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APPLICATION OF TA AND KINETIC STUDY TO COMPATIBILITY AND STABILITY PROBLEMS IN SOME COMMERCIAL DRUGS
Remarks on statistical data

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Abstract

A thermal analysis and kinetic study on decomposition processes of some commercial drugs have been carried out to find their thermal stability.

DSC/TG curves of some commercial drugs were compared with those of their active components, the excipients, the active component/excipient and the excipient/excipient mixtures.

A kinetic study was carried out using both isothermal and dynamic TG curves. Both active components and commercial drugs tested show a first order decomposition mechanism. The kinetic data showed that excipients cause a decrease of the kinetic stability of the active components.

Statistical analysis allowed us to select reliable kinetic parameters related to decomposition processes. This procedure showed that the values obtained by extrapolation, outside the temperature range where the processes occurred must be used with caution. Indeed half-time and shelf-time values, commonly used at room temperature, seemed to be unrealistic.

Keywords: active components, commercial drugs, kinetic analysis, statistical analysis, TG/DSC

Introduction

Thermal analysis is a routine method for the analysis of drugs and substances of pharmacological interest [1–4]. The active component, during the manufacture of commercial drug, is mixed with other compounds (excipients). The last ones sometimes cause variation in the physical-chemistry properties of the active component. The chemical reactivity of the mixture can be modified, at high temperature, leading to uncontrollable reactions with consequent danger situations.

Unless incompatibility is evident (e.g. the formation of a eutectic melting below room temperature) it is necessary to carry out a thermal stability study that usually re-

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quires weeks or months. However thermal analysis allows us to obtain some data more rapidly.

Although this technique will not completely replace the classical stability program that implies a long-time observation, it can provide an early alert to compatibility problems and indicate the most favourable directions to pursue for a successful formulation.

The following considerations must be made before the application of thermal analysis: i) the 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, suitable mechanism, activation energy and stability time values at various temperatures. In the present work all these quantities are provided by a kinetic analysis of solid state decomposition processes.

Moreover, an attempt was made in order to find at a given temperature the shelf-life (the length of time for which a drug preserves its activity) or half-life (the isothermal decomposition of half-product, which can be determined by heating a sample quickening its decomposition process. So, the values obtained at room temperature must be interpreted with caution.

Thermal analysis carried out both on pure active components and on some solid mixture of active component/excipient or excipient/excipient allows to visualize interactions among them and to individuate the excipients that are thermally incompatible with the active component.

This work aims to study thermodynamic and kinetic properties of decomposition processes of drugs having phosphomycin as an active component. Moreover, an attempt to determine if quantities related to thermal behaviour of decomposition processes can be extrapolated to room temperature was made.

Phosphomycin is one of the most interesting phosponates. It was isolated from streptomyces and was found to exert antibiotic activity against both gram positive and gram negative infections [5–9].

TG/DSC curves of commercial drugs were compared with those of the pure components and of some of their mixtures, so the interactions among them have been studied.

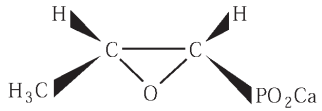
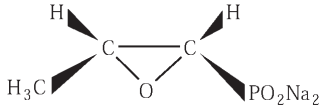
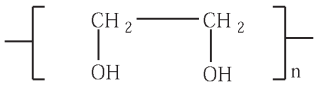
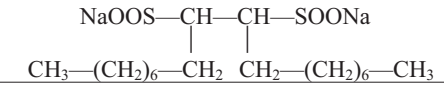
The kinetic study allowed to individuate the decomposition mechanisms for the commercial drugs studied, stressing the influence of the excipients on the decomposition mechanism of the active component.

An attempt to point out the different thermal behaviour of the drugs produced by using different operative methods was also made.

Experimental

Crinos S. P. A supplied pure Phosphomycin calcium salt (Ca–F) and the commercial drug (Fosfocin) containing Ca–F (active component) together with 9.03% (mass/mass) of poly(ethylenglycol) (PEG) and 0.2% (mass/mass) of sodium dioctylsulphosuccinate (SDSS) (Table 1).

Table 1 List of the studied pure component with their abbreviation names, structural and empirical formulas

Components	Abbreviation	Structural formulas	Empirical formulas
Calcium fosfomycin	Ca–F		$C_3H_5CaO_4P$
Disodium fosfomycin	Na_2–F		$C_3H_5Na_2O_4P$
Succinic acid	SA	HOOC–CH_2–CH_2–COOH	$C_4H_6O_4$
Poly(ethylenglycol)	PEG		
Sodium dioctylsulphosuccinate	SDSS		$C_{18}H_{36}Na_2O_4S_2$

Italfarmaco (Milan) supplied pure Phosphomycin disodium salt (Na_2–F) and the commercial drug (Fosfotricina) containing Na_2–F as active component with 10.7% (mass/mass) of succinic acid (SA) while Merck supplied pure Succinic acid (Table 1).

Thermoanalytical measurements were carried out on a Stanton-Redcroft 625 Simultaneous TG/DSC thermoanalyser 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. Both the metals and organic compounds were of purity over than 99.9%.

For decomposition studies under dynamic and static conditions samples of 5–6 mg were weighed in aluminium pans placed in an argon-filled dry box. The TG/DSC equipment was flushed with air or argon 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 rate was always 5 K min^{-1} (in non-isothermal experiment) and at least three runs were made for each compound studied.

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. All the compounds tested were used as received without any purification treatment.

Simultaneous TG/DSC is a very useful tool for investigating organic compounds, since it combines (in a single run) mass loss and heat change measurements. In this way, transformations occurring even with small mass changes (chemical reactions, decomposition, vaporisation and oxidation processes) can be distinguished from those occurring without a mass change (melting, crystallisation, polymorphic changes).

The quantities used to characterize the compounds submitted to non-isothermal measurements were the percentage mass loss and the corresponding onset temperatures (T_0) for the TG technique.

In DSC technique, enthalpy values related to various processes were considered together with the peaks temperature T_p that could provide valuable information in the analytical study of organic compounds. T_p is the temperature at which the process theoretically occurs at the highest rate, but it is also the temperature at which the maximum rate of heat change between the sample and the environment takes place.

For example, some α-amino acids [10] were identified on the basis of T_p alone because these values are distinct and do not overlap with those of the adjacent α-amino acids on the decomposition scale.

