IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
**Research Article**
August 2018 Vol.:13, Issue:1


# Solubility Enhancement of Ciprofloxacin by Co-Crystallization Technique

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

**Suryakant V. Kadam*, Yogesh N. Gavhane**

*Govt. College of Pharmacy, Karad.*

**Submission:** 19 July 2018
**Accepted:** 27 July 2018
**Published:** 30 August 2018



**Keywords:** co-crystal, ciprofloxacin, solubility

**ABSTRACT**

This research aims to prepare co-crystal of Ciprofloxacin (Cipro)-nicotinamide (Nico) by a solvent-assisted grinding method with a variation of concentration in coformer to improve the solubility of Cipro. Co-crystal were developed by solvent evaporation with 1:1, 1:2, 1:3, 1:4 and 1:5 molar fraction, the prepared Cipro – Nico cocrystal were characterized for differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FT-IR), and *in vitro* dissolution. FTIR study showed that the co-crystals might have the hydrogen bonding between the drug and coformer. DSC thermogram showed that CIPRO- NICO co-crystal showed the endothermic peak in the range of 245-252 $^{0}$C. XRPD diffractogram showed that CIPRO-NICO co-crystal in chloroform exhibited new diffraction peaks. Dissolution study showed that there was a significant increase of CIPRO- NICO co-crystal dissolution rate in 0.1 N HCl compared to the pure Cipro. The study concludes that CIPRO-NICO co-crystal in chloroform were successfully formed and the dissolution rate of co-crystals increase significantly.

## INTRODUCTION

Co-crystals are solids that are crystalline materials composed of two or more molecules in the same crystal lattice Pharmaceutical co-crystals have, however, been termed as co-crystals that are formed between a molecular or ionic active pharmaceutical ingredient and a benign co-crystal former that is a solid under ambient conditions. Solubility is an important parameter for evaluating the properties of a pharmaceutical co-crystal. A pharmaceutical co-crystal is a novel approach to improve the physicochemical properties such as solubility of compounds[1]. Either pharmaceutical industry focuses on the development of the new solid dosage forms or the new drug delivery systems for the drugs. This will be based on the problems faced by drugs during their development. In general, developers and regulatory authorities prefer pharmaceutical crystal forms, because crystallization tends to afford highly pure products that are superior with respect to reproducibility and scalability. Moreover, a unique crystalline form may exhibit distinctive physicochemical properties and could, in turn, affect the dissolution, manufacturing, physical stability, permeability, and oral bioavailability of an API. Thus, it is apparent that selection of an appropriate crystal form for downstream development and processing is of primary importance in pharmaceutical development. A typical crystal form selection process comprises two stages of development after a target API molecule has been selected: discover as many pharmaceutical crystal forms as possible; then examine the physicochemical properties of the newly discovered crystal forms[2]. At the stage of crystals preparation, primary approaches are used. The more straightforward approach is largely based on trial-and-error.

Ciprofloxacin is a synthetic broad-spectrum fluoroquinolone antibiotic. Ciprofloxacin binds to and inhibits bacterial *DNA gyrase*, an enzyme essential for DNA replication. This agent is more active against Gram-negative bacteria than Gram-positive bacteria. Ciprofloxacin is the classic drug which is practically insoluble in water[3,4]

Nicotinamide is a GRAS status co-crystallizing compound. It is a primary amide with two hydrogen bond donors (NH2) and an acceptor(C=O), demonstrate a remarkable ability to form hydrogen bonds for the formation of an intermolecular drug molecule: co-crystal former synthon. A second hydrogen bond acceptor is the lone pair on the N atom of the pyridine ring. This makes the molecule very versatile for a variety of hydrogen-bonded interactions, which makes Nicotinamide be excipient of choice.[2,4]

## MATERIALS

Ciprofloxacin (Cipro) was procured from Yarrow chemicals, Mumbai. Nicotinamide (Nico) was purchased from Loba chem. All the other chemicals used were of analytical grade.

## METHOD

## SOLVENT ASSISTED CO GRINDING METHOD

This technique is considered to be a very good alternative to solid-state grinding in the development of pharmaceutical co-crystals. The technique involves the grinding of two different materials as that of solid-state grinding along with a little quantity of solvent which is acting as a catalyst for the development of co-crystals.

