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Pharmaceutical Cocrystals of Nitrendipine with Improved Solubility and Dissolution Characteristics

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Abstract Nitrendipine is used in the treatment of hypertension. It comes under BCS class II and has a poor dissolution rate and water solubility. In the present study, pharmaceutical cocrystals of nitrendipine with 4-hydroxy benzoic acid were prepared using crystal engineering, an innovative method for improving solubility. 4-hydroxy benzoic acid was used as a co-former to prepare cocrystals of nitrendipine in the ratios of 1:1 and 1:2. Nitrendipine cocrystals were prepared using cooling co-crystallization. The prepared cocrystals were assessed for in vitro dissolution characteristics, saturation solubility, and stability. Analytical measures such as Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and powder X-ray diffraction (PXRD), and differential scanning calorimetry (DSC) were also used to analyze cocrystals for their purity and to confirm the formation of cocrystals. By using the cooling co-crystallization process, nitrendipine and 4-hydroxy benzoic acid crystallize together in an equimolar ratio. When compared to pure nitrendipine, the nitrendipine - 4-hydroxy benzoic acid cocrystals have a dissolving rate that is 3-4 times faster. Co-crystallization may increase nitrendipine's water solubility and rate of dissolution, which could be a solution to the drug's bioavailability issue. X-ray diffraction revealed crucial hydrogen bonding and interactions, while differential scanning calorimetry confirmed improved dissolution kinetics and higher equilibrium solubility in the optimized nitrendipine cocrystal formulation. Nitrendipine's solubility and dissolution rate are improved by the cocrystal formulation, according to the results of research on its solubility, dissolution, and stability.

Keywords Cocrystallization, Nitrendipine, Solubility, Dissolution

1. Introduction

In the research and development hypotheses of discovery-oriented pharmaceutical corporations, drug compounds with limited aqueous solubility are increasing [1]. A significant number of new chemical entities have entered the poorly soluble drug category over the past ten years, which frequently results in poor oral bioavailability [2]. The biopharmaceutical classification system (BCS) categorizes drugs into four groups based on their solubility and permeability. Poor absorption and bioavailability are significant challenges faced by drugs in BCS Class II and Class IV due to their low water solubility, complicating the drug development process [3]. The difficulty of crystal engineering appeared in its cutting-edge form in the late 1980s and early 1990s [4]. A little later, the field of natural crystal engineering saw how well it might be applied to the interior of medicinal cocrystals and salts. These were referred to as "co-crystals which may be fashioned between a molecular or ionic energetic pharmaceutical ingredient

(API) and a cocrystal former that may be a strong below ambient circumstances" by Anthony and Osselton [5]. Due to the prevalence of strong hydrogen bonds in cocrystals, proton transfer from the acid donor to the base acceptor might happen, which would cause salt to form. This phenomenon arises from the nature of hydrogen bonding interactions [6]. Salts, amorphous materials, co-crystals, including amorphous dispersions, and hydrates or solvates are examples of the various forms in which pharmaceutical solid forms can be found [7]. Ongoing research aims to determine whether cocrystals can address challenges related to an Active Pharmaceutical Ingredient's (API) bioavailability, solubility, and other physical or chemical limitations. The potential of cocrystals to enhance these properties is currently under investigation [8].

Cocrystals provide a novel method for improving the solubility of non-ionizing medicines that ordinarily are incapable of forming pharmaceutical salts [9]. With their well-defined stoichiometry, cocrystals represent a homogeneous crystalline phase. Unlike amorphous pharmaceutical forms, thermodynamic stability is possible for cocrystals in the solid state. Additionally, compared to the medicine itself, they offer a significant solubility advantage, surpassing the solubility of polymorphs by several orders of magnitude [10]. Pharmaceutical companies spend a lot of effort and money on the discovery of new medications [11]. More than 60% of novel drug compounds show low water solubility among recently identified drugs [12]. In order to enhance the solubility of pharmaceuticals with poor water solubility, researchers have explored different approaches including solid dispersion, salt formation, size reduction, and complexation [13]. These methods have been developed to address the challenge of increasing the solubility of weakly soluble or water-insoluble pharmaceuticals.

To increase their solubility, a significant proportion of BCS Class II drugs are transformed into salts, representing a fundamental technique employed to modify the physical properties of active pharmaceutical ingredients (APIs). Salt formation is widely utilized as a strategy to increase solubility in these drugs [14]. However, the API must possess an appropriate (simple or acidic) ionizable site for the salt production process to work. However, cocrystals offer an alternative method by which any API, regardless of its acidic, basic, or ionizable groupings, can conceivably co-crystallize [15]. In the context of improving solubility, cocrystal formation is therefore regarded as a practical and innovative crystal engineering technique [16]. Cocrystals are created using a variety of methods, including supercritical fluid technique, reaction cocrystallization, cooling co-crystallization, and slowly evaporating at ambient temperature [17].

Since the natural state of nitrendipine has been electrically neutral, it satisfies all requirements for cocrystal formation. The presence of favorable proton distribution between the donor and acceptor in the structure facilitates the formation of hydrogen bonds between the active pharmaceutical ingredient (API) and the co-former in a cocrystal. Cocrystals can serve as a valuable and effective strategy for enhancing the apparent solubility of BCS Class II and Class IV medications, according to research on crystal engineering in the pharmaceutical industry. Improving apparent solubility is a critical challenge in developing optimized formulations for newly discovered chemical entities (NCEs) within the pharmaceutical industry [18].

Nitrendipine, classified as a BCS Class II drug, is a calcium channel blocker prescribed for the management of hypertension. It functions by blocking calcium channels to regulate blood pressure levels [19]. Nitrendipine's limited dissolution and low absorption are linked to pharmacokinetic variations in people [20]. In the current study, 4-hydroxy benzoic acid was used as a suitable co-former to create cocrystals of nitrendipine, utilizing different drug: co-former ratios of 1:1 and 1:2 during cooling crystallization to improve the solubility and dissolution characteristics [21, 22].

