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# Thermal behavior of fluconazole-active substance and tablet

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**ABSTRACT**

*The thermal decomposition of Fluconazole-active substance and tablet were studied using differential scanning calorimetry (DSC) and thermogravimetry (TG). Thermal analysis was supplemented using X-ray powder diffraction and infrared spectroscopy to characterize samples. It was observed that the active substance showed a slight different thermogravimetric profile in commercial sample, due to the presence of the excipients in drug (tablet). DSC studies of binary mixtures, fluconazole and excipients (lactose monohydrate, microcrystalline cellulose and magnesium stearate) showed, with the exception of microcrystalline cellulose, that endothermic peaks of drug was broadened and shifted to lower temperature. These differences may be due to the small interactions that have not been confirmed by FT-IR spectroscopy. Through non-isothermal conditions, the activation energy for the decomposition reaction of Fluconazole active substance and tablet were determined. It was revealed the lower thermal stability of fluconazole-tablet compared with the active substance.*

**Key words**: Fluconazole, TG, DSC, XRD, activation energy

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## INTRODUCTION

Fluconazole (2, 4-difluoro-1', 1'-bis (1H-1, 2,4-triazol- 1-ylmethyl) benzyl alcohol -$C_{13}H_{12}F_2N_6O$, (306.27 g/mol$^{-1)}$ is a triazole antifungal agent with high oral efficiency. Fluconazole is used against superficial and systemic candidiasis and in the treatment of cryptococcal infections for patients with the acquired immunodeficiency syndrome. [1, 2]

This active pharmaceutical ingredient (API) crystallizes in more than one solid form (polymorphs). [3, 4]

Excipients are known to facilitate administration and release of an active component, as well as to protect it from the environment. These latter are considered pharmaceutically inert but physical and chemical interactions with an active component are possible [5]. Interaction between drugs and excipients can alter stability and bioavailability of drugs, thereby, affecting its safety and/or efficacy. [6]

The thermal analysis is a routine method applied for drugs characterization and is useful in the pre-formulation stage in the development of solid dosage forms [7, 8]. Also determining the temperature range when a certain medicine substance is stable regarding its structure as well as its pharmaceutical action is crucial for the stocking of the drug, for its technological transformations and for the obtaining technology of the right formulas [9].

Thermal studies were performed on pure fluconazole [10] in order to study the change between its polymorphic forms and to evaluate its thermal behavior through DSC methods and kinetic studies. Elisana et al, used the FWO method with kinetic of zero order to assess activation energy (95.83 KJmol$^{-1}$ +- 2.76).

This paper aims to study the thermal stability of Fluconazole in Tunisian commercial tablet using DSC, TG and kinetic dynamic methods.

## EXPERIMENTAL SECTION

Pure substance of Fluconazole was obtained from Drugs Quality Control Laboratory of Tunis as pure compound readily available to be used for medical purpose. Commercial product (tablet) was purchased in a local drugstore. This latter contains lactose monohydrate, magnesium stearate and cellulose microcrystalline.

Physical mixtures were prepared in proportion 1:1 (fluconazole: excipient) by simple mixing.

The Differential Scanning Calorimetric curves were obtained in a DSC-131 cell (SETARAM) using aluminum crucibles with about 2 mg of samples, under dynamic nitrogen atmosphere. The temperature range was from 30°C to 300°C at heating rate of 10°C $min^{-1}$.

TG experiments were performed with a SRTARAM SETSYS 1750 TG/DTA instrument in the temperature range of 20-500°C, with ≈ 2.2 mg of samples under helium atmosphere and the heating rates of 2.5, 5, 10, 15 and 20°C.$min^{-1}$. The X-ray diffractograms of the powders were recorded between 5° and 35° (2θ), at room temperature, using a PANalytical X'Pert PRO with a copper anticathode.

## RESULTS AND DISCUSSION

1. Characterization of Fluconazole

Polymorphic changes in the drug are important since they might affect the dissolution rate and bioavailability. So, it was necessary to study the polymorphic states of fluconazole in the tablet [11].

Figure.1 shows the pure substance of Fluconazole (FP) and commercial Fluconazole (CF) diffractograms. The diffraction lines of the pure substance sample were identical to those of crystalline polymorph III, while the commercial pharmaceutical product matched polymorph II [3, 4].

