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# Preliminary assessment on cocrystals of nicotinamide:cinnamic acid and nicotinamide:p-coumaric acid at different solvents and ratio

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## ABSTRACT

Cocrystal plays an important role in the pharmaceutical industry to improve the low solubility and bioavailability of drugs. In this study, the cocrystal formation screening was carried out for nicotinamide(NIC) as the API (Active Pharmaceutical Ingredient) with two coformers; cinnamic acid (CIN), and *p*-coumaric acid (COU) using recrystallization method with different solvents (methanol, ethanol, and acetonitrile) and molar ratios of NIC:CIN and NIC:COU of 1:1, 1:2 and 2:1. The NIC:CIN and NIC:COU mixtures were characterized using Differential Scanning Calorimetry (DSC), Powder X-ray Diffraction (PXRD), and Fourier Transform Infrared (FTIR) to assess the formation of cocrystal. All characterization data for NIC:CIN mixtures showed that the use of different types of solvents and molar ratios have no significant effect on the formation of the cocrystal. The characterization data showed the formation of similar NIC:CIN cocrystal with no polymorphism with a melting temperature of 96–98 $^{o}$C for all mixtures. The diffraction pattern of all NIC:CIN also showed similar new peaks at 2θ of 6.7°, 17.7°, 20.6°, 22.4°, and 25.1°. The DSC and PXRD data of NIC:CIN were supported by FTIR which revealed similar hydrogen bonding interaction for all NIC:CIN mixtures. The characterization of NIC:COU mixture revealed four different cocrystal forms with melting points of 118 °C, 152 °C, 160 °C, and 169 °C. The PXRD data of NIC:COU mixture also showed different diffraction patterns signifying distinct crystalline identities which supported with different FTIR spectrum validating the difference in hydrogen bonding interaction. It was observed that the use of different types of solvents did not give significant effects on the formation of NIC:CIN and NIC:COU cocrystals.

**Keywords:** *Nicotinamide, Cocrystal Pre-Characterization, DSC, PXRD, FTIR*

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## INTRODUCTION

Cocrystallization is an alternative method used to circumvent the problems associated with the active pharmaceutical ingredient (API) with low bioavailability [1]. Cocrystal can be defined as a stoichiometric multi-component system interacting non-covalently where all components present in solid under ambient condition [2-4]. The pharmaceutical industry has drawn significant interest in the formation of cocrystals over the last two decades, which are acknowledged as the pharmaceutical cocrystal [5-10]. The pharmaceutical cocrystal is defined as a compound composed of API and an appropriate coformer, those substances available are generally recognized as safe (GRAS) [1]. The coformer selection mostly depends on the synthon formation approach, which constructs the supermolecule by utilizing the specific interaction between the functional groups of the molecules in the crystal lattice [11]. The cocrystallization is recognized as an important method available to obtain the crystalline forms of molecules where salts or solvates are desired [12].

The method widely used to assess the cocrystal formation is through the solid dispersion method [13, 14]. The use of heat, solvent, or combination of heat and solvent during the preparation of the solid dispersion may produce polymorphic forms of the cocrystal [13]. The recrystallization method is referred to as a very fast crystallization method, which has much in common with the actual crystallization that governed the same law [15].

Nicotinamide ($C_6H_6N_2O$, pyridine-3-carboxamide), Figure 1(a) also known as niacinamide is an amide compound produced in vivo from the nicotinic acid (vitamin $B_3$), used as API in the formation of the cocrystal in this study. The amide group and pyridine ring enable the heterosynthon formation with the carboxylic acid group [16] of the coformers. Cinnamic acid (CIN), Figure 1(b) and *p*-coumaric acid (COU), and Figure 1(c) with the carboxylic acid functional group were used as the coformer for the cocrystal formation with the NIC. The additional hydroxyl group on COU molecules act as the additional site for hydrogen bonding formation that serves as hydrogen bond donor to form the NIC:COU cocrystal.

NIC used as the API was reported to have four polymorphs with melting points of 126-128 $^{o}$C, 112-117 $^{o}$C, 107-111 $^{o}$C, and 101-103 $^{o}$C, which were prepared with different crystallization conditions [13]. The use of different NIC polymorphs may form different cocrystal forms with CIN, and COU. Thus, the modification of crystallization conditions such as the molar ratio of the precursors and the solvent used for the preparation of the solid dispersion may change the cocrystal form compared to the published cocrystal of NIC:CIN [17] and NIC:COU [18].

