

PREPARATION AND CHARACTERIZATION OF IBUPROFEN COCRYSTALS BY USING SOLVENT DROP GRINDING METHOD

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Article Received on
18 April 2014,

Revised on 14 May 2014,
Accepted on 07 June 2014

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ABSTRACT

Ibuprofen is a non-steroidal anti-inflammatory BCS class II drug of low solubility and high permeability. Pharmaceutical cocrystals of Ibuprofen were prepared with cocrystal formers, such as benzoic acid, 3-aminobenzoic acid, and cinnamic acid, to improve drug solubility. Solvent drop grinding method was successful to make Ibuprofen cocrystals. All new crystalline forms were characterized by IR spectroscopy, differential scanning calorimetry, and X-ray diffraction to confirm their purity and homogeneity. Cocrystals with benzoic acid, 3-aminobenzoic acid and cinnamic acid showed a faster

powder dissolution rate than the reference active pharmaceutical ingredient (API). Cocrystals of Ibuprofen with benzoic acid showed the highest solubility (7 times as compared with API) while cocrystals with Ibuprofen and 3-aminobenzoic acid and cinnamic acid showed comparably good solubility (3 times faster than the API) up to 60 min. The study showed cocrystals is an emerging trend to modify physicochemical properties of drug to enhance their pharmaceutical properties.

Keywords: Cocrystals, Cocrystallization, Ibuprofen, Grinding.

1.INTRODUCTION

The improvement of the physicochemical properties, biopharmaceutical and in-vivo of active pharmaceutical ingredients (APIs) has become a major concern in the pharmaceutical industry. Both branded and generic pharmaceutical companies spend considerable efforts and resources on the discovery of new crystalline forms of their APIs. This intense research has been driven by the need for improving undesirable properties of APIs witnessed in the commercialization pipelines^{1,2}. Pharmaceutical cocrystals is reliable method to improve drug

physicochemical and mechanical properties such as solubility, dissolution rate, stability, hygroscopicity, compressibility and in vivo performance without altering their pharmacological behavior and, hence, are a potential new alternative in the selection of optimal solid forms in drug product development^{3,4}. Pharmaceutical cocrystals can be defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non-covalent interactions, primarily hydrogen bonding⁵. The resulting multi-component crystalline phase maintains the intrinsic activity of the parent API. The screening of cocrystal is based upon some traditional methods such as solvent evaporation, crystallization from melts and grinding^{6,7}. Cocrystals can be considered for non-ionizable drugs for which salts cannot be attained. Also, for ionizable drugs, the number of suitable cocrystal ligands can exceed the number of suitable counterions⁸.

Ibuprofen [(+/-) 2-(p-isobutylphenyl)propanoic acid ($(\text{CH}_3)_2\text{CHCH}_2\text{-C}_6\text{H}_4\text{CH}_2\text{CHCO}_2\text{H}$)] is well known as a non-steroidal anti-inflammatory (NSAID), analgesic and antipyretic agent. It is a weakly acidic drug having high permeability through stomach because it remains 99.9% unionized in stomach (pKa of Ibuprofen- 4.43, pH of gastric fluid - 1.2). Ibuprofen is mostly permeable through stomach but due to its solubility limitation it can't enter into systemic circulation and gastric emptying time is 30 min to 2 hr. After this time ibuprofen goes into small intestine where it is solubilized but can't permeate through its membrane (Ibuprofen having pH dependent solubility and permeability). To improve dissolution of such drug is challenging and rational. However, commercially available ibuprofen particles are needle-like with rough surfaces and show poor flowability, poor compaction behaviour and a tendency to stick to the tablet punches. To overcome these problems, a suitable size and shape of ibuprofen crystal is desirable that could be directly compressed⁹.

