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Synthesis and Characterization of Two New Co-Crystals: p-Aminobenzoic Acid with Isonicotinamide and Pyrazine (1:1)

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ABSTRACT

Two co-crystals of p-aminobenzoic acid with isonicotinamide and pyrazine were prepared in acetone-ethanol solution by solvent evaporation method in the 1:1 cytochiometric ratio. Their structures were characterized by FT-IR, 1H NMR and 13C NMR spectroscopies, powder X-Ray diffraction and differential scanning calorimetry (DSC) method. Both of the structures have shown the COOH/N heterosynthon. The thermal stability of the co-crystals was investigated by using DSC and it was determinated that the melting points of the co-crystals 1 and 2 were lower and in-between from those of their coformers, respectively.

Keywords:
P-aminobenzoic acid; Isonicotinamide; Pyrazine; Co-crystal

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INTRODUCTION

Co-crystals are made up of two or more molecular or ionic compounds combining at a cytochiometric rate, having a different crystallographic pattern than the precursor compounds, and being two or multi-component molecular crystals [1–3]. Molecules forming them are connected to each other by intermolecular interactions such as hydrogen bonds, π-π stacking interactions, C-H…π and Van der Waals forces [4,5]. The most preferred methods used in the preparation of the co-crystals are precipitation, slurry formation, cooling crystallization, grinding, as well as the evaporation that is the most common method. These methods can be applied differently within themselves [6–10]. Co-crystals have been widely used in the field of pharmacology, cosmetics, agriculture, paint, food, optoelectronic and photonic device industries in recent years. A co-crystal usually has some different properties than its constituent compounds, such as resolution, crystallization, melting point, optical properties, biocompatibility and thermodynamic stability [4, 11–14]. In previous studies, two new co-crystals composed of benzoic acid derivatives and pyridine derivatives have been reported. Many different biological activities of these organic ligands and their metal complexes have been investigated, and these complexes have been proven to be more biologically active compounds than free ligands. This phenomenon is not only for metal complexes but also for the co-crystals [15, 16].

p-Aminobenzoic acid is one of the B group vitamins, having drug property. In addition to vitamin properties, its antiviral, antioxidant, anticoagulant, fibrinolytic, antifungal, sunscreen protective properties are known, and it is used in diagnostic tests of gastrointestinal diseases. p-Aminobenzoic acid, one of the anthranilic acid derivatives, is a compound having a group of amine and a carboxylate groups attached to the benzene ring. These groups that are involved in its structure provide the formation of supramolecular structures by non-covalent interactions with heterocyclic rings which has aromatic ring nitrogen atoms and amide groups [17–19]. The isonicotinamide and pyrazine, which are used as co-formers in the formation of the co-crystals, have aromatic ring nitrogen atom that can form heterosynthon bonds with p-aminobenzoic acid. In addition, isonicotinamide is an antibacterial, antituberculosis compound capable of forming hydrogen bonds with oxygen and nitrogen atoms by means of potential donor atoms in amide group [20–25]. Pharmacological properties of pyrazine and its derivatives are also known. The increase in pharmacological and pharmacokinetic properties of co-crystals, in comparison to its constituent compounds, leads to an enhancement in the potential of its use as a drug. If at least one of the compounds forming the co-crystals is an active pharmaceutical

ingredient (API) and the other compound has a pharmacological use, it is regarded as a pharmaceutical crystal [2, 26–28]. In this context, we synthesized two new co-crystals of p-aminobenzoic acid that is an active pharmacological compound (API), with isonicotinamide and pyrazine in the 1:1 cytochiometric ratio, through solvent evaporation method. We examined the structures of these synthesized co-crystals with the method of 1H NMR, 13C NMR and FT-IR Spectroscopy, Differential Scanning Calorimetry (DSC) and Powder X-Ray Diffraction Analysis (XRPD).

