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DESIGN, DEVELOPMENT AND EVALUATION BIGEL BASED TOPICAL DRUG DELIVERY OF AMPHOTERICIN-B AND KETOCONAZOLE IN THE TREATMENT OF FUNGAL INFECTION

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Abstract

Topical drug delivery systems provide an efficient means of treating localized fungal infections by enhancing therapeutic efficacy while minimizing systemic side effects. This study aimed to design, develop, and evaluate a bigel-based formulation for the topical delivery of amphotericin-B and ketoconazole, two potent antifungal agents. Bigel, which combine the properties of hydrogels and organogels, offer a unique matrix for improving drug stability, release profiles, and skin permeation. The development process involved optimizing formulation variables such as the hydrogel to organogel ratio, polymer concentrations, and drug loadings. The resulting bigel was characterized for its physicochemical properties, including rheological behavior, spreadability, and stability. The optimized bigel exhibited favorable viscoelastic properties and a stable matrix conducive to the sustained release of both antifungal agents. In vitro release studies indicated a controlled and prolonged release of amphotericin-B and ketoconazole, suggesting potential for extended antifungal activity. Ex vivo permeation studies using human cadaver skin demonstrated enhanced skin penetration, attributed to the dual-phase nature of the bigel, facilitating deeper drug delivery to the infection site.

Efficacy studies against fungal pathogens such as Candida albicans and Aspergillus fumigatus showed significant antifungal activity, with notable inhibition zones and minimal inhibitory concentrations comparable to conventional formulations. Furthermore, cytotoxicity assays on human skin fibroblasts confirmed the safety of the bigel for topical application.

In conclusion, the bigel-based topical delivery system for amphotericin-B and ketoconazole presents a promising alternative for fungal infection treatment, combining enhanced drug stability, controlled release, and improved skin permeation with a favorable safety profile. Future research will focus on clinical evaluations and further optimization for commercial application.

Keywords: Bigel, Topical Drug Delivery, Ketoconazole, Amphotericin-B, Fungal Infection, Optimization, Candida Albicans,

Introduction

Fungal infections, ranging from superficial to systemic, pose significant health challenges, particularly in immunocompromised individuals. Traditional systemic antifungal therapies often lead to severe side effects and drug resistance, emphasizing the need for localized treatment options that can offer high efficacy with reduced systemic exposure. Topical drug delivery systems emerge as an effective alternative, providing targeted therapy that minimizes systemic toxicity and enhances patient compliance. Amphotericin-B and ketoconazole are two potent antifungal agents widely used in the treatment of fungal infections. Amphotericin-B, a polyene antibiotic, exhibits broad-spectrum antifungal activity but is associated with significant nephrotoxicity when administered systemically. Ketoconazole, an imidazole antifungal, effectively treats superficial and systemic infections but also carries the risk of systemic side effects. Developing a topical formulation that can harness the efficacy of these drugs while minimizing adverse effects is crucial for improving patient outcomes.

Bigel, hybrid systems composed of both hydrogel and organogel phases, offer a novel platform for topical drug delivery. The unique structure of bigel combines the hydrophilic nature of hydrogels with the lipophilic properties of organogels, creating a versatile matrix that can encapsulate and stabilize hydrophobic and hydrophilic drugs simultaneously. This dual-phase system enhances drug stability, controls release rates, and improves skin permeation, making it an ideal candidate for topical delivery of amphotericin-B and ketoconazole.

This study aims to design, develop, and evaluate a bigel-based formulation for the topical delivery of amphotericin-B and ketoconazole. By optimizing the formulation variables and characterizing the physicochemical properties of the bigel, we aim to create a stable and effective delivery system. In vitro release studies, ex vivo permeation studies, and efficacy tests against common fungal pathogens will be conducted to assess the potential of the bigel formulation. Additionally, cytotoxicity studies will evaluate the safety of the formulation for topical application.

Material and Method:

Dummy Gel

Table: Hydrogel

Ingredients (mg)	**DH1**	**DH2**	**DH3**
Carbopol	100 mg	-	-
HPMC	-	100 mg	-
Guar Gum	-	-	100 mg
Propylene Glycol	510 mg	510 mg	510 mg
Methyl Paraben	10 mg	10 mg	10 mg
Propyl Paraben	0.25 mg	0.25 mg	0.25 mg
Water	9.3 ml	9.3 ml	9.3 ml
Total	≈10 gm	≈10 gm	≈10 gm

Table 2: Organogel

Ingredients (mg)	**DO1**	**DO2**	**DO3**
Coconut Oil	2000 mg	-	-
Arachis Oil	-	2000 mg	-
Almond Oil	-	-	2000 mg
DMSO	3ml	3ml	3ml
Span-60	4.99 ml	4.99 ml	4.99 ml
Methyl Paraben	10 mg	10 mg	10 mg
Propyl Paraben	0.25 mg	0.25 mg	0.25 mg
Total	≈10 gm	≈10 gm	≈10 gm

We gathered all of the chemicals and materials in the exact amounts specified in the recipe and table up top. While stirring continuously at 500 rpm for about 1 hour, dissolve span-60 in DMSO and add the aforementioned oils one by one. It was then mixed with propylene glycol, methyl paraben, propyl paraben, and triethanolamine while being kept at 60°C. A final weighing was performed using oil. Before the assessment test, all the samples were left to equilibrate at room temperature for 24 hours.

Preparation of Bigel:

For the production of a bigel, the heated organogel was mixed with the hydrogel while stirring constantly at 500 rpm until the mixture was homogenous, and then cooled to room temperature. Using different proportions of hydrogel and Organogel, nine different bigel formulations were created. Color, uniformity, consistency, and phase separation were the visual attributes used to assess the prepared bigels.

API Containing Gel

Table 3: Hydrogel (API containing)

Ingredients (mg)	**DCH1**	**DCH2**	**DCH3**
ketoconazole	200mg	200mg	200mg
Carbopol	100mg	-	-
HPMC	-	100mg	-
Guar Gum	-	-	100mg
Propylene Glycol	510mg	510mg	510mg
DMSO	1ml	1ml	1ml
Methyl Paraben	10mg	10mg	10mg
Propyl Paraben	0.25mg	0.25mg	0.25mg
Water	8.1ml	8.1ml	8.1ml
Total	≈10gm	≈10gm	≈10gm

All of the components, including the active drug (ketoconazole), were gathered in accordance with the formula that is shown in the table that is located above. Ketoconazole, 200 milligrams, should be dissolved in one milliliter of DMSO. Following the preparation of the drug ethanol, water, and propylene glycol solution, Beaker-A was used to label the solution. In solution A, add 100 mg of cabolpol/HPMC/Guar Gum while stirring continuously at a speed of 500 revolutions per minute for about two hours. In addition to triethanolamine, propylene glycol, methyl paraben, and propyl paraben were added to it while the temperature was maintained at 25 degrees Celsius. Water was used to determine the final weight. Prior to carrying out the assessment test, each of the samples was given a period of twenty-four hours at room temperature to acclimate to the environment.

