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Thermal behaviour of cephalexin in different mixtures

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Abstract The thermoanalytical curves (TA), i.e. TG, DTG and DTA for pure cephalexin and its mixtures with talc, magnesium stearate, starch and microcrystalline cellulose, respectively, were drawn up in air and nitrogen at a heating rate of 10 °C min^{-1}. The thermal degradation was discussed on the basis of EGA data obtained for a heating rate of 20 °C min^{-1}. Until 250 °C, the TA curves are similar for all mixtures, up this some peculiarities depending on the additive appears. These certify that between the pure cephalosporin and the excipients do not exists any interaction until 250 °C. A kinetic analysis was performed using the TG/DTG data in air for the first step of cephalexin decomposition at four heating rates: 5, 7, 10 and 12 °C min^{-1}. The data processing strategy was based on a differential method (Friedman), an integral method (Flynn–Wall–Ozawa) and a nonparametric kinetic method (NPK). This last one allowed an intrinsic separation of the temperature, respective conversion dependence on the reaction rate and less speculative discussions on the kinetic model. All there methods had furnished very near values of the activation energy, this being an argument for a single thermooxidative degradation at the beginning (192–200 °C).

Keywords Cephalexin · Thermal stability · Kinetic parameters · NPK method

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Introduction

The term 'cephalosporins' refers to a variety of semisynthetic antibiotics derived from cephalosporin C, a natural antibiotic isolated in 1945 from *Cephalosporium acremonium*. Cephalosporins contain the 7-aminocephalosporanic acid nucleus, which consists of a fused β-lactam-dihydrothiazine system, also termed as cephem. They are the most important class of drugs against infectious diseases caused by bacteria, and their interactions in human body were recently studied [1, 2].

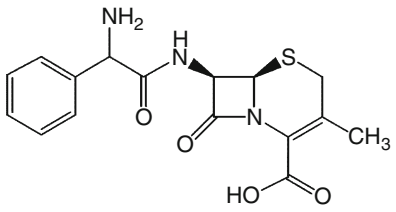
The continued popularity and worldwide use of parenteral and oral cephalosporins, is predominantly related to both a proved track record of broad-spectrum antibacterial activity (against several *Gram-positive* and *Gram-negative bacteria*) as well as excellent safety during more than 30 years of clinical experience [3, 4].

Cephalexin (6R,7R)-7-[[(2R)-2-amino-2-phenylacetyl]-amino]-3-methyl-8-oxo-5–thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (see Scheme 1) is a first-generation cephalosporin antibiotic. It is used to treat urinary tract infections, respiratory tract infections (including sinusitis, otitis media, pharyngitis, tonsillitis, pneumonia, and bronchitis), and skin and soft tissue infections [5].

Thermal analysis is one of the most frequently used instrumental techniques on pharmaceutical researches to solve technological problems. [6, 7]

Thermoanalytical techniques can be applied successfully to investigate different materials, which have pharmaceutical relevance [8, 9].

Thermal techniques are widely applied alone or as combined with microscopy, spectroscopy (UV, IR), X-ray powder diffractometry and mass spectrometry during preformulation (tablet fabrication, capsules, powders, etc.) and for characterization of drugs [10, 11].



Scheme 1

Thermoanalytical techniques are also used for incompatibility studies between drug(s) and excipient(s) upon preformulation. Incompatibility can lead to the loss of biological activity of drugs, complex formation, acid–base interactions and formation of eutectic mixtures [12].

In our previous paper [13], we proved the importance and utility of the kinetic analysis in estimations on the thermal behaviour of different pharmaceuticals.

The aim of this work is to evaluate the thermal behaviour of cephalexin and some possible interactions between this compound and different pharmaceutical excipients. The strategy of the kinetic analysis is that used in our mentioned paper.

Experimental

The cephalexin (6*R*,7*R*)-7-[[(2*R*)-2-amino-2-phenylacetyl] amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2 ene-2-carboxylic acid was obtained from Antibiotice Iaşi (lot: 01061042/550513-00416). Excipients tested were: magnesium stearate (Union Derivan Spain, lot: 01067215/592781), talc powder (Luzenac Pharma Italy, lot: 010 67235/S450/06), microcrystalline cellulose. The mixed samples consisted of equal masses of cephalexin and each excipient was weighed individually into amber glass flasks to originate mass of approximately 2 g of mixture. Physical mixtures were prepared in proportion (m/m) 1:1 (cephalexin: excipient) by simple mixing.

