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FORMULATION, CHARACTERIZATION, AND OPTIMIZATION OF AN ITRACONAZOLE BIGEL FOR IMPROVED ANTIFUNGAL EFFICACY AND ENHANCED SKIN RETENTION

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Abstract- The present study was aimed at the formulation and evaluation of a Luliconazole-loaded nanoemulgel for effective topical treatment of fungal skin infections. Nanoemulgel formulations were prepared using different concentrations of HPMC, Carbopol 940, coconut oil, Tween 80, and other suitable excipients to enhance drug solubility, skin penetration, and therapeutic efficacy. Preformulation studies, including melting point determination, solubility analysis, Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), and UV spectrophotometric analysis, confirmed the purity and compatibility of Luliconazole with the selected formulation components. Nine formulations (F1–F9) were developed and evaluated for pH, viscosity, spreadability, extrudability, drug content, and in vitro drug release. The formulations exhibited acceptable physicochemical properties with pH values ranging from 6.8 to 7.5, indicating suitability for topical application. Among all formulations, F8 demonstrated optimum performance with satisfactory spreadability, excellent extrudability, and enhanced drug release characteristics. Drug release kinetic studies revealed that the release pattern followed the Korsmeyer–Peppas model, indicating a diffusion-controlled release mechanism. Stability studies confirmed that the optimized formulation remained physically and chemically stable under different storage conditions. The developed Luliconazole nanoemulgel showed promising potential as an effective topical drug delivery system, offering improved drug release, enhanced bioavailability, prolonged retention, and better patient compliance for the management of fungal infections.

Keywords- Luliconazole; Nanoemulgel; Topical Drug Delivery; Antifungal Therapy; Carbopol 940; HPMC; Coconut Oil; Drug Release Kinetics; Korsmeyer–Peppas Model; Stability Studies; Skin Permeation; Fungal Infections

I. INTRODUCTION

The last two decades have seen unprecedented changes in the pattern of fungal infections in humans. These diseases have assumed a much greater importance be cause of their increasing incidence in persons with the acquired immunodeficiency syndrome AIDS in recipients of solid organ or haematopoietic stem cell transplants HSCT in persons with haematological malignancies and in other debilitated or immunocom promised individuals. Although gains have been made in the treatment and prevention of fungal infections, major changes in health care practices have resulted in the emergence of new atrisk populations. Fungi are a varied group of eukaryotic organisms that are essential to many ecological functions including breaking down organic matter and recycling nutrients. They can appear as single celled forms like yeasts or as multicellular filamentous structures such as molds. Fungi inhabit a wide range of environments including soil, water and living organisms like plants and animals they hold significant ecological and medical importance.[1]

II. MATERIALS AND METHODS

2.1 METHODS

Analysis of Luliconazole

1. **Differential Scanning Calorimetry**

During the course of this inquiry, the melting point of the Luliconazole sample that was used was determined via the utilisation of Differential Scanning Calorimetry (DSC). This differential scanning calorimeter comes with a sub-ambient attachment that is filled with liquid nitrogen. At a rate of twenty millilitres per minute, the device was operated using nitrogen pure gas. Using duplicate samples of 5 mg in crimped aluminium samples pans, the DSC analysis was performed throughout a temperature range of 50-2000 degrees Celsius at a rate of 100 degrees Celsius per minute. When calibrating the DSC equipment, indium was the element of choice.

2. **Fourier Transform Infra Red Spectroscopy (FTIR)**

The infrared (IR) examination of the sample was performed in order to identify the qualitative compounds using the sample. The infrared analysis offers a comprehensive picture of the interactions that take place between the medicine and the excipients at play. As part of the preparation process, a pressure compression machine was used to grind roughly 5 mg of sample with 100-120 mg of potassium bromide. The pellet, which had a diameter of approximately 01 mm, was made from the medication. After being installed in the infrared chamber, the sample pellet was scanned at a wavelength ranging from 4000 cm-1 to 400 cm-1.

3. **Ultraviolet absorption**

In order to determine the wavelength maxima and absorbance of the drug, as well

as to calibrate the standard curve of the medication, an ultraviolet spectroscopy examination was performed on the drug. The procedure is carried out by creating different concentrations of the medication in a solution (methanolic Phosphates Buffer, pH 7.4) and then performing spectroscopy in the region of 240 to 400 nm in order to acquire the absorbance for the relative concentration of the drug components.

- **Solubility**

Based on the findings of Higuchi and Connors, the determination of soluble substances was carried out. The ability of Luliconazole to dissolve in a variety of solvents was found to be studied. A amount of the medication that was in excess was added to 10 millilitres of each solvent, which was then placed in screw-capped glass test tubes and shaken for a period of twelve hours at room temperature. After filtering and diluting the solution, a spectrophotometric analysis was performed at 205 nm to evaluate the solubility of the substance.

- **Partition coefficient**

The partition coefficient of Luliconazole was determined in n-octanol: phosphates buffer pH 7.4 system. An accurately weighed (500mg) amount of Luliconazole was added into 10 ml each of n- octanol and aqueous phase in a screw capped tube. The mixture was shaken for 20 hours until equilibrium was reached. Phases were separated; the aqueous phase was filtered, diluted and the amount of Luliconazole solubilized in aqueous phase was determined by measuring the absorbance at 205 nm spectrophotometrically.

The partition coefficient of Luliconazole was calculated from the ratio between the concentration of Luliconazole in organic and aqueous phase using following equation.

$$P_{o/w} = (C_{Oil} / C_{pH\ 7.4})_{equilibrium}$$

Calibration curve of Luliconazole

A. **Determination of Absorption maxima**

A UV absorption maxima was determined by scanning a 2 to 10 ug/ml solution of Luliconazole in 5% (v/v) methanolic Phosphate buffer pH 7.4 between 200-400nm.

