Enhancement of Solubility and Dissolution rate of Ciprofloxacin using Cocrystallization Technique

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Abstract:
Drug-coformer Cocrystals of Ciprofloxacin and Nicotinamide were synthesized by using solvent grinding Technique. The Ciprofloxacin a BCS Class IV drug act as API and Nicotinamide act as conformer. The Ciprofloxacin and Nicotinamide in the molar ratio 1:1 Ciprofloxacin (0.1 g/mol i.e 0.331 gm) Nicotinamide (0.1 g/mol i.e 0.122gm) were used in the formation of Cocrystals. The Cocrytsals of Ciprofloxacin and Nicotinamide were characterized by FTIR, DSC, XRD and SEM analysis. The melting point, solubility, in vitro dissolution and stability studies were conducted for the cocrystals. The formation of Ciprofloxacin and Nicotinamide Cocrystals were supported and confirmed based on the data of the FTIR, DSC and XRD. The SEM also showed change in the habit of Cocrystals compared to pure drugs. The Ciprofloxacin and Nicotinamide Cocrytsals showed 4.57-fold increase in the solubluity in water compared to Ciprofloxacin. The dissolution rate Cocrytsals Ciprofloxacin and Nicotinamide were also dramatically improved compared to pure drugs. The pharmacokinetic study of Ciprofloxacin and Nicotinamide Cocrystals showed increased in the bioavailability of fixed dose combination.

Keywords: Solubility, Cocrystals, Physico-chemical properties, XRD, SEM

INTRODUCTION

The pharmaceutical formulations field evolves and adapts to new therapeutic needs as it continuously changes[1]. A considerable number of newly reported active chemicals exhibit low water solubility and dissolution rates, which may equate to poor bioavailability, especially when administered orally[2]. Crystal engineering, one of the current options for mitigating these flaws offers several possibilities for development of single- component or multi component alterations of an active compound, including pharmaceutical co-crystal synthesis[3].Co-crystal are crystalline complexes of active compounds that forms a distinct crystalline lattice via non covalent bonds, specifically hydrogen bonds. The primary advantage of co-crystallization is that preservation of drugs intrinsic pharmacological properties, while the physicochemical profile.Because combined therapies are frequently prescribed for the effective treatment of variety of pathologies, drug-drug co-crystals represents a promising line of research. The advantages of co-crystals of multiple active compounds may outweigh the disadvantage of conventionally combined drugs[4].Co-crystal is defined as a crystalline material consisting of two or more compound, at least two of which are held together by weak interaction, and at least one of which is a co-crystal former. According to the present invention, The co-crystals may however, includes one or more solvate molecules in the crystalline lattice. "Co-crystal former" as used herein is defined as Ciprofloxacin with which Nicotinamide is able to form co-crystals. In a further personification of the co-crystal invention's, the Ciprofloxacin and Nicotinamide ratio is chosen in such a way that, when compared to Nicotinamide alone or a comparable mixture of Nicotinamide and ciprofloxacin , the solubility , dose of response, dissolution, bioavailability and efficacy of the co-crystal increased and the hygroscopicity of the co-crystal decreased. Nicotinamide-Ciprofloxacin mixture is defined as a mixture of Nicotinamide and ciprofloxacin that is only a physical mixture with no coupling forces between the compounds and thus does not include salts or another co-crystals. Ciprofloxacin being the co-crystal former with nicotinamide is a highly interesting drug. The Grinding method in co-crystallization is divided into two techniques: dry and solvent-drop grinding. Dry grinding (mechanochemistry) is aimed at modifying crystalline phase formation through two mechanisms: molecular diffusion due to displacement, and cleavage planes formation in each cell unit. Solvent-drop grinding is performed by adding a small amount of specific solvent to the grinding process, an amount that can affect the process of co-crystal formation. Solvent-drop grinding possesses several advantages over dry grinding, including shorter time of co-crystal phase formation and possibility of obtaining pure co-crystal [5].

MATERIAL AND METHODS

Chemicals: Ciprofloxacin was obtained as gift sample from Nicolus Piramal, Indore, India.
Nicotinamide was purchased from Balaji Drugs, Mumbai. All the chemicals such as Microcrystalline cellulose Talc, starch, magnesium stearate were purchased fron SD Fine chemicals , Mumbai.

Preparation of Co-crystal:

Co-crystal prepared with nicotinamide as coformer:

Using solvent drop grinding techniques, a pharmaceutical co-crystal of ciprofloxacin was created with co-formers. Ciprofloxacin (0.1 g/mol, or 0.331 gm) and nicotinamide (0.1 g/mol, or 0.122 gm) are weighted, and Cocrystal was made by pulverising the two substances in a mortar and pestle at a 1:1 molar ratio for 90 minutes while also adding a few drops of ethanol (about 10% of the weight of the entire solid). The solid powder was then scraped from the mortar walls and placed in a container for future research [6].