It was anticipated the main synthon formation which may be utilized for the formation of cocrystal between nicotinamide with cinnamic acid, and *p*-coumaric acid is acid dimer, O-H···O, amide dimer, N-H···O, acid pyridine heterosynthon, O-H···N and C-H···O, and acid amide heterosynthon O-H···O and N-H···O [1]. The reported NIC:CIN cocrystal was synthesized using

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the ethanol solvent [17]. However, the NIC:COU cocrystals with four polymorphs were synthesized using different crystallization conditions such as the variety of solvent used, method of crystallization, and also the molar ratio of the compound used [18].

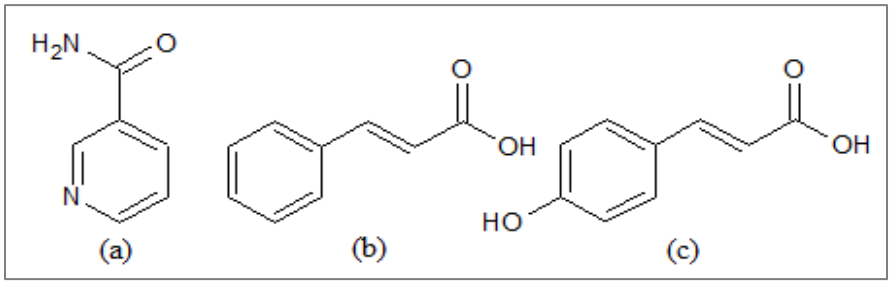


**Figure 1:** Molecular structure of (a) nicotinamide (NIC), (b) cinnamic acid (CIN), and (c) *p*-coumaric acid (COU).

The formation of cocrystal polymorph often occurs when different crystallization conditions are applied to the mixture [19-21]. Polymorphism is defined as the ability of a substance to crystallize in more than one distinct crystal habit (different crystal packing arrangements and/or different conformations), which has a great impact on the bioavailability of the drug [12]. In 2003, the number of cocrystal polymorphs deposited to the Cambridge Structural Database (CSD) was 46 cocrystals, and this number kept increasing in recent years [12]. Various examples of cocrystal polymorphs have been reported [22] such as ethenzamide with saccharin, gentisic acid, and ethylmalonic acid [23-26] and carbamazepine with malonic acid, 4-hydroxybenzoic acid, isonicotinamide, 4-aminobenzoic acid, and nicotinamide [27-32]. Other cocrystal polymorphs reported were temozolomide with 4,4'-bipyridine-*N,N'*-dioxide [33], caffeine with glutaric acid [34], tryptamine with hydrocinnamic acid [35], meloxicam with salicylic acid [36, 37], and piroxicam with 4-hydroxybenzoic acid [38]. The existence of the cocrystal polymorphs increases the availability of the solid API forms which can alter specific physicochemical properties. The study of polymorphic form is a vast area, where McCrone had said that "every compound has different polymorphic form, and the number of polymorphic forms known for a particular substance is proportional to the time and energy spent in the research done on that compound" [12].

The ability of NIC:COU cocrystal [18] to form polymorphs with the use of different types of solvents direct this study to explore more on the effects of different molar ratios. CIN was chosen as another coformer to be cocrystallized with NIC due to the similarity of the molecular structure with COU. In addition, there was only one reported NIC:CIN cocrystal [17] and to date, there are no cocrystal polymorphs for NIC:CIN deposited in Cambridge Structural Database (CSD). Hence, this study aims to investigate the ability of different crystallization conditions

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(molar ratio and solvent) through recrystallization method to form the cocrystal polymorph of NIC:CIN and NIC:COU compared to the reported cocrystals structures.

## EXPERIMENTAL

### *Recrystallization Method*

The preparation of NIC:CIN and NIC:COU mixture and the characterization procedure were based on the previous study [39]. The mixture of NIC:CIN and NIC:COU were prepared using the rotary evaporator (Rotavapor R-210, BUCHI, Switzerland) at 50 °C (water bath temperature), 50 mbar (vacuum pressure), and 200 rpm speed. The mass of the mixture with respect to the molar ratio of the compounds is tabulated in Table 1. Prior, the mixture was completely dissolved in methanol (MeOH), ethanol (EtOH), or acetonitrile (ACN), where the amount of solvent was varied based on the solubility of the mixture in the respective solvent. The amount of solvent used to prepare NIC:CIN and NIC:COU mixture are as in Table 2. The dried mixture from the rotary evaporator was ground using the mortar and pestle to obtain the uniform size solid powder.

