RESEARCH ARTICLE

Development and Evaluation of Flurbiprofen-Ferulic Acid Co-crystal With Enhanced Solubility and Dissolution Rate

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ABSTRACT

Flurbiprofen, a BCS class II NSAID, was combined with GRAS molecules to create new co-crystal forms using crystal engineering techniques such as solvent drop grinding and evaporation. Analysis with XRD, DSC, and FTIR confirmed purity and co-crystal formation. X-ray crystal data revealed hydrogen bonding and interactions, while DSC showed changes in thermal behavior. The co-crystals, particularly the flurbiprofen-ferulic acid co-crystals, had increased solubility and faster dissolution than pure drug.

Keywords: Flurbiprofen, Co-Crystals, Ferulic Acid, Co-Former.

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INTRODUCTION

The characteristics of active pharmaceutical components, including stability, particle size, flow ability, flavor, compatibility, hygroscopicity, and solubility, significantly influence the effectiveness and production costs of solid dosage forms.[1] Rate of dissolution and solubility of drug molecules affect oral drug absorption. 40% of market medicines and 90% of new compounds face low water solubility issues placing them in BCS classes II and IV, leading to reduced absorption in the GI tract and impacting drug effectiveness.[2,3] The physicochemical traits of pharmaceutical solids significantly affect therapeutic products. The crystal lattice and atomic packing directly influence material properties, allowing changes in packing arrangements to modify solid drug characteristics.[4] Two or more neutral chemicals are present in pharmaceutical co-crystals, bonded non-covalently (e.g., π-π stacking, van der Waals, hydrogen bonding). The components are approved pharmaceuticals, with at least one being an API.[5] Pharmaceutical co-crystallization, a novel technique in dosage form design, offers altered physicochemical attributes for API without impacting its intended pharmacological qualities by providing alternatives to salts, solvates, and polymorphs through crystalline modification.[6]

Flurbiprofen, a propionic acid derivative, is an NSAID with analgesic and antipyretic properties. Marketed as tablets, these compounds have limited bioavailability due to low water solubility and dissolution rates.[7] The research aimed to enhance flurbiprofen's solubility and dissolution rate by creating co-crystals with co-formers like ferulic acid due to their suitable molecular structures that facilitate hydrogen bonding between the API and conformer.

MATERIALS AND METHODS

Materials

Flurbiprofen was procured from Aarti Pharmaceuticals, Mumbai, India. Other chemicals have been purchased from Mumbai, India Loba Chemie Pvt. Ltd. The remaining components were all of the analytical or chromatographic grades.

Selection of Co-former and its Ratio

Six conformers were chosen based on mechanochemistry due to their ability to form hydrogen bonds and Serve as proton donors and acceptors with only ferulic acid, yielding an improved rate of dissolution and solubility. Stoichiometric ratios, such as a 1:1 ratio of API to ferulic acid, were crucial in the selection process.

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Method

Flurbiprofen - ferulic acid (1:1) co-crystal synthesis by solvent drop method[8]

A stoichiometric ratio (1:1) of drug & coformer was grinding with ethanol added dropwise in a mortar and pestle for 15 minutes. Co-crystals were obtained after evaporating the solvent, with flurbiprofen's absorption maxima found at 247 nm through spectroscopic analysis.

Flurbiprofen - ferulic acid (1:1) cocrystal synthesis by solvent evaporation method[9-11]

Flurbiprofen Co crystals were created using the solvent evaporation method with a constant 1:1 stoichiometric ratio for flurbiprofen (247 mg) and ferulic acid (194.12 mg) dissolved in ethanol. After evaporating the solvent at room temperature, the Co-crystals were obtained successfully for further experiments.

Characterization of Flurbiprofen, Ferulic Acid and co Crystal

Determination of melting point-[12]

The capillary method was used to determine the drug, coformer, and co-crystal melting points.

Solubility analysis[13-15]

Flurbiprofen and FPN-FA cocystal were produced using solvent evaporation and drop methods. Excess materials were placed in glass tubes, covered with foil, and then submerged in 10 ml of distilled water and PBS pH 7.2. After 24 hours of stirring, the suspension was filtered and analyzed using a UV spectrophotometer (Shimadzu 1900) after dilution with distilled water and phosphate buffer (pH 7.2).

Fourier-transform infrared spectroscopy[16]

The FTIR (Bruker Tensor II) was used to analyze the IR spectra of the drug, co-former, and co-crystals for consistent interactions. Samples were scanned between 4000 to 400 cm^{-1} to collect data.

