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KINETIC ANALYSIS OF SINGLE OR MULTI-STEP DECOMPOSITION PROCESSES
Limits introduced by statistical analysis

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Abstract

A kinetic study on decomposition processes of some penicillin and some commercial drugs was carried out. As expected by the complex structures of penicillins, several steps with different activation energies occurred in their decomposition processes.

Model-fitting and model-free kinetic approach were applied to non-isothermal and isothermal data.

In the model-fitting methods the kinetic triplets ($f(\alpha)$, A and E_a) that defines a single reaction step resulted in being at variance with the multi-step nature of penicillins decomposition.

The model-free approach represented by isothermal and non-isothermal isoconversional methods, gave dependences of the activation energies on the extent of conversion. The complex nature of the multi-step process of the studied compounds was more easily revealed using a broader temperature range in non-isothermal isoconversional method. The failure in the model fitting method did not allow calculating storage times. Model-fitting and model-free methods, both isothermal and non-isothermal, showed that F1 mechanism is able to describe decomposition processes for drugs (having Phosphomycin salts as active component) for which a single decomposition process occurs. Statistical analysis allowed us to select reliable kinetic parameters related to the decomposition processes for these last compounds. This procedure showed that the values obtained by extrapolation, outside the temperature range where the processes occurred must be used with caution. Indeed half-life and shelf-life values, commonly extrapoled at room temperature, seemed to be unrealistic.

Keywords: Arrhenius parameters, drugs, isothermal, multi-step, non-isothermal, statistical analysis, thermal decomposition

Introduction

It is well-known that solid compounds submitted to heating treatment undergo simple or multi-step thermal decomposition processes in relation to the complexity of their structures.

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Thermal analysis, which studies these processes, is a routine method for the study of drugs and substances of pharmacological interest [1–4].

For example, as regards storage time values study 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 step reaction of decomposition and a severe statistical analysis [5].

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 danger problems occurring at high temperatures and it can indicate the most favourable directions to pursue a successful formulation.

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

From this fact the need to determine thermal stability i.e. the temperature range over which a substance does not decompose with an appreciable rate.

Moreover, as in the case of fire, the loss of drugs from disposal sites through the vapour phase is the main pathway, a kinetic study on the vaporisation process of these compounds attempts to determine the most probable mechanism and the kinetic parameters involved.

As regards the evaluation of the kinetic parameters there are two opinions:

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.

Before the application of thermal analysis to pharmaceutical compounds the following considerations must be made: 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 decomposition rate, the suitable mechanism and the activation energy values at various temperatures.

This work aims to study kinetic behaviour of decomposition processes of some penicillins having complex structures (ampicillin, benzylpenicillin, carbenicillin, oxacillin, cloxacillin dicloxacillin) and of some drugs having phosphomycin salts (which shows a simple structure) as active component. These compounds have been the subject of previous works [5, 6].

Recently many authors [7–15] have brought about a great improvement as regards kinetic analysis.

Kinetic analysis of 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

$$d\alpha/dt = k(T)f(\alpha) \quad (1)$$

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

$$d\alpha/dt = A\exp(-E_a/RT)f(\alpha) \quad (2)$$

where A (the pre-exponential factor) and E (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

$$d\alpha/dT = (A/\beta)\exp(-E_a/RT)f(\alpha) \quad (3)$$

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.

For compounds having 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. The use of Eqs (2) and (3) determines reactions model that does not represent multi-step kinetics.

For this reason one cannot justify the establishment of the reaction mechanism from $f(\alpha)$ alone.

Also for a simple decomposition step one cannot justifiably expect that identical values of Arrhenius parameters result from isothermal and non-isothermal experiments which are necessarily conducted in different regions of temperature.

Moreover, the application of non-isothermal model-fitting (methods) approaching to single-rate data fails to achieve a clean separation between the rate temperature dependence $k(T)$ and the reaction model $f(\alpha)$. Almost any $f(\alpha)$ can satisfactorily fit the data by virtue of the Arrhenius parameters compensation effects, thus substituting the true unknown reaction model. For this reason the single heating rate data for the determination of kinetic parameters should be avoided. The application of these models to isothermal parameters gives rise to more reliable values of Arrhenius parameters that, however, are likely to conceal the kinetic complexity. 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 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.

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.

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.

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

Experimental

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 mechanisms 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.

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

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

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 degree of conversion (α)-time plots $\alpha=f(t)$ 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 α=0.5) have subsequently been constructed.

Curves $\alpha=f(t/t_{0.5})$ were compared with the theoretical ones reported in literature [16, 17] 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 constant rate k were determined at different temperatures from the slope of the straight line obtained by plotting $g(\alpha)$ *vs.* time (least-square method). These values were subsequently inserted in the Arrhenius equation together with the corresponding temperature values T:

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

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

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

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

where the obtained t and T are the time and temperature values which make constant the function $g(\alpha)$. By using the logarithmic form of Eq. (7) it can be written:

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

and rearranging it, one obtains

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

By plotting $\ln t$ *vs.* $1/T$ 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 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.

Non-isothermal methods

In order to study chemical and physical properties variation related to non isothermal processes it has become usual to associate 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 and co-workers [18–21] have carried out a computer program that plots theoretical $d\alpha/dT$ curve by using Eq. (3) when the hypothesised mechanism $f(\alpha)$ and the 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 in being 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 (d) or sharp (s),

ii) the half width defined as the peak width on the differential plot of $d\alpha/dT$ *vs.* 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 [18] 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 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:

$$\ln[(\beta d\alpha/dT)/f(\alpha)] = \ln k = \ln A - E_a/RT \quad (10)$$

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

$$\log[g(\alpha)] = -0.4567(E/RT) - 2.3115 + \log(AE_a/R\beta) \quad (11)$$

where Doyle's approximation is valid in a temperature range of 100 K [22].

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

$$\ln[(\beta d\alpha/dT)/f(\alpha)] \textit{ vs. } 1/T \quad (12)$$

$$\log[g(\alpha)] \textit{ vs. } 1/T \quad (13)$$

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 regressions straight lines, 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 E_a values related to isoconversional non-isothermal method the Ozawa–Flynn–Wall equation

$$\log\beta = -0.4567(E_a/RT) - 2.3115 + \log(AE_a/R) - \log[g(\alpha)] \quad (14)$$

was applied to non-isothermal TG curves.

Finally, some importance was given to the parameters determining the stability times for the drugs: storage's times at a given fraction of compound decomposed α at various temperatures were obtained by the expression

$$t\alpha = g(\alpha)/A\exp(-E_a/RT) \quad (15)$$

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

If the kinetic triplet $g(\alpha)$, A and E_a obtained from isothermal model-fitting method fails in the description of the kinetic complexity the values of these quantities extrapolated to room temperature are not acceptable. Anyway, as well as in the case where a single reaction step occurs, a severe statistical analysis is required to accept extrapolation at room temperature [5].

