

Formulation and Evaluation of Luliconazole–Fumaric Acid Cocrystals for Solubility Enhancement**Rithik Yadav¹, Sunil Sain², Megha Singh³**¹Research Scholar, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan, India²Associate Professor, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan, India³HOD, UVR Group of Labs, Greater Noida (U.P.), India

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Abstract

Luliconazole is an imidazole antifungal drug with poor aqueous solubility, which may limit its dissolution and formulation performance. The present study aimed to develop luliconazole cocrystals using fumaric acid as a coformer to improve solubility and dissolution. Fumaric acid was selected based on in-silico binding energy studies, showing the lowest binding energy of -11.341 kcal/mol. Luliconazole–fumaric acid (LUZ-FUM) cocrystals were prepared in a 1:1 molar ratio by solvent evaporation using ethanol and evaluated for drug content, FTIR, PXRD, DSC, solubility, antifungal activity, and in-vitro dissolution. The prepared cocrystals showed a drug content of $94.39 \pm 1.21\%$ and improved solubility compared with pure luliconazole and the physical mixture, with the highest solubility of 157.65 ± 0.04 $\mu\text{g/mL}$ at pH 1.2. FTIR, PXRD, and DSC results supported the formation of a new crystalline phase. In-vitro dissolution showed approximately 80% of the drug release from the cocrystals after 60 min, compared with 24% from the physical mixture and 12% from pure luliconazole. The cocrystals also showed improved antifungal activity against *Candida albicans*. Overall, cocrystallization with fumaric acid demonstrated potential for enhancing the solubility and dissolution performance of luliconazole.

Keywords: Luliconazole, Pharmaceutical cocrystals, Fumaric acid, Solubility enhancement, Dissolution enhancement, Solvent evaporation.

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Introduction

The pharmaceutical industry focuses on developing effective medicinal products with adequate bioavailability and desirable physicochemical properties. Among these properties, aqueous solubility and dissolution are important factors influencing the pharmaceutical performance of poorly water-soluble drugs. A significant number of active pharmaceutical ingredients (APIs) exhibit poor aqueous solubility, with many belonging to Biopharmaceutics Classification System (BCS) Class II.

Various approaches have been investigated to improve the solubility and dissolution of poorly soluble drugs, including particle size reduction, solid dispersions, surfactants, lipid-based formulations, and solid-state modification through crystal engineering. Crystal engineering can generate different solid forms such as polymorphs, hydrates, solvates, salts, co-amorphous systems, and pharmaceutical cocrystals.

Pharmaceutical cocrystals are crystalline materials consisting of an active pharmaceutical ingredient and a suitable coformer within the same crystal lattice in a defined stoichiometric ratio. Their formation is generally governed by non-covalent interactions, particularly hydrogen bonding, without covalent modification of the drug molecule. Selection of a suitable coformer is important because intermolecular interactions can influence crystal packing and properties such as solubility, dissolution, morphology, thermal behavior, and stability.

Luliconazole is a relatively new imidazole-class antifungal drug. Its antifungal activity is associated with inhibition of lanosterol 14 α -demethylase involved in ergosterol biosynthesis, thereby disrupting fungal cell membrane formation and inhibiting fungal growth. Previous investigations have indicated that cocrystal engineering can

improve the solubility, dissolution, and physicochemical properties of luliconazole.

In the present study, luliconazole–fumaric acid (LUZ-FUM) cocrystals were developed and evaluated. Fumaric acid was selected from candidate coformers based on in-silico binding-energy evaluation, showing the lowest binding energy of -11.341 kcal/mol. LUZ-FUM cocrystals were prepared in a 1:1 molar ratio by solvent evaporation using ethanol and characterized using optical microscopy, FTIR, PXRD, DSC, and SEM. The cocrystals were further evaluated for drug content, aqueous solubility, in-vitro dissolution, and antifungal activity against *Candida albicans*.

Aim

This study aimed to develop luliconazole Fumaric acid cocrystal to enhance the drug's solubility and dissolution behavior, thereby improving its overall bioavailability.

Objective

- The main objective of this study is to prepare luliconazole cocrystals using the solvent evaporation method.
- To improve the aqueous solubility of luliconazole through cocrystal formation with suitable coformers.
- To enhance the dissolution rate of luliconazole, thereby improving its overall formulation performance.

Materials and Methods

Materials: Luliconazole, fumaric acid, ethanol, isopropyl alcohol, ethyl acetate were used for formulation development.

Methods: Preformulation Studies: Luliconazole was evaluated for UV absorption, FTIR, solubility and partition coefficient. The λ_{max} of the drug was determined by UV spectroscopy and found to be 295nm.

Preparation of Cocrystals: Luliconazole Cocrystals were prepared by the solvent evaporation method using fumaric acid as the coformer. The drug and

coformer were weighed according to their molecular weights and mixed in molar ratios of 1:1, 2:1, 1:2, and 1:3. Both components were dissolved in 20 mL ethanol and stirred to obtain a homogeneous solution. The solution was kept undisturbed for 2–3 days to allow slow solvent evaporation and cocrystal formation. The resulting cocrystals were collected by filtration using Whatman filter paper and air-dried.

