J Therm Anal Calorim (2011) 104:307–313
DOI 10.1007/s10973-010-1185-y

# Thermal characterization of antimicrobial drug ornidazole and its compatibility in a solid pharmaceutical product

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Received: 8 August 2010 / Accepted: 11 November 2010 / Published online: 7 January 2011


**Abstract** The ornidazole drug substance presents melt at approximately 90 °C ($\Delta T$ = 85–98 °C), which is critical for its use on pharmaceutical manufacturing process. This work aimed the thermal characterization of ornidazole raw-material synthesized by three different manufacturers from India, China, and Italy, using the thermoanalytical techniques of DTA, DSC, and TG, besides the verification of its stability and compatibility as a solid pharmaceutical product by the analysis of its binary mixtures (BM) with excipients and a tablet formulation. The characterization includes the thermal decomposition kinetic investigation by Ozawa model using Arrhenius equation and drug purity determination by Van't Hoff equation. The DSC purity determination and precision were compared with results from UV–Vis spectrophotometric and liquid chromatography, showing an adequate correlation before being recommended as a general method for purity assay. The drug raw-materials presented similar quality and zero-order kinetic behavior, besides showing differences on thermal stability. The drug presented compatibility with the tested excipients since the BM studied presented melting at the same temperature range as the drug and a decomposition temperature similar to the drug for two of the BM, and at a higher temperature for the others three of the BM evaluated, which presented excipients with higher molecular structure, capable of spatial coating on the small drug molecule promoting a physical interaction pharmaceutical acceptable. The tablet was processed by wet granulation and compressed under normal conditions of pressure and temperature, maintaining the physical properties of solid drug approving the manufacturing process used. In this study, the thermal analysis was used with success as an alternative method to characterize, quantify, and perform a preformulation study.

**Keywords** Ornidazole · Excipients · Purity assay · Thermal analysis · Compatibility

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## Introduction

The ornidazole [1-(2-hydroxy-3-chloropropyl)-2-methyl-5-nitro-imidazole] (Fig. 1), a synthetic derivative of 5-nitro-imidazoles, has anti-protozoan and antibacterial properties against anaerobic bacteria. The antimicrobial activity of this compound is due to reduction of the nitro group to a more reactive amine group that attacks microbial DNA, inhibiting further synthesis, and leading to degradation of existing DNA [1, 2]. Ornidazole has a chemical structure and a pharmacological action similar to metronidazole. The metronidazole is considered as the drug of choice of the pharmacological class, however, the ornidazole has some therapeutic advantages compared with metronidazole, presenting a higher half-life time, 12–14 h versus 6–8 h, respectively, resulting in the reduction of both the dose

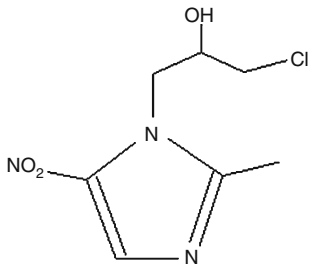


**Fig. 1** Chemical structure of ornidazole

frequency and treatment duration in respect of most major clinical infections [3, 4].

In the development of a solid pharmaceutical product of ornidazole drug substance, the drug low melting point is critical for supporting some of the manufacturing processes available without change its physical state, which may present interference in its bio-availability or chemical entirety. Therefore, previous knowledge of the physical–chemical characteristics of the drug and excipients is necessary, as well as the investigation of their compatibility, the kinetics determination, and degradation parameters. The thermoanalytic techniques are widely used in the pharmaceutical industries as fast and precise techniques of quality control and products development [5–8], including thermal characterization [9–12], drugs stability studies [13–15], preformulation and compatibility studies [16, 17], as well as manufacturing process study and suppliers' qualification [18].

