Formulation and Evaluation of In-Situ gel for Antifungal Activity

[1]Sawant Viraj, [2]Miss. Mane Kirti, [3]Dr. Gurav Yogesh
[1]virusawant36@gmail.com, [2]mane.kirti091@gmail.com, [3]grddsvp@gmail.com

Abstract:
The present study focuses on the formulation and evaluation of a Luliconazole-loaded in-situ gel intended for topical antifungal therapy. In-situ gel systems offer a novel approach to drug delivery by undergoing a sol-to-gel transformation in response to physiological stimuli such as temperature, pH, or ionic interactions. This mechanism facilitates localized, sustained release and enhances drug retention at the application site, thereby improving therapeutic efficacy and patient compliance. Luliconazole, a potent imidazole antifungal agent, was incorporated into a thermosensitive gel matrix using polymers like Poloxamer 407, HPMC, CMC, methyl cellulose, and sodium alginate. The formulations were characterized for pH, viscosity, gelation temperature and time, clarity, drug content, and in vitro antifungal activity against *Candida albicans*. The optimized formulation (F2) exhibited superior gel strength, desirable viscosity, controlled drug release, and a larger zone of inhibition compared to marketed preparations. These findings suggest that in-situ gel systems are promising platforms for effective and patient-friendly topical antifungal therapy.

Key Words: Luliconazole, in-situ gel, antifungal activity, thermosensitive gel, sustained release, topical delivery, Poloxamer 407, Candida albicans.

INTRODUCTION

Topical drug delivery systems have emerged as an essential platform for the localized treatment of skin and mucosal infections, offering distinct advantages such as bypassing hepatic first-pass metabolism, reducing systemic side effects, and enhancing patient compliance through direct site-specific action. However, conventional topical formulations like creams, ointments, and gels often fall short due to poor retention at the application site, rapid wash-off, inconsistent drug release, and the need for frequent application, all of which compromise therapeutic efficacy and user adherence. These limitations have led researchers to explore advanced drug delivery systems that ensure prolonged drug availability, controlled release, and better bio adhesion to the site of infection.

One such promising approach is the development of in-situ gel systems, which are liquid at room temperature but transform into a gel upon exposure to physiological triggers such as temperature, pH, or ionic changes. Thermosensitive in-situ gels, in particular, have gained attention in dermatological applications because they gel upon contact with skin temperature, ensuring ease of application and extended retention. These systems not only provide a sustained release profile but also form a protective layer over the skin, creating a barrier that enhances drug penetration and maintains the drug concentration at the infection site for a longer duration. Poloxamer 407, a synthetic triblock copolymer, is widely used as a thermoresponsive agent due to its reversible sol-gel transition property. When combined with other viscosity-enhancing polymers such as Hydroxypropyl Methylcellulose (HPMC), Carboxymethyl Cellulose (CMC), Methyl Cellulose (MC), and Sodium Alginate (SA), it provides a stable, non-irritating, and effective gel matrix ideal for topical drug delivery.

Luliconazole is a novel, broad-spectrum antifungal agent belonging to the imidazole class, effective against dermatophytes and Candida species. It functions by inhibiting the biosynthesis of ergosterol, a vital component of the fungal cell membrane, leading to increased membrane permeability and cell death. Luliconazole is primarily used to treat superficial mycotic infections such as tinea pedis, tinea corporis, and candidiasis. However, its conventional dosage forms offer limited bioavailability, poor water solubility, and require frequent applications, which may affect patient compliance and clinical outcomes. Therefore, the incorporation of Luliconazole into a thermosensitive in-situ gel system offers a strategic advantage, enabling better solubilization, controlled release, and enhanced antifungal efficacy at the site of infection.

The present study aims to formulate and evaluate a Luliconazole-loaded in-situ gel using Poloxamer 407 as the main thermogelling polymer, in combination with hydrophilic agents like HPMC, CMC, MC, and SA. Ethanol is used as a co-solvent to enhance the solubility of Luliconazole, and Benzalkonium Chloride is added as a preservative to ensure microbial stability. The objective is to develop a gel that is clear, stable, pH-compatible with skin, and capable of forming a gel upon application, while providing prolonged antifungal activity with minimal irritation. The formulated gels will be subjected to a comprehensive evaluation for parameters including pH, viscosity, clarity, gelation temperature and time, drug content, antifungal activity against Candida albicans, and in vitro drug release to study the release kinetics. The optimized formulation will be compared with a marketed preparation to determine its performance and therapeutic superiority.

Thus, this research explores a novel approach to enhance the topical delivery of Luliconazole using an in-situ gel system, which holds the potential to improve therapeutic efficacy, reduce dosing frequency, and significantly enhance patient compliance in the management of superficial fungal infections.

MATERIAL AND METHODS:

Materials:

The in-situ gel formulation was prepared using pharmaceutical-grade Poloxamer 407 as the primary thermosensitive gelling agent. Hydroxypropyl Methylcellulose (HPMC), Methyl Cellulose (MC), Sodium Alginate (SA), and Carboxymethyl Cellulose (CMC) were used as viscosity enhancers and gel stabilizers. Benzalkonium Chloride was included as a preservative to prevent microbial contamination. All materials used were of analytical grade and suitable for topical pharmaceutical formulations.

Methods:

Melting Point:

The melting point of Luliconazole was determined using the capillary tube method. A small quantity of the pure drug was placed into a capillary tube sealed at one end using a flame. This capillary tube was then attached to a thermometer with a thread and immersed in a Thiele's tube containing liquid paraffin. The setup was gradually heated and the temperature at which the drug began to melt was recorded as its melting point.

Solubility study of the Drug (Luliconazole)

The solubility of Luliconazole was performed in Methanol.

UV Spectroscopy:

A drug solution of 10 ug/ml in distilled water was prepared, scanned taking appropriate solvent as blank spectrum was recorded by using twin beam UV/visible spectrophotometer was used to measure the UV absorption of a prepared medication solution in the 200-400) nm range.