Characterization of the cocrystals: The prepared cocrystals were characterized by Differential Scanning Calorimetry (DSC), solubility studies, FTIR, in-vitro dissolution, drug content determination, and in-silico studies to evaluate the interaction and compatibility between luliconazole and fumaric acid

Results and Discussion

Pre Formulation Studies:

Physical Properties of Luliconazole:

Luliconazole was observed as a white to slightly off-white, fine crystalline powder and was odourless. The observed physical characteristics were consistent with reported literature, confirming its suitability for further experimental studies [32].

Melting Point Determination: The melting point of luliconazole was determined by the capillary tube method and was found to be $150\text{--}152^\circ\text{C}$, which was consistent with the reported value of 152°C . The result confirmed the purity and identity of the drug sample [33].

Standard Calibration Curve: A standard calibration curve of luliconazole was prepared in 0.1 N HCl, and absorbance was measured at 295 nm using a UV-visible spectrophotometer. The calibration curve showed good linearity over the selected concentration range, with a regression equation of $y = 0.0666x + 0.0406$ and a correlation coefficient ($R^2 = 0.9901$). The results confirmed the suitability of the UV spectrophotometric method for quantitative estimation of luliconazole.

Table 1: Values depicting the calibration curve of luliconazole.

Concentration of luliconazole ($\mu\text{g/ml}$)	Absorbance
2	0.205 ± 0.07
4	0.324 ± 0.03
6	0.432 ± 0.06
8	0.609 ± 0.03
10	0.681 ± 0.05
12	0.831 ± 0.06

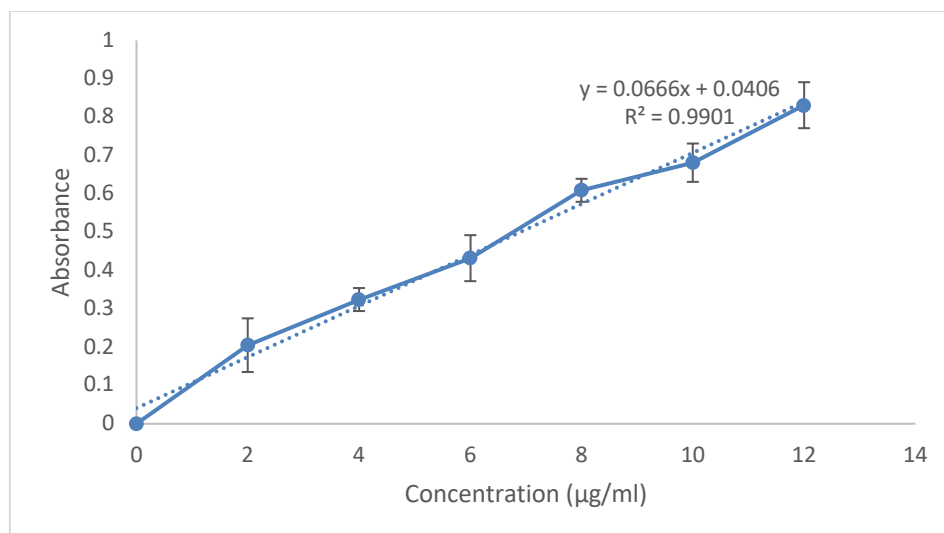


Figure 1: Standard calibration curve of luliconazole in 0.1 N HCl

Solubility Studies: The solubility of luliconazole was evaluated in ethanol, isopropyl alcohol, ethyl acetate, and distilled water to identify a suitable solvent for cocrystal preparation. Among the tested solvents, ethanol showed the highest solubilizing capacity. Luliconazole was freely soluble in

ethanol, sparingly soluble in isopropyl alcohol, and slightly soluble in ethyl acetate and distilled water.

Based on these findings, ethanol was selected as the preferred solvent for the preparation of luliconazole–fumaric acid cocrystals.[34]

Table 2: Luliconazole solubility in different solvents

S. No	Solvent	Solubility (µg/ml)
1.	Ethanol	15.96±0.03
2.	Isopropyl Alcohol	13.59±0.07
3.	Ethyl acetate	10.30±0.08
4.	Distilled water	0.09±0.03

Selection of the Coformer: A suitable coformer was selected using in-silico molecular docking to evaluate its interaction potential with luliconazole. Four coformers—fumaric acid, benzoic acid, malonic acid, and oxalic acid—were evaluated based on their binding energies, which were –11.341, –5.215, –9.012, and –6.639 kcal/mol, respectively. Fumaric acid showed the lowest

binding energy (–11.341 kcal/mol), indicating the strongest and more stable interaction with luliconazole.

Therefore, fumaric acid was selected as the most suitable coformer for the preparation of luliconazole cocrystals [35].

