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Original Article

Comparative Evaluation of Co-Crystallization Methods for the Solubility Enhancement of Poorly Water-Soluble Drug of BCS Class II

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ABSTRACT

Background: The practice of co-crystallizing 2 or more components has gained increasing popularity to create novel materials with enhanced performance and properties compared to those composed solely of pure components. **Objectives:** The present study is aimed to increase solubility of Piroxicam by preparing co-crystals using methods of co-crystallization using various co-formers in different solvents. **Materials and Methods:** The Co-crystals of Piroxicam were prepared using solvent evaporation and slow cooling methods of co-crystallization. The co-formers used in the study were benzoic acid, citric acid and PABA. The prepared Co-crystals were evaluated for solubility and dissolution rate. The Co-crystals were characterized by, Fourier Transform Infrared Spectroscopy (FTIR), Powder X-ray Diffractometry (PXRD) and Scanning Electron Microscopy (SEM). **Results:** The formation of co-crystals by solvent evaporation and slow cooling methods were done with benzoic acid, citric acid and PABA as co-formers and ethanol, acetone and acetonitrile as the solvent was done. It was confirmed based on melting point, PXRD data, FTIR and SEM. The aqueous solubility and dissolution rate showed improved rates as compared to pure drug. **Conclusion:** The prepared co-crystals showed improved rates as compared to pure piroxicam.

Keywords: Co-crystallization, Co-crystals, Improved bioavailability, Piroxicam, Slow cooling, Solvent evaporation.

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INTRODUCTION

Solid dosage forms, such as tablets and capsules, are widely used for drug delivery due to their convenience, compactness and stability during storage. However, there are instances where the Active Pharmaceutical Ingredients (APIs) cannot be formulated in their pure form due to stability issues. As a result, understanding and managing the chemistry of the solid state becomes a crucial aspect of pharmaceutical development. Alternative forms of drug delivery may offer faster API release, but the solid state remains the preferred choice for its practicality and long-term storage suitability.[1]

Pharmaceuticals with low water solubility often encounter difficulties associated with insufficient and inconsistent oral bioavailability, resulting in variations in clinical response.[2] Drug substances belonging to class II of the biopharmaceutics classification system, characterized by high permeability but low solubility, face limitations in oral absorption due to their poor solubility. Consequently, the growing prevalence of drug substances with solubility challenges poses a significant obstacle to the advancement of drug development.[3]

However, these challenges can be overcome through the proper formulation of the drug. One possible approach involves leveraging various polymorphs, such as anhydrous forms and solvate/hydrate forms, to enhance the drug's bioavailability and address these concerns effectively.[2]

Polymorphism is a phenomenon observed in many pharmaceutical solids, wherein a substance can exist in multiple crystalline phases. These phases differ in the arrangement and conformation of molecules within the crystal lattice. Polymorphic solids display distinct physicochemical properties, encompassing variations in shape, compressibility, melting point, crystal habit, colour, density, solubility and dissolution rate. In recent years, polymorphism has gathered significant attention due to

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the realization that different polymorphs of a specific drug can exhibit varying solubilities. As a result, certain polymorphs may demonstrate superior therapeutic activity compared to others, especially when the drug has limited solubility.[1,2]

The practice of co-crystallizing 2 or more components has gained increasing popularity to create novel materials with enhanced performance and properties compared to those composed solely of pure components.[4] The growing interest in co-crystals, which are crystal forms comprising two or more neutral molecules within a crystal lattice, has emerged across various research fields, including the pharmaceutical industry. This interest has been driven by studies displaying the ability of co-crystal formation to enhance the physical properties of the individual compounds involved.[5]

Polymorphic forms of drugs exhibit varying degrees of stability and can undergo spontaneous conversions from metastable to stable forms under the influence of factors like temperature, pressure and processing conditions. Having a comprehensive understanding of these transformations is crucial in drug formulation. Consequently, the development of dosage forms can be optimized by focusing on metastable forms that offer high solubility and stability. The investigation of polymorphic changes in drugs entails the use of several techniques, including Differential Scanning Calorimetry (DSC), Optical microscopy, Hot Stage Microscopy (HSM), X-ray Powder Diffraction (XRPD), Fourier Transform Infrared spectroscopy (FT-IR) and Thermogravimetric Analysis (TGA), among others.[6]

In the process of selecting a co-crystallization method, numerous factors need to be taken into account. These factors encompass the lability, solubility, stability and susceptibility of both the Active Pharmaceutical Ingredient (API) and the co-former to form polymorphs, solvates, or amorphous states. It is equally important to consider the scalability of the chosen method, particularly in relation to industrial applications.[6]

MATERIALS AND METHODS

Materials

Piroxicam was a gift sample from the Shri Bhavani Pharmaceuticals Hubballi (Karnataka, India). Benzoic acid, PABA and citric acid were purchased from Molychem Mumbai (India). Other solvents were of analytical grade and the solvents used were acetone, acetonitrile, ethanol.