The TG/DTG/DTA curves were drawn up on Perkin Elmer DIAMOND devices, in dynamic air atmosphere (100 mL min^{-1}), with a heating rate of 5, 7, 10 and 12 °C min^{-1} until 550 °C.

The evolved gas analysis (EGA) was carried out by a coupled TG/FTIR technique, using a Perkin Elmer SPECTRUM 100 devices with a IR gas chamber connected to the exit of the DIAMOND furnace. The same air flow of 100 mL min^{-1} and a heating rate of 20 °C min^{-1} were used. The FTIR spectra were processed by the Sadtler Gas Vapor Library.

Thermal behaviour

Cephalexin, in both air and nitrogen (Figs. 1, 2), had rather the same behaviour, a clear decomposition step in a very narrow range, 180–200 °C. The single and well developed DTG indicates probably a single step process. The exothermic DTA, even in nitrogen, is due to enough oxygen atoms in the molecule for the beginning of an intramolecular oxidation. The same values of the DTG and DTA maximum indicate a relative low exothermic effect.

After this first step, the molecule is partially destroyed, so that after 200 °C it is a range unimportant.

Regarding the eventually interaction between the pure cephalexin and different excipients, according to data in Fig. 3, no changes until 200 °C take place. Supplementary decomposition steps appear up to 300 °C. Characteristics of the first thermodegradation step are presented in Table 1.

EGA for cephalexin in air

The first signal in the gas chamber appears at 9.7 min, i.e. at 194 °C and the spectrum corresponds to a mixture of carbon dioxide and water vapour. But quickly, at 200 °C also benzene was identified. These are arguments for a rapid thermooxidation, beginning with depletion of carbon and hydrogen and followed by deeper destroying.

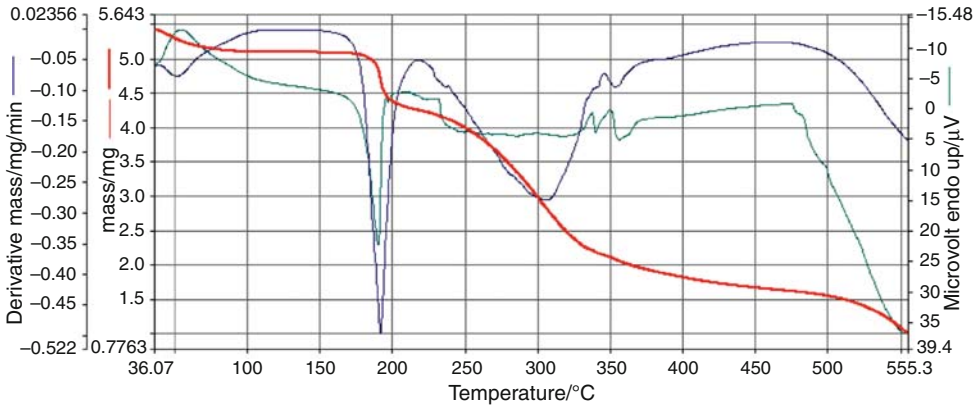


Fig. 1 The thermoanalytical curve obtained in air at heating rate of 10 °C min^{-1} for cephalexin