Table 3: Binding interaction data between the coformer and the drug

Coformer	Binding energy (Kcal/mol)
Fumaric acid	-11.341
Malonic acid	-9.012
Oxalic acid	-6.639
Benzoic acid	-5.215

Preparation of Luliconazole–Fumaric Acid Cocrystals: Luliconazole–fumaric acid cocrystals were prepared by the solvent evaporation method using drug: coformer molar ratios of 1:1, 2:1, 1:2, and 1:3. Luliconazole and fumaric acid were dissolved in 20 mL ethanol with stirring to obtain a homogeneous solution, followed by slow solvent evaporation and drying. The 1:1 formulation (F1) showed the highest solubility (29.57 ± 0.02 µg/mL)

compared with the other formulations and was therefore selected as the optimized batch. For the optimized formulation, 354 mg of luliconazole and 116 mg of fumaric acid were used in a 1:1 molar ratio than dissolved in 20 mL ethanol along with 5 mL isopropyl alcohol and 5 mL ethyl acetate. After slow evaporation, the resulting crystalline material was collected, dried, and designated as LUZ-FUM cocrystals.

Table 4: Quantitative composition of Luliconazole-fumaric acid cocrystals batches.

Formulation	(Drug: Coformer) (Molar Ratio)	Luliconazole (mg)	Fumaric Acid (mg)	Ethanol	Solubility ($\mu\text{g/mL}$; at 37 $^{\circ}\text{C}$) 7.4 pH buffer
F1	1.1	354	116	20ml	29.57 $\pm$ 0.02
F2	2.1	708	116	20ml	22.42 $\pm$ 0.12
F3	1.2	354	232	20ml	26.82 $\pm$ 0.01
F4	1.3	354	348	20ml	27.45 $\pm$ 0.07

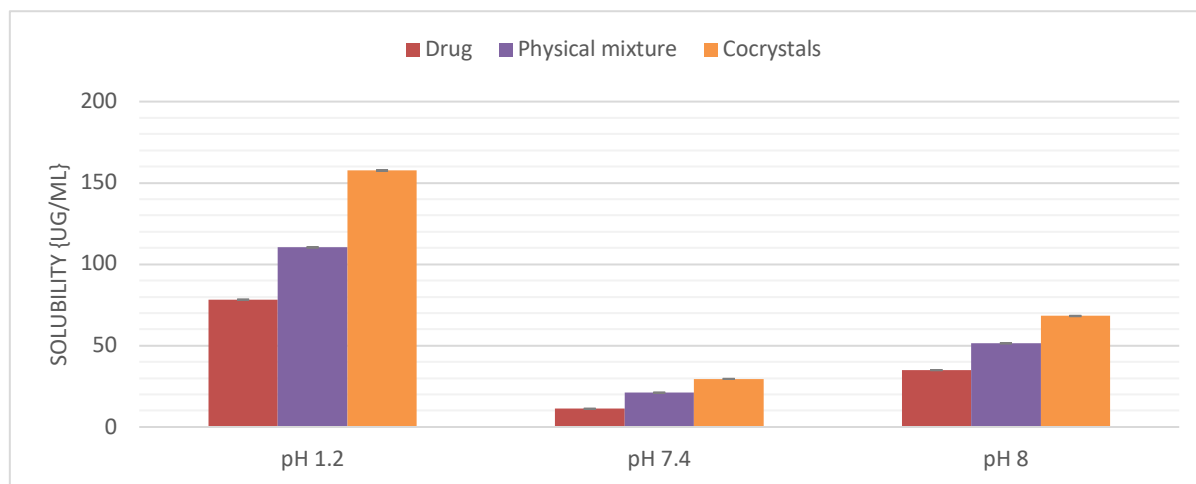
Characterization of cocrystals: Solubility Determination: The solubility of pure luliconazole, physical mixture (PM) of luliconazole and fumaric acid, and luliconazole–fumaric acid cocrystals (LUZ-FUM) were evaluated in pH 1.2, 7.4, and 8 buffer media [11]. LUZ-FUM cocrystals showed higher solubility than both pure luliconazole and PM in all tested media.

At pH 1.2, the solubility of pure luliconazole, PM, and LUZ-FUM was 78.25 $\pm$ 0.02, 110.39 $\pm$ 0.11, and 157.65 $\pm$ 0.04 $\mu\text{g/mL}$, respectively. At pH 7.4,

the corresponding values were 11.20 $\pm$ 0.09, 21.08 $\pm$ 0.15, and 29.57 $\pm$ 0.02 $\mu\text{g/mL}$, while at pH 8, they were 34.95 $\pm$ 0.03, 51.45 $\pm$ 0.11, and 68.22 $\pm$ 0.12 $\mu\text{g/mL}$, respectively.[12] The solubility enhancement followed the order LUZ-FUM > PM > pure luliconazole, with the highest solubility observed for LUZ-FUM at pH 1.2 (157.65 $\pm$ 0.04 $\mu\text{g/mL}$). The improved solubility of the cocrystals may be attributed to modification of the crystal lattice and intermolecular interactions between luliconazole and fumaric acid. The results are presented in Table 5 and Figure 2.