Methods

Solvent evaporation: The co-crystal preparation process commenced by dispensing piroxicam and the selected co-former into a suitable solvent, with careful consideration of an optimal molar ratio. This ratio was determined based on the evaluation of the number of theoretical hydrogen bond donor and acceptor sites in both piroxicam and the co-former. The specific drug-to-co-former ratios used were 1:6, 1:4 and 1:3. Subsequently, the solvent was allowed to evaporate naturally at room temperature. Any excess solvent was eliminated by subjecting the co-crystals to a hot air oven set at 70°C for duration of 30 min. The remaining traces of solvent were removed by storing the co-crystals in a desiccator for a period of 2 weeks.[6-8,17]

Slow cooling methods

Piroxicam crystals were prepared using supersaturation by cooling crystallization technique, which involves the use of various organic solvents. This method is widely employed in crystal manufacturing due to its simplicity, convenience and effectiveness. It is a time-efficient process that yields a high quantity of crystals with excellent variety and cost-effectiveness. To begin the process, a measured quantity of piroxicam was dissolved in solvents such as acetone, ethanol and acetonitrile, in the ratio required by each specific co-former. The dissolution took place at a temperature of 60°C using a hot plate. The solution was then cooled to 37°C and allowed to crystallize for a period of 24 hr. Afterwards, the solution was further cooled to room temperature and left for an additional 24 hr to complete the crystallization process. The resulting crystals were collected, surface-dried using filter paper and stored in a desiccator to maintain their quality.[6,9,10]

Absorption maxima

Absorption maxima was determined using stock solution II (100 µg/mL) of Piroxicam. It was calculated using a 6.8 pH buffer as reagent blank and was subjected to scanning between the wavelength range of 200-400 nm. After scanning the absorption maxima was found to be 353 nm.

Selection of Co-former

The selection of co-formers is typically based on either Hansen's solubility parameter or ΔpKa. These criteria are used to determine the compatibility and potential for co-crystal formation between the drug and the co-former.

Based on Hansen Solubility Parameter

Hansen solubility parameter can be calculated using various sub-methods, including Fedors, Hoy's and Van Krevelen methods. For the specific case of Piroxicam, these methods can be employed to calculate the Hansen solubility parameter.[11-13]

Following a similar approach, Hansen Solubility Parameter (HSP) values were calculated for several selected co-formers based on the literature and their availability in the laboratory. The reported findings suggest that co-crystal formation is likely to occur if the value of Δ δ is less than 5 MP (as proposed by Krevlens) and the value of Δ δ is less than 7MP (as suggested by Greenhalgh).[12]

The discrepancies in solubility parameter values between piroxicam and the 21 different co-formers were computed. The

chosen co-formers were benzoic acid, citric acid and PABA. These co-formers were employed in the production of co-crystals. Moreover, these co-formers underwent additional verification based on other criteria for the selection of co-formers.

Based on ΔpKa value

The ΔpKa value (ΔpKa=pKadrug-pKaco-former) is commonly used as an indicator to predict the likelihood of co-crystal or salt formation. When the ΔpKa value is greater than 3, it is generally indicative of salt formation. On the other hand, if the ΔpKa value is less than 0, there is a possibility of crystal formation. If the ΔpKa value falls within the range of 0 to 3, it suggests the potential for salt or co-crystal formation, or even the formation of a complex involving partial proton transfer.[14]

The pKa values were gathered from the available literature and subsequently, the ΔpKa values were calculated and compiled in Table 1. While all the ΔpKa values fall within the co-crystal category, they are not considered definitive indicators on their own. Therefore, additional investigations were conducted utilizing techniques such as melting point analysis, Fourier-Transform Infrared Spectroscopy (FTIR), X-Ray Diffraction (XRD) and Scanning Electron Microscopy (SEM) to further evaluate the potential co- crystal formation.

Preparation of co-crystals

From various methods that were used in the preparation of co-crystals were, solvent evaporation method and slow cooling method were selected for the preparation of co-crystals. The ratio that was employed in the preparation of co-crystals was benzoic acid (1:6), citric acid (1:4) and PABA (1:3).

