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# Characterization of citric acid-nicotinamide cocrystals prepared by the grinding method for enhanced stability of effervescent products

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## ABSTRACT

Effervescent dosage forms contain acidic and basic components that react upon dissolution in water to releasing carbon dioxide ($CO_2$). In this study, citric acid was selected as the acidic component due to its affordability, high water solubility, and greater acidity than tartaric acid, while sodium bicarbonate was used as the basic component. However, citric acid is highly hygroscopic and can react prematurely with sodium bicarbonate under high humidity conditions (>20% RH, 25 °C), leading to undesirable premature effervescent reactions during manufacturing. To address this issue, this study aimed to modify a cocrystal of citric acid with nicotinamide as a co-former to enhance stability. Cocrystals were prepared using the grinding method at molar ratios of 1:1 (CN-Cocrystal 1:1) and 1:2 (CN-Cocrystal 1:2). The resulting solids were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier-transform infrared spectroscopy with attenuated total reflectance (FTIR-ATR), scanning electron microscopy (SEM), and moisture interaction testing. PXRD results showed new crystalline phases for both cocrystals, with distinct diffraction peaks at 2θ values of 17.1132°; and 21.761° (1:1); and 16.9117°; 20.2717°; and 20.9566° (1:2). DSC thermograms exhibited new endothermic peaks at 107.01 °C (1:1); and 114.28 °C (1:2). FTIR spectra revealed shifts in the -OH group of citric acid and the -NH group of nicotinamide, indicating hydrogen bonding. SEM analysis confirmed distinct surface morphologies for the cocrystals compared to the pure compounds. Notably, moisture interaction testing demonstrated that both cocrystals maintained tablet diameter up to 120 minutes, while the control tablets showed significant dimensional changes. In conclusion, co-crystallization of citric acid with nicotinamide enhances moisture resistance and prevents premature effervescent reactions, with CN-Cocrystal 1:2 showing superior physical characteristics, making it a promising candidate for effervescent formulations.

**Keywords**: Citric acid, Cocrystals, Effervescent, Grinding, Nicotinamide

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## INTRODUCTION

Effervescent formulations consist of acidic and basic components that react rapidly upon exposure to water, resulting in the liberation of carbon dioxide gas. This reaction facilitates the disintegration of the dosage form and enhances the release of active pharmaceutical ingredients (APIs). The effervescent also generates foam within the formulation as a visible indication of the reaction (Kailas Anil et al., 2022). Citric acid was selected as the acidic component in this study due to its relatively low cost, high water solubility, and greater acidity than tartaric acid (Setiana & Kusuma, 2018). In effervescent formulations, citric acid also serves to mask the bitter taste of the drug and improve its palatability (Lambros et al., 2022). Sodium bicarbonate was employed as the basic component in this formulation (Patel & Siddaiah, 2018).

Citric acid can react with sodium bicarbonate to produce effervescence when exposed to high humidity conditions (above 20% relative humidity at 25 °C), leading to a premature effervescent reaction (Pagire et al., 2020). This phenomenon refers to unintended interactions between the acidic and basic components during the manufacturing process, resulting in effervescence prior to tablet compression. It is typically indicated by foaming and stickiness of the acid–base mixture. Such premature reactions can adversely affect the quality and integrity of the final dosage form (Zheng et al., 2019). Therefore, formulation modifications are necessary to prevent this issue during the development of effervescent products. In this study, modification was applied to the citric acid component by forming a citric acid-nicotinamide cocrystal. A previous study found that citric acid, after co-crystallization, successfully inhibited premature effervescent reactions (Dhondale et al., 2023; Pagire et al., 2020).

Cocrystal is a solid material composed of two or more solid molecules (in a specific stoichiometric ratio) that form a distinct crystalline lattice under certain conditions and are held together by intermolecular interactions, such as hydrogen bonds and Van der Waals forces (Karagianni et al., 2018; Nawatila et al., 2017). In this study, two components were utilized citric acid as the pharmaceutical compound and nicotinamide as the co-former. A co-former is a secondary molecule that interacts with an APIs through bonding mechanisms, such as hydrogen bonding, to form a new crystalline structure with enhanced stability against moisture (Singh et al., 2023). Nicotinamide is a vitamin B derivative that has a significant role in forming intermolecular hydrogen bonds. The ability of the nitrogen atom in the nicotinamide pyridine ring to form strong hydrogen bonds with carboxylic acid groups has made it a favorable compound for cocrystal formation (Kamis et al., 2020). Furthermore, nicotinamide is classified as "GRAS" (Generally Recognized as Safe), indicating that it is considered safe for use in food and pharmaceutical products (Wathoni et al., 2022).