This study aimed the characterization of antimicrobial drug ornidazole raw-material, synthesized by three differents manufacturers, and the compatibility evaluation of this drug as a solid pharmaceutical product by analyzing physical binary mixtures (BM) of the drug associated with specified pharmaceutical excipients and a tablet formulation (TF). The characterization includes the thermal decomposition kinetic investigation using Ozawa model [19] and Arrhenius equation [20], and the drug purity determination by Van't Hoff equation [21]. The accuracy and precision of purity results obtained with thermal analysis were compared with the results obtained by UV–Vis spectrophotometric and HPLC methods [22].

## Materials and methods

The ornidazole drug (MW = 219.63 g $mol^{-1}$) analyzed was synthesized by three different manufactures, denominated as A (from India, declared assay of 100.12%), B (from China, declared assay of 99.0%), and C (from Italy, declared assay 99.28%). The working standard was donated by Gemine Exports. The reference medicine Tiberal® (Roche) was bought from the market (batch B1080).

The drug substance purity determination and the decomposition kinetic investigation were conducted for all suppliers (A, B, and C). Then, the BM samples (1:1, w/w) and the TF, used on the stability study, were conducted just with the raw material from supplier A, because of the large amount of material available.

All pharmaceutical excipients studied (corn starch, croscarmellose sodium, magnesium stearate, microcrystalline cellulose 101, and polyvinylpyrrolidone) were donated by Apsen Farmacêutica S.A. The TF consists of all excipients tested by the BM, being manufactured by wet granulation process, where granules were dried in a hot air-circulating chamber (50 °C) and compressed by an industrial rotary compressor. With thermocouples used to measure the temperatures reached in the compression process, characterized as exothermic, the temperatures of the process was assumed to be about 90 °C.

### Differential thermal analysis (DTA) and differential scanning calorimetry (DSC)

The DTA was used for samples' characterization and compatibility investigation, whereas the DSC was used for drug purity determination. The DTA curves of drug, excipients, BM, and TF were obtained using a Shimadzu DTA-50 cell. Alumina pan with 8.0 mg (± 0.5) of samples under a nitrogen flow at 50 mL $min^{-1}$ and heating rates of 10 °C $min^{-1}$ up to 500 and 30 °C $min^{-1}$ up to 900 °C, were used as process conditions.

The DSC curves were obtained using a Shimadzu DSC-50 cell. Aluminum pan with 5.0 mg (±0.5) of samples under a nitrogen flow at 50 mL $min^{-1}$ and heating rate of 10 °C $min^{-1}$ up to 500 °C was used for the process. The DTA and DSC cells were calibrated using indium ($T_{fus}$ = 156.6 °C; $\Delta H$ = 28.54 J $g^{-1}$) and zinc ($T_{fus}$ = 419.6 °C; $\Delta H$ = 108.40 J $g^{-1}$).

### Thermogravimetry (TG)

For kinetic determination, non-isothermal TG curves were obtained using a Shimadzu thermobalance, model TGA–50H. Platinum pan with 8.0 mg (±0.5) of sample under a nitrogen flow at 50 mL $min^{-1}$ and heating rates of 10, 15, and 20 °C $min^{-1}$ up to 900 °C was used for the process.

#### Purity determination

A UV–Vis Spectrophotometric and High Performance Liquid Chromatography (HPLC) methods were used to quantify the ornidazole drug [22], and the data obtained with these two methods were used for the precision and

accuracy comparison with the obtained data using the thermal analysis method and the Van't Hoff equation.

## Results and discussion

### Thermal characterization of ornidazole

The ornidazole' DTA curve showed an endothermic process characteristic of melting in the range of 85–98 °C, with a melting peak at 90 °C and enthalpy value of 122 J $g^{-1}$, corresponding to the melting range described in literature [3]. The exothermic process, characteristic of decomposition, was evidenced in the range of 212–236 °C, with decomposition peak at 228 °C and enthalpy value of 514 J $g^{-1}$ (Fig. 2).

