

## CHARACTERISATION, EVALUATION AND DENSITY FUNCTIONAL ANALYSIS OF CILNIDIPINE-NICOTINAMIDE COCRYSTALS DEVELOPED BY LIQUID ASSISTED GRINDING TECHNIQUE: A SUSTAINABLE APPROACH FOR ENHANCED SOLUBILITY

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### ABSTRACT

**Objective:** Improving the solubility of poorly water-soluble drugs has always been a challenge in drug development. This study aimed to enhance the aqueous solubility of a poorly water-soluble drug, Cilnidipine, by cocrystallisation method using liquid-assisted grinding (LAG) technique with Nicotinamide as the coformer. The study also aimed to understand the mechanism of cocrystal formation by quantum mechanical calculations.

**Methods:** The Cilnidipine-Nicotinamide cocrystals were prepared in various stoichiometric ratios using the liquid-assisted grinding (LAG) technique. The cocrystals obtained were characterised by vibrational spectroscopy, thermal methods such as differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and surface morphology by field emission scanning electron microscopy (FE-SEM). The cocrystals were evaluated for saturation solubility, and the mechanistic study of cocrystal formation was performed using the Gaussian 09 software package.

**Results:** FT-IR spectra of the formulated cocrystal indicated the intermolecular hydrogen bond formation between N-H of Nicotinamide and the nitro group of Cilnidipine. DSC analysis showed a single endotherm at 96.76 °C, PXRD patterns were different from that of the reactants, and FE-SEM analysis revealed the changes in the surface morphology of the obtained cocrystal. The prepared cocrystal showed a 26.36-fold enhancement in the aqueous solubility of Cilnidipine. The DFT study demonstrated the formation of a strong intermolecular hydrogen bonding between the nitrogen atom of Cilnidipine and the amide hydrogen atom of Nicotinamide in cocrystal formed.

**Conclusion:** This study highlights the potential of the liquid-assisted grinding method for preparing cocrystals as a sustainable and reliable approach to address the challenges posed by poorly water-soluble drugs.

**Keywords:** Cocrystals, Cocrystals Cilnidipine, Cilnidipine Nicotinamide, Liquid-assisted grinding, Solubility enhancement, Green, Sustainable

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### INTRODUCTION

Several factors are involved in determining the absorption of a drug from an oral solid dosage form. These include the release of the drug from the dosage form, its ability to dissolve in gastrointestinal (GI) fluids, and its permeability through the gastrointestinal tract (GIT). Over the past few years, many newly discovered drugs have been classified as BCS class II (highly lipophilic and poor aqueous solubility). For these drugs, the ability to dissolve in the GI fluids is critical in determining their bioavailability [1]. There are various methods that formulation scientists can utilise to address this issue. In recent years, cocrystallisation has emerged as a promising approach for enhancing the aqueous solubility of such active pharmaceutical ingredients (API) without altering their pharmacological activities [2]. Cocrystals offer several potential benefits, such as improved aqueous solubility and consequent increase in bioavailability, better mechanical properties, and stability [3]. Pharmaceutical cocrystals are crystalline materials of two or more different molecules in a specific stoichiometric ratio. One of the components is an API, while the other is a coformer held together by nonionic and non-covalent bonds [4].

Poorly controlled hypertension increases the risk of cardiovascular, renal, and endocrine disorders. To manage hypertension, dihydropyridine class of calcium channel blockers (CCBs) such as Cilnidipine are commonly used as first-line agents, alone or in combination with other antihypertensive drugs [5]. Cilnidipine blocks both L-type and N-type calcium channels and is the recommended medication for treating hypertension in patients with chronic renal diseases and diabetes mellitus [6–8]. Cilnidipine is a BCS class II drug, insoluble in water and with a reported bioavailability of less than 13% [9]. The pKa value of Cilnidipine is

11.39. The N-H of the dihydropyridine ring can serve as a hydrogen bond donor, and eight electronegative atoms, such as the oxygen atom of the NO<sub>2</sub> group and the ester functional group, serve as hydrogen bond acceptors [10]. Because of these properties, Cilnidipine is an ideal candidate for developing cocrystals with compatible coformers having complementary hydrogen bonding sites [11].

