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Multi-step decomposition processes for some antibiotics A kinetic study

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Abstract

In the present study, a kinetic analysis on decomposition processes of some oxacillin salts (oxacillin, cloxacillin and dicloxacillin) was carried out to identify their kinetic parameters. As expected by their complex structures, several steps with different activation energies occurred in the decomposition processes.

The application of the model-fitting kinetic method to multi-step decomposition process results to be unsuitable for the non-isothermal data. As far as isothermal data are concerned this method gives rises to more reliable results which, however, are likely to conceal the kinetic complexity.

The model-free approach represented by isothermal and non-isothermal isoconversional methods, gives different dependencies of the activation energies as a function of the extent of conversion and allows detecting multi-step processes over a wide temperature range.

Keywords: Isothermal; Non-isothermal; Activation energy; Arrhenius parameters; Thermal decomposition; Oxacillin; Cloxacillin; Dicloxacillin

1. Introduction

Antibiotics for humans are mostly given therapeutically, whereas veterinary antibiotics are also used precautionary as feed additives. Penicillin G is frequently used in veterinary practice for treatment of ovine mastitis and microbial infections.

A modest quantity of this compound in milk might be responsible for allergic reactions in humans [1,2]. Moreover, penicillin is used for starter culture inhibition in the manufacture of fermented dairy products such as cheese, buttermilk and yoghurt [3,4].

Most antibiotics are water soluble (e.g. tetracyclines, sulphonamides, and some β-lactam antibiotics) and excreted with the urine as parent compounds (e.g. tetracycline and β-lactam antibiotics) or metabolites (e.g. sulphonamides and macrolides) [5]. Macrolides (e.g. Tylorsin) and pleuromutilin derivatives (e.g. Tiamulin) are, on the other hand, less water soluble and excreted with faeces. Application of manure as fertiliser on fields may thus contain antibiotics or antibiotic residues and may affect the ecosystem in the environment [5]. For this reason, an important question is the natural degradation of these compounds. One factor influencing this process is the temperature. Hence, knowledge of thermal behaviour may provide information on the fates of these compounds and the formation of their derivatives in the environment. Kinetic analysis allows obtaining at high temperatures some information on thermal decomposition mechanisms.

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At this regard, a thermal analysis using simultaneous TG–DSC measurements as well as a kinetic investigation on their liquid–gas phase processes by a dynamic TG technique of pesticides have been already carried out in our laboratory [6–8].

Moreover, thermal analysis is also a routine method for the analysis of drugs and substances of pharmacological interest [9–12]. For example, as regards the study of storage times that usually requires weeks or months, kinetic analysis allows us to obtain some data more rapidly by heating a sample and by quickening its decomposition process. This procedure requires a single decomposition step and a severe statistical analysis [10].

Although this technique cannot completely replace the classical stability program that implies long time observation it can provide, on the other hand, an early alert to dangerous problems occurring at high temperatures and indicate the most favourable directions to pursue a successful formulation.

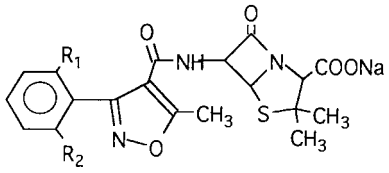
In fact, it is well known that at high temperature the chemical reactivity of drug active components, both pure and in the mixture, can be modified, thus leading to uncontrollable reactions with consequent dangerous situations.

For this reason, it is important to determine the thermal stability (i.e. the temperature range over which a substance does not decompose with an appreciable rate).

Moreover, being the vapour phase the main way in which the loss of drugs from disposal sites occurs, a kinetic study is useful to determine the most probable mechanisms and the kinetic parameters.

There are two opinions as regards the evaluation of the kinetic parameters: (i) kinetic parameters do have a physical meaning and can be used to help in elucidating the solid reaction mechanisms; (ii) kinetic parameters do not have a physical meaning but can help in predicting the rate of the process for drastic conditions, e.g. very high temperature. It seems to be acceptable that kinetic calculations may not be the most efficient means of determining a reaction mechanism, however, they can be useful for drawing reasonable mechanistic conclusions [20].

Before developing the application of thermal analysis to pharmaceutical compounds, it is useful to make the following considerations: (i) the chemical analysis of the compound structure is able to supply useful expectations on its stability; (ii) the presence of an oxygen atom in the compound structure permits the decomposition process without the presence of air; (iii) the presence of a notable exothermic process at low temperature requires the knowledge of the decomposition rate, the suitable mechanism and the activation energy values at various temperatures.



Scheme 1. Structural formulas of oxacillin (R_1 = H; R_2 = H), cloxacillin (R_1 = Cl; R_2 = H), dicloxacillin (R_1 = Cl; R_2 = Cl).

This work aims to study the kinetic behaviour of decomposition processes of some penicillin's having very similar structures.

TG–DSC curves of these substances allow also to obtain some information on the physical properties (melting, solid–gas phase transitions) related to thermal decomposition processes. The structures of the examined compounds (oxacillin, cloxacillin, dicloxacillin) are represented in Scheme 1.

2. Experimental

Penicillin sodium salts (Table 1) were supplied by the Istituto Biochimico Italiano (oxacillin) and by Farmitalia (cloxacillin and dicloxacillin).