Furthermore, thermal analysis of different series of dipeptides was carried out by simultaneous TG/DSC measurements and the thermal behaviour of these compounds was compared to that of each free α-amino acid contained in the dipeptides [11, 12].

Kinetic procedure

As non-isothermal TG curves show complex shapes, both TG isothermal and dynamic curves have been used to study kinetic data. For this purpose the following isothermal method was adopted.

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

$$g(\alpha)=kt \tag{1}$$

where k is the specific constant rate and $g(\alpha)$ is a mathematical expression related to some 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) describe, respectively, diffusion, chemical reaction and nucleation mechanisms.

Degree of conversion α (fraction of reacted compound) is given by the expression:

$$\alpha(t)=[(\%m_i-\%m_t)]/[(\%m_i-\%m_f)] \tag{2}$$

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-time plots $\alpha=f(t)$ were constructed by using experimental percentage mass data taken from TG isothermal curves performed at different constant temperatures lying in the temperature range where decomposition processes occur.

Generalised reduced time plots, in which α values for each curve are reported as a function of the ratio $t/t_{0.5}$, ($t_{0.5}$ is the experimental time corresponding to α=0.5) have subsequently been constructed.

The curves $\alpha=f(t/t_{0.5})$ were compared with theoretical ones reported in literature [13, 14] to individuate the most probable mechanisms. The mathematical expressions $g(\alpha)$ describing the possible decomposition mechanisms, together with experimental α and t values corresponding to a fixed temperature were inserted in Eq. (1). The $g(\alpha)$ expression best linearizing this equation was chosen as that describing the most probable mechanism.

The values of kinetic constant rate k (s^{-1}) are 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:

$$\ln k=\ln A-E_a/RT \tag{3}$$

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

At this regard 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 [15–16] affirm that in most of kinetic studies of solid state de-

compositions, 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 often been 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 extrapolated values must be interpreted with caution, 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 activation energy and constant rate values calculated in the experimental range temperature, can be assumed as significant. Then it is interesting to submit Eqs (1) and (3) to a linear regression analysis which supplies the precise form of the mathematical function relating to 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 [17–22].

Furthermore, it must bear in mind that 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.* ($E_a \pm \sigma_{E_a} t_{CL,v}$, $A \pm \sigma_A t_{CL,v}$) due to the experiments variability. In the mentioned intervals, the true values of the regression function parameters (intercept a, regression coefficient b) lie with fixed degree of probability.

Besides an alternative procedure was used to verify that activation energy value E related to decomposition process remains constant and a single mechanism occurs in the 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. (1), one obtains

$$g(\alpha)=A[\exp(-E_a/RT)]t \tag{4}$$

where the obtained t and T are the time and temperature values which make the function $g(\alpha)$ constant. By using the logarithmic form of Eq. (4):

$$\ln g(\alpha) = \ln A - E_a/RT + \ln t \quad (5)$$

and rearranging it, one obtains

$$\ln t = -\ln A + \ln g(\alpha) + E_a/RT \quad (6)$$

By plotting ln$t$ *vs.* $1/T$ according to Eq. (6) the activation energies were found at any given α values from the slope of a regression straight line. The change in E_a values for the variation of α is negligible. This regression was also submitted to statistical analysis.

Finally, the kinetic data obtained were compared with those of a non-isothermal method (McCarty and Green) based on a first order mechanism [23]. The kinetic analysis of this method included the calculation of activation energy E_a relating to the phase transition processes, the pre-exponential factor A, and the reaction order. This implementation of the McCarty–Green method is restricted to the first-order reactions (F_1). The starting equation for this method is:

$$d\alpha/dT = (A/\beta)\exp(-E_a/RT)(1-\alpha) \quad (7)$$

Rearranging Eq. (7) and integrating yields:

$$-\ln(1-\alpha) = (AE_a/\beta R)p(x) \quad (8)$$

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

$$p(x) = \{(x+3)/[x(x+1)(x+4)e^x]\} \quad (9)$$

On taking natural logarithms of both sides of Eq. (8) one can obtain:

$$\ln[-\ln(1-\alpha)] = \ln(AE_a/\beta R) + \ln p(x) \quad (10)$$

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

$$dF(\alpha)/dx = d\ln p(x)/dx \quad (11)$$

Taking into account that $x = E_a/R$ one obtains $dx = (E_a/R)d(1/T)$. Substituting the dx algorithm in Eq. (11) and rearranging it can be written:

$$E_a = R[dF(a)/d(1/T)]/[d\ln p(x)/dx] \quad (12)$$

Data for the construction of this plot are taken from the TG curve. The numerator in Eq. (12) 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. (8). 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 can be fitted by a first-order reaction equation. The Arrhenius parameters values (A and E_a) obtained using this integral method are a function of F_1 mechanism (first-order reaction).

Finally, some importance was given to the parameters determining the stability times of the drugs: half-life time (isothermal decomposition of half-product) and shelf-life time (isothermal decomposition of small prefixed extent of product).

For decomposition processes following first order reaction $g(\alpha)=-\ln(1-\alpha)$, half-life and shelf-life times at various temperatures were obtained by expression

$$t_\alpha = -\ln(1-\alpha)/k(T) \quad (13)$$

using, respectively, α=0.5 and small α values (0.01, 0.02, 0.03, 0.04).

Results and discussion

Features of the thermal processes

Trends of thermal behaviour for the examined compounds are shown in Figs 1a, 1b, and 1c. Values of the thermodynamic quantities relating to TG/DSC curves are reported in Tables 2–4. The enthalpy values are given in kJ g^{-1} to compare pure compounds with their mixtures.

TG and DSC curves of the commercial drug named Fosfocin shows three steps of mass loss to which one endothermic and two exothermic processes correspond (Figs 1a and 1c, curves 7, Tables 2 and 3).

To explain thermal behaviour of this compound the TG/DSC curves of active component (Ca–F), excipients (PEG, SDSS) and their mixtures (Ca–F/PEG, Ca–F/SDSS PEG/SDSS) were carried out.

DSC curve of Ca–F (Fig. 1c curve 1 and Table 3) shows that both the second endothermic and exothermic processes of commercial drug belong to the active component.

The first decomposition process (8.3%) for this compound (Fig. 1a, curve 1, Table 2) could be related to the loss of water of crystallisation nature.

The second exothermic mass loss could be related to a formation of a stable compound or to an oxidative decomposition process.

