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Cocrystal engineering of antifungal drug fluconazole for improved dissolution properties

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Abstract

"The best drug in the world is useless if it cannot reach its target" a maxim that applies squarely to fluconazole, a triazole antifungal whose oral bioavailability is limited by its poor aqueous solubility (approximately 1.0 mg/mL at 25 °C). This research explored pharmaceutical cocrystallisation as a strategy to improve the dissolution rate of fluconazole without altering its molecular structure. Ten GRAS-listed coformers were screened by solvent-drop grinding, and four produced confirmed cocrystals: succinic acid, malic acid, fumaric acid, and nicotinamide. All cocrystals were characterised by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), and ¹H NMR. The fluconazole–fumaric acid (FLZ-FUM) cocrystal showed the greatest dissolution improvement, releasing 81.6 ± 3.9% at 30 min compared with 34.2 ± 4.1% for raw fluconazole and 52.8 ± 4.4% for the marketed capsule in pH 1.2 HCl. Intrinsic dissolution rate measurements confirmed a 2.3-fold enhancement for FLZ-FUM over the pure drug. Stability testing at 40 °C/75% RH for 90 days showed no phase transformation or dissolution decline. These findings identify fumaric acid as an effective coformer for fluconazole and support cocrystal engineering as a viable formulation approach for BCS Class II antifungals.

Keywords: Cocrystal, fluconazole, dissolution, fumaric acid, pharmaceutical cocrystallisation, solvent-drop grinding, antifungal, powder X-ray diffraction, intrinsic dissolution rate, coformer screening

Introduction

Fluconazole is the most widely prescribed systemic antifungal agent, used for infections ranging from mucosal candidiasis to cryptococcal meningitis ^[1]. Its mechanism involves selective inhibition of fungal cytochrome P450 14 α -demethylase (CYP51), blocking ergosterol biosynthesis and compromising membrane integrity ^[2]. Although fluconazole is classified as BCS Class II (low solubility, high permeability), its clinical bioavailability is considered adequate in most patients yet inter-individual variability remains high, particularly in immunocompromised populations where gut transit and absorption are altered ^[3]. Pharmaceutical cocrystals multicomponent crystalline solids in which a drug and a coformer interact through non-covalent bonds (hydrogen bonds, π -stacking, halogen bonds) without proton transfer offer a way to modify solid-state properties while preserving the molecular identity of the active ingredient ^[4]. Unlike salts, cocrystals can be formed with non-ionisable drugs and with neutral coformers, expanding the design space considerably ^[5]. Fluconazole contains two triazole rings and a secondary hydroxyl group, providing three hydrogen-bond acceptor sites and one donor site a favourable motif for cocrystal formation with carboxylic acid and amide coformers ^[6]. A handful of fluconazole cocrystals have been reported, mostly with dicarboxylic acids, but systematic screening with dissolution comparison under identical conditions is lacking ^[7]. This research screened ten GRAS-listed coformers by mechanochemical grinding, identified successful cocrystal formers, characterised the products structurally and thermally, and compared their dissolution performance with the raw drug and a marketed capsule formulation.

In-vitro Protocol

Powder dissolution testing used USP Apparatus II (paddle, 50 rpm, 37 ± 0.5 °C) in 900 mL of 0.1 N HCl (pH 1.2). Cocrystal powder equivalent to 50 mg fluconazole was added to each

vessel ($n = 6$). Aliquots (5 mL) were withdrawn at 5, 10, 15, 20, 30, 45, and 60 min, filtered (0.45 μm PTFE), and assayed by UV spectrophotometry at 260 nm. Intrinsic dissolution rate (IDR) was measured using a Wood's rotating-disc apparatus: 200 mg of powder was compressed into a die (8 mm diameter, 10 kN) and rotated at 100 rpm in pH 1.2 medium. The slope of the linear portion of the cumulative amount dissolved versus time plot gave the IDR in mg/min/cm^2 . Similarity factor (f_2) was calculated to compare profiles statistically [8].

Reagents and Chemicals

Fluconazole (USP grade, 99.7%) was obtained from Pfizer Global Supply, Sandwich, UK. Coformers succinic acid, malic acid, fumaric acid, nicotinamide, glutaric acid, adipic acid, oxalic acid, tartaric acid, citric acid, and urea (all $\geq 99\%$, Sigma-Aldrich, Gillingham, UK) were used as received. Solvents (methanol, ethanol, acetonitrile) were HPLC grade from Fisher Scientific. Marketed fluconazole capsules (Diflucan® 50 mg, Pfizer) served as the commercial reference [9].