Characterization of Piroxicam co-crystals

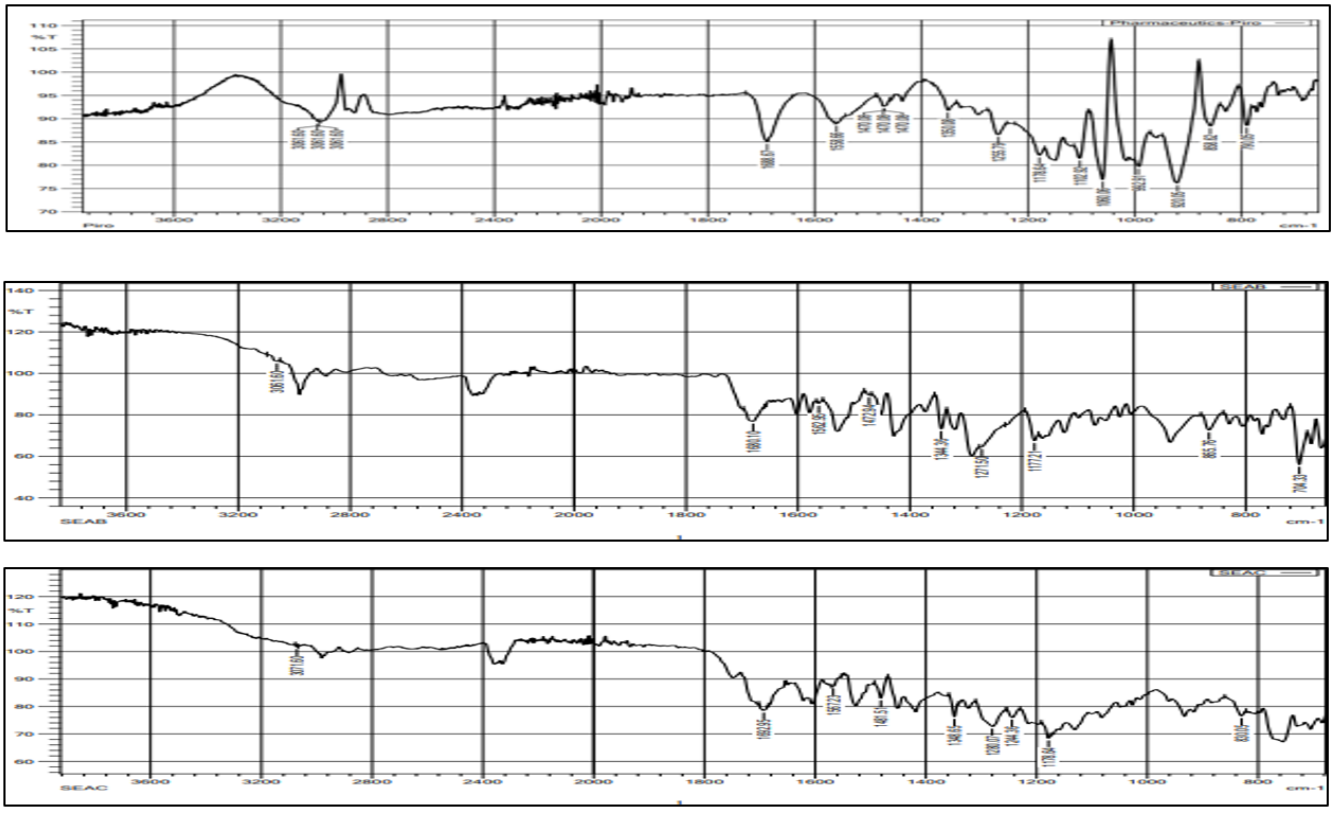
After an extensive review of the literature, methods were developed to characterize the prepared co-crystals of piroxicam. Several parameters and techniques were employed for the characterization, including solubility analysis, drug content determination, dissolution studies, Fourier-Transform Infrared spectroscopy (FTIR), X-ray Diffraction (XRD) and Scanning Electron Microscopy (SEM). The following section outlines the detailed procedures that were followed for each characterization study.

Melting point

The melting points of piroxicam co-crystals were determined using the open capillary tubes method. Samples of the co-crystals were filled into the capillaries and then inserted into the melting point apparatus. The melting points of the co-crystals were recorded at different time intervals over a period of three weeks, following the previously explained procedure. The obtained results were carefully documented and reported.[15]

Estimation of drug content in co-crystals

A precise amount of 10 mg of co-crystals was weighed accurately and transferred into a 10 mL volumetric flask. The co-crystals