Several methods can be employed to develop cocrystal systems, including grinding, solvent evaporation, slurry, ultrasonication, and others (Pawar et al., 2021). Grinding is a technique that involves milling the APIs and the co-former using a ball mill chamber containing quartz balls and a small amount of solvent. The solvent acts as a catalyst to enhance the interaction between components in a controlled ratio (Karagianni et al., 2018). Based on the study by Panzade, cocrystals prepared at molar ratios of 1:1 and 1:2 using nicotinamide as a co-former were successfully formed. The successful co-crystallization was evidenced by specific intermolecular interactions between the APIs and the nicotinamide co-former, indicating the generation of a new crystalline phase that led to alterations in the material's physicochemical properties. In this study, ethanol was used as the solvent, and the molar ratios of citric acid to nicotinamide were set at 1:1 and 1:2, respectively (Panzade & Shendarkar, 2019).

The variation in the molar ratios of citric acid to nicotinamide (1:1 and 1:2) is expected to influence the physical characteristics of the resulting cocrystals as well as the moisture interaction properties within the effervescent system. The physical characteristics of the cocrystals will be compared with those of the physical mixture and the individual pure components (citric acid and nicotinamide). The evaluation of cocrystal properties includes organoleptic, crystallinity profile

using Powder X-Ray Diffraction (PXRD), thermal behavior using Differential Scanning Calorimetry (DSC), infrared spectra profiling using Fourier Transform Infrared-Attenuated Total Reflection Spectroscopy (FTIR-ATR), and surface morphology characterization using Scanning Electron Microscopy (SEM). In addition, the moisture interaction properties will be assessed in a simulated effervescent system composed of the modified citric acid in cocrystal form and sodium bicarbonate as the basic component.

Based on the above, this study was conducted to characterize citric acid cocrystals using nicotinamide as a co-former at molar ratios of 1:1 and 1:2, employing the grinding method for the preparation of the acidic component in an effervescent system. Accordingly, the aim of this research is to identify the cocrystal composition with the most optimal physical characteristics and moisture interaction properties in preventing premature effervescent reactions. Studies investigating the influence of different citric acid–nicotinamide cocrystal molar ratios on these properties in effervescent formulations remain limited. Therefore, this study was designed to further explore these aspects and contribute to a better understanding of the potential role of cocrystal stoichiometry in improving the stability of effervescent pharmaceutical preparations.

## MATERIALS AND METHOD

### Materials

The materials used in this study included food-grade citric acid monohydrate (Shandong Ensign, China), food-grade nicotinamide (Hangzhou Rebtech Novel Material, China), food-grade sodium bicarbonate (Ihjuchem, Mongolia), food-grade lactose (Grande, USA), and 96% pharmaceutical-grade ethanol (Merck, Germany) as the solvent.

### Methods

#### Preparation of citric acid-nicotinamide cocrystal (CN-Cocrystal)

In this study, two cocrystal systems were prepared, consisting of citric acid-nicotinamide at a molar ratio of 1:1 (CN-Cocrystal 1:1) and 1:2 (CN-Cocrystal 1:2), with citric acid as a control.

Citric acid and nicotinamide were weighed according to the specified quantities (Table 1) and moistened with three drops of ethanol. The mixture was then transferred into a ball mill jar (Erweka 401, Germany) with quartz balls of appropriate size and quantity (4 balls with a diameter of 30 mm). The grinding process was carried out for 30 minutes at 120 rpm. The resulting powder was stored in a desiccator and subsequently subjected to characterization (Eesam et al., 2021).

**Table 1. Cocrystal system design**

| No. | Materials | Control | CN-Cocrystal 1:1 molar ratio | CN-Cocrystal 1:2 molar ratio |
|---|---|---|---|---|
| 1 | Citric Acid Monohydrate | 1.00 g | 1.00 g | 1.00 g |
| 2 | Nicotinamide | - | 0.58 g | 1.16 g |

#### Preparation of citric acid-nicotinamide physical mixture (CN-PM)

Citric acid and nicotinamide were weighed according to the specified quantities. Both powders were homogeneously mixed in a mortar using spatula without any energy or grinding. The powder was stored in a desiccator and subsequently subjected to characterization.

