NEVIRAPINE COCRYSTAL MOTIF USING A GREEN APPROACH– PREPARATION, CHARACTERIZATION AND DISSOLUTION STUDIES.

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ABSTRACT

Nevirapine (NE) is a BCS class II drug used in the prevention of HIV/AIDS, specifically HIV-1. Its inadequate physicochemical characteristics, such as its low affinity for water and slow dissolution rate, continue to be a barrier to creating new formulations. In this study, cocrystal formation is a contingent feature that involves ionic or non-covalent intermolecular interactions between an active moiety and a coformer in a crystal lattice for creating NE cocrystals with favourable physicochemical characteristics. The coformers chosen were Nicotinamide (NA) and Succinimide (SI) which demonstrated encouraging results in terms of enhanced water solubility and dissolution rate. NE cocrystals were synthesised in 1:1 stoichiometric ratio utilising liquid-assisted grinding method with liquid acetone, which acted as a catalyst to accelerate reaction kinetics. Analytical methods such Fourier transform (FTIR), Powder X-ray diffraction (XRD), SEM, and differential scanning calorimeter were used to analyse the novel cocrystals of NE. All of the studies revealed the formation of cocrystals with increased solubility and dissolution rates. The thermal stability The dissolution studies revealed that NE-NA (1.94-fold) and NE-SI (1.86-fold) were more soluble than pure NE. The NE-NA and NE-SI cocrystals in phosphate buffer at pH 6.8 exhibit higher dissolution rates than pure NE. The positive attributes of cocrystallization in strengthening the drug's physicochemical features were shown by changes in the chemical environment, an enhancement in solubility, and an increase in dissolution rate.

Keywords: Nevirapine, Nicotinamide, Succinimde, Cocrystallization, solubility and Dissolution rate.

Introduction

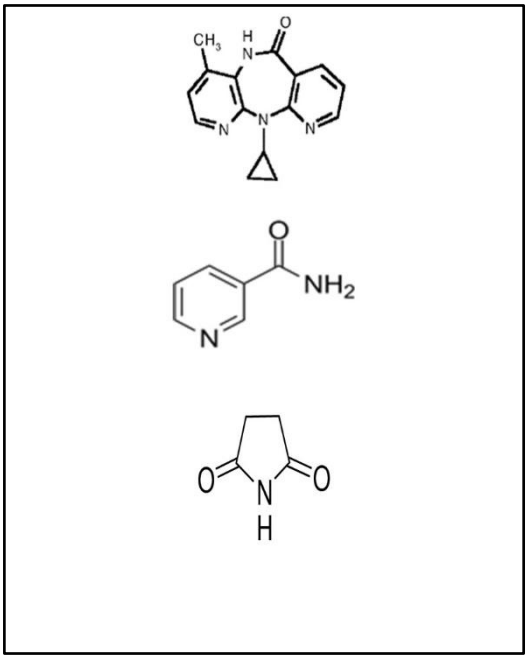
One of the most common ways to administer medication is orally. However, oral administration is complicated by the high lipophilicity of 50% of medicines. Because they are relatively insoluble in water, drugs in Biopharmaceutical Classification System (BCS) Classes II and IV have low bioavailability. As a consequence, medication absorption is hampered. Therefore, enhancing drugs solubility and oral bioavailability is a concern for scientists [1]. Cocrystal technology has rekindled interest in the pharmaceutical industry because it provides a unique scientific research approach for tailoring and improving the physicochemical properties of active pharmaceutical ingredient (API) while maintaining therapeutic efficacy for the easy administration of improved medicines [2]. To improve the drug's properties, the molecular linkages can be altered utilising the pharmaceutical cocrystallization process. Cocrystals are made up of a multicomponent system that includes API and a stoichiometric amount of a pharmaceutically approved GRAS (Generally Recognised as Safe) coformer that are physically coupled by non-ionic and non-covalent bonds. The coformer interacts with the supramolecular synthon approach between API's acidic and basic functional groups, potentially resulting in a hydrogen bond or non-covalent connection [3].

