Nebivolol Hydrochloride-Amino Acid Zwitterionic Cocrystals with Superior Physicochemical Characteristics

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ABSTRACT

Cocrystallization of drugs with coformers is a promising method for modifying drug substance solid state qualities such as solubility and dissolution. The current study aimed to create, synthesize, and analyze Nebivolol hydrochloride cocrystals by screening several coformers. The type II biopharmaceutical medication Nebivolol hydrochloride (NBH), used to treat hypertension, has great permeability, limited water solubility, and a slow dissolving rate. This remains a barrier to the creation of innovative formulations. In this paper, we focus on the formation of the first NBH zwitterionic cocrystals while using less hazardous zwitterionic amino acids as coformers, such as L-proline P) and L-glutamine (G). The zwitterionic cocrystals of NBH were synthesized using liquid-aided grinding and slow solvent evaporation procedures by using a molar ratio (1:1) of the drug and zwitterion coformers. The cocrystals revealed a distinctive characteristic in X-ray diffraction studies, FT-IR spectra, SEM images, and DSC thermograms. The infrared study demonstrated the displacement of NBH distinctive bands. The X-Ray Powder Diffraction pattern indicated co-crystallinity and a significant difference in the 2θ value of intense peaks. Differential scanning calorimetry (DSC) spectra of cocrystals revealed changed endotherms correlating to melting point. Dissolution studies revealed that the zwitterionic NBH cocrystals disintegrated faster in vitro by 89.3% and 84.7% respectively.

Key Words: *Pharmaceutical cocrystals, Nebivolol hydrochloride, L-proline, L-glutamine, Solubility and dissolution studies*

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INTRODUCTION

In recent years, drug cocrystal design has rapidly progressed from absolute obscurity to an extensively researched category of crystal formations in the field of crystal engineering and science. They considerably increase the variety of active pharmaceutical ingredients (API) crystal forms and allow for improvements in physicochemical characteristics like solubility, dissolution rates, stability, hygroscopicity, and bioavailability that are relevant for clinical use. It is important to emphasize that in the pharmaceutical cocrystallization approach, cocrystals comprise a multicomponent system of active pharmaceutical ingredients (API) with a stoichiometric amount of a pharmaceutically acceptable conformer incorporated in the crystal lattice, without altering the pharmacological activity of the drug. Cocrystal is formed between API molecules or ions having donor or acceptor moieties that are capable of forming supramolecular synthon through non-covalent interactions between the molecules, π-π interactions, and hydrogen bonds with the generally

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recognized as safe (GRAS) coformers having functional groups [1, 2]. There are several ways to make cocrystals, including slow evaporation at ambient temperature [3, 4] reaction cocrystallization [5], cooling co-crystallization [6], the grinding process [7], and supercritical fluid approach [8]. In addition to these techniques, novel techniques including hot-stage microscopy and approaches with ultrasound assistance are also documented [9]. It was evident from both conventional and new approaches that the grinding technique with a few modifications, such as the inclusion of a tiny quantity of solvent (LAG), and solvent evaporation at normal temperature, is better suited for the formation of cocrystals.

The long-acting α-blocker nebivolol hydrochloride is used to treat hypertension. Owing to its limited solubility in water (0.0091 grams /10 Cm^3) and dissolving rate, it has a lower bioavailability (11%). The main objective of the current work is the potential for creating cocrystals using coformers to enhance the solubility and dissolution rate [10]. In the current work, an eco-friendly pharmaceutical cocrystallization process a "green method" adopting solvent-free procedures or minimal use of solvents is used to synthesize Nebivolol cocrystals. Researchers have also been searching for lower-risk amino acids to act as the secure coformer that results in the required API physicochemical features. In terms of structure, amino acids, particularly L-proline and L-glutamine (which improve API solubility and gastrointestinal absorption) are promising coformer candidates because they have zwitterionic moieties, which facilitate strong acquaintances, and functional groups that can generate hydrogen bonds that improve stability [11]. Nebivolol hydrochloride structure, which is already in salt form and is electrically neutral by nature, satisfies all the requirements for the successful creation of cocrystals. In the structure, it exhibits successful donor and acceptor protonation, which aids in the creation of non-covalent interaction between the drug and the coformer.