#### Physical characterization of CN-Cocrystal

##### Organoleptic

The organoleptic evaluation aimed to identify the color, taste, odor, and morphology of the powder. This assessment was conducted on citric acid (CA), nicotinamide (NIC), CN-PM, and CN-Cocrystal 1:1 and CN-Cocrystal 1:2.

**Characterization using PXRD**

This characterization was performed using a PXRD instrument (Phillips X'Pert Diffractometer, The Netherlands) to determine changes in the degree of crystallinity of CA, NIC, CN-PM, CN-Cocrystal 1:1 and 1:2. Sample was weighed 5-10 mg, and the measurement conditions were set at 40 kV voltage and 40 mA current (Winantari et al., 2017). The samples were scanned over a range of 2θ of 5°–50° (Abdullah et al., 2022).

**Characterization using DSC**

This characterization was conducted to analyze the thermal profiles of each material using a DSC instrument (Mettler Toledo, USA). The sample was weighed 3–4 mg were placed in aluminum pans and analyzed at a heating rate of 10 °C/min over a temperature range of 30–300 °C under a nitrogen atmosphere with a flow rate of 50 mL/min (Chaturvedi et al., 2017; Patil et al., 2023).

**Characterization using FTIR-ATR**

This characterization was performed using a FTIR-ATR instrument (Agilent Cary 630, USA) to observe shifts in the wavenumber of each material. Approximately 1–2 mg of sample was weighed and placed directly onto the ATR crystal, then constant pressure was applied to ensure adequate contact. The analysis was carried out at room temperature within a wavelength range of 400–4000 $cm^{-1}$ (Gozali et al., 2012; Tupe et al., 2023).

**Characterization using SEM**

This characterization was conducted to examine the surface morphology of the particles using a SEM instrument (FEI Inspect S50, Czech Republic). A 5 mg sample was prepared and coated with a thin layer of palladium-gold prior to analysis. The sample was scanned with an electron beam at an accelerating voltage of 30 kV and a current of 12 mA. Observations were carried out at magnifications of 100× and 500× (Abdullah et al., 2022; Umar et al., 2022).

**Moisture interaction**

This evaluation aimed to observe the influence of ambient humidity (50-60% RH) and ambient temperature (22-27ºC) on effervescent tablet simulations prepared using a combination of acid and base components. The acidic component used was citric acid cocrystals (CN-Cocrystal 1:1 and 1:2), while the basic component was sodium bicarbonate. The effervescent tablet simulations were formulated by mixing the acid and base components at a 1:3 (w/w) ratio, with lactose monohydrate added as a filler to achieve a tablet weight of 1 grams (Table 2) (Jacob et al., 2009).

**Table 2. Formula of effervescent tablet simulations for moisture interaction testing**

| No. | Materials | Control (grams) | CN-Cocrystal 1:1 molar ratio (grams) | CN-Cocrystal 1:2 molar ratio (grams) |
|---|---|---|---|---|
| 1 | Acid Component: | | | |
| | Citric Acid Monohydrate | 0.1875 | - | - |
| | CN-Cocrystal 1:1 | - | 0.1875 | - |
| | CN-Cocrystal 1:2 | - | - | 0.1875 |
| 2 | Base Component: | | | |
| | Sodium Bicarbonate | 0.5625 | 0.5625 | 0.5625 |
| 3 | Lactose Monohydrate* | 0.2500 | 0.2500 | 0.2500 |

*Lactose monohydrate comprising 25% of the total mixture

The mixture was then compressed into tablets using a manual tablet press. The resulting tablets were placed in petri dishes, and the change in tablet diameter was measured at time intervals of 0, 15, 30, 60, 90, and 120 minutes under ambient room conditions using a caliper (Zheng et al.,

2019). Subsequently, each sample at each time was also measured for moisture content (%MC) using a moisture analyzer (OHAUS MB120, USA). A specific amount of sample was accurately weighed and dried at 105°C until a constant weight was achieved. %MC was calculated using the following equation: %MC = (initial weight-final weight) / (initial weight) x 100.

