNGAL INFECTION AND WHITE PATCHES ON SKIN

Chinmay Dahariya*[1], Anju Mishra[1], Ghanshyam Rathore[1] and Jhakeshwar Prasad[2]

[1]School of Pharmacy, Chouksey Engineering College, Lal Khadan, Masturi - Jairamnagar Rd, Bilaspur, (CG), Pin 495004.

[2]RITEE College of Pharmacy, Chhatauna, Mandir Hasaud, Raipur – 492101, C.G. India.

***Corresponding Author: Chinmay Dahariya**

School of Pharmacy, Chouksey Engineering College, Lal Khadan, Masturi - Jairamnagar Rd, Bilaspur, (CG), Pin 495004.

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ABSTRACT

The present study has been undertaken to development of Ketoconazole and Curcumin Topical Delivery Lotion for Treatment of Fungal Infection. Superficial fungal infections of the hair, skin are common yet often difficult to treat. Dermatophytes are one of the most common causes of tinea (capitis, manuum, pedis, cruris, corporis, barbae) and onychomycosis. Candidal infections and pityriasis versicolor, caused by Malassezia furfur, lipophilic yeast, are also among the most widespread superficial cutaneous fungal infections. Topical antifungal agents are compounded into different types of vehicles, such as creams, lotions, gels, or sprays. When applied to the skin surface, they readily penetrate into the stratum corneum to either kill the fungi or inhibit their growth, achieving clinical and mycologic eradication. Ketoconazole belongs to the class of drugs called azole antifungals. It works by stopping the growth of the fungus. The main classes of topical antifungal treatment modalities include the polyenes, the azoles, and the allylamine/benzylamines. Other topical antifungal agents include ciclopirox, a hydroxypyridone, thiocarbonate, haloprogin, and selenium sulfide. The high synergistic activity of combinations is encouraging and the potential drug delivery system for the combination of ketoconazole and Curcumin.

KEYWORDS: Fungal infection; Topical drug delivery systems; Ketoconazole; Curcumin.

1. INTRODUCTION

Fungal infection is one of the major burden of skin disease worldwide. The reported prevalence of fungal infection is about 40 million people in developing & underdeveloped countries. Fungi usually attack the skin surface during the initial phase and later invade into the deeper layer by desquamation. Candida species is one of the fungi which are most superficial cutaneous infection.[1,2,3,4,5] Fungal infection expressed in deeper layer of skin called cutaneous mycoses". Cutaneous fungal infections are commonly known as "Dermatophytes". Fungi commonly involved in different dermatomycoses include Tinea corporis, Tinea pedis and Tinea cruris.[6,7,8] Once, fungal infection further penetrates deeper skin tissue is known as "Subcutaneous mycosis".[9] Anti-fungal chemotherapy is used in the treatment of both superficial and deep fungal infection. Figure 1 show fungal infections commonly seen in the different layers of skin. Topical delivery of anti-fungal drugs is perhaps the best route against major skin dermatophytes, ensuring its direct access and higher retention rate at the target. Topical delivery further contributes to reduced systemic toxicity and avoid pre-systemic metabolism. Various drugs like ketoconazole, itraconazole, clotrimazole are used as topical administration to skin by spreading or rubbing.[10,11,12] Advantages of topical delivery further include site specific drug delivery, reduce systemic toxicity, increase patient compliance, increase the efficacy of treatment and improve bioavailability.[13] On the other hand, topical delivery of anti-fungal drugs can cause adverse skin reactions like allergic reaction and itching.[14,15,16] Further, conventional formulation needs high dose and repeated administration, associated with an increased risk of both local and systemic toxicity.

For this reason, novel drug delivery system is envisaged with an objective to reduce local side effects and increase their therapeutic efficacy. Ketoconazole is an imidazole antifungal that can be fungistatic to fungicidal depending on fungal sensitivity and serum levels of the drug. Ketoconazole is used to treat skin infections such as athlete's foot, jock itch, ringworm, and certain kinds of dandruff. This medication is also used to treat a skin condition known as pityriasis (tinea versicolor), a fungal infection that causes a lightening or darkening of the skin of the neck, chest, arms, or legs. Curcumin is a bright yellow chemical compound isolated from Curcuma longa

L. (turmeric) plants (Zingiberaceae).[17] Turmeric has been historically used in herbalism as a traditional medical remedy for cutaneous and gastrointestinal inflammation, weight control, and poor digestion.[18–20] Recently, conventional medicine is directing a lot of effort towards identifying novel, low-cost, safe molecules that may be used in the treatment of inflammatory, neoplastic, and infectious diseases. Numerous in vitro and in vivo studies have examined curcumin's anti-inflammatory, anticancer, and antimicrobial properties, both individually and combined with traditional treatments.