B. **Preparation of Calibration Curve**

10 mg of Luliconazole was weighed accurately and dissolved 5ml methanol in a 100 ml of volumetric flask and volume was made up to with the Phosphate buffer pH 7.4. Two ml of this solution was diluted to 10 ml with pH 7.4 Phosphate buffer to obtain a stock solution of 20ug/ml.**3.**

2.2 Formulation of Dummy Gel

Table 1: Hydrogel

Ingredients (%	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**

w/w)									
HPMC	0.5	1.0	2.0	-	-	-	-	-	-
Coconut Oil	-	-	-	2.5	3.5	5.0	-	-	-
Carbopol 940	-	-	-	-	-	-	1.0	1.5	2.0
Tween 80 (Surfactant)	10.0	10.0	10.0	12.0	12.0	12.0	15.0	15.0	15.0
Triethanolamine	pH 6.5–7.0	pH 6.5–7.0	pH 6.5–7.0	pH 6.5–7.0	pH 6.5–7.0	pH 6.5–7.0	pH 6.5–7.0	pH 6.5–7.0	pH 6.5–7.0
Methylparaben	0.1	0.1	0.1	0.15	0.15	0.15	0.2	0.2	0.2
Distilled Water	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

2.3 Preparation of Nanoemulgel

Table 2: Nanoemugel (API containing)

Ingredients (% w/w)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Luliconazole	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
HPMC	0.5	1.0	2.0	-	-	-	-	-	-
Coconut Oil	-	-	-	2.5	3.5	5.0	-	-	-
Carbopol 940	-	-	-	-	-	-	1.0	1.5	2.0

Tween 80	10.0	10.0	10.0	12.0	12.0	12.0	15.0	15.0	15.0
Triethanolamine	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Methylparaben	0.1	0.1	0.1	0.15	0.15	0.15	0.2	0.2	0.2
Distilled Water	87.4	86.9	85.9	83.35	82.35	80.85	81.8	81.3	80.8

2.4 Standard Curve of Luliconazole

Table 3: Absorbance Luliconazole

Concentration	**Absorbance (255.2 nm)**
0.0	0
2.0	0.128±0.002
4.0	0.253±0.003
6.0	0.378±0.001
8.0	0.522±0.002
10.0	0.647±0.003
12.0	0.795±0.001
14.0	0.920±0.001

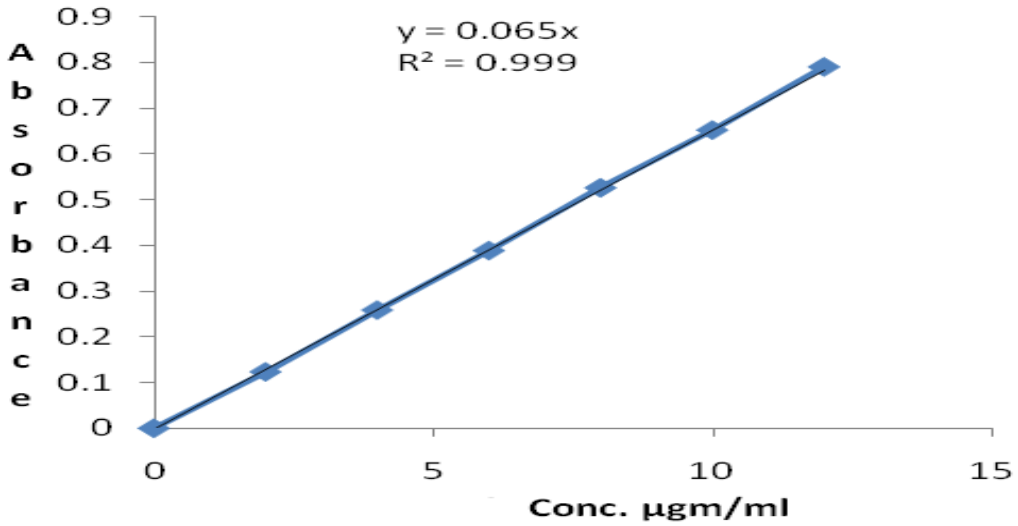

Figure 1: Calibration Curve Luliconazole

2.5 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

2.6 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 296 nm for Luliconazole, 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

2.7 Determination of pH

After transferring 50 grams of each gel formulation into a beaker containing 10 milliliters, the pH of the gel was measured using a digital pH meter. For maximum success in treating skin infections, the pH of the topical gel composition must range from 3 to 9.

2.8 Spreadibility

After one minute, the spreadability of the gel formulation was assessed by measuring the diameter of one gram of gel placed between two horizontal plates, each measuring 20 centimeters by 20 centimeters. Two hundred fifty grams was the standard weight affixed to the upper plate.

2.9 Extrudability

The gel formulations were contained in an aluminum or collapsible metal tube. The tube was actuated to extrude the material; the extrudability of the formulation was confirmed. 6.8

2.10 Viscosity Estimation

The viscosity of the gel was measured using a Brookfield viscometer DVII model equipped with a T-Bar spindle and a helipath stand.

a) Selection of spindle: The Spindle T 95 was employed to test the viscosity of all the gels.

b) Sample container size: The viscosity was measured using 50 gm of gel filled in a 100 ml beaker.

c) Spindle immersion: The T-bar spindle (T95) was lowered perpendicular in the centre taking care that spindle does not touch the bottom of the jar.

d) Measurement of viscosity: The T-bar spindle (T95) was employed to ascertain the viscosity of the gels. The elements influencing viscosity, such as temperature, pressure, and sample size, were controlled throughout the procedure. The helipath T-bar spindle was adjusted vertically, providing viscosity measurements at various locations along the path. The torque measurement consistently exceeded 10%. The viscosity of gels was recorded as the average of three tests made within one minute.