In the current study, the production of the first NBH zwitterionic cocrystals under the oversight of the cocrystal technology idea may be of interest using amino acids, which are natural zwitterions under physiological preferences. Because the penta cyclic ring "side chain" reduces the molecular structure restricted and rigid, proline appears to be prevalent in cocrystal formation [12].

To emphasize the role of first NBH zwitterionic cocrystal in enhancing physicochemical properties of NBH and to demonstrate the significance of the zwitterionic cocrystal in the pharmaceutical field, L-proline and L-glutamine were selected as the coformer for the reasons listed below. From a structural standpoint, L-proline and L-glutamine possess all characteristics found in other common amino acids, including the presence of an ammonium-carboxylate synthon, which acts as a donor or acceptor for hydrogen bonds, as well as the ability to strengthen crystal lattices through the use of non-covalent hydrogen bonds, which are typically more powerful than neutral hydrogen bonds. L-proline in particular is thought of as a restricted, rather stiff amino acid with a penta cyclic ring, which is rare among amino acids but which may provide it an entropic edge over other amino acids in the creation of NBH cocrystals. L-proline has the best solubility among all the amino acids from a natural standpoint, and because of this, it is well recognised as a solubilizing excipient that is employed in pharmaceutical synthesis research. From each of these perspectives, we can forecast the possibility of using L-proline and L-glutamine as coformers in conjunction with NBH to improve its qualities as well as some novel insight on altering NBH using amino acid zwitterions [13, 14].

With the use of liquid-assisted grinding and solvent evaporation, Nikam *et al*. [10] produced cocrystals of NBH utilizing coformers such as 4-hydroxy benzoic acid and nicotinamide. Tilborg, Anaëlle, *et al*. [15] highlighted the cocrystal formations containing L-Proline, a zwitterionic amino acid, and naproxen.

The primary goal of this effort is to improve aqueous solubility and comprehend the physicochemical properties of NBH medication. Donor ($-NH_2$) and acceptor (–COOH) groups, of amino acids frequently establish hydrogen bonds with hydroxyl groups of NBH. This was done to deal with challenges with the drug's poor water solubility, dissolution, and stability to increase its efficacy.

The morphology and physical properties of nebivolol hydrochloride and the unique cocrystal were characterized using differential thermogram, PXRD, FTIR, and electron beam-focused microscopy techniques.

MATERIALS AND METHODS

Materials

Nebivolol hydrochloride (NBH) gift sample received from Global Calcium Pvt. Ltd., Bangalore. Other high purity Chemicals L-proline, L-glutamine, and methanol were procured. Every other resource used in the study was of industrial grade.

Selection of the coformer and its proportion

Nebivolol hydrochloride has –OH groups and the -NH group, which are both visible in **Figure 4**. When examining the functional groups of NBH, a coformer with the group of amide and carboxylic acids may have a chance of forming hydrogen bonds. There are a large number of appropriate conformers accessible for pharmaceutical cocrystal engineering according to GRAS, a thorough pathway from the literature, however, L-proline and L-glutamine were chosen as two coformers based on prior literature studies [16, 17]. The acidic and basic functional groups of API can establish hydrogen bonds or non-

covalent interactions with the coformers. For the current investigation, zwitterionic substances such as L-proline and L-glutamine were used at a 1:1 stoichiometric molar ratio.

Novel NBH cocrystal preparation by liquid assisted grinding

NBH (441 mg), L-proline (122 mg), and a few drops of methanol as a solvent were added to a clean mortar and pestle in an equimolar 1:1 stoichiometric ratio. Then the ingredients were mechanically ground for 40 minutes. This mechanical grinding method uses green chemistry, making it environmentally beneficial. The novel cocrystals of NBH were collected and preserved after grinding. The cocrystals at a 1:1 stoichiometric molar ratio of the coformers and API suggested better physicochemical attributes, such as dissolution rate and aqueous solubility.

