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FORMULATION AND EVALUATION OF TOPICAL ITRACONAZOLE NANOGEL

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Keywords:

Itraconazole, Inclusion complex, Nanocomposite, Topical gel (Nanogel)

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ABSTRACT: Itraconazole is a triazole antifungal category drug used for the treatment of local &Systemic fungal infections. Itraconazole is not recommended to neutropenic and other immune-compromised patients who have difficulty swallowing the oral capsule formulation, and it has many side effects. Commercially, Itraconazole topical gel preparation is not available in the market; thus, this formulation is made for better patient compliance, reduces the drug dose, and avoids side effects like liver damage and kidney damage avoiding first-pass metabolism. The gel was formulated by preparing nanocomposite with polymer inclusion complex by microwave-induced diffusion technique. Which ultimately results in enhancing the water solubility of nanocomposites. The resultant polymer-based nanocomposite retains the inherent properties nanoparticles, while providing higher stability, and this nanocomposite is incorporated into the gel base. Prepared nanogel Prepared nanogel is characterized by pH determination, Spreadability, Viscosity measurement, In-vitro diffusion, antifungal activity. Among the formulation, F_3 was selected as the best formulation having % CDR of 76.57 % & more Antifungal activity than the marketed formulation. The results indicated that nanocomposite-based nanogel is a promising approach for the transdermal delivery of Itraconazole.

INTRODUCTION: Nowadays, one of the common dermatological problems related to the skin is a fungal infection. The physicians have extended choices for treatment from solid dosage to semisolid dosage form to liquid dosage formulation. Between them, topical formulation clear transparent gel is mostly accepted in cosmetics and pharmaceuticals [1]. The fungal infection may be attributed to superficial infections affecting the skin, nails, hairs, and mucous membranes or systemic affecting the body as a whole.

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Subcutaneous infection is mainly restricted to the subcutaneous tissue and dermis but may be severe to the epidermis and deeper; for example, systemic bone infections tend to occur more frequently in immunocompromised patients such as those with AIDS [2]. There are some common species to result in infection, such as Aspergillus, Candida, Cryptococcus, Tenia, Pneumocystis, and Histoplasma.

This species causes fungal infections such as finger and toenail infection, athlete's foot, Yeast infection, oral thrush, and ringworm [3]. Onychomycosis is a common antifungal infection of the nail bed with nail deformity, pain and disability primarily caused by *Trichophyton rubrum*, which is dermatophytes [4]. There are many oral formulations of the drug in marketed formulation for curing fungal infection, such as ketoconazole, griseofulvin, Itraconazole,

fluconazole, ketoconazole and terbinafine which is not used currently. However, oral therapy results in some disadvantages such as drug interaction, side effects, high cost of medication, and the duration of treatment. Systemic use of azole category drug cause hepatotoxicity, especially during extended use. Therefore topical delivery of drugs has various advantages over systemic administration [5]. Topical application of the drug offers many advantages, such as the delivery of the prescription to the site of action for an extended period at the affected site, increasing the contact time, and mean resident time of the drug at the applied area.

Nanocomposite hydrogel, which is molecular networks physically or covalently cross-linked with nanoparticles or nanostructure, have been suggested as innovative means to overcome some of the challenges associated with using hydrogel in control drug delivery system [6]. Current advances in the field of pharmacology and nanotechnology have drawn attention to nanoparticles as novel drug delivery systems [7]. There are various types of nanoparticles, such as carbon-based nanomaterial's, polymeric nanoparticles, and metallic nanoparticles are merged with the polymeric network to create reinforced nanocomposite hydrogel [8]. The nanocomposite is defined as multiphase solid material where at least one phase has one, two, or three dimensions in are nano-size range. Microwave-induced diffusion (MIND) is a green and effective method for generating nanocomposites. These nanoparticles are incorporated into the gel base and form nanocomposites nanogel [9].

MATERIAL AND METHOD: Itraconazole to be gift sample from Alembic Ltd, Gujarat. Polymer 2-hydroxy propyl beta-cyclodextrin, Carbapol 974 p, Propylene glycol, Triethanolamine, Methylparaben, Tween 20 from Himedia Laboratories Pvt. Ltd Mumbai. Methanol, DMSO obtained from S.D fine chemicals Mumbai.

