RESEARCH PAPER

# FORMULATION AND CHARACTERIZATION OF ITRACONAZOLE TABLETS FROM NANOSUSPENSION

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***ABSTRACT***
Itraconazole, a broad-spectrum antifungal agent, exhibits poor aqueous solubility, limiting its oral bioavailability. This study aimed to enhance the solubility and therapeutic efficacy of itraconazole by developing a nanosuspension-based tablet formulation for sustained release. The nanosuspension was prepared using the antisolvent precipitation method, followed by high-shear homogenization and ultrasonication. The optimized nanosuspension (F4) was spray-dried into nanogranules and compressed into tablets containing various polymers including HPMC K100, Carbopol 934, and Eudragit RL. The optimized formulation (F6) containing HPMC K100 demonstrated superior sustained release properties, achieving 99.27% drug release over 12 hours following zero-order kinetics. Characterization studies confirmed nanoscale particle size (307 nm), uniformity, and stability with a zeta potential of −30.5 ± 2.84 mV. The FTIR and DSC analyses indicated no significant drug–excipient interactions and confirmed thermal stability. The developed nanosuspension-based itraconazole tablet presents a promising approach for improving solubility, bioavailability, and sustained antifungal efficacy of poorly soluble drugs.
**Keywords:** Itraconazole, nanosuspension, sustained release, solubility enhancement, HPMC K100, tablet formulation, zero-order kinetics, antifungal agent
**Abbreviations:** BCS: Biopharmaceutics Classification System; DSC: Differential Scanning Calorimetry; FTIR: Fourier-Transform Infrared Spectroscopy; HPMC: Hydroxypropyl Methylcellulose; PDI: Polydispersity Index; SEM: Scanning Electron Microscopy; RH: Relative Humidity.
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## INTRODUCTION

Fungal infections remain a significant global health concern, particularly among immunocompromised individuals, and are associated with high morbidity and mortality worldwide [(1–3)]. Itraconazole, a triazole antifungal agent, demonstrates broad-spectrum activity against dermatophytes, yeasts, and Aspergillus species but suffers from poor aqueous solubility, resulting in low and variable oral bioavailability [(4–6)]. According to the Biopharmaceutics Classification System (BCS), itraconazole is classified as a Class II drug exhibiting high permeability but poor aqueous solubility, making dissolution the rate-limiting step for oral absorption[(6,7)], necessitating formulation strategies to enhance dissolution rate and absorption. Nanotechnology-based approaches, particularly nanosuspensions, have emerged as promising strategies for improving the dissolution rate, saturation solubility, and oral bioavailability of poorly water-soluble drugs[(8–11)]. Nanosuspensions are submicron colloidal dispersions consisting of pure drug particles stabilized by surfactants or polymers, generally possessing particle sizes below 1 μm [(10–12)], offering increased surface area and improved dissolution. The present study focuses on formulating and characterizing itraconazole nanosuspensions and converting them into sustained-release tablets to achieve prolonged therapeutic efficacy and enhanced bioavailability.

## Materials and Methods

### Materials

Itraconazole was obtained from JK Chemicals, Chennai. Stabilizers like Poloxamer 188, Tween 80, and polymers such as HPMC K100, Eudragit RL, and Carbopol 934 were used. All reagents were of analytical grade.

**Preformulation Studies**

**Physicochemical Characterization:** The organoleptic properties, melting point (via capillary method), and loss on drying (LOD) of itraconazole were determined.

**Solubility Studies:** Itraconazole solubility was assessed in water, phosphate-buffered saline (PBS, pH 7.4), alcohol, and dichloromethane using the shake flask method. The shake-flask method is considered the standard technique for equilibrium solubility determination of poorly soluble drugs [(13)]. Samples were vortexed for 10 minutes, incubated at 37 ± 1°C for 48 hours, centrifuged at 5000 rpm for 15 minutes, and the supernatant was analyzed after filtration through a 0.45 µm filter.

**Drug-Excipient Compatibility**

Fourier-transform infrared (FTIR) spectroscopy was performed (Shimadzu FTIR 8400S) over a range of 4000–400 $cm^{-1}$. FTIR spectroscopy is widely used to evaluate drug–excipient compatibility by identifying possible chemical interactions between formulation components [(14)].Itraconazole was mixed with key excipients (e.g., HPMC K100, Carbopol 934, Eudragit RL, Tween 80, Poloxamer 188) at a ratio of 1:100 (drug:KBr) and pressed into pellets.

