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Preparation and Characterization of Flurbiprofen-Arginine Co-crystals

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ABSTRACT:

Flurbiprofen is a minimal solubility, greater permeability non-steroidal anti-inflammatory medication classified as BCS class II drug. To enhance the drug's physicochemical properties, pharmaceutical co-crystals of Flurbiprofen were made with arginine as the co-crystal former. Flurbiprofen co-crystals were successfully prepared using the solvent drop grinding process. IR spectroscopy, differential scanning calorimetry, and X-ray diffraction were used to validate the integrity and uniformity of all proposed crystal structures. When compared to pure active pharmaceutical component, co-crystals with arginine exhibited a greater powder dissolving rate (API). When compared to the pure active pharmaceutical ingredient, co-crystals of flurbiprofen with arginine demonstrated a 5.2 times gradual increase in solubility. Co-crystals are an evolving approach for modifying and enhancing physicochemical aspects of drugs to improve their medicinal effects, as per the research.

KEYWORDS: Flurbiprofen Co-crystals, Co-crystals, Cocrystallization, Flurbiprofen.

1. INTRODUCTION:

Weak biopharmaceutical qualities, instead of toxic effect or inefficacy, account for less than 1% of pharmaceutically active compounds that reach the market non the pharmacological sector. Solubility is still a prominent concern among these biological qualities (1). Synthesis without making and breaking covalent bonds is a very difficult as most crystalline molecular solids are homomeric (2). Co-crystallization of active pharmaceutical ingredients (APIs) with coformers is a yet another method for enhancing essential physicochemical features of APIs while preserving their chemical nature and pharmacological action. Solid dispersion, polymorphic modifications, micronization, Nanonization, complexation, salt production, emulsification, solubilization, and co-solvency are some of the processes used (3). The definition of co-

crystals proposed by the FDA in the draft guidance is as "Solids that are crystalline materials composed of two or more molecules in the same crystal lattice (4)." A pharmaceutical cocrystal constitutes active pharmaceutical ingredient and a coformer (5,6).

Physical properties of active pharmaceutical ingredients (APIs) such as crystallinity, solubility, hygroscopicity, stability, particle size, flow, filterability, density, and taste are constantly being improved by pharmaceutical scientists (7). When crystalline solid forms are needed, scientists look for polymorphs, hydrates, solvates, salts, and, more recently, cocrystals of an API (8). APIs are chemical structures that have functional groups that can participate in molecular recognition (9).

A cocrystal is a solid substance that contains at least two elements, which could be electrons, ions, or molecules. The prerequisite that the elements be solid in their stable form at ambient temperatures is often added to this approach. The ambient phase distinction, however, has been suggested to be subjective (10).

There are two parts to a cocrystal. The first part is the API, and the second is the coformer. Coformers are mostly pharmacological excipients, however they could also be other effective active medicinal components. Food additives and preservatives could also be utilized as coformers. The API to coformer ratio is often 1: 1, 1: 2, or vice versa. The coformer is usually a small organic acid molecule, and one that can hydrogen bind with the target API is desirable because it promotes API solubility (11).

Flurbiprofen (Figure 1) is a non-steroidal anti-inflammatory agent, one of the propionic acid group, with significant anti-inflammatory, analgesic and antipyretic properties (12). Rheumatoid arthritis, degenerative joint disease, osteoarthritis, ankylosing spondylitis, acute musculoskeletal problems, low back pain, and other illnesses are treated with it (13). It is chemically known as 2-(3-fluoro-4-phenylphenyl) propanoic acid. Flurbiprofen's anti-inflammatory activity is mediated through reversible suppression of cyclooxygenase (COX), the enzyme that converts arachidonic acid to prostaglandin G2 (PGG2) and PGG2 to prostaglandin H2 (PGH2) in the prostaglandin production pathway. Flurbiprofen is a medication classified as BCS class II, indicating it has a low solubility (14,15).