Novel NBH cocrystal preparation by slow solvent evaporation

The novel zwitterionic NBH cocrystals were designed employing a solvent evaporation approach with L-glutamine as a coformer. When NBH (500 mg) and L-glutamine (140 mg) are combined in a molar ratio of 1:1, cocrystals are generated.15 cm^3 of methanol was used to dissolve the NBH, and 5 cm^3 of distilled water were used to dissolve the coformer. After thoroughly dissolving the substance to create a clear solution, both solutions were ultrasonically treated while being agitated. A solution of L-glutamine in water was dropped gradually into a methanol solution containing NBH and placed on the magnetic stirring device, which stirred continuously until the solvent was fully evaporated. To dry, the cocrystals were placed overnight in a glass container with a moisture-removing drying agent[13]. A schematic representation of the synthesis of cocrystals is shown in **Figure 1.**

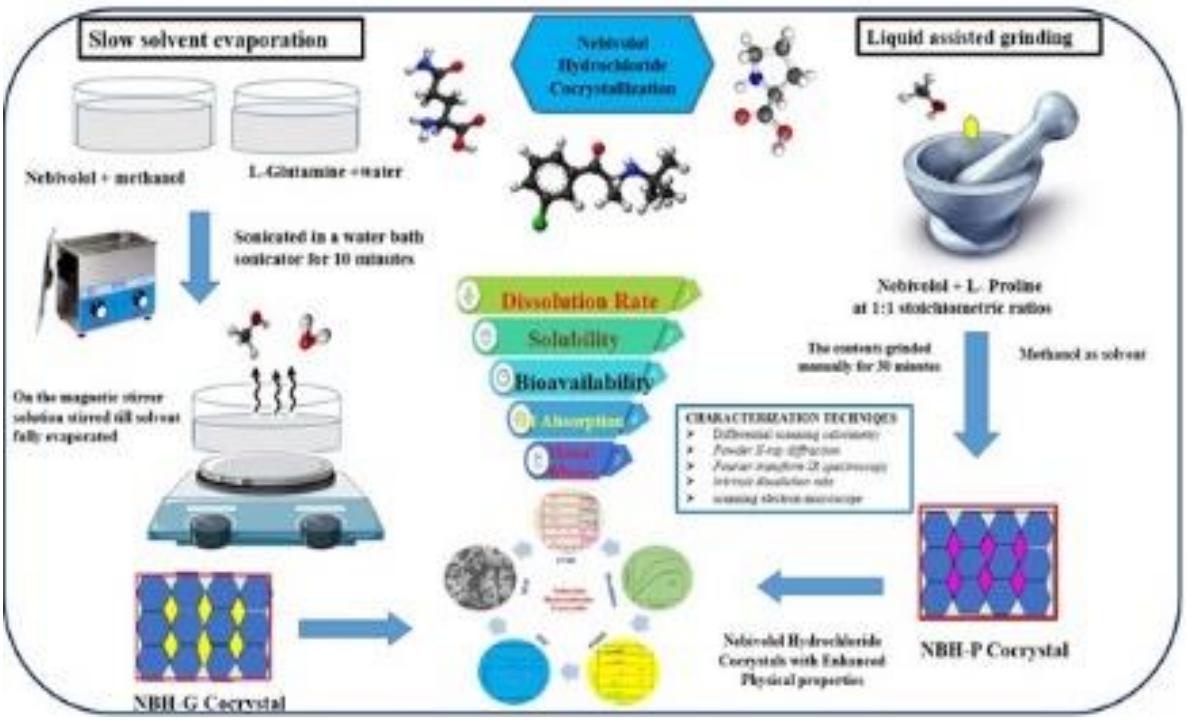


Figure 1. Schematic representation of synthesis of cocrystals

Identification methods

Powder X-ray diffraction analysis

The X-ray diffraction (XRD) data of synthesized samples and pure form has been recorded using an X-ray diffractometer Si (L ithium) *position-sensitive detector* Copper X-ray source (λ =1.5406Å). The measurements were taken between angular ranges of 4° to 40°.

Fourier transform ınfra-red spectroscopy analysis

Fourier Transform Infra-red analysis (FTIR) of NBH and cocrystals was obtained using a Bruker-2 with an attenuated total reflection detector and a DLATGS detector with a spectral resolution of 2 cm^{-1}. After adding 2 mg of each material to the sample cell, spectra between 4000 and 500 cm^{-1} were acquired. The data collected was evaluated using Origin software.

