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# Formulation And Evaluation of Spray-Dried Ternary Solid Dispersions of Amorphous Itraconazole

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**Abstract**

Although it is extensively utilized to treat both systemic and superficial fungal infections, the therapeutic efficacy of itraconazole is severely constrained due to its extremely low oral bioavailability and extremely poor water solubility. The purpose of this research was to create and assess amorphous itraconazole spray-dried ternary solid dispersions with improved solubility properties by means of hydrophilic carriers such as polyvinylpyrrolidone K30 (PVP K30) and Sylysia® 350. The melt-quench process was used to create the amorphous itraconazole, which was then spray-dried into binary and ternary solid dispersions. The drug content was adequate in all formulations, indicating that the spray drying process was effective in incorporating the medicine. Pure crystalline itraconazole, amorphous itraconazole, and binary solid dispersions all performed poorly in comparison to the ternary solid dispersion containing PVP K30 and Sylysia® 350 (F3), which achieved the best dissolution performance. Amorphization, greater wettability, increased surface area, drug molecular dispersion, and the synergistic action of the hydrophilic polymer and porous silica carrier were all factors in the enhanced solubility.

**Keywords:** Itraconazole, Amorphous, Spray Drying, Ternary, Chromatography

## I. Introduction

When it comes to increasing the oral bioavailability and solubility of medications that are not very water-soluble, solid dispersions have shown to be a very useful formulation strategy. Oral administration of many recently found pharmaceutical compounds is hindered by their slow dissolving rate and lack of therapeutic effectiveness due to their poor water solubility. Many potential new drugs fall under the Biopharmaceutics Classification System (BCS) Classes II and IV, which are defined by poor solubility and high or low permeability, respectively. These chemicals may be very difficult to create drugs for because of their unpredictable bioavailability, delayed beginning of action, and variable absorption. Among these medications, itraconazole stands out as a prime example of an antifungal agent that is both lipophilic and weakly soluble in water. Its main limitation in terms of clinical efficacy is its low solubility in gastrointestinal fluids.

Patients with systemic or superficial fungal infections due to species like Candida, Aspergillus, Histoplasma, Blastomyces, or Cryptococcus are often treated with itraconazole, a broad-spectrum triazole antifungal medication. The antifungal effect of the medicine is achieved by limiting the production of ergosterol, a crucial element of fungal cell membranes, by

specifically inhibiting the enzyme lanosterol 14α-demethylase, which is reliant on cytochrome P450. Despite being very effective against a wide range of fungal infections, itraconazole has a very low water solubility (usually less than 1 ng/mL under neutral circumstances), which causes it to be absorbed unevenly from the intestines. The oral bioavailability of this substance varies greatly from patient to patient due to variables such as stomach acidity, food consumption, and individual physiological characteristics. As a result, research into pharmaceutical formulations has mostly focused on ways to improve itraconazole's dissolving properties.

The extraordinary capacity of amorphous solid dispersions to improve medication solubility without changing the chemical structure of the active medicinal ingredient has brought them considerable renown among the many formulation approaches created to circumvent solubility restrictions. The medicine that has trouble dissolving in water is either coarsely or molecularly dispersed within a hydrophilic polymeric carrier in a solid dispersion system. Transforming a crystalline medicine into an amorphous one increases its molecular mobility and free energy by removing the long-range molecular order that is typical of crystalline materials. Therefore, in comparison to its crystalline form, the amorphous form has a much quicker dissolving rate and a much greater apparent solubility. Amorphous solid dispersions are among the most promising methods for tackling the solubility-related issues with BCS Class II medicines because of their features.

Itraconazole has several medicinal benefits in its amorphous form that are not present in its crystalline one. The unusually delayed drug release of crystalline itraconazole is due to its highly organised lattice structure, which needs a great deal of energy to break when dissolved. On the other hand, amorphous itraconazole does not have this stiff molecular configuration, hence it dissolves more easily in biological fluids. Rapid supersaturation is promoted by the enhanced thermodynamic activity of the amorphous phase, leading to a much better drug concentration inside the gastrointestinal system. On the other hand, due to its larger free energy, the amorphous form is intrinsically metastable and has a tendency to recrystallise during storage or after administration. The advantages of improved solubility may be diminished over time due to this instability. Consequently, one of the biggest problems in formulating amorphous itraconazole is keeping it in its amorphous form during the product's shelf life.