The TG–DSC measurements were carried out on a Stanton-Redcroft 625 Simultaneous TG–DSC connected to an Olivetti 250 computer. Instrument calibration was performed with standard indium, gallium, lead, tin, zinc, naphthalene and benzoic acid samples of known temperatures and enthalpies of melting. Purity of both metals and organic compounds is over

Table 1
Names, empirical formulas and molecular weights for the oxacillin derivatives studied (sodium salts)

Sample	Names	Empirical formula	Molecular weight
1	Oxacillin	$C_{19}H_{18}N_3NaO_5S$	423.42
2	Cloxacillin	$C_{19}H_{17}ClN_3NaO_5S$	457.87
3	Dicloxacillin	$C_{19}H_{17}Cl_2N_3NaO_5S$	492.31

99.9%. The compounds studied were used as received without further purification and their purity is over 99%.

Samples of 8–10 mg were weighed in aluminium pans placed in a nitrogen-filled dry box. The TG–DSC system was flushed with air stream both below (flow rate 30 ml min^{-1}) and above (flow rate 50 ml min^{-1}) the open pans. In this way the gas evolved during the thermal decomposition experiment was continuously removed. The heating rates chosen were 1, 2, 5 and 10 K min^{-1} (in non-isothermal experiment) and at least two runs were made for each compound. For isothermal measurements, the prefixed temperature was reached using a heating rate of 8 K min^{-1}. All the thermodynamic parameters were calculated using Stanton-Redcroft Data Acquisition System, Trace 2, Version 4.

The simultaneous TG–DSC system is a very useful tool for investigating organic compounds since it combines, in a single run, weight loss and heat change processes.

In this way, transformations that occur even with small weight changes (chemical reactions, decomposition, vaporisation, and oxidation processes) can be distinguished from those occurring without weight change (melting, crystallisation and polymorphic changes).

In non-isothermal measurements, the quantities used to characterise the compounds were the mass loss percentage in TG technique and the corresponding onset temperatures (T_o).

In differential scanning calorimetry technique, enthalpy values related to various processes were considered together with the temperature peaks T_p that could provide valuable information in the analytical study of organic compounds. Ideally, T_p is the temperature at which the process occurs most rapidly, but is also the temperature at which the maximum rate of heat change between the sample and the environment takes place. Some α-amino acids [14] were identified on the basis of the values of T_p, which are distinct and do not overlap those of the adjacent α-amino acids on the decomposition scale.

Furthermore, thermal analysis of different series of dipeptides, by simultaneous TG–DSC measurements, was carried out. The thermal behaviour of these compounds was compared to that of independent free α-amino acids contained in the dipeptides [15,16].

3. Kinetic procedure

Recently, many authors [17–25] have brought about a great improvement as regards to kinetic analysis. Kinetic analysis of a decomposition process is traditionally expected to produce an adequate kinetic description of the process in terms of the reaction model and of the Arrhenius parameters using a single-step kinetic equation

$$\frac{d\alpha}{dt} = k(T)\,f(\alpha) \tag{1}$$

where t is the time, T the temperature, α the extent of conversion and $f(\alpha)$ the reaction model. The temperature dependence of the rate constant is introduced by replacing $k(T)$ with the Arrhenius equation, which gives

$$\frac{d\alpha}{dt} = A \exp\left(-\frac{E_a}{RT}\right) f(\alpha) \tag{2}$$

where A (the pre-exponential factor) and E_a (the activation energy) are the Arrhenius parameters and R is the gas constant. For non-isothermal conditions, $d\alpha/dt$ in Eq. (2) is replaced with $\beta(d\alpha/dT)$, where β is the heating rate, giving

$$\frac{d\alpha}{dT} = \left(\frac{A}{\beta}\right) \exp\left(-\frac{E_a}{RT}\right) f(\alpha) \tag{3}$$

The three components ($f(\alpha)$, E_a and A) called "kinetic triplet" define both in Eqs. (2) and (3) a single-step reaction that disagrees with the multi-step nature of decomposition that usually occurs in the solid state.

As the studied compounds have complex structures, it can be hypothesised that several steps with different energies will be involved.

If a process involves several steps with different activation energies, the relative contributions of these steps to the overall reaction rate will vary with both temperature and extent of conversion. This means that the effective activation energy determined from the analysis of the results will also be a function of these two variables. Following the model-fitting method the $k(T)$ term is determined by the form of the $f(\alpha)$ chosen. In isothermal kinetics, these terms are separated (k values are constant in isothermal condition). The evaluation of the $f(\alpha)$ term is achieved by fitting various reaction models to experimental data.

On the contrary, a single non-isothermal experiment provides information on both $k(T)$ and $f(\alpha)$ terms but not in a separate form. For this reason, almost any $f(\alpha)$ can satisfactorily fit experimental data by virtue of the variation in the Arrhenius parameters that compensate the difference between the assumed model for $f(\alpha)$ and the true but unknown one [20].

Moreover, isothermal and non-isothermal experiments, necessarily conducted in different regions of temperature, provide single decomposition steps that cannot supply identical values of the Arrhenius parameters.

However, the application of these models to isothermal parameters gives rise to more reliable values of Arrhenius parameters that are likely to conceal the kinetic complexity [19,20].

Anyway, the complex nature of a multi-step process can be more easily detected when using a broader temperature range in the non-isothermal method. In the narrow ranges used under isothermal conditions, the differences between different models are much less visible and lead to a statistically acceptable description of the multi-step by one set of kinetic parameters. An alternative approach to kinetic analysis is the model-free methods that allow us for evaluating Arrhenius parameters without choosing the reaction model. The isoconversional methods make up the best representation of the model-free approach. These methods yield the variation of the effective activation energy as a function of the extent of conversion [17,19,20].

The knowledge of the dependence of E_a on α allows detecting multi-step processes and predicting some mechanistic conclusions on the reaction kinetics over a wide temperature range [17,19]. The isoconversional methods could also yield similar dependencies of the activation energy on the extent of conversion for isothermal and non-isothermal experiments, but direct comparison between these two methods should not be made because they cover different range of temperatures [19,20].