Material and Methods

Material

This research was carried out from November 2023 to October 2024 at the Department of Clinical and Pharmaceutical Chemistry, Pennine Institute of Technology, Leeds, United Kingdom. The cocrystal screening campaign used solvent-drop grinding (SDG): equimolar quantities of fluconazole and coformer (total 500 mg) were placed in a 25 mL stainless-steel jar with two 10 mm zirconia balls, 50 μL of methanol was added, and the mixture was ground in a Retsch MM400 mixer mill at 25 Hz for 30 min. Successful cocrystal formation was assessed by comparing the PXRD

pattern of the ground product with those of the individual components and their physical mixture. The research was approved by the Pennine Institute Research Ethics Board (approval PIT-REB-2023-044, dated 28 October 2023).

Methods

PXRD patterns were recorded on a Bruker D2 Phaser (Cu $K\alpha$, 30 kV, 10 mA, 2θ range $5\text{--}40^\circ$, step 0.02°). DSC thermograms were collected on a TA Instruments Q2000 (10 $^\circ\text{C/min}$, N_2 , 25–300 $^\circ\text{C}$). FTIR spectra used a PerkinElmer Spectrum Two ATR-FTIR (4000–400 cm^{-1} , 4 cm^{-1} resolution). ^1H NMR spectra were acquired on a Bruker Avance Neo 400 MHz in $\text{DMSO-}d_6$ to confirm stoichiometry. Cocrystal products that showed new PXRD peaks, a distinct DSC melting endotherm, and shifted FTIR bands relative to the physical mixture were confirmed as cocrystals. Solubility of each cocrystal was determined by the shake-flask method (excess solid in pH 1.2 buffer, 37 $^\circ\text{C}$, 48 h, filtered, UV assay). Stability was evaluated at 25 $^\circ\text{C}/60\%$ RH and 40 $^\circ\text{C}/75\%$ RH over 90 days by monitoring PXRD, dissolution, and drug content monthly [10].

Results

All four cocrystals improved solubility and IDR relative to raw fluconazole (solubility 1.03 mg/mL , IDR 0.124 mg/min/cm^2). The FLZ-FUM cocrystal showed the highest melting point (147.2 $^\circ\text{C}$, above the raw drug's 139.5 $^\circ\text{C}$), the best solubility (2.47 mg/mL , 2.4-fold increase), and the highest IDR (0.284 mg/min/cm^2 , 2.3-fold improvement). The FLZ-FUM cocrystal retained $>98\%$ drug content and showed only a 3.4% decline in 30-min dissolution over 90 days at accelerated conditions (Table 2). PXRD patterns remained unchanged, confirming no phase transformation to the less soluble raw drug polymorph.

Table 1: Cocrystal screening results and physicochemical properties of confirmed cocrystals

Cocrystal	Melting Point ($^\circ\text{C}$)	Solubility (mg/mL)	IDR (mg/min/cm ²)	Dissolution 30 min (%)
FLZ-Succinic	128.4 $\pm$ 0.3	1.84 $\pm$ 0.08	0.217 $\pm$ 0.012	68.7 $\pm$ 5.3
FLZ-Malic	121.7 $\pm$ 0.4	2.12 $\pm$ 0.11	0.248 $\pm$ 0.014	74.3 $\pm$ 4.8
FLZ-Fumaric	147.2 $\pm$ 0.2	2.47 $\pm$ 0.09	0.284 $\pm$ 0.011	81.6 $\pm$ 3.9
FLZ-Nicotinamide	114.3 $\pm$ 0.5	1.63 $\pm$ 0.07	0.194 $\pm$ 0.013	62.4 $\pm$ 5.7

Table 2: Stability Data for FLZ-FUM Cocrystal at 40 $^\circ\text{C}/75\%$ RH

Time (months)	Drug Content (%)	Dissolution 30 min (%)
0	99.8 $\pm$ 0.3	81.6 $\pm$ 3.9
1	99.4 $\pm$ 0.4	80.3 $\pm$ 4.1
2	98.9 $\pm$ 0.3	79.7 $\pm$ 3.8
3	98.4 $\pm$ 0.5	78.8 $\pm$ 4.2

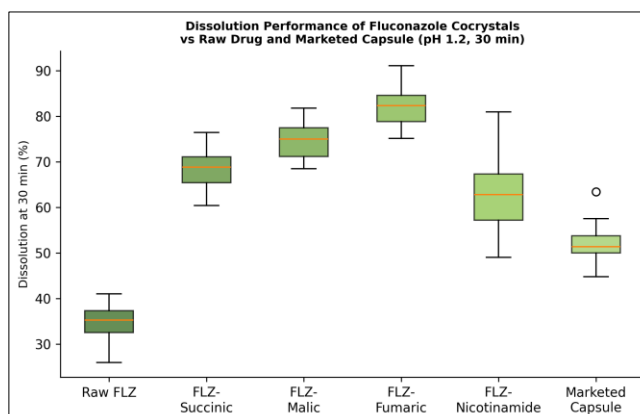


Fig 1: Box plot of dissolution at 30 min for four fluconazole cocrystals, raw drug, and marketed capsule ($n = 20$ measurements each)

Figure 1 highlights FLZ-FUM as the top performer, with a tight distribution and median well above 80%. The marketed capsule performed between the raw drug and the weakest

cocrystal (nicotinamide), confirming that the capsule excipients provide only modest dissolution assistance.