Table 4: Organogel (API Containing)

Ingredients (mg)	**DCO1**	**DCO2**	**DCO3**
Amphotericin-B	200mg	200mg	200mg
Coconut Oil	2ml	-	-
Lemon Oil	-	2ml	-
Almond Oil	-	-	2ml
DMSO	3 ml	3 ml	3 ml
Span-60	4.79mg	4.79mg	4.79mg
Methyl Paraben	10mg	10mg	10mg
Propyl Paraben	0.25mg	0.25mg	0.25mg
Total	≈10gm	≈10gm	≈10gm

Every chemical and ingredient was gathered in accordance with the formula that is shown in the table that is located above. Amphotericin B, 200 milligrams, was dissolved in three milliliters of DMSO, and the name label A was affixed over it. Span-60 should now be added to solution –A. After adding the required quantity of coconut oil, lemon oil, and almond oil to solution A, stir the mixture constantly at a speed of 500 revolutions per minute for about one hour. A temperature of sixty degrees Celsius was maintained while propylene glycol, methyl paraben, propyl paraben, and triethanolamine were added to it. Oil was used to determine the final weight. Before carrying out the assessment test, each of the samples was given a period of twenty-four hours at room temperature to acclimate to the environment.

Preparation of Bigel of Amphotericin-B and Ketoconazole

Table 5: Bigel formulation

Formulation	**BG1**	**BG2**	**BG3**	**BG4**	**BG5**	**BG6**	**BG7**	**BG8**	**BG9**
Ratio	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1
Hydrogel+ Organogel Code	DH1+ DCO1	DH1+ DCO2	DH1+ DCO3	DH2+ DCO1	DH2+ DCO2	DH2+ DCO3	DH3+ DCO1	DH3+ DCO2	DH3+ DCO3

Following the addition of the heated organogel to the hydrogel, the mixture was constantly agitated at a speed of 500 revolutions per minute in line with the table that was shown earlier. In order to establish a uniform mixture, this step was taken, and after that, the mixture was allowed to cool down to the temperature of the surrounding environment. The combination of hydrogel and organogel in a wide range of varied proportions resulted in the creation of nine distinct bigel compositions. Following the completion of the preparation process, the bigels were visually checked and evaluated for their color, homogeneity, uniformity, and phase separation (phase separation).

Evaluation for Gel:

Standard curve of Amphotericin-B

By dissolving 100 mg of amphotericin-B that had been accurately weighed in a tiny amount of 0.1M hydrochloric acid, and then adding more 0.1M hydrochloric acid to bring the total volume

up to the acceptable levels, the required volume of 100 ml was successfully accomplished. 0.1M hydrochloric acid was used in order to reach the desired concentration of 0, 2, 4, 6, 8, 10, and 12 µg/ml for each ml of stock solution. This concentration was necessary for the experiment. To determine the absorbance of the sample that had been slightly diluted, a spectrophotometric measurement was performed at 415 nm using 0.1M hydrochloric acid and a UV-spectrophotometer. While the absorbance was shown along the Y axis, the concentration was plotted along the X axis. The concentration was measured in micrograms per milliliter.

Table 6: Absorbance Amphotericin-B

Concentration	Absorbance (415 nm)
0.0	0
2.0	0.173±0.001
4.0	0.318±0.001
6.0	0.464±0.006
8.0	0.627±0.003
10.0	0.771±0.003
12.0	0.953±0.005

All values are expressed as mean (± SD), *n* = 3

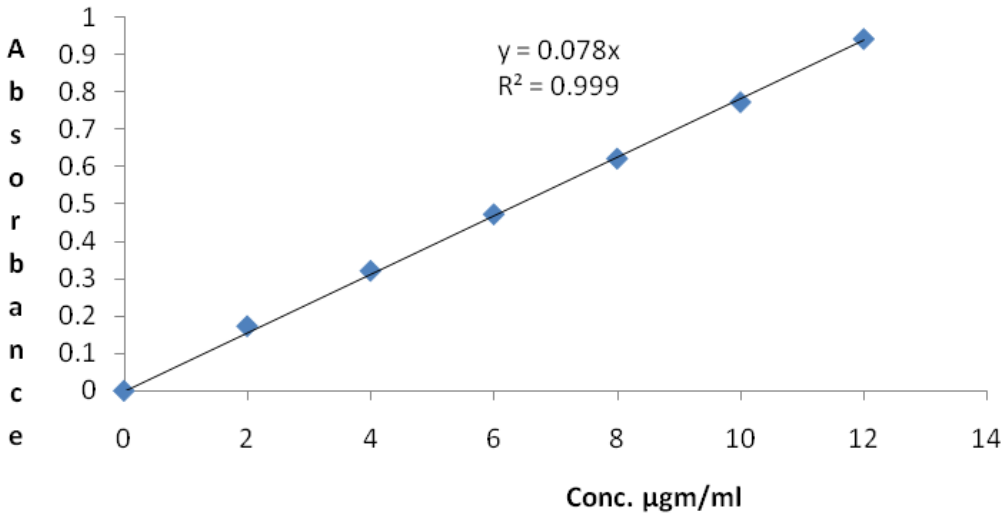

Fig. 1: Calibration Curve Amphotericin-B

Standard curve of ketoconazole

The absorption spectrum of the ketoconazole was measured using a Shimadzu UV Visible Spectrophotometer while it was being described in methanol, which served as the solvent. When

the medication was scanned between 180 and 400 nm, its value of λmax was observed to be 255.nm. Plotting absorbance readings at various doses of the medication using a UV spectrophotometer allowed for the generation of a standard curve for ketoconazole. Using the concentration (in micrograms per milliliter) as the X-axis and absorbance as the Y-axis, the standard plot was created.

