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
absorption of the pharmaceutical agent. DSC was
proposed as a rapid and precise method to determine
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 effectiveness (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.

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 accessory 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·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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Article published: May 2015
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 disappear, nor other new ones can be observed 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 occurred 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, hydroxyethylcellulose and the binary mixture (bottom)

Fig.4 FT-IR spectra of pioglitazone, mannitol and the binary mixture (bottom)
Investigation of thermally induced interactions between pioglitazone and some excipients by FT-IR and DSC analysis

**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 definitively confirm interactions between the two molecules.

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

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

Fig.2 DSC curves of pioglitazone, silicon dioxide and the binary mixture (1:1, w/w)

Fig.3 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...
representation 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.

ACKNOWLEDGMENT: This paper was supported by grant POSDRU/159/1.5/S/133391

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