## CHARACTERIZATION OF CO-CRYSTALS

### Fourier transformation infrared spectroscopy (FTIR):

In this study, A FTIR spectrum was obtained using a Bruker ATR spectrometer the sample was scanned over the range of 4000-450cm$^{-1}$. The sample placed on the sample holder directly and the IR spectrum of the sample are obtained on the computer screen.

### Saturation solubility studies:

Saturation solubility was performed with distilled water and in triplicate according to the method reported by Higuchi and Connors. Excess of pure drug and co-crystals were added to 10 ml of distilled water taken in a screw cap tube and shaken for 24 h in a rotary flask shaker at a room temperature to achieve the equilibrium. Appropriate aliquots were then withdrawn and filtered through Whatman filter paper after suitable dilutions analyzed by spectrophotometrically at 276 nm.

### Drug Content Determination:

Co-crystals equivalent to 10mg ciprofloxacin were taken in 10 ml volumetric flask containing 0.1 N HCl The drug and adjusted to the volume with the same solvent to obtain a stock solution. The solution was filtered through further suitable dilutions were done. The absorbance was recorded at a max of 276 nm using double beam UV Spectrophotometer[5].

**Differential Scanning Calorimetry (DSC):**

DSC was performed in and thermal behavior of the drug (Ciprofloxacin) and the solid dispersion prepared. About 5 mg of the sample was sealed in the aluminum pans and heated at the scanning rate of 10˚C/min, a temperature range of 80ºC to 400ºC under nitrogen atmosphere[11].

**X ray Powder Diffractometry (XRPD):**

For characterization of crystalline state, the X-ray diffraction (XRD) patterns for Ciprofloxacin and the solid dispersion system prepared were determined using X-ray diffractometer with a copper target, at a voltage of 40 kV and current of 40MA. The rate of the scanning was 0.30°C /min[11].

**In vitro drug release:**

The I.P Apparatus No. 2 (Paddle) was used for all the in vitro dissolution studies. 100mg of the pure drug or its equivalent amount of co-crystals were added to dissolution medium. The volume of 900 ml of 0.1 N HCl was used as dissolution media, at 50 rpm and 37 ± 0.5ºC. Appropriate aliquots were withdrawn at a suitable time interval (5, 10, 15, 30 45, 60 min.) and filtered through Whatman filter paper need with 0.1 N HCl. Sink conditions were maintained throughout the study. The samples were then analyzed at a max of 276 nm by UV/visible spectrophotometer.

**RESULT AND DISCUSSION**

**FTIR Analysis for Hydrogen bonding:**

Further characterized by IR spectroscopy. IR spectra of pure ciprofloxacin and formulations were determined by Attenuated total reflectance mode of IR spectroscopy. Analysis by IR spectroscopy was carried out to access any possible interaction between drug and coformer used for crystallization. IR spectra of and theres are shown below.

An IR spectrum of ciprofloxacin showed the principal peaks at 3737.47 cm−1 (N-H Stretch of primary and secondary amines and amides), 1584.92 cm−1 (C=O Stretch of amide), 1495.27 cm−1 (C- H bend of alkanes ), 2321.05 cm−1 (C-N Stretch OF Amines), 1175.65 cm-1 (C-f stretch of fluoride), and 649cm−1 (C-H stretch of alkenes),

3737.47 cm−1 (N-H stretch), 3040.73 cm−1 (Aromatic stretch), 1283.76 cm−1 (C=C stretching), 1614.73 cm−1 (co-acid), 2841.25 cm−1 (OH acid)

The IR spectrum of Nicotinamide 3600.63 cm -1 (Two OH stretch of alcohol, phenols), 3144.49 cm-1 (Two N-H stretch of primary and secondary amines and amides), 1673.05 cm-1 (stench of aldehyde group), 1389.39 cm-1 (C=C stretch of Alkene), 697.5 cm-1 (C-H stretch of alkene).

The spectra of all samples were nearly identical and main absorption bands of ciprofloxacin appeared in all of the spectra of untreated drug and formulations. This indicated that there were no any differences between internal structure and conformations of these samples and no any changes occurred at molecular level during the crystallization[5-7] AS shown comparative IR spectra in the table no.1 frequency of functional group in co-crystals is remains constant in therefore there is no addition or subtraction of functional groups participates in weak hydrogen bonds. Binding of the drug and co former may be having the weak hydrogen bonding.