Table 7: Absorbance Ketoconazole

Concentration	Absorbance (255 nm)
0.0	0
2.0	0.127±0.002
4.0	0.254±0.003
6.0	0.379±0.001
8.0	0.521±0.002
10.0	0.648±0.003
12.0	0.794±0.001

All values are expressed as mean (± SD), *n* = 3

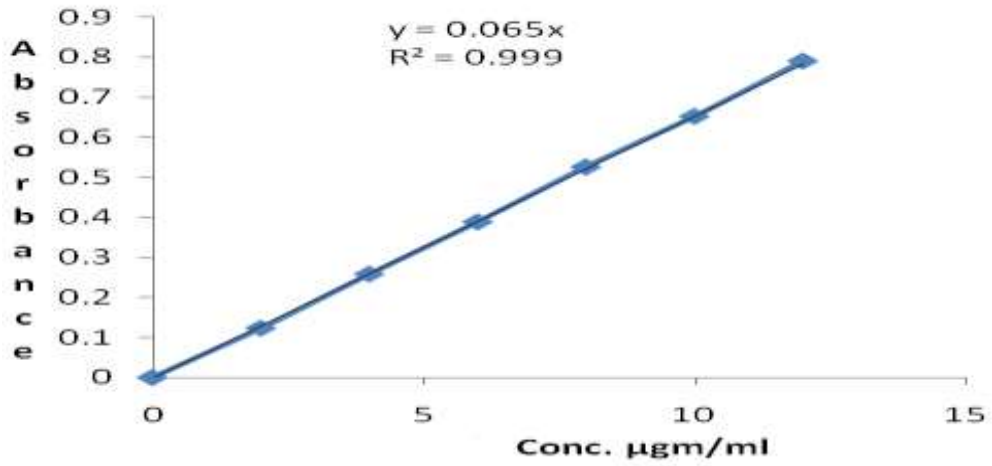

Fig. 2: Calibration Curve Ketoconazole

Percentage Yield

The container that was empty was both the container in which the gel formulation was housed and the container itself were weighed, and then the gel formulation was weighed once again. After that, the practical yield was calculated by subtracting the weight of the empty container from the weight of the container containing the gel formulation. The formula was then used to determine the percentage of yield that was obtained

% Yield = Practical Yield / Theoretical Yield X 100

API content

A total of ten grams of each gel formulation were weighed and then put into a volumetric flask that contained twenty milliliters of alcohol. The mixture was swirled for thirty minutes. After 100 milliliters of liquid had been added, it was filtered. An additional 1 ml of the solution described above was diluted with alcohol until it reached a volume of 10 ml, and then another 1 ml of the solution was diluted with alcohol until it reached a volume of 10 ml. At a wavelength of 415 nm for amphotericin-B and 255 nm for ketoconazole, the absorbance of the solution was determined using spectrophotometric analytical techniques. Here is the formula that was used to determine the amount of drug present.

Drug Content = Absorbance / Slope X Dilution Factor X 1/1000

Determination of pH

Following the transfer of 50 grams of each gel formulation into a beaker containing 10 milliliters, the pH of the gel was determined with the use of a digital pH meter. When treating skin infections, the pH of the topical gel formulation should be between 3 and 9 for optimal results.

Spreadability

Following a duration of one minute, the spreadability of the gel formulation was evaluated by measuring the diameter of a single gram of gel between two horizontal plates measuring 20 centimeters by 20 centimeters. Two hundred and fifty grams was the customary weight that was fastened on the top plate.

Extrudability

The gel compositions were housed in an aluminium or collapsible metal tube. The tube was pushed to extrude the material; the extrudability of the formulation was verified.

Viscosity estimation

The determining the viscosity of the gels. The factors like temperature, pressure and sample size etc. Which affect the viscosity was maintained during the process. The helipath T-bar spindle was moved up and down giving viscosities at a number of points along the path. The torque reading was always greater than 10%. The average of three readings taken in one minute was noted as the viscosity of gels.

***In vitro* diffusion study**

The abdominal skin of pig, weighing 20–25 gm of 8–10 w old was clean the skin with hot water cotton swab. 5 gm of gel was applied uniformly to the skin. The skin was mounted between the compartments of the Franz diffusion cell with stratum corneum facing the donor compartment. Reservoir compartment was filled with 100 ml phosphate buffer of pH 6.8. The study was carried out at 37±1 °C and the speed was adjusted until the vortex touches the skin and it carried

out for 4½ h. 5 ml of the sample was withdrawn from the reservoir compartment at 30 min interval and absorbance was measured spectrophotometrically at 255 nm. Each time the reservoir compartment was replenished with the 5 ml volume of phosphate buffer pH 6.8 solutions to maintain a constant volume.

PREFORMULATION STUDIES

S. .No.	Drug	Physical appearance	Melting point (°C)
1.	Ketoconazole	White	152°C
2.	Amphotericin B	Yellow	172°C

Table No: 8

S. No.	Drug	Solubility				
		Dimethyl sulphoxide	Dimethyl formamide &Methanol	Benzene & Ethanol (95%),	Ether & Water	(DMSO)
1.	**Ketoconazole**	(-)	(-)	(-)	(-)	(+++)
2.	**Amphotericin B**	(+++)	(++)	(-)	(-)	(+++)

Table No: 9

Analytical Profile of Active Drug (DSC & FTIR)

a) Amphotericin-B:

Figure 8.1 displays the Amphotericin-B DSC thermogram. Amphotericin-B's DSC thermogram revealed a strong peak at 1720C. By comparing a compound's identification to that of a genuine sample, one can verify the presence of functional groups in an unknown molecule using infrared spectra. The acquired infrared spectra were explained for significant groupings of chromophores. Peaks were visible in the IR spectra at 3240, 1650, 1280, 950, 840, and 510 cm-1. The different peaks are shown in Figure 4.

