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Original Research Article

Enhancing the Pharmaceutical Properties of Ibuprofen through Spherical Agglomeration-Co-Crystallization with Nicotinamide: A Comprehensive Study of Micromeritic, Tabletability, and Dissolution Characteristics

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ABSTRACT

Developing efficient methods for cocrystal production is crucial to improving drug solubility and bioavailability. This study utilized the spherical agglomeration-co-crystallization (SA-CC) method to produce spherical ibuprofen-nicotinamide (IBU-NICO) cocrystals. This method used ethanol (ETA) as a solvent and a mixture of deionized water and PEG-4000 as an anti-solvent, enhancing the micromeritic properties of the cocrystal. The addition of dichloromethane (DCM) facilitated the formation of spherical particles via rapid viscous phase transition. Fourier-transform infrared (FTIR) spectroscopy identified significant molecular interactions, such as hydrogen bonding between the ibuprofen carboxyl and nicotinamide acylamino groups, ensuring cocrystal stability. Hot-stage microscopy (HSM) and scanning electron microscopy (SEM) analyses demonstrated that cocrystals exhibited lower thermal stability but improved dissolution rates due to their amorphous-crystalline structures and rough, porous surfaces. Differential scanning calorimetry (DSC) showed altered thermal profiles with a reduction of 7.21ºC, indicating modified crystal lattice structures. Powder X-ray diffraction (PXRD) confirmed the formation of new crystalline phases. Micromeritic evaluations revealed favorable particle size distribution (PSD) with an average size of 5 mm, enhanced flowability, and compressibility, with cocrystals showing superior tensile strength (2.36 MPa at 207.97 MPa) and dissolution rates 2.82 times higher than pure IBU at pH 6.8. These findings highlight the potential of the SA-CC method to produce cocrystals with enhanced drug properties, paving the way for improved pharmaceutical formulations.

***Keywords*:** Spherical agglomeration-co-crystallization, Ibuprofen cocrystals, Micromeritic, Dissolution enhancement

Introduction

The pharmaceutical industry continually faces the challenge of developing effective tablet formulations for active pharmaceutical ingredients (APIs) with poor manufacturability and dissolution properties.[1] Direct compression (DC) is the preferred method owing to its cost-effectiveness and compatibility with continuous manufacturing. However, DC struggles with APIs that exhibit poor flowability, low solubility, and inadequate tabletability, crucial factors for achieving high drug loading and ensuring therapeutic absorption.[2,3] Cocrystallization has emerged as a promising strategy to enhance the solubility and dissolution rates of poorly soluble drugs.[4,5] Cocrystals are crystalline materials composed of an API and a coformer, interacting through non-covalent bonds within the same crystal lattice.[6,7] This technique can significantly improve the physicochemical properties of drugs without altering their molecular structure. Nicotinamide (NICO), a form of vitamin B3, has been identified as an effective coformer for ibuprofen (IBU) due to its ability to form strong hydrogen bonds and enhance solubility.[8,9]

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Spherical cocrystallization further enhances the benefits of cocrystallization by improving the micromeritic properties of cocrystals, such as particle size, shape, and bulk density.[10] Techniques like spherical agglomeration (SA) and quasi-emulsion solvent diffusion (QESD) were employed to create spherical agglomerates of cocrystals.[11] These methods can improve the flowability and compressibility of pharmaceutical powders, making them more suitable for DC tablet formulations.[12]

This study focuses on the spherical cocrystallization of IBU with NICO using a spherical agglomeration-based spherical cocrystallization (SA-CC) method. This process involves mixing a good solvent containing the crystalline drug with an anti-solvent to precipitate cocrystals, followed by the addition of a bridging liquid, such as Polyethylene glycol 4000 (PEG-4000), which acts to bind and coat the particles, forming spherical agglomerates. Compared to the QESD method, SA-CC offers distinct advantages in controlling particle morphology and enhancing the micromeritic properties of the resulting cocrystals.[13,14]