2.11 In Vitro Diffusion Study

The abdomen skin of a pig, weighing 20–25 grams and aged 8–10 weeks, was cleansed using a hot water cotton swab. 5 grams of gel were evenly applied to the skin. The skin was positioned between the chambers of the Franz diffusion cell, with the stratum corneum oriented towards the donor compartment. The reservoir compartment was filled with 100 cc of phosphate buffer at pH 6.8. The experiment was conducted at 37±1 °C, with the velocity modified until the vortex made contact with the skin, lasting for 4½ hours. 5 ml of the sample was extracted from the reservoir compartment at 30-minute intervals, and absorbance was quantified spectrophotometrically at 260 nm. Each time, the reservoir compartment was supplied with 5 ml of phosphate buffer solution at pH 6.8 to sustain a steady volume.

2.12 Skin Irritation Study

This research was conducted on healthy Wistar rats. The animals were categorized given two groups: control and Gel formulations BG1. The skin on the back, covering an area of 5 cm^2, was shaved one day prior to the commencement of the

research. The research was conducted over a duration of four days. Upon conclusion of the trial, the animals were monitored for any signs of dermal irritation.

2.13 Ex-Vivo Studies

Antifungal sensitivity: The antifungal sensitivity test is conducted on all fungal colonies of Tinea Versicolor in the current investigation. For this experiment, wells with a diameter of 6 mm were utilized, upon which a stock of bigel was put. A SDA plate is inoculated with Tinea Versicolor using the spread plate technique, allowed to rest for 5 minutes, and thereafter incubated for 24 hours at 37°C. Following incubation, the plates were examined to assess the formulation's sensitivity to the test at a certain dose, indicated by the zone of inhibition.

Pathogenic fungi used: The pathogenic fungi Tinea Versicolor used in the current study were obtained from NIA, Jaipur.

- **Media preparation: Composition of Sabouraud Dextrose Agar media**

  Agar - 15 gms.

  Peptone - 10 gms.

  Dextrose - 40 gms.

  Distilled water - to make 100 ml.

  pH – 5.6

- **Sterilization culture media:** The flask holding the medium was cotton-plugged and subjected to sterilization in an autoclave at 15 psi (121°C) for 15 minutes.

- **Preparation of plates:** Subsequent to sterilization, the molten agar in the flask was promptly dispensed (20 ml per plate) into sterile Petri dishes placed on a flat surface. The prepared plates are incubated at 37°C overnight to assess their sterility. The plates were dried at 50°C ± 0.5°C for 30 minutes before to use.

- **Revival of the fungi culture:** The cultures utilized in the investigation were acquired in lyophilized form. The lyophilized cultures were aseptically inoculated into sterile nutrient broth and incubated for 24 hours at 37°C ± 0.5°C. Post-incubation, growth is noted as turbidity. The broth cultures were subsequently inoculated onto nutrient agar plates using a loop and incubated for 24 hours at 37°C ± 0.5°C to achieve pure cultures, which were then preserved as stocks for future investigation.

- **Antifungal sensitivity:** The antifungal sensitivity test is applied to all the fungal colonies included in the current investigation. For this experiment, 6 mm diameter wells were utilized, with a stock of bigel put to them. A nutritional agar plate is inoculated with specific bacteria using the spread plate technique, let to rest for 5 minutes, and thereafter incubated for 24 hours at 37°C. Following incubation, plates were examined to assess the sensitivity of extracts to the test at a certain

concentration, indicated by the zone of inhibition.

2.14 Stability Studies

Stability studies: Optimized formulations of Luliconazole bigel underwent accelerated stability testing under storage conditions of 4 ± 1°C and at room temperature (25 ± 1°C) with 60 ± 5% relative humidity. Both formulations were preserved in screw-capped amber glass bottles at 4 ± 1°C and 25 ± 1°C. Samples were examined for vesicle size and drug content after 7, 14, 21, and 28 days of storage under specified conditions.

(a) Effect of storage temperature on vesicle size: The vesicle size of the formulations maintained at 4±1°C and 25±1°C was assessed using a Zetasizer (Malvern Instrument, UK) at intervals of 7, 14, 21, and 28 days.

(b) Effect of storage temperature on drug content: Following a designated storage duration of 7, 14, 21, and 28 days, the drug content of both formulations was assessed. The drug concentration in liposomal gel was quantified spectrophotometrically as previously described (6.4.5.).

III. RESULTS

In the proposal study nanoemulgel of Luliconazole were prepared and evaluated for their use to obtain Local Fast release and Increased bioavailability by preventing from first pass metabolism

3.1 Preformulation Studies

S. No.	Drug	Physical appearance	Melting point
1.	Luliconazole	White	152°C

S. No.	Drug	Solubility				
		Phosphate Buffer	Dimethyl formamide &Methanol	Benzene & Ethanol (95%),	Ether & Water	(DMSO)
1.	**Luliconazole**	(-)	(-)	(-)	(-)	(+++)

3.2 ANALYTIC PROFILE OF ACTIVE DRUG (DSC & FTIR)

a) Luliconazole: The DSC thermogram of Luliconazole is shown in Figure 8.3. The DSC thermogram of Luliconazole 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 2.