The three raw materials' authenticity and quality can be verified since no significant differences between the averages from the melting and decomposition peaks were obtained on analyzing the work standard and the raw materials available by DTA, using Turkey's statistical test with 5% significance (Fig. 2 and Table 1). The TG curves showed a similarity in the thermal decomposition behaviors of the raw materials and work standard, being thermally stable until 232 °C, presenting a main stage of decomposition between 232 and 264 °C, with a mass loss of 47%, equivalent to the molecular weight of 103 g $mol^{-1}$.

### Kinetic investigation by Ozawa

The Ozawa model was used to determine the kinetic parameters, such as apparent activation energy ($E_a$), frequency factor ($A$), and reaction order ($n$), using the data obtained with the dynamic thermogravimetry study (TG) (Table 2). The calculated data showed one kinetic behavior of zero-order for ornidazole. The kinetic parameters of thermal decomposition from the raw materials analyzed under three heating rates (10, 15, and 20 °C $min^{-1}$), considering the same fraction decomposed ($\alpha = 0.1$–$0.9$), presented the following ascending order B < C < A. This result suggests that the raw material ornidazole from the manufacturer B showed, under the heating rates of 15 and 20 °C $min^{-1}$, mass loss occurring in the main stage at lower temperatures than those of A and C. This TG profile differentiation can be assigned by differences between crystalline and physical characteristics of the compounds, which could be confirmed by the Scanning Electron Microscopy (SEM) and the X-ray diffraction (DRX) analyses.

**Table 1** Thermal behavior of ornidazole raw-materials supplied by manufactures A, B and C

| Ornidazole | $T_{fus}$/°C | $\Delta H_{fus}$/ J $g^{-1}$ | $T_{decomposition}$/°C | $\Delta H_{decomposition}$/ J $g^{-1}$ |
|---|---|---|---|---|
| Standard | 90.45[a] | −122.43 | 228.17[b] | 514.36 |
| Supplier A | 92.17[a] | −121.81 | 227.95[b] | 495.49 |
| Supplier B | 90.77[a] | −119.71 | 228.77[b] | 542.28 |
| Supplier C | 92.12[a] | −123.38 | 227.87[b] | 530.14 |

[a,b] Equal letters indicate, with 95% of security, no significant difference among the respective averages and among suppliers

**Table 2** Ornidazole raw materials' thermal decompositions kinetic, manufactures A, B, and C

| Ornidazole | Reaction order/$n$ | $A$/$min^{-1}$ | $E_a$/Kj $mol^{-1}$ |
|---|---|---|---|
| A | 0 | 8.908E + 11 | 126.44 |
| B | 0 | 1.321E + 04 | 50.39 |
| C | 0 | 1.343E + 08 | 91.07 |

### Ornidazole purity determination by Van't Hoff equation

The Van't Hoff equation is based on purity determination of substances that exhibit melting peaks defined by

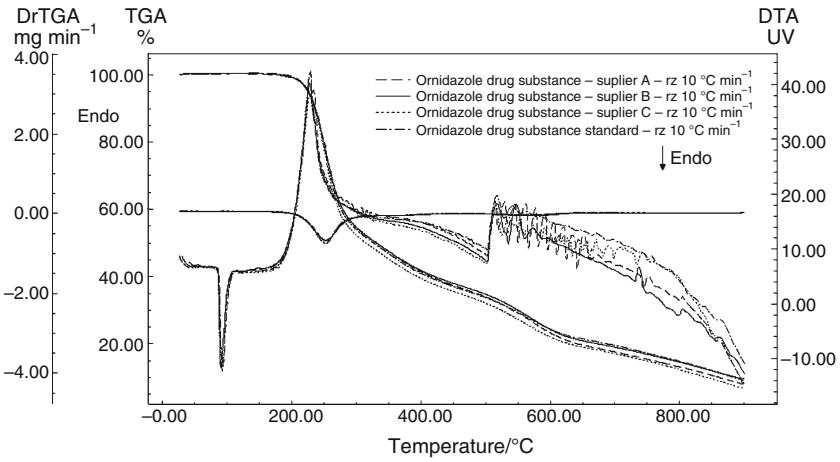


**Fig. 2** DTA and TG curves of ornidazole: work standard and raw materials, supplied by manufactures: A, B and C

evaluating several parameters, such as small fractions of impurities, peak shift, and other parameters involving the extent of drug purity. The data obtained by DSC were treated with the Van't Hoff equation to determinate the drug purity. The values obtained were compared with values obtained by two other analytic techniques developed and validated [22].

