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# Dissolution Enhancement Of Itraconazole By Loading On Parteck SLC Mesoporous Silica Followed By Hot Melt Extrusion.

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***Abstract***
*The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. Thus, this study suggests that a combined approach of loading mesoporous silica (Parteck® SLC 500) entrapment followed by solid dispersion with Poloxamer 188 by hot melt extrusion process successfully improved dissolution of Itraconazole.*

*Among the various approaches, ITZ was loaded onto mesoporous silica (Parteck® SLC 500) via the incipient wetness impregnation method. The optimized drug-loaded batch was extruded with polyvinyl alcohol (PVA) and Poloxamer 188 in varying ratios. The formulations were characterized by Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray powder diffraction (XRD). In-vitro dissolution studies were conducted to assess the drug release profiles.*

*The optimized formulation containing PVA and Poloxamer 188 in a 1:2 ratio demonstrated a 4.5-fold improvement in dissolution rate compared to pure ITZ, achieving 87% drug release within 20 minutes. DSC and XRD results confirmed the conversion of ITZ from a crystalline to an amorphous state. While FTIR results confirmed the absence of chemical interactions between ITZ and the excipients.*

*From the above results, it was concluded that the combination of mesoporous silica loading and HME proved to be an efficient method for enhancing ITZ dissolution, offering a robust approach for improving the bioavailability of poorly water-soluble drugs.*

***Keywords****: ITZ, dissolution enhancement, mesoporous silica, polyvinyl alcohol, Poloxamer 188, hot extrusion.*

## INTRODUCTION-

Itraconazole (ITZ), a triazole antifungal drug, is widely used to treat systemic and localized fungal infections. However, its poor aqueous solubility (0.0004 mg/mL in water) limits its bioavailability and poses challenges for oral delivery. Classified under Biopharmaceutics Classification System (BCS) Class II, ITZ is characterized by low solubility but high permeability, making dissolution a rate-limiting step in its absorption. Enhancing the dissolution profile of ITZ is critical for improving its therapeutic efficacy and patient outcomes.

Mesoporous silica, such as Parteck® SLC 500, features a high surface area and pore volume, enabling the entrapment of poorly soluble drugs within its nanostructures. This enhances the surface interaction between the drug and the dissolution medium, leading to improved solubility and dissolution rates. Furthermore, loading ITZ into mesoporous silica can prevent recrystallization, maintaining the drug in a more soluble amorphous state.

Hot melt extrusion is a well-established technique for producing amorphous solid dispersions by dispersing drugs at a molecular level within polymer matrices. This method offers advantages such as solvent-free processing, scalability, and the ability to combine multiple excipients to enhance drug solubility. Polymers like polyvinyl alcohol (PVA) and Poloxamer 188 are commonly used in HME due to their thermal stability and ability to form solid dispersions that enhance drug release.

**MATERIAL AND METHOD -**

Materials

Drug: Itraconazole (ITZ) was provided by Zenvision Pharma LLP.

Excipients: Parteck® SLC 500 (mesoporous silica), Polyvinyl Alcohol (PVA), and Poloxamer 188 were procured from Merck.

Solvents: Analytical-grade dichloromethane and methanol were used.

**Method -**

Hot Melt Extrusion (HME)

ITZ was loaded onto Parteck® SLC 500 using the incipient wetness impregnation method. The optimized ITZ-loaded mesoporous silica batch was processed using a twin-screw extruder (Thermo Fisher Pharma Mini HME).

The drug-loaded silica was blended with PVA and Poloxamer 188 in three ratios: 1:1, 1:2, and 2:1.The mixture was fed into the extruder at a screw speed of 100 rpm and a processing temperature of 170°C.The extrudates were cooled, milled into granules, and stored in airtight containers for further analysis.

**RESULTS AND DISCUSSION**

Drug Loading Efficiency

| **Batch** | **Itracanazole %** | **Mesoporous Silica%** |
|---|---|---|
| A1 | 30% (4.8g) | 70% (11.2g) |
| A2 | 25% (4g) | 75% (12g) |
| A3 | 20% (3.2g) | 80% (12.8g) |

Batch A2 (25:75 drug-to-silica ratio) exhibited the highest loading efficiency of 96%.