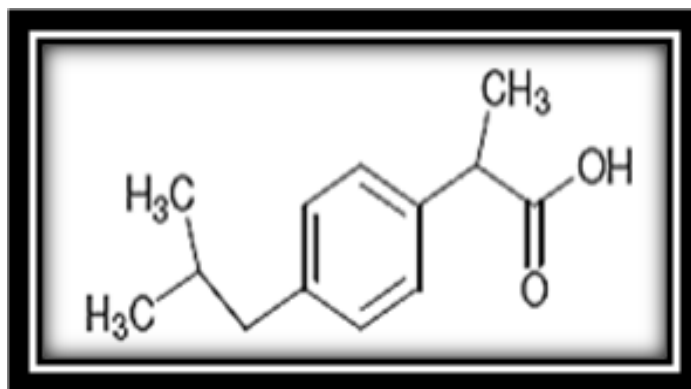


Figure 1: Structure of Ibuprofen

Pharmaceutical cocrystals of Ibuprofen were prepared with cocrystal formers, such as oxalic acid, benzoic acid, 3-aminobenzoic acid, 4-aminobenzoic acid, urea, salicylic acid, cinnamic acid, succinic acid and citric acid, to improve drug solubility. Solvent drop grinding method was used as it is a ecofriendly method. New crystalline forms were characterized by IR spectroscopy, differential scanning calorimetry, and X-ray diffraction to confirm their purity and homogeneity.

2. MATERIALS AND METHODS

2.1 Materials

Ibuprofen was received as a gift sample from the Kaytross ACG Life Sciences Ltd., Maharashtra, India. Other chemicals and solvents were obtained from different commercial suppliers.

2.2 Preparation of Cocrystals

Pharmaceutical cocrystals of Ibuprofen were prepared with different cocrystal formers using solvent drop grinding method. Ibuprofen- Benzoic acid, 3- aminobenzoic acid and cinnamic acid cocrystal was prepared by grinding 1:1 molar ratio in a pestle and mortar for 180 minutes with addition of a few drops of methanol. The solid powder was then scratched from walls of mortar and stored in vial. The solid obtained in experiments were then characterized using various analytical techniques.

3. PRELIMINARY CHARACTERIZATION

3.1 Melting point

Melting point of the sample Ibuprofen- benzoic acid, 3- aminobenzoic acid and cinnamic acid cocrystal were determined by open capillary method by using melting point apparatus. The melting point was done in triplicate. (Omega Scientific Industries, India).

3.2 IR Spectroscopy

Infrared spectroscopy analysis of Ibuprofen- Benzoic acid, 3- aminobenzoic acid and cinnamic acid cocrystal 1:1 was performed by Attenuated Total Reflectance (ATR Bruker Alpha).

3.3 Differential scanning calorimetry

The DSC thermogram of Ibuprofen- Benzoic acid, 3- Aminobenzoic acid and cinnamic acid cocrystal 1:1 was recorded by differential scanning calorimeter equipped with a computerized

data station. The DSC measurements were performed on a DSC 60, Shimadzu, Japan instrument. Accurately weighed sample were placed in a sealed aluminium pans before heating under nitrogen flow (20ml/min) at a scanning rate of $10^{\circ}\text{C}/\text{min}$. An empty aluminium pan was used as a reference. Melting point was determined for identification of API and cocrystal former.

3.4 X-ray Diffraction

For characterization of crystalline state, the powder x-ray diffraction (XRD) pattern of Ibuprofen- Benzoic acid, 3- Aminobenzoic acid and cinnamic acid cocrystal 1:1 was determined. Powder X-ray diffraction (XRD) was carried out using a Bruker AXS Advance D-8 scanner with filter Ni, Cu- $K\alpha$ radiation, voltage 40kV and a current 20mA. The scanning rate employed was $1^{\circ}/\text{min}$ over the 5° to 50° diffraction angle (2θ) range.

3.5 Scanning Electron Microscopy

Scanning electron microscopy of Ibuprofen- Benzoic acid, 3- Aminobenzoic acid and cinnamic acid cocrystal 1:1 was carried to determine the external morphology. The sample was mounted directly onto the SEM sample holder using double sided sticking tape and images were recorded at the required magnification at acceleration voltage of 10 kV using scanning electron microscope (JSM 6930, Jeol Datum Ltd. Japan).

3.6 Phase Solubility

The phase solubility of Ibuprofen- Benzoic acid, 3- Aminobenzoic acid and cinnamic acid cocrystal 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 above solvent, in vials. The samples were kept at equilibrium for a period of 72 hrs in incubator at $37 \pm 0.5^{\circ}\text{C}$ with occasional shaking. The supernatant collected from vials was filtered through whatman filter paper and analyzed by UV-Visible spectrophotometer (V630, Jasco) at respective wavelength.