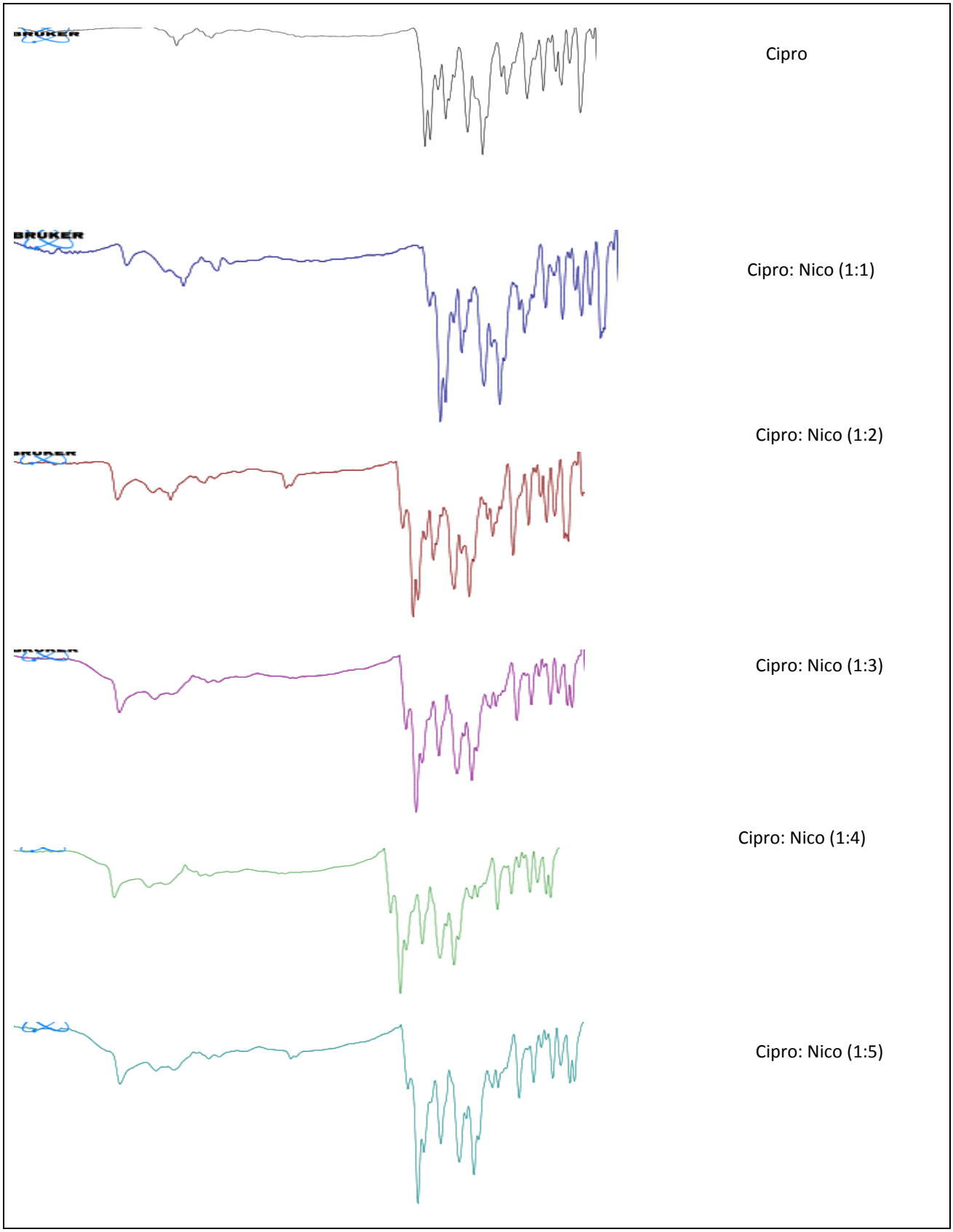



**Fig no. 1: FT-IR graph**

**Table no. 1: Comparative IR study**

| Functional group | Wave number($cm^{-1}$) | | | | | |
|---|---|---|---|---|---|---|
| | ciprofloxacin | Batch (1:1) | Batch (1:2) | Batch (1:3) | Batch (1:4) | Batch (1:5) |
| C=O Stretch of ket on | 1584.92 | 1585.95 | 1585.48 | 1580.79 | 1580.21 | 1581.21 |
| C- f stretch of fluoride | 1175.65 | 1175.96 | 1176.30 | 1180.81 | 1180.42 | 1179.87 |
| Aromatic stretch | 3040.73 | 3042.56 | 3042.61 | 3149.62 | 3146.84 | 3041.10 |
| CO-acid | 1614.73 | 1614.74 | 1614.74 | 1615.23 | 1615.23 | 1615.23 |
| OH acid | 2841.25 | 2854.83 | 2844.89 | 2837.86 | 2779.58 | 2839.81 |