## RESULT AND DISCUSSION

### Organoleptic

The visual observations of the pure materials, physical mixture, and cocrystals are presented in Figure 1. All six powders were white and odorless. In the 1:1 molar ratio of citric acid-nicotinamide, both the physical mixture (CN-PM 1:1) and the cocrystal form (CN-Cocrystal 1:1) produced powders that were relatively clumpy (slightly moist) compared to the 1:2 molar ratio. This observation suggests that the proportion of nicotinamide in the mixture influences the stability of the resulting powder. A higher amount of nicotinamide contributes to the formation of a more ideal and non-sticky citric acid cocrystal (Pagire et al., 2020).


**Figure 1. Visual appearance of pure materials, physical mixture, and cocrystal. (A) Citric acid, (B) Nicotinamide, (C) CN-PM 1:1, (D) CN-PM 1:2, (E) CN-Cocrystal 1:1, (F) CN-Cocrystal 1:2**

### Characterization using PXRD

The formation of cocrystals is primarily characterized using PXRD. If the resulting PXRD pattern of the solid product is different from the original components, it can be concluded that a new solid phase has been formed (Nawatila et al., 2017). Differences in the diffractogram profiles are indicated by the appearance of new diffraction peaks in the cocrystal and the disappearance of characteristic peaks from the constituent components (Alatas et al., 2013). As shown in Table 3 and Figure 2, CN-Cocrystal 1:1 exhibits the formation of a new crystalline phase with diffraction peaks at 2θ angles of 17.1132° and 21.761°, with corresponding peak intensities (height) of 67.78 and 100.15, respectively, indicating successful cocrystal formation. Furthermore, CN-Cocrystal 1:2 shows an even greater number of new crystalline peaks compared to CN-Cocrystal 1:1, with new peaks observed at 2θ values of 16.9117°; 20.2717°; and 20.9566°, having peak intensities (height) of 184.95; 442.55; and 166.84; respectively. The emergence of new crystalline peaks and the disappearance of characteristic peaks from the starting materials confirm the successful formation of cocrystal powders in both systems.

**Table 3. The results of the diffractogram profile observations of the 2θ (°) and height (cts) of citric acid, nicotinamide, CN-PM 1:1, CN-PM 1:2, CN-Cocrystal 1:1, CN-Cocrystal 1:2**

| Citric acid | | Nicotinamide | | CN-PM 1:1 | | CN-PM 1:2 | | CN-Cocrystal 1:1 | | CN-Cocrystal 1:2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **2θ (°)** | **Height (cts)** | **2θ (°)** | **Height (cts)** | **2θ (°)** | **Height (cts)** | **2θ (°)** | **Height (cts)** | **2θ (°)** | **Height (cts)** | **2θ (°)** | **Height (cts)** |
| - | - | - | - | 5.9614 | 74.81 | - | - | - | - | - | - |
| **11.3311** | 991.46 | 11.2428 | 170.42 | 11.516 | 139.36 | 11.2663 | 186.2 | - | - | 11.1874 | 86.81 |
| **14.9477** | 1606.21 | 14.9304 | 2016.47 | - | - | 14.722 | 3972.52 | 14.8923 | 66.22 | 14.8113 | 355.73 |
| **15.2214** | 28706.79 | - | - | 15.2932 | 185.7 | 15.9341 | 67.34 | 15.1939 | 124.22 | 15.1688 | 611.74 |
| - | - | - | - | 17.0477 | 100.76 | - | - | 17.1132 | 67.78 | 16.9117 | 184.95 |
| **18.9669** | 1483.31 | - | - | 18.4635 | 199.43 | 18.9911 | 77.28 | 18.752 | 78.07 | 18.5438 | 128.64 |
| - | - | - | - | - | - | - | - | - | - | 20.2717 | 442.55 |
| - | - | - | - | - | - | - | - | - | - | 20.9566 | 166.84 |
| - | - | - | - | - | - | - | - | 21.761 | 100.15 | - | - |