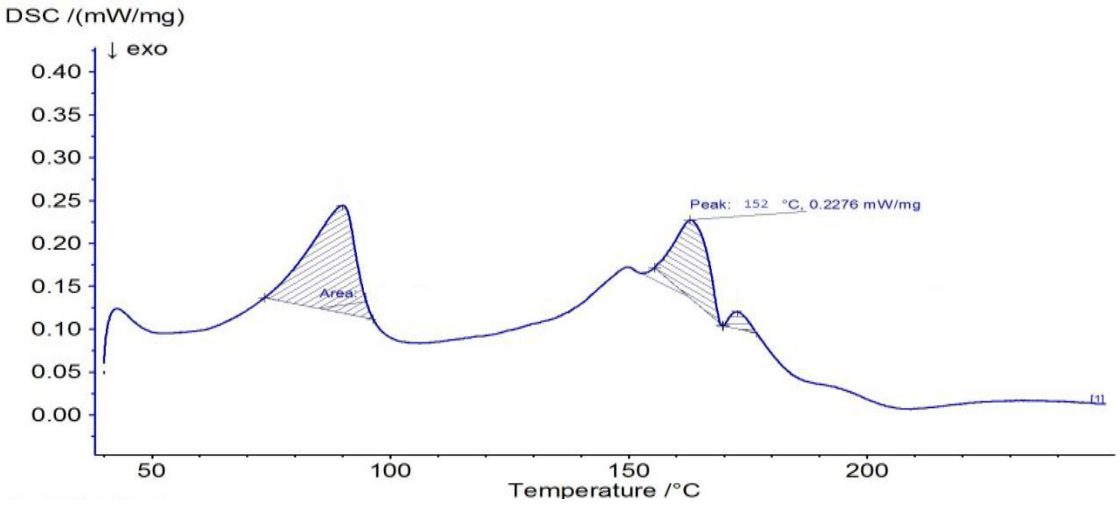

Figure 2: DSC Thermogram of Luliconazole

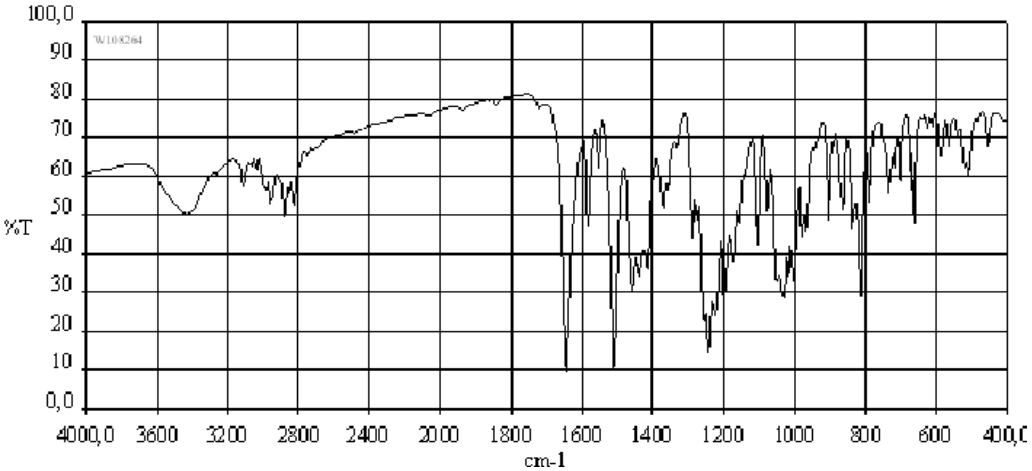

Figure 3: IR Spectra of Luliconazole

Table 4: FTIR Spectra of Luliconazole

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

a) DSC of Luliconazole and various polymers (Compatibility Study)