**Determination of saturation solubility:**

The saturation solubility of pure drug and Co-crystals are given in table Prepared Co-crystals have shown increased solubility in comparison to the pure drug. The saturation solubility of Cipro: Nico co-crystals was increased than that of Ciprofloxacin. The difference in saturation solubility of Cipro:Nico co-crystal and ciprofloxacin is highly significant, The saturation solubility of Cipro:Nico(1:1), Cipro:Nico(1:2), Cipro:Nico(1:3), Cipro:Nico(1:4) & Cipro:Nico(1:5) is increases 2.84, 2.86, 2.84, 2.7 & 2.58 fold respectively. The saturation solubility of all the Co-crystals is improved than that of pure ciprofloxacin.

**Table no.2 : Saturation solubility of ciprofloxacin and co-crystals in Distilled water**

| System/parameter | Concentration µg/ml) |
|---|---|
| Cipro:nico(1:1) | 77.8±0.1 |
| Cipro:nico(1:2) | 78.2±0.3 |
| Cipro:nico(1:3) | 77.7±0.25 |
| Cipro:nico(1:4) | 74.6± 0.4 |
| Cipro:nico(1:5) | 70.8±0.3 |
| Cipro | 27.3±0.45 |

**Determination of drug content:**

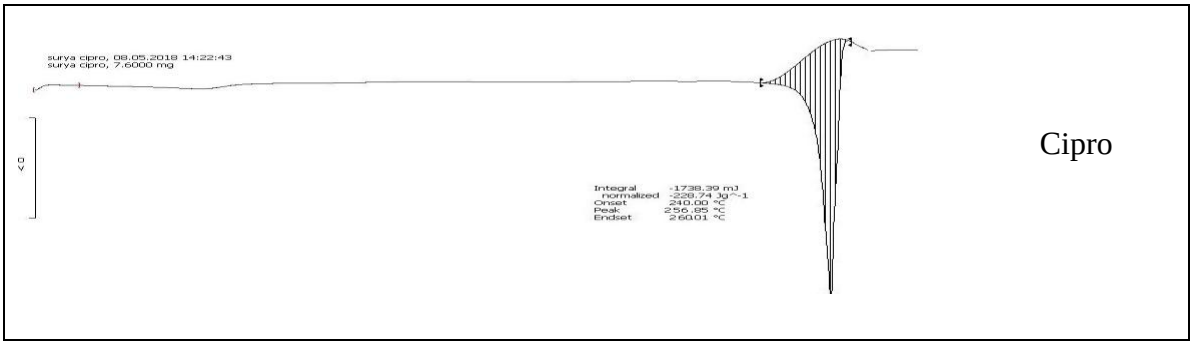
Percentage drug contents of synthesized ciprofloxacin co-crystals with nicotinamide. In various batches (1:1, 1:2, 1:3, 1:4,& 1:5) Shown in the table no3.

**Table no.3:% drug content**

| Formulation type | Ratio | Percent Drug Content±SD |
|---|---|---|
| CIPRO: NICO | 1:1 | 92.0±0.8895 |
| CIPRO: NICO | 1:2 | 91.71±1.38 |
| CIPRO: NICO | 1:3 | 91.84±1.088 |
| CIPRO: NICO | 1:4 | 92.89±0.74 |
| CIPRO: NICO | 1:5 | 92.10±0.44 |

**Differential Scanning Calorimetry (DSC):**

Are usually formed by a strong physical interaction between an API and a co-former. The existing physical interaction expected to be between an API and a co-former is hydrogen bond formation between polar functional groups of API and co-former. This interaction results in moderate to complete alterations in molecular arrangement of co-crystal formed, thus giving a new melting point and /or solubility. On the basis of PXRD studies which indicated completely different diffractograms of newly formed co-crystals from either an API or co-former. Thus, the strength of hydrogen bonding will definitely influence the melting point characteristics of a co-crystal. Thus, it could be concluded that the alteration in the melting point of an API could be possible via co-crystallization resulting in a co-crystal with a melting point of either in between that of the API and Co-Former or lower than the API or co-form er.[9]