Vitiligo is a common autoimmune disease that progressively destroys melanocytes in the skin, resulting in the appearance of patchy depigmentation. This disfiguring condition frequently affects the face and other visible areas of the body, which can be psychologically devastating. The onset of vitiligo often occurs in younger individuals and progresses for life, resulting in a heavy burden of disease and decreased quality of life. Presentation patterns of vitiligo vary, and recognition of these patterns provides both diagnostic and prognostic clues. Recent insights into disease pathogenesis offer a better understanding of the natural history of the disease, its associations, and potential for future treatments.

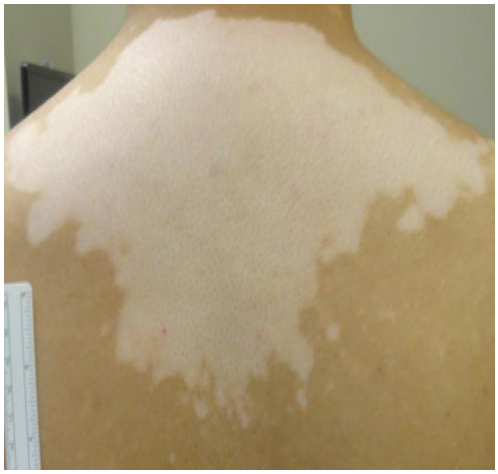


Fig 1: Vitiligo. Lesion on the upper aspect of the back before narrowband ultraviolet B light phototherapy.

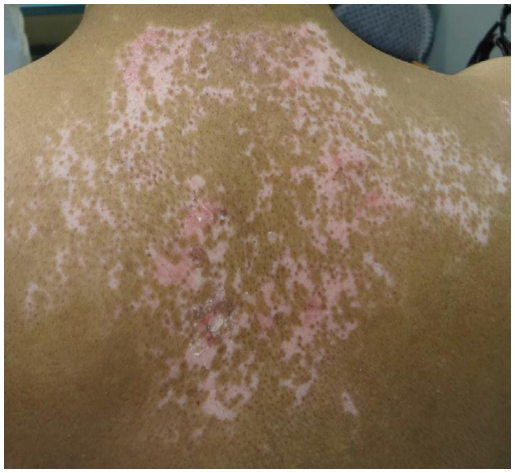


Fig 2: Vitiligo. Lesion on the upper aspect of the back after 5 months of narrow and ultraviolet B light phototherapy.

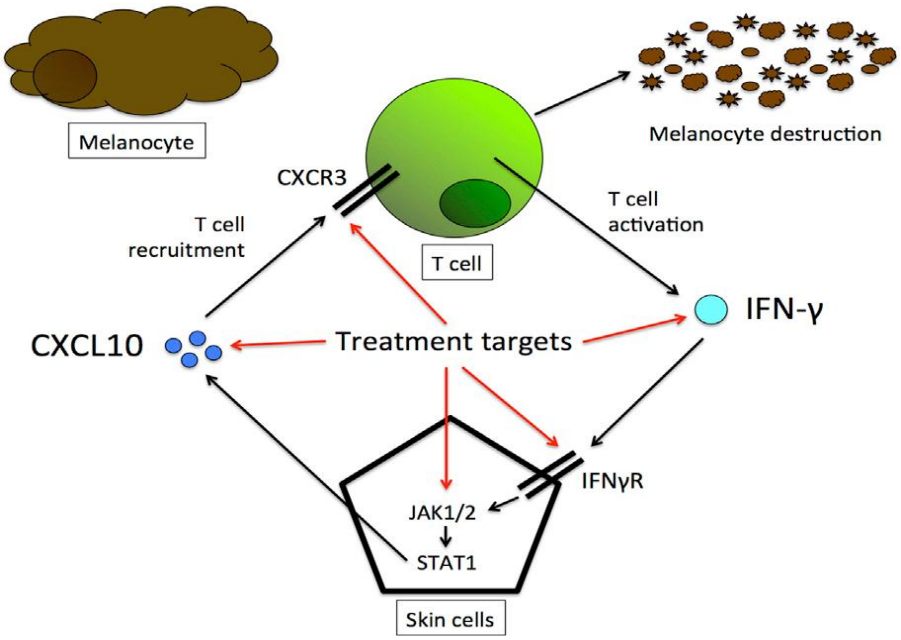


Fig 3: Schematic diagram of current understanding of vitiligo pathogenesis.