Standard calibration curve in methanol

Preparation of stock solution in Methanol:

Standard stock solution was prepared by taking 10 mg in 10 ml of methanol (1000µg/ml). The stock solution scanned in the range 400-200 nm by UV spectrophotometer. The solution showed maximum absorbance at 297 nm.

FTIR:

FTIR spectroscopy by comparing the absorption peaks of Luliconazole with those of a standard reference spectrum, the compound was identified using Fourier transform infrared spectroscopy. Hydraulic pressing was used to compress a finely powdered mixture of Luliconazole (1-2 mg) and dry potassium bromide (KBr) into a thin, clear pellet in a 1:100 ratio. An FTIR spectrophotometer was used to examine the pellet,

with a resolution of 4 cm^{-1}, across a scanning range of 4000-400 cm^{-1}. By looking for distinctive peaks in the resultant spectrum that match to Luliconazole functional groups, we were able to positively identify the medicine.

DRUG EXCIPIENT COMPATIBILITY STUDY

FTIR spectroscopy

The FTIR method was used to conduct the research of medication excipient compatibility. The diffraction reflectance scanning technique was used to scan the optimized batch samples throughout a wave number range of 500-4000 cm^{-1}.

Differential Scanning Calorimetry

Using a modified differential scanning calorimetric (DSC), measurements were taken. The lead-hermetically-covered aluminum pans were utilized for the optimal batch sample. Under a nitrogen environment, the heating range for the sample was 60–300 °C, with a constant rate of temperature increase of 10°C/min (50–60 ml/min). The formulation's resulting thermograms were acquired.

Formulation of in-situ gel

Cold Method

- The in-situ gel of Luliconazole was prepared using the cold method.
- Poloxamer 407 was slowly added to cold distilled water (4–8°C) with continuous stirring to avoid clumping and refrigerated overnight to ensure complete hydration.
- Separately Methyl Cellulose (MC), Carboxymethyl Cellulose (CMC), and Hydroxypropyl Methylcellulose (HPMC) were dispersed in small amounts of water and allowed to swell completely.
- These hydrated polymer solutions were then combined to form a uniform blend. Luliconazole was dissolved in a suitable solvent such as ethanol and Benzalkonium Chloride was added as a preservative.
- The drug solution was added slowly into the cold polymer base with constant stirring. The Ph of the formulation was adjusted to 5.5–6.5 using a dilute NaOH solution.
- Finally, the volume was made up with cold water, and the formulation was stored at 4°C to maintain its liquid state until use.

Table: Formulation Batches of in-situ Gel

Batch	Drug (mg)	Pluronic f-127 (gm)	HPMC (g)	SA (g)	MC (g)	CMC (g)	Water (ml)
F1	100	1.4	0.05	0.2	0.05	0.05	10
F2	100	1.6	0.1	0.2	0.1	0.1	10
F3	100	1.8	0.2	0.2	0.2	0.2	10
F4	100	2.0	0.3	0.2	0.3	0.3	10
F5	100	2.2	0.4	0.2	0.4	0.4	10

F1 F2 F3 F4 F5

Appearance

- All formulations (F1–F5) were visually inspected in transparent glass containers under ambient light.
- Gels were observed against white and black backgrounds for clarity, color, homogeneity, and presence of particulates.
- Acceptable formulations appeared clear to slightly translucent, colorless to pale yellow, smooth, and free from undissolved particles.

Clarity

- Clarity was assessed visually in glass vials under natural light against contrasting backgrounds.
- Gels were graded as clear, slightly hazy, or turbid.
- Clear gels indicated good dispersion and stability, essential for patient acceptability.

Gelation Temperature and Time

- Measured using the tube inversion method.
- Gelation temperature: point at which formulation showed no flow within 10 seconds on inversion.
- Gelation time: time required to form a non-flowing gel at that temperature.
- Ensured formulations remained liquid at room temp and gelled at skin temp (32–37 °C).

pH Measurement

- pH was measured using a calibrated digital pH meter.
- 1 g gel dispersed in 10 mL distilled water; pH recorded at room temperature in triplicate.
- pH values ranged between 5.0 and 7.0 to match skin pH and minimize irritation.

Antifungal Activity

The antifungal efficacy of the formulated Luliconazole in-situ gel was evaluated using the agar well diffusion method against *Candida albicans*. Sabouraud Dextrose Agar (SDA) plates were prepared and inoculated with fungal suspension. Wells of 6–8 mm diameter were created using a sterile cork borer and filled with 100 µL each of the formulated gel and a marketed Luliconazole gel for comparison. The plates were incubated at 25–28°C for 48–72 hours. After incubation, the zones of inhibition around each well were measured in millimeters to assess antifungal activity.

Figure No.12 Antifungal activity

The antifungal activity of the formulated Luliconazole in-situ gel was evaluated against *Candida albicans* and compared with a marketed gel and saline control using the agar diffusion method. After 72 hours of incubation, the in-situ gel showed a larger zone of inhibition (28.6 ± 1.2 mm) than the marketed gel (24.3 ± 1.0 mm), while the control showed no activity. The superior antifungal effect of the formulation is attributed to enhanced penetration and sustained drug release.

Viscosity Measurement

The viscosity of the Luliconazole-loaded in-situ gel formulations was measured using a Brookfield viscometer with spindle no. 63 or 64 at varying speeds (10–100 rpm). About 10 g of each formulation was tested at room temperature (25 ± 2°C) to assess rheological behavior. All formulations exhibited pseudoplastic (shear-thinning) flow, which is desirable for easy application and better spreadability. Values were recorded in centipoise (cP), and each reading was taken in triplicate.

Drug Content

Drug content was determined by dissolving an accurately weighed gel sample equivalent to 1 mg of Luliconazole in methanol or phosphate buffer (pH 7.4), followed by sonication and filtration. The filtrate was diluted and analyzed spectrophotometrically at 296–298 nm. Results, calculated from a standard calibration curve, confirmed uniform drug distribution, with values close to 100%, indicating formulation accuracy. All analyses were done in triplicate.