A number of options for supramolecular association are produced in a cocrystallization experiment by the interaction of many hydrogen bonding groups. Internal factors include an unbalanced donor-acceptor ratio, unfavourable shape, and molecular conformational flexibility. The solvent, stoichiometric ratio, and temperature are examples of external impacts on crystallisation conditions. As a result of cocrystallization, an entirely new cocrystal may form. Even while each of these aspects is important in and of itself, from a practical standpoint, controlling the production of a single chemical in the environment is the most important. Because of its -NH and C=O groups, NE can elicit a wide range of supramolecular patterns in the current work to generate cocrystals [4].

Pharmaceuticalcocrystals can be achieved by using various conventional methods like cooling cocrystallization, grinding method, anti-solvent crystallization, slurry cocrystallization and supercritical fluid method, hot stage microscopy, and ultrasound assisted. The liquid aided grinding method is seen as a more appealing and environmentally friendly solution to the manufacture of multicomponent medicinal solid forms. This approach is considered an eco-friendly procedure that can be carried out in solvent-free circumstances, and it has become a significant synthetic tool in the pharmaceutical sector. The addition of a minimal amount of solvent to dry API solid prior to grinding plays catalytic role to accelerate the kinetics of cocrystal formation [3, 5].

NE is a class of medications called non-nucleoside reverse transcriptase inhibitors (NNRTIs). It reduces the viral load in the blood by binding to Human Immunodeficiency Virus Type 1 (HIV-1) reverse transcriptase and inhibiting RNA plus-strand initiation. Nevirapine is marketed under the brand name Viramune [6, 7]. NE is a benzodiazepine derivative. The presence of amide (-NH group and C=O) in NE propound create cocrystal via non-covalent interaction, i.e., hydrogen bond with coformers with GRAS such as Nicotinamide and

Succinimide coformers. The cocrystals of NE-NA and NE-SI using Nicotinamide and Succinimide as coformers were prepared by liquid assisted grinding method using acetone as a solvent in 1:1 molar stoichiometric ratio. The new cocrystals synthesised using the green synthesis methodology described above have physicochemical features such as solubility and dissolution, which boost GI absorption substantially. Several previous attempts to increase NE solubility have been made. Using the neat grinding process, Nalte et al. (2015) produced cocrystals of NE using maleic acid [8], Costa et al. (2019) of the production of multicomponent systems of NE with seven potential coformers: salicylic acid, 3-hydroxybenzoic acid, 4-hydroxybenzoic acid, saccharin, theophylline, caffeine, and urea. Using the solid drop grinding method, [9] Sathisaran et al. (2021) synthesised cocrystals using trimesic acid and paracetamol as coformers [10].These cocrystal discoveries proved that it is possible to alter and improve physico chemical properties of NE by preparing NE cocrystals. Accordingly, the objective of the present work was to prepare, formulate and evaluate the NE cocrystal by screening various coformers and to evaluate the modified changes in the solubility and in the dissolution rate. The chemical structures of NE and coformers are shown in the **Figure.1**



(Figure 1) Chemical Sketch of (a) Nevirapine (NE) (b) Nicotinamide (NA), (c) Succinamide (SI)

Materials and Methods

Materials:

Nevirapine (NE) was generously offered by Nargund College of Pharmacy, Bangalore. Ragavendra Chemicals Ltd supplied acetone, Succinimide, and Nicotinamide. Analytical-grade chemicals were used throughout the investigation.

Coformer selection and its Proportion.

The use of a preset library of pharmaceutically acceptable/approved chemicals in an effort to cocrystallize them is known as "tactless" cocrystal screening, and it is a common method for choosing coformers. Nicotinamide and Succinimide were chosen as two coformers based on this. With the basic and acidic functional groups of API, the coformers can engage non -covalently or via hydrogen bonds. However, only Nicotinamide and Succinimide demonstrated encouraging results in terms of enhanced water solubility and dissolution rate. The initial (1:1) molar ratio for amides was chosen for API and coformers [5].

