

Application of thermal analysis to the study of antituberculosis drugs–excipient compatibility

Edilene Pereira Lavor · Marco Vinícius M. Navarro · Fátima D. Freire ·
Cícero F. S. Aragão · Fernanda Nervo Raffin · Euzébio Guimarães Barbosa ·
Túlio F. A. de Lima e Moura

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Abstract First-line drugs (rifampicin, RIF; isoniazid, INH; ethambutol, ETA; and pyrazinamide, PZA) recommended in conventional treatment of tuberculosis were analyzed in 1:1 w/w binary mixtures with microcrystalline cellulose MC 101 (CEL) and lactose supertab[®] (LAC) by differential scanning calorimetry (DSC), thermogravimetry (TG), differential thermal analysis (DTA), and Fourier transformed infrared analysis (FTIR) as part of development of fixed dose combination (FDC) tablets. Evidence of interaction between drug and pharmaceutical excipients was supposed when peaks disappearance or shifting were observed on DTA and DSC curves, as well as decreasing of decomposition temperature onset and TG profiles, comparing to pure species data submitted to the same conditions. LAC was showed to interact with RIF (absence of drug fusion and recrystallization events on DSC/DTA curves); INH (thermal events of the mixtures different from those observed for drug and excipient pure in DSC/DTA

curves); PZA (decrease on drug fusion peak in DSC/DTA curves), and ETA (shift on drug onset fusion and absence of pure LAC events on DSC/DTA curves). In all cases, an important decrease on the temperature of drug decomposition was verified for the mixtures (TG analysis). However, FTIR analysis showed good correlation between theoretical and experimental drug–LAC spectra except for INH–LAC mixture, evidencing high incompatibility between these two species and suggesting that those interactions with PZA and RIF were thermally induced. No evidence of incompatibilities in CEL mixtures was observed to any of the four-studied drugs.

Keywords Excipient compatibility · Thermal analysis · FTIR · Antituberculosis drugs

E. P. Lavor
Laboratório de Desenvolvimento de Medicamentos, Programa de Pós-Graduação em Ciências Farmacêuticas, Universidade Federal do Rio Grande Do Norte (UFRN), R. Brigadeiro Cordeiro de Farias, s/n, Petrópolis, Natal, RN CEP 59010-180, Brazil

M. V. M. Navarro · F. D. Freire
Programa de Pós-Graduação em Desenvolvimento e Inovação Tecnológica em Medicamentos, Universidade Federal do Rio Grande Do Norte (UFRN), Campus Universitário, s/n, Lagoa Nova, Natal, RN CEP 59078-970, Brazil

C. F. S. Aragão
Laboratório de Controle de Qualidade de Medicamentos, Departamento de Farmácia, Universidade Federal do Rio Grande Do Norte (UFRN), R. Brigadeiro Cordeiro de Farias, s/n, Petrópolis, Natal, RN CEP 59010-180, Brazil

F. N. Raffin · T. F. A. de Lima e Moura (✉)
Laboratório de Desenvolvimento de Medicamentos, Departamento de Farmácia, Universidade Federal do Rio Grande Do Norte (UFRN), R. Brigadeiro Cordeiro de Farias, s/n, Petrópolis, Natal, RN CEP 59010-180, Brazil
e-mail: mouratf@hotmail.com

E. G. Barbosa
Laboratório de Química Farmacêutica, Departamento de Farmácia, Universidade Federal do Rio Grande Do Norte (UFRN), R. Brigadeiro Cordeiro de Farias, s/n, Petrópolis, Natal, RN CEP 59010-180, Brazil

Introduction

As tuberculosis has been declared by World Health Organization (WHO) to be a global emergency, a number of combination of first class drugs medications (rifampicin, isoniazid, pyrazinamide, and ethambutol) are in use nowadays with emphasis to FDCs of the three or four of nominated drugs [1, 2]. However, efforts to combat the disease through the use of these drugs are not problem free [1–4].

A rational development of medications should be done to minimize the risk of undesirable results that is why it is essential to characterize physicochemical properties, assess its stability, as well as compatibility between active substance and excipient throughout the manufacturing process and storage, aiming to obtain a good quality final product [4, 5]. In addition, bioavailability of drugs can be influenced by formulation factors, the active ingredient quality, excipients, as well as compatibility and the process used in manufacturing and packing [3, 6].