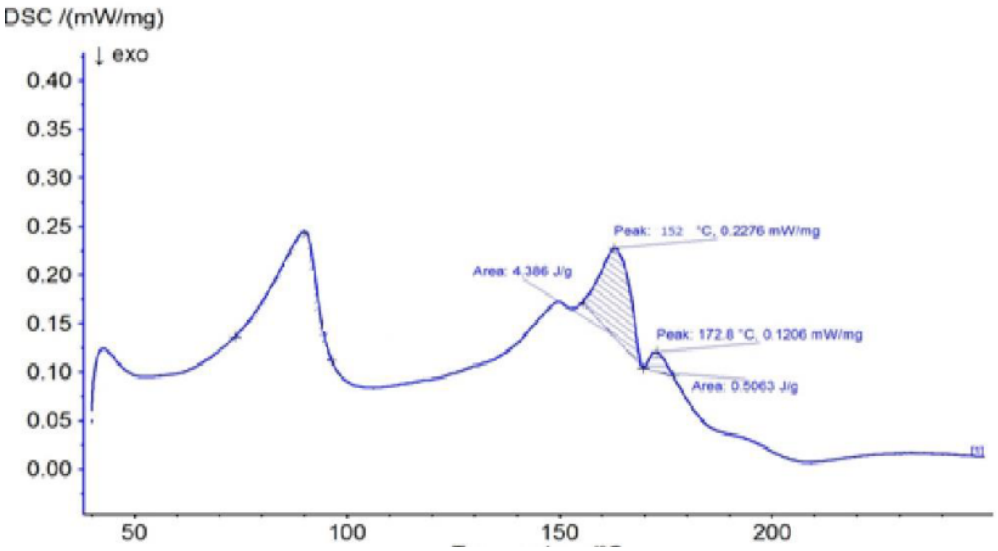

Figure 5: DSC Luliconazole

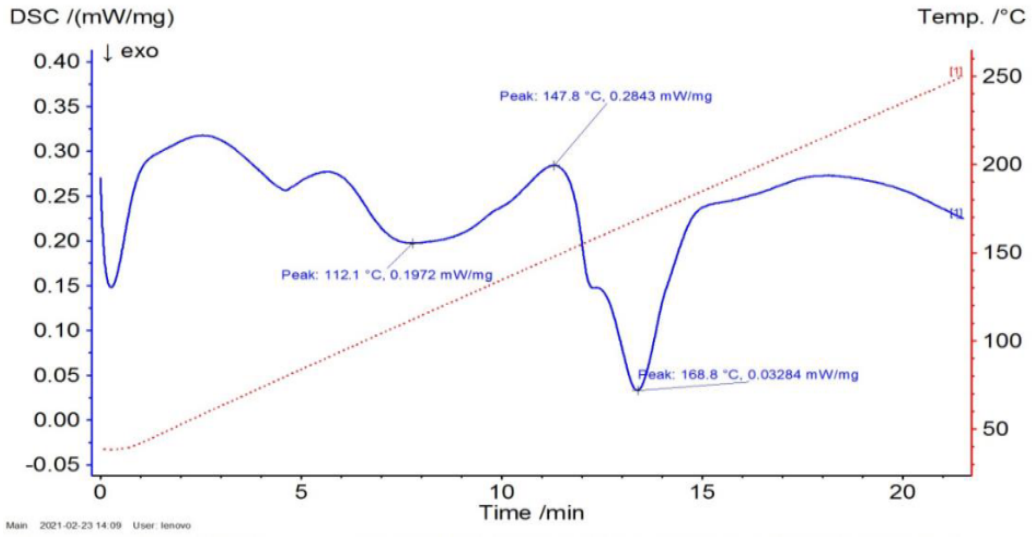

Figure 6: DSC Carbopol+ Coconut oil +Luliconazole

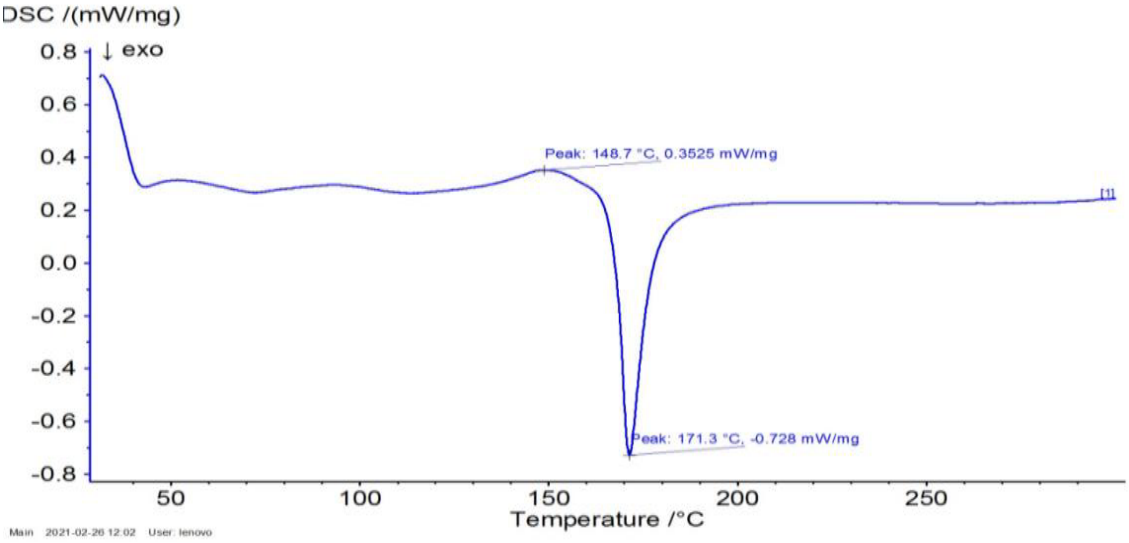

Figure 7: DSC HPMC +Coconut oil+ Luliconazole

3.3 Physical Evaluations

a) pH:

The pH of the prepared formulations was determined using a digital pH meter. The results showed that the pH ranged between 6.8 and 7.5.

b) Viscosity Measurements:

The viscosity of the gel formulations was measured using a Brookfield Viscometer (DV-II model) equipped with a T-Bar spindle and Helipath stand, which ensures precise readings. To maintain the accuracy of the results, variables such as temperature, pressure, and sample size—which can influence the gel's rheological behavior—were kept constant. Since some materials are highly temperature-sensitive and even slight variations can significantly alter viscosity, the testing was conducted at a controlled temperature of 25ºC. This is because viscosity generally decreases with increasing temperature and vice versa.

