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Dedicated to the memory of
Professor Ioan Silaghi-Dumitrescu (1950 – 2009)

THERMAL BEHAVIOUR OF ACTIVE COMPOUNDS *VERSUS* PHARMACEUTICAL COMPOUNDS FOR SOME BENZODIAZEPINES

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The thermal behaviour of diazepam, nitrazepam and oxazepam was studied under non-isothermal conditions and dynamic nitrogen atmosphere, in comparison with pharmaceutical products containing the corresponding active substances. Also, the FT–IR spectra of the same samples were recorded.
The main conclusion of this comparative study was that the TG/DTG and DSC diagrams, together with the FT–IR spectra constitute believable data for the discrimination between the pure substances and any pharmaceutical form.

INTRODUCTION

The thermal analysis is a routine method to analyze drugs and substances of pharmaceutical interest. The application of thermal methods, especially TG, DTG and DSC is very important when solving pharmaceutical problems, like for example the determination of purity level, qualitative and quantitative analysis of the medicinal compositions, stability tests, kinetic parameters' determination, etc.[1-7]

In an earlier paper[8] was demonstrated the possibility to analyzed the thermal "sensitive" part of a molecule by means of an adequate processing of the thermogravimetric data in connection with the FT–IR spectra.

In this work, the thermo-analytical techniques have been used to study the diazepam's, nitrazepam's and oxazepam's (pure substances: I–III) thermal behaviour in non-isothermal conditions, in comparison with the pharmaceutical products (I P–II P) which contain the same active compounds.

Also, the FT–IR spectra of pure substance and the pharmaceuticals were drawn up in order to establish an easy way for sample identification by means of a simultaneous analysis of TG/DTG and DSC curves and FT–IR spectra.

The influence of heating rate on the thermal decomposition was followed through DSC technique.

The active compounds studied are presented in Fig. 1.

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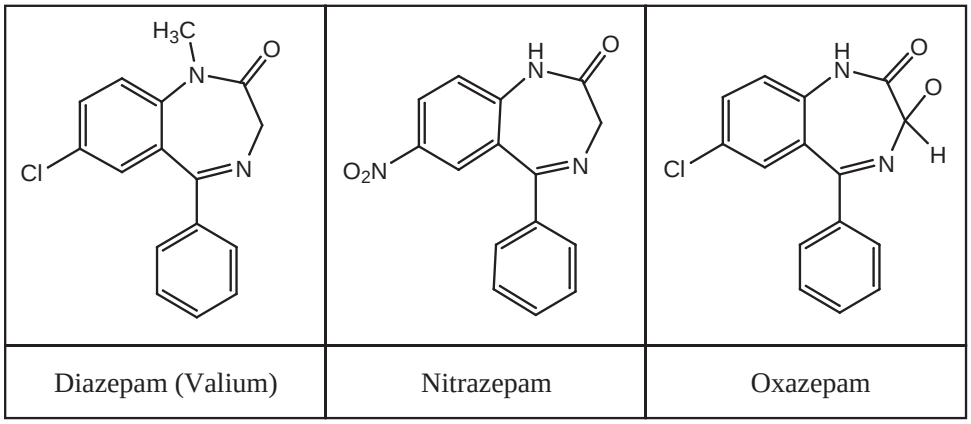

Fig. 1 – Structural formula of the benzodiazepines.

RESULTS AND DISCUSSION

1) The TG/DTG curves for the studied samples are presented in Figs. 2-4, and curves DSC in Figs. 5-7.

The main observations are summarized in Table 1.

From the presented data (Table 1) results a simple manner in which the concerned samples can be differentiated: diazepam's decomposition (as an active compound) takes place in a single step, with a peak at 300°C (curve DTG); this also appears, clearly enough, in the pharmaceutical product (I P).

The nitrazepam has as characteristic two (endothermic) peaks, at 150°C and respectively at 250°C. They are also present in the pharmaceutical product (II P), being well accentuated.

