Chettinad Health City Medical Journal
Volume 13, Issue 3 - 2024, Pg. No. 65-74
Peer Reviewed & Open Access Journal

Research Article

Improving the Dissolution Characteristics of Itraconazole by Formulating Cocrystal with the Use of Appropriate Conformers Using Solvent Evaporation Method

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DOI: https://doi.org/10.24321/2278.2044.202447

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How to cite this article:
Kanabar V, Radadiya J, Gadhiya H. Improving the Dissolution Characteristics of Itraconazole by Formulating Cocrystal with the Use of Appropriate Conformers Using Solvent Evaporation Method. Chettinad Health City Med J. 2024;13(3):65-74.

Date of Submission: 2023-10-11
Date of Acceptance: 2024-04-16

A B S T R A C T

Introduction: Itraconazole BCS class II drugs have low solubility. Their solubility improves made cocrystal. Cocrystals can be made by many methods like solvent evaporation, cooling crystallisation, and freeze-drying.

Method: In this study, cocrystals were prepared by slow solvent evaporation method with the use of an appropriate coformer with a suitable stoichiometric ratio and COSMO-RS software. Itraconazole and the coformer were dissolved in the proper solvent or solvent mixture and swirled on a magnetic stirrer for 45 minutes at 600 rpm until the product was totally dry. Cocrystal characterisation was done on this product. To create cocrystals, organic acid coformers such as benzoic acid, salicylic acid, caffeine, oxalic acid, and nicotinamide were utilised. Prepared cocrystals were evaluated on the basis of FTIR spectra, DSC thermogram, powder X-ray diffraction, in vitro dissolution study and saturation solubility study.

Results: The FTIR, DSC, and PXRD results indicated that there was no cocrystallisation in organic acid coformers. The usage of amino acids such as glycine, alanine, cysteine, and proline followed. Of these, glycine and alanine showed promise in FTIR, DSC, PXRD, saturation solubility research, and in vitro dissolution studies. Alanine and oxalic acid showed promising results in powder X-ray diffraction.

Conclusion: In the current study, itraconazole cocrystals were effectively created by slow solvent evaporation and had better-dissolving properties than pure itraconazole. Additionally, it was shown that the manufactured cocrystal had a greater saturation solubility than pure itraconazole. Co-crystallisation is therefore a viable method to enhance medication solubility properties without compromising structural integrity and pharmacological effectiveness.

Keywords: Cocrystal, Itraconazole, Oxalic Acid, Cystine, Anti-Fungal Disease, Solvent Evaporation Method

Introduction

The oral delivery of new drugs is challenging due to the poor solubility of many drug molecules. Solubility is critical for achieving the desired concentration of drugs in the bloodstream to produce a pharmacological response. Many drugs fall under the BCS – Biopharmaceutical Classification System as Class II or IV drugs, with low aqueous solubility and slow dissolution rates.[1] Solubility enhancement techniques like particle size reduction, solid dispersions, and nanosuspensions have been used to increase bioavailability. Other techniques include supercritical fluid processes, cryogenic techniques, complex formation-based techniques, cosolvency, hydrotrophy, microemulsion, co-crystals, nanocrystals, self-emulsifying drug delivery systems, and liquisolid compacts.[2]

BCS Class II drugs, which have high permeability but low solubility, are particularly vulnerable to bioavailability issues related to drug solubility and dissolution.[3] Therefore, improving the solubility of such drugs through formulation development is a key approach to enhancing their therapeutic potential. By increasing the solubility and bioavailability of poorly water-soluble drugs, it may be possible to improve their efficacy and reduce the risks and costs associated with drug development and production.[4]

Crystal Engineering

Crystal engineering is a field of chemistry that designs and synthesises molecular solid-state structures to improve the properties of drugs, particularly their solubility and bioavailability. Pharmaceutical cocrystals, formed by combining a coformer molecule with the drug molecule, are a promising approach for improving the solubility and dissolution rate of poorly soluble drugs, including those belonging to BCS class II and IV.[5] Crystal engineering can potentially improve patient outcomes and provide more effective treatment options by enhancing the solubility of these drugs.

Cocrystals

Cocrystals were first discovered in the 1800s and early 1900s. The first reported cocrystal, quinhydrone (cocrystal of quinone and hydroquinone (1:1) stoichiometric ratio), was prepared by Friedrich Wohler in 1844.[6] Cocrystals are defined as homogenous crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds.[7]

Cocrystals are multi-component crystals held together by non-covalent interactions and are gaining interest in the pharmaceutical industry due to their ability to improve the properties of API – Active Pharmaceutical Ingredient Synthon theory can guide cocrystal formation, but other factors also play a role. The "spring and parachute" effect can be applied in cocrystals to improve the solubility and dissolution rate of poorly soluble drugs. The cocrystal former acts as a protective layer around the API molecules, while the API acts as a "spring" that releases the drug molecules in a controlled manner over time.[8] The traditional approach is salt formation for improving the drug solubility, but it proves to be unsuccessful for the drugs that are non-ionisable, and for the sensitive moieties that are liable to decomposition. Such problems do not take place in cocrystals. Cocrystals between the API and coformer molecules are formed using non-covalent interactions like hydrogen bonding, stacking, van der Waals forces, halogen bonding, and electrostatic interactions.[9]