3.4 DSC OF NANOEMULGEL FORMULATION

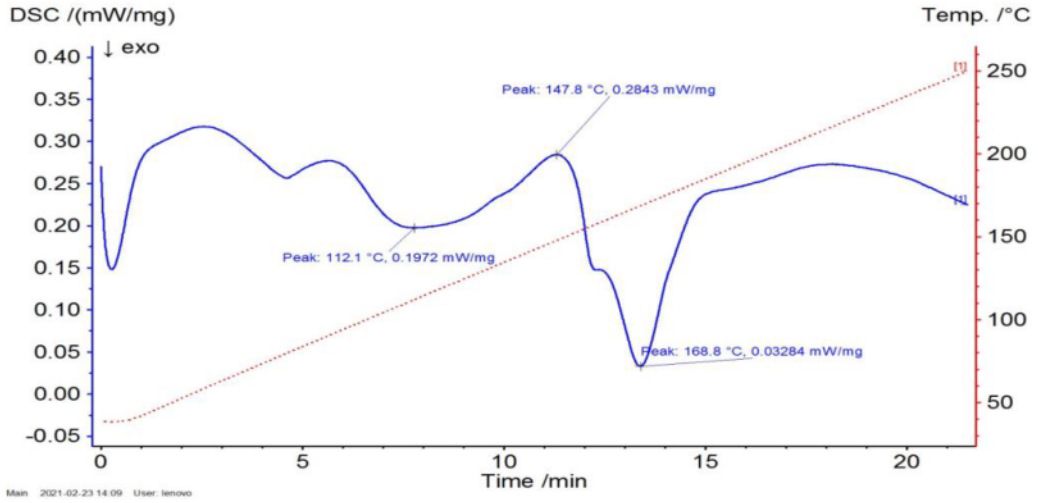

Figure 8: DSC Nanoemulgel Formulation

3.5. 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 inTable8.2

Table 5: Extrudability of Nanomeulgel formulations

Formulation	Extrudability
F1	++++
F2	++++
F3	++

F4	++
F5	++
F6	+++
F7	++
F8	+++
F9	++

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

3.6.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.

Table 6: Spreadability of gel formulations

Formulation	**Time taken (minutes)**	**Spreadability (cm)**
F1	20	8.1
F2	20	7.9
F3	20	5.4
F4	20	4.7
F5	20	5.4
F6	20	6.5

F7	20	5.4
F8	20	5.5
F9	20	5.2

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

Table 7: Scanning of Luliconazole in different solvents

S. No.	**Solvent Used**	**Concentration of final aliquots solution (10 µg/ml)**	
		λ_{max}	**Absorbance**
1.	DMSO	296	0.661
2.	Ethanol	296	0.628
3.	Methanol	296	0.715
5.	Phosphate Buffer (pH 6.8)	296	0.621

3.7 Standard Curve of Luliconazole

The Luliconazole was characterized in methanol as solvent by measuring absorption spectrum using Shimadzu UV Visible Spectrophotometer. The drug exhibited λmax at 296 nm when scanned between 180-400 nm. Standard curve of Luliconazole was obtained by plotting absorbance values at different concentrations of the drug UV- spectrophotometer. The standard plot was made with concentration (µg /ml) on X axis and Absorbance on Y axis.

Preparation of Calibration curve of Luliconazole in DMSO:

Table 8: Absorbance of Luliconazole in DMSO

Concentration	**Absorbance (296 nm)**

0.0	0
2.0	0.125±0.003
4.0	0.259±0.002
6.0	0.384±0.003
8.0	0.528±0.002
10.0	0.653±0.003
12.0	0.786±0.001

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

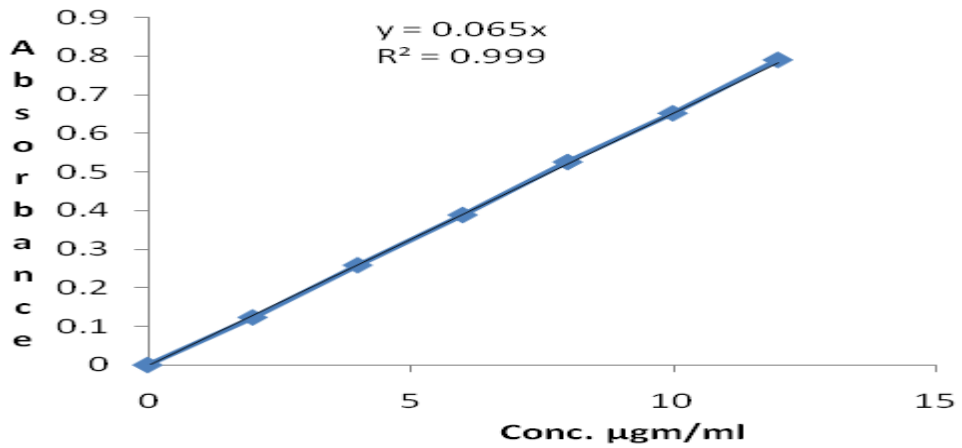

Figure 9: Standard curve of Luliconazole

Preparation of Calibration curve of Luliconazole in Ethanol:

Table 9: Absorbance of Luliconazole in Ethanol

Concentration	**Absorbance (296 nm)**
0.0	0

2.0	0.131±0.001
4.0	0.252±0.002
6.0	0.351±0.002
8.0	0.493±0.001
10.0	0.606±0.001
12.0	0.741±0.002

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

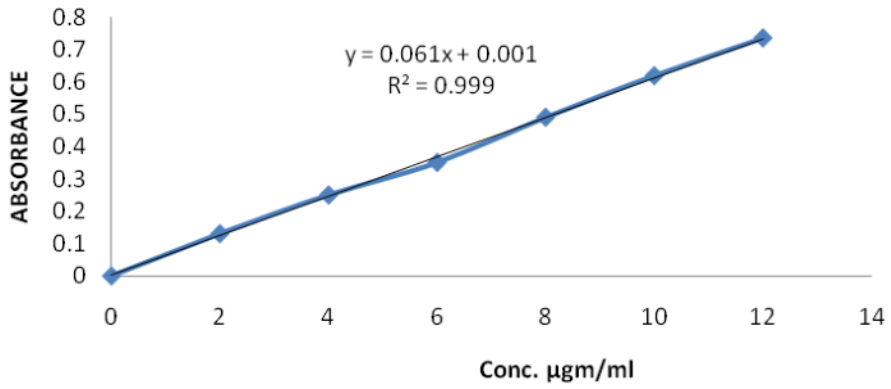

Figure 10: Standard Curve Luliconazole (Ethanol)

