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Screening of multicomponent crystals of L-tryptophan with three isomers of pyridinedicarboxylic acids

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ABSTRACT

Multicomponent crystallization of L-tryptophan with three different isomers of pyridinedicarboxylic acids, namely, 2,3-pyridinedicarboxylic acid (2,3-PDA), 2,5-pyridinedicarboxylic acid (2,5-PDA) and 2,6-pyridinedicarboxylic acid (2,6-PDA), were screened using conventional solution cocrystallization technique. Whereas the new phases derived from the amino acid with 2,3-PDA or 2,5-PDA were analyzed using powder X-ray diffraction and thermal analysis techniques, the crystalline phase synthesized from 2,6-substituted isomer was further characterized by single crystal X-ray diffraction. Structural analysis revealed that the amino acid exists in the zwitterionic form interacting with the neutral 2,6-PDA by strong intermolecular hydrogen bonding. The components in the co-crystal self-assemble leading to a three dimensional hydrogen bonded closed packed network structure. Isothermal calorimetric titration showed that among the three isomers, 2,6-PDA showed relatively strong binding interaction towards the amino acid in water at 298 K. All the crystals exhibit marginal quenching of fluorescence properties of L-tryptophan in the solid state.

1. Introduction

Over the last two decades, multicomponent crystalline materials (either salt or co-crystals) derived from various active pharmaceutical ingredients (APIs) have been explored towards the development of drug formulations as well as to improve the physical and chemical properties such as solubility, dissolution rate, stability and hygroscopicity [1–7]. These multicomponent solids have further been directed towards purification, separation, absolute configuration determination and development of solid state applications [8–16]. Amino acids like many APIs are known as potential salt and co-crystal formers because of their high ionizable ability and solubility in water. They have been used in various pharmaceutical applications [17–22]. Tryptophan "an essential amino acid" is required for normal functioning in humans and act as a biochemical precursor for the production of neurotransmitter serotonin and the vitamin niacin [22–24]. Literature survey shows that host–guest or supramolecular inclusion complexes of tryptophan are very limited. The supramolecular complexes of L-tryptophan with acetic acid, formic acid, pyridine-2,4-dicarboxylic acid, D-(R)-mandelate and fumaric acid has been investigated [25–30]. Single-crystal investigation of L-tryptophan with high $Z' = 16$ is also known [31]. Solid state supramolecular assemblies of D-tryptophan with S-naproxen and cucurbit[6]uril has been reported recently [32,33]. Lack of crystal structures for the amino acid may be due to absence of any ionizable side chain in the molecule and thus, it deserves further attention. Tryptophan has been used as an important intrinsic fluorescent probe to estimate the nature of microenvironment of the tryptophan [34,35]. It has also been reported that the intrinsic fluorescence emissions of a folded protein are related to the excitation of tryptophan residues [36]. However, these fluorescence parameters are strongly influenced by the tryptophan environment. It has been investigated that the presence of nearby protonated acidic groups such as aspartic acid or glutamic acid causes significant quenching of tryptophan fluorescence [37].

Pyridinedicarboxylic acids (PDA) are known for various host–guest supramolecular complexes in the form of hydrogen bonded assemblies [38,39]. Presence of large number of hydrogen bond donor–acceptors and freely rotating bonds enable them as potential co-crystal formers. The current work explores multicomponent crystals of L-tryptophan with three different pyridinedicarboxylic acids (Fig. 1) in an attempt to expand the series of known co-crystals containing L-tryptophan, to examine the structural changes, binding ability and variation of fluorescence properties of L-tryptophan upon interacting with these PDAs.

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2. Experimental procedure

2.1. Materials

L-Tryptophan (98%), 2,3-pyridinedicarboxylic acid (quinolinic acid) (99%), 2,5- pyridinedicarboxylic acid (isocinchomeronic acid) (98%), and 2,6-pyridinedicarboxylic acid (dipicolinic acid) (99%), were purchased from Sigma-Aldrich Co., which were of the best available purity and were used without further purification unless otherwise indicated. Ethanol (Bengal chemicals) and Milli Q water from Merck Millipore was used both as solvent and for crystallization purpose.

2.2. Screening of multicomponent crystals

Screening of multicomponent crystals were conducted by dissolving a molar ratio of 1:1 mixture of L-tryptophan (105 mg) with three different isomers of pyridinedicarboxylic acids (83.5 mg) independently in a minimum amount of ethanol and water mixture. The resulting pale yellow or colorless solutions were stirred for 3 h at ambient temperature. The solutions thus obtained in each case were filtered and left at ambient condition for crystallization.

2.3. Optical microscopy

Optical micrographs of the crystals were taken under the polarization microscope (BX-51, Olympus, Japan) equipped with CCD camera (XC10).