Fourier transform infrared spectroscopy (FTIR):

Using an infrared spectrophotometer, all of the co-crystals of ciprofloxacin made with coformer and the pure drug itself were scanned and recorded in the 4000-400 cm-1 range (Agilent, India). Using a mortar and pestle, the co-crystal samples were triturated with dried potassium bromide. The mixture was consistently held in an appropriate die after being ground into a fine powder and compacted into a pellet shape using a hydraulic press. In the IR spectrophotometer, the produced pellet was mounted in an appropriate holder (Carry, 630) [7]

Differential scanning calorimetry (DSC):

Thermograms were produced after calibration by heating all of the samples (5 mg) of the pure drug (Ciprofloxacin) and its co-crystals made with coformer at a constant heating rate of 100C/min with chart speed of 20 ml/min under a nitrogen atmosphere. Automatic calculations determined the precise peak temperatures, melting point, and heat of fusion. All of the samples were subjected to a scan temperature range of 200C to 4000C.(Metropolitan Toledo) [7]

Powder X-ray diffraction spectroscopy (PXRD):

The X-ray diffractometer (BRUKER D8 ADVANCE, Germany) was used to obtain the X-ray diffraction pattern of Ciprofloxacin and its co-crystals prepared with as coformer at 40 kV, 30 mA, and a scanning rate of 10 /min at the diffraction angle 2 over the range of 10-600 using Cu (as an anode) radiation of wavelength 1.5406A0. [7]

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was used to examine the morphology of crystals made of ciprofloxacin,and cocrystal. While cocrystals display a distinct size, shape, and crystal with the formation of clumps, ciprofloxacin and nicotinamide displayed irregularly sized particles with amorphous structures. This shows the crystals of pure drugs and cocrystal changing in size and shape.[7]

Solubility studies:

Ciprofloxacin and co-crystal solubility was investigated in media such as (distilled water). The excess amount (52.63 mg) of co-crystal was transferred to a glass stopper containing 50 ml of medium and stirred using a magnetic stirrer at a speed of 150 rpm for 24 hours at 37 0.50C. Whatman filter paper No. 1 was then used to filter out the solution. The concentration was calculated spectrophotometrically at 278 nm after making the appropriate dilution. (USP Electrolab)[8]

Dissolution studies:

The USP dissolution test apparatus was used to conduct dissolving tests on Ciprofloxacin powder and co-crystal, with the basket moving at 50 rpm and the medium temperature set to 37°C (0.5°C). Co-crystal was taken and put inside a capsule, equating to 50 mg of Ciprofloxacin. The capsule was retained in the basket and the dissolution process was carried out for 60 min. To maintain the sink condition, the sample (5 ml) was removed at intervals of 10,20,30,40,50,and 60 min. After passing through a Whatman filter, a UV Spectrophotometer set to 278 nm was used to measure the solution's absorbance. (Electrolab, USP))[8]

Formulation of Co-crystals into Tablet:

Preparation of Tablet:

Following the addition of magnesium sterates as lubricant and Crossprovidone, the correct weight quantity of the medicine and other co-crystals were added to microcrystalline cellulose, starch, and talc, which were then correctly combined. The powder mixture was compressed into a tablet form.[9]

Table No-:1 Formulation of tablet

Ingredient	Quantity taken (mg)	
Ciprofloxacin	250	-
Ciprofloxacin -Nicotinamide Co-crystal	-	250
Microcrystalline cellulose	37.6	37.6
Mag. Sterates	0.4	0.4
Starch	10	10
Talc	1.0	1.0
Crosprovidone	1.0	1.0

Post compression parameter:

Hardness

The hardness of a tablet determines how resistant it is to breaking during shipping, storage, transportation, and handling before use. Three tablets from each formulation were tested using the Pfizer hardness tester to determine

their hardness. Between two taster jaws, the tablet was held between them along its oblong axis. The measurement at this moment should be 0 kg/cm2. After that, the tablet was subjected to continual pressure until it broke. At this stage, the value was indicated as kg/cm2.[10]

Friability

The strength of a tablet is measured by its friability. The friability was examined using an electrolab friabilator. The friability of 20 tablets for each formulation was calculated. By using a plastic chamber that rotates at a speed of 25 rpm and drops the tablet to a distance of 6 inches with each revolution, this test subjects a number of tablets to the combined effect of shock and abrasion.A sample of 20 preweight tablets was placed in a friabilator and run for 100 revolutions, or 4 minutes, before the tablets were dedusted and reweighed. Generally speaking, a weight decrease of less than 1% is acceptable. The formula for percent friability (%F) was as follows.[10]

$$\% F = (\text{Initial weight} - \text{Final weight}) / \text{Initial weight} \times 100$$

Weight variation test

By taking 20 tablets and accurately weighing oneself, the weight variation test was conducted. It was determined what the typical tablet weighed.[10]

Drug Content

Twenty tablets and triturate were consumed in order to ascertain the drug content. The same quantity of powder (5 mg) was dissolved in DMSO (5 mL), and 50 mL of water was added. This mixture was then sonicated for 15 minutes. The solution was filtered using Whatman filter paper number 41. It underwent spectrophotometric examination at 278 nm following the appropriate water dilutions (Shimadzu 1800, Japan). The drug content was determined using the ciprofloxacin calibration curve in a DMSO and distilled water solution.[10]

Disintegration time

The phrase "disintegration" describes how a tablet fragments into smaller pieces. The in-vitro disintegration time of a tablet was estimated using disintegration test apparatus that complied with I.P. criteria. Place a tablet in each of the 6 tubes in the basket. A disc should be put to each tube. Use distilled water that is maintained at a constant 37 °C to operate the machinery. The assembly should be raised and lowered 28 to 32 times per minute in distilled water maintained at 37°C. It was noted how long, in seconds, it took for the tablet to fully disintegrate, leaving no recognisable bulk inside the apparatus. (The Gupta Agencies of Haryana)[10]

In vitro dissolution studies:

Dissolution tests on the ciprofloxacin tablet and the co-crystal tablet were performed using the USP dissolving test apparatus with the basket rotating at 50 rpm and the 900ml medium at 370.50C. The dissolving procedure took place over the course of 60 minutes with the tablet kept in a basket. At intervals of 10, 20, 30, 40, 50, and 60 minutes, samples (5 ml) were taken to maintain the sink's condition. The solution's absorbance at 278 nm was determined using a UV Spectrophotometer after passing through a Whatman filter. in the USP Electrolab. [10]

PHARMACOKINETIC STUDY IN RATS [13]

Protocol for pharmacokinetic studies on the Cocrystals of Carvedilol was approved by Institutional Animal Ethical Committee (1336/AC/10/CPCSEA). The *in-vivo* kinetic study was performed by administering the pure and Cocrystals of Carvedilol to rats orally and blood samples were collected at regular time intervals to calculate the concentration of drug in plasma.