3.7 Flow properties

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

4. RESULT 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 1.

Table no. 1: Melting point of Ibuprofen, Cocrystal former and cocrystals

Sr.no.		Sample	Observed Melting point ($^{\circ}\text{C}$)
1	API	Ibuprofen	74-78
2	Cocrystal former	Benzoic acid	120-123
		3-aminobenzoic acid	176-179
		Cinnamic acid	130-134
3	Cocrystals	Ibuprofen- benzoic acid	56-62
		Ibuprofen- 3-aminobenzoic acid	62-68
		Ibuprofen- Cinnamic acid	63-68

It was found that melting point of cocrystals get decreased as compared to API and cocrystal former.

4.2 IR Spectroscopy

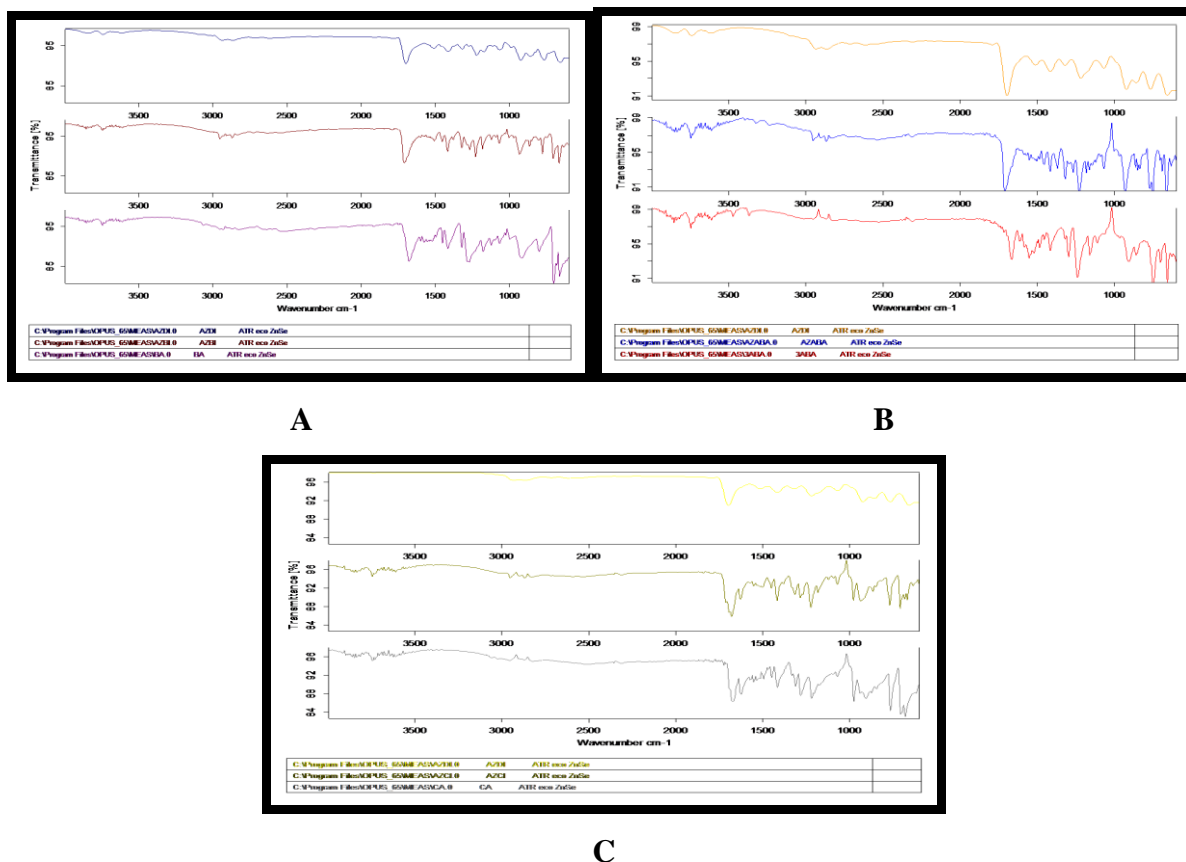


Figure 2: A: IR spectra of Ibuprofen, IBU-BA, benzoic acid, B: IR spectra of Ibuprofen, IBU-3ABA, 3-aminobenzoic acid. C: IR spectra of Ibuprofen, IBU-CA, cinnamic acid.