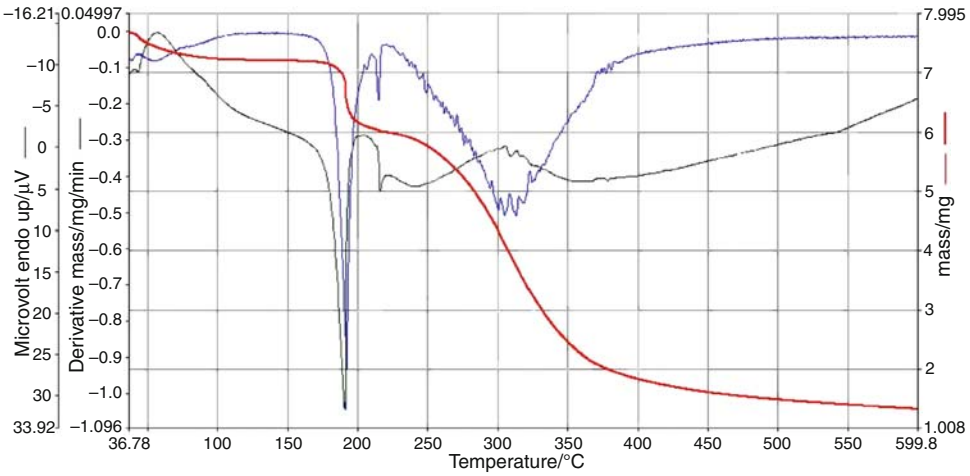


Fig. 2 The thermoanalytical curve obtained in nitrogen at heating rate of 10 °C min^{-1} for cephalexin

Kinetic analysis

Three different methods for TG/DTG data processing were used, i.e. the method by Flynn–Wall [14] and Ozawa [15] (FWO), the method by Friedman [16], respectively, the non-parametric kinetic (NPK) method [17–19].

(i) The FWO isoconversional method requires the temperature measurement at certain conversions α for experiments performed at different heating rates β. The experimental data were processed according to Eq. 1

$$\ln \beta = \ln \frac{AE}{Rg(\alpha)} - 5.331 - 1.052 \cdot \frac{E}{RT} \quad (1)$$

where β is the heating rate, α is the conversion degree at temperature T, $f(\alpha)$ is the conversion function and A, respectively, E is the pre-exponent factor and the activation energy in the Arrhenius equation and

$$g(\alpha) = \int_{\alpha_0}^{\alpha} f(\alpha)\mathrm{d}\alpha$$

is the integral form of the conversion function $f(\alpha)$. The value of the activation energy E at a certain α will be determined. The FWO method is a *model-free method* because its application does not require the explicit form of the conversion function. The data are presented in Fig. 4.

(ii) The differential-isoconversional method by Friedman.
At constant conversion, the differential form of the reaction rate can be written

$$\ln\left(\beta \frac{\mathrm{d}\alpha}{\mathrm{d}T}\right)_{\alpha} = \ln[A \cdot f(\alpha)] - \frac{E}{RT} \quad (2)$$

where β is the heating rate, α is the conversion degree at temperature T, $f(\alpha)$ is the conversion function and A, respectively, E the pre-exponent factor and the activation energy in the Arrhenius equation. The Friedman's method is also a 'model free' method. The data are presented in Fig. 5. By the both mentioned methods, there are significant and non-monotonous variations of the E versus α and this is a doubtless indication for complex processes. Therefore, a more sophisticated kinetic method is necessary.

(iii) The non-parametric kinetic method [17–23].
By this method, the reaction rates $\beta \cdot \mathrm{d}\alpha/\mathrm{d}T$, measured from several experiments at different heating rates, β, were interpolated as a surface in a three-dimensional (3D) space ($\beta \cdot \mathrm{d}\alpha/\mathrm{d}T$, α, T). This surface is organized as an x_{ij} matrix M, where the rows correspond to different degrees of conversion α_i, and the columns correspond to different temperatures T_j. Based on the assumption that the reaction rate can be expressed as a product of two independent functions, $f(T)$ and $g(\alpha)$, an element i, j of the matrix $\mathbf{M}$ is $\mathbf{M}_{i,j} = f(T_j) \cdot g(\alpha_i)$.
By the singular value decomposition algorithm [24], the matrix is decomposed according to equation

$$\mathbf{M} = \mathrm{U}(\mathrm{diagS})\mathrm{V}^T \quad (3)$$

A vector $\mathbf{u}_1$ given by the first column of U is analyzed versus α to determine the conversion function; we suggest the Šesták–Berggren equation [25]:

$$g(\alpha) = \alpha^m(1-\alpha)^n \quad (4)$$

A similar vector $\mathbf{v}_1$, corresponding to V is checked for an Arrhenius type temperature dependence.
In case of a multi-step process, for example with two simultaneous reactions of rates r_1 and r_2,

