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The mechanism and kinetics of the thermal decomposition of telbivudine

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ABSTRACT

The thermal decomposition of Telbivudine (LdT) was measured with thermogravimetry (TG), differential scanning calorimetry (DSC), and thermogravimetric analysis coupled with Fourier transform infrared spectroscopy (TGA–FTIR). The infrared spectra of LdT, its gaseous products, and the remainders of thermal decomposition at various temperatures were determined. The molecular bond orders were calculated by GAMESS program of quantum chemistry, and the mechanism of thermal decomposition of LdT is discussed. The kinetic parameters of thermal decomposition such as activation energy E_a and the pre-exponential factor A were obtained with the Ozawa method. The prospective lifetime of LdT was estimated with the Dakin equation. The results indicated that the thermal decomposition of LdT is a two-step process. Fracture of the peptide bond connecting the thymine and furan rings occurs in the initial step. Under nitrogen atmosphere, the temperature range of decomposition is from 198 °C to 314 °C, the E_a and A of the thermal decomposition process at the initial stage are 120.9 kJ mol^{-1} and 1.66×10^{11} min^{-1}, respectively. In air, the temperature range of decomposition is from 199 °C to 309 °C, and the corresponding E_a and A are 133.0 kJ mol^{-1} and 3.89×10^{12} min^{-1}, respectively. The thermal stability of LdT is very good under routine temperatures.

1. Introduction

Telbivudine (LdT), which chemical name is 1-(2-deoxy-β-L-*erythro*-pentofuranosyl)-5-methyl pyrimidine-2,4(1*H*,3*H*)-dione, is an antiviral drug used to treat hepatitis B infection. It is marketed by the Swiss Pharmaceutical Company Novartis under the trade names Sebivo (Europe) and Tyzeka (United States). Clinical trials have shown it to be significantly more effective than lamivudine or adefovir and less likely to cause resistance [1–6].

Thermoanalytical techniques have been widely applied in the pharmaceutical field for several purposes including purity determination of drugs, composition analysis of drugs and raw materials, melting point testing, crystal formation and change tests, thermal stability of medicines, evaluation of the validity, thermal decomposition kinetics, identification of natural drug, and the process optimization of drug [7–10].

Thermal stability studies and the thermal decomposition mechanism of LdT have important theoretical significance for further understanding of the chemical properties of LdT. It may also have the practical consequences for the production, processing and storage of LdT. Surprisingly however; research on the thermal stability of LdT has not yet been reported. In this paper, the thermal decomposition processes of LdT under nitrogen and air atmospheres were measured with thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). The volatile species that evolved during decomposition were measured with thermogravimetry coupled with Fourier transform infrared spectroscopy (TGA/FTIR), and the residues of thermal decomposition from different stages were distinguished with infrared spectroscopy. The molecular bond orders were calculated with GAMESS program of quantum chemistry, and the mechanism of the thermal decomposition of LdT is discussed. The kinetics of thermal decomposition of LdT were studied with the Ozawa method [11–13]. The apparent activation energy E_a and pre-exponential factor A of thermal decomposition reaction were obtained according to the thermogravimetric curve data under different heating rates. The prospective lifetime of LdT under different temperatures was estimated to provide reference for the correct and reasonable use of this drug.

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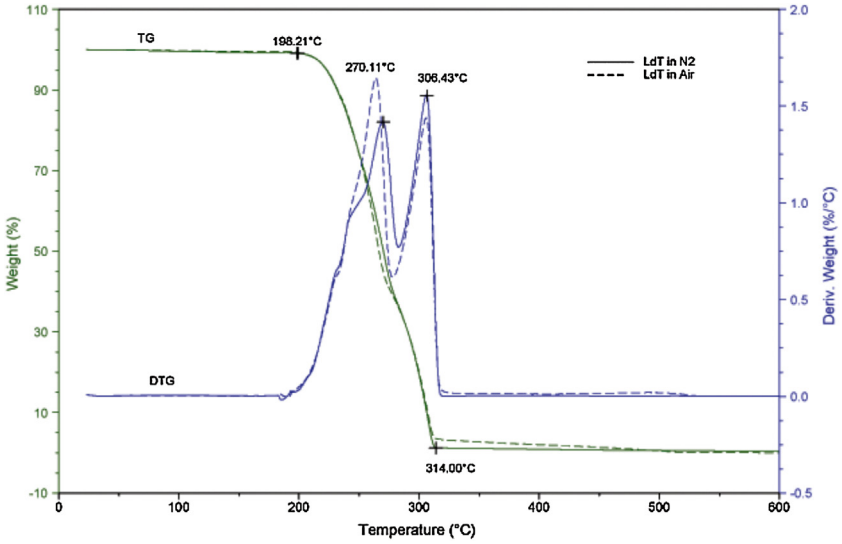

Fig. 1. The TG and DTG curves of LdT (heating rate: 10 °C min^{-1}).