TG and DSC curves related to the same exothermic process and performed in argon stream show % mass loss and enthalpy values allowing to consider the second hypothesis true (Tables 2 and 3, bracketed values).

It was also noted (Fig. 1c, curves 1, 7 and Table 3) that the peak temperature and the enthalpy values of the second endothermic process for commercial drug and of the endothermic process of active component are close while in the second exothermic process of the former compound the same quantities decrease with respect to those of the exothermic process of the latter.

Both the first endothermic and exothermic processes of commercial drug (Fig. 1c, curve 7) can be related to melting and strong exothermic decomposition processes of PEG respectively, as it can be seen by its DSC curve (Fig 1c, curve 2). Moreover, while temperatures of the peaks related to the melting processes for both

Table 2 Extent of the thermal decomposition of Fosfocin and of its components and related solid mixtures in air stream as obtained from TG data. Data in brackets are obtained from TG experiments performed in argon stream

Compounds	Stages of thermal decomposition								
	I			II			III		
	T_e/K	Δm/%	ΔT/K	T_e/K	Δm/%	ΔT/K	T_e/K	Δm/%	ΔT/K
Fosfocin	450.6	6.9	425–450	475.0	6.9	450–490	518.4	14.9	490–675
Ca–F				473.6	8.3	445–495	550.1 (565.2)	10.6 (12.2)	495–675 (510–655)
Ca–F+PEG	447.8	39.2	420–470	465.8	21.8	470–720			
Ca–F+SDSS				463.3	8.41	420–500	501.6	13.5	510–690
PEG							499.0	81.7	480–530
SDSS	325.5	3.1	300–450	543.2	66.4	450–570	577.1	17.2	570–750
PEG+SDSS				475.5	54.0	463–555	558.1	35.7	555–610

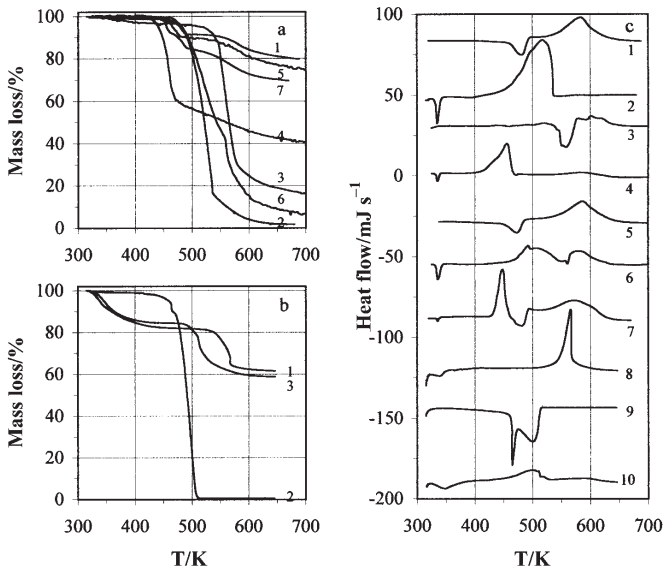


Fig. 1 TG curves (a) of Ca–F (1), PEG (2), SDSS (3), mixture of Ca–F and PEG (4), mixture of Ca–F and SDSS (5), mixture of PEG and SDSS (6), and Ca–F/PEG/SDSS (7); TG curves (b) of Na_2–F (1), SA (2) and Fosfotricina (3) and DSC curves (c) of Ca–F (1), PEG (2), SDSS (3), mixture of Ca–F and PEG (4), mixture of Ca–F and SDSS (5), mixture of PEG and SDSS (6), and Ca–F/PEG/SDSS (7), Na_2–F (8), SA (9) and Fosfotricina (10)

compounds were found to be close, for the commercial drug the peak temperature and the enthalpy values related to the first exothermic process are shifted towards lower values with respect to those of the excipient.

Different peak temperature and enthalpy values, in the same processes, for components in the pure phase and in the commercial drug, can be related to their reciprocal interactions.

As this regards the following considerations can be made:

i) DSC curve of Ca–F/PEG mixture shows a reciprocal reduction of the two exothermic processes (Fig. 1c, curve 4).

ii) DSC curve of SDSS shows an endothermic decomposition process in a temperature range close to that where the exothermic process of PEG occurs (Fig. 1c, curve 3).

iii) In DSC curve of Ca–F/SDSS mixture (Fig. 1c, curve 5) the same thermal behaviour of Ca–F was found (no interaction).

iv) In DSC curve of PEG/SDSS (Fig. 1c, curve 6) mixture the two excipients interact each other with subdivision in two parts of the exothermic process of PEG.

Na_2–F and succinic acid compose the second commercial drug (Fosfotricina), respectively, as active component and as excipient. Both for the commercial drug and active component there are two steps of decomposition (Fig. 1c, curves 8 and 10).

Table 3 Thermodynamic parameters for the thermal decomposition of Fosfocin and of its components and related solid mixtures as obtained from DSC data. Data in brackets are obtained from TG experiments performed in argon stream

Compounds	Stages of thermal decomposition											
	320–390 K			420–450 K			450–500 K			525–625 K		
	T_e/K	T_p/K	ΔH/kJ g^{-1}	T_e/K	T_p/K	ΔH/kJ g^{-1}	T_e/K	T_p/K	ΔH/kJ g^{-1}	T_e/K	T_p/K	ΔH/kJ g^{-1}
Fosfocin	330.7	336.0	8.9	436.8	451.9	–395.5	465.3	486.1	149.8	529.7	575.9	–530.3
Ca–F							459.5 (454.6)	481.2 (473.3)	204.8 (249.9)	535.7 (526.9)	584.1 (573.9)	–923.0 (–354.6)
Ca–F+PEG	332.5	335.8	55.0	427.8	456.3	–1107.8				540.7	586.1	–245.1
Ca–F+SDSS							449.9	472.7	249.9	539.4	587.3	–989.7
PEG+SDSS	333.0	335.7	110.5				471.0	492.3	–813.0	562.2	579.2	471.0
PEG	332.1	335.1	126.0				464.4	517.6	–2593.7			
SDSS										513.1	558.0	205.3

Table 4 Thermodynamic parameters for the thermal decomposition of Fosfotricina and of its components as obtained from TG and DSC measurements

Compounds	From TG measurements				From DSC measurements								
	315–420 K		420–620 K		320–390 K			430–530 K			530–625 K		
	T_e/K	Δm/%	T_e/K	Δm/%	T_e/K	T_p/K	ΔH/kJ g^{-1}	T_e/K	T_p/K	ΔH/kJ g^{-1}	T_e/K	T_p/K	ΔH/kJ g^{-1}
Fosfotricina	321.2	12.4	503.1	26.8	329.5	350.0	121.0	448.5	495.2	–346.1	532.5	549.0	–72.9
Na_2–F	317.3	17.7	548.4	19.0	323.7	339.0	46.0				547.2	566.3	–818.7
SA			477.8	99.7				464.9	500.5	773.8			

Diffuse form of TG curves (Fig. 1b, curves 1 and 3) related to endothermic mass loss, both in the two compounds, could be due to the loss of water molecules bonded by Van deer Waals forces (humidity).