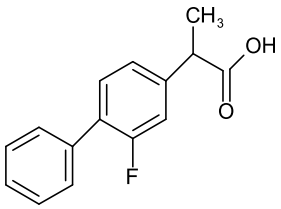

Figure 1: Structure of Flurbiprofen

To enhance pharmaceutical drug solubility, pharmaceutical co-crystals of Flurbiprofen were produced with cocrystal former such as arginine. Because it is an environmentally benign process, the solvent drop grinding approach was utilized. IR spectroscopy, Differential Scanning Calorimetry, and X-ray Diffraction were used to ascertain the quality and uniformity of new crystal structures.

2. MATERIALS AND METHODS:

2.1. Material:

Flurbiprofen was purchased from the Aarti Pharmaceuticals, Mumbai, Maharashtra, India. Other chemicals and solvents were obtained from different commercial suppliers.

2.2. Preparation of Co-crystals:

Flurbiprofen pharmaceutical co-crystals were synthesized utilizing the solvent drop grinding process with several co-crystal formers. Following trial batches with various coformers, the Flurbiprofen-Arginine co-crystal was chosen based on solubility improvement. The mole fraction of drug and conformer was taken in a pestle and mortar for optimized minutes with the addition of a few drops of methanol, and the procedure was chosen. The solid powder was then scraped from the mortar walls and placed in a vial. Using full factorial design, both proportion and grinding time were optimized. Various analysis approaches were used to characterize the solid formed throughout the trials.

2.3. Experimental design for preparation of co-crystals of Flurbiprofen using solvent drop grinding method:

To create a 3^2 factorial design, three factors at two levels were chosen. **Table 1** lists the factors and levels that were employed, whereas **Table 2** lists the nine experiments that were planned.

Table 1: Factors and their levels

Levels / Factors	Low	Mid	High
Drug : Conformer Ratio	1:1	1:1.5	1:2
Grinding time (min)	30	45	60

Table 2: Details of the nine formulations in the 3^2 factorial design

Sr. no.	API (Wt. in mg)	Co-Former (wt. in mg)	Grinding Time (in min)
1	244	187	23.79
2	244	205.38	45
3	244	168.62	45
4	244	187	66.21
5	244	200	30
6	244	200	60
7	244	174	60
8	244	187	45
9	244	174	30

3. PRELIMINARY CHARACTERIZATION:

3.1. Melting point

Digital melting point apparatus (Analab Scientific Instrument Pvt. Ltd.) were used to study the melting point of Co-Crystal former.

3.2. IR Spectroscopy

Infrared spectroscopy analysis Flurbiprofen-arginine co-crystals was performed by Attenuated Total Reflectance (ATR Bruker Alpha).

3.3. Differential scanning calorimetry

2–5 mg of the sample was placed in T zero aluminium pans, which were subsequently covered with a perforated aluminium lid and squeezed with a DSC crimper. The sample was maintained in a crimped aluminium pan in the thermal analysis chamber. As a reference, an empty pan was used. The temperature of

the DSC device was calibrated using indium as a reference. To maintain an inert atmosphere, nitrogen gas was purged continuously at a flow rate of 30 ml/min. Thermograms were acquired by heating the samples from 30° to 350° at a rate of 10°/min. DSC studies were carried out with nearly comparable numbers of samples for better comparisons.

3.4. X-ray Diffraction

An X-ray diffractometer was used to determine the PXRD pattern of pure drug and manufactured cocrystal (Flurbiprofen-L-Arginine LAG) at room temperature. Monochromatic Cu radiation was achieved using Ni-filtration and a system of 1.0^{o} and 0.3 mm divergent and receiving slides, respectively. With a voltage of 40 kV and a current of 30 mA, the diffraction pattern was measured over a 2 range of 10-80o with a sampling pitch of 0.02^{o} and a scan speed of 4^{o}/min.