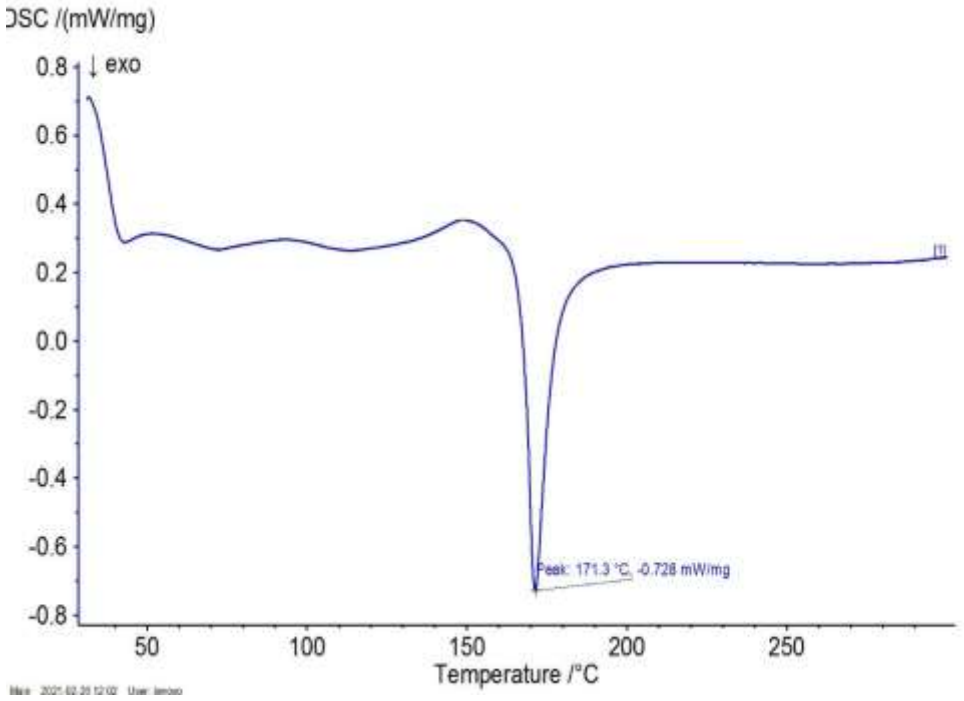

Figure 3: DSC Thermogram of Amphotericin-B

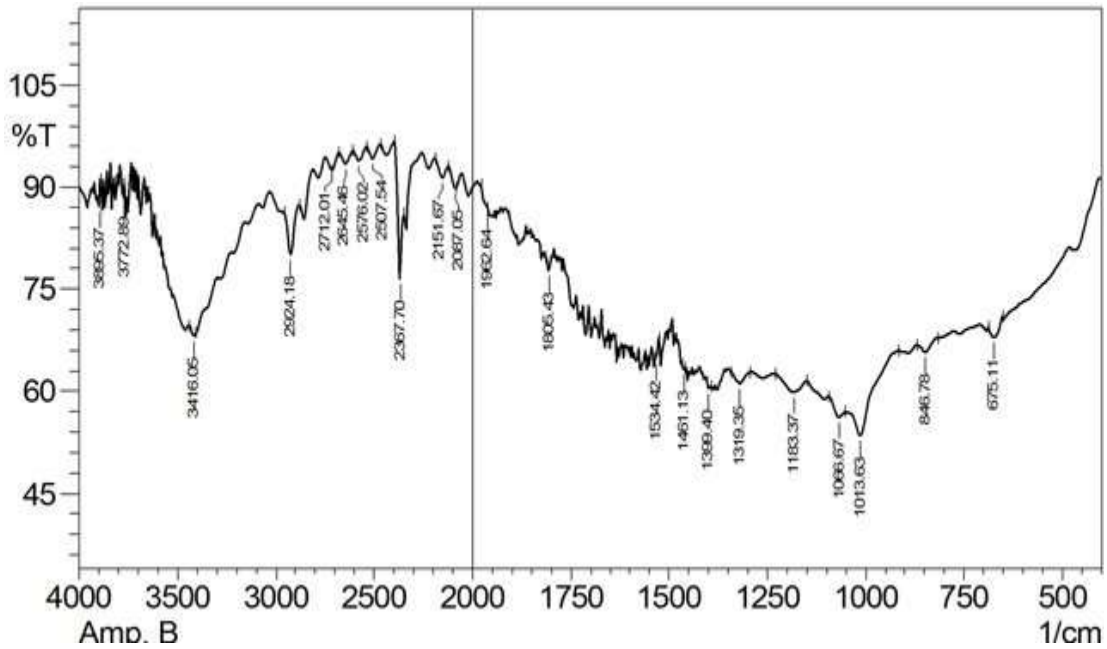

Figure 4: IR Spectra of Amphotericin-B

Table 9: FTIR Spectra of Amphotericin-B

Functional Group	Observed Value (cm^{-1})
N-H stretch	1563
C-C stretch	1592
C=O stretch	1695
CH_2, CH_3	2931
CH Polyene stretch	3365

b) Ketoconazole: The DSC thermogram of Ketoconazole is shown in Figure 5. The DSC thermogram of Ketoconazole showed sharp peak at 162^0C. The identity of a compound was confirmed by comparison with that of an authentic sample and verification of the presence of functional groups in an unknown molecule was done by IR spectra**.** The IR spectra obtained was elucidated for important chromophore groups. The IR spectra showed peaks at 3640, 1450, 1057, 1250, 810 and 690 cm^{-1}. The various peaks are depicted in Figure 6.