2. Materials and Methods

The drug sample of nitrendipine was gifted from USV Ltd., Mumbai, India. In this work, only analytical-grade chemicals and solvents were used and bought from Loba Chemie Pvt. Ltd. Mumbai.

2.1. Synthesis of Nitrendipine Cocrystals

Trial batches of the nitrendipine cocrystals were prepared to utilize 4-hydroxy benzoic acid and nicotinamide as co-formers, which may form hydrogen bonds (good proton donor and acceptor). But nitrendipine's water solubility and dissolving rate are improved by batches of co-crystal formation by 4-hydroxy benzoic acid [22]. As a result, it is believed that 4-hydroxy benzoic acid is a better co-former for the formulation of nitrendipine cocrystals. Nitrendipine and 4-hydroxy benzoic acid were used in a 1:1 or 1:2 ratio to create cocrystals of the compound using the cooling crystallization process. Nitrendipine and 4-hydroxy benzoic acid were dissolved in methanol and heated in a reflux condenser at 100 ℃ with continuous stirring for 2 h. The resultant mixture was cooled overnight before being filtered to produce the cocrystals. Then the solution was filtered to get rid of the insoluble [23-25].

2.2. Characterization of Nitrendipine Cocrystals

2.2.1. Solubility Analysis

In a volumetric flask with an aluminum foil lid, nitrendipine and nitrendipine -4-hydroxy benzoic acid co-crystals were added to 10 ml of pure water separately. For

24 h, at a temperature of 37 ℃±0.5 ℃, the volumetric flasks were shaken. A 0.45 µm Millipore filter was used to filter the solutions, and the filtrate was then subjected to spectrophotometric analysis at 232 nm by UV spectrophotometer (UV1800, Shimadzu, Japan) [26].

2.2.2. Differential Scanning Calorimetry (DSC)

Thermograms for nitrendipine, 4-hydroxy benzoic acid, and their respective cocrystals were acquired using a (Mettler DSC 1 star from Mettler-Toledo, Switzerland). The samples were enclosed in perforated aluminum pans and subjected to a uniform heating rate of 10 ℃/min. Nitrogen purging was employed, and the temperature range spanned from 30 ℃ to 350 ℃ during the experiment [27-29].

2.2.3. Powder X-Ray Diffraction (PXRD)

The powder X-ray diffraction data of nitrendipine, cocrystals, and their components were recorded using a (Bruker AXS D8 Advance Germany). The measurement setup included a Cu X-ray source with a wavelength of 1.5406 Å, a Si (Li) PSD detector, and an angular range spanning from 3 ° to 135 °. The cocrystals' powder X-ray diffraction patterns were compared to those of the bulk drug and co-former in a comparative analysis [30].

2.2.4. Fourier Transform - Infrared Spectroscopy (FTIR)

The FTIR spectra of nitrendipine, 4-hydroxy benzoic acid, and their cocrystals were recorded using an FTIR instrument (FT/IR-4000, Jasco, Japan). The spectra were captured between the wavelengths of 4000 and 400 cm-1, utilizing a high-intensity ceramic source light source and a DLATGS detector. The spectral resolution was set at 2 cm-1. The data were collected using appropriate software for analysis [31].

2.2.5. Analysis of Surface Roughness and Crystal Morphology

Scanning electron microscopy (Joel® JSM-6390LV, Japan) was used to determine the exterior morphology of nitrendipine and its cocrystals. A double sticky tape was attached to an aluminum stub, and the product for evaluation was then sprinkled over it. The aluminum stub was then placed inside the chamber. The item was randomly scanned at 10 kV acceleration voltages, and photomicrographs were taken [32].

2.2.6. *In vitro* Dissolution Study

Utilizing a Type II (paddle-type) dissolving apparatus (TDT-08L, Electrolab, India), a dissolution study was conducted at 37±0.5 ℃ and 50 RPM for nitrendipine and its cocrystals in phosphate buffer 0. N hydrochloric acid. The samples were removed for 60 min at the 10-minute interval and replaced with a fresh dissolution media. The samples had been diluted adequately and filtered as quickly as possible using Whatman filter paper, and then examined at 232 nm using a UV spectrophotometer (UV1800, Shimadzu, Japan) [33-35].

2.3. Development of Immediate-Release (IR) Tablets Containing Nitrendipine Cocrystals

A nitrendipine cocrystal, equivalent to a drug dose of 10 mg, along with other ingredients, was carefully weighed and put through a sieve with a mesh size of 60. The mixture was then thoroughly blended in a vertical blender for a duration of 30 minutes. The resulting mixture was then immediately compressed into tablets. The tablet weight was 100 mg. The composition of tablets containing nitrendipine cocrystals is shown in Table 1. Using a Cadmach multistation tablet compression machine from Karnavati, India, round concave tablets with a diameter of 6 mm were prepared [36-38].

Table 1. Composition of immediate-release tablets of nitrendipine cocrystals

Sr. No.	Ingredients	Quantity (gm)
1.	Nitrendipine cocrystals equivalent to 10 mg of nitrendipine	19.90
2.	Lactose, spray dried 250 DC grade 34	25
3.	Magnesium stearate	1.5
4.	Starch	5
5.	Microcrystalline cellulose	48.6

2.4. Evaluation of Pre-Compression Parameters

Before the compression process, the powder blends intended for tablet production underwent an evaluation of various parameters including bulk density, flow properties, tapped density, and compressibility. The powder's flow characteristics were evaluated using the angle of repose, and its compressibility was examined using Carr's index and Hausner's ratio. These evaluations provided insights into the flow and compressibility characteristics of the powder blends [39].

2.5. Evaluation of Post-Compression Parameters

2.5.1. Variations in Weight and Thickness

Using a digital Vernier caliper, the thickness of the tablets was measured. Each tablet's thickness was tested for five tablets which were chosen at random. The outcomes are presented as mean and standard deviation (S.D.). The average weight of the 20 randomly selected pills was determined using an electronic balance. The weights of each pill were measured and contrasted with average weights [40].

