Eng. Sci., 2021, **15**, 129–137

Engineered Science
DOI: https://dx.doi.org/10.30919/es8d1501

Introduction of Plasticity to Change Mechanical Behaviour of Pharmaceutical Crystals by Co-Crystallization: A Solution of Long Standing Problem in Isoniazid

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Abstract

Three co-crystals of the anti-tuberculosis drug Isoniazid (INH) with three analogous aromatic carboxylic acid namely phathalic acid (PA), isophthalic acid (IPA) and trimesic acid (TMA), were rationally designed and synthesized by slow evaporation method. Qualitatively, two-dimensional (2D) structure shows shearing behaviour on application of a mechanical stress, whereas the interlocked crystals are associated with brittleness in nature. Interestingly, co-crystallization of INH with PA converts its brittle nature of single crystal to shearing (plasticity) crystal *i.e.*, three-dimensional (3D) interlocked packing to 2D layer structure in INH/PA. Whereas, the co-crystals of INH/IPA and INH/TMA show brittle (non-plasticity) nature by keeping same 3D interlocked crystal packing as of INH. Improving the mechanical behaviour of single crystal of INH enhance its pharmaceutical acceptability and crystalline stability.

Keywords: Crystal Engineering; crystal structure; isoniazid; pharmaceutical co-crystal; structure-mechanical properties.
Received: 16 June 2021; Accepted: 3 August 2021.
Article type: Research article.

1. Introduction

The mechanical behaviour of organic materials has gained extensive attention to the researches of several disciplines due to its controlling ability of new materials in solid state. For example, in organic semiconductor devices,[1] Organic Light-Emitting Diodes (OLEDs),[2] polymer science,[3] biophysics,[4] formulation of active pharmaceutical ingredients(APIs) in pharmaceuticals,[5] *etc* are governed by mechanical properties and controlling dislocations. However in the context of of industrial-scale pharmaceutical manufacturing, it plays a crucial role in the manufacturing and performance of pharmaceutical products. The bulk properties of a drug like hardness, strain rate sensitivity, granularity and its ability to flow will depend on its mechanical properties which is important for easy tableting and formulation.[6,7] Manifestation of structure-property correlation is the key factor for the successful design and control of properties in desired materials.[8] In this context, understanding of the precise nature of intermolecular interactions among the atoms in a molecule and their role in directing the structures is important. Consequently, to a great extent, the structure determines the physical and chemical properties of a solid material at a given temperature.[8]

It is well-known that 2D layer structure is favorable to enhance the plasticity in molecular crystals.[8] With decreasing plasticity, the hardness of the crystals increases, which makes a crystal brittle. In presence of a planner co-former that promotes 2D layer formation and enhances the plasticity introduces several favorable properties like improving solubility and permeability, elevation of melting point, photostability, hydration stability and the half life of APIs.[9] Sometime, a multicomponent co-crystals with more than one drug molecules help against multi-drug resistance. The plasticity in co-crystals mainly can absorb the external energies in form of heat, light or mechanical forces in form of potential energy and releases slowly as a kinetic energy and comes to the normal state. This feature makes the 2D plastic co-crystals resistant against the unwanted external energies and make useful for practical uses. Shearing or bending behaviour is known in anisotropic crystals with 2D layer packing or with strong and weak (nonspecific) interactions in perpendicular directions, respectively. Brittle nature is observed in isotropic crystals due to similar interactions in all the dimensions. Thus, the plastic materials are favorable for tablet formation due to its bond area enhance ability under compaction pressure. To achieve 2D layer structure, co-crystallization is very useful technique. The co-crystal of an API has gaining popularity in the

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pharmaceutical industry for desired physicochemical properties like stability, solubility, bioavailability, mechanical properties, *etc* without affecting the pharmacological behavior of the drug.[10-15]

Isoniazid (INH) is the first-line medication in prevention and treatment of tuberculosis.[16] There was no evidence for the polymorph[17] of INH and it is brittle in nature. phthalic acid (PA), IPA and trimessic acid (TMA) are used as plasticizers, chemical strength improving and rigid building block developing materials, respectively.[18-20]