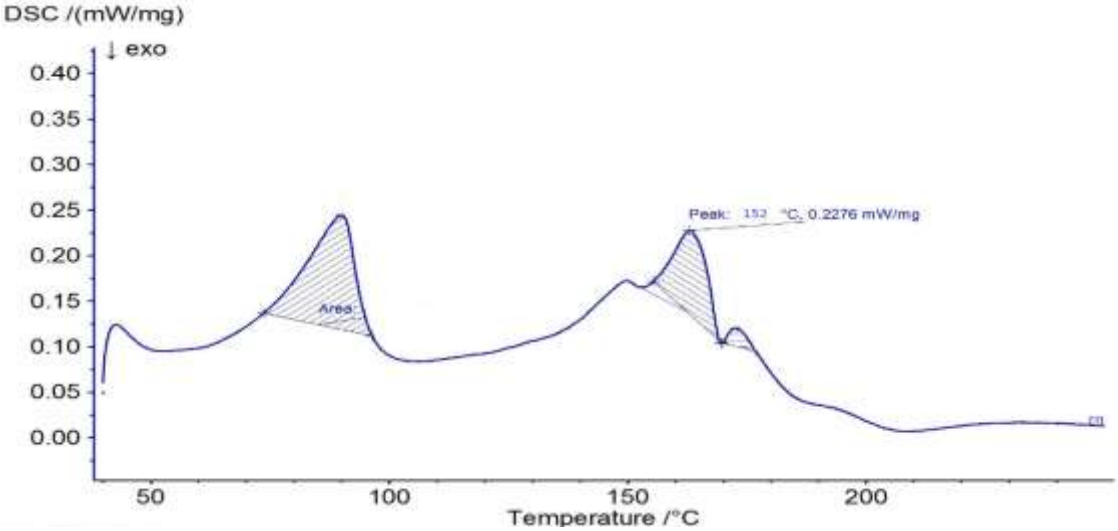

Figure 5: DSC Thermogram of Ketoconazole

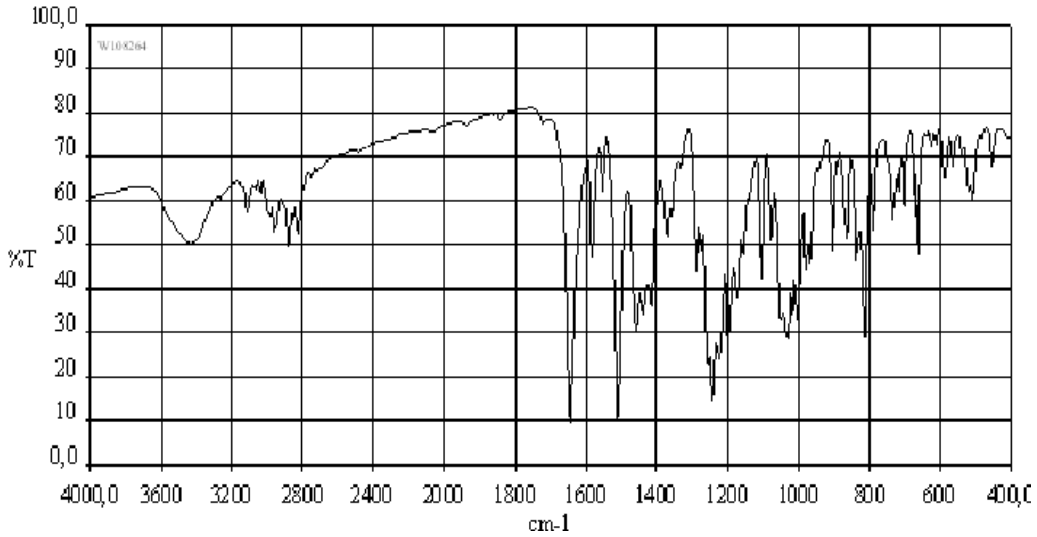

Figure 6: IR Spectra of Ketoconazole

Table 10: FTIR Spectra of Ketoconazole

Functional Group	**Observed Value (cm^{-1})**
C-C stretch	1579
C-N stretch	1429
CH_2 stretch	2585
CH stretch	2954
C-N stretching	3150

c) DSC of Amphotericin-B, Ketoconazole and various polymers (Compatibility Study)