Differential Scanning Calorimetry[17]

The sample's thermal behavior was analyzed using differential scanning calorimetry with TA Instrumentation's SDT Q 600. Samples of pure API, conformer, and novel co-crystals (4–5 mg each) were scanned in sealed aluminum pans, with an empty pan as a reference, under nitrogen purge (30 mL/min) at a rate of 10°C/min from 25 to 450°C.

X-ray Diffractometer[18,19]

XRD spectroscopy was conducted on the drug and co-crystals using a Bruker D8 Advance X-ray Diffractometer.

Scanning Electron Microscopy[20,21]

Using JEOL detectors (JSM-6360), which are made in Japan, SEM was employed to look at the differences in shape between the new co-crystals and the pure drug. Particles were mounted on aluminum stabs, vacuum-coated with gold, and photographed at different magnifications.

Intrinsic Dissolution Rate Measurement[22]

Using a USP apparatus II dissolution apparatus, an intrinsic dissolution study was conducted with 900 mL pH 7.2 phosphate buffer at 37°C and 50 rpm. The dissolution tests for the drug and co-crystals lasted 60 minutes, with samples withdrawn every 10 minutes and analyzed at 247 nm using a Shimadzu 1900 UV spectrophotometer.

Stability Studies[23]

The formulations underwent stability tests for three months in triplicate at 40°C & 75% RH to detect changes. Solubility & *in-vitro* drug release were used to evaluate stability.

RESULTS AND DISCUSSION

Co-formers, co-crystals, and drug melting points were identified to assess purity and crystallinity. Variations in melting points between the drug, co-former, and co-crystals indicate unique crystal formations and potential improvements in solubility and physio-chemical properties.

Solubility Analysis

A solubility analysis was done using distilled water and PBS (pH 7.2). Pure flurbiprofen had concentrations of 0.47 & 5.83 mg/mL in water & PBS, respectively. FPN-FA co-crystal formation by grinding method raised solubility to 6.23 & 9.75 mg/mL in water & PBS. The evaporation of solvent technique increased flurbiprofen solubility by 9.64 mg/mL in water & 9.94 mg/mL in PBS, endorsing co-crystals for flurbiprofen formulations.

Fourier-Transform Infrared Spectroscopy:

Figure 2 depicts the FTIR data for plain flurbiprofen, ferulic acid, and their co-crystals. Changes in intermolecular interactions compared to the original molecules were observed. Distinct peaks for flurbiprofen include O-H stretch at 2724 cm^{-1}, C=O at 1697 cm^{-1}, and F stretch at 1216 cm^{-1}. Ferulic acid exhibited a sharp peak at 3334 cm^{-1} for O-H stretch and peaks at 1662 cm^{-1} for C=O stretch. Co-crystals prepared *via* evaporation method showed shifts in peaks: the O-H peak of flurbiprofen moved from 2424 to 2720 cm^{-1}, the C=O peak of ferulic acid shifted from 1662 to 1660 cm^{-1}, and the C-F peak from 1216 to 1206 cm^{-1}. Co-crystals produced by the solvent drop method displayed shifts in peak positions for the parent molecules: O-H from 2424 to 2726 cm^{-1} and C=O of ferulic acid from 1662 to 1692 cm^{-1}. Broad peaks in the 2500 to 3000 cm^{-1} range suggest O-H stretching and hydrogen bonding in both methods. Peaks in the 400 to 800 cm^{-1} range indicate interactions between halogen and hydrogen, hinting at synthon formation at the *F atom*.

Table 1: Melting point

S. No.	*Name of compound*	*Melting Point (°C)*
1	Flurbiprofen	117
2	Ferulic Acid	172
3	Co-crystal Prepared by Solvent Drop Method	164
4	Co-crystal Prepared by Solvent Evaporation Method	108

Table 2: Solubility analysis

S. No.	*Solvent*	*Flurbiprofen (mg/mL)*	*Co-crystal solvent drop method (mg/mL)*	*Co-crystal by solvent evaporation method (mg/mL)*
1	water	0.47	6.23	9.64
2	PBS pH 7.2	5.83	9.75	9.94

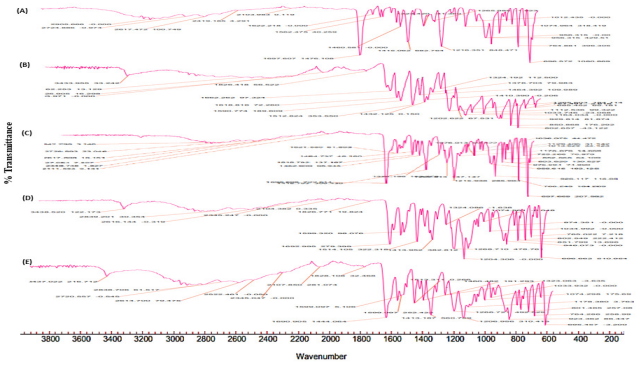

Figure 1: FTIR spectra of (a) Flurbiprofen; (b) Ferulic acid (c) Co-crystal prepared by solvent drop method; (d)) Co-crystal prepared by the evaporation of solvent method