The objectives of this study were to evaluate the micromeritic, mechanical, solubility, and dissolution properties of the spherical IBU-NICO cocrystals. Specifically, we aim to assess particle size, flowability, bulk density, tabletability, hardness, comparative solubility, and intrinsic dissolution rates. We hypothesize that spherical cocrystallization will significantly enhance these properties, improving manufacturability and therapeutic efficacy. [10,15,16]

This research is novel in its application of the SA-CC method to enhance the properties of IBU, thereby addressing the limitations of DC in processing APIs with poor manufacturability. Our findings could contribute significantly to the pharmaceutical formulation field,

offering new insights into improving drug solubility and tabletability through advanced cocrystallization techniques.

Materials and Methods

Materials

IBU, used as the active pharmaceutical ingredient (API), was obtained from Triman Ltd. NICO, serving as the coformer, and was sourced from Sigma Aldrich. PEG-4000 was procured from Merck, Germany. The solvents employed in the study included DCM and ETA, both of analytical grade, acquired from Merck. Deionized water was prepared according to laboratory specifications.

Preparation of IBU-NICO Cocrystal Agglomerates

The spherical agglomeration-based cocrystallization (SA-CC) method was utilized to prepare the cocrystal agglomerates. Specifically, IBU (1.03 g) and NICO (0.61 g) were dissolved in ETA (3 mL) with continuous stirring until a clear solution was achieved. This solution was introduced into an anti-solvent, deionized water (80 ml) containing PEG-4000 at 10°C. The mixture was agitated at a speed of 500 rpm to facilitate the precipitation of cocrystals. DCM (1 mL) was subsequently added dropwise to promote the formation of spherical agglomerates. The resulting agglomerates were filtered and dried at 40°C for 30 minutes.

FTIR Spectroscopy Analysis

Fourier Transform Infrared (FTIR) Spectroscopy investigated the chemical interactions and bonding characteristics of IBU and IBU-NICO cocrystals. Samples were prepared by finely grinding the cocrystals and analyzing them using an FTIR-630 Infrared Spectrometer (Agilent, Germany) in Attenuated Total Reflectance (ATR) mode. Spectra were collected over 4000 to 650 cm^{-1}, ensuring detailed capture of all relevant chemical signatures. Each spectrum was the result of 32 scans to maximize accuracy and reliability.

Hot Stage Microscopy (HSM)

A small amount of the sample was prepared on a microscope slide and covered with a cover slip to ensure uniform heating and prevent contamination. The slide was then placed on a pre-calibrated polarized microscope (All-Pro, China) equipped with a temperature controller. The sample was observed in real-time as it underwent thermal transitions, and photomicrographs were captured using a CCD camera (ToupTek Photonics, China).[17]

Powder X-ray Diffractometry (PXRD)

The crystallographic properties of the IBU-NICO cocrystals were characterized using a powder X-ray diffractometer equipped with Cu Kα radiation (1.54059 Å). The samples were scanned between 5 and 40° 2θ with a step size of 0.02° and a dwell time of 1 s per step. The X-ray tube operated at a voltage of 40 kV and a current of 40 mA. This analysis provided detailed information on the crystal structure and phase purity of the cocrystals.[18]

DSC analysis

Thermal properties of the cocrystal powders were analyzed using a differential scanning calorimeter (DSC; Q2000, TA Instruments, New Castle, DE). Approximately 5-8 mg of each sample was placed in hermetically sealed aluminum pans (Tzero). The samples were heated from 30 to 200°C at 10°C/min under a nitrogen purge at a 50 mL/min flow rate. The DSC instrument was calibrated for temperature and cell constant using high-purity indium. This method allowed for the assessment of melting points, crystallization behavior, and thermal stability of the cocrystals.[19]

Scanning Electron Microscopy (SEM)

