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INVESTIGATION OF THERMALLY INDUCED INTERACTIONS BETWEEN PIOGLITAZONE AND SOME EXCIPIENTS BY FT-IR AND DSC ANALYSIS

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ABSTRACT: This aim of this paper is to determine potential thermally induced drug-excipient interactions between pioglitazone, a drug in the thiazolidinediones group and a series of different excipients. The drug is used in the treatment of type II diabetes mellitus by decreasing insulin resistance. The study was performed on the active compound, on the excipients and on the binary mixtures. (1:1, w/w), using two of the most important methods of investigation of compatibility between a pharmaceutical agent and excipients: FT-IR spectroscopy and DSC analysis. Results showed that no interactions occur that alter the molecular structure of the active compound.

KEYWORDS: Pioglitazone · Excipients · FT-IR · DSC analysis

INTRODUCTION:

As any oral formulation, pioglitazone tablets are a mix of the active substance with various excipients. One commercial available pioglitazone based drug contains the following excipients: mannitol, carmellose calcium, hydroxypropylcellulose and magnesium stearate. Excipients are added to the galenic form of a drug to enhance manufacturing, administration or absorbtion of the pharmaceutical agent. DSC was proposed as a rapide and precise method to determine any drug-excipient interactions (Chaves *et al. 2013;* Kumar et al. 2014). Ideally, excipients are inert and do not interact in any way with the active compound but sometimes they can initiate or participate to chemical processes involving the pharmaceutical agent, hence they may alter the therapeutic effectivenes (Nishath *et al.* 2011).

FT-IR spectroscopy is a very suitable method to determine any interactions between a pharmaceutical active compound and excipients because the spectra will show any modification of the functional groups that are present in the molecular structure of the drug. If there is a good compatibility between a drug and an excipient, this can be determined by evaluating the FT-IR spectrum of the binary mixture.

This study also provides informations about the thermal effects of pioglitazone, that are recorded when the sample is heated. One of the best techniques available to investigate de thermally induced interactions is differential scanning calorimetry (DSC) because it gives us valuable informations about any thermal effects that occurs in the sample. So in order for us to draw the conclusions we performed DSC analysis for pioglitazone, the excipients and binary mixtures (1:1, w/w) of the active compound and the excipient.

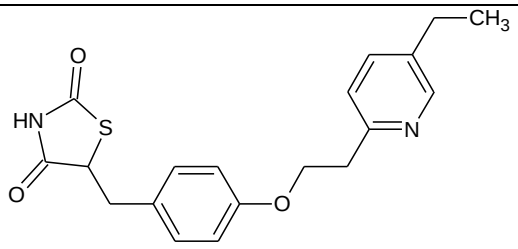

Fig.1 The chemical structure of pioglitazone

MATERIALS AND METHODS:

The pharmaceutical agent, pioglitazone hydrochloride, was purchased from Sigma (lot #022M4747V) and was further used as received from the producer. The excipients used in this study are: mannitol (Fluka), hydroxyethylcellulose (Merck), magnesium stearate (UTCHIM), microcrystalline cellulose (Aldrich), talc (Fluka) and silicon dioxide (Aldrich).

The FTIR spectra for pioglitazone, the excipients and the binary mixtures were recorded with a Perkin Elmer Spectrum Two spectrometer equipped with an UATR accesory for solid samples. Data recorded was further processes by Perkin Elmer Spectrum software.

DSC data was recorded on a Perkin Elmer Pyris Diamond DSC while the samples were sealed in aluminum crucibles. The temperature programe was set from 40 to 350°C with a heating rate of $10°C \cdot min^{-1}$, while all the data was processes by Perkin Elmer Pyris software.

