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Thermal studies of isoniazid and mixtures with rifampicin

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Abstract Rifampicin–Isoniazid mixture is a frequently used product in the treatment of tuberculosis. Rifampicin exhibits polymorphism and exists in two polymorphic forms: the stable form I and the metastable form II. The aim of this work was to evaluate the thermal behavior of the binary mixtures of polymorphs I and II of rifampicin and isoniazid by using DSC. Mixtures of different forms (rifampicin form I and II) showed interaction with isoniazid indicating that the mixtures are less stable compared to the drug alone. Interaction was observed in case of both polymorphs of rifampicin.

Keywords Drug development · Isoniazid · Rifampicin

Introduction

Rifampicin (RIF) and isoniazid (INH) are drugs available for the treatment of tuberculosis. They are administered separately or as fixed-dose combination (FDC) in both intensive and continuous phase for the treatment of all patient categories [1]. Their chemical structures are given in Fig. 1.

Fixed dose anti-tubercular products combine the most effective drugs in one formulation; this minimizes the adaptation of monotherapy by patients and hence reduces the chances of developing drug resistances [1].

However, poor bioavailability of rifampicin from a number of FDC dosage forms with isoniazid has been reported [2, 3]. This variable bioavailability of rifampicin is considered as a major obstacle in the effective implementation of this kind of products and reasons cited include physiological, polymorphism, manufacturing/processing, solid state, drug decomposition in formulations, drug decomposition in situ in stomach and bioavailability assessment procedure [4]. Unfortunately the origin and cause of the problem is not clearly understood.

Polymorphism of rifampicin is attributed as an important factor because of the alteration of bioavailability from solid oral dosage forms. It is well known that changes in polymorphic forms can affect the solubility and dissolution properties of a drug [5].

Rifampicin has two polymorphs, form I and form II, which might responsible for the differences in hydrogen bonding, conformational changes and ionization states, which allow different crystalline packing of the complex structure to occur [6].

Agrawal et al. [5] characterized solid-state properties of standard form I, form II, amorphous and commercial samples of rifampicin by using differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), hot stage microscopy (HSM), thermogravimetric analysis (TG), X-ray powder diffraction (XRD), solid-state nuclear magnetic resonance (NMR) and molecular

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Fig. 1 Chemical structures of (**1**) rifampicin and (**2**) isoniazid

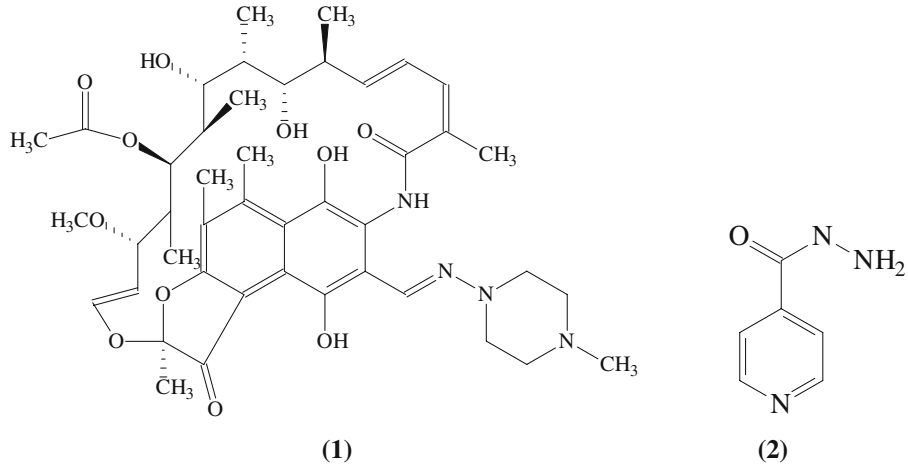

Table 1 Samples evaluated by DSC

Sample	Abbreviation
Rifampicin polymorph form I	RIF I
Rifampicin polymorph form II	RIF II
Isoniazid	INH
Isoniazid:Rifampicin polymorph form I*	INH:RIF I
Isoniazid:Rifampicin polymorph form II*	INH:RIF II

*The model mixtures were assessed at a mass ratio of 1:1

modeling. In addition, intrinsic dissolution of standard samples, powder dissolution as well as particle size distribution of all the samples were carried out in order to study the influence of polymorphism on rate and extent of dissolution. It was found that rifampicin exists in different combinations of form I, form II and amorphous and there is slight differences in solubility due to polymorphic forms.

