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THERMAL DECOMPOSITION KINETICS OF CEFADROXIL

Adriana FULIAŞ,[a*] Nicolae DOCA,[b] Gabriela VLASE,[b] Bogdan TIŢA,[a] Dumitru TIŢA[a] and Titus VLASE[b]

[a] "Victor Babeş"University of Medicine and Pharmacy, Faculty of Pharmacy, 2 Eftimie Murgu Square, Timişoara, RO–300041, Roumania
[b] West University of Timişoara, Research Centre for Thermal Analysis in Environmental Problems, 16 Pestalozzi Street, Timişoara, RO–300115, Roumania

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The thermoanalytical curves TG/DTG/DTA for pure cefadroxil were drawn up in air at different heating rates. A kinetic analysis was performed using the TG/DTG data in air for the first step of cefadroxil 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 (Kissinger–Akahira–Sunose) and a nonparametric kinetic method (NPK). The NPK method leads to a value for activation energy similar to the value obtained using the KAS method, so it can be argued that decomposition takes place mainly in a single step, according to a first-order reaction.

INTRODUCTION

Cefadroxil, a first-generation cephalosporin antibiotic, is used to treat urinary tract infections, skin and skin structure infections, pharyngitis, and tonsillitis. Like all *beta*-lactam antibiotics, cefadroxil binds to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, causing the inhibition of the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that cefadroxil interferes with an autolysin inhibitor.[1-3]

The studies of thermal stability and degradation mechanism are very important and useful. Kinetic analysis of thermal decomposition processes has been the subject interest for many investigators all along the modern history of thermal decomposition. On one side, kinetic data are essential for describing any kind of device, in which the thermal decomposition takes place; on the other side, kinetics is intrinsically related whit the decomposition mechanism.[4,5] Knowledge of kinetic parameters, such as the reaction rate, activation energy and pre-exponent factor, is one of the keys to determine the reaction mechanism in the solid-state reactions. Practically, the kinetic triplet is needed to provide a mathematical description of the processes. If the kinetic triplet is determined correctly, it can be used to reproduce the original kinetic data as well as to predict the process kinetics outside the experimental temperature region.[6]

Thermoanalytical analysis is one of the most commonly used technologies to study a variety of primary reactions of decomposition of solids and estimate the kinetics parameters of these processes.[7] It is well known that the determination of kinetic parameters by non-isothermal methods offers advantages over conventional isothermal studies. The conventional non-isothermal single scan method, which cannot detect the complex nature of the solid-state reaction, has been replaced by multiple scan method at different heating rates using isoconversional and iso-temperature calculation procedures.[8] Among the iso-conversional methods, Friedman (FR) method,[9] and Kissinger–Akahira–Sunose (KAS) method,[10,11] respectively the modified non-parametrical method

* Corresponding author: adrifulias@yahoo.com

(NPK)[12-14] have been widely used to estimate the kinetic parameters.

The purpose of this study was to assess the thermal behaviour for cefadroxil monohydrate by determining the kinetic parameters and to evaluate the complexity of the studied process.

Cefadroxil's formula is presented in Fig. 1.

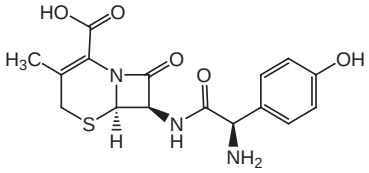


Fig. 1 – The chemical structure of the cefadroxil.

RESULTS AND DISCUSSION

Thermal behaviour of the cefadroxil monohydrate is characterized by the existence of two stages in which can be identified both the TG and DSC curves, the following processes that occur are still numerous and consist in destroying the whole product from dihydrotiazinic cycle decomposition (cephem structure).

The results of TG/DTG/DTA obtained for cefadroxil monohydrate during heating at β=5°C·min^{-1} in air atmosphere are presented in Fig. 2.

The kinetic analysis is performed for the second decomposition process, which took place in the temperature range 185–225°C. The first decomposition process corresponds to removal of water molecule from the composition of the hydrate. The dehydration of the sample with loss of one water molecule took place in the range 50–150°C. The observed mass loss due to this dehydration was 5.16%, respectively the calculated value for one water molecule is 4.72%. The second process involves the destruction of cefadroxil molecule, because of that reason and because of the relatively high temperature it is considered that the kinetic analysis does not present more interest for the following processes.