2.4. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction patterns were recorded on a Bruker D2 Phaser (Germany) diffractometer with Cu Kα (1.542 Å) radiations operated at 30 kV and 10 mA. The data were collected over a 2θ angle range of 5–50° with a step scan of 0.02° with 2 s exposure time.

2.5. Single crystal X-ray diffraction (SCXRD)

Single crystal data of co-crystal **3** were collected on Oxford SuperNova microfocus based single crystal diffractometer where the data refinement and cell reductions were carried out by CrysAlisPro software®. The crystal was kept at 293.0 K during data collection. Structures were solved by direct methods and were refined by full-matrix least-squares on F^2 using SHELXL software. The H-atoms attached to O and N was located in the difference Fourier synthesis maps, and refined with isotropic displacement coefficients.

2.6. Differential scanning calorimeter (DSC) and thermogravimetry (TG) analysis

DSC analyses were performed on a TA Instruments Q20 differential scanning calorimeter. An amount of 5–10 mg of samples is kept in aluminum pan and the thermal behavior was monitored under nitrogen environment at a heating rate of 5 °C/min over a temperature of 30–350 °C. TGA analyses were performed in Mettler Toledo TGA/SDTA851^e under nitrogen atmosphere from 30 °C to 400 °C with a heating rate of 5 °C/min.

2.7. Infrared spectroscopy (IR)

Infrared spectra (KBr pellets) of these crystals were recorded with a Perkin Elmer Spectrum two FTIR spectrophotometer. Each spectrum was scanned in the spectral region 4000–400 cm^{-1} at a resolution of 2 cm^{-1} with a minimum of 32 scans. The alkali halide is dried at approximately 110 °C for two to three hours before making the pellets.

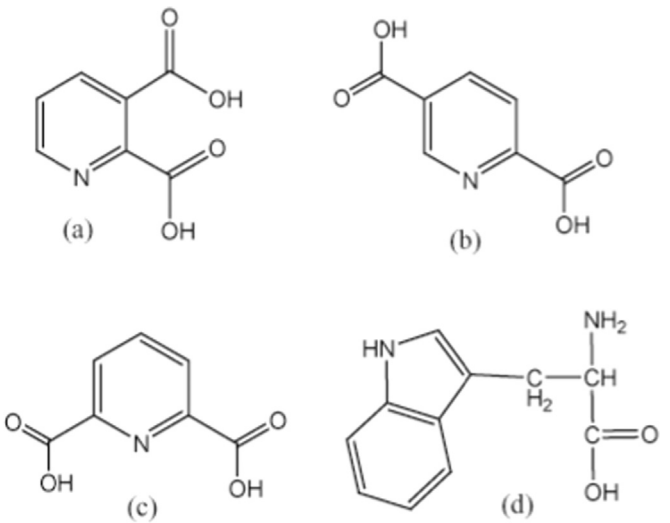

Fig. 1. Chemical sketches of (a) 2,3-pyridinedicarboxylic acid, (b) 2,5-pyridinedicarboxylic acid, (c) 2,6-pyridinedicarboxylic acid and (d) L-tryptophan.

2.8. Fluorescence studies

Horiba Fluoromax-4 spectrometer is used for measuring the fluorescence properties of these crystals. The equipment is designed with solid sample holder at an angle of 60° to measure the fluorescence of the finely powdered samples in the solid state. The experiments were carried out with similar amounts of sample under identical conditions.

2.9. Isothermal titration calorimetry

Isothermal calorimetric titrations (ICT) were carried out on a GE Healthcare iTC200 Microcalorimeter. The experiments were performed at 25 °C dissolving both the co-formers in water to minimize solvation enthalpy with 25 injections keeping the time interval 90 s.

3. Results and discussion

3.1. Microscope images of crystals

The crystal morphologies of the compounds **1–3** observed under a microscope are shown in Fig. 2. The crystal **1** is microcrystalline solids in nature, whereas crystal **2** having relatively bigger in size with regular structure and uniform surface. Despite of the bulk solids of each component of crystal **1** and **2** being white in color, the new crystals appeared as pale yellow. Co-crystal **3** is colorless with well defined morphology suitable for crystal structure determination.

3.2. Monitoring the crystals by powder XRD results

Powder XRD is utilized more frequently to demonstrate the formation of a crystalline molecular complexes or co-crystals. In the initial screening, when the powder diffraction patterns of the crystalline materials of **1–3** contained new peaks, different from the peaks of the initial compounds, i.e., the pyridinedicarboxylic acids and the amino acid, indicating the formation of a new phase. The powder XRD patterns of co-formers and the new phases of