All raw materials presented purity in accordance with the specification limit established between 98 and 101% (dried basis), for being approved for medicine production process. No statistically significant differences among the raw materials from different manufacturers and among different analytic techniques were shown, with 5% significance, according to the Turkey statistical test (Table 3).

Based on the results, the results obtained by the thermal analysis method proved to be statistically comparable to the other two methods, spectroscopy and chromatography, which are traditionally accepted by the pharmacopoeias and, therefore, could be considered as an alternative method for this drug assay in the quality control laboratories (Table 3).

**Table 3** Drug purity determination

| Ornidazole | DSC/% | HPLC/% | UV/Vis Spectro/% |
|---|---|---|---|
| Standard | 99.68 a/1 | 100.10 b/1 | 100.48 c/1 |
| Supplier A | 98.12 a/2 | 99.69 b/2 | 100.22 c/2 |
| Supplier B | 98.09 a/3 | 99.22 b/3 | 100.39 c/3 |
| Supplier C | 98.03 a/4 | 99.28 b/4 | 99.90 c/4 |
| RSD | 0.097 | 0.916 | 0.235 |

a, b, c: Equal letters indicate, with 95% of security, no significant difference among the respective averages among suppliers' assay. 1, 2, 3, 4: Equal numbers indicate, with 95% of security, no significant difference among the respective average among techniques assay

Preformulation study

Through the BM DTA curves, it can be observed that there were no significant variations in drug melting points ($T_{fus}$) for all BM studied. On the other hand, for the decomposition peak, a significant shift in three of the five BM studied was observed. The shift showed that this process occurred at higher temperatures and can be considered as a physical interaction, without chemical reactions, because once mixed together, the two components of the BM are replaced by a different thermal behavior. In this case, the thermal stability was prolonged, since the BM have to be at higher temperatures to start the process of thermal decomposition of the drug. These three BM are composed of croscarmellose sodium (MW: 263.19761 g $mol^{-1}$), microcrystalline cellulose 101 (MW: 111.14176 g $mol^{-1}$), and polyvinylpyrrolidone (MW: 504.43708 g $mol^{-1}$). All these excipients have a large molecular structure when compared with the ornidazole molecule. Once the drug melts, it can be incorporated by the excipients' molecules and this fact may be protecting the drug and delaying its decomposition (Fig. 3 and Table 4).

The TG curves showed that practically for all the BM, the first event of mass loss, noncharacteristic from the drug decomposition, was associated with the loss of surface water present in the excipients, as can be seen when analyzing the TG curves of excipients alone. The decomposition main stage was unchanged in the percentage of mass lost for all the five BM studied; however, the TG curves evidenced that three of these BM presented the decomposition main stage at higher temperatures, which can be correlated with the DTA results. Also, two of these three BM still showed a new second decomposition stage, these being the BM with the magnesium stearate, which showed a minor secondary event and the BM with polyvinylpyrrolidone, which showed a significant secondary event (Fig. 4).