Hot Melt Extrusion

| **Batches (Contains5gm of ITZ Loaded mesoporous silica ≈ 1.5gm of Itraconazole)** | **Polymer ratio (Polyvinyl alcohol: Poloxamer-188)** | **Weight of polymer mixture (gm.)** | **Temperature (°C)** | **Screw torque (Revolution per minute)** |
|---|---|---|---|---|
| A | 1:1 | 5 | 170 | 100 |
| B | 1:2 | 7.5 | 170 | 100 |
| C | 2:1 | 7.5 | 170 | 100 |
| B1 | 1:2 | 7.5 | 170 | 100 |

**Table 1. Batches for extrusion (Polyvinyl alcohol: Poloxamer-188)**

| **Batches (Contains5gm of ITZ Loaded mesoporous silica ≈ 1.5gm of Itraconazole)** | **Polymer ratio (HPMC k-50: Poloxamer-188)** | **Weight of polymer mixture (gm.)** | **Temperature (°C)** | **Screw torque (Revolution per minute)** |
|---|---|---|---|---|
| D | 1:1 | 5 | 170 | 100 |
| E | 1:2 | 7.5 | 170 | 100 |
| F | 2:1 | 7.5 | 170 | 100 |

| | | | | |
|---|---|---|---|---|
| E1 | 1:2 | 7.5 | 170 | 100 |

**Table 2. Batches for extrusion (HPMC k-50: Poloxamer-188)**

4gm. of loaded powder and different ratios of polymers (Polyvinyl alcohol and Poloxamer 188) and (HPMC K-50 and Poloxamer 188) as shown in Table 1 and 2, was fed into the feeder for the formulation of extrudates using THERMO SCIENTIFIC Pharma mini hot melt extruder. The obtained extrudates were milled using a rapid mixer granulator (Merck) to form granules. The granules were further evaluated for processability parameters and dissolution. The outcome of this systematic assessment led to the identification of an optimized batch, honed through a judicious selection of polymer ratios and formulation strategies. Building upon this achievement, a pivotal experiment was undertaken. The same optimal polymer ratio was employed in the context of hot melt extrusion alone referred as Batch B1 and E1 at same torque speed and temperature as those used for optimized batch. This strategic decision was intended to explore the variation in drug release, setting the meaningful stage for comparisons.

Drug-Excipient Compatibility – Atr:
FTIR spectra showed no significant shifts in characteristic peaks, indicating compatibility between ITZ and excipients.

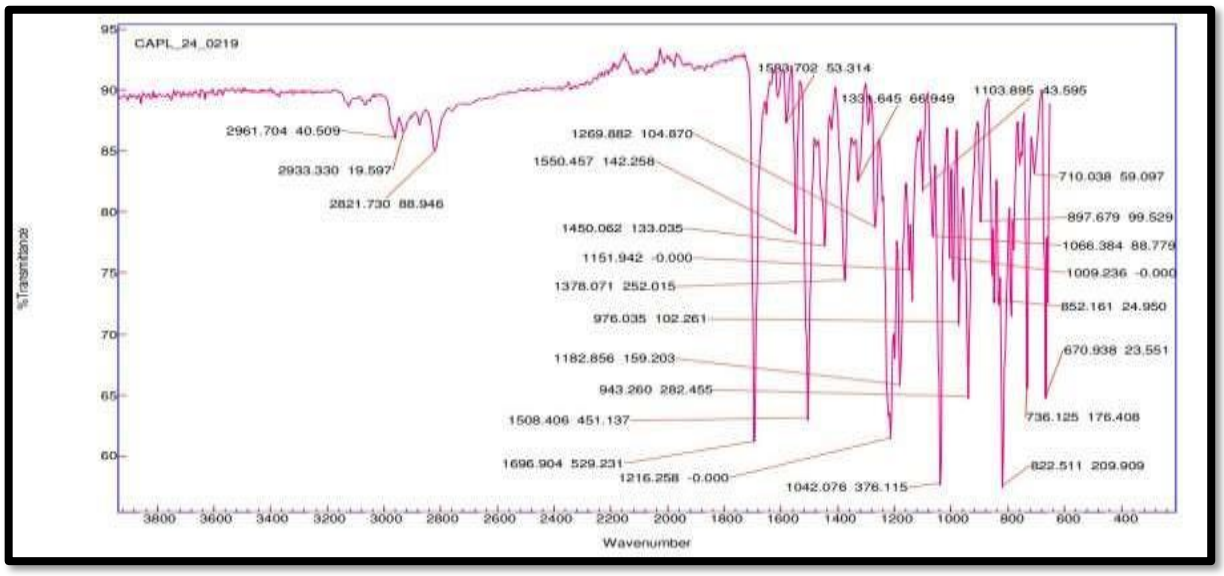


Figure 1: FTIR spectra of pure Itraconazole

| Sr. No | Functional group | Range (Expected) ($cm^{-1}$) | Observed ($cm^{-1}$) |
|---|---|---|---|
| 1. | C-H | 3000-2850 | 2961 |
| 2. | -C=O | 1870- 1650 | 1696 |
| 3. | -C=N | 1650-1550 | 1583 |
| 4. | -C-N | 1230-1020 | 1151 |
| 5. | C=C | 1600-1500 | 1550 |