**Table 1:** The mass of NIC:CIN and NIC:COU mixture used for reprecipitation.

| Molar ratio | NIC:CIN (mg) | NIC:COU (mg) |
|---|---|---|
| 1:1 | 122 : 148 | 122 : 164 |
| 1:2 | 122 : 296 | 122 : 328 |
| 2:1 | 244 : 148 | 244 : 164 |

**Table 2:** Volume of solvents used to prepare the NIC:CIN and NIC:COU mixture.

| Solvents | NIC:CIN (mL) | NIC:COU (mL) |
|---|---|---|
| MeOH | 40 | 20 |
| EtOH | 30 | 30 |
| ACN | 20 | 40 |

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### *Differential Scanning Calorimetry (DSC)*

The DSC is a characterization method based on the heat of the reaction involved in the thermal change during the analysis. It is used to determine the melting point and purity of the compound, where the heat of the reaction is directly proportional to the mass quantity of the compound analysed [16]. The mixture of NIC:CIN and NIC:COU were analysed using a Mettler Toledo DSC, where the temperature and cell constant were calibrated using indium. The mixture (1-3 mg) was crimped in a non-hermetic aluminium DSC pan and heated (30 °C – 300 °C) at 10 °C/min under a continuous nitrogen purge (40 mL/min).

### *Powder X-ray Diffraction (PXRD)*

The PXRD is commonly used as a tool to determine the different crystalline phases of a compound, which has unique diffraction patterns for each structure. This method enables us to distinguish the presence of new crystallographic motifs, polymorph, or cocrystal [16]. A Rigaku powder diffractometer with Cu-$K_\alpha$ radiation ($\lambda = 1.5406$ Å) source was used at 40 kV and 40 mA to analyse the sample in the range of $2\theta$=5°-55° with scanning speed of 2°/min, and a step size of 0.02°.

### *Attenuated Total Reflection – Fourier Transform Infrared (ATR-FTIR)*

The infrared spectroscopy enables great information about the interactions between molecules in the crystal lattice. The ATR accessory results in a fast and non-destructive analysis with no sample preparation [16]. The Perkin Elmer spectrophotometer with 1 $cm^{-1}$ spectral resolution was used to determine the interaction between the nicotinamide and the coformers. The background spectrum was collected before analysis, which consisted of moisture and carbon dioxide band that will be deducted from the sample spectrum. The data collected was over the range of 4000-400 $cm^{-1}$.

## RESULTS AND DISCUSSION

### *Differential Scanning Calorimetry (DSC)*

The melting temperature of NIC, CIN, and COU is 129.94 °C, 134.44 °C [40], and 221.62 °C respectively as shown in Figure 2. The higher melting point of COU is concurrent with other studies [40-43] which due to the high thermal stability that is induced by the highly regular and abundant rigid benzene ring, the conjugated structure formed by the benzene ring, the double-carbon bonds in the COU chain [44] and the presence of hydroxyl group at the *-para* position on the benzene.

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The formation of NIC:CIN and NIC:COU cocrystals can be determined by the melting event of a mixture that is located in between (130-134 °C for NIC:CIN and 130-222 °C for NIC:COU) or below the melting points of the precursors (<130 °C) [45, 46], which is observed in all mixtures prepared. Figure 3 shows the melting points of all NIC:CIN cocrystals prepared using different molar ratios and solvents. The varieties of molar ratios and solvents used in the preparation of the cocrystals showed no significant difference with melting points of 96 °C to 98 °C.

