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Thermal kinetic studies on the decompositions of cefuroxime lysine in different atmospheres and heating rates

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Abstract The thermal decomposition of a new antibiotic agent, cefuroxime lysine, was investigated by thermogravimetry analysis/derivative thermogravimetry and differential scanning calorimetry (DSC) methods in anoxic and oxidative environments. The influence of heating rates (including 5, 10, 15, and 20 °C/min) on the thermal behavior of cefuroxime lysine was revealed. By the methods of Kissinger and Flynn–Wall–Ozawa, the thermal kinetic parameters of activation energy and pre-exponential factor for the exothermic processes under non-isothermal conditions were calculated using the analysis of corresponding DSC curves.

Keywords Cefuroxime lysine · Thermal decomposition · Kinetic

Introduction

Cefuroxime lysine, a new cefuroxime salt considered as the second-generation cephalosporins, has been invented by the Shenzhen Qingdazhong Biotech Co. Ltd. having the patent number of 201010191440.1 in China. Being a new drug having better solubility and stability, as compared with cefuroxime sodium, the thermal stability and decomposition kinetic characteristics of cefuroxime lysine have to be determined for its further application and development (Fig. 1). Thermal analysis is a useful and commonly used technique for fast evaluation of thermal stability and behavior, degradation temperature, absorbed moisture content, crystallized water content, melting point, crystallization, purity, and thermal decomposition kinetics. Currently, the commonly used methods are mainly depending on thermogravimetry analysis (TG)/derivative thermogravimetry (DTG) and differential scanning calorimetry (DSC) methods [1–5]. The thermal stabilities and decomposition kinetics of cefuroxime lysine are critical for the quality control during the manufacturing process. Unfortunately, the detailed studies on the thermal analysis of cefuroxime lysine are missing. Thus, the thermal properties of cefuroxime lysine were revealed here by TG/DTG and DSC methods. In addition, the influence of heating rate and atmosphere on the thermal behavior of cefuroxime lysine was investigated here. Moreover, the kinetic parameters for chemical decomposition were calculated by using the methods of Kissinger and Flynn–Wall–Ozawa [6–8].

Experimental

Cefuroxime lysine, in a crystal III form, was supplied by the Shandong Luoxin Pharmacy Stock Co., Ltd. with a purity of over 97.6%, as determined by HPLC-UV method. The analyses by TG and DSC of cefuroxime lysine were carried out with SHIMADZU TGA-50 or SHIMADZU DSC-60 thermal analysis instruments, performing on a TA-60 thermal analyzer. Thermal properties were examined by TG and DSC methods under a nitrogen atmosphere or an air atmosphere, and which was purged with a gas flow rate of 40 mL/min. The measurements were carried out from room temperature to 350 °C at four different heating rates of 5, 10, 15, and 20 °C/min. Approximately 2.5 mg of the sample was placed in an aluminum pan and Al_2O_3 was selected as the reference material.

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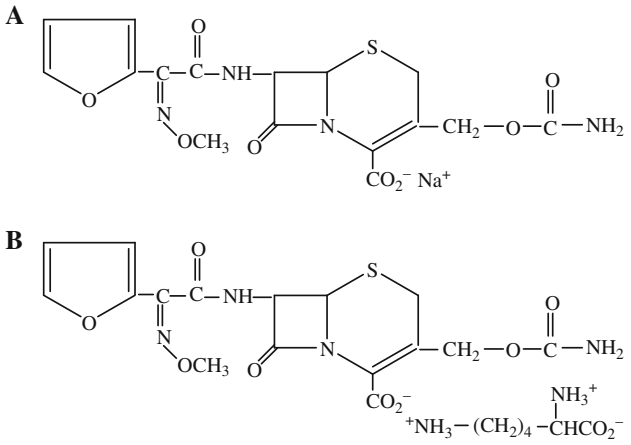

Fig. 1 Chemcial structure of cefuroxime sodium (**a**) and cefuroxime lysine (**b**)

