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ENHANCEMENT OF IBUPROFEN'S PHYSICOCHEMICAL PROPERTIES BY DEVELOPING ITS COCRYSTALS

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ABSTRACT
Pharmaceutical cocrystals, which are formed when an active pharmaceutical ingredient (API) and a pharmaceutically acceptable coformer interact noncovalently, have become a popular method for improving the physicochemical characteristics of drug moiety without alter pharmacological activity. For the selection of the drug and coformer , the ΔpKa technique and CSD software were employed. The Cocrystals were prepared using the solvent evaporation method and their characterization was performed using DSC, XRD and FTIR techniques. In vivo anti-inflammatory activity was evaluated using 24 Wistar rats. In the present study, in vitro dissolution studies revealed increased solubility profile for the cocrystals when compared with the pure drug and a marketed formulation. Furthermore, the cocrystals demonstrated enhanced in vivo anti-inflammatory potentials compared to reference drug. The results of this research revealed that the physicochemical properties of BCS class II APIs can be significantly improved without altering or affecting their therapeutic efficacy.

KEYWORDS: Ibuprofen, Cinnamic acid, API, Cocrystallization, XRD analysis, Dissolution

INTRODUCTION
Many drugs that come from drug development pipelines are known to exhibit issues such as poor water solubility, and low stability. A number of approaches have been researched to enhance the pharmaceutical properties of drugs.[1] The most popular approach is to prepare cocrystals.[2] Pharmaceutical cocrystallization is currently getting widespread attention due to its potential to modify the physicochemical properties of APIs without affecting their basic pharmacological properties.[3] The pharmaceutical sector progressively concerned with improving the physicochemical characteristics and biological efficacy of active pharmaceutical ingredients (APIs) such as ibuprofen from BCS class II, it is a widely used nonsteroidal drug (NSAID) with analgesic, antipyretic and anti-inflammatory properties. It is also a non-selective inhibitor of the cyclooxygenase-2 enzyme. Ibuprofen is widely used as a therapeutic drug, but it is also a poorly water-soluble drug that can limit its dissolution rate and, therefore, its bioavailability. Ibuprofen has low aqueous solubility and this is one of the major challenges in the development of the pharmaceutical formulations especially with regard to rapid onset of action and consistent therapeutic efficacy.[4] A cocrystal is a form of crystal engineering in which two or more molecules within the same crystal lattice are linked by noncovalent bonding. Several approaches have been successfully used to create ibuprofen cocrystals.[5,6] The most popular technique for cocrystallization with different coformers is solvent evaporation.[7] While other techniques are grinding, crystallization, and melting.[8] Cinnamic acid, specifically, has emerged as frequently used conformer for ibuprofen cocrystal formation. A basic principle of cocrystal design is the presence of supramolecular synthons. Supramolecular chemistry plays a major role in cocrystallization technique as it manipulates the self-assembly of crystalline materials. Cocrystal formation influenced by intermolecular interactions such as hydrogen bonding, van der waals, and π-π stacking interactions. Cinnamic acid has functional groups that are suitable for synthon formation, such as two hydrogen bond acceptors and one hydrogen bond donor, which can help to build strong hydrogen bonded synthons with ibuprofen (IBP).[9-12] Cinnamomum cassia (Chinese cinnamon) , Panax ginseng contain cinnamic acid , a naturally occurring aromatic carboxylic acid.[13] In order to choose the acidic or basic medication and the conformer for co-crystallization over salt or eutectic mixture formation, the pka value-based method[14] provides a line. Furthermore, Δpka value between IBP and cinnamic acid is less than 1 which indicates cocrystal formation rather than salt formation.[15] Various methods, such as CSD software, were used to pick appropriate coformer. In silico frameworks and screening tools are increasingly utilized to streamline this selection process by predicting molecular similarities [31]. Such advanced screening methods help target screening strategies, address operational challenges, and identify unique therapeutic opportunities [32, 33]. The present study is focussed on using cinnamic acid as coformer (from generally recognised as safe GRAS list) to prepare cocrystals. Cinnamic acid and ibuprofen interact synergistically due to their complementary anti-inflammatory potential as both components target COX pathway.[8] Various techniques can be used for conformer selection but in this study ΔpKa value calculation method is selected.

A previous study by Rathi at el. Reported the preparation of curcumin-cinnamic acid cocrystals using solvent evaporation method and cocrystal formation was supported with DSC, FTIR, XRD.[16]
Thus, in this study, we explored the preparation of ibuprofen cocrystals with cinnamic acid by the solvent evaporation technique. The drug and coformer were added to a mortar and pestle with addition of methanol as solvent. FTIR, XRD and DSC techniques were used to characterize the cocrystals. Cocrystals' in vitro drug release was calculated in 0.05M phosphate buffer medium and compared the with marketed formulation as well as the pure drug. In vivo anti-inflammatory activity was also performed on carrageenan induced Wistar rats to analyse the potential of the cocrystals.

MATERIAL AND METHOD

Ibuprofen and cinnamic acid were purchased from Sigma-Aldrich Chemical Limited. Analytical grade ethanol was obtained from Rankem chemicals. Carrageenan was procured from CHD Ltd, New Delhi. Cocrystals were prepared by using solvent evaporation method. The animal study was performed as per IAEC guidelines and approved by Institutional Animal Ethics Committee. 28 Albino Wistar rats weighing about 195 g body weight were selected for study from the animal house of institute. The study was authorised by the Institutional Animal Ethics Committee (IAEC) of the institute under proposal/reference No. 1204/PO/ReBiBt/S/2008/CCSEA/25-16 dated 05/08/24. Rats were divided into 7 groups, with 4 animals in each group. Ibuprofen and cinnamic acid both were co-crystallised with each other with the help of ethanol as solvent. Both powders were used in a 1:2 stoichiometric ratio i.e. 206.29 mg ibuprofen and 296.32 mg of cinnamic acid in weight were used for cocrystals formation by solvent evaporation method. The solution was kept to allow slow evaporation over 2 days at room temperature. The co-crystallized product was collected and stored in a desiccator[17] (Fig.1).

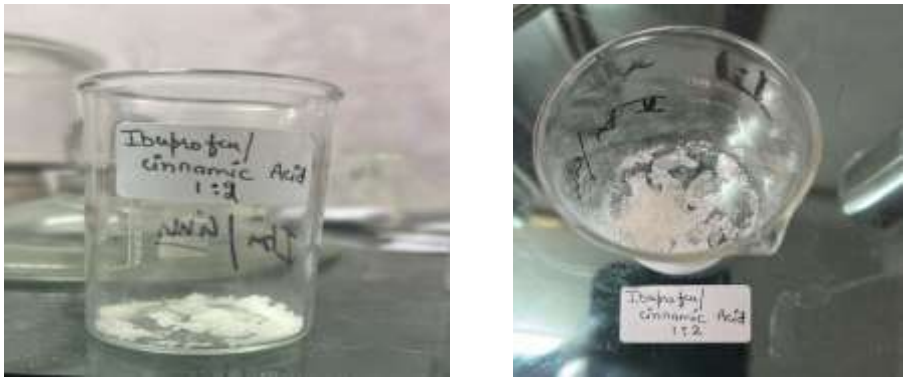

Figure 1: Cocrystals of ibuprofen: cinnamic acid (1:2)