Preparation of Nanocomposite-Based Nanogel: Physical mixture of Itraconazole and 2- Hydroxy propyl beta-cyclodextrin was made by homogeneous mixing. The weight-to-weight ratio of the drug to the carrier was taken from 1-0.5 to1-3 keep the drug constant. The physical mixture was prepared by homogeneous mixing of drug and carrier in mortar and pestle. To this mixture 5ml of water was added for each gram of the drug carrier mixture to make homogeneous slurry. The water was added for the hydration of the polymer. A fixed amount of dispersion was placed in a glass beaker and irradiated with microwave radiations for a different time at power 640w (power grill 20 black ONIDA) with continuous stirring. Composites were grind in mortar and pestle. The composites of the drug with polymer were denoted with symbol ITZ- 2-HP-β-CD [10]. optimization of various batch composite (drug carrier mixture ratio) for nanogel preparation is done by testing drug content study, further do TEM for particle size analysis in nano size. To prepare nanogel, These nanocomposite (optimised drug-carrier mixture) containing drug dissolve in methanol. This solution adds pre-soaked carbapol gel with continuous stirring and adjusts the PH with Triethanolamine [11].

TABLE 1: FORMULATION OF NANOGEL

Sr. no.	Ingredients % w/w	F1	F2	F3
1	Itraconazole (Nanocomposite) (gm)	0.01%	0.01%	0.01%
2	Carbapol (gm)	1.5	2	1
3	Propylene glycol(ml)	2	2	2
4	Methanol (ml)	5	5	10
5	Tween 20 (ml)	1	1.25	1.50
6	Methyl paraben (gm)	0.03	0.03	0.03
7	Glycerine (ml)	10	10	10
8	Triethanolamine (ml)	q.s	q.s	q.s

Characterization of Prepared Nanocomposite and Nanogel:

Melting Point: The melting point is the primary criterion for selecting a drug for the formulation. With the help of melting point apparatus (veego), the drug was filled in a capillary glass tube placed in melting point apparatus containing liquid paraffin oil as a heating medium & the melting point of Itraconazole was recorded [12].

Fourier Transform Infrared Spectroscopy (FTIR): Drug–FTIR did an excipients

compatibility study. FTIR spectrum of pure drug Itraconazole, HP-β-CD, and nanocomposite (Drug – polymer combination) was recorded. The drug and polymers, separately and in combination with each other, were mixed with KBr in the ratio of 1:100 for the determination of spectrum range from 400cm^{-1} to 4000cm^{-1} using FT-IR Spectrophotometer (Shimadzu DR-8031, Japan) [13].

Drug Content Analysis: The drug content study determined the amount of drug incorporated in the nanocomposites Amount of Itraconazole in Nanocomposites determined by dissolving them in 25 ml of methanol.

The resulting solution was filtered through a 0.2-micron membrane filter. The Itraconazole content in the methanolic extracts was analysed by using a UV-visible spectrophotometer at a wavelength of 270 nm, methanol as blank & absorbance of polymer 2-HP-β-CD negligible [13, 14].

Transmission Electron Microscopy (TEM): Transmission electron microscope examined for the particle size and shape of drug crystal dispersed in the polymer. TEM (TEM: JEOL/JEM 2100) images were obtained by dry powder redispersed in water and placed on a Cu grid, and then the grid was inserted into the TEM column for examination [15].

Characterization of Nanogel [16, 17]:

pH: pH of the final formulation was determined by using a pH meter. The weight quantity of 5 gm of each nanogel formulation was transferred in 10 ml of beaker and measured using the digital pH meter (Systronics MK VI, Mumbai).

Total Drug Content: Content of Drug concentration in nanogel measured by UV-Visible spectrophotometer. Itraconazole content in gel was measured by dissolving known quantity nanogel into solvent methanol by sonication. Absorbance was measured after suitable dilution at 270 nm in a UV-VIS spectrophotometer (UV-1800, Shimadzu, Japan).

Rheological Study: The viscosity of different nanocomposite gel formulations was determined at 37°C using a brook field viscometer (Brookfield DV-E viscometer). The spindles S-96 were dipped in a beaker containing Nanogel, and viscosity was recorded at different rpm.

Spreadability: It indicates the extent of the area to which gel readily spreads on application to the skin or affected part. The therapeutic potency of a formulation also depends upon its spreading value. Spreadability is calculated in terms of time in seconds taken by two slides to slip off from the gel which is placed in between the slides under the direction of a certain load. The longer the time taken for separating two slides, the better the spreadability. It is calculated by using the formula:

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

Where, M = wt. tied to upper slide L = length of glass slides T = time taken to separate the slides.

