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# Design and In Vitro Assessment of Itraconazole Topical Gel for Fungal Infections

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**Abstract: The current study's objective is to create and evaluate an itraconazole antifungal gel. Itraconazole, a derivative of imidazole, is used to treat local and systemic fungal infections. The goal of this formulation is to increase patient compliance while reducing the dosage of the drug. When incorporated into the gel foundation, the resultant polymer-based nanocomposite preserves the inherent properties of nanoparticles while providing enhanced stability. The generated formulations were tested for physical appearance, pH, viscosity, spreadability, drug content, in vitro drug release, and antifungal activity using Candida albicans and Aspergillus Niger. The gel containing 1% w/w itraconazole and Carbopol 934p as the gelling agent has the best qualities. Its steady drug concentration (98.6 ± 0.5%), appropriate pH (6.4 ± 0.2), respectable viscosity, and adequate in vitro drug release over 8 hours were all noteworthy. Antifungal testing revealed significant inhibitory zones, indicating strong antifungal activity comparable to that of commercial therapies. The study concludes that topical gel formulation of itraconazole is a promising alternative to oral therapy for superficial fungal infections because it provides targeted delivery with enhanced efficacy and less systemic exposure. To confirm clinical efficacy and safety, more in vivo studies are recommended. Developing and testing a topical antifungal gel with itraconazole is the goal of this project in order to increase local drug delivery, minimise systemic side effects, and enhance patient adherence. Physical appearance, pH, viscosity, spreadability, drug content, in vitro drug release, and antifungal effectiveness against Candida albicans were all assessed for the produced formulations. According to the findings, the optimised gel demonstrated notable antifungal effectiveness, prolonged drug release, and favourable physicochemical characteristics. Additionally, the formulation held up well in conditions of accelerated storage.**

***Keywords:*** *Itraconazole, Topical Gel, Carbopol, Skin, Viscosity, Aspergillus Niger.*

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## I. INTRODUCTION

These days, one of the most common dermatological conditions is fungal infections of the skin. Infection is caused by microscopic organisms that penetrate the epithelial tissue. The fungus kingdom includes yeasts, moulds, rusts, and mushrooms, which are commonly found on the skin, mouth, colon, rectum, vagina, stomach, and throat. Every time this kind of organism grows, it might produce symptoms of infection in the mouth, skin, vagina, and intestine. Doctors can choose from a variety of therapy alternatives, including liquid dose formulation, solid dosage, and semisolid dosage form. One kind of topical formulation that is frequently utilised in both medicinal and cosmetic applications is clear transparent gels.

Currently, fungal skin infections are among the most prevalent dermatological diseases. Microscopic organisms that infiltrate the epithelial tissue are the source of infection. The yeasts, moulds, rusts, and mushrooms that are frequently found on the skin, mouth, colon, rectum, vagina, stomach, and throat are all members of the fungal kingdom. This type of organism may cause infection symptoms in the mouth, skin, vagina, and intestine each time it grows. A range of therapy options is available to physicians, such as semisolid dosage form, solid dosage, and liquid dose formulation. Clear transparent gels are one type of topical formulation that is commonly used in both medical and cosmetic applications.

The word "Gel" was first used to describe a semisolid material in the late 1800s, based more on pharmacological than molecular properties. According to the U.S.P., gels are semisolid systems made up of a mixture of small inorganic particles or large organic molecules. Interpenetrated and surrounded by liquid. In three dimensions, the inorganic particles form a "house of cards" structure. By exploiting the differences between fungal and mammalian cells, two antifungal drugs eliminate the fungal organism without posing a threat to the host.

Topical antifungal therapy is a crucial adjuvant in the management of dermatophytosis. Topical therapy is also often necessary for specific disorders, such as dermatophytosis in neonates and pregnant women. One of the most effective ways to administer drugs that undergo first-pass metabolism is. It is often effective in treating fungal infections. Systemic fungal infections are treated with itraconazole, a triazole derivative. By inhibiting an enzyme

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that depends on cytochrome P-450, this triazole antifungal medication stops the synthesis of ergosterol.

Aspergillosis, blastomycosis, histoplasmosis, and cryptococcal meningitis have all been treated with it. It is a BCS class II drug that has weak solubility and high permeability. Itraconazole's extremely low solubility results in a poor oral bioavailability of 55%. The study reported here focuses on the formulation of topical itraconazole gels using the synthetic polymers Xanthum gum and Carbopol 934p.