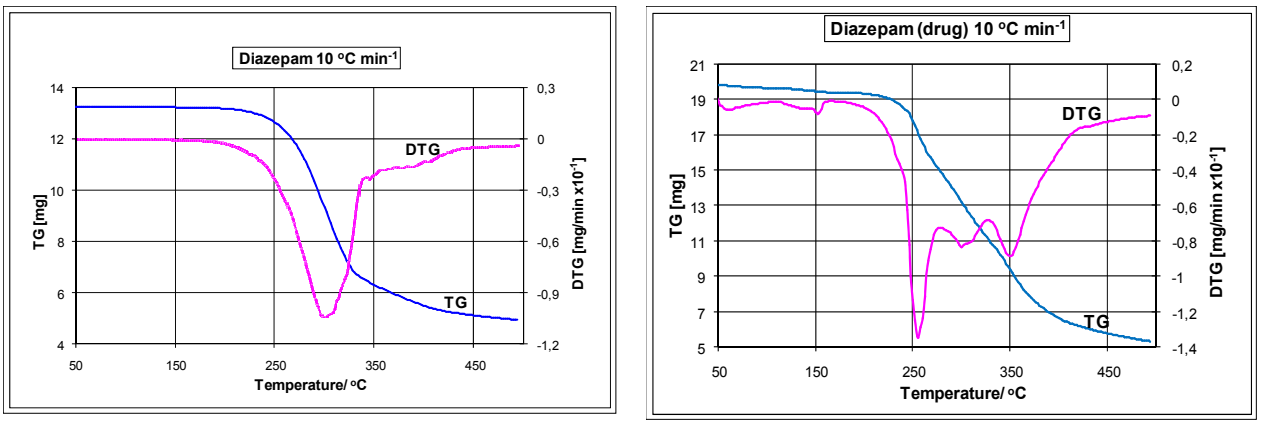

Fig. 2 – TG/DTG curves for I and I P.

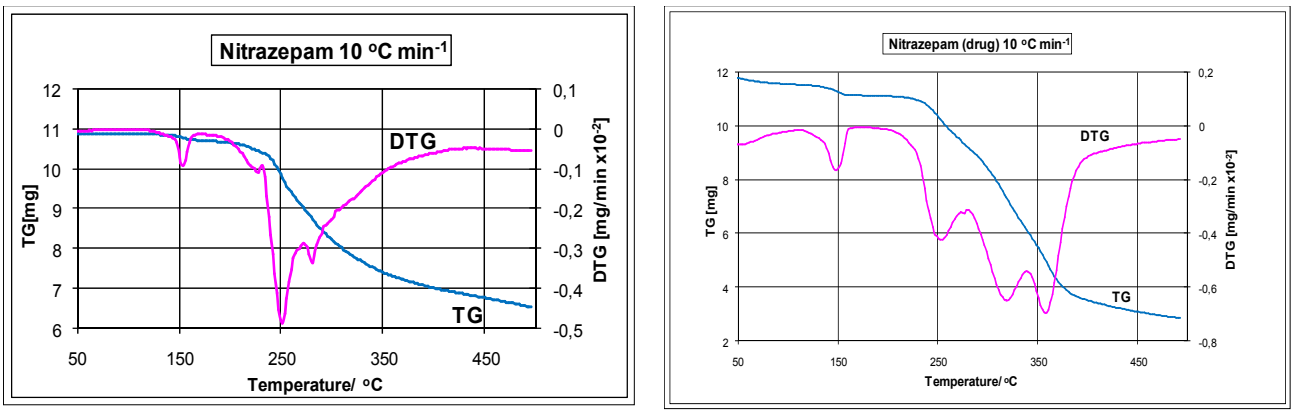

Fig. 3 – TG/DTG curves for II and II P.