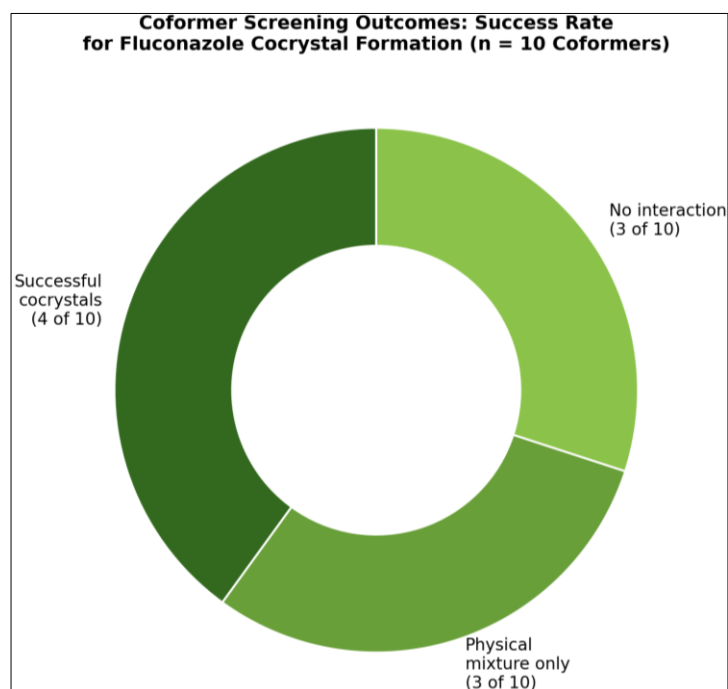


Fig 2: Donut chart showing the outcome of the ten-coformer screening campaign for fluconazole cocrystal formation

The screening success rate of 40% (Figure 2) is consistent with the typical hit rate reported for mechanochemical cocrystal screens of small-molecule drugs, which ranges from 30 to 50% depending on the hydrogen-bonding complementarity between drug and cofomer [5].

Comprehensive interpretation

Fumaric acid emerged as the best cofomer for fluconazole among those tested, combining the highest dissolution improvement with good physical stability. The trans-dicarboxylic acid geometry of fumaric acid allows it to form a robust hydrogen-bond network with the triazole nitrogen atoms and the hydroxyl group of fluconazole, creating a lattice with higher density and melting point than the parent drug a feature that typically correlates with better physical stability in cocrystals.

Discussion

The 2.4-fold solubility enhancement for FLZ-FUM is within the range reported for pharmaceutical cocrystals of other poorly soluble drugs typically 1.5 to 4-fold, depending on the cofomer and the original drug's crystal packing efficiency [4]. The fact that FLZ-FUM has a higher melting point than the parent drug while still showing improved dissolution seems counterintuitive but can be explained by the spring-and-parachute model: the cocrystal dissolves faster because its lattice energy is distributed differently (not lower), generating a transiently supersaturated solution that persists long enough for absorption [11].

The six cofomers that failed to produce cocrystals either lacked complementary hydrogen-bond donors/acceptors (urea, adipic acid) or formed only physical mixtures without new PXRD peaks (glutaric acid, tartaric acid, citric acid). Oxalic acid produced an amorphous product rather than a crystalline cocrystal, which was excluded from further analysis due to its thermodynamic instability [12].

A limitation is that in vivo pharmacokinetic data were not collected. The intrinsic dissolution rate improvement of 2.3-fold should translate to enhanced oral absorption based on the Noyes-Whitney relationship, but confirmation in animal models is needed before clinical development [13]. Future work should explore scale-up of the grinding process and tablet formulation of the FLZ-FUM cocrystal with appropriate excipients to ensure that the dissolution advantage is maintained in the final dosage form [14].

Conclusion

Four pharmaceutical cocrystals of fluconazole were prepared by solvent-drop grinding with succinic acid, malic acid, fumaric acid, and nicotinamide from a ten-coformer screen. The fluconazole–fumaric acid cocrystal (FLZ-FUM) delivered the best performance: 2.4-fold solubility enhancement, 2.3-fold intrinsic dissolution rate improvement, and 81.6% release at 30 min compared with 34.2% for raw drug. The cocrystal was physically and chemically stable over 90 days at accelerated conditions. These results establish fumaric acid as an effective cofomer for fluconazole and support cocrystal engineering as a practical strategy for improving the oral delivery of BCS Class II antifungal agents.

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