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Thermal characterization of the solid state and raw material fluconazole by thermal analysis and pyrolysis coupled to GC/MS

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Abstract This article had studied the thermal characterization of the raw material and different fluconazole crystals, obtained through recrystallization with different solvents using thermoanalytical techniques (TG, DTA, DSC-50, DSC Photovisual, DSC-60) and Pyr-GC/MS. The results confirmed that the fluconazole volatilizes without decomposition until 250 °C. Pyr-GC/MS showed hexachlorobenzene like impurities in fluconazole raw material.

Keywords Thermal analysis · Pyrolysis · Fluconazole

Introduction

The fluconazole (FLU) is an antifungal drug, derived from the triazole, with a wide action range [1]. There are many applications of thermal analysis in the pharmaceutical industry, for example, for identification, characterization of active and inactive ingredients, routine analysis, quality control, stability study, and polymorphism. It comes about as an analytical method capable of producing fast and reproducible results [2–16].

This study aims at the thermal characterization of the raw material and crystals fluconazole, obtained through the recrystallization of three different solvents (acetone, methanol, and chloroform), using the thermal techniques (TG, DTA, DSC-50, DSC Photovisual, DSC-60) and the pyrolysis coupled to the gas chromatography interfaced to spectrometry of mass (Pyr-GC/MS), to determine the kinetic parameters of thermal stability and degradation products.

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Experimental

Materials

Fluconazole (A) obtained from China, and crystals (B), (C) and (D) were obtained from raw material fluconazole recrystallization with different solvents such as methanol, acetone and chloroform.

It was weighed 100.0 mg of fluconazole raw material and solubilized in methanol, acetone, and chloroform separately; after solubilization, few quantities of raw material fluconazole was added in the solutions to obtain saturated solutions. The saturated fluconazole solutions were kept in refrigeration for 24 h. The crystals were obtained from solvents for filtration and vacuum drying.

Thermal analysis

The calorimetric curves of fluconazole raw material (A) and crystals (B), (C), and (D) were recorded using a Shimadzu Calorimeter, model DSC-50, calibrated with standard indium under the same conditions as the samples were measured. The DSC curves were recorded at a heating rate

of 2.0, 5.0, 10.0, 20.0, and 40.0 °C/min from room temperature up to 250.0 °C in nitrogen (50.0 mL/min). It was weighed about 2.0 mg of raw material and crystals fluconazole. DSC photovisual data were recorded applying a Shimadzu Calorimeter model DSC-50 coupled to a model VCC-520 photovisual system connected to an Olympus microscope and to a Sony camera in nitrogen (50.0 mL/min) at a heating rate of 10.0 °C/min from room temperature up to 250.0 °C. The DSC photovisual system was connected to a computer using Assimetrix software. The pictures of the samples were visualized and recorded at real time according to their DSC curves observing the phase transition of the samples. The DSC cooling/heating curves of the fluconazole and crystals were obtained after two cycles of sequential heating and cooling [16], and recorded using a Shimadzu calorimeter model DSC-60, coupled to a model EK90/SH cooling system Peltier, in nitrogen (30.0 mL/min) at heating rates of 5.0, 10.0 and 20.0 °C/min. The sample was heated up to 160.0 °C, and held at this temperature for 3 min before cooling to room temperature at the same heating rates. The sample cooled to room temperature was reheated up to 160.0 °C under similar conditions. The DTA curves of fluconazole (A) were recorded using a Shimadzu differential thermal analyzer model DTA-50 in nitrogen (50.0 mL/min) at a heating rates (10.0, 20.0 and 40.0 °C/min), up to the temperature of 900.0 °C. The drug was characterized through its typical transition phases, using a TASYS program, from Shimadzu. Thermogravimetric curves were recorded in a Shimadzu thermobalance model TGA-50H apparatus calibrated with calcium oxalate monohydrate. The dynamic and isotherm curves were obtained in nitrogen (50.0 mL/min) and synthetic air (20.0 mL/min). The dynamic TG curves were recorded at a heating rate of 10.0, 20.0, and 40.0 °C/min from ambient up to 900.0 °C. Isothermal curves were recorded at 155.0, 160.0, 165.0, 170.0, and 175.0 °C for 300 min. The sample mass was 5.0 ± 0.5 mg. The kinetic parameters of decomposition were calculated using the Arrhenius equation on the basis of TG isothermal data [17]. The reaction order (n), frequency factor (A), and activation energy (Ea) were determined using the Ozawa model for the TG dynamic data in the synthetic air atmosphere [6]. TG data were analyzed using Tasys software from Shimadzu.