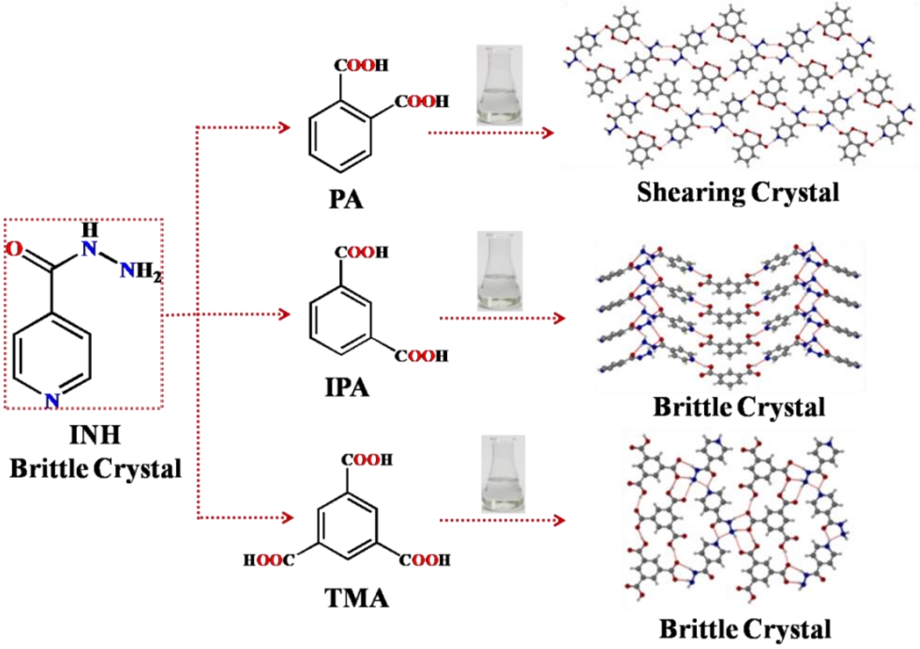
The mechanical behaviour of any API is an important factor for stability. Because brittle nature of a crystal is contrary to the formation of good quality tablet and a medicinally weak tablet will have very poor stresses to packaging, carrying and during treatment. So, a moderate strength tablet is highly desirable (either shearing or bending nature).[21] To resolve these unfavourable parameters of pharmaceutical industries, crystal engineering community can come with some innovative crystal engineering strategies. Isoniazid (INH) has drawn a renewed interest to the crystal engineering community due to its ability to form a robust interaction with carboxylic acid containing molecules.[22] There are few reports of isoniazid (INH) co-crystals in the literature,[22-29] which are limited mostly to crystal structure reports. Some reports on the modification of hydrazide group on INH by forming adducts with some keto compounds, followed by its co-crystallization with other hydrogen bonding co-formers. INH is also known to form co-crystals with another drug molecule.[23,24] But mechanical behaviour of INH and its co-crystals was not studied so far. Thus just forming some co-crystal without any medicinal goal is basically not relevant for developing an API. The main problems in INH should be solved by introducing the plastic behaviour. In order to introduce the plastic property, for making the drug stable against light, mechanical forces and temperature, we need to make the crystal structure 2D hydrogen bonded without compromising the solubility in water.

In this study, we used INH as model due to brittle nature of its single crystal. To improve the mechanical behaviour, we co-crystallize with three analogous planner aromatic acid molecules, namely; PA, IPA and TMA, assuming the 2D pllaner co-crystal formation. Interestingly only PA forms co-crystal with layer packing structure which convey shearing nature in the crystal. Whereas the other two analogous acids; IPA and TMA co-crystallize with INH in 3D interlocked packing results brittle in nature. Here we designed and synthesized three co-crystals among them only one co-crystal showed shearing behaviour which improve the mechanical behaviour of INH for the first time. This engineering tool will open a new door for using INH in the medicinal field.

2. Methods and Experimental Section

Materials Isoniazid drug and all co-crystal formers were purchased from Sigma-Aldrich. Commercially available solvents were used as received without further purification.

Single Crystal Preparation Isoniazid drug and co-crystal former in a definite stoichiometric ratio were subjected to grind in an agate mortar and pestle for 10 min. After grinding, the mixture was transferred to a 10 mL conical flask followed by addition of 10% methanol-acetonitrile mixture. The suspension was heated until a clear solution was obtained. The resulting mixture was boiled for 10 min followed by filtered into a fresh conical flask. The filtrate was left to evaporate slowly at ambient conditions. (Scheme 1) The single crystals suitable for X-ray diffraction studies were obtained in 4–6 days. The molecular strrructure of INH and other three coformers are depicted in Scheme 2.



Scheme 1. Schematic diagram of co-crystallization process.

Crystallography Co-crystals of Isoniazid were individually mounted on a glass tip. Intensity data were collected on a Brukar's KAPPA APEX II CCD Duo system with graphite-monochromatic Mo Kα radiation (λ = 0.71073 Å). The data were collected at 296 K temperature for INH/IPA, INH/PA and 100 K for INH/TMA co-crystals. Data reduction was performed using Bruker SAINT software.[30] Crystal structures were solved by direct methods using SHELXL-97 and refined by full-matrix least-squares on F2 with anisotropic displacement parameters for non-H atoms using SHELXL-97.[31] Hydrogen atoms associated with carbon atoms were fixed in geometrically constrained positions. Hydrogen atoms associated with oxygen and nitrogen atoms were included in the located positions. Structure graphics shown in the figures were created using the X-Seed software package version 2.0.[32]

Differential Scanning Calorimetry (DSC) DSC was conducted on a Mettler-Toledo DSI1 STAR^e instrument. Accurately weighed samples (2–3 mg) were placed in hermetically sealed aluminum crucibles (40 µL) and scanned from 30 to 300 °C at a heating rate of 5 °C/min under a dry nitrogen atmosphere (flow rate 80 mL/min). The data were managed by STAR^e software. The melting points are listed in Table 1.