Advantages of Cocrystals

1. Cocrystals can enhance the dissolution rate and solubility of an API without chemical modification of the API.[10]
2. Theoretically, all types of molecules in an API (weakly ionisable or non-ionisable) are able to form cocrystals.[11]
3. There's no requirement to create or break the covalent bonds.[12]
4. It can improve dissolution rate, bioavailability, permeability, and physical and chemical stability.[13]
5. The FDA – Food and Drug Administration has released guidelines regarding the approval of pharmaceutical cocrystals as applicants for New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDA).[14]
6. It offers scope for change of an amorphous or non-crystalline API to an easy-to-handle crystalline form (into a readily handled, stable crystalline solid).

Cocrystal Design and Screening

Finding a suitable coformer for successful cocrystal formation is a tough task. Since a coformer interacts non-ionically with API within a crystal structure, it should be non-toxic, free of adverse effects, and non-volatile.[15,16]

1. Hansen solubility parameters
2. Supramolecular synthons
3. Structural resemblance
4. Virtual coformer screening approaches (e.g., conductor-like screening model for real solvents (COSMO-RS))
5. Surface site interaction point (SSIP) method
6. Cloud-computing crystal structure prediction (CSP)

Virtual Coformer Screening Approaches

As shown in Fig.1, Material sparing, rapid screening, ease of understanding, and the ability to obtain relevant results are all advantages of computational cocrystal screening methods over traditional ones. The excess enthalpy between the API-coformer mixture and pure components was determined by using the conductor-like screening model for real solvents (COSMO-RS).[17]

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202447

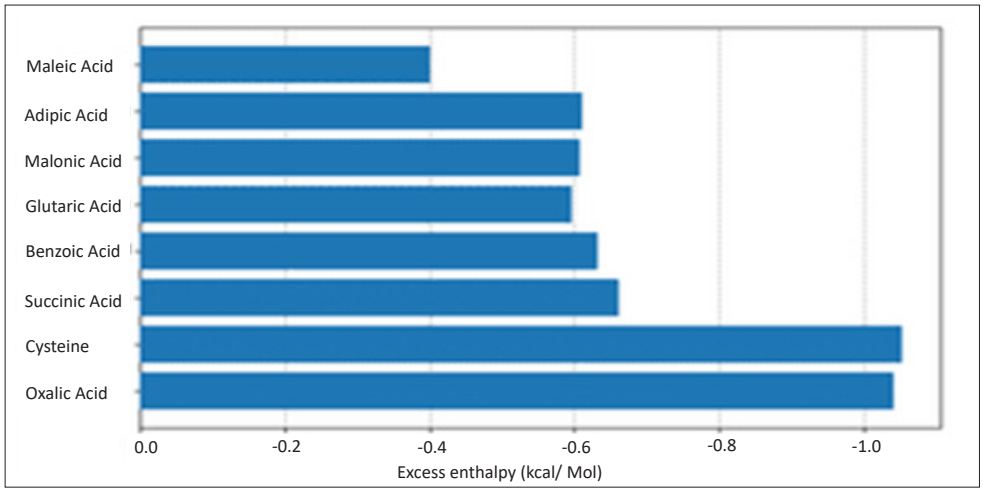

Figure 1.COSMO-RS Software

Preparation Methods of Cocrystals

Cocrystals are prepared by two major processes: Solution crystallisation and Solid-state crystallisation.[18,19]

Solution-Based Methods

- Solvent evaporation
- Cooling crystallisation
- Reaction crystallisation
- Spray drying
- Freeze drying
- Supercritical fluid technology

Solvent-Free Methods

- Hot melt extrusion
- Wet grinding or liquid-assisted grinding
- Dry grinding

Solvent Evaporation

Preparing cocrystals may be done easily and reliably using solvent evaporation.

Superior quality: The process of solvent evaporation can yield pure and superior cocrystals.

Single crystals: Single crystal cocrystals that are useful for structural study are frequently made using this method.

Co-crystal screening: This is a frequently used technique. Using this method, supersaturation is produced by removing the solvent from a solution containing both coformers and evaporating it. A cocrystal nucleates and grows as a result of this. The cocrystals should be gathered before the solution entirely evaporates to guarantee pristine crystals.