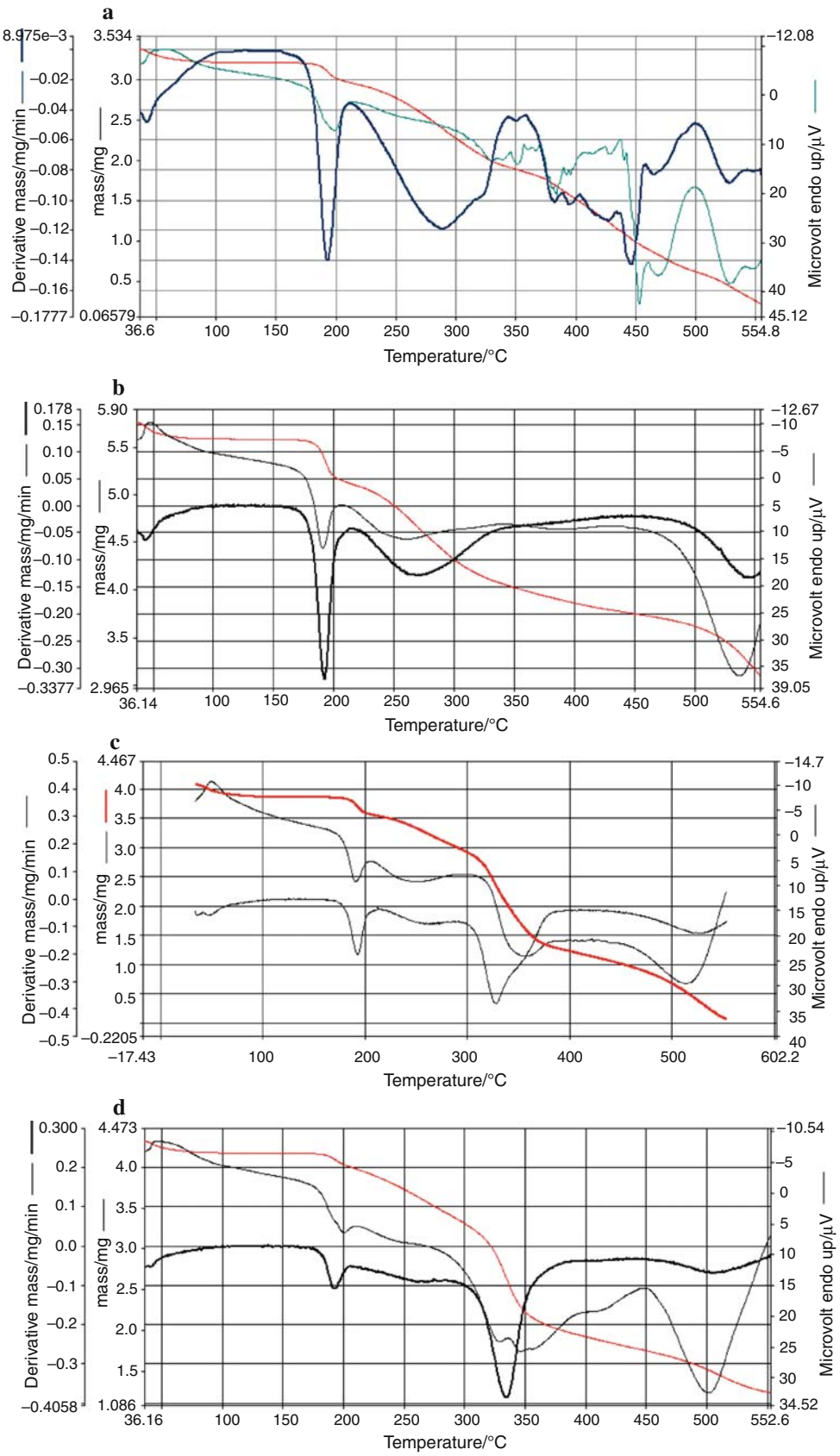


Fig. 3 The thermoanalytical curve obtained in air at heating rate of 10 °C min^{-1} for:
a cephalexin + stearate magnesium;
b cephalexin + talc;
c cephalexin + cellulose;
d cephalexin + excipients

Table 1 Characteristics of the first thermodegradation step

Sample	T initial/°C	T final/°C	DTG max./°C	Δm/%
Cephalexin (Fig. 1)	150	220.3	190	16.07
Cephalexin + stearate magnesium (1:1) (Fig. 3a)	161.8	215.2	190	14.81
Cephalexin + talc (1:1) (Fig. 3b)	150	215	193.3	8.67
Cephalexin + cellulose (1:1) (Fig. 3c)	170	214	192	7.14
Cephalexin + excipients (1:1:1:1) (Fig. 3d)	166.7	206.7	190	4.1