This study aimed to enhance the aqueous solubility of Cilnidipine by utilising the cocrystallisation technique with Nicotinamide (pyridine-3-carboxamide) as the coformer. Nicotinamide is a valuable coformer in the pharmaceutical industry as it has multiple hydrogen bond acceptor and donor sites [12]. ΔpKa value for the Cilnidipine-Nicotinamide system is less than one, favouring the formation of cocrystals [13, 14]. Moreover, Nicotinamide is a water-soluble vitamin (vitamin B<sub>3</sub>) used in foods and nutrient supplements and is included in the GRAS list (generally regarded as safe) [15–17]. This study adopted the liquid-assisted grinding (LAG) technique to prepare Cilnidipine-Nicotinamide cocrystals. The LAG method involves grinding solid reactants while incorporating a minimal amount of solvent (micro-liter), making it a swift and dependable method for discovering cocrystals [18]. This process is considered eco-friendly since it uses minimal organic solvents, making it a sustainable option for cocrystal preparation [19]. Methanol was used as the solvent in this study, as it can modify the wettability of the solid surface of Cilnidipine and facilitate cocrystal formation [20]. The resulting cocrystals were characterised using Fourier-transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and field emission scanning electron microscopy (FE-SEM). A computational technique based on Density Functional Theory (DFT) using the Gaussian approach was used to study the mechanism of intermolecular and intramolecular interactions within the

Cilnidipine-Nicotinamide cocrystal system [21]. Ultimately, the prepared cocrystals were assessed for saturation solubility to ascertain the improvement in aqueous solubility of Cilnidipine achieved through the prepared cocrystals.

## MATERIALS AND METHODS

The materials used were Cilnidipine (PubChem: 5282138), Nicotinamide (PubChem: 936) and Methanol (PubChem: 887). Cilnidipine was obtained from Pure Chem Pvt. Ltd., Gujarat, while Nicotinamide was purchased from Merck and Methanol (HPLC grade) was sourced from SD Fine-Chem Limited in Mumbai. The ultra-pure grade water collected from the Milli-Q® water purification system (Millipore, Germany) was used for the study. All other chemicals used in the study were analytical grade (AR).

**Table 1: Ratio of cilnidipine and nicotinamide in the cocrystals**

| Ingredients      | CN1 (1:0.5) | CN2 (1:1) | CN3 (1:2) |
|------------------|-------------|-----------|-----------|
| Cilnidipine (g)  | 0.4952      | 0.4952    | 0.4952    |
| Nicotinamide (g) | 0.0611      | 0.1221    | 0.2442    |

### Fourier-transform infrared spectroscopy analysis

The FT-IR analysis of Cilnidipine, Nicotinamide, their physical mixtures and prepared products was carried out by KBr pelleting technique [23], using Nicolet iS10 FT-IR Spectrometer, ThermoFisher, USA. The spectra were recorded from 4000 to 400  $\text{cm}^{-1}$ .

### Differential scanning calorimetric analysis

The DSC analyses were conducted in DSC Q20V24.11, TA Instruments, USA. About 5 mg of the sample was accurately weighed and transferred to an aluminium pan. The pan was crimped using a crimping machine and placed in the sample chamber, and an empty aluminium pan was kept in the blank chamber. Dry nitrogen gas was continuously purged into the chamber, and the spectra were recorded from 30 °C to 300 °C at a heating rate of 10 °C/min.

### Powder X-ray diffraction (PXRD) measurements

The powder X-ray diffractometer, Ultima IV (Rigaku, Japan), with Cu-K $\alpha$ -X radiation as source ( $\lambda = 1.5405 \text{ \AA}$ ) at 40 kV/30 mA, was used to record powder X-ray diffractograms of samples. 2 $\theta$  angle was measured from 5°–80° at a step size of 0.02°/0.5 s using Nickel as the filter. The diffraction pattern was obtained by plotting 2 $\theta$  against the intensity.

### Saturation solubility analysis of cilnidipine-nicotinamide cocrystals

Accurately weighed and transferred 100 mg each of pure Cilnidipine and CN2 to vials containing 10 ml of ultrapure water. The vials were shaken continuously at 100±10 agitations/min in a shaker water bath at room temperature for 24 h. It was then centrifuged, the supernatant was separated and filtered using Whatman filter paper No: 10, and the drug content was estimated using an ultraviolet (UV) spectrophotometer.