**Preparation of Itraconazole Nanosuspension**

**Stabilizer and Drug Solutions:** An aqueous stabilizer solution was prepared by dissolving Poloxamer 188 or Tween 80 in distilled water. Separately, itraconazole was dissolved in ethanol. The itraconazole solution was added dropwise into the stabilizer solution under continuous stirring. [15]

**High-Shear Homogenization and Ultrasonication:** The resultant suspension was homogenized at 10,000 rpm for 20 minutes[16]. Ultrasonication minimizes particle agglomeration and further reduces particle size through cavitation effects [(17)] and subsequently sonicated for 20 minutes while maintaining the temperature below 25°C.

**Centrifugation:** The nanosuspension was centrifuged at 10,000 rpm for 30 minutes to separate the sediment. The supernatant (nanosuspension) was collected for further evaluation.

**Table 1** Preparation of Itraconazole Nanosuspension

| Formula | Itraconazole (mg) | Ethanol (mL) | Stabilizer |
|---|---|---|---|
| F1 | 100 mg | q.s. to 10 mL | Tween 80(1%) |
| F2 | 100 mg | q.s. to 10 mL | Tween 80(2%) |
| F3 | 100 mg | q.s. to 10 mL | P-188(1%) |
| F4 | 100 mg | q.s. to 10 mL | P-188(2%) |

**Evaluation of Nanosuspension**

The nanosuspension was characterized for:

**Particle Size and Polydispersity Index (PDI):** Using dynamic light scattering (DLS) methods. Dynamic light scattering (DLS) is the most widely used technique for determining nanoparticle size distribution and polydispersity index [(18)]

**Zeta Potential:** Zeta potential provides information regarding colloidal stability, with values greater than ±30 mV generally indicating good physical stability [(19)]. Measurements indicated surface charge and stability.

**Viscosity:** Determined using a Brookfield viscometer.

**Drug Content and Entrapment Efficiency:** Quantified via UV spectrophotometry at 254 nm.

**Turbidity and Redispersibility:** To assess the uniformity and stability of the suspension.

**Morphological Analysis:** Scanning electron microscopy (SEM) was employed to examine particle shape and surface characteristics.[20]

**Nanogranule Formation:** The nanosuspension was converted into granules using the spray drying technique.

**Tablet Compression:**

The spray-dried granules were blended with excipients (e.g., HPMC K100, Carbopol 934, Eudragit RL) and lubricants (magnesium stearate, colloidal silicon dioxide) before being compressed into tablets using a 16-station rotary tablet press.

**Table 2** Tablet Formulation

| **Ingredients** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
|---|---|---|---|---|---|---|---|---|---|
| **Itraconazole granules**(Itraconazole NS equivalent to Itraconazole 100mg) | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 |
| **Carbopol 934** | 5 | 10 | 15 | – | – | – | – | – | – |
| **HPMC K100** | – | – | – | 5 | 10 | 15 | – | – | – |
| **Eudragit RL** | – | – | – | – | – | – | 5 | 10 | 15 |
| **Magnesium Stearate** | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| **Sodium Lauryl Sulfate** | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| **Colloidal Silicon Dioxide** | 18.8 | 13.8 | 8.8 | 18.8 | 13.8 | 13.8 | 18.8 | 13.8 | 13.8 |
| **Lactose Monohydrate** | 21 | 21 | 21 | 21 | 21 | 16 | 21 | 21 | 16 |
| **Total Weight (mg)** | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |

**Evaluation Parameters:**
Pre-compression parameters (bulk density, tapped density, Hausner's ratio, compressibility index) and post-compression parameters (hardness, friability, weight variation, drug content uniformity) were assessed.

***In Vitro* Dissolution Studies:**
Performed using a USP Type II dissolution apparatus in 0.1 N HCl at 37°C ± 5°C with a rotation speed of 50 rpm. Samples were withdrawn at hourly intervals up to 12 hours and analyzed spectrophotometrically.

**Release Kinetics:**
The dissolution data were fitted to various kinetic models (zero order, first order, Higuchi, Korsmeyer–Peppas) to determine the drug release mechanism.

**Thermal Analysis and Stability:**
Differential Scanning Calorimetry (DSC) was used to confirm the thermal stability. Accelerated stability testing was performed at 40 ± 2°C/75 ± 5% relative humidity over three months.

