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TG/DTG/DTA DATA USED TO DETERMINE THE THERMAL BEHAVIOUR OF PIOGLITAZONE

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ABSTRACT: Pioglitazone is a drug from the thiazolidinediones group and it is used in the treatment of type II diabetes mellitus by decreasing insulin resistance. Thermal degradation involves different reactions like pyrolysis, hydrolysis, decarboxylation, isomerization, rearrangement and polymerization of the active substance, hence the importance of studying the thermal behaviour of pharmaceutical compounds. This study was performed using just one heating rate of 10°C·min^{-1}, in air atmosphere. Data collected from TG/DTG/DTA analysis was used to determine the thermal behavior and thermal stability of the pharmaceutical active agent.

Keywords: Pioglitazone, Thermal behavior, FTIR, Diabetes, TG/DTG/DTA

INTRODUCTION:

Pioglitazone hydochloride is used as an oral therapeutic agent that acts by decreasing insulin resistance, hence it is used in the treatment of diabetes, more accurate on type II diabetes mellitus (Sripalakit *et al.*2007). Pioglitazone, also known as (5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4 thiazolidinedione), is a member of the drug group known as the thiazolidinediones or "insulin sensitizers", is not chemically or functionally related to the alpha-glucosidase inhibitors, the biguanides, or the sulfonylureas. Pioglitazone targets insulin resistance and, hence, is used alone or in combination with insulin, metformin, or asulfonylurea as an antidiabetic agent. Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption (Sripalakit *et al.*, 2007; Attia *et al.*, 2013). This compound binds well to proteins found in plasma and it is metabolized in the liver by an enzime system (Sripalakit *et al.*, 2007).

Modelling drug molecules involves creating organic structures that interact with receptors or facilitate the metabolic process and it is these precise structures that make them ofter vulnerable to degradation. The most important degradation reactions are: hydrolysis, oxidation, isomerization, polimerization and photolysis. Of course, the molecules mainly susceptible to hydrolysis are esters, amides or lactones while oxidation may occur easier in aldehydes, alcoholos, phenols, alkaloids and different unsaturated compounds. Isomerization is very tricky as it may turn a compound into its optical or geometrical isomer and thus cancel its therapeutic effects (Nishath *et al.*, 2011).

Drug development is more and more related to thermal analysis techniques as they provide very rigorous informations about the thermally induced effects on the molecular structure of a certain drug. In the last decade there was a large scale use of the more efficient hyphenated thermoanalytical techniques that provide more reliable experimental data, hence a better interpretation of the physico-chemical alterations that occur during the thermal degradation process. The various thermoanalytical techniques such as thermogravimetry (TG), derivative thermogravimetry (DTG), differential thermal analysis (DTA), evolved gas analysis (EGA) or differential scanning calorimetry (DSC) are widely used in quality control, drug-excipient interaction studies, thermal stability and purity of the pharmaceutical products (Attia *et al.*, 2012).

This study was performed to understand the thermal stability of pioglitazone, as the main component in drugs related to the treatment of type II diabetes mellitus. The thermogravimetric data collected from this study will be used further to determine possible thermally induced interactions between pioglitazone and some excipients used in the galenic form of the drug.

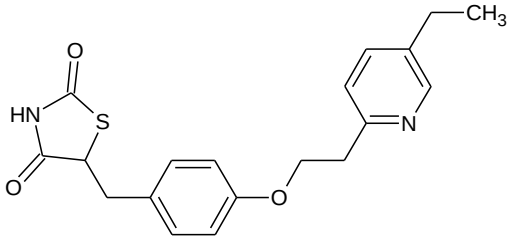

Fig.1 The chemical structure of pioglitazone

MATERIALS AND METHODS:

The pharmaceutical agent, pioglitazone hydrochloride, was purchased from Sigma (lot #022M4747V) and was further used as received from the producer.

To evaluate the thermal behavior of pioglitazone, samples were submitted to a controlled temperature program from 40 to 500°C in air flow of 100 mL·min^{-1}.

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The samples were heated at a heating rate of 10°C·min^{-1}. This analysis was performed on a Perkin Elmer TG/DTA thermobalance, while the data was processes by Perkin Elmer Pyris.

RESULTS AND DISCUSSIONS:

FT-IR analysis of the pharmaceutical active compound was performed in order to confirm that pioglitazone was handled in good conditions during transportation and storage and that no damage was induced to the molecular structure of the drug.

Figure 2 represents the FT-IR spectrum of pioglitazone which confirms the stretching vibrations of: CO−NH−CO at 1741cm^{-1}, C=N in pyridines at 1652cm^{-1}, aryl =C−O at 1230 cm^{-1} or C−S at 602 cm^{-1}. There are also in plane deformations of the 1,4 disubstituted benzene at 1175, 1065 and 1037 cm^{-1}.