3.5. Scanning Electron Microscopy

The morphology of the co-crystals was studied using a scanning electron microscope (SEM) with an energy dispersive X-ray source (EDX). Carbon coating was applied on the specimen in order to boost electron beam conductivity. The reference voltage was 15 KV and the current was 87000nA.

3.6. Solubility

The phase solubility of Flurbiprofen-arginine co-crystals was determined. The solubility of drug and cocrystals were determined by taking an excess amount of drug (50 mg), cocrystals (equivalent to 50 mg of drug) and added them in 10 ml of solvent, in vials. The samples were kept at equilibrium for a period of 48 hrs in variable shaker (Biotechnics India). The supernatant collected from vials was filtered through Whatman filter paper and analyzed by UV-Visible spectrophotometer (Lab India 3000) at respective wavelength.

3.7. Flow properties

Flow properties and compressibility were calculated by determining bulk density, tapped density angle of repose, compressibility index and Hausner ratio.

4. RESULTS AND DISCUSSION:

4.1. Melting point determination:

Melting point of the drug sample and cocrystals were determined by open capillary method by using melting point apparatus and found to be shown in Table 3.

Table no. 3: Melting point of Flurbiprofen, Co-crystal former and co-crystals

Sr. No	Sample	Observed Melting Point (^{0}C)
1.	Flurbiprofen	112-114
2.	Arginine	240-244
3.	Flurbiprofen-Arginine co-crystals Co-crystals	74-78