RESULTS AND DISCUSSIONS:

FT-IR analysis

FT-IR spectroscopy was performed for a sample of pioglitazone to determin the characteristic functional groups in order to make our first assumptions about the possible interactions between the pharmaceutical agent

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and the excipients taken in account (Albu *et al.* 2015) [5]. The next step was evaluating the FT-IR spectra of the binary mixtures. Of course prior to this, FT-IR spectra of each excipient was recorded as well. It is correct to assume that if no characteristic peaks disapear, nor other new ones can be observerd on the FT-IR spectra of the binary mixture, then probably no chemical interactions occur between the two components. This is not a very precise method, but it can eliminate some uncertainties.

Figures 2 to 7 show the split overlap of the FT-IR spectra of pioglitazone, each of the excipients and the binary mixture (1:1, w/w). After a complete analysis of the FT-IR spectra recorded we noticed that no interactions involving degradation of any functional groups or molecular structure occured in the binary mixture of pioglitazone and each of the excipients. The only modifications on the spectra are due to overlapping of more intense peaks.

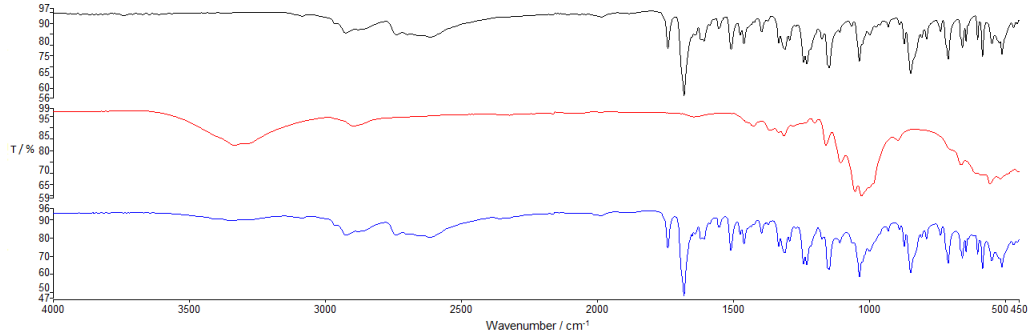

Fig.2 FT-IR spectra of pioglitazone, microcrystalline cellulose and the binary mixture (bottom)

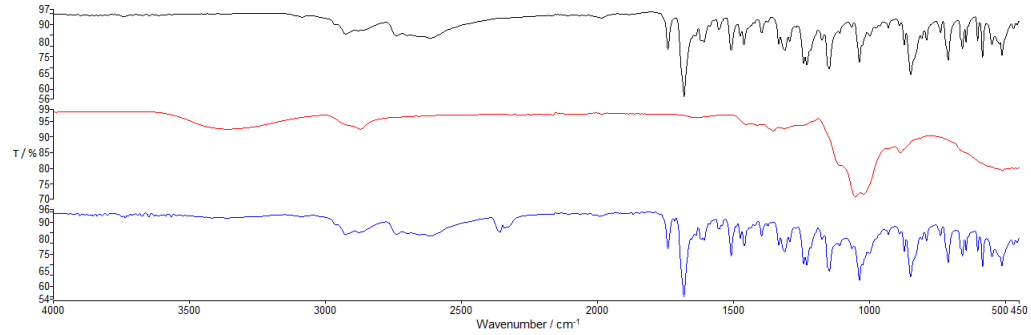

Fig.3 FT-IR spectra of pioglitazone, hydroxuethylcellulose and the binary mixture (bottom)