The particle morphology and surface features of the IBU-NICO cocrystals were evaluated using scanning electron microscopy (SEM; JEOL 6500F, JEOL Ltd., Tokyo, Japan). Samples were sputter-coated with a thin layer of platinum (~75 Å) using an ion-beam sputter (IBS/TM200S; VCR Group Inc., San Clemente, CA) and mounted onto carbon tapes. The SEM was operated in SEI mode with an acceleration voltage of 5 kV, and a high vacuum (10^{-4} to 10^{-5} Pa) was maintained during imaging. This provided a detailed visual characterization of the surface morphology and particle size of the cocrystals.[20]

PSD Measurement

The PSD of the IBU-NICO cocrystal agglomerates was determined using ImageJ software and OriginLab. The cocrystal agglomerates were placed on a black background. Using an optical microscope with a high-resolution camera, multiple images were captured. These images were then analyzed with ImageJ, where the scale was calibrated, and particles were identified and measured. The resulting data, including particle size and distribution, were exported to OriginLab for further statistical analysis, creating frequency distributions and histograms. This method ensured a comprehensive and reliable characterization of the PSD, which is critical for evaluating the micromeritic properties of cocrystals.[21]

Tabletability

To assess the tabletability of the IBU-NICO cocrystal agglomerates, samples weighing 350 ± 2 mg were prepared. These samples were placed into a die with a diameter of 12 mm and compressed under varying pressures ranging from 35 to 278 MPa using a hydraulic press (Perkin Elmer, US). Prior to the compaction process, the punch and die were lubricated with magnesium stearate to ensure smooth operation and prevent sticking. After compaction, the tablets were stored for 24 hours to equilibrate. Following this period, the diameter (d) and height (h) of the tablets were measured using a Mitutoyo caliper (Japan). The crushing strength (F) of the tablets was then measured using a Digital Tablet hardness tester (B-One, China). The tensile strength (σ) of the tablets was calculated using the following equation 1:

$$\sigma = \frac{2F}{\pi dh} \quad (1)$$

Flowability and Compressibility

The flowability and compressibility of the IBU-NICO cocrystal agglomerates were assessed by measuring the angle of repose, bulk density (BD), and tapped density (TD). The angle of repose was determined by allowing 10 grams of the sample to flow through a funnel and form a cone on a flat surface. The height (h) and radius (r) of the cone were measured, and the angle of repose (θ) was calculated using the equation 2:

$$tan(\theta) = \frac{h}{r} \quad (2)$$

BD was measured by gently filling a graduated cylinder with the sample and noting the volume. TD was measured after mechanically tapping the cylinder until no further volume change was observed. The Carr Index (CI) and Hausner Ratio (HR) were then calculated using the following equations 3 and 4:

$$CI = \left(\frac{TD-BD}{TD}\right) \times 100 \quad (3)$$

$$HR = \frac{TD}{BD} \quad (4)$$

All measurements were performed in triplicate to ensure accuracy and reliability.

Intrinsic dissolution

The dissolution performance of the tablets was assessed in 500 mL of solutions at pH levels 1.2, 4.5, and 6.8, maintained at a temperature of 37 ± 0.5 °C, with paddle stirring at 50 rpm. Tablets were compressed at 70 MPa and contained 200 mg of IBU-NICO. Samples of the medium (10 mL) were collected at predetermined intervals of 5, 10, 20, 30, 40, 50, and 60 minutes and filtered through a membrane with a 0.45 µm pore size. The concentration of IBU was measured using a UV/Vis spectrophotometer (Cary 60, Agilent, Germany) at a

wavelength of 223 nm, employing a calibration curve and suitable background correction to eliminate NICO interference.

Statistical analysis

All statistical analyses were performed using OriginPro 9.0. Descriptive statistics, including mean and standard deviation, were calculated for each set of experimental data. Linear regression analysis was conducted for dissolution intrinsic to determine the relationship between drug release and time. Graphical representations of the data, including scatter plots, histograms, and trend lines, were generated to visualize the results. The significance of the regression coefficients was evaluated to assess the strength and direction of the relationships observed.

