Preparation and Pharmaceutical Characterization of Supra molecular Complex of Isoniazid with L(+) Tartaric acid

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Abstract:
Concept of supramolecular synthons represent a new archetype toward the design of novel pharmaceutical multiple components of crystalline phases with desired physicochemical properties. The active pharmaceutical ingredient Isoniazid is the major component in "triple therapy" used to treat tuberculosis and it is a potentially flexible supramolecular reagent to synthesis cocrystals and molecular complexes. In this study, we utilized this concept as recurring design strategy in supramolecular synthesis of pharmaceutical molecular complex of isoniazid with L (+) tartaric acid, a GRAS compound. The supramolecular interaction of isoniazid with dicarboxylic acids resulted in both valid co-crystals and organic salts depending on the nature of the dicarboxylic acid. The pure drug and the prepared molecular complex were characterized by infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), Scanning electron microscopy (SEM) and subjected to Preliminary pharmaceutical characterization such as solubility, micromeritic studies, Invitro dissolution studies and Antitubercular activity. DSC, SEM and FTIR analysis confirm the formation of molecular complex. From the pharmaceutical characterization, prepared molecular complex was showing decreased solubility, similar dissolution profile in all mediums and improved micromeritic properties, but it has less antitubercular activity when compare with pure drug.
Keywords: molecular complexes, pharmaceutical compounds, Preliminary pharmaceutical characterization

INTRODUCTION:

Concepts of crystal engineering represent a new paradigm toward the design and synthesis of novel pharmaceutical multiple component crystalline phases with pharmaceutically accessible additives [1] based on supramolecular architectures, which are used as robust structural units to control the structures of single- and multi-component solid phases with desired composition, physicochemical and mechanical properties [2-6]. In addition, the approach of supramolecular synthesis [7,8] can offer considerable benefits over conventional covalent synthesis in which compounds are prepared by stepwise breaking and making of covalent bonds. Particularly, supramolecular synthon approach facilitates self assembly of molecules with high molecular weight and without altering the covalent structure of components.

Investigating how these molecules assemble by non-covalent integrations to form multiple component crystalline complexes or phases is important for the design and Synthesis of pharmaceuticals [9-14]. The enhanced physicochemical and pharmaceutical properties of multiple component crystalline complexes compared to the single component crystal of pharmaceuticals have been reported, such as solubility, dissolution rate [15, 16], chemical and physical stability, hygroscopicity [17], and moisture uptake [18-22]. The explanation to designing these extended synthons lies in identifying non-covalent intermolecular interactions that direct molecular assembly [23-27]. The strength and directional nature of hydrogen bonds is the master key today and most useful interactions in building in building the desirable self-assembly of molecules in the solid state. Many drug molecules are known to form hydrogen bonded molecular complexes in solution and in the solid state and are therefore good supramolecular reactants with other components. Actually, hydrogen bonds have been engaged in the formation of multiple crystalline supramolecular architectures of binary and ternary composition where at least one of the components is a pharmaceutical [28-35].

A Cambridge Structural Database (CSD) investigation of supramolecular architectures concerning primary amides reveals that 84% form amide-amide dimers, while 14% form catemers in the lack of other competing hydrogen bond donors and/or acceptors. Conversely in the presence of chemically distinct but complementary functional groups such as aromatic nitrogen moieties or carboxylic acids, primary amides tend to produce supramolecular heterosynthons. Supramolecular heterosynthons provides an opportunity for design of multi-component crystals of pharmaceuticals wherein one molecule have a primary amide and a second molecule called coformer contains the functional group that is complementary to the primary amide. Carboxylic acid-pyridine supramolecular heterosynthon has emerged as a reliable key in construction of molecular complexes between homologous alkane dicarboxylic acids and isonicatine amide [36]. We have utilized this concept as frequent design approach in supramolecular synthesis of pharmaceutical multiple component crystalline phases involving isoniazid. Isoniazid (INH, pyridine-4-carbohydrazide) is used as a first-line antitubercular agent, in combination with other antitubercular drugs for the effective treatment of active disease and also used for prevention of tuberculosis in individuals who have been exposed to active disease. The supramolecular interactions of Isoniazid with dicarboxylic acids resulted in both co-crystals and organic salts based on the nature of the dicarboxylic acid. Co-crystals (of 2:1