4.2. IR Spectroscopy:

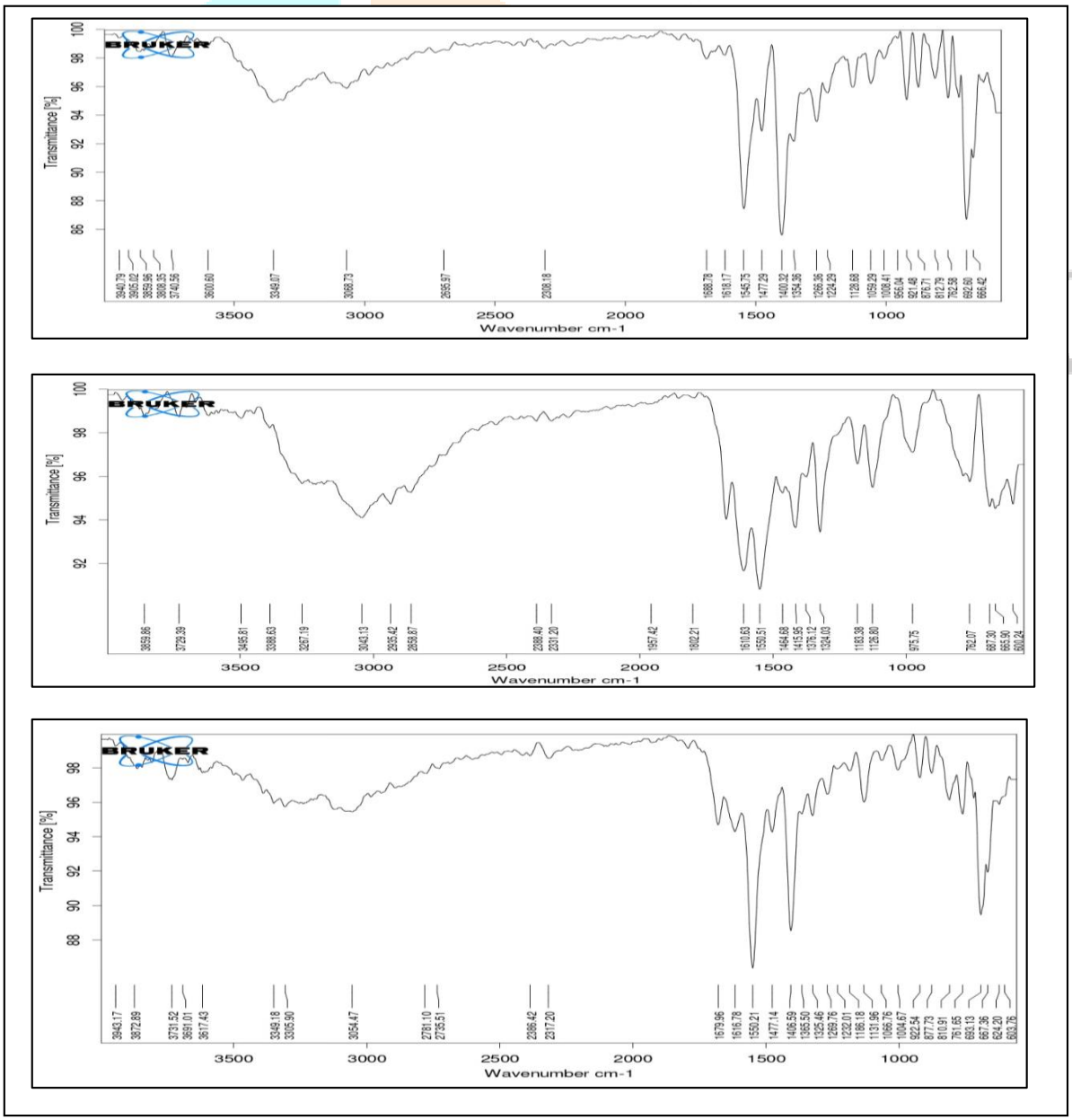

Figure 2: IR spectra of Flurbiprofen, Arginine and Flurbiprofen-Arginine co-crystals.

Infrared spectroscopy is useful for identifying novel crystalline forms in the early stages. According to the comparison, the new crystalline form is represented by peak shifts. The shift at the –C=O stretch, as well as the C-O stretch, strongly suggest the establishment of a hydrogen bond between Flurbiprofen and Arginine. There's no additional signal, reveals presence of Co-Crystal.

4.3. Differential Scanning Calorimetry (DSC):

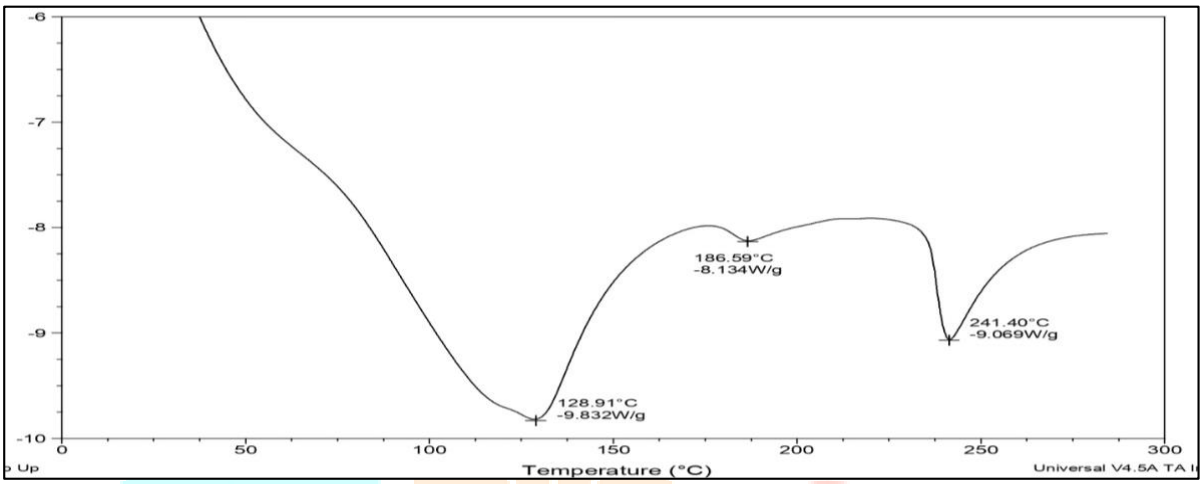

Figure 3 (A): DSC thermogram of Flurbiprofen.