MATERIALS AND INSTRUMENTS

p-Aminobenzoic acid, pyrazine, ethanol and acetone (Sigma Aldrich, Germany) and isonicotinamide (Aldrich, Germany) were purchased commercially available and used as received without purification. IR spectra (from solid samples) were recorded in the range of 600–4000 cm^{-1} with a Perkin Elmer Frontier™ FT-IR Spectrometer using a Diamond ATR accessory. Resolution was set up to 4 cm^{-1}, signal/noise ratio was estabilished by 16 scans. ^{1}H and ^{13}C NMR spectra were obtained with help of Bruker 400 Mhz spectrometer at ambient temperature using DMSO-d_6 as solvent. Powder X-Ray Analysis were carried out Philips X'Pert Pro diffractometer with Cu, Kα radiations, 40 kV of voltage and a current of 35 mA. The samples were analyzed from 5° to 75° (2°θ) with 0.2° min^{-1} and a step size of 0.02°. The DSC analyses were carried out a Perkin Elmer Diamond DSC analyzer at heating rates of 10 °C min^{-1}, using a nitrogen atmosphere and a scanning range of 60–400 °C.

Preparation of Co-crystals

To obtain Co-crystal 1, p-aminobenzoic acid (10 mmol, 1.37 g) and isonicotinamide (10 mmol, 1.22 g) were stirring and heating at about 60 °C for thirty minutes in beakers in acetone:ethanol (1:1) solution. Prepared solution was kept to evaporate for three days and obtained crystals were filtered and washed with acetone:ethanol (1:1) solution.

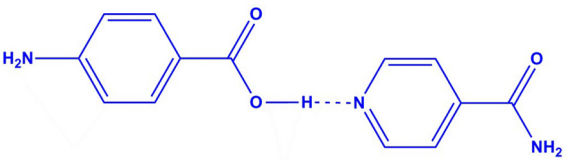

Figure 1. The molecular structure of Co-crystal 1.

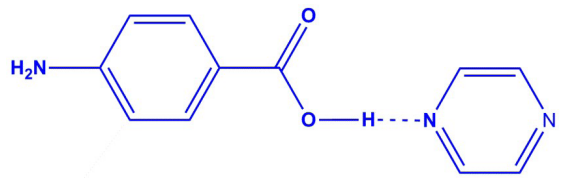

Figure 2. The molecular structure of Co-crystal 2.

To prepare Co-crystal 2, p-aminobenzoic acid (20 mmol 2.74 g) and pyrazine (10 mmol, 0.80 g) were stirring and heating at about 60 °C for thirty minutes in beakers in acetone:ethanol (1:1) solution. Prepared solution was kept to evaporate for two days and obtained crystals were filtered and washed with acetone:ethanol (1:1) solution.

RESULTS AND DISCUSSION

Evaluation of Structures

The structures of co-crystal 1 and 2 are given in Fig. 1 and 2, respectively. The co-formers are connected by O—H…N hydrogen bonds.

NMR Spectroscopy

4ABA-INA

^{1}H NMR (400MHz, DMSO-d6) δ 5.85 (s, 2H, NH2), 6.61 (d, 2H, ArH; J=8.80 Hz), 7.69 (d, 2H, ArH; J=8.80 Hz), 7.78 (s, 1H, NH), 7.80 (d, 2H, ArH; J=6.00 Hz), 8.30 (s, 1H, NH), 8.71 (d, 2H, ArH; J=6.00 Hz), 12.04 (s, 1H, OH); ^{13}C NMR (100MHz, DMSO-d6) δ 112.78 (2C), 117.43, 121.44 (2C), 131.30 (2C), 141.34, 150.09 (2C), 153.04 (Ar-C), 166.62, 167.66 (C=O) (Fig. 3).

4ABA-py

^{1}H NMR (400MHz, DMSO-d6) δ 5.88 (s, 2H, NH2), 6.61 (d, 2H, ArH; J=6.00 Hz), 7.70 (d, 2H, ArH; J=8.80 Hz), 8.63

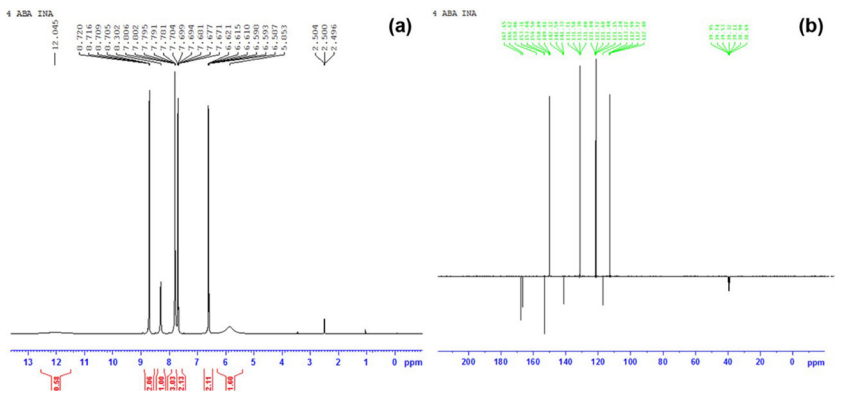

Figure 3. ^{1}H (a) and ^{13}C NMR (b) NMR Spectra of of Co-crystal 1.