2. MATERIALS AND METHODS

Drug and Chemical Reagents

Ketoconazole was purchased from Hegde & Hegde Pharmaceutical LLP Malabar Hill, Mumbai, Maharashtra, Curcumin, Acetyl alcohol, Tween - 80, Glycerin, Triethanolamine and Benzyl alcohol was

purchased from Kashiwal Chemicals Raipur, Chhattisgarh, India. All other chemicals used was of highest analytical grade-commercially available. Drug excipients compatibility studies by FT-IR**.** IR spectra of drug were obtained using FT-IR Drug and excipients were analyzed by IR spectral studies using KBr. Pellet technique. In this method, the drug and KBr were mixed at the ratio of 1:1. Then these mixtures were pressed in to a pellet. The FT-IR spectra were recorded using KBr pellet method in the region 400-4000 cm-1. Spectra were recorded forpure drug.

3. RESULTS AND DISCUSSION

The lotion is Yellowish, appealing appearance and smooth texture, and they were all homogenous with no signs of phase separation. The pH of the lotion was found to 6.2. The pH should not be too acidic as it may cause skin irritation and should not be too alkaline as it may cause scaly skin. Viscosity was measured by Brookfield viscometer and it was found to be 150 cps. The shows results for drug content. All the formulations gave satisfying results for the percentage drug content. The result was found to be 9.74. The results for Extrudability are shown good extrudability. The following values were recorded for spread ability of formulated lotion and it has been found 2cm that the formulations have good spread ability. Results for physical evaluation of ketoconazole. Found to be the evaluation parameters like spread ability- easy, wash ability- washable, colour- yellowish, odor- odorless etc of the formulated gels were studied. Determination of λmax: The λmax was found to be 208 nm. The partition coefficient of ketoconazole was determinedin n-octanol: PBS buffer (pH 7.4) system. Melting point of ketoconazole is 146 °c. Thin layer chromatography: Rf value of ketoconazole was found to be 0.65. Determination of λmax: The λmax was found to be 424 nm. Melting point of Curcumin is 183°c. Thin layer chromatography: Rf value of Curcumin found to be 0.75.