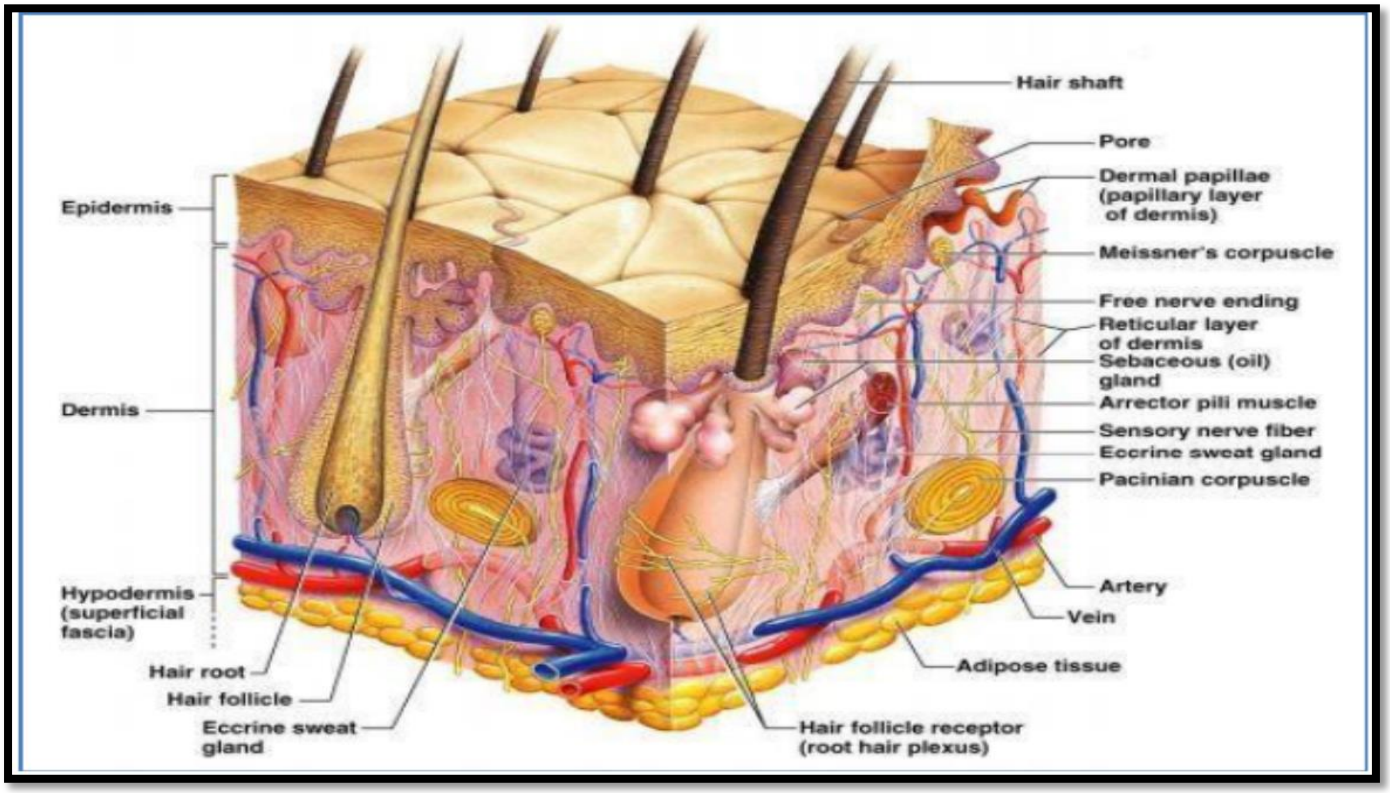


Fig 1 Structure of Skin

## II. METHODOLOGY

➢ *Analytical Methods*

- *Amax Determination Of Itraconazole*

Itraconazole 10 mg was dissolved in methanol and diluted to a concentration of 10µg/ml. The λ was determined by scanning between 220 nm and 300 nm. The chosen wavelength for λmax was 265 nm. The drug solution was further analysed using the same method, and at 265 nm, the final standard solution's absorbance was measured.

➢ *Calibration curve of Itraconazole:*

- *Preparation Of Standard Solution:*

Itraconazole was made into a standard stock solution in methanol. A little amount of methanol was used to dissolve 100 mg of itraconazole, which had been precisely weighed into a 100 mL volumetric flask. 6.8 phosphate buffer was used to make up the volume to achieve a concentration of 100 µg/ml (SS-I). To obtain a concentration of 100µg/ml, 10 ml of the solution was taken out and diluted to 100 ml.