2.5.2. Hardness and Friability

For each batch, a random selection of five tablets was

made, and their hardness was measured using a Monsanto hardness tester. The hardness's mean value and standard deviation were computed. Additionally, a Roche friabilator of the USP type was used to assess the tablets' friability. Pre-weighed tablets were put inside a plastic chambered friabilator that was attached to a motor, and they were rotated for 4 minutes at a speed of 25 rpm. After de-dusting and reweighing the tablets, the percentage of weight loss was calculated using the formula percent friability = ((initial weight - final weight) / initial weight) × 100 [41].

2.5.3. *In vitro* Disintegration Time

A digital tablet disintegration test device (ED2L, Electrolab, India) was used to assess the tablets' in vitro disintegration time (DT) at a temperature of 37 ℃, with 0.1 N hydrochloric acid as the dissolution medium. The amount of time in seconds it took for the tablet to completely dissolve was recorded as the disintegration time, leaving no residue in the device [41].

2.5.4. Drug Content

The weight and powder content of twenty tablets were measured. Nitrendipine equivalent powder (10 mg) was precisely weighed and dissolved in a small amount of methanol. 0.1 N hydrochloric acid was added to the solution to further dilute it, and a UV-visible spectrophotometer (UV1800, Shimadzu, Japan) was used to measure the drug concentration at a 252 nm wavelength [42].

2.5.5. *In vitro* Drug Release Study

The USP dissolving test apparatus (TDT-08L, Electrolab, India) was used for the drug release investigations, and the paddle method was used. The trials were carried out at a temperature of 37 ± 0.5 ℃ with the paddle revolving at a speed of 50 rpm and 900 cc of 0.1 N hydrochloric acid as the dissolve media. 5 ml samples were taken out of the dissolution medium and replaced with an equal volume of fresh medium at specified intervals of 10 minutes. The samples were then passed through a 0.45 m membrane filter and examined with a UV spectrophotometer (1800, Shimadzu, Japan) at a wavelength of 232 nm [42].

2.6. Stability Analysis

For the stability assessment, tablet samples were put inside glass vials of USP type I and hermetically sealed with rubber plugs and aluminum covers. These vials were afterwards kept in a stability chamber (Remi, India) that was kept at temperature and humidity conditions conforming to ICH standards (40 ℃ and 75% RH). The tablet samples' (n=3) physical attributes, drug content %, and in vitro drug release were assessed at intervals of 0, 1, 2, and 3 months to monitor any potential changes over time. [43].

3. Results and Discussion

3.1. Solubility Analysis

Table 2 presents the solubility data of nitrendipine and nitrendipine - 4-hydroxy benzoic acid cocrystals in distilled water. Pure nitrendipine exhibited an aqueous solubility of 0.0142 mg/ml. However, the aqueous solubilities of nitrendipine - 4-hydroxy benzoic acid cocrystals with ratios of 1:1 and 1:2 were found to be 0.1184 mg/ml and 0.07814 mg/ml respectively. These solubility values were higher compared to the solubility of pure nitrendipine, indicating an enhancement in solubility achieved through cocrystallization. The solubility of nitrendipine - 4-hydroxyl benzoic acid cocrystals with a 1:1 ratio showed an 8-fold increase and a 1:2 ratio showed a 5.28-fold increase. Hence cocrystal formulation appears to hold a lot of promise for improving the solubility of medications that aren't very soluble [44].

Table 2. Aqueous solubility of nitrendipine and its cocrystals

Sr. No.	Chemical species	Solubility* (mg/ml)
1.	Nitrendipine	0.0142 ± 0.0042
2.	Nitrendipine 4-hydroxyl benzoic acid (1:1)	0.1184 ± 0.0106
3.	Nitrendipine 4-hydroxyl benzoic acid (1:2)	0.0781 ± 0.0093

*Mean ± S.D., n=3

3.2. Differential Scanning Calorimetry (DSC)

Figure 1 illustrates the DSC data obtained for plain nitrendipine and its cocrystals. The DSC curve for plain nitrendipine exhibited a distinct and sharp endothermic peak observed at 159.49 ℃, indicative of its melting point. Contrasted with the endotherm of the pure drug sample, the nitrendipine - 4-hydroxyl benzoic acid co-crystals revealed a sharp endothermic peak at 157.38 ℃, indicating a little shift in the peak. As a result of its decreased concentration solubility in the cocrystal formulation, the 4-hydroxyl benzoic acid melts as the endothermic peak vanishes [45].