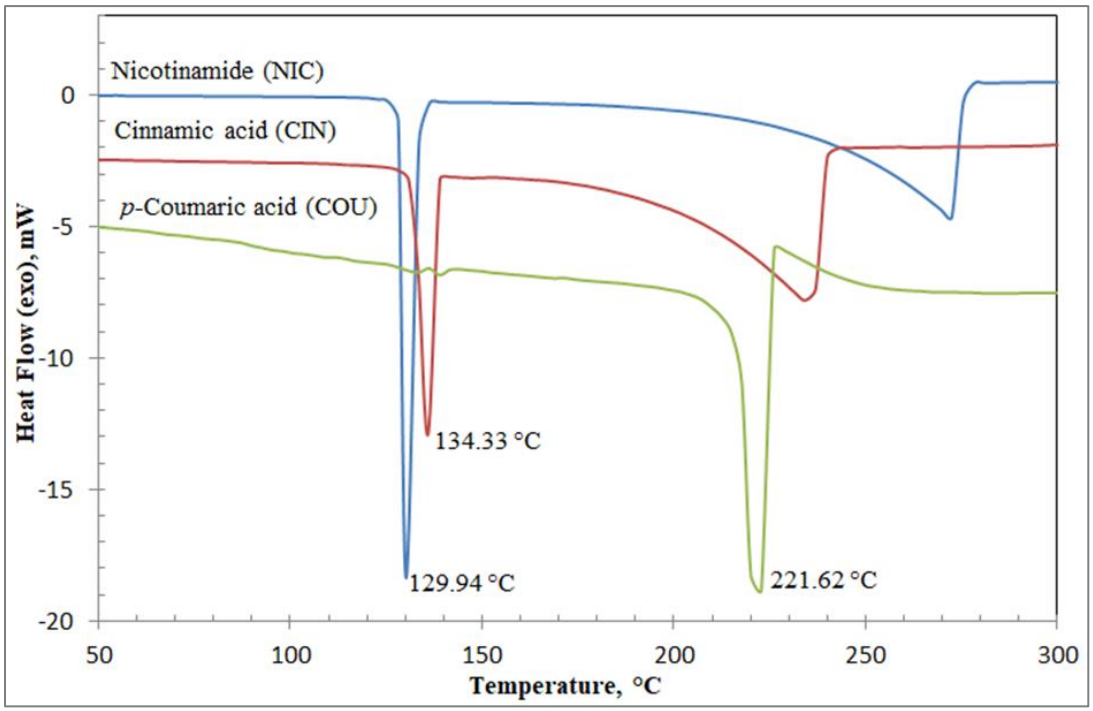


**Figure 2:** The melting points of NIC, CIN, and COU

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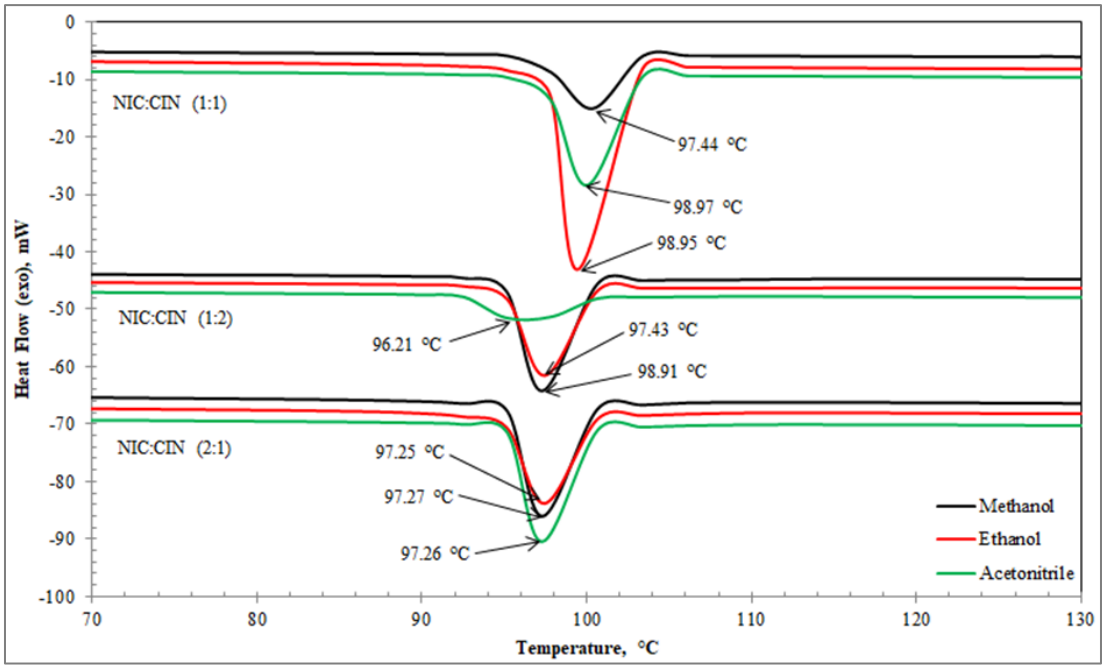


**Figure 3:** The melting points of NIC:CIN cocrystals prepared with different molar ratios and solvents

However, the NIC:COU cocrystals showed different melting events with phase transition due to the temperature change as shown in Figure 4. For NIC:COU (1:1) cocrystal, the solvent has been observed as the factor for the formation of three different cocrystal forms with melting points of 119 $^{o}$C, 152 $^{o}$C, and 160$^{o}$C. Both of the NIC:COU (1:2) cocrystals prepared using methanol and acetonitrile showed two melting points at 159 $^{o}$C and 169 $^{o}$C.

On the other hand, the NIC:COU (1:2) cocrystal prepared using ethanol only shows a single exotherm at 171 $^{o}$C, which is still comparable to the second exotherm of the other two similar molar ratio cocrystals prepared using methanol and acetonitrile. All of the NIC:COU (2:1) cocrystals show almost similar melting points at 118-119 $^{o}$C and 151-152 $^{o}$C for all of the solvents used. The slight difference (~1 $^{o}$C) between the NIC:COU (2:1) cocrystals may also form different crystal structures, which will be confirmed with PXRD and FTIR analysis. From the DSC data, it can be presumed that the NIC:COU cocrystal prepared from different molar ratios and solvents resulted in four different crystal forms with melting points of 118-119 $^{o}$C, 151-152 $^{o}$C, 159-161 $^{o}$C, and 169-171 $^{o}$C.