**Results**

**Table 3. Organoleptic properties of Pure Drug**

| S.No. | Test | Specification | Observation |
|---|---|---|---|
| 1 | Colour | White powder | White |
| 2 | Odour | Odourless | Odourless |
| 3 | Appearance | Crystalline | Crystalline powder |

**Table 4 Melting Point**

| Drug | Specification | Observation |
|---|---|---|
| Itraconazole | 166.2°C | 165°C±1.33 |

**Table 5 Loss on Drying**

| Drug | Specification | Observation |
|---|---|---|
| Itraconazole | ≤ 1.0%,% | 1.2% |

**FTIR and Compatibility Analysis**

FTIR analysis confirmed that the characteristic peaks of itraconazole were preserved in the presence of excipients, indicating no significant chemical interaction and ensuring formulation compatibility. [14,21]

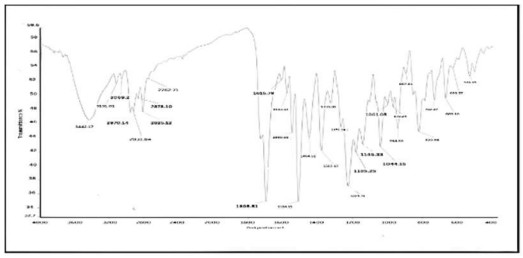


Fig 1. FTIR Spectrum of Itraconazole

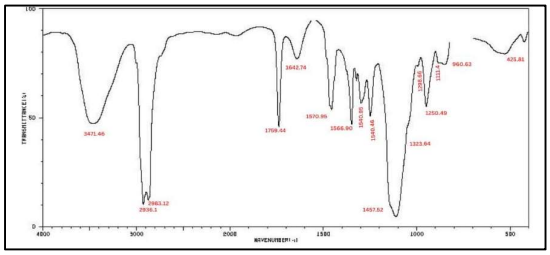


Fig 2 FTIR Spectrum of Tween 80

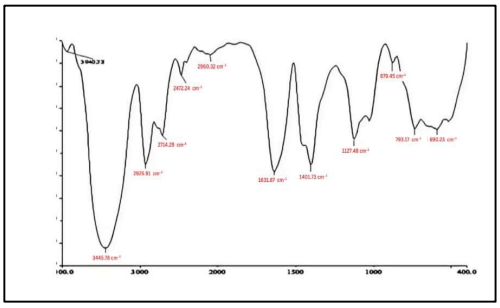


Fig 3. FTIR Spectrum of Eudragit RL

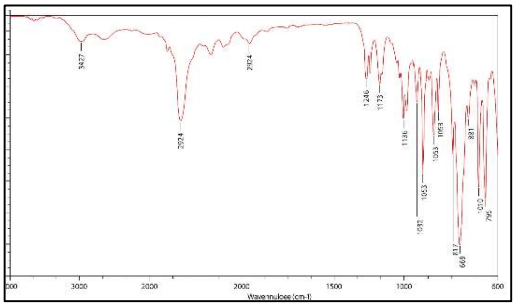


Fig 4. FTIR of Spectrum Poloxamer 188

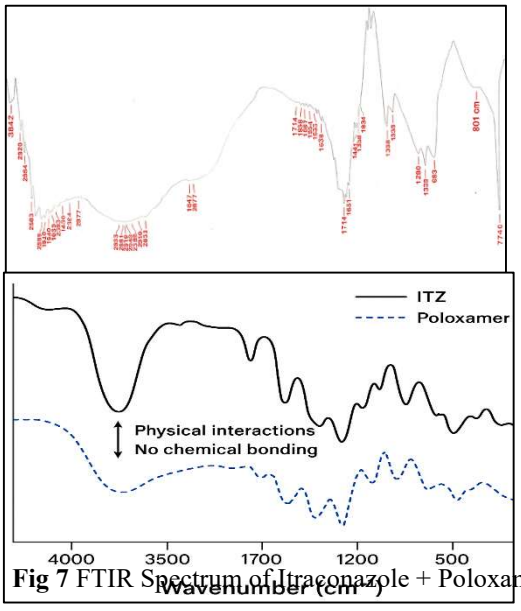



**Fig 7** FTIR Spectrum of Itraconazole + Poloxamer 188

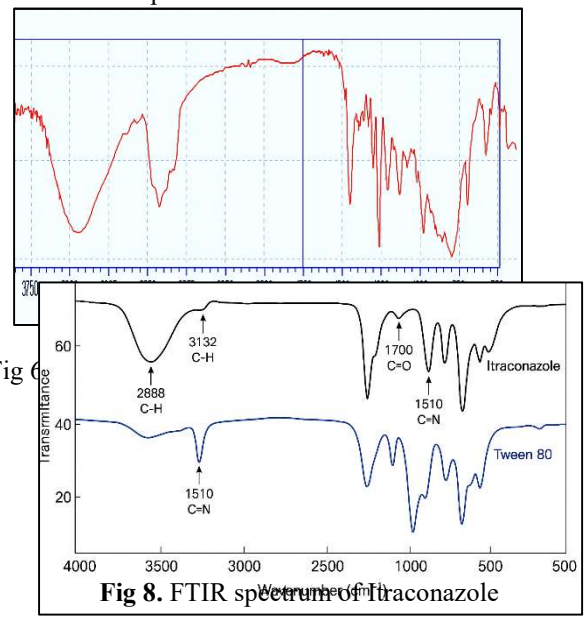



**Fig 8.** FTIR spectrum of Itraconazole

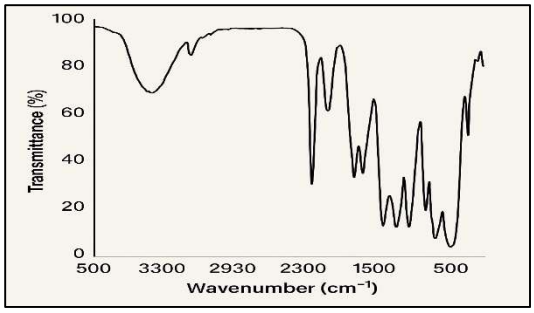



Fig 9. FTIR spectrum of (ITZ+ Carbopol 934+Other Excipients.

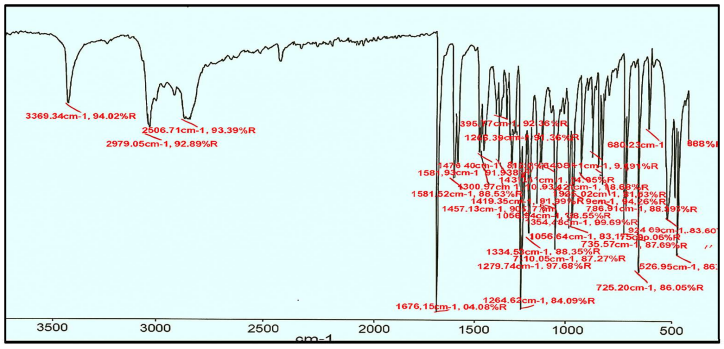



Fig 10. FTIR spectrum of (ITZ+ HPMC K100M+Other Excipients)