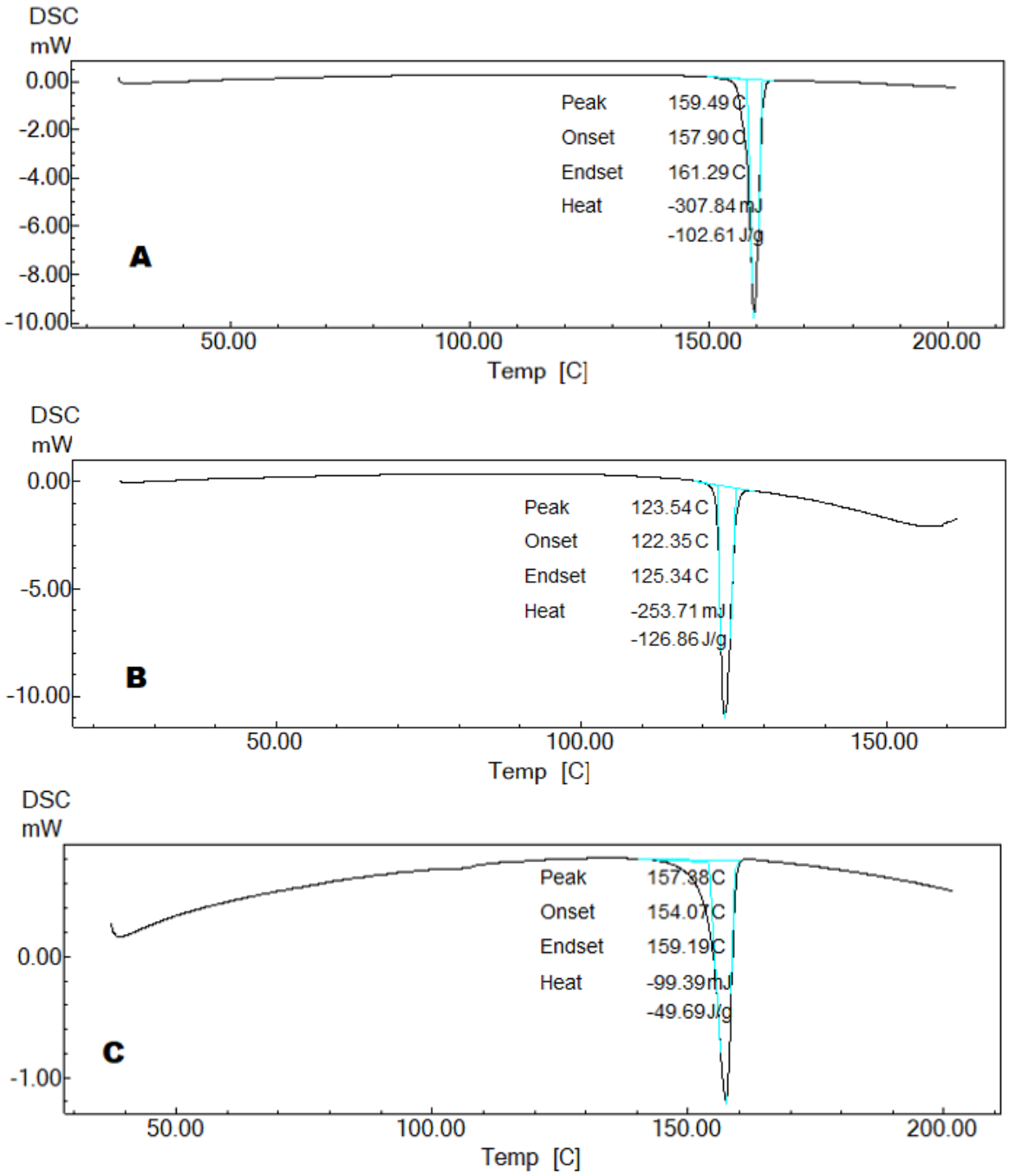


Figure 1. DSC thermograms of (A) pure nitrendipine, (B) 4-hydroxy benzoic acid and (C) nitrendipine - 4-hydroxy benzoic acid co-crystals

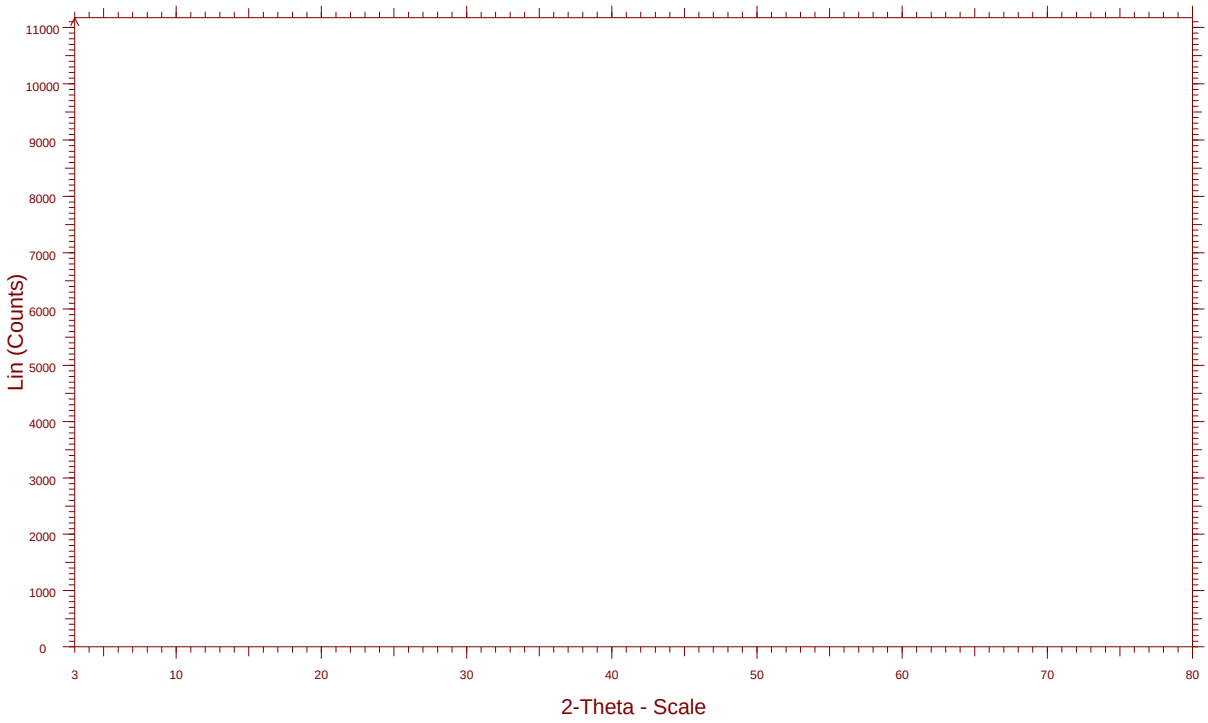
3.3. Powder X-Ray Diffraction (PXRD)

Figure 2 presents the X-ray diffraction data for both plain nitrendipine and its cocrystals. As a BCS Class II drug, nitrendipine demonstrates a low water solubility, which is reflected in its X-ray diffraction pattern. The XRD pattern of co-crystals of nitrendipine with benzoic acid demonstrates the development of fresh additional peaks with heightened intensities. The three strongest peaks in the pure drug's X-ray diffraction pattern were at 13.580°, 14.452°, and 22.948° at 2θ, and a succession of acute and intense diffraction peaks was used to emphasize the pure nitrendipine's crystalline condition. Sharp additional peaks were seen in X-ray diffraction pattern of the cocrystals at 14.440°, 18.540°, 18.760°, and 18.998° at 2θ. These peaks indicated the formation of cocrystals.