Results and discussion

TG/DTG analysis of cefuroxime lysine

The TG/DTG profiles of cefuroxime lysine at different heating rates and environments after thermal decomposition were presented in Fig. 2. As shown in Fig. 2, the thermal decomposition processes of cefuroxime lysine, both under nitrogen and air, could be revealed basically by three maximum peaks in the TG/DTG profiles, which therefore strongly suggested the degradation of cefuroxime lysine could be mediated by three mass-loss stages. From the DTG curves, the maximum rate of mass loss corresponding to the peak temperature of degradation, i.e., the value for T_p, was revealed. In parallel, the onset temperature of degradation (T_{onset}) could be calculated from the TG curves by extrapolating the curves at the peak of degradation to the initial mass [9]. The characteristic temperatures and corresponding mass loss (%) in the first (I) and second (II) thermal decomposition processes were being listed in Table 1.

The temperature range of the first degradation stage was 68.50–100.77 °C, having a mean mass loss of 2.314%, which might be because of an increased amount of absorbed water. At the second stage of degradation between 176.41 and 191.31 °C, the mass loss was 12.30%, and thereafter the TG curves showed a strong mass loss after this temperature. From the experimental results, it was obvious that the TG curves could be migrated, both in nitrogen or air atmospheres, toward the higher temperature side with an increase of heating rates. It was interesting to observe that the TG curves in nitrogen and air atmospheres were highly similar at the heating rates of 5, 10, 15 °C/min. However, a higher fluctuation of mass loss, measured by DTG curves, in air atmosphere as compared with that of in nitrogen atmosphere, was revealed here, and which suggested that cefuroxime lysine should be recommended to store in the absence of oxygen.

DSC analysis of cefuroxime lysine

The non-isothermal DSC curves at the heating rates of 5, 10, 15, and 20 °C/min were determined both in nitrogen and air atmosphere (Fig. 3). As shown in Fig. 3a, a slight endothermic peak at about 82 °C was revealed, and a significant endothermic peak was observed at about 179 °C

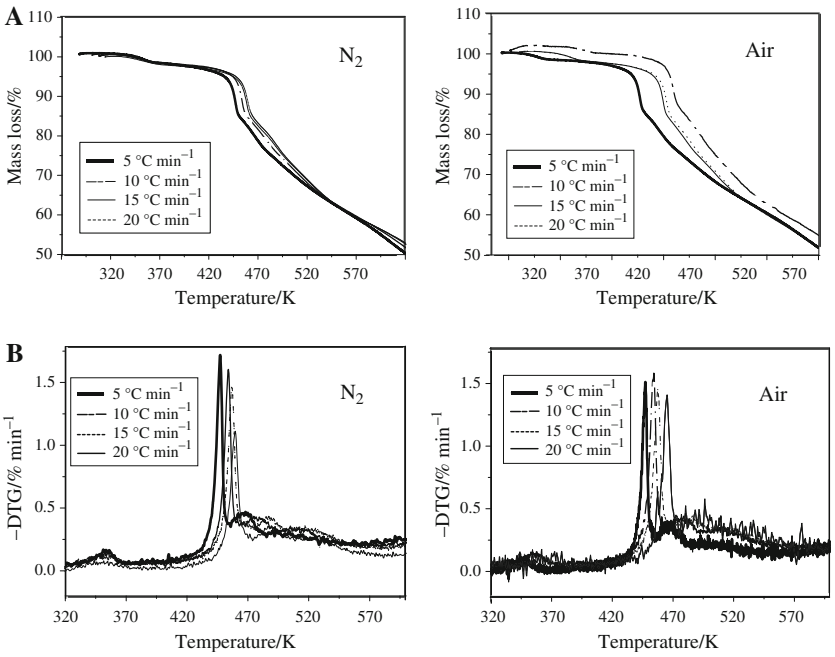

Fig. 2 The TG (**a**) and DTG curves (**b**) of cefuroxime lysine under nitrogen (N_2) and air at the heating rates of 5, 10, 15, and 20 °C min^{-1}, as indicated