Results and discussion

Features of the thermal processes and kinetics

Trends of thermal behaviour (TG/DSC curves) at β=5 K min^{-1} for the examined compounds are shown in Fig. 1. From these curves it can be seen that the penicillins undergo a more complex decomposition process than that of fosfocin and fosfotricin.

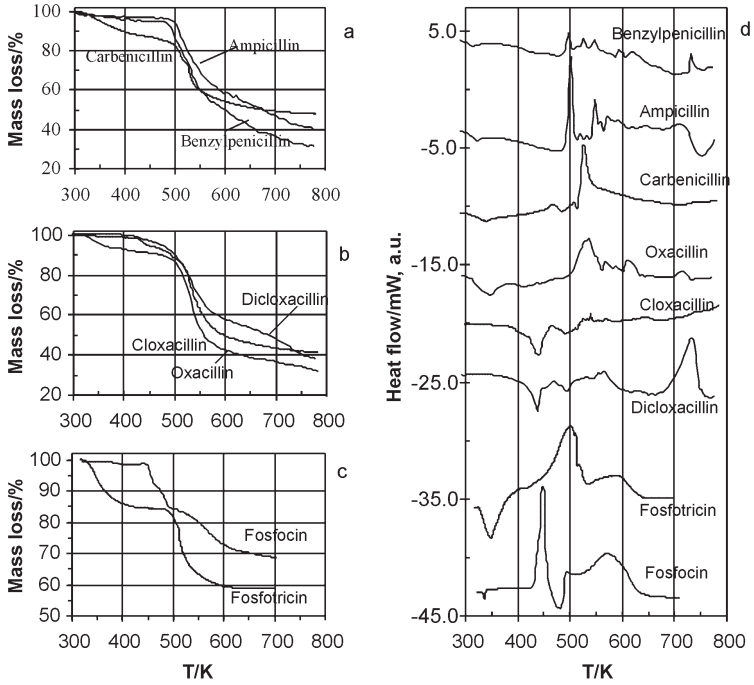

Fig. 1 Simultaneous TG (a, b, and c plots) and DSC (d plot) curves for the examined pharmaceutical compounds

One example of $\alpha=f(t)$ isothermal experimental curves of penicillin salts is given for the two steps of benzylpenicillin decomposition processes, chosen at different temperatures (lying in the experimental temperature range) in Figs 2a and 2b. In α-time plots carried out at different temperatures the t values related to the same α values were divided by the corresponding $t_{0.5}$. Obtained α *vs.* $t/t_{0.5}$ plots do not depend on the model function $f(\alpha)$ but on the temperature only so that the curves were normalised.

The generalised reduced times plots derived from the isoconversional curves have been compared with the generalised reduced theoretical ones reported in literature [16, 17].

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 processes the experimental normalized curves at various temperatures for, benzylpenicillin, ampicillin, carbenicillin, oxacillin, cloxacillin and

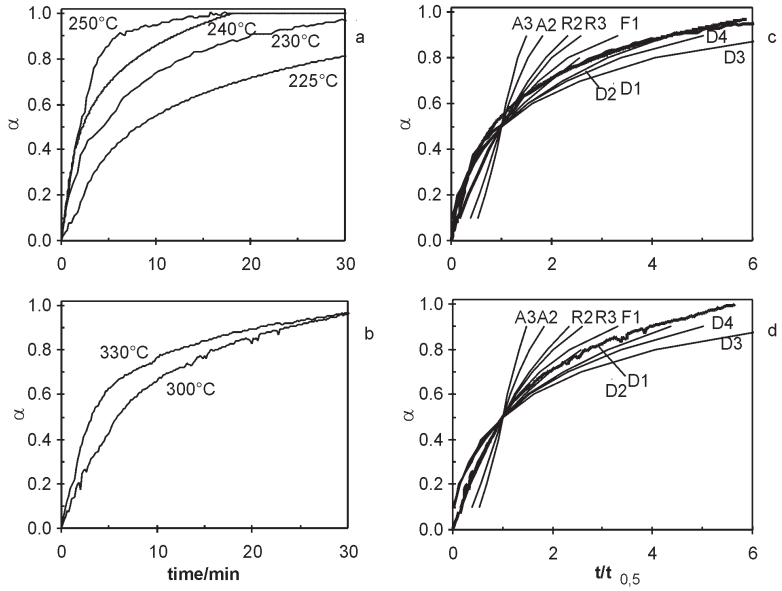

Fig. 2 α *vs.* time plots for the first and the second decomposition processes of benzylpenicillin (a and b, respectively). Reduced time isothermal plots for the first and the second decomposition processes of benzylpenicillin carried out at fixed temperatures lying in the actual decomposition temperature range (c and d, respectively)

Table 1 E_a (kJ mol^{-1}) and ln$A$ (s^{-1}) values obtained by a linear regression analysis on Arrhenius equation according to the isothermal model-fitting method for all the decomposition processes of some penicillin drugs

Kinetic parameters	Step	Kinetic models								
		D1	D2	D3	D4	F1	R2	R3	A2	A3
						Benzylpenicillin				
E_a	I	79.1	116.0	101.9	89.7	117.9	83.1	73.7	113.9	112.6
ln$A$		11.7	20.5	16.7	13.0	22.1	12.5	9.2	20.5	19.9
E_a	II	–5.8	5.2	4.3	–0.8	6.0	–4.5	–9.4	2.5	1.1
ln$A$		–8.7	–6.5	–7.1	–8.9	–5.1	–8.7	–10.7	–6.6	–7.2
						Ampicillin				
E_a	I	275.5	275.4	275.2	275.3	275.3	275.5	275.6	275.4	275.5
ln$A$		58.2	58.0	57.2	56.8	59.2	57.9	57.0	58.5	58.2
E_a	II	38.3	39.8	42.2	40.6	40.7	38.3	36.5	38.6	37.8
ln$A$		–0.2	0.0	–0.3	–1.1	1.4	–0.4	–1.7	0.2	–0.3
						Carbenicillin				
E_a	I	70.0	70.6	71.6	71.0	71.0	69.9	69.0	69.9	69.5
ln$A$		9.2	9.2	8.6	8.0	10.5	8.9	7.7	9.5	9.0
E_a	II	25.8	23.5	19.8	22.3	21.9	25.5	28.2	25.0	26.0
ln$A$		–2.4	–3.1	–4.6	–4.6	–2.2	–2.8	–3.1	–2.3	–2.4
						Oxacillin				
E_a	I	169.9	170.9	172.3	171.4	171.0	169.5	168.1	169.3	168.7
ln$A$		37.0	37.0	36.6	35.9	38.3	36.6	35.4	37.2	36.7
						Cloxacillin				
E_a	I	98.2	98.4	98.5	98.4	98.4	98.2	97.9	98.2	98.1
ln$A$		19.8	19.7	18.9	18.4	20.9	19.5	18.5	20.1	19.7
						Dicloxacillin				
E_a	I	86.3	87.4	89.2	88.0	88.1	86.3	84.9	86.4	85.9
ln$A$		16.8	16.9	16.5	15.8	18.3	16.6	15.3	17.2	16.7
E_a	II	164.7	165.0	165.5	121.8	165.1	164.6	164.3	164.7	164.5
ln$A$		26.1	26.0	16.9	16.9	27.2	25.9	24.9	26.5	26.1

dicloxacillin, partially overlap with some of the theoretical ones related to various mechanisms (in Figs 2c and 2d an example related to benzylpenicillin is given). This result allows to conclude that a superimposed series of reactions occur.