- *Preparation Of Working Standard Solutions:*

Additionally, 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, and 1 ml aliquots were pipetted into 10 ml volumetric flasks from (BSS-II). Using pH 6.8 phosphate buffer, the volume was adjusted to achieve final concentrations of 2, 4, 6, 8, and 10 µg/ml, respectively. At 265 nm, the absorbance of every quantity was determined.

➢ *Characterization of Gel*

- *Organoleptic Characteristics:*

The formulations' psych rheological qualities, such as colour, texture, phase separation, scent, and feel (greasiness, grittiness) upon application, were evaluated.

- *Wash Ability:*

The skin was treated with a tiny amount of gel. I tested to see if the gel was fully washable after giving it a water wash.

- *Spread Ability:*

A modified wooden block and glass slide setup was used to measure it. A fixed glass slide and a moving pan with a glass slide attached were both covered with a calculated amount of gel. For five minutes, the gel was sandwiched between the two glass slides. The weight kept coming off. The following formula was used to determine spreadability:

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$$S = M/T$$

Where,

S is the Spreadability in g/s,
The M is the mass in grams &
T is the time in seconds.

- *pH:*

One gram of gel was dissolved in thirty millilitres of distilled water to create a solution with a pH of seven. By touching the probe of a digital pH meter to the samples, the pH of the gel was ascertained.

- *Content Homogeneity And Drug Content:*

1g of gel was constantly agitated for 48 hours while dissolving in 100 mL of phosphate buffer (pH 6.8) using a magnetic stirrer.

➢ *In Vitro Release Studies from Dialysis Membrane*

An open-ended diffusion cell that was specifically created in our lab according to the literature was used to investigate the skin penetration of itraconazole from the formulation. The diffusion cell's effective permeation area was 2.4 cm, whereas the receptor cell's volume was 200 ml. A constant temperature of 37 ± 0.5°C was maintained. 200 millilitres of pH 6.8 buffer were kept in the receptor compartment, which was continuously agitated at 100 rpm using a magnetic stirrer. The donor and receptor compartments were separated by a prepared dialysis membrane. The dialysis membrane was coated with the formulation, and the diffusion cell's contents were continuously stirred.

Following appropriate dilution, 5 ml of the samples were taken out of the diffusion cell's receptor compartment at prearranged intervals and examined using a spectrometric technique at 265 nm. Fresh pH 6.8 buffer in an equivalent volume was promptly added to the receptor phase. Drug release investigations were carried out in triplicate.

## III. MATERIALS & METHODS

- Itraconazole (Active Pharmaceutical Ingredient) (98%).
- Gelling Agents: Carbopol 934p, Xanthum gum, Guar gum.
- Penetration Enhancers: Propylene Glycol, DMSO.
- Preservatives: Methylparaben, Propylparaben, Sodium Benzoate.
- Triethanolamine, potassium hydroxide flakes, and sodium hydroxide flakes are pH adjusters.
- Solvent: Ethanol, Water.

Table 1 Materials Required

| S.NO | INGREDIENTS | Manufacturer |
|---|---|---|
| 1 | Itraconazole | Lab grade |
| 2 | Carbopol(934p) & Xanthum gum | Lab grade |
| 3 | Propylene Glycol& DMSO | Lab grade |
| 4 | Methylparaben, Propylparaben & Sodium Benzoate | Lab grade |
| 5 | Triethanolamine& sodium hydroxide flakes & Potassium hydroxide flakes | Lab grade |

## FORMULATION & DEVELOPMENT

After adding the required quantity of Carbopol (934p) to water, the mixture was left to soak in a beaker for a full day. In other beakers, the drug was dissolved in PEG and DMSO. The drug solution was mixed with the gel base. Propyl and methyl parabens were added to the gel as supplements. Triethanolamine was used to bring the gel's pH down to 5.5. The necessary volume of distilled water was added to the gel's final volume.