Infrared spectroscopy helps in preliminary identification of new crystalline form. From comparison indicated shifts at peaks of functional group represents the new crystalline form. It is confirmed from shift at $\text{C}=\text{O}$ stretch and also $\text{C}-\text{O}$ stretch strongly indicate formation of hydrogen bond in between Ibuprofen and benzoic acid, 3-aminobenzoic acid and cinnamic acid.

4.3 Differential Scanning Calorimetry (DSC):

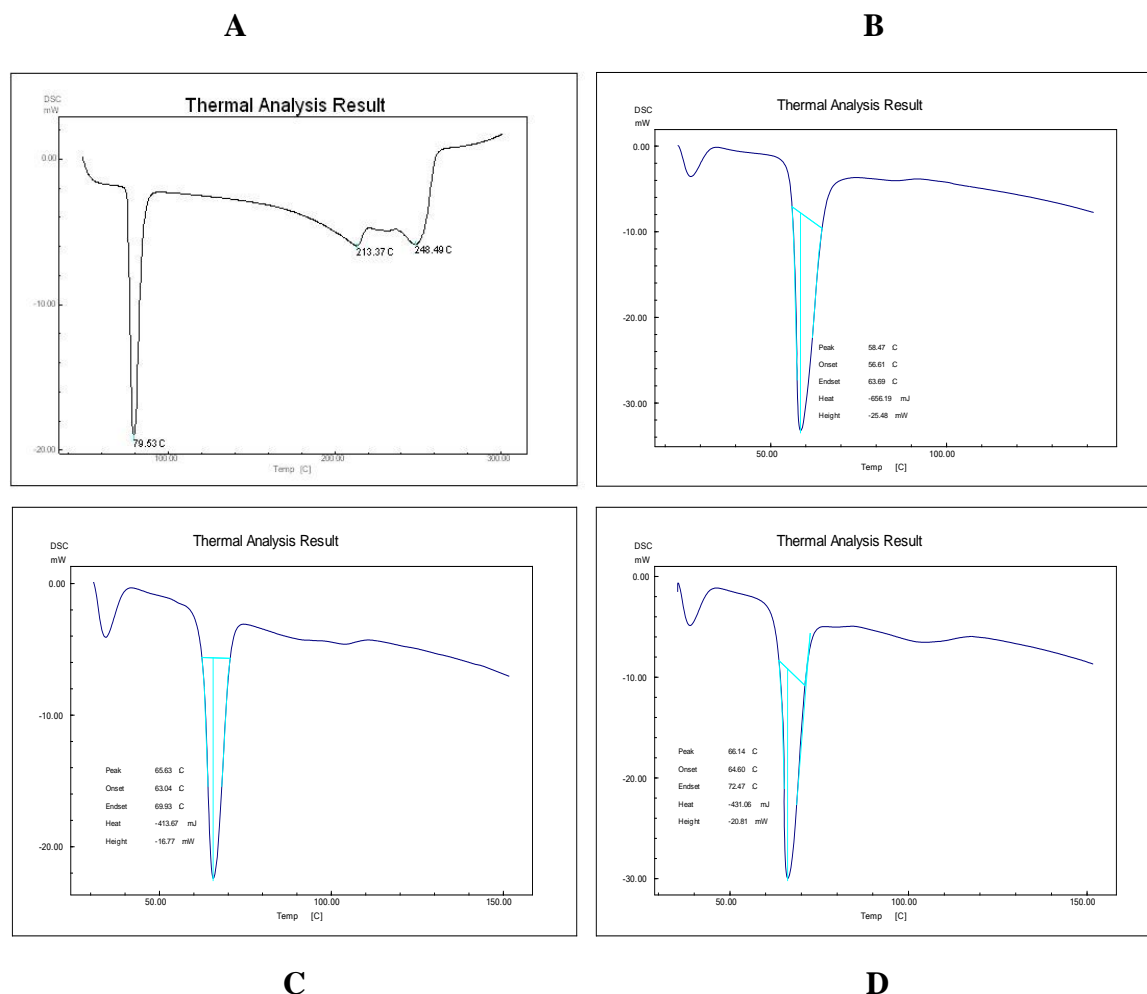


Figure 3: A: DSC thermogram of Ibuprofen.

B: DSC thermogram of Ibuprofen- benzoic acid.

C: DSC Thermogram of Ibuprofen- 3- amino benzoic acid.