stoichiometry) of isoniazid with adipic, succinic and malonic acids and the organic salts (of 1:1 stoichiometry) of isoniazid with oxalic or D-tartaric acid are reported. In this research article, we report an organic salt of isoniazid with L(+)-tartaric acid of 1:1 stoichiometry.

MATERIALS AND METHODS:

Isoniazid was purchased from Lobe chemie Pvt.Ltd, Mumbai and used without further purification. L(+)-tartaric acid was procured from Qualigens Fine Chemicals, Mumbai. All other chemicals and reagents used were of analytical reagent grade.

Preparation of Co-crystals:

Isoniazid (0.137g, one mmol) and L(+) Tartaric acid (co-crystal formers, 0.15g, one mmol) were dissolved separately in 10 mL of methanol with warming and mixed together. Solution was cooled to room temperature and kept for slow evaporation for 6 h. The crystals were isolated by filtration through a membrane (0.45 µm) and dried in the air.

Infra-red Spectroscopy:

Infra red (IR) spectroscopy studies of INH, L(+) Tartaric acid and supramolecular complex were recorded in a FTIR spectrophotometer (Thermo-IR 200) Potassium bromide pellet method was employed and background spectrum was collected under identical 4000 cm^{-1} at a spectral resolution of 2 cm^{-1}.

Differential Scanning Calorimetry (DSC):

DSC was performed using DSC- (NETZSCH DSC 204) calorimeter to study the thermal behavior of INH, L(+) Tartaric acid and prepared co-crystal. The samples were heated in hermetically sealed aluminum pans under nitrogen flow (30 ml/min) at a scanning rate of 10 ◦C/min from 50 ◦C to 300 ◦C. Empty aluminum pan was used as a reference.

Scanning Electron microscopy (SEM)

The surface characteristics of the pure drug and prepared supramolecular complex were studied by SEM (ZEISS Electron Microscope, EVO MA 15). Powder samples were mounted onto aluminum stubs using double sided adhesive tape and sputter coated with a thin layer of gold at 10 Torr vacuum before examination. The specimens were scanned with an electron beam of acceleration potential of 20 kV and the images were collected as secondary electron mode.

Measurement of flowability and packability:

Measurement of flowability:

The bulk density (BD) and tapped bulk densities (TBD) were investigated in triplicate by using Density apparatus. The Carr's index (%) and the Hausner's ratio (HR) were calculated by using BD and TBD. The angle of repose of Isoniazid was assessed by fixed funnel method. The Carr's index represents the compressibility, and there is a correlation between the compressibility index and the flowability of the pure drug and prepared supramolecular complex.

$$CI = \left[\frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}}\right] \times 100$$

$$HR = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Where CI = Carr's index, and HR = Hausner's ratio.

Measurement of Packability:

The packability of the pure drug and prepared supramolecular complex were determined in triplicate by tapping them in to a 25-ml measuring cylinder (using a Density apparatus). Initially, 25 g was weighed and then was gently poured into a measuring cylinder. The volume of samples was recorded. The poured density (loose bulk density) was calculated from mass and the volume. The cylinder was then tapped and the volume was recorded after each 100 taps until the volume did not vary significantly. The compressibility was determined by measuring the tapped density according to the modified Kawakita (I) and Kuno (II) equation

$$\left[\frac{n}{C}\right] = \left[\frac{1}{ab}\right] + \left[\frac{n}{a}\right] \ldots\ldots\ldots\ldots (I)$$

Where n = tap number, C = degree of volume reduction which can be calculated according to the equation III, a and b = constant for packability and flowability.