Differential scanning calorimetry analysis

A differential thermogram was used to examine the materials' melting behavior. Each sample, weighing 1.5 to 2.5 mg of NBH, coformers, and unique cocrystals, was scanned using a DSC 823e calorimeter made by the Swiss

company Mettler Toledo. Every single sample was placed inside a 40-microliter sealed aluminum pan, with an empty sealed aluminum pan used as a standard. Using nitrogen gas flow at a rate of 20 ml/min, all samples were scanned at a rate of 10 °C per minute between RT and 300°C

Solubility analysis

The NBH, NBH-P, and NBH-G were dissolved in 10 mL of distilled water and placed in glass vials with caps. The resulting slurries were then stirred orbital shaker running at 100 rpm for 24 hours at room temperature. The quantity of NBH, NBH-P, and NBH-G solubilized was then measured spectrophotometrically at 280 nm using a UV-1900 Series Model (S/N): UV-1900i (A12535780084) after each solution had been filtered through a paper filter.

Morphology analysis

The morphology of the NBH and NBH cocrystals (NBH-P and NBH-G) were examined using SEM (SEM; Hitachi S3400, Japan). The particles were mounted on aluminum skewers and covered with gold while under vacuum to prepare them for examination. At various magnifications, the samples were photographed under a microscope.

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 API and cocrystals at pH 7.4 to replicate an actual intestinal environment. The paddle was rotating at a speed of 100 rpm and the water bath temperature was 37 °C. A sample was obtained to determine the concentration at 10, 20, 30, 40, 50, 60, and up to 120 minutes. For each sample, three runs of dissolution test were performed. The concentration was calculated at 280 nm using a UV spectrophotometer.

RESULTS AND DISCUSSION

NBH, a third-generation beta-blocker drug that has been authorized by the FDA for the treatment of hypertension with a water solubility barrier, is used in the present study as an API to cocrystallize with L-proline and L-glutamine. Using the solvent evaporation method, NBH and L-glutamine were combined with water and methanol as solvents. NBH and L-proline were combined with a few drops of methanol as solvent using the liquid-assisted grinding method. A 1:1 molar ratio [18] of NBH and zwitterionic coformers is employed to create the required cocrystal.

Powder X-ray diffraction analysis

Powder X-ray diffraction (XRD) analysis is utilized to confirm the phase transition and purity of the current cocrystal since it is a practical and sensitive characterization method for crystalline solid-state forms. In their solid states, most medications can be found in crystalline, amorphous polymorph, and solvate forms, among others. The physicochemical characteristics of these forms can also vary greatly [19]. **Figure 2** displays the XRD spectra of the API, coformers, and unique cocrystals. The crystalline form of the NBH was confirmed by XRD **(Figure 2)**, which revealed clear, distinct peaks at 2θ= 5.89º, 11.9º, 12.62º, 16.3º, 18.4º, 21.21º, 22.7º, 24.84º, and 25.42º. The XRD pattern of the cocrystals of NBH-P and NBH-G reveals the emergence of new peaks with higher intensities. The NBH-P cocrystals made using the solvent-aided grinding approach peaked at 2θ = 8.8°, 13.3°, 14.8°, 17.43°, 19.3°, 23.1°, and 26.5°. However, for NBH-G 2θ = 6.8°, 11.7°, 16.9°, 17.3°, 19.3°, 23.7°, and 24.8° cocrystals made using the solvent evaporation approach revealed additional peaks. This confirms the formation of cocrystals [20].