Thermogravimetric Analysis (TGA) TGA was performed on a Mettler-Toledo TGA/SDTA 851^e instrument. Approximately 10–15 mg of the sample was added to an aluminum crucible and heated from 30 to 350 °C at a rate of 10 °C/min under continuous nitrogen purge.

IR Spectroscopy Transmission infrared spectra of the solids were obtained using a Fourier-transform infrared spectrometer (PerkinElmer 502). KBr samples (2 mg in 20 mg of KBr) were prepared and 10 scans were collected at 4 cm^{-1} resolution for each sample. The spectra were measured over the range of 4000–400 cm^{-1}.

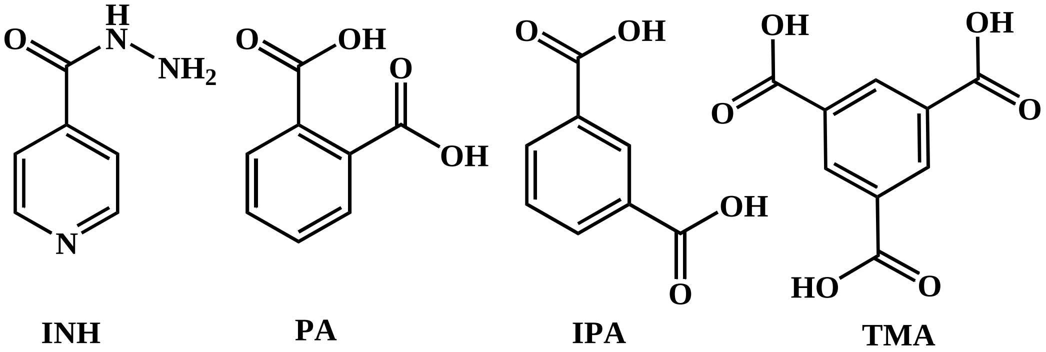
Optical Microscopy The crystal images were taken by using Leica M80 microscope.

3. Results and discussion

3.1. Crystal structure analysis

Crystal structures analysis were done to rationalize the hydrogen bonding preferences of acceptors and donors in the presence of other competing functional groups. The same batches of samples were used for IR spectroscopy. Crystallographic data are listed in Table 2. Hydrogen bond table (Table S1, Supporting Information) and the ORTEP diagrams for all the co-crystals are included in the Supporting Information (Figs. S1–S3).

Isoniazid/Phthalic acid (1:1), (INH/PA) The salt INH/PA crystallizes in the triclinic *P*-1 space group with one molecule of each INH and PA in the asymmetric unit. The INH molecule has a pyridyl N-atom, one terminal primary amine group (–NH_2), a secondary amine group (>NH) and a carbonyl group (>C=O). The co-former, PA molecule, which possesses two strong hydrogen bonding carboxylic acid groups at the ortho-position to each other, form an intramolecular hydrogen bonding via the hydroxyl group of carboxylic acid (O3–H3C···O4; d/Å, θ/°; 1.27(4) Å, 174(4)°). The proton of the second carboxylic acid group transfers to the pyridyl N-atom, thus forming a salt. In the structure, the INH molecules form dimer via synthon 1 involving the terminal primary amine group (–NH_2) and carbonyl group (>C=O) (see Scheme 3; N3–H3A···O1; 2.17(3) Å, 145(2)°). This leads to the formation of 1D tape as shown in Fig. 1a.



Scheme 2. Molecular structures of the compounds used for co-crystallization in this study.

Table 1. New isoniazid (171–173 °C)^a co-crystals with various carboxylic acid co-formers and corresponding melting points.

Co-crystal structure code	Coformer name (code)	Co-crystal, mp(°C)T_{max} from DSC	Coformer, mp (°C)^a
INH/PA	phathalic acid (PA)	146	210–211
INH/IPA	isophthalic acid (IPA)	199	341–343
INH/TMA	trimesicacid (TMA)	260.33	> 300

^{a} Melting point values as reported in Sigma-Aldrich chemical catalog.

Table 2. Crystallographic Data and Structure Refinement Parameters of INH Co-Crystals.