$$C = \frac{(V_0 - V_n)}{V_0} \ldots\ldots\ldots\ldots (III)$$

The plot of $\left[\frac{n}{C}\right]$ versus n is linear and the compactibility $\frac{1}{a}$ and cohesivity $\frac{1}{b}$ are obtained from the slope $\frac{1}{a}$ and the intercept $\frac{1}{ab}$ of the plot of the modifed Kawakita equation. The data were also analysed by Kuno equation:

$$\ln(\rho_f - \rho_n) = -kn + \ln(\rho_f - \rho_0) \ldots\ldots\ldots\ldots (II)$$

where ρ_f, ρ_n and ρ_0 are the apparent densities at equilibrium, nth tapped and initial state, respectively, and k is the constant.

Drug content:

For the determination of drug content, prepared supramolecular complex (100 mg) were dissolved in 100 ml distilled water and the solution was analyzed spectrophotometrically for drug content after sufficient dilution with distilled water. The study was performed in triplicate.

Saturation Solubility:

Saturation solubility studies of INH and INH-L(+) Tartaric acid co-crystal were performed in triplicate according to method reported by Higuchi and Connors.[39] In this saturation solubility study, an excess quantity of Isoniazid, prepared co-crystals was placed in the vials containing 10 ml of different pH Medias. The vials were agitated in incubator shaker (100 agitations / min) for 4 hr at room temperature. The solution was then filtered through a membrane (0.45µm) and the amount of the drug dissolved was analyzed spectrophotometrically (UV-1700, Shimadzu, Japan) at 266 nm (0.1N HCl), and 262 nm (Distilled water and pH 6.8 phosphate buffer).

In vitro dissolution studies:

The *in vitro* dissolution studies were carried out in triplicate using eight-station USP type II dissolution apparatus (Lab India, Model Disso 2000 Tablet dissolution test apparatus, Mumbai, India). Dissolution studies were carried out using 900mL of 0.1N HCl, distilled water and pH 6.8 phosphate buffer at 37 ± 0.5°C and 50 rpm. 5 mL of sample was withdrawn after suitable time interval and replaced each time with 5mL fresh medium. The solutions were immediately filtered through 0.45 mm membrane filter, diluted and the concentration of Isoniazid was determined spectrophotometrically at respective λmax (0.1N HCl - 266 nm, distilled water - 262 nm and pH 6.8 phosphate buffer - 262.5 nm).

Anti-Tubercular activity:

The anti mycobacterial activity of compounds were assessed against M. tuberculosis using microplate Alamar Blue assay (MABA). In this method, 200µl of sterile deionzed water was added to all outer perimeter wells of sterile wells plate to minimized evaporation of medium in the test wells during incubation. The wells plate received 100 µl of the Middlebrook 7H9 broth and serial dilution of untreated drug and prepared cocrystal were made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/ml. Plates were covered and sealed with parafilm and incubated at 37ºC for five days. After this time, 25µl of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth.

RESULT AND DISCUSSION:

Isoniazid is used as a first-line treatment for tuberculosis, in combination with other drugs for the treatment of active disease. The pyridine ring of INH is excellent hydrogen bonding acceptor for mono and di-carboxylic acids and the possible attaching point for any heterosynthons. The carbohydrazide group of isoniazid has both good hydrogen bonding acceptor (O and N atoms) and donor (3 H atoms) functionality. Hence, it is a potentially versatile supramolecular reagent to prepare molecular complex such as co-crystals and salts. In this study isoniazid-L(+)tartaric acid molecular complex was prepared by solution precipitation method.

