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FORMULATION AND EVALUATION OF MUCOADHESIVE GEL FOR ORAL CANDIDIASIS

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Keywords:

Oral candidiasis, Pathogenesis, Mucoadhesive strength, *In-vitro* antifungal

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ABSTRACT: Oral candidiasis (OC) is a common fungal infection characterized by white patches on the oral mucosa, often triggered by factors like immunosuppression and medication use. It can affect anyone, regardless of age or background. The formulation of mucoadhesive gels for the treatment of oral candidiasis is a promising area of research. The gel enhances the residence time of the drug at the site of infection, thereby improving therapeutic efficacy. This study aimed to develop a mucoadhesive gel for oral candidiasis treatment using an inclusion complex of itraconazole and beta-cyclodextrin. Different concentrations of mucoadhesive polymers (Carbopol 940) and absorption enhancers (Poloxamer 188 and propylene glycol) were used. The pH of the gels ranged from 6.5 to 7.2. The viscosity varied between 300 and 600 cps. The gelation temperature was 30°C to 35°C. Spreadability ranged from 4.7 to 4.83 cm. The drug content was found to be 90% to 95%. Mucoadhesive force ranged from 3549 to 3917 dyne/cm^2. Drug release lasted 6 hours, with 95 to 99% cumulative release. *In-vitro* antifungal activity showed a zone of inhibition of 10 to 15 mm against *Candida albicans*. The mucoadhesive gels exhibited favourable physicochemical properties and demonstrated potential for oral candidiasis treatment and therapeutic efficacy for treating oral candidiasis.

INTRODUCTION: Oral candidiasis (OC) is a fungal infection caused by Candida yeast overgrowth in the oral cavity. It manifests as white patches on the mouth's surfaces, which can be scraped off to reveal red areas underneath. OC can affect anyone, and certain factors like immune suppression, underlying medical conditions, and medication use can trigger its development. Weakened immune systems and certain medical conditions increase the risk of OC, as does the use of antibiotics, corticosteroids, and immune-suppressants [1].

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Pathogenesis: Oral candidiasis results from the interplay between the immune system, oral microbiome, and Candida species, with Candida overgrowth, triggered by factors like adhesion to oral surfaces, biofilm formation, and immune responses, particularly involving innate and adaptive immune cells, cytokines, and chemokines. Immunocompromised individuals are more vulnerable to oral candidiasis due to impaired immune function. Various host factors, including oral mucosal changes, dry mouth, and antibiotic use, can influence its development. The pathogenesis of white and erythematous candidiasis differs to some extent [2].

***Ex-vivo* Mucoadhesive Drug Delivery System:** Mucoadhesive drug delivery systems utilize mucoadhesion to enhance drug effectiveness by increasing bioavailability, stability, and retention time at mucosal surfaces.

They can be classified as bioadhesion or mucopenetration mechanisms. Mucoadhesive gels are commonly used for oral, nasal, ocular, vaginal, and rectal drug delivery, with oral mucoadhesive gels used for local oral treatments and systemic drug delivery, bypassing first-pass metabolism. These gels employ mucoadhesive polymers to achieve sustained drug release and improved therapeutic efficacy [3].

Advantages [4]:

- Enhanced drug bioavailability and efficacy at the target site.
- Reduced dosing frequency, improving patient compliance.
- Bypass first-pass metabolism, increasing drug availability.
- Improved drug stability, protecting against degradation.
- Customizable drug release profiles through formulation design.
- Non-invasive administration without injections or invasive procedures.
- Versatility for various mucosal surfaces.

Disadvantages [5]:

- Variability in mucoadhesive performance affecting consistency.
- Potential irritation or allergic reactions at the application site.
- Limited drug loading capacity, restricting high-dose delivery.
- Interference with normal physiological functions.
- Possible discomfort or inconvenience during application or administration.

Triazole antifungals are a class of antifungal medications commonly used for the treatment of oral candidiasis. Some examples of triazole antifungals include fluconazole, itraconazole, and voriconazole. These drugs are typically administered orally in conventional dosage forms, such as tablets or capsules, for the treatment of oral candidiasis [6]. However, these conventional dosage forms may have limitations in terms of drug retention, prolonged contact with the affected mucosal surfaces, and controlled drug release at the site of infection. To overcome these challenges, the use of a mucoadhesive gel as a drug delivery system for oral candidiasis may offer potential advantages [7].