NE Cocrystals Preparation by Liquid-Assisted Grinding

NE-NA and NE-SI combination cocrystallization was accomplished via mechanochemical grinding, also known as the liquid-assisted grinding technique. An equimolar 1:1 stoichiometric ratio of NE (266 mg), NA (122 mg) and NE (266 mg), SI (122 mg) was transferred to clean mortar pestle with the addition of a few drops of acetone. The contents were grinded manually for 40 minutes. After grinding these cocrystals were collected and stored. Figure.2 depicts the schematic representation of synthesis of NE cocrystals via green approach.

(Figure 2) A Schematic representation of synthesis of NE cocrystals via green approach

Fourier transform infrared spectroscopy analysis

FTIR analysis of NE, NA, SI and NE cocrystals was recorded using Bruker α -2 with attenuated total reflection containing DLATGS detector with 2 cm^{-1} spectral resolution. Then, 2 mg of each sample was placed on the sample cell and spectra recorded through the wavelength of 4000–400 cm^{-1}. The obtained data was analysed using Origin software.

Differential scanning calorimetry analysis

Differential scanning calorimetry was used to examine the material's melting behaviour. Each sample, weighing 2 mg of pure drug, co-formers, and unique cocrystals, was scanned using a DSC 823e calorimeter made by the Swiss company Mettler Toledo. With an empty, sealed aluminium pan acting as a reference, each and every specimen was sealed in a 40 microliter aluminium pan. With nitrogen gas flowing at a rate of 20 ml/min, all samples were scanned at a rate of 5 °C per minute between RT and 300 °C.

Powder X-ray diffraction analysis

Powder X-ray diffraction data recording was done using powder X -ray diffractometer (Bruker AXS D8 Advance, Germany). Conditions used for measurement: Si (Li) PSD detector, Cu X-ray source (λ=1.5406 Å), 3° to 135° angular range. Powder X-ray diffraction data obtained were compared with bulk drug and co-formers.

Solubility analysis

Excess amounts of each material NE, NA, SI, and cocrystals placed in 10 ml distilled water in glass tubes sealed with aluminium foil. Resultant suspension stirred for 72 h and filtered. Filtrate obtained was diluted with distilled water and analysed spectrophotometrically using a UV-spectrophotometer.

SEM analysis

Using a scanning electron microscope (SEM; Hitachi S3400, Japan), the NE and NE cocrystals (NE-NA and NE-SI) were studied for their surface morphology. Prior to examination, the particles had been gold sputtered at room temperature.

Intrinsic dissolution rate measurement

A USP equipment dissolution tank with 900 cc of phosphate buffer as the dissolving media was used to perform studies on the intrinsic dissolution of pure drug and cocrystals at pH 7.4 in order to replicate an actual intestinal environment. The water bath temperature was 37 °C, and the paddle rotated at a speed of 100 rpm. One millilitre of each sample was used to calculate the concentrations at 10, 20, 30, 40, 50, 60 70, 80, 90,100, 100,110 and 120 minutes respectively. There were three runs of each dissolving test. The concentration was calculated at 293 nm using a UV spectrophotometer.