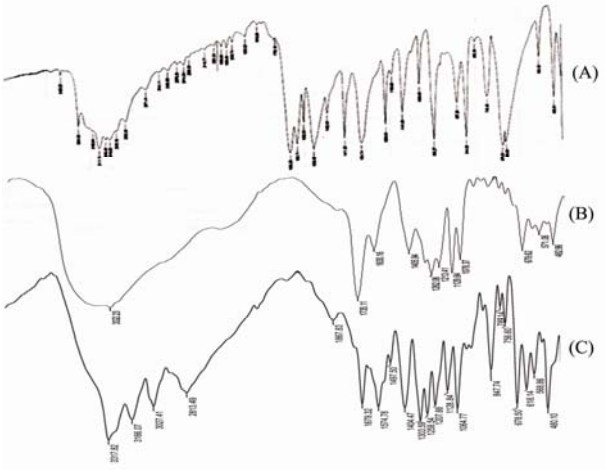

Figure No. 1 FTIR spectrums of (a) Isoniazid, (b) L(+)tartaric acid and (c) Molecular complex I

The possible interaction between the drug and the L(+)tartaric acid were studied by IR spectroscopy. The FT-IR spectrum of INH showed a strong C=O stretch (Amide) band around 1668 cm^{-1}, free NH_2 at 1220 cm^{-1}, N-H bend at 1633 cm^{-1} and 1411.9 $cm^{-1}$of pyridine. FTIR spectrum of L(+)tartaric acid showed a characteristic OH peak at 3322.23 cm^{-1} and C=O peak at 1735.11 cm^{-1}. The prepared molecular complex shows The asymmetric stretching vibration frequencies of ionized carboxylic group of tartaric acid were attributed to 1574.78 cm^{-1}. Protonated amino group of INH were observed between 3317.82 cm^{-1} and 3166 cm^{-1}. It indicates the formation of isoniazid-L(+)tartaric acid molecular complex.

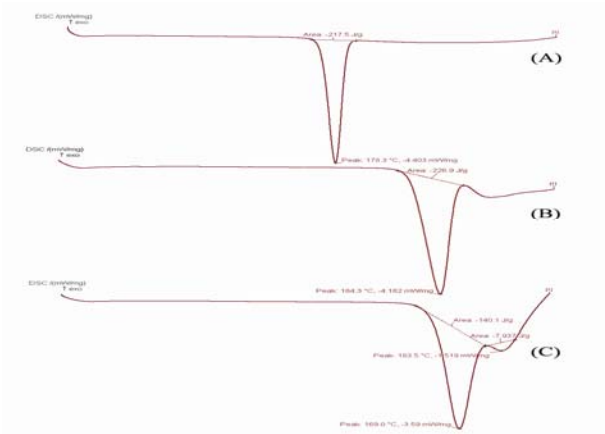

Figure No: 2 DSC thermo grams of (a) Isoniazid, (b) L(+)tartaric acid and (c) Molecular complex I

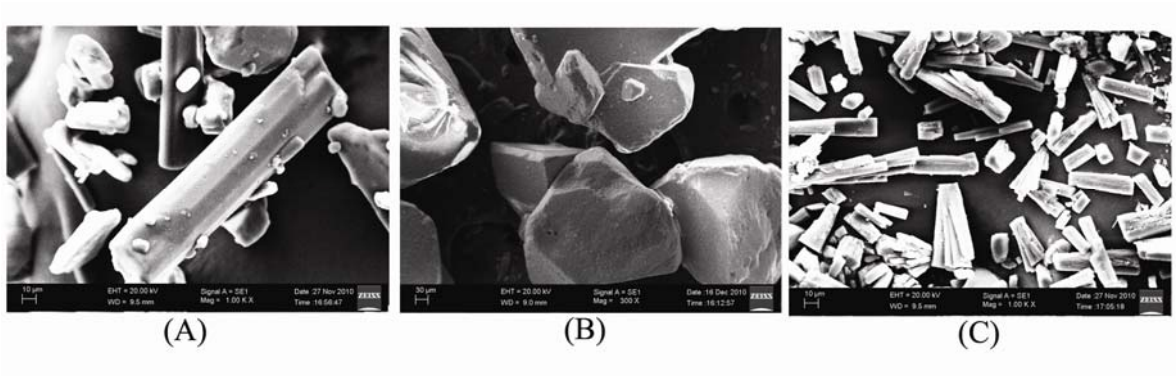

Figure No 3 : SEM photographs of (a) Isoniazid, (b) L(+)tartaric acid and (c) Molecular complex I