Solvent evaporation is a popular method for synthesising cocrystals, where the API and coformer are dissolved in a suitable solvent in a proportional stoichiometry, and allowed to evaporate slowly. This method is primarily used for creating high-quality single crystal structures, suitable for X-ray crystallography. The resulting cocrystals can be characterised using various analytical techniques, but may not be suitable for all systems. Other methods such as slurry conversion or antisolvent addition may be more appropriate in certain cases.[20]

Materials and Method

Identification of Drug

Drug identification is a crucial step in a pre-formulation inquiry. The substance is identified using the melting point, DSC, FTIR and UV spectrophotometry.[21]

Determination of Melting Point

A previously sealed glass capillary method was used to carry it out. The temperature was measured when the lopinavir powder melted in a capillary that was put on a thermometer dipped in liquid paraffin and heated with a blue flame burner.[22]

Differential Scanning Colorimetry (DSC)

It gauges the variation in heat flow based on the relationship between a sample's temperature and a reference material. It is feasible to determine any thermal modifications unique to the cocrystal by contrasting the DSC curves of pure drug, coformer, and cocrystals. This knowledge helps in enhancing the cocrystal's manufacturing and processing for its stability and appropriateness as a medicinal constituent.[20]

Fourier Transform Infra-Red (FTIR) Spectrophotometry

In order to create a spectrum that contains information about functional groups, FTIR spectrophotometry examines the infrared light absorption/ transmission by a sample. To confirm identification and purity, the pure itraconazole's spectrum was collected in the 450–4000 cm^{-1} region and compared to accepted reference spectra.[20]

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202447

Powder X-Ray Diffraction

Powder X-Ray Diffraction (PXRD) is used to determine a sample's crystal structure and unit cell size. To ensure purity, a 200 mg sample was compared to the original medication. PXRD is a crucial technology for analysing pharmaceuticals.[23]

Determination of Maximal Absorption Values (Λ MAX) in 6.8 pH Phosphate Buffer by UV Spectrophotometry

Preparation of Stock Solution

100 mg of itraconazole was taken in a 100 mL volumetric flask. 30 mL of methanol and 70 mL of pH 6.8 buffer solution were added up to the mark to give a final strength of 1000 µg/mL. From this stock solution, a series of 50 to 900 µg/mL concentrations were prepared with the same solvent mixture and scanned from 200–400 nm in a UV spectrophotometer by UV probe.[23]

Method of Cocrystal Preparation

Cocrystal preparation was carried out by the slow solvent evaporation method. The drug and co-former were solubilised in a suitable solvent or solvent mixture and then stirred at 600 rpm on a magnetic stirrer for 45 min. The solvent evaporated slowly and a dry product was obtained that was used for further characterisation of cocrystals.[23]

Preliminary Trials

Cocrystals were firstly produced by solvent evaporation method for A1 to A7 described in Table 2, in which drug and co-former solubilize in suitable solvent and follow the procedure mentioned in above point.[24]

Evaluation Parameters

Microscopical Determination

To conduct a preliminary examination, a microscope was utilised to conduct a microscopical examination of the pure drug and the generated cocrystal. Pure drug and cocrystal were observed at both 10x and 45x, and morphological alterations were compared to pure drug microscopical characteristics.[24]

Calibration Curve of Drug in Methanol

10 mg of itraconazole was weighed accurately and added into a 100 mL volumetric flask. The volume was made up to 100 mL with methanol. The concentration of the obtained stock solution was 100 µg/mL. Aliquots of 0.2, 0.6, 1.0, 1.4, 1.8, 2.2, and 2.6 mL of stock solution were pipetted out into 10 mL volumetric flasks and the volume was made up to 10 mL with methanol to obtain concentrations of 2, 6, 10, 14, 18, 22 and 26 µg/mL respectively. The absorbance was measured against a blank at 262 nm using a UV-visible spectrophotometer Figure 3. Determination of λ_{max} was done by scanning the above sample from 200 to 400 nm in a UV spectrophotometer.[24] Table 3 describes the different absorbance.

Table.1 List of Instruments

S. No.	Name of Instrument	Manufacturer/ Source
1	UV spectrophotometer (UV-1900)	Shimadzu, Japan
2	Analytical weighing balance	Shimadzu, Japan
3	Dissolution test apparatus USP	Electrolab, Mumbai
4	FTIR	Shimadzu, Japan
5	DSC	Shimadzu, Japan

UV – Ultraviolet
FTIR – Fourier Transform Infrared Spectroscopy
DSC – Differential Scanning Calorimetry

Table 2.Batches of Formulation

Batches	Drug (mg)	Co-Former (mg)	Ratio	Solvent (mL)	Crystal Obtained
A1	141.2	Benzoic acid (24.4)	1:1	Methanol (5)	Not obtained
A2	141.2	Oxalic acid (19)	1:1	Methanol (5)	Obtained
A3	141.2	Oxalic acid (38)	1:2	Methanol (5)	Obtained
A4	141.2	Cysteine (25)	1:1	Methanol (5)	Obtained
A5	141.2	Glutaric acid (26)	1:1	Methanol (5)	Not obtained
A6	141.2	Glycine (15)	1:1	Methanol (5)	Obtained
A7	141.2	Alanine (18)	1:1	Methanol (5)	Obtained
A8	141.2	Alanine (35)	1:2	Methanol (5)	Obtained

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DOI: https://doi.org/10.24321/2278.2044.202447