Henwood et al. [6] also studied crystal properties of several rifampicin raw materials by X-ray diffraction (XRD), infrared (IR) spectroscopy and differential scanning calorimetry (DSC). The solubility and dissolution behavior in water, buffer pH 7.4 and 0.1 M HCl were also measured. The results showed that although the amorphous powders were more soluble than form II it did not lead to improved dissolution. In fact, in contrast to expectations an increase in amorphous content significantly reduced the dissolution rate of the powders in water and buffer pH 7.4. This behavior was attributed to the electrostatic properties of the very fine particles in the amorphous powders.

Desription of the thermal behavior of isoniazid using DSC are scarce. Kaur and Sodhi, [7] reported the thermal characteristics of organomercury complexes with isoniazid by differential thermal analysis (DTA), differential scanning calorimetry (DSC), infrared (IR) spectroscopy and mass spectroscopy (MS).

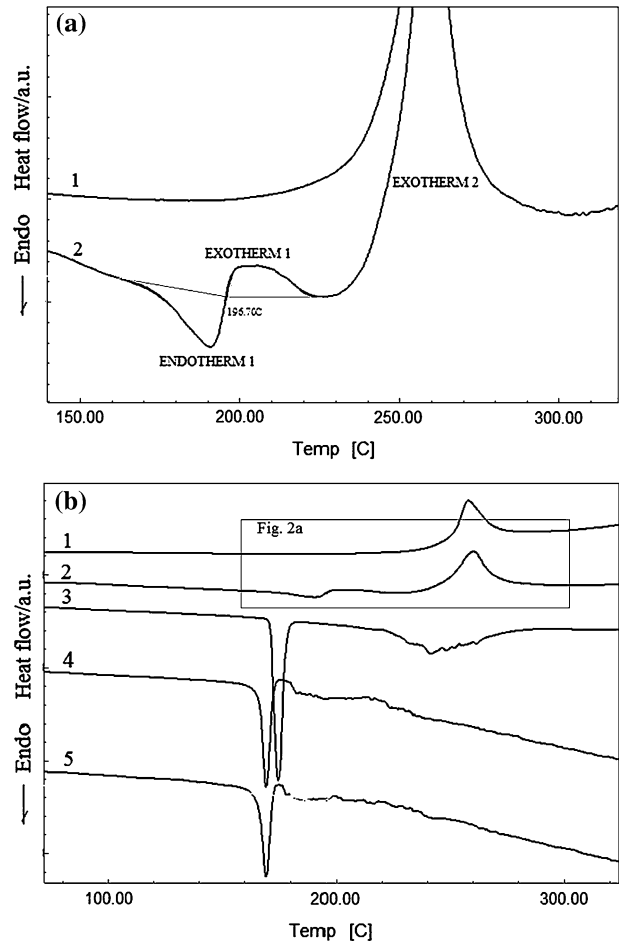

Fig 2 DSC curves of (1) RIF I; (2) RIF II. (3) INH; (4) INH:RIF I; (5) INH:RIF II. The figure **a** shows in detail the transitions of the (1) RIF I and (2) RIF II

Wesolowski and Konarski, [8] studied on the thermal decomposition by TG and DTA of tuberculostatic drugs, including isoniazid.

In Brazil, FDC capsules produced by public manufacturers and distributed by the Health Ministry contain

Table 2 Main thermal events taken from the DSC curves

Samples	DSC: transition temperature (*onset–endset*, °C) (enthalpy, ΔH, J g^{-1})		
	Endotherm	Exotherm 1	Exotherm 2
RIF I	–	–	251–270 ($\Delta H = 167$ J g^{-1})
RIF II	181–197 ($\Delta H = -31$ J g^{-1})	197–219 ($\Delta H = 23$ J g^{-1})	236–268 ($\Delta H = 187$ J g^{-1})
INH	171–178 ($\Delta H = -207$ J g^{-1})	–	–
INH:RIF I	166–173 ($\Delta H = -131$ J g^{-1})	–	–
INH:RIF II	166–173 ($\Delta H = -126$ J g^{-1})	–	–

To describe better the interaction between the two compounds the use of other solid state methods (e.g. FTIR, HSM, TG, XRD, NMR, molecular modeling and dissolution) are necessary

rifampicin and isoniazid at a 1.5:1 ratio. Despite the studies concerning these drugs separately, there is no DSC data on their mixtures.

The aim of this work was to evaluate the thermal behavior of the binary mixtures of rifampicin polymorphs I and II and isoniazid through DSC.