The mucoadhesive gel formulation can be customized to include the triazole antifungal drug, along with appropriate mucoadhesive polymers and excipients, to optimize mucoadhesion, drug release, and stability. This formulation approach can potentially overcome the limitations of conventional dosage forms and enhance the effectiveness of triazole antifungals in the treatment of oral candidiasis [8]. Itraconazole, a triazole antifungal, has poor aqueous solubility, limiting its effectiveness for oral candidiasis. To overcome this, inclusion complexes of itraconazole with beta-cyclodextrin have been developed. These complexes enhance solubility and dissolution by encapsulating itraconazole within beta-cyclodextrin's hydro-phobic cavity [9]. The objective of this research work is to formulate and evaluate a mucoadhesive gel as a drug delivery system for oral candidiasis, focusing on the preparation and characterization of the gel, measurement of its *ex-vivo* mucoadhesive strength, and assessment of its *in-vitro* antifungal activity.

MATERIALS AND METHODS: Itraconazole from SMS Pharmaceuticals (Hyderabad), Carbopol 940(DELLOL), poloxamer 188 (Simson Pharma), beta-cyclodextrin (Manas Aktteva Biopharma), and propylene glycol (Niram Chemicals) were procured. All other materials used were of analytical grade.

Preformulation Study:

Melting Point: The melting point of the drug was determined using the capillary technique. The drug sample was placed in a sealed capillary tube and heated gradually in a digital melting point apparatus. The temperature at which the drug completely melted was recorded as its melting point. The process was repeated three times for accuracy [10].

FTIR Analysis: Compatibility studies were conducted using FT-IR spectral analysis to detect any potential chemical interaction between the drugs and polymers. Samples of the drug, polymer powder, and physical mixture of different drug-polymer combinations were prepared and formed into pellets with potassium bromide. The samples were scanned using a Bruker FTIR spectrophotometer, ranging from 4000 - 500 cm-1. The obtained spectra were compared and analyzed for the presence of functional group peaks to assess compatibility [11].

Preparation of Formulation of Itraconazole Mucoadhesive Oral Gel: The gel was developed by enhancing the water solubility of Itraconazole by preparing an inclusion complex. Equal proportions of the drug and beta-cyclodextrin were mixed with ethanol and dried. The dried complex was then powdered and utilized in the formulation of the mucoadhesive gel.

Poloxamer 188 was mixed with a small amount of water at 5°C. The gel contained 1% medication, along with absorption enhancers and propylene glycol. Carbopol 940 was mixed separately with water, and the Poloxamer 188 solution was combined with the carbopol 940-water mixture. After 1 hour of mixing, the mixture was diluted to a final volume of 25 mL using distilled water. The resulting gel formulation was stored at room temperature for further use [12].

TABLE 1: FORMULATION TABLE OF MUCOADHESIVE GEL

Formulation code	Drug (% w/v)	Carbopol 940 (% w/v)	Poloxamer 188 (% w/v)	Propylene glycol (ml)	Distilled water (upto 25 ml)
F 1	1	1	0.5	1	q.s
F 2	1	1.5	1	1	q.s
F 3	1	2	1.5	1	q.s
F 4	1	2.5	2	1	q.s
F 5	1	3	2.5	1	q.s

Characterization of Mucoadhesive Gel:

pH of Mucoadhesive Gel: In a beaker containing 15mL of pH 6.8 PBS, one gram of gel was placed. Following that, surface pH measurements were taken at 0.30, 1.0, 1.30, 2, 3, 4, 5, and 6 h intervals [13].

Viscosity Studies: Gel thickness was resolved to utilize a Brookfield Viscometer (Variant 5.1). The estimations were taken with a T-molded shaft No. 63. Viscosity was determined at various rpms after one minute equilibration period at each rpm. Samples were transferred to the spindle with a spatula to avoid formulation shearing, and the viscometer was adjusted at room temperature [14].

The sample viscosity was calculated by increasing the experimental reading by the shear rate.