In order to obtain the above-cited values both TG isothermal and dynamic curves have been carried out.

3.1. Isothermal methods

For the isothermal model-fitting method the following procedure was adopted.

It is well known that isothermal kinetics of solid-state reactions can be represented by the equation

$$g(\alpha) = kt \tag{4}$$

where k is the specific constant rate and $g(\alpha)$ is an integral mathematical expression related to a mechanism of solid phase reactions.

Three groups of mathematical expressions (D_1, D_2, D_3, D_4), (R_2, R_3, F_1) and (A_2, A_3, A_4) describe diffusion, chemical reaction and nucleation mechanisms, respectively [26,27].

The degree of conversion α (fraction of compound decomposed) is given by the expression

$$\alpha(t) = \frac{\%m_i - \%m_t}{\%m_i - \%m_f} \tag{5}$$

where $\%m_i$ is the initial percent mass; $\%m_t$ the percent mass at time t and $\%m_f$ the final percent mass, as they are collected from an isothermal TG experiment.

The α–time plots were constructed using experimental percentage mass data taken from TG isothermal curves performed at different constant temperatures, lying in the temperature range where decomposition processes of the studied compounds occur. Generalised reduced time plots, in which α values for each curve are reported as a function of the ratio $t/t_{0.5}$ ($t_{0.5}$ being the experimental time corresponding to $\alpha = 0.5$) have subsequently been constructed.

The curves $\alpha = f(t/t_{0.5})$ were compared with the theoretical ones reported in the literature [26,27] to individuate the most probable mechanisms. The mathematical expressions $g(\alpha)$ describing the possible decomposition mechanisms together with the experimental α and t values corresponding to a fixed temperature were inserted in Eq. (4). The values of kinetic rate constant k were determined at different temperatures from the slope of the straight line obtained by plotting $g(\alpha)$ against time (least-squares method). These values were subsequently inserted in the Arrhenius equation together with the corresponding temperature values T:

$$\ln k = \ln A - \frac{E_a}{RT} \tag{6}$$

supplying activation energy and pre-exponential factor values from the slope and intercept of a regression straight line.

If no expression was found to describe the kinetic complexity, an alternative procedure, the so-called

isothermal isoconversional method, was used to verify the energy value variation related to the multi-step in the actual experimental temperature range.

From isothermal TG curves, a set of temperature, T, and time t values were obtained for fixed values of α. Substituting $k = A\exp(-E_a/RT)$ in Eq. (4), one obtains

$$g(\alpha) = A\exp\left(-\frac{E_a}{RT}\right)t \tag{7}$$

where the obtained t and T are the time and temperature values, respectively, which make the function $g(\alpha)$ constant. By using the logarithmic form of the above equation:

$$\ln g(\alpha) = \ln A - \frac{E_a}{RT} + \ln t \tag{8}$$

and rearranging, it can be obtained

$$\ln t = -\ln A + \ln g(\alpha) + \frac{E_a}{RT} \tag{9}$$

By plotting $\ln t$ against $1/T$ according to Eq. (9) the activation energies were found at any given α values from the slope of a regression straight line.

It must be taken into account that in the isothermal mode, the reactions are very slow at the lowest temperatures, so that the experiments will be limited by long times to reaction completion and by low detection limits, while for high temperatures the reaction will be too fast.

These restrictions imply that the experimental isothermal domain of temperature available is limited, hence the possible separation of several reactions with isothermal isoconversional method will depend on this. Furthermore, the complexity of the process could be concealed if different processes have similar activation energy.

To avoid this fact model-fitting and isoconversional non-isothermal methods can be applied.

3.2. Non-isothermal methods

In order to study the variation of the chemical and physical properties related to non-isothermal processes, it has become usual to associate a mathematical relationship with a particular model of mechanism, but there are several models giving the same mathematical expression and the same model giving two, three or more alternative expressions.

Dollimore et al. [28–31] have carried out a computer program that plots a theoretical $d\alpha/dT$ curve by using Eq. (3) when the hypothesised mechanism $f(\alpha)$ and suitable values of both A and E_a are introduced.

This approach may be considered as the reverse of the Arrhenius non-isothermal kinetics in which A and E_a are calculated both from the α–T plots and a proper mechanism. The shape of the theoretical curve obtained in this way results to be only a function of the mechanism and allows determining the following parameters:

(i) Initial (T_i) and final (T_f) temperature of TG curve as diffuse or sharp.
(ii) The half width defined as the peak width on the differential plot of $d\alpha/dT$ against T measured at half height.
(iii) The value of α_{max} at the maximum rate of the process (at T_p) in the α–T plot.

The comparison of these characteristic quantities (half width, α_{max}, T_i and T_f) for experimental curves with those reported in literature [28] shows more than one possible mechanism for each compound. In order to select the appropriate mechanism for each compound and to determine the kinetic parameters A and E_a the following method can be used.

The α values, calculated from TG curves as a function of the temperature together with those of $d\alpha/dT$ (the reverse of DTG) are inserted in the mathematical expressions of $f(\alpha)$ and used in the Arrhenius differential equation:

$$\ln\left[\frac{\beta(d\alpha/dT)}{f(\alpha)}\right] = \ln k = \ln A - \frac{E_a}{RT} \tag{10}$$

The α values are also inserted in the mathematical integral expression $g(\alpha)$ and used together with β in the Satava integral equation

$$\log[g(\alpha)] = -0.4567\left(\frac{E_a}{RT}\right) - 2.3115 + \log\left(\frac{AE_a}{R\beta}\right) \tag{11}$$

where Doyle's approximation is valid in a temperature range of 100 K [8].