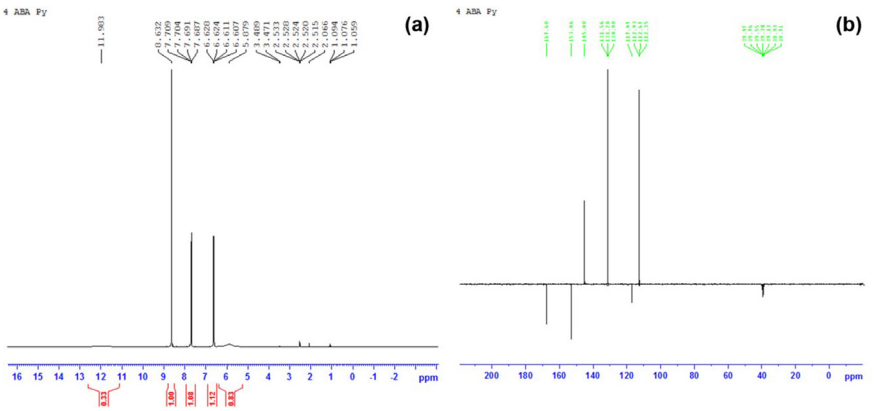

Figure 4. ^{1}H (a) and ^{13}C NMR (b) Spectra of of Co-crystal 2.

(s, 4H, pirazin-H), 11.98 (s, 1H, OH); ^{13}C NMR (100MHz, DMSO-d6) δ 112.67 (2C), 117.07, 131.28 (2C), 145.08 (4C), 153.06 (Ar-C), 167.60 (C=O) (Fig. 4).

FT-IR Spectroscopy

The formation of co-crystals 1 and 2 were determined by evaluating the changes in the vibration modes of the functional groups of the their co-formers (Fig. 5 and 6). The co-formers of synthesized co-crystals contains an aromatic amine (from the p-aminobenzoic acid) and a heteroamide (from the isonicotinamide) group. The vibration bands of these are observed at 3363 cm^{-1} and 3227 cm^{-1}; 3363 cm^{-1} and 3177 cm^{-1}, respectively [29]. In co-crystals, these streching frequences cocrystal 1 an co-crystal 2 were appeared at 3355 cm^{-1} and 3177 cm^{-1}; 3331 cm^{-1} and 3210 cm^{-1}, respectively. The p-aminobenzoic acid and isonicotinamide display to characteristic absorption bands at 1660 cm^{-1} and 1658 cm^{-1} related to carboxyl and carbonyl streches, respectively [29]. These bands were observed at 1688 cm^{-1} and 1651 cm^{-1} in co-crystal's spectra, while in the spectra of co-crystal 2, a single peak related to the carboxyl strech was observed at 1662 cm^{-1}. The-

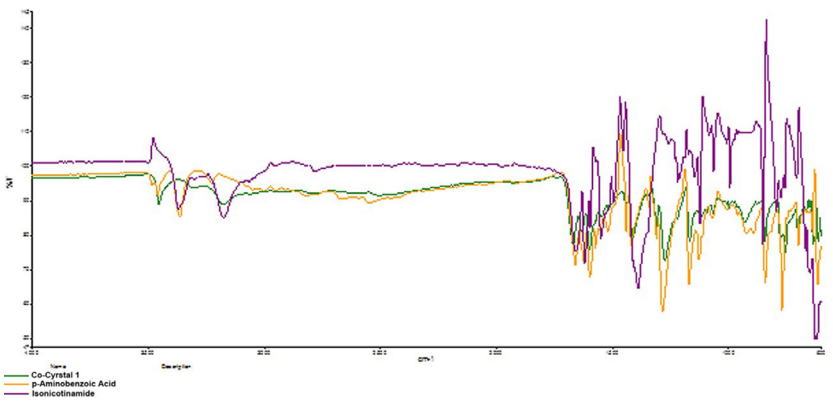

Figure 5. FT-IR Spectra of Co-Crystal 1 and its co-formers.