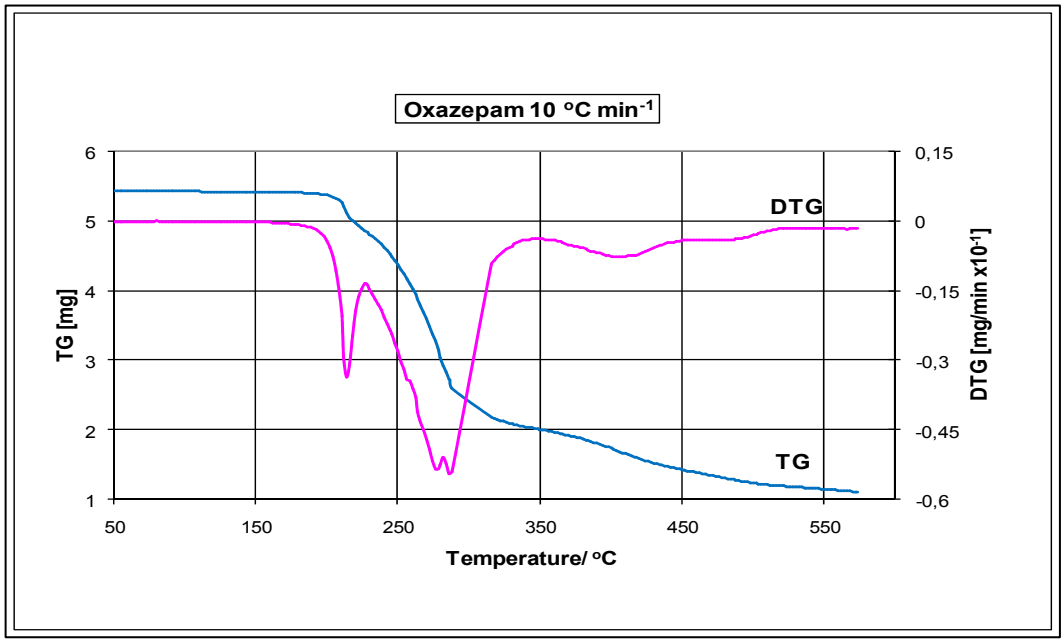

Fig. 4 – TG/DTG curves for oxazepam III.

Table 1

Characteristics of the thermal behaviour of the studied samples

Sample	Range of mass loss, °C	Maximum of DTG, °C	Mass loss, Δm, %
I	220–360	300	61.7
I P	230–420	250; 300; 350	73.0
II	140–150; 210–400	150; 250; 280	40.2
II P	140–160; 240–400	150; 250; 320; 360	72.4
III	210–350	215; 270–285	79.6

Regarding oxazepam, there are present, as well, two (endothermic) peaks, at 215°C and respectively at 270–285°C. Just as expected, the pharmaceutical (commercial) products show supplementary decomposition steps in comparison to the active compounds. These steps are accentuated on the DTG curves, by the corresponding peaks and are due to the presence of excipients, in fact to their possible interactions with the active substance. Also, the loss mass, in wt.%, is higher for pharmaceutical products in comparison to the active substance.

According to the DSC curves, the active substances, as well as the pharmaceutical products act in the same manner thermally, but still showing some differences regarding the nature and the number of the processes taking place, which was expected.