Results and Discussion

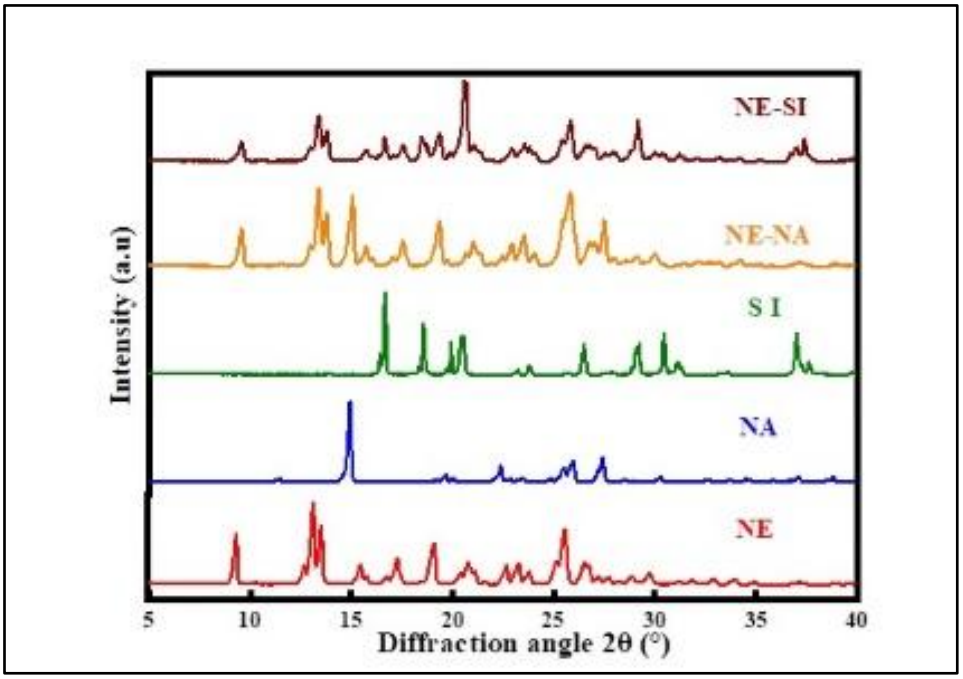
Liquid-assisted grinding technique has been shown to be an effective method for the synthesis of cocrystals since it is an environmental friendly process that can be completed in solvent-free conditions or with the presence of catalytic amounts of solvent [5].Cocrystals are one of the outputs of the pharmaceutical cocrystallization process, characterised by ionic or non-covalent intermolecular interactions between two or more distinct molecules in a crystal lattice, in which one molecule should be an active moiety and the other a coformer. The coformer identified from the GRAS list should predominantly comprise a group capable of creating molecular synthons with the active moiety. Amides and imides appear to be excellent options as practical companions in this scenario [11].

According to the findings of the Fourier transform (FTIR), Powder X-ray diffraction (XRD), SEM, and Differential scanning calorimeter, all cocrystallization products have characteristic patterns that are distinct from either NE or those of the corresponding coformers, indicating the formation of new solid forms.

Powder X-ray diffraction analysis

To determine the crystalline phases that were produced during the creation of the cocrystals, a Powder X-ray Diffraction (XRD) study was conducted. Each sample generated diffraction pattern was compared to the diffraction pattern of its parent NE. Figure. 3 displays the XRD patterns of pure NE, NE-NA, NE- SI cocrystals respectively. It showed that the XRD patterns of cocrystals were distinct from those of the drug NE.

The principal diffraction peaks corresponding to NE and coformers were found at diffraction angles 2θ values of NE = 9.1°, 13.4°, 14.6°, 19.3°, 23.4°, 23.9° and 26.3°, NA =14.9°, 22.2°, 27.5°, 37° and 38.8° and SI = 16.7°, 19.9°, 20.5°, 26.6°, 29.2o respectively. Similar outcomes were reported in the earlier experiment, and the coformers had distinctive diffraction peaks at unique 2θ values [8, 12]. In comparison to the drug and coformers, additional diffraction peaks were observed, suggesting the creation of a novel crystalline solid form. The new peaks that weren't found in the drug and coformers were NE-NA =11.5°, 12.9°, 13.6 °,15° (Intense peak), 17.6°, 21.2°and 25.8° (Intense peak), and NE-SI =9.6°, 13.7°, 15.8°, 16.7°, 17.6°, 18.6°, 20.3° (Intense peak), 23°, 29°and 37.4°[13] .