## Preparation of cocrystals of cilnidipine with nicotinamide as cofomer by LAG

The LAG method was adopted to prepare cocrystals of Cilnidipine with Nicotinamide as the cofomer. Cilnidipine and Nicotinamide in the stoichiometric ratio, as shown in table 1, were taken in an agate mortar and pestle and manually ground at room temperature with the addition of 100  $\mu\text{l}$  (2 drops) of methanol at 10 min intervals for 45 min [22]. The obtained products were dried at room temperature in a desiccator and used as such for further characterisation and evaluation [18]. The physical mixtures (CNPM) were prepared by physically mixing the components in the same molar ratio used to prepare the respective formulation.

### Field emission scanning electron microscopy analysis

FE-SEM analyses of the samples were carried out in Gemini 300 (Carl Zeiss, Germany). The gold-sputtered samples were analysed under an inert argon atmosphere at an accelerating voltage of 20 kV.

### Computational method

Density functional theory calculations of the Cilnidipine–Nicotinamide (1:1) cocrystal system were performed using the Gaussian 09W program to study the possible mechanism of cocrystal formation [24]. The structures of Cilnidipine and Nicotinamide, downloaded from the PubChem database, were converted from the standard data format (SDF) to Gaussian Job File (GJF) using the Open Babel application [25, 26]. The optimised structures of the cocrystal and its components were obtained by DFT calculations using the B3LYP/6-311++G (d,p) level of theory [27].

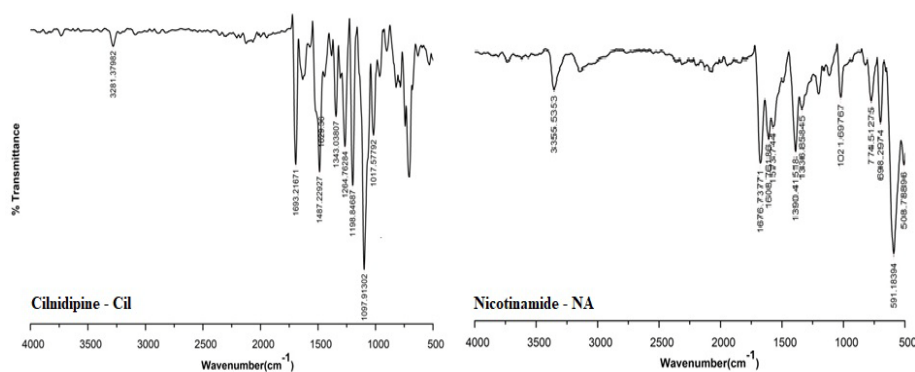
## RESULTS AND DISCUSSION

### Preparation of cocrystals of cilnidipine with nicotinamide as cofomer by LAG

The LAG technique using trace amounts of methanol as solvent was used to prepare cocrystals of Cilnidipine with Nicotinamide. Grinding the components using micro-liters of methanol facilitated the formation of cocrystals with Nicotinamide [19].

### Fourier-transform infrared spectroscopic analysis

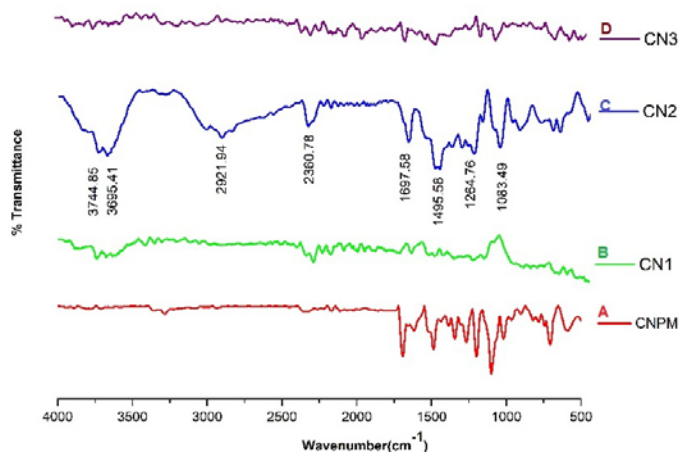
FT-IR spectroscopy is a valuable technique used to characterise the cocrystals. It provides helpful information about the intermolecular and intramolecular interactions, especially hydrogen bond formation in a cocrystal [20]. The FT-IR spectra of Cilnidipine and Nicotinamide are given in fig. 1.