DSC experiments were carried out to study the thermal behavior of the molecular complex I in relation to the individual components. DSC thermal data are shown in fig. DSC study of isoniazid and L(+) tartaric acid shows endothermic peak at 178.3^{0}C and 184.3^{0}C while DSC study of prepared cocrystal shows sharp endothermic peak at 163.9^{O}C, the sharp endothermic values of molecular complex I and the individual components agreed with the measured melting range in the melting point determination. The thermal profile of molecular complex I was distinct, with a different melting transition from that seen with either of the individual components. This indicates the formation of novel molecular complex. This single endothermic transition indicates the absence of any unbound or absorbed solvent or water and also demonstrates the stability of the phase until the melting point.

SEM photography of prepared molecular complex shows uniform rod shaped crystals while INH shows small rod like crystals and L(+)tartaric acid shows irregular particles. This indicates the formation molecular complex.

Table 1 Evaluation Parameters of Isoniazid and Molecular complex I

	Isoniazid	**Molecular complex I**
Bulk density	0.59±0.027	0.38±0.004
Tapped	0.723±0.029	0.45±0.006
Angle of Repose*	23.5±0.17^o	21.13±0.570
Carr's Index*	17.02±2.009	15.48±0.17
Hauser Ratio*	1.205±0.028	1.18±0.002
Packability study:		
a*	0.007±0.0015	0.009±0.0019
b*	0.149±0.014	0.16±0.014
K*	0.0143±0.015	0.0118±0.011
Solubility studies:		
0.1N HCl	143.18±2.925	75.59003±1.907528
Distilled Water	141.06±1.75	55.5836±2.214685
pH 6.8 phosphate buffer	112.6±1.84	72.28208±1.858842

* Each value represents mean ± S.D. (n = 3)

Pure drug isoniazid exhibited poor flowability and compressibility as indicated by high value of Carr's index (17.02±2.009%), Hausner's ratio (1.205±0.028) and angle of repose (23.5±0.17^o). This could be due to the rod shape and small size of powder with stickiness, which put hurdles in the uniform flow of powder from the funnel. The prepared molecular complex I showed improved flowability and compressibility as showed by high value of Carr's index (15.48±0.17%), Hausner's ratio (1.18±0.002) and angle of repose (21.13±0.57^o)when compared to pure drug.

The solubility studies of isoniazid showed 147.60±1.80, 113.15±6.64and 107.65±2.18 mg/ml, while the prepared molecular complex showed 75.59±1.90, 55.58±2.21 and 72.28±1.85 mg/ml in 0.1N HCl, distilled water and Phosphate buffer 6.8pH respectively. This decrease of solubility may enhance its solid state stability.

Invitro dissolution studies were done for isoniazid and molecular complex I in 0.1 N HCl, distilled water and pH 6.8 phosphate buffer, and the powder dissolution profiles for Isoniazid and molecular complex I are shown in fig. respectively. The time for peak dissolution for both pure drug and molecular complex I was independent of pH. Both isoniazid and molecular complex I have similar dissolution profile in different pH medium. However, the dissolution rate for pure drug slightly higher.

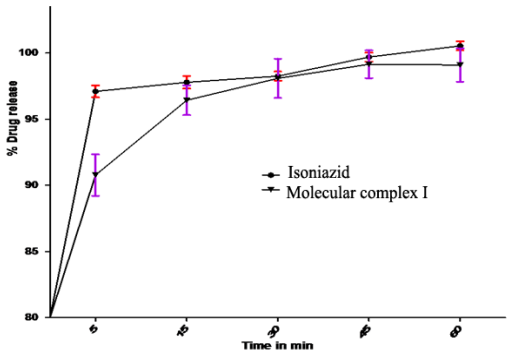

Figure No. 4 -Dissolution profiles of isoniazid and Molecular complex I respectively, in 0.1N HCl medium