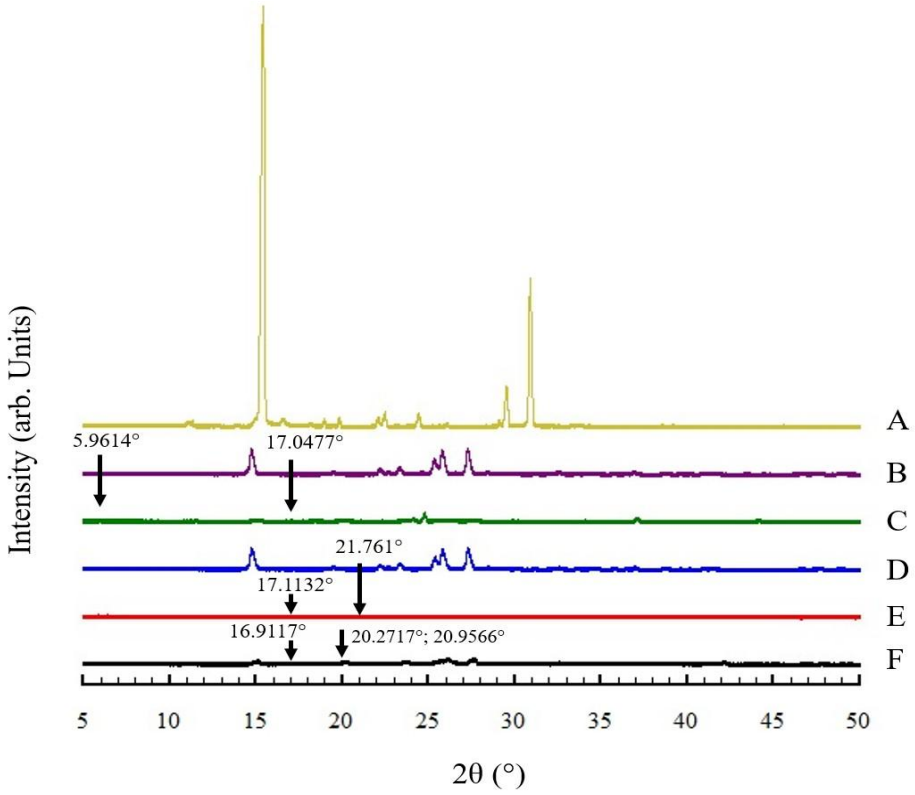



**Figure 2. PXRD diffractogram of pure materials, physical mixture, and cocrystal. (A) Citric acid, (B) Nicotinamide, (C) CN-PM 1:1, (D) CN-PM 1:2, (E) CN-Cocrystal 1:1, (F) CN-Cocrystal 1:2**

CN-PM 1:2 exhibits no evidence of new solid crystalline phase formation. In contrast, CN-PM 1:1 exhibited a new solid crystalline phase with diffraction peaks at 2θ angles of 5.9614° and 17.0477°. However, this phenomenon is presumed to be associated with hygroscopic materials, which may have influenced the diffraction pattern of new peaks. In this context, the observed additional peaks are not considered to represent the intended crystalline phase formation.

**Characterization using DSC**

The PXRD findings are further supported by the DSC results, as presented in Figure 3. Citric acid exhibited two specific melting points at 68.08 °C and 146.05 °C, with corresponding enthalpy values of −144.89 J/g and −52.58 J/g, respectively. The endothermic peak at 68.08 °C indicates the loss of water, confirming the monohydrate form of citric acid used in this study. Nicotinamide showed a single melting point at 129.50 °C with an enthalpy of −179.00 J/g. Both physical mixtures displayed complex endothermic peaks corresponding to the melting transitions of the individual components, indicating no thermal interaction and confirming the absence of cocrystal formation. In contrast, the DSC thermograms of CN-Cocrystal 1:1 and 1:2 revealed distinct new endothermic peaks at 107.01 °C and 114.28 °C, respectively. These unique thermal events, absent in either of the pure components, strongly indicate the formation of new solid phases, thus confirming successful cocrystal formation in both systems (Abdullah et al., 2022; Masuda et al., 2012).