Pharmaceutical researchers use appropriate polymeric carriers that may stabilise the amorphous structure via molecular interactions to circumvent the instability that is often associated with amorphous medications. Hydrophilic polymers like HPMC, HPMCAS, PVP, PVP-VA, PEG, Soluplus®, and Eudragit® derivatives are promising candidates for stabilising amorphous itraconazole. As a result of hydrogen bonding, dipole-dipole interactions, and van der Waals forces, these polymers bind to drug molecules and reduce their mobility, making them less likely to recrystallise when stored. Polymeric carriers not only stabilise the system, but they also accelerate hydration, prevent crystal nucleation, and maintain supersaturation even as they dissolve. The oral absorption and dissolution characteristics of itraconazole are greatly enhanced by these combined actions.

There are a number of different ways to make itraconazole amorphous solid dispersions, and each has its own set of benefits that are dependent on the drug's and carrier materials'

physicochemical qualities. One of the most popular and lucrative processes is hot-melt extrusion, which allows for continuous solvent-free production while still producing high-quality drug-polymer mixtures. Spray drying is another common method that quickly evaporates solvents from drug-polymer mixtures, turning them into small, amorphous particles. This creates uniform dispersions that are easier to dissolve. Solvent evaporation, freeze drying, electrospinning, co-precipitation, supercritical fluid technology, and KinetiSol® processing are some more methods. When choosing a production procedure, it's important to examine issues including thermal stability, compatibility with polymers, residual solvent, scalability, and regulatory compliance.

Multiple supplementary processes control the improved solubility attained by amorphous solid dispersions. Particles of smaller sizes have more surface area to dissolve, and those with better wettability may be dissolved more quickly. The drug's molecular dispersion allows for quicker dissolving kinetics by removing the need to disturb the crystal lattice. Creating supersaturated medication solutions also greatly enhances the concentration gradient that propels absorption in the intestines. To further delay the crystallisation of dissolved drug molecules, certain polymers also act as precipitation inhibitors, keeping the solution supersaturated for lengthy periods of time. Increased therapeutic effectiveness, less variability in absorption, better pharmacokinetic performance, and greater plasma drug concentrations are all results of these processes working together.

## II. Review Of Literature

Hong, Z. et al., (2018). The goal of this study was to compare the dissolving properties of Sporanox with those of an amorphous solid dispersion of itraconazole that was created using hot-melt extrusion technology in an effort to design a novel formulation. The carriers employed were Solu plus, Kolli don VA64, HPMGAS, and Eudragit EPO, which were chosen based on the solubility parameter and glass transition temperature. An amorphous solid dispersion was effectively produced and studied using MT-DC, X-ray powder diffraction (XRPD), polarised light microscopy (PLM), and Fourier transform infrared (FT-IR) after modulated temperature-differential scanning calorimetry (MT-DSC) was used to screen candidate carriers. was that there was a contact between the polymer and the amorphous form of the ITZ solid dispersion. We conducted in vitro dissolution and kinetic solubility studies on solid dispersions with drug loadings of 30% and 50%. The solubility rate of itraconazole was much enhanced when utilising Solu plus (3=7) as a carrier at an extrusion temperature of 17P t, in comparison to Sporanox. For 30 days under a 40% relative humidity environment, the solid dispersion of itraconazole did not exhibit any crystal structure. The solubilisation of amorphous itraconazole may be better understood and future formulations can be developed based on the results of this study, which suggest that the molecular level miscibility between Solu plus and amorphous itraconazole is likely the major reason.