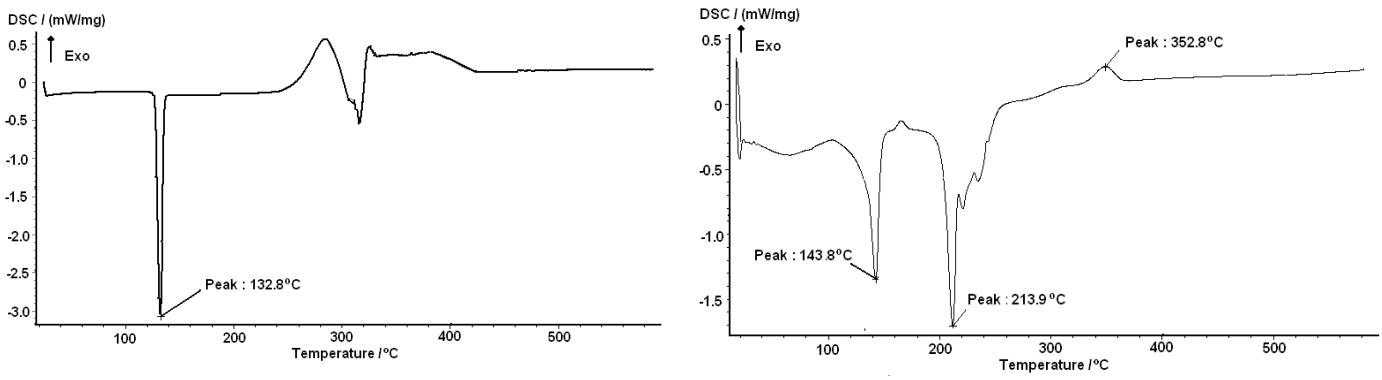

Fig. 5 – DSC curves for I and I P.

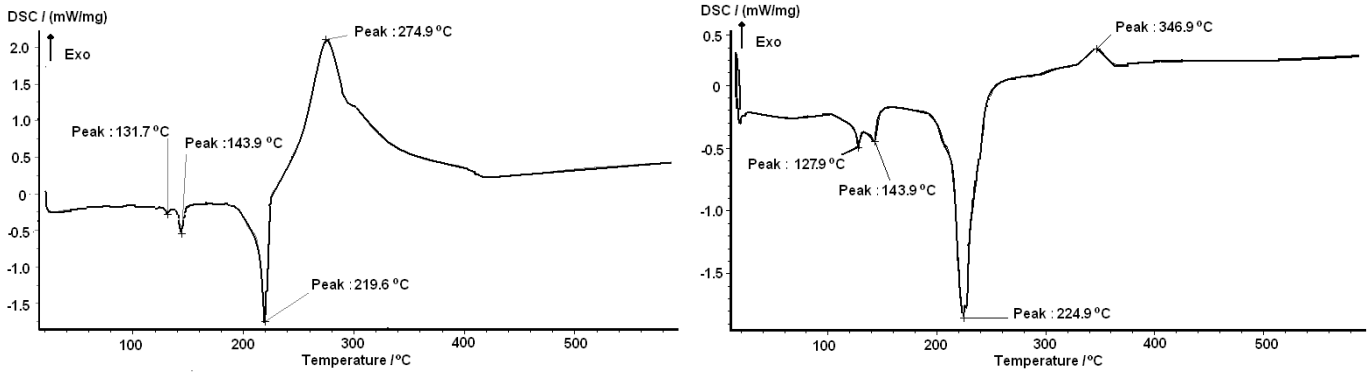

Fig. 6 – DSC curves for II and II P.

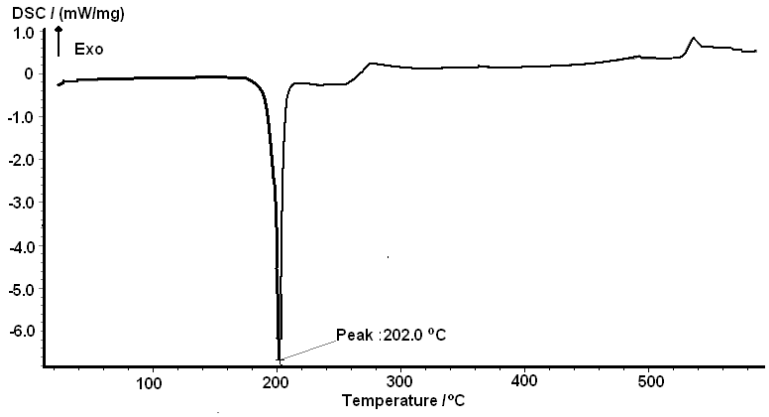

Fig. 7 – DSC curve for III.

A practical example for the influence of the heating rate is the variation mode of the melting point, it values being determined from the DSC curves and included in Table 2.

The TG/DTG and DSC curves shifted to higher temperatures with increasing heating rate.

2) The FT–IR spectra are presented in Figs. 8–10.