Cipro

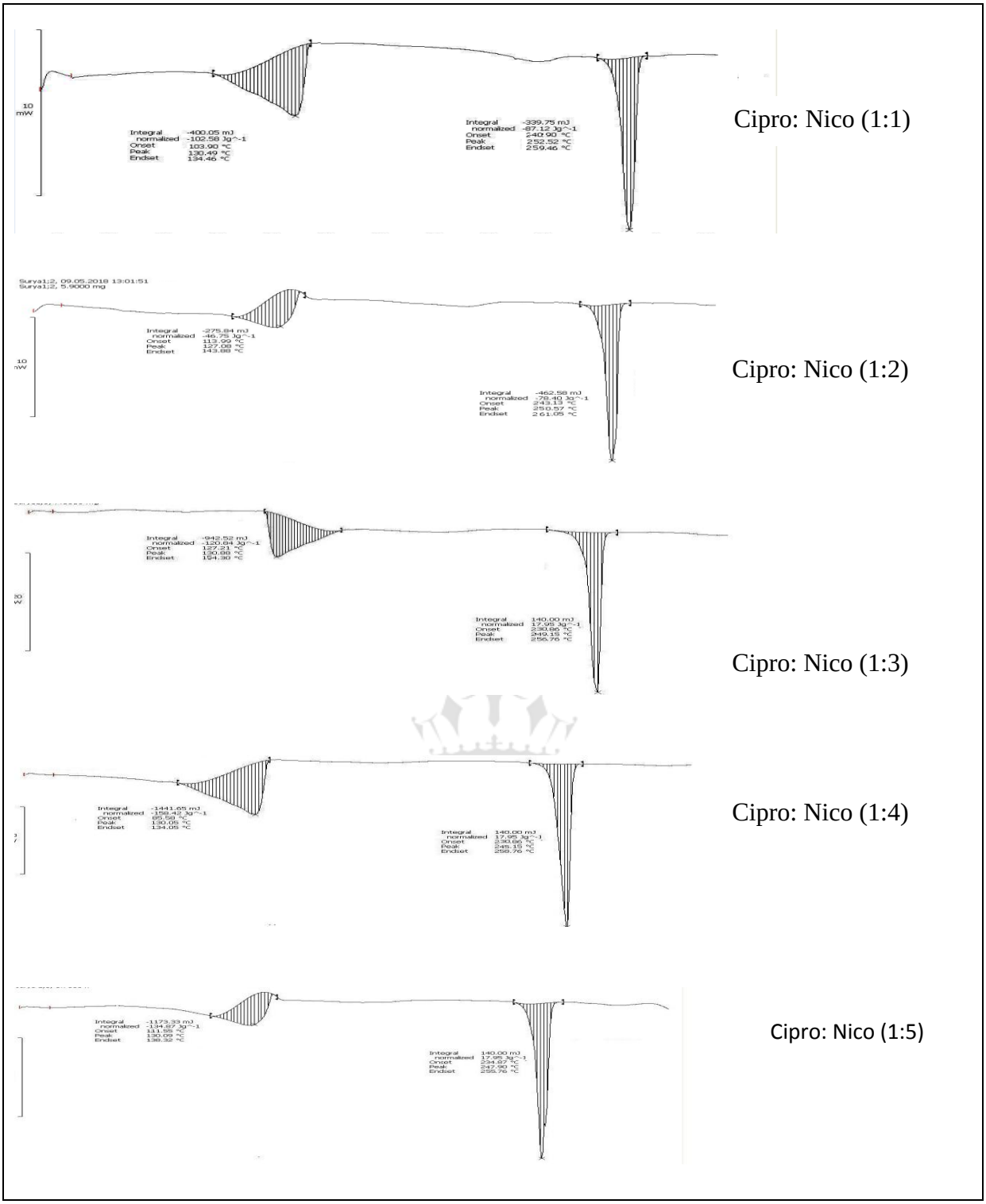



**Fig no. 2 DSC thermogram**

**XRPD results showing 2θ values with high peak intensity:**

As shown in figures unique XRPD pattern indicate different 2θ values of the drug and co-crystals shows peak intensities at various diffraction angles (2θ). It can be seen that the crystals and co-crystals drug possessing the different internal structure with significant

habit modification. Further, the relative intensities of their XRPD peaks were modified which might be attributed to the different crystal habits and arrangement of molecules.[8]The e of crystallinity (RDC) by equation RDC= I sample /I ref and table 4 indicates the value of RDC for different samples. The XRPD pattern of prepared co-crystals exhibited changes in both numbers and intensities of peaks compared to pure ciprofloxacin at specific angles. From peak intensities of Cipro:Nico(1:1), Cipro:Nico(1:2), Cipro:Nico(1:3), Cipro:Nico(1:4), Cipro:Nico(1:5) it can be concluded that there is an increase in crystallinity of co-crystals compared to pure ciprofloxacin which attributes to improvement in the dissolution profile of sample and can be justified by dissolution result.[9]