Davis, Mark et al., (2018). The study focused on the downstream processing characteristics of a stable amorphous itraconazole form that had improved solubility. The powder processing characteristics of this ternary amorphous solid dispersion were drastically altered depending on whether it was prepared using hot melt extrusion or spray drying. Scanning electron microscopy was used to examine the shape and size of the particles. Rheometric, compaction

modelling, and a dissolution kit were used to investigate flow, compression, mixing, and dissolution. In comparison to the milled extrudate, the spray dried material had less sensitive flow and was less affected by aeration. Various flow measuring methods, including the Flow Function, the Relative flow function, the Flow rate index, the Aeration rate, the Hausner ratio, and the Carr index, showed good agreement with one another. Both powders showed no signs of instability in terms of agglomeration, de-agglomeration, or attrition, according to the stability index. Research on tablet ability and compressibility revealed that, in comparison to extruded material, spray-dried material may be crushed into compacts with greater strength. Compression and flow were both affected by the addition of low-moisture, freely-flowing excipients to the powder mixture. Research on the porosity of extrudate and blended extrudate formulations showed that the densification process might be affected by mixing. After the powders were mixed, they were compacted into four 500 mg tablets, with 100 mg of amorphous itraconazole in each. from dissolving experiments showed that the medication was released more rapidly and fully from the spray-dried material, and that the addition of excipients to the mixture affected the dissolution process even more.

Duarte, Iris et al., (2014). The study focused on the downstream processing characteristics of a stable amorphous itraconazole form that had improved solubility. The powder processing characteristics of this ternary amorphous solid dispersion were drastically altered depending on whether it was prepared using hot melt extrusion or spray drying. Scanning electron microscopy was used to examine the shape and size of the particles. Rheometric, compaction modelling, and a dissolution kit were used to investigate flow, compression, mixing, and dissolution. In comparison to the milled extrudate, the spray dried material had less sensitive flow and was less affected by aeration. Various flow measuring methods, including the Flow Function, the Relative flow function, the Flow rate index, the Aeration rate, the Hausner ratio, and the Carr index, showed good agreement with one another. Both powders showed no signs of instability in terms of agglomeration, de-agglomeration, or attrition, according to the stability index. Research on tablet ability and compressibility revealed that, in comparison to extruded material, spray-dried material may be crushed into compacts with greater strength. Compression and flow were both affected by the addition of low-moisture, freely-flowing excipients to the powder mixture. Research on the porosity of extrudate and blended extrudate formulations showed that the densification process might be affected by mixing. After the powders were mixed, they were compacted into four 500 mg tablets, with 100 mg of amorphous itraconazole in each. from dissolving experiments showed that the medication was released more rapidly and fully from the spray-dried material, and that the addition of excipients to the mixture affected the dissolution process even more.

Davis, Mark et al., (2017). Itraconazole (ITZ), HPMCP, and Solu plus have been produced in a variety of 17 ternary formulations by the use of spray drying. After one year at 40 °C/75% RH, all formulations of ITZ remained amorphous, demonstrating the remarkable stability of these amorphous solid dispersions (ASDs) against crystallisation. The physicochemical characteristics of the ASDs after processing and storage, as well as any interactions between components, were characterised using a variety of solid-state analytical methods, including as PXRD, DSC, small angle X-ray scattering, FTIR, and solid-state NMR. The correlation between polymer concentration and PSD was shown by microtrap laser scattering research.

Results from dissolution experiments showed that in acidic environments, ITZ concentrations were highest for formulations with a greater Solu plus content.

Subramanian, Rajarajan et al., (2009). This study's overarching goal is to test the effects of spray drying on the solid dispersion of the poorly water-soluble drug itraconazole using PEG/HPMC polymer blends as a model drug. The researchers will also use ternary mixing to prepare solid dispersions of itraconazole and will evaluate the polymer blends using DSC, XRD, and in vitro dissolution testing to determine the impact of polymer compatibility on the degree of molecular dispersion. In order to assess the condition of the ternary solid dispersion phases in the glass transition state, thermal analysis of DSC and XRD graphs were examined. When it came to invitro release, the amorphous nature of the formulations with a PEG/HPMC ratio of 15/85 (w/w) performed better.