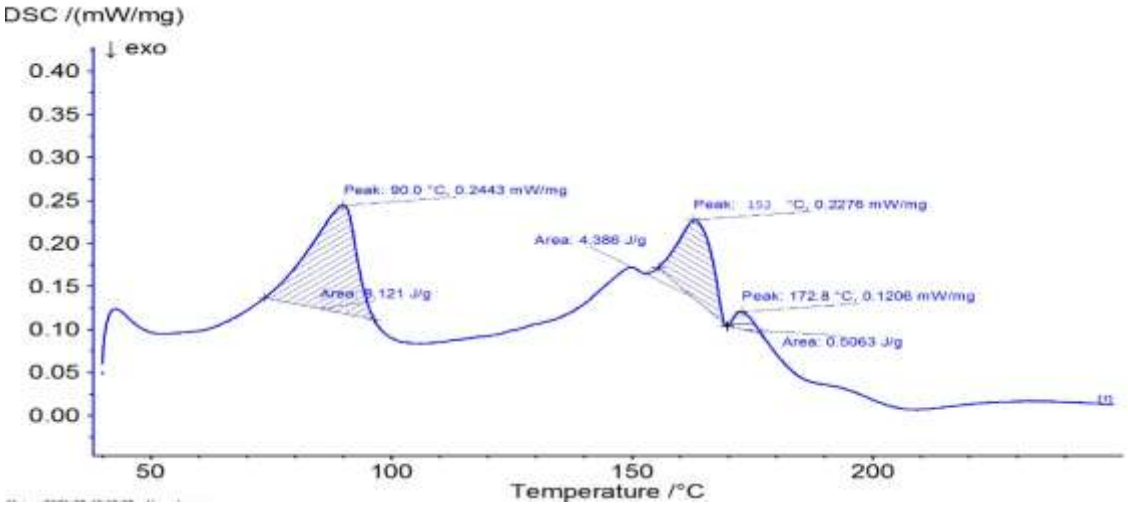

Fig.7 DSC Amphotericin-B and Ketoconazole

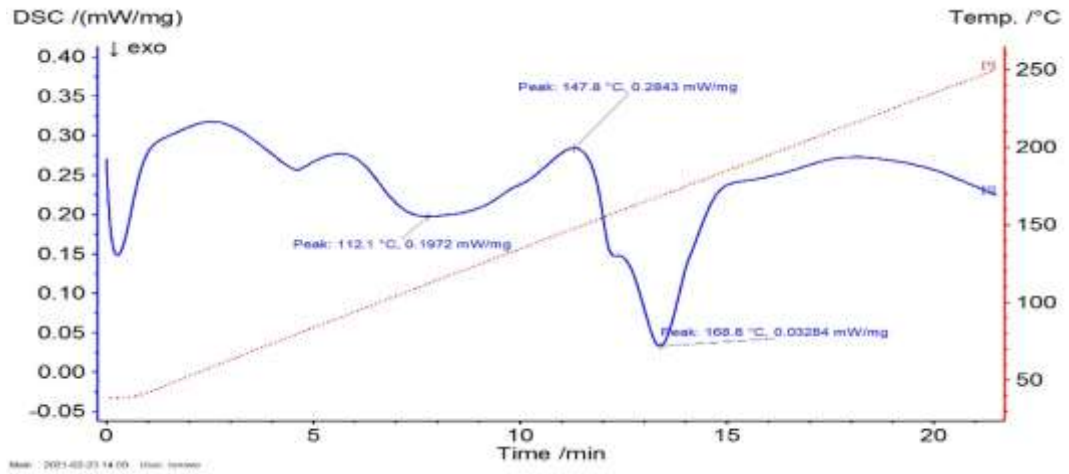

Fig.8 DSC Carbopol+Coconut oil+Amphotericin-B+Ketoconazole

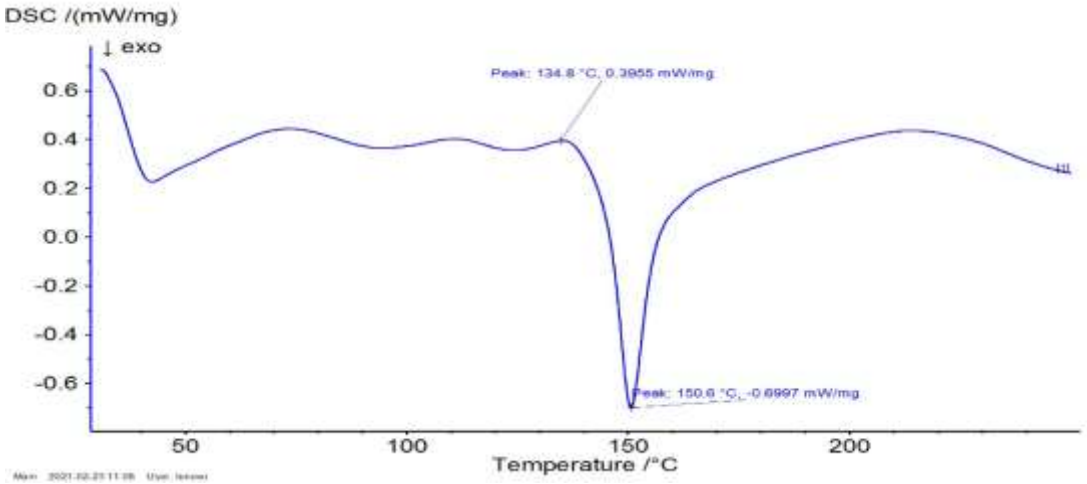

Fig.9 DSC Carbopol+ Arachis Oil +Amphotericin-B + Ketoconazole

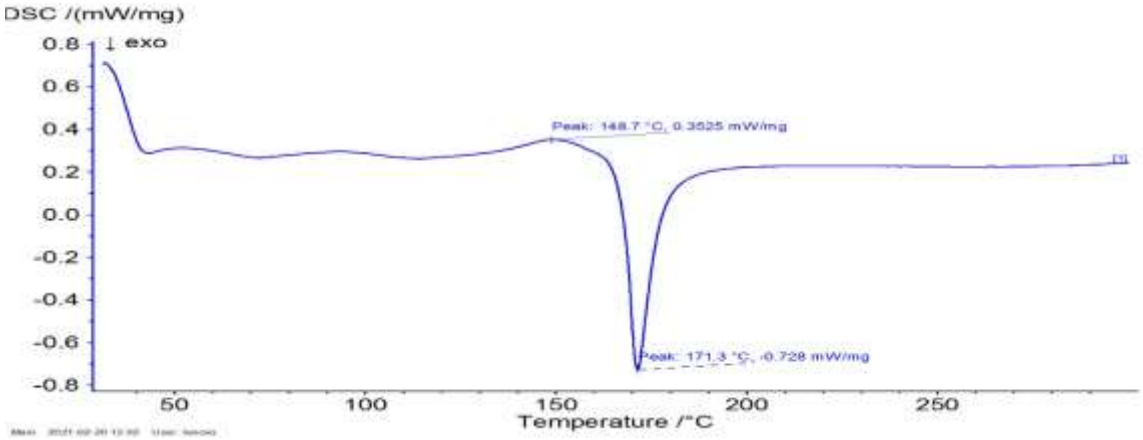

Fig. 10 DSC HPMC +Coconut oil+ Amphotericin-B+ Ketoconazole

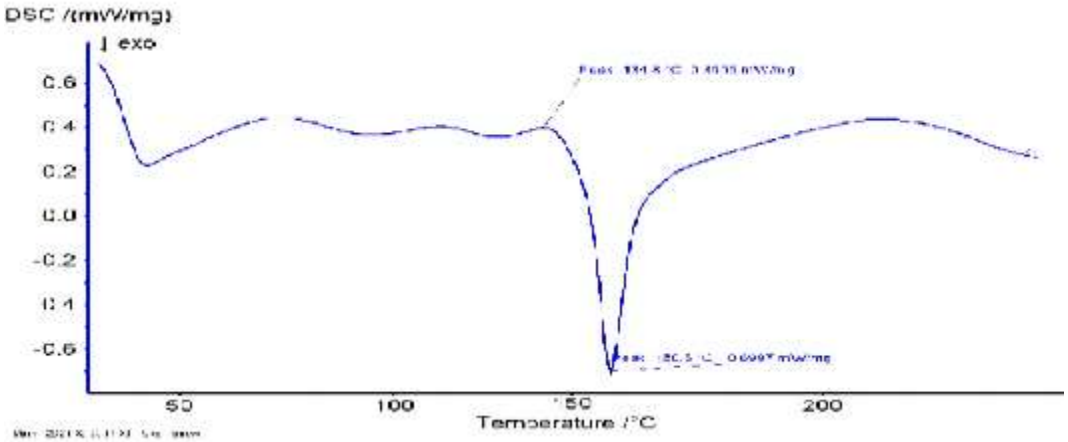

Fig.11 DSC HPMC +Almond oil+Amphotericin-B+Ketoconazole

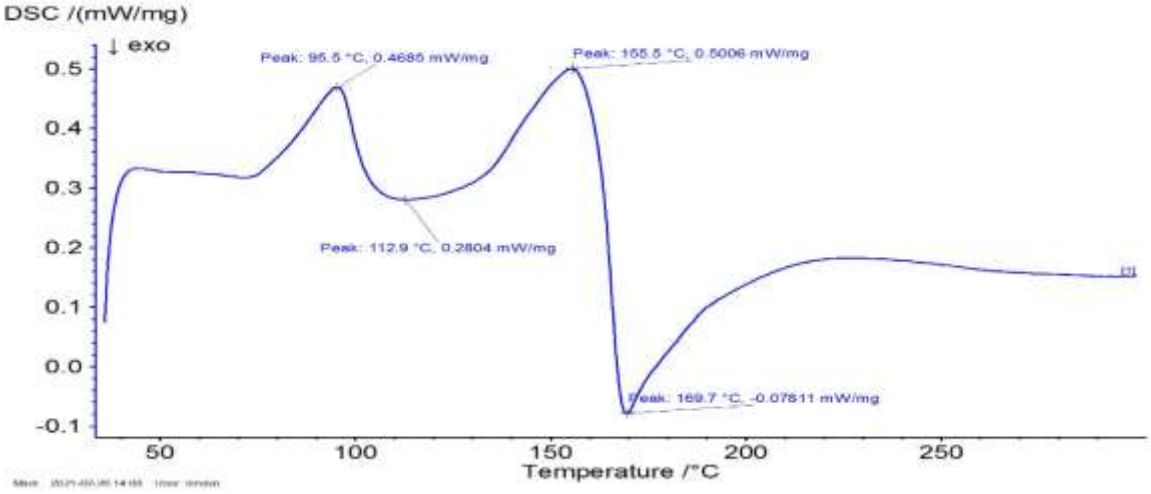

Fig. 12 DSC HPMC+ Arachis Oil +Amphotericin-B + Ketoconazole

PHYSICAL EVALUATIONS

a) pH:

pH of prepared formulation was evaluated by Digital pH meter. The pH of prepared formulations observed in range 6.8 to 7.5.