Alkhamis et al. reported that polymorphic form II is a metastable form that is converted to the more stable form III under the effect of compression or during the storage in standard ambience conditions of temperature and humidity [12].

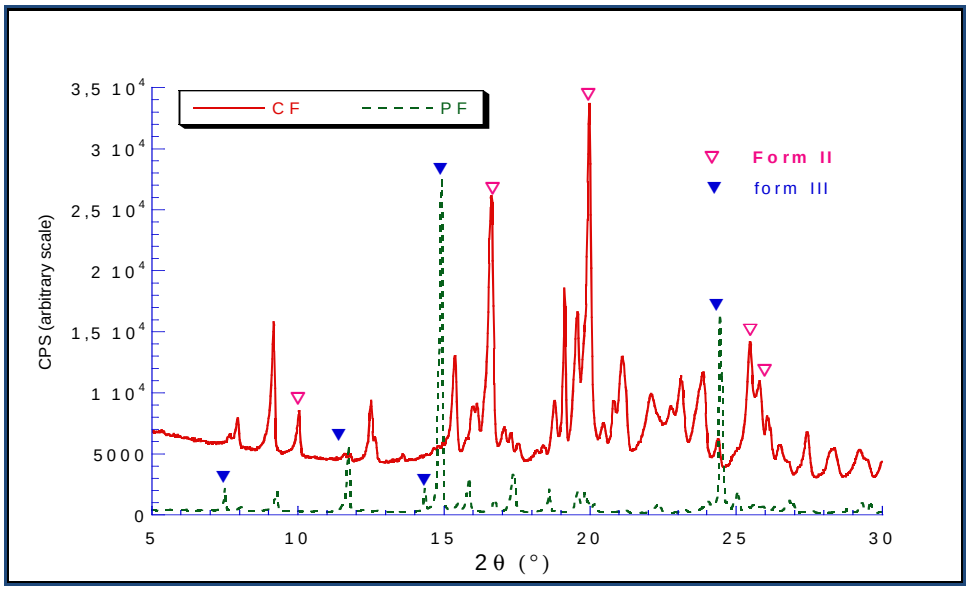


**Figure.1 X-ray diffraction (XRD) patterns for: Pure Fluconazole (PF) and commercial Fluconazole (CF)**

Figure.2 presents Differential scanning calorimetric DSC curves of the pure Fluconazole (FP) and commercial samples (CF).

The endothermic peaks at about 100 and 140°C are due respectively to the dehydration and melting of Fluconazole. For the commercial product, the temperature of the endothermic peak ($T_{onset}$) of Fluconazole has decreased from 139.23°C to 135.75°C.

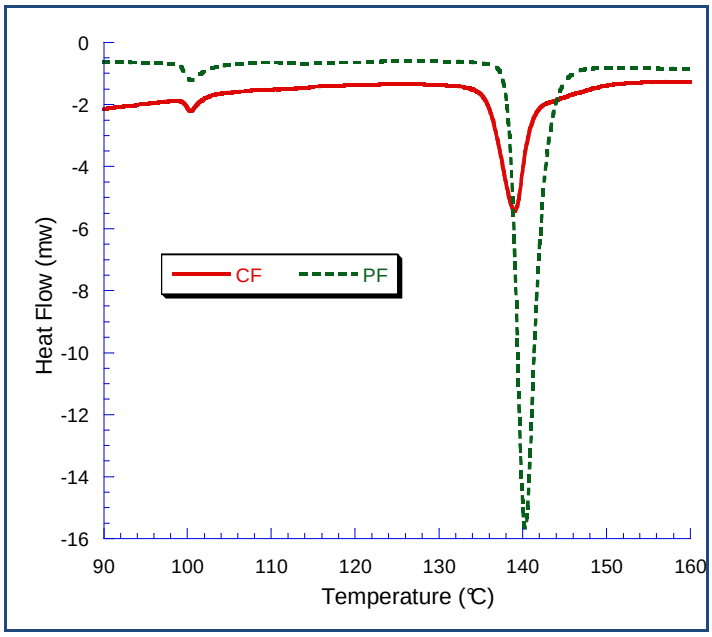


**Figure.2 DSC curves of pure Fluconazole (PF) and commercial Fluconazole (CF) in dynamic nitrogen atmosphere and heating rate 10°C.min$^{-1}$**

Figure.3 shows the TG curves of the Fluconazole (PF) and Fluconazole (CF). TG curve of PF shows a large mass loss taking place in the domain range of 175-295°C with a mass loss of 99.68% which corresponds to the volatilization of Fluconazole as showed by Elisana et al [10] using a gas phase chromatograph coupled to mass spectrometry (GC/MS).