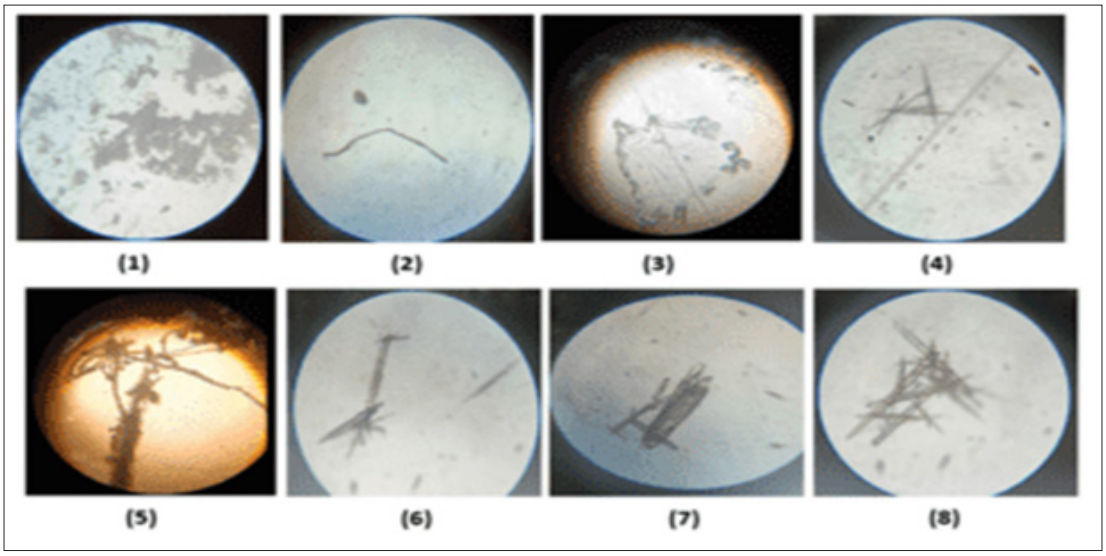

Figure 2.Microscopical Evaluation of Prepared Batches
((1): A1, (2): A2, (3): A3, (4): A4, (5): A5, (6): A6, (7): A7, (8): A8)

Table 3.Absorption Data of Itraconazole in Methanol at 262 nm

Concentration (ppm)	Absorbance 1	Absorbance 2	Absorbance 3	Mean ± SD
0	0.000	0.000	0.000	0.000 ± 0.000
2	0.087	0.091	0.108	0.095 ± 0.011
6	0.275	0.267	0.282	0.275 ± 0.008
10	0.483	0.499	0.493	0.492 ± 0.008
14	0.636	0.627	0.644	0.636 ± 0.009
18	0.827	0.821	0.813	0.82 ± 0.007
22	1.020	0.997	1.008	1.008 ± 0.012
26	1.212	1.214	1.196	1.207 ± 0.010

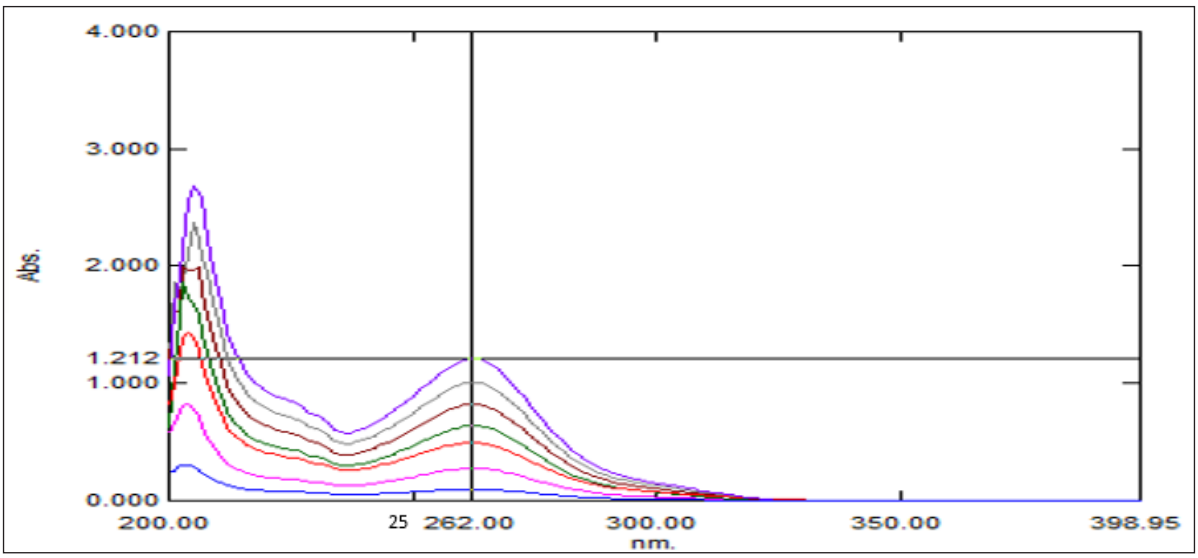

Figure 3.Calibration Spectrum of Itraconazole in Methanol (262 nm)