Viscosity (cps) = (300 / N) measured value, N = revolutions per minute

Gelation Temperature: The gelation temperature was determined by gradually heating the given amount of sample of Carbopol 940 and poloxamer188 of each formulation in phosphate buffer 6.8 in a beaker placed on a temperature-regulated water bath while continuously stirring at 50 revolutions per minute. The gelation temperature was identified visually when the gel solidified, indicated by the cessation of movement of the magnetic bar, and the corresponding temperature of the water bath was recorded[15].

Spreadability: The Spreadability of the formulation was measured by spreading 0.5 g of the gel on a circle of 2 cm diameter premarked on a glass plate and then a second glass plate was employed. Half a kilogram of weight was permitted to rest on the upper glass plate for 5 min. The diameter of the circle after spreading the gel was determined [16].

Drug Content: The drug content of each gel formulation was determined by weighing 10 grams of the formulation, mixing it with 20 ml of PBS (pH 6.8) in a volumetric flask, and swirling it for 30 minutes.

The resulting solution was filtered, and a 1:10 dilution was prepared. Spectrophotometric measurements of the diluted solutions at 263 nm were taken, and the drug content was calculated using the absorbance values, slope, dilution factor, and the formula provided [17].

Drug content = (Absorbance/Slope) × Dilution factor × (1/1000) [17]

***Ex-vivo* Measurement of Mucoadhesive Force:** To measure the mucoadhesive force of the gel, goat buccal tissue segments were securely attached to glass vials using a rubber band and placed in a 36.5°C environment. One vial was paired with another on a movable skillet, and 1 gram of poloxamer gel was applied to the buccal tissue surface. Gradually increasing loads were applied to the vial setup until separation occurred, and the minimum load required was recorded as the bioadhesive strength in grams of force. This process was repeated using fresh buccal tissue fragments for accurate and consistent measurements [18, 19].

***In-vitro* Drug Release Study:** A modified Franz dispersion cell was utilized to concentrate on the medication arrival of the fluconazole bioadhesive gel dissemination tubes with an inner width of 2cm and a cellophane film toward one side will be utilized. The cylinder was loaded up with two grams of gel. This collection was soaked in a measuring glass filled with 20 ml of Phosphate buffer solution (pH 6.8) and kept over a thermostatically controlled stirrer set to 37°C. The items in the receptacle were mixed at 300 rpm with a Teflon-covered dot. To keep up with the sink conditions, the examples (2ml) were removed at 0.30, 1, 2, 3, 4, 5, and 6 h and supplanted with phosphate buffer (pH 6.8). The drug content of the sample was determined using spectrophotometry [19-23].

***Ex-vivo* Permeation of Drug through the Buccal Mucosa:** *Ex-vivo* permeation tests were conducted on freshly excised buccal tissue from goats within two hours of collection. The tissue was handled carefully, and the mucosa was separated while preserving the basal membrane. After cleaning and inspection, the buccal mucosa was stored in pH 6.8 phosphate-buffered saline at 4°C for 24 hours before the permeation studies. The permeation studies used modified Franz diffusion cells with a 2 cm internal diameter. The goat buccal mucosa was placed at one end of the diffusion tube, and 2 grams of the gel formulation under investigation were added. The setup was immersed in a beaker containing 20 ml of pH 6.8 PBS and maintained at 37±1°C using a thermostatically controlled magnetic stirrer operating at 600 rpm. Samples (2 ml) were withdrawn at predetermined time intervals: 0.30, 1, 2, 3, 4, 5, and 6 hours. Each withdrawn sample was replaced with an equal volume of pH 6.8 PBS to maintain the system's volume and composition. Drug content analysis was performed on each sample to determine the extent of drug permeation through the buccal tissue [20-25].

***In-vitro* Antifungal Study:** The agar-cup diffusion method was employed for the tests using Candida albicans cultures (AJ 005123) and Sabouraud dextrose agar as the growth medium. The Candida albicans strain was diluted in a sterile 0.85% NaCl solution to achieve a concentration of 10^6 CFU/mL. A sterile swab was used to seed the culture onto agar plates by dragging it uniformly across the surface. Wells with a diameter of 6 mm was made in the seeded agar plates, and 20 mg of itraconazole gel and 20 mg of the commercial formulation (1%) were added to separate wells. The plates were frozen briefly and then incubated at 37°C for 24-48 hours. The diameter of the zone of inhibition around each well was measured and compared to the manufactured formulation and the marketed formulation [25-28].

