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Synthesis, characterization, solubility and stability studies of hydrate cocrystal of antitubercular Isoniazid with antioxidant and anti-bacterial Protocatechuic acid

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ABSTRACT

Isoniazid is an important component used in "triple therapy" to combat tuberculosis. It has reduced Tabletting formulations stability. Anti-oxidants are obligatory to counter oxidative stress, pulmonary inflammation, and free radical burst from macrophages caused in tuberculosis and other diseases. In the present study a hydrate cocrystal of Isoniazid with anti-oxidant and anti-inflammatory and anti-bacterial Protocatechuic acid (3,4-dihydroxybenzoic acid) in 1:1 is reported. This Cocrystal may have improved tabletting stability and anti-oxidant properties. Cocrystal structure analysis confirmed the existence of pyridine-carboxylic acid synthon in the Cocrystal. Other synthons of different graph sets involving N–H···O and O–H···N bonds are formed between hydrazide group of isoniazid and coformer. Solubility studies revealed that cocrystal is less soluble as compared to isoniazid in buffer at pH 7.4 at 22 °C while stability studies at 80 °C for 24 h period disclosed the fact that cocrystal has higher stability than that of isoniazid.

1. Introduction

Crystal engineering [1] has discovered a relatively new solid form of Active Pharmaceutical Ingredient (API) known as Pharmaceutical cocrystal. Crystal engineering falls into the domain of Supramolecular Chemistry [2], popularized when the Nobel Prize of the year 1987 in chemistry was awarded to the founders of this field. Cocrystals are "a stoichiometric multi component crystal in which all its components are neutral and solid under ambient conditions when in pure form" [3], and can be formatted through several types of interactions, including hydrogen bonding, pi-stacking, and van der Waals forces.

Pharmaceutical cocrystals provides a way to alter the physico-chemical properties of API [4]. Pharmaceutical dual drug cocrystals may have properties like retained molecular structure with improved bioavailability, increased resistance to hydrate formation and improved compaction properties for tablet formulation of two APIs into one dose.

Study of synthons and creation of hydrogen bonds between synthons is the core of the field of cocrystallization. Hydrogen bond is energetic, directional [5,6] and is utilized in synthetic schemes to create specific assemblies [7–11]. Carboxylic acid - pyridine hydrogen bond in the formulation of cocrystals is an established fact due to strong donor and strong acceptor functionality of the carboxylic and pyridine functional groups respectively. This is in accordance to Etter's rules for the formation of hydrogen bonds [12,13].

Isoniazid (Antitubercular drug) is the popular name of pyridine-carboxylic acid hydrazide or isonicotinic acid hydrazide (INH). It is odorless white crystalline powder with molecular weight 137.14 g/mol having empirical formula of $C_5H_5N_3O$(Fig. 1a). It is the primary constituent of "triple therapy" used to effectively treat tuberculosis as it is highly active against *Mycobacterium tuberculosis* since 1952.

Crystalline isoniazid is stable for long time while its Tablet formulations undergo oxidative degradation under high temperature and humid climatic conditions (40 °C, 75% RH) [14]. Exposure to light and presence of other drugs (pyrazinamide, ethambutol) being used in combination therapy also enhance isoniazid tablet's

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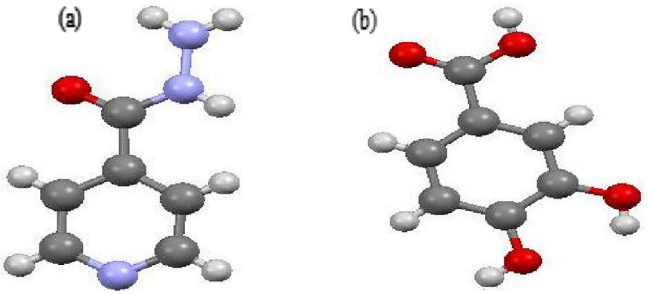

Fig. 1. (a) Structural formulas of Isoniazid (b) Structural formulas of Protocatechuic acid.

degradation [15,16]. It is therefore important to develop stable formulations of isoniazid.