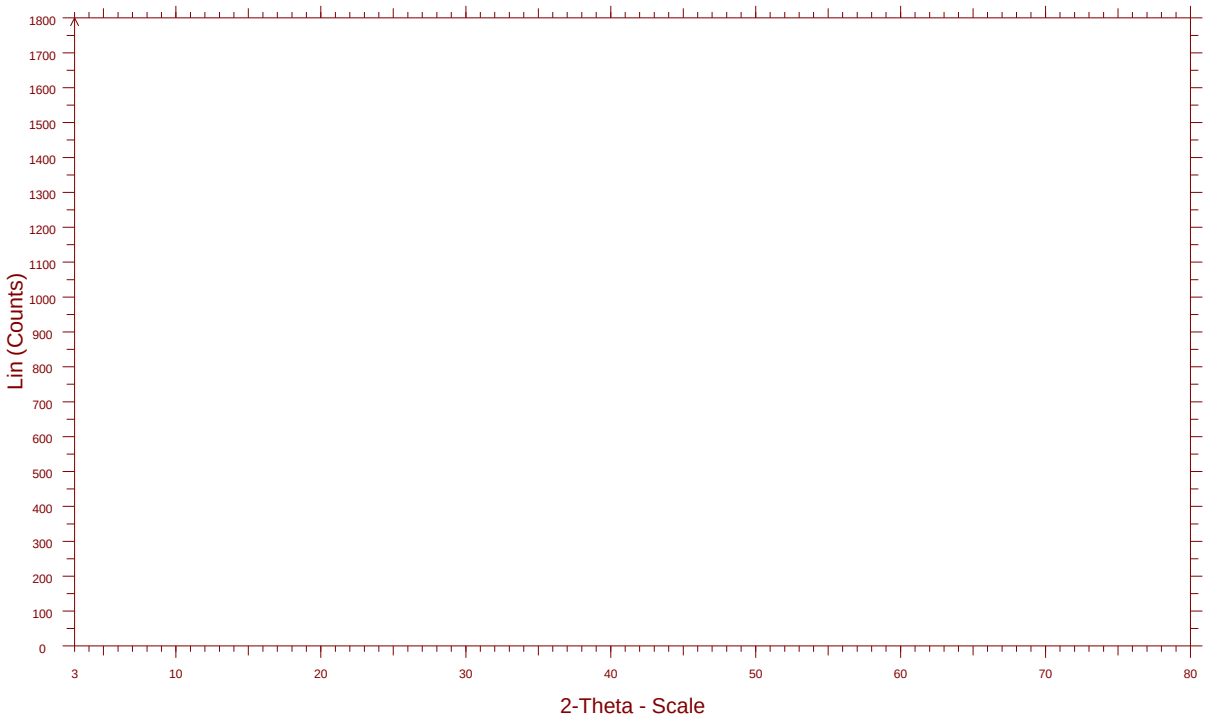
3.4. FTIR

Figure 3 illustrates the FTIR spectra obtained for nitrendipine, 4-hydroxy benzoic acid, and nitrendipine - 4-hydroxy benzoic acid cocrystals, enabling the examination of the drug's effects on the cocrystals. In the FTIR spectrum of nitrendipine, distinctive peaks corresponding to different

functional groups, including N-H, O-H, C-C, and C-H were observed. In the cocrystals, additional peaks appeared alongside nitrendipine's distinctive peaks as a result of hydrogen bonds forming between the drug and co-former. Notably, a peak associated with C=O stretching, indicating the presence of an aldehyde moiety, was detected in the cocrystals at a wavenumber of 1698.02 cm-1. A second peak was seen in the 1348 cm-1 range, indicating the presence of CH3 bending. Hydrogen bonding can be seen as a peak with a stretch between 2950 and 3050 cm^{-1}. Peaks at 1208.15 cm^{-1} demonstrated C-O-C stretch [46].