The Arrhenius parameters can be calculated by means of the following two linear relationships:

$$\ln\left[\frac{\beta(d\alpha/dT)}{f(\alpha)}\right] \text{ vs. } \frac{1}{T} \tag{12}$$

$$\log[g(\alpha)] \text{ vs. } \frac{1}{T} \tag{13}$$

where $f(\alpha)$ and $g(\alpha)$ are the mathematical expressions related to the mechanisms according to the two methods. From the coefficient and the intercept of the regression straight lines, the E_a and A parameters can be calculated.

Finally, the values of A and E_a and related mechanisms represented by $f(\alpha)$ were inserted in Eq. (3) and the theoretical DTG curves are reconstructed and compared to the experimental ones.

Values of triplets obtained in this way can be used in non-isothermal model-fitting method.

To obtain the E_a values related to isoconversional non-isothermal method the Ozawa–Flynn–Wall equation was applied to non-isothermal TG curves:

$$\log\beta = -0.4567\left(\frac{E_a}{RT}\right) - 2.3115 + \log\left(\frac{AE_a}{R}\right) - \log[g(\alpha)] \tag{14}$$

Finally, some importance was given to the parameters determining the stability times for the drugs: storage times at a given degree of conversion α at various temperatures were obtained by the expression

$$t_\alpha = \frac{g(\alpha)}{[A\exp(-E_a/RT)]} \tag{15}$$

by using the mathematical expressions $g(\alpha)$ describing the possible decomposition mechanisms and $\alpha = 0.5$ or small values (0.05 and 0.10).

If triplet kinetic $g(\alpha)$, A and E_a obtained from isothermal model-fitting method fails in the description in kinetic complexity, the values of these quantities extrapolated to room temperature are not acceptable. Anyway, as well as in the case that a single-step reaction occurs, a severe statistical analysis is required to accept extrapolation at room temperature [13].

4. Results and discussion

4.1. Features of the thermal processes

Trends of thermal behaviour at $\beta = 5\,\mathrm{K\,min^{-1}}$ for the examined compounds are shown in Fig. 1. The

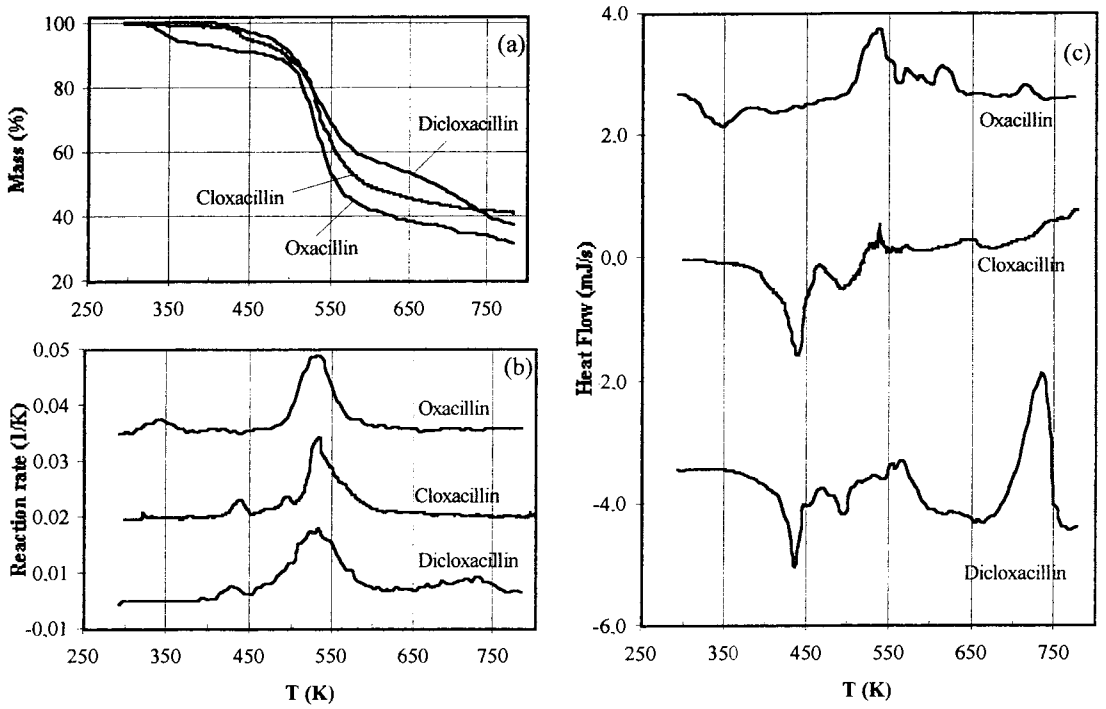


Fig. 1. Simultaneous TG–DTG–DSC curves for the antibiotics examined performed at $5\,\mathrm{K\,min^{-1}}$ under air stream.

Table 2
Onset temperatures (T_o) and mass loss percentage obtained from dynamic TG measurements ($\beta = 5\,K\,min^{-1}$) for the oxacillin derivatives studied (sodium salts)

Compounds	Dehydration step		Decomposition step	
	T_o (K)	Mass loss (%)	T_o (K)	Mass loss (%)
Oxacillin	321.6	8.1	504.2	59.2
Cloxacillin	372.7	5.4	478.7	52.8
Dicloxacillin	402.5	5.2	487.9	38.6
			648.8	18.3

values of the thermodynamic quantities relating to TG–DSC curves are reported in Tables 2 and 3.