Extrudability Test (Tube Test): The extrudability test is based upon the determination of weight required to extrude a 0.5 cm ribbon of nanogel in 10 sec from lacquered collapsible aluminium tube. The extrudability value was calculated using the following formula:

$$\text{Extrudability} = \text{Weight applied to extrude Nanogel from tube (gm)} / \text{Area (cm}^2\text{)}$$

***In-vitro* Diffusion Study:** The *in-vitro* skin study was performed by using Franz diffusion cells with an effective diffusion area of 2 cm^2. The dialysis membrane was soaked for 12 h and clamped between the donor and receptor compartments of the cell. The Nanocomposites gel containing Itraconazole (10mg) was placed in the donor comportment. The receptor compartment was filled with a phosphate buffer with PH 5.5 as the medium and maintained at 37± 1°C and stirred at 600 rpm samples were withdrawn from the receptor compartment at regular intervals for period 8 hours with the same amount replaced to maintain sink condition. The sample was analyzed by UV–visible spectrophotometer at 270 nm. The amount of Itraconazole released at various time intervals was calculated with the help of a calibration curve with phosphate buffer PH 5.5 and plotted against time.

Antifungal Activity: Antimicrobial activity was studied by Preparation of Agar medium and determining ITZ's and the complex's activity. The medium was prepared by dissolving 65 gm of Sabouraud Dextrose Agar (mycological peptone 10 mg, dextrose 10 mg, agar no. 1) in one liter of distilled water was heated with frequent agitation

and boiled for 1 min to dissolve the power completely. Autoclaving was conducted at 121°C for 10 min. The agar was poured into 150 mm diameter plastic plates and left to solidify. Wells of 6 mm diameter were punched out using a steel borer. An agar cup diffusion technique was applied using *Candida albicans* and *Candida parapsilosis* as the test organism.

The ITZ nanocomposite gel was tested by placing a 100ul sample of the equivalent of 8 ug/ml ITZ nanocomposite gel in dimetylsulfoxide (DMSO) in each well. The diameter of zone of inhibition was measured after 24 h incubation at 37°C. The activity of ITZ nanocomposites nanogel and marketed formulation compared by this test.

Stability Test: According to ICH guidelines, prepared Itraconazole nanogel formulations were stored away from light in the collapsible tube at 40±2°C/75% RH and 30±2°C/60% RH for 2 months. After storage, the samples are tested for their Physical appearance, pH and Drug content.

RESULT:

Melting Point: The melting point of Itraconazole was found to be 169.2°C which corresponds to the melting point of Itraconazole.

FTIR: The absorbance peaks at 945.12, 1379.10, 1697.36, 2823.79 & 3319.25 cm^{-1} corresponding to ITZ pure drug.

The peak absorbance at 945.12 to 3319.25 cm^{-1} was shifted to lower frequencies at 898.83, 1377.12, 1696.31, 2847.79 & 3308.75 cm^{-1}, respectively. This finding supports the hypothesis that ITZ molecules have suffered a chemical change during the complexation process.

The prominent absorbance peak of HPBCD at 3400 cm^{-1} (OH), 2930 cm^{-1} (C-H), 1157 cm^{-1}(C-O) for stretching vibrations, 1655 cm^{-1} (H-O-H) for bending vibration and 1030 cm^{-1} were observed in all prepared ITZ-HPBCD complexes indicating the presence of a host-guest interaction and confirming complex formation.