**Table 3. Interpretation of IR spectra of Itraconazole**

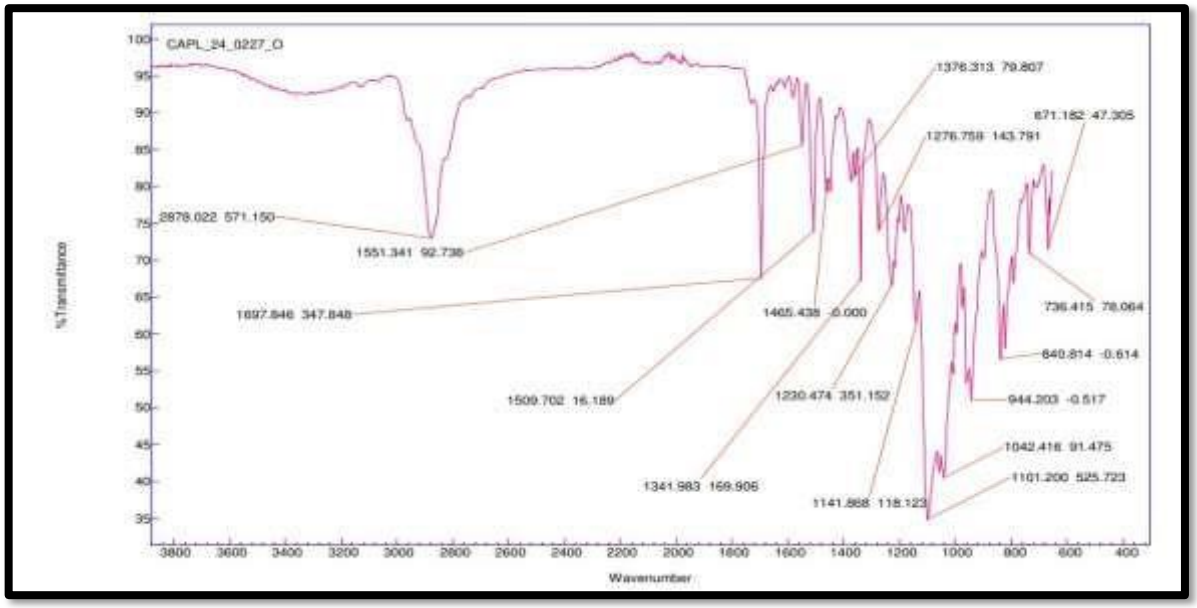


**Figure 2: IR Spectra of physical mixture 1**

| Sr. No. | Functional group | Range (Expected) ($cm^{-1}$) | Observed ($cm^{-1}$) |
|---|---|---|---|
| 1 | -C-O | 1250-1050 | 1230 |
| 2 | -C-H | 3300-2700 | 2878 |
| 3 | -C-C | 1600-1500 | 1551 |
| 4 | -C=O | 1780-1650 | 1697 |