**Fig. 1: FT-IR spectra of (A) Cilnidipine (Cil) and (B) Nicotinamide (NA)**

The Cilnidipine showed the characteristic peaks at  $3281\text{ cm}^{-1}$  (N-H stretching),  $1693\text{ cm}^{-1}$  (C=O stretching) and  $1525\text{ cm}^{-1}$  (N-O symmetrical stretching) and  $1343\text{ cm}^{-1}$  (N-O asymmetrical stretching)

and that of Nicotinamide at  $3355.53\text{ cm}^{-1}$  (N-H asymmetrical stretching),  $3147.48\text{ cm}^{-1}$  (N-H symmetrical stretching),  $1676.73\text{ cm}^{-1}$  (C=O stretching) and  $1608.76\text{ cm}^{-1}$  (N-H bending) [9].



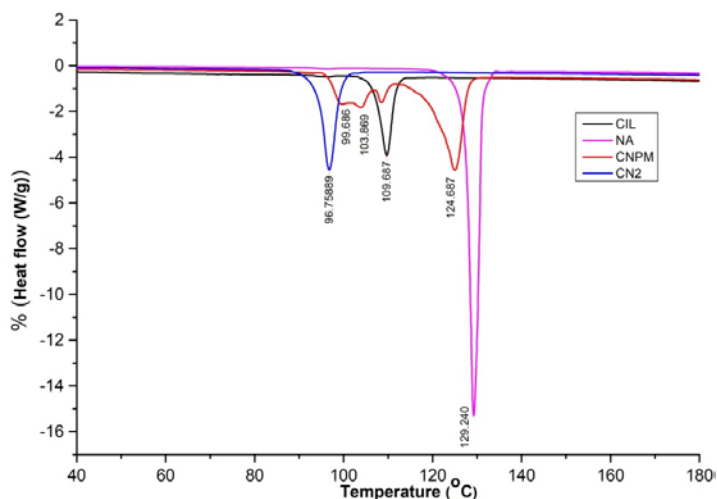
**Fig. 2: FT-IR Spectra of (A) Physical mixture of cilnidipine and nicotinamide (CNPM), formulations of cilnidipine-nicotinamide in the molar ratio: (B) 1:0.5-CN1, (C) 1:1-CN2, (D) 1:2-CN3**

The FT-IR spectra of the physical mixture and various formulations (CN1, CN2 and CN3) are shown in fig. 2. The spectra of the physical mixture (CNPM) showed all the characteristic peaks of its components, thus indicating the absence of any chemical or physical interactions between Cilnidipine and Nicotinamide. The FT-IR spectra of CN1 and CN3 were similar to that of the physical mixture, indicating that the cocrystal formation has not occurred in these two formulations. In the formulation CN2, containing equimolar amounts of Cilnidipine and Nicotinamide, a considerable broadening of peaks and shift in the positions of the characteristic peaks of Cilnidipine and Nicotinamide were observed. A shift in the position and broadening of the -N-H

stretching peak of Nicotinamide to  $3900\text{--}3400\text{ cm}^{-1}$  indicated the formation of hydrogen bonds. A band broadening from  $1550\text{ cm}^{-1}$  to  $1450\text{ cm}^{-1}$  suggested the involvement of the nitro group of Cilnidipine in hydrogen bonding. FT-IR study indicated the formation of cocrystals in formulation CN2 [28].

#### Differential scanning calorimetric analysis

DSC is a rapid and sensitive technique commonly employed to identify, characterise and screen cocrystals [29]. DSC thermograms of Cilnidipine, Nicotinamide, their physical mixture (CNPM) and cocrystal -CN2 are shown in fig. 3.



**Fig. 3: Overlain DSC thermograms of cilnidipine (Cil), Nicotinamide (NA), their physical mixture (CNPM) and cilnidipine-nicotinamide cocrystal (CN2)**

The thermogram of Cilnidipine showed a single sharp melting endotherm at  $109.69\text{ }^{\circ}\text{C}$  and Nicotinamide at  $129.24\text{ }^{\circ}\text{C}$ , corresponding to their respective melting points. During DSC analysis of Cilnidipine and Nicotinamide, a single endothermic peak indicated that they melted without decomposing, making it possible to use this method for cocrystal screening [29]. An equimolar physical mixture of Cilnidipine and Nicotinamide (CNPM) showed endothermic peaks at  $99.69\text{ }^{\circ}\text{C}$ ,  $103.87\text{ }^{\circ}\text{C}$ ,

