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Isoniazid cocrystals with anti-oxidant hydroxy benzoic acids

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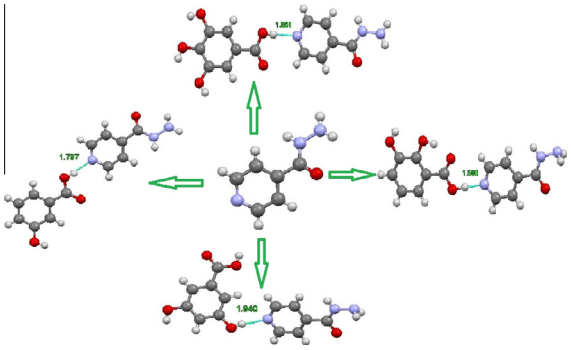
HIGHLIGHTS

- Cocrystals of isoniazid with four anti-oxidant hydroxy benzoic acids.
- Single crystal XRD studies of the isoniazid–hydroxy benzoic acid cocrystals.
- Infra-red (IR) studies of the isoniazid–hydroxy benzoic acid cocrystals.
- Differential Scanning Calorimetric (DSC) studies of the Isoniazid–hydroxy benzoic acid cocrystals.

GRAPHICAL ABSTRACT



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ABSTRACT

Isoniazid is the primary constituent of "triple therapy" used to effectively treat tuberculosis. In tuberculosis and other diseases, tissue inflammation and free radical burst from macrophages results in oxidative stress. These free radicals cause pulmonary inflammation if not countered by anti-oxidants. Therefore, in the present study cocrystals of isoniazid with four anti-oxidant hydroxy benzoic acids have been reported. Gallic acid, 2,3-dihydroxybenzoic acid, 3,5-dihydroxybenzoic acid, and 3-hydroxybenzoic acid resulted in the formation of cocrystals when reacted with isoniazid. Cocrystal structure analysis confirmed the existence of pyridine–carboxylic acid synthon in the cocrystals of isoniazid with Gallic acid, 2,3-dihydroxybenzoic acid and 3-hydroxybenzoic acid. While cocrystal of 3,5-dihydroxybenzoic acid formed the pyridine–hydroxy group synthon. Other synthons of different graph sets are formed between hydrazide group of isoniazid and coformers involving N—H···O and O—H···N bonds. All the cocrystals were in 1:1 stoichiometric ratio.

Introduction

Supramolecular Chemistry [1,2] gained attention when Nobel Prize of the year 1987 in chemistry was awarded to the founders of this field. This domain can be portrayed as "chemistry beyond the molecule" [3] and can be applied in the field of crystal engineering. It is described as "the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties" [4]. Cocrystallization of two or more pure compounds by crystal engineering to create a new functional material such as pharmaceutical cocrystal is of great academic and industrial interest [5]. Cocrystal can be defined as "a stoichiometric multi component crystal in which all its components are neutral and solid under ambient conditions when in pure form" [6], and can be constructed through several types of interactions, including hydrogen bonding, pi-stacking, and van der Waals forces.

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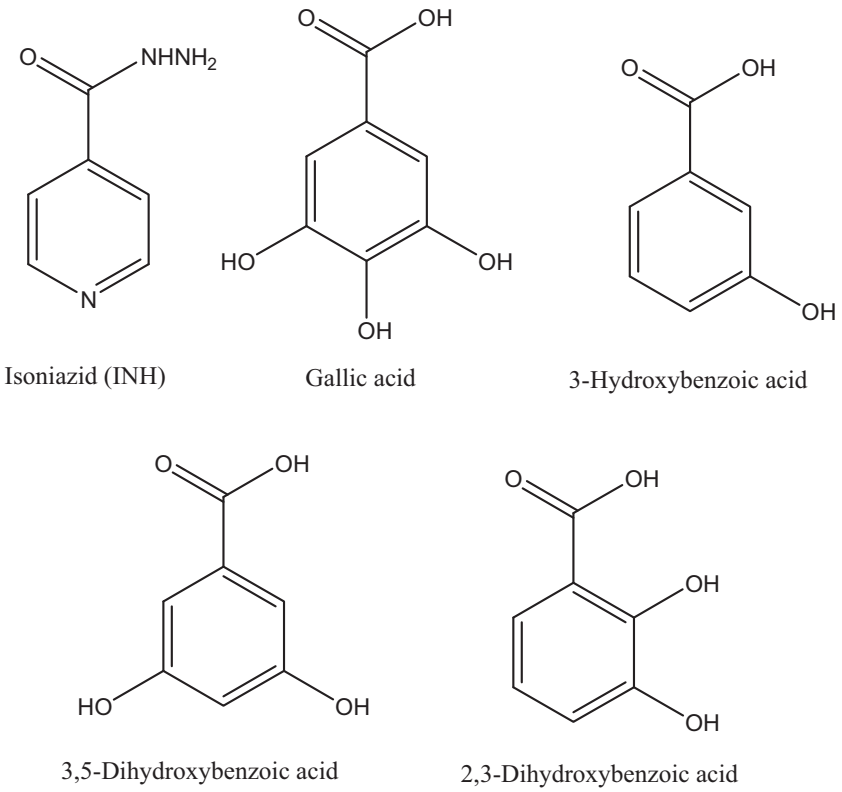