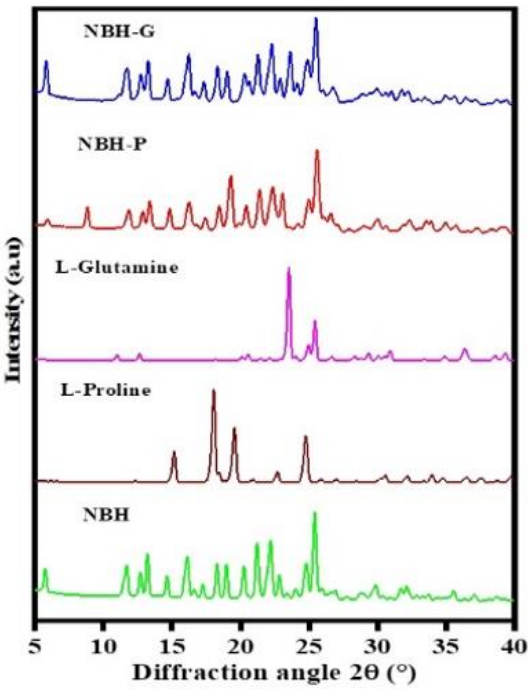


Figure 2. Powder XRD pattern of NBH and co-crystals

Fourier transform ınfra-red spectroscopy

FTIR analysis was accepted as a persuasive justification technique in endorsing the formation of zwitterionic cocrystals, for the idea that the frequencies of vibrational patterns linked to the active moieties would be influenced when changes like hydrogen bonding occur in these groups due to the formation of novel crystalline form [14]. **Figure 3** depicts the FTIR spectra of NBH and cocrystals. The FTIR spectra of NBH showed distinctive peaks caused by different functional groups. O-H stretching of alcohol is at 3185 cm^{-1}, N-H stretching of amine is at 3376 cm^{-1}, aromatic C-H is at 2964.85 cm^{-1}, C-C stretch is at 1498 cm^{-}

[1], halogen C-X is at 869 cm^{-1}, and C-F is at 1141 cm^{-1}, respectively [19]. L-Proline unique peaks were found to be at 1609, 2352, and 3053 cm^{-1}, which correspond to the carboxylic acid C-O, N-H, and O-H stretching, respectively [21]. As shown in **Figure 3**, the distinctive O-H stretching peak of the carboxylic acid for L-glutamine was assigned at 3166 cm^{-1}, and a broad multiple peak for the N-H stretch of the amide was assigned at 3401 cm^{-1}.

Since non-covalent interaction hydrogen bonding developed in the zwitterionic cocrystal, a change in the IR spectrum between the cocrystal and its related starting components was also noticed. Several IR peaks changed consequently, as shown in **Figure 3**.

The investigation of the spectra reveals a wave number shift from the N-H stretch (Amine) 3376 shifted to 3409 cm^{-1}, the O-H stretch (Alcohol) 3185 shifted to 3172 cm^{-1}, and the 1609 C-O stretching of the carboxylic acid of L-Proline shifted to 1625 cm^{-1}. This shift is indicative of the formation of a hydrogen bond between the NBH and L-Proline. Hydrogen bonding may be seen in the peak in the 2400–3400 cm^{-1} stretch range.

The O-H peak of the alcoholic group of NBH was displaced from 3185 to 3177 cm^{-1}, and the -N H peak of L-Glutamine was shifted from 3401 to 3409 cm^{-1}, while the carbonyl group was shifted from 1681 to 1623 cm^{-1}. The change of the frequency that generated due to the formation of hydrogen bonds flanked by the OH group of NBH and Zwitter ionic carboxylic O group of amino acid coformers O-H----O. This is in agreement with the literature reports [22]. An outline of possible cocrystal structures of NBH-P and NBH-G are shown in **Figures 4a and 4b** respectively.