The main thermal analyses used in the pharmaceutical industry are differential scanning calorimetry (DSC) and thermogravimetry (TG) for the development of pharmaceutical formulations, to check thermal characterization of drugs, compatibility studies in the development of a new pharmaceutical formulation, polymorphs identification, stability assessment, used in quality control, since variations in the physicochemical properties of drug can have an impact on therapeutic levels, manufacturing, commercial, and legal [6–11].

DSC or DTA alone does not provide conclusive results about incompatibilities between components of a mixture; however, it is an extremely agile, clean, and simple technique to perform and interpret, for providing secure evidences of interactions between these components. In a decision tree, the absence of any evidence of incompatibility in a mixture resulting of a DSC or DTA analysis dispenses the use of complementary techniques, which are often time consuming, complex, and difficult to implement. On the other hand, if a resulting DSC or DTA curve of a mixture presents shift towards lower or higher temperature above 5 °C, disappearance of the characteristic peaks or shows new peaks/thermal events which were absent in the curves of pure compounds, then there is evidence of any thermally induced interaction which justifies the use of complementary analytical techniques such as XRD, NMR, liquid chromatography–tandem mass spectrometry (LC–MS/MS), and FTIR analysis [5, 12–15].

IR spectrum gives a fingerprint of a sample, as each material is a unique combination of atoms, therefore IR spectroscopy can be used as a powerful tool for qualitative identification of different materials [16]. FTIR offers ease of spectra collection and interpretation because its ease of operation, minimal sample preparation, and it is fast, high

sensitive, reliable, and robust analysis; furthermore, FTIR can be applied to powdered or aqueous samples and the spectrometer can be modified in order to analyze very small samples [17, 18].

The main aim of this study was to assess compatibility of antituberculosis drugs—rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (ETA) and common pharmaceutical excipients [microcrystalline cellulose (CEL) and supertab lactose (LAC)] in binary mixtures by DSC, TG, DTA, and FTIR as a part of the development of FDC tablets.

Experimental

Drugs and excipients

RIF 100.47 % from Novartis Co., Ltd, INH 99.60 % from AMSAL CHEM Co., Ltd, PZA 99.09 % from Davilson Co., Ltd, ETA 98.94 % from Hildose Co., Ltd, Microcrystalline cellulose MC 101[®] and Lactose Supertab[®] supplied by Blanver Farmoquímica Co., Ltd.

Preparation of the samples

Binary mixtures were prepared at 1:1 (w/w) rate between active and excipients ingredients; by homogenizing for 10 min through a geometrical dilution method.