## III. Materials And Methods

### Materials

A free sample of itraconazole was provided by Glenmark Pharma of Mumbai, India. Sponsored by Signet Chem. Lab., PVP K30 and sylysia® 350 were kindly provided. Fuji Sylysia Chemical Ltd. of Japan and Mumbai, India, respectively. We only used analytical grade reagents. Throughout the experiment, double-distilled water was used.

### Preparation of an amorphous state

In order to prepare the amorphous state of ITR, the melt quench cooling process was used. After the ITR crystals were melted in a steel container at carefully controlled temperatures, they were cooled by immersing them in a close-knit freezing mixture of ice and sodium chloride for about one to one and a half hours. Desiccators were used to hold the solidified substance until more research could be conducted.

### Thin layer chromatography

The potential deterioration of the medication during the formation of the amorphous phase was detected using thin-layer chromatography (TLC). Silica gel G used as the stationary phase, while a mobile phase consisting of a chloroform: benzene (40:10) combination was used simultaneously. A sealed container with an atmosphere filled with iodine vapour was used to keep the plate for a few minutes in order to see the spots. At each step, the drug's behaviour on the TLC was characterised by determining and verifying the relative mobility, or Rf value.

### Preparation of binary and ternary amorphous solid dispersions (SDs)

The spray drying method was used to create AITR SDs. AITR, AITR mixed with PVP K30 or sylysia® 350 (1:1 w/w), and AITR mixed with PVP K30 and sylysia® 350 (1:1:1 w/w) were dissolved in enough chloroform to produce clear solutions. Subsequently, the solutions were subjected to a series of conditions in order to facilitate spray drying. These conditions included an inlet temperature of 60 °C, an outlet temperature of 45 °C, a cool temperature of 35 °C, a feed rate of 8-10 ml/min, an atomisation air pressure of 2 kg/cm2, and an aspiration rate of 60 mBar. The formulations were placed in a desiccator and coded according to the information in table 1 pending further examination.

**Table 1: Codes for all systems**

| Batch Code | Description of System |
|---|---|
| CITR | Pure crystalline itraconazole |
| AITR | Spray-dried amorphous itraconazole |
| F1 | Binary dispersion with PVP K30 |
| F2 | Binary dispersion with Sylysia® 350 |
| F3 | Ternary dispersion with PVP K30 and Sylysia® 350 |

**Determination of drug content**

The solution was adjusted to a final volume of 100 ml using distilled water after dissolving 10 mg of SDs in 10 ml of methanol. Afterwards, a 0.45-µm filter was used to filter the samples, and a UV-Visible spectrophotometer (Shimadzu1800, Japan) was used to conduct spectrophotometric analysis at λmax 262 nm to determine the drug concentration. The experiments were repeated three times, and the results are shown as the average.

**Fourier transformation infrared spectroscopy (FTIR)**

Using a Jasco V550 spectrophotometer from Japan, we were able to get the Fourier transform infrared spectra of pure CITR, PVP K30, sylysia® 350, and all binary and ternary SDs. Dry potassium bromide was used to fully mix the samples before they were compacted into discs. The 10-milligram portions of each sample were examined using a scanning frequency range of 4,000 to 400 cm -1.

**Dissolution studies**

The Disso 2000 equipment from LabIndia, India, was used to conduct dissolution tests for all binary and ternary SDs in accordance with the USP II technique (paddle method). To model the dissolution of the ITR in the stomach, a dissolving medium consisting of enzyme-free simulated gastric fluid (SGF) kept at 37 ± 0.5 °C and spun at 100 rpm was used. To the dissolving media was added a quantity of formulation that was 100 mg of ITR dosage. The sink condition was maintained by immediately replacing an equivalent amount of fresh dissolving medium each time with a 10-, 20-, 30-, 45-, 60-, and 90-minute interval for sampling. After that, the samples were diluted appropriately and passed through a 0.45 µm membrane filter. The spectrophotometric analysis was completed using a UV-visible spectrophotometer (Shimadzu-1800, Japan) at λmax 262 nm. Triplicate runs of each study were performed.

**Statistical analysis**

Mean standard deviation was used to represent the data, and suitable methods were used for statistical analysis wherever needed.