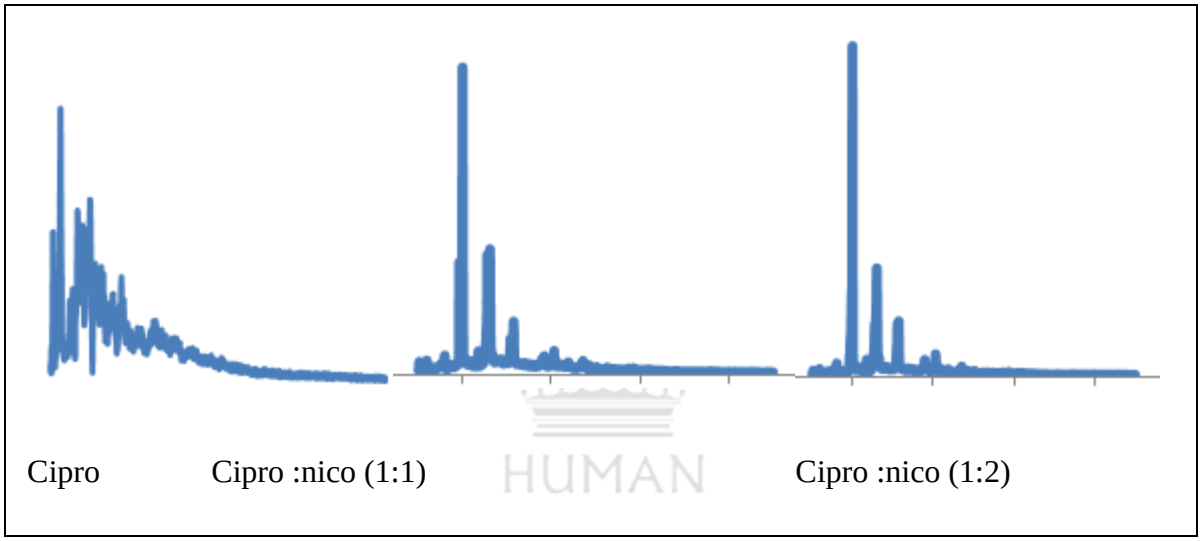



**Fig. no. 3: XRPD pattern**

From the XRPD results, the relative degree of the crystallinity was calculated and results conclude that crystallinity of co-crystals was increased compared to pure ciprofloxacin.

**Table no.:4: Relative degree of crystallinity**

| 2θ | 1:1 | 1:2 | 1:3 | 1:4 | 1: 5 |
|---|---|---|---|---|---|
| 10.44 | 2.5 | 1.32 | 2.08 | 6.9 | 2.6 |
| 10.24 | 2.5 | 1.83 | 2.8 | 4.3 | 1.3 |
| 15.97 | 1.9 | 1.45 | 1.9 | 1.7 | 3.3 |
| 19.88 | 4.6 | 7.6 | 1.9 | 2.2 | 1.3 |
| 20.07 | 9.5 | 7.3 | 1.6 | 1.2 | 1.3 |
| 23.56 | 1.05 | 1.25 | 1.5 | 1.5 | 1.42 |
| 23.72 | 1.64 | 1.76 | 1.7 | 1.17 | 2.60 |

***In vitro* drug release:**

In the dissolution studies of pure ciprofloxacin and its co-crystals with Nicotinamide, in batches (1:1, 1:2, 1:3, 1:4,& 1:5) showed improvement in dissolution profile. Dissolution curves of pure ciprofloxacin and co-crystals in 0.1 N shown in fig. 40. The co-crystals have improved the dissolution rate of ciprofloxacin as compared to the original drug. Percent drug dissolved in 60 min.