TG and DSC curves of oxacillin show a step of weight loss in which exothermic processes occur. A dehydration process was also found (endothermic process). For cloxacillin there is a decomposition step with exothermic and endothermic processes, while at low temperature a dehydration process occurs.

Dicloxacillin shows a dehydration process and two steps of decomposition with endothermic and exothermic processes in the first and a sharp exothermic process in the second one. This behaviour clearly allows to hypothesise that these compounds undergo complex decomposition processes.

An attempt to individuate kinetic parameters of superimposed reactions can be made by means of a kinetic analysis.

4.2. Kinetics

The $\alpha = f(t)$ isothermal experimental curves of oxacillin salt for the decomposition process chosen at different temperatures (lying in the experimental temperature range) are given in Fig. 2.

At a given extent of conversion, the correspondent t values where divided by $t_{0.5}$ for each experimental temperature. The obtained $\alpha(t/t_{0.5})$ values do not depend on temperatures but on the model function only. The dependencies of α on the reduced time $t/t_{0.5}$, the so-called generalised reduced time plots, derived from the isoconversional curves. The experimental $\alpha(t/t_{0.5})$ values have been compared with the generalised reduced theoretical ones reported in the literature [23,24].

Theoretical curves were constructed in the following way: by substituting the values $k = A\exp(-E_a/RT)$ in the expressions $d\alpha = kf(\alpha)\,dt$, one obtains $d\alpha = A\exp(-E_a/RT)f(\alpha)\,dt$, where the hypothesised mechanism $f(\alpha)$ and the suitable values of both A and E_a are introduced. The shape of the theoretical curves obtained in this way proves to be only a function of the mechanisms and the temperatures. These curves were normalised in the same manner as the experimental ones.

In the decomposition process the experimental normalised curves at various temperatures for oxacillin partially overlap with some of the theoretical ones

Table 3
Onset, peak temperatures (T_o and T_p, respectively) and enthalpy changes calculated from DSC measurements for the compounds studied (sodium salts)

Compounds	Dehydration step			Decomposition step		
	T_o (K)	T_p (K)	ΔH (kJ mol^{-1})	T_o (K)	T_p (K)	ΔH (kJ mol^{-1})
Oxacillin	314.3	347.5	55.4	503.9	515.0	−97.7
					520.1	
					530.4	
				559.7	567.5	−25.4
					608.7	
Cloxacillin	414.5	439.4	74.8	476.3	492.1	19.3
				511.7	518.8	−28.5
					532.2	
					565.1	
Dicloxacillin	419.1	438.7	65.1	479.8	494.6	17.3
				531.7	558.7	−33.8
					562.5	
				685.8	734.1	−214.1

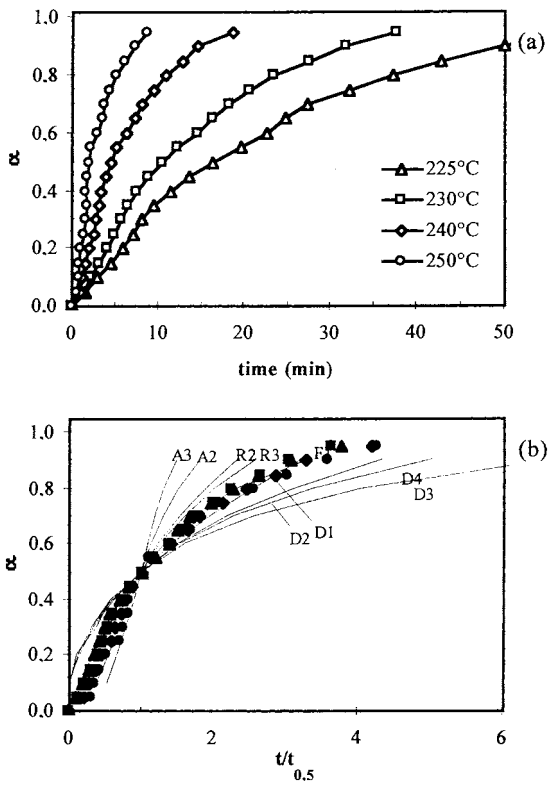


Fig. 2. α vs. time (a) and reduced time isothermal plots (b) carried out at fixed temperatures (in the actual decomposition temperature range).

related to various mechanisms (Fig. 2). This result allows a superimposed series of occurring reaction to be established.

In order to apply the model-fitting method, the mathematical integral expressions $g(\alpha)$ together with the experimental α and t values (corresponding to a fixed temperature) were inserted in Eq. (4). The values of the kinetic rate constant k were determined at different temperatures from the slope of the straight line obtained by plotting $g(\alpha)$ against time (least-squares method). These values were subsequently inserted in the Arrhenius equation together with the corresponding temperature values T supplying activation energy and pre-exponential factor values from the slope and intercept of regression straight line (Tables 4 and 5).

The values of activation energies for the decomposition process are nearly constant varying from 168.1 to 172.3 kJ mol^{-1} (Table 5). In the narrowed temperature range used under isothermal conditions the differences between the different models are much less visible and lead to a statistically acceptable description of the multi-step process by one set of kinetic parameters.

The Dollimore's computer program used in non-isothermal method cannot be applied to our experimental curves due to the complexity of decomposition process (as it can be seen in Fig. 3). The change in E_a values in the isoconventional methods was obtained by using Eqs. (9) and (14).