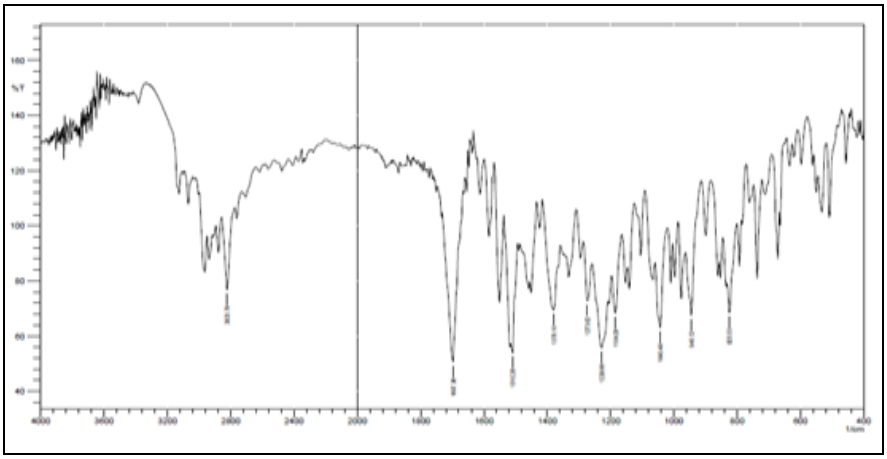

FIG. 1: FTIR OF DRUG ITZ

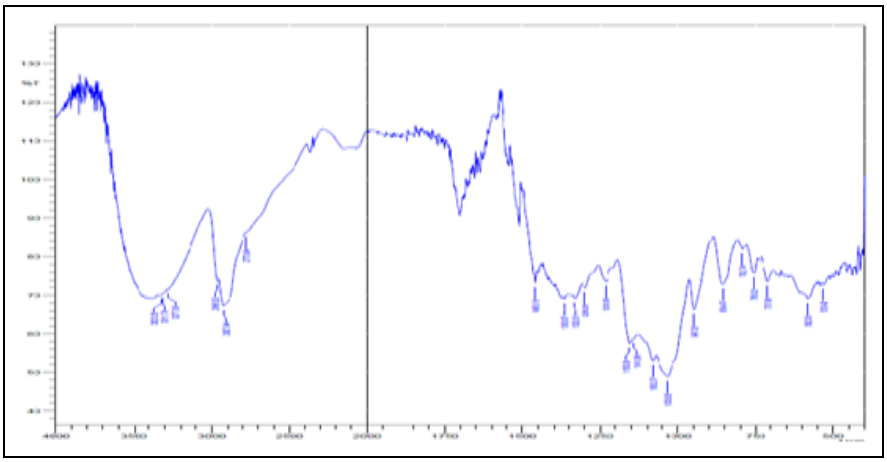

FIG. 2: FTIR OF DRUG HPBCD

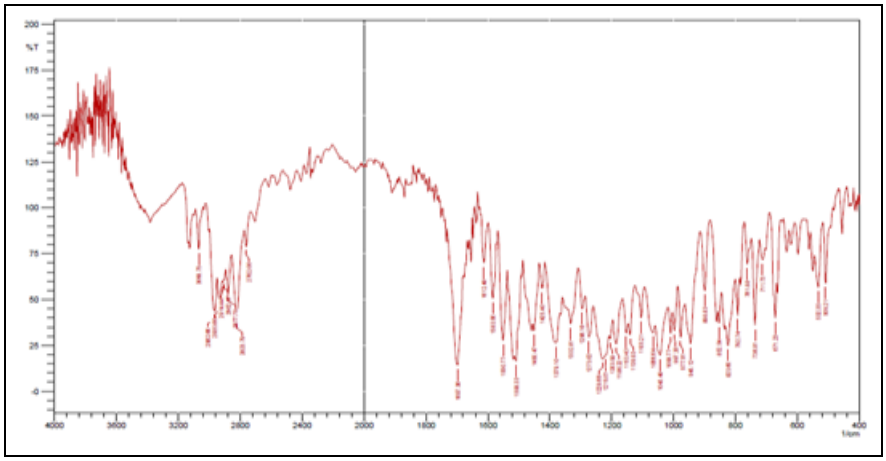

FIG. 3: FTIR OF NC

Drug Content: Entrapment efficiency of the drug in nanocomposite is determined by drug content analysis. It is found to be 94 to 97.27 % of the drug was incorporated in Nanocomposites.

TABLE 2: DRUG CONTENT ANALYSIS OF NANOCOMPOSITE

Sr. no.	Ratio	Drug Content
1	1:1	94.23%
2	1:2	95.68%
3	1:3	97.27%

TEM (Transmission Electron Microscopy): A transmission electron microscope study was performed to confirm the size and shape of the drug crystal dispersed in the polymer.

From **Fig. 4** and **5,** it can be concluded that drug crystals are irregular in shape and dispersed in the polymer. Drug crystals and polymers completely embedded with each other form complex sizes in nm.