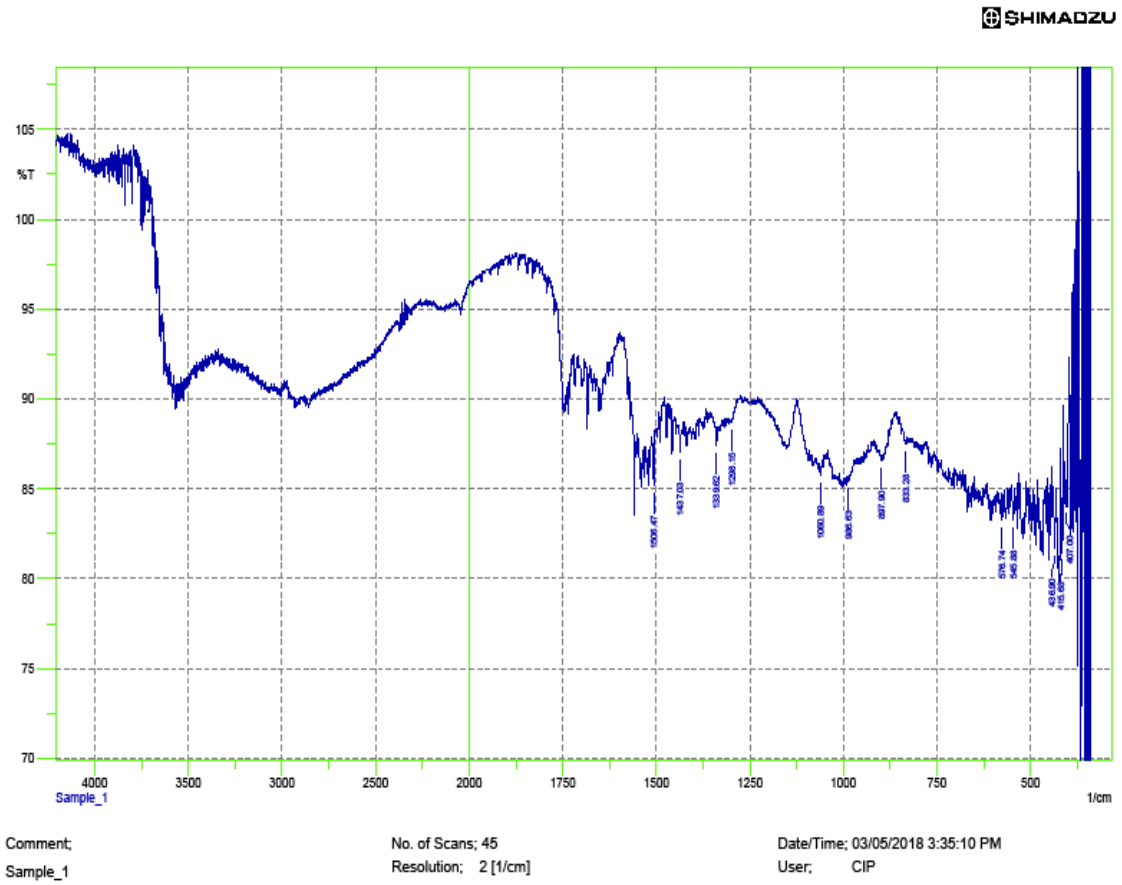
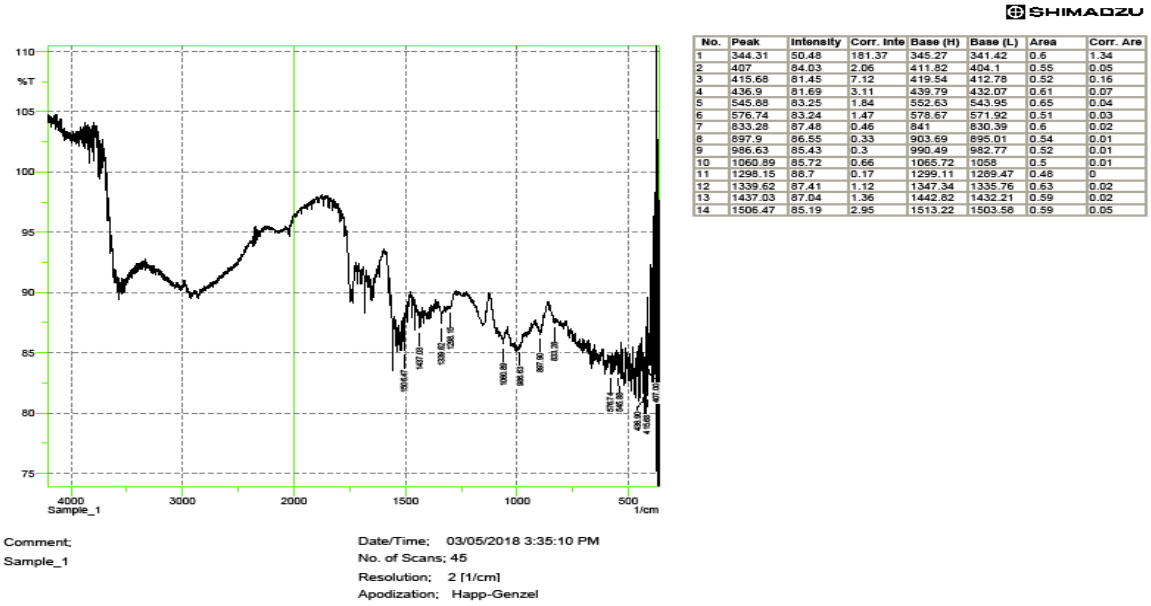


Fig 4: FT IR spectrum of ketoconazole.

