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THE INFLUENCE OF STORAGE CONDITIONS ON THE POLYMORPHIC STABILITY OF ZOLPIDEM TARTRATE HYDRATE

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The polymorphic stability of a drug substance is a very important topic in the pharmaceutical industry. Differential scanning calorimetry, thermogravimetric analysis with the support of X-ray powder diffraction and infrared spectroscopy were used as screening techniques for testing structural changes of zolpidem tartrate hydrate stored under different conditions. Obtained data suggested that first structural changes occurred at the temperature of 25°C after 2 months of storage. DSC analysis showed that there was a two-step process of water elimination and lack of a phase transition in the temperature range from 130 to 170°C in comparison with an initial sample.

Keywords: *drug substance, DSC, infrared spectroscopy (IR), polymorphic stability, thermogravimetric analysis (TG/SDTA), X-ray powder diffraction (XRPD), zolpidem tartrate*

Introduction

The knowledge about active pharmaceutical substance stability is essential in order to know how long such a product can be kept in storage and distribution conditions. The long-term tests of the stability are performed at regular periods in time for samples that have been stored under different conditions of humidity and temperature [1, 2]. The studies of a drug substance kept under different conditions give additional information about its stability and structural changes. The results obtained by thermoanalytical techniques are required for the complete characterisation of physicochemical properties of a drug [3–6].

The aim of this paper is the investigation of influence of temperature and time on the structural changes of zolpidem tartrate hydrate.

Zolpidem tartrate (Fig. 1), (2,3-dihydroxybutanedioic acid; N,N-dimethyl-2-[4-methyl-8-(4-methylphenyl)-6,9-diazabicyclo[4.3.0]nona-2,4,7,9-tetraen-7-yl]-ethanamide) is indicated for the short-term treatment of insomnia [7, 8].

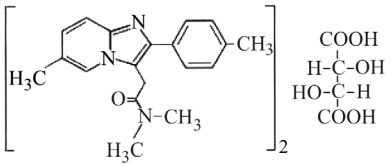

Fig. 1 The chemical structure of zolpidem tartrate [7]

Experimental

Zolpidem tartrate was produced at the Pharmaceutical Research Institute in Warsaw. The measurements were performed for the initial sample of zolpidem tartrate and following samples: stored at the temperature of 5°C for 2 years, at 25°C in the humidity of 60% for 2 months, at 25°C in 60% for 2 years, at 40°C in 75% for 1 and 6 months. Samples were characterized by a very low solvents content (below 0.1%).

Thermal analyses were carried out by means of the DSC822 with IntraCooler and the TGA/SDTA 851 cells (Mettler Toledo) in the nitrogen atmosphere. Accurately weighed samples (5–7 mg) were packed in the aluminum pan with the pierced lid. For both experiments, samples were heated from 30 to 260°C, with the scanning rate of 10°C min^{-1}. The two-minute isothermal step at 30°C preceded the dynamic temperature regime for DSC measurements. The DSC instrument was calibrated using indium and zinc as standards, however for the TG instrument indium and aluminium were used. TG measurements were blank curve corrected.

XRPD studies were performed by means of the MiniFlex diffractometer (Rigaku Corporation, Tokyo Japan) using $CuK_{\alpha 1}$. Samples were pressed on a glass plate. The instrument was operated in the continuous scan mode in the range from 3 to 40°.

The IR spectra were recorded on a Perkin-Elmer FT-IR BX spectrometer. Solid samples were measured in KBr pellets. A spectral resolution of 4 cm^{-1} was used.

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Results and discussion

TG and DSC characterisation

TG and DSC curves of the initial and stored samples of zolpidem tartrate are shown in Fig. 2. Thermogravimetric and DSC results of the initial sample and the sample stored at 5°C for two years were similar (Figs 2a and b). The thermogravimetric analysis of these samples revealed that the first endothermic peak was connected with the presence of water of crystallization. In the temperature range from 130 to 170°C, endo- and exothermic peaks can indicate a phase transition that completely disappeared for samples stored at 25 and 40°C. Furthermore, TG and DSC curves of samples stored at higher temperatures, revealed visible changes in the area of the crystallization water elimination (Figs 2c–f). TG and DSC curves of the samples stored at 25°C for two months and two years showed a two-step process of water elimination. However, further temperature increase, up to 40°C, brought about one-step of water evaporation but in the lower temperature range (Figs 2e and f).