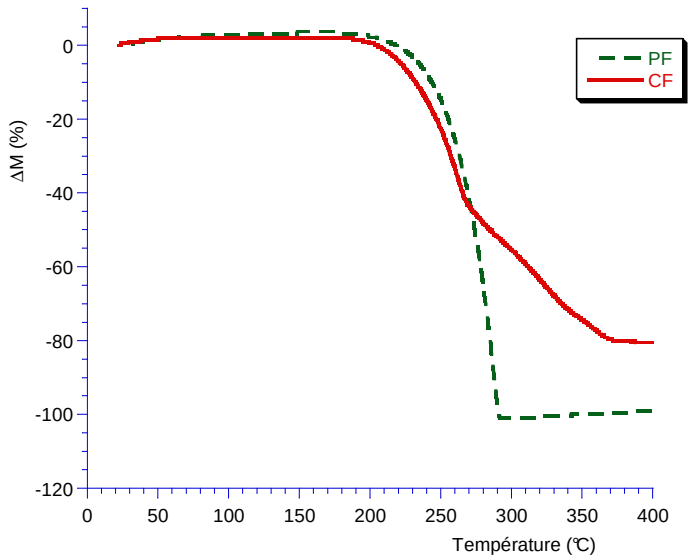


**Figure.3 TG curves of pure Fluconazole (PF) and commercial Fluconazole (CF) in dynamic nitrogen atmosphere and heating rate 10°C.min-1**

TG curves of Fluconazole (PF) present two successive mass losses, 44.26 and 36.11%. The first occurring at 280°C is assigned to Fluconazole volatilization, and the second part is related to excipient degradation.

In order to target the excipient responsible to the peak shift, binary mixtures (Figure.4) of fluconazole with lactose monohydrate, microcrystalline cellulose and magnesium stearate showed was subjected to DSC studies. As shown in figure.5, endothermic peaks of drug was broadened and shifted to lower temperature with the exception of microcrystalline cellulose. This is indicative of a possible interaction, but not necessarily corresponding to an incompatibility because there was no disappearance or appearance of new bands in IR spectra confirming no change has occurred in the drug structure.

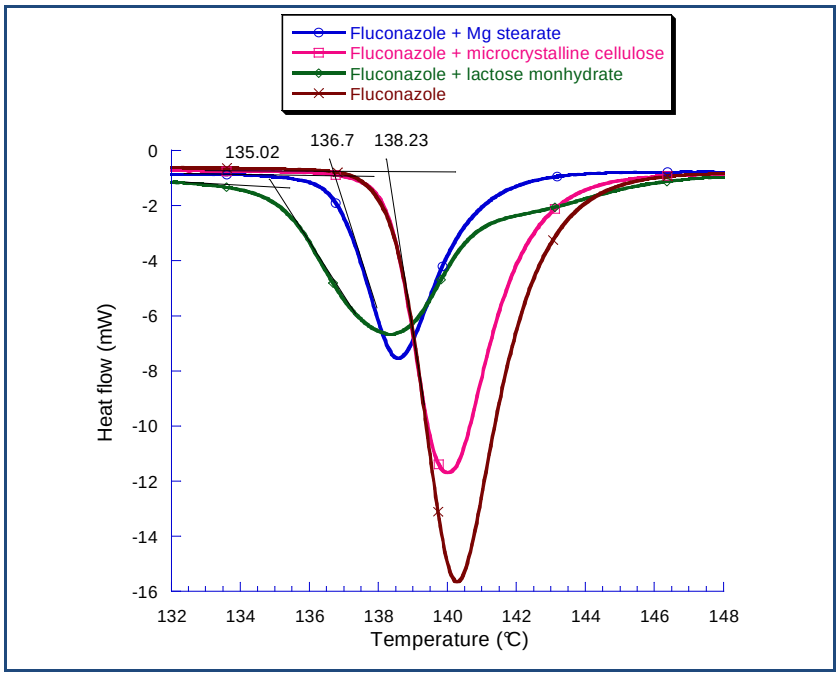


**Figure. 4 DSC curves of Fluconazole and excipients obtained in dynamic nitrogen atmosphere and heating rate 10°C min $^{-1}$**