**Table 4: Interpretation of IR Spectra of physical mixture 1**

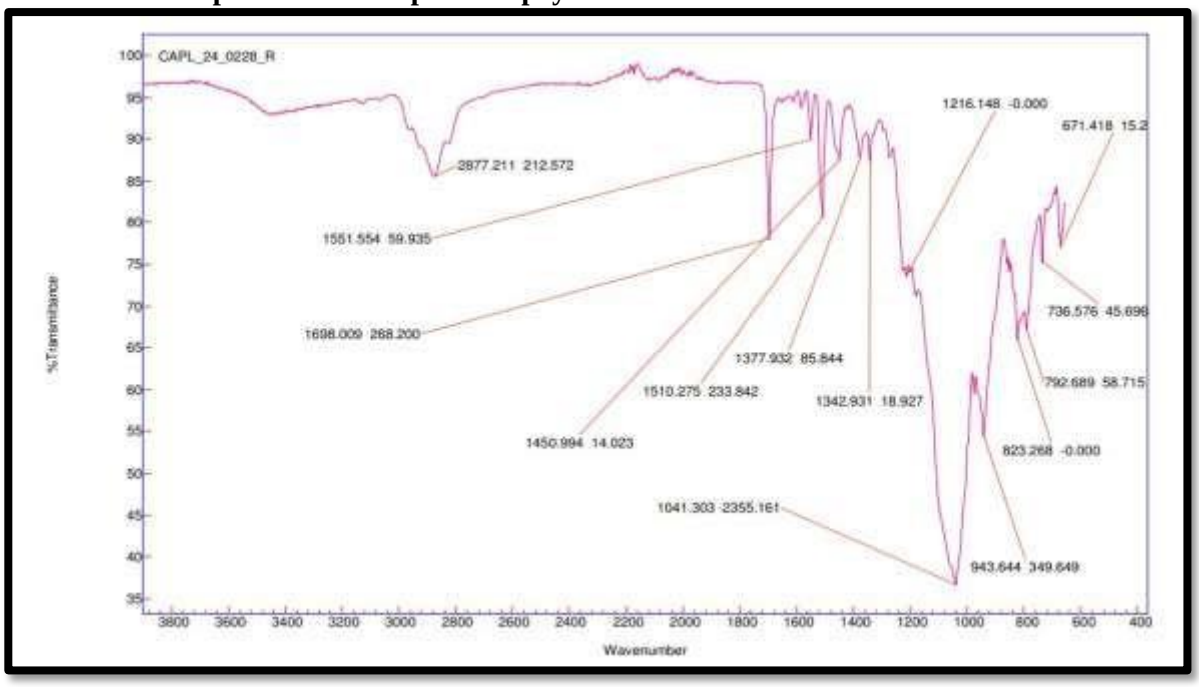


**Figure 3: IR Spectra of physical mixture 2**

| Sr. No. | Functional group | Range (Expected) ($cm^{-1}$) | Observed ($cm^{-1}$) |
|---|---|---|---|
| 1 | -C-O | 1250-1050 | 1216 |
| 2 | -C-H | 3300-2700 | 2877 |
| 3 | -C-C | 1600-1500 | 1510 |
| 4 | -C=O | 1780-1650 | 1698 |

**Table 5: Interpretation of IR Spectra of physical mixture 2**

Differential Scanning Calorimetry

The DSC thermogram depicted in following figures, reveals distinct features for the compounds under study. Notably, ITZ exhibits a characteristic melting peak observed at 173.03°C. Whereas, Poloxamer 188 presents a sharp peak at 60.83°C, and polyvinyl alcohol displays a peak at 80.93°C and Hpmc k-50 presents a sharp peak at 270.48°C. Upon closer analysis of the optimized batch, namely batch B and batch E, it becomes evident that the previously observed ITZ melting peak at 173.03°C is no longer present. Conversely, in A batch, shifts in peak positions was observed at 166.16°C. This shift in peak, is may be due to the presence of Polyvinyl alcohol as it acts as a plasticizer, and helps in reduction of the melting temperature of ITZ. Thus, the absence of a peak in batch B and Batch E strongly suggests the transformation of the ITZ crystalline structure into an amorphous state.