XRPD analysis

XRPD patterns of the initial and stored zolpidem tartrate samples under different conditions are compared in Fig. 3. There were not any visible changes between powder diffractograms of the initial sample and the sample stored at the temperature of 5°C for 2 years (Figs 3a and b). First distinguishable diffraction peaks appeared at 10.2 and 14.0° for the sample stored at 25°C for 2 months (Fig. 3c). Similar changes were observed for the sample stored at 25°C for 2 years (Fig. 3d). Additionally, there was lack of the peak at 16.5° in comparison with the initial sample. The most representative diffraction peaks at 6.5, 8.9 and 19.8° of samples stored at 5 and 25°C were absent

TG curves of Fig. 2					
	a	b	c	d	e
step	–2.8181% –0.1886 mg	–2.6087% –0.1656 mg	–1.2309% –81.7308E-03 mg	–2.1023% –0.1296	–2.4203% –0.1617 mg
left limit/°C	29.80	29.76	29.78	29.82	29.67
right limit/°C	139.96	140.02	108.69	113.06	139.95
step			–1.4619% –97.0650E-03 mg	–0.1669% –10.2892E-03 mg	
left limit/°C			108.69	113.06	
right limit/°C			139.93	139.93	

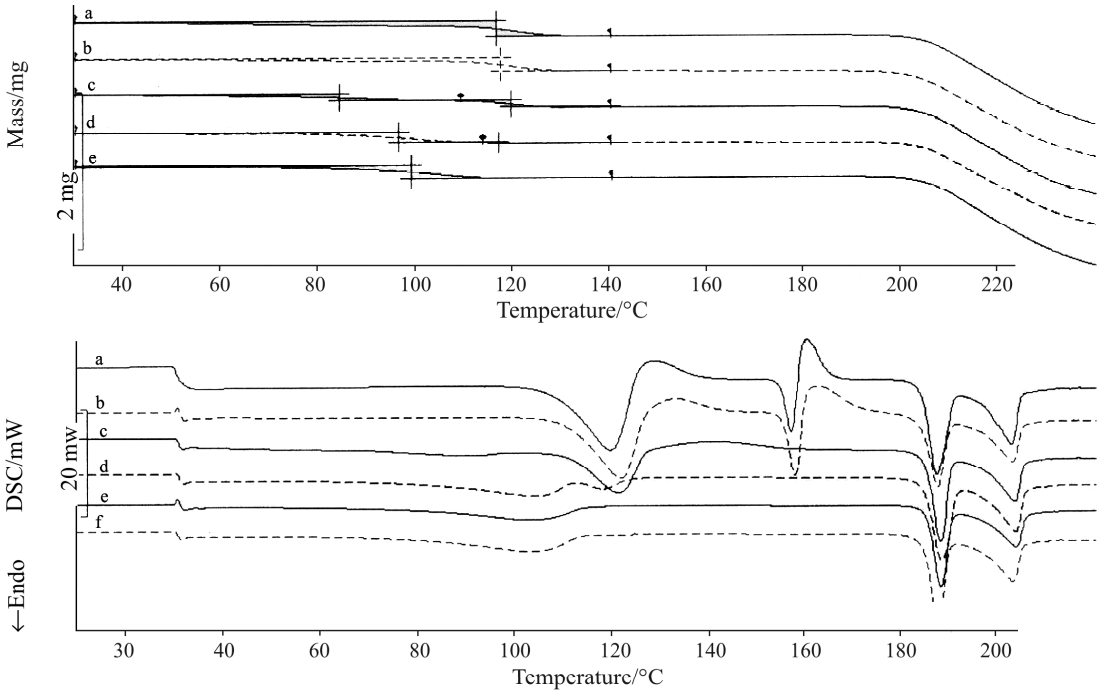

Fig. 2 TG and DSC curves of a – the initial sample and samples of zolpidem tartrate hydrate: stored b – at 2 years at 5°C, c – at 2 months at 25°C, d – at 2 years at 25°C, e – at 1 month at 40°C; and DSC curves of the sample of zolpidem tartrate hydrate stored f – at 6 months at 40°C the initial and stored samples of zolpidem tartrate hydrate