	INH/PA	INH/IPA	INH/TMA
Chemical Formula	$C_8H_5O_4$, $C_6H_8N_3O$	$C_8H_6O_4$, $2(C_6H_7N_3O)$	$C_9H_5O_6$, $C_6H_8N_3O$
Formula weight	303.27	440.42	347.28
Cryst sys	Triclinic	Orthorhombic	Orthorhombic
Space group	*P*-1	*Pmn*2$_1$	*Pca*2$_1$
a (Å)	6.9494(4)	42.012(7)	29.100(8)
b (Å)	9.2686(6)	6.2346(12)	3.7511(9)
c (Å)	11.0237(7)	3.8005(7)	13.255(4)
α (°)	97.879(4)	90.00	90
β (°)	99.814(4)	90.00	90
γ (°)	100.141(4)	90.00	90
Vol (Å^3)	678.43(7)	995.5(3)	1446.9(7)
D_{calcd}(g/cm^3)	1.485	1.469	1.594
μ (mm^{-1})	0.115	0.112	0.129
θ range (°)	2.03- 25.110	3.58 - 20.62	2.80 - 24.86
Z	2	2	4
range h	–8 to +8	–53 to +49	–37 to +37
range k	–11 to +11	–7 to +7	–4 to +3
range l	–12 to +13	–3 to +4	–16 to +16
Reflns collected	12196	7746	13042
Independent reflns	2397	2081	3125
Obsdreflns	1788	1179	2243
T (K)	296	296	100(2)
$R1$	0.0401	0.0504	0.0503
$wR2$	0.1169	0.1208	0.1225
GOF	1.015	0.917	0.875
CCDC No.	868957	868958	868959

The two primary NH protons from either side of the dimer are linked to carbonyl C=O from two adjacent PA molecules via N–H···O (synthon 2) hydrogen bond (N2–H2A···O5; 1.95(2) Å, 163(2)°) and (N1–H1A···O2; 1.81(3) Å, 178(3)°) (Fig. 1a). The INH molecule offers the second hydrogen atom of terminal primary amine group (–NH_2) for binding with the carboxylic acid group of PA of the next layer via synthon 3 (N3–H3B···O4; 2.35(4) Å, 167(3)º (Fig. 1b). The separation between two consecutive layers is 3.466 Å.

Isoniazid/Isophthalic acid (1:1), (INH/IPA) The co-crystal, INH/IPA, crystallizes in orthorhombic *Pmn*2$_1$ space group with one molecule of each co-former in the asymmetric unit. Here IPA adopts a planer conformation. IPA forms two strong O–H⋯N (O2–H2A⋯N1; 1.82(6) Å, 160(7)°) hydrogen bonds by the carboxylic acid groups and pyridyl N-atom from INH *via* synthon 4. The two hydrogen atoms from primary amine group (–NH_2) of INH form N–H⋯O hydrogen bonds with the carbonyl group (>C=O) of other two INH (N3–H3A⋯O1; 2.18(5) Å, 175(5)°) molecules. The secondary amine group (>NH) of INH forms N–H⋯N hydrogen bond (N2–H2B⋯N3; 2.03(6) Å, 160(4)°) with primary amine N-atoms of two INH molecule *via* synthon 5 leading to the formation of puckered tetramers (Fig. 2a), which form the infinite hydrogen bonding chain. IPA molecules act as a bridge between two infinite chains (as seen in Fig. 2b) along the *a*-axis. Both the co-former molecules are stabilized by the π⋯π interactions between the aromatic rings.

Isoniazid/Trimesic acid (1:1), (INH/TMA) The salt INH/TMA crystallizes in the orthorhombic *Pca*2$_1$ space group with one molecule of each in the asymmetric unit. In this bi-component system INH forms a salt by accepting proton from one of the carboxylic acid groups of TMA to pyrimidine N atom of INH. This hydrogen forms a bifurcated hydrogen bonding with carbonyl O-atom and primary amine N-atom of another INH *via* synthon 6 (N1–H1C⋯O1; 2.02(5) Å, 138(4)° and N1–H1C⋯N3; 2.07(5) Å, 140(4)°) (Fig. 3a). Two hydrogen atoms of primary amine group of INH form hydrogen bond with the carbonyl O-atom of carboxilate group of one TMA and carbonyl O-atom of carboxylic acid group of another TMA (N3–H1B⋯O4; 2.04(5) Å, 164(5)° and N3–H1A⋯O6; 2.21(5) Å, 135(4)°). The hydrogen atom of secondary amine group of INH and the hydrogen atom of carboxyl group of another TMA forms hydrogen bond with