D: DSC Thermogram of Ibuprofen-cinnamic acid.

The DSC thermogram of Ibuprofen- Benzoic acid, 3- aminobenzoic acid and cinnamic acid cocrystals was recorded by using a differential scanning calorimeter with a computerized data station. DSC experiment was carried out to study the thermal behaviour of the Ibuprofen- benzoic acid, 3- aminobenzoic acid and cinnamic acid cocrystals had shown a single

endothermic peak maxima at 58.47, 65.63 °C and 66.14 °C due to melting of cocrystals. The thermal behaviour was distinct, with a different melting transition from that seen with either of the individual component; this suggest formation of new phase cocrystals. The melting point of cocrystals was found to be below the melting point of both the drug and cocrystal former.

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

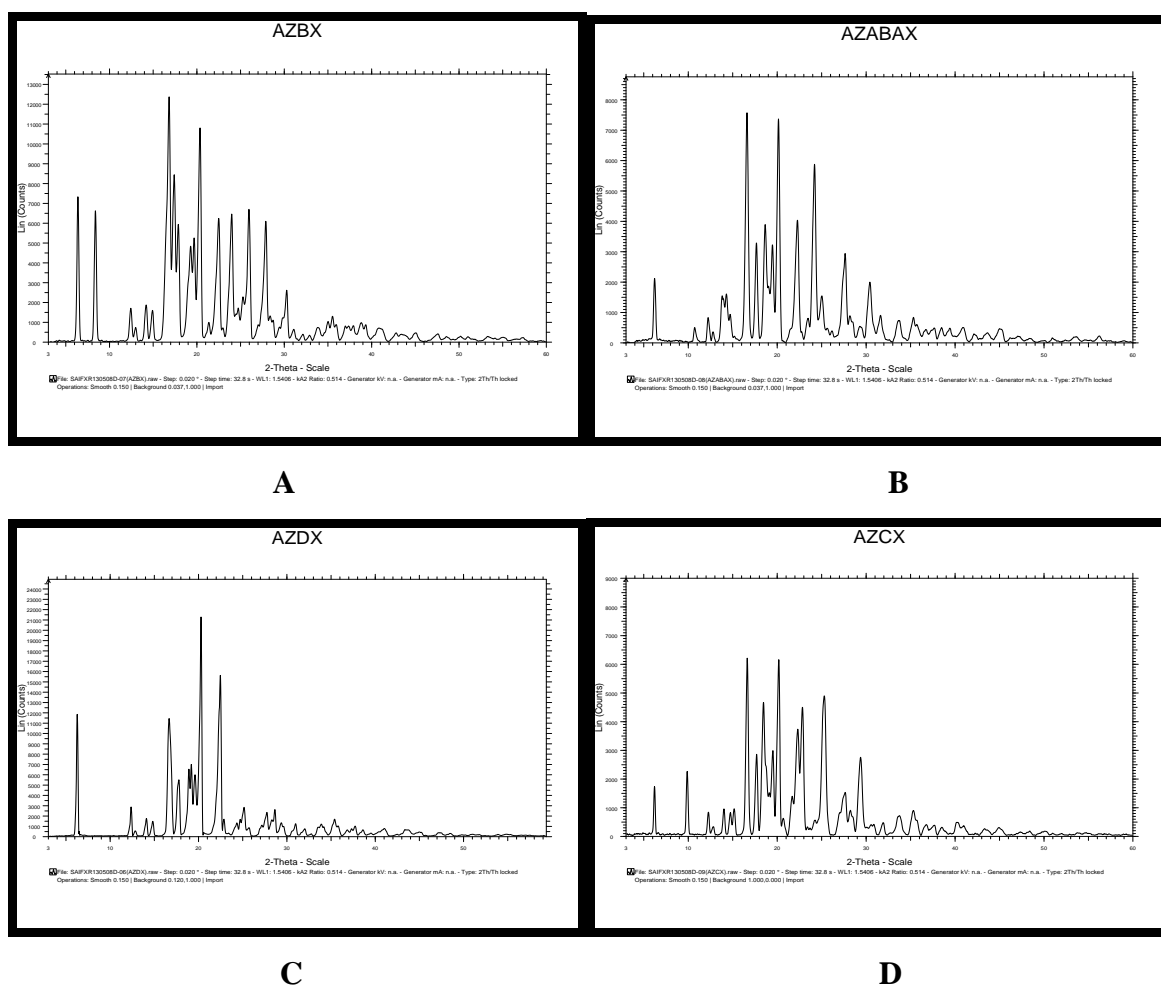


Figure 4: A: XRD Patterns of Ibuprofen.