b) Viscosity measurements:

The Helipath T- Bar spindles were rotated up and down in the sample giving variable viscosities at a number of points programmed over the time. The readings taken over a period of 60 seconds at 6 to 10 rpm were averaged to obtain viscosity. The viscosity of prepared various gel formulations was resulted as 27040±25 to 51250±20CPS.

DSC of Bigel Formulation

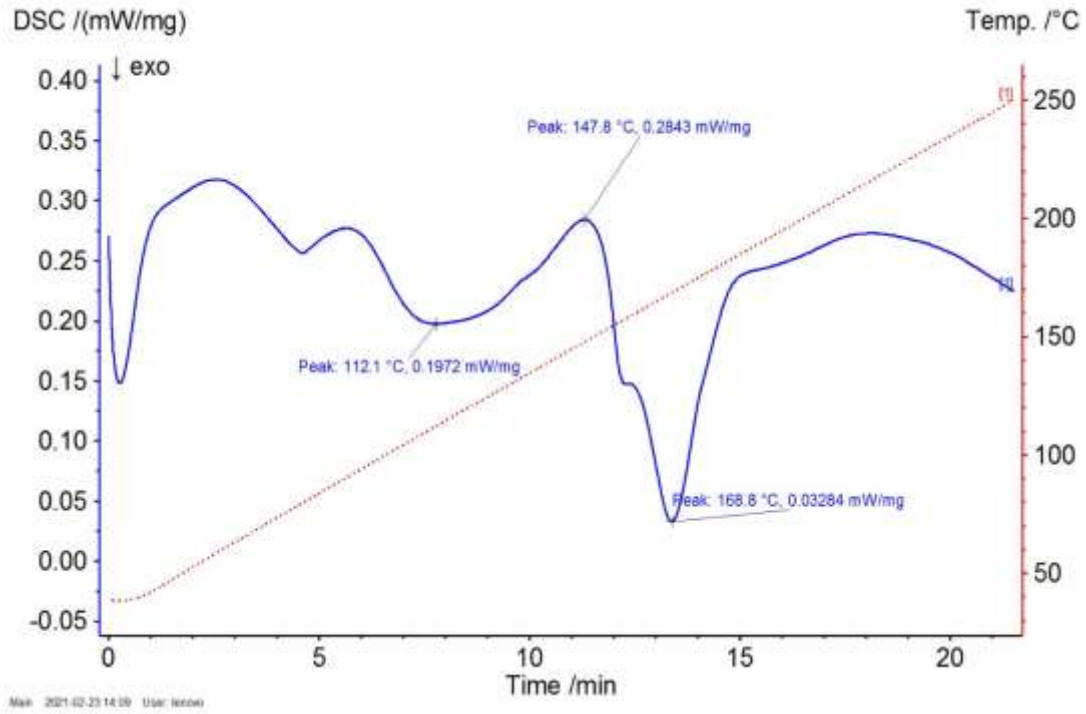

Fig. 11 DSC Bigel Formulation

Extrudability

The extrudability of the gel formulations were checked as per the procedure. Extrudability of carbopol and HPMC gels were excellent than Guar gum gel and the results were shown in Table 11

Formulation	Extrudability
BG1	++++
BG2	++++
BG3	+
BG4	++
BG5	++
BG6	++
BG7	++
BG8	+
BG9	++

++++Excellent, ++Good, +Not satisfactory

Table 11: Extrudability of gel formulations

Determination of Spreadability

The Spreadability of gels was determined as per the procedure. From Spreadability data is observed that the formulation with carbopol-934 showed maximum (8cm), where as the

formulations with carbopol-940, HPMC and Guar gum were showed significant Spreadability. The results were tabulated in Table 12

Formulation	Time taken (minutes)	Spreadability (cm)
BG1	20	8.0
BG2	20	7.8
BG3	20	5.4
BG4	20	4.7
BG5	20	5.5
BG6	20	6.3
BG7	20	5.4
BG8	20	5.6
BG9	20	5.2

Table 12: Spreadability of gel formulations

SCANNING AND DETERMINATION OF MAXIMUM WAVELENGTH (λ_{MAX})

Table 13 Scanning of Amphotericin-B in different solvents

S. No.	Solvent Used	Concentration of final aliquots solution (10 µg/ml)	
		λ_{max}	Absorbance
1.	DMSO	415	0.762
2.	Ethanol	415	0.646
3.	Methanol	415	0.710
5.	Phosphate Buffer (pH 6.8)	415	0.662

Table 14 Scanning of Ketoconazole in different solvents

S. No.	Solvent Used	Concentration of final aliquots solution (10 µg/ml)	
		λ_{max}	Absorbance
1.	DMSO	255	0.661
2.	Ethanol	255	0.628
3.	Methanol	255	0.715
5.	Phosphate Buffer (pH 6.8)	255	0.621

Standard curve of Amphotericin-B

100 mg of accurately weighed Amphotericin-B was dissolved in little amount of DMSO, Ethanol, Methanol and Phosphate Buffers volume 100 ml. So that each ml of stock solution required concentration of 0, 2, 4, 6, 8, 10 and 12 µg/ml was made up with particular solvent. . The standard plot was made with concentration (µg /ml) on X axis and Absorbance on Y axis.