Table 2

Values of the melting point at the heating rates of 5, 7, 10, 12 and 15°C·min^{-1}

Compound	Melting point (°C)				
	5°C·min^{-1}	7°C·min^{-1}	10°C·min^{-1}	12°C·min^{-1}	15°C·min^{-1}
Diazepam	131.3	131.6	132.8	132.9	136.7
Nitrazepam	215.7	217.5	219.6	219.9	220.9
Oxazepam	195.1	199.0	202.0	204.2	207.5

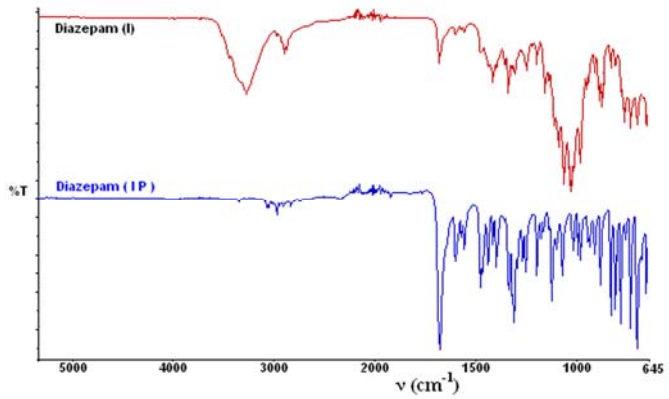

Fig. 8 – FT–IR spectra of I in comparison with I P.

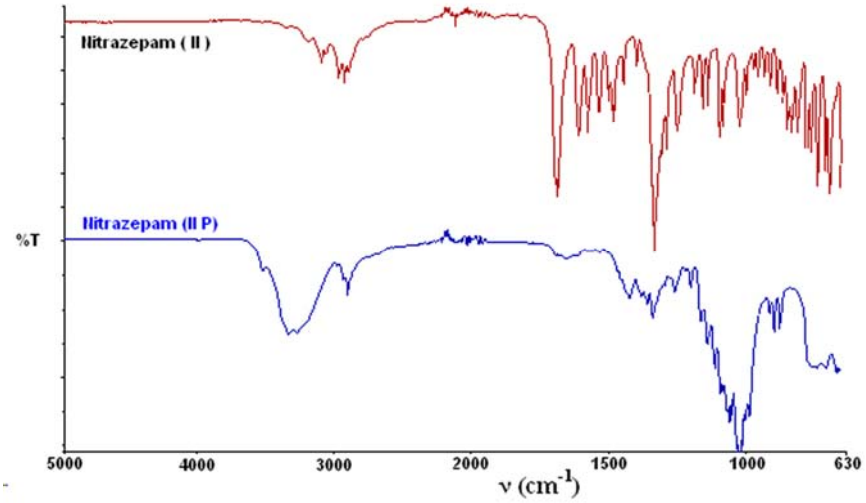

Fig. 9 – FT–IR spectra of II in comparison with II P.

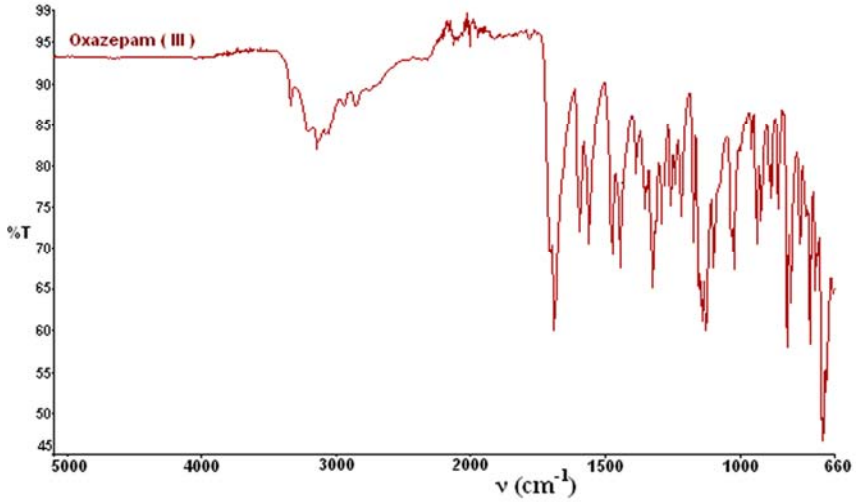

Fig. 10 – FT–IR spectrum of III.