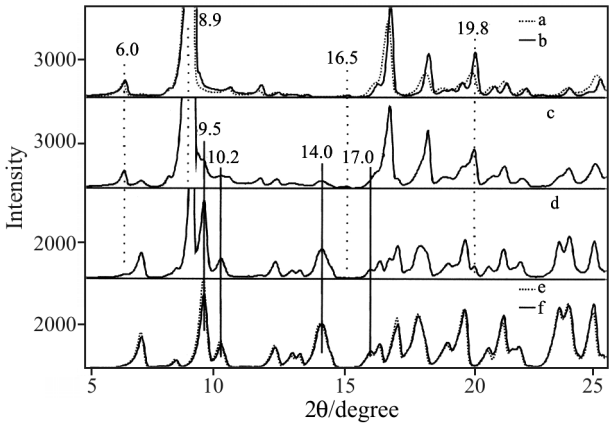

Fig. 3 X-ray diffraction patterns of a – the initial zolpidem tartrate and samples: stored b – at 5°C for 2 years, c – at 25°C for 2 months, d – at 25°C for 2 years, e – at 40°C for 1 month and f – at 40°C for 6 months

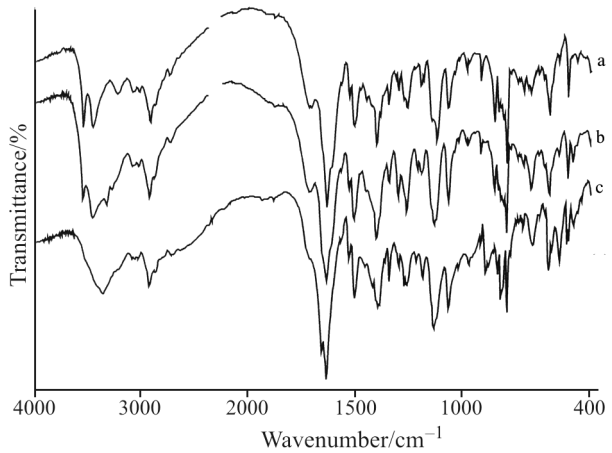

Fig. 4 IR spectra of zolpidem tartrate samples in KBr pellets: a – the initial sample, the sample stored b – at 25°C for 2 months and c – at 40°C for 6 months

in diffractograms of samples stored at 40°C for 1 and 6 months (Figs 3e and f). Characteristic peaks that appeared and disappeared during the duration of storage process are pointed by full and dotted straight lines, respectively.

IR studies

The IR spectra of selected zolpidem tartrate samples are shown in Fig. 4. There were not any visible changes in IR spectra of the initial sample and the sample stored at the temperature of 5°C for 2 years. First small changes appeared for the sample stored at 25°C for 2 months in the region of O–H stretching vibration that was involved in the hydrogen bonds region from ~3600 to ~3150 cm^{-1} (Fig. 4b). The most important changes occurred for the sample stored at 40°C also in the region of O–H stretching vibrations involved in the hydrogen bonds region. There was one broad structured band with maximum ~3353 cm^{-1}. Additional changes occurred in the region of C=O and C=N stretching vibrations from ~1760 to ~1580 cm^{-1} and in the region from ~930 to ~750 cm^{-1}.

Conclusions

The studies clarified that the water molecule has been incorporated into the zolpidem tartrate crystal lattice.

It has been shown that storage conditions have substantial influence on the zolpidem tartrate stability. First structural changes occurred at the temperature of 25°C after 2 months of storage but the most rapid transformation appeared to be at the temperature of 40°C.

The results demonstrated that DSC technique is a very useful tool for a quick screening of structural changes occurring during long-term stability tests. TG provides solutions of potential problems with solvates. Thermal analysis results supported by XRPD and IR measurements ensure reliable interpretation of pharmaceuticals studies.

References

1 CPMP/ICH/2736/99: Stability testing of new drug substances and products (second revision).
2 J. T. Carstensen, Drug stability, principles and practises, edited by J. T. Carstensen and C. T. Rhodes, Marcel Dekker, Inc, New York 2000, pp. 145–148.
3 R. K. Khankari and D. J. W. Grant, Thermochim. Acta, 248 (1995) 61.
4 D. Giron, J. Therm. Anal. Cal., 64 (2001) 37.
5 D. Giron, J. Therm. Anal. Cal., 73 (2003) 441.
6 M. R. Caira, A. Foppoli, M. E. Sangalli, L. Zema and F. Giordano, J. Therm. Anal. Cal., 77 (2004) 653.
7 http://pubchem.ncbi.nlm.nih.gov
8 Eu. Pharm. 5th Edition, Vol. 2, 2005, p. 2734.

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