Table 1 The data of thermogravimetry for cefuroxime lysine in first (I) and second (II) thermal decomposition process

Atmosphere	Heating rates/°C min^{-1}	T_{onset}/°C		T_p/°C		$W_{mass\ loss}$/%	
		I	II	I	II	I	II
Nitrogen	5	74.88	172.9	81.25	175.5	2.531	11.90
	10	68.50	178.8	78.04	182.0	2.383	12.62
	15	74.83	182.5	81.60	185.9	2.425	12.16
	20	79.67	183.4	80.72	187.3	2.124	12.66
Air	5	74.52	173.2	71.64	175.7	1.968	12.016
	10	70.59	179.3	79.87	182.2	2.694	12.60
	15	73.66	183.1	84.03	186.1	2.306	11.30
	20	80.35	188.3	90.21	191.3	2.080	13.16

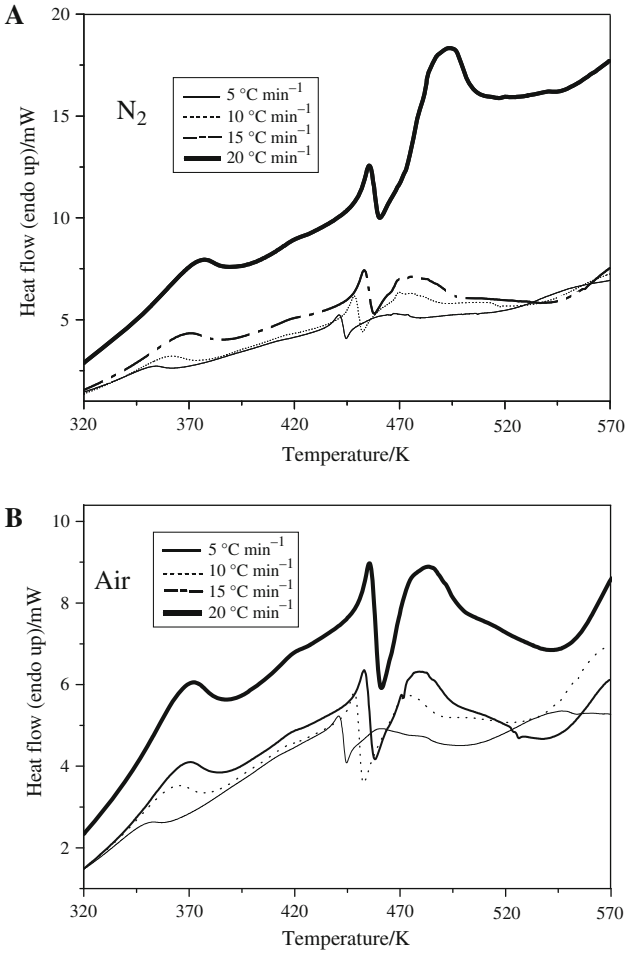

Fig. 3 The DSC curves of cefuroxime lysine at the heating rates of 5, 10, 15, and 20 °C min^{-1} under nitrogen (N_2) and air. The heat flow under all the heating rates, as indicated here, had an upward endothermic peak

corresponding to the melting process. Lastly, a sharp exothermic peak at the maximum of 184 °C was revealed. The melting enthalpy change (ΔH_m, J/g) and the peak temperature at different heating rates were summarized in Table 2. The results indicated that there was an upward shift in the peak temperature of the exothermic peak.

Thermal decomposition kinetics

In order to obtain the thermal kinetic parameters, e.g., the activation energy, E and the pre-exponential factor, A of the exothermic decomposition of cefuroxime lysine, the methods of multiple heating rates, namely Kissinger method and Flynn–Wall–Ozawa method, were employed. These "model-free" methods are multi-rate methods and free from kinetic model, which could allow the activation to be obtained independently [10]. The relevant equations are as follows:

Kissinger equation:

$$\ln\frac{\beta}{T_P^2} = \ln\frac{AR}{E} - \frac{E}{RT_P} \tag{1}$$

where β is the heating rate, T_P is the maximum peak temperature of a DSC scan at that rate, and R is the gas constant of 8.314 J/K/mol.