In Vitro Drug Release Studies

In vitro drug release was assessed using a Franz diffusion cell with a cellulose membrane and phosphate buffer (pH 7.4) at 37 ± 0.5°C. A fixed amount of gel (equivalent to 1 mg of drug) was applied to the membrane, and receptor fluid samples were withdrawn at intervals up to 8 hours. Each sample was analyzed using UV spectroscopy at ~297 nm. Cumulative drug release was calculated and plotted over time to evaluate the sustained release profile of the formulations.

RESULT AND DISUSSION

Melting point:

Melting point determination was used to confirm that the chemical was pure. According to the given criteria, Luliconazole has a melting point of 151 °C.

λ max of Luliconazole in Methanol.

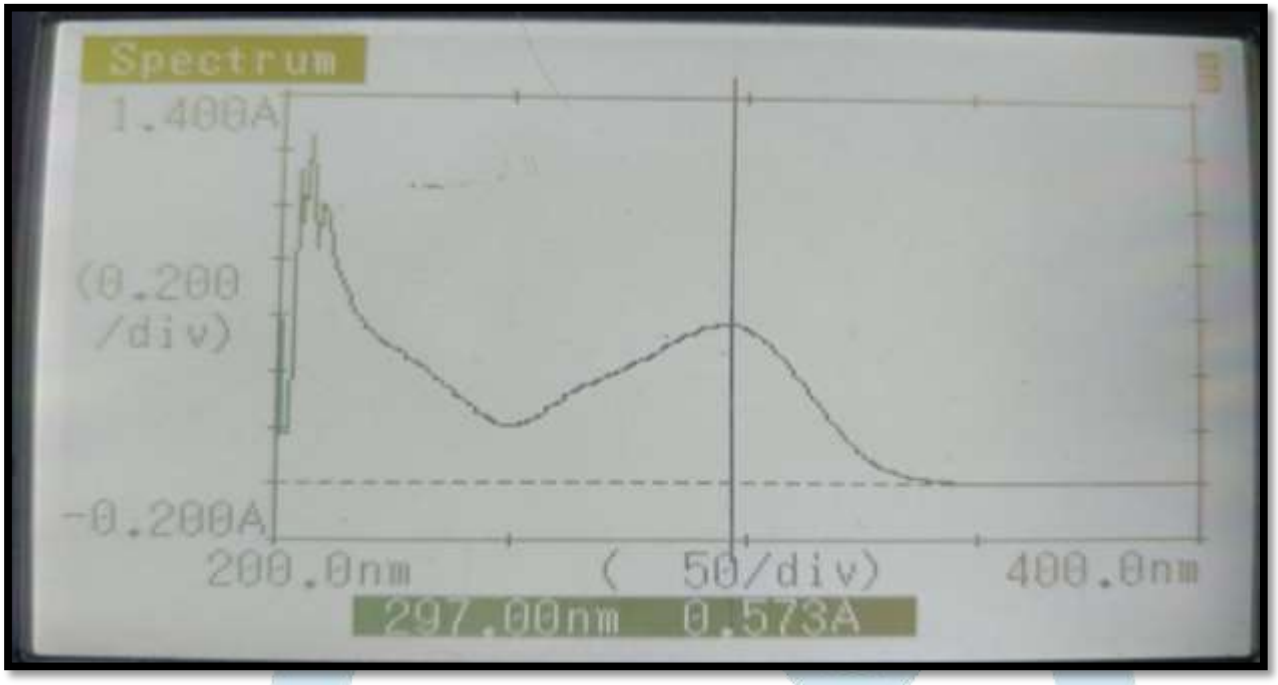

Fig. λ max of Luliconazole in Methanol.

The Wavelength of Luliconazole was found to be 297nm.

Calibration Curve in Methanol

A standard calibration curve of Luliconazole was prepared in Methanol using a UV-Visible spectrophotometer. Solutions in the concentration range of 1 to 5 µg/mL were prepared and their absorbance measured at 297 nm (λmax). A graph of absorbance versus concentration was plotted, showing a linear relationship, which was used to calculate drug concentrations in various analyses.