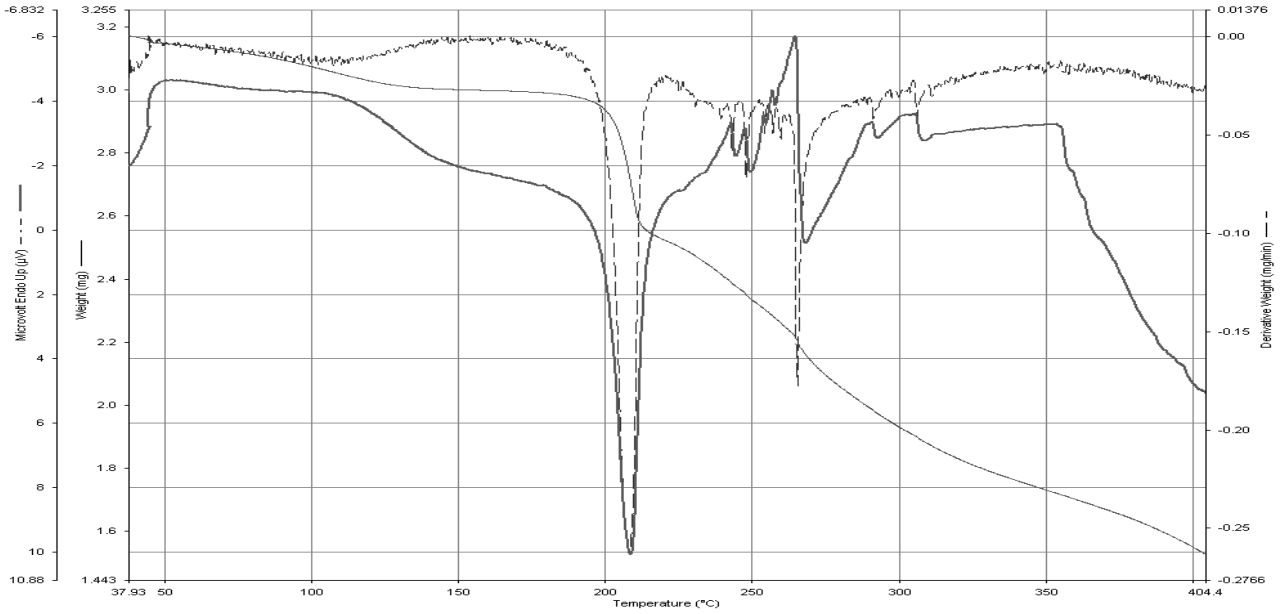


Fig. 2 –The thermoanalytical curves TG/DTG/DTA obtained in air at β=5°C·min^{-1} for cefadroxil monohydrate.

a) Friedman method

Friedman's isoconversional method [9] is based on the equation:

$$\ln(\beta\frac{d\alpha}{dT}) = \ln[A \cdot f(\alpha)] - \frac{E}{R \cdot T} \qquad (1)$$

The necessary data for $\ln(\beta\frac{d\alpha}{dT})$ *vs.* (1/T) graphical representation (corresponding to the Friedman method) were taken from the chart of the reaction rate versus temperature for cefadroxil, under non-isothermal conditions (Fig. 3). In Fig. 4, it is represented the Friedman's family of straight lines, from the slope of those lines being calculated the activation energy according to equation 1.

The activation energy's values corresponding of the second decomposition process, the most important one, according to the degree of conversion are presented in Table 1.