Drug release kinetics: Mathematical models were used to analyze drug release kinetics and mechanisms from the formulations. Four models were considered:

- Zero-order kinetic model ($A_t = A_0 - K_o t$),
- First-order kinetic model (Log C = log Co - $2.303K_t$),
- Higuchi model ($Q = Kt^{(1/2)}$),
- Korsmeyer-Peppas equation ($M_t/M_\infty = Kt_n$).

The model with the highest 'r-value, indicating the best fit to the release data, was selected. These models provide insights into drug release behavior and mechanisms, including constant release, concentration-dependent release, diffusion-based release, and various release mechanisms characterized by the release exponent 'n' [29-30].

Stability Studies: Stability studies were conducted at 45°C and 75% RH for three months to assess

their stability. After storage, the formulation was subjected to FTIR analysis, pH, spreadability, and drug content [29-32].

RESULT AND DISCUSSION:

FTIR Analysis: The Fourier Transform Infrared (FTIR) analysis of the physical mixture of Itraconazole, Carbopol 940, Poloxamer 188, and beta-cyclodextrin revealed the presence of various functional groups. The observed IR peaks indicated the presence of C-N (1103.70 cm^{-1}), C-C (1453.27 cm^{-1}), C_6H_5 (1551.16 cm^{-1}), C-O-C (1100.58 cm^{-1}), OH (3395.54 cm^{-1}), CH_2 (2872.35 cm^{-1}), and C=O (1699.42 cm^{-1}) groups in the mixture. These peaks correspond to specific chemical bonds and provide valuable information about the molecular composition of the physical mixture. The FTIR analysis confirmed the presence of these functional groups, suggesting the successful incorporation of the components in the mixture. These findings contribute to the understanding of the chemical interactions and compatibility between the constituents, which is important for formulating effective drug delivery systems.

Melting Point: The melting point of the drug was found to be 164.3± 1.5 °C.

pH of the Formulated Mucoadhesive Gel: The surface pH of the buccal mucoadhesive gel remained stable throughout the 6-hour test period, ranging from 6.7 to 7.0. This pH range is within the neutral range of saliva (5.8 to 7.1). The consistent pH readings indicate that the polymeric blend used in the gel formulation is suitable for oral administration, minimizing the risk of adverse effects or discomfort.

Viscosity: The table shows viscosity measurements of different formulations, with the highest viscosity observed in formulation F5 containing Poloxamer, Carbopol, and polyethylene glycol. The use of different absorption enhancers significantly influenced the viscosity, highlighting their impact on flow properties. Viscosity is a crucial parameter that affects gel application, adherence, and drug release, making its optimization important for optimal bioadhesive gel performance. The obtained viscosity data aids in the selection and optimization of absorption enhancers to achieve the desired viscosity range for optimal gel functionality.

Gelation Temperature: The gelation temperature of a bioadhesive gel is crucial for its effectiveness, with an ideal range of 30 to 36°C. Poloxamer 188, known for its thermosensitive gelling properties, was selected for the formulation. However, using Poloxamer 188 alone did not achieve the desired gelation temperature range. By combining Poloxamer 188 with carbopol 940, successful gelation at physiological temperature was achieved. The gelation temperature is influenced by the concentration and content of carbopol 940 and Poloxamer 188, with the temperature change associated with the molecular configuration shift of Poloxamer 188 from a zigzag to a meander structure.

Spreadability: The spreadability of the gels was in the range of 4.7±0.01 to 5.3±0.20 cm after 5 minute. The viscosity of gel formulations F3 and F4 prepared was adequate, hence showed high spreadability and good extrudability.

***Ex-vivo* Mucoadhesive Strength:** A gel's bioadhesive force is determined by its ability to attach to the buccal mucosa. Hydrophilic polymers can form strong connections with the mucosal chains of oligosaccharides, resulting in a significant mucoadhesive force. A balanced mucoadhesive force is important to prevent the gel from being washed away while avoiding potential damage to the mucous membranes.