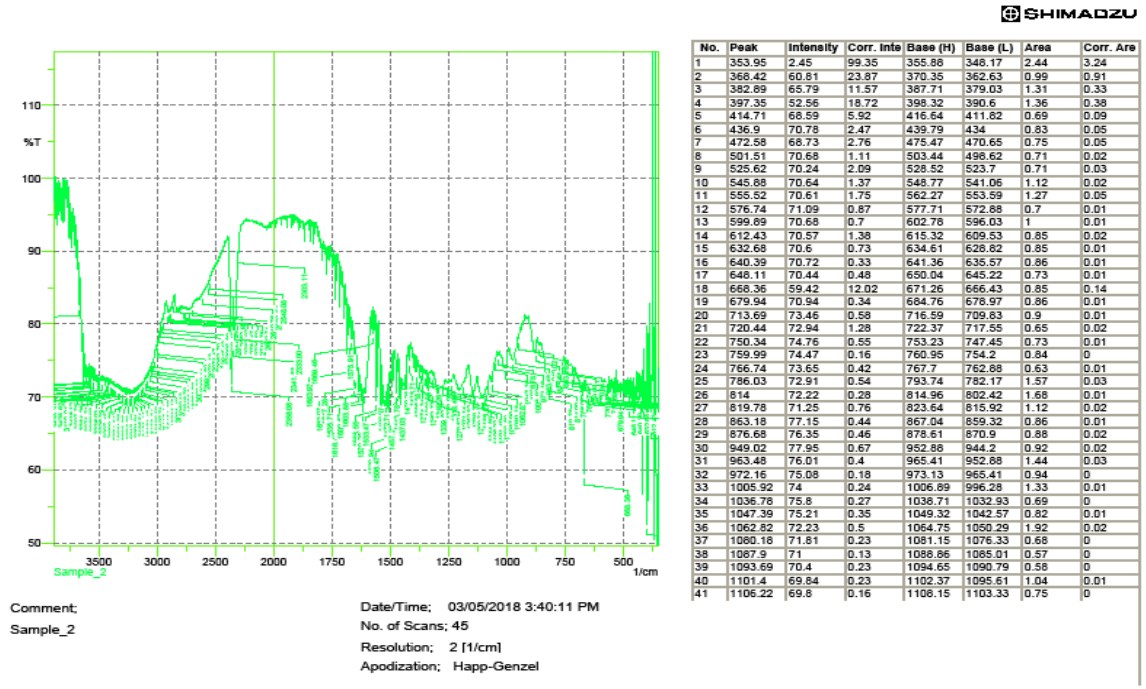
The IR spectrum of ketoconazole revealed the presence of peak at 3085.89 cm–1 due to N-H stretching while peaks at 2927.74 and 2740.66 cm–1 is due to aliphatic C-H stretching. Strong absorption peaks observed at 1743.53 and 1689.53 cm–1 were assigned to drug carbonyl stretching vibration (C=O). A peak at 1612 cm–1 indicates the aromatic ring and a peak at 1238 cm–1 is due to C-O Ar group. Peaks obtained in spectrum of pure drug (immediate & after 15 days) were similar to that given in standard.



No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	344.31	50.48	181.37	345.27	341.42	0.6	1.34
2	407	84.03	2.06	411.82	404.1	0.55	0.05
3	415.68	81.45	7.12	419.54	412.78	0.52	0.16
4	436.9	81.69	3.11	439.79	432.07	0.61	0.07
5	545.88	83.25	1.84	552.63	543.95	0.65	0.04
6	576.74	83.24	1.47	578.67	571.92	0.51	0.03
7	833.28	87.48	0.46	841	830.39	0.6	0.02
8	897.9	86.55	0.33	903.69	895.01	0.54	0.01
9	986.63	85.43	0.3	990.49	982.77	0.52	0.01
10	1060.89	85.72	0.66	1065.72	1058	0.5	0.01
11	1298.15	86.7	0.17	1299.11	1289.47	0.48	0
12	1339.62	87.41	1.12	1347.34	1335.76	0.63	0.02
13	1437.03	87.04	1.36	1442.82	1432.21	0.59	0.02
14	1506.47	85.19	2.95	1513.22	1503.58	0.59	0.05

Fig 5: FT IR spectrum of ketoconazole (After 15 days).

Peaks obtained in spectrum of pure drug (immediate & after 15 days) were similar to that given in standard.