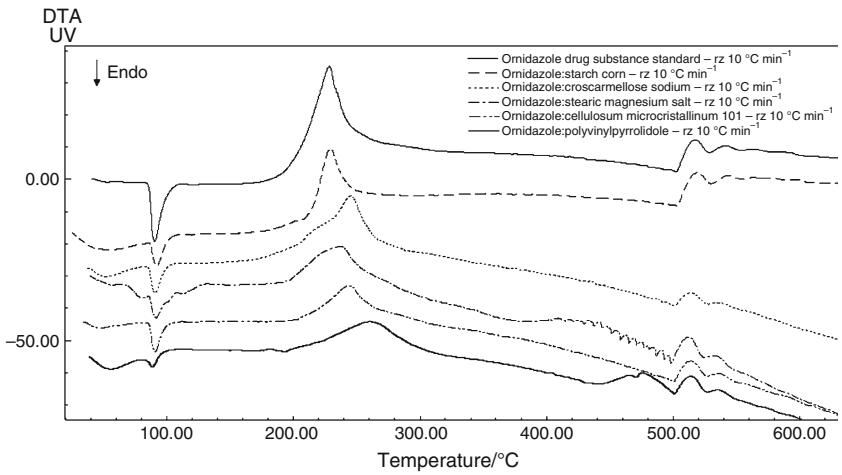


**Fig. 3** DTA curves of ornidazole BM with pharmaceutical excipients (1:1)

**Table 4** DTA curves of ornidazole BM

| Sample | $T_{fus}$/°C | $\Delta H_{fus}$/J g$^{-1}$ | $T_{decomposition}$/°C | $\Delta H_{decomposition}$/J g$^{-1}$ |
|---|---|---|---|---|
| Ornidazole | 90.45 | −122.43 | 228.17 | 514.36 |
| Ornidazole + Corn Starch | 92.27 | −47.07 | 229.58 | 284.67 |
| Ornidazole + Croscarmellose sodium | 90.92 | −53.62 | 245.19 | 339.64 |
| Ornidazole + Magnesium stearate | 92.03 | −24.86 | 230.08 | 399.52 |
| Ornidazol + Microcrystalline cellulose 101 | 91.75 | −54.24 | 244.83 | 135.73 |
| Ornidazol + Polyvinylpyrrolidone | 89.08 | −15.89 | 260.68 | 471.76 |