Selection of co-former

Cocrystal formation depends on the choice of an appropriate coformer. Formation of a synthon between two molecules eventually results in co-crystallization. Ibuprofen was chosen for cocrystallization due to its low solubility in water and limited bioavailability. The ΔpKa value method was utilised to predict cocrystal formation.[18] The appropriate range of Δpka value obtained 0.64 i.e.between 0 to 1 for formation of cocrystals. This value was calculated by subtracting ΔpKa value of cinnamic acid (3.76) from the ΔpKa value of ibuprofen (4.4).[19] For the determination of synthon formation ,CSD software was used. By CSD analysis, the COOH group (figure 2) of both ibuprofen and cinnamic acid was found to be most favourable group for synthon formation. Thus, both components formed a homosynthon through hydrogen bonding.[20,21]

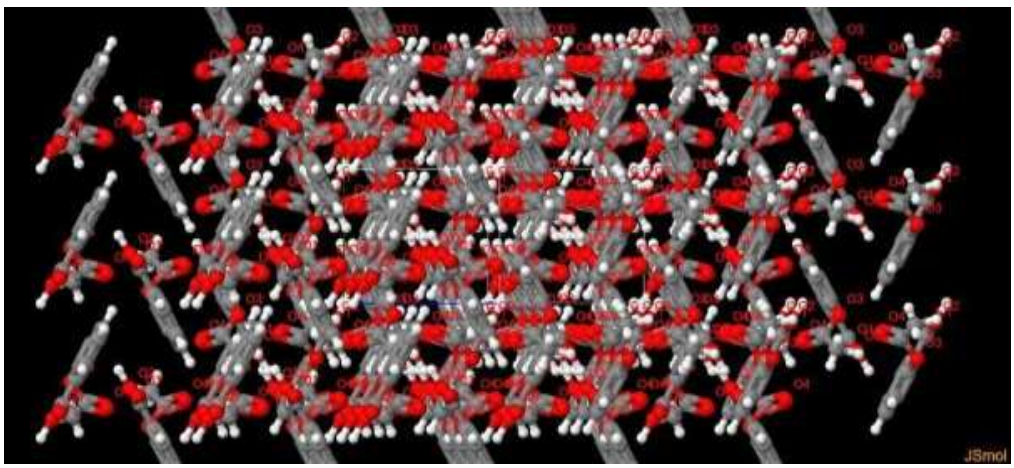

Figure 2: Packing of Ibuprofen

Characterization

Absorption maxima determination: In this work, absorption maxima were determined using UV-spectroscopy. To make the stock solution, dissolve 100 mg of pure drug in 1000 ml of 0.05M buffer solution (phosphate buffer) pH 7.2. UV spectrophotometer to scan in 200-400 nm range at concentration of 7µg/ml.[22]

Preparation of calibration curve:
Ibuprofen was dissolved in methanol, resulting in a stock solution with a concentration of 100µg/ml. The stock solution was subsequently diluted to achieve final concentration of 2, 4, 6, 8, and 10 µg/ml. Plotting the calibration curve required determining the absorbance at 222 nm.[23]

DSC Analysis:
For DSC analysis of cocrystals, a DSC Q10 V9.9 Build 303 US apparatus was used. The aluminium pan containing 2mg of samples was heated between 20 ^{0}C and 160 ^{0}C in nitrogen gas atmosphere with a flow rate of 60ml/minute. As reference, empty aluminium pan was used.[8]

FT-IR Analysis:
The FTIR of ibuprofen, cinnamic acid, their physical mixture, and cocrystals was analyzed using the KBr disc technique on instrument FT-IR Alpha Bruker 12060280, Germany. The spectrum was recorded over the range of 4000- 400 cm^{-1}.

XRD study:
The XRD model "XPERT PRO" instrument was used to analyze XRD study of pure ibuprofen, cinnamic acid, their physical mixture and cocrystals using continuous scanning at a 2θ angle. We compared the diffraction profiles of the new solid phase with standard pattern of pure drug and physical mixture to confirm the formation of new solid phase.[24]

Dissolution study:
Dissolution study of pure Ibuprofen, its cocrystals and marketed formulations were performed using type II USP paddle apparatus (Electro Lab) in 0.05M, 7.2 pH phosphate buffer as dissolution medium. For 90 minutes, paddle speed and temperature remain 50rpm and 30+0.5 ^{0}C respectively. Before dissolution test cocrystals filled in empty shells of capsules. 50 mg of pure drug was used for study. Samples were withdrawn every 15 minutes for 90 minutes, and an equal amount of dissolution medium was added after each sample withdrawal. Samples were diluted appropriately and examined spectrophotometrically at 222 nm to calculate amount of drug.[25]

Anti-inflammatory activity (in vivo)
In vivo anti-inflammatory activities were conducted at the institutional animal house after approval from thr Institutional Animal Ethics Committee (IAEC). As previously reported, the carrageenan-induced rat paw edema model was used to analyze and evaluate anti-inflammatory effect of pure Ibuprofen and cocrystals. Wistar rats were used for experiment after divided into four groups, each group with six animals in each group (Table 1). Before the start of experiment all animals were kept on fasting for 24 hours (overnight) and kept under airconditioned housing facilities. Pure Ibuprofen was used as standard at dose 50 mg/Kg. Group I was injected with carrageenan (0.05ml of 1% solution), group II injected with polymer cinnamic acid at 50 mg/kg, group III received 50 mg/kg of pure drug (ibuprofen) and group IV injected 50 mg/kg dose of cocrystals to evaluate antiinflammatory activity.[26] Because of enhanced dissolution profile of drug after cocrystallization, half dose (50mg/kg) of cocrystals was used. The rats were given a subcutaneous injection of 0.05 ml of 1% carrageenan solution in plantar side of left hind paw after 30 minutes of treatment. Paw was submerged in mercury. Paw volume was measured by using Plethysmograph just after carrageenan administration and upto five hours at every one hour interval for inflammation progression. % inhibition was calculated by using formula given,
% Inhibition= [paw volume of control (mean)- paw volume of treated (mean)/paw volume of control (mean) × 100]

Table 1: Anti-inflammatory study (in vivo)

Sr. no.	Groups	Treatment	Dose	Route of administration
1	I (control)	Carageenan	0.05 ml of 1% solution	Injected in plantar side of left hind paw
2	II	Cinnamic Acid	50mg/kg	Oral route
3	III	Ibuprofen Pure	50mg/kg	Oral route
4	IV	Ibuprofen:Cinnamic Acid cocrystals	50mg/kg	Oral route

*no. of rats= 24 (six in each group)

Stability study
According to USP and ICH guidelines, accelerated stability studies were performed. For 6 months, the samples were stored in tiny glass beakers wrapped with aluminium foil in a stability chamber with humidity of 75% RH ± 5% and a temperature of 400±2^{0}C. Samples were taken out at intervals of 0, 3, and 6 months, and their drug content was assessed by the HPLC technique. The drug content was assessed using Area Under Curve (AUC).[26]

RESULT & DISCUSSION
Absorption maxima determination
A UV-spectrophotometer scanned a solution at a concentration of 7.5 µg/ml between 200-400 nm. At 222 nm, maximum absorption was observed. Figure 3 shows the absorption maxima of ibuprofen.