2. Kinetic study

The kinetic study of fluconazole is carried out through its thermal decomposition, under non-isothermal conditions, for the active substance and tablet.

The kinetic parameters were determined from TG curves, using the integral methods, Flynn-Wall-Ozawa (FWO) [13, 14] and Kissinger-Akahira-Sunrose (KAS) [15, 16].

The theory of this kinetic study is based on the equation of solid-gas reaction [17]:

$$\frac{d\alpha}{dt} = K(T).f(\alpha) = A.\exp(-\frac{E}{R.T}) \quad (1)$$

Where A is the Arrhenius pre-exponential factor, R is the gas constant, E is the activation energy, α is the reacted fraction, T is the process temperature and f (α) accounts for the reaction rate dependence on α. The kinetic model, f (α) is an algebraic expression which is usually associated with a physical model that describes the kinetics of the solid state reaction [18]

Equation (1) is a general expression that describes the relationship among the reaction rate, reacted fraction and temperature independently of the thermal pathway used for recording the experimental data. In case the experimental data were recorded at a constant reaction rate $\beta = \frac{dT}{dt}$, Equation (1) can be written as follows [19]:

$$\frac{d\alpha}{dt} = \frac{A}{\beta}.exp\,(-\frac{E}{R.T}) \quad (2)$$

***Flynn-Wall-Ozawa's isoconversional*** method (FWO) is based on the adequate temperature to certain values of the conversion α.For experiments conducted at various rates of heating β; the equation corresponding to the method is as follow:

$$ln\,\beta = ln\,\frac{A.E}{R.g(\alpha)} - 5.331 - 1.052 - \frac{E}{R.T} \quad (3)$$

The plot ln β vs. (1/T) is linear and form the slopes of the straight lines (-E/R), the values of the activation energy (E) were obtained (Figure 5.a-b).