Table 2 Formulation of Gel

| INGREDIENTS | IF1 | IF2 | IF3 | IF4 |
|---|---|---|---|---|
| Itraconazole (gm) | 2 | 2 | 2 | 2 |
| Carbopol 934p(F1)/ Xanthum gum(F2)/ Guar gum (F3)/HPMC(F4) (gm) | 1.5 | 1.5 | 1.5 | 1.5 |
| Dimethyl Sulfoxide (DMSO) (ml) | 4 | 4 | 4 | 4 |
| Methyl paraben/ Ethyl paraben (gm) | 0.2/0.5 | 0.2/0.5 | 0.2/0.5 | 0.2/0.5 |
| Propylene glycol (PEG) | 10 | 10 | 10 | 10 |
| Triethanolamine (ml) | Q. S | Q. S | Q. S | Q. S |
| Water (ml) | 100 | 100 | 100 | 100 |

## IV. RESULTS

➢ *Preformulation Studies*

- *Description:*

The following table shows the results of these tests, which were carried out by the protocol:

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Table 3 Table Showing the Description of Itraconazole (API)

| TEST | DESCRIPTION |
|---|---|
| Colour | A white to slightly yellowish powder |

- *Result:*
  The results were found as per specifications.

- *Solubility:*
  The following table shows the results of these tests, which were carried out following the protocol:

Table 4 Solubility of Itraconazole (API) in Various Solvents

| SOLVENTS | SOLUBILITY |
|---|---|
| Water | Insoluble |
| pH 6.8 Phosphate buffer | Soluble |
| DMSO | Freely soluble |
| Ethanol | Freely soluble |

- *Melting Point:*
  The following table shows the results of these tests, which were carried out under the protocol:

Table 5 Showing the Melting Point of API's

| MATERIAL | MELTING POINT | MELTING POINT RANGE |
|---|---|---|
| Itraconazole | 167ºc | 166-170ºc |

- *Result:*
  The Result was found to be within the limit.

➢ *Analytical Study*

- *Calibration Curve in Ph 6.8 Phosphate Buffer Standard Calibration Curve*

Table 6 Concentration and Absorbance.

| S.NO | CONCENTRATION | ABSORBANCE |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 0.115 |
| 3 | 4 | 0.221 |
| 4 | 6 | 0.322 |
| 5 | 8 | 0.425 |
| 6 | 10 | 0.526 |

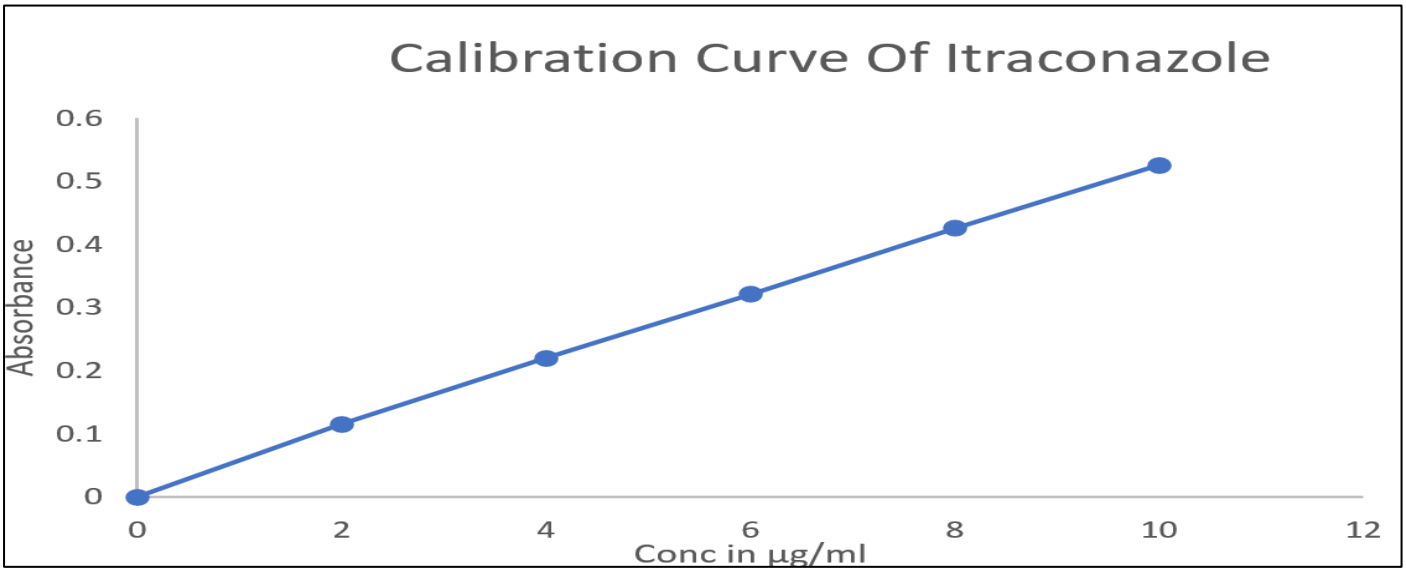


Fig 2 Calibration Curve of Itraconazole Drug.