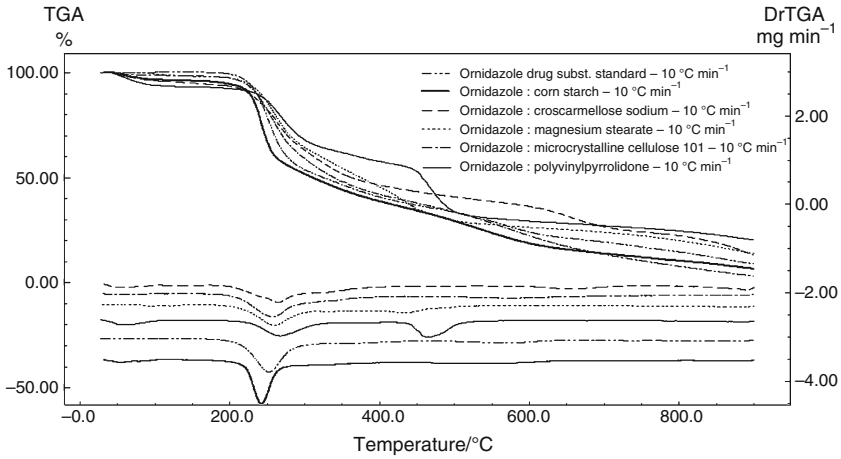


**Fig. 4** TG curves of ornidazole BM with pharmaceutical excipients (1:1)

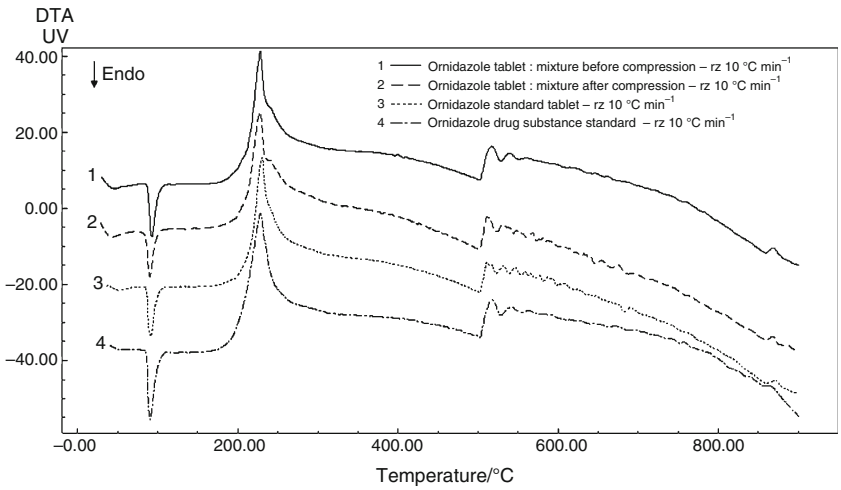


**Fig. 5** DTA cruves of ornidazole FT: powder mixture before compression, tablet formulation after compression, and reference tablet available from the market

It could be proved that the compression process did not affect the thermal properties of the powder mixture submitted to the manufacture process, proving that the ornidazole drug synthesized by the manufacturer A, evidenced as the most stable crystalline solid among the three raw materials evaluated, since it did not melt or change the crystalline form under stress conditions (pressure and temperature). The thermal profile of the tablet is very similar to the drug profile, without displacing the peaks of melting and decomposition, and showing the absence of physical and chemical interactions between the drug and the excipients studied, these samples have the real proportions of each raw material (excipients and drug) in the formulation, being more representative and conclusive than the BM studied (Fig. 5 and Table 5).

**Table 5** DTA curves of ornidazole TF

| Sample | $T_{fus}$/°C | $\Delta H_{fus}$/J g$^{-1}$ | $T_{decomposition}$/°C | $\Delta H_{decomposition}$/J g$^{-1}$ |
|---|---|---|---|---|
| Ornidazole | 90.45[a] | −122.43 | 228.17[b] | 514.36 |
| BM before compression | 92.26[a] | −88.79 | 228.17[b] | 724.42 |
| BM after compression | 89.95[a] | −75.07 | 227.61[b] | 132.29 |
| Reference Tablet | 91.02[a] | −86.61 | 230.34[b] | 498.23 |

[a,b] Equal letters indicate, with 95% of security, no significant difference among the respective averages and among the samples

## Conclusions

Based on the results, it can be understood that ornidazole raw materials from the three different manufacturers can be considered adequate to medicine production presenting satisfactory quality and bacause of their authenticity, as well as showing the same differences on their respective thermal profiles, which can be assigned by differences between the crystalline and physical characteristics of the compounds, which could be confirmed by a SEM and DRX analyses and showed that the raw material from the manufacturer B presented less thermal stability than the manufacturer C, which in turn showed less thermal stability than the manufacturer A.

The drug decomposition kinetic parameters determined by the Ozawa method presented kinetics of zero order, which is a linear form of kinetics. The determination of drug purity showed no statistically significant differences among the purities of the raw materials, and the analytical techniques had demonstrated both precision and accuracy. The DSC method can be considered as an alternative method for drug quantification/purity analysis, since the results presented by this technique does not differ significantly from the results presented by the analytic techniques of HPLC and UV–Vis spectrum that are widely used and recognized worldwide.

The DTA curves showed no significant variation on the drug melting peaks in the BM evaluated, but showed for the three of the five BM studied a shift on the decomposition peak. This change in the thermal behavior showed a greater stability of the mixtures and evidenced a physical interaction between these compounds, which can be accepted pharmaceutically.

The BM TG curves showed no harmful changes in the characteristics of the drug decomposition main stage. For some of the BM presented, this stage in higher temperatures is in accordance with the DTA results. The study of the TF presented no physical–chemical interactions between the drug and excipients submitted to the manufacturing process, thereby approving the formulation and the process for medicine production.

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