Table 5: Solubility study of LUZ, LUZ-FUM physical mixture, and LUZ-FUM cocrystals

S.no.	API/PM/CC	Solubility ($\mu\text{g/ml}$) 1.2 pH buffer	Solubility ($\mu\text{g/ml}$) 7.4 pH buffer	Solubility ($\mu\text{g/ml}$) 8 pH buffer
1.	LUZ	78.25 $\pm$ 0.02	11.20 $\pm$ 0.09	34.95 $\pm$ 0.03
2.	LUZ-FUM (Physical mixture)	110.39 $\pm$ 0.11	21.08 $\pm$ 0.15	51.45 $\pm$ 0.11
3.	LUZ-FUM (cocrystals)	157.65 $\pm$ 0.04	29.57 $\pm$ 0.02	68.22 $\pm$ 0.12

**Figure 2: Bar representation of solubility in 1.2 pH buffer, pH 7.4 buffer, and 8 pH buffer**

Drug Content: The drug content of the prepared luliconazole–fumaric acid cocrystals (LUZ-FUM) and physical mixture was determined by UV spectroscopic analysis. The LUZ-FUM cocrystals showed a drug content of 94.39 $\pm$ 1.21%, whereas the physical mixture exhibited a drug content of 91.53 $\pm$ 1.13%. The higher drug content observed for the cocrystals indicated satisfactory incorporation of luliconazole in the prepared cocrystalline system

Optical Microscopy Analysis: Optical microscopy showed that the prepared LUZ-FUM cocrystals

formed well-defined rectangular, rod-shaped, and plate-shaped crystals, indicating successful formation of a crystalline phase.

The rod-like and small-sized crystals provided greater surface area for interaction with the dissolution medium, which may contribute to improved solubility and dissolution [14][15].

Similar morphological changes have been reported to improve the dissolution behavior of poorly soluble drugs [16].

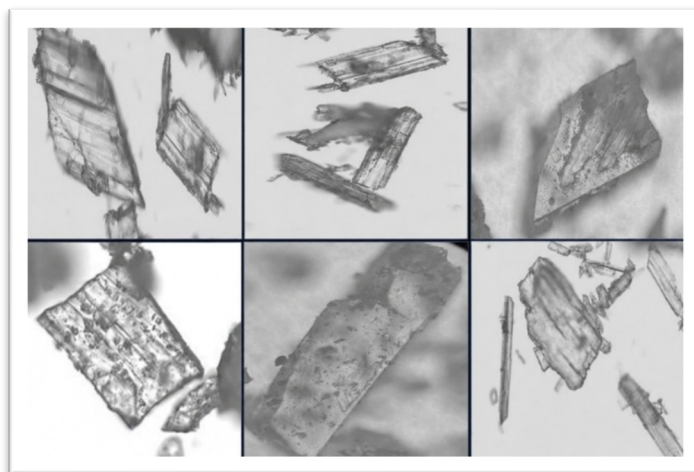


Figure 3: Microscopic images of prepared LUZ-FUM cocrystals

SEM Analysis: Scanning Electron Microscopy (SEM) was used to examine the surface morphology of pure luliconazole, LUZ-FUM physical mixture, and LUZ-FUM cocrystals at different magnifications (250 $\times$ –1000 $\times$). Pure luliconazole showed irregular particles with rough surfaces, dense aggregation, and non-uniform distribution [17]. The physical mixture exhibited

similar morphology, with block-like agglomerates, rough layered surfaces, and occasional cracks [18]. In contrast, LUZ-FUM cocrystals showed more uniform particles and well-defined needle-shaped crystalline structures with smooth surfaces. These morphological changes supported the formation of a distinct crystalline system [19]. The SEM images are presented in Figures 4.