All major characteristic peaks of Itraconazole are retained across all mixtures. No significant shifts or disappearance of peaks observed. Indicates chemical compatibility between Itraconazole and the selected excipients

**Calibration Curve of Itraconazole In 0.1 Hcl**

The calibration curve for Itraconazole in 0.1N HCl showed a linear relationship between concentration and absorbance follows ***Beer-Lambert's law***

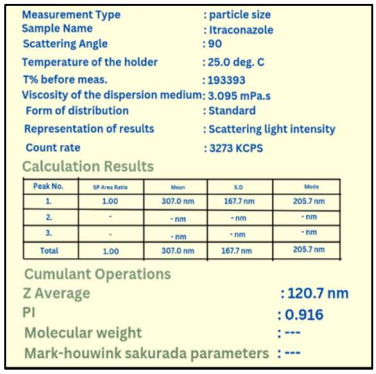
**Nanosuspension Characterization**

**Particle Size and PDI:**

The optimized nanosuspension (F4) exhibited a mean particle size of 307 nm and a narrow PDI, indicating a uniform distribution reported for enhancing dissolution and oral bioavailability of poorly soluble drugs [8,11,15]

**Zeta Potential:**

A zeta potential of −30.5 ± 2.84 mV confirmed physical stability by preventing aggregation.



| | |
|---|---|
| Measurement Type | : particle size |
| Sample Name | : Itraconazole |
| Scattering Angle | : 90 |
| Temperature of the holder | : 25.0 deg. C |
| T% before meas. | : 193393 |
| Viscosity of the dispersion medium | : 3.095 mPa.s |
| Form of distribution | : Standard |
| Representation of results | : Scattering light intensity |
| Count rate | : 3273 KCPS |

Calculation Results

| Peak No. | SP Area Ratio | Mean | S.D | Mode |
|---|---|---|---|---|
| 1. | 1.00 | 307.0 nm | 167.7 nm | 205.7 nm |
| 2. | - | - nm | - nm | - nm |
| 3. | - | - nm | - nm | - nm |
| Total | 1.00 | 307.0 nm | 167.7 nm | 205.7 nm |

Cumulant Operations

| | |
|---|---|
| Z Average | : 120.7 nm |
| PI | : 0.916 |
| Molecular weight | : --- |
| Mark-houwink sakurada parameters | : --- |