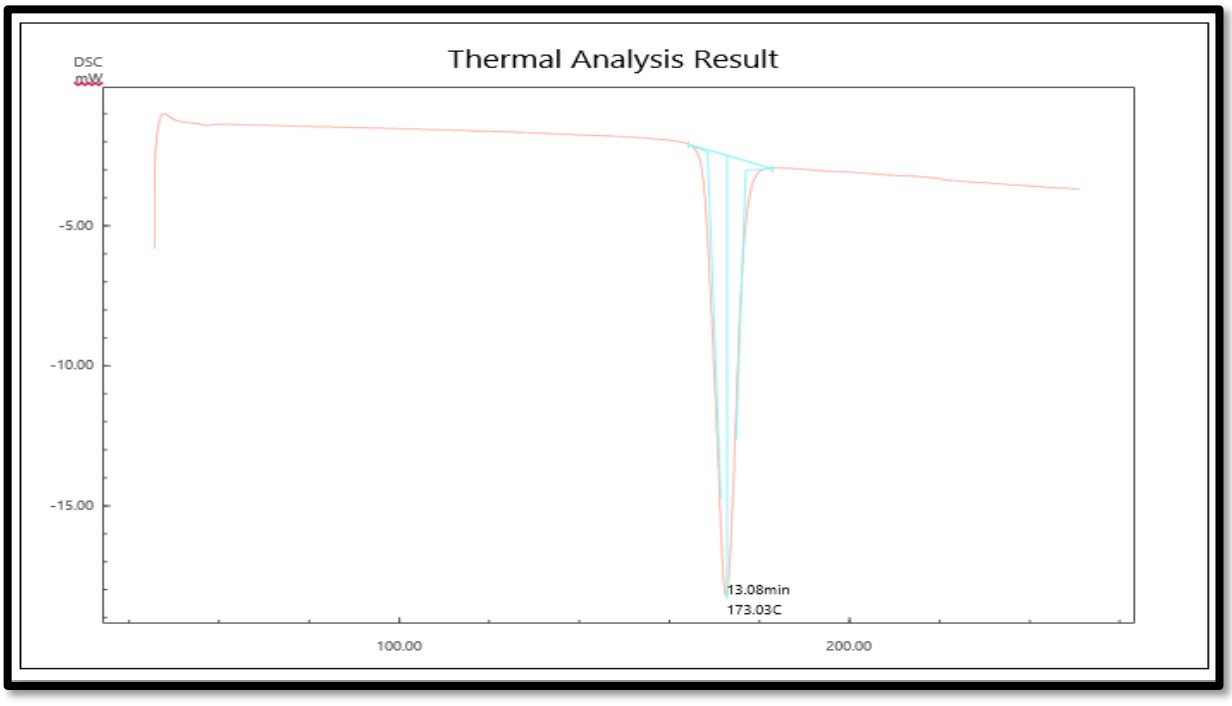


**Figure 4: DSC of Itraconazole**

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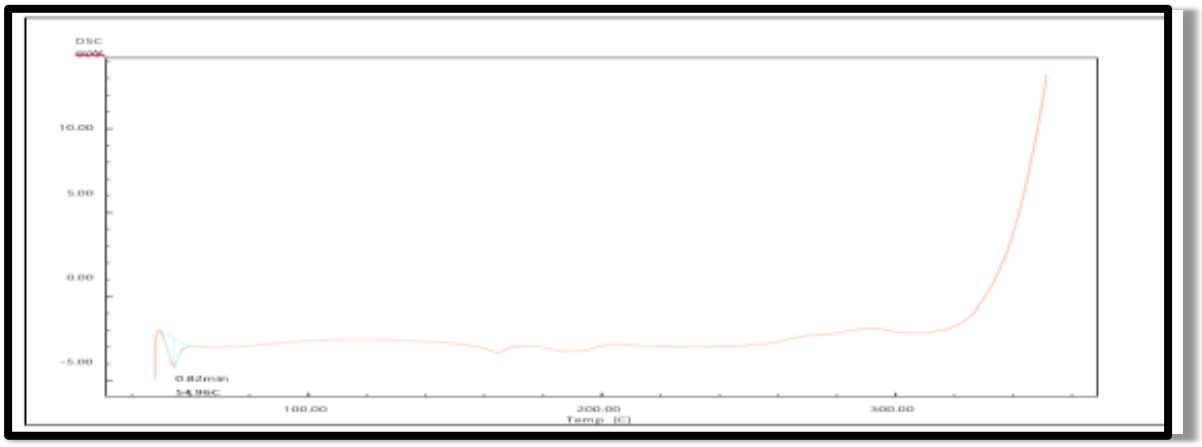