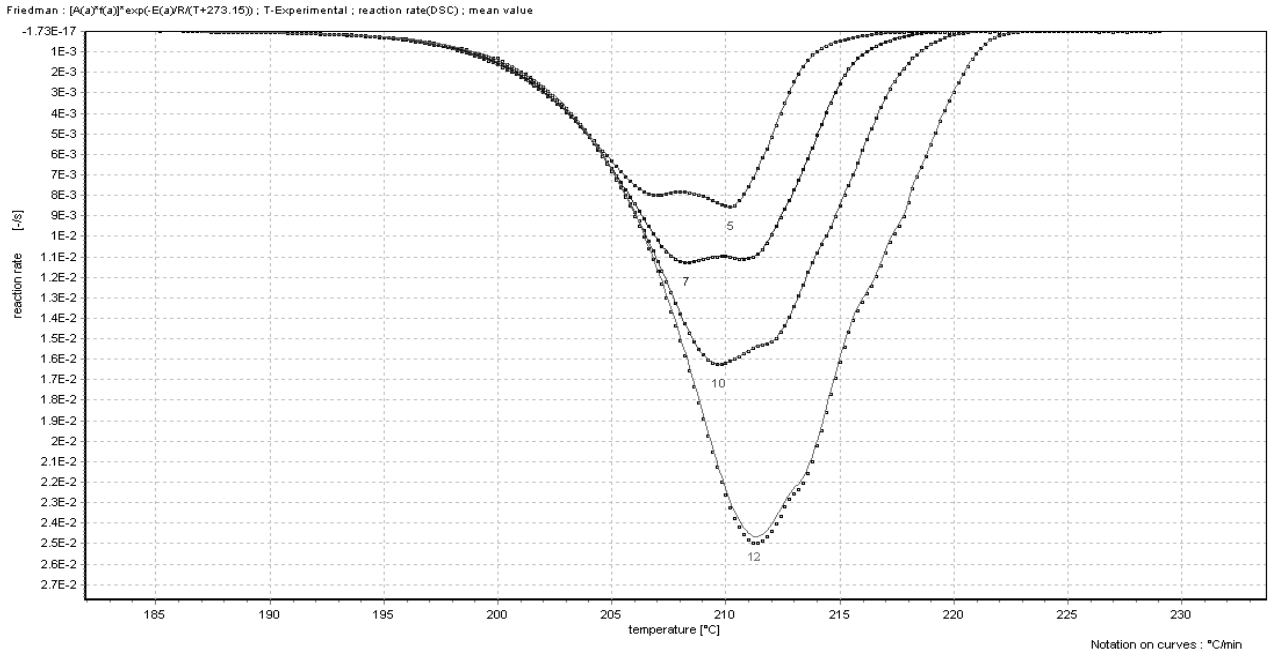


Fig. 3 – Graphical representation of the reaction rate *vs.* temperature for cefadroxil corresponding to four heating rates (non-isothermal regime).