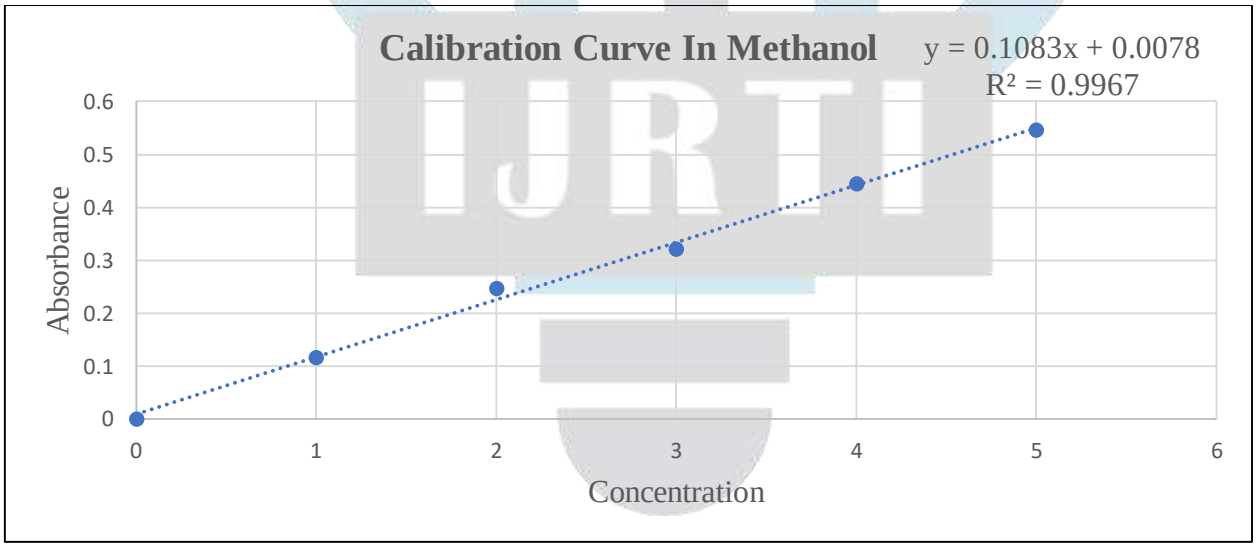

Figure: Calibration Curve in Methanol

Table: Calibration Curve of Luliconazole in Methanol

Conc. (PPM)	Abs
0	0
1	0.115
2	0.246
3	0.321
4	0.444
5	0.546

Estimation of Luliconazole by IR Spectroscopy

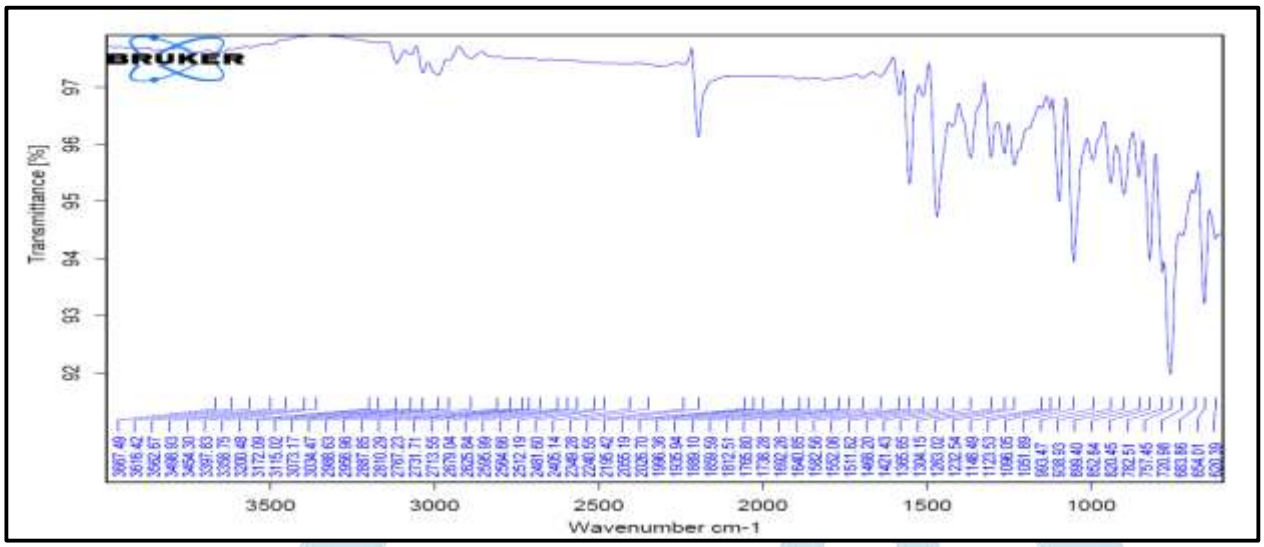

Figure: IR Spectroscopy of Luliconazole

Table 14: Functional groups and wavenumber of Luliconazole

Functional Group	Reported Wavenumber (cm^{-1})	Observed Wavenumber (cm^{-1})
C=O (Ester)	1735–1750	1738.28
C=N (Imidazole Ring)	1550–1640	1640.85, 1582.56, 1552.06
Aromatic C=C	1450–1600	1511.62, 1468.20
C–Cl (Aryl Chloride)	600–800	782.51, 757.45, 720.98, 683.86, 654.01
C–O (Ester)	1050–1300	1263.02, 1232.54, 1148.49, 1123.53, 1096.05, 1051.89
C–H (Aromatic)	3000–3100	3115.02, 3073.17, 3034.47
C–H (Alkyl)	2850–2960	2956.96, 2887.85

Estimation of Luliconazole by Differential Scanning Calorimetry (DSC)

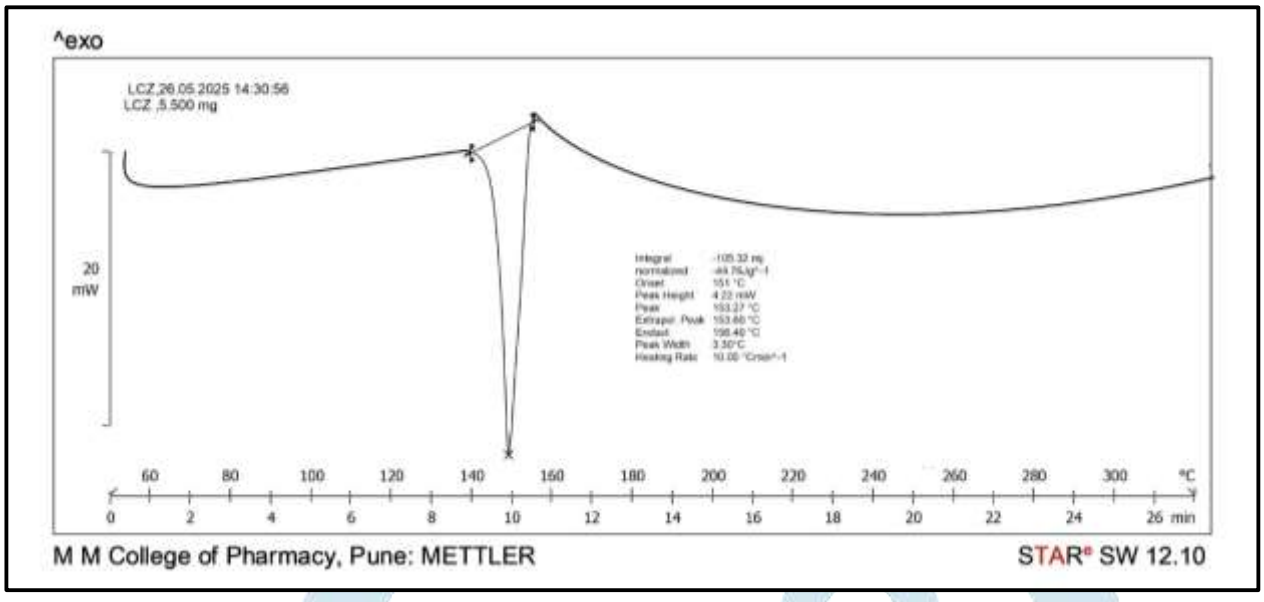

Figure: Differential Scanning Calorimetry of Luliconazole

DSC analysis of Luliconazole showed a sharp endothermic peak at 153.27 °C, confirming its crystalline nature, high purity, and thermal stability.