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202447

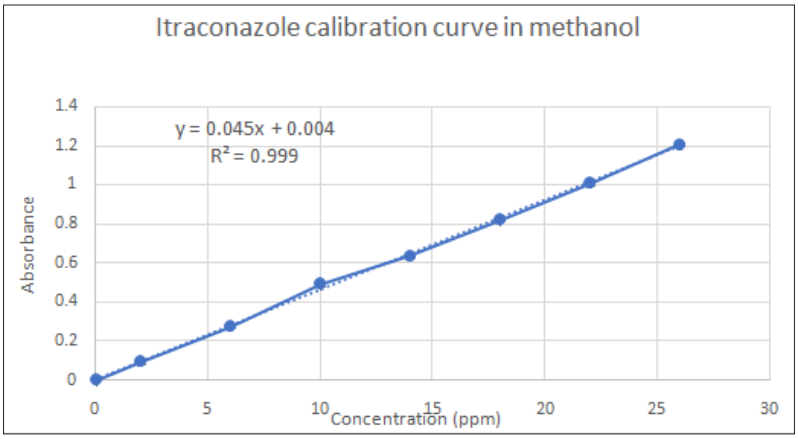

Figure 4.Itraconazole Calibration Curve methanol in Phosphate buffer pH 6.8 containing 0.1% SLS

Calibration Curve of Drug in Phosphate Buffer

As shown in Figure 4, 10 mg of itraconazole was weighed accurately and added into a 100 mL volumetric flask. The volume was increased to 100 mL with methanol. The concentration of the obtained stock solution was 100 µg/mL. Aliquots of 0.2, 0.6, 1.0, 1.4, 1.8, 2.2 and 2.6 mL of stock solution were pipetted out into 10 mL volumetric flasks and the volume was increased to 10 mL with phosphate buffer (pH 6.8) containing 0.1% sodium lauryl sulphate to obtain concentrations of 2, 6, 10, 14, 18, 22 and 26 µg/mL respectively. The absorbance was measured against a blank at 262 nm (Table 4) using a UV-visible spectrophotometer.[24]

Figure 5 describes the calibration curve of itraconazole in pH 6.8 phosphate buffer containing 0.1% sodium lauryl sulphate.

Fourier Transform Infra-Red Spectrophotometry

An IR spectrum was taken for the drug. It was recorded with a Thermo-scientific FT-IR spectrophotometer in the range 450–4000 cm^{-1} using a resolution of 4 cm^{-1} and the sample was diluted by mixing with KBr powder and pressed to obtain self-supporting disks. Figures 6 and 7 show the FTIR spectra of itraconazole and reference drug. The FTIR spectrum of the sample drug was compared with the reference FTIR spectrum of the pure drug and mentioned in Table 5.

Table 4.Absorption Data of Itraconazole at 262 nm

Conc (ppm)	Absorbance 1	Absorbance 2	Absorbance 3	Mean ± SD (n = 3)
0	0	0	0	0.000 ± 0.000
2	0.101	0.084	0.114	0.100 ± 0.015
6	0.221	0.206	0.232	0.220 ± 0.013
10	0.380	0.366	0.390	0.379 ± 0.012
14	0.537	0.525	0.547	0.536 ± 0.011
18	0.685	0.671	0.693	0.683 ± 0.011
22	0.845	0.837	0.856	0.846 ± 0.010
26	1.011	0.998	1.019	1.009 ± 0.011

Table 5.FTIR Data of Pure Drug

Functional Group	Basic IR Bands (cm^{-1})	Itraconazole IR Bands (cm^{-1})
C=O stretch	1698.30	1697.8
(Aromatic) R-C-H bonding	671.82	672.8
(Aromatic) R-C-C bonding	1551.91	1564.1
(Ether linkage) R-O-R	1381.38	1377.3
(Aromatic) R-C=C bonding	1510.36	1511.4
(Alkyl) R-C-H stretch	2964,2823	2965.1,2823.5
Mono substituted benzene	824.37	821.9

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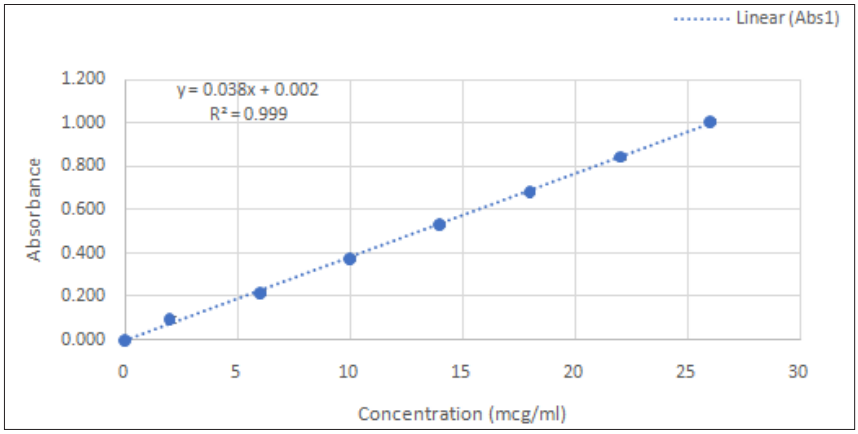