Pyrolysis—GC/MS

A pyrolyzer coupled to a Shimadzu gas phase chromatograph, model GCMS-QP5050A was used for the studies of pyrolysis. The oven was programmed with the following temperature 70.0 °C (initial) and at a heating rate of 10.0 °C/min up to 290.0 °C. The temperature of the ions source was 300.0 °C. The identification of the compounds was made comparing their mass spectra with the Wiley/NBS library. The sample's volume corresponds to a little fluconazole crystal put in platinum crucible and introduced to the pyrolyzer at the temperatures of 250.0, 500.0, and 750.0 °C, separately for each experiment.

Results and discussion

The DSC-50 curves of fluconazole raw material (A) and crystals (B, C and D) were better characterized at a heating rate of 2.0 °C min^{-1} (Fig. 1). The calorimetric curve of the raw material fluconazole (A) showed an endothermic peak corresponding to the melting point temperature at 138.4 °C. The calorimetric curves of the crystals B, C, and D present different thermal behaviors. The crystals showed two endothermic peaks in the melting point of the fluconazole, for the crystal B in the temperatures of 136.7 and 138.6 °C, the crystal C showed endothermic peaks in the temperatures of 135.1 and 138.9 °C and the crystal D showed endothermic peaks of 136.0 and 138.5 °C, corresponding to the presence of two polymorphs formed in the process of recrystallization in different solvents.

The images captured at room temperature in the DSC photovisual show the drug and crystals without visible alterations (Fig. 2). The following images correspond to the melting process of the samples. For the sample A, it is possible to observe the phase transition at the temperatures 138.5 and 139.6 °C, which occurs in a uniform manner in all the sample extensions. The images captured for crystals B, C, and D show two events at temperatures 138.3, 138.6, and 138.2 °C, respectively: the melting process of the first polymorphic form (less stable), and the polymorph form more stable staying unaltered. In the figures captured at the temperatures of 138.7, 138.9, and 138.5 °C were observed the melting of the second form for the crystals B, C, and D, respectively. The images confirm the presence of polymorphs forms visualized in the conventional DSC curves. At the temperatures 220.3, 221.6, 220.1, and 225.4 °C for

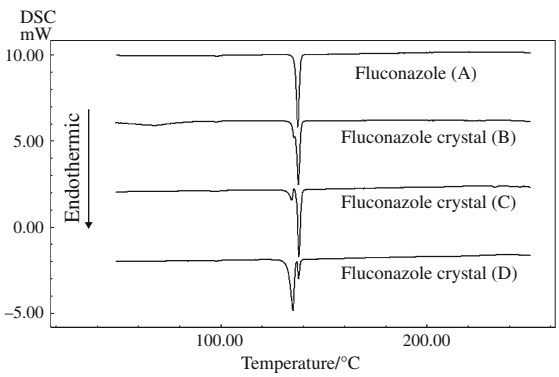

Fig. 1 Calorimetric curves of the fluconazole and its crystals at the heating rate of 2.0 °C/min