In order to apply the model-fitting method the above cited 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 kinetic constant rate k were determined at different temperatures from slope of the straight line obtained by plotting $g(\alpha)$ *vs.* time (least-square method). These values were subsequently inserted in the Arrhenius equation together with the corresponding temperature values T supplying E_a and pre-exponential factor values from the slope and intercept of regression straight-line (Table 1).

For benzylpenicillin the values of activation energies related to the first step of decomposition vary from 79.1 to 117.9 while for the second one some negative values were found, thus confirming that the model-fitting model disagrees with the multi-step nature of the decomposition process.

Activation energies related to the first decomposition step for ampicillin are quite constant (275.5 kJ mol^{-1}) for all the $g(\alpha)$ model function while for the second one (Table 1) they ranged from 36.5 to 42.2 kJ mol^{-1}. Carbenicillin shows quite constant activation energy values for the first decomposition step (about 70 kJ mol^{-1}) and values varying from 19.8 to 28.2 kJ mol^{-1} for the second one. Activation energies related to the decomposition steps of oxacillin are varying from 168.1 to 172.3 kJ mol^{-1} while for cloxacillin E_a values calculated result to be quite constant (about

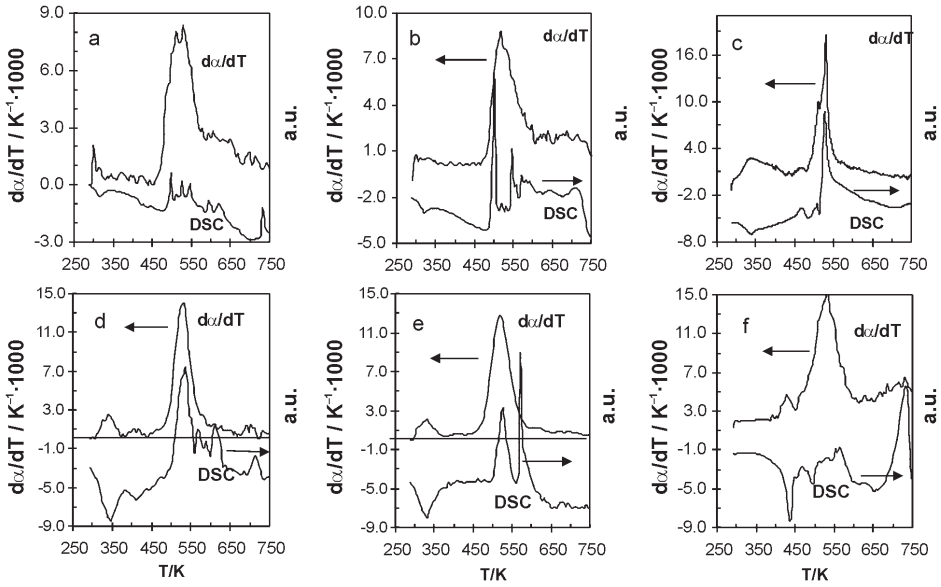

Fig. 3 dα/dT and DSC curves for a – benzylpenicillin, b – ampicillin, c – carbenicillin, d – oxacillin, e – cloxacillin and f – dicloxacillin

98 kJ mol^{-1}) (Table 1). E_a values for both the first and the second decomposition steps of dicloxacillin are nearly constant (about 86 and 165 kJ mol^{-1}, respectively).

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 the decomposition processes (as it can be seen in Fig. 3).

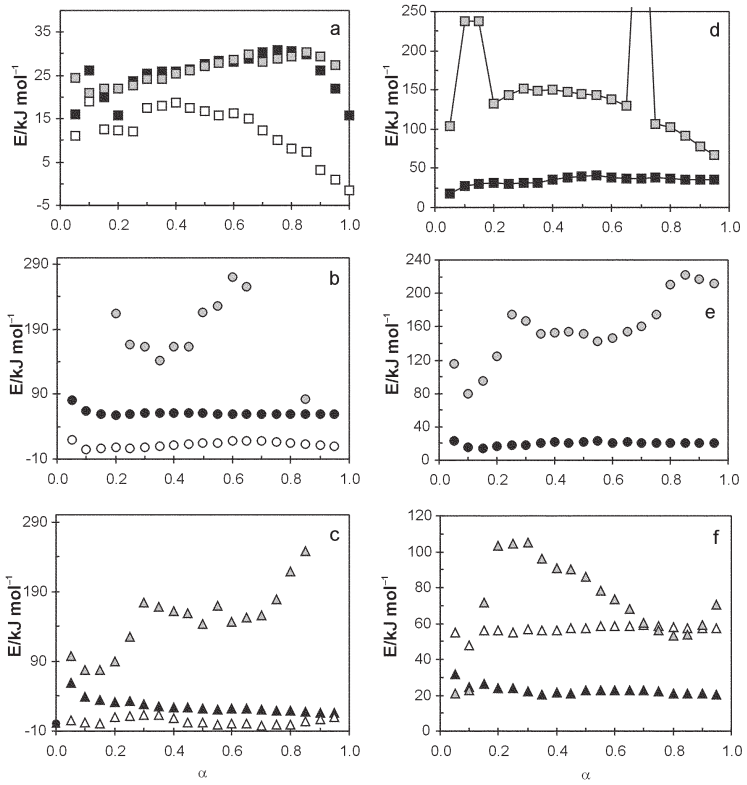

Fig. 4 E_a values as a function of α obtained from dynamic isoconversional method (grey lines) as well as from isothermal model-fitting method (black and white lines for the first and second decomposition steps, respectively). a – benzylpenicillin, b – ampicillin, c – carbenicillin, d – oxacillin, e – cloxacillin and f – dicloxacillin

The change in E_a values reported in Fig. 4 were obtained by isoconversional methods by using Eqs (9) and (14).