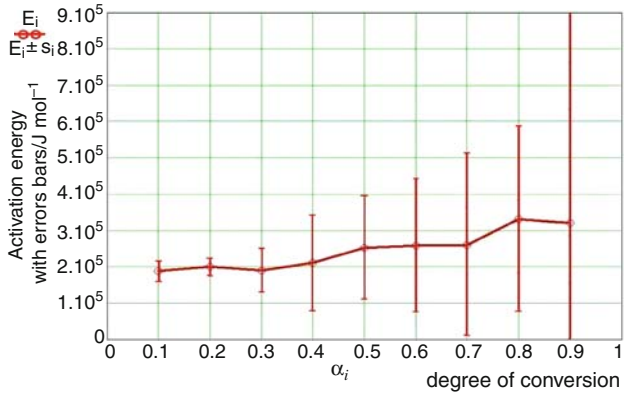


Fig. 4 Activation energy (FWO) versus degree of conversion

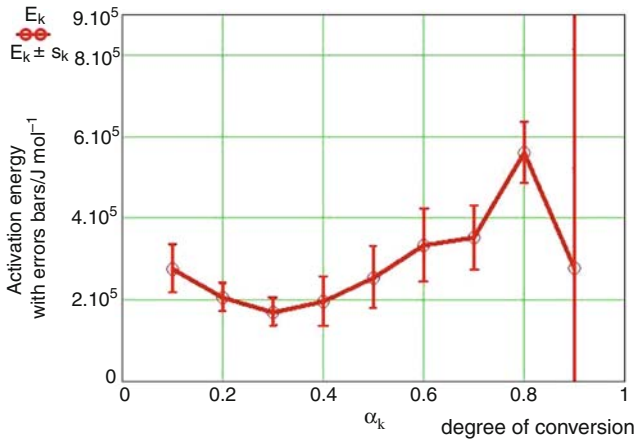


Fig. 5 Activation energy (FR) versus degree of conversion

$$r = r_1 + r_2 = f_1(T) \cdot g_1(\alpha) + f_2(T) \cdot g_2(\alpha) \quad (5)$$

the initial matrix became

$$\mathbf{M} = \mathbf{M}_1 + \mathbf{M}_2 \quad (6)$$

and the contribution of each step to the observed process is expressed by the explained variance, λ, so that $\sum \lambda_i = 100\%$.

The data are systematized in Table 2. Only steps with $\lambda \geq 10\%$ are considered. The explained variance, λ, seems the percent from the variation of the experimental data explained by the proposed processes. According to the data in Table 2, the decomposition is a complex process, the secondary one having also a physical step ($m \neq 0$). The main process (explained variance is 77%) is a chemical step with a first order kinetic.

Table 2 Kinetic analysis by NPK method

Process	λ/%	E/kJ mol^{-1}	A/min^{-1}	n	m	$\sum\lambda \cdot$ E/ kJ mol^{-1}
Main	77.2	220.2 ± 9.7	$8.04 \cdot 10^{23}$	1	–	248.0 ± 38.2
Secondary	18.9	412.4 ± 162.2	$3.4 \cdot 10^{45}$	1.66	1	

Table 3 Comparative value of the activation energy

Main value $\overline{E_a}$/kJ mol^{-1}		
FWO	Friedman	NPK $\sum\lambda \cdot$ E
245.9 ± 50.8	290.8 ± 136.9	248.0 ± 38.2

According to the data in Table 3, a comparison of the E value obtained by the three used methods is acceptable only with the following remarks:

- the narrow values (especially by FWO and NPK methods) are rather of formal significance;
- the difference in the standard deviation by FWO, respectively, FR method is due to the differential character of the last one.
- by the NPK method allowed a separation of the temperature, respective conversion dependence of the reaction rate; indeed together with A and E also the m and n values were obtained, without any supplementary hypothesis.

Conclusions

- The thermal degradation of cephalexin under non-isothermal conditions in air and in nitrogen was observed. The thermooxidation take place in a first step

in a very narrow temperature range. Arguments on the first degradation of the molecule were brought by EGA
- Mixture of cephalexin with different excipients proved that now interactions between these and active compounds take place
- A kinetic analysis using three different methods confirmed that the first decomposition step is a complex process of both chemical and physical nature.

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