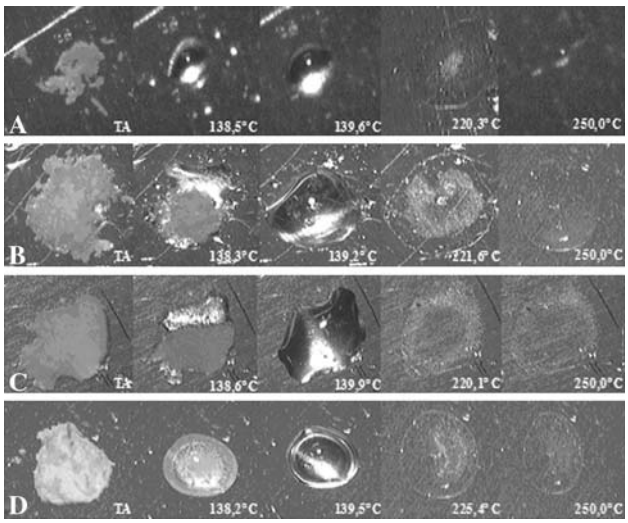

Fig. 2 Images from the DSC-photovisual of the fluconazole A and its crystals recrystallized in methanol, acetone, and chloroform (B, C, and D) at the ambient temperature, onset, peak, and 250.0 °C

the samples A, B, C, and D respectively, it is seen a white spot possibly from the crystallization of the samples. At the temperature of 250.0 °C, it is observed a volatilization of the samples studied.

The DSC-60 curves of fluconazole raw material and its crystals B, C, and D showed to be better characterized at the heating rate of 5.0 °C min^{-1}. The data obtained for the samples in the first heating cycle are similar to the ones obtained in the DSC-50. The sample (A) showed an endothermic peak typical of melting at a temperature of 138.9 °C. The samples B, C, and D showed two endothermic peaks corresponding to the melting of two polymorphs forms at the temperatures (137.9 and 139.4 °C), (137.8 and 139.9 °C), and (138.2 and 139.9 °C), respectively. In the second heating cycle, the sample (A) showed an endothermic peak at 32.8 °C corresponding to the glass transition, followed by an exothermic peak at 91.7 °C possibly from the crystallization, and two endothermic peaks at the temperatures 138.7 and 139.5 °C (Fig. 3). The characteristic of the two different crystalline forms melting, obtained after cooling of the fluconazole melting in the first heating and cooling cycle [6]. For the crystals B, C, and D in the second heating cycle the processes of glass transition are evidenced at the temperatures 31.7, 36.2 and 34.1 °C, of crystallization at the temperatures 91.3, 94.7 and 95.7 °C, respectively, and two endothermic peak's characteristic of two crystalline forms melting processes (similar to the first heating cycle), at the temperatures (138.2 and 139.5 °C) for the crystal B, (137.9 and 138.0 °C) for the crystal C and (138.0 and 138.8 °C) for the crystal D. In the first and second cooling cycles, no thermal phenomena were observed in all the samples studied.

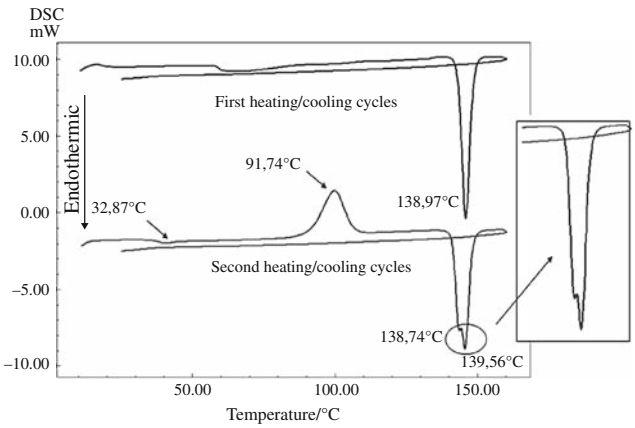

Fig. 3 DSC-cooling curves of the fluconazole A, in the heating/cooling cycles, at a rate of 5.0 °C/min

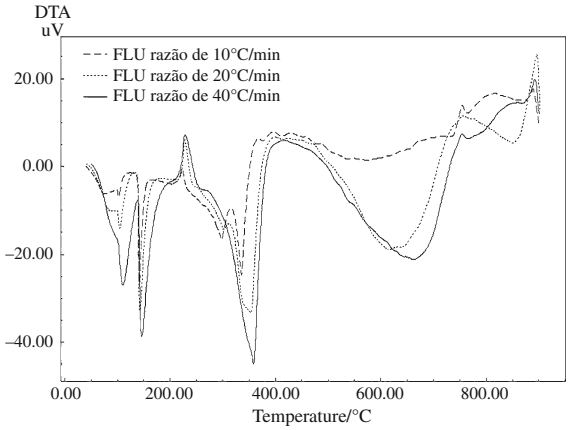

Fig. 4 Differential thermal analysis curves of the fluconazole A, at the heating rates of 10.0, 20.0, and 40.0 °C/min