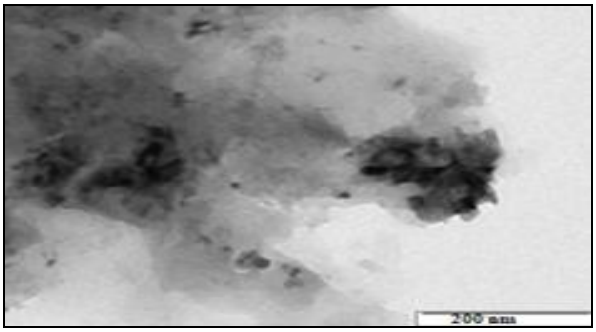

FIG. 4:

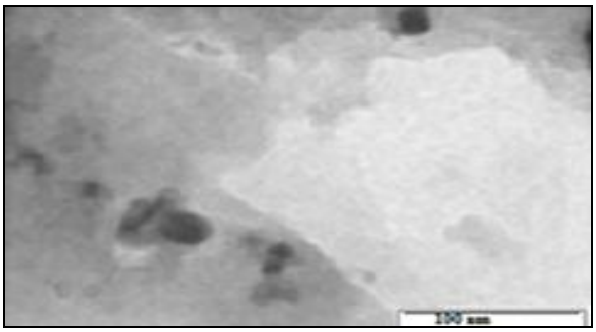

FIG. 5:

Determination of pH: Since the topical system is directly applied to the skin pH should be compatible with the skin pH. pH of all formulations were found to be between 5.4-5.6, which is acceptable for skin permission.

TABLE 3: PH OF NANOGEL

Formulations	pH (Mean±S.D.)
F_1	5.42 ±0.06
F_2	5.36 ±0.06
F_3	5.56 ±0.03

Viscosity Measurement: To study the Rheological behaviour of the Nanogel viscosity measured. This system indicates that it was shear thinning, showing a decrease in viscosity at the increasing shear rates. As the shear stress increases, the normally disarranged molecules of the gelling materials are caused to align their long axis in the flow direction. Such orientation reduces the internal resistance of the material and hence decreases the viscosity.

TABLE 4: VISCOSITY OF THE NANOGEL

Sr. no.	Rpm	Viscosity in (CP)
1	10	22800
2	30	17500
3	50	11600

Drug Content Determination: The drug content of all formulations was found to be in the range of 94% to 97.62%; hence, uniformity of drug content was found satisfactory.

TABLE 5: % DRUG CONTENT OF THE NANOGEL

Sr. no.	Formulations	Drug content (%)
1	F_1	94.23 ± 4.04
2	F_2	95.52 ± 0.57
3	F_3	97.62 ± 3.60

Spreadability: It depends upon the viscosity of the formulation and the physical characteristics of the polymers used in the formulation. A more viscous formulation would have poor spreadability. It indicates the extent to which gel readily spreads on application to the skin or affected area. F_3 formulation spreading coefficient 11.64 gm cm^2 may be due to the optimum concentration of the gelling agent.

TABLE 6: SPREADABILITY OF NANOGEL

Formulations	Spread ability ($gm.cm^2$)
F_1	10.70
F_2	11.06
F_3	11.64

Extrudability Test: The extrudability of the Nanogel depends upon the viscosity of that Nanogel. The less viscous the Nanogel, lesser the force required to remove it from tube, thus showing better extrudability. The extrudability data of formulated Nanogel is shown in the following table.

TABLE 7: EXTRUDABILITY TEST

Formulations	Extrudability
F_1	++
F_2	+
F_3	+++

(+ = Fair, ++ = good and +++ = excellent) F3 showed best extrudability than other formulations as it contained Carbapol 974 p in 1%.

***In-vitro* Diffusion Study:** The higher drug release was observed with formulation F_3. This may be due to the minimum amount of gelling agent, *i.e.*, Carbapol 974p. The minimum amount of gelling agent causes less viscous formulation than other Nanogel formulations, leading to less packed nanogel matrix which easily get braked, thus higher drug release.

TABLE 8: CUMULATIVE AMOUNT OF ITRACONAZOLE DIFFUSED (%) FROM NANOGEL FORMULATIONS USING MODIFIED DIFFUSION CELL

Time (Hrs.)	% Cumulative Drug Release		
	F_1	F_2	F_3
0	0	0	0
1	8.811 ± 0.057	13.65 ± 0.023	22.64 ±1.016
2	13.97 ± 3.072	18.54 ±2.011	29.34 ±0.057
3	19.34 ± 1.047	26.13 ± 0.034	36.68± 0.026
4	26.15 ± 0.010	31.53 ± 1.032	46.91± 0.025
5	37.42 ± 0.074	44.24 ± 0.057	54.38± 0.015
6	46.23 ± 0.011	51.19 ± 0.059	61.79 ± 0.02
7	51.63 ±1.015	58.24 ± 0.043	68.46 ±0.073
8	58.94 ± 0.025	65.33 ± 0.023	76.57 ±0.058