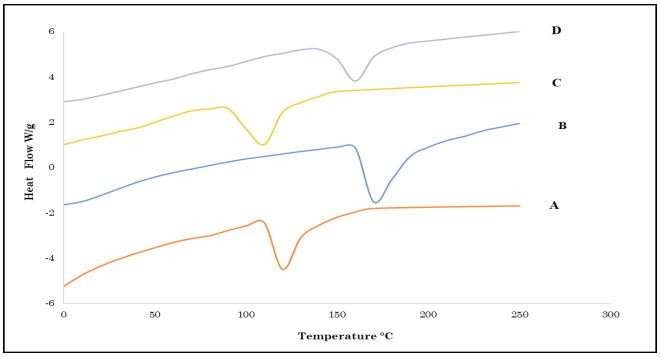

Figure 2: DSC graph of a) Flurbiprofen, b) Ferulic acid, c) Co-crystal prepared by Solvent drop method, d) Co-crystal prepared by the evaporation of solvent method

Differential Scanning Calorimetry

Figure 3 shows DSC data for plain flurbiprofen, ferulic acid, and their co-crystals. Pure flurbiprofen had a melting point of 117.25°C, and ferulic acid showed an endothermic peak at 174°C. FPN-FA Co-crystals created by the solvent drop method had an endothermic peak at 108.45°C, lower than both individual compounds' melting points, indicating a new crystalline form. In contrast, the FPN-FA Co-crystals prepared by the solvent evaporation method exhibited an endothermic peak at 160.5°C, showing an increase in flurbiprofen's melting point new solid crystal formation between flurbiprofen and ferulic acid.

Powder X-ray Diffraction

Figure 5 displays XRD spectra of flurbiprofen and FPN-FA co-crystals. Flurbiprofen exhibits peaks at 7.14°, 10.79°, 15.84°, and 20.56°, indicating its semi-crystalline nature.The FPN-FA co-crystal, obtained by solvent drop method, displays unique

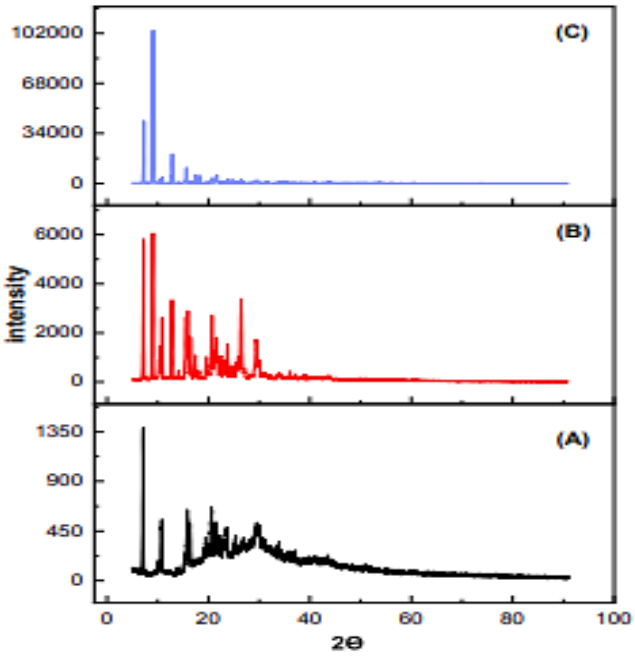

Figure 3: XRD patterns of a) Flurbiprofen, b) Co-crystal prepared by Solvent drop method, c) Co-crystal prepared by the evaporation of solvent method