The DTA curves of the fluconazole (Fig. 4) proved that the drug presented melting endothermic processes similar to the DSC. At the rates of 10.0, 20.0, and 40.0 °C min^{-1}, it is possible to observe at the temperatures of 99.4 °C ± 0.31, 99.3 °C ± 0.07, 100.5 °C ± 0.45, respectively, an endothermic peak typical of water loss. The endothermic peaks of melting of FLU are observed at the rates of 10.0, 20.0, and 40.0 °C min^{-1} at the temperatures of 138.5 °C ± 0.28, 138.8 °C ± 0.19, and 139.8 °C ± 0.82, respectively. It was also possible to observe at the different heating rates, in the temperature interval from 216.1 to 319.8 °C, an exothermic peak followed by two endothermic peaks, possibly due to the crystallization of the sample, following of volatilization, confirming the white spot at the temperature 220.3 °C and the sample absence in the photovisual at the temperature of 250.0 °C.

The dynamic thermogravimetric curves obtained in the synthetic air atmosphere, at the heating rate of 10.0 °C/min,

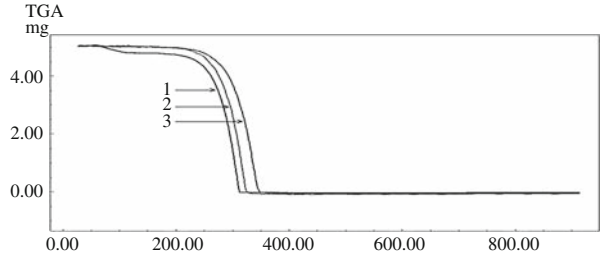

Fig. 5 Thermogravimetric dynamic of the fluconazole A, at the heating rates of **(1)** 10.0, **(2)** 20.0, and **(3)** 40.0 °C/min

have shown that the fluconazole presents a mass loss from 4.16 to 4.57% before the melting temperature at the average initial temperature (T_i) in 65.8 °C (± 0.53) and average final temperature (T_f) at 110.2 °C (±0.40), corresponding to the water loss of the sample [18]. The following phase corresponds to the mass loss of the FLU with the average T_i at 240.4 °C (±2.2) and T_f at 310.8 °C (±1.87), with a mass loss from 94.02 to 94.32%. The behavior of the fluconazole in the dynamic curves at the heating rate of 20.0 and 40.0 °C shows to be similar in the mass loss percentages. The temperature of the mass loss is dislocated to higher temperatures with the increase of the heating rate (Fig. 5).

Ozawa's model, for the TG dynamic data, has been employed in the kinetic studies to evaluate the kinetic parameters, activation energy (E_a), frequency factor (A) and reaction order (n). The data has evidenced a thermal process with kinetic of zero order for the fluconazole, with the values of E_a (95.83 KJ/mol ± 2.76), frequency factor (2.831×10^8 min^{-1} ± 0.57×10^8), in the decomposed fraction α10. With the data from the TG isothermal curves, the rate constants of mass loss were calculated, at the analyzed temperatures, following the Arrhenius equation considering the zero order of decomposition determined by the Ozawa method. According to the coefficients of correlation, the isothermal data confirm zero order of decomposition (Table 1).