B: XRD Patterns of Ibuprofen- benzoic acid.

C: XRD Patterns of Ibuprofen- 3- amino benzoic acid.

D: XRD Patterns of Ibuprofen- cinnamic acid.

The pure Ibuprofen and IBU-BA exhibited intense crystalline peak between 5° to 50° . Characteristic diffraction peaks at 6.2° , 16.6° , 17.7° , 20.2° , 22.4° , 25.1° , 27.7° and 28.6° were observed with intense peak at 20.2° indicating crystalline nature of Ibuprofen. Ibuprofen-benzoic acid shows characteristic at 6.3° , 8.3° , 16.7° , 17.3° , 20.3° , 22.4° , 23.9° , 25.9° and 27.8° and intense peak was observed at 16.7° indicating crystalline nature of IBU-BA. The shift in intense peak indicate formation of new crystalline form. Ibuprofen- 3- amino benzoic acid shows characteristic at 6.1° , 14.2° , 16.4° , 17.5° , 20.1° , 22.2° and 24.1° and intense peak was observed at 16.4° indicating crystalline nature of IBU-3ABA. The shift in intense peak indicate formation of new crystalline form. Ibuprofen- cinnamic acid shows characteristic at 6.1° , 9.81° , 16.3° , 18.4° , 19.4° , 19.9° , 22.2° , 22.7° , 25.2° and 29.3° and intense peak was observed at 16.3° indicating crystalline nature of IBU-CA. The shift in intense peak indicate formation of new crystalline form.