Poloxamers, in combination with the hydrophilic bioadhesive polymer Carbopol, successfully bind to the mucosal chains, resulting in a moderate mucoadhesive force. The addition of Carbopol 940 further enhances the gel's strength and effectively increases the bioadhesive force.

TABLE 2: PHYSIOCHEMICAL CHARACTERISTICS

Formulation	pH	Gelation temperature °C	Viscosity at 100 rpm (cPs)	Spreadability (cm)	Mucoadhesive strength (N)	% Drug content
F 1	6.8±0.03	39±0.5	1260±10	4.7±0.01	0.34±0.02	98±1
F 2	6.7±0.05	38±0.5	1413±10.40	4.76±0.01	0.37±0.01	98.2± 0.08
F 3	6.9±0.02	37±0.05	1619±5.50	4.8±0.10	0.38±0.03	97±1.2
F 4	7.1±0.03	35±0.7	1813±8.54	4.83±0.05	0.45±0.02	96.5±1.1
F 5	6.9±0.04	29±0.1	2343±8.50	4.7±0.20	0.51±0.04	95±1

Drug Release Profile: The concentration of Carbopol 940 increases from 1% in F1 to 3% in F5. Generally, increasing the concentration of a thickening agent like Carbopol 940 can affect the drug release and dissolution properties of the formulation. It may lead to a slower drug release, potentially increasing drug content.

The concentration of Poloxamer 188 increases from 1.5% in F2 to 3% in F5. Poloxamer 188 is a surfactant and can influence the solubility and dispersibility of the drug. The increase in Poloxamer 188 concentration may enhance drug solubility, potentially affecting the drug content. The formulation F4 was identified as the best formulation among all the formulations, exhibiting a pH of 7.1±0.03. The viscosity of F4 was measured at 1813±8.54 cPs, and its mucoadhesive strength was determined to be 3831±10.40 dyne/cm^2.

The spreadability of F4 was found to be 4.83±0.05 cm, which was considered adequate for the gel application, given its appropriate viscosity. The gelation temperature of F4 was recorded at 35±0.7 °C, indicating that it achieved the desired gel consistency. Gelation at a temperature below 30°C would have made administration difficult due to solidification at room temperature, while gelation beyond 36°C could have resulted in a liquid gel, potentially leading to leakage from the buccal mucosa.

TABLE 3: DRUG RELEASE PROFILE OF DIFFERENT FORMULATIONS

	% cumulative drug release				
Time	**F1**	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
30	5.18±0.01	4.04±0.03	3.90±0.1	3.20±0.01	2.10±0.15
60	12.14±0.01	10.54±0.30	9.72±0.19	8.30±0.09	8.10±0.15
120	25.44±0.45	22.68±0.16	23.32±0.45	20.10±0.16	18.20±0.15
180	40.40±0.80	45.10±1.0	40.17±0.53	38.33±0.25	33.33±0.5
240	58.0±0.5	56.54±0.27	54.83±0.33	52.90±0.09	50.66±0.36
300	80.08±0.72	76.30±0.60	71.13±0.69	73.65±0.71	70.40±0.55
360	99.78±0.39	98.94±0.67	98.10±0.15	97.64±0.12	96.99±0.40