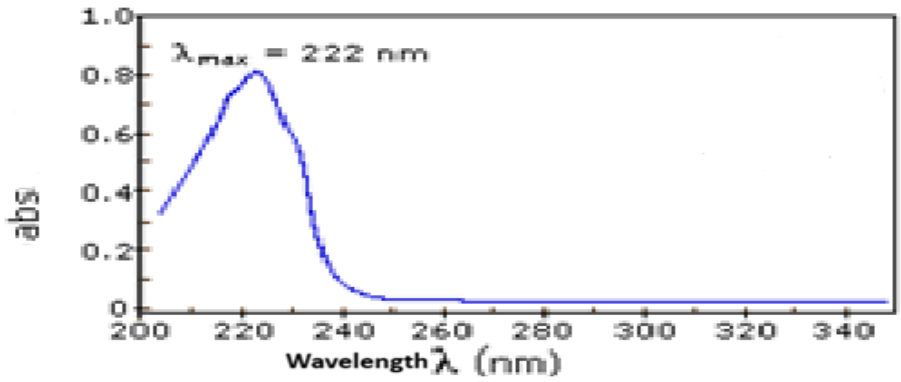

Figure 3: Absorption maxima of ibuprofen

Calibration curve preparation

Various concentrations of ibuprofen were measured in methanol. Absorbance was measured at λmax 222 nm. A graph was plotted between absorbance and concentration. The R-value was found to be 0.997, determined using the calibration curve and shown in table 2 and figure 4.

Table 2: Concentration vs absorbance data

Concentration (µg/ml)	Absorbance
2µg/mL	0.139± 0.14
4µg/mL	0.270±0.22
6µg/mL	0.419±0.17
8µg/mL	0.541±0.38
10µg/mL	0.714±0.21

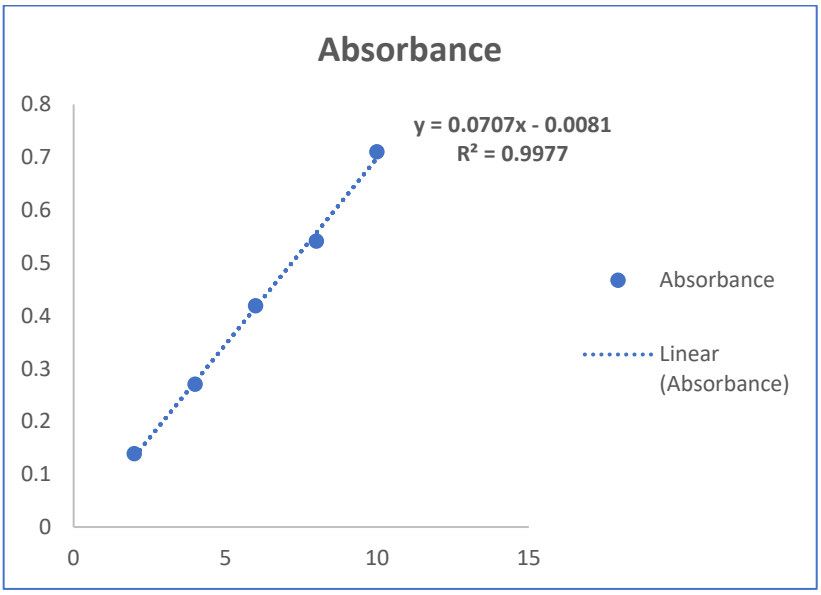

Figure 4: Calibration curve of ibuprofen

DSC Analysis:

DSC is the most informative technique for revealing information about the cocrystallization. Heating at a rate of 5^0C/min resulted in a product formed through solvent evaporation. A DSC Q10 V9.9 Build 303, a USA instrument was used for DSC analysis. A sharp endothermic peak in DSC thermogram of ibuprofen is observed at its melting point of 81.04^0C(Figure 5).Similarly, a sharp endothermic peak observed at 137.28^0C in thermogram of cinnamic acid (figure 6). The absence of any additional peaks in both thermograms demonstrated the purity of the obtained samples. Instead of comparable peaks for both ibuprofen and cinnamic acid, the thermogram of the physical mixture displayed a peak at 71.77^0C and 108.17^0C that shows the physicochemical interaction of ibuprofen and cinnamic acid (figure 7).Finally the DSC thermogram of cocrystals shows a clear endothermic peak at 70.41^0C; no other peaks were observed, indicating that the drug was completely co-crystallized (figure 8).