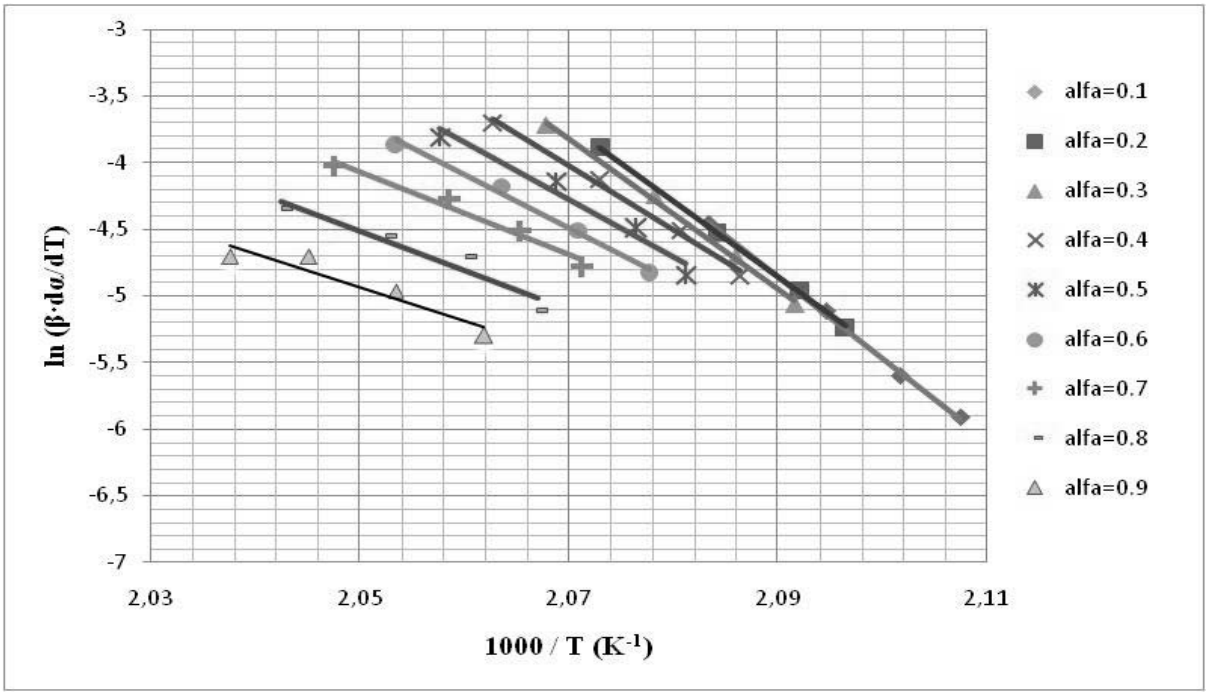


Fig. 4 – Graphical representation $\ln(\beta\frac{d\alpha}{dT})$ *vs.* (1/T). Friedman diagram for cefadroxil.

Table 1

Activation energy's values obtained by Friedman isoconversional method for cefadroxil monohydrate

	Conversion degree α								
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
E_a **kJ/mol**	510.3 ±1.0	475.9 ±0.5	468.3 ±1.4	399.5 ±2.8	355.7 ±12.8	331.1 ±3.6	259.1 ±7.5	245.8 ±19.9	194.9 ±22.8

It is noted a significant variation of the activation energy depending on the conversion degrees. This fact indicates that the decomposition process is complex, respectively the existence of more than one process. In this case it is necessary to use other kinetic methods of study, more developed in an attempt to determine and separate these processes, yet unknown as number. The activation energy's values decrease throughout the $0 < \alpha < 1$ range, which may suggest a sequence of reversible reactions (unlikely given to the fact that some degradation products are in gaseous form) or a sequence of successive reactions.

b) Kissinger–Akahira–Sunose method

This method is based on measuring the temperature corresponding to fixed values of the α conversion for experiments at different heating rates β. It is plotting $\ln\frac{\beta}{T^2}$ *vs.* 1/T and the slope of the straight line being equal to $-E_a/R$. If it is noticed a change of the E_a values function of α, the result can be interpreted as a multistage reaction mechanism. This method is based on the following equation:

$$\ln\frac{\beta}{T^2} = \ln\frac{A\cdot R}{E\cdot g(\alpha)} - \frac{E}{R\cdot T} \qquad (2)$$

c) Non-parametric kinetics method (NPK)

The non-parametric kinetics (NPK), developed[12-13] and modified[14-17] a few years ago, represents a special approach for processing the kinetic data. The method introduces a new point of view in kinetic analysis. It is also based on the single-step kinetics approximation, so that the basic relationship for the analysis of kinetic data represents Eq. 3, the general rate equation:

$$\frac{d\alpha}{dT} = k(T)\cdot f(\alpha) \qquad (3)$$

The experimental values of reaction rates are arranged in a matrix which is expressed as a product of two vectors containing information on k(T) and f(α). The most important feature of the method is that it enables to decouple the vectors related to the temperature and conversion functions without the need of any assumptions about their functionality. Validity of Eq. 3 is the only assumption made in the development of NPK method.