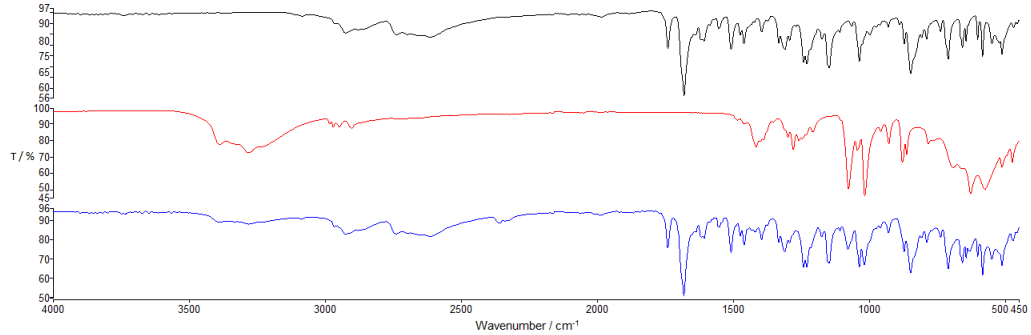

Fig.4 FT-IR spectra of pioglitazone, mannitol and the binary mixture (bottom)

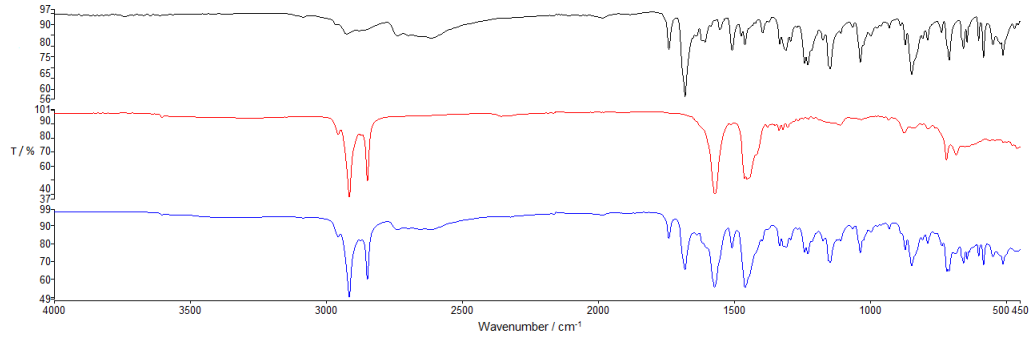

Fig.5 FT-IR spectra of pioglitazone, magnesium stearate and the binary mixture (bottom)

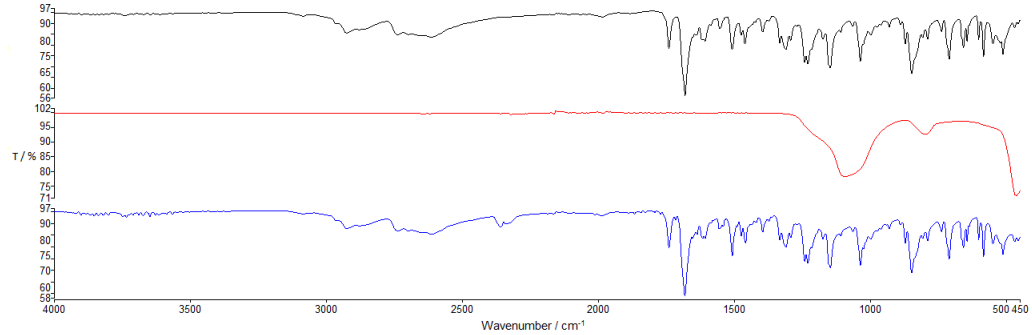

Fig.6 FT-IR spectra of pioglitazone, silicon dioxide and the binary mixture (bottom)

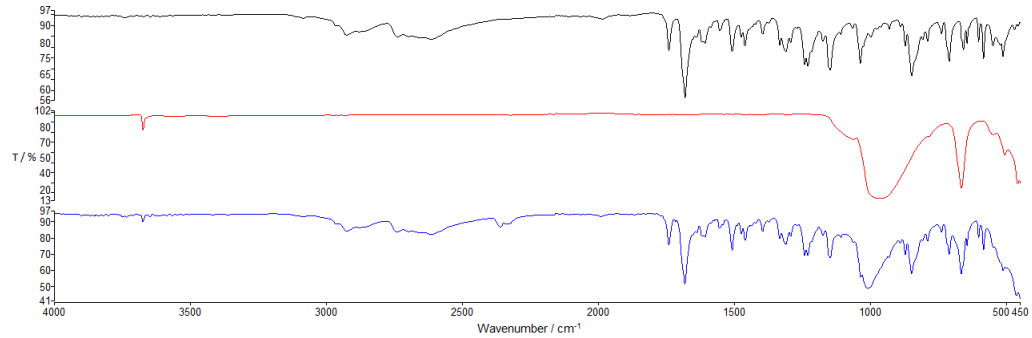

Fig.7 FT-IR spectra of pioglitazone, talc and the binary mixture (bottom)