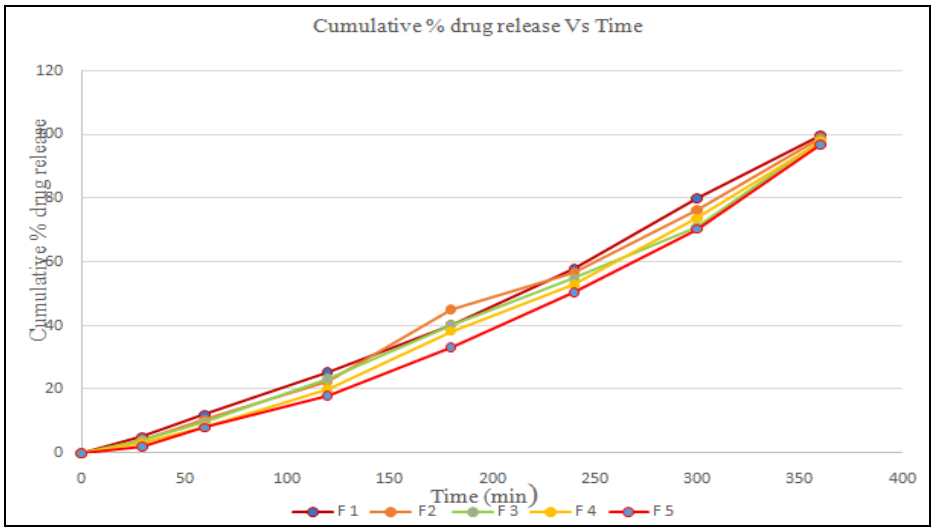

FIG. 1: CUMULATIVE % DRUG RELEASE GRAPH

***Ex-vivo* Permeation of Formulation F4 through Goat Buccal Mucosa:** The permeation flux of the drug through the buccal mucosa was determined to be 104.51 µg/cm²·h.

The partition coefficient (K_P), calculated as the ratio of the flux (J) to the initial concentration (C_O), was found to be 0.20×10^{-}1 cm/h. Additionally, the drug permeation through the buccal mucosa was observed to be 72.6%. By measuring the flux, researchers can assess the effectiveness of different drug delivery systems, formulations, or enhancers in enhancing drug permeation. It helps in optimizing the formulation parameters to achieve the desired flux for therapeutic efficacy.

In-vitro Antifungal Activity:

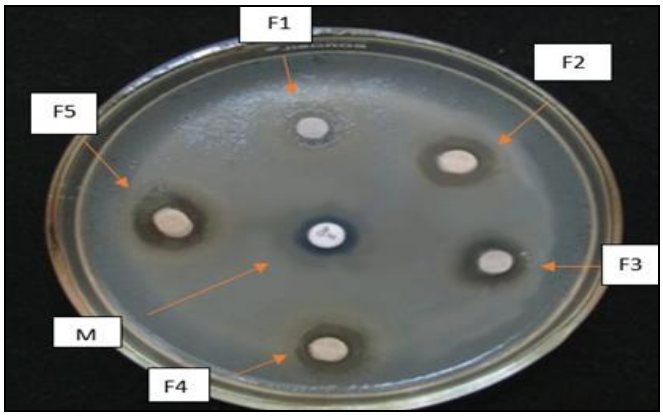

FIG. 2: ANTIFUNGAL ACTIVITY BY AGAR DIFFUSION METHOD

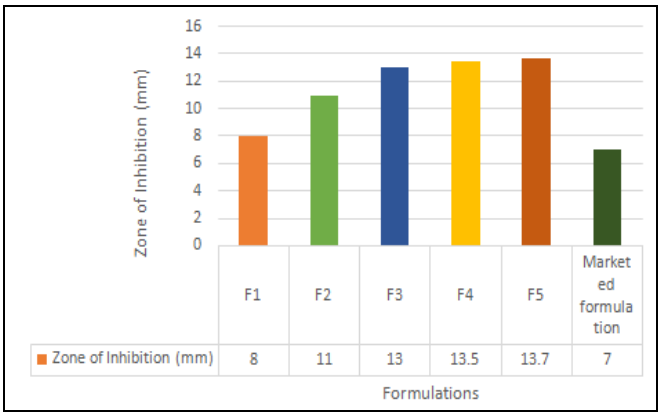

FIG. 3: GRAPH SHOWING ZONE OF INHIBITION (MM)

The analysis of the data indicates that there is a statistically significant difference between the means of column A (Formulated gel) (mean = 11.80) and column B (Marketed gel) (mean = 7.000) (t(8) = 4.538, p = 0.0019, two-tailed). The difference in means (B - A) is -4.800, with a 95% confidence interval of -7.239 to -2.361. The effect size, measured by R-squared (eta squared), is 0.7202, indicating a large effect. Additionally, the F-test comparing variances revealed a significant difference between the groups (F (4, 4) = Infinity, p < 0.0001). These findings suggest that the two groups differ significantly in terms of their means, with formulated gel having higher values compared to marketed gel.