Figure 5.Itraconazole Calibration Curve in pH 6.8 Phosphate Buffer

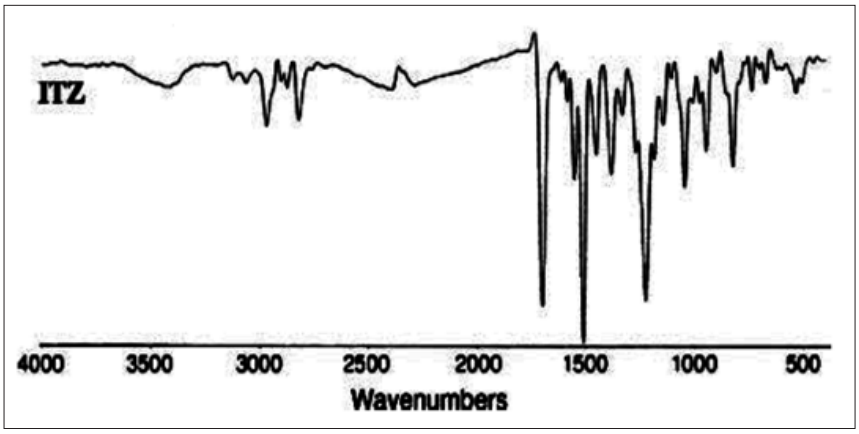

Figure 6.Itraconazole FTIR Reference Spectra[26]

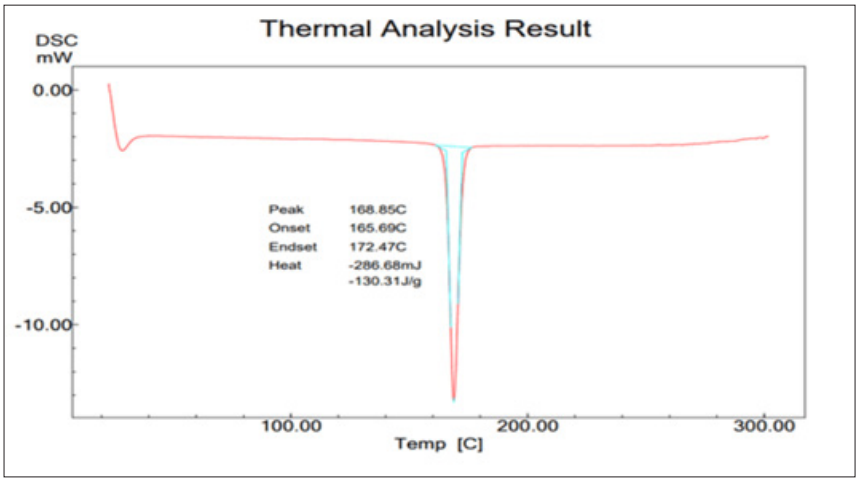

Figure 7.Itraconazole FTIR Spectra

Differential Scanning Calorimetry Study

Thermal analysis was done for pure drug. Approximately 5–10 mg of sample drug was hermetically sealed in an aluminium pan and exposed to purging nitrogen gas at 20 mL/min flow rate, at a scanning rate of 2 °C min^{-1} from 0 to 300 °C. Fig 8 and 9 describes the DSC study of our drug and reference drug.[25]

Powder X-Ray Diffraction

PXRD is used to provide the unit cell dimension information by phase identification. A total of 200 mg of the sample was used for the PXRD analysis that was compared with the pure drug.[25]

Figure 10 indicates the PXRD of pure drug, as well Figure 11 indicates the PXRD of pure drug reference.

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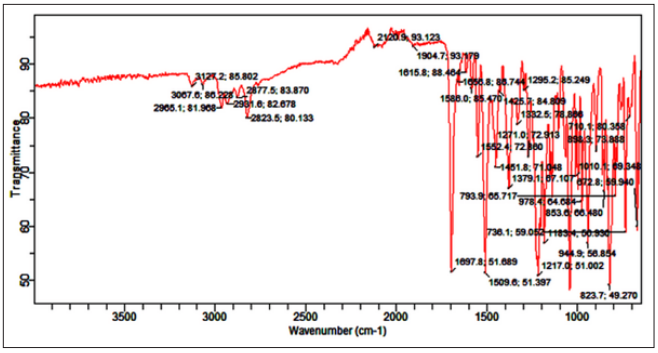
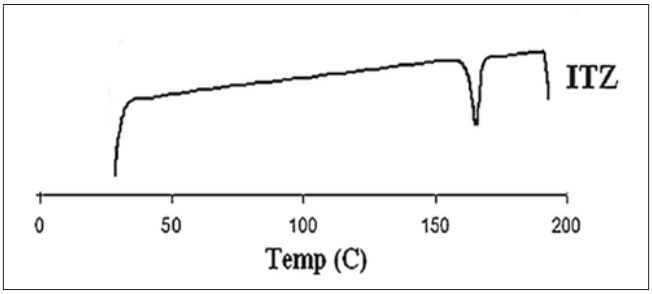