Compatibility Study-Fourier Transformed Infrared Spectroscopy

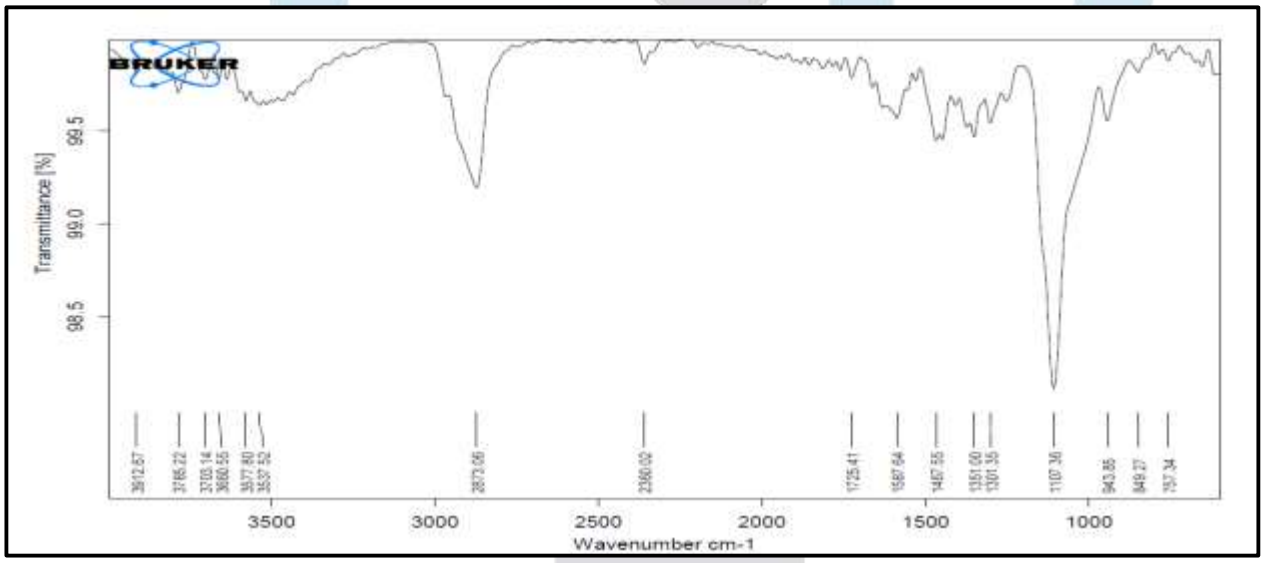

Figure: FTIR spectrum of Optimized Batch F2

Table: Interpretation FTIR spectrum of Optimized Batch F2

Functional Group	Reported Wavenumber (cm^{-1})	Observed Wavenumber (cm^{-1})
C=N (Imidazole Ring)	1550–1640	1587.64
Aromatic C=C	1450–1600	1467.55
C–Cl (Aryl Chloride)	600–800	757.34
C–O (Ester)	1050–1300	1107.36
C–H (Alkyl)	2850–2960	2873.06

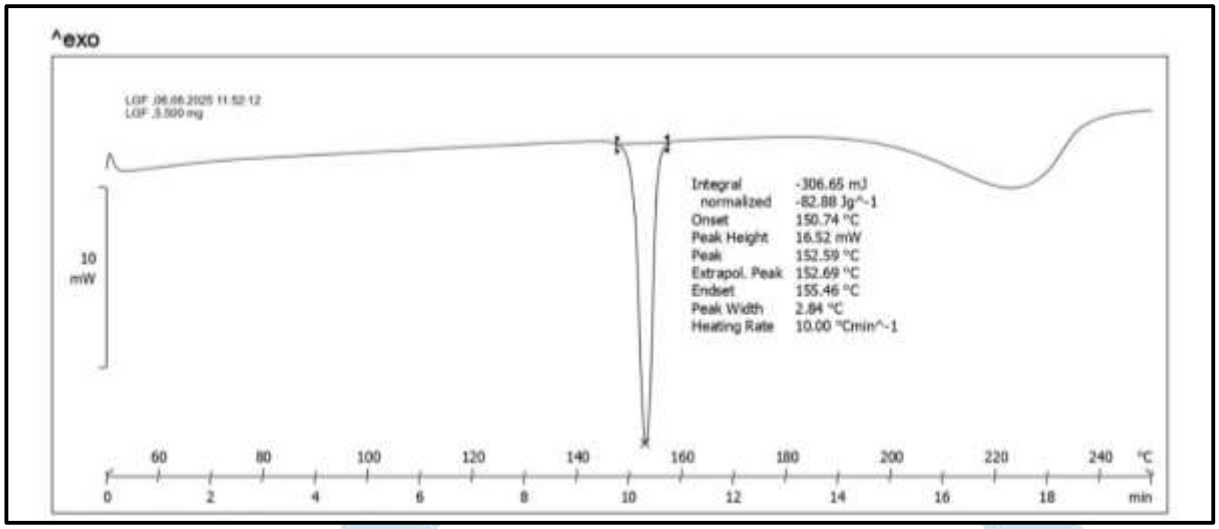

Figure: DSC of Optimize batch F2

DSC was performed to assess the thermal behavior and compatibility of Luliconazole with formulation excipients. The pure drug showed a sharp endothermic peak at 153.60 °C, indicating its crystalline nature and high purity. In the physical mixture with Poloxamer 407, HPMC, CMC, MC, and sodium alginate, the drug's melting peak was retained with slight broadening, suggesting minor physical interactions but no chemical incompatibility. This confirmed the thermal stability and compatibility of Luliconazole with all excipients used in the in-situ gel formulation.