Flynn–Wall–Ozawa equation:

$$\log\beta = \log\frac{AR}{Rg(\alpha)} - 2.315 - 0.4567\frac{E}{RT_P} \tag{2}$$

where $g(\alpha)$ is the integral function of conversion.

Thermodynamic parameters of activation equation [11–13]:

$$Ae\frac{-E}{RT} = ve\frac{-\triangle G^{\neq}}{RT} \tag{3}$$

$$v = K_B T/h \tag{4}$$

$$\triangle H^{\neq} = E - RT \tag{5}$$

$$\triangle G^{\neq} = \triangle H^{\neq} - T\triangle S^{\neq} \tag{6}$$

where $\Delta G^{\neq}$, $\Delta H^{\neq}$, $\Delta S^{\neq}$ are the free energy, enthalpy and entropy of activation, respectively. While, K_B is the

Table 2 The enthalpy and peak temperature of cefuroxime lysine under different heating rates

Heating rate/°C min^{-1}	5		10		15		20	
	Endo	Exo	Endo	Exo	Endo	Exo	Endo	Exo
Nitrogen								
ΔH_m/J g^{-1} K^{-1}	0.0924	0.0384	0.0852	0.0381	0.0857	0.0381	0.0654	0.0379
T_p/°C	171.2	174.6	178.4	182.4	183.2	188.0	185.5	190.7
Air								
ΔH_m/J g^{-1} K^{-1}	0.0792	0.0357	0.0929	0.0496	0.0801	0.0364	0.0884	0.0388
T_p/°C	170.9	174. 7	178.2	182.7	183.0	188.0	185.4	191.2

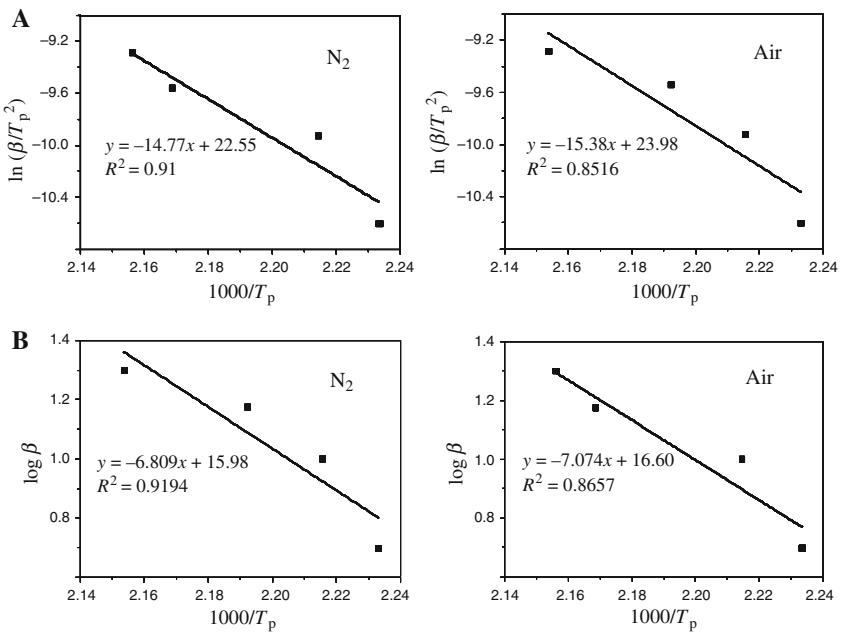

Fig. 4 The plot of $\ln(\beta/T_p^2)$ and $\log \beta$ versus $1/T_p$ for cefuroxime lysine under nitrogen (N_2) and air using the methods of Kissinger and Flynner–Wall–Ozawa. The coefficients of regressions, calculated from the lines, were included here

Table 3 The kinetic parameters for the degradation of cefuroxime lysine calibrated using the methods of Kissinger and Flynner–Wall–Ozawa