DSC analysis

DSC is one of the thermoanalytical methods used to investigate drug molecules (Fulias *et al. 2013;* Duda-Seiman *et al. 2011*), but DSC is also one of the well-developed techniques used in detection of incompatibilities in drug/drug and drug/excipient interactions. DSC is able to measure energy directly and allows precise measurements of heat capacity, hence any interactions of the pharmaceutical agent and the excipient are quickly observed. Any chemical process involves a thermal effect so if any differences appear regarding the peaks on the DSC curve of the binary mixture, that are not noticeable on the DSC curve of the active compound or of the excipient, then we can definitly can confirm interactions between the two molecules.

Figures 8 to 13 represent the overlaped DSC curves of pioglitazone with each of the excipients and in the binary mixture.

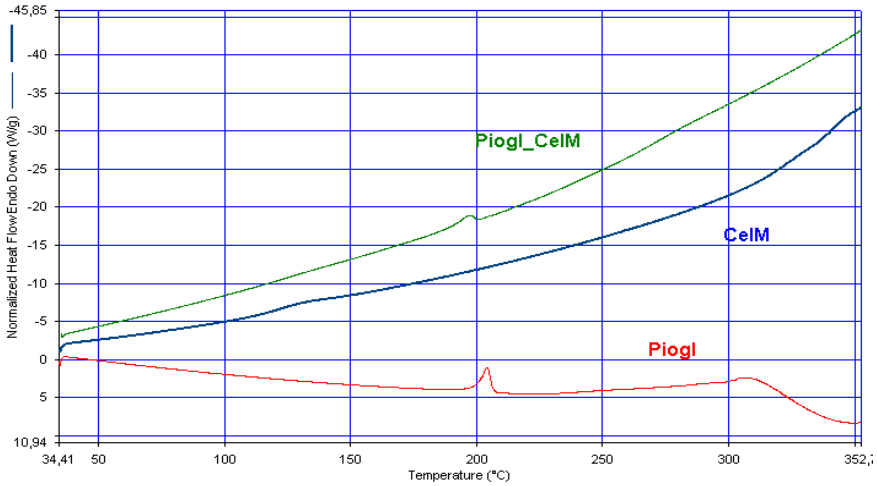

Fig.8 DSC curves of pioglitazone, microcrystalline cellulose and the binary mixture (1:1, w/w)