**Figure 5: BATCH B DSC**

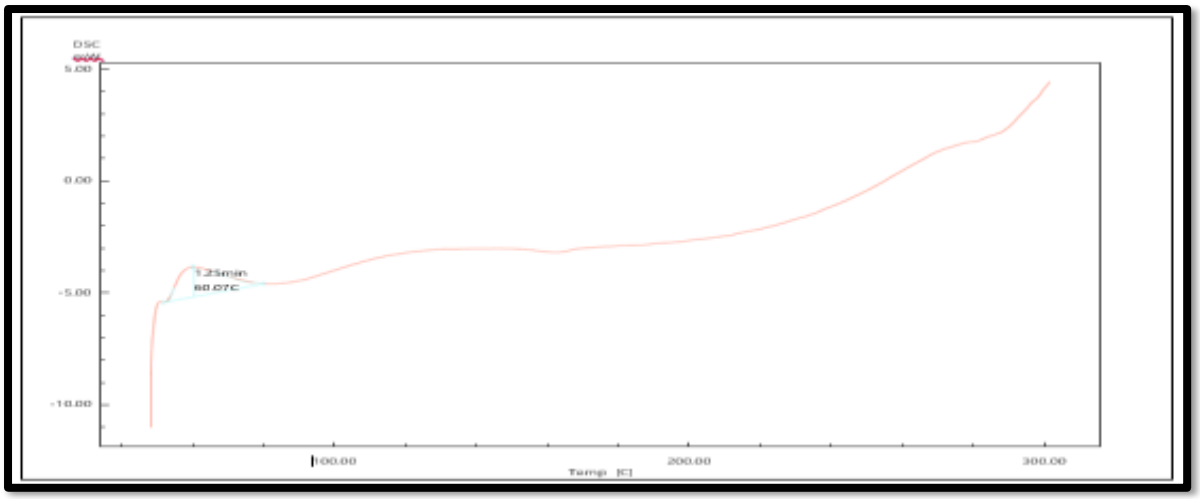


**Figure 6: BATCH E DSC**

X- Ray Powder Diffraction Study

XRPD analysis confirmed the crystalline nature of ITZ with sharp peaks at 11°, 14°, 18°, 20°, and 24°. In contrast, Batch B (PVA: Poloxamer 188, 1:2) and Batch F (HPMC: Poloxamer 188, 1:2) exhibited distinct peaks at 20° and 25°, with Batch F also showing a peak at 22°, indicating partial amorphization. Batches B and E were identified as optimized formulations due to their superior dissolution performance. The enhanced dissolution is attributed to the higher proportion of Poloxamer 188 (1:2 ratio), as its crystalline structure promotes improved solubility, aligning with findings in the literature.

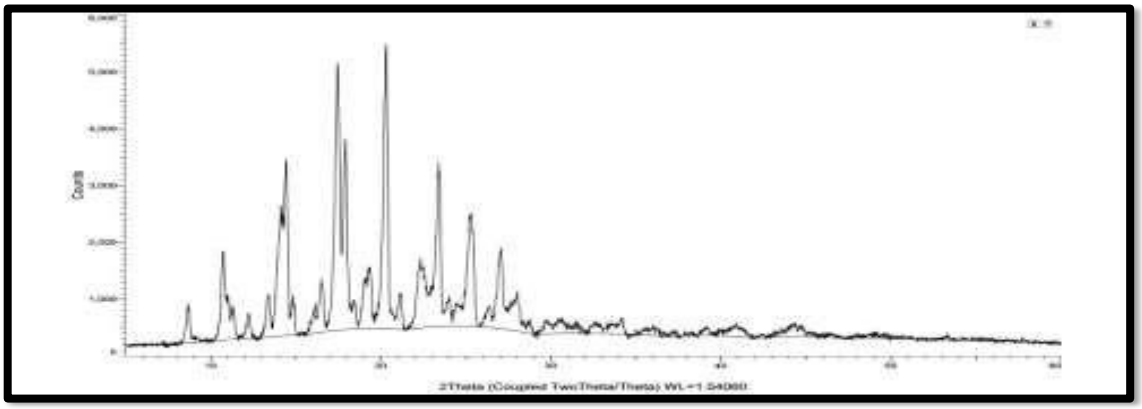


**Figure 7: XRD of Itraconazole**

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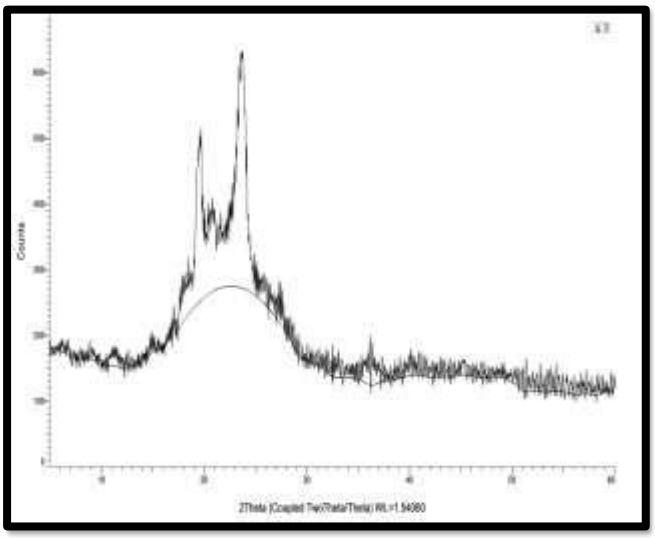