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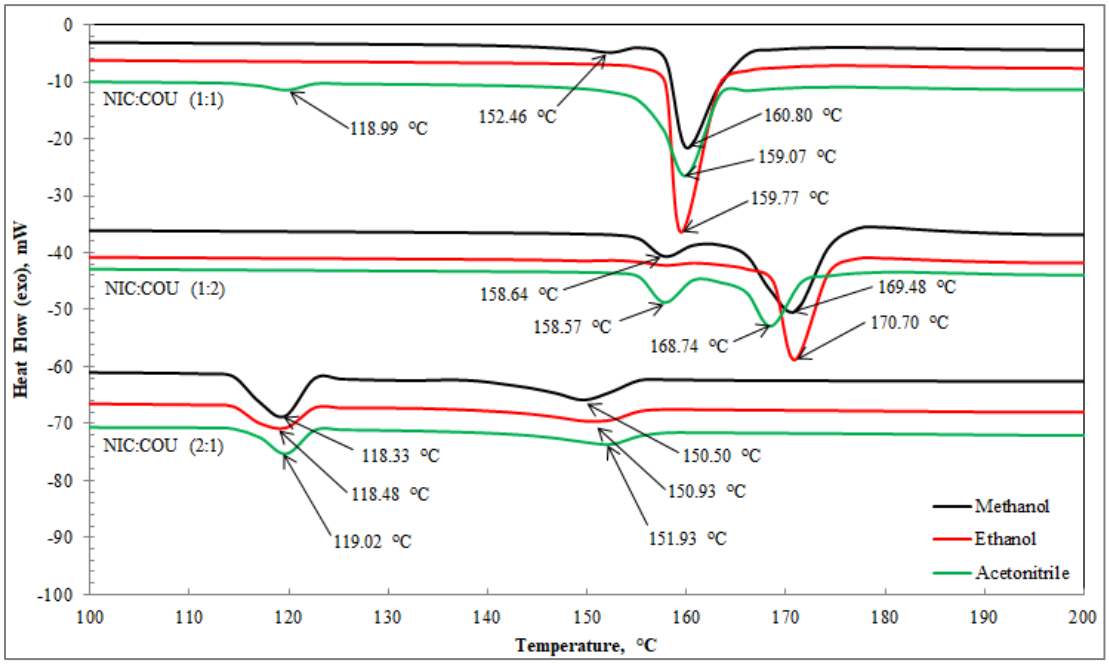


**Figure 4:** The melting points of NIC:COU cocrystals prepared with different molar ratios and solvents

### *Powder X-ray Diffraction (PXRD)*

The PXRD patterns of NIC, CIN, and COU are presented in Figure 5, and the cocrystals of NIC:CIN and NIC:COU prepared from different molar ratios and solvents are presented in Figure 6 and Figure 7 respectively. The characteristic peaks of NIC, CIN, and COU are in agreement with literatures at 2θ of 13.3° and 14.8° for NIC [47, 48], 9.7° for CIN [45, 49], and 22.2° for COU.

All the NIC:CIN cocrystals in Figure 6 show similar diffraction patterns with new diffraction peaks observed at 2θ of 6.7°, 17.7°, 20.6°, 22.4°, and 25.1°. The similarity of the PXRD patterns concurrent with the DSC results. These results prove that the different molar ratios and solvents used in the preparation of the NIC:CIN cocrystal have no significant effect on the crystal structure. The characteristic peak observed in NIC:CIN (1:2) at 2θ of 9.6° corresponds to the characteristic peak of CIN which is used in excess to produce the mixture.