RESULTS AND DISCUSSION

In the present research work, the cocrystals of Ciprofloxacin and Nicotinamide were prepared by Solvent drop grinding method using ethanol as a solvent. Various trail batches has prepared using others methods and varying concentration of coformers, but cocrystals were formed by solvent grinding methods . Thecorystals were characterix=zed by various methods such as FTIR, DSC, XRD and SEM.Also cocrystals were evaluated for solubility and dissolution . Finaly the cocrystals were incorporated in the tablets and its evaluation were carried out.

Infrared spectroscopy

Ciprofloxacin showed characteristic peaks at 1699.74 cm-1 for C=O stretching , 1267.33 cm-1 for O=H bending , 2683.76 cm-1 for C-H stretching, and 1621.43 cm-1 for N-H bending. As a result of the drug and coformer contributing and accepting hydrogen to establish hydrogen bonds, the IR spectra of commercial drugs exhibit modest differences in their distinctive peaks when compared to the numerous Ciprofloxacin co-crystals formed in the presence of coformers. These findings suggested that although drug and coformer contact is minimal when cocrystals are created, the chemical makeup of drug molecules is unaffected.

Table No-2: FTIR data of pure drug & co-crystal

Sr. no	Crystal codes	C=O stretching	O-H bending	C-H stretching	N-H Bending
1	Pure drug	1699.74	1267.33	2683.76	1621.43
2	Coformer	1673.65	-	-	1673.95
3	Physical Mixture	1699.74	1308.34	2765.76	1621.43