Figure 8 : BATCH B XRD

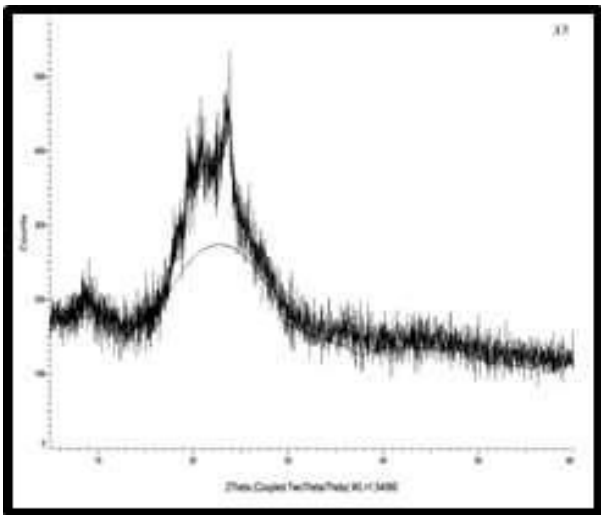

Figure 9: BATCH E XRD

In-Vitro Drug Release

In our investigation into drug release, we observed that Batch B and Batch E (with a 1:2 ratio of Poloxamer 188) showed the highest drug release, reaching 73.86% and 51.22%, respectively, within 20 minutes. This enhanced release is attributed to the solubility-boosting effect of Poloxamer 188, which has a solubility of 0.77 mg/mL in USP buffer, slightly higher than polyvinyl alcohol (0.75 mg/mL). Batch B and Batch E, with the 1:2 ratio, demonstrated the best performance, outperforming Batch B1 and E1, which were prepared using hot melt extrusion alone. The combination of mesoporous silica loading and hot melt extrusion led to enhanced dissolution, with the formulations showing more than 50% similarity to the marketed product CANDITRAL® SB in drug release.

| **Time (min)** | **% Cumulative drug release (±Standard deviation)** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Pure ITZ** | **ITZ loading batches with mesoporous silica** | | | **Extrudates batches after loading with mesoporous silica** | | | **Extrudes by using HME only** | **CANDITRAL® SB 65** |
| | | A1 | A2 | A3 | A | B | C | B1 | |
| 10 | 2.11 | 0.89 | 1.62 | 1.06 | 67.56 | 73.86 | 66.56 | 61.69 | 71.41 |
| 20 | 2.13 | 4.69 | 5.62 | 2.99 | 73.05 | 78.68 | 72.19 | 63.08 | 85.16 |
| 30 | 2.39 | 5.63 | 8.39 | 5.71 | 78.68 | 86.41 | 76.07 | 65.12 | 88.43 |
| 40 | 2.95 | 7.51 | 11.07 | 8.15 | 82.90 | 91.72 | 81.89 | 71.54 | 92.59 |
| 50 | 3.5 | 11.05 | 14.66 | 10.14 | 90.21 | 98.07 | 88.67 | 76.89 | 96.45 |
| 60 | 5.38 | 14.95 | 18.35 | 13.79 | 95.77 | 104.76 | 91.94 | 83.11 | 114.45 |

**Table 6. % Cumulative drug release as per USP for batches pva: plx**

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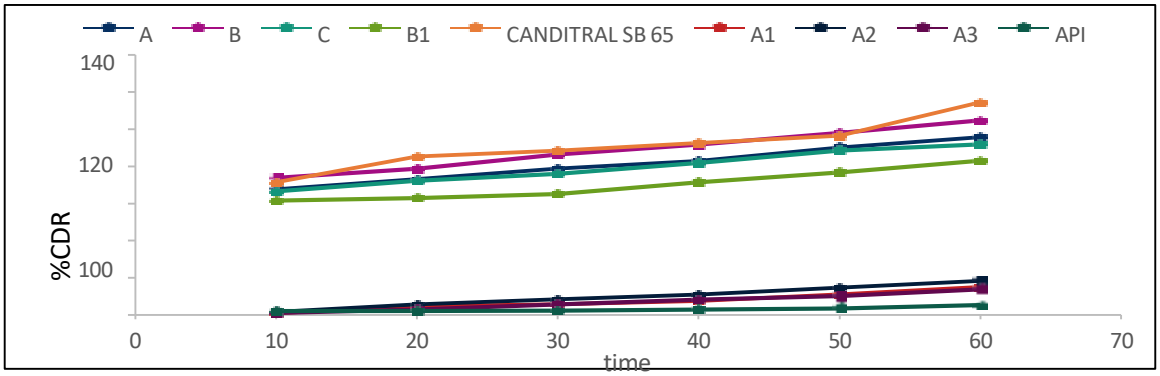