No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	353.95	2.45	99.35	355.86	348.17	2.44	3.24
2	368.42	60.81	23.87	370.35	362.63	0.99	0.91
3	382.89	65.79	11.57	387.71	379.03	1.31	0.33
4	397.35	52.56	18.72	398.32	390.6	1.36	0.38
5	414.71	68.59	5.92	416.64	411.82	0.69	0.09
6	436.9	70.78	2.47	439.79	434	0.83	0.05
7	472.58	68.73	2.76	475.47	470.65	0.75	0.05
8	501.51	70.68	1.11	503.44	498.62	0.71	0.02
9	525.62	70.24	2.09	528.52	523.7	0.71	0.03
10	545.88	70.64	1.37	548.77	541.06	1.12	0.02
11	555.52	70.61	1.75	562.27	553.59	1.27	0.05
12	576.74	71.09	0.87	577.71	572.88	0.7	0.01
13	599.89	70.68	0.7	602.78	596.03	1	0.01
14	612.43	70.57	1.38	615.32	609.53	0.85	0.02
15	632.68	70.6	0.73	634.61	628.82	0.85	0.01
16	640.39	70.72	0.33	641.36	635.57	0.86	0.01
17	648.11	70.44	0.48	650.04	645.22	0.73	0.01
18	668.36	59.42	12.02	671.26	666.43	0.85	0.14
19	679.94	70.94	0.34	684.76	678.97	0.86	0.01
20	713.69	73.46	0.58	716.59	709.83	0.9	0.01
21	720.44	72.94	1.28	722.37	717.55	0.65	0.02
22	750.34	74.76	0.55	753.23	747.45	0.73	0.01
23	759.99	74.47	0.16	760.95	754.2	0.84	0
24	766.74	73.65	0.42	767.7	762.88	0.63	0.01
25	786.03	72.91	0.54	793.74	782.17	1.57	0.03
26	814	72.22	0.28	814.96	802.42	1.68	0.01
27	819.78	71.25	0.76	823.64	815.92	1.12	0.02
28	863.18	77.15	0.44	867.04	859.32	0.86	0.01
29	876.68	76.35	0.46	878.61	870.9	0.88	0.02
30	949.02	77.95	0.67	952.88	944.2	0.92	0.02
31	963.48	76.01	0.4	965.41	952.88	1.44	0.03
32	972.16	75.08	0.18	973.13	965.41	0.94	0
33	1005.92	74	0.24	1006.89	996.28	1.33	0.01
34	1036.78	75.8	0.27	1038.71	1032.93	0.69	0
35	1047.39	75.21	0.35	1049.32	1042.57	0.82	0.01
36	1062.82	72.23	0.5	1064.75	1050.29	1.92	0.02
37	1080.18	71.81	0.23	1081.15	1076.33	0.68	0
38	1087.9	71	0.13	1088.86	1085.01	0.57	0
39	1093.69	70.4	0.23	1094.65	1090.79	0.58	0
40	1101.4	69.84	0.23	1102.37	1095.61	1.04	0.01
41	1106.22	69.8	0.16	1108.15	1103.33	0.75	0

Fig 6: FT IR spectrum of ketoconazole+ Sodium starch glycolate (After 15 days).

Thin Layer Chromatography

Using silica gel as the coating substance and a mixture of 4 volumes of methanol, 4 volumes of dichloromethane, 2 volumes of ammonia (~260 g/l) TS, and 1 volume of acetonitrile as the mobile phase. Apply separately to the plate as 1-cm bands, 5 µl of each of 2 solutions containing (A) 10mg of Ketoconazole per mL, and (B) 10 mg of Ketoconazole RS per mL Placean evaporating-dish containing 50ml of ammonia (~260g/l) TS in the chromatographic chamber. Expose the plate to the ammonia vapour in the closed chamber for 15 minutes. Withdraw the plate and transfer to another chromatographic chamber containing the mobile phase to develop. After removing the plate from the chromatographic chamber, allow it to dry in air for about 15 minutes, and examine the chromatogram in ultraviolet light (254nm and 365nm).

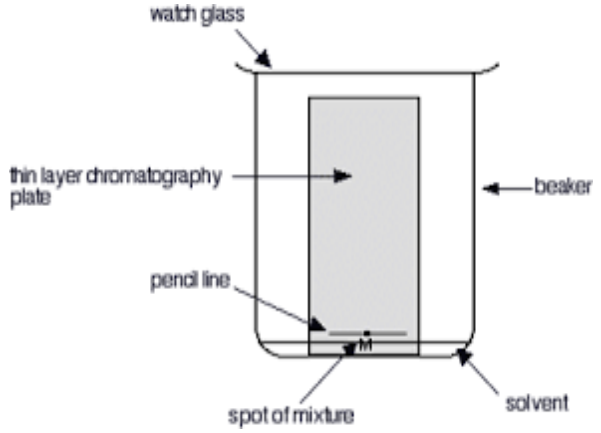


Fig 7: TLC Plate.