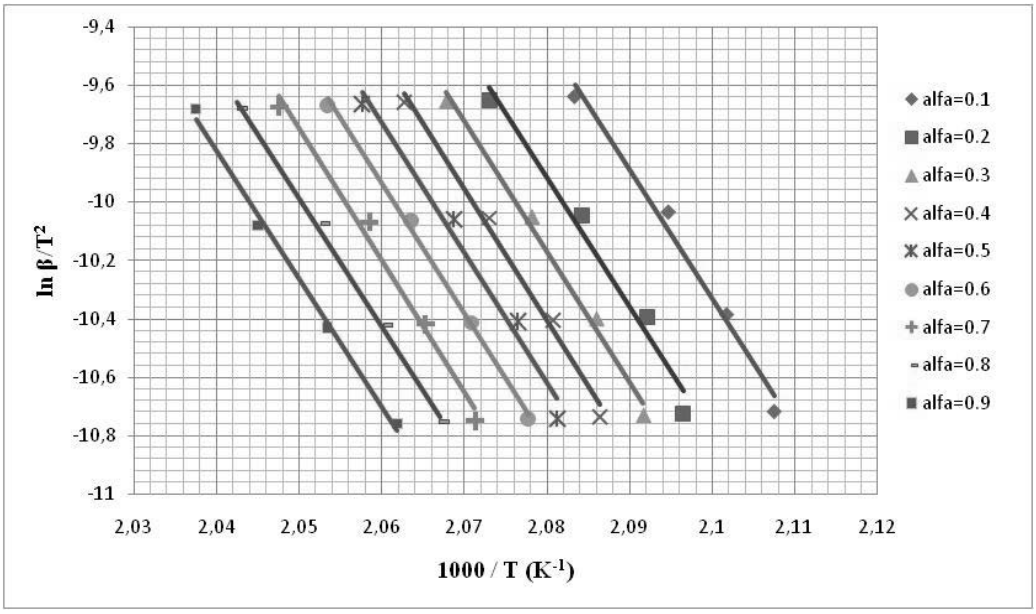


Fig. 5 – Graphical representation of $\ln\frac{\beta}{T^2}$ *vs.* (1/T). KAS diagram for cefadroxil monohydrate.

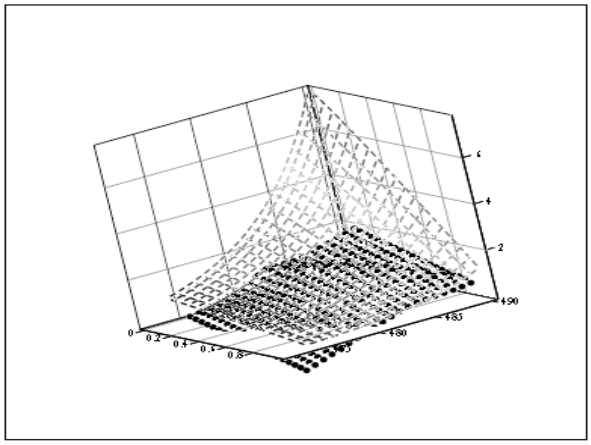
Table 2

The activation energy values obtained by the KAS method for cefadroxil monohydrate

	Conversion degree α								
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
E_a kJ/mol	283.1 ±5.5	283.3 ±8.9	283.2 ±3.3	287.1 ±3.4	284.1 ±7.4	286.5 ±1.5	283.0 ±4.5	285.8 ±1.1	290.8 ±2.2

The experimental points obtained at different heating rates are represented in a 3D system and interpolated as a continuous reaction rate surface. This surface is discretizated into a square matrix M which is decomposed, using the singular value decomposition algorithm,[17] into the product of three matrixes:

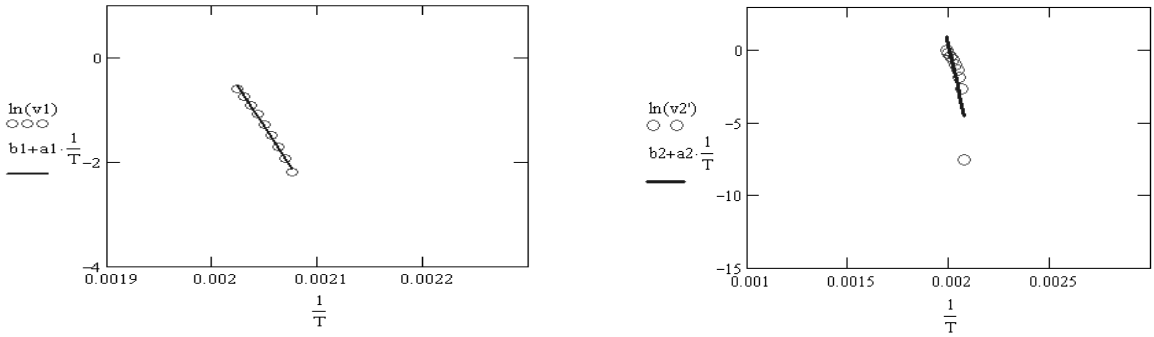
$$M = U(\text{diag } S)V^T \quad (4)$$



L,(X,Y,Z)

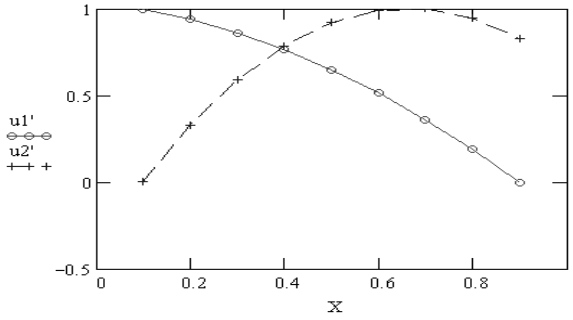
Fig. 6 – The reaction surface for cefadroxil monohydrate, in 3D space with coordinates ($\beta\frac{d\alpha}{dT}$; α; T.).