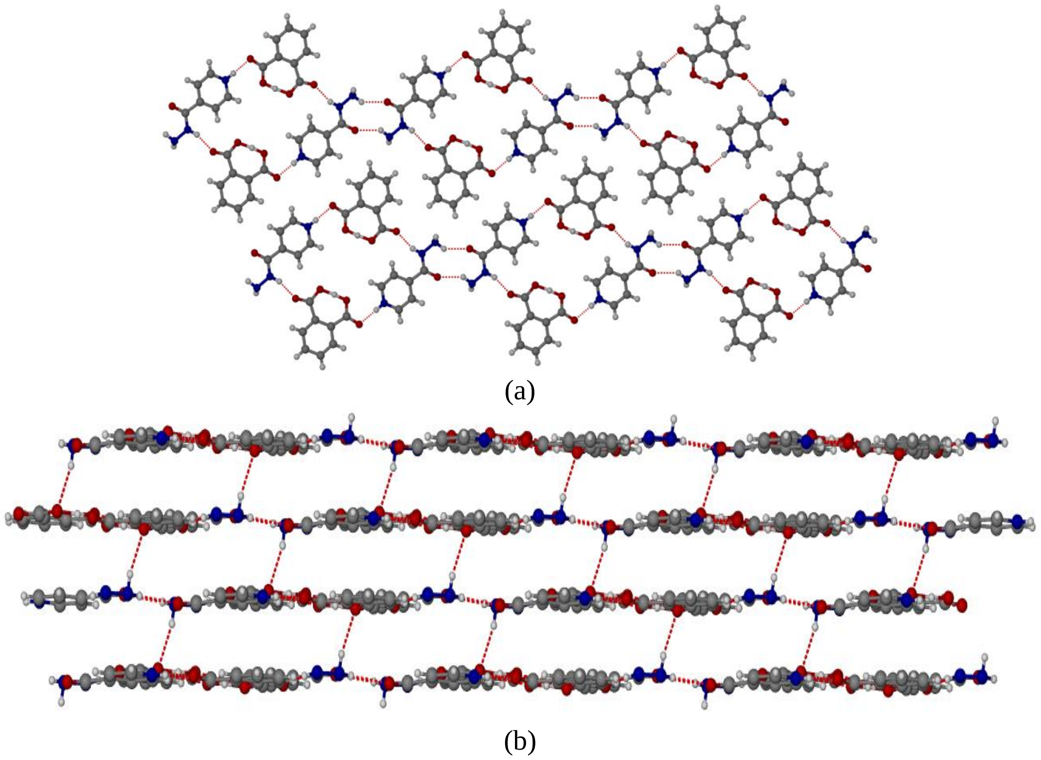
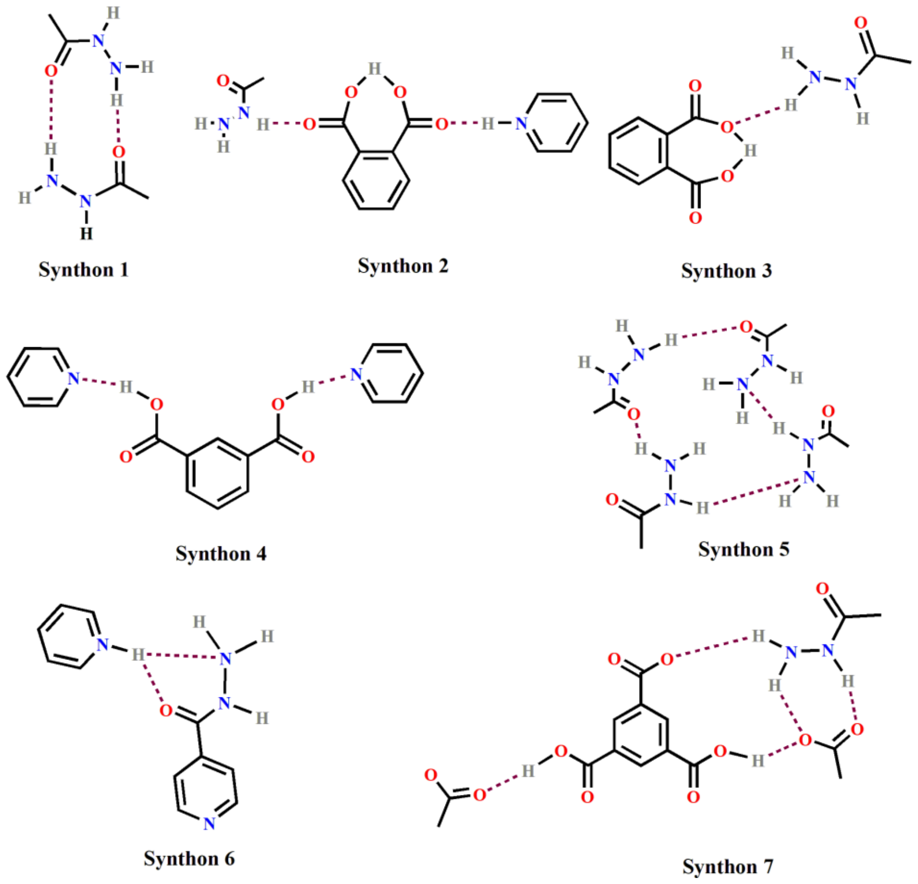
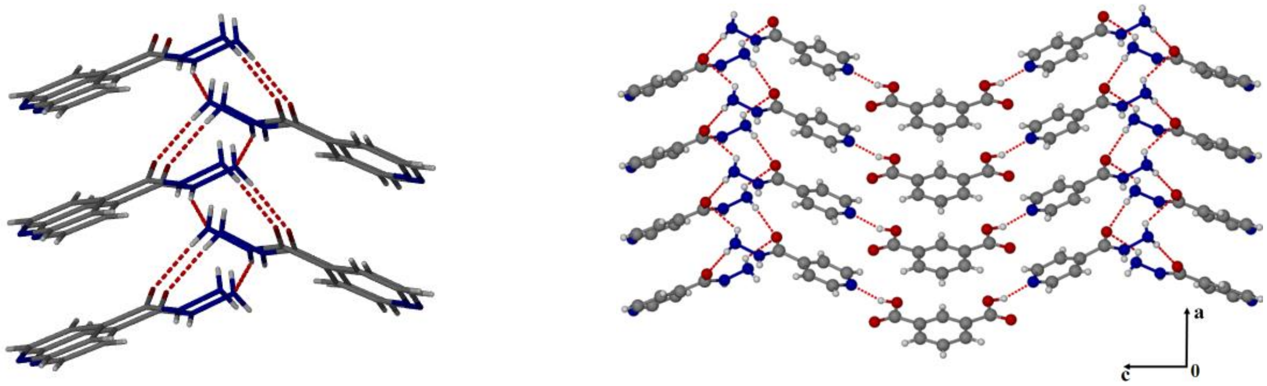