Results and Discussion

The SA-CC method employed for the cocrystallization of IBU and NICO provided several advantages over traditional cocrystallization techniques. Using ETA as a solvent and deionized water containing PEG-4000 as an anti-solvent ensured the formation of cocrystals and enhanced their micromeritic properties. Previous studies have demonstrated that the choice of solvent and anti-solvent can significantly influence the morphology and size of cocrystals, impacting their downstream processing and dissolution characteristics.[22] DCM played a crucial role in promoting the sphericity of the agglomerates. Its addition to the cocrystal slurry rapidly formed a viscous phase that eventually hardened into spherical particles. This step is critical in controlling the agglomeration kinetics and the final morphology of the particles.[23]

Spectrum FTIR analysis

FTIR Spectroscopy analysis provides crucial insights into the chemical structure and interactions within the IBU-NICO cocrystal formed by the spherical agglomeration method (Figure 1). For IBU, characteristic peaks were observed at 2953 cm^{-1}, indicating the C-H stretch, and peaks at 2727 cm^{-1} and 2631 cm^{-1} corresponding to the O-H groups. The C=O stretch was visible at 1703 cm^{-1}. Additional peaks at 1321 cm^{-1}, 1229 cm^{-1}, and 1069 cm^{-1} were attributed to C-O stretches, with a fingerprint region peak at 778 cm^{-1}. The cocrystal spectrum showed significant shifts indicating interactions between IBU and NICO. The NH_2 group of NICO shifted from 3550 cm^{-1} to 3399 cm^{-1}. Similarly, the O-H groups in IBU shifted slightly from 2727 cm^{-1} to 2728 cm^{-1} and from 2631 cm^{-1} to 2633 cm^{-1}. The C=O stretch in IBU shifted from 1703 cm^{-1} to 1700 cm^{-1}, and the C-O stretch of NICO showed a notable shift from 1592 cm^{-1} to 1508 cm^{-1}.
These shifts suggest strong hydrogen bonding between the carboxyl group of IBU and the acylamino group of NICO, which is critical for the formation and stability of the cocrystal. These FTIR results, together with previous studies,[9] confirm that the spherical agglomeration method effectively promotes the formation of IBU-NICO cocrystals with potentially superior drug properties.

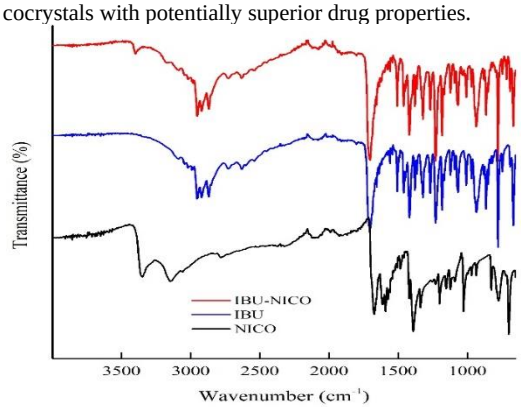

Figure 1: FTIR spectra comparison of pure ibuprofen (IBU), nicotinamide (NICO), and spherical ibuprofen-nicotinamide cocrystal (IBU-NICO)

Morphological Analysis of Cocrystals

HSM Observations

HSM was employed to investigate the thermal behavior and crystal habit of IBU and IBU-NICO cocrystals (Figure 2). The distinct morphological characteristics observed at different temperatures for IBU and its cocrystals with NICO elucidate the thermal stability and the effects of cocrystallization. The rod-like IBU crystals were at lower temperatures, and as temperature increased, these crystals began to melt, underscoring their thermal limits.
Interestingly, the IBU-NICO cocrystals displayed a different behavior. Amorphous and crystalline structures at 45°C could indicate incomplete crystallization, potentially due to the rapid cooling process used during cocrystallization, which may inhibit complete crystal formation. Compared to pure IBU, the early onset of melting at 72°C suggests that the cocrystals have lower thermal stability than the pure drug. This could enhance the dissolution rate, as lower melting points often correlate with improved solubility and faster dissolution rates.[24,25]