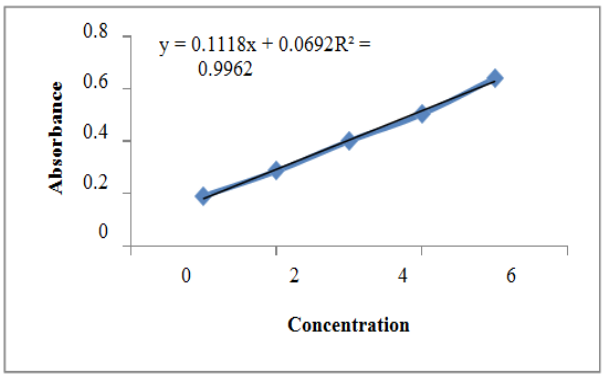


Fig 8: Determination of maximum wavelength of Curcumin by UV.

Table 1: Standard calibration curve of ketoconazole.

S. No.	Concentration	Absorbance
1.	0.1	0.191
2.	0.2	0.286
3.	0.3	0.401
4.	0.4	0.504
5.	0.5	0.641
6.	Slop	0.111
7.	Correlation	0.996

Table 2: Drug content analysis of Drug content analysis of Curcumin (1:1).

S. No.	Theoretical drug content per 100 ml (lg/ml)	Percentage drug content	Practical drug content per 100 ml (lg/ml)	Percentage drug content (%)
1.	10	100	25	27.3%

Table 3: Drug content analysis of Curcumin (1:2).

S. No.	Theoretical drug content per 100 ml (lg/ml)	Percentage drug content	Practical drug content per 100 ml (lg/ml)	Percentage drug content (%)
1.	10	100	16.66	28.5%

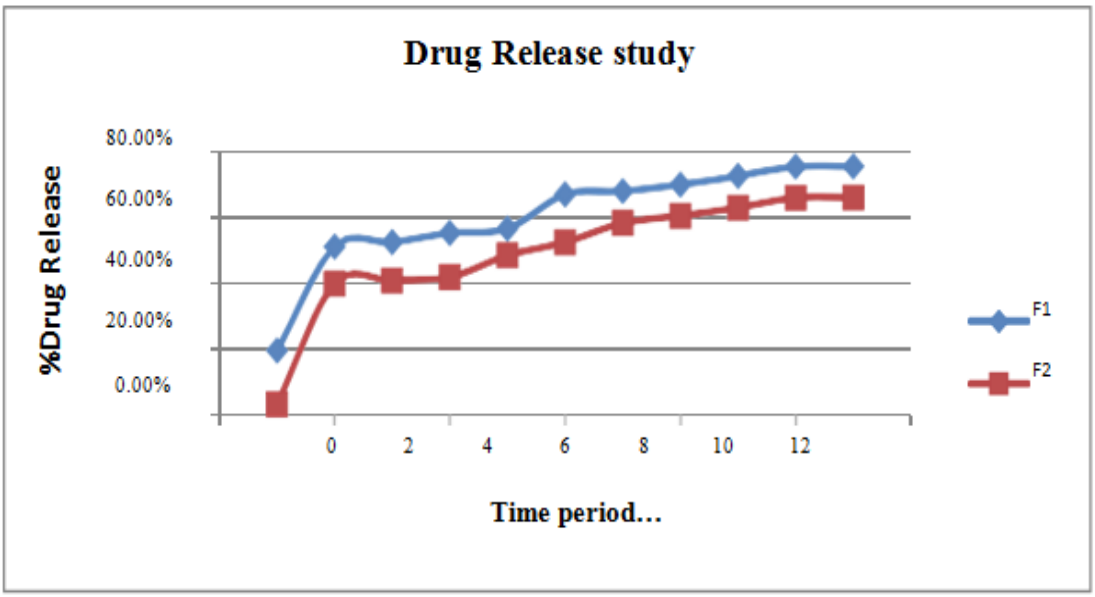


Fig 9: Drug release study of Curcumin 1:1 and 1:2.

Table 4: Formulation code for lotion preparation.