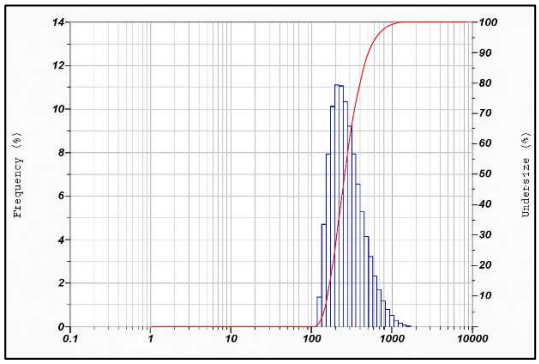



**Fig 11. Zeta Potential**

The average particle size was found to be in a nanorange, i.e., <1 µm in the range of 150–350 nm, from this study, it has been concluded that there is a size reduction of particles,, it was confirmed by zeta size by zeta sizer is determined as **307 nm.**

| | |
|---|---|
| Measurement Type | : Zeta Potential |
| Sample Name | : Itraconazole-Zeta |
| Temperature of the holder | : 25.0 deg. C |
| Viscosity of the dispersion medium | : 0.898 mPa.s |
| Conductivity | : 0.119 mS/cm |
| Electrode Voltage | : 3.4 V |

Calculation Results

| Peak No. | Zeta Potential | Electrophoretic Mobility |
|---|---|---|
| 1. | -30.5mV | -0.000235 |
| 2. | -mV | -cm2/Vs |
| 3. | -mV | -cm/Vs |

| | |
|---|---|
| Zeta potential (Mean) | : -30.5mV |
| Electrophoretic mobility mean | : -0.000235 |

**Fig 12**. Zeta Potential

From zeta potential was found to be −30.5±2.84 mV for nanosuspension, and it indicates that there is physical stability due to sufficient thickness of diffusive layer to prevent particle aggregation and allow for a longer residence time for the particles by ionic interaction with the drug molecules

**Viscosity and Redispersibility:**

With a viscosity of 25 cP, the nanosuspension demonstrated sufficient fluidity for processing and excellent redispersibility upon settling.

**Table 6** Viscosity and Redispersibility

| Parameter | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| Viscosity (cP) | 120 | 80 | 50 | 25 |
| Re-Dispersibility Index (RI) (%) | 60 | 75 | 85 | 96.74 |

**Turbidity Measurement**

Turbidity directly correlates to particle uniformity: higher turbidity suggests more suspended particles. **F4** maintains close to the original turbidity after redispersion, signifying excellent suspension stability.

**Drug Entrapment and Content:**

High entrapment efficiency and consistent drug content were achieved, ensuring adequate dosing

**Table 7** Drug Entrapment and Content

| Batches | Drug Content | % drug entrapment efficiency |
|---|---|---|
| F1 | 93.22± 1.02 | 92.01± 0.2 |
| F2 | 93.05± 1.63 | 92.04± 1.03 |
| F3 | 94.02± 2.1 | 93.01± 1.33 |
| F4 | 95.82± 1.03 | 94.26± 1.02 |

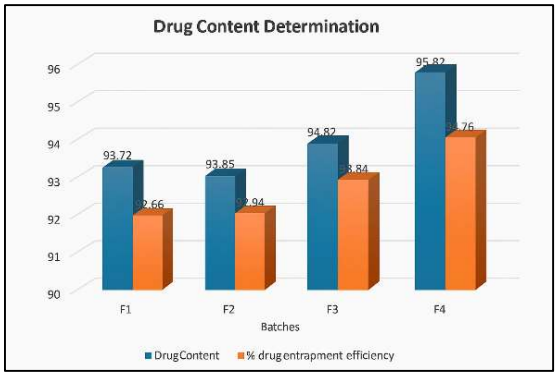



**Fig 13** Drug Entrapment

**Morphological Study**

Surface morphology and shape were visualized by SEM for F4. The particles appeared with smooth surface and wavy.

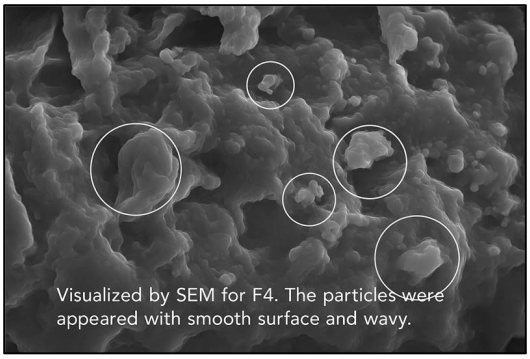



**Fig 14.** Morphological Study

**Precompression Parameters of Nanogranules**

**Table 8** Precompression Parameters

| Formulation | Bulk Density (g/cm³) | Tap Density (g/cm³) | Hausner's Ratio | Carr's Index (%) |
|---|---|---|---|---|
| F 4 | 0.421± 0.12 | 0.472± 1.01 | 1.1±0.3 | 10.21±1.2 |