Fig. 1. Structural formulas of cocrystal components.

Pharmaceutical cocrystal is relatively new solid form of Active Pharmaceutical Ingredient (API) that has appealed the scientists as a mean of altering the physicochemical properties of API [7]. Pharmaceutical cocrystallization is an opportunity for the optimization of important physiochemical properties of an API while retaining its molecular structure and having improved bioavailability, increased resistance to hydrate formation, improved compaction properties for tablet formulation of two APIs into one dose. In spite of the fact that relationship between crystal structure and physicochemical properties of cocrystals has been studied [8–11], but still not completely understood. For example, no logical explanation of the variation in melting points of cocrystals can be given because of complicated nature of hydrogen bonding present in a cocrystals [12]. The melting point is also influenced by other intermolecular interactions, molecular conformations, packing, and entropy factors [13,14].

Study of hydrogen bond is heart of all intermolecular interactions [15]; it is energetic and directional [16,17] in nature and has been successfully identified in different environments among specific sets of functional groups having hydrogen bond formation capacity. It is therefore utilized in synthetic schemes to create specific assemblies [18–22]. Carboxylic acid–pyridine hydrogen bond in cocrystals is an established fact. It is due to strong donor and strong acceptor functionality of the carboxylic and pyridine functional groups respectively as described by Etter's rules for the formation of hydrogen bonds [23,24]. A numbers of cocrystals of isoniazid have been made with this hydrogen bond [25–30].

Isoniazid is highly active against *Mycobacterium tuberculosis* and is the primary constituent of "triple therapy" used to effectively treat tuberculosis since 1952. It is very versatile supramolecular reagent to synthesize novel supramolecular structures. Pyridine ring of INH is excellent hydrogen bond acceptor for carboxylic acids and bears possible attaching point for other heterosynthons. The carbohydrazide group of isoniazid has both functionalities of good hydrogen bonding acceptor in form of O and N atoms and donor in the form of three H atoms. Therefore, it is a potentially very important supramolecular reagent to synthesize cocrystals. Cocrystals of isoniazid having carboxylic-pyridine synthons with 4-aminosalicylic acid [31], 2-hydroxybenzoic acid, 4-hydroxybenzoic acid, 2,4-dihydroxybenzoic acid [32], malonic acid, succinic acid, glutaric acid, adipic acid, and pimelic acid [32–34] sebacic acid, suberic acid, cinnamic acid [35], tartaric acid [36], and 2,2-dithiodibenzoic acid have been reported.

Crystalline isoniazid is reported to be stable for long time periods however, its tablet formulations undergo degradation, particularly under high temperature and humid climatic conditions (40 °C, 75% RH) [37,38]. Exposure to light and presence of other drugs (pyrazinamide, ethambutol) being used in combination therapy also enhance isoniazid tablet's degradation [39,40]. It is therefore important to develop stable formulations of isoniazid.

In tuberculosis and other diseases, tissue inflammation and free radical burst from macrophages results in oxidative stress. These free radicals cause pulmonary inflammation if not countered by anti-oxidants [41–43]. On the other hand oxidation reaction is the main reason of degradation of molecules (APIs). The shelf life of pharmaceutical formulations depends on their ability to resist to oxidation of APIs. Anti-oxidants are used to stop the oxidation processes. Therefore, in the present study cocrystals of isoniazid with gallic acid, 2,3-dihydroxy benzoic acid, 3,5-dihydroxy benzoic acid and 3-hydroxy benzoic acid, which are known anti-oxidants, have been developed by slow evaporation method, and characterized by Fourier transform infrared spectroscopy (FTIR), single crystal X-ray diffraction (XRD) and Differential Scanning Calorimetry (DSC). Fig. 1 shows the structural formulas of the cocrystal components.