S. No.	Ingredients	F1	F2	F3	F4	F5
1	Ketoconazole (gm)	3	3	3	3	3
2	Curcumin (gm)	4	4	4	4	4
3	Benzyl alcohol (ml)	1	1	1	1	1
4	Tween 80 (ml)	1.5	1.25	1	1.75	1
5	Glycerine (ml)	5	10	50	10	20
6	Triethanolamine (gm)	3	2.5	2.1	2	3.2
7	Octyl stearate (gm)	2	2.1	1	3	2

4. EVALUATION AND CHARACTERIZATION OF LOTION

Table 5: Drug content of the formulations.

Formulation Code	Drug Content
F1	95.4
F2	92.86
F3	93.4
F4	96.74
F5	95.113

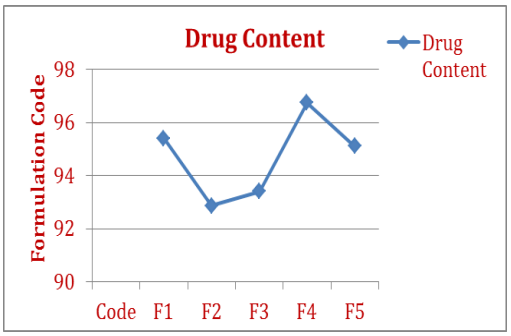


Fig. 10: The *In vitro* drug content of ketoconazole lotion.

Table 6: *In-vitro* drug release.

Formulation Code	Percentage ketoconazole Released after 1 hour	Percentage ketoconazole Released after 3 hours	Percentage Ketoconazole Released after 6 hours
F1	15.2	24.5	62.3
F2	14.1	23.3	56.5
F3	12.7	20.6	52.4
F4	11.5	22.7	50.5
F5	13.6	17.5	47.3

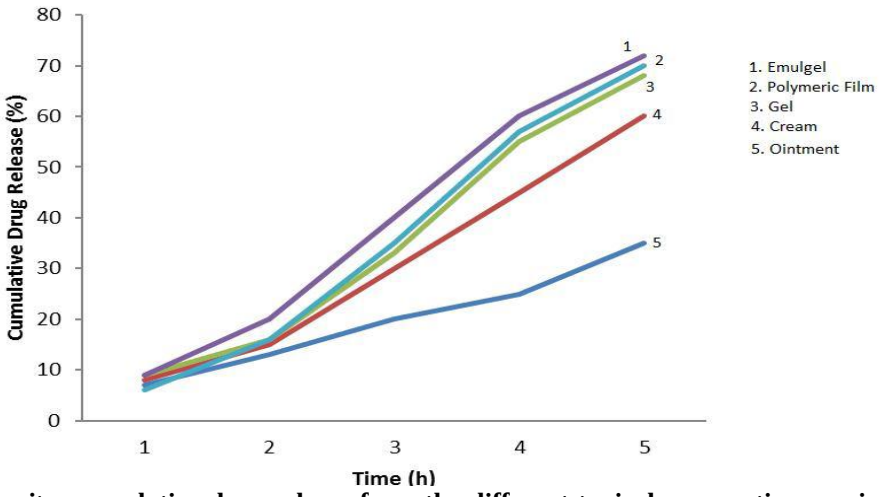


Fig. 11: The *In vitro* cumulative drug release from the different topical preparations against time as tested by Franz diffusion cell.

5. CONCLUSION

The formulation of antifungal agents along with ketoconazole and antifungal activity. The results of different chemical and physical tests of lotion showed that it could usetopically in order to protect against skin infections caused by fungus or bacteria. Ketoconazole is an imidazoles derivative, used for the topical as well as systemic fungal infections. The bioavailability of ketoconazole is 90%. In thepresent study, an attempt was made to formulate topical lotion of miconazole for efficient delivery of drug across the skin. A suitable method of analysis of drug was UV spectrophotometric. ketoconazole showed maximum absorption at a wavelength of 208 nm in phosphate buffer. Various formulations (F1, F2…F5) were developed by using Triethanolaminefor local release of ketoconazole for the treatment of fungal infections by using Tween 80. Developed formulations of ketoconazole were evaluated for the physiochemical parameters such as drug content, viscosity, spread ability, in vitro diffusion. Viscosity studies of various formulations revealed that formulation F1 is bettercompare to others. Thus, the objective of the present work of formulation and evaluating of ketoconazole.

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