$108.49\text{ }^{\circ}\text{C}$  and  $124.68\text{ }^{\circ}\text{C}$  corresponding to the melting endotherm of cocrystal, eutectic, Cilnidipine and Nicotinamide respectively. Yamashita *et al.* showed that these thermal events are typical of mixtures capable of forming cocrystals [30]. Cilnidipine-Nicotinamide cocrystal (CN2) gave a distinct endothermic peak at  $96.76\text{ }^{\circ}\text{C}$ , distinguishable from those of its components. The appearance of a sharp melting endotherm and a shift in the peak's position in CN2 indicated the formation of a

new crystalline phase. The lower melting point of CN2 than its components contributed to its enhanced water solubility [31].

#### Powder X-ray diffraction analysis

PXRD analysis is used to study changes in the crystal lattice of molecules, making it a valuable tool for characterising cocrystals. When there is a crystal lattice change, a molecule's unique PXRD pattern is altered [32]. The PXRD pattern of Cilnidipine (CIL), Nicotinamide (NA), and the cocrystal CN2 are given in fig. 4. The characteristic  $2\theta$  positions of Cilnidipine are  $5.86^\circ$ ,  $11.74^\circ$ ,  $12.3^\circ$ ,  $14.26^\circ$ ,  $16.52^\circ$ ,  $18.74^\circ$ ,  $19.96^\circ$ ,  $21.8^\circ$ ,  $25.0^\circ$ ,  $26.12^\circ$ , while the peaks for Nicotinamide are  $13.14^\circ$ ,  $14.64^\circ$ ,  $22.12^\circ$ ,  $25.26^\circ$ ,  $25.74^\circ$ , and  $27.22^\circ$ . The CN2 exhibited peaks at  $5.80^\circ$ ,  $11.82^\circ$ ,  $14.72^\circ$ ,  $16.44^\circ$ ,  $21.7^\circ$ ,  $23.24^\circ$  and  $25.74^\circ$ . The  $2\theta$  positions of CN2 are more intense,

unique and different from its components, which confirm the formation of a new crystalline phase.

#### Saturation solubility measurements of cilnidipine-nicotinamide cocrystals

The saturation solubility analysis of Cilnidipine and formulation CN2 were determined in water, and the results are tabulated in table 2. The results showed that pure Cilnidipine is practically insoluble in water with an aqueous solubility of  $5.53 \pm 0.26 \mu\text{g/ml}$ . The aqueous saturation solubility of the formulation CN2 was  $145.77 \pm 0.021 \mu\text{g/ml}$  and thus exhibited 26.36 folds improvement in aqueous solubility compared to the pure Cilnidipine. This enhancement in aqueous solubility is due to the ability of the cofomer Nicotinamide to decrease the solvation barrier of the cocrystal of Cilnidipine [33].

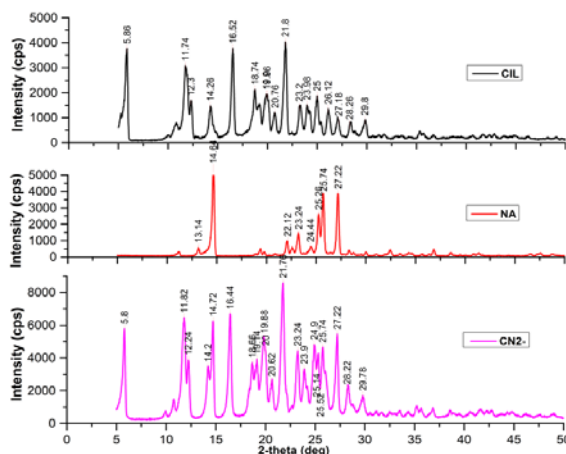


Fig. 4: PXRD pattern of cilnidipine (CIL), nicotinamide (NA) and cilnidipine-nicotinamide cocrystal (CN2)

Table 2: Saturation solubility studies of cilnidipine-nicotinamide cocrystals in water

| Sample (n=3) | Solubility in water ( $\mu\text{g/ml}$ ) | No: of folds increase in solubility |
|--------------|--|-------------------------------------|
| Cilnidipine  | $5.53 \pm 0.26$                          | -                                   |
| CN2          | $145.77 \pm 0.021$                       | 26.36                               |

The value given is the mean  $\pm$  SD (n = 3).