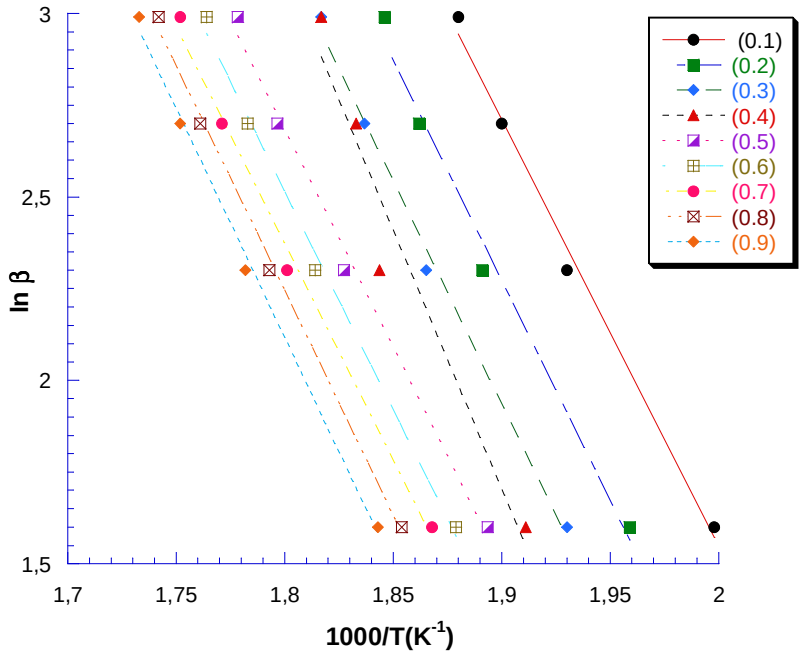


**Figure.5-a The Flynn-Wall-Ozawa's diagrams for pure Fluconazole (PF) at different conversion degrees**

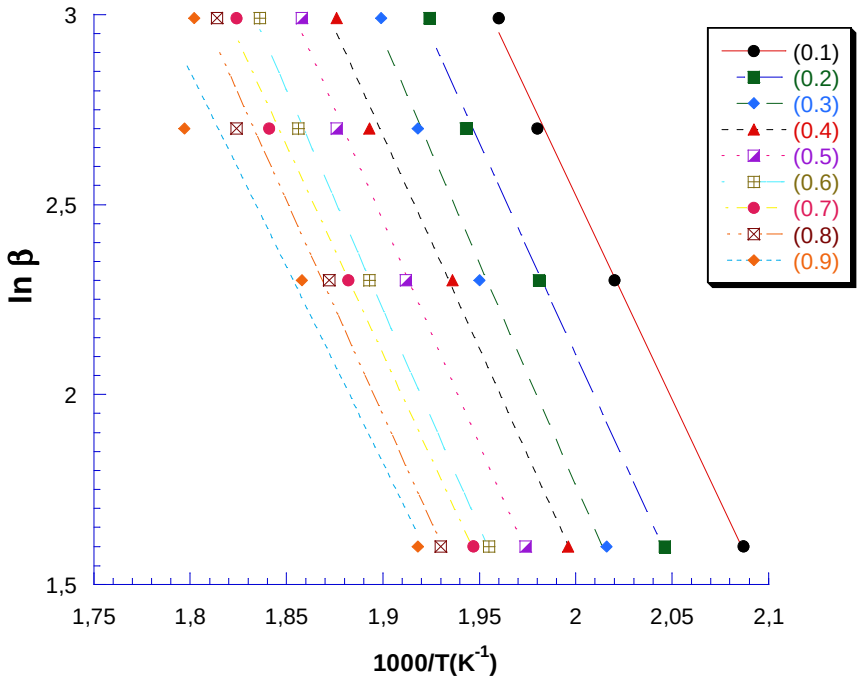


**Figure.5-b The Flynn-Wall-Ozawa's diagrams for commercial Fluconazole (CF) at different conversion degrees**

The ***Kissinger-Akahira-Sunose*** method (KAS) is based on the following equation:

$$\ln\left(\frac{\beta}{T_\alpha^2}\right) = ln\frac{A.R}{E.g(\alpha)} - \frac{E}{R.T_\alpha^2} \quad (4)$$

This method utilizes the adequate temperatures ($T_\alpha$) for certain values of the conversion α for experiments undertaken at various rates of heating β.

From the slopes of the straight lines obtained by the graphic representation of $ln\left(\frac{\beta}{T_\alpha^2}\right)$ vs. $\left(\frac{1}{T_\alpha}\right)$ the activation energy was determined (Figure 6.a-b).