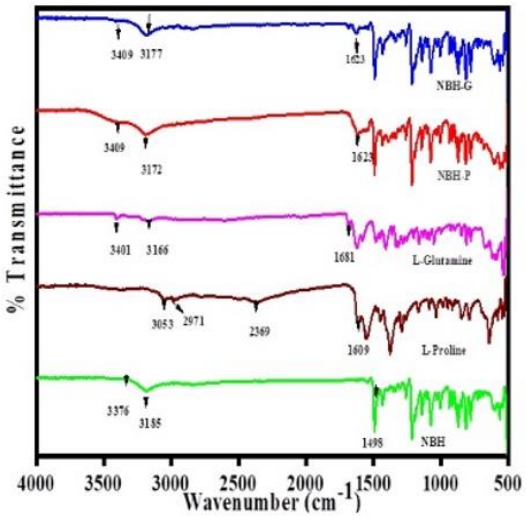
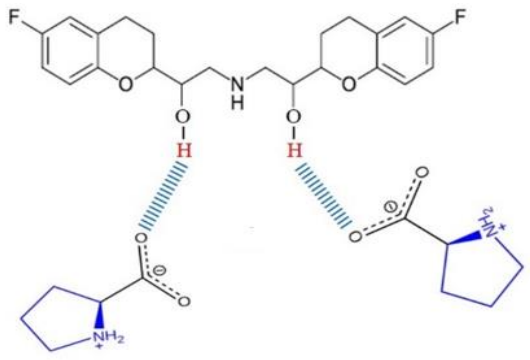
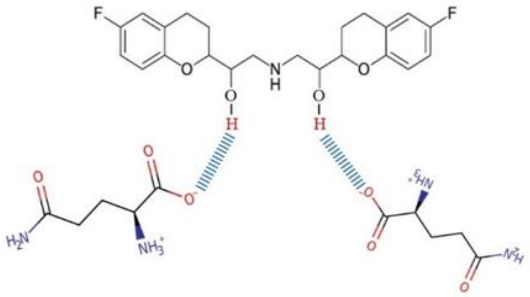


Figure 3. FTIR Spectra of NBH and cocrystals



a)



b)

Figure 4. The 3- hetero supramolecular synthon between (a) NBH and L-proline and (b) NBH and L-glutamine.

DSC analysis

It is the most popular quick, practical, and effective approach for analyzing the cocrystal formation between API and coformer. **Figure 5** depicts the DSC thermograms of NBH, coformers L-proline, L-glutamine, and new cocrystals NBH-P, NBH-G. NBH and coformers display an endothermic peak on the DSC curve of their starting materials that may be ascribed to melting at temperatures of 224°C, 220°C, 194 °C, 169 °C, and 174 °C, respectively. Between the melting points of NBH and the coformers, the single endothermic peak lies at 169 and 174 °C, respectively. Cocrystals' NBH-P and NBH-G melting points should be attributed to these peaks. The observed melting point of the cocrystals is different from that of the parent drug molecule and the coformers. These changes indicate the establishment of the cocrystals of NBH-P and NBH-G [23]. Perlovich's research indicates that compared to the initial materials, 55.3% of cocrystals have an intermediate melting point, 28.9% have a low melting point, and 14.5% have a higher endotherm. NBH-P and NBH-G have melting values of 169 °C and 174 °C, respectively, which are typical for 1:1 stoichiometric cocrystals. This suggests that the cocrystal melting point is in the middle of the NBH and the coformers melting points. The position and form of endothermic melting peaks in a DSC analysis serve as a depiction of the distinctive character of cocrystals. Crisp and narrow endothermic

peaks are seen in novel cocrystals, suggesting a high degree of crystallinity and purity [24].

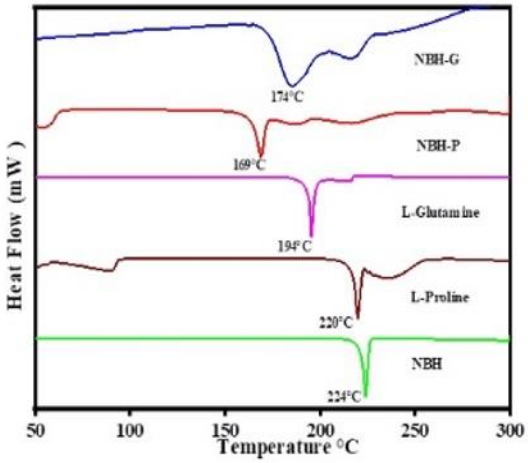


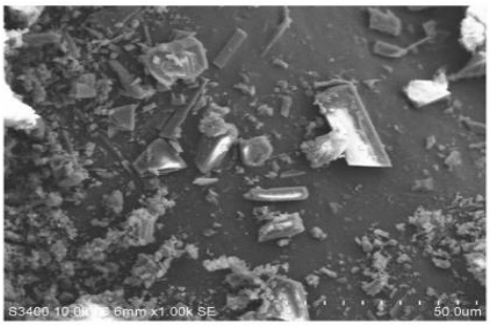
Figure 5. DSC thermograms of NBH and Cocrystals