The sharp exothermic enthalpy value related to the second mass loss for active component (Fig. 1c, curve 8, Table 4) is lowered by the melting and decomposition processes (both endothermic) of the excipient (Fig. 1c, curve 9, Table 4). The above-cited exothermic process appears, in commercial drug, in form of two smaller exothermic processes.

Isothermal kinetics

As previously said kinetic analysis was carried out to determine the most probable decomposition mechanism for active components and to verify if it is influenced by the presence of the excipients.

$\alpha=f(t)$ isothermal experimental curves of Ca–F, Fosfocin, Na_2–F and Fosfotricina decomposition processes chosen at different temperatures (lying in experimental temperature range) are given in Fig. 2 (plots a, b, c and d).

The generalized reduced times plots (Figs 3a, b, c and d), in which time values have been scaled to $t/t_{0.5}$ have been derived from the isoconversion curves in Fig. 2 and have been compared with the generalized theoretical ones reported by literature [13–14].

t values that, in curves at different temperatures, are related to the same α values were divided by the corresponding $t_{0.5}$ that depends on temperature only, so the curves were normalised.

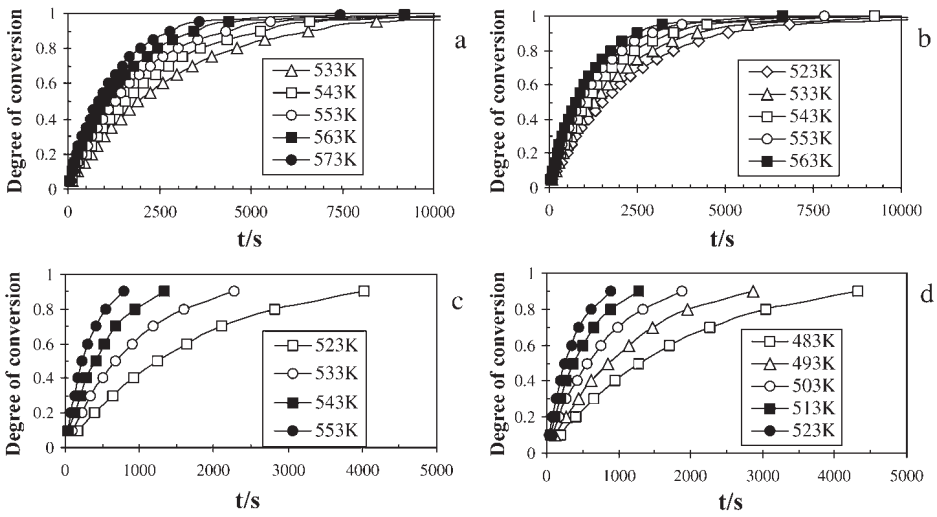


Fig. 2 Isoconversion plots at different fixed temperatures for pure Ca–F (curves a), Fosfocin (curves b), Na_2–F (curves c) and Fosfotricina (curves d)

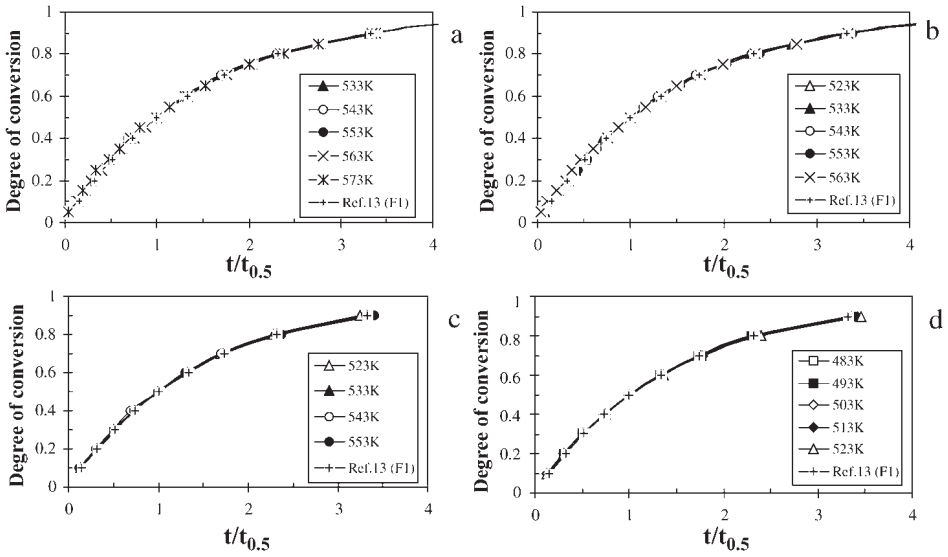


Fig. 3 Generalized reduced time *vs*. at different fixed temperatures for pure Ca–F (curves a), Fosfocin (curves b), Na_2–F (curves c) and Fosfotricina (curves d)

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

Table 5 Kinetic constant values obtained from isothermal TG curves according to the Eq. (1).

Compounds	k (s^{-1})·10^{-4}									
	483 K	493 K	503 K	513 K	523 K	533 K	543 K	553 K	563 K	573 K
Na_2–F					5.72	10.08	17.06	28.96		
Fosfotricina	5.29	8.05	12.04	17.91	25.74					
Ca–F						3.52	4.43	5.35	6.64	8.14
Fosfocin					5.95	5.85	10.06	11.38	27.93	

[a]From the slope of a linear regression analysis applied to Eq. (1)

The experimental normalised curves at various temperatures (Figs 3 a, b, c, d) overlap with the theoretical one related to mechanism F_1. This result allows to conclude that for the commercial drugs and active components studied F_1 (first reaction order) is the most probable decomposition mechanism in the above-mentioned temperature range. This behaviour was also confirmed by inserting in Eq. (1), at different temperatures (lying in the range where decomposition occurs) the mathematical ex-

pressions related to various mechanisms [14]. Figures 4a and b, 5a and b show that F_1 mechanism best linearizes the experimental values.