Experimental

Materials

Rifampicin (polymorph form I and II) and isoniazid samples used in this work were purchased by the Nucleus of Research on Food and Pharmaceuticals (NUPLAM, Natal, Brazil).

Samples and binary mixtures

Pure isonoazid, polymorphs I and II of rifampicin and their binary mixtures were investigated by DSC. (Sample names and their abbreviations can be seen in Table 1.)

DSC curves were recorded using Shimadzu DSC-60 cell. About 2 mg of samples were placed to aluminium sample holders. Dynamic N_2 atmosphere (flow rate: 50 mL min^{-1}) and 10 °C min^{-1} heating rate in 25–360 °C temperature range was used. DSC cell was calibrated with indium (*m.p.* 156.6 °C) and zinc (*m.p.* = 419.6 °C).

Results and discussion

The DSC curves of rifampicin form I and II are shown in Fig. 2a, curves **1** and **2**, respectively. The main thermal events are shown in Table 2. Form I directly decomposes as it is indicated by a sharp exothermic peak between 251–270 °C ($\Delta H = 167$ J g^{-1}). Form II exhibits distinct melting endothermic peak in the 181–197 °C temperature range ($\Delta H = -31$ J g^{-1}), followed by crystal transformation to form I between 197–219 °C ($\Delta H = 23$ J g^{-1}), which is a characteristic of solid-liquid-solid transition [5] and decomposition of form I in the range of 236–268 °C ($\Delta H = 187$ J g^{-1}).

According to Fig. 1b, curve **3** and Table 2 a single endothermic event was observed between 171–178 °C ($\Delta H = -207$ J g^{-1}), which corresponds to the melting of isoniazid according to [9]. Around 220 °C degradation of the substance takes place.

The DSC curves of the mixtures of different forms of rifampicin (Fig. 2b, curve **4** and **5**) suggest an interaction with isoniazid with displacement of the melting point of isoniazid (Fig. 2b, curve **3,** see the variation of onset temperatures from 171 to 166 °C) which indicates the decreased thermal stability of the mixture compared to the pure drug. This interaction occurred independently of the polymorphic form used. The corresponding enthalpy changes of mixtures (INH:RIF I, $\Delta H = -131$ J g^{-1} and INH:RIF II, $\Delta H = -126$ J g^{-1}) showed no significant alteration.

Conclusions

Binary mixtures of different polymorphs of rifampicin, (INH:RIF I and INH:RIF II) showed interaction with isoniazid, which can indicate that products containing the mixture of these drugs exhibit lower thermal stabilities compared to the drug alone.

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References

1. Agrawal S, Panchagnula R. Biopharmaceutic and pharmacokinetic aspects of variable bioavailability of rifampicin. Int J Pharm. 2004;271:1–4
2. Seifart HI, Parkin DP, Donald PR. Stability of isoniazid, rifampicin and pyrazinamide in suspensions used for the treatment of tuberculosis in children. Pediatr Infect Dis. 1999;10:827–31.

3. Shishoo CJ, Shah SA, Rathod IS, Savale SS, Kotecha JS, Shah PB. Stability of rifampicin in dissolution medium in presence of isoniazid. Int J Pharm. 1999;190:109–23
4. Singh S, Mariappan TT, Sankar R, Sarda N, Singh B. A critical review of the probable reasons for the poor/variable bioavailability of rifampicin from anti-tubercular fixed-dose combination (FDC) products, and the likely solutions to the problem. Int J Pharm. 2001;228:5–17.
5. Agrawal S, Ashokraj Y, Bharatam PV, Pillai O, Panchagnula R. Solid-state characterization of rifampicin samples and its biopharmaceutic relevance. Eur J Pharm Sci. 2004;22:127–44.
6. Hewood SQ, Liebenberg W, Tiedt LR, Lotter AP, Villers MM. Solubility and dissolution properties of generic rifampicin raw materials. Drug Dev Ind Pharm. 2000;26:403−8.
7. Kaur J, Sodhi GS. Thermal studies on some biologically active organomercury (II) complexes. J Therm Anal Calorim. 2001;65: 249–55.
8. Wesolowski M, Konarski T. Characteristics of the thermal decomposition of antituberculosis drugs. J Therm Anal. 1995;45:1199–204.
9. Armijo CJV. Aplicação de métodos termo-analíticos e espectroscópicos na avaliação do comportamento do fármaco isoniazida frente a adjuvantes tecnológicos. Dissertation, Postgraduate Program in Pharmaceutical Sciences, UFRGS, 2003.