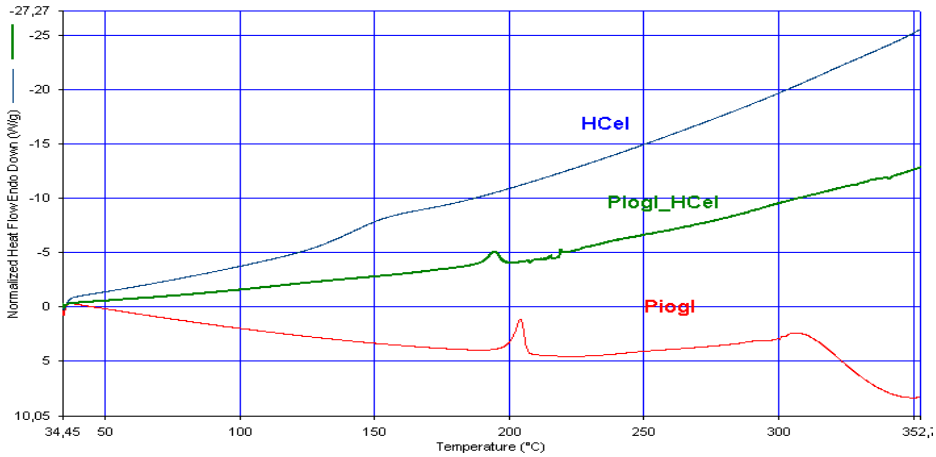

Fig.9 DSC curves of pioglitazone, hydroxyethylcellulose and the binary mixture (1:1, w/w)

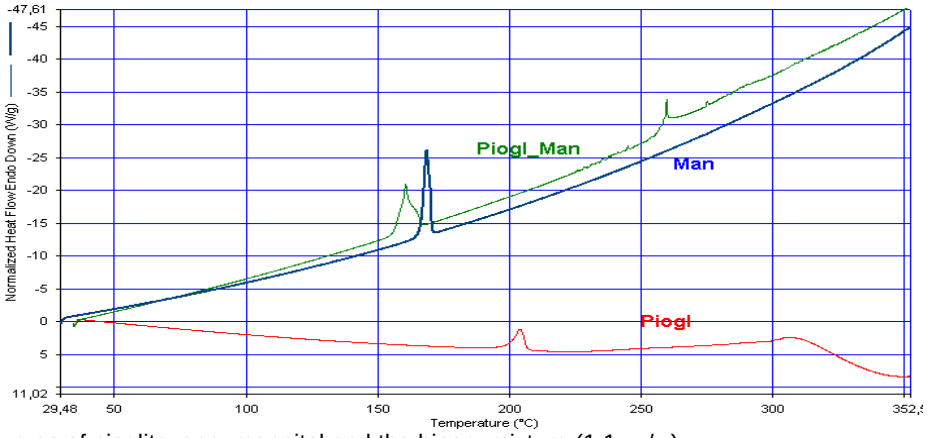

Fig.10 DSC curves of pioglitazone, mannitol and the binary mixture (1:1, w/w)

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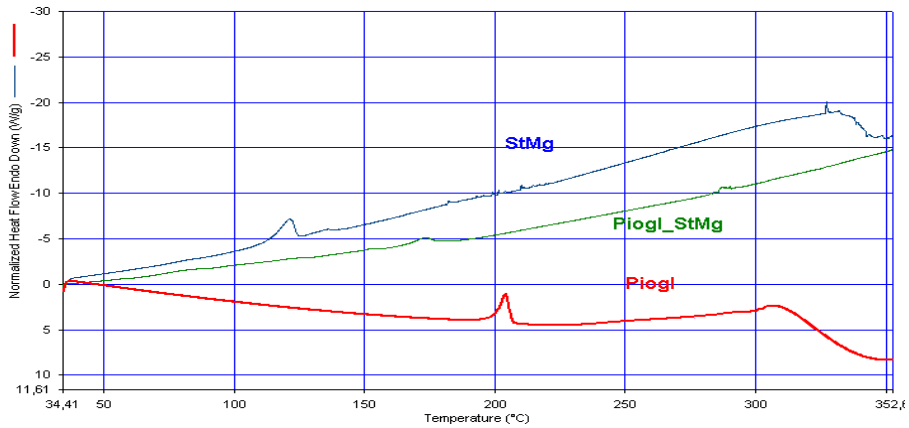

Fig.11 DSC curves of pioglitazone, magnesium stearate and the binary mixture (1:1, w/w)