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➢ *FTIR STUDIES*

Infrared spectra were compared and analysed for functional group non-involvement and any shifting of functional peaks. It is evident from the spectra that the medication, the mixes, and the chosen carriers do not interact. Therefore, there were no interactions between each other and the selected carrier was determined to be consistent with entrapping the chosen itraconazole.

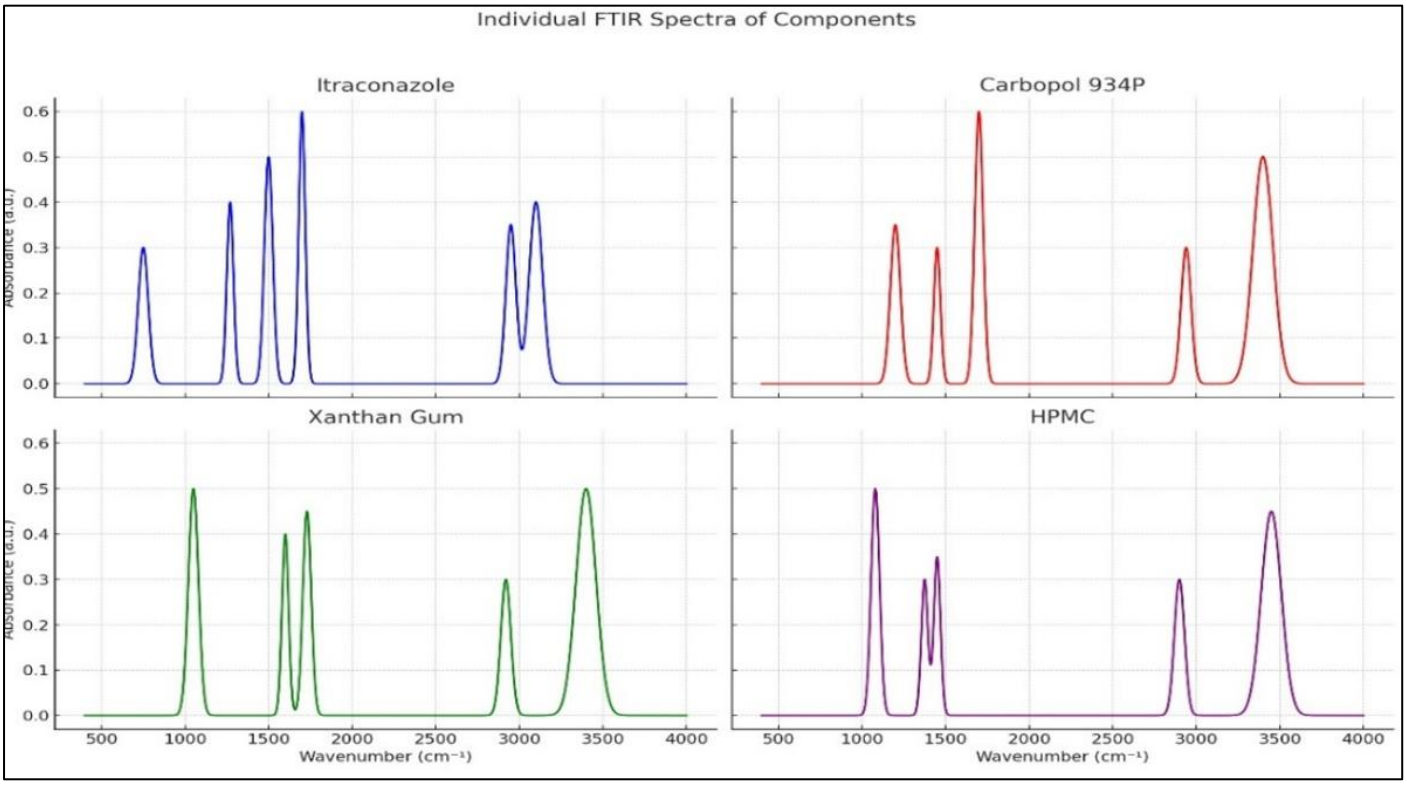


Fig 3 FTIR Spectra of ITRACONACOLE, CARBOPOL 934p, XANTHUM Gum and HPMC.