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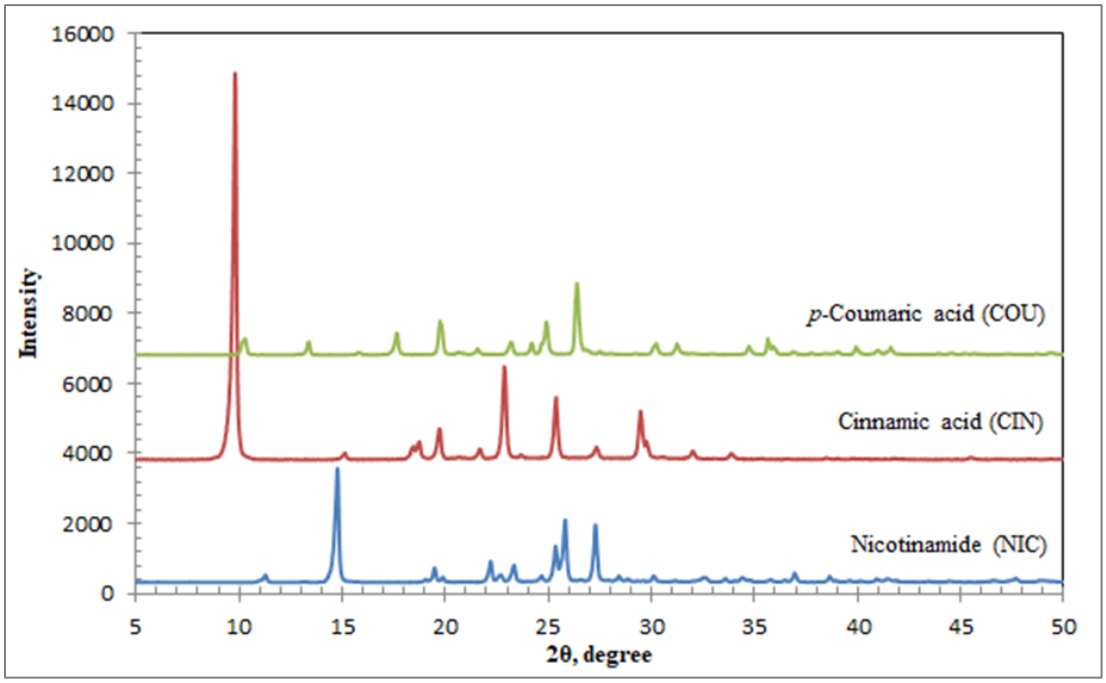


**Figure 5:** The diffraction patterns of NIC, CIN, and COU

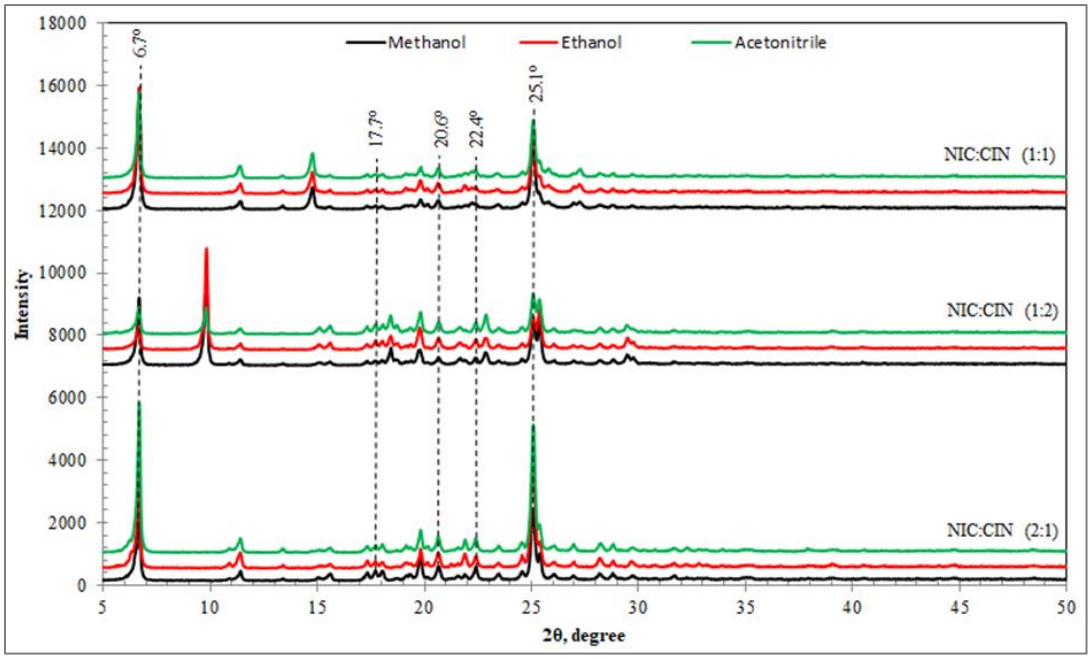


**Figure 6:** The diffraction patterns of NIC:CIN cocrystals prepared with different molar ratios and solvents

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Figure 7 shows the NIC:COU cocrystals prepared from different molar ratios and solvents. The NIC:COU (1:1) cocrystals prepared using different solvents showed different diffraction patterns, where the cocrystal prepared using methanol revealed eleven new diffraction peaks at 2θ of 5.9º, 11.8º, 14.8º, 15.7º, 16.7º, 17.1º, 18.2º, 18.9º, 20.0º, 23.8º and 24.6º.