By inserting $g(\alpha)$ values related to F_1 mechanism in Eq. (1), at the different above-cited temperatures (Figs 6a, b, c and d), the constant rate values (k) for the decomposition processes of the four compounds were found (Table 5).

k values were subsequently inserted in Arrhenius Eq. (3) thus allowing to calculate E_a and A values for the cited processes (Table 6).

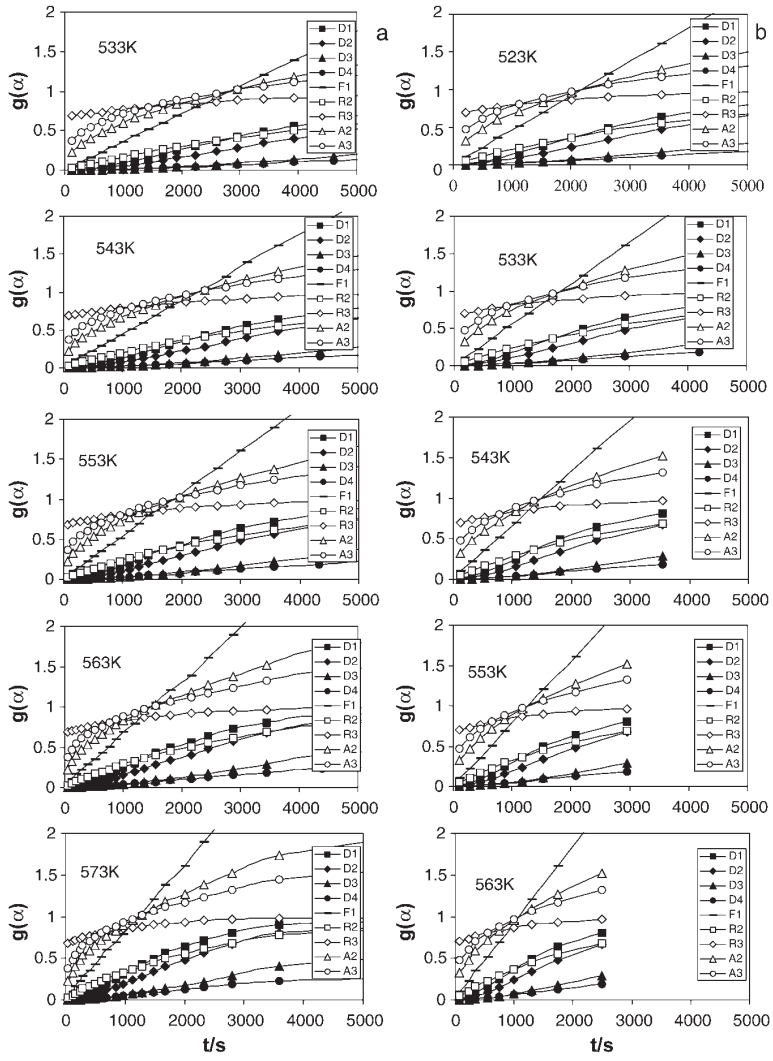


Fig. 4 Integral plots of $g(\alpha)$ *vs.* time representing all possible reaction mechanisms at different fixed temperatures for pure Ca–F (curves a), Fosfocin (curves b)

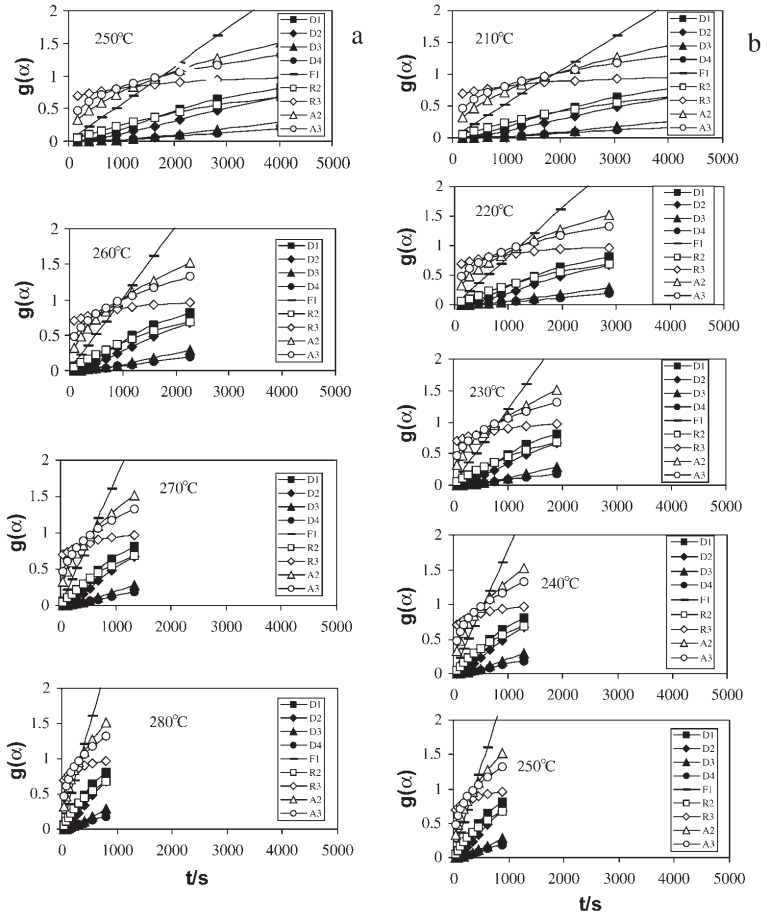


Fig. 5 Integral plots of $g(\alpha)$ *vs.* time representing all possible reaction mechanisms at different fixed temperatures for pure Na_2–F (curves a) and Fosfotricina (curves b)

Table 6 Kinetic parameters according to Arrhenius equation. Comparison between values obtained by non-isothermal procedure [23] with those of the isothermal method according to Eq. (1)

Compounds	Non-isothermal method			Isothermal method	
	T_{onset}[a]/K	E_a/kJ mol^{-1}	ln$A$/s^{-1}	E_a/kJ mol^{-1}	ln$A$/s^{-1}
Na_2–F	546.1	127.4	29.9	129.7	22.4
Fosfotricina	480.6	84.9	21.8	83.3	13.2
Ca–F	535.6	54.9	12.6	52.9	4.0
Fosfocin	500.5	42.5	10.3	36.1	1.3

[a]Extrapoled from TG measurements

To test the significance of the regression parameters related to Eqs (1), (3) and (6) a statistical analysis was carried out (Tables 7, 8 and 10, respectively).