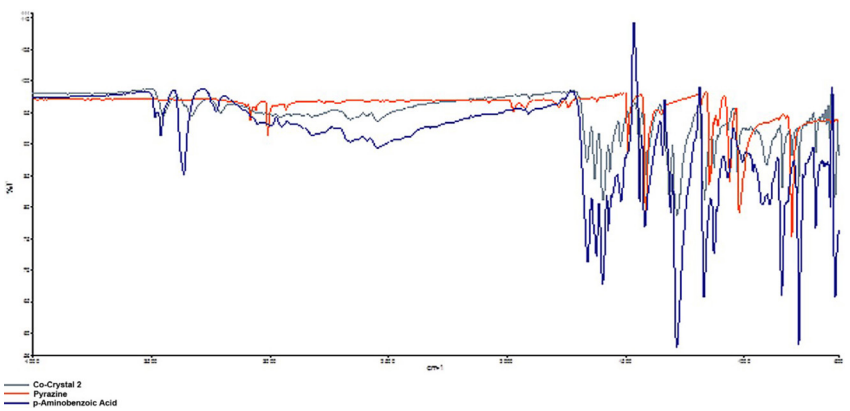

Figure 6. FT-IR Spectra of Co-Crystal 2 and its co-formers.

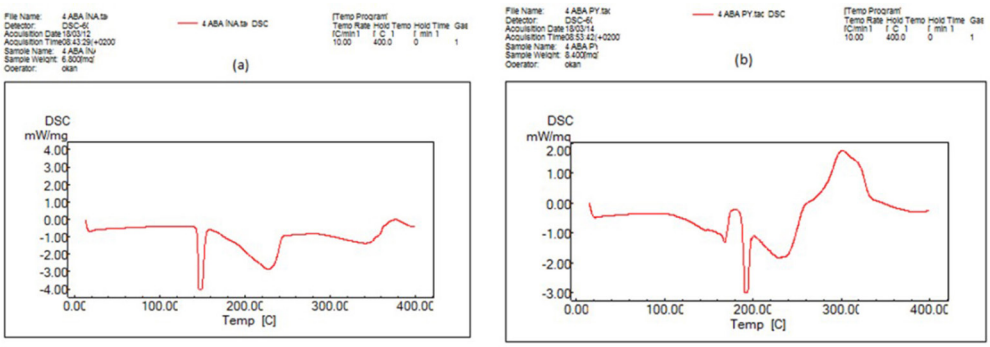

Figure 7. DSC curves of Co-crystal 1 and Co-crystal 2

se vibrational shifts can be attributed to the presence of hydrogen bonds in the co-crystals. C-N strech and N-H bends were shown at 1410 cm^{-1} and 1310 cm^{-1} (co-crystal 1) and 1411 cm^{-1} and 1315 cm^{-1} (co-crystal 2), respectively.

DIFFERENTIAL SCANNING CALORIMETRY AND POWDER X-RAY DIFFRACTION

Melting points of co-crystals and starting materials were measured with a melting point determination device (Fig. 7 a-b). These values for co-crystal 1, co-crystal 2, p-aminobenzoic acid, isonicotinamide and pyrazine are 145-157 °C, 169-170 °C, 187-189 °C, 155-156 °C and 52-53 °C, respectively. DSC analysis were performed to determine the melting points of the co-crystals. According to the results of the DSC analysis, co-crystal 1 is thermally stable up to 143 °C. The melting point of crystal 1 is lower (146 °C) than the melting points of the starting components p-aminobenzoic acid and isonicotinamide. This proves that the thermal stability of the crystal is less than that of the co-formers. The melting point of co-crystal 2 at 168 °C is higher than the melting point of pyrazine and lower than the melting point of p-aminobenzic acid. It can be said that thermal stability is higher than pyrazine and less than p-aminobenzoic acid depending on these values [30,31].