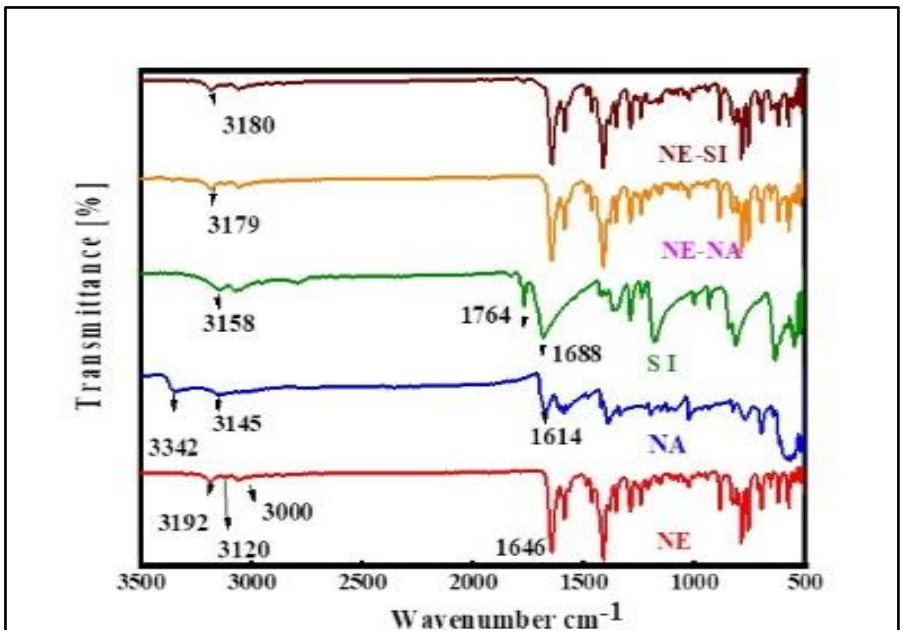
(Figure 3) Powder X-ray diffraction pattern of NE and Cocrystals

Fourier Transform IR spectroscopy

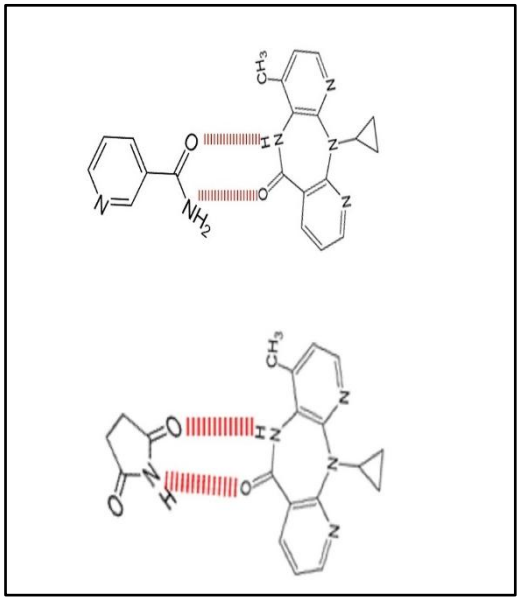
The functional groups of the API and coformers create hydrogen bonds, which lead to the formation of the cocrystals, as it is seen in Figure. 5.The FTIR spectrum of NE (Figure 4) reveals the existence of the typical peaks for seven membered cyclic, which were measured at 3192 cm^{-1} due to -NH absorption bands and C-N at 3120 cm^{-1}, 3000 cm^{-1} due to aliphatic -C-H absorption bands, 1646 cm^{-1} C-O stretching vibration of cyclic amide 1700 cm^{-1} aromatic C = O absorption bands, 1286 cm^{-1} and C = N absorption bands as indicated in **Table 1**. The IR spectra of NA exhibited an absorption band at 3145 cm^{-1} for primary amide NH_2 stretching, 3342 cm-1 for the pyridine ring area, 1593 cm^{-1} for NH bending, and 1614 cm^{-1} for aromatic C=C peaks, as given in **Table 2**. SI has a hydrogen bonded to the imide nitrogen. This type of imide will display an imide N-H stretch, which falls at 3158 cm^{-1}. A double carbonyl stretch is one of a SI spectral characteristics. These peaks are identified in Figure. 4 and lies at 1764 and 1688 cm^{-1} as shown in **Table 3**.