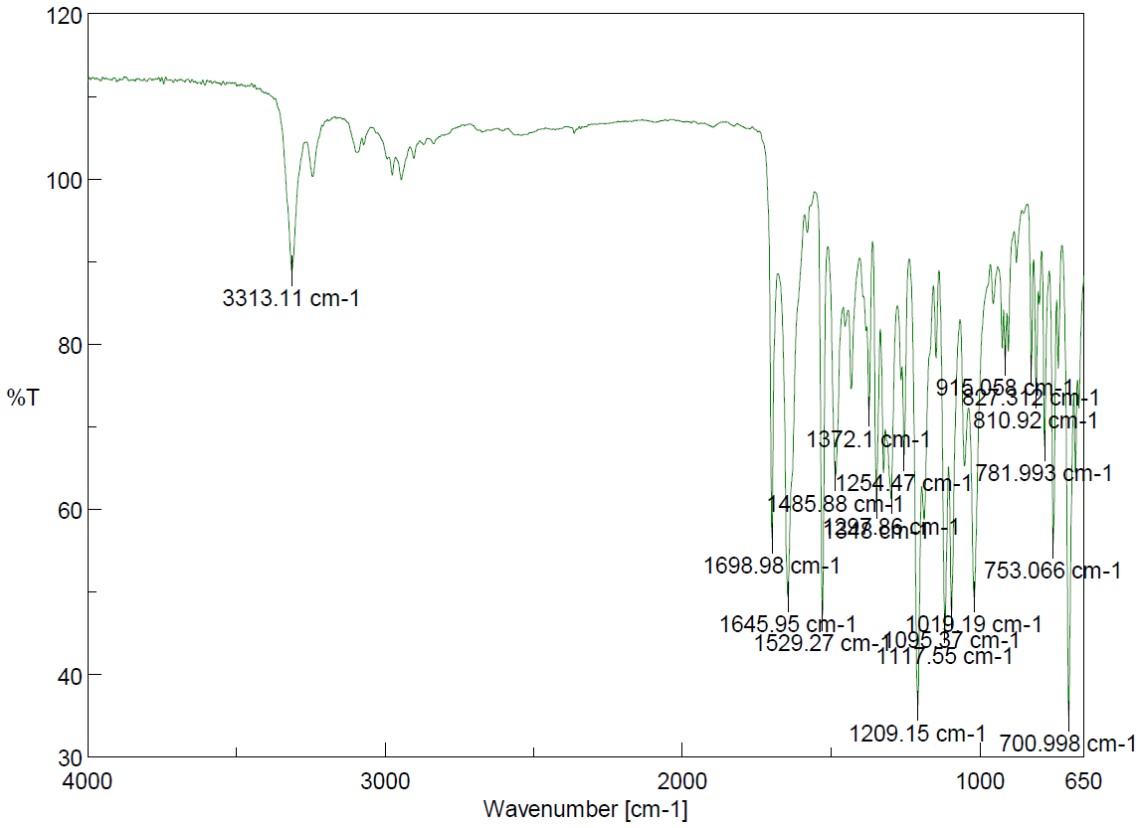


(A)



(B)

Figure 2. Powder XRD curve of (A) pure nitrendipine and (B) nitrendipine - 4-hydroxy benzoic acid cocrystals


120
100
80
60
40
30
%T
4000
3000
2000
1000
650
Wavenumber [cm-1]
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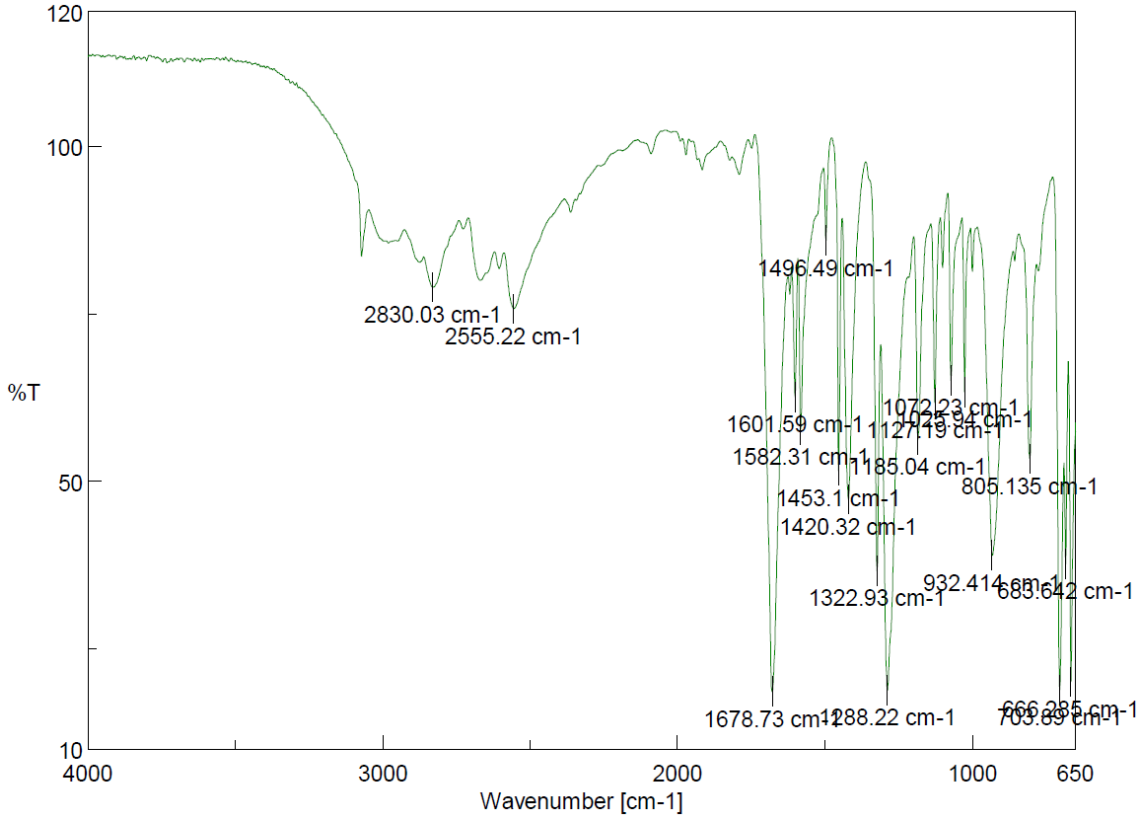
1698.98 cm-1
1645.95 cm-1
1529.27 cm-1
1485.88 cm-1
1372.1 cm-1
1254.47 cm-1
1209.15 cm-1
1117.55 cm-1
1095.37 cm-1
1019.19 cm-1
915.058 cm-1
827.312 cm-1
810.92 cm-1
781.993 cm-1
753.066 cm-1
700.998 cm-1

(A)