Based on the melting points of NIC:COU (1:2) cocrystals, it was suspected that the cocrystals prepared using methanol and acetonitrile will form a similar crystal form, hence similar diffraction patterns. The NIC:COU (1:2) cocrystal prepared using methanol revealed new diffraction peaks at 2θ of 5.9º, 15.7º, 16.7º, 18.2º, 18.9º, 20.0º, 23.8º and 24.6º. In conjunction, the NIC:COU (1:2) cocrystals prepared using ethanol, and acetonitrile revealed the absence of diffraction peaks of 2θ at 5.9º, 15.7º and 18.2º, and 2θ at 5.9º and 18.2º respectively. The slight difference in the diffraction peaks is presumed not to have a significant effect on the crystal structure.

The NIC:COU (2:1) cocrystals prepared using methanol and ethanol revealed several new diffraction peaks at 2θ of 5.9º, 11.8º, 15.7º, 16.7º, 17.1º, 18.2º, 18.9º, 20.0º, 23.8º and 24.6º. However, NIC:COU (2:1) cocrystal prepared using acetonitrile revealed a distinct diffraction pattern with new diffraction peaks observed at 2θ of 14.8º, 15.7º, 16.7º, 18.9º, 20.0º, and 24.6º. The difference in the NIC:COU (2:1) cocrystal diffraction patterns explained the slight difference in the melting points of NIC:COU (2:1) cocrystals as discussed in the previous section.

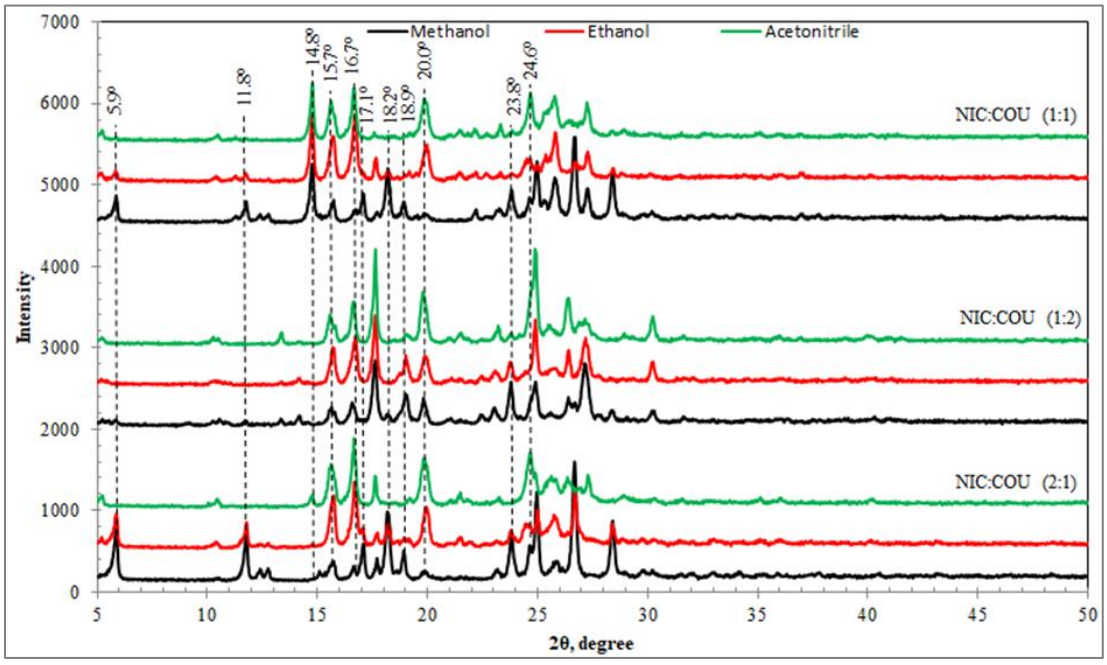


**Figure 7:** The diffraction patterns of NIC:COU cocrystals prepared with different molar ratios and solvents

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### *Fourier Transform Infrared (FTIR)*

Table 3 and Table 4 represent the summary of peak position in the mixtures compared to the precursors. The functional groups of NIC, CIN, and COU were only observed at significant peaks that were able to form the hydrogen bonding. The peaks shift of NIC were observed at the C=O and -$NH_2$ of amide, and nitrogen atom at the pyridine ring. The peaks shift of CIN, and COU were observed at the –COOH (carboxylic acid), and –OH (phenol). The peaks shift of NIC:CIN cocrystals prepared from different molar ratios and solvents did not demonstrate a significant difference, signifying the similar hydrogen bonding interaction. These results justify the similarity of melting points and the diffraction patterns as discussed in the previous sections.