2. Experimental

2.1. Reagents

The LdT was supplied by Hangzhou Coben Pharmaceutical Co. Ltd. (China). The HPLC purity was 99.5%; it was used without further purification.

2.2. Experimental methods

TG-DTG-DSC Simultaneous Thermal Analysis: The TG, DTG and DSC curves of LdT were obtained with a SDT-Q600 Simultaneous Thermal Analyzer (TA Instruments Inc., USA) using an alumina ceramic crucible containing 10 mg of sample under either nitrogen or air atmospheres (100 mL min^{-1}). The heating rate was 10 °C min^{-1} from ambient to 600 °C.

Residues of thermal decomposition: The residues of the thermal decomposition were prepared in a SDT-Q600 simultaneous thermal analyzer using an alumina ceramic crucible containing 10 mg of sample under nitrogen atmosphere at a flow rate of 100 mL min^{-1} and heating rate of 10 °C min^{-1} from room temperature to the selected temperature. Endpoints included: beginning of weight loss, DTG peak, and end of first weight loss, etc.

Infrared spectra of solid samples: The IR absorption spectra of LdT and its solid residues of thermal decomposition were carried out with the Nicolet iS 10 FT-IR spectrophotometer (Thermo Fisher Scientific Inc. USA). The spectra were collected by accumulating 32 scans at a resolution of 4 cm^{-1} from 4000 to 400 cm^{-1} using a KBr pellet technique.

TGA/FTIR: The TGA/FTIR analysis was conducted on a SDT-Q600 Thermal Analyzer coupled with a Nicolet iS10 Fourier-transform infrared spectrometer using a stainless steel transfer line and gas cell. Approximately 10 mg of sample was heated from room temperature to 400 °C at 10 °C min^{-1}. These experiments were carried out in both dry nitrogen and dry air. The flow rate of gases into the TGA/FTIR cell was 80 mL min^{-1}. Both the gas cell for IR detection and the connection line transferring evolved gases from TGA to FTIR were kept at 250 °C to prevent gas condensation. The IR spectra of the evolved gases were collected at 8 cm^{-1} resolution with co-adding of 32 scans per spectrum from 4000 to 500 cm^{-1}.

2.3. Kinetic analysis

Thermal decomposition kinetic analysis and lifetime estimation of LdT used the software package provided by manufacturer. Five different heating rates were used: 2.0, 5.0, 10.0, 15, 20 °C min^{-1} under a dynamic atmosphere with a flow rate of 100 mL min^{-1}.

2.4. Quantum chemical methods

The molecular structure and structure optimization of LdT used ChemDraw software attached to ChemOffice (Version: Ultra 11.0.1, Cambridgesoft, 2007). The GAMESS package is a general ab initio quantum chemistry package attached to ChemDraw and was used to calculate molecular energy, charge distribution and bond order. We used the HF/3-21G level. The calculation accuracy and convergence threshold were the default values in all programs. All the calculations used a PC.

3. Results and discussions

3.1. The thermal decomposition process of LdT

The TG and DTG curves of LdT in nitrogen and air atmosphere at a heating rate of 10 °C min^{-1} are shown in Fig. 1. We can see from the TG curves that the thermal decomposition of LdT is approximately a continuous decomposition process with decomposition beginning at 198 °C. By 314 °C, the decomposition is nearly complete. There are two obvious peaks on the DTG curves that suggest that the thermal decomposition processes of LdT in two atmospheres are actually a two-step processes. Under nitrogen, the DTG peaks are at 270.1 °C and 306.4 °C. In air, the peaks are at 262.3 °C and 300.6 °C. Except for these two differences, the TG and DTG curves of LdT in air and nitrogen are quite similar with the same form, size, initial decomposition temperature, temperature of DTG peak, and rate of weight loss. This suggests that the thermal decomposition processes of LdT in nitrogen and in air atmosphere are essentially the same.

The TG and DSC curves of LdT under nitrogen and air are shown in Fig. 2. The DSC curves are remarkably similar despite the different atmosphere. Before the LdT began to lose weight, the DSC curves have an obvious endothermic peak. This