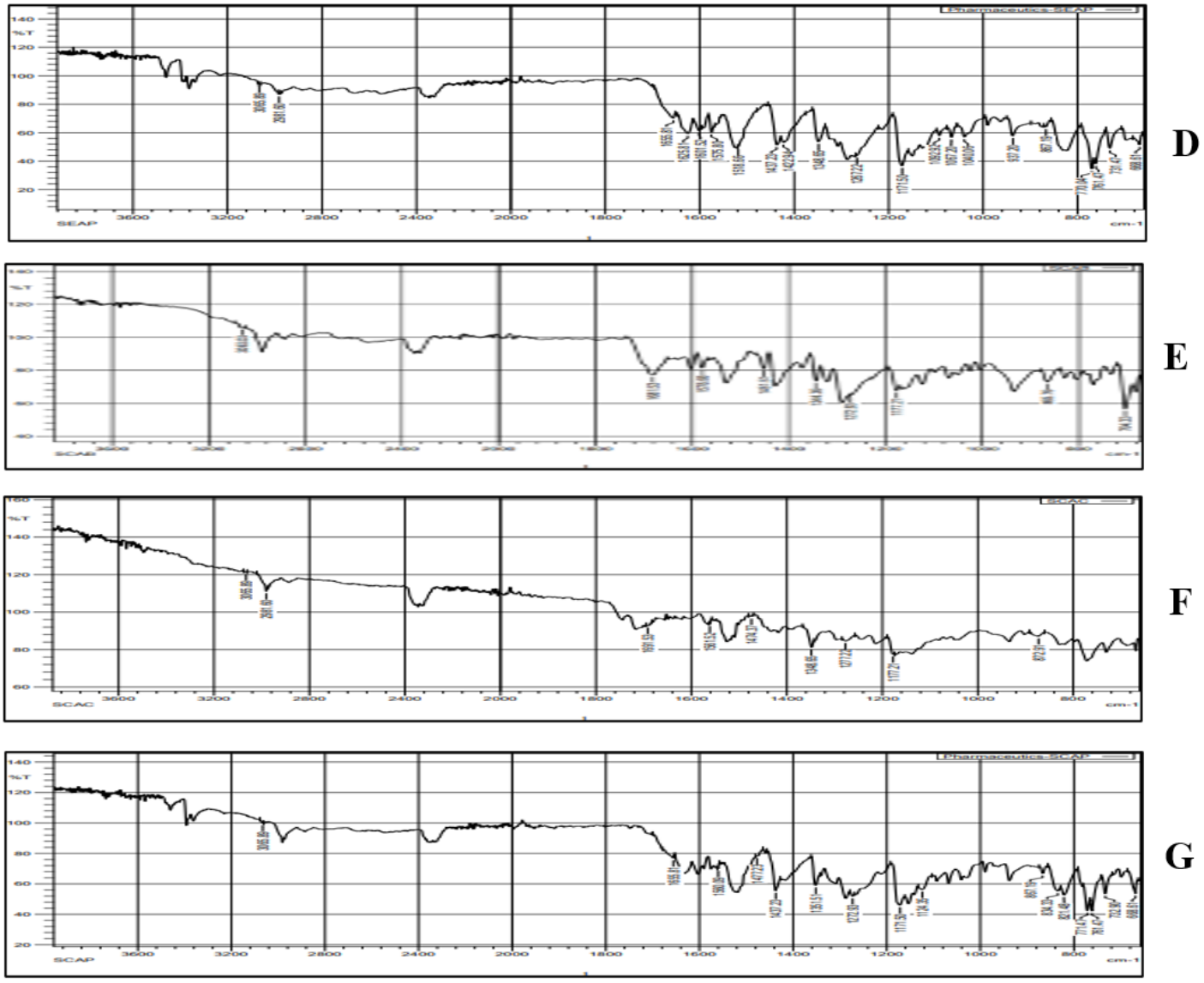


Figure 1: (A) FTIR spectrum of piroxicam, (B) FTIR spectrum of piroxicam-benzoic acid co-crystals, acetone as solvent by solvent evaporation method, (C) FTIR spectrum of piroxicam-citric acid co-crystals, acetone as solvent by solvent evaporation method, (D) FTIR spectrum of piroxicam-PABA co-crystals, acetone as solvent by solvent evaporation method, (E) FTIR spectrum of piroxicam-benzoic acid co-crystals, acetone as solvent by slow cooling method, (F) FTIR spectrum of piroxicam-citric acid co-crystals, acetone as solvent by slow cooling method, (G) FTIR spectrum of piroxicam-PABA co-crystals, acetone as solvent by slow cooling.

were dissolved by adding a small quantity of ethanol and then the volume was adjusted to 10 mL. From this prepared solution, 1 mL was withdrawn and diluted to 10 mL using a 6.8 pH buffer solution. The resulting solution was then used to measure the absorbance and the value was recorded. The percentage of drug content was calculated based on these measurements and documented.[16]

Aqueous solubility studies

The solubility of piroxicam was investigated in distilled water. For this study, 10 mL of distilled water was added to a 25 mL volumetric flask. Excess quantities of the prepared co-crystal and the piroxicam Active Pharmaceutical Ingredient (API) were separately added to the flasks. To achieve solubility equilibrium, the flasks were placed onto a rotary shaker apparatus and operated at room temperature (25ºC) and a speed of 75 rpm for approximately 24 hr. Once equilibrium was reached, samples were withdrawn as aliquots, filtered using Whatman filter paper and further diluted using a 6.8 pH buffer solution. The resulting samples were then analyzed at a wavelength of 353 nm.[17,18]

In vitro Dissolution studies

Dissolution studies were conducted using the USP dissolution test apparatus II with the aid of paddles and a 6.8 pH buffer solution. Both the API and the prepared co-crystals were weighed, approximately 25 mg each and filled into empty hard gelatin capsules. The dissolution process took place in 900 mL of 6.8 pH buffer solutions, maintaining a temperature of 37±0.5ºC

Table 1: pKa and ΔpKa values of co former.

Sl. No.	Co-formers	pKa	ΔpKa	Inference
1	Citric Acid	14.4	-9.1	Co-crystals
2	PABA	4.98	0.32	Co-crystals
3	Benzoic Acid	4.20	1.1	Co-crystals

and a stirring speed of 50 rpm. Samples were withdrawn at regular time intervals of 10, 20, 30, 40, 50 and 60 min. To prepare the samples for analysis, they were filtered through 0.45 µm filter paper. Further dilutions were performed using a 6.8 pH buffer solution and the samples were analyzed using spectrophotometry at a wavelength of 353 nm. The 6.8 pH buffer solution was used as a blank during the analysis.[17,19]

Infrared spectroscopy

To obtain FTIR spectra of piroxicam co-crystals with different co-formers, the co- crystals were mixed with potassium bromide and pellets were prepared following the procedure. The FTIR spectra of these co-crystals were then acquired. A comparison was made between the obtained spectra and the FTIR spectrum of the commercial sample (API) of piroxicam. The observed spectra were carefully documented and reported.[20,21]

Powder X-ray diffraction studies

The Piroxicam (API) and prepared co-crystals were subjected to X-ray Powder Diffraction (PXRD) analysis using Ni-filtered Cu Kα radiation with a wavelength of 1.542 Å. The samples were scanned over a range of 5 to 100° (2θ) at a scanning speed of 5/min, using an X-ray source operating at 40 kV and 40 mA. The obtained results from the PXRD analysis were documented and reported.[21]

Scanning Electron Microscope (SEM)

Scanning Electron Microscope (SEM) studies were conducted to examine the surface morphology of Piroxicam (API) and its co-crystals. In this process, an electron gun was positioned above the SEM, emitting an electron beam that was directed towards the sample. Electromagnetic coils surrounding the sample's surface caused the beam to scan back and forth in a series, thereby scanning the sample as well. Instead of passing through the specimen, the electron beams directly bounced off its surface. Like a television, the electrons reflected onto the sample, generating high-resolution, sharp and three-dimensional images. SEM requires less specimen preparation compared to other techniques. In this study, piroxicam and the prepared co-crystals were subjected to scanning electron microscopy. The obtained results from the SEM analysis were carefully examined and reported, providing valuable insights into the surface characteristics of the samples, particularly in the context of nanomaterials science and co-crystals.[22]