**Tablet Evaluation**

**Table 9** Tablet formulations (F1–F9) were prepared and evaluated.

| Formulation Code | Hardness (Kg/Cm²) | Percent Friability (%) | Drug Content (%) |
|---|---|---|---|
| F1 | 5.5 ± 0.62 | 0.2 ± 0.05 | 99.5 ± 0.04 |
| F2 | 6.5 ± 0.62 | 0.15 ± 0.05 | 98.5 ± 0.05 |
| F3 | 6 ± 0.62 | 0.12 ± 0.05 | 98.3 ± 0.04 |
| F4 | 6.8 ± 0.62 | 0.14 ± 0.05 | 99.5 ± 0.01 |
| F5 | 6.2 ± 0.62 | 0.18 ± 0.05 | 98.4 ± 0.07 |
| F6 | 7 ± 0.62 | 0.1 ± 0.05 | 99.7 ± 0.02 |
| F7 | 6.3 ± 0.62 | 0.17 ± 0.05 | 99.3 ± 0.04 |
| F8 | 5 ± 0.62 | 0.25 ± 0.05 | 99.1 ± 0.02 |
| F9 | 6.4 ± 0.62 | 0.22 ± 0.05 | 98.9 ± 0.03 |

**Weight Variation**

**Table 10** Weight Variation

| Tablet No. | F1 (mg) | F2 (mg) | F3 (mg) | F4 (mg) | F5 (mg) | F6 (mg) | F7 (mg) | F8 (mg) | F9 (mg) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 150.38 | 151.49 | 149.2 | 151.53 | 148.34 | 149.59 | 147.79 | 151.38 | 147.47 |
| 2 | 150.38 | 149.24 | 150.83 | 152.74 | 146.69 | 150.03 | 149.76 | 148.53 | 149.87 |
| 3 | 150.23 | 150.45 | 149.78 | 150.48 | 147.72 | 150.03 | 150.62 | 149.43 | 149.27 |
| 4 | 150.24 | 149.53 | 149.48 | 151.38 | 150.14 | 149.72 | 150.23 | 150.61 | 148.68 |
| 5 | 150.38 | 147.88 | 150.39 | 152.29 | 146.99 | 150.19 | 148.86 | 150.2 | 149.43 |
| 6 | 150.58 | 150 | 149.99 | 152.4 | 151.78 | 149.59 | 149.45 | 149.73 | 151.21 |
| 7 | 150.45 | 149.09 | 150.53 | 148.66 | 150.44 | 149.44 | 148.38 | 148.98 | 150.49 |
| 8 | 150.24 | 149.68 | 151.57 | 150.78 | 148.49 | 150.91 | 150.8 | 150.35 | 148.83 |
| 9 | 150.23 | 151.01 | 150.23 | 152.13 | 147.27 | 150.05 | 148.1 | 149.89 | 151.38 |
| 10 | 145.24 | 150.31 | 150.61 | 152.55 | 146.52 | 150.05 | 149.16 | 150.91 | 149.27 |

| Tablet No. | F1 (mg) | F2 (mg) | F3 (mg) | F4 (mg) | F5 (mg) | F6 (mg) | F7 (mg) | F8 (mg) | F9 (mg) |
|---|---|---|---|---|---|---|---|---|---|
| 11 | 150.04 | 149.83 | 150.96 | 151.67 | 149.83 | 150.03 | 150.05 | 151.78 | 149.27 |
| 12 | 150.01 | 148.66 | 149.03 | 151.81 | 150.14 | 149.59 | 150.63 | 148.71 | 150.63 |
| 13 | 150.45 | 150.74 | 151.11 | 150.62 | 147.43 | 150.25 | 147.94 | 149.13 | 150.38 |
| 14 | 150.04 | 149.98 | 149.92 | 151.97 | 148.77 | 150.69 | 150.36 | 150.98 | 149.58 |
| 15 | 145.24 | 149.39 | 148.88 | 150.9 | 148.03 | 149.59 | 148.74 | 150.03 | 150.92 |
| 16 | 150.04 | 151.75 | 150.83 | 150.78 | 151.63 | 150.15 | 149.62 | 150.61 | 150.17 |
| 17 | 145.24 | 150.69 | 151.48 | 151.2 | 149.99 | 150.05 | 149.01 | 150.61 | 149.99 |
| 18 | 145.24 | 148.79 | 150.69 | 148.8 | 149.68 | 150.05 | 149.91 | 150.48 | 151.05 |
| 19 | 150.45 | 150.45 | 149.88 | 150.78 | 149.68 | 150.03 | 149.62 | 150.72 | 150.02 |
| 20 | 145.24 | 148.79 | 150.69 | 151.2 | 151.63 | 149.99 | 151.74 | 151.08 | 150.51 |
| Total average weight | 149.02 | 149.89 | 150.3 | 151.23 | 149.06 | 150 | 149.54 | 150.21 | 149.92 |