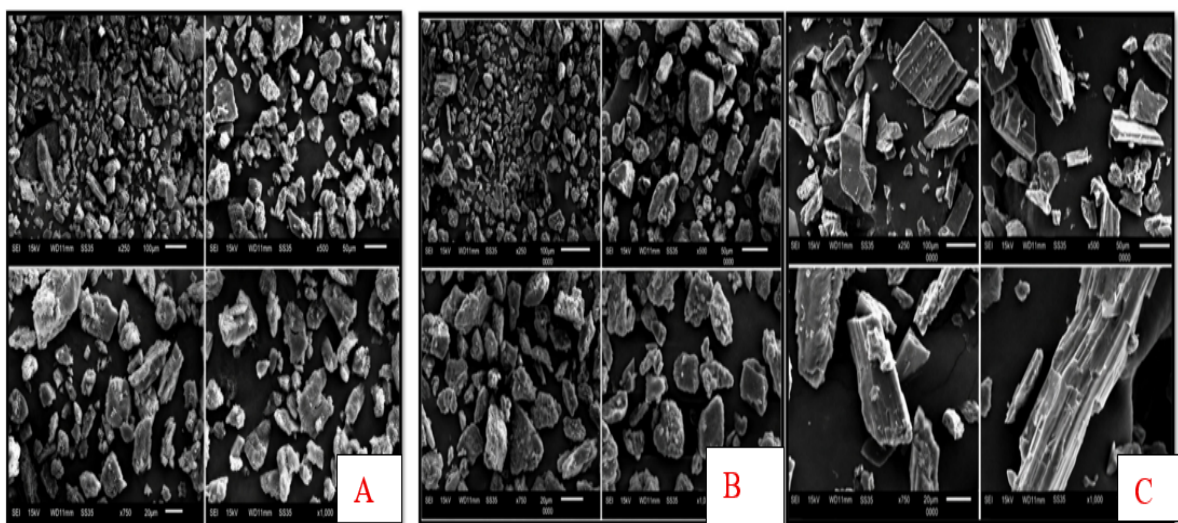


Figure 4: [A] shows SEM photomicrograph of pure Luliconazole, [B] shows SEM photomicrograph of LUZ-FUM, and [C] shows SEM photomicrograph of LUZ-FUM cocrystals at (a) 250 $\times$ magnification (b) 500 $\times$ magnification (c) 750 $\times$ magnification (d) 1000 $\times$ magnification

Differential Scanning Calorimetry (DSC) Analysis: DSC analysis was performed to evaluate the thermal behavior of pure luliconazole, LUZ-FUM physical mixture, and LUZ-FUM cocrystals.

Pure luliconazole exhibited a sharp endothermic peak at 152.197 $^{\circ}$ C, confirming its crystalline nature and consistency with reported findings [20]. The physical mixture showed endothermic peaks at 121.05 $^{\circ}$ C and 219.95 $^{\circ}$ C, possibly associated with

eutectic formation and fumaric acid melting, respectively. A minor exothermic peak at 298.93 $^{\circ}$ C indicated possible thermal decomposition [21]. In contrast, LUZ-FUM cocrystals exhibited a distinct endothermic peak at 281.61 $^{\circ}$ C and an exothermic peak at 317.91 $^{\circ}$ C. The substantial shift in thermal behavior compared with pure luliconazole supported the formation of a new crystalline phase and suggested improved thermal stability [22].