4	Co-crystal	-	1267.34	2683.77	1617.74

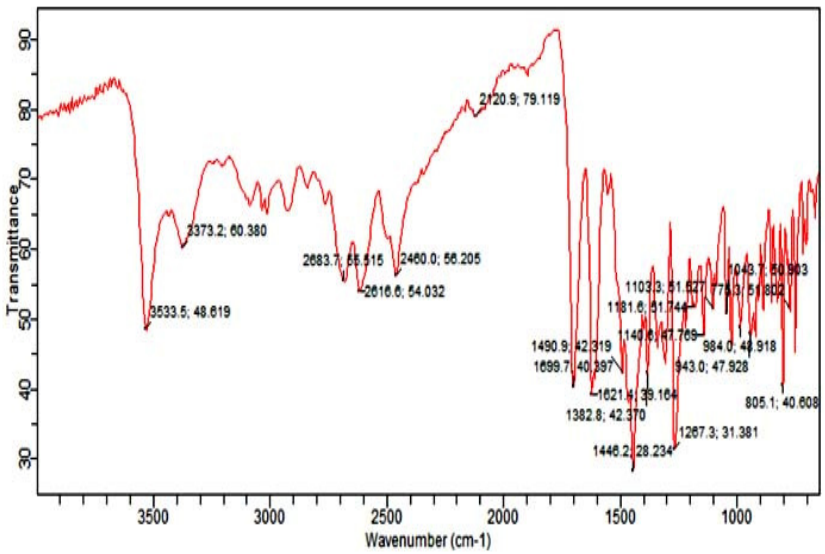

Fig No-1(a): FTIR spectra of Ciprofloxacin

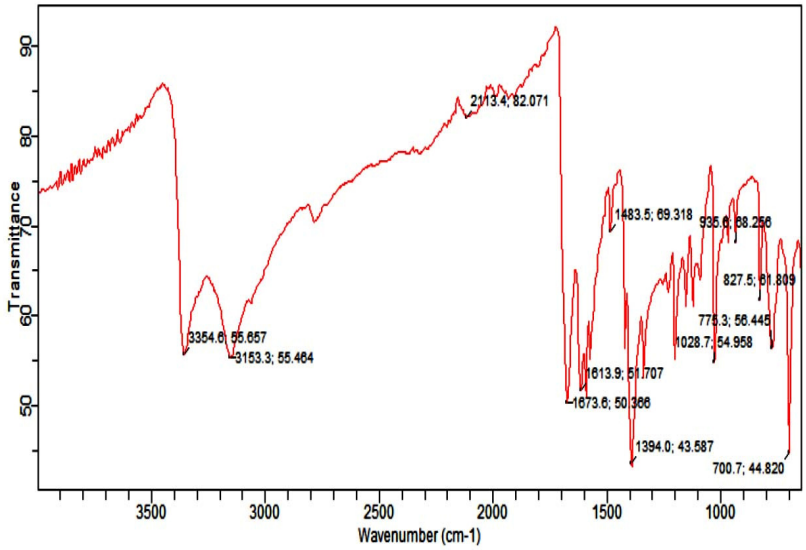

Fig No-1 (b): FTIR spectra of Nicotinamide coformer

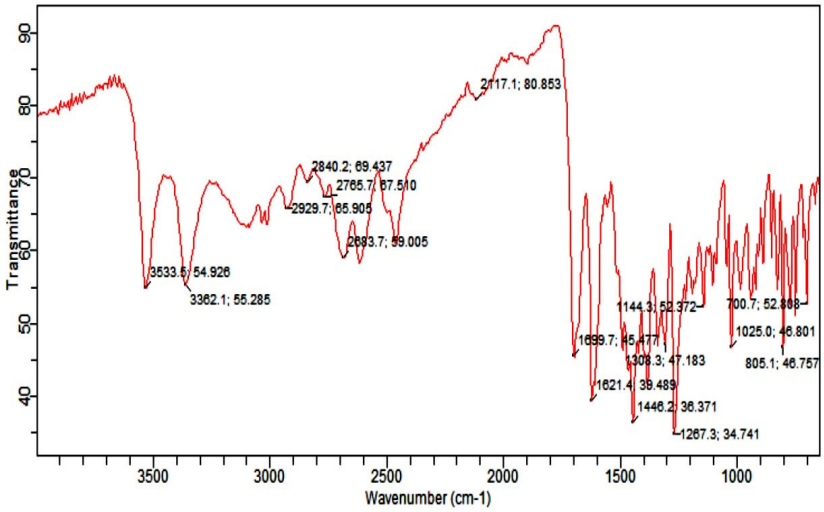

Fig No1-(c): FTIR spectra of Ciprofloxacin Nicotinamide physical mixture

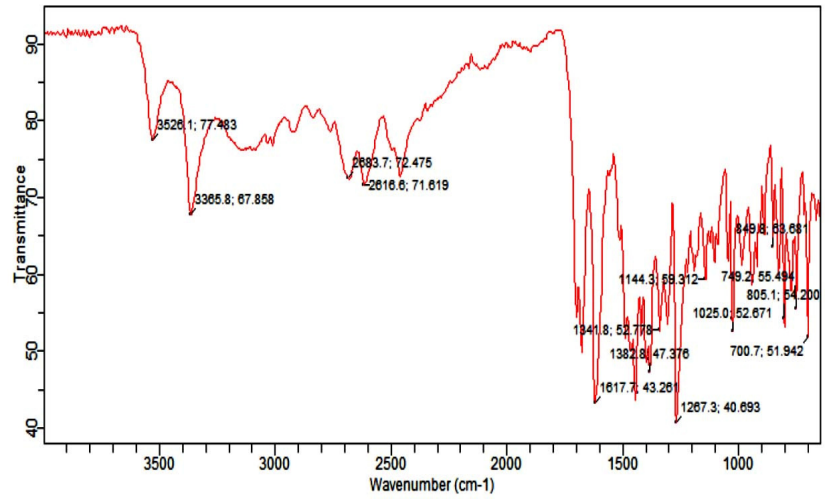

Fig No-1(d): FTIR spectra of Ciprofloxacin nicotinamide co-crystal

Differential scanning calorimetry

All of the co-crystals made using the solvent drop grinding technique displayed the antibiotic Ciprofloxacin's distinctive endothermic peak. When the co-crystal exhibits distinct melting points, DSC is typically co-crystal composition of medicinal powders. The graphs below depict the temperature behaviour of co-crystals and pure medication. Ciprofloxacin occurred on a sharp endothermic peak at roughly 139.660C, which corresponds to its melting point, according to the DSC curve. The co-crystals produced with nicotinamide as the coformer, however, displayed a shift of the endothermic peak towards a lower temperature, at 134.450C, respectively. The drop in the drug's melting point in co-crystals is shown by the endothermic peak's shift towards a lower temperature. The greater solubility of the medication is explained by this lower melting point.

Table No-2: DSC data of pure drug and modified co-crystals

Sr. no.	Crystal form	DSC data		
		Melting point (⁰C)	Peak fusion point (⁰C)	Heat of fusion (J/g^-1)
1	Ciprofloxacin	147.95	139.66	635.50
2	Ciprofloxacin Nicotinamide co-crystal	140.57	134.45	992.00

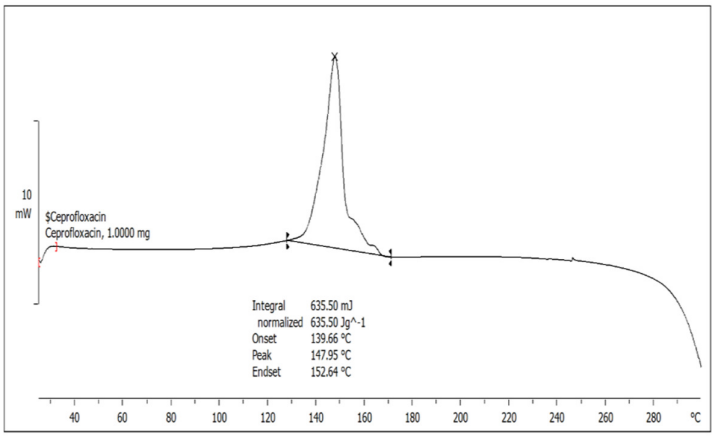

Fig No-2(a): DSC Thermogram of pure drug (Ciprofloxacin)