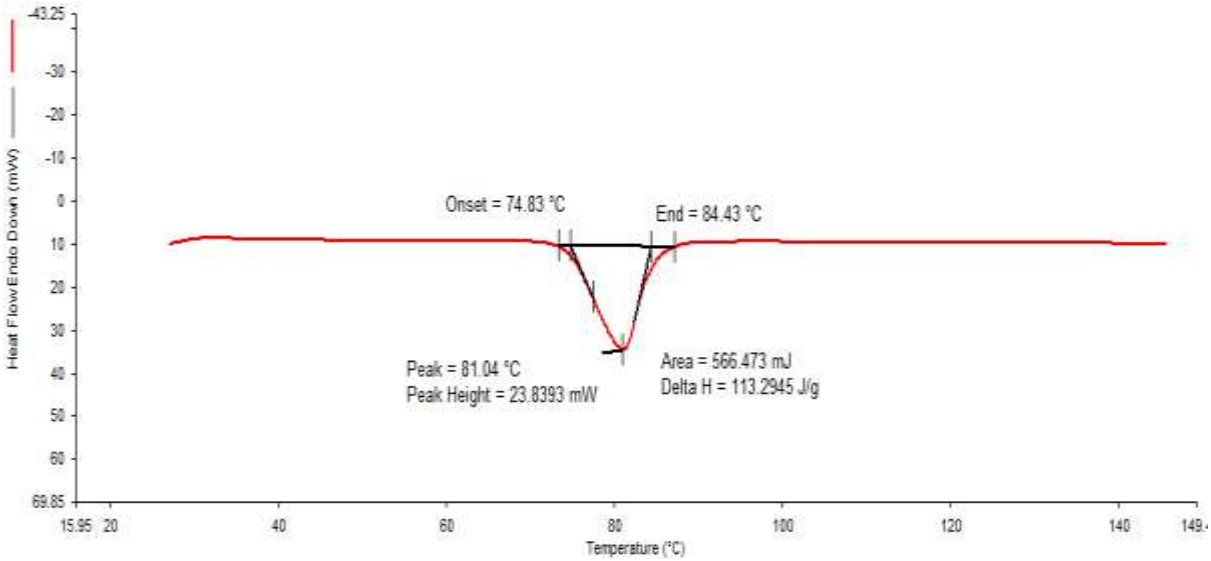

Figure 5: DSC thermogram of ibuprofen

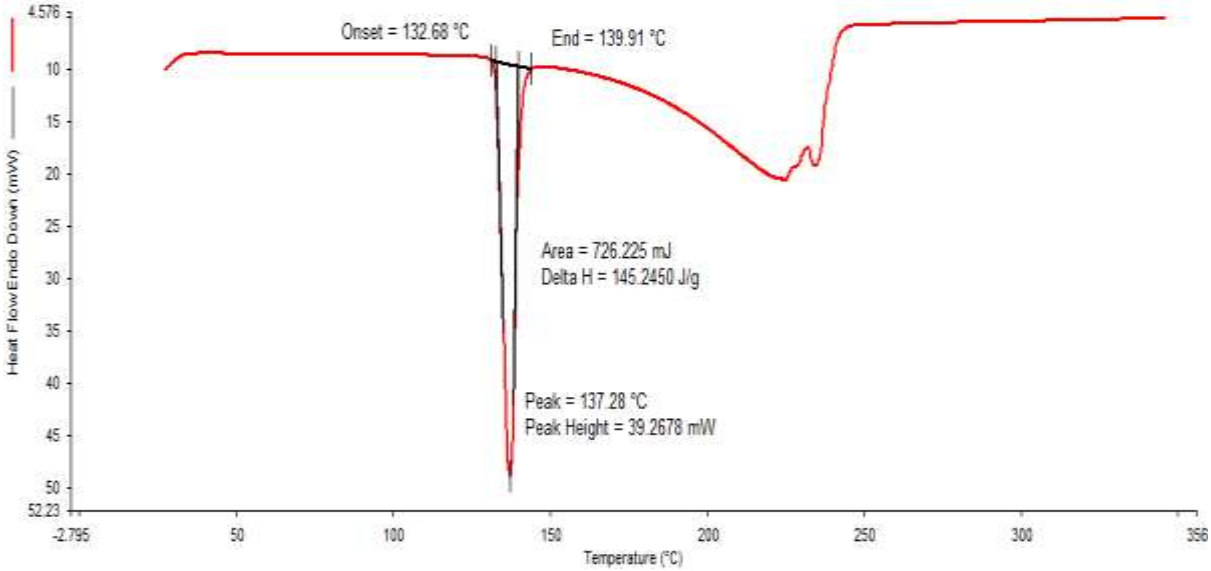

Figure 6: DSC thermogram of cinnamic acid

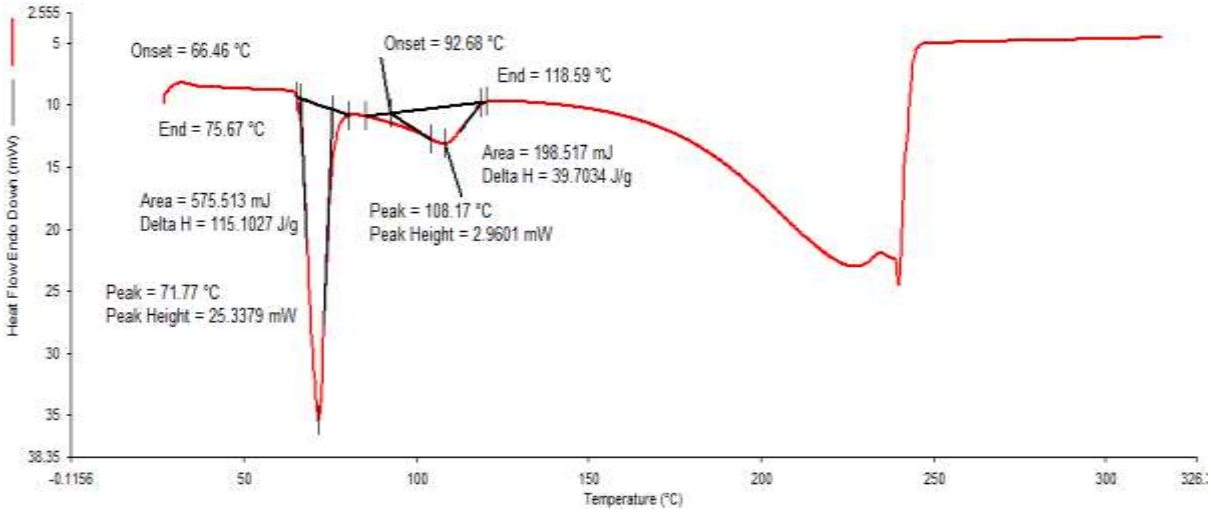

Figure 7: DSC thermogram of physical mixture

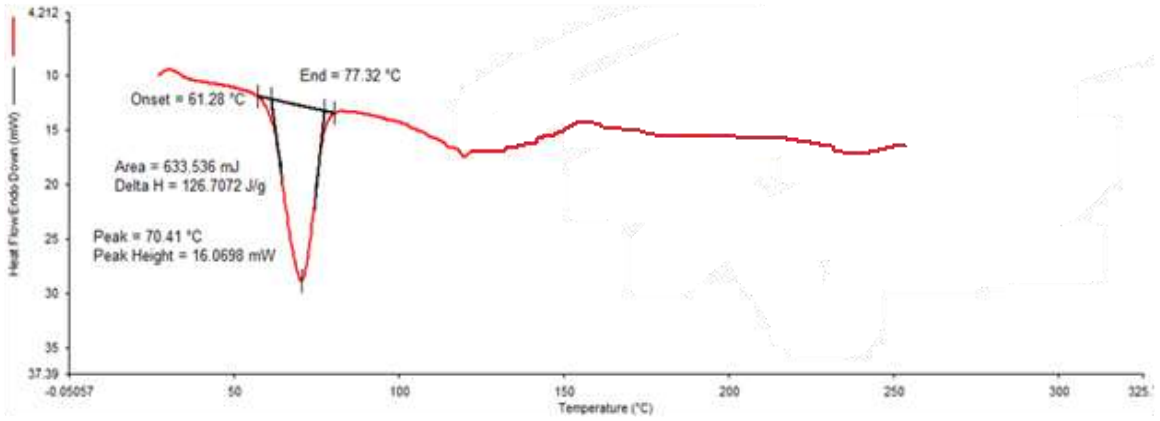

Figure 8: DSC thermogram of cocrystals

FTIR study

Figure 9-12 shows characteristics peaks of ibuprofen, cinnamic acid, physical mixture and cocrystals respectively. The characteristic peaks in the FTIR spectra of ibuprofen obtained at 1718cm-1, 3643cm^{-1}, 2957cm^{-1} and 2872.13cm^{-1} which can be attributed to C=O and O-H stretching of the carboxylic group, C-H stretching (aromatic), C-H stretching (aliphatic). These spectra confirmed the presence of a carboxylic acid group in the structure of ibuprofen. In the case of cinnamic acid, prominent peaks were obtained at 1672.36 cm^{-1}, 3061.16cm^{-1}, 1170.84cm^{-1}, 2833.50cm^{-1} for C=O stretching, O-H stretching, C-O stretching, C-H stretching, respectively. This demonstrated that, in the absence of solvent addition, there was no chemical interaction between the drug and the coformer physical mixture. The FTIR spectrum of cocrystals revealed the creation of homosynthon by hydrogen bonding between the COOH group of both drug and conformer following the addition of solvent to the ibuprofen and cinnamic acid physical mixture in a ratio of 1:2. The cocrystals' FTIR spectra shows peaks at 2937.71cm^{-1} and 1710.93cm^{-1} for the O-H bond and C-O stretching. The peak for the carbonyl group (-C=O) shifted from 1716 to 1626 cm^{-1}. The IR data indicate the formation of cocrystals of ibuprofen and cinnamic acid.