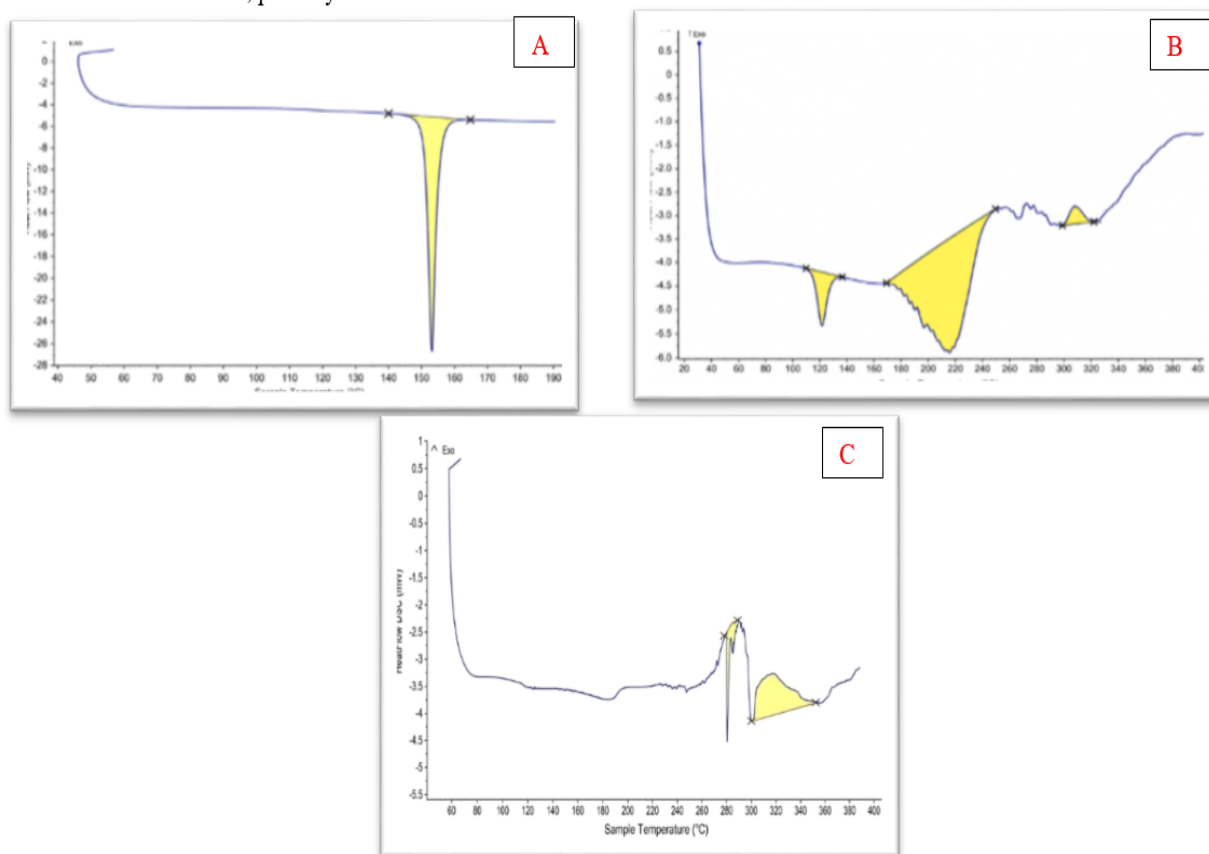


Figure 5: [A] shows DSC thermogram of pure Luciconazole, [B] shows DSC thermogram of LUZ-FUM, and [C] shows DSC thermogram of LUZ-FUM cocrystals

Powder X-ray Diffraction (PXRD) Analysis: PXRD analysis confirmed the crystalline nature of pure luciconazole, with characteristic peaks at $2\theta = 12.25^\circ$, 18.33° , and 24.44° [23].

The physical mixture showed major peaks at 18.31° , 18.44° , and 28.88° , indicating that both components retained their crystalline characteristics

[24]. In comparison, LUZ-FUM cocrystals exhibited peaks at 13.73° , 18.40° , 23.36° , and 25.78° , with a maximum relative intensity of 100% at 18.40° .

The changes in peak positions and intensities supported the formation of a new crystalline phase [25]. PXRD patterns are shown in Figures 6.

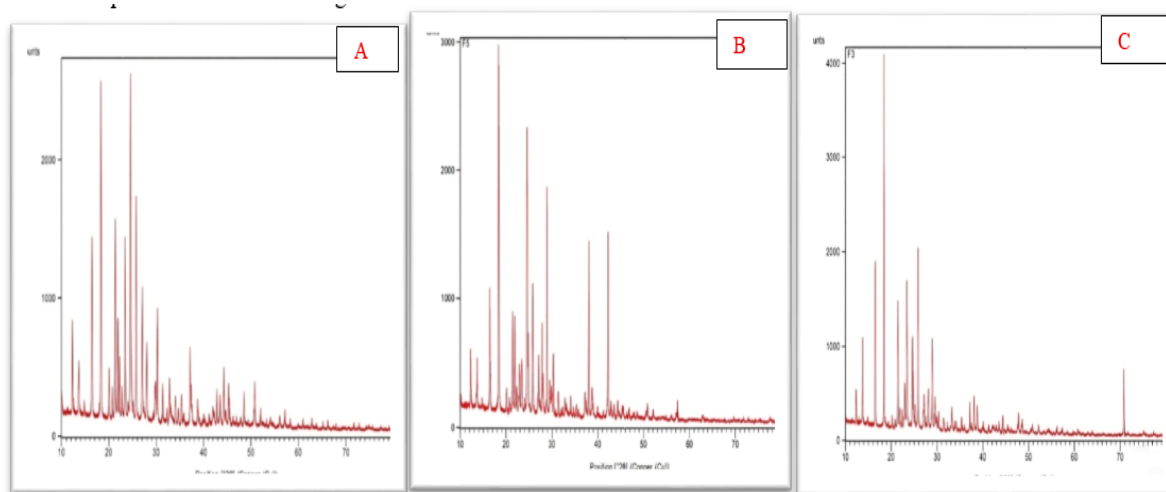


Figure 6: [A] shows PXRD spectra of pure Luciconazole, [B] shows PXRD spectra of LUZ-FUM, and [C] shows PXRD spectra of LUZ-FUM cocrystals at (a) 250x magnification (b) 500x magnification (c) 750x magnification (d) 1000x magnification

Fourier Transform Infrared Spectroscopy (FTIR) Analysis: FTIR analysis was performed to identify characteristic functional groups and intermolecular interactions in pure luliconazole, LUZ-FUM physical mixture, and LUZ-FUM cocrystals. The physical mixture showed characteristic absorption bands of both components, indicating physical blending without significant chemical modification [26]. Compared with pure luliconazole, the cocrystals exhibited

shifts in characteristic absorption bands and the appearance of new bands.

These spectral changes suggested intermolecular hydrogen bonding between luliconazole and fumaric acid, supporting successful cocrystal formation [27]. The FTIR spectra are presented in Figures 7-9, and the corresponding peak assignments are summarized in Tables 6-8.