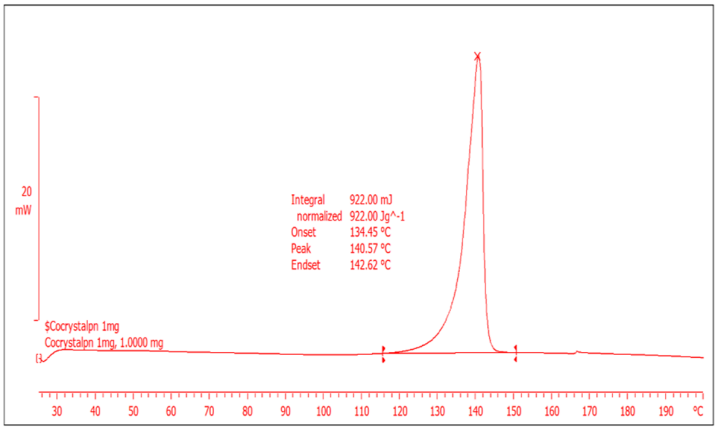

Fig No-2 (b): DSC Thermogram of Drug-Nicotinamide Co-Crystal

Powder X-ray Diffraction

The X-ray diffractometer was used to study the X-ray diffraction patterns of several co-crystals. When compared to different co-crystals, the pure drug's X-ray diffraction pattern shows a greater number of peaks. Drug-nicotinamide co-crystal XRD spectra show a reduced number of peaks but an increase in peak strength. At 2 = 1.54060, distinctive diffraction peaks were seen. It is possible that particles crystallised using the solvent drop co-grinding method in the presence of co-coformer did not undergo structural modification because the XRD spectra of pure drug and co-crystals obtained in the presence of co-crystal coformer showed essentially similar diffraction patterns (2 values).However, the variations in the relative strengths of their peaks may be explained by variations in the sample's crystal structure and behaviour, which may be explained by variations in the drug's solubility in the sample's crystals media.

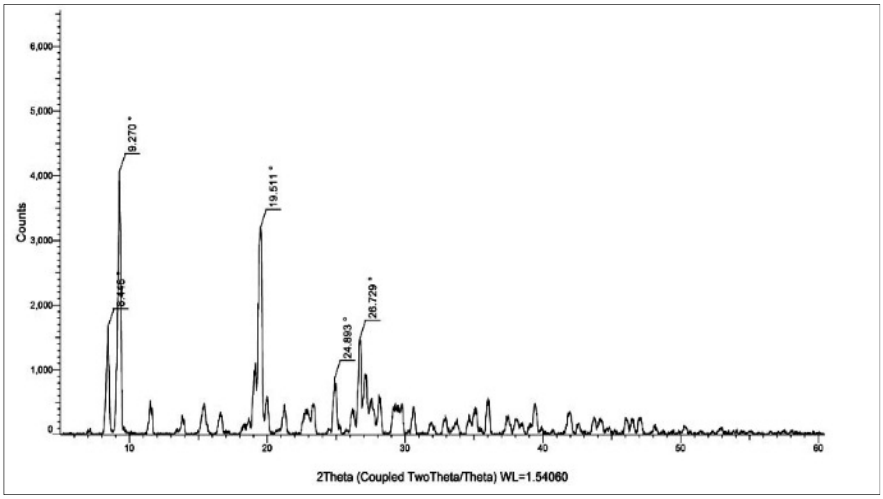

Fig No- 3 (a): XRD Spectra of pure drug (Ciprofloxacin)

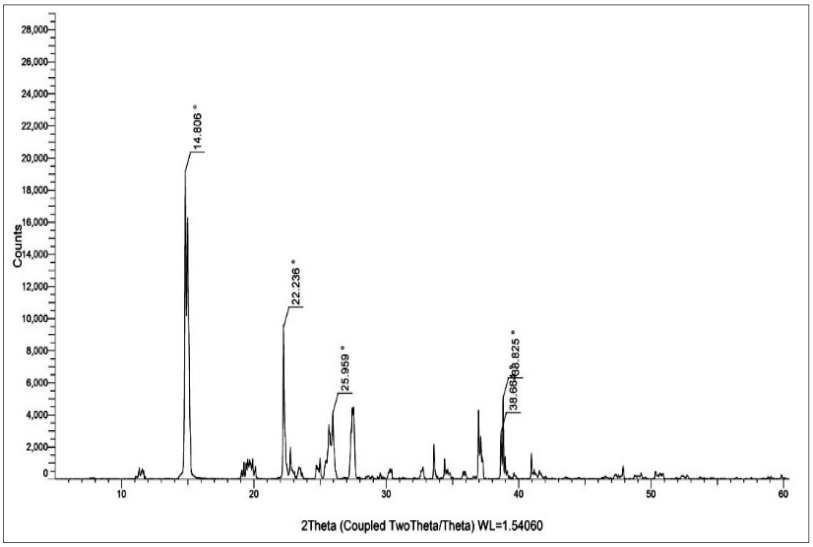

Fig No-3 (b): XRD Spectra of Coformer(Nicotinamide)