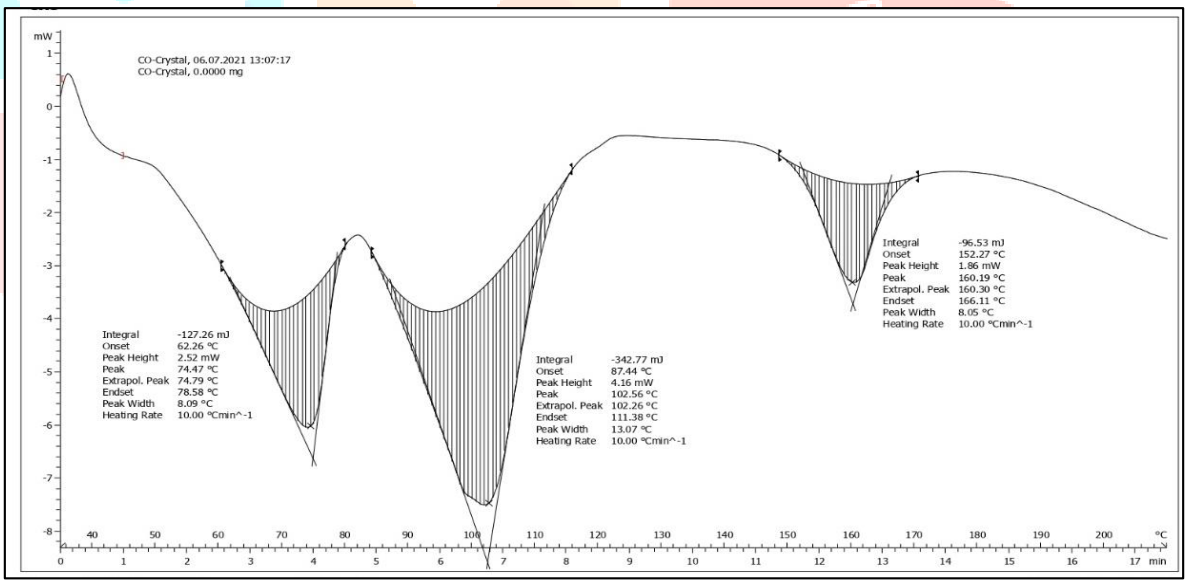

Figure 3 (B): DSC thermogram of Flurbiprofen-Arginine Co-crystals.

A differential scanning calorimeter with an automated data station was used to obtain the thermogram of Flurbiprofen. The melting of Flurbiprofen resulted in a single endothermic peak maxima at 111.38^{0}C on the thermogram. Due to melting of cocrystals, flurbiprofen-arginine co-crystals showed a single endothermic peak maximum at 74.470C. The thermal behavior was distinct, with a melting transition that differed from that of either of the separate components; this suggests the creation of novel phase cocrystals. The melting point of cocrystals was discovered to be lower than the drug's and cocrystal's melting points. A single endothermic transition for the cocrystals indicates the absence of any unbound or absorbed solvent or water and also demonstrates the stability of the phase until the melting point.