Fig. 1 Crystal packing of INH/PA salt. (a) Formation of tetrameric motiffs through N–H···O linkages that result in 1D tape (top view). (b) Side view of 2D layers formed by parallel 1D tapes. The layers are packed one over the other via π-stacking and N–H···O interactions. This plane is expected to be the weakest interaction plane. (Color index; O-red, N-blue, H-white).



Scheme 3. Synthons expected and/or observed in the INH co-crystals.



(a) (b)

Fig. 2 (a) Infinite hydrogen bonding chain formed by INH molecules. (b) Crystal packing to show the bridging of two adjacent infinite chains by IPA molecules (view along b-axis). (Color index; O-red, N-blue, H-white).

carboxylate group of a TMA (N2–H2A···O5; 1.97(6) Å, 167(6)° and O7–H7···O4; 1.61(5) Å, 170(5)°) *via* synthon 7 leading to a 3D interlocked packing (Fig. 3b). In this structure carboxyl group of another TMA forms hydrogen bond with carboxilate group of a TMA *via* synthon 7 (O3–H3···O5; 1.83(5) Å, 157(5)°). The aromatic rings in the salt are stabilized by the π-stacking interactions along *b*-axis.

3.2. Structure-Mechanical properties

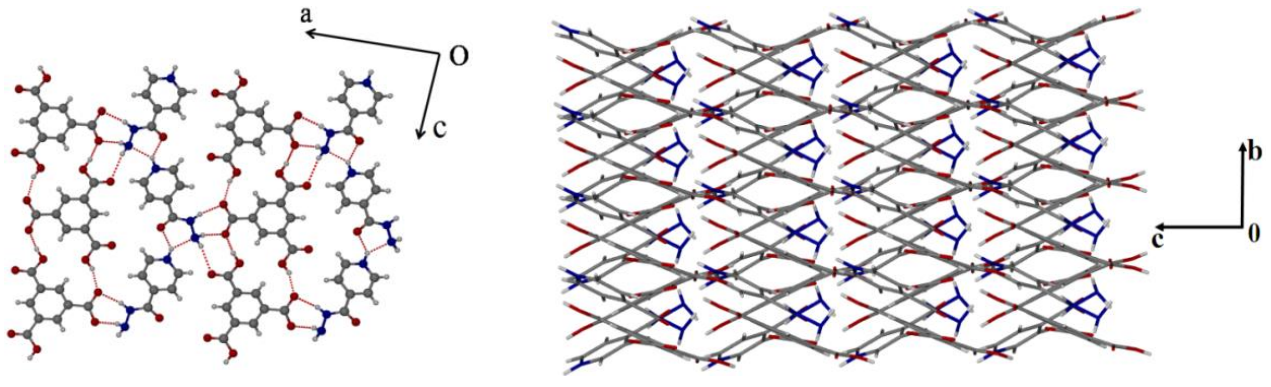
The mechanical behaviour of crystals depends on the features of crystal packing arrangement.[14,33,34] Depending on the mechanical behaviour the molecular crystals are classified into two categories, soft (shearing and bending) and hard (brittle) types. The crystal packing of single component isoniazid is nearly isotropic in nature, due to which the crystals are brittle (Fig. S13). Mechanical studies are performed on the single crystals of all co-crystals, using forceps and needle under a stereomicroscope. The co-crystals namely INH/PA is the shearing type, while the others, INH/IPA and INH/TMA are brittle in this series. INH/PA was found to be soft and showed smooth shear deformation on application of a mechanical stress parallel to the 2D layers in the crystal (Figs. 4a and b).