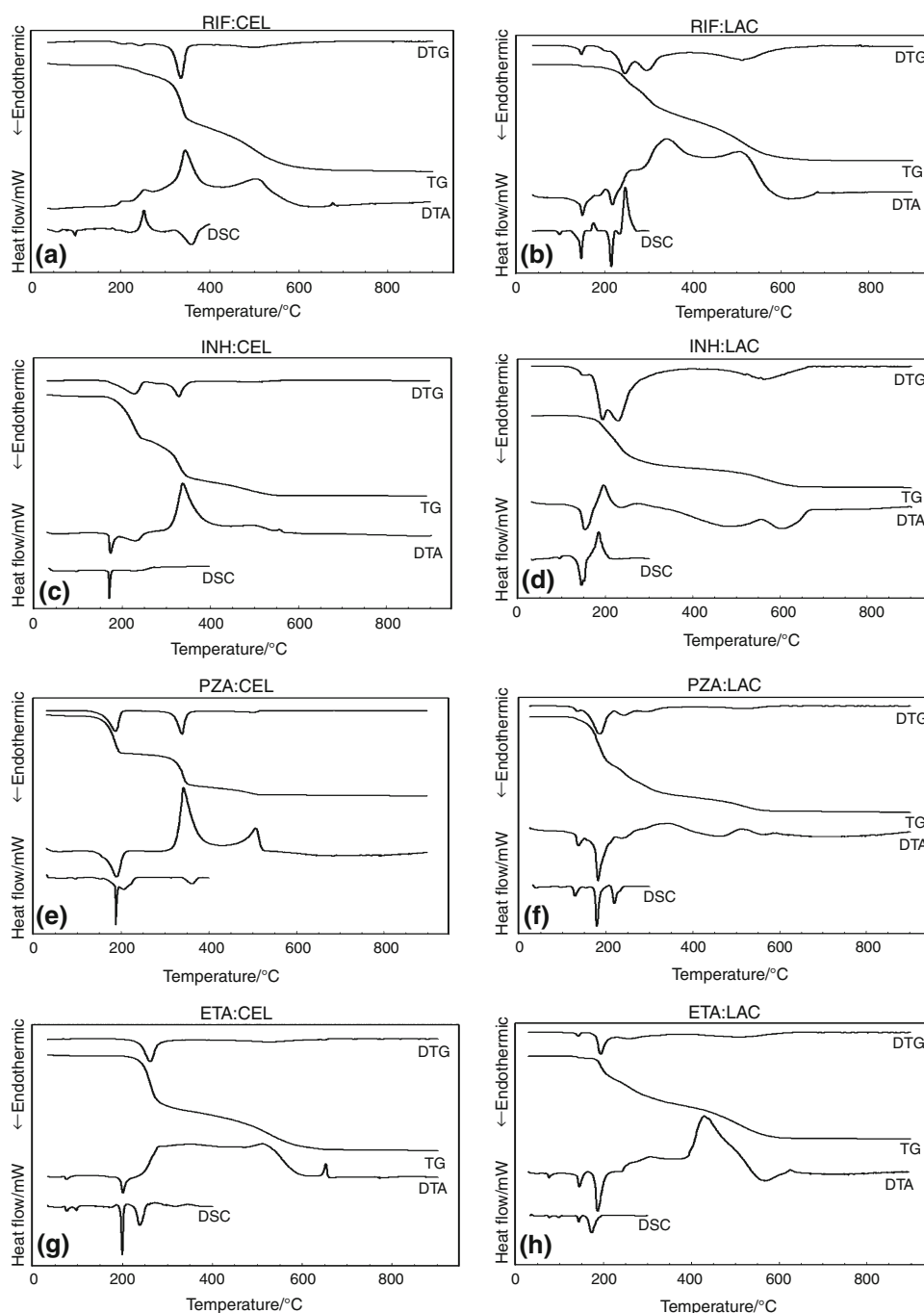
Measurements

DSC curves were obtained by using a Shimadzu DSC-60 cell, using closed aluminum pans with about 2 mg of samples, under dynamic atmosphere of N₂ (50 mL min⁻¹) at a heating rate of 10 °C min⁻¹ in the temperature ranging from 25 to 400 °C to CEL and from 25 to 300 °C to LAC.

Highly pure Zn and In were used to calibrate the DSC equipment where experiments were run at 200 and 500 °C, respectively. Through their melting points (156.65 and 419.50 for In and Zn, respectively) the areas under the peaks were determined. Once the correction of the calibration temperature was performed, the heat calibration was corrected in which the enthalpy value for In and Zn were 28.5 and 100.5 J g⁻¹, respectively. Further, new experiments were performed to assure that the melting temperature varied in the range of ±0.5 °C and the values of ΔH in the range of ±1.0 J g⁻¹. Once these parameters were reached, the calibration was accomplished.

On the other hand, the DTA equipment was calibrated using In, where it was heated up to 200 °C followed by the correction of the calibration temperature. Next, another

Fig. 1 DSC, TG, and DTA curves of binary mixtures of antituberculosis drugs and excipients: **a** RIF + CEL, **b** RIF + LAC, **c** INH + CEL, **d** INH + LAC, **e** PZA + CEL, **f** PZA + LAC, **g** ETA + CEL, and **h** ETA + LAC



experiment was run with the purpose of checking whether the melting temperature varied in ± 0.5 °C.

TG/DTG and DTA curves were obtained using a thermobalance Shimadzu model TGA 60 in the temperature interval between 25 and 900 °C, using aluminum pan with 4 mg of samples, under dynamic atmosphere of synthetic air (50 mL min^{-1}) at the heating rate of 10 °C min^{-1} .