In contrast to the pure drug and coformer, the IR bands in the cocrystal were considerably displaced, showing that the drug and coformer interacted. Both cocrystals spectra showed a shift in the peak at 3179 and 3180 cm^{-1}, indicating the cocrystals development. The intermolecular hydrogen connection between the oxygen atom in the drug and the hydrogen of the major amide N-H and imide N-H may be the cause for the peak shift at 3362, 3293 cm^{-1}in the cocrystals. Similar alterations in the IR spectra of other drugs, such as fenofibrate and zaltoprofen with nicotinamide, were observed and interpreted as an indication of cocrystal formation. The production of a cocrystal of fenofibrate and nicotinamide was indicated by changes in the IR peaks of fenofibrate. Possible hydrogen bonding interactions between the drug and the coformer have been attributed for the alterations [14]. Changes in IR peak intensities were used to further confirm the formation of the cocrystal in this particular case of the NE-NA, NE- SI cocrystals [12, 15].

An outline of possible cocrystal structures of NE- NA and NE-SI are depicted in Fig. 5 (a) and (b) respectively.



(Figure 4) FTIR Spectra of NE and Cocrystals



(Figure 5). Outline of possible cocrystal structures of (a) NE- NA and (b) NE-SI

Table 1. The FTIR wavenumber vibrational assignments of NE in FTIR

Functional groups	Reported value (cm^{-1})	Observed value (cm^{-1})	Functional groups	Reported value (cm^{-1})
-NH stretching and C-N for 7 membered ring	3300-3000	3192, 3120	-NH stretching and C-N for 7 membered ring	3300-3000
-CH Aliphatic stretching	3000–2850	3000	-CH Aliphatic stretching	3000–2850
-C=N stretching	1250-1340	1286	-C=N stretching	1250-1340

Table 2. The FTIR wavenumber vibrational assignments of NA in FTIR

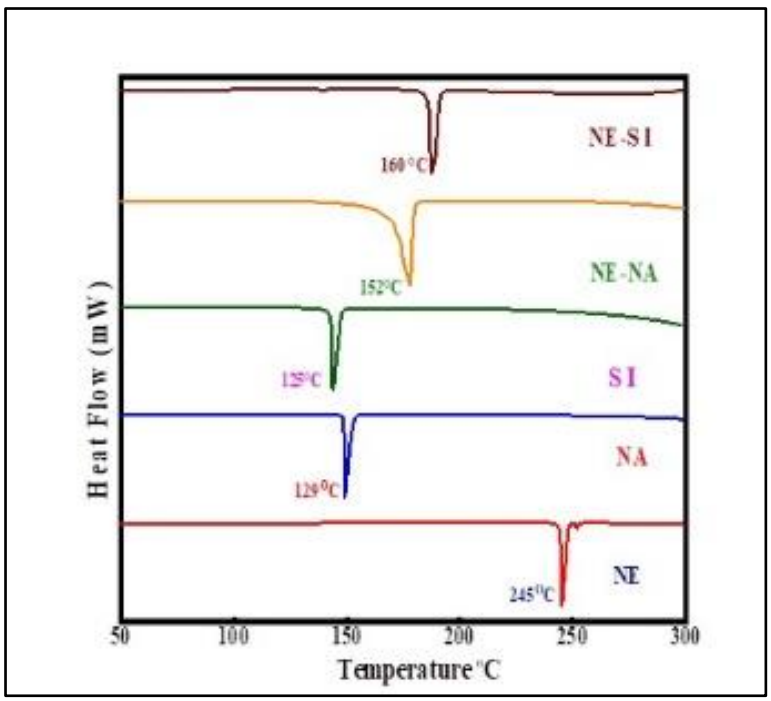
Functional groups	Reported value (cm^{-1})	Observed value (cm^{-1})	Functional groups	Reported value (cm^{-1})
-NH_2 stretching	3500-3100	3350	-NH_2 stretching	3500-3100
-C=O aromatic stretching	1670- 1640	1673	-C=O aromatic stretching	1670- 1640