In this structure the layers are formed *via* strong N–H···O (see Fig. 1a) hydrogen bonds. These layers are connected through long N–H···O interactions (see Fig. 1b). So, it is marginally shearing type. But, the formation of robust layers with weak interlayer interactions is necessary for smooth shearing in 2D layer crystals.[8,35] In this crystal, slices come out easily while performing the shearing experiment.

Crystals of 2D layer packing with comparable interlayer and intralayer interactions do not show such shearing and simply break (*i.e.*, shear stress > cleavage stress). It was observed inINH/IPA, where strong O–H···N interactions are present within the layers and strong N–H···N and N–H···O interactions are present between the layers (Fig. 2b). In case of INH/TMA co-crystal, the structure is 3D interlocked, with isotropic distribution of strong interactions (Fig. 3a). So, during mechanical stress the crystals simply break (Figs. S8 and S9).

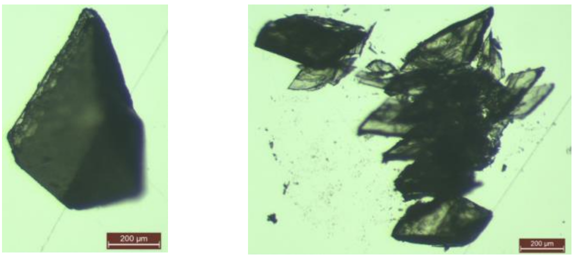
3.3. Thermal properties

The DSC and TGA experiments helped to establish their thermal stabilities with respect to the commercial sample of isoniazid. The DSC traces and thermogravimetric data for the isoniazid co-crystals are presented in Fig. 5a. The DSC thermograms for all the INH co-crystals, except INH/PA, showed a single endothermic transition corresponding to the



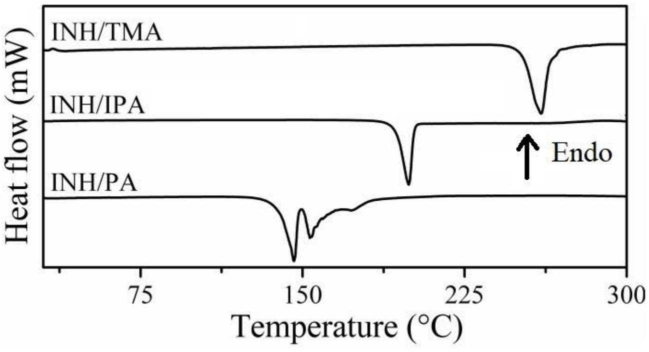
(a) (b)

Fig. 3 (a) Top view along b-axis, (b) the 3D corrugated packing along C-axis, for clarity bonds are not shown. Hydrogen bonds are not shown for clarity. (Color index; O-red, N-blue, H-white).

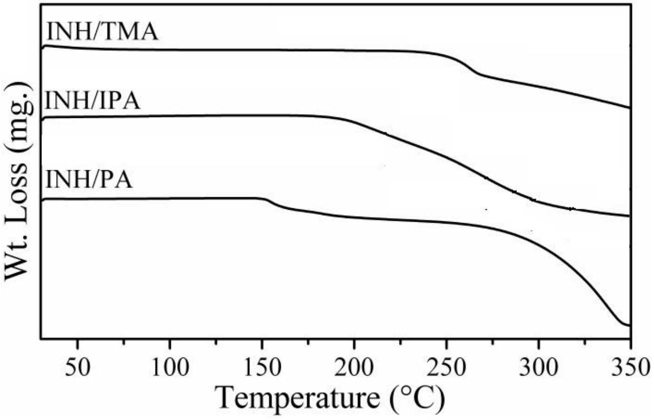


(a) (b)

Fig. 4 Optical images of INH/PA crystal (a) before and (b) after (right) shearing, respectively.