4.5 Scanning Electron Microscopy

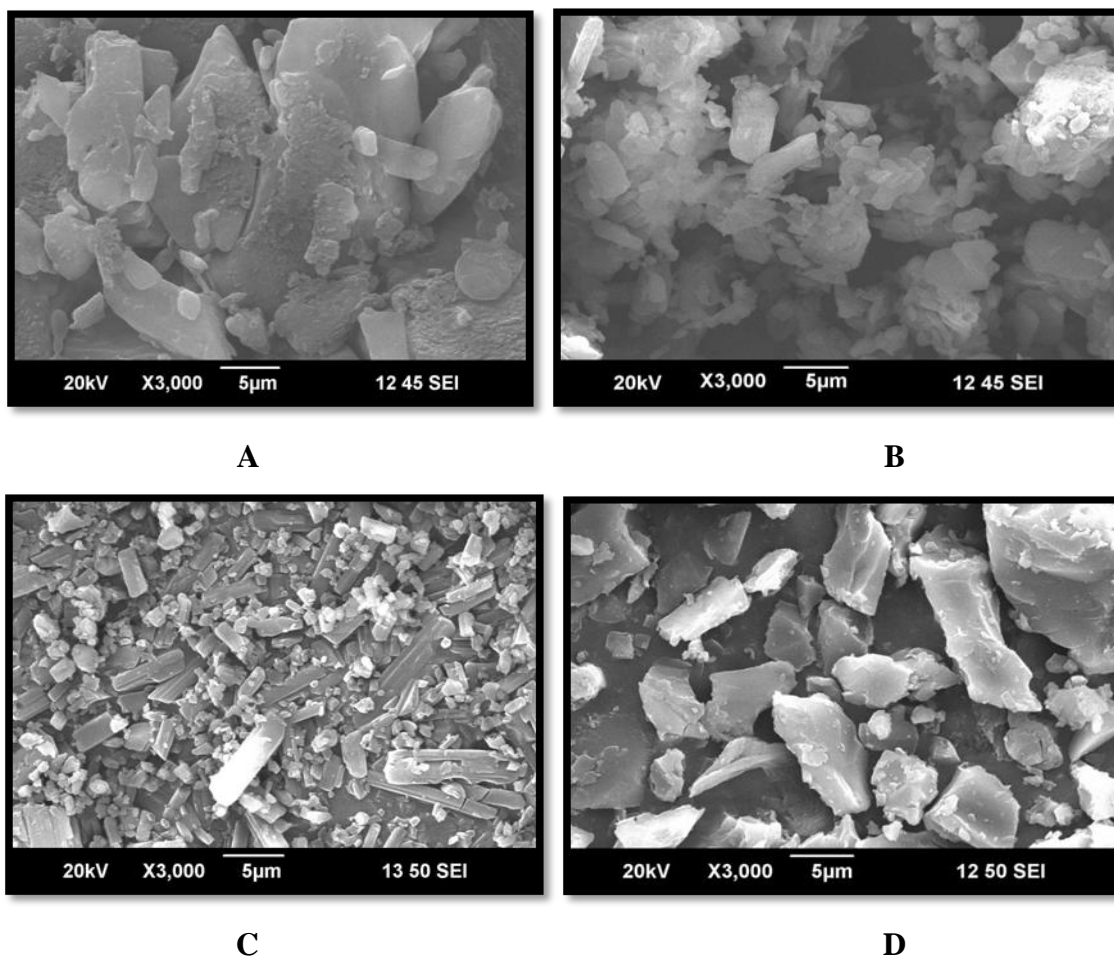


Figure 5: A: Scanning Electron Microscopy of Ibuprofen.

B: Scanning Electron Microscopy of Ibuprofen.

C: Scanning Electron Microscopy of Ibuprofen.**D: Scanning Electron Microscopy of Ibuprofen.**

SEM of Ibuprofen indicated needle shaped fracture surface. Ibuprofen- Benzoic acid, 3-aminobenzoic acid and cinnamic acid cocrystals indicated change in surface morphology, development of irregular shaped crystal were seen.

4.6 Phase 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 2.

Table no. 2: Phase solubility of Ibuprofen- Benzoic acid, 3- aminobenzoic acid and cinnamic acid

Sr. No.	Sample	Solubility (mg/ml)	Increase in Solubility (folds)
1	Ibuprofen	0.40	-
2	Ibuprofen-benzoic acid	3.08	7.62
3	Ibuprofen- 3-amino benzoic acid	1.60	3.96
4	Ibuprofen-cinnamic acid	1.41	3.49

4.7 Flow properties

The flow properties of Ibuprofen with benzoic acid, 3-aminobenzoic acid and cinnamic acid cocrystals have been determined and compared in Table 3 shows the flowability represented in terms of the angle of repose, Carr's index and Hausner ratio of cocrystals were much improved compared to those of the original drug crystals.

Table no. 3: Comparison of flow properties of Ibuprofen, Ibuprofen- Benzoic acid, 3- aminobenzoic acid and cinnamic acid

Sr. No.	Evaluation Parameters	Ibuprofen	Ibuprofen-benzoic acid	Ibuprofen- 3- amino benzoic acid	Ibuprofen-cinnamic acid
1	Angle of Repose	41.18 ± 0.22	24.77 ± 0.40	28.17 ± 0.17	33.17 ± 0.36
	Inference	Very poor	Good	Good	Excellent
2	Bulk Density	0.404 ± 0.006	0.314 ± 0.005	0.333 ± 0.029	0.315 ± 0.004

3	Tap Density	0.603 ± 0.015	0.353 ± 0.005	0.366 ± 0.015	0.370 ± 0.017
4	Carr's index	33.33 ± 0.32	10.53 ± 0.48	12.22 ± 0.41	15.82 ± 0.19
	Inference	Poor	Good	Good	Excellent
5	Hausner Ratio	1.5 ± 0.04	1.11 ± 0.02	1.13 ± 0.02	1.18 ± 0.02
	Inference	Extremely Poor	Good	Good	Excellent

5. CONCLUSION

Ibuprofencocrystals was formed with different cocrystal formers to overcome various problems associated with an API. Cocrystals of Ibuprofen with benzoic acid, 3-aminobenzoic acid and cinnamic acid was prepared by using solvent drop grinding method. Cocrystals was confirmed by melting point, ATR-IR, DSC, XRD, SEM. Cocrystals of Ibuprofen with benzoic acid showed the highest solubility (7 times as compared with API) while cocrystals with Ibuprofen and 3-aminobenzoic acid and cinnamic acid showed comparably good solubility (3 times faster than the API) up to 60 min. The study successfully demonstrateCocrystals has shown increased solubility, flow properties and compressibility.

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