Table 3. The FTIR wavenumber vibrational assignments of SI in FTIR

Functional groups	Reported value (cm^{-1})	Observed value (cm^{-1})	Functional groups	Reported value (cm^{-1})
-NHstretching	3150-3250	3158	-NHstretching	3150-3250
-C=O (Imide) a stretching	1900- 1600	1764,1688	-C=O (Imide) a stretching	1900- 1600

Differential scanning calorimetry analysis

In order to ascertain the formation of cocrystal and the purity, DSC investigations were carried out. Figure.6 shows a sharp-edged endothermic DSC curve of NE and cocrystals. The single endothermic peak observed at 245°C indicates the melting point of pure NE. The same melting point for drug NE was found in the literature [16]. The melting point of the coformers NA and SI are 129°C and 125°C accordingly. According to Perlovich's research [17], 14.5% of cocrystals have a greater endotherm than the starting materials, 28.9% of them have a low melting point, and 55.3% of them have an intermediate melting point. The new crystalline solid form thermal behaviour was different from that of the drug and its coformers. The melting point of the cocrystals NE-NA and NE-SI were found to be at 152°C and 160°C, respectively (Figure.6) which are typical for 1:1 stoichiometric cocrystals. This shows that the cocrystal melting point is intermediate between the NE and the melting points of the coformers. In a DSC study, the location and shape of endothermic melting peaks serve as a representation of the unique characteristics of cocrystals.



(Figure 6) DSC of NE and Cocrystal

Solubility analysis

Solubility analysis was performed in distilled water, pure NE showed 0.0892 mg/ml concentration at 24 h (RT 25 °C) with continuous stirring. The cocrystals NE-NA, NE-SI, showed

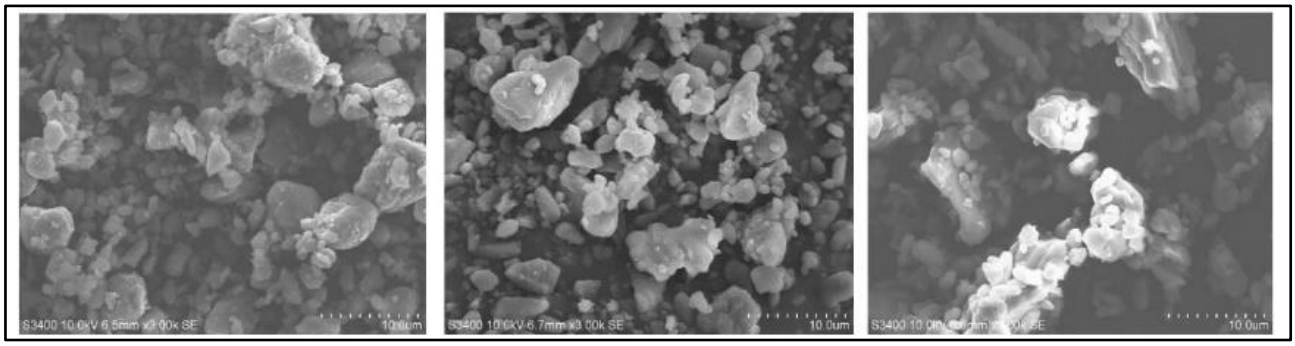
increase in aqueous solubility of 0.1726 mg/ml and 0.16554 mg/ml respectively (**Table 4)** and confirms potential in cocrystals to sight for new and efficient formulation of NE.