For the isoconversional isothermal method related to the first decomposition step (498–523 K) of the benzylpenicillin (Fig. 4a) the activation energy decreases

from 27 to 15 kJ mol^{-1} in the 0.1–0.2 range of α, increases from 15 to 29 kJ mol^{-1} in the 0.2–0.8 range and decreases from 29 to 15 kJ mol^{-1} in the 0.8–1.0 range.

For the second decomposition step (573–603 K) the activation energy decreases from 19 to 12 kJ mol^{-1} in 0.1–0.2 range extent, increases from 12 to 17 kJ mol^{-1} in the range from 0.2 to 0.4 and decreases from 17 to 3 kJ mol^{-1} in the 0.4–0.9 range (Fig. 4a). By applying Eq. (14) the E_a values decrease from 25 to 21 kJ mol^{-1} in the 0.05–0.1 range, increase from 21 to 29.4 kJ mol^{-1} in the 0.1–0.8 range while in the 0.8-0.95 range decrease from 31 to 27 kJ mol^{-1} (Fig. 4a).

In the 0.25–0.85 range of α the E_a dependences are very close both for isothermal (for the first decomposition step only) and non-isothermal experiments while they are completely different at the beginning and at the end of reaction.

However, direct comparison between these two methods should not be made because non-isothermal method experiments cover a much wide range of temperatures (312–700 K) than those of isothermal ones (498–523 K).

For isoconversional isothermal method related to the first decomposition step (498–523 K) of the ampicillin, the activation energy with the exception of 0.0–0.1 range extent, results to be constant at about 60 kJ mol^{-1} (Fig. 4b). In the second decomposition step (573–603 K) the activation energy, in the 0.1–1.0 range, varies from 5 to 18 kJ mol^{-1}.

In the non-isothermal isoconversional method E_a values assume in the range of degree of conversion 0.2–0.6 high values varying from 142 to 270 kJ mol^{-1} while in isothermal isoconversional method the above cited temperature restrictions limit the separation of superimposed reactions.

For the first decomposition step of carbenicillin the isothermal isoconversional method provides activation energy values that decrease (in the 0.5–0.95 range of degree of conversion) from 60 to16 kJ mol^{-1} (Fig. 4c). For the second step E_a values are kept in the range $-1<E_a<12$ kJ mol^{-1}. For the non-isothermal isoconversional method the activation energy values are very high. These values increase from 77 (for α equal to 0.1) to 177 kJ mol^{-1} (for α equal to 0.3) while decrease up to 143.49 and subsequently sharply increase up to 247 kJ mol^{-1} when α is equal to 0.5 and 0.85, respectively. For oxacillin the activation energies related to the isoconversional isothermal method increase from 20 (at 0.05 extent of conversion) to 40 kJ mol^{-1} (at 0.5 extent of conversion). In the 0.5–0.95 the E_a values results to be constant (about 40 kJ mol^{-1}, Fig. 4d).

In the non-isothermal isoconversional method E_a values assume in the whole range of α high values varying from 66.26 to 237.35 kJ mol^{-1}.

For cloxacillin isoconversional isothermal method the activation energy results to be constant 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 142.47 to 216.59 kJ mol^{-1} (Fig. 4e).

For isoconversional isothermal method related to the first decomposition step of dicloxacillin the activation energy results to be constant at about 20 kJ mol^{-1}, while in

Table 2 Storage time values (years) at fixed conversion of 10 and 50% according to the isothermal model-fitting method for all the decomposition processes of some penicillin drugs

Storage times	Step	Kinetic models								
		D1	D2	D3	D4	F1	R2	R3	A2	A3
						Benzylpenicillin				
$t_{10\%}$	I	0.2	44.4	1.5	0.4	375.0	2.2	17.1	1143.1	1935.2
$t_{50\%}$		4.5	1316.7	54.4	13.9	2467.2	12.3	20.4	2931.9	3626.0
$t_{10\%}$ (**)	II	**0.2**	**0.9**	**0.2**	**0.2**	**6.6**	**1.5**	**23.1**	**20.3**	**33.1**
$t_{50\%}$ (**)		**4.8**	**27.2**	**8.8**	**6.6**	**43.2**	**8.8**	**27.5**	**52.0**	**62.1**
						Ampicillin				
$t_{10\%}$ (*)	I	30.2	17.7	8.5	14.0	106.1	202.6	7207.2	689.8	1487.1
$t_{50\%}$ (*)		754.3	525.4	305.6	440.8	698.2	1156.5	8580.2	1768.9	2786.4
$t_{10\%}$ (**)	II	**1901.6**	**1576.7**	**1299.3**	**1487.0**	**11673.5**	**13040.4**	**307941.0**	**46932.0**	**86459.0**
$t_{50\%}$ (**)		**47540.3**	**46740.2**	**46429.0**	**46909.7**	**76798.0**	**74428.9**	**366596.4**	**120376.7**	**162004.2**
						Carbenicillin				
$t_{10\%}$ (***)	I	**60.3**	**40.0**	**23.2**	**33.6**	**256.6**	**401.6**	**12129.0**	**1373.0**	**2750.7**
$t_{50\%}$ (***)		**1507.6**	**1187.2**	**829.9**	**1060.5**	**1688.1**	**2292.4**	**14439.3**	**3521.5**	**5154.1**
$t_{10\%}$ (**)	II	**119.0**	**45.8**	**11.3**	**28.9**	**205.6**	**764.7**	**44873.7**	**2394.1**	**6224.5**
$t_{50\%}$ (**)		**2975.7**	**1356.4**	**402.7**	**910.4**	**1352.5**	**4364.3**	**53421.1**	**6140.7**	**11663.3**
						Oxacillin				
$t_{10\%}$	I	16304	11876	7590	10336	73949	102095	2718845	339730	643779
$t_{50\%}$		407603	352051	271210	326047	486499	582713	3236720	871380	1206293
						Cloxacillin				
$t_{10\%}$	I	0.131	0.082	0.040	0.066	0.499	0.871	28.664	2.976	6.225
$t_{50\%}$		3.274	2.423	1.529	2.092	3.284	4.972	34.123	7.630	11.664
						Dicloxacillin				
$t_{10\%}$ (**)	I	0.020	0.015	0.010	0.013	0.103	0.137	3.711	0.480	0.923
$t_{50\%}$ (**)		0.511	0.448	0.372	0.424	0.680	0.785	4.418	1.231	1.730
$t_{10\%}$ (**)	II	100.37	67.78	40.32	0.00	432.27	667.58	20138.97	2292.35	4621.53
$t_{50\%}$ (**)		2509.21	2009.36	1440.86	0.12	2843.81	3810.26	23974.97	5882.25	8659.68

(*) storage time values $\cdot 10^{12}$; (**) storage time values $\cdot 10^{6}$; (***) storage time values $\cdot 10^{3}$

the second decomposition step the activation energies are constant about 60 kJ mol^{-1} (Fig. 4f).