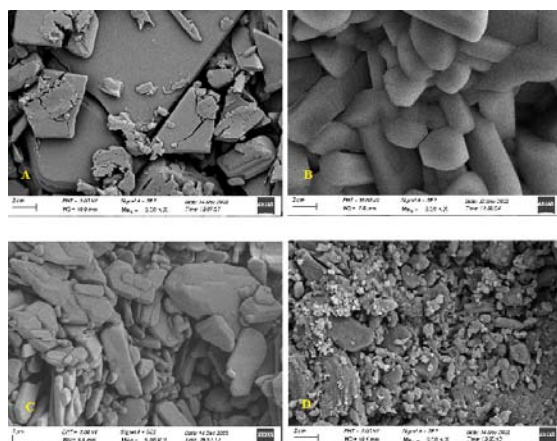


Fig. 5: FESEM images of (A) Cilnidipine (B) Nicotinamide (C) Physical mixture (CNPM) and (D) Cocrystal formulation (CN2). (Magnification: 5.00K X; resolution: 2  $\mu\text{m}$ )

#### Field emission-scanning electron microscopy

FE-SEM images of Cilnidipine, Nicotinamide, physical mixture (CNPM) and cocrystal formulation CN2 are given in fig. 5.

The FE-SEM analysis revealed that Cilnidipine, in its pure form, appeared as smooth, flat, and rectangular crystalline plates, while Nicotinamide was in the form of tubular solids. The physical mixture of the two substances did not show any

noticeable change in the surface morphology of either Cilnidipine or Nicotinamide. However, in CN2, there was a significant reduction in the size of the Cilnidipine particle with a change in surface morphology.

#### Computational analysis-DFT studies

The optimised structure of cilnidipine, nicotinamide and cilnidipine-nicotinamide cocrystal (CN2) are shown in fig. 6 to 8.

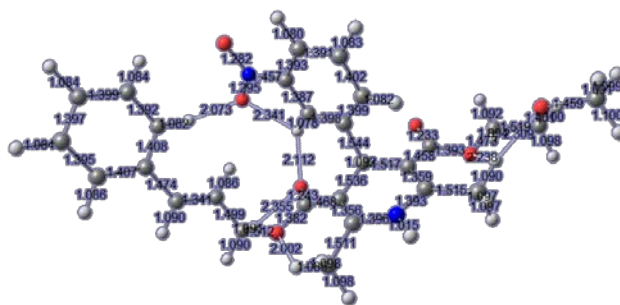


Fig. 6: Optimized structure of cilnidipine

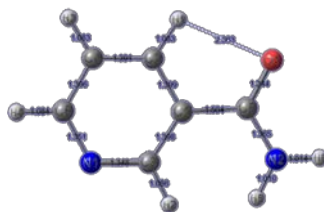


Fig. 7: Optimized structure of nicotinamide

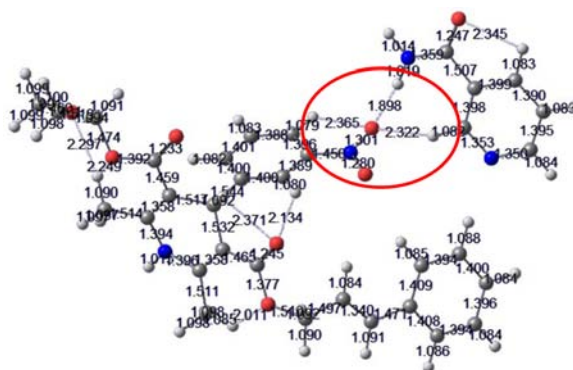


Fig. 8: Optimized structure of cilnidipine-nicotinamide cocrystals with intermolecular hydrogen bonding

The geometrical parameters of Cilnidipine, Nicotinamide and Cilnidipine-Nicotinamide cocrystal (CN2) were calculated, and the details of bonds involved in intermolecular and intramolecular hydrogen bonds are tabulated in table 5.

Considerable changes in the geometrical parameters of CN2 from that of its components were noted, including the formation of two intermolecular hydrogen bonds between Cilnidipine and Nicotinamide.