Clarity and Homogeneity:

Table: Clarity and Homogeneity

Formulation Code	Clarity	Homogeneity
F1	Clear	Uniform
F2	Clear	Uniform
F3	Clear	Uniform
F4	Slightly cloudy	Slightly gritty
F5	Clear	Uniform

The clarity and homogeneity of the Luliconazole-loaded in-situ gel formulations were assessed visually under natural light against white and black backgrounds. Formulations F1, F2, F3, and F5 appeared clear and uniform, indicating good dispersion and stability, while F4 was slightly cloudy and gritty, likely due to incomplete polymer dispersion. Among all, F2 showed the best physical appearance, making it the most suitable for topical application.

Gelation temperature and time

Table: Gelation temperature and time

Formulation Code	Gelation Temperature (°C) (Mean ± SD)	Gelation Time (sec)
F1	31.5 ± 0.2 °C	45 seconds
F2	32.0 ± 0.1 °C	40 seconds
F3	34.0 ± 0.3 °C	50 seconds
F4	30.5 ± 0.2 °C	60 seconds
F5	33.5 ± 0.2 °C	48 seconds

Gelation temperature and time were evaluated to ensure the formulations undergo sol-to-gel transition near skin temperature (~32 °C). All formulations showed gelation temperatures between 30.5 ± 0.2 °C and 34.0 ± 0.3 °C, suitable for topical use. F1, F2, F3, and F5 were within the ideal range, while F4 had the lowest gelation temperature (30.5 °C), indicating potential for early gelation. Gelation times ranged from 40 to 60 seconds, with F2 showing the most desirable profile—32.0 ± 0.1 °C gelation temperature and a short 40-second gelation time.

pH Measurement:

Table: pH of all Formulations

Formulation Code	Ph (Mean ± SD)
F1	5.40 ± 0.05
F2	6.00 ± 0.05
F3	6.20 ± 0.04
F4	5.10 ± 0.06
F5	5.70 ± 0.03

The pH of the Luliconazole-loaded in-situ gel formulations ranged from 5.10 ± 0.06 to 6.20 ± 0.04, all within the acceptable dermal range (5.0–6.5). Measured using a digital pH meter, the results confirmed skin compatibility. Formulation F3 had the highest pH (6.20), F4 the lowest (5.10), and F2 exhibited an ideal pH of 6.00 ± 0.05, making it suitable for safe topical application without irritation.

Table: Viscosity of all Formulations

Formulation Code	Viscosity (cP) (Mean ± SD)
F1	820 ± 12 cP
F2	870 ± 10 cP
F3	910 ± 15 cP
F4	760 ± 18 cP
F5	890 ± 14 cP

The viscosity of Luliconazole-loaded in-situ gel formulations (F1–F5), measured at room temperature using a Brookfield viscometer, ranged from 760 ± 18 cP to 910 ± 15 cP. F3 showed the highest viscosity (910 cP), while F4 had the lowest (760 cP). Formulation F2 displayed an optimal viscosity of 870 ± 10 cP, indicating a good balance between spreadability and gel stability, making it well-suited for topical application.

Table: Drug Content of all Formulations

Formulation Code	Drug Content (%) (Mean ± SD)
F1	85.8 ± 1.0
F2	92.2 ± 0.8
F3	87.5 ± 1.3
F4	78.0 ± 1.5
F5	88.5 ± 1.4

Drug content analysis of Luliconazole-loaded in-situ gels (F1–F5) showed values ranging from 78.0 ± 1.5% to 92.2 ± 0.8%, indicating satisfactory drug loading. Formulation F2 had the highest drug content (92.2%), suggesting efficient entrapment and uniform distribution, likely due to optimal polymer composition. In contrast, F4 showed the lowest content (78.0%), possibly due to poor dispersion. These findings support F2 as the most effective formulation.

In vitro drug release:

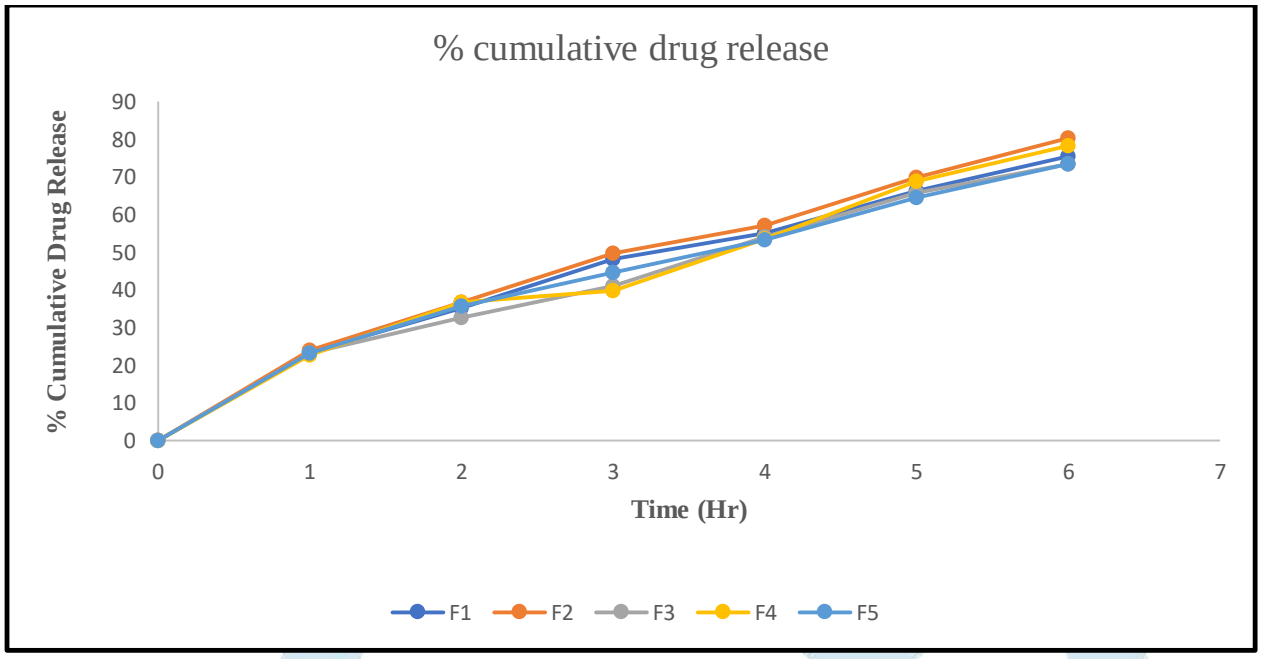

Figure: *in-vitro* release profile for formulations F1-F5

In vitro drug release of Luliconazole-loaded in-situ gels (F1–F5) was studied over 6 hours using a Franz diffusion cell. Formulation F2 showed the highest cumulative drug release (80.43%), followed by F4 (78.31%), F1 (75.53%), and both F3 and F5 (73.41%). The superior release from F2 is attributed to its optimal polymer composition enabling better gelation and diffusion. Kinetic analysis revealed that F2 followed zero-order release, indicating a diffusion-controlled mechanism and confirming its suitability as the optimized formulation for sustained topical delivery.

CONCLUSION:

Luliconazole-loaded in-situ gel formulations were successfully developed and evaluated for enhanced topical antifungal therapy. Among the batches, F2 was optimized based on its clarity, ideal gelation temperature (32.0 °C), optimal viscosity (870 cP), high drug content (92.2%), and maximum drug release (80.43% at 6 hours). FTIR and DSC studies confirmed drug-excipient compatibility. The optimized formulation exhibited good spreadability, appropriate pH, and superior antifungal activity, indicating improved bioavailability and localized efficacy. Overall, this thermosensitive in-situ gel offers a promising approach for sustained topical delivery of Luliconazole in the treatment of superficial fungal infections.

REFERENCES

1. Alsaidan, O. A., Zafar, A., Yasir, M., Alzarea, S. I., Alqinyah, M., & Khalid, M. (2022). Development of ciprofloxacin-loaded bilosomes in-situ gel for ocular delivery: Optimization, in-vitro characterization, ex-vivo permeation, and antimicrobial study. *Gels, 8*(11), 687. https://doi.org/10.3390/gels8110687.

2. Bajwa, M., Tabassam, N., Hameed, H., Irfan, A., Zaman, M., Khan, M. A., Shazly, G. A., Mehboob, T., Riaz, T., & Jardan, Y. A. (2023). Thermo-responsive sol-gel-based nano-carriers containing terbinafine HCl: Formulation, in vitro and ex vivo characterization, and antifungal activity. *Gels, 9*(10), 830. https://doi.org/10.3390/gels9100830.

3. Bhattaccharjee, S., Beck-Broichsitter, M., & Banga, A. K. (2020). In situ gel formation in microporated skin for enhanced topical delivery of niacinamide. *Pharmaceutics, 12*(5), 476. https://doi.org/10.3390/pharmaceutics12050476.

4. Chaiwut, C., Tadtong, S., Akachaipaibul, P., Jiaranaikulwanitch, J., Singh, S., Okonogi, S., Syukri, D. M., & ChittasuPho, C. (2024). Thermosensitive in situ ophthalmic gel for effective local delivery and antifungal activity of ketoconazole nanoparticles. *Gels, 11*(1), 13. https://doi.org/10.3390/gels11010013.

5. Choudhury, A., Verma, R., Sinha, D., Sahu, S., & Roy, A. (2014). Development and characterization of topical phyto-formulation for antifungal activity. *Journal of Applied Pharmaceutical Research, 2*(2), 18–21.

6. Dhalkar, P. V., Jagtap, S. S., Jadhav, S. T., Redkar, M. R., & Karande, B. S. (2019). Formulation and evaluation of in-situ gel model naproxen. *Asian Journal of Pharmacy and Technology, 9*(3), 204–207.

7. Garala, K., Joshi, P., Shah, M., Ramkishan, A., & Patel, J. (2013). Formulation and evaluation of periodontal in situ gel. *International Journal of Pharmaceutical Investigation, 3*(1), 29–35. https://doi.org/10.4103/2230-973X.107002.

8. Gözcü, S., & Polat, K. H. (2023). Thermosensitive in situ gelling system for dermal drug delivery of rutin. *Turkish Journal of Pharmaceutical Sciences, 20*(2), 78–84. https://doi.org/10.4274/tjps.galenos.2023.72834.

9. Harish, N. M., Prabhu, P., Charyulu, R. N., Gulzar, M. A., & Subrahmanyam, E. V. (2009). Formulation and evaluation of in-situ gels containing clotrimazole for oral candidiasis. *Indian Journal of Pharmaceutical Sciences, 71*(4), 421. https://doi.org/10.4103/0250-474X.57291.

10. Kasar, P. M., Kale, K. S., & Phadtare, D. G. (2018). Formulation and evaluation of topical antifungal gel containing itraconazole. *Research Journal of Topical and Cosmetic Sciences, 9*(2), 49–52. https://doi.org/10.5958/2321-5844.2018.00009.6

11. Kolawole, O. M., & Cook, M. T. (2023). In-situ gelling drug delivery systems for topical drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics, 184*, 36–49. https://doi.org/10.1016/j.ejpb.2023.02.011

12. Kurniawansyah, I. S., Rusdiana, T., Sopyan, I., Desy Arya, I. F., Wahab, H. A., & Nurzanah, D. (2023). Comparative study of in situ gel formulation based on the physicochemical aspect: Systematic review. *Gels, 9*(8), 645. https://doi.org/10.3390/gels9080645