**Dissolution Profile:** *In vitro* testing revealed a sustained drug release, with F6 achieving 99.27% release over 12 hours. [22,23]

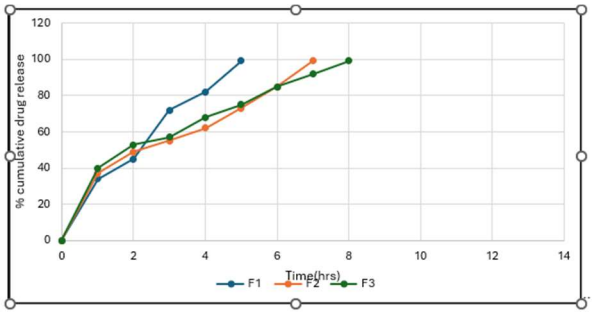



**Fig 15**. Itraconazole containing Carbopol 934(F1-F3)

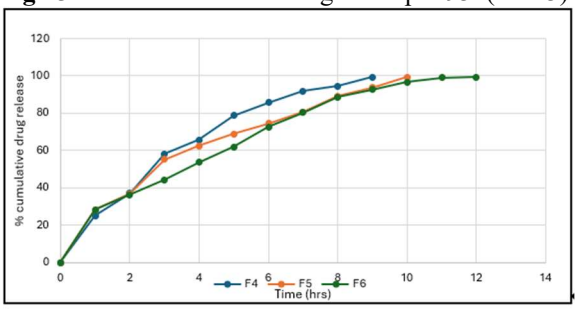



**Fig 16**. Itraconazole containing +HPMC K100(F4-F6)

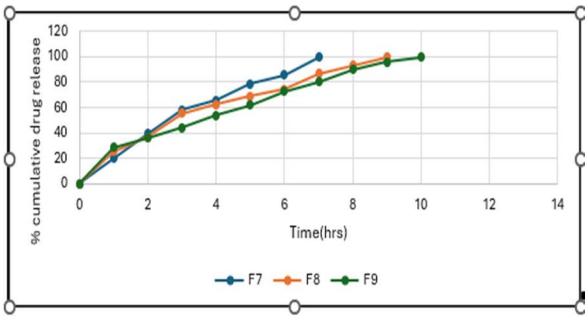



**Fig 17.** Itraconazole containing Eudragit RL(F7-F9)

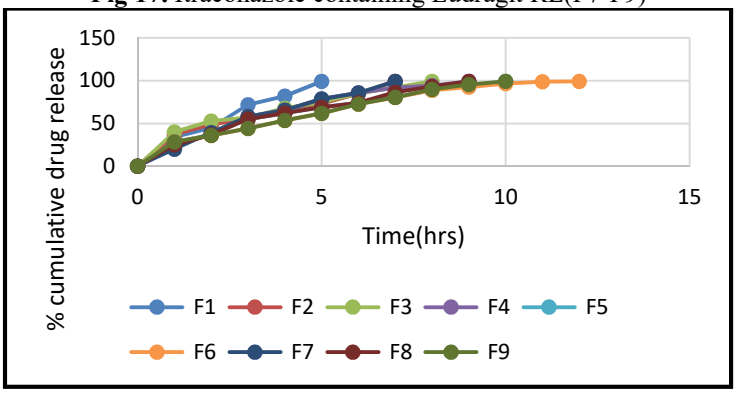



**Fig 18.** *In-vitro* drug release studies of Itraconazole tablet F1 to F9

**F6 eventually reached 99.27% drug release at 12 hours,** other formulations like either released too quickly or reached their maximum release earlier.This balance in F6 ensures prolonged drug availability. F6 (HPMC K100) demonstrates the most suitable profile for sustained drug release, with controlled release extending over 12 hours. Its ability to avoid burst release and gradually deliver the drug makes it a superior choice compared to other formulations (F1–F9) for ensuring therapeutic effectiveness over an extended period.