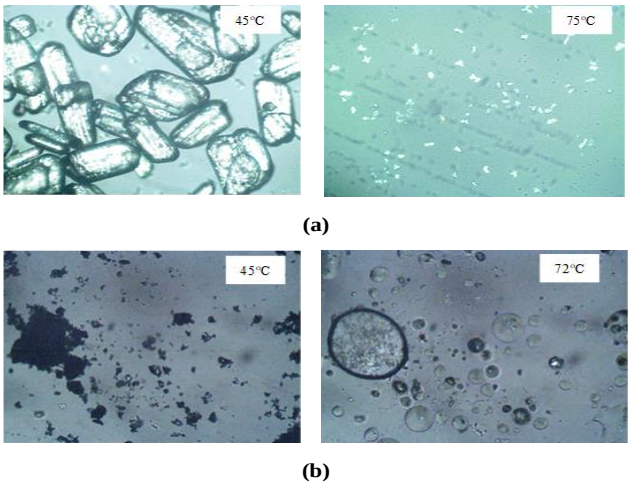

Figure 2: HSM analysis of thermal behavior and morphology of pure ibuprofen (IBU) and ibuprofen-nicotinamide cocrystals (IBU-NICO)

Scanning Electron Microscopy Insights

The SEM image of pure IBU (Figure. 3a) displays a typical crystal morphology with relatively uniform, small particle sizes, showcasing a relatively smooth surface. In contrast, the spherical cocrystal of IBU-NICO (Figure. 3b) exhibits a significantly altered morphology. The image shows a large, rough, and porous spherical agglomerate.
The rough and porous texture of the cocrystals is particularly advantageous for dissolution properties, as it allows for more extensive solvent penetration and a greater surface area exposed to the dissolution medium. The spherical agglomerates facilitate better flow properties and more uniform packing during tablet formulation, enhancing the compressibility and handling of the drug formulation.

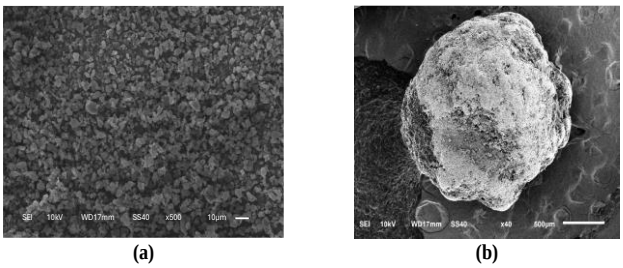

Figure 3: SEM analysis of ibuprofen crystals (a) and spherical ibuprofen-nicotinamide cocrystal (b)

Thermal Behavior by DSC

DSC was employed to assess the thermal properties of IBU alone and its cocrystals with NICO (Figure 4), offering insights into their stability and the effects of cocrystallization on their thermal behavior.

The DSC thermogram for IBU showed a peak at 71.41°C; the enthalpy change recorded was -47.18 J/g, and the peak height reached -11.65 mW. These values are typical for IBU, reflecting its well-defined melting behavior and consistent with literature values indicating its thermal stability under standard conditions.[26,27]

In contrast, the IBU-NICO cocrystals exhibited a distinctly different thermal profile. The peak melting temperature was lower, at 64.20°C, with the heat flow measured at -39.45 J/g, with a peak height of -8.79 mW. This reduction in melting temperature and enthalpy change compared to pure IBU suggests that cocrystallization with NICO alters the crystal lattice, possibly due to weaker interactions within the cocrystal structure, which lowers the energy required for melting.[28,29]