(a)



(b)

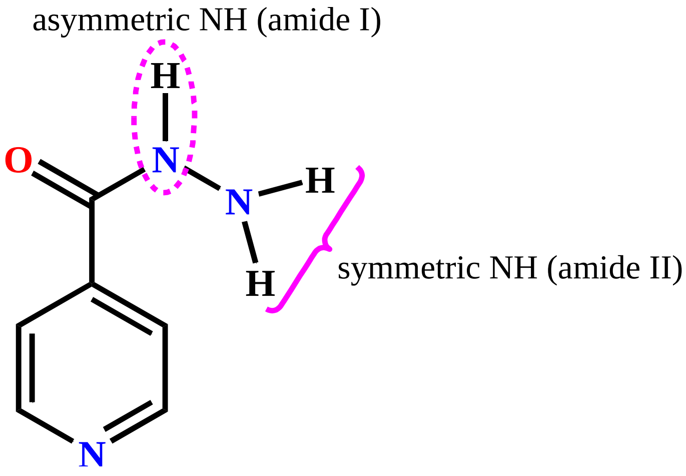
Fig. 5 Thermal property analysis of INH co-crystals.
(a) DSC and (b) TGA of INH co-crystals.

melting. The thermogram in the case of INH/PA showed a complicated pattern with a major endotherm at 146 °C, along with a sharp additional endotherm at 153.99 °C a small endotherm at 173 °C. This complicated pattern could be due to multiple phase transitions, but further studies are required to confirm the exact reasons. DSC plots reveal that the thermal stability of four co-crystals is higher than that of the commercial isoniazid where the rest of the three are lower. The least stable among the co-crystals is INH/PA.

In the TGA experiment of INH/PA co-crystal, the first weight loss corresponds to the decomposition of co-crystal, and second loss is for decomposition of INH (Fig. 5b). The TGA experiments confirmed purity of rest of the co-crystals as there wasshowed only single weight loss.

3.4. Infrared Spectroscopy

One of the reliable techniques to ascertain the formation of co-crystals is infrared spectroscopy (IR spectroscopy). Generally, co-crystals show the stretching frequency (*vs*) bands of both the co-formers correlated with characteristic shifts. For the IR spectroscopy of all the INH co-crystals (in the region 400–4000 cm^{-1}) (Figs. S4-S6), one or two single crystals were chosen by inspecting them under an optical microscope. A comparison of the νs shifts gave an estimate of the relative strengths of the hydrogen bonds formed between the functional groups in co-crystals.[36-38]



Scheme 4. Representation of symmetric and asymmetric amine group.

In the single component INH crystals, two stretching frequency bands at 3304 and 3111 cm^{-1} are assigned to the asymmetric NH (amide I) and symmetric NH (amide II) stretching frequencies of amine groups respectively (Scheme 4), while the two bands at 1667 and 1556 cm^{-1} are assigned to the stretching frequencies of carbonyl group to amide I and amide II groups respectively. Whereas, in the co-crystals, the INH exists in either amine or salt form to make hydrogen bonded synthons 4, 5 or 2, 6 with the co-formers; hence the associated stretching bands appear at different frequencies. Similarly, the INH amine also involves in different synthons (1, 3 or 7) in different co-crystals. The infrared stretching frequencies with the associated shifts (in brackets) in comparison with free INH are given in Table 3.

4. Conclusion

Three new co-crystals of INH have been designed, synthesized and characterized. Among these three co-crystals, INH/PA shows shearing behaviour where as INH/IPA and INH/TMA are brittle in nature. Mechanical behaviour and controlling of dislocations of a compound is important in the formulation of APIs in pharmaceutical industries. INH is known to be brittle in nature which is a long standing problem. Co-crystallization of INH with three co-formers reveal improved mechanical behaviour for INH/PA. Improving the mechanical behaviour reveals an acceptable solution for the tablet formation by introducing 2D layer

Table 3. Infrared stretching frequencies for INH amine (NH) and carbonyl (C=O) groups in free INH and co-crystals[a].

Peak assignment	INH	INH/PA	INH/IPA	INH/TMA
amine ν(NH)asym (cm^{-1}) (amide I)	3304	3293 (–11)	3317 (+13)	3278 (–26)
amine ν(NH)sym (cm^{-1}) (amide II)	3111	3053 (–58)	3195 (+84)	3104 (–7)
carbonyl ν(C=O)(cm^{-1}) (to amide I)	1667	1636 (–31)	1659 (–8)	1654 (–13)
carbonyl ν(C=O)(cm^{-1}) (to amide II)	1556	1499 (–57)	1553 (–3)	1535 (–21)

[a] The values given in brackets are the frequency shifts in comparison with the corresponding groups in single component INH crystals.

structure in INH co-crystal. Further study on mechanical behaviour of these co-crystals is under investigation. This work might be fruitful solution for this API to improve the mechanical behaviour and this technique should be useful in wide variety of other API too.

Acknowledgments

PPB gratefully acknowledged Prof. C. Malla Reddy from IISER Kolkata for providing experimental facility, Dr. P. Sahoo (NIMS, Japan) for his constructive criticism during revision and thanks the Collaborative Research Funds under TEQIP III and Dumka Engineering College, also thankful to SRM University Sikkim for completing the total project.

Supporting information

Geometrical parameters of molecules from crystal structures, infrared spectra, ORTEP diagrams, optical images of mechanical behavour of crystals. CCDC 868957–868959. For ESI and crystallographic data in CIF.

Conflict of interest

There are no conflicts to declare.

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