Figure 8.DSC Study Graph



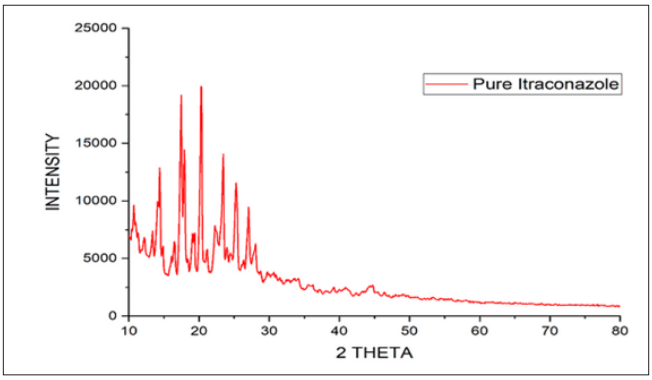


Figure 9.Reference DSC Study Graph[26]

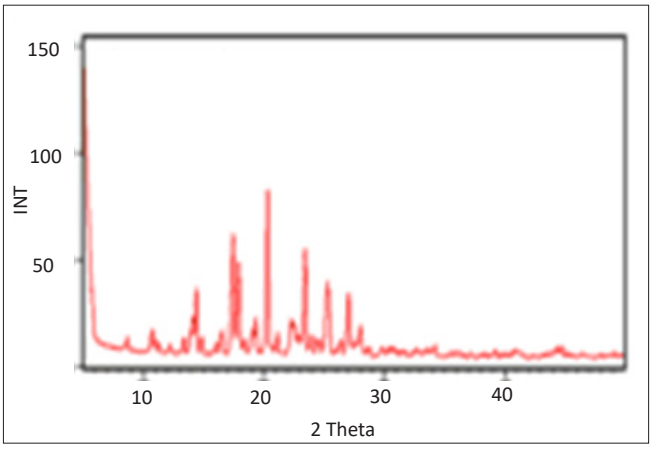


Figure 10.PXRD of Pure Drug

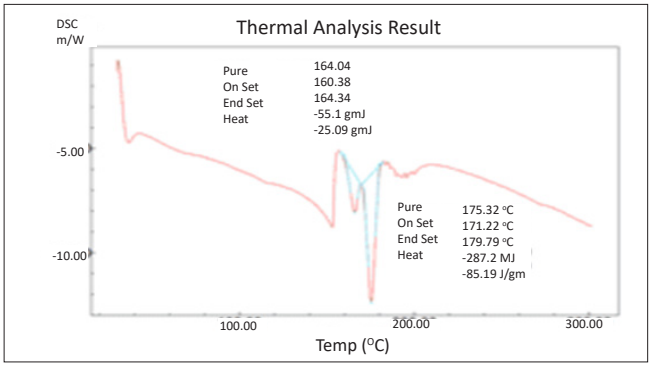


Figure 11.PXRD of Pure Drug Reference

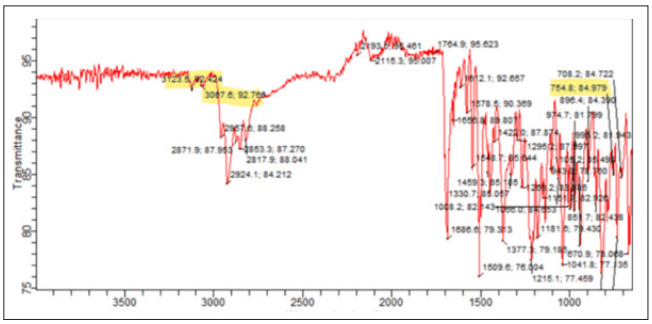


Figure 12.FTIR Spectra of A3

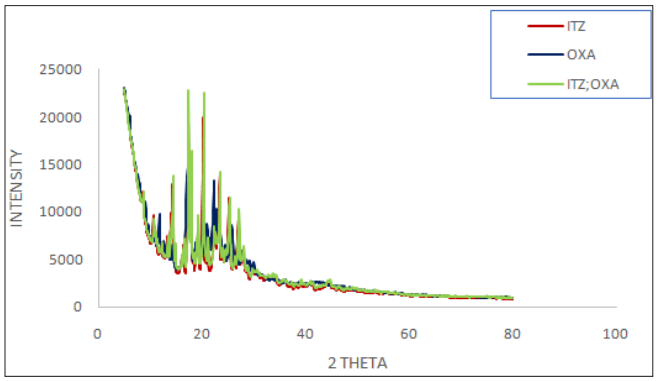


Figure 13.PXRD Spectra of A3

Result

Differential Scanning Calorimetry

The thermogram of itraconazole, oxalic acid, and itraconazole and oxalic acid in a ratio of 1:1 showed endothermic peaks at 168 °C, 190 °C, and 175 °C (Figure 11). The prepared batch showed that there was a shifting of peaks or reduction in energy which resulted in cocrystallisation.