4.4. X-Ray Diffraction:

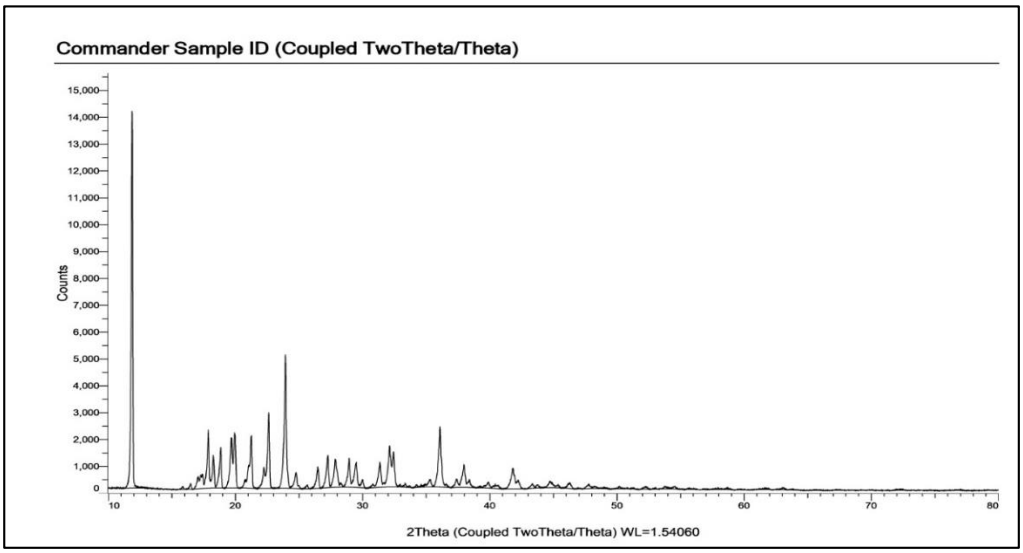

Figure 4 (A): XRD pattern of Flurbiprofen

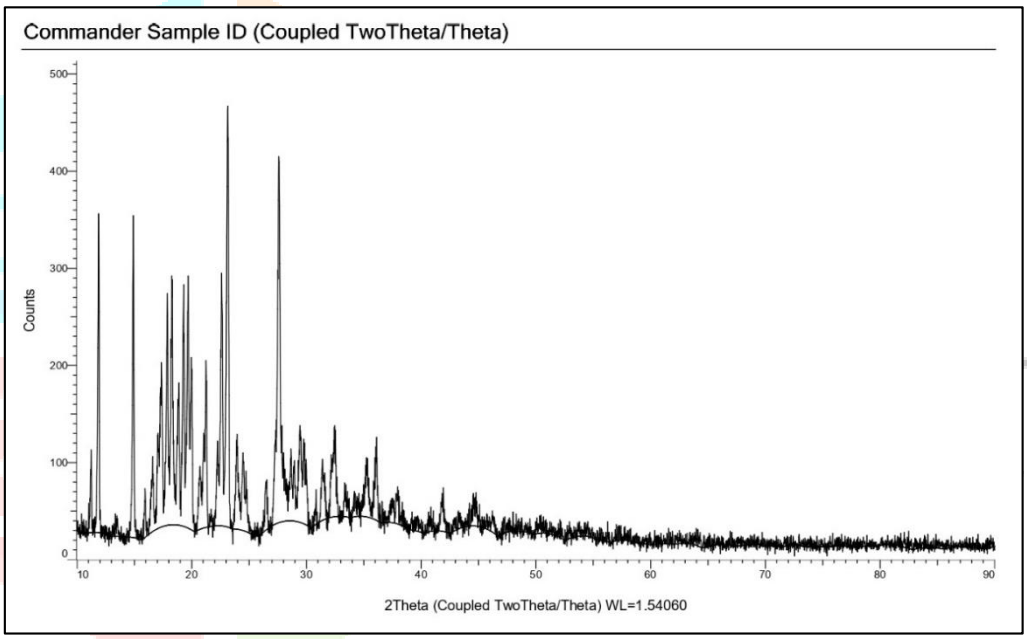

Figure 4 (B): XRD Patterns of Flurbiprofen-Arginine Co-crystals.

Between 150 and 350, flurbiprofen and flurbiprofen-arginine Co-Crystals showed a significant crystalline peak. Diffraction peaks at 15.760, 18.110, 23.320, 27.170, 32.250, and 35.150 were observed, with a strong peak at 20.20 suggesting Flurbiprofen's crystalline composition. While Flurbiprofen-Arginine Co-Crystals display characteristic characteristics and intense peak was seen at 15.70, demonstrating Flurbiprofen-Arginine Co-Crystals crystalline nature. The creation of a new crystalline form is indicated by a shift in the intensity peak.