## IV. Results And Discussion

### Thin-layer chromatography

In order to detect any loss of ITR during melting, TLC experiments were carried out. Rf values were around 0.82 in both the crystalline and amorphous forms. It was established that the medication remained stable throughout melting since the amorphous state run showed no extra spots and identical Rf values.

### Fourier transformation infrared spectroscopy (FTIR)

A closer look at CITR's infrared spectra reveals many distinct peaks, as shown in Figure 1 A: 3142 cm-1 for C-H aromatic, 2995 cm-1 for C-H aliphatic, 1725 cm-1 for C=O, amide carbonyl, 1400 cm-1 for C=N, 1480 cm-1 for C=C aromatic, 1237 cm-1 for C-N, ring stretch, heterocyclic, 1030 cm-1 for C-O-C, and 1080 cm-1 for C-Cl. For AITR, there was hardly any change to the broad spectrum, except for a little shift in a few of distinctive peaks (Figure 1 D). The absorption bands of ITR assigned to C-H aliphatic stretch and C=O amide carbonyl stretch were moved towards lower intensity and expanded in the spectra for the binary SDs of amorphous drug with PVP K30 (Figure 1 E) and with sylysia® 350 (Figure 1 F). Another possible explanation for the wide peak at 3495 cm-1 is that the medicine and PVP K30 form hydrogen bonds.

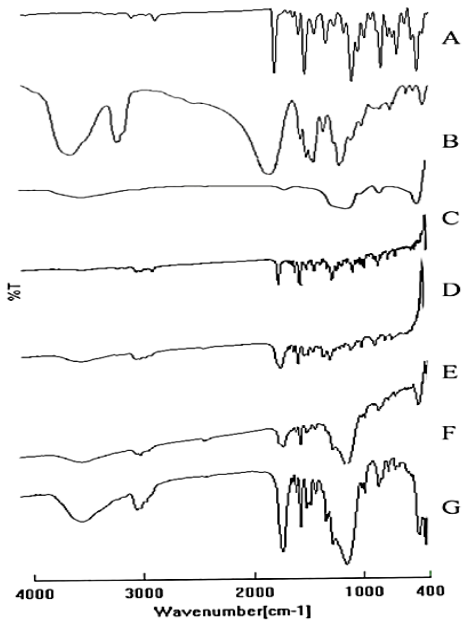


**Fig. 1: FTIR spectra of all systems. (A) Crystalline Itraconazole, (B) Polyvinylpyrrolidone K30, (C) sylysia® 350, (D) Amorphous Itraconazole, (E) F1, (F) F2 and (G) F3**

Figure 1 shows that in the ternary solid dispersion system, there is strong hydrogen bonding between the silanol groups of the ternary components (sylysia® 350) and the functional groups of the ITR. This is shown by the lack of peaks corresponding to the C-H aliphatic and C-H

aromatic stretch. The significant physical interaction between the drug and polymer may also explain why all of the other peaks that correspond to the ITR spectrum were present, but with lower peak intensities and smoothed down. The lack of extra spectra peaks in both binary and ternary SDs suggests that the medication and carriers, including the ternary component, did not interact chemically in any way.

**Drug content**

From 82.52 ± 1.93% to 96.46 ± 1.8%, the percentage of drug content in all formulations was determined (n = 3 for each formulation).

**Dissolution studies**

Figure 4 displays the CITR and AITR dissolution curves as well as their standard deviations in SGF without enzyme at 37 ± 0.5 °C. All formulations clearly outperformed the CITR and AITR systems in terms of ITR dissolving profile ($p < 0.001$). The dissolution data assessment was based on the percentage of medication dissolved at 5 minutes (DP5), 15 minutes (DP15), and the dissolution efficiency at 15 minutes (DE15), as shown in table 2.