Isoniazid is very useful supramolecular reagent to synthesize novel supramolecular structures; this is due to the fact that Pyridine ring and carbohydrazide group of Isoniazid act as hydrogen bond acceptor for carboxylic acids in form of O and N atoms and donor in the form of three H atoms respectively. Therefore, INH is a potential supramolecular reagent to synthesize pharmaceutical cocrystals. In past cocrystals of isoniazid [17–24] with Carboxylic–pyridine synthons have been reported. Hydroxy benzoic acids, Gallic Acid, 4-aminosalicylic acid, dicarboxylic acids, terephthalic acid, tartaric acid and 2,2-dithiodibenzoic acid have been synthesized. Moreover, hydrazide–hydrazide hydrogen bonds are also present in the pharmaceutical cocrystals of isoniazid.

Oxidative stress in tuberculosis and some other diseases is common due to tissue inflammation and free radical burst from macrophages. These free radicals results in pulmonary inflammation if not countered by anti-oxidants [25–27]. Oxidation reactions are the main reasons of degradation of APIs which decreases the shelf life of pharmaceutical formulations. Anti-oxidants are required to combat above said oxidative stress and degradation.

In the present study Hydrate cocrystal of Isoniazid with an antioxidant, antibacterial Protocatechuic acid (Fig. 1b) is synthesized by slow evaporation method and characterized by Fourier Transform Infrared spectroscopy (FTIR), Single crystal X-ray diffraction and Differential Scanning Calorimetry (DSC) studies.

Table 3
Single Crystal XRD data of Cocrystals (C-01).

Cocrystal	C-01
Empirical formula	$C_{26}H_{30}N_6O_{12}$
Formula Weight	618.56
Temperature (K)	293(2)
Wavelength (Á)	0.71073
Crystal System	Monoclinic
Space Group	*P 21*
Cell formula unit-Z	1
a (Á)	6.9626(5)
b (Á)	22.664(5)
c (Á)	8.8114(5)
α (°)	90
β(°)	100.124(4)
γ(°)	90
Volume (Á3)	1368.8(3)
Absorption coefficient (mm^{-1})	0.121
R factor (%)	6.26

Table 4
Hydrogen bond distances in Isoniazid-Cocrystals (C-01).

Atoms	D–H (Aº)	H···A (Aº)	D···A (Aº)	<D–H···A (deg)
Cocrystal C-01				
O8–H8···N6	0.932	1.676	2.593	167.12

Moreover, the Solubility, Stability and Spectral studies were also performed to investigate and compare the properties of cocrystal with that of isoniazid.

2. Experimental section

All the chemicals were used as received from the supplier without any further purification.

Melting point was studied by using a Gallenkamp (UK) 50 Hz 220/240 V melting point apparatus. The IR spectra were recorded on Varian 640-IR spectrophotometer.

Single crystal X-ray diffraction data was collected by using Bruker Kappa APEX II CCD diffractometer equipped with a graphite monochromator at 296 K. Fine focus of molybdenum Kα tube was used. Data was collected using APEX2 software, SAINT for indexing the reflections and determining the unit cell

Table 1
Physical data of Isoniazid and Cocrystals (C-01).

Code	Physical appearance	Melting point (°C)	Stability	Solubility	λmax
Isoniazid	White crystal	172 °C	93.86%	76.30 mg/mL	263 nm
Protocatechuic acid	Light brown	221 °C	93.40%	12.40 mg/mL	258 nm
C-01	Orange Prism	185 °C	94.46%	6.57 mg/mL	252 nm

Table 2
IR spectral data of Cocrystals (C-01).

Functional groups	Isoniazid υ cm^{-1}	Protocatechuic acid	C-01 υ cm^{-1}
Asymmetric $-NH_2$ stretching	3302	–	3248
Aromatic C–H Stretching	3010	3176	–
C–O Stretching	1662	1667	1651
C–N Stretching	1602	–	1612
Aromatic ring Vibration	1492	1528,1465	1526, 1493
Pyridine ring	1411	–	1407
Carboxylic acid OH	–	2632	–