**Table no. 5: % drug release**

| % DRUG RELEASE | | | | | | |
|---|---|---|---|---|---|---|
| **Time** | **A(1:1)** | **B(1:2)** | **C(1:3)** | **D(1:4)** | **E(1:5)** | **DRUG** |
| **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| **5** | 77.92±1.06 | 79.34±1.0 | 76.5±0.97 | 66.03±1.08 | 65.6±1.20 | 54.94±1.2 |
| **10** | 78.39±1.11 | 79.81±0.99 | 76.73±1.0 | 68.44±0.96 | 67.73±1.04 | 56.84±0.92 |
| **15** | 78.86±1.08 | 80.28±1.32 | 77.21±0.81 | 68.92±1.40 | 68.92±1.08 | 59.21±1.09 |
| **30** | 79.57±1.14 | 81.23±0.86 | 77.92±0.81 | 69.86±1.34 | 69.39±1.03 | 61.81±1.06 |
| **45** | 80.05±0.99 | 81.47±1.52 | 78.39±1.07 | 70.81±1.24 | 69.63±1.69 | 62.52±1.68 |
| **60** | 80.28±1.06 | 81.94±1.10 | 78.63±0.94 | 73.18±1.05 | 72.23±1.20 | 63.94±0.86 |

The faster dissolution of ciprofloxacin co-crystal due to changes in size and shape, crystallinity pattern and crystal habit. It is also seen that batch1:2 co-crystal having a higher dissolution than co-crystals of 1:1.batch 1:1 co-crystal having a higher dissolution than co-crystals of batch 1:3.batch 1:3 co-crystals having a higher dissolution than co-crystals of batch 1:4 & 1:5

**CONCLUSION**

In conclusion, modification of Ciprofloxacin by co-crystallization method resulted in the crystallization of Ciprofloxacin. Due to co-crystals formed in crystallization greatly affected crystal habit. The crystals showed significant improvement in dissolution rate, solubility and flow properties than Ciprofloxacin drug. As dissolution, data is a good primary indicator for in-vivo performance. There was no polymorphic form of Ciprofloxacin observed from X-ray powder diffraction and DSC pattern. Hence, the change of crystals Properties may result from the alteration of crystal habit.

## ACKNOWLEDGMENT

Thanks to all G.C.O.P.K. organization for the support for completion of the work. Special thanks to Guide Yogeshkumar Gavhane Sir. Thanks to my all friends.

## REFERENCES

1) Shubhangi a bagde, Kanchan p Upadhye, Gauri r Dixit, formulation and evaluation of poorly water-soluble drug, IJPSR, 2018, 4988-4997.
2)Sevukaranjan M, Tanuja B, Riyaz sodanapalli, synthesis and characterization of pharmaceutical co-crystals, 2011, 1288-1293.
3)Sandeep kalepu, Vijaykumar nekkanti, insoluble drug delivery strategies, Acta Pharmaceutica sinica, B,2015.
4)www.pubchem.com
5) United sStates pharmacopeia XXXI. "The official compendia of standards", The United states pharmacopoeial Convention, Rockville, 2008,217.
6) Mulye SP, Jamadar S A, Karekar P S, Pore Y V, Dhawale S C. "Improvement in physicochemical properties of ezetimibe using a crystal engineering technique", An International Journal on science and technology of wet and dry particulate system. 2012,222, 131-138.
7) Flory K. "Analytical profiles of drug substances", Elsevier publications, Academic press 18. 1989,221-288.
8) R. P. Patel, H Patel, AH. Baria, "Formulation and Evaluation of Liposomes of Ciprofloxacin", Int J Drug Deliv Tech. 2009, volume 1,Issue 1, 16-23.
9) Patel R. P, Patel H, Baria AH. "Formulation and Evaluation of Carbopol Gel
Containing Liposomes of Ciprofloxacin", (Part-II), Int J Drug Deliv Tech. 2009, volume 1, Issue 2, 42 – 45.
10) Vanshiv S, Rao R. "Physicochemical characterization and in vitro dissolution of oxcarbazepine and β-cyclodextrin inclusion complexes", Indian Drugs.2008, 45, 815-820.
11)Sinko P J. "Micromeritics, Martins Physical Pharmacy and Pharmaceutical Sciences". Lippincott Williams and Wilkins.5th edition. 557.
12)Labhasetwar V, Deshmukh S V, Dorle A K, "Studies on some crystalline forms of ibuprofen", Drug dDevelopment and Industrial Pharmacy, 1993, volume 19, 631-641