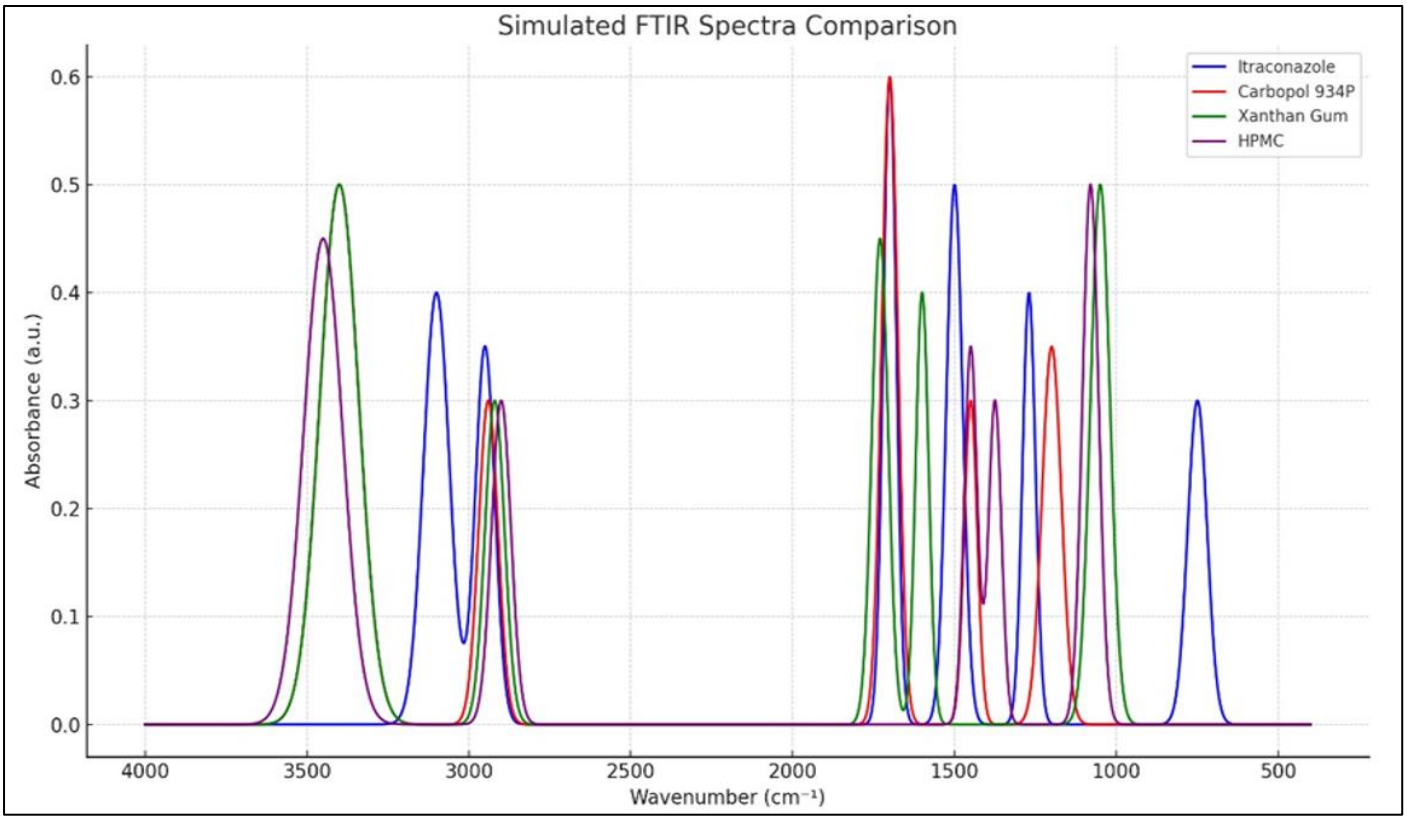


Fig 4 FTIR SPECTRA of ITRACONAZOLE FINAL FORMULATION

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Table 7 Values of FTIR for Each Peak

| WAVENUMBER REGION ($CM^{-1}$) | FUNCTIONAL GROUP | MATERIALS EXHIBITING PEAK |
|---|---|---|
| ~3400 | O–H stretching (hydrogen bonded) | Carbopol, Xanthan Gum, HPMC |
| ~2950–2920 | C–H stretching (aliphatic) | All |
| ~1730–1700 | C=O stretching (carbonyl) | Itraconazole, Carbopol, Xanthan Gum |
| ~1600–1500 | Aromatic C=C or $COO^-$ stretch | Itraconazole, Xanthan Gum |
| ~1375–1450 | $CH_2$ bending, methyl bending | Carbopol, HPMC |
| ~1270–1050 | C–O, C–O–C stretching | All |
| ~740–800 | C–Cl stretching or aromatic bending | Itraconazole |

➢ *Evaluation of Prepared Gel:*

- *Physical Evaluation:*

The organoleptic attributes, occlusiveness, and washability of each itraconazole formulation have been investigated.