Table 6: FTIR stretching frequencies of luliconazole

Wavenumber (cm ⁻¹)	Functional group
3787.25	O-H
3029.50	C-H
2375.55	C≡N
1690.50	C=O
1570.25	C=C
1389.10	C-N

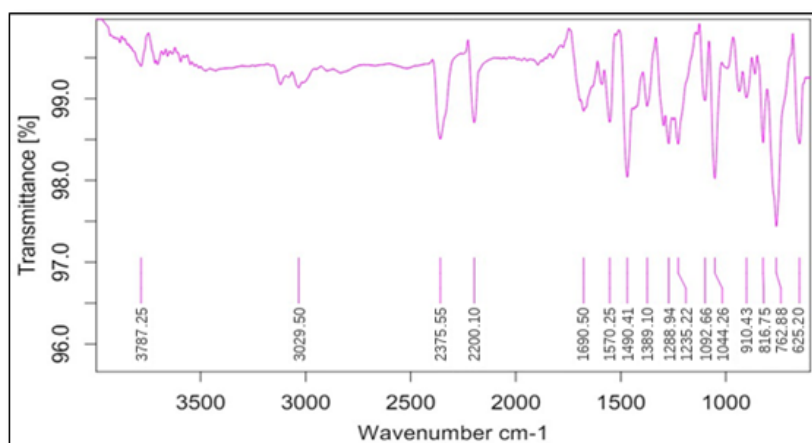


Figure 7: IR spectrum of luliconazole

Table 7: FTIR stretching frequencies of LUZ-FUM physical mixture

Wavenumber (cm ⁻¹)	Functional Group
3030.18	C-H
1659.91	C=O
1567.50	C=C
1265.75	C-N

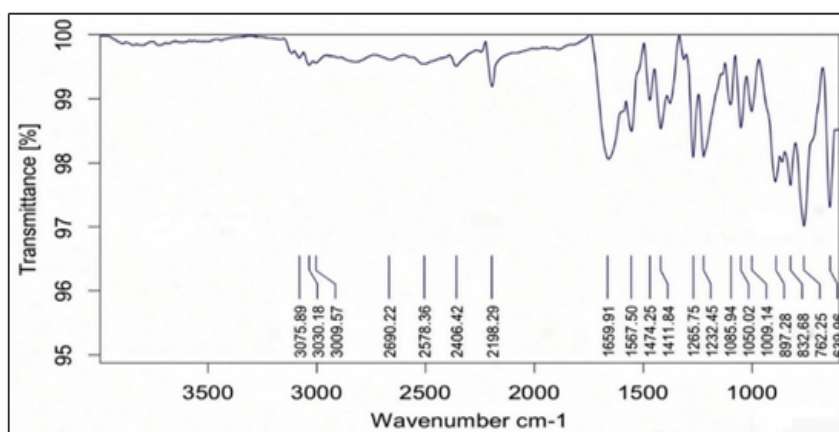
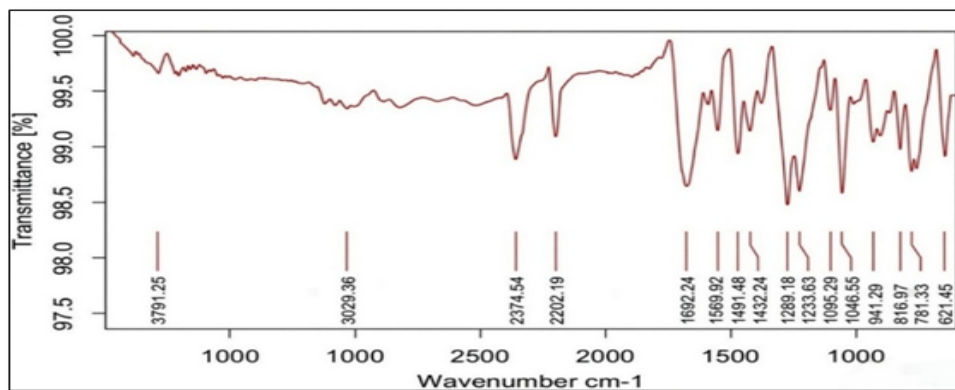


Figure 8: IR spectrum of LUZ-FUM mixture

Table 8: FTIR stretching frequencies of LUZ-FUM Cocrystals

Wavenumber (cm-1)	Functional Group
3791.25	O-H
3029.36	C-H
2374.54	C≡N
1692.24	C=O
1569.92	C=C
1432.24	C-H
1289.17	C-N

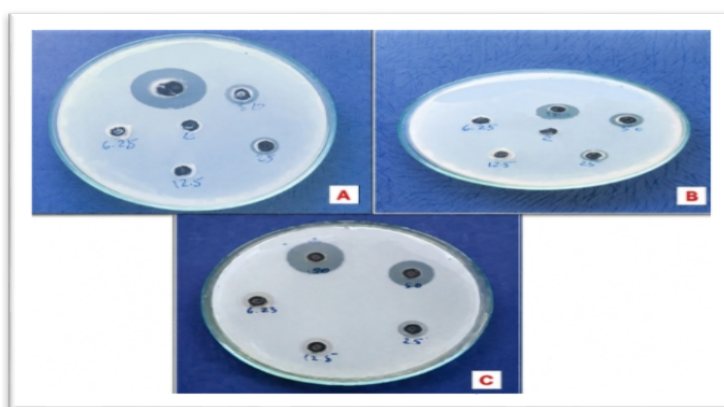
**Figure 9: IR spectrum of LUZ-FUM cocrystals**

In-vitro Antifungal Activity: Antifungal activity against *Candida albicans* (ATCC-24433) showed that LUZ-FUM cocrystals had better activity than pure luliconazole and the physical mixture [28,29].