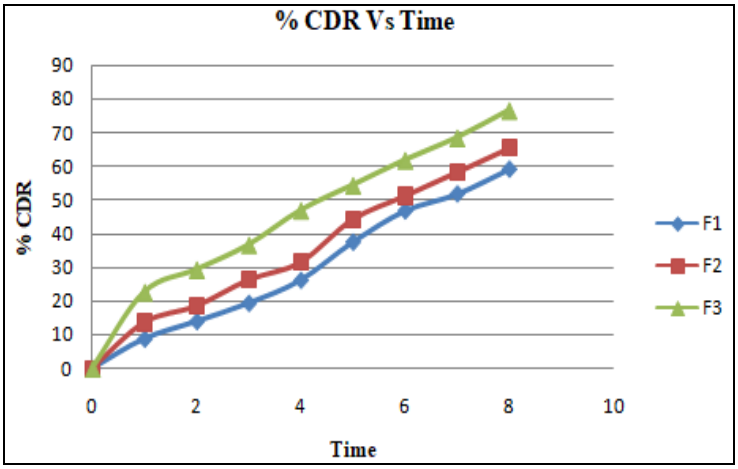

FIG. 6: RELEASE PROFILE OF ITRACONAZOLE NANOGEL

Drug Release Kinetics: The release rate of the drug from F_3 formulation is best fitted to the Higuchi matrix model.

TABLE 9: DRUG RELEASE KINETICS

Formulation cod	Zero Order Kinetics	First Order Kinetics	Higuchi Model
F_3	0.9524	0.8951	0.9861

Antifungal Activity: Antimicrobial activity was studied for the ITZ Nanogel F3 and the marketed formulation. The antifungal activity against *Candida albicans* and *Candida parapsilosis* was studied it was observed that ITZ Nanogel show the more zone of inhibition area as compared to the marketed formulation against both organism. *C. parapsilosis* was found to be more sensitive than the *C. albicans* due to this zone of inhibition for *C. parapsilosis* found.

TABLE 10: ZONE OF INHIBITION OF FORMULATION NANOGEL AND MARKETED PREPARATION

Sample	Mean Diameter of the Zone of Inhibition with *C. albicans* (mm)±SD	Mean diameter of the zone of the inhibition with *C. parapasilosis* (mm) ±SD
ITZ Nanogel (F3)	36.33 ±2.5018	37.16 ± 1.52
Marketed Formulation	34.70 ± 0.57	35.64 ± 1.04

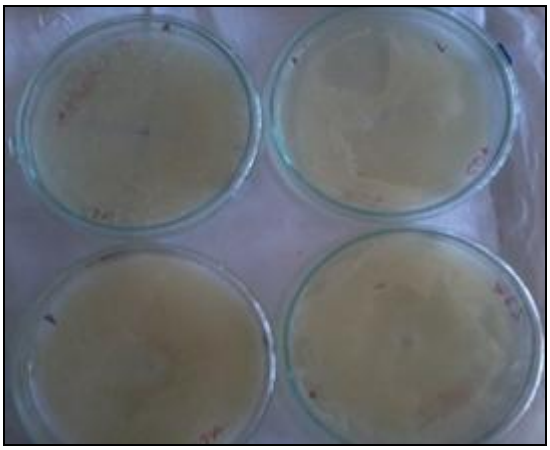

FIG. 7: ZONE OF INHIBITION OF NANOGEL FORMULATION

Stability Studies: There was no significant change during the stability study. The following result concludes that formulation was stable at 30 ± 2ºC 60% RH due to decreasing small value of drug content.

TABLE 11: STABILITY STUDIES

Sr. no.	Properties	Observation
1	Colour (Initial)	White
2	Colour (After two Month)	White
3	PH (initial)	5.56
4	PH (After two Month)	5.56
5	% Drug content at 30± 2ºC 60% RH	96 ± 1.15 %
6.	% Drug content at 40 ± 2º C 75% RH	60 ± 0.08 %

CONCLUSION: The optimized batch of nanocomposite shows a better percentage yield. IR spectra indicate that there is a formation of a complex in the drug and carrier. From the TEM results, Drug crystal and polymer completely embedded with each other form complex having a size of nm. The optimized nanocomposite incorporated into nanogel F3 formulation shows a greater % drug release. The antifungal activity also shows a good result compared to the marketed formulation. Thus, the objective of the present work of preparation and evaluation of Itraconazole nanocomposite based on nanogel has been achieved with success.

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