Crystallographic Properties by PXRD

The PXRD pattern for pure IBU exhibits sharp peaks at specific 2θ values (6.4, 16.9, 20.2, 22.4, and 17.6), indicating its crystalline nature with well-defined crystallography (Figure 5). NICO displays its characteristic diffraction peaks, indicating a crystalline structure with different peak positions than IBU, reflecting its distinct crystal lattice. The diffractogram of the IBU-NICO spherical cocrystal reveals new peaks at 2θ values of 9.5, 12.5, and 15.7, compared to the individual components, indicative of a new crystalline phase resulting from the cocrystallization process. Notably, some intense peaks of pure IBU and NICO either disappear or reduce in intensity. In contrast, new peaks emerge, suggesting significant molecular interaction and possibly forming a stable cocrystal structure. These new peak formations in the IBU-NICO cocrystal suggest strong molecular interactions, likely through hydrogen bonding between IBU carboxylic and NICO amide groups. These interactions are crucial in stabilizing the cocrystal structure, potentially altering its solubility and dissolution rate.[29] The appearance of new diffraction peaks confirms the successful formation of a unique cocrystal phase, distinct from the parent compounds.[30]

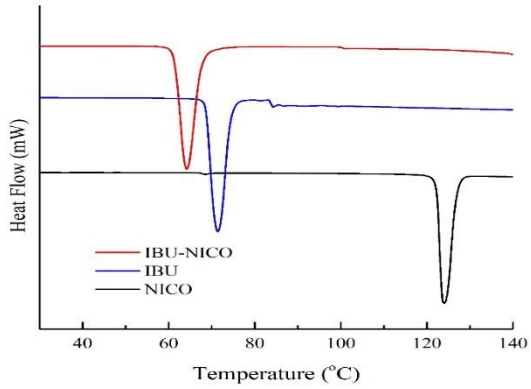

Figure 4: DSC thermograms of pure ibuprofen (IBU) and ibuprofen-nicotinamide cocrystals (IBU-NICO)

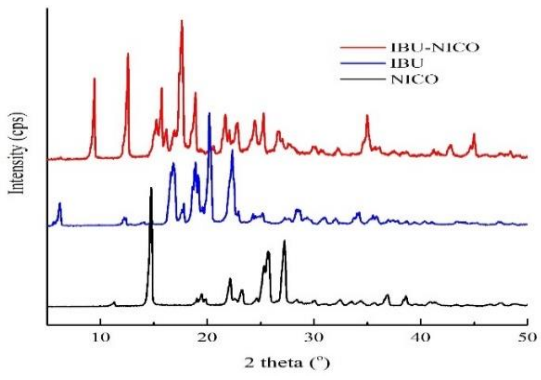

Figure 5: PXRD patterns of pure ibuprofen (IBU), nicotinamide (NICO), and ibuprofen-nicotinamide cocrystals (IBU-NICO)

Micromeritic Properties

Particle Size Distribution Measurement

The particle size distribution (PSD) analysis, as evidenced by the histogram and accompanying particle image (Figure 6), offers significant insights into the micromeritic properties of the IBU cocrystals produced through the advanced spherical agglomeration method. The histogram demonstrates an unimodal distribution with a pronounced peak centered around 5 mm, indicating that most particles fall within this size range.

The particle image corroborates the histogram data, showcasing relatively uniform spherical particles. This homogeneity in particle size is crucial for ensuring consistent dissolution rates, which directly impacts the bioavailability of the drug. As observed, the spherical nature of the particles likely contributes to improved flow properties and reduced inter-particle friction, which are desirable characteristics in pharmaceutical formulations.[31,32] In our case, the advanced spherical agglomeration method has produced cocrystals with a favorable PSD, thus potentially enhancing both the micromeritic properties and the dissolution profile of IBU.