The NIC:COU (1:1) cocrystals prepared using different solvents revealed different peak shift patterns, which supports the DSC and PXRD results. The NIC:COU (1:2) cocrystals prepared using methanol and acetonitrile do not demonstrate similar hydrogen bonding patterns as presumed in the PXRD. The difference in the hydrogen bonding interactions may form different crystal structures of NIC:COU (1:2) cocrystals. The NIC:COU (2:1) cocrystals prepared using ethanol and acetonitrile possessed similar hydrogen bonding interaction with no O-H···N observed compared to the NIC:COU (2:1) cocrystal prepared using methanol. These results also show that the characterization of cocrystal formation needs several methods that support each other to come out with reliable data. The cocrystal formation could be observed by the characterization methods used in this study; DSC, PXRD, and FTIR, which help to explain the difference in the physical properties of the mixture. The characterization methods used in this study can provide complementary data on the physicochemical characteristics of a solid in pharmaceutical product development [47].

**Table 3:** FTIR data for NIC, CIN, and NIC:CIN cocrystal based on different crystallization conditions

| Functional Group | NIC | CIN | NIC:CIN (1:1) | | | NIC:CIN (1:2) | | | NIC:CIN (2:1) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | MeOH | EtOH | ACN | MeOH | EtOH | ACN | MeOH | EtOH | ACN |
| C=O (amide) | 1674 | - | 1683 | 1669 | 1686 | 1668 | 1669 | 1668 | 1669 | 1669 | 1674 |
| Asymmetric -$NH_2$ | 3354 | - | 3320 | 3351 | 3316 | 3317 | 3350 | 3333 | 3333 | 3353 | 3342 |
| Symmetric –$NH_2$ | 3145 | - | 3122 | 3182 | 3121 | 3118 | 3180 | 3127 | 3122 | 3180 | 3132 |
| -N- (pyridine) | 1393 | - | 1389 | 1391 | 1389 | 1389 | 1391 | 1390 | 1389 | 1391 | 1390 |
| O-H···N | - | - | 1942 | 1889 | 1942 | 1942 | 1900 | 1942 | 1942 | 1888 | 1941 |
| O-H (acid) | - | 3027 | 3055 | 3002 | 3025 | 3064 | 3005 | 3026 | 3061 | 3005 | 3022 |

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**Table 4:** FTIR data for NIC, COU, and NIC:COU cocrystals based on different crystallization conditions

| Functional Group | NIC | COU | NIC:COU (1:1) | | | NIC:COU (1:2) | | | NIC:COU (2:1) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | MeOH | EtOH | ACN | MeOH | EtOH | ACN | MeOH | EtOH | ACN |
| C=O (amide) | 1674 | - | 1671 | 1662 | 1667 | 1674 | 1679 | 1667 | 1678 | 1678 | 1667 |
| Asymmetric $-NH_2$ | 3354 | - | 3395 | 3425 | 3355 | 3395 | 3435 | - | 3397 | 3440 | 3356 |
| Symmetric $-NH_2$ | 3145 | - | 3176 | 3167 | 3181 | 3167 | 3158 | 3178 | 3166 | 3154 | 3177 |
| -OH (phenol) | - | 3425 | 3356 | 3378 | 3424 | 3355 | 3388 | 3426 | 3359 | 3374 | 3426 |
| -N- (pyridine) | 1393 | - | 1398 | 1410 | 1404 | 1399 | 1411 | 1422 | 1396 | 1392 | 1394 |
| O-H···N | - | - | 1897 | - | 1900 | 1900 | - | - | 1896 | - | - |
| O-H (acid) | - | 3029 | 3058 | 3014 | 2905 | 3064 | 3017 | 2899 | 3055 | 3011 | 2902 |

## CONCLUSION

The cocrystal formation of NIC:CIN and NIC:COU was investigated through a reprecipitation method with different molar ratios and solvents. The characterization data from DSC, PXRD, and FTIR revealed the formation of a similar cocrystal form for NIC:CIN cocrystals. On the other hand, four different cocrystal forms of NIC:COU were synthesized from different molar ratios and solvents. The molar ratio and the type of solvent used were the crucial factor in the formation of different crystal forms of NIC:COU, which was contrary to the NIC:CIN cocrystals. The stability of NIC:CIN cocrystal may be the factor of the formation of similar cocrystal forms regardless of the molar ratio and different types of solvents used to synthesize the cocrystal. However, the variation of molar ratios and solvents used to show different interactions through hydrogen bonding, thermal instability, and crystal phase between NIC and COU. The formation of different cocrystal structures for NIC:COU has also been suspected due to the additional hydroxyl group serve as the additional site for the hydrogen bonding to form. The additional site for hydrogen bonding can be used for the molecules to interact differently, thus forming a new crystal lattice.

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