4.5. Scanning Electron Microscopy:

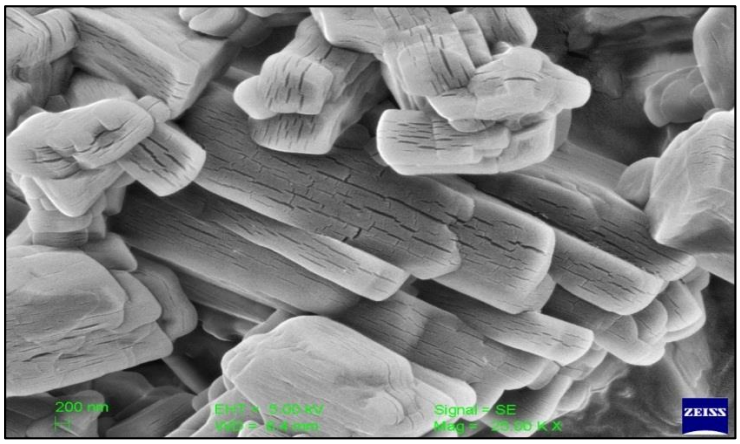

Figure 5 (A): Scanning Electron Microscopy of Flurbiprofen.

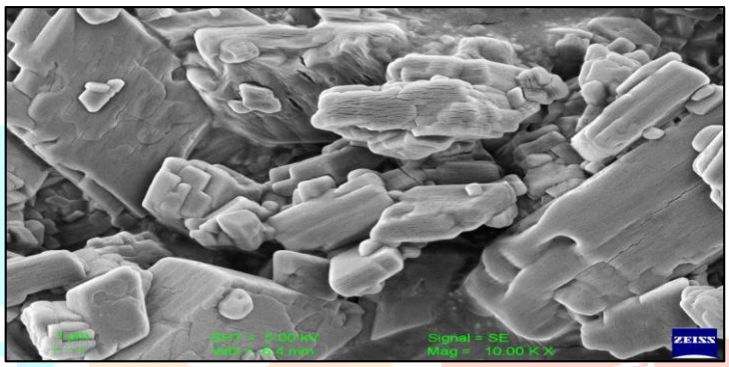

Figure 5 (B): Scanning Electron Microscopy of Flurbiprofen-Arginine co-crystals.

In the case of pure Flurbiprofen, the fracture surface was needle-shaped, but the SEM of Flurbiprofen-Arginine Co-Crystals revealed a change in surface morphology, with the creation of irregular plate-shaped crystals as shown in Figure 5.

4.6. Solubility:

Solubility studies were performed in order to analyze solubility enhancing properties of cocrystals. Solubility studies gave the basis for selection of best ratio that is to be forwarded for formulation. The results of the same are shown in Table no. 4.

Table no. 4: Solubility of Flurbiprofen and Flurbiprofen Arginine co-crystals

Sr. No.	Sample	Solubility (μg/ml)	Increase in Solubility (folds)
1	Flurbiprofen	10	-
2	Flurbiprofen-Arginine co-crystals	52	5.2

4.7. Flow properties:

The flow characteristics of Flurbiprofen, Flurbiprofen Arginine co-crystals were determined and compared in Table no. 5. The flowability of cocrystals was substantially enhanced when compared to the original drug crystals in terms of angle of repose, Carr's index, and Hausner ratio.