Table 7 Statistical parameters obtained by the linear regression analysis (in the form $y=a+bx$) applied on Eq. (1). The data are referred to the most suitable mechanism (F_1) at the lowest and higher fixed temperatures

Parameters	Ca–F		Fosfocin		Na_2–F		Fosfotricina	
	523 K	553 K	483 K	523 K	523 K	573 K	523 K	563 K
a	0.2	0.2	0.2	0.02	-0.01	0.01	0.01	0.02
σ_a	$5.7\cdot10^{-2}$	$5.6\cdot10^{-2}$	$5.1\cdot10^{-2}$	$5.0\cdot10^{-2}$	$5.6\cdot10^{-3}$	$8.1\cdot10^{-3}$	$2.8\cdot10^{-3}$	$5.0\cdot10^{-3}$
c.i.	±0.2	±0.2	±0.1	±0.01	±0.02	±0.03	±0.01	±0.02
b	0.00028	0.00066	0.00037	0.00257	0.00057	0.00290	0.000539	0.000539
σ_b	$1.1\cdot10^{-5}$	$2.6\cdot10^{-5}$	$1.3\cdot10^{-5}$	$1.2\cdot10^{-5}$	$2.9\cdot10^{-6}$	$2.1\cdot10^{-5}$	$1.4\cdot10^{-6}$	$1.2\cdot10^{-5}$
c.i.	±0.00003	±0.00007	±0.00004	±0.00003	±0.00001	±0.00007	±0.00005	±0.00004
$\sigma_{y/x}$	$1.9\cdot10^{-1}$	$1.9\cdot10^{-1}$	$1.7\cdot10^{-1}$	$9.2\cdot10^{-3}$	$1.0\cdot10^{-2}$	$1.5\cdot10^{-2}$	$5.3\cdot10^{-3}$	$9.2\cdot10^{-3}$
r^2	0.9731	0.9732	0.9782	0.9999	0.9998	0.9996	1.0000	0.9999
t_a	2.87	3.10	3.04	4.62	0.91	1.55	3.06	4.62
CL_a*	0.99	0.995	0.995	0.9995	0.8	0.9	0.99	0.995
T_b	25.49	25.55	28.42	20.13	197.02	135.16	387.46	220.78
CL_b*	0.9995	0.9995	0.9995	0.9995	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*)

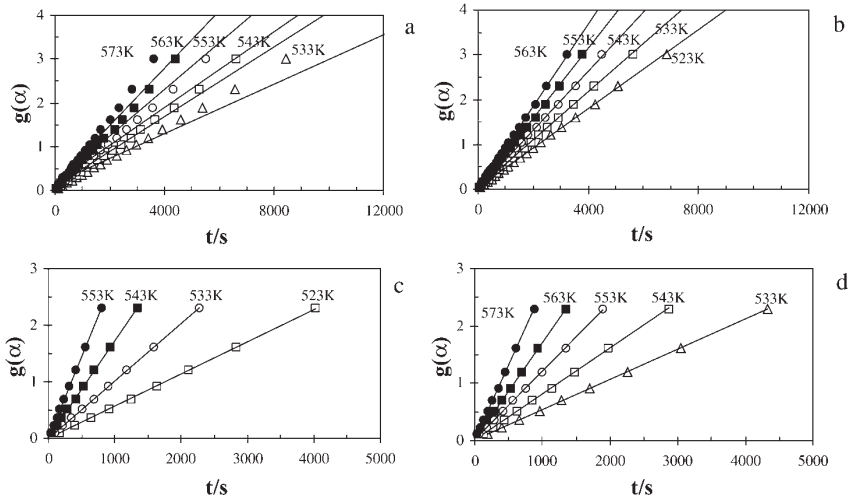


Fig. 6 Integral plots of $g(\alpha)$ *vs.* time according to the most suitable reaction mechanisms (F_1) at different fixed temperatures for pure Ca–F (curves a), Fosfocin (curves b), Na_2–F (curves c) and Fosfotricina (curves d)

To test the significance of the regression parameters related to Eqs (1), (3) and (6) a statistical analysis was carried out (Tables 7, 8 and 10, 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 7 and 8. For Eq. (1) the regression was not forced through the origin. An intercept was drawn with the least-squares treatment, but it was normally indistinguishable from zero.

Table 8 Statistical parameters obtained by applying a linear regression analysis on ln*k vs.* 1/*T* (Eq. (3)) in the form *y=a+bx*

Parameters	Ca–F	Fosfocin	Na_2–F	Fosfotricina
a	4	1	22	13
σ_a	$1.7\cdot10^{-1}$	$2.9\cdot10^{-1}$	$1.7\cdot10^{-1}$	$7.6\cdot10^{-2}$
c.i.	±2	±3	±2	±1
b	–6.4	–4.3	–15.6	–10.0
σ_b	$9.5\cdot10^{-2}$	$1.5\cdot10^{-1}$	$9.1\cdot10^{-2}$	$3.8\cdot10^{-2}$
c.i.	±0.3	±0.5	±0.3	±0.1
$\sigma_{y/x}$	$9.9\cdot10^{-3}$	$1.9\cdot10^{-2}$	$7.0\cdot10^{-3}$	$4.8\cdot10^{-3}$
r^2	0.9993	0.9965	0.9999	1.0000
t_a	23.07	4.38	131.88	174.49
CL_a **	0.9995	0.975	0.9995	0.9995
t_b	66.77	29.28	171.11	263.63
CL_b **	0.9995	0.9995	0.9995	0.9995

*The degree of freedom ν is 3 for all the regressions except for that of Na_2–F (ν=2)
**The null hypotheses applied to the regression equation (NH: *a*=0; *b*=0) are rejected for the given confidence level (*CL*)

Linear regressions applied to Eq. (1) for the commercial drugs and the active components (at the given highest and lowest experimental temperatures) were carried out to verify the reliability of k values (Table 7).

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. t values of a and b were calculated by the expressions:

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

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 [25]. 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 of Eq. (1) shows (Table 7) that for active component Na_2–F the null hypothesis A=0 was accepted with CL<0.95 at 523.15 nd 553.15 K while B=0 is rejected at CL=0.9995 for both temperatures.