**Table 2: Initial Dissolution Profile of CITR, AITR, and Solid Dispersions in SGF**

| System | DP5* | DP15* | DE15* |
|---|---|---|---|
| Crystalline Itraconazole | 2.39 ± 1.7 | 4.45 ± 1.5 | 2.88 ± 0.67 |
| Amorphous Itraconazole | 10.40 ± 2.8 | 10.37 ± 3.9 | 5.80 ± 2.5a |
| F1 | 20.32 ± 2.3 | 22.21 ± 2.7 | 10.83 ± 3.4a |
| F2 | 43.08 ± 3.4 | 45.91 ± 4.8 | 23.69 ± 2.7b |
| F3 | 63.54 ± 4.1 | 62.53 ± 4.2 | 32.92 ± 3.1b |

* Mean ± S.D. (n = 3); S.D.: Standard deviation; DP5: % Drug dissolved at 5 min; DP15: % Drug dissolved at 15 min; DE15: Dissolution efficiency at 15 min; a no significant difference compared to CITR ($p > 0.05$); b significant difference compared to CITR and AITR ($p < 0.001$).

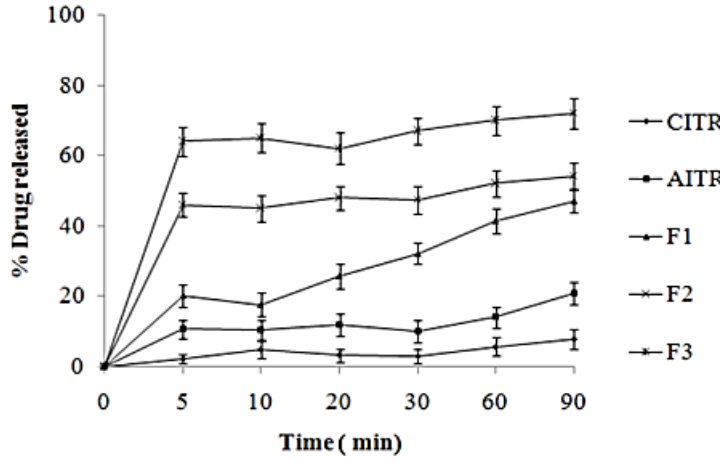


**Fig. 2: Initial dissolution profile of all systems including pure drug in simulated gastric fluid (SGF) without enzyme at 37 ± 0.5 °C**

Within 90 minutes in the dissolving medium, CITR demonstrated a drug release of just 7.71±1.26%. Although CITR had a higher rate of ITR release than AITR and binary systems prepared with PVP K30 (F1), there was no statistically significant difference ($p>0.05$) between the three. This could happen when an amorphous medicine reaches an equilibrium state and changes from an amorphous solid to a cohesive supercooled liquid around the glass transition temperature. In addition, the amorphous form of ITR may have a poor dissolving profile due to aggregation and high adherence of individual particles. The binary system that was produced with sylysia® 350 (F2) showed a considerably better p profile compared to the pure medication, with a DE15 of 23.69 ± 2.7%.

Increased surface area by spray drying and the hydrophilic nature of the carrier both lead to a better rate of breakdown and a greater extent of ITR. The porous ternary component sylysia® 350 was used in the F3 ternary dispersion system. Among the many possible explanations for the enhanced solubility of ITR, the hydrophilic properties of silicon dioxide particles stand out. The silanol groups on the surfaces of fine silica particles with a high specific surface area allow them to make hydrogen bonds with drug molecules, allowing them to absorb them. The drug molecules become more dispersible in the carrier system and their wettability is further enhanced as a result of this interaction. Adsorbed drug molecules also enhanced solubility due to their amorphous nature.'

## V. Conclusion

This research proved that amorphous itraconazole spray-dried ternary solid dispersions are a great way to make the medicine more soluble and faster to dissolve. The ternary solid dispersion of PVP K30 and Sylysia® 350 (F3) outperformed the pure drug and binary formulations in terms of dissolving performance and stability. Results from FTIR and TLC analyses verified that the chosen excipients were compatible with the medicine and that it was stable. The increased wettability, synergistic impact of the polymer and porous carrier, and the amorphous character of itraconazole were shown to be responsible for the enhanced dissolution. The research found that spray-dried ternary solid dispersions are a good way to

make itraconazole and other medications that aren't very water-soluble more bioavailable and effective when taken orally.

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