For isoconversional isothermal method (Fig. 4) related to the decomposition step the activation energy values increase from 20 kJ mol^{-1} at 0.05 extent of conversion to 40 kJ mol^{-1} at 0.5 extent of conversion. In the range 0.5–0.95 the values remain constant about 40 kJ mol^{-1}.

In the whole range of the degree of conversion, the E_a values obtained from non-isothermal isoconversional method assume high values varying from 66.3 to 237.3 kJ mol^{-1} (Fig. 4), while in isothermal isoconversional method the restrictions due to a narrower range of temperatures limit the separation of superimposed reactions. From these results, it can be seen that the complex nature of a multi-step process can be more easily detected when using a broader temperature range.

The isothermal normalised curves of cloxacillin partially overlaps with the theoretical ones but the values calculated with isothermal fitting method result to be (Table 5) constant about 98 kJ mol^{-1} thus confirming the statistically acceptable description of the multi-step decomposition by one set of kinetic parameters. Dollimore's method shows that the non-isothermal fitting method cannot be applied to our experimental curves (Fig. 3).

For the isoconversional isothermal method, the activation energy shows constant values nearly about 20 kJ mol^{-1} while for the non-isothermal isoconversional method the activation energy decrease from 115 to 79.53 kJ mol^{-1} in the range of degree conversion 0.05–0.10. Subsequently, this quantity assumes high values ranging from 95.1 to 216.6 kJ mol^{-1} (Fig. 4).

This behaviour confirms that more than one reaction occurs in the decomposition process examined. For dicloxacillin also the normalised curves of first and

Table 4
Linear regression parameters obtained from Arrhenius equation according to the isothermal model-fitting method for each decomposition step

Regression parameters[a]	Kinetic models								
	D_1	D_2	D_3	D_4	F_1	R_2	R_3	A_2	A_3
Oxacillin									
a	37.0	37.0	36.6	35.9	38.3	36.6	35.4	37.2	36.7
b	−20.43	−20.56	−20.72	−20.62	−20.57	−20.38	−20.21	−20.27	−20.29
r^2	0.9986	0.9988	0.9991	0.9989	0.9989	0.9986	0.9983	0.9986	0.9984
F	2865	3327	4215	3596	3539	2792	2339	2788	2574
Cloxacillin									
a	19.78	19.66	18.90	18.40	20.86	19.50	18.53	20.11	19.72
b	−11.81	−11.83	−11.85	−11.84	−11.83	−11.81	−11.78	−11.81	−11.80
r^2	0.9611	0.9615	0.9619	0.9617	0.9610	0.9601	0.9591	0.9595	0.9587
F	99	100	101	100	99	96	94	95	93
Dicloxacillin (step I)									
a	16.82	16.92	16.54	15.79	18.28	16.56	15.33	17.21	16.71
b	−10.38	−10.51	−10.73	−10.58	−10.59	−10.38	−10.22	−10.40	−10.33
r^2	0.9653	0.9680	0.9680	0.9668	0.9675	0.9659	0.9651	0.9664	0.9661
F	111	114	121	116	119	113	110	115	114
Dicloxacillin (step II)									
a	26.13	26.00	25.26	15.79	27.22	25.86	24.92	26.49	26.11
b	−19.80	−19.85	−10.73	−19.91	−19.86	−19.80	−19.76	−19.81	−19.79
r^2	0.9785	0.9810	0.9831	0.9523	0.9812	0.9787	0.9765	0.9784	0.9773
F	191	207	232	80	208	184	166	181	172

[a] The regression equation is $y = a + bx$.

second steps of decomposition partially overlap with the theoretical ones related to various mechanisms. However, the values of activation energies, calculated with the isothermal fitting model (Tables 4 and 5) in the first and second steps of decomposition for all $g(\alpha)$, are nearly constant (about 86 and 165 kJ mol^{-1}, respectively).

For the isoconversional isothermal method related to the first decomposition step the activation energy (Fig. 4) shows a value of about 20 kJ mol^{-1}, while in

Table 5
E_a and ln A values obtained by a linear regression analysis on Arrhenius equation according to the isothermal model-fitting method

Kinetic parameters	Step	Kinetic models								
		D_1	D_2	D_3	D_4	F_1	R_2	R_3	A_2	A_3
Oxacillin										
E_a (kJ mol^{-1})	I	169.9	170.9	172.3	171.4	171.0	169.5	168.1	169.3	168.7
ln A (s^{-1})		37.0	37.0	36.6	35.9	38.3	36.6	35.4	37.2	36.7
Cloxacillin										
E_a (kJ mol^{-1})	I	98.2	98.4	98.5	98.4	98.4	98.2	97.9	98.2	98.1
ln A (s^{-1})		19.8	19.7	18.9	18.4	20.9	19.5	18.5	20.1	19.7
Dicloxacillin										
E_a (kJ mol^{-1})	I	86.3	87.4	89.2	88.0	88.1	86.3	84.9	86.4	85.9
ln A (s^{-1})		16.8	16.9	16.5	15.8	18.3	16.6	15.3	17.2	16.7
E_a (kJ mol^{-1})	II	164.7	165.0	165.5	121.8	165.1	164.6	164.3	164.7	164.5
ln A (s^{-1})		26.1	26.0	16.9	16.9	27.2	25.9	24.9	26.5	26.1