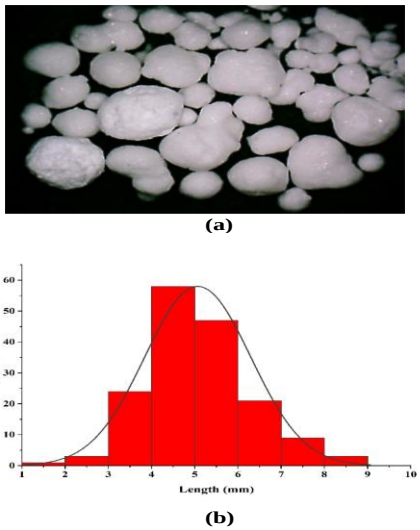

Figure 6: Morphology (a) and particle size distribution (b) of ibuprofen-nicotinamide cocrystals produced by spherical agglomeration-based spherical cocrystallization (SA-CC)

Flowability and Compressibility

The micromeritic evaluation in Table 1 provides a comprehensive comparative analysis between IBU and spherical IBU-NICO cocrystals produced via SA-CC. The bulk density of pure IBU is 0.57 g/mL, significantly higher than the 0.32 g/mL observed for IBU-NICO. Similarly, the tap density of IBU at 0.71 g/mL exceeds the 0.37 g/mL for IBU-NICO. These differences suggest that IBU-NICO particles are less densely packed in both loose and tapped states, likely due to their spherical morphology, which provides more interstitial space.

The Hausner ratio, which indicates the degree of powder flowability, is markedly improved for IBU-NICO (1.07) compared to pure IBU (1.31). Carr's Index, a measure of compressibility, is substantially lower for IBU-NICO at 6.16%, compared to 23.52% for pure IBU. These values confirm that IBU-NICO exhibits superior flowability and compressibility.

The angle of repose for IBU-NICO is 25.50°, indicative of excellent flow characteristics. Pure IBU did not flow at all, making it impossible to measure its angle of repose. The enhanced flowability of IBU-NICO can be attributed to its spherical shape, which reduces inter-particle friction and facilitates better movement.[33] The improved

micromeritic properties of IBU-NICO have significant implications for ensuring uniform mixing and tableting, reducing variability in dosage forms.[31]

Tabletability

The tensile strength analysis of IBU and its cocrystal (IBU-NICO) under varying compaction pressures reveals significant differences in mechanical properties, as illustrated in Figure 7. As the compaction pressure increases, both formulations show an initial increase in tensile strength, reaching their respective peaks at different pressures. IBU tablets reached a maximum tensile strength of 1.32 MPa at 166.37 MPa, whereas the IBU-NICO cocrystals peaked much earlier at a significantly higher tensile strength of 2.36 MPa at 207.97 MPa. Beyond these pressures, the tensile strength of both formulations began to decrease, with IBU-NICO maintaining a consistently higher tensile strength than IBU even at the highest compaction pressure of 249.56 MPa (0.78 MPa for IBU and 2.19 MPa for IBU-NICO).

The enhanced tensile strength of IBU-NICO cocrystals can be attributed to the intermolecular interactions between IBU and NICO, which likely contribute to a more robust crystal lattice structure.[34] This enhancement in mechanical properties suggests that cocrystallization with NICO significantly improves the compressibility and compaction behavior of IBU, making it a superior candidate for tablet formulation in terms of mechanical strength.[35]

These findings align with those from a previous study, in which the cocrystallization of IBU with NICO demonstrated similar improvements in mechanical properties. Specifically, the study found that IBU cocrystals with NICO significantly improved tablet tensile strength, attributed to higher lattice energy and bonding strength. The cocrystal exhibited a higher molar enthalpy of fusion, indicating a stronger crystal lattice, contributing to the enhanced mechanical properties observed.[9,36]

Dissolution Performance

The dissolution profiles of IBU and its cocrystal with NICO reveal significant differences between the two pH environments tested, pH 1.2 and pH 6.8 (Figure 8). At pH 1.2, the cocrystal dissolution rate was approximately 2.25 times that of pure IBU at 60 minutes. At pH 6.8, this enhancement increased to approximately 2.82 times. This significant increase suggests that cocrystal dissolution is more efficient in a slightly basic environment, which is closer to the physiological pH of the small intestine.