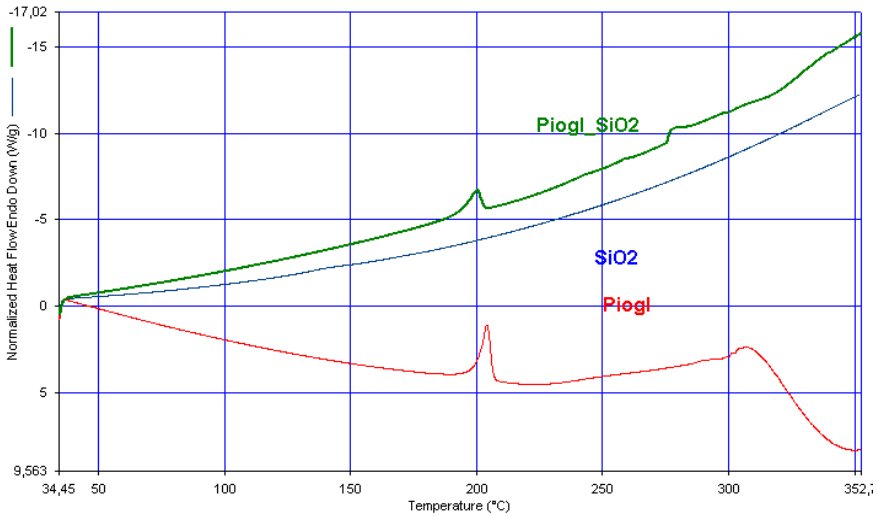

Fig.12 DSC curves of pioglitazone, silicon dioxide and the binary mixture (1:1, w/w)

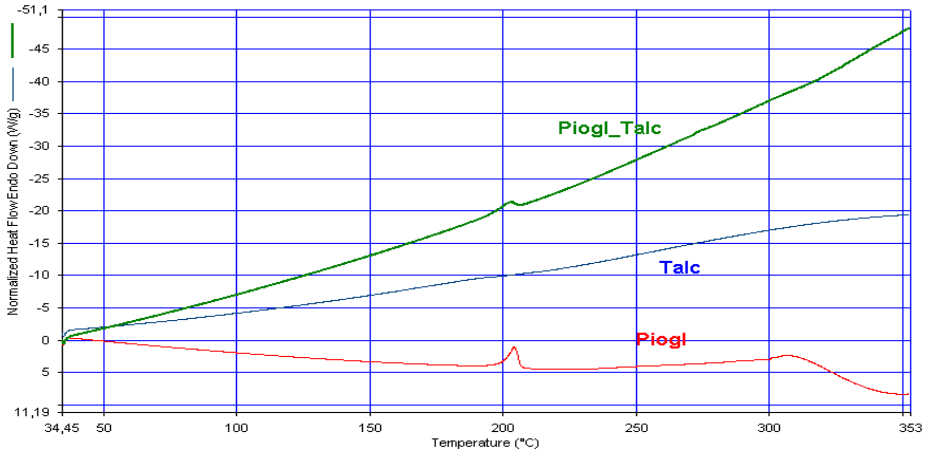

Fig.13 DSC curves of pioglitazone, talc and the binary mixture (1:1, w/w)

CONCLUSIONS:

In this paper we investigated the compatibility between an antidiabetic agent, pioglitazone hydrochloride, and 6 different excipients. Incompatibility between drug and excipient can alter stability and bioavailability of drugs, thereby, affecting its safety and/or therapeutic effect. Drug–excipient compatibility studies are an essential step in the development of a stable solid dosage form.

This study performed two of the most important methods of investigating drug-excipient interactions: DSC and FT-IR analysis. All the data gathered helped us to conclude that no interactions that could alter the molecular structure of the pharmaceutical active compound are to occur at room temperature. On the other hand, DSC showed that the binary mixtures of pioglitazone with magnesium stearate and hydroxyethylcellulose have an ideal thermal behavior i.e. the DSC curve of the mixture is a mean

reprezentation of the compounds that form the mixture. The other mixtures show a slightly more pronounced exothermic effect than we could predict from the DSC curves of pioglitazone and of the excipients. Although this is an observation that is to be taken into consideration, we must emphasise that the mixtures show only the peaks found on the DSC curves of the compounds outside the mixture.

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