For the non-isothermal isoconversional method the activation energy assumes in the range of degree conversion 0.1–0.2, values varying from 20 to 100.67 kJ mol^{-1}. Subsequently these values decrease from 104.82 to 70.20 in the range 0.20–0.95.

This behaviour allows to hypothesise that more than one reaction occurs in the decomposition processes of all the compounds considered and that the complex nature of multi-step processes can be more easily detected when using a broader temperature range.

Finally storage time values for thermal decompositions of penicillin salts were calculated (Table 2) by inserting the suitable kinetic triplet values obtained by isothermal fitting model in Eq. (15). Scattered values displayed by the compounds in the different mechanisms clearly indicate that the failure in the model-fitting method makes unsuitable extrapolated at room temperatures. For drugs having phosphomycin salts as active components (fosfocin and fosfocitrin) the following procedure was performed.

The experimental normalised curves at various temperatures (Fig. 5) overlap with the theoretical one related to mechanism F1. This result allows to conclude that for the commercial drugs studied F1 (first reaction order) is the most probable decomposition mechanism in the above-mentioned temperature range. This behaviour was also confirmed by inserting in Eq. (4) the mathematical expressions related to various mechanisms (at different temperatures lying in the range where decomposition occurs) and showing that F1 mechanism best linearizes the experimental values Fig. 6).

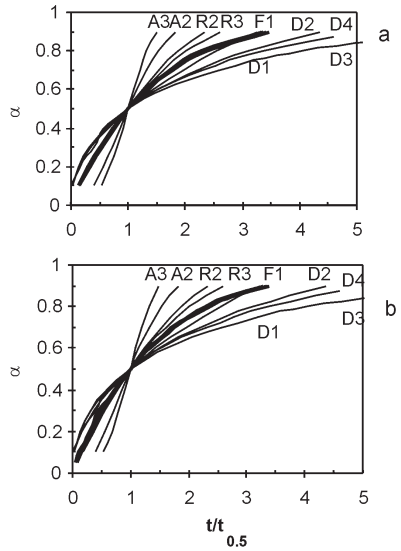

Fig. 5 Reduced time isothermal plots for the decomposition process of fosfotricin (a) and fosfocin (b) carried out at fixed temperatures lying in the actual decomposition temperature range

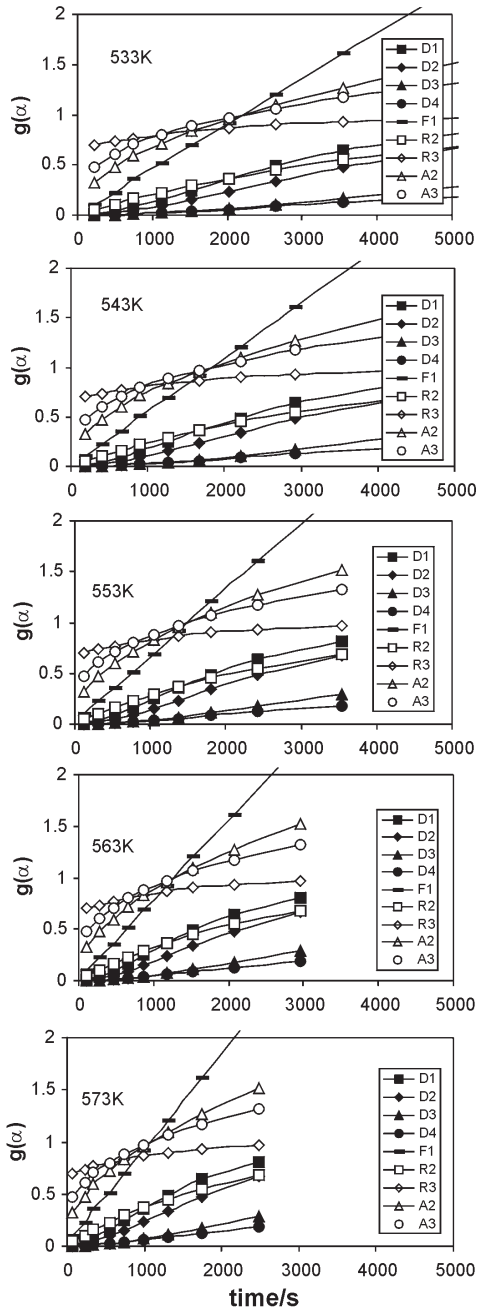

Fig. 6 Integral plots of $g(\alpha)$ *vs.* time representing all possible reaction mechanisms at different fixed temperatures for fosfocin

Table 3 E_a (kJ mol^{-1}) and ln$A$ (s^{-1}) values obtained by a linear regression analysis on Arrhenius equation according to the isothermal model-fitting method for the decomposition processes of fosfotricin and fosfocin drugs

Storage times	Step	Kinetic models								
		D1	D2	D3	D4	F1	R2	R3	A2	A3
						Fosfotricin				
E_a	I	83.3	83.3	83.4	83.3	83.3	95.1	83.2	83.3	83.3
ln$A$		16.3	16.1	15.3	14.8	17.3	18.9	15.2	16.6	16.3
						Fosfocin				
E_a	I	46.4	46.2	45.7	46.0	46.0	46.4	46.8	46.4	46.6
ln$A$		6.0	5.8	4.9	4.5	6.9	5.7	4.9	6.3	6.0

By inserting $g(\alpha)$ values related to F1 mechanism in Eq. (4), at different above cited temperatures, the rate constants values (k) for the decomposition processes of the two compounds were found.

The k values were subsequently inserted in Arrhenius Eq. (6) thus allowing calculating E_a and A values for the cited processes (Table 3). In the range of α 0.05–0.95 quite constant E_a values (about 83 and 46 kJ mol^{-1}) both for the two above cited drugs were found.

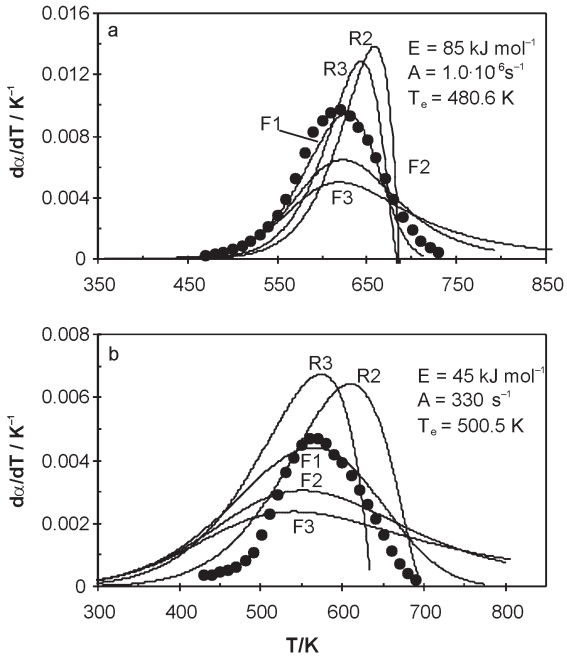

Fig. 7 Reconstructed dα/dT plots for fosfotricin (a) and fosfocin (b) and comparison with theoretical dα/dT plots that follow particular decomposition mechanisms

Dollimore method shows that non-isothermal model-fitting can be used (Fig. 7).