**Release Kinetics**

The drug release profile of the F6 formulation best fitted the zero-order kinetic model ($R^2$ = 0.991), indicative of a constant drug release rate independent of concentration. Additional kinetic modeling (Higuchi and Korsmeyer–Peppas) supported a diffusion-controlled mechanism. [23,24]

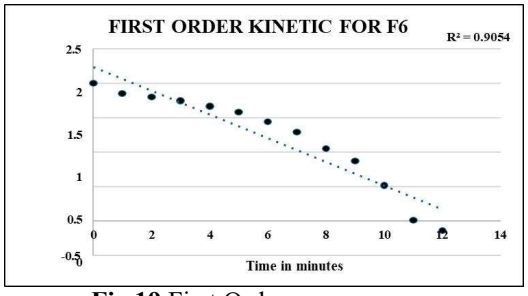



**Fig 19** First Order

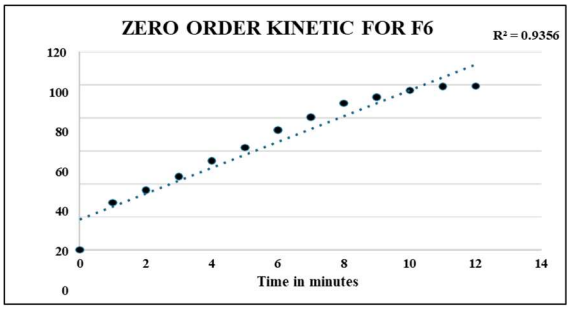



**Fig 20**. Zero Order

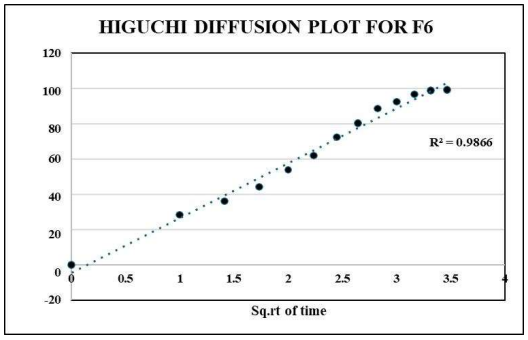



**Fig 21** Higuchi

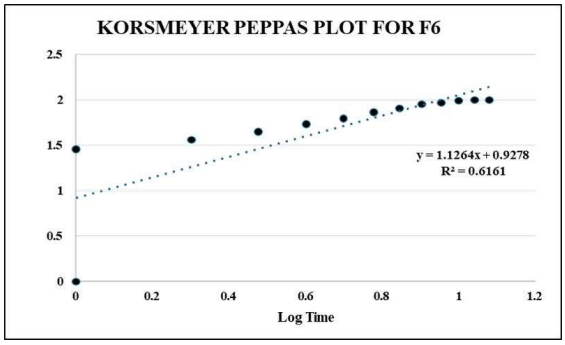



**Fig 22**. Korsmeyer Peppas

**Thermal and Stability Analysis**

DSC analysis confirmed that the thermal characteristics of itraconazole were preserved post-formulation. Accelerated stability studies under ICH conditions (40°C/75% RH for three months) demonstrated that the optimized formulation (F6) maintained its dissolution profile and drug content without significant degradation.

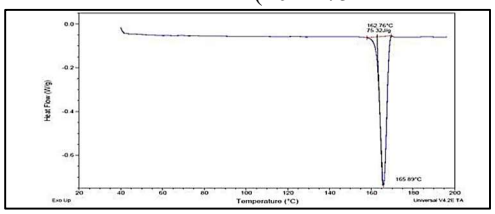


**Fig 23** DSC of Itraconazole pure drug

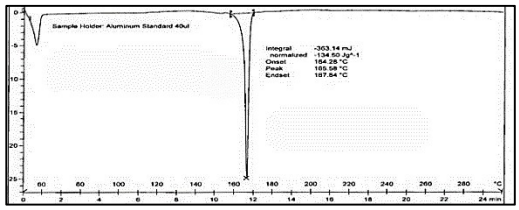



**Fig 24** DSC of F6 Formulation

**Discussion**

This study demonstrated the potential of nanosuspension technology in enhancing the solubility and bioavailability of poorly soluble drugs such as itraconazole The developed nanosuspension-based tablet represents an effective strategy for improving the dissolution, oral bioavailability, and sustained release of poorly soluble itraconazole, consistent with previous reports on nanocrystal-based drug delivery systems [11,25]. The reduction in particle size to the nanometer range significantly increased surface area, promoting rapid dissolution. HPMC K100 acted as an effective sustained-release polymer, ensuring consistent

drug release over 12 hours while preventing burst effects. The zero-order release pattern indicates concentration-independent release, which is desirable for maintaining steady plasma levels. The stability data confirm that the formulation remains physically and chemically stable under accelerated conditions. These findings align with previous reports on nanosuspension-based delivery systems, supporting their use as a viable strategy for improving therapeutic performance of poorly soluble antifungal agents. Future studies should focus on *in vivo* pharmacokinetic evaluation to confirm enhanced bioavailability and therapeutic efficiency.

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