Atmosphere	Methods	E/kJ mol^{-1}	log A/S^{-1}	r	$\Delta G^{\neq}$/kJ mol^{-1}	$\Delta H^{\neq}$/kJ mol^{-1}	$\Delta S^{\neq}$/J mol^{-1}
Nitrogen	Kissinger	122.8	16.25	0.954	94.7	119.0	−53.81
	Ozawa	124.0	16.39	0.959	94.7	120.2	−56.47
Air	Kissinger	127.8	16.88	0.923	94.4	124.1	−65.83
	Ozawa	128.8	17.00	0.930	94.3	125.0	−68.09

Boltzmann constant of 1.3807×10^{-23}J s, and h is the Planck constant of 6.625×10^{-34}J s.

The values of $\ln(\beta/T_p^2)$ or $\ln\beta$ were plotted against the values of $1/T_p$. A straight line through the data points was obtained by linear regression. The activation energy, E, was determined from the slope, and the pre-exponential factor, A, was determined from the equation, $A = \beta E[\exp(E/RT_p)]/RT_p^2$. The typical kinetic plots by Kissinger and Flynn–Wall–Ozawa methods for cefuroxime lsyine in nitrogen and air atmospheres are shown in Fig. 4. In addition, the kinetic parameters for the degradation are listed in Table 3.

From the results of Table 3, the values of E and A obtained using Kissinger method were 122.8, 127.8 kJ/mol and $10^{16.25}$, $10^{16.88}$ s^{-1} in nitrogen and air, respectively. Meanwhile, the values of E and A obtained by Ozawa method were 124.0, 128.8 kJ/mol and $10^{16.39}$, 10^{17} s^{-1} in nitrogen and air, respectively. The values of $\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ of the major exothermic decomposition reaction

for cefuroxime lysine were 94.7, 119.0 kJ/mol, and −53.81 J/mol under nitrogen condition, while the values of 94.4, 124.1 kJ/mol, and −65.83 J/mol under air condition were also determined by Kissinger method. The results were confirmed by Flynn–Wall–Ozawa method without a significant difference, which indicated that cefuroxime lysine should have good thermal stability, and which could be stored for a sufficient time at room temperature.

Conclusions

The reaction atmosphere is an important factor, which is considerably affecting the degradation route of medicine, especially during its storage, transportation, and application. Therefore, the thermal stability for cefuroxime lysine in anoxic and oxidative atmospheres has been investigated in this study. The results demonstrated that the reaction atmosphere was an important factor in influencing the decomposition of cefuroxime lysine. In this study, a recommendation was given that cefuroxime lysine should be stored in the absence of oxygen. The thermal behavior and decompositions of cefuroxime lysine, studied using TG and DSC in different heating rates and atmospheres, indicated that the chemical could be sublimated at about 179 °C before it was decomposed.

The values of the kinetic parameters obtained by Kissinger and Flynn–Wall–Ozawa methods for cefuroxime lysine have a good correlation. However, it should be recognized that the values of E, A, $\Delta H^{\neq}$, and $\Delta S^{\neq}$, calculated using Flynn–Wall–Ozawa method, are a little higher than those calculated using Kissinger method without any significant difference. On the other hand, the values of $\Delta G^{\neq}$, $\Delta H^{\neq}$, and $\Delta S^{\neq}$ of cefuroxime lysine in nitrogen and air atmospheres were calculated and compared. Analyzing the values of E, A, $\Delta H^{\neq}$, and $\Delta S^{\neq}$ in anoxic and oxidative atmosphere, one could observe that these values were slightly higher in air, as compared with that in nitrogen. These results indicated that the two analytic methods described here in determining the kinetic parameters for non-isothermal decomposition were valid, feasible, and conventional. Using the estimated kinetic parameters of cefuroxime lysine, calculated using Kissinger and Flynn–Wall–Ozawa methods, the predicted mass loss could fit well with the experimental data, which indicated the validity and applicability of the estimated parameters as described in this study.

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