Table 4. Aqueous solublity of NE and Cocrystals

Chemical species	Solubility (mg/ml)	Increased ratio	Chemical species
NE	0.0892		NE
NE- NA cocrystal	0.1726	1.94	NE- NA cocrystal

Scanning electron microscopy (SEM)

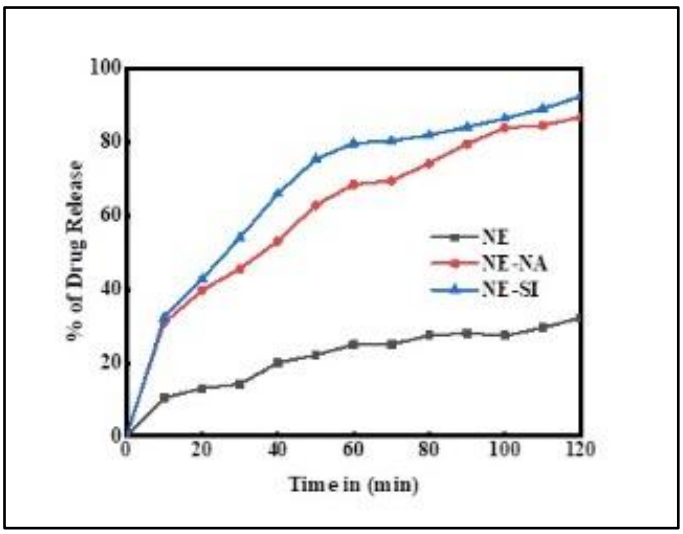
SEM was used to examine the morphology of pure NE, NE-NA and NE-SI cocrystals. Pure NE has shown block-shaped particles. The majority of the cocrystals formed had a distinctive size, irregular shape, and morphology. This alteration in crystallographic habits denotes the creation of cocrystals. SEM images of the pure (NE) and cocrystal samples (NE-NA, NE-SI) are shown in Figure. 7 a –c. The final particle shape was affected by the coformer utilised for the cocrystallization of NE, as seen in Figure. 7[18, 16].



(Figure 7) Scanning electron microscopy (SEM) images of **(a)** NE, **(b)** NE-NA, **(c)** NE-SI

Dissolution studies:

Pure drug NE, NE-NA, and NE-SI cocrystal dissolution profiles were created using phosphate buffer pH 6.8 as the dissolving media. In a phosphate buffer with a pH of 6.8, 32.23% of the NE was found to have been released in 120 minutes (Figure 8). In 120 minutes, the percentage of the drug release of NE-NA and NE-SI was observed to vary from 86.7.97% to 92.3%, respectively. The cumulative proportion of medication release was increased by around 50–60%.NE-NA, NE- SI cocrystals and raw nevirapine were dissolved in 6.8 phosphate buffer, and the comparative intrinsic dissolution data are shown in Fig. 8. The gastrointestinal absorption of drugs is accelerated by an increase in dissolution rate. It is advantageous to use pharmaceutical cocrystallization techniques to increase the solubility of API [19].



(Figure 8) Dissolution Studies of NE and cocrystals

Financial support:: None

Conclusion

By using a liquid-assisted grinding technique, nevirapine cocrystals NE-NA, NE- SI were effectively synthesised using NA and SI as coformers. In this work, it is emphasised that mechanochemical approaches, which are non-toxic, sustainable, and environmentally benign, have a considerable commercial advantage over other conventional methods of producing NE cocrystals. Novel cocrystals were analysed by using XRD, FTIR, DSC, SEM, and dissolution tests. The development of distinct molecular structures as a result of NE cocrystal formation was demonstrated by changes in infrared peaks, XRD 2θ values, melting point in DSA peaks, and surface appearance by SEM. The peak shift in the IR spectra provides additional evidence for the hydrogen bond that was supported by NE and the coformers. According to our findings, nevirapine cocrystals (NE-NA and NE-SI) demonstrate, favourable physicochemical characteristics which in turn improves therapeutic efficacy and drug delivery.

Overall, nevirapine cocrystals provide an achievable strategy for enhancing NE therapeutic potential and broadening its range of uses for the treatment of HIV/AIDS. The efficacy of the therapy, patient compliance, and treatment results as a whole may all be improved with continued research and development in this field.

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Conflict of interest: None

Ethics statement: None.

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