The IR spectra were obtained in an IRPrestige-21—Schimadzu measured in % Transmittance, later converted to absorbance. The number of scans was 10 and the resolution was 4.0 cm^{-1} ranging from 400 to $4,000 \text{ cm}^{-1}$. In order to

detect interactions between the active and excipients ingredients a correlational IR analysis was performed. Such analysis was carried out by importing the IR spectral data in ASCII format into Matlab software. The spectral region from 400 to $1,940 \text{ cm}^{-1}$ was considered in this approach. A theoretical IR spectrum of the active and excipients ingredients was built but the linear combination of the experimental spectra of the drugs and excipients. Subsequently, the Pearson correlation (r) between the theoretical and experimental drug-excipient IR spectra was calculated. The deviation from ideality ($r = 1$) was interpreted as an

indication of problems for a particular drug–excipient mixture analyzed. The comparison of the IR spectra of pure and binary drug mixture is widely used in the pharmaceutical literature. We are proposing an approach, in spite of being simple, seems not to have been used straightforwardly by authors in this field.

Results and discussion

In our previous work, we showed the main thermal events for tuberculostatic drugs by using TG and DSC analysis, where we highlighted the fusion ranges for RIF, INH, PZA, and ETA of 181–196 °C ($\Delta H = -11 \text{ J g}^{-1}$), 173–177 °C ($\Delta H = -222 \text{ J g}^{-1}$), 192–195 °C ($\Delta H = -195 \text{ J g}^{-1}$), and 196–204 °C ($\Delta H = -110 \text{ J g}^{-1}$), respectively. The onset temperature for the first decomposition step of RIF, INH, PZA, and ETA were 190, 170, 150, and 232 °C, respectively. Superposition of DSC, DTA, and TG/DTG curves indicated that among the four drugs studied, ETA was the only one whose fusion did not occur with concurrent decomposition [7]. The main thermal events considered for the interaction and compatibility studies were the melting and the first decomposition step of the drugs as well as the excipients. A temperature range up to 400 °C was arbitrarily chosen for the DSC experiments.

DSC and DTA curves of CEL showed two endothermic peaks in the range between 89 and 102 °C ($\Delta H = -5 \text{ J g}^{-1}$) and 326–369 °C ($\Delta H = -140 \text{ J g}^{-1}$), where the first one can be attributed to the elimination of superficial water and the second to its decomposition by pyrolysis [11]. DSC curve of LAC has a similar profile when compared to those of lactose monohydrate, showing an endothermic peak between 144 and 153 °C ($\Delta H = -132 \text{ J g}^{-1}$), which corresponds to the loss of water of crystallization, followed by an exothermic peak between 193 and 209 °C ($\Delta H = 10 \text{ J g}^{-1}$) corresponding to a

crystalline transition of anhydrate lactose from α to β . Fusion of β -lactose occurs between 213 and 225 °C ($\Delta H = 139 \text{ J g}^{-1}$), with its decomposition occurring right after [19–21].

The thermal curves for binary mixtures of RIF, INH, PZA, and ETA with CEL (Fig. 1a, c, e, g), show all thermal events related to the isolated species with a superposition of the individual curves. Since these curves are the sum of thermal events observed in the individual components it is likely to assume that no interaction took place between these species and therefore, the absence of physical–chemical incompatibilities cannot be ruled out.

DSC/DTA curves of RIF:LAC showed that the dehydration, crystalline transition, and fusion of LAC as well as the exothermic decomposition of RIF were preserved. However, the fusion and recrystallization peaks of RIF disappeared. In addition, TG/DTG curves for RIF:LAC binary mixture showed that the decomposition started 63 °C lower than that of the pure drug. This finding suggests that some interaction between LAC and RIF took place. Although the dissolution of RIF in the melted LAC could be possible, a shift in the decomposition temperature to a significant lower value is an evidence of drug/excipient interaction thermally induced (Table 1).

DSC and DTA curves of INH:LAC (Fig. 1d) show that although the dehydration peak of LAC was preserved, the onset temperature shifted 20 °C below that observed for pure lactose. Furthermore, all other peaks in the individual curves were replaced by a single exothermic peak in the DSC curve for the binary mixture. The onset temperature of the first decomposition step of the mixture on the TG/DTG curve decreased 30 °C compared to that of pure INH, suggesting strong interaction between INH and LAC. This interaction may be ascribed to a Maillard-type reaction, a well-known reaction that occurs between a reducing sugar, e.g., lactose and primary or secondary amine. Since isoniazid have a primary amine group bound to a secondary

Table 1 Enthalpy changes associated to the thermal events determined by DSC measurements for each binary mixture *active component/excipient*