Table 3

Characteristics of the FT–IR spectra for active substances

Common bands for all the three compounds		
Wave number, cm^{-1}		Assignments
1650–1580		C=C and C=N
1175–1125		trisubstituted benzene
1070–1000		trisubstituted benzene
1022		monosubstituted benzene
816		C–H stretching in heterocycles
Specific bands		
Compound	Wave number, cm^{-1}	Assignments
Diazepam	1700–1680	stretching of C=O in acyl dimmers
	1470–1435	asymmetric C–CH_3
	1385–1370	asymmetric C–CH_3
	984	δ_{CH3} in heterocycles
	740	monochloro derivatives
Nitrozepam	1550–1510	asymmetric NO_2 in aromatics
	1365–1335	asymmetric NO_2
	860–840	C–N stretching
Oxazepam	3500–3300	OH group and hydrogen banded OH
	1700–1680	stretching of C=O in acyl dimmers
	740	monochloro derivatives

Using the FT–IR spectra, a facile identification of the active compound is possible. According to the data systematized in Table 3, the three active compounds show common and specific well defined bands. For example, for diazepam (I) the simultaneous presence of bands due to methyl and chloride is characteristic. As for nitrazepam, the specific band is that corresponding to the nitro group, when in the case of oxazepam, the presence of bands due to hydroxyl and chloride is characteristic. The assigning from Table 3 is according to.[17,18]

From the FT–IR spectra form and wave number where characteristic bands appear, the active substance and its pharmaceutical form can be easily differentiated. According to spectra from Figs. 8 and 9, the pharmaceuticals present bands at 3280, 3329 and 2900 cm^{-1}, a range where the active compounds don't have characteristic bands.

The melting point is commonly used as a preliminary identification parameter for crystalline organic compounds. In comparison with the melting point determined by using the classical methods, the determination under a dynamic flow of dry nitrogen can provide a reliable value for the fusion temperature.

This justifies the usage of DSC as a routine technique for the identification and quality control of the active substances created for pharmaceutical usage, by melting point.

A considerable effect of heating rate on the thermal decomposition of benzodiazepines may due to a complexity of the thermal rearrangement of examined compound to the intermediate products.

The simultaneous analysis of the TG–DTG–DSC and FT–IR data constitutes a credible and secure method of control and just evaluation in the practice of the pharmaceutical benzodiazepines.

EXPERIMENTAL

The active substances (I–III) were available as pure compounds, able to be used for medical purposes. They are obtained from Terapia SA/ Ranbaxy, Cluj-Napoca, Roumania.

The pharmaceuticals (IP–IIP) were commercial products, containing different (qualitative and quantitative) excipients.

TG/DTG experiments were performed with a Perkin-Elmer Diamond thermobalance, in the temperature range of 25–600°C, under an atmosphere dynamic of nitrogen at a flow rate of 100 $ml \cdot min^{-1}$. Samples with the mass in the range of 5–25 mg were put into aluminium crucibles, at a heating rate of $10°C \cdot min^{-1}$

DSC curves were recorded with a Netzsch differential scanning calorimeter, model DSC–04, using aluminium crucibles with samples of 2 mg, in a dynamic nitrogen atmosphere, with a constant flow of 50 $ml \cdot min^{-1}$ and heating rates of 5, 7, 10, 12 and $15°C \cdot min^{-1}$, up to a temperature of 600°C.

Fourier transform infrared (FT–IR) spectra were recorded to the room temperature, in the range of 4000–400 cm^{-1}, as powder, on a Perkin–Elmer spectrum 100 device using the U–ATR technique.

CONCLUSIONS

The thermal and infrared analysis was simultaneously performed for the three benzodiazepines and their pharmaceutical forms. There have been observed significant differences between the TG/DTG curves of the pure compound and those of the pharmaceutical products.

Also, between the FT–IR spectra of the two compounds categories, there are significant differences.

Less significant differences have also been observed on the DSC curves.

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