For Ca–F, Fosfomicin and Fosfotricina the null hypotheses A=0 and B=0 are rejected at both temperatures (Table 7).

Equation (1) related to Na_2–F passes through the origin while this is not true for the two drugs and for the active component Ca–F.

The degree of CL related to null hypothesis A=0 shows that at the lowest temperature the linearity of Eq. (1) decreases both for the active components and the drugs (Table 7).

This allows to hypothesize that outside the experimental temperature range the degree of linearity significance of Eq. (1) could not give reliable values of constant rates k.

The same consideration can be made (Table 8) for the Arrhenius equation (i.e. for Fosfocin the hypothesis A=0 was rejected at CL=0.975 while for the other compounds CL=0.9995.

Degree of significance

a and 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 7–8) where the probability that the true parameters values lie is given by (100 CL)%.

$t_{CL,\nu}$ is chosen from proper tables [25] 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 a statistical point of view in physical terms.

Statistical analysis applied to Eq. (1) shows that the degree of significance of the regression parameter *a*, for all the compounds studied decreases at lower temperature. In the Arrhenius equation applied to the Fosfocin decomposition the probability to find the true value of *a* in the confidence interval results to be 97.5%, while for other compounds the probability of this parameter is 99.95%.

Table 9 Values of kinetic parameters E_a (kJ mol^{-1}) and A (s^{-1}) as a function of the degree of conversion α according to Eq. (6)

Compounds	ΔT/K	α	E_a/kJ mol^{-1}	A/s^{-1}
Na_2–F (4)[a]	523–563	0.3	129.8	$3.2\cdot10^{11}$
		0.6	133.0	$8.8\cdot10^{11}$
		0.9	129.8	$3.1\cdot10^{11}$
Fosfotricina (5)[a]	483–533	0.3	85.0	$5.0\cdot10^{7}$
		0.6	83.9	$3.7\cdot10^{7}$
		0.9	83.5	$3.4\cdot10^{7}$
Ca–F (5)[a]	533–573	0.3	57.5	$9.0\cdot10^{3}$
		0.6	53.6	$3.8\cdot10^{3}$
		0.9	54.1	$4.2\cdot10^{3}$
Fosfocin (5)[a]	523–563	0.3	46.3	$1.2\cdot10^{3}$
		0.6	43.3	$5.8\cdot10^{2}$
		0.9	43.8	$4.2\cdot10^{2}$

[a]The number of regression points n for each studied compound are reported in brackets

Using Eq. (6) the negligible change in E_a values confirms that F_1 is the only mechanism occurring in the whole temperature range of the decomposition process (Table 9).

The statistical analysis applied to Eq. (6) shows (Table 10) 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 all the other compounds the probability for the same parameter is 99.95%.

The kinetic constant rates of commercial drugs were found to be greater than those of their active components (Table 5) while for the activation energy values the reverse is true (Table 6). Kinetic data of both commercial drugs have been obtained by means of non-isothermal method that utilises a dynamic TG curve alone based on F_1 mechanism have been done in the same table.

The good accordance between these kinetic data and those of the isothermal method confirms that all the components undergo F_1 mechanism of decomposition.

In the case of a relatively simple process [26], 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 experimental data (temperature range of isothermal and non-isothermal experiments are

Table 10 Statistical parameters obtained by applying a linear regression analysis on ln*t vs.* 1/*T* (Eq. (6)) in the form *y=a+bx*

Param.	Ca–F			Fosfocin			Na_2–F			Fosfotricina		
	α=0.3	α=0.6	α=0.9	α=0.3	α=0.6	α=0.9	α=0.3	α=0.6	α=0.9	α=0.3	α=0.6	α=0.9
a	–6	–4.2	–3	–3	–2	–1	–23	–23	–22	–16	–15	–14
σ_a	$3.8\cdot10^{-1}$	$4.2\cdot10^{-2}$	$1.9\cdot10^{-1}$	$9.7\cdot10^{-1}$	$2.0\cdot10^{-1}$	$9.1\cdot10^{-2}$	$7.4\cdot10^{-1}$	$3.1\cdot10^{-1}$	$1.3\cdot10^{-1}$	$3.4\cdot10^{-1}$	$2.2\cdot10^{-1}$	$1.3\cdot10^{-1}$
c.i.	±2	±0.2	±1	±6	±1	±1	±7	±3	±1	±2	±1	±1
β	7	6.4	6.5	5	4	4.5	16	16	16	12	12	11.7
σ_b	$2.1\cdot10^{-1}$	$2.3\cdot10^{-2}$	$1.1\cdot10^{-1}$	$4.9\cdot10^{-1}$	$1.0\cdot10^{-1}$	$4.6\cdot10^{-2}$	$4.0\cdot10^{-1}$	$1.6\cdot10^{-1}$	$7.3\cdot10^{-2}$	$1.9\cdot10^{-1}$	$1.2\cdot10^{-1}$	$7.3\cdot10^{-2}$
c.i.	±1	±0.1	±0.6	±3	±1	±0.3	±4	±2	±1	±1	±1	±0.4
$\sigma_{y/x}$	$2.2\cdot10^{-2}$	$2.4\cdot10^{-3}$	$1.1\cdot10^{-2}$	$6.1\cdot10^{-2}$	$1.2\cdot10^{-2}$	$5.7\cdot10^{-3}$	$3.1\cdot10^{-2}$	$3.1\cdot10^{-2}$	$5.6\cdot10^{-3}$	$2.0\cdot10^{-2}$	$1.3\cdot10^{-2}$	$7.9\cdot10^{-3}$
r^2	0.9972	1.0000	0.9992	0.9698	0.9985	0.9997	0.9987	0.9998	1.0000	0.9993	0.9997	0.9999
t_a	15.84	100.35	17.54	3.34	8.34	8.96	31.73	76.60	159.06	47.24	68.13	103.74
CL_a **	0.9995	0.9995	0.9995	0.95	0.99	0.99	0.9995	0.9995	0.9995	0.9995	0.9995	0.9995
t_b	32.79	276.80	60.51	9.81	44.91	99.02	39.33	97.97	214.33	63.68	98.24	159.79
CL_b **	0.9995	0.9995	0.9995	0.99	0.9995	0.9995	0.9995	0.9995	0.9995	0.9995	0.9995	0.9995

*The degree of freedom ν is 3 for all the regressions except for that of Na_2–F (ν=2)

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

not the same, 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 [26]. 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 excipients decrease the kinetic stability of the active components and if commercial drug named Fosfotricina is more stable than Fosfocin (from a kinetic point of view) the simulated α *vs.* temperature and α *vs.* time curves for the couples Fosfotricina/Fosfocin, Fosfotricina/Na_2–F and Fosfocin/Ca–F, using F_1 mechanism and non-isothermal and isothermal kinetic parameters of Table 6, have been constructed (Fig. 7).