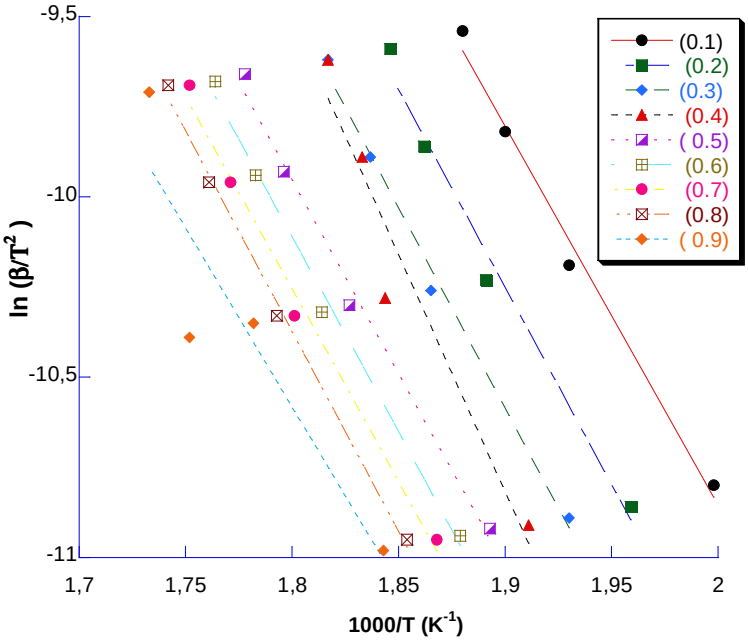


**Figure.6-a The Kissinger-Akahira-Sunose's diagrams for pure Fluconazole (PF) at different conversion degrees**

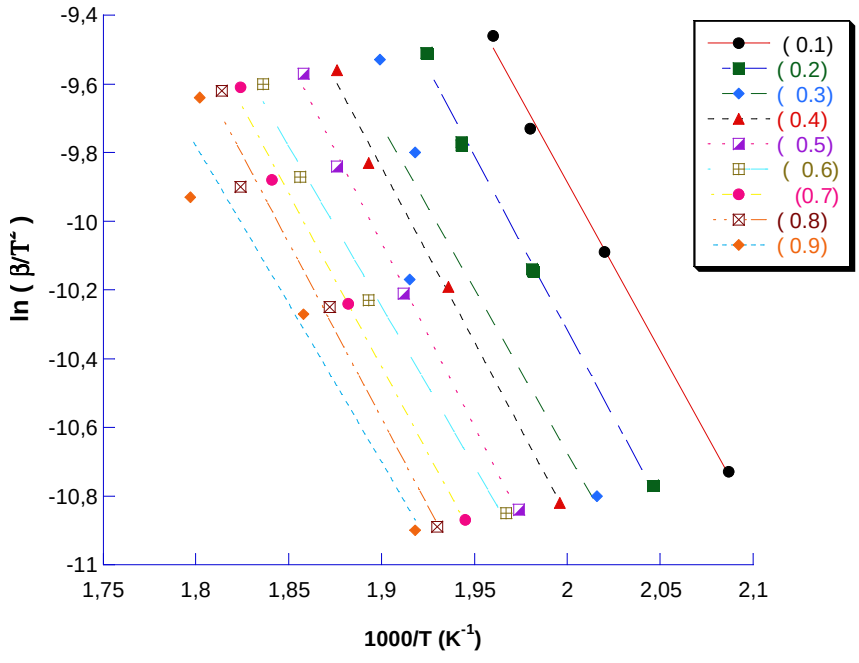


**Figure.6-b The Kissinger-Akahira-Sunose's diagrams for commercial Fluconazole (CF) at different conversion degrees**

By comparison of results (Table 1), estimated by the two different integral methods (FWO and KAS), it was revealed the relative lower values of activation energy, with conversion degree, of fluconazole in tablet compared with the pure substance.

**Table 1: Values of the activation energy obtained by the Flynn-Wall-Ozawa and Kissinger-Akahira-Sunose 3333methods for pure Fluconazole (PF) and commercial Fluconazole (CF)**

| Methods | E, ($kJmol^{-1}$), for conversion degree,α | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **0.1** | **0.2** | **0.3** | **0.4** | **0.5** | **0.6** | **0.7** | **0.8** | **0.9** | **Mean value** |
| **FWO (PF)** | 92.29 | 94.68 | 96.16 | 111.93 | 93.74 | 94.143 | 93.258 | 96.805 | 98.732 | 96.86 |
| **KAS (PF)** | 87.23 | 90.86 | 92.31 | 109 | 89.27 | 89.92 | 88.76 | 92.19 | 82.27 | 91.31 |
| **FWO (CF)** | 84.79 | 88.23 | 92.42 | 88.68 | 92.79 | 90.88 | 86.72 | 88.8 | 81.48 | 88.31 |
| **KAS (CF)** | 81.35 | 84.22 | 79.02 | 84.39 | 89.10 | 77.54 | 83.91 | 84.92 | 76.66 | 82.34 |

## CONCLUSION

The study of thermal behavior of pure substance and commercial product of Fluconazole evidenced that the presence of excipients decreases to some extent the thermal stability of this drug. This trend is confirmed through the kinetic and the compatibilities studies. The kinetic study showed lower values of activation energy for the active substance in commercial product. The DSC curves of the binary mixture (Fluconazole/lactose monohydrate, Fluconazole/magnesium stearate) showed a lowering of the melting temperature of the active substance. However, FT-IR results did not evidence any interaction.

The thermal study can be used in the pre-formulation and production steps for quality control of solid drug and can enhance the credibility of some commercial drug.

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