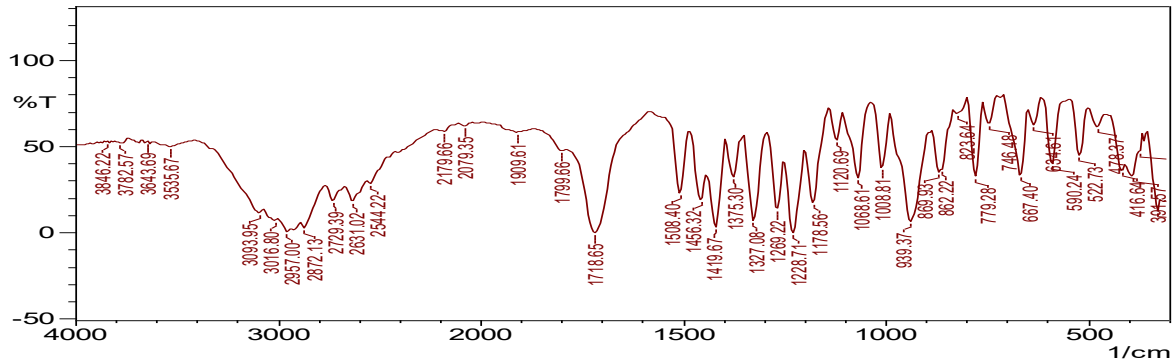

Figure 9: FTIR spectrum of ibuprofen

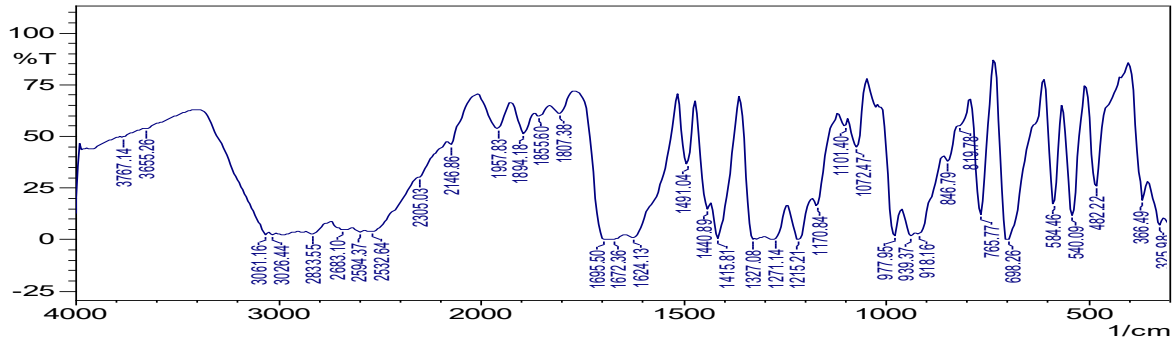

Figure 10: FTIR spectrum of cinnamic acid

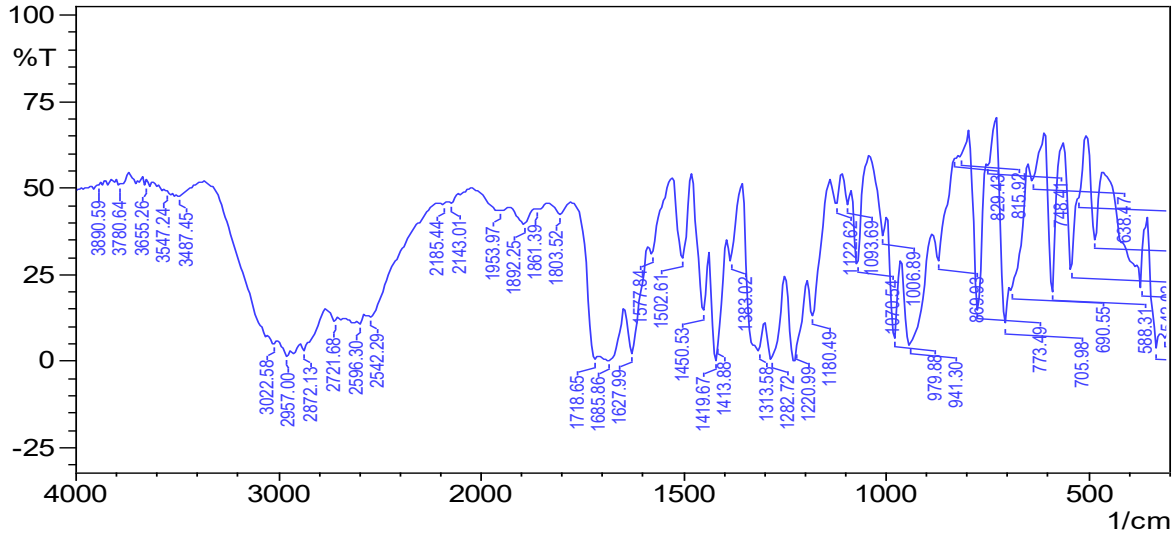

Figure 11: FTIR spectrum of physical mixture

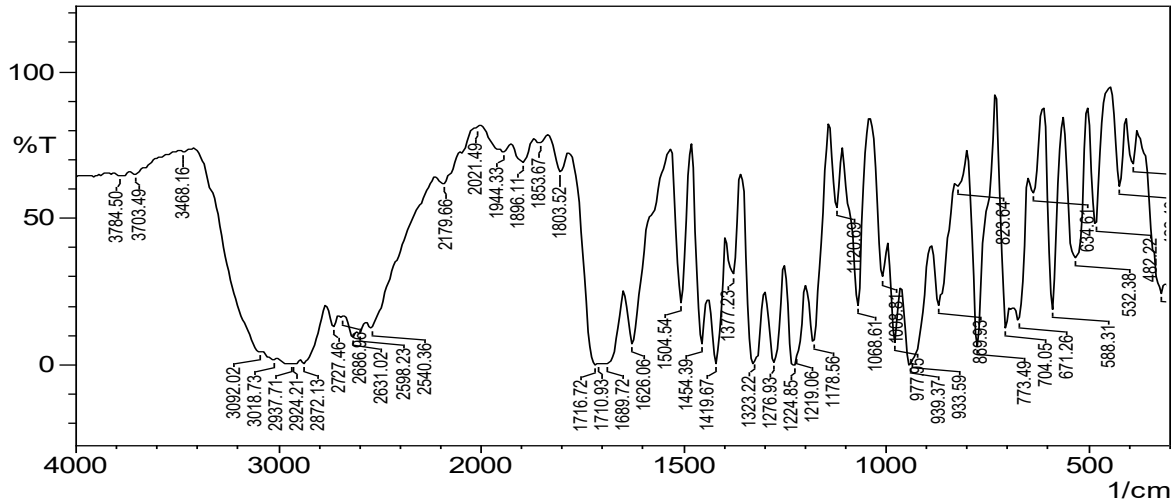

Figure 12: FTIR spectrum of cocrystals

XRD Analysis

Ibuprofen's XRD spectrum showed distinct peaks at 14.34, 16.14, 16.61, 22.17 and 26.14 with relative intensities of 44.85, 71.11, 58.71, 100 and 32.39 (figure 13). The XRD spectrum of cinnamic acid revealed distinct peaks at 7.9682, 8.1026, 16.3212, 17.1394, 25.5124, and 28.2124 with relative intensities of 72.62, 85.34, 62.71, 100, 22.45, and 21.12 respectively (figure 14). The XRD spectrum of ibuprofen and cinnamic acid physical mixture showed distinct peaks on 2θ angle position at 8.1392, 16.2711, and 22.2043with relative intensities 100, 35.64, and 4.86 (figure 15). XRD spectrum of the cocrystals revealed characteristic peaks on the 2θ angle position at 8.1151, 14.3321, 15.6800, 20.8074, and 22.1549 with relative intensities of 100, 63.27, 59.28, 78.91, and 81.94 respectively[27] (figure 16).