Table 3: Intermolecular and intramolecular hydrogen bonding in cilnidipine, nicotinamide and its cocrystal with their bond length in Å

| Definition                       | Bond involved                     | Bond length (Å)          |                           |       |
|----------------------------------|-----------------------------------|--------------------------|---------------------------|-------|
|                                  |                                   | Cilnidipine <sup>a</sup> | Nicotinamide <sup>b</sup> | CN2   |
| R (6-9)                          | O6-N9                             | 1.282                    | -                         | 1.301 |
| R (7-9)                          | O7-N9                             | 1.295                    | -                         | 1.280 |
| R (7-39) <sup>#</sup>            | O7-H39                            | 2.341                    | -                         | -     |
| R (7-60) <sup>#</sup>            | O7-H60                            | 2.073                    | -                         | -     |
| R (6-48) <sup>#</sup>            | N6-H48                            | -                        | -                         | 2.365 |
| R (3-14)                         | N2-H5                             | -                        | 1.010                     | 1.019 |
| R (3-15)                         | N2-H6                             | -                        | 1.014                     | 1.014 |
| R (3-8)                          | N2-C5                             | -                        | 1.365                     | 1.359 |
| R (1-8)                          | C5=O1                             | -                        | 1.244                     | 1.247 |
| R (2-6)                          | N1-C3                             | -                        | 1.348                     | 1.353 |
| R (1-10)/†R (65-74) <sup>#</sup> | †O65-H74                          | -                        | 2.363                     | 2.345 |
| R (6-75) <sup>*</sup>            | O6 <sup>a</sup> -H75 <sup>b</sup> | -                        | -                         | 2.322 |
| R (6-78) <sup>*</sup>            | O6 <sup>a</sup> -H75 <sup>b</sup> | -                        | -                         | 1.898 |

<sup>#</sup>intramolecular hydrogen bonding; <sup>\*</sup>intermolecular hydrogen bonding. †Numbering of atoms of Nicotinamide changed in CN2

In the optimised structure of Cilnidipine, two intramolecular hydrogen bonds (R(7-39); bond length-2.073 Å and R(7-60); bond length of 2.341 Å) were observed, both involving oxygen atom of the

nitro group and hydrogen atom of the phenyl ring present in the side chain of dihydropyridine nucleus of Cilnidipine. However, these two intramolecular hydrogen bonds disappeared in the Cilnidipine-



Nicotinamide cocrystal. Instead, two new intermolecular hydrogen bonds were formed, namely R(6-75) and R(6-78), with bond lengths of 2.322 Å and 1.898 Å, respectively. The R(6-75) bond was formed between the nitro oxygen of Cilnidipine and the C2 hydrogen atom of the pyridine nucleus of Nicotinamide (-N-O $\cdots$ H-C=), while the second intermolecular hydrogen bond, R(6-78), formed between the nitro oxygen of Cilnidipine and the amide hydrogen of Nicotinamide (-N-O $\cdots$ H-N-). The hydrogen bond between the oxygen (O6) of the nitro group and the amide hydrogen (-N-O $\cdots$ H-N-) had a bond length of 1.898 Å, comparable to the strong hydrogen bonds of a carboxylic acid with a hydroxyl group (-C=O $\cdots$ H-O-; bond length-1.884 Å) and between a carboxylic acid and an amino group (-C=O $\cdots$ H-N-; bond length-2.011 Å). This indicated that the hydrogen bond in CN2 was also strong [34]. As a result of intermolecular hydrogen bonding, the length of N-H and C=O bonds were increased in Nicotinamide by 0.009 Å and 0.003 Å and the N2-C5 bond in pyridine nucleus of Nicotinamide was decreased by 0.006 Å, which was consistent with many reported studies [35]. This confirmed the involvement of the oxygen atom of the nitro group of Cilnidipine and the amide hydrogen atom of Nicotinamide in forming intermolecular hydrogen bonding in CN2.

## CONCLUSION

An eco-friendly approach, liquid-assisted grinding, was adopted to prepare the Cilnidipine-Nicotinamide cocrystals to enhance the poor solubility of Cilnidipine. The FT-IR, DSC, PXRD and FE-SEM studies confirmed that the cocrystals had been successfully formed. The aqueous solubility of Cilnidipine in CN2 was increased by 26-fold compared to the pure drug. Additionally, DFT analysis revealed that two strong intermolecular hydrogen bonds are formed between the nitro group of Cilnidipine and hydrogen atoms of Nicotinamide. Thus, the successful formation of Cilnidipine-Nicotinamide cocrystals by liquid-assisted grinding method demonstrates the potential application of this technique as a sustainable and promising approach to tackle the challenges posed by poorly water-soluble drugs.

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## AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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