A non-isothermal method (McCarty and Green) based on a first order mechanism was used [23]. The kinetic analysis of this method included the calculation of activation energy E_a related to the phase transition processes, the pre-exponential factor A, and the reaction order. This implementation of the McCarty and Green method is restricted to the first order reactions (F1). The starting equation for this method is:

$$d\alpha/dT=(A/\beta)\exp(-E_a/RT)(1-\alpha) \quad (16)$$

Rearranging Eq. (16) and integrating yields:

$$-\ln(1-\alpha)=(AE_a/\beta R)p(x) \quad (17)$$

where x is the substituted variable for the quantity E_a/RT, and $p(x)$ represents a series expansion approximating the resulting integral:

$$p(x)=\{(x+3)/[x(x+1)(x+4)\ e^x]\} \quad (18)$$

On taking natural logarithms of both sides of Eq. (17) one can obtain:

$$\ln[-\ln(1-\alpha)]=\ln(AE_a/\beta R)+\ln p(x) \quad (19)$$

Assigning $F(\alpha)=\ln[-\ln(1-\alpha)]$ and then differentiating with respect to x:

$$dF(\alpha)/dx=d[\ln p(x)]/dx \quad (20)$$

Taking into account that $x=E_a/R$ one obtains $dx=(E_a/R)d(1/T)$. Substituting the dx algorithm in Eq. (20) and rearranging it can be written:

$$E_a=R[dF(\alpha)/d(1/T)]/\{d[\ln p(x)]/dx\} \quad (21)$$

Data for the construction of this plot are taken from the TG curve. The numerator in Eq. (21) is the slope of a plot of $F(\alpha)$ *vs.* $1/T$ whereas the denominator can be estimated from the series:

$$d[\ln p(x)]/dx=1/(x+3)-(1/x)-[1/(x+1)]-[1/(x+4)]-1$$

Since the numerator is also a function of E_a the software uses an initial guess of 125.56 kJ mol^{-1} for the activation energy. A series of iterative calculations is performed to refine the value of E_a to within 0.42 J. Once E_a has been determined, the pre-exponential factor A is calculated by the Eq. (17). This method considers mass losses consistently lower than 10% for the calculation of activation energy [24].

Indeed it was usually considered that the initial portion of the TG curves could be fitted by a first-order reaction equation. The Arrhenius parameters values (E_a and $\ln A$) obtained using this integral method are a function of F1 mechanism result to be 84.9 and 21.8 for the fosfotricin and 42.5 and 10.3 for fosfocin, respectively. The good accordance between these kinetic data and those of the isothermal method allows to hypothesize that the two compounds undergo F1 mechanism of decomposition.

In the case of relatively simple process [25], the kinetics of which can be described by a single kinetic triplet (E_a, A and $g(\alpha)$) the differences in kinetic triplet values derived from isothermal and non-isothermal data is primarily determined by ex-

perimental data: temperature range of isothermal and non-isothermal experiments are not the same and truly isothermal conditions cannot be accomplished for very low and very high ranges of the extent of reaction α.

Moreover, substances showing a process at lower activation energy values will not necessarily decompose at lower temperatures [25]. In fact, it can be reminded that activation energy alone can determine the reaction rate of a process only when A and $g(\alpha)$ are the same.

In order to decide if commercial drug named fosfotricin is more stable than fosfocin (from a kinetic point of view) the simulated α *vs.* temperature curve for the couples fosfotricin/fosfocin, using F1 mechanism and non-isothermal and isothermal kinetic parameters of Table 2 have been constructed (Fig. 8). The process having higher activation energy occurs in a higher temperatures range.

Using both Eqs (9) and (14) the values in E_a values confirms (Fig. 9) that F1 is the only mechanism occurring in the whole temperature range of the decomposition process.

In the range 0.4–1.0 of α (where the actual decomposition occurs) fosfocin shows constant E_a values of about 42 kJ mol^{-1} (isoconversional isothermal method) (Fig. 9) and 50 kJ mol^{-1} (non-isothermal method) (Fig. 10). In the same range of degree of conversion fosfotricin shows a constant E_a value of about 84 kJ mol^{-1} for the

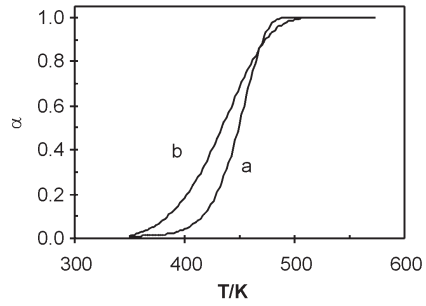

Fig. 8 Experimental α *vs.* time plots for the decomposition process of a – fosfotricin and b – fosfocin

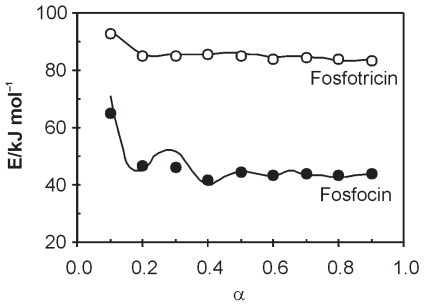

Fig. 9 Comparison between E_a values as a function of α obtained from isothermal model-fitting method (mechanism F1) (circles) and those from isothermal isoconversional method (black lines)

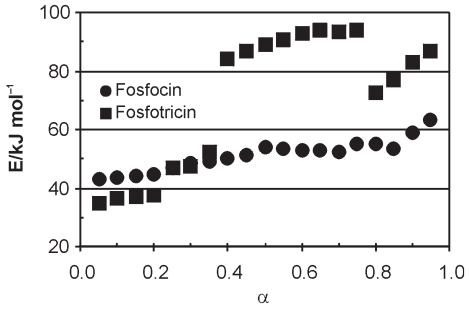

Fig. 10 E_a values as a function of α obtained from non-isothermal isoconversional method for fosfotricin and fosfocin compared with those extrapoled by means of the McCarthy–Green method [5] (84.9 and 42.5 kJ mol^{-1}, respectively)

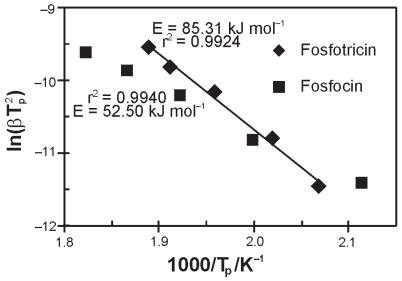

Fig. 11 Kissinger plot for non-isothermal decomposition processes of fosfotricin and fosfocin

isothermal isoconversional method (Fig. 9) and values ranging from 80 to 95 kJ mol^{-1} for the non-isothermal isoconversional method (Fig. 10).