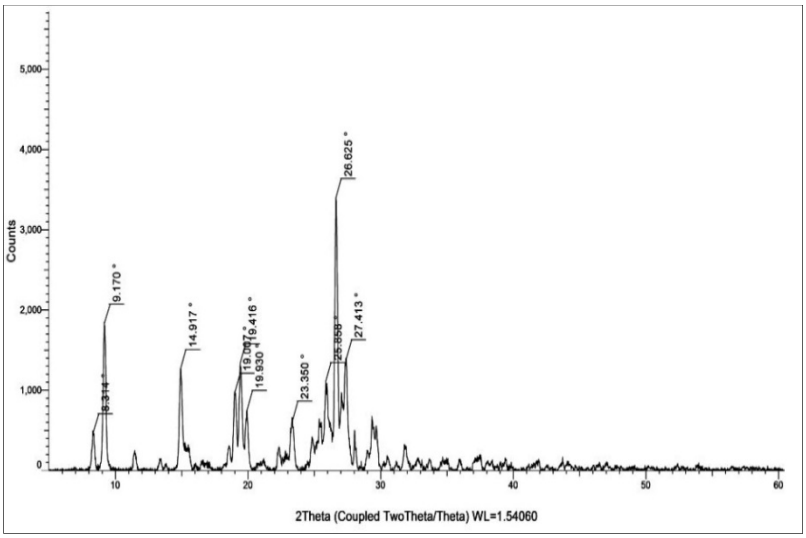

Fig No-3 (c): XRD Spectra of Co-crystal

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was used to examine the morphology of crystals made of ciprofloxacin,and cocrystal. While cocrystals display a distinct size, shape, and crystal with the formation of clumps, ciprofloxacin and nicotinamide displayed irregularly sized particles with amorphous structures. This shows the crystals of pure drugs and cocrystal changing in size and shape

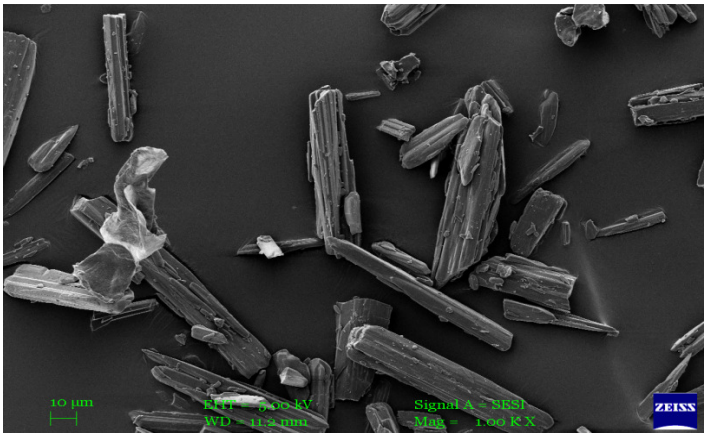

Fig No- 4 (a): SEM Spectra of Ciprofloxacin (Mag = 1.00 KX)

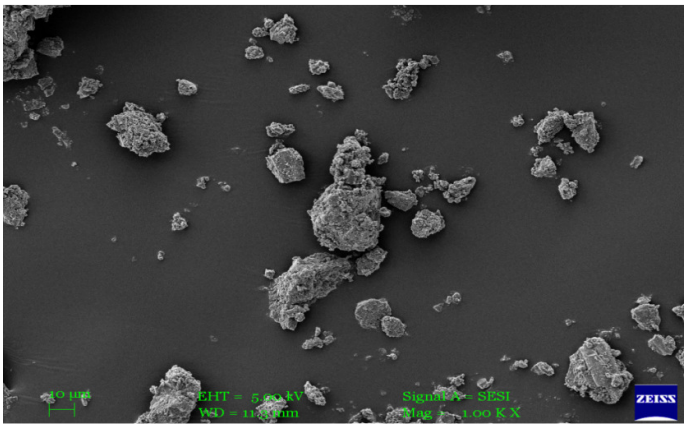

Fig No-4 (b): SEM Spectra of Cocrystal (Mag = 1.00 KX)

Solubility studies

The solubility study revealed that the co-crystals grown in the presence of nicotinamide as coformer were soluble (12.0 g/ml), with a 4.57-fold increase in solubility when compared to the pure drug. The co-crystals were grown in the presence of ciprofloxacin, which was the least soluble (2.625 g/ml) (Ciprofloxacin).

Table No-3: Solubility data of various co-crystal forms.

Sr. no.	Co-Crystal	Solubility (µg/ml)
1	Ciprofloxacin	2.625
2	Ciprofloxacin-Nicotinamide co-crystal	12.0

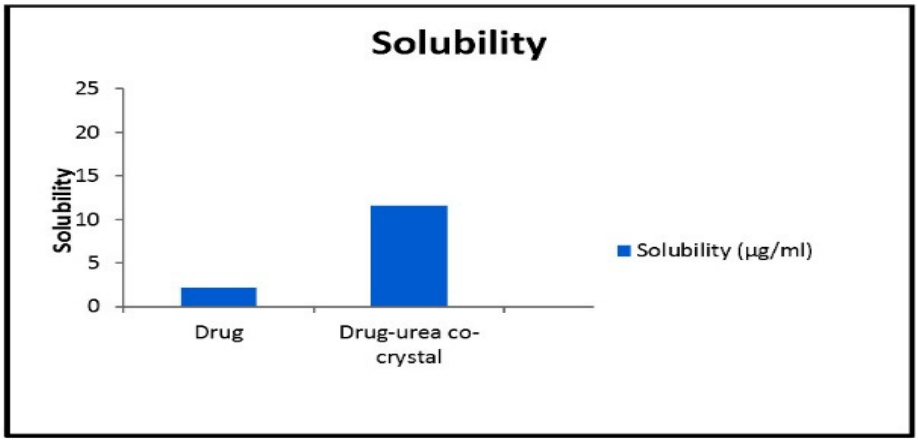

Fig No-5: Solubility study of Ciprofloxacin co- crystal

Dissolution studies

The varied forms' dissolution curves revealed variations in dissolution rates that were consistent with the crystallinity and solubility ordering. The outcome of dissolving studies is graphicalally represented as % release vs. time. The drug-nicotinamide co-crystal had the highest rate of dissolution. Nicotinamide is necessary for the formation of co-crystals since coformer significantly increased the rate of disintegration.