In-Vitro Release

a) Drug release profile of Formulation BG1

i) Amphotericin-B

Table-15 BG1 In-Vitro Release

Time (minutes)	Absorbance at 415nm	Concentration (µg/ml)	Amount of drug release(mg)	Percentage drug release*
30	0.215	10.651	2.130	21.30
60	0.471	16.879	3.374	33.74
90	0.601	29.475	5.894	58.94
120	0.715	35.856	7.170	71.70
150	0.757	38.591	7.718	77.18
180	0.771	42.894	8.578	85.78

ii) Ketoconazole

Table-16 BG1 In-Vitro Release

Time (minutes)	Absorbance at 272nm	Concentration (µg/ml)	Amount of drug release (mg)	Percentage drug release*
30	0.186	09.016	1.803	18.03
60	0.365	14.699	2.939	29.39
90	0.481	27.086	5.417	54.17
120	0.52	33.888	6.777	67.77
150	0.617	37.884	7.576	75.76
180	0.676	40.098	8.019	80.19

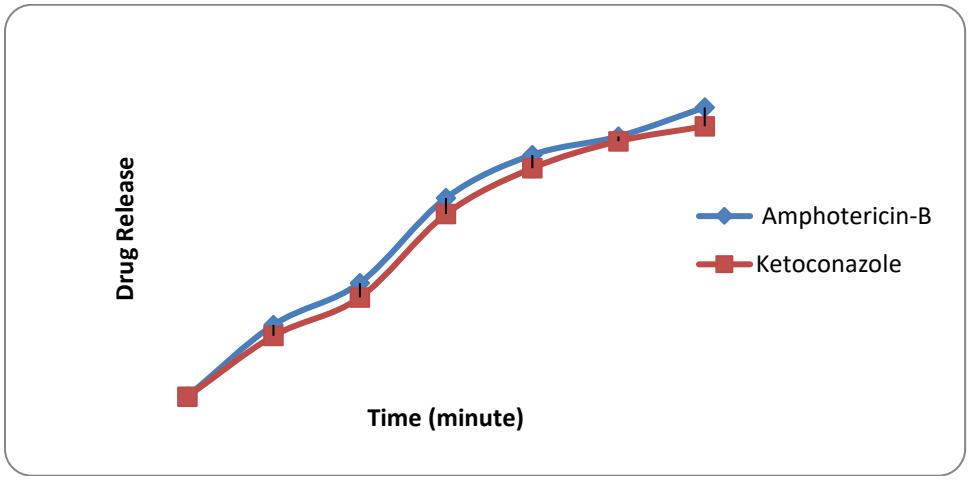

Fig. 11 In-Vitro Release for Formulation BG1

Table 17: Release kinetics and release mechanism of from various Formulations

Model	**BG1**	**BG2**	**BG3**	**BG4**	**BG5**	**BG6**	**BG7**	**BG8**	**BG9**
Zero Order	0.998	0.981	0.995	0.981	0.995	0.985	0.991	0.984	0.985
First Order	0.961	0.963	0.959	0.962	0.979	0.988	0.975	0.989	0.973
Higuchi	0.963	0.979	0.972	0.989	0.972	0.974	0.969	0.978	0.966
Korsmeyer Peppas	0.999	0.991	0.997	0.994	0.989	0.992	0.989	0.994	0.988

Next the Release data obtained were subjected for Kinetic treatment to know the type and order of drug release. From the in-vitro drug release profile it is evident that the kinetic of drug release is first order for all the prepared formulations as the plot between log percent drugs retained versus time showed good linearity. The coefficient of determination of R^2 values much closer to 1 for Kosmayer plots, thus indicating the drug release followed a diffusion controlled mechanism.

Skin Irritation Test

The primary skin irritation test was performed on healthy albino rabbits, weighing between 2.0-3.5 kg. The gel formulation film was prepared and used as test patches, while adhesive tape (USP) was used as control. The test was conducted on unbraided skin of the rabbits. The control and test patches were placed on the left and right dorsal surfaces of the rabbits respectively. The patches were removed after 24 hours with the help of alcohol swab and the skin was examined for erythema and edema, and it's shown in figure No.26 & 27.

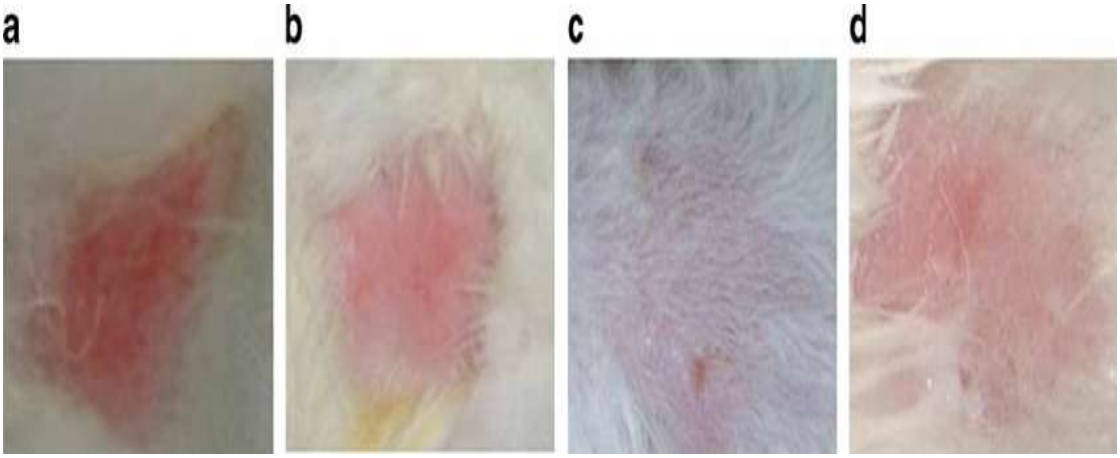

Figure 12: **Skin appearance after 24 hrs for irritation test**

Antifungal sensitivity: The antifungal sensitivity test is employed on to the all the fungi colony of Tinea Versicolor under present study. For this experiment 6 mm diameter wells, stock of bigel applied on it. A SDA plate is seeded with Tinea Versicolor with the help of spread plate technique and left for 5 minutes then incubated for 24 hours at 37^{o}C. After incubation, plates were observed to see the sensitivity of formulation towards test at particular concentration in the form zone of inhibition.

Conclusion:

Bigel-based topical drug delivery systems represent a promising approach for the treatment of fungal infections, offering enhanced efficacy, improved patient compliance, and reduced systemic toxicity. The design, development, and optimization of bigel formulations containing Amphotericin-B and ketoconazole hold significant potential in addressing the unmet needs of current antifungal therapy. From this investigation, it was concluded that formulation BG1 with 1% Carbopol-934 may be the best formulation having good in vitro release profile, stability and bioavailability. Based on the results from the study further utility of the dosage form may depend on pharmacokinetic data. Forthcoming research work of Antifungal activity may contribute in the challenging area.

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