Solubility analysis

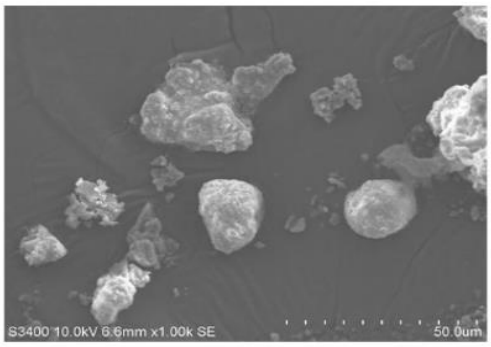
Solubility is a fundamental aspect yet it is difficult to overcome since it is one of the primary factors that drives the processes of medication absorption, transportation, metabolism, and excretion. During drug development and design, researchers modify and test the qualities of various drugs [14]. Approximately 100 mg of each NBH, NBH-P, and NBH-G cocrystals were added to 10 ml of distilled water, which was then constantly agitated for 24 hours at room temperature to verify the solubility. The concentration of the pure drug (NBH) was 847 ± 18 µg/ml and the concentration of cocrystals found to be NBH-P (177 9± 48 µg/ml) and NBH-G (1575 ± 26 µg/ml). For the NBH, and cocrystals NBH-P and NBH-G, which demonstrated an increase in water solubility.

Scanning electron microscopy analysis

The SEM images for NBH, NBH-P, and NBH-G are shown in **Figures 6a-6c** respectively. The NBH exhibited rectangular morphology as shown in **Figure 6a**. This is in agreement with the literature [21]. Due to agglomeration, a spherical morphology was observed in NBH-P **(Figure 6b)** and rod-like morphology in NBH-G **(Figure 6c)**. The SEM images are inconsistent with XRD data.



a)



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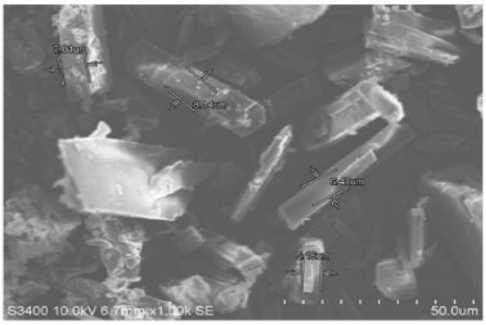

c)

Figure 6. Scanning electron microscopy (SEM) images of (a) NBH, (b) NBH-P and (c) NBH-G

Calibration curve and dissolution studies

The calibration curve yielded a high magnitude correlation value which is equal to 0.9998. The NBH content quantity and the drug release percentage upon dissolution were calculated using the following calibration curve equation:

$$Y = 0.0086\ X + 0.0132, \quad X = \text{amount of NBH}, \qquad (1)$$

Y = the ratio of the area that was determined for each time point.

Among the NBH ratios of concentration to area at various time points, the equation demonstrates a solid linear connection. The correlation coefficient r value is quite near to one, illustrating the significant link between the concentration and the area ratio [25].

Figure 7 shows the in vitro dissolution patterns of the cocrystals NBH-P and NBH-G in comparison to those of the pure drug NBH. The zwitterionic NBH cocrystals showed a greater in vitro dissolution rate. After 60 minutes, pure drug NBH releases 47.26% of its active ingredient, whereas cocrystals release 81.6% (NBH-P) and 79.4% (NBH-G) respectively. The fast rate of prepared cocrystal dissolution can be attributed to the NBH crystallinity changing as a result of potential hydrogen bond interactions with coformers [26].