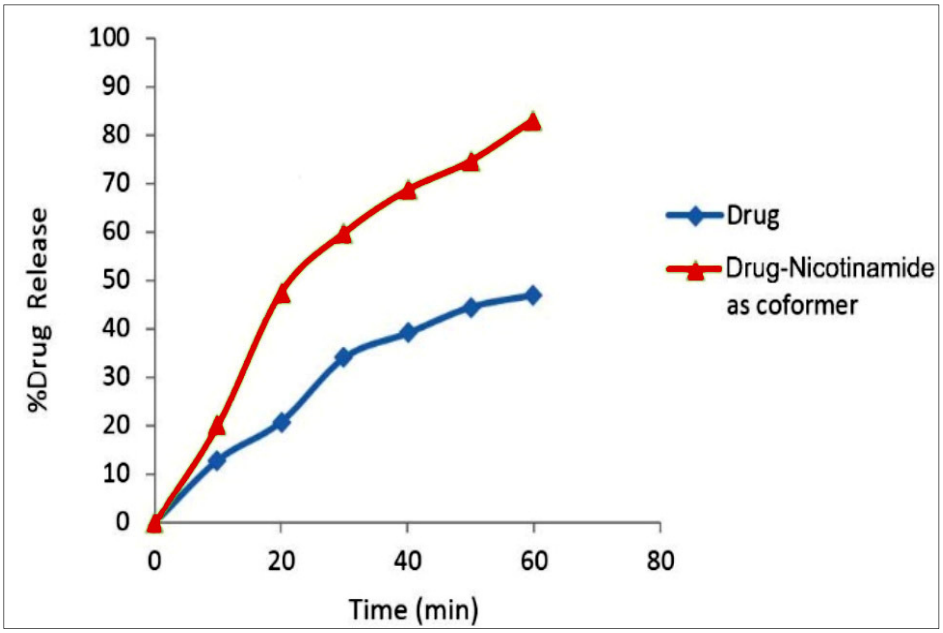

Fig No-6: Dissolution study of Ciprofloxacin co-crystal

Table No-4: Post compression parameter

Formulation	Hardness (Kg/cm2)	Friability (%)	Weight variation (mg)	Drug Content (W/W)	Disintegration Time (Sec)
Ciprofloxacin	4.8±0.4	0.444±0.15	Passes	97.33 ± 0.03	190 ± 2
Ciprofloxacin - Nicotinamide co-crystal	5.9±0.66	0.442±0.09	Passes	99.9 ±0.99	153 ± 2

The overall look of the tablets, their visual identity, and their "elegance" are crucial for their acceptability; all of the formulations were off-white, smooth, spherical, and flat-faced, with no obvious fissures. The Roche friabilator was used to measure the friability, which was found to be drug-0.444% and drug-Nicotinamide co-crystal 0.442%. This parameter was considered given the tablet's good mechanical resistance. Weight fluctuation was 7.5% of the weight or less within the pharmacopoeia's guidelines. The percentage drug contents of the manufactured co-

crystals were determined to be between 97.33 and 0.03 weight percent to 99.9 and 0.99 weight percent. The disintegration period of the tablet formulation was discovered to be between 153 and 190 seconds.

Pharmacokinetic Study

The drug concentration of each plasma samples were determined by extrapolating the linearity graph with peak area at above said predetermined time interval (0, 0.5, 1, 2, 4 and 8). The plasma drug concentration-time curve of pure Ciprofloxacin and Ciprofloxacin Cocrystals were plotted and presented in Figure 5 and other pharmacokinetic parameters (Table 5) were calculated by non compartmental model using PK solution 2.0 software.

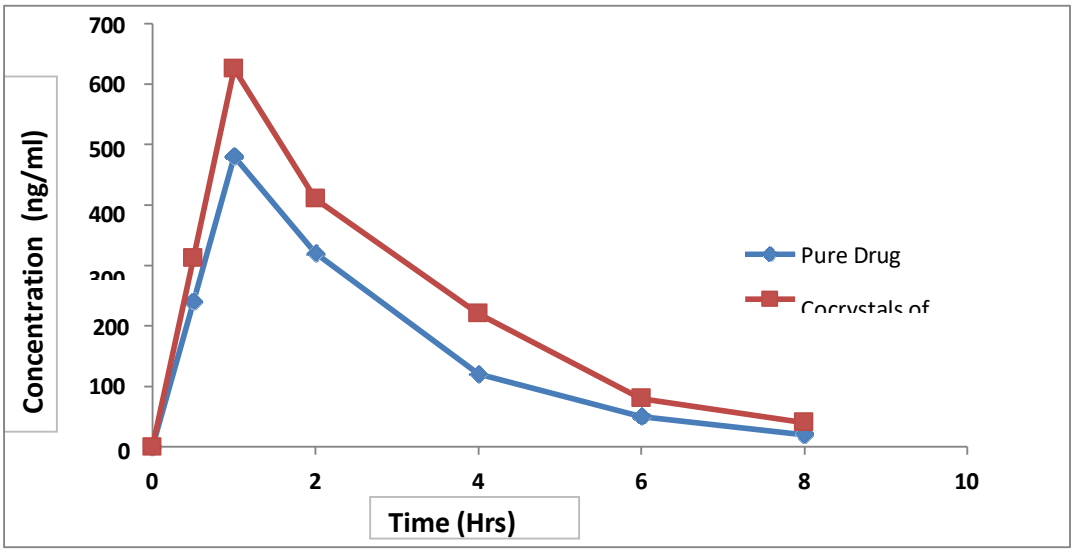

Figure 6. Mean plasma concentration-time profile of pure Ciprofloxacin and Ciprofloxacin Cocrystals after single oral administration