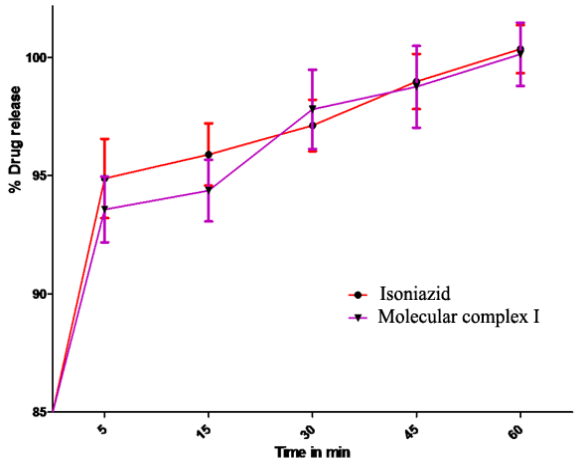

Figure No.5- Dissolution profiles of isoniazid and Molecular complex Irespectively, in Distilled water.

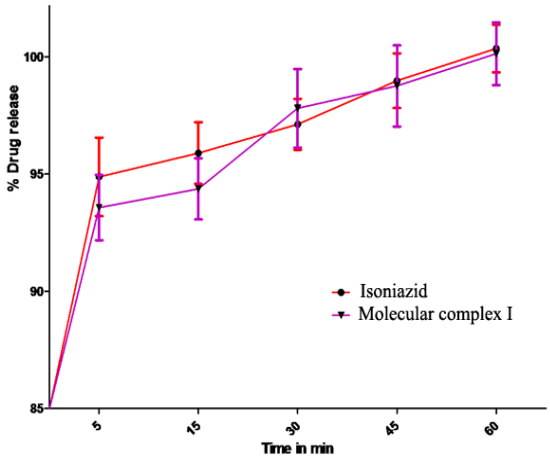

Figure No.6 Dissolution profiles of isoniazid and Molecular complex I respectively, in pH 6.8 phosphate Buffer.

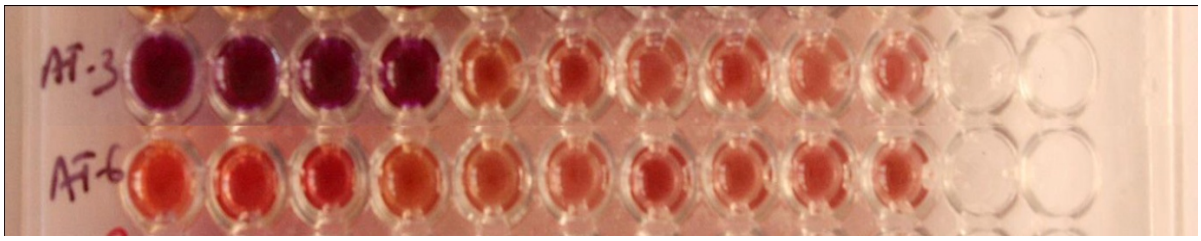

Figure No. 7. Microplate Alamar Blue assay of Isoniazid, Molecular complex I

The *in vitro antitubercular activity* of isoniazid and molecular complex I were assessed against M. tuberculosis using MABA, from our results (Fig.), both compounds shows activity upto 12.5µg/ml and 25µg/ml respectively. This indicates the molecular complex I has less antitubercular activity compare with pure drug.

CONCLUSION:

The results presented here demonstrate that reaction crystallization allows for the effective and rapid formation of Supra molecular Complex under ambient conditions, between isoniazid and L(+) Tartaric acid. It is well known that isoniazid can exhibit problems ranging from poor micromeritic properties and photo-instability. We do solve the issue of poor micromeritic properties of isoniazid by this complex with similar In-vitro dissolution. The issue of photo-instability of isoniazid will be addressed in future papers.

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