Table 2: FTIR spectral assignments of piroxicam and piroxicam co-crystals

Vibrational Band Assignment	Piroxicam cm^{-1}	Co-crystals cm^{-1}
Aromatic CH stretching	3061.60	3063.03, 3065.89, 3065.89, 3061.60, 3071.60, 3065.89
C-C stretching	1255.79	1272.93, 1277.22, 1272.93, 1271.50, 1280.07, 1267.22
Amide C=O stretching	1688.67	1681.53, 1691.53, 1655.81, 1680.10, 1692.95, 1655.81
C=C stretching	1558.66	1578.66, 1561.52, 1560.09, 1562.95, 1567.23, 1575.80
Asymmetric C-H bending	1470.08	1451.51, 1474.37, 1477.23, 1472.94,
Symmetric C-H bending	1350.08	1344.36, 1348.65, 1351.51, 1344.36, 1348.65, 1348.65
S =O symmetric stretching	1178.64	177.21, 1177.21, 1171.50, 117721, 1178.64, 1171.50
Aromatic CH bending	858.62	865.76, 872.91, 867.19, 865.76, 830.05, 867.19

RESULTS AND DISCUSSION

Melting point

Upon examination it can be observed that piroxicam exhibits a melting point of 197.6±0.577°C (n=3). This value aligns closely with the literature reference range of 198-200°C. Based on this observation, it can be concluded that the tested sample is authentic. To further confirm its authenticity, additional support can be obtained through FTIR analysis.

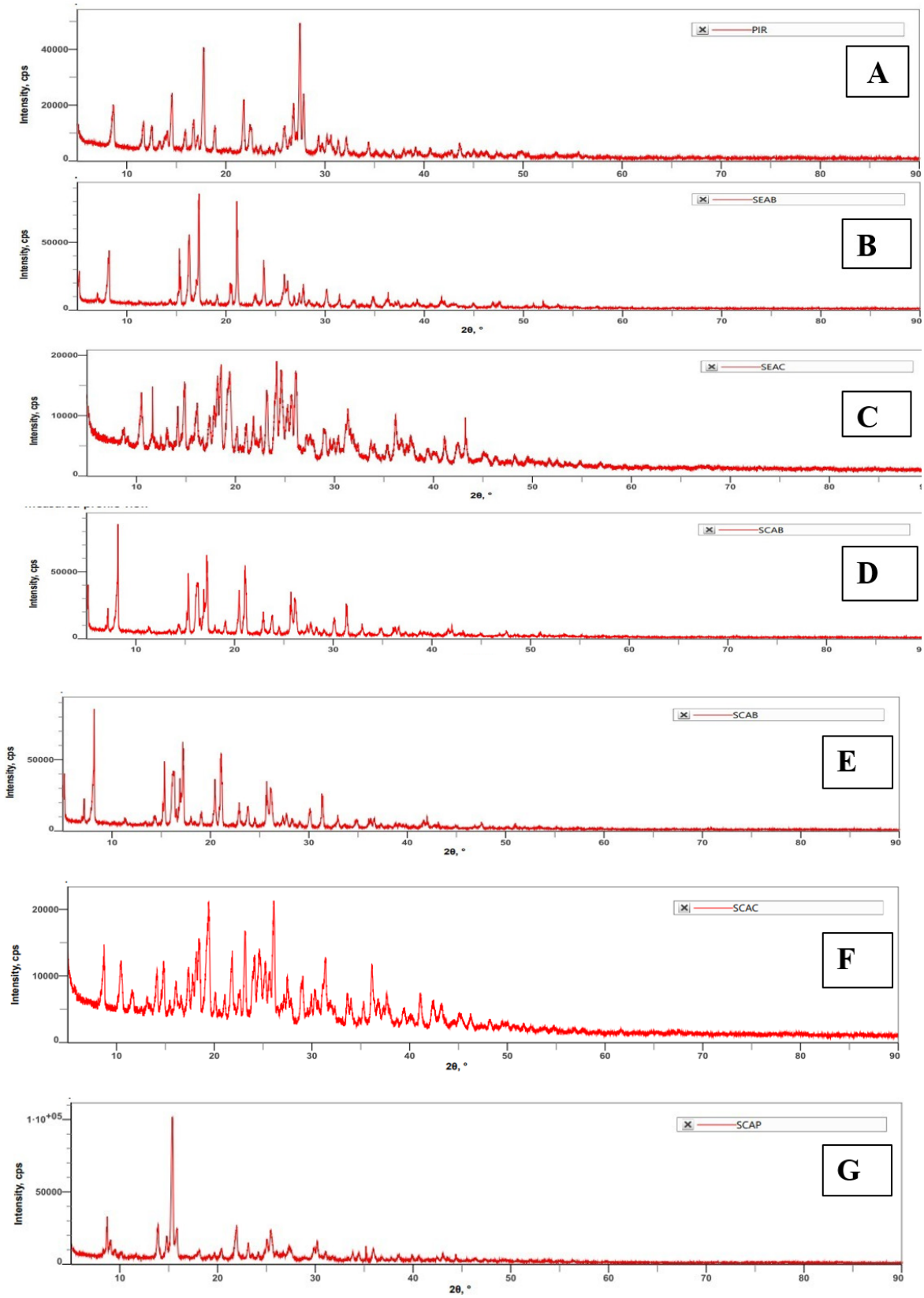


Figure 2: (A) XRD pattern of piroxicam API, (B) XRD of piroxicam-benzoic acid co-crystals, acetone as solvent by solvent evaporation method, (C) XRD of piroxicam-citric acid co-crystals, acetone as solvent by solvent evaporation method, (D) XRD of piroxicam-PABA co-crystals, acetone as solvent by solvent evaporation method, (E) XRD of piroxicam-benzoic acid co-crystals, acetone as solvent by slow cooling method, (F) XRD of piroxicam-citric acid co-crystals, acetone as solvent by slow cooling method, (G) XRD of piroxicam-PABA co-crystals, acetone as solvent by slow cooling method.