This improvement may be attributed to enhanced solubility and dissolution, facilitating drug diffusion through the agar medium [30]. Results are presented in Table 9 and Figure 10.

Table 9: In-vitro antifungal activity (MIC) of the test Sample

S. No.	Sample	Antimicrobial Efficacy as Zone of Inhibition (in mm) at different concentrations of Samples against <i>Candida albicans</i>				
		100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml
1	Cocrystals	18 mm	10 mm	11 mm	8 mm	0 mm
2	PM	16 mm	13 mm	9 mm	0 mm	0 mm
3	Pure drug	14 mm	9 mm	8 mm	0 mm	0 mm

**Figure 10: Experimental images of in-vitro antifungal activity against *Candida albicans* (A) LUZ-FUM cocrystal (B) Luliconazole (C) LUZ-FUM physical mixture**

In-vitro Dissolution Study: The in-vitro dissolution behavior of pure luliconazole, LUZ-FUM physical mixture, and LUZ-FUM cocrystals was evaluated over a period of 60 minutes. After 60

minutes, pure luliconazole exhibited approximately 12% drug release, whereas the LUZ-FUM physical mixture and LUZ-FUM cocrystals showed 24% and 80% of the drug release, respectively.

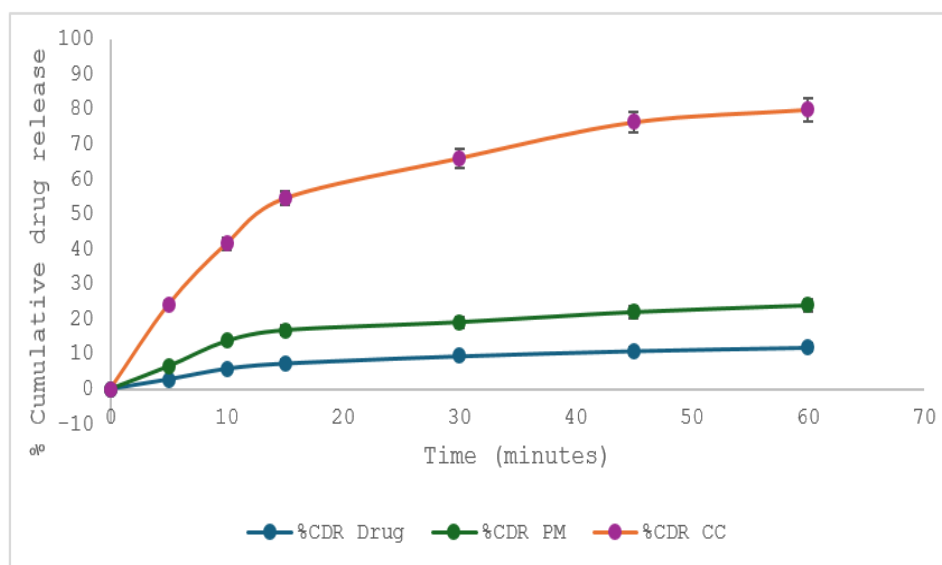


Figure 11: In-vitro dissolution profile of the luliconazole, LUZ-FUM physical mixture, and LUZ-FUM cocrystals

Stability study: The stability of the prepared LUZ-FUM cocrystals was evaluated under $40 \pm 2^\circ\text{C}/75\% \text{RH}$ with open exposure (petri plate) for a period of 2 months and 100 mg of Strength.

Table 10: Stability Results of cocrystals

Condition		40°C ±2°C/ 75% RH			
Test	Specifications	Initial	15 days	1 month	2 months
Dissolution (%)	(900 ml) 0.1 N HCl, USP II 50 RPM)	80.21±0.023	79.82±0.001	79.51±0.012	79.18±0.018
Drug content (%)	0.1 N HCL	94.43±1.23%	93.89±0.017	93.27±0.013	92.78±0.018
Solubility (µg/ml)	pH 1.2, pH 7, pH 8.4	84.17	82.21	79.23	78.39

Conclusion

The present study demonstrated that fumaric acid-based cocrystallization successfully improved the physicochemical properties of luliconazole. FTIR, PXRD, DSC, and SEM confirmed the formation of a new crystalline phase. LUZ-FUM cocrystals showed enhanced solubility, dissolution, and antifungal activity compared with pure luliconazole and the physical mixture, with approximately 80% drug release after 60 min.

The cocrystals also showed good stability under the investigated conditions, indicating that LUZ-FUM cocrystallization is a promising approach for improving the performance of poorly water-soluble luliconazole.

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