Table 8 Physical Evaluation

| | |
|---|---|
| Organoleptic Characteristics: | The colour is golden brown.<br>Gracelessness: Not oily<br>Grittiness: Not at all gritty.<br>Application simplicity: applied quickly and easily.<br>Skin irritation: Not at all |
| Washability: | Washing is simple and leaves no residue on the skin's surface. |
| Physical evaluation: | IF1-WHITE<br>IF2-WHITE<br>IF3-WHITE<br>IF4-WHITE |

- *Measurement of pH:*

A digital pH meter was used to measure the prepared gels' pH. The electrode was immersed in the gel, and readings were recorded from a pH meter. The pH values for all formulations were in the range of 6.5 to 6.8.

Table 9 pH Measurements

| FORMULATION CODE | PH |
|---|---|
| IF1 | 6.1 |
| IF2 | 6.3 |
| IF3 | 6.6 |
| IF4 | 6.2 |

- *Viscosity Study:*

Viscosity measurements were done on a Brookfield viscometer by selecting a suitable spindle number and rpm. A 50 ml beaker containing 50 g of preparation was placed till the spindle groove was dipped, the rpm was adjusted, and the dial reading was measured after three minutes. From the reading obtained, viscosity was calculated by using the factor. Three iterations of the process were conducted, and the mean of the observations was noted.

- *Spread Ability:*

A sample of 0.1 g of each formula was pressed between two slides (divided into squares of 5 mm sides) and left for about 5 minutes, where no more spreading was expected. Spread circle diameters were measured in centimetres and used as a benchmark for spreadability. The results obtained are the average of three determinations.

- *Extrudability Study:*

Filling the gel in the collapsible tubes allowed researchers to assess the extrudability of various gel formulations the extrudability was determined in terms of the weight in grams required to extrude a 0.5 cm ribbon of gel.

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Table 10 Evaluation of Gel

| Formulation code | Viscosity(cps) | Spreadability(gm·cm/sec) | Extruded amount (%) | Drug Content (%) |
|---|---|---|---|---|
| IF1 | 45670 | 11.50 | 82.25 | 93.07 |
| IF2 | 52680 | 11.75 | 86.15 | 94 |
| IF3 | 43590 | 12.45 | 84.60 | 95.4 |
| IF4 | 48569 | 11.98 | 80.08 | 92.25 |

- *Drug Content:*

Ten grammes of each gel formulation, weighed, were added to a 250 millilitre volumetric flask with twenty millilitres of alcohol, and the mixture was swirled for half an hour. The volume was filtered after being increased to 100 millilitres. One millilitre of the aforementioned solution was diluted with ten millilitres of alcohol, and then again with ten millilitres of alcohol. Using spectrophotometry, the solution's absorbance was determined at 260 nm. Drug content was calculated by the following formula:

Drug content = absorbance/slope× dilution factor× 1/100

- *In Vitro Diffusion Studies:*

The drug release from the formulations was determined by using the apparatus, which consists of a cylindrical glass tube (with 22-mm internal diameter and 76 mm height), which was opened at both ends. A cellophane membrane that had been soaked in medium for 24 hours was covered with 1 gm of gel, which is equal to 10 mg of itraconazole, and it was adhered to one end of the tube. The entire structure was secured such that the gel-containing tube's lower end barely touched (1-2 mm deep) the diffusion medium's surface, which is 100 millilitres of pH 7.4 phosphate buffer.