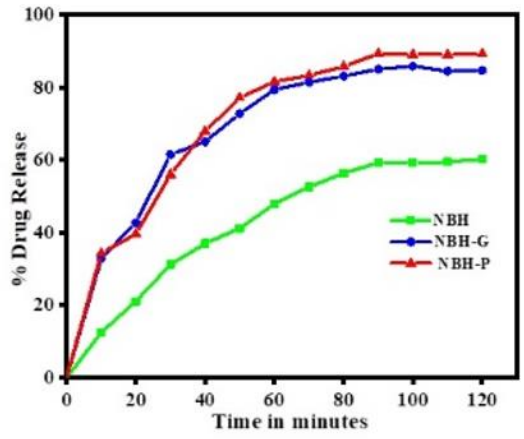

Figure 7. Dissolution studies of NBH and cocrystals

NBH's undesirable physicochemical attributes frequently prevent them from delivering the therapeutic advantages promised to them. Cocrystals are crystalline substances amalgamated through one of the latest approaches for improving drug physicochemical attributes composed of non-covalent intermolecular interaction between active moiety and coformer in the same crystal lattice in a particular stoichiometric ratio. Amino acids seem to be an excellent choice as a practical companion in this scenario. Amino acids fall within the GRAS category since they are also extremely inexpensive and low in toxicity.

The establishment of a novel phase is demonstrated by the emergence of new peaks that have elevated intensities in the current cocrystals seen during PXRD analysis. PXRD data confirms that the drug changed from its partly crystalline state to a novel crystalline structure in both cocrystals. This distinct phase may be attributed to the formation of cocrystals owing to the hydrogen bond interaction between NBH and a coagent substance.

The FTIR spectrum suggested that there was good interaction between NBH and coformers as evidenced by spectral alterations, such as a small displacement of the NBH-P and NBH-G distinctive peaks. A change in the peaks of NBH and conformers to the O-H peak of the alcoholic group of NBH, the N-H stretch of amine, and C=O stretching, respectively, suggests that hydrogen bonding is exceptionally likely to occur. The frequency shift is caused by the creation of the NBH--O-H----O Carboxylic O group of amino acid coformers, which are flanked by the OH groups of NBH and Zwitterionic amino acids. This is consistent with the reports in the literature [22]. The findings of this study additionally supported the use of DSC as a tool to complement information gleaned from FTIR and PXRD spectra. On the DSC curve of their starting materials, NBH and coformers show an endothermic peak that may be attributed to melting at temperatures of 224°C, 220°C, 194°C, 169°C, and 174°C, respectively. The single endothermic peak for the cocrystals NBH-P and NBH-G is located at 169 and 174 °C, respectively. These modifications show that NBH-P and NBH-G cocrystals have formed.

Comparing the apparent solubility of novel cocrystals to that of pure NBH. The solubility of plain NBH was 847.18 µg/ml, but that of NBH cocrystals was 177.48 and 1575.26 µg/ml, respectively, which is about 2.1-fold and 1.86-fold greater than that of the parent molecule.

Cocrystals NBH-P and NBH-G exhibited spherical and rod-like surface forms, contrasting the flat rectangular surface of pure NBH. This change recommends that the intermolecular hydrogen bonds between the drug and the coformer influence the cocrystals' habits.

The quantity of NBH-P and NBH-G drug release was seen to range between 81.6% and 79.4% during 120 minutes. There was an increase of around 40–50% in the cumulative fraction of drug release. An increase in dissolution rate quickens the pace of drug absorption through the gastrointestinal tract. The approach employed to put the concept of cocrystals into practice was effectively discussed in earlier literature, which might be useful for the process advancement in subsequent research.

CONCLUSION

The first zwitterionic cocrystal of NBH with L-glutamine and L-proline was magnificently formed in the current study. The evaluations of the prepared cocrystals by XRD, FTIR, DSC, SEM, and dissolution studies all indicated the formation of novel crystal lattices NBH-P and NBH-G. The changes in infrared peaks, XRD 2θ values, melting point in DSA peaks, and surface morphology by SEM all indicated that unique molecular structures were formed as a result of the formation of NBH cocrystals. The peak shift in IR spectra also confirms the establishment of hydrogen bonds flanked by NBH and the coformers. These findings indicate that NBH-P and NBH-G cocrystals may be a prospective agent with improved in vitro dissolution routine, demonstrating the capacity of L-proline and L-glutamine to enhance their properties through the cocrystallization process. As effective cocrystal formers, zwitterionic amino acids may now be used in a wider range of therapeutic applications.

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Ethics statement: None

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