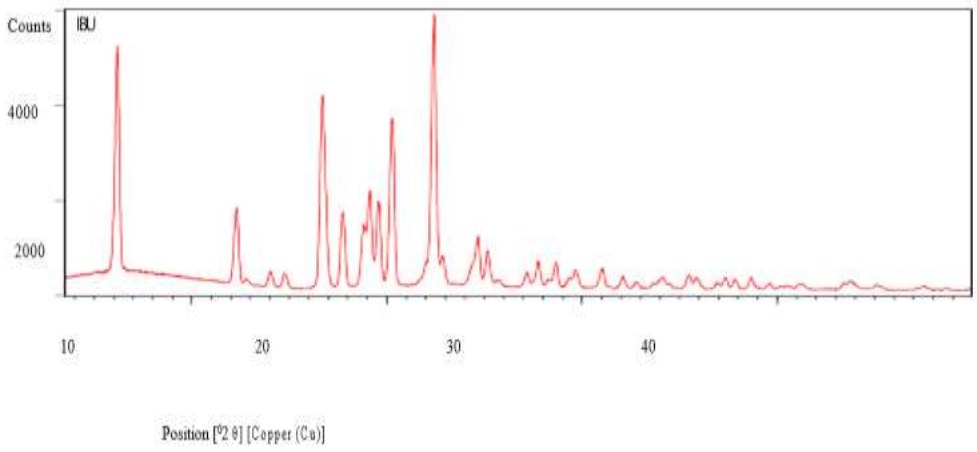

Figure 13: XRD spectrum of ibuprofen

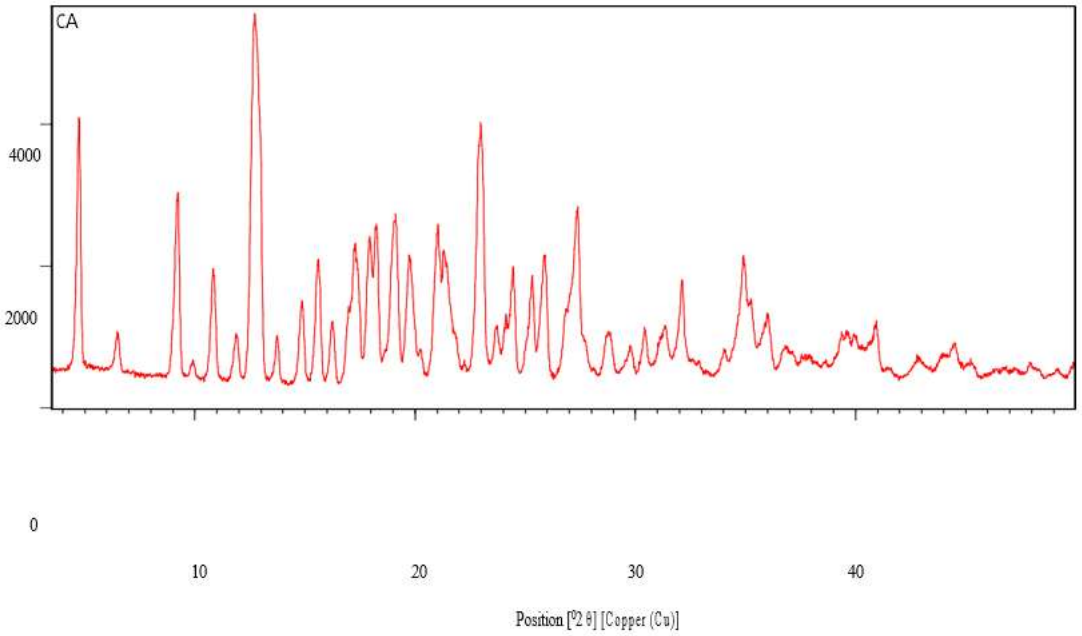

Figure 14: XRD spectrum of cinnamic acid

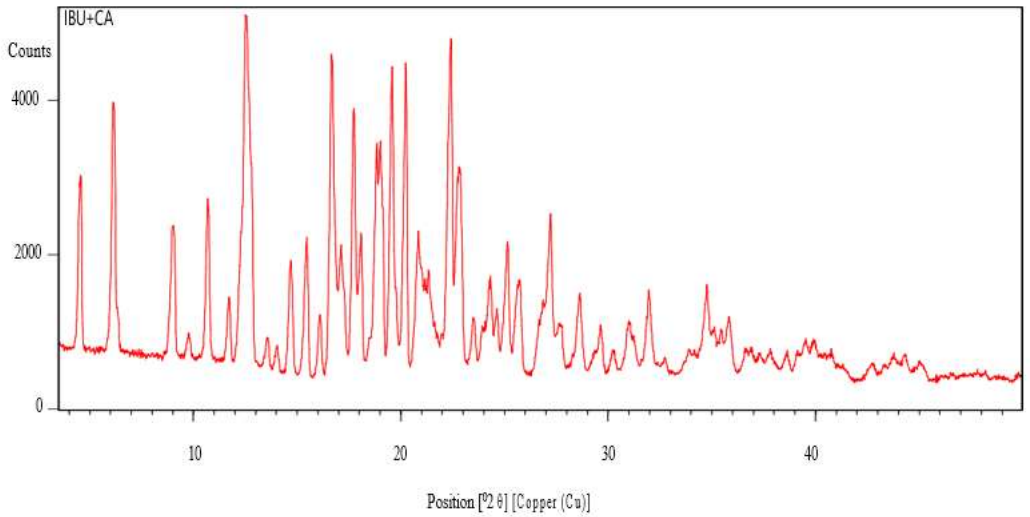

Figure 15: XRD spectrum of physical mixture (IBU+CA)