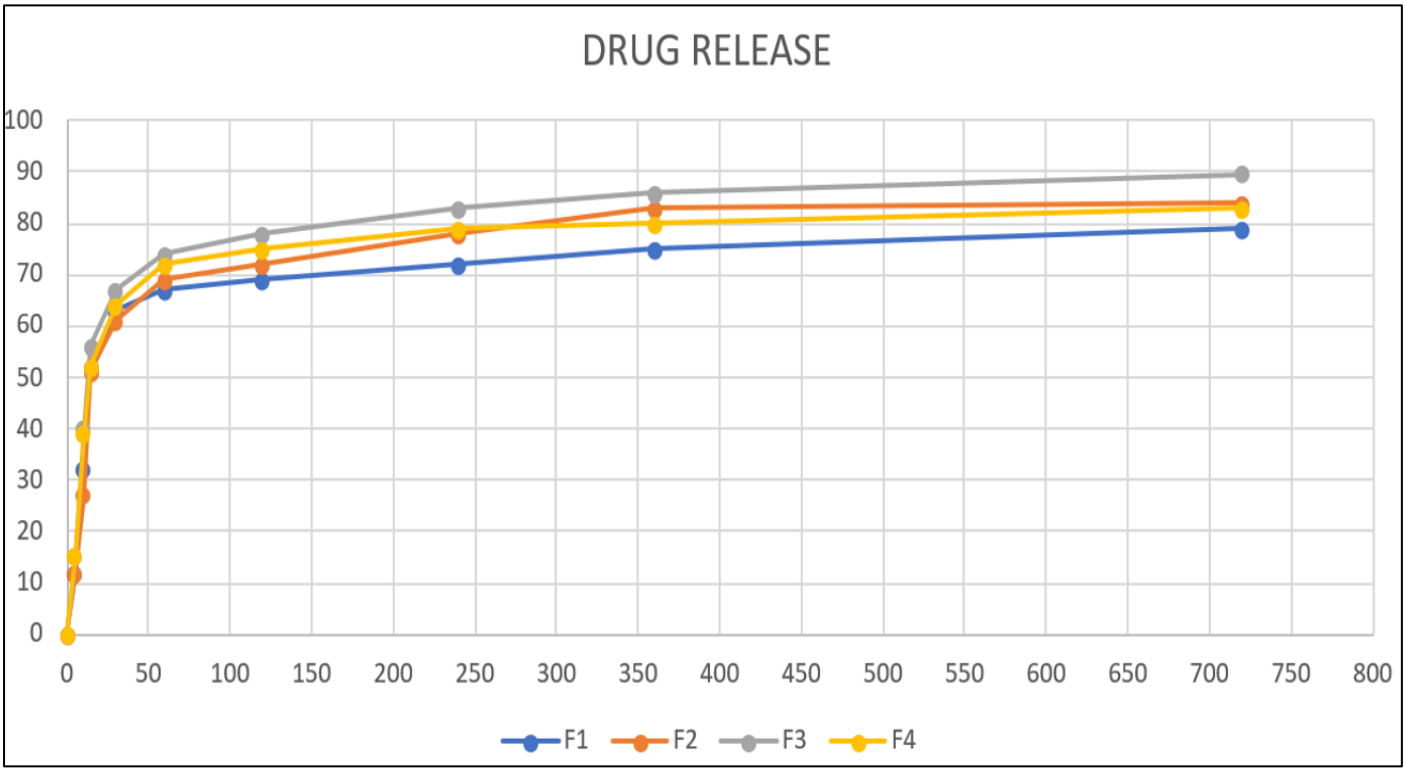


Fig 5 In-Vitro Release Study for F1-F4

Table 11 In Vitro Diffusion Studies

| TIME | CONCENTRATION | F1 | F2 | F3 | F4 |
|---|---|---|---|---|---|
| 10 | 0 | 0 | 0 | 0 | 0 |
| 20 | 50 | 12 | 12 | 15 | 15 |
| 30 | 10 | 32 | 27 | 40 | 39 |
| 40 | 15 | 52 | 51 | 56 | 52 |
| 50 | 30 | 63 | 61 | 67 | 64 |
| 60 | 60 | 67 | 69 | 74 | 72 |
| 70 | 120 | 69 | 72 | 78 | 75 |
| 80 | 240 | 72 | 78 | 83 | 79 |
| 90 | 360 | 75 | 83 | 86 | 80 |
| 100 | 720 | 79 | 84 | 89.7 | 83 |

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## V. CONCLUSION

The study successfully formulated a topical gel containing itraconazole with satisfactory physicochemical properties and enhanced antifungal activity. Among the tested formulations, xanthum gum-based gel demonstrated the most promising results in terms of drug release, spreadability, and microbial inhibition. Topical delivery of itraconazole offers a promising strategy for treating superficial fungal infections by improving local drug concentration, minimising systemic side effects, and enhancing patient adherence. This formulation can be further optimised and tested through in vivo studies and clinical trials for commercial application**.**

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