Preparation of Calibration curve of Luliconazole in Methanol:

Table 10: Absorbance of Luliconazole in Methanol

Concentration	**Absorbance (296 nm)**
0.0	0
2.0	0.153±0.001

4.0	0.291±0.002
6.0	0.455±0.002
8.0	0.589±0.001
10.0	0.721±0.001
12.0	0.847±0.002

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

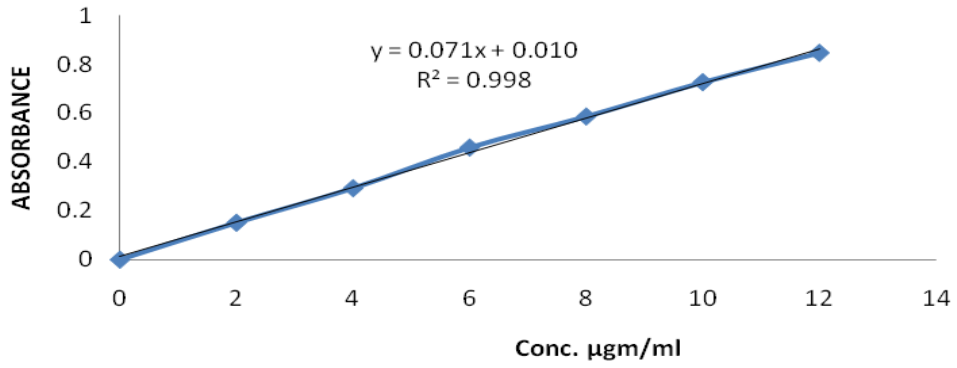

Figure 11: Standard Curve Luliconazole (Methanol)