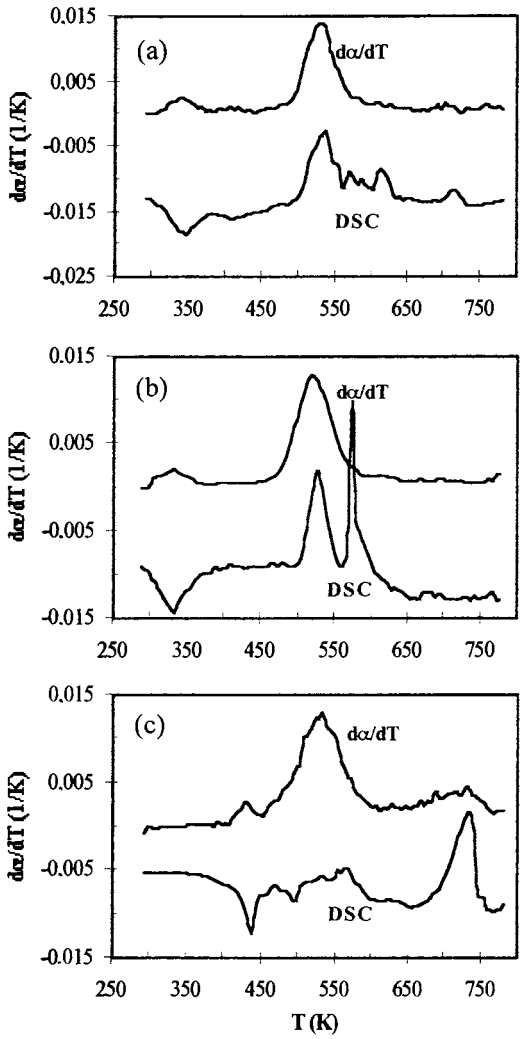


Fig. 3. Comparison between DSC and dα/dT curves for oxacillin (a), cloxacillin (b) and dicloxacillin (c). A multi-step nature of decomposition reaction is underlined by several exothermic effects in the range 450–650 K.

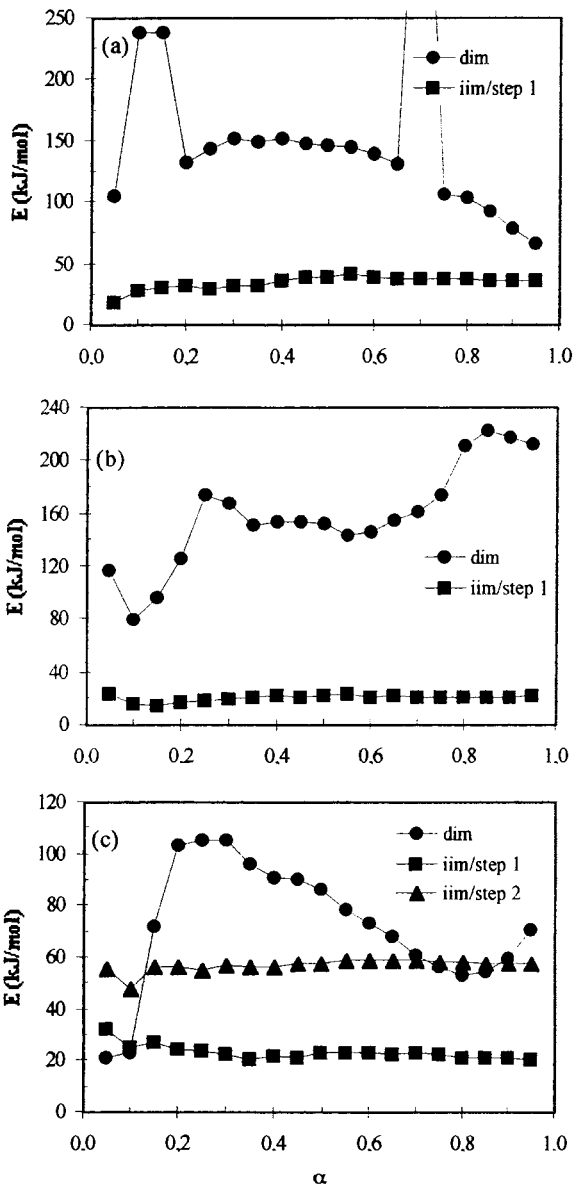


Fig. 4. Dependence of E_a on α determined using both the dynamic isoconversional method (dim) and the isothermal isoconversional method (iim) for oxacillin (a), cloxacillin (b) and dicloxacillin (c).

the second decomposition step the activation energies shows a value of about 60 kJ mol^{-1}.

For non-isothermal isoconversional method in the range of degree of conversion 0.1–0.2, the activation energy (Fig. 4) assumes values varying from about 20 to 105 kJ mol^{-1}. Subsequently, these values decrease from about 105 to 70 kJ mol^{-1} in the range 0.3–0.95. This behaviour allows to hypothesise that more than one reaction occurs in the decomposition process.

Finally, half-life times for the drugs examined were calculated by inserting the triplet kinetic values obtained by isothermal fitting model in Eq. (15) (Table 6). Scattered values displayed by the compounds in the different mechanisms clearly indicate

Table 6
Storage time values (years) at 25 °C for a conversion of 5, 10 or 50% (half-life) for each decomposition step

Conversion (%)	Storage time (years)								
	D_1	D_2	D_3	D_4	F_1	R_2	R_3	A_2	A_3
Oxacillin									
5	4076	3917	1831	2524	36001	50375	2654111	237042	506444
10	16304	11876	7590	10336	73949	102095	2718845	339730	643779
50	407603	352051	271210	326047	486499	582713	3236720	871380	1206293
Cloxacillin									
5	0.033	0.020	0.010	0.016	0.243	0.430	27.981	2.076	4.897
10	0.131	0.082	0.040	0.066	0.499	0.871	28.664	2.976	6.225
50	3.274	2.423	1.529	2.092	3.284	4.972	34.123	7.630	11.664
Dicloxacillin (step I)									
5	0.005	0.004	0.003	0.003	0.050	0.068	3.623	0.335	0.726
10	0.020	0.015	0.010	0.013	0.103	0.137	3.711	0.480	0.923
50	0.511	0.448	0.372	0.424	0.680	0.785	4.418	1.231	1.730
Dicloxacillin (step II)[a]									
5	25	17	10	9.2×10^{-4}	210	329	19659	797.56	3636
10	100	68	40	3.8×10^{-3}	432	668	10139	1143.07	4622
50	2509	2009	1441	1.2×10^{-1}	2844	3810	23975	2931.89	8660

[a] Storage time values $\times10^6$.

that the failure in the model-fitting method makes unsuitable kinetic parameters extrapolated at room temperature.