Table 5: Pharmacokinetic Parameter of pure Ciprofloxacin and Ciprofloxacin Cocrystals

Pharmacokinetic Parameter	**Pure Ciprofloxacin**	**Ciprofloxacin Cocrystals**
AUC 0-t(ng/ml * hr)	2219±243.1	3024±352.5
AUC 0-∞(ng/ml * hr)	2833±365.2	4500±345.8
Cmax (ng/ml)	480±25.6 ng/ml	625±28.4 ng/ml
Tmax (hrs)	1.0±0.0hr	1.0±0.0hr
t1/2(hrs)	1.20±0.6	1.90±0.8
Ke(hrs)	0.28±0.22	0.32±0.21
Relative Bioavailability	--	1.59

The *in vivo* pharmacokinetic parameters of pure Ciprofloxacin and Ciprofloxacin Cocrystals were studied in Wistar rats. The measured mean Ciprofloxacin plasma concentrations versus time after single oral administration in male Wistar rats using0.5% oral Solution. The pharmacokinetic parameters calculated from the non-compartment model using linear trapezoidal method are described in (Table 5). The pharmacokinetic parameters of Ciprofloxacin obtained from non-compartmental analysis using a linear trapezoidal method after a single oral dose of 10 mg/kg of Ciprofloxacin to Wistar rats. The t1/2, Tmax and Cmax of the drug was found to be about 1.20±0.6 hr, 1.0±0.0hr, and 480±25.6 ng/ml respectively along with AUC0-t of 2219±243.1 ng/mL*h. In contrast, the Ciprofloxacin Cocrystals demonstrated higher Cmax and AUC0-t as compared to pure Ciprofloxacin (Cmax= 625± 28.4ng/ml, AUC_{0-t} = 3024±352.5). Conversely, the Tmax of the Ciprofloxacin Cocrystals was same as compared to the pure Ciprofloxacin. The relative bioavailability of Ciprofloxacin Cocrystals formulation was found to be about 2.4 folds higher, which may be due to conversion of drug into its new solid phase which is having high internal energy that promotes quick dissolution and hence higher bioavailability was observed.

CONCLUSION

When co-crystals were generated using nicotinamide as a co-crystal coformer using the solvent drop grinding method, the FTIR results demonstrated that there was no chemical interaction between the medication and co-crystal coformer. The DSC, XRD, and SEM data indicated that no transition had occurred, but that there had been a considerable change in the co-crystal size and habit due to the presence of co-crystal coformer. The sample processed using the solvent drop grinding method had the highest level of solubility, and using ethanol as the solvent significantly increased the rate at which Ciprofloxacin dissolved. Therefore, crystallisation is a technology that has promise for increasing the solubility and rate of dissolution of ciprofloxacin.

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REFERENCES

1] Jones W, Motherwell WD, Trask AV. Pharmaceutical cocrystals: An emerging approach to physical property enhancement. MRS bulletin. 2006;31(11):875-9.

2] Zaworotko M. Crystal engineering of co-crystals and their relevance to pharmaceuticals and solid-state chemistry. Inacta Crystallographica A-Foundation And Advances 2008, 1 (Vol. 64, Pp. C11-C12). 2 Abbey Sq, Chester, Ch1 2hu, England: Int Union Crystallography.

3] Rodríguez-Hornedo N, Nehm SJ, Jayasankar A. Cocrystals: design, properties and formation mechanisms. Encyclopedia of pharmaceutical technology. 2007;1:615-35.

4] Duarte AR, Ferreira AS, Barreiros S, Cabrita E, Reis RL, Paiva A. A comparison between pure active pharmaceutical ingredients and therapeutic deep eutectic solvents: Solubility and permeability studies. European Journal of Pharmaceutics and Biopharmaceutics. 2017, ;114:296-304.

5] Butler JM, Dressman JB. The developability classification system: application of biopharmaceutics concepts to formulation development. Journal of pharmaceutical sciences. 2010;99(12):4940-54.

6] Thenge, R., Patel, R. ., Kayande, N. ., & Mahajan, N. Co-Crystals of Carvedilol: Preparation, Characterization And Evaluation: Co-Crystals of Carvedilol. International Journal of Applied Pharmaceutics, 2020, 12(1), 42–49. Https://Doi.Org/10.22159/Ijap.2020v12i1.35640

7] Thenge RR. Crystal modification of aceclofenac by spherical crystallization to improve solubility dissolution rate and micromeritic properties. J Pharma Res 2012;5:974-7.

8] RR Thenge, VB Patond, VS Adhao, PV Ajmire, LN Barde, NM Mahajan, NP Tekade, Preparation And Characterization of Co-Crystals of Diacerein, Indonesian J. Pharm. 2017, 281 : 34 – 41.DOI: 10.14499/indonesianjpharm28iss1pp34.

9] ND Deshmukh, RR Thenge, NM Mahajan, Formulation and Evaluation of Bisoprolol Fumarate Fastdissolving Tablet by Direct Compression Techniques, IJPRBS, 2012; 1(5): 364-378.

10] NP. Tekade, NS. Bhajipale, V. Ganesan, RR. Thenge, DR. Dewade1, Orodispersible Tablets Of Lansoprazole: Formulation, Characterization AndIn VitroEvaluation, International Journal of ChemTech Research, 2010, 2,1, 400-405.