3.8. Drug release of F1-F9 formulation

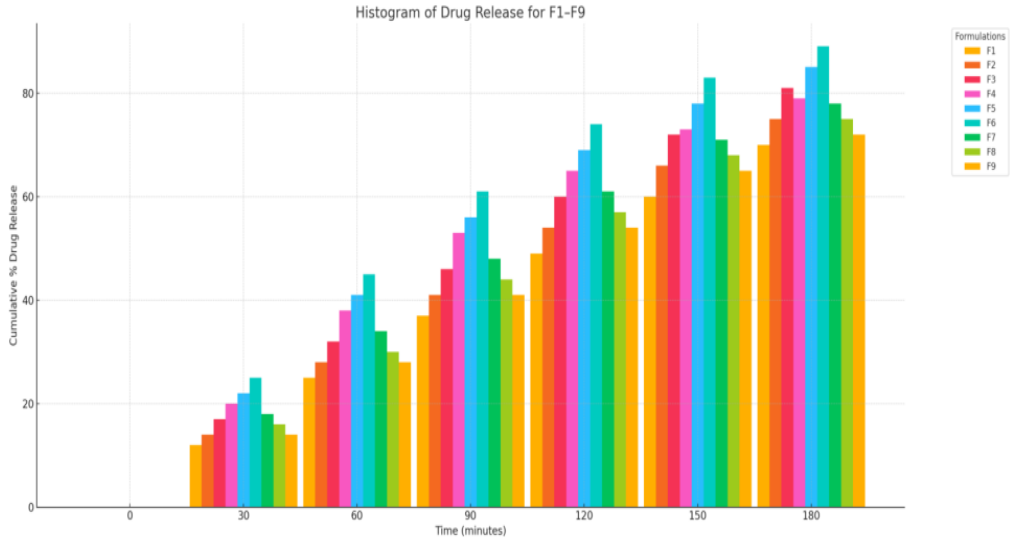

Figure 12: Graph of F1-F9 Formulation

3.9 Drug Release Kinetic

3.9.1 Zero order

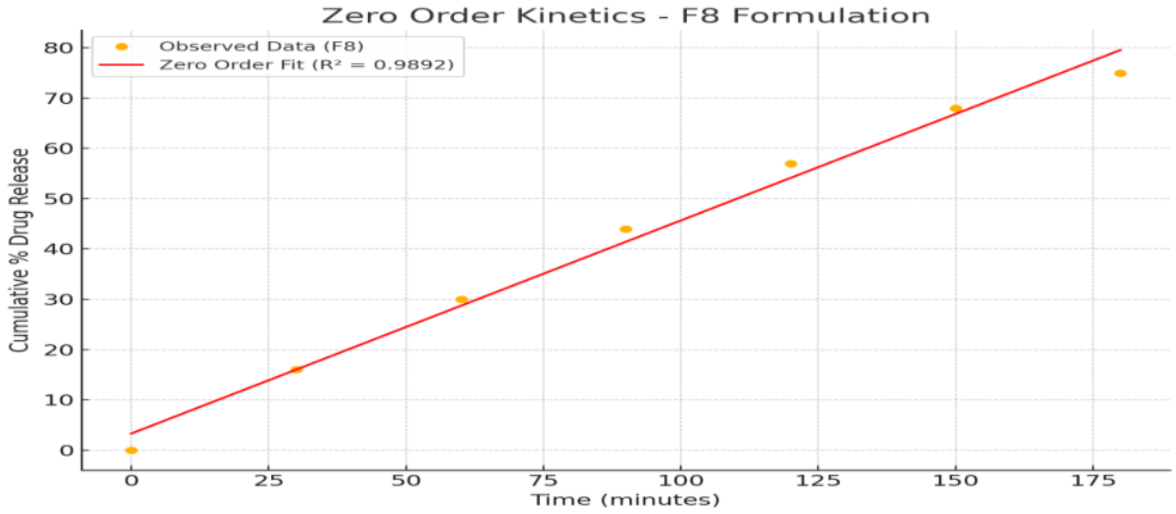

Figure 13: Graph of Zero Order Kinetics

3.9.2 First order

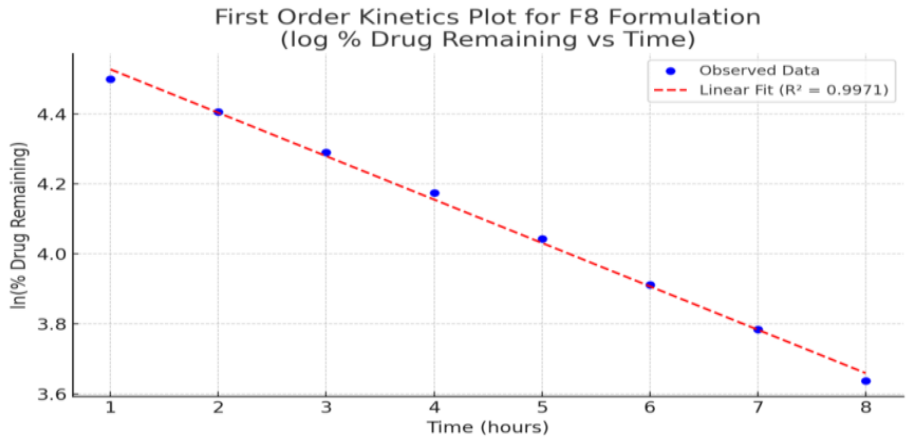

Figure 14: Graph of First order Kinetics

3.9.3 Higuchi

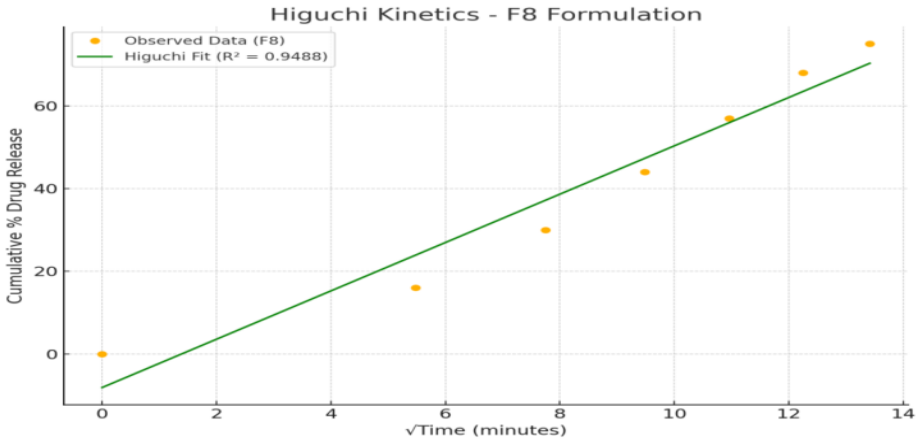

Figure 15: Graph of Higuchi kinetics

3.9.4 Korsmeyer peppas

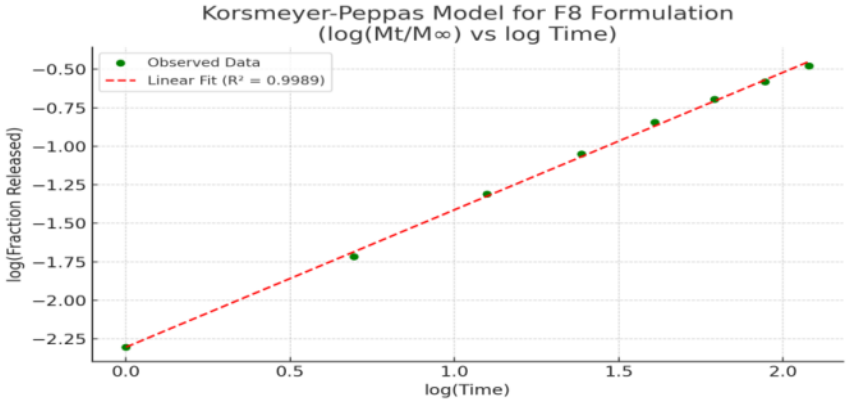

Figure 16: Graph of Korsmeyer-Peppas

Table 11: kinetic Equation parameter of formulation F8

Formulation Name	Zeroorder	Firstorder	Higuchi	KorsymerPeppas
F8	R^2	R^2	R^2	R^2
	0.9892	0.9971	0.9488	0.9989

Discussion: Mathematical models are commonly used to predict the release mechanism and compare release profile. For all optimized formulations, the % drug release vs time (zero order), log% drug remaining vs time (first order), log% drug release vs square root of time (higuchi plot) and log fraction drug releasevs log time (korsmeyer peppas) were plotted. Considering the determination coefficient, Korsmeyer modelfit the release data.

IV. Conclusion

The present study successfully developed and evaluated a Luliconazole-loaded nanoemulgel for topical antifungal delivery. The optimized formulation exhibited acceptable pH, good spreadability, excellent extrudability, and enhanced drug release characteristics. Compatibility studies confirmed the stability of Luliconazole with the selected excipients, while kinetic analysis indicated a diffusion-controlled drug release mechanism following the Korsmeyer–Peppas model. The formulation remained stable during storage and demonstrated potential for improved topical delivery, enhanced bioavailability, and effective management of fungal skin infections.

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