120
100
50
10
%T
4000
3000
2000
1000
650
Wavenumber [cm-1]
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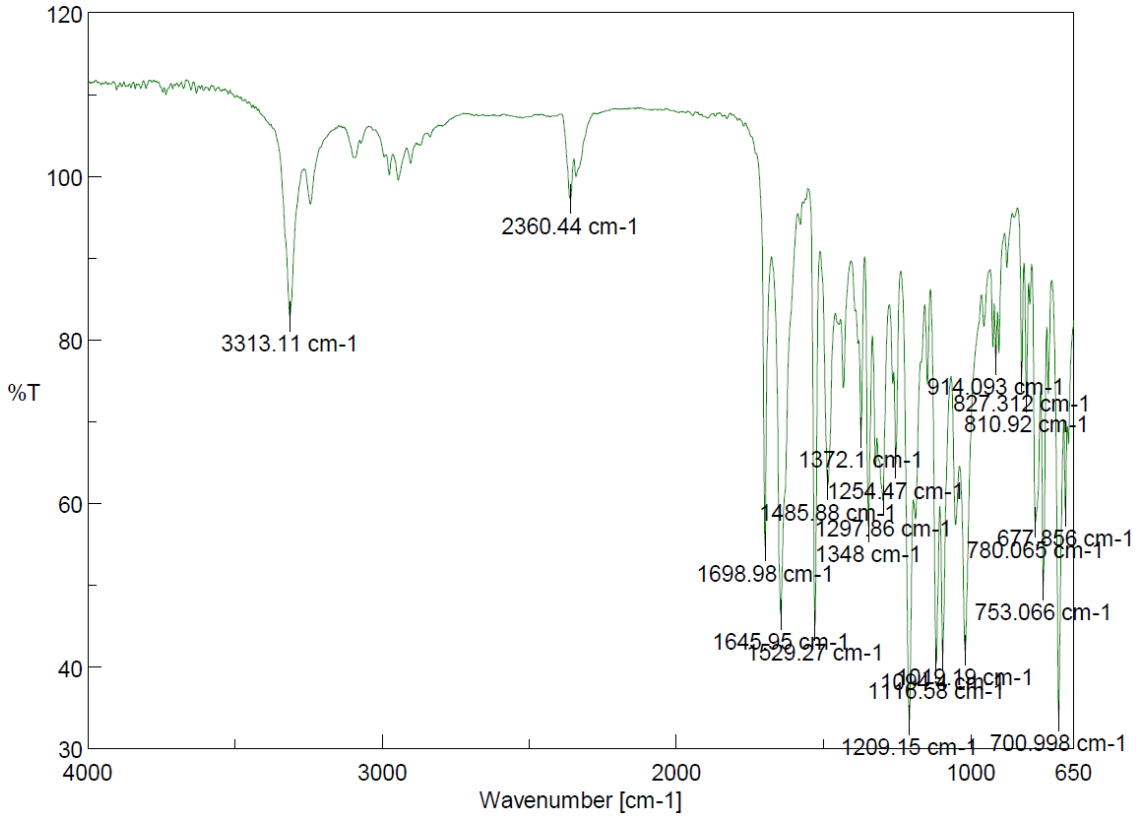
1601.59 cm-1
1582.31 cm-1
1496.49 cm-1
1453.1 cm-1
1420.32 cm-1
1322.93 cm-1
1288.22 cm-1
1185.04 cm-1
1127.19 cm-1
1072.23 cm-1
805.135 cm-1
685.642 cm-1

(B)



(C)

Figure 3. FTIR spectra of (A) pure nitrendipine; (B) 4-hydroxy benzoic acid; (C) nitrendipine -4-hydroxy benzoic acid cocrystals

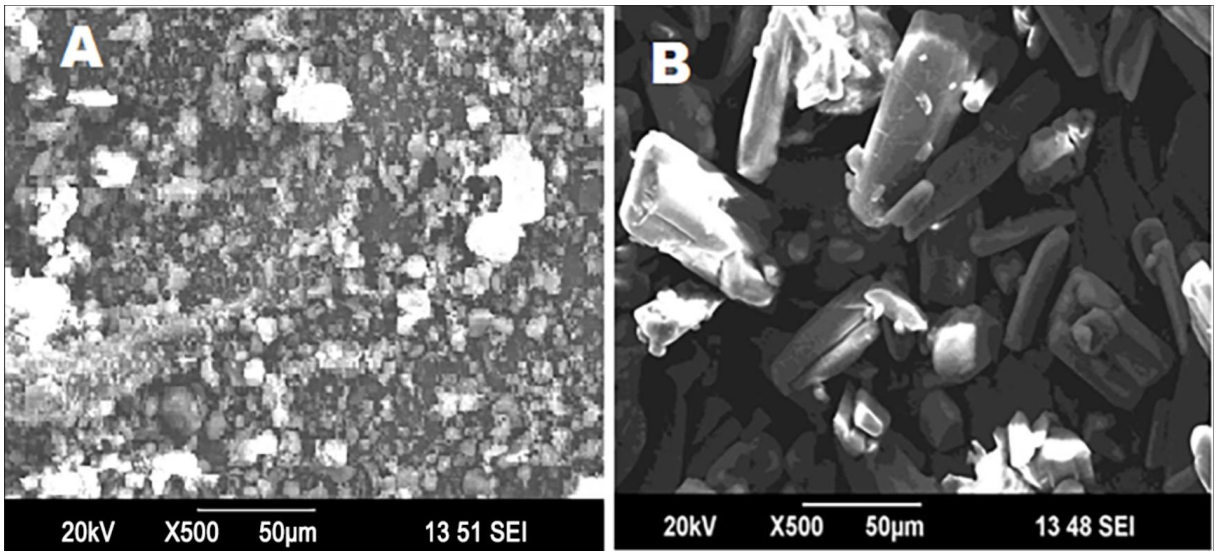


Figure 4. SEM photomicrograph of (A) nitrendipine; (B) Nitrendipine- 4-hydroxy benzoic acid co-crystals

3.5. Surface Roughness and Crystal Morphology

Scanning electron microscopic (SEM) image of nitrendipine cocrystals reveals the creation of crystal structure with irregular shape and smooth surface as compared to the SEM image of pure nitrendipine (Figure 4) [47].

3.6. *In vitro* Dissolution

Figure 5 displays the *in vitro* dissolving data for nitrendipine and its cocrystals in 0.1 N hydrochloric acid. Nitrendipine dissolved at a rate of 59.03% in 60 min as compared to 89.73% and 80.16% for cocrystals with the differing co-former ratios of 1:1 and 1:2 respectively. The amount of nitrendipine released from the cocrystals was consistently greater than the amount of plain nitrendipine at each time point. According to the data, a significant improvement in the dissolution rate in cocrystals over pure drug was seen [48].