Table 3: Solubility studies, Percent dissolution and Percent drug content.

Sl. No.	API/ co-crystals		Aqueous solubility (mg/mL)	Percent dissolution at 60 min	Percent drug content
1	Piroxicam		0.0198	34.8594	
2	Acetone (slow cooling)	Benzoic acid	16.68	99.96	100.3±0.45
		Citric acid	13.1	91.8542	98.3±0.45
		PABA	13.36	95.5355	99.96± 0.2
3	Acetone (solvent evaporation)	Benzoic acid	15. 84	95.8648	99.96±0.2
		Citric acid	11.98	90.7644	96.96±0.8
		PABA	12.14	86.3933	93.3±0.4
4	Acetonitrile (Slow cooling)	Benzoic acid	8.48	91.3327	95.23±0.89
		Citric acid	6.78	81.7742	93.86±0.5
		PABA	5.1	86.743	95.23±0.45
5	Acetonitrile (solvent evaporation)	Benzoic acid	7.9	86.0037	94.3±0.95
		Citric acid	6.18	80.8765	93.2±0.2
		PABA	4.68	85.8840	94.9±1.21
6	Ethanol (Slow cooling)	Benzoic acid	4.06	75.8342	96.9±0.8
		Citric acid	3.58	59.4463	73.96±0.8
		PABA	3.18	61.8308	84.3±0.95
7	Ethanol (solvent evaporation)	Benzoic acid	3.89	73.0473	96.60±0.585
		Citric acid	3.33	56.5746	72.16±2.528
		PABA	2.91	60.102	82.21±0.984

FTIR spectrum

As described in the methodology section, the Fourier Transform Infrared Spectroscopy study was carried out for active pharmaceutical ingredients. IR spectrum of piroxicam is shown in Figure 1. The peaks listed in Table 2 can be regarded as characteristic peaks of piroxicam. The wave numbers corresponding to different functional groups in the literature match the values obtained from the sample analysis. This alignment strongly suggests that the tested sample is indeed piroxicam. Thus, this test provides further confirmation of the sample's authenticity.

Solid samples of piroxicam co-crystals were prepared in KBr pellets. The FTIR spectra for the co-crystals of piroxicam from various co-formers and solvents are shown in Figure 1. The FTIR spectrum of piroxicam is compared with the various co-crystals formed. From the structure of piroxicam, the characteristic bands were identified and given in Table 2. The data for the co-crystals is compared with the data obtained for the API, which is also shown in the same Table.

Fourier-Transform Infrared (FTIR) spectroscopy is a useful tool to investigate the interactions between drugs and co-formers. The characteristic peak of piroxicam appeared at 3061.60 cm^{-1} (aromatic CH stretching), 1255.79 cm^{-1} (C-C stretching), 1688.67 cm^{-1} (amide C=O stretching), 1558.66 cm^{-1} (C=C stretching), 1470.08 cm^{-1} (asymmetric C-H bending), 1350.08 cm^{-1} (symmetric C-H bending), 1178.64 cm^{-1} (S=O symmetric stretching), 858.62 cm^{-1} (aromatic CH bending). The FTIR spectra with various co-crystals show the various vibrational bands which are shown in Table 2. There are not any new peaks in the spectra of the co-crystals suggesting that there is no interaction between the drug and co-former. The FTIR spectra of the prepared co-crystals exhibit noticeable shifts in the functional groups compared to pure piroxicam. This shift suggests the formation of new bonds during the co-crystal formation process. Hence, FTIR spectroscopy serves as a reliable tool to confirm the formation of co-crystals.

Solubility behavior of piroxicam co-crystals

Solubility data of co-crystals of piroxicam in purified water have been obtained after shaking for 24 hr at 25°C and are shown in Table 3. Perusal to this order indicates that all the co-crystals have shown higher aqueous solubility than the commercial sample which was found to be 0.0198 mg/mL for piroxicam. Thus, the solubility of piroxicam is increased with the formation of co-crystals.