Table no. 5: Comparison of flow properties of Flurbiprofen and Flurbiprofen Arginine co-crystals

Sr. No.	Evaluation Parameters	Pure Drug	Flurbiprofen-Arginine Co-Crystals
1	**Angle of Repose**	42.32 ± 0.20	20.17± 0.78
	Inference	Passable	Excellent
2	**Bulk Density**	0.83 ± 0.012	0.71 ± 0.021
3	**Tap Density**	0.901 ± 0.002	0.653 ± 0.014
4	**Carr's index**	39.43 ± 0.39	12.15 ± 0.14
	Inference	Very Poor	Excellent
5	**Hausner Ratio**	1.64 ± 0.34	1.09 ± 0.05
	Inference	Very Very Poor	Excellent

4.8. Formulation of Flurbiprofen-Arginine Co-Crystals tablets:

The optimized formulae for Flurbiprofen Arginine co-crystals tablet had decided on trial and error basis of hardness and disintegration time of tablets.

Table no. 6: Formulation of Flurbiprofen-arginine Co-Crystals tablets

Formulation / **Ingredients (mg)**	**Flurbiprofen-Arginine Co-Crystals (mg)**
Flurbiprofen arginine cocrystal	175
Microcrystalline cellulose PH 102	120
Lactose	10
Magnesium stearate	5
Starch	10

4.9. In-vitro drug release study of Flurbiprofen-Arginine Co-Crystals tablets vs. Marketed Formulation:

The drug release study of tablets formulation was carried out to compare the dissolution efficiency of Flurbiprofen Arginine co-crystals tablets marketed tablets.

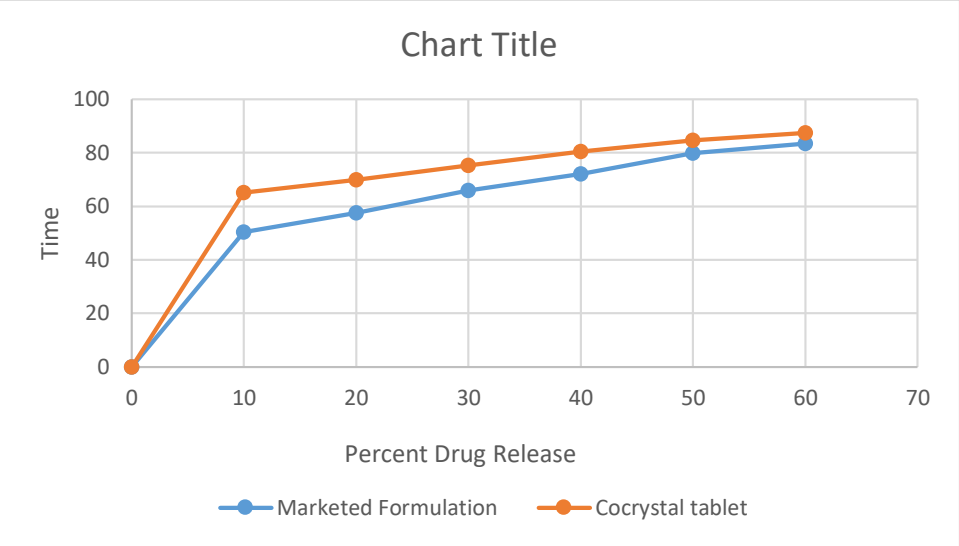

Figure 5: Comparison of % Drug release in phosphate buffer pH 6.8

Marketed tablet (Ar Flur) gave 79.48% drug release in phosphate buffer pH 6.8 after 1 hour. While co-crystals tablet gave 85.63% release in phosphate buffer pH 6.8 after 1 hour, this show that cocrystal formulation shows better result than marketed tablet.

5. CONCLUSION:

To improve the physicochemical difficulties associated with an API, flurbiprofen cocrystals were produced using an arginine cocrystal forming. The solvent drop grinding process was used to make Flurbiprofen with arginine cocrystals. Melting point, ATR-IR, DSC, XRD, and SEM all confirmed the presence of cocrystals. Flurbiprofen with arginine cocrystals had a 5.2-fold improvement in solubility and a better dissolving profile than the API. Co-crystals were shown to have higher solubility, dissolution, flow characteristics, and compressibility in the study.

6. ACKNOWLEDGEMENTS:

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