Sample	1st event		2nd event		3rd event		4th event	
	$\Delta T/^\circ\text{C}$	$\Delta H/\text{J g}^{-1}$	$\Delta T/^\circ\text{C}$	$\Delta H/\text{J g}^{-1}$	$\Delta T/^\circ\text{C}$	$\Delta H/\text{J g}^{-1}$	$\Delta T/^\circ\text{C}$	$\Delta H/\text{J g}^{-1}$
RIF + LAC	146–151	–35.0	194–208	7.0	213–223	–73.0	242–260	100.0
RIF + CEL	94–102	–5.0	244–260	35.0	337–378	–35.0	–	–
INH + LAC	139–148	–20.0	150–156	–55.0	174–192	–110.0	–	–
INH + CEL	91–100	–5.0	168–174	–80.0	–	–	–	–
PZA + LAC	124–138	–55.0	175–184	–175.0	213–225	–70.0	–	–
PZA + CEL	92–100	–3.0	186–192	–52.0	197–229	–55.0	340–374	–68.0
ETA + LAC	73–81	–5.0	94–101	–5.0	140–148	–15.0	165–181	–75.0
ETA + CEL	73–82	–5.0	94–101	–5.0	196–202	–50.0	230–251	–60.0

ΔT temperature range between onset and endset temperature of each thermal event

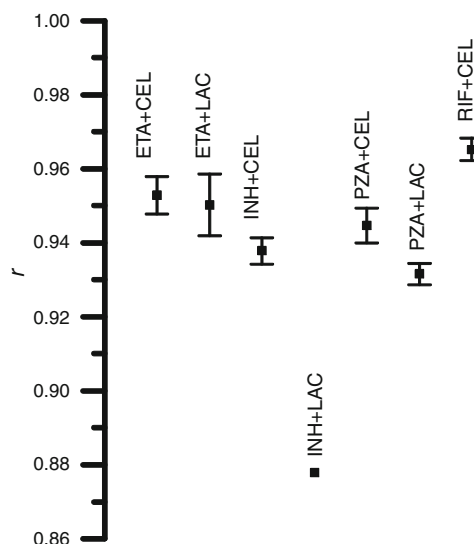


Fig. 2 Plot of the Pearson's correlation (r) between the theoretical and experimental drug-excipient IR spectra

nitrogen of the acetamide group, it is likely that this drug could undergo Maillard-type reactions under optimal conditions [20, 21].

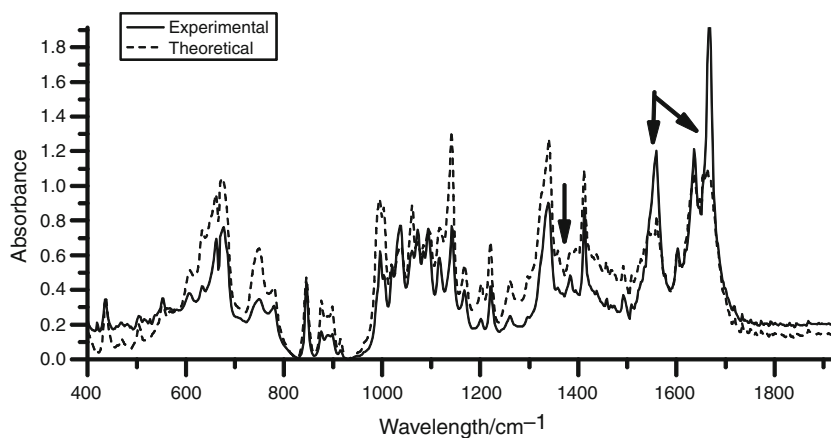
TG/DTG curves for PZA:LAC mixture show that the loss of mass occurred in five different steps: between 129 and 145, 145 and 204, 204 and 264, 264 and 471, and 471 and 589 °C, with mass loss of 3, 43, 19, 23, and 10 %, respectively. DSC and DTA curves of the binary mixture PZA:LAC also show a decrease of around 13 °C in the onset temperature of the melting point as well as disappearance of thermal events that were initially observed in the isolated species (Fig. 1f). In addition, a marked reduction of 21 °C was observed on the onset of the first decomposition step of the TG curve of the mixture compared to that of the pure drug. It is important to note that PZA has a primary amine that forms a carboxamide (acetamide) moiety, which is able to undergo Maillard-type

reactions and therefore, the interaction observed can be considered strong evidences of thermal-induced incompatibilities between the drug and excipients.