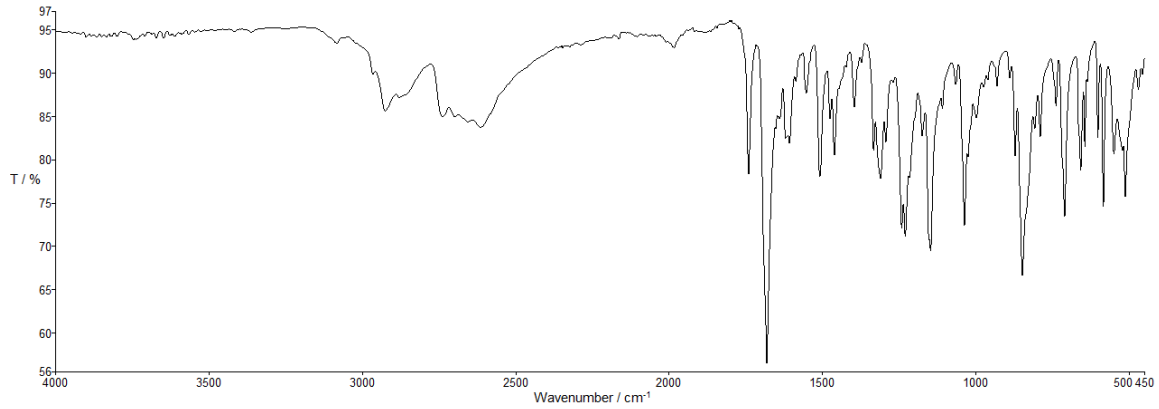

Fig.2 The FT-IR spectrum of pioglitazone

TG/DTG/DTA analysis

The thermal degradation process of pioglitazone revealed several degradation steps within the temperature range of 166 and 336°C. As in other of our studies regarding pharmaceutical compounds (Fulias *et al.*,2013; Anghel *et al.*, 2013; Duda-Seiman *et al.*, 2011) the thermal behavior was recorded at the heating rate of 10°C·min^{-1}, in air flow. Figure 2 shows the TG/DTG/DTA curves recorded in the mentioned conditions.

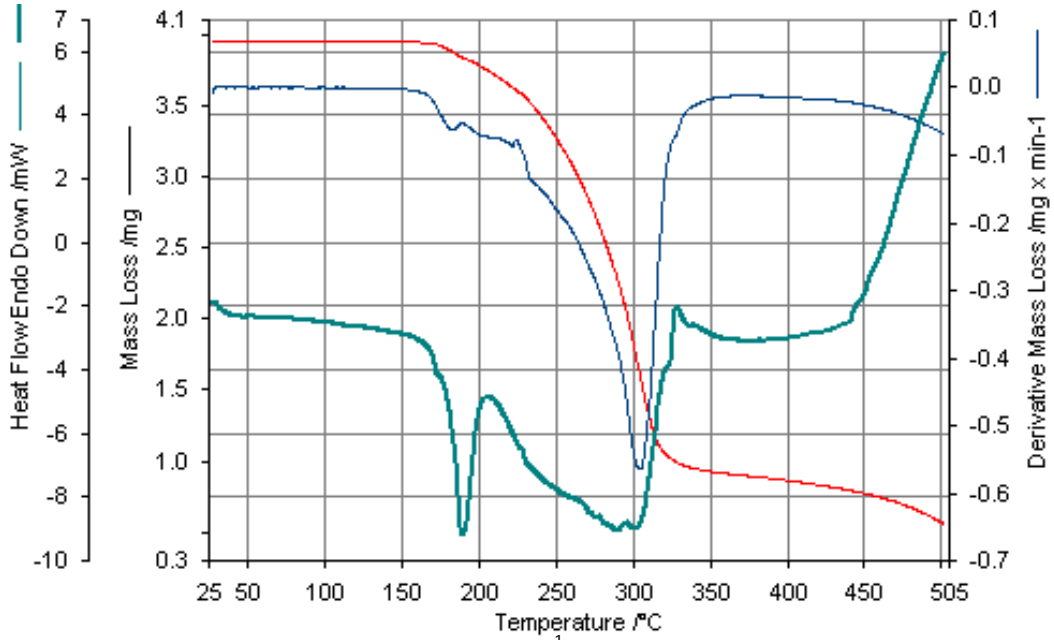

Fig.2 TG/DTG/DTA curves of pioglitazone, in air, 100 mL·min^{-1} at a heating rate of 10°C·min

Table 1
Thermoanalytical data for pioglitazone

Compound	Process	T_i/°C	T_f/°C	$T_{max\ DTG}$/°C	Δm/%
Pioglitazone	I	166	188	183	2.487
	II	189	228	225	6.597
	III	230	322	303	63.895
	IV	323	336	328	1.796

As we can see from table 1, the thermal degradation process of pioglitazone is a complex one, consisting of four steps. The first two correspond to an endothermic effect with a cumulated $\Delta H=80.5\ J\cdot g^{-1}$. This first step mainly involves the melting process of pioglitazone. The main degradation step stretches on a temperature range of almost 100°C and it is also endothermic, but with a thermal effect of much higher value, $\Delta H=354\ J\cdot g^{-1}$. The last thermal event noticed on the TG/DTG curve is a small exothermic process, but as mentioned it is small both as thermal effect and mass loss.

CONCLUSIONS:

The thermal stability of the pharmaceutical active compound was investigated is showing a four step thermally induced degradation with a significant mass loss of over 70% of the sample. The main thermal degradation process was recorded in the temperature range of 230 and 322°C with a mass loss of 63.895% of the sample. Both endothermic and exothermic effects can be noticed on the DTA curve of the process.

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