Finally, based on FTIR, interaction between the drug and co-former was observed and according to the DSC analysis, only one co-former is yielding in A3, indicating that co-crystallization has happened in this co-former.

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Fourier Transform Infra-Red Spectrophotometry

Itraconazole showed characteristic peaks at 2965.1 cm^{-1}, 2823 cm^{-1}, and 672.8 cm^{-1} corresponding to the stretching vibration of -OH and -CH_2. Oxalic acid showed characteristic peaks at 3039 cm^{-1}, 3075 cm^{-1}, and 764 cm^{-1} corresponding to stretching vibration of -OH and -CH_2.

The FTIR spectra (Figure 12) of the prepared batch showed a change with itraconazole that suggests an interaction between itraconazole and oxalic acid, and breaking of hydrogen bonding between the drug and coformer.

The PXRD spectra (Figure 13) of batch A3 showed suppression of peaks of pure itraconazole but there was a generation of five new peaks at 14.98 °C, 16.38 °C, 20.5 °C, 23.9 °C, and 28 °C. It may chance of generation of cocrystals in different ratios of coformer.

The PXRD spectra (Figure 13) of batch A3 showed a significant change in spectra. There were five new peaks generated at 14.90 °C, 16.38 °C, 20.5 °C, 23.9 °C and 28 °C in the itraconazole–oxalic acid 1:2 ratio spectrum that suggests that co-crystallisation had occurred.

Saturation Solubility Study

An excess of cocrystal or itraconazole was added to 10 ml of 6.8 pH phosphate buffer. The samples were shaken for 48 hours at 37 °C and 150 rpm in a rotary shaker. After 48 hours, the solution was filtered through Whatman filter paper, diluted with 6.8 pH phosphate buffer, and spectrophotometrically measured at 262 nm against 6.8 pH phosphate buffer as a blank. Table 6 identifies the outcomes of pure itraconazole, A2, and A3 for saturation solubility study.

Table 6.Saturation Solubility Study

Batch	Ratio	Absorbance	Concentration (µg/mL)	Fold
Pure itraco-nazole	-	0.495	12.87	0.00
A2 (ITZ: OXA)	1:1	0.654	17.02	1.32
A3 (ITZ: OXA)	1:2	1.968	51.33	3.98

In Vitro Dissolution Study

In *vitro* dissolution of pure drug or cocrystal (50 mg of ITZ) was performed by USP apparatus II (Paddle type) at a rotating speed of 50 rpm and a controlled temperature of 37 ± 0.5 °C in 6.8 pH phosphate buffer as a dissolution media (900 mL). Table 7 presents the dissolution data of itraconazole and cocrystal.

Table 7.Dissolution Data of Itraconazole and Cocrystal

Time (min)	Drug Release (ITZ) (%)	Physical Mixture (1:1)	ITZ:OXA Cocrystal
10	3.48 ± 0.44	3.52	15.31 ± 0.62
20	4.46 ± 0.34	5.38	48.53 ± 0.33
30	5.92 ± 0.74	6.79	81.55 ± 1.59
45	7.52 ± 0.25	8.52	98.08 ± 0.89
60	9.09 ± 0.62	9.32	102.00 ± 0.31
90	11.52 ± 0.98	14.88	-
120	15.18 ± 0.71	21.22	-

Discussion

Itraconazole and coformer are solubilised into the appropriate solvent or solvent mixture and stirred on a magnetic stirrer for 45 min at 600 rpm. The solvent was allowed to slowly evaporate till a completely dry product was obtained. This product was subjected to characterisation for cocrystals. The organic acid coformers like benzoic acid, oxalic acid, caffeine, glutaric acid, gallic acid, and nicotinamide was used to formulating cocrystals. In organic acid coformers, the FTIR, DSC and PXRD data suggested cocrystallisation.

Next, oxalic acid was employed and the findings of the saturation solubility research, in vitro dissolution study, FTIR, DSC, and PXRD were all encouraging. Cocrystals of itraconazole and oxalic acid were produced in two different stoichiometric ratios (1:1) and (1:2), with encouraging outcomes.

Conclusion

In the present research work, the cocrystal of itraconazole was successfully prepared in various stoichiometric ratios with oxalic acid by slow solvent evaporation method. Prepared cocrystals had improved dissolution characteristics compared to pure itraconazole and physical mixtures. It was also discovered that the saturation solubility of prepared cocrystal was higher as compared to pure itraconazole. Thus, it can be concluded that co-crystallisation is a promising approach to improve drug dissolution characteristics without altering structural integrity and pharmacological activity.

Source of Funding: None

Conflict of Interest: None

ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202447

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ISSN: 2278-2044
DOI: https://doi.org/10.24321/2278.2044.202447