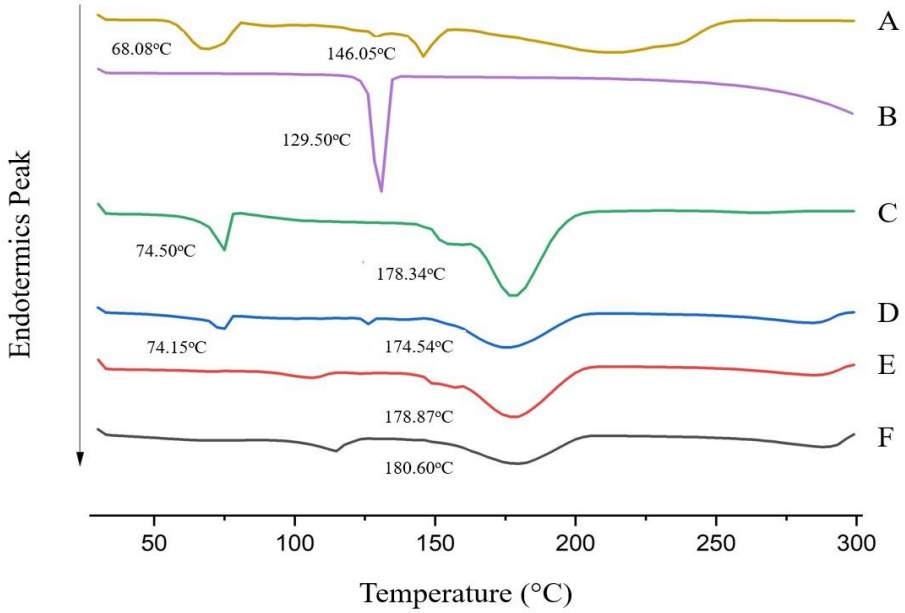



**Figure 3. DSC thermogram of pure materials, physical mixture, and cocrystal. (A) Citric acid, (B) Nicotinamide, (C) CN-PM 1:1, (D) CN-PM 1:2, (E) CN-Cocrystal 1:1, (F) CN-Cocrystal 1:2**

**Characterization using FTIR-ATR**

FTIR spectroscopy is commonly employed to evaluate alterations of the chemical and physical structures at the molecular level. The FTIR spectrum of the cocrystal exhibited notable shifts in the absorption bands corresponding to the characteristic functional groups of the original pure compounds (Shewale et al., 2015). Figure 4 shows that both physical mixtures still exhibit similar absorption peaks corresponding to the functional groups of the individual components (citric acid and nicotinamide). This indicates that no molecular interaction occurred between citric acid and nicotinamide in the physical mixtures.

In contrast, the FTIR spectrum of CN-Cocrystal 1:1 revealed noticeable shifts in the absorption frequencies of the citric acid -OH functional group from 3309, 3226, and 3011 $cm^{-1}$ to 3185, 2946, and 2517 $cm^{-1}$. Additionally, the -NH functional group of nicotinamide shifted from 3354, 3151, and 3060 $cm^{-1}$ to 3432, 3414, and 3358 $cm^{-1}$. These changes formed a distinct double peak, which is characteristic of the -$NH_2$ group. A similar pattern was observed in CN-Cocrystal 1:2, where the -OH stretching frequencies of citric acid shifted from 3309, 3226, and 3011 $cm^{-1}$ to 3185, 2946, and 2487 $cm^{-1}$. The -NH stretching frequencies of nicotinamide also shifted from 3354, 3151, and 3060 $cm^{-1}$ to 3432, 3414, and 3354 $cm^{-1}$, again forming a characteristic -$NH_2$ double peak. These spectral shifts indicate the formation of hydrogen bonds between the two components. Specifically, two -OH groups from citric acid interact with the nitrogen atom of the nicotinamide pyridine ring through hydrogen bonding. Additionally, the C=O group of citric acid is also involved in C–H···O=C interactions with nicotinamide, further supporting the formation of a new cocrystal structure (Verma et al., 2019).