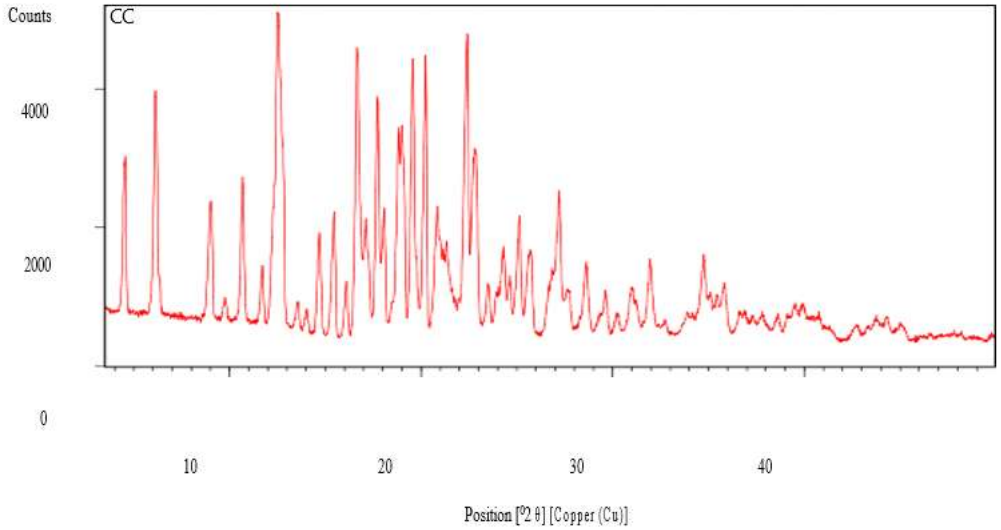

Figure 16: XRD spectrum of cocrystals

Table 4: XRD data of ibuprofen, cinnamic acid, physical mixture and cocrystals

Position (^{0}2θ)	FWHM total (^{0}2θ)	d-spacing (^{0}A)	Relative intensity (%)	Area [cts*2 θ]
Ibuprofen				
11.2412	0.1145	11.86892	13.48	82.49
11.8625	0.1298	5.62691	19.80	116.83
14.3443	**0.1412**	**5.32889**	**44.85**	171.38
16.1445	**0.1378**	**4.01109**	**71.11**	461.84
16.6143	**0.1437**	**5.60121**	**58.71**	151.18
19.1878	0.1321	3.38595	32.28	174.41
22.1767	**0.1301**	**4.00014**	**100**	547.12
26.1427	**0.1501**	**3.13287**	**32.39**	279.12
Cinnamic Acid				
7.9682	**0.1489**	**10.08670**	**72.62**	**712.12**
8.1026	**0.1481**	**10.90312**	**85.34**	**921.48**
16.1232	**0.2823**	**5.16936**	**62.71**	**1032.17**
17.1394	**0.0189**	**5.49282**	**100.00**	**687.64**
25.5124	**0.1642**	**3.18720**	**22.45**	**601.13**
28.2146	**0.2416**	**3.23011**	**21.12**	**417.56**
33.5742	**0.1741**	**2.56010**	**16.74**	**376.53**
Physical Mixture (1:1)				
8.1392	**0.0815**	**12.24545**	**100.00**	**4085.41**
16.2711	**0.1239**	**8.78581**	**35.64**	**2084.21**
17.2045	0.1308	5.68445	6.31	349.12
19.1501	0.1114	5.34355	2.96	288.21
22.2043	**0.2116**	**4.87101**	**4.86**	**466.20**
30.1247	0.2301	3.2681	2.40	491.01
32.8921	0.0828	5.11201	2.54	28.84
25.8412	0.2145	2.8912	0.95	154.23
24.4456	0.0456	3.7541	1.12	47.25
Cocrystals				
6.2789	0.1391	14.14181	13.36	37.92
8.1151	**1.3161**	**9.70326**	**100.00**	**248.48**
11.2618	0.0706	8.30547	24.96	97.85
11.8564	0.2146	10.90924	51.20	127.16
14.3321	**0.5234**	**6.34346**	**63.27**	**380.12**
15.6800	**0.1802**	**5.68662**	**59.28**	**142.88**
16.6034	0.1187	5.22203	51.28	285.51
20.8074	**0.1134**	**4.26101**	**78.91**	**278.02**
22.1549	**0.0904**	**2.21580**	**81.94**	**64.36**
30.5812	0.2451	4.19021	69.98	72.14
38.7728	0.0546	5.13320	43.55	112.201

Dissolution study (in vitro drug release)

Ibuprofen, its cocrystals and marketed formulation (Momentact 400mg capsules, In life Healthcare) were reported for in vitro drug release in phosphate buffer pH 7.2. Pure ibuprofen released 16.29%, 20.86%, 31.50%, 36.92%, 40.92%, 43.18%, and 45.25% at different time intervals of 5, 10,15, 30, 45, 60, and 90 minutes, while the physical mixture released 17.32%, 26.21%, 36.14%, 39.98%, 41.01%, 44.12%, and 46.64%%. In figure 17, cocrystals showed release of approximately 41.22%, 58.42%, 70.06%, 78.24%, 89.92%, 92.49%, and 94.48% whereas marketed formulations showed release of 20.66%, 33.35%, 42.65%, 51.18%, 59.48%, 60.45%, and 66.54% respectively. Three reading were taken and data mean and standard deviation (n=3) were reported[28]. Table 5 shows the percentage release of the drug ibuprofen, physical mixture, cocrystals, and marketed formulation.

Table 5: % drug release cumulative data for ibuprofen, physical mixture, cocrystals and marketed formulation

Time (minute)	Pure drug (%)	Physical mixture (%)	Cocrystals (%)	Marketed formulation (%)
0	0	0	0	0
5	16.29	17.32	41.22	20.66
10	20.86	26.21	58.42	33.35
15	31.50	36.14	70.06	42.65
30	36.92	39.98	78.24	51.18
45	40.92	41.01	89.92	59.48
60	43.18	44.12	92.49	60.45

90	45.25	46.64	94.48	66.54
Data± S.D (n=3)				

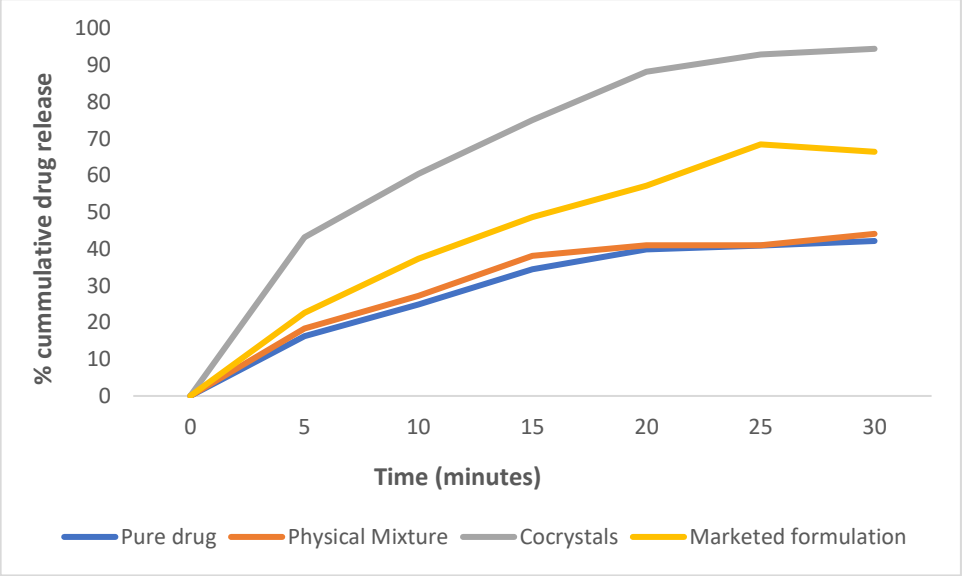

Figure 17: Comparison of drug release

In vivo anti-inflammatory activity

Table 6 and Figure 18 showed the anti-inflammatory effects of cocrystals on edema caused by carrageenan in the hind paws of rats. Group 2 received only polymer cinnamic acid in dose 50 mg/Kg compared to standard drug. Both groups 3 and 4, received equivalent dose of pure drug ibuprofen and cocrystals in dose 50mg/Kg. Rats in group 1 or control group that received only saline treatment did not exhibit inflammation reduction. However, all dose treated groups given reduced inflammation, while group with cocrystals showed greatest reduction. After 5 hours of carrageenan administration, the volume of each paw decreased. The paw volumes were 0.988±0.02, 0.758±0.03, 0.829±0.09, and 0.714±0.06 for groups 1 to 4, respectively . When in vivo anti-inflammatory activity results applied for one way ANOVA test, carrageenan induced group showed a significant value of **p<0.01.[29]