Finally, by applying the Kissinger method the E_a value for fosfotricin results to be 83.31 kJ mol^{-1} while for fosfocin the E_a value is 52.50 kJ mol^{-1} (Fig. 11).

Statistical considerations

Although for fosfocin and fosfotricin there is a single decomposition process described by one mechanism, the E_a values obtained must be considered with caution. At this regards it is well known that in some chemical-physical equations (i.e. Hammet and Arrhenius equations) a physical significance is usually assigned (using both r and standard deviation) to the regression parameters (i.e. activation energy E_a) without an evaluation of their estimation significance. With regards to this fact Galway and Brown [26–27] affirm that in most kinetic studies of solid state decompositions, the accuracy of the activation energy values E_a is frequently difficult to assess. Reproducibility of measurements is not always good and a few values have been confirmed independently.

E_a values have been often reported by using several significant figures, without the provision of realistic estimates of the measurements uncertainties. Moreover the

Arrhenius plots are generally assumed to be linear for solid state reactions and few tests are made for possible deviations.

For this equation, the error on k is much greater than those on temperature and its validity is limited to the temperature range where the process occurs, so that extrapolated values must be interpreted with caution. This occurs because the relationship between the two variables could not be linear out of the experimental temperature range or the linearity degree significance could not give reliable values for the dependent variable. This makes unreliable the significance degree of k values extrapolated out of the experimental temperature range where the Arrhenius equation is applied. For this reason, only the activation energy and the rate constant values calculated in the experimental temperature range can be assumed as significant. Then it is interesting to submit Eqs (4) and (6) to a linear regression analysis which supplies the precise form of the mathematical function relating to the two variables and tests how the experimental results support the theoretical relationship within the limits of the experimental error of the measurements. In this context, more useful tests are needed: the standard deviation on the slope σ_b and on the intercept σ_a, the standard deviation of the regression $\sigma_{y/x}$, the Student t-test for the intercept and the slope values of the linear regression [28–33].

Furthermore, it must be reminded that a statistical analysis cannot supply absolute answers, but only allows the experimental results to be compared and explained in terms of probability. Indeed, for this kind of analysis, an introduction of absolute data (confidence level, distribution error, etc.) is needed to explain the results in positive or negative ways.

The standard deviation and the Student t-test related to the regression coefficient (slope) and to the intercept ensure the linearity of the relationship and allow calculating, in terms of probability, the confidence intervals c.i. ($E_a \pm \sigma_{E_a} t_{CL,\nu}$, $A \pm \sigma_A t_{CL,\nu}$) due to the experiments variability. In the mentioned intervals the true values of the regression function parameters (the intercept a and the regression coefficient b) lie with a fixed degree of probability. To test the significance of the regression parameters related to the Eqs (4), (6) and (9) a statistical analysis was carried out (Tables 4, 5 and 6, respectively).

The values of regression parameters a and b together with their standard deviations σ_a and σ_b, the confidence interval (c.i.), the degree of freedom ν and the square correlation coefficient r^2 are given in Tables 4 and 5. For Eq. (4) the regression was not forced through the origin. An intercept was drawn with the least-squares treatment but it was normally indistinguishable from zero.

Linear regressions applied to Eq. (4) for the commercial drugs (at the given highest and lowest experimental temperatures) were carried out to verify the reliability of k values (Table 4).

Table 4 Statistical parameters obtained by the linear regression analysis (in the form $y=a+bx$) applied on Eq. (4). The data are referred to the most suitable mechanism (F1) at the lowest and higher fixed temperatures

Parameters	Fosfocin		Fosfotricin	
	483 K	523 K	523 K	563 K
a	0.2	0.02	0.01	0.02
σ_a	0.051	0.050	0.003	0.005
c.i.	±0.1	±0.01	±0.01	±0.02
b	0.00037	0.00257	0.000539	0.000539
σ_b	0.00001	0.00001	0.000001	0.00001
c.i.	±0.00004	±0.00003	±0.00005	±0.00004
$\sigma_{y/x}$	0.17	0.009	0.005	0.009
r^2	0.9782	0.9999	1.0000	0.9999
t_a	3.04	4.62	3.06	4.62
CL_a*	0.995	0.9995	0.99	0.995
T_b	28.42	20.13	387.46	220.78
CL_b*	0.9995	0.9995	0.9995	0.9995

*the null hypotheses applied to the regression equation (NH: a=0; b=0) are rejected for the given confidence level (CL)

Test of linearity

A test of linearity for a linear regression can be obtained by means of the coefficient and intercept regression significance. This can be made using two null hypotheses tested by the Student t-test. The t values of a and b were calculated by the expressions:

$$t_a=(a-A)/\sigma_a;\ t_b=(b-B)/\sigma_b$$

where a and b are the intercept and the slope of the regression equation, respectively while σ_a and σ_b their standard deviations, A and B prefixed values.

The calculated t_a and t_b for A=0 and B=0 were compared to those of a handbook of statistical tables [34]. If $t_{calc}>t_{CL,\nu}$, where ν is the degree of freedom and CL the confidence level for the regression significance, then for $CL<0.95$ the null hypothesis is accepted (chemical hypothesis) while for $CL>0.999$ its rejection is highly significant.

Regression analysis applied to Eq. (4) shows that for fosfocin and fosfotricin the null hypotheses A=0 and B=0 are rejected at both lowest and higher temperatures (Table 4). For the two drugs the regression do not pass through the origin.

The degree of CL related to null hypothesis A=0 shows that at lowest temperature the linearity of Eq. (4) decreases both for the drugs (Table 4). This allows to hypothesize that, outside the experimental temperature range, the degree of linearity significance of Eq. (4) could not give reliable values of constant rates k.

Degree of significativity

σ_a and σ_b values (in the regression equation) representing the standard deviations of parameters allow to determine the confidence interval (c.i.) $a \pm \sigma_a t_{CL,\nu}$, $b \pm \sigma_b t_{CL,\nu}$ (Tables 5, 6 and 7) where the probability that the true parameters values lie is given by (100*CL*)%.

$t_{CL,\nu}$ is chosen from proper tables [34] at a *CL* (confidence level) and for ν degree of freedom. A significative level can be obtained by choosing *CL* values ranging from 0.99 to 0.999.