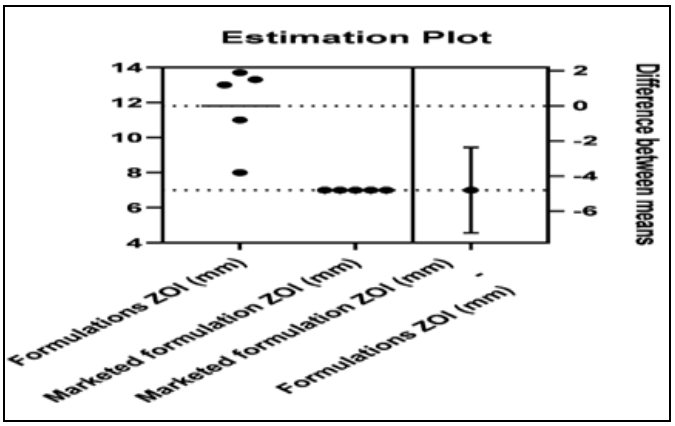

FIG. 4: ESTIMATION PLOT OF ZOI OF FORMULATIONS VS MARKETED FORMULATION

Stability Study of Formulation F4: The FTIR analysis of the formulation F4 revealed the presence of several functional groups: C-N (1103.70 cm^{-1}), C-C (1453.27 cm^{-1}), C_6H_5 (1551.16 cm^{-1}), C-O-C (1100.58 cm^{-1}), OH (3395.54 cm^{-1}), CH_2 (2872.35 cm^{-1}), and C=O (1699.42 cm^{-1}). These peaks remained unchanged even after storing the F4 formulation at 45°C and 75% RH for three months. The retention of these peaks indicates the stability of the formulation and suggests the successful incorporation of the components. Additionally, minimal variations were observed in terms of appearance, pH, spreadability, and drug content. Based on these findings, it can be concluded that the formulation exhibits excellent physical and chemical stability.

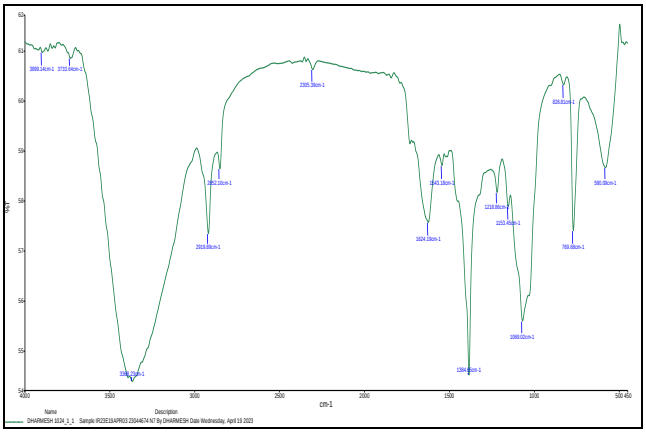

FIG. 5: FTIR FOR FORMULATION F4

TABLE 4: PHYSIOCHEMICAL CHARACTERISTICS OF F4

Appearance	Spreadability (cm)	pH	Drug content (%)
Viscous gel	4.9±0.03	7.1±0.05	96.8±1.2

CONCLUSION: The inclusion complex of itraconazole and beta-cyclodextrin improved drug solubility and dissolution. The gel exhibited favourable properties: pH 6.5-7.2, viscosity 300-600 cps, gelation temperature 30-35°C, and Spreadability was found to be 4.7-4.83 cm.

Mucoadhesive force ranged from 0.34 to 0.51N. Drug content was 90-95%. *In-vitro* antifungal activity showed 10-15 mm zone of inhibition against *Candida albicans*. The drug release profile indicated sustained release over 6 hours, with 95-99% cumulative release. The best formulation, F4, had pH 7.1±0.03, viscosity 1813±8.54 (cPs), mucoadhesive strength 3831±10.40 (dyne/cm2), and Spreadability 4.83±0.05 cm. It achieved gelation at 35±0.7 °C indicating that it achieved gelation within the desired temperature range. The controlled drug release enhanced itraconazole's bioavailability and therapeutic efficacy for oral candidiasis.

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Author Contributions: Nematullah: literature search, drafting and corrections, Dr. Richa Srivastava: conceptualization, discussion and revision, final corrections.

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