The faster dissolution at pH 6.8 can be attributed to the higher solubility of IBU in a less acidic environment. IBU, a weak acid with a pKa of approximately 4.5, is more soluble at higher pH levels.[37] This is because, at a pH above its pKa, IBU exists primarily in its ionized form, which is more soluble in aqueous solutions. Therefore, in a basic medium like pH 6.8, a larger proportion of IBU is ionized, increasing solubility and, consequently, a higher dissolution rate. The improved dissolution characteristics of the IBU-NICO cocrystal can be attributed to the synergistic interactions between IBU and NICO, which likely disrupt the crystal lattice of IBU, enhancing its solubility and dissolution rate in aqueous environments.

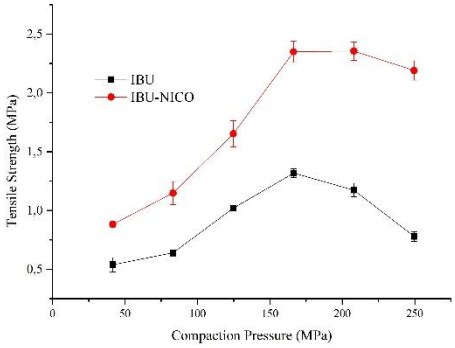

Figure 7: Tensile strength comparison of pure ibuprofen (IBU) and ibuprofen-nicotinamide cocrystals (IBU-NICO) under varying compaction pressures

Table 1: Comparative Analysis of Micromeritic Properties Between Pure IBU and Spherical IBU-NICO

Parameters	IBU (n=6)	IBU-NICO (n=6)
Bulk density (g/mL)	0.57±0.02	0.32±0.01
Tap density (g/mL)	0.71±0.08	0.37±0.03
Hausner Ratio	1.31±0.07	1.07±0.03
Carr's Index (%)	23.52±3.85	6.16±2.80
Flowability (g/s)	No flowing	6.97±0.59
Angle of repose (°)	No flowing	25.50±2.51

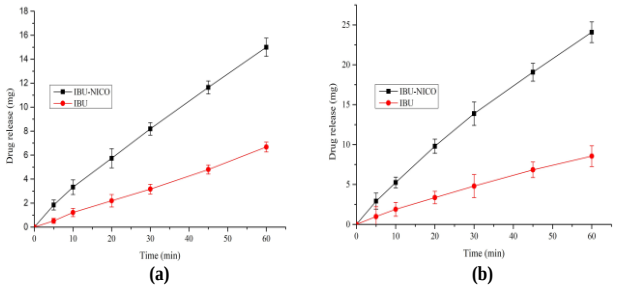

Figure 8: Intrinsic dissolution profiles of pure ibuprofen (IBU) and ibuprofen-nicotinamide cocrystals (IBU-NICO) at pH 1.2 (a) and pH 6.8 (b)

Conclusion

The cocrystallization of IBU with NICO using the spherical agglomeration method (SA-CC) significantly enhances the mechanical and micromeritic properties of IBU, making it a superior candidate for pharmaceutical tablet formulation. The advanced SA-CC method, utilizing ETA and deionized water with PEG-4000, promotes the formation of robust cocrystals with enhanced properties, surpassing those achieved through traditional cocrystallization techniques. Adding DCM further improves the sphericity and uniformity of the agglomerates, which is critical for consistent downstream processing.

The spherical IBU-NICO cocrystal enhances tabletability properties and dissolution performance and improves micromeritic properties, making it a highly promising formulation for pharmaceutical applications. These advancements highlight the potential of cocrystallization as a strategic approach to optimizing the physicochemical properties of APIs.

Subsequent research may investigate the stability of these cocrystals under varied storage conditions, providing essential insights into their viability for prolonged pharmaceutical use. This investigation establishes a foundational basis for developing sophisticated drug formulations that are more productive, reliable, and tailored to specific therapeutic requirements.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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