The results of NPK analysis are systematized in Table 3. These data were obtained from the linearization of the vector v (Fig. 7) and of the vector u with different correlation functions to identify the reaction model (Fig. 8):



** principal process ** secondary process

Fig. 7 – Linearization of vector **v** for cefadroxil – active substance.



++++ $f_i = (1-x_i)^1$ $corr(u'_1, f)=0.999$

oooo $f_i = (x_i)^{1/3}$ $corr(u'_2, f)=0.997$

Fig. 8 – Conversion functions for the two decomposition processes characterizing cefadroxil monohydrate.

In Table 3 the results obtained by the application of NPK method are presented. It is noted that the main process is a first order chemical reaction (n=1) unaccompanied by any physical process (m=0). The secondary process requires a higher activation energy comparative with the value required in the first process, but it contributes to the unit process in a small proportion (explained variance $\lambda = 0.036$). The secondary process is accompanied by a physical process (m=1/3).

Table 3

Kinetic analysis for cefadroxil–active substance, the NPK method

	Process	λ (%)	E (kJ·mol^{-1})	A (min^{-1})	n	m	Ec. S–B	∑λ·E (kJ·mol^{-1})
Cefadroxil active substance	1	95.4	258.6±7.1	$1.33\cdot10^{27}$	1	–	(1–α)	264.5±9.8
	2	4.6	385.4±83.8	$1.07\cdot10^{37}$	–	1/3	$\alpha^{1/3}$	

EXPERIMENTAL

The active substance which was utilized in this study is cefadroxil with IUPAC name (*6R,7R*)–7–{[(*2R*)–2–amino–2–(4–hydroxyphenyl)acetyl]amino}–3–methyl–8–oxo–5–thia–1–azabicyclo[4.2.0]oct–2–ene–2–carboxylic acid. This substance was obtained from Antibiotice Iaşi (lot: 01061042/550513–00416).

Thermogravimetrical analysis (TG and DTG) was performed on Perkin–Elmer DIAMOND equipment in temperature range 25–550°C, using an air atmosphere and under dynamic conditions in order to study the thermal stability of the active substance. Samples with the mass in the range of 2 to 5 mg were put into aluminium crucibles, at a heating rate, β, of 5, 7, 10 and 12°C·min^{-1}.

CONCLUSIONS

The thermal behaviour of cefadroxil monohydrate was estimated by a comparative kinetic study using three different kinetic methods. According to the values from Table 2, using the Kissinger–Akahira–Sunose isoconversional integral method, the variation of the activation energy depending on the degree of conversion does not exceed the required value of 10%, which is consistent with data obtained from the application of NPK method. According to these data there are two processes, but the secondary one has a very small contribution ($\lambda = 0.036$), so it can be argued that the decomposition takes place mainly in a single step as a first order chemical reaction (n=1). The NPK method leads to a similar value of activation energy E_a with the value obtained using the KAS method (Table 4).

According to the data from Table 3, it is clear that 96%, so the first process is a chemical process with the reaction order n=1. The approaching of the average value of the activation energy determined by the KAS method – an isoconversional integral method, which takes account of the decomposition reaction's history – and NPK, is justified.

Regarding the dependence of E_a *vs.* α, according to Friedman method, this is an important one and it is probably due to differential processing of the kinetic data.

The kinetic data obtained from applying the three kinetic methods differ depending on the method used, but the differences were framed in a narrow range, the values obtained by application of NPK and KAS methods, being actually equal.

Table 4

The main values of E_a obtained by comparative kinetic methods

	Mean value $\overline{E_a}$ (kJ·mol^{-1})		
Cefadroxil *active substance*	**Kissinger–Akahira–Sunose**	**Friedman**	**NPK (∑λ·E)**
	285.2±2.6	360.1±7.1	264.5±9.8

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