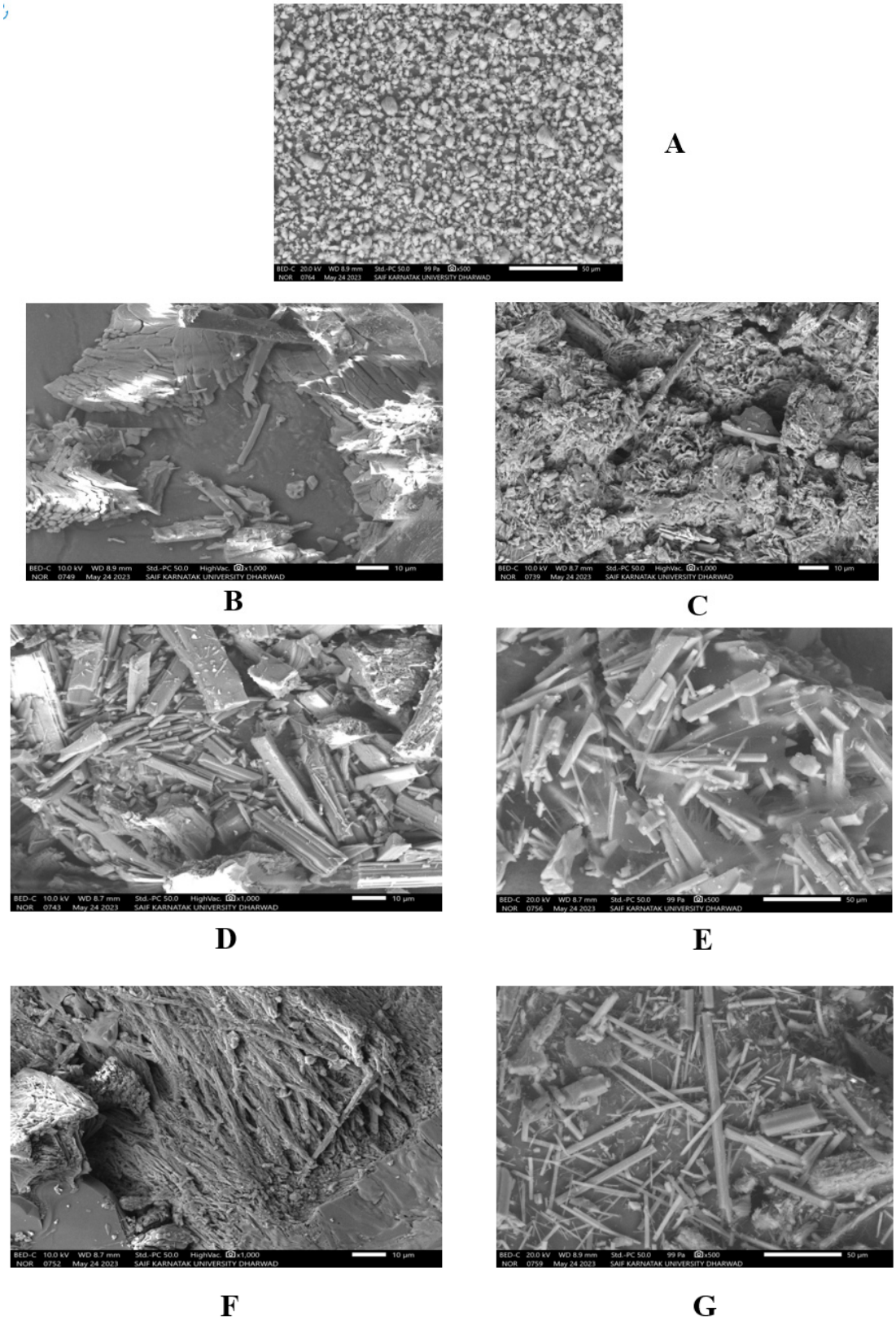


Figure 3: (A) SEM of piroxicam API, (B) SEM of piroxicam-benzoic acid co- crystals, acetone as solvent by solvent evaporation method, (C) SEM of piroxicam-citric acid co-crystals, acetone as solvent by solvent evaporation method, (D) SEM of piroxicam-PABA co-crystals, acetone as solvent by solvent evaporation method, (E) SEM of piroxicam-benzoic acid co-crystals, acetone as solvent by slow cooling method, (F) SEM of piroxicam-citric acid co-crystals, acetone as solvent by slow cooling method, (G) SEM of piroxicam-PABA co-crystals, acetone as solvent by slow cooling method.

Table 4: Powder X-ray diffraction.

Sl. No.	Drug and conformer	Peak 2θ values	Intensity	Inference
1	Piroxicam	8.6	3484.18	
		17.75	5752.38	
		21.80	3000.69	
2	Benzoic acid-acetone co-crystals by slow cooling.	8.1	9295.2	Co-crystals
		16.24	8868.17	
		21.04	5870.02	
3	Citric acid-acetone co-crystals by slow cooling.	8.72	2149.03	Co-crystals
		17.35	1213.17	
		18.46	2329.01	
4	PABA-acetone co-crystals by slow cooling.	8.71	2939.43	Co-crystals
		15.38	16716.76	
		21.93	4198.58	
5	Benzoic acid-acetone co-crystals by solvent evaporation.	8.18	8552.6	Co-crystals
		16.26	7391.54	
		21.08	7848.89	
6	Citric-acid-acetone co-crystals by solvent evaporation.	10.49	2012.74	Co-crystals
		19.34	3933.97	
		24.62	2862. 8	
7	PABA-acetone co-crystals by solvent evaporation.	9.13	2937.79	Co-crystals
		18.42	8288.34	
		21.1	59.66.52	

Estimation of drug content in co-crystals

The percentage drug contents of prepared co-crystals were found to be in the range of 72.16% to 100.3% (Table 3).

Dissolution behavior of piroxicam co-crystals

The different molecular packing associated with different co-crystals of a drug substance can give rise to different physical properties that cause different behavior, such as dissolution rate and consequently have a significant effect on piroxicam's bioavailability and its effective clinical performance. 6.8 pH buffers was used as a dissolution medium for dissolution studies. Dissolution study was performed by using dissolution apparatus type II that is paddle type. The data obtained from dissolution studies and processing of the data are shown in Table 3. The order of piroxicam co-crystals based on the % drug dissolution at 60 min, the co-crystals with acetone as solvent showed higher dissolution rate, followed by co-crystals prepared by acetonitrile as solvent, followed by ethanol. This result was supported by the solubility of these co-crystals in the 6.8 pH buffer. Therefore, based on the dissolution values, piroxicam with acetone as solvent was selected for further studies. Dissolution was studied with a pure drug and compared it with prepared co-crystals. Pure drug percentage release was found to be 34.85 % which was less than prepared co-crystals. Thus, the prepared co-crystals showed a better dissolution profile compared to pure drug.