**Figure 10: Drug release profile**

| Time (min) | % Cumulative drug release (±Standard deviation) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pure ITZ | ITZ loading batches with mesoporous silica | | | Extrudates batches after loading with mesoporous silica | | | Extrudes by using HME only | CANDITRAL® SB 65 |
| | | A1 | A2 | A3 | D | E | F | E1 | |
| 10 | 2.11 | 0.89 | 1.62 | 1.06 | 40.68 | 51.22 | 43.04 | 41.22 | 71.41 |
| 20 | 2.13 | 4.69 | 5.62 | 2.99 | 46.77 | 57.21 | 48.44 | 46.79 | 85.16 |
| 30 | 2.39 | 5.63 | 8.39 | 5.71 | 50.56 | 61.94 | 53.90 | 53.61 | 88.43 |
| 40 | 2.95 | 7.51 | 11.07 | 8.15 | 53.32 | 69.77 | 59.17 | 62.13 | 92.59 |
| 50 | 3.5 | 11.05 | 14.66 | 10.14 | 61.39 | 78.43 | 66.56 | 68.81 | 96.45 |
| 60 | 5.38 | 14.95 | 18.35 | 13.79 | 67.11 | 81.71 | 71.33 | 72.09 | 114.45 |

**Table 7. % Cumulative drug release as per USP for batches hpmc: plx**

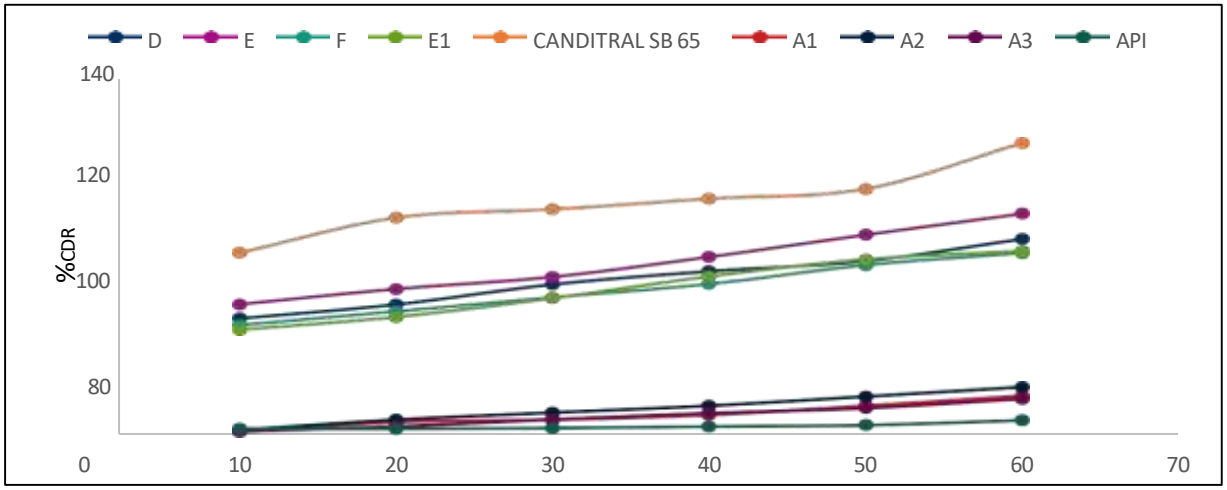


**Figure 11: Drug release profile**

## CONCLUSION

This study successfully exploits the synergistic benefits of two approaches: mesoporous silica loading and hot melt extrusion to achieve significant enhancements in the dissolution characteristics of ITZ. Employing a two-step approach, involving the loading of ITZ onto mesoporous silica followed by hot melt extrusion with a carefully balanced [Polyvinyl alcohol: Poloxamer-188 (1:2)] and [HPMC: Poloxamer-188 (1:2)] ratio showed the highest drug release to address the inherent solubility limitations of the ITZ. The achieved enhancements in dissolution profiles and comparative evaluations against a marketed formulation provide a strong foundation for further exploration and application in drug delivery. So, the study underscores the pivotal role of mesoporous silica (Parteck® SLC 500), Poloxamer-188, and the hot melt extrusion process in achieving our solubility enhancement objectives. The observed results align with our initial aim, demonstrating the potential of this integrated approach to transform the dissolution behavior of Itraconazole.

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