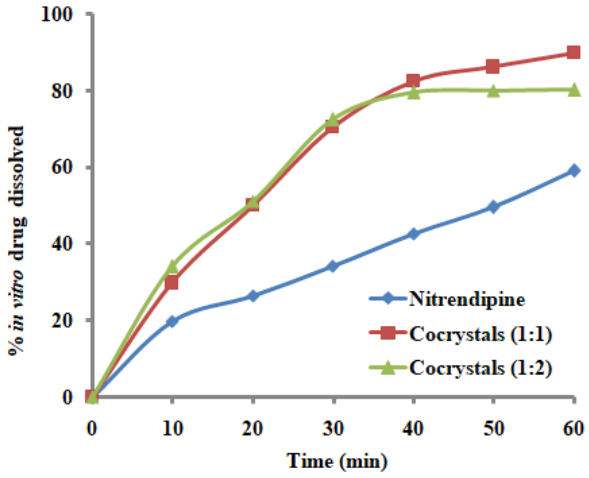


Figure 5. % *in vitro* drug dissolved from nitrendipine, co-crystals (1:1) and cocrystals (1:2)

3.7. Evaluation of Pre-Compression Parameters

Table 3 displays the outcomes for various tablet powder pre-compression parameters. The findings suggest that the powder blend exhibits favorable flow and compression properties, indicating its suitability for tablet formulation.

Table 3. Pre-compression parameters for powder blend

Sr. No.	Evaluation parameter	Results*
1.	Angle of Repose	33.27 ±0.37
2.	Bulk Density	0.303 ±0.01
3.	Tap Density	0.352 ±0.01
4.	Carr's index	14.98 ±0.22
5.	Hausner ratio	1.17 ±0.058

*Mean ±S.D., (n=3)

3.8. Evaluation of Post-Compression Parameters

Tablets containing nitrendipine cocrystals were prepared by compressing the powder blend using a 6 mm punch on a rotary tablet machine (Karnavati, India). The tablets obtained from the formulation were subjected to a comprehensive evaluation, including an assessment of their appearance, hardness, thickness, friability, drug content, disintegration time, weight variation, and in vitro drug release. A comparative analysis was also conducted to compare these parameters with a marketed formulation for benchmarking purposes. The results obtained are shown in Table 4 which were within the standard limits [48].

Table 4. Post-compression parameters for tablets

Sr. No.	Evaluation parameters	Results*
1.	Appearance	Elegant
2.	Thickness (cm)	3.07 ±0.22
3.	Hardness (kg/cm^2)	3.5 ±0.84
4.	Friability (%)	0.21 ±0.08
5.	Weight variation (mg)	102.7 ±5.18
6.	Disintegration time (sec)	90 ±8.24
7.	% drug content	99.03 ±1.38

*Mean ±S.D., (n=3)

3.9. Comparison of *In vitro* Drug Release of Tablet Formulation with Marketed Formulation

To compare the dissolution efficiency, an in vitro drug release study was conducted on a tablet formulation containing nitrendipine cocrystals, in comparison to marketed nitrendipine tablets (Cardif®). The obtained results, as presented in Table 5, indicate that the tablets containing nitrendipine cocrystals exhibited slightly higher drug release compared to the marketed nitrendipine tablets.

Table 5. In *vitro* release of nitrendipine from tablet of nitrendipine cocrystals and marketed nitrendipine tablet (Cardif®)

Time (min)	% Cumulative drug release	
	Tablet of nitrendipine cocrystals	Marketed nitrendipine tablet (Cardif®)
10	55.60 ±0.17	45.8 ±0.21
20	66.5 ±0.30	55.5 ±0.19
30	76.5 ±0.42	64.6 ±0.19
40	85.2 ±0.48	69.5 ±0.38
50	89.2 ±0.45	73.0 ±0.41
60	94.5 ±0.36	79.06 ±0.25

*Mean ±S.D., (n=3)

Table 6. Results for tablet formulation during stability studies

Parameters/Time	Initial	1st month	2nd month	3rd month
Physical appearance	White color	No change	No change	No change
Drug content* (%)	95.22 ±0.33	95.65 ±0.22	95.10 ±0.25	95.05 ±0.82
In vitro* drug release	94.9 ±0.35	93.52 ±0.33	93.65 ±0.59	95.02 ±0.92

*Mean ±S.D., (n=3)

3.10. Stability Studies

The stability of tablet formulation of cocrystals of nitrendipine was assessed using studies on accelerated stability. The tablet formulation containing nitrendipine cocrystals underwent stability testing under conditions of 40 ℃ and 75% RH for a duration of 3 months. The results obtained for physical appearance, percentage of drug content, and in vitro drug release during the stability studies are depicted in Table 6. These findings suggest that the tablets containing nitrendipine cocrystals remained stable throughout the study period.

4. Conclusions

When nitrendipine was co-crystallized with 4-hydroxy benzoic acid by cooling co-crystallization, it had a significantly higher solubility and dissolution rate than the parent molecule. Numerous analytical techniques, including FTIR, DSC, and XRD were used to analyze optimized cocrystal formulation and validated the development of nitrendipine - 4-hydroxy benzoic acid cocrystals. Nitrendipine's solubility and dissolution rate are improved by the cocrystal formulation, according to the results of research on its solubility, dissolution, and stability. By using the cooling co-crystallization process, nitrendipine and 4-hydroxy benzoic acid crystallize together in an equimolar ratio. When compared to pure nitrendipine, the nitrendipine - 4-hydroxy benzoic acid cocrystals have a dissolving rate that is 3-4 times faster. Co-crystallization may increase nitrendipine's water solubility and rate of dissolution, which could be a solution to the drug's bioavailability issue. In light of this, it represents a novel strategy for increasing the solubility of a poor candidate with less need for excipients, rapid method development, and minimal solvent usage in the case of an organic-based solvent approach.

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Disclosure Statement

The authors report there are no competing interests to declare.

Conflict of Interest Statement

Authors Shubhangi R. Sonawane and Sanjay B. Patil declare that they have no conflict of interest.

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