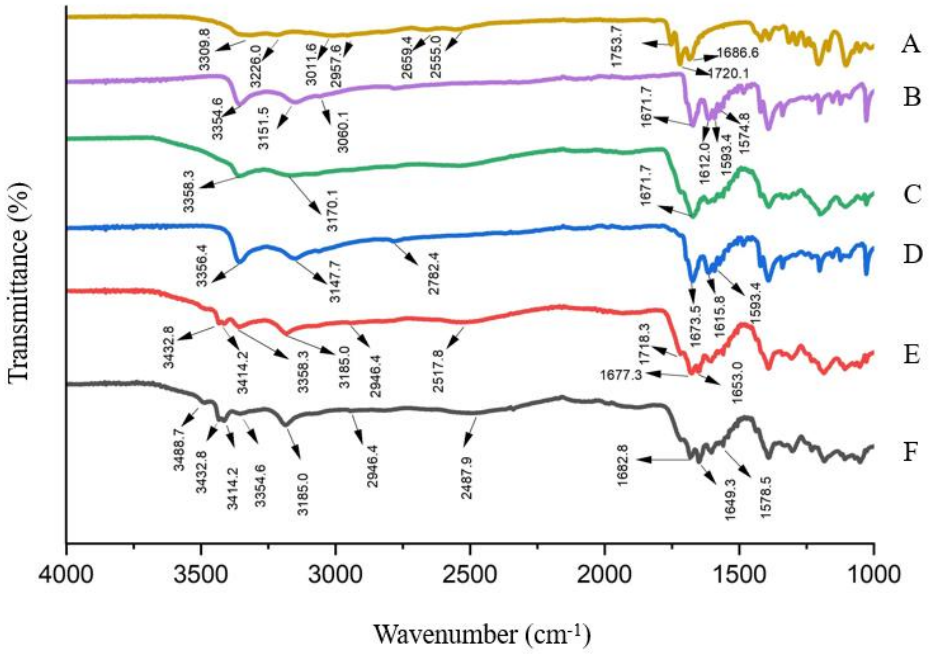
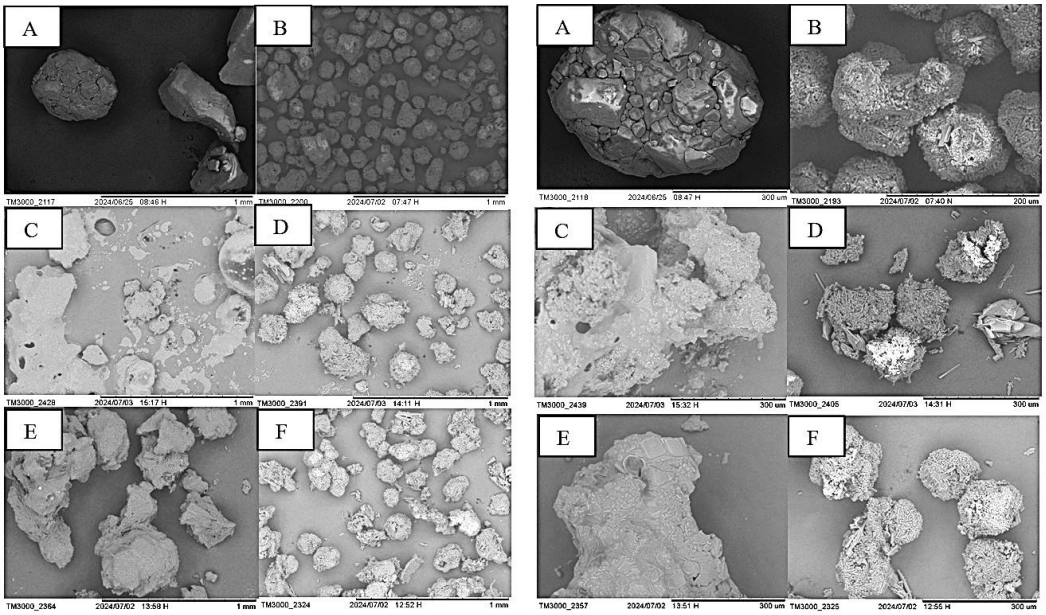



**Figure 4. FTIR spectroscopy of pure materials, physical mixture, and cocrystal. (A) Citric acid, (B) Nicotinamide, (C) CN-PM 1:1, (D) CN-PM 1:2, (E) CN-Cocrystal 1:1, (F) CN-Cocrystal 1:2**

**Characterization using SEM**

The surface morphologies of the pure components, physical mixtures, and cocrystals were observed using SEM and are presented in Figure 5. Observations were carried out at a magnification of 100 times (with a scale of 1 mm) and 250 times (with a scale of 300 micrometers). The surface morphology of citric acid exhibited a block-like structure with an irregular surface texture. Nicotinamide showed an acicular (needle-like) shape with a tendency to agglomerate. In the CN-PM 1:1 physical mixture, the particles appeared highly hygroscopic, as evidenced by the presence of moisture or adhering water droplets visible on the powder surface in Figure 5. Meanwhile, CN-PM 1:2 still displayed distinguishable morphologies corresponding to both citric acid and nicotinamide, indicating no structural transformation. In contrast, both cocrystal systems demonstrated surface morphologies distinct from those of the original components. CN-Cocrystal 1:2 exhibited a more granular surface morphology compared to CN-Cocrystal 1:1. These changes in particle morphology

relative to the pure materials suggest that citric acid was successfully co-crystallized with nicotinamide as the co-former (Khan et al., 2020).