The degradation products corresponding to the phase of mass loss of the fluconazole were identified through pyrolysis coupled to GC–MS. The pyrogram obtained at the temperature of 250.0 °C can be visualized in the Fig. 6, where two peaks have been detected, the first corresponding to the hexachlorobenzene and the second identified as fluconazole, confirming that at the temperature of 240.0 °C, the mass loss observed in the thermogravimetric curve (Fig. 5), does not correspond to the degradation of the drug, but to the volatilization of the fluconazole in its intact molecular form. The pyrograms were also obtained at the temperatures of pyrolysis of 500.0 and 750.0 °C, (Figs. 7 and 8, respectively), where the products of degradation of the fluconazole were detected in the state of

Table 1 Kinetic constants (k) of the isothermal decomposition of the fluconazole A, at the temperatures 155.0, 160.0, 165.0, 170.0, 175.0 °C ($n = 3$)

Sample	Kinetic parameters	Temperatures				
		175.0 °C	170.0 °C	165.0 °C	160.0 °C	155.0 °C
Fluconazole	k_0 (r^2)	1.063×10^{-5} (0.9999)	8.928×10^{-5} (0.9998)	7.438×10^{-5} (0.9997)	3.673×10^{-5} (0.9997)	2.506×10^{-5} (0.9992)
	k_1 (r^2)	7.905×10^{-5} (0.9980)	6.542×10^{-5} (0.9973)	$5,181 \times 10^{-5}$ (0.9977)	2.412×10^{-5} (0.9991)	1.614×10^{-5} (0.9990)
	k_2 (r^2)	1.345×10^{-4} (0.9915)	1.086×10^{-4} (0.9918)	8.725×10^{-5} (0.9937)	3.959×10^{-5} (0.9981)	2.637×10^{-5} (0.9985)

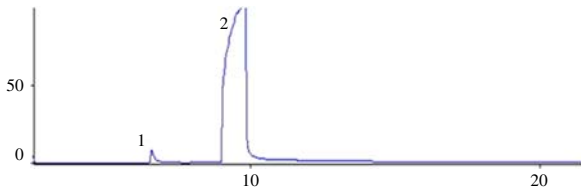

Fig. 6 Pyrogram obtained for the FLU, at the temperature of 250.0 °C, showing tow peak the first corresponding to hexachlorobenzene and the second identified as fluconazole

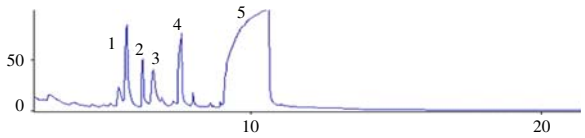

Fig. 7 Pyrogram obtained for the FLU, at the temperature of 500.0 °C, showing the degradation products of the process of thermal decomposition of the drug in the form of gas; **(1)** 1H-1,2,3-triazole,4-5-diphenil, **(2)** 1-methil-trans-4-isopropilciclohexano, **(3)** 3,3-difluor-1,2-dipropyl-cyclopropano, **(4)** 2-etil-6-phenylpiridina, and **(5)** fluconazole

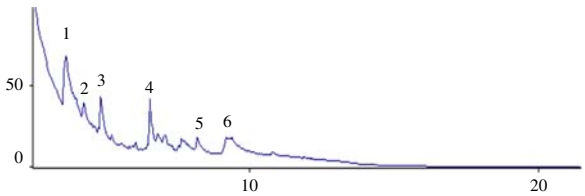

Fig. 8 Pyrogram obtained for the FLU, at a temperature of 750.0 °C, showing the degradation products of the process of thermal decomposition of the drug in the form of gas; **(1)** 2-metil-5,6,7,8-tetrahidro-quinixolona, **(2)** 2,5-diethilpirazine, **(3)** 9H-fluorano-2-carbonitrila, **(4)** 3,4,5,6-tetrahidro-1 H-enzo[1, 6]naftilpiridona 2-3H, **(5)** 1H purin-6-amina,N(3-methil-2-butenil, and **(6)** fluconazole

gas. The pyrograms of the crystals B, C, and D also present hexachlorobenzene as impurity.

Conclusions

The fluconazole mass loss showed kinetic process of zero order both Ozawa and Arrhenius equations. The first step in TG dynamic curves corresponds to the volatilization of the fluconazole process confirmed by the techniques DSC, DSC-photovisual, DTA, and Pyr-GC/MS. Different polymorphs from fluconazole were obtained from recrystallization processes in solvents and temperature. The hexachlorobenzene was found as impurity in the raw material and crystals studied.

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