TG/DTG curves of ETA-LAC mixture show loss of mass in three steps: between 172 and 236, 236 and 378, and 378 and 624 °C, with losses of 28, 29, and 40 %, respectively. Decomposition started at 60 °C below of that observed for pure ETA, which is in consonance with DCS/DTA data. DSC and DTA curves for ETA:LAC (Fig. 1h) also show a change in the onset temperature of the melting peak of ETA as well as the disappearance of some characteristic peaks related to LAC. However, it should be noted that although ETA has a secondary amino group in its structure (less prone to undergo Maillard reactions than primary amino groups), the disappearance of peaks of LAC cannot be unequivocally related to some interaction/incompatibility because the exothermic crystalline transition peak of LAC (between 193 and 209 °C) coincides with the melting peak of ETA (between 196 and 204 °C). Besides, the melting/decomposition peaks of LAC (between 213 and 225 °C) also coincides with the decomposition peak of ETA (215–278 °C).

It is worth mentioning that although current DSC has an unquestionably value for incompatibility studies, their results can hardly be interpreted directly and usually need to be confirmed by other analytical techniques such as FTIR analysis. The correlational analysis between theoretical and experimental drug-excipients IR spectra is shown in Fig. 2. The comparison of the IR spectra between pure drug and excipient and their mixture is useful to pinpoint drug-excipient interactions. The very same analysis was carried out, but in an automatic and quantitative fashion by the calculation of the Pearson's correlation of computer generated (theoretical) mixture spectra and actual mixtures. We propose that the more the computed correlations deviate from the unit, the more drug-excipient interactions are present. Figure 2 shows the results for such analysis made in triplicates.

Fig. 3 Overlapping of experimental and theoretical IR spectra. The arrows indicate to the major peaks displacement when comparing the spectra



The values are shown in squares (■) and the standard deviation of three different experimental IR spectra correlation analysis is shown in error bars.

It can be observed in Fig. 2 that the INH + LAC mixture was the sample that mostly deviate for the ideal correlation ($r = 1$). This can be related to a reaction of LAC and INH molecules resulting in a greater difference in the IR spectra. INH is known to be incompatible with reducing sugar that bears aldehydes in its structure due to condensation reaction of LAC with INH which may explain such correlation deformation [20]; such reactions are stronger with primary amino groups and less evident with secondary amino groups which explains the low reactivity observed in RIF-LAC mixture. The second most unstable mixture is the PZA + LAC. The amide group in PZA has low reactivity compared with INH amine probably due to the withdrawing effect of oxygen in nitrogen vicinity. Another advantage of the IR spectra correlation analysis relative to the thermal analysis is the lack of heat-induced alterations to the mixture. Therefore, among mixtures containing lactose stability followed the sequence INH:LAC < PZA:LAC < ETA:LAC < RIF:LAC.

The remaining drugs showed almost perfect correlation with the theoretical drug-exipients IR spectra. Figure 3 shows the main pattern dislocation in the IR spectra. A peak in $1,380\text{ cm}^{-1}$ and the peaks in $1,558$ and $1,666\text{ cm}^{-1}$, the later likely to be related to carbonyl bond stretching, are significantly modified.

It is noteworthy that even taken into account that in experiments in TG, DSC, and DTA samples are subjected to a thermal stress that will not be experienced by a formulation containing these species, it is well known that Maillard-type reactions play important role in stability reactions in pharmaceutical formulation [22] and as the drugs studied in this work contain primary and secondary amino moieties able to undergo Maillard reactions our results show clear indications of possible incompatibilities that should not be neglected in the development of formulation containing lactose or other reduction sugars with these antituberculosis drugs.

Conclusions

DSC, DTA, and TG/DTG curves for all binary mixtures with cellulose did not show interaction. However, fusion peaks on DSC curves of the drugs with lactose shifted to lower temperatures and the absence of events characteristic of the pure compounds as well as the anticipated decomposition of the drugs showed by TG/DTG curves suggest physicochemical interactions. A classical interaction with incompatibility effect of isoniazid and pyrazinamide with the reducing sugar lactose was revealed by the analysis of

the Pearson's correlation of IR spectra being the former more evident. Such approach proved to be a useful tool to analyze drug-exipient interactions.

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