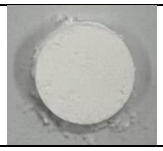
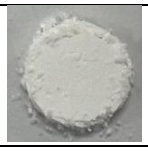
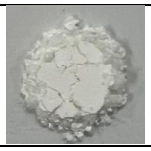

100 x Magnification 250 x Magnification

**Figure 5. SEM morphology of pure materials, physical mixture, and cocrystal. (A) Citric acid, (B) Nicotinamide, (C) CN-PM 1:1, (D) CN-PM 1:2, (E) CN-Cocrystal 1:1, (F) CN-Cocrystal 1:2**

**Moisture interaction**

Moisture interaction testing was conducted to assess the influence of environmental humidity on the simulated effervescent tablets, observed at time intervals of 0, 15, 30, 60, 90, and 120 minutes, using changes in tablet diameter as the evaluation parameter (Jacob et al., 2009). The testing was conducted in a room with ambient humidity 50% + 2% RH and temperature 25,8°C + 0,5°C. Control tablets were prepared using pure citric acid as an acidic component and pure sodium bicarbonate as the basic component for comparison purposes. As shown in Table 4, no observable change in tablet diameter occurred in the simulated effervescent tablets formulated with CN-Cocrystal 1:1 and CN-Cocrystal 1:2 as the acidic components up to 120 minutes, in contrast to the control tablets. This observation is further supported by the moisture content data, which indicate that both CN-cocrystal 1:1 and CN-cocrystal 1:2 exhibited comparatively lower %MC values than the control, ranging from 2.43–3.35% and 1.16–3.23%, respectively. In contrast, the control tablets demonstrated a marked increase in %MC over time, reaching 7.07% at 120 minutes. This result indicates that the co-crystallization of citric acid effectively provides moisture protection, thereby preventing the occurrence of premature effervescent reactions. Nicotinamide, acting as a co-former, forms hydrogen bonds with citric acid, which helps reduce the water-absorbing capacity of the system. Consequently, the cocrystal exhibits improved resistance to moisture and enhanced physicochemical stability (Dhondale et al., 2023).

**Table 4. Results of moisture interaction of tablet effervescent simulation with CN-Cocrystal 1:1 and 1:2**

| Minute | 0 | 15 | 30 | 60 | 90 | 120 |
|---|---|---|---|---|---|---|
| Control tablet |  |  |  |  |  |  |
| Du/D*<br>%MC | 1.00±0.00<br>3.43±0.30 | 1.11±0.12<br>3.58±0.39 | 1.16±0.08<br>4.28±0.77 | 1.34±0.07<br>4.91±0.38 | 1.40±0.09<br>5.52±0.97 | 1.45±0.05<br>7.07±2.61 |
| CN-Cocrystal 1:1 |  |  |  |  |  |  |
| Du/D*<br>%MC | 1.00±0.00<br>2.43±0.35 | 1.00±0.00<br>2.79±0.43 | 1.00±0.00<br>3.04±0.50 | 1.00±0.00<br>3.05±0.22 | 1.00±0.00<br>3.14±0.14 | 1.00±0.00<br>3.35±0.07 |
| CN-Cocrystal 1:2 |  |  |  |  |  |  |
| Du/D*<br>%MC | 1.00±0.00<br>1.16±0.72 | 1.00±0.00<br>1.74±0.74 | 1.00±0.00<br>2.37±0.32 | 1.00±0.00<br>2.58±0.46 | 1.00±0.00<br>2.72±0.53 | 1.00±0.00<br>3.32±1.21 |

*Du = diameter at the minute
D = initial diameter
%MC = percentage of moisture content

## CONCLUSION

Citric acid as the acidic component in the effervescent system, was successfully converted into a cocrystal form using nicotinamide as a co-former through the grinding method. Both cocrystal formulations, CN-Cocrystal 1:1 and CN-Cocrystal 1:2, demonstrated significant improvements in maintaining the stability of the effervescent system and in preventing premature effervescent reactions during the manufacturing process. However, CN-Cocrystal 1:2 exhibited superior performance in terms of physical characteristics compared to CN-Cocrystal 1:1, indicating its greater potential as an optimized formulation.

## ACKNOWLEDGEMENT

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