Powder X-ray Diffraction

The powder state crystalline material will have a different X-ray peak pattern of varying intensities at a particular position. The XRD of piroxicam API is compared with the XRD of piroxicam-co-crystals. The characteristic changes are given in Table 4. The XRD spectrum of piroxicam is given in Figure 3(A) and that of piroxicam- co-crystals are given in the Figure 2 (B), (C), (D), (E), (F), (G).

Different X-ray peaks are present in the API and with the help of XRD we can come to know that the material we were working on is amorphous or crystalline in nature. The θ values of the standard drug are used to compare it with the samples to be examined. The XRD scanning of pure Piroxicam indicated intense peaks of crystallinity. A perusal of Table 4 and Figure 2 indicates that the crystallogram patterns of co-crystals show variation in formed peak intensity when compared to that of the pure piroxicam. Along with the peaks of piroxicam spectra showed some new peaks as well. Hence it was concluded that there were some physical and/or chemical bonding changes incurred between

pure piroxicam and co-formers which resulted in the formation of co-crystals. This was supported by FTIR spectral data. Heights in the diffraction patterns of the co- crystal's crystallinity was determined with the pure piroxicam.

Scanning Electron Microscopy

The topography of the piroxicam co-crystals was smooth. Perusal to Figure 3 indicates that the topography of the co-crystals is not smooth due to the presence of co- former on their surfaces. In all the figures smaller particles of co-formers can be seen on the bigger particles of piroxicam. Probably because of this property, piroxicam-co-former co-crystals exhibited different physical properties.

Comparative Evaluation

Co-crystallization is a process of increasing the solubility of the API which is from BCS class II which possesses low solubility and high permeability, so to increase the solubility of the API, co-formers are used. Two methods which were employed in this project are solvent evaporation method and slow cooling method.

Comparison of both the methods were observed visually

Solvent required in the process of slow cooling method is comparatively less as compared to solvent evaporation to dissolve the API and the co-formers.

Since heat is used in the process of slow cooling method the process of formation of co-crystals is comparatively faster as compared to solvent evaporation method.

The yield produced in slow cooling was more compared to the solvent evaporation method.

As per the results obtained in this study, it shows that in slow cooling method the dissolution and solubility studies are slightly better compared to solvent evaporation method.

CONCLUSION

The study demonstrated the ability of converting the pure drug form into co-crystals improved the dissolution rate and the solubility of the drug. The formation of co-crystals by co-crystallization methods with co-formers and solvents was confirmed based on melting point, PXRD data, FTIR and SEM.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This study explores the co-crystallization of piroxicam, a Biopharmaceutical Classification System (BCS) Class II drug with low solubility and high permeability, to enhance its solubility and dissolution rate. Solvent evaporation and slow cooling were used to prepare piroxicam co-crystals using co-formers such as benzoic acid, citric acid and Para-Aminobenzoic Acid (PABA) in varying molar ratios. Solvent evaporation involved allowing the solvent to evaporate naturally at room temperature, followed by drying in a hot air oven and desiccation. In contrast, the slow cooling method employed supersaturation by cooling crystallization, offering higher yields with less solvent usage and faster co-crystal formation.

Characterization of the prepared co-crystals was conducted using melting point determination, Fourier-Transform Infrared Spectroscopy (FTIR), Powder X-ray Diffraction (PXRD) and Scanning Electron Microscopy (SEM). The melting point analysis confirmed the authenticity of piroxicam, while FTIR spectra revealed shifts in functional group bands, indicating new bonds and co-crystal formation. PXRD demonstrated variations in crystallinity between the pure drug and co-crystals, further confirming co-crystal formation. SEM analysis highlighted surface morphology changes, showing smaller co-former particles on larger piroxicam particles, which influenced the physical properties of the co-crystals.

The study also evaluated the solubility, drug content and dissolution profiles of the co-crystals. The solubility of piroxicam co-crystals in purified water significantly increased compared to the pure drug. Drug content ranged from 72.16% to 100.3%, while dissolution studies revealed a notable enhancement in the dissolution rate of co-crystals compared to the pure drug, with the acetone-prepared co-crystals exhibiting the highest dissolution rate.

A comparative evaluation of the two methods showed that the slow cooling method required less solvent, yielded more co-crystals and demonstrated slightly better dissolution and solubility performance compared to solvent evaporation. Overall, this study concluded that converting piroxicam into co-crystals using these methods effectively enhanced its solubility and dissolution rate, with the structural and physical changes confirmed through various analytical techniques.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **FTIR:** Fourier Transform Infrared Spectroscopy; **PXRD:** Powder X-ray Diffraction**; SEM:** Scanning Electron Microscopy**; PABA:** Para-Aminobenzoic Acid**; DSC:** Differential Scanning Calorimetry**; HSM:** Hot Stage Microscopy**; XRPD:** X-ray Powder Diffraction**; TGA:** Thermogravimetric Analysis**; HSP:** Hansen Solubility Parameter**; ΔpKa:** Difference in pKa values between the drug and co-former**;**

Nm: Nanometer**; mL:** Milliliter; **°C:** Degree Celsius**; Rpm:** Revolutions per minute**; USP:** United States Pharmacopeia**; Min:** Minute**; Δ:** Solubility parameter**; 2θ:** Scattering angle in X-ray diffraction**; µM:** Micrometer**.**

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