The diffractograms of the co-crystals and their co-formers are shown in Fig. 8-9. Significant differences were observed between the diffractograms of the crystals and the initial substrates. The characteristic diffraction peaks of p-aminobenzoic acid are 9.37, 6.40, 5.79, 4.07 and 2.51 at 2°θ. For the isonicotinamide, these peaks are 4.99, 4.72, 4.56, 4.26, 3.85, 3.81, 3.44, 3.36 and 2.89 2°θ. pyrazine presents diffraction peaks at 4.99, 4.66, 3.54, 3.21, 3.04, 2.75 2°θ. Significant differences were observed between the diffractograms of the crystals and the initial substrates. Co-crystal 1 indicates different peaks from p-aminobenzoic acid and isonicotinamide in: 10.99, 7.09, 5.77, 5.12, 4.82, 3.92, 3.53, 3.49, 3.17 and 3.10 2°θ. Co-crystal 2 presents different peaks from p-aminobenzoic acid and pyrazine in: 8.87, 6.30, 5.61, 4.43, 3.96, 3.33, 3.22, 2.66 and 2.50 2°θ. The diffraction peaks of 5.12, 3.92 and 3.49 2°θ (for co-crystal 1) and 5.61 and 4.43 2°θ (for co-crystal 2) are evidence of the formation of new crystallographic structures.

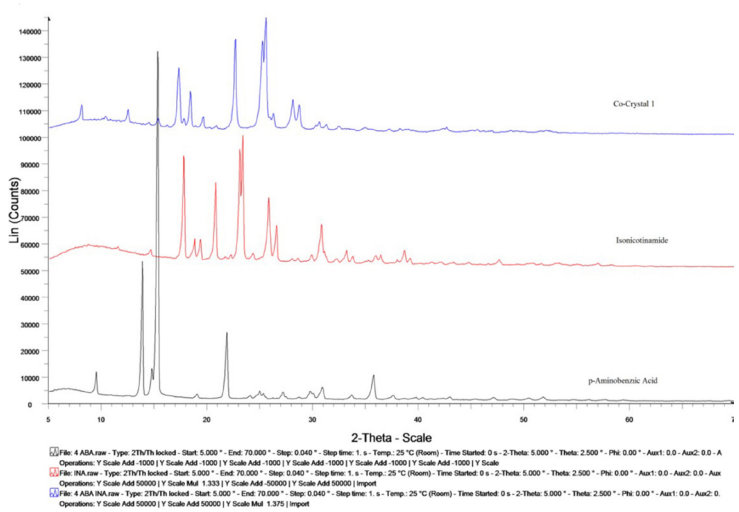

Figure 8. XRD Patterns of Co-crystal 1 and its coformers

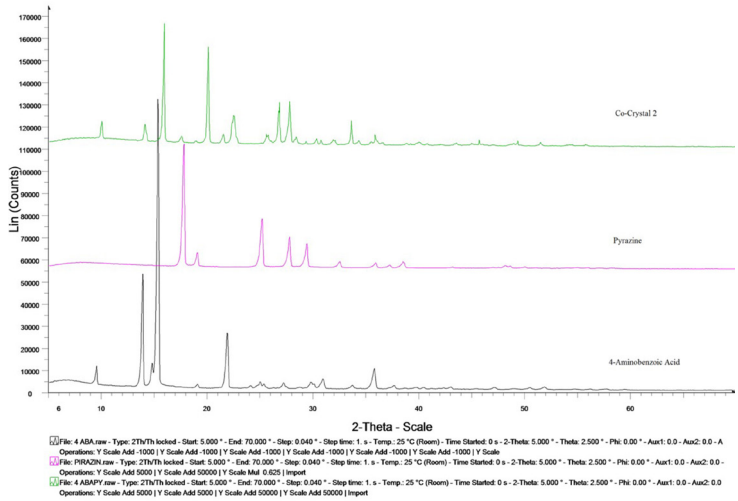

Figure 9. XRD Patterns of Co-crystal 2 and its coformers

CONCLUSION

Co-crystals of 4-aminobenzoic acid with isonicotinamide and pyrazine have been successfully synthesized and characterized by powder X-ray diffraction, FTIR spectroscopy, DSC analysis. The cocrystal 1 and 2 exhibited the carboxylic acid/heterocyclic ring's nitrogen atom heterosynthon. In the synthesized co-crystals, there are hydrogen bonds between the isonicotinamide/pyrazine ring nitrogen atom and the COOH group of the p-aminobenzoic acid. The co-crystals demonstrate same stoichiometry with 1:1 ratio. Because the p-aminobenzoic acid, isonicotinamide and pyrazine which are the coformers of our co-crystals, show pharmacologically properties, the synthesized compounds are likely to have pharmacological potential.

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