Significative interval does not indicate, for example, that *b* parameter is significant but that in the considered interval there is a probability ranging from 99 to 99.9% to find the true value of *b*. It is clear that the more the *CL* is close to 1, the more *b* could be discussed by statistical point of view in physical terms.

Statistical analysis applied to Eq. (4) shows that the degree of significance of the regression parameter *a*, for the compounds studied, decreases at lower temperature. In the Arrhenius equation applied to the decomposition of fosfocin, the probability to find the true value of a in the confidence interval results to be 97.5%, while for the other compound the probability of this parameter is 99.95% (Table 5).

Table 5 Statistical parameters obtained by appliyng a linear regression analysis on ln*k vs.* 1/*T* (Eq. (3)) in the form $y=a+bx$

Parameters	Fosfocin	Fosfotricin
a	1	13
σ_a	0.29	0.08
c.i.	±3	±1
b	–4.3	–10.0
σ_b	0.15	0.04
c.i.	±0.5	±0.1
$\sigma_{y/x}$	0.02	0.005
r^2	0.9965	1.0000
t_a	4.38	174.49
CL_a **	0.975	0.9995
T_b	29.28	263.63
CL_b **	0.9995	0.9995

*the degree of freedom ν is 3 for all the regressions
**the null hypotheses applied to the regression equation (NH: $a=0$; $b=0$) are rejected for the given confidence level (*CL*)

The statistical analysis applied to Eq. (9) shows (Table 6) that the linear regression for fosfocin is uncertain and the value of its parameter *a* is true with 95 and 99% of probability while for the other compound the probability for the same parameter is 99.95%.

Table 6 Statistical parameters obtained by appliyng a linear regression analysis on ln*t vs.* 1/*T* (Eq. (9)) in the form *y=a+bx*

Parameters	Fosfocin			Fosfotricin		
	α=0.3	α=0.6	α=0.9	α=0.3	α=0.6	α=0.9
a	–3	–2	–1	–16	–15	–14
σ_a	0.97	0.20	0.09	0.34	0.22	0.13
c.i.	±6	±1	±1	±2	±1	±1
b	5	4	4.5	12	12	11.7
σ_b	0.49	0.10	0.05	0.19	0.12	0.07
c.i.	±3	±1	±0.3	±1	±1	±0.4
$\sigma_{y/x}$	0.061	0.012	0.006	0.020	0.013	0.008
r^2	0.9698	0.9985	0.9997	0.9993	0.9997	0.9999
t_a	3.34	8.34	8.96	47.24	68.13	103.74
CL_a**	0.95	0.99	0.99	0.9995	0.9995	0.9995
T_b	9.81	44.91	99.02	63.68	98.24	159.79
CL_b**	0.99	0.9995	0.9995	0.9995	0.9995	0.9995

*the degree of freedom ν is 3 for all the regressions
**the null hypotheses applied to the regression equation (NH: *a*=0; *b*=0) are rejected for the given confidence level (*CL*)

Table 7 Half-time and shelf-life values t_α at fixed temperatures (1 year is about $3.1\cdot10^7$ s)

Compounds	*T*/K	From Eq. (15)				
		$t_{0.01}$ (s)	$t_{0.02}$ (s)	$t_{0.03}$ (s)	$t_{0.04}$ (s)	$t_{0.50}$ (s)
Fosfotricin	298.15	$7.3\cdot10^6$	$1.4\cdot10^7$	$2.2\cdot10^7$	$2.9\cdot10^7$	$5.0\cdot10^8$
	373.15	$8.5\cdot10^3$	$1.7\cdot10^4$	$2.5\cdot10^4$	$3.4\cdot10^4$	$5.9\cdot10^5$
	483.15	$1.9\cdot10^2$	$3.8\cdot10^2$	$5.7\cdot10^2$	$7.7\cdot10^2$	$1.3\cdot10^3$
	493.15	$1.2\cdot10^2$	$2.5\cdot10^2$	$3.8\cdot10^2$	$5.1\cdot10^2$	$8.5\cdot10^2$
	503.15	$8.3\cdot10^1$	$1.7\cdot10^2$	$2.5\cdot10^2$	$3.4\cdot10^2$	$5.7\cdot10^2$
	513.15	$5.6\cdot10^1$	$1.1\cdot10^2$	$1.7\cdot10^2$	$2.3\cdot10^2$	$3.8\cdot10^2$
	523.15	$3.9\cdot10^1$	$7.8\cdot10^1$	$1.2\cdot10^2$	$1.6\cdot10^2$	$2.7\cdot10^2$
Fosfocin	298.15	$5.8\cdot10^3$	$1.1\cdot10^4$	$1.7\cdot10^4$	$2.3\cdot10^4$	$4.0\cdot10^5$
	373.15	$3.1\cdot10^2$	$6.2\cdot10^2$	$9.4\cdot10^2$	$1.2\cdot10^3$	$2.1\cdot10^4$
	523.15	$1.7\cdot10^2$	$3.4\cdot10^2$	$5.1\cdot10^2$	$6.9\cdot10^2$	$1.5\cdot10^3$
	533.15	$1.7\cdot10^2$	$3.4\cdot10^2$	$5.2\cdot10^2$	$7.0\cdot10^2$	$1.3\cdot10^3$
	543.15	$1.0\cdot10^2$	$2.0\cdot10^2$	$3.0\cdot10^2$	$4.0\cdot10^2$	$1.1\cdot10^3$
	553.15	$8.8\cdot10^1$	$1.8\cdot10^2$	$2.7\cdot10^2$	$3.6\cdot10^2$	$9.1\cdot10^2$
	563.15	$3.6\cdot10^1$	$7.2\cdot10^1$	$1.5\cdot10^2$	$1.5\cdot10^2$	$7.6\cdot10^2$

Finally, half-life and shelf-life values for the commercial drugs and active components have been calculated using Eq. (15).

From these values (Table 7) it can be noted that both for these quantities the values obtained outside the decomposition temperature range of the experiments (i.e.

298.15 and 373.15 K) seem to be unrealistic with respect to those obtained in the above-cited range.

This is surely due to the low degree of significance of k values extrapolated at room temperature using Eq. (4).

Conclusions

Pharmaceutical substances submitted to thermal treatment undergo single or multi-step decomposition processes as a function of their structures.

Kinetic calculations applied to multi-step decomposition processes for some penicillin salts are not most efficient means of determining reaction mechanisms, but they can be useful for drawing reasonable mechanistic conclusions.

Using isothermal and non-isothermal TG data model-fitting and isoconversional methods show that F1 mechanism can describe decomposition processes for drugs (having phosphomycin salts as active component) for which a single decomposition process occurs. Moreover, statistical analysis shows that only in the temperature range where decomposition occurs Arrhenius parameters assume reliable values.

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