13. Wong, Y. L., Pandey, M., Choudhury, H., Lim, W. M., Bhattamisra, S. K., & Gorain, B. (2021). Development of in-situ spray for local delivery of antibacterial drug for Hidradenitis suppurativa: Investigation of alternative formulation. *Polymers, 13*(16), 2770. https://doi.org/10.3390/polym13162770

14. Zafar, A., Alsaidan, O. A., Imam, S. S., Yasir, M., Alharbi, K. S., & Khalid, M. (2022). Formulation and evaluation of moxifloxacin loaded bilosomes in-situ gel: Optimization to antibacterial evaluation. *Gels, 8*(7), 418. https://doi.org/10.3390/gels8070418

15. Ambalal Purohit, A., Chavan, D. U., Marques, S. M., et al. (2022). Formulation and evaluation of a novel cubosomal emulgel for topical delivery of luliconazole. *Tenside Surfactants Detergents, 59*(5). https://doi.org/10.1515/tsd-2022-2442

16. Dandagi, P. M., Pandey, P., Gadad, A. P., & Mastiholimath, V. S. (2020). Formulation and evaluation of microemulsion-based luliconazole gel for topical delivery. *Indian Journal of Pharmaceutical Education and Research*, *54*(2), 293–301.

17. Malothu, N., Babu, B., Reddy, D. P., & Rathod, M. S. (2023). Formulation and evaluation of luliconazole nanosponge gel using experimental design. *Indonesian Journal of Pharmacy*, 34(1), 27–38.

18. Purohit, A. A., et al. (2025). Luliconazole-loaded nanostructured lipid carriers for the treatment of dermatophytosis in guinea pigs. *Journal of Fungi, 11*(4), 324.

19. Samarth, R. M., et al. (2024). Luliconazole-loaded nanofibers for prolonged retention and antifungal effect. *Journal of Materials Science: Materials in Medicine*. https://doi.org/10.1007/s10856-024-06815-w

20. Helal, D. A., El-Rahman, D. A., Abdel-Halim, S. A., & El-Nabarawi, M. A. (2012). Formulation and evaluation of fluconazole topical gel. *International Journal of Pharmacy and Pharmaceutical Sciences, 4*(5), 176–183.

21. Madhavi, A., et al. (2019). Enhanced solubility and skin retention of luliconazole using nanocrystal hydrogel. *Asian Journal of Pharmaceutical Sciences, 14*(6), 668–678.

22. Zafar, A., et al. (2023). Development of fluconazole nanoparticles with poloxamer 407 and HPMC for ocular delivery. *Polymers, 15*(1), 209. https://doi.org/10.3390/polym15010209

23. Chhajed, S. S., Laddha, U. D., Sonawane, S. S., et al. (2024). PLGA-luliconazole nanoparticles loaded gel: Formulation and evaluation. *Indian Journal of Pharmaceutical Education and Research, 58*(1s), s187–s195.

24. Yallavula, J., Mandava, K., & Madhav, V. (2023). Topical gel containing solid-lipid nanoparticles loaded with luliconazole. *International Journal of Pharmaceutical Research and Technology, 13*(2), 52–64.

25. Mishra, S., & Gupta, R. A. (2022). Formulation and evaluation of niosomal gel of antifungal luliconazole. *Journal of Drug Delivery and Therapeutics, 12*(6–Suppl), 5705–5713.

26. Kaur, M., Singh, G., Shivgotra, R., et al. (2020). Luliconazole vesicular-based gel formulations for enhanced topical delivery. *Journal of Liposome Research, 30*(4), 388–406.

27. Rani, R., & Pathak, K. (2012). Formulation of thermoreversible in situ gel of itraconazole for vaginal use. *Pharmacology & Pharmacy, 3*, 469–478. https://doi.org/10.4236/pp.2012.34063

28. Basak, R., & Bandyopadhyay, R. (2014). Encapsulation of hydrophobic drugs in Pluronic F127 micelles: drug loading and release properties. *arXiv preprint arXiv:1406.7073*.

29. de Ruiter, R., Royon, L., Snoeijer, J. H., & Brunet, P. (2018). Spreading of a drop from a gel: Influence of gelation dynamics. *arXiv preprint arXiv:1801.01323*.

30. Kumar, R., et al. (2020). Development of luliconazole nanoemulsion for ocular and topical applications. *International Journal of Nanomedicine, 15*, 7877–7893.

31. Choudhury, H., Pandey, M., Gorain, B., et al. (2020). Nanoemulsion-based gel of luliconazole for effective topical delivery: formulation and evaluation. *Pharmaceutical Development and Technology, 25*(2), 131–140.

32. Wadhwa, J., Nair, A., & Kumria, R. (2012). Temperature-sensitive hydrogels for oral drug delivery. *Journal of Pharmacy and Bioallied Sciences, 4*(S1), S319–S326.

33. Parhi, R., & Suresh, P. (2012). Controlled release of etoricoxib from Poloxamer 407 and Carbopol 934P based thermoreversible gel. *Tropical Journal of Pharmaceutical Research, 11*(6), 889–895.

34. Kurniawansyah, I. S., Sari, D. K., Wathoni, N., & Muchtaridi, M. (2023). Comparative review on temperature-, pH-, and ion-triggered in-situ gels. *Gels, 9*(2), 139. https://doi.org/10.3390/gels9020139

35. Patel, M., & Patel, R. (2020). In situ gelling system for sustained delivery of fluconazole. *International Journal of Pharmaceutical Sciences and Research, 11*(2), 815–822.

36. Kaur, P., & Rana, A. C. (2013). Temperature and pH-triggered in situ gel for ocular delivery of moxifloxacin. *International Journal of Pharmacy and Pharmaceutical Sciences, 5*(2), 747–752.

37. Wong, Y. L., Pandey, M., Choudhury, H., Lim, W. M., Bhattamisra, S. K., & Gorain, B. (2021). Development of in-situ spray for local delivery of antibacterial drug for Hidradenitis suppurativa. *Polymers, 13*(16), 2770. https://doi.org/10.3390/polym13162770