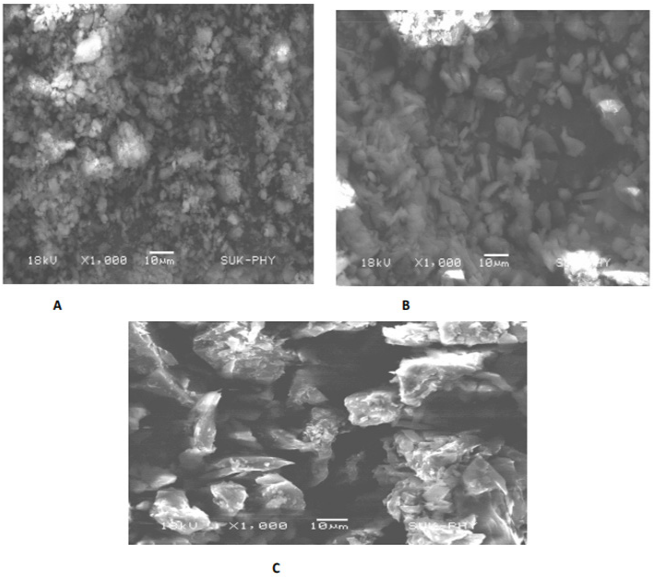

Figure 4: SEM a) flurbiprofen; b) co-crystal prepared by solvent drop method; c) co-crystal prepared by the evaporation of solvent method

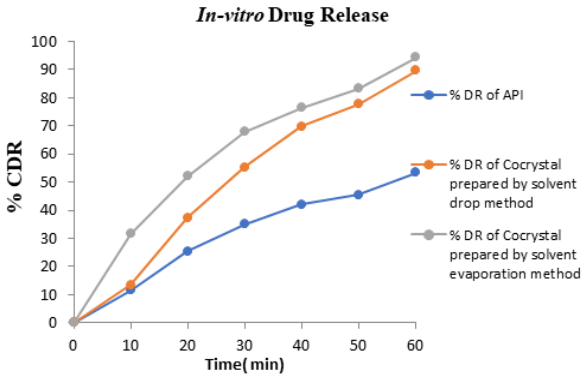

Figure 5: %cumulative drug release for co-crystals and pure API

Table 3: Solubility analysis of co-crystals after stability study

Storage condition 40 ± 5°C/75 ± 5% RH	*Solubility (mg/mL)*	
	Co-crystal prepared by solvent drop method	*Co-crystal prepared by solvent evaporation method*
	water	
Initial	6.23 ± 0.53	9.64 ± 0.13
1 month	6.20 ± 0.45	9.72 ± 0.29
2 month	6.26 ± 0.2	9.58 ± 0.18
3 month	6.18 ± 0.32	9.68 ± 0.23

Table 4: Intrinsic dissolution rate of co-crystals after stability study

Storage condition 40 ± 5 °C/75 ± 5% RH	*%CDR*	
	solvent drop method	*solvent evaporation method*
Initial	89.66 ± 0.54	94.32 ± 0.92
1 month	88.23 ± 0.67	95.12 ± 0.73
2 month	90.21 ± 1.2	93.65 ± 0.65
3 month	88.87 ± 0.45	94. 04 ± 0.32

peaks at 7.23°, 9.01°, 10.86°, 12.79°, 15.62°, and 26.45° that are not present in the drug. Another preparation method yields FPN-FA co-crystal with unique peaks at 7.27°, 9.08°, 10.92°, 12.79°, 12.88°, 15.69°, and 21.70°, representing novel XRD patterns for flurbiprofen. The new co-crystals show signature peaks, indicating a new phase formed by the drug's crystalline transformation in both co-crystallization methods, supported by XRD results. DSC and FTIR studies suggest a new phase involving hydrogen bonding between the co-former and the drug, potentially forming co-crystals.

Scanning Electron Microscopy

Figure 5 shows SEM data for plain flurbiprofen and co-crystals. Plain flurbiprofen particles were plate-shaped with erratic surfaces. The co-crystal made by solvent drop method was smooth and rod-shaped, while the one from solvent evaporation was stick-shaped. Hydrogen bonds between the components may have influenced the co-crystals' appearance.

Intrinsic Dissolution Rate

Comparing dissolution data of flurbiprofen, co-crystals were made using different methods. Pure API released 53.28% after 1-hour, while solvent drop method and evaporation method Co-crystals released 89.66 and 94.32%, respectively, after 1-hour, showing notable improvement over pure drug.

Stability Study

The stability study lasted three months at 40 ± 5°C and 75 ± 5% humidity, revealing that both co-crystals remained stable. Results suggest no significant changes in the co-crystals. Tables 3 and 4 show findings on drug release and solubility for *in-vitro* studies.

CONCLUSION

The study created pharmaceutical co-crystals of flurbiprofen to overcome challenges in its absorption into the bloodstream. Co-crystals prepared using solvent drop and evaporation techniques had better solubility and dissolution rates than the original compound. The analysis confirmed co-crystal formation through PXRD, DSC, and IR. Stability tests revealed the co-crystal remained stable for three months under accelerated environmental conditions.

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