5. Conclusion

The application of the model-fitting method to a multi-step decomposition process results to be unsuitable for the non-isothermal data. For the isothermal data this method gives rise to apparently reliable results that, however, are likely to conceal the kinetic complexity. A viable alternative to the model-fitting method is the model-free isoconversional method.

By this method, both isothermal and non-isothermal data can be analysed and the E_a vs. α plots can reveal complexities in reaction kinetics. Due to the wide temperature range covered, the non-isothermal method gives a more complete picture of the decomposition process. Finally, kinetic calculations are not able to determine the decomposition mechanisms for the studied compounds. The failure in the model-fitting method to define multi-step decomposition processes makes unsuitable the storage times extrapolated at room temperature.

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References

[1] J.M. Dewduey, R.G. Edwards, J. R. Soc. Med. 77 (1984) 866.
[2] V. Burgat, Allergy and residues, in: Safety and Quality in Food, Bureau European d'Information pour Development de la Santé Animale (DSA), Elsevier, Amsterdam, 1984, 143 pp.
[3] P.K. Orberg, W.E. Sandine, Appl. Environ. Microb. 49 (1985) 538.
[4] K.M. Shahani, P.J. Whalen, Significance of antibiotics in food and feed, in: W.A. Moats (Ed.), Agricultural Uses of Antibiotics, American Chemical Society, Washington, DC, 1986, 88 pp.
[5] B. Halling-Sorensen, Chemosphere 40 (2000) 731.
[6] F. Rodante, G. Marrosu, G. Catalani, Thermochim. Acta 82 (1984) 319.
[7] F. Rodante, G. Catalani, M. Guidotti, J. Therm. Anal. 53 (1998) 937.
[8] F. Rodante, S. Vecchio, G. Catalani, M. Guidotti, J. Therm. Anal. Calorim. 60 (2000) 605.
[9] M. Nebuloni, in: G. Della Gatta, A. Lucci (Eds.), Principi Ed Applicazioni di Calorimetria ed Analisi Tecnica, Piccin, Padova, 1984.

[10] U. Biader Ceipidor, M. Tomassetti, R. Curini, Thermochim. Acta 56 (1982) 125.
[11] M. Tomassetti, G. D'Ascenzo, R. Curini, Thermochim. Acta 60 (1983) 1.
[12] M. Tomassetti, L. Campanella, L. Sorrentino, G. D'Ascenzo, Thermochim. Acta 70 (1983) 5.
[13] F. Rodante, S. Vecchio, J. Therm. Anal. Calorim. 63 (2001) 433.
[14] F. Rodante, G. Marrosu, G. Catalani, Thermochim. Acta 194 (1992) 197.
[15] F. Rodante, G. Marrosu, G. Catalani, Thermochim. Acta 197 (1992) 147.
[16] F. Rodante, F. Fantauzzi, G. Catalani, Thermochim. Acta 287 (1996) 351.
[17] S. Vyazovkin, C.A. Wight, Thermochim. Acta 340–341 (1999) 53.
[18] M.E. Brown, M. Maciejewski, S. Vyazovkin, R. Nomen, J. Sempere, A. Burnham, J. Opfermann, R. Strey, H.L. Anderson, A. Kemmer, R. Keuleers, J. J Enssens, H.O. Desseyn, C.-R. Li, T.B. Tang, B. Roduit, J. Malek, T. Mitsuhashi, Thermochim. Acta 355 (2000) 125.
[19] M. Maciejewski, Thermochim. Acta 355 (2000) 145.
[20] S. Vyazovkin, Thermochim. Acta 355 (2000) 155.
[21] A.K. Burnham, Thermochim. Acta 355 (2000) 165.
[22] B. Roduit, Thermochim. Acta 355 (2000) 171.
[23] N. Sbirrazzuoli, Y. Giraud, L. Elegant, Thermochim. Acta 293 (1977) 25.
[24] S. Vyazovkin, N. Sbirrazzuoli, Macromol. Rapid Commun. 20 (1999) 387.
[25] S. Vyazovkin, N. Sbirrazzuoli, Anal. Acta 355 (1997) 175.
[26] J.H. Sharp, G.W. Brindley, B.N. Narahari Achar, J. Am. Ceram. Soc. 49 (7) (1966) 379.
[27] I. Halikia, P. Neou-Syngouna, D. Kolitsa, Thermochim. Acta 320 (1998) 75.
[28] D. Dollimore, Thermochim. Acta 203 (1992) 7.
[29] D. Dollimore, T.A. Evans, Y.F. Lee, G.P. Pee, F.W. Wilburn, Thermochim. Acta 196 (1992) 255.
[30] D. Dollimore, T.A. Evans, Y.F. Lee, F.W. Wilburn, Thermochim. Acta 198 (1992) 249.
[31] X. Gao, D. Chen, D. Dollimore, Thermochim. Acta 223 (1993) 333.