Table 6: Data of anti-inflammatory activity

Time	Group 1*	Group 2*	Group 3*	Group 4*
1	0.567 ±0.04**	0.476 ±0.02**	0.538 ±0.01**	0.436 ±0.02**
2	0.750 ±0.04**	0.686 ±0.01**	0.709 ±0.01**	0.606 ±0.06**
3	0.864 ±0.03**	0.789 ±0.02**	0.778 ±0.02**	0.711 ±0.03**
4	0.939 ±0.03**	0.841 ±0.03**	0.819 ±0.02**	0.727 ±0.03**
5	0.988 ±0.02**	0.758 ±0.03**	0.829 ±0.09**	0.714 ±0.06**

Group 1: Control; Group 2: Cinnamic acid (50mg/Kg); Group 3: Pure drug (50mg/Kg); Group 4: Cocrystal (50mg/Kg)
*Mean±S.D. (n=6); **p<0.01 compared to carrageenan control group

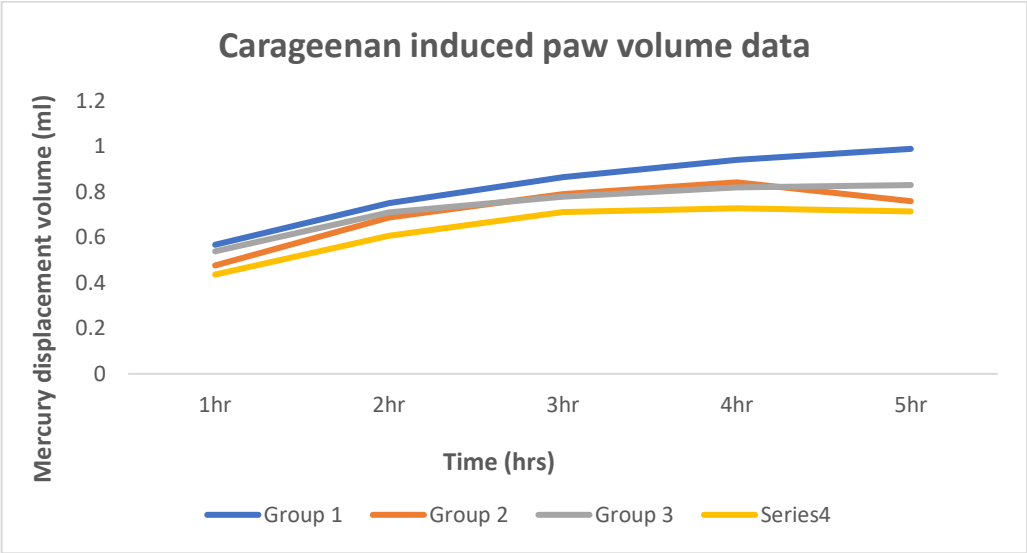

Figure 18: Paw volume with time

Figure 19: (a,b) injection of 0.05ml of 1% solution of carrageenan in hind paw (c, d) Inflammation after carrageenan (e, f) measurement of inflammation by plethysmometer

Stability studies

The stability profile exhibited by the cocrystals and the pure drug were 78% and 63% after six months, respectively. The drug content was evaluated by AUC. The AUC for ibuprofen was found to be 145742, 125147, 88451 and AUC for cocrystals was obtained 142445, 129452, and 99523 at an intervals of 0, 3, and 6 months respectively. The stability profile of ibuprofen was significantly improved by the co-crystallization technique. Both the pure drug and the cocrystals followed first order kinetics where the Concentration of the remaining drug is directly proportional to the rate of drug degradation.[30]

Table 7: Concentration of samples with their AUC

Concentration (mcg/ml)	AUC
2	28874
4	51613
6	79966
8	106647
10	129029
12	155342

Table 8: Stability data at 0, 3, and 6 months interval

Time (Month)	% Drug Remaining (Aceclofenac)*	% Drug Remaining (Cocrystals)*
0	99.04±0.027	98.26± 0.041
3	79.26±1.019	95.12±4.11
6	63.16±0.411	78.58± 0.484
Mean± S.D (n=3)		

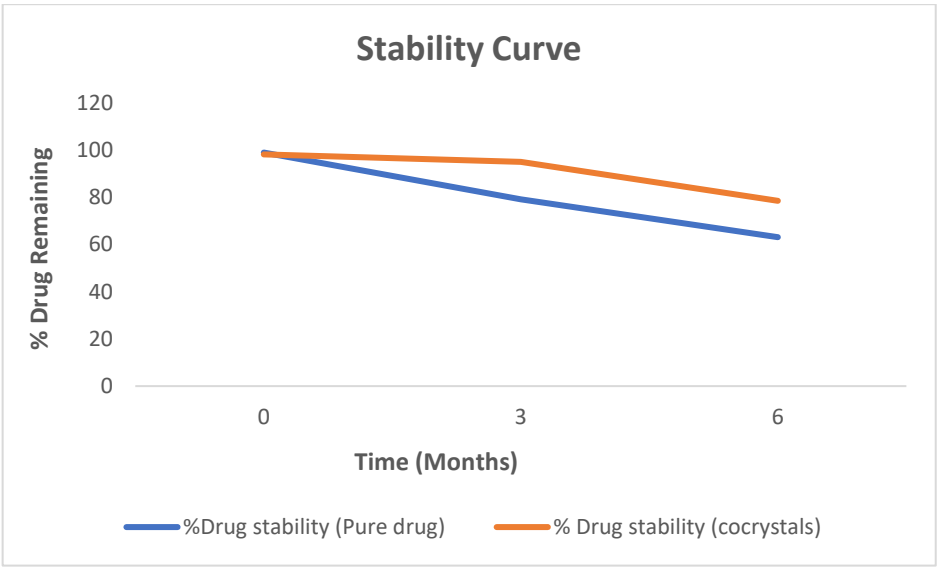

Figure 20: Stability data at 0, 3 and 6 months interval

CONCLUSION

In this study, Ibuprofen and cinnamic acid were successfully co-crystallized in a 1:2 stoichiometric ratio using the solvent evaporation technique with methanol. In contrast to drug and conformer, DSC analysis showed a sharp endothermic peak that confirms the interaction and formation of cocrystals. This interaction was further supported by FT-IR and XRD analysis, which showed the clear involvement of the -COOH functional group. When compared to the pure drug and marketed formulation, the cocrystals dissolution profile showed a much higher drug release. The study clearly indicates that these cocrystals have the potential to improve the in vitro dissolution of poorly water-soluble drugs, which can lead to better activity in vivo. Finally, the accelerated stability studies show that the co-crystallization process successfully improve the stability and properties of the drug compound. However, further bioavailability, toxicological, and the clinical studies are still required to successfully launch this formulation into the commercial market.

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8. AUTHORS CONTRIBUTION

SA: Conceptualization, methodology, and initial drafting. GV: Data validation and study design supervision and manuscript finalization. RS: Reviewing, editing and refining the manuscript. All authors have approved the final version and agreed to be accountable for the work.

9. CONFLICT OF INTEREST

The authors declare no conflict of interest.

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