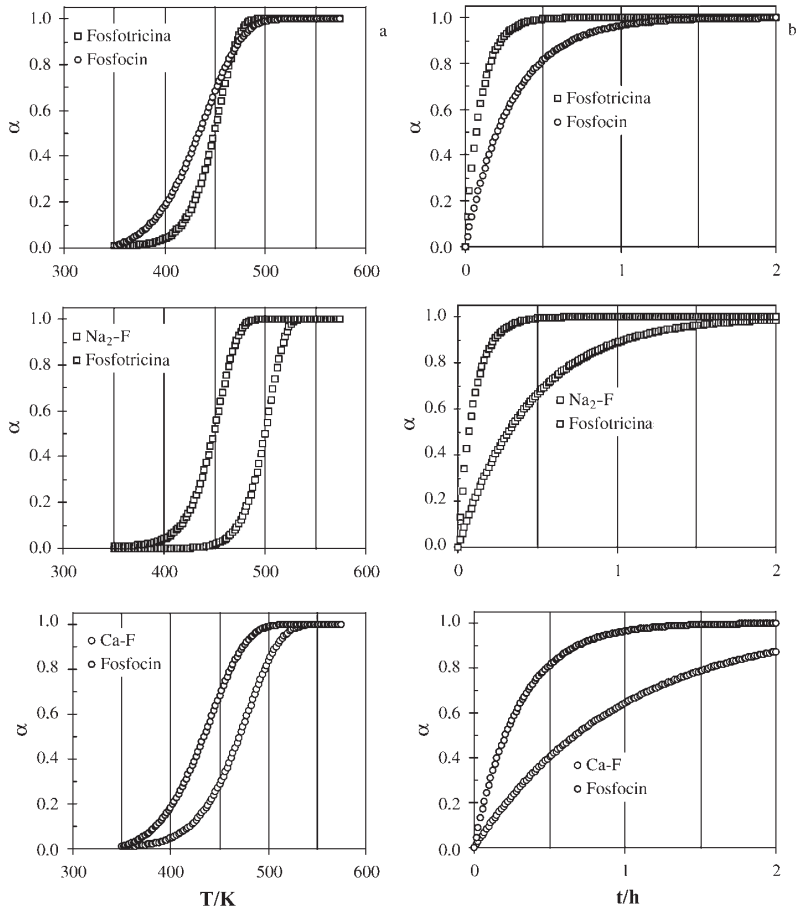


Fig. 7 Simulated α *vs.* temperature (curves a) and α *vs.* time (curves b) plots obtained by using kinetic parameters reported in [14] according to the non-isothermal and isothermal methods, respectively

For all the couples of curves considered the process having higher activation energy occurs in a higher temperatures range (Fig. 7a) or reachses its completion (α=1) in a longer time (Fig. 7b).

Finally, half-life and shelf-life values for the commercial drugs and active components have been calculated using the expression (13).

From these values (Table 11) it can be observed that excipients lower both the half–life and shelf–life times of active component. It can be noted that both for these quantities the values obtained outside the decomposition temperature range of the experiments (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. (1).

Table 11 Half-time and shelf-life values t_α at fixed temperatures for the studied compounds (1 year is about $3.1\cdot10^7$ s)

Compounds	T/K	From Eq. (13)				
		$t_{0.01}$/s	$t_{0.02}$/s	$t_{0.03}$/s	$t_{0.04}$/s	$t_{0.50}$/s
Na_2-F	298.15	$9.9\cdot10^{10}$	$2.0\cdot10^{11}$	$3.0\cdot10^{11}$	$4.0\cdot10^{11}$	$7.2\cdot10^{12}$
	373.15	$2.7\cdot10^{6}$	$5.4\cdot10^{6}$	$8.1\cdot10^{6}$	$1.1\cdot10^{7}$	$1.8\cdot10^{8}$
	523.15	$1.7\cdot10^{2}$	$3.5\cdot10^{2}$	$5.3\cdot10^{2}$	$7.1\cdot10^{2}$	$1.2\cdot10^{3}$
	533.15	$1.0\cdot10^{2}$	$2.0\cdot10^{2}$	$3.0\cdot10^{2}$	$4.0\cdot10^{2}$	$6.9\cdot10^{2}$
	543.15	$5.9\cdot10^{1}$	$1.2\cdot10^{2}$	$1.8\cdot10^{2}$	$2.4\cdot10^{2}$	$4.1\cdot10^{2}$
	553.15	$3.5\cdot10^{1}$	$7.0\cdot10^{1}$	$1.0\cdot10^{2}$	$1.4\cdot10^{2}$	$2.4\cdot10^{2}$
Fosfotricina	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	$3.9\cdot10^{1}$	$7.8\cdot10^{1}$	$1.2\cdot10^{2}$	$1.6\cdot10^{2}$	$2.7\cdot10^{2}$
Ca-F	298.15	$3.4\cdot10^{5}$	$6.8\cdot10^{5}$	$1.0\cdot10^{6}$	$1.4\cdot10^{6}$	$2.3\cdot10^{7}$
	373.15	$4.7\cdot10^{3}$	$9.3\cdot10^{3}$	$1.4\cdot10^{4}$	$1.9\cdot10^{4}$	$3.2\cdot10^{5}$
	533.15	$2.8\cdot10^{2}$	$5.7\cdot10^{2}$	$8.6\cdot10^{2}$	$1.1\cdot10^{3}$	$1.9\cdot10^{3}$
	543.15	$2.3\cdot10^{2}$	$4.6\cdot10^{2}$	$6.9\cdot10^{2}$	$9.2\cdot10^{2}$	$1.6\cdot10^{3}$
	553.15	$1.9\cdot10^{2}$	$3.8\cdot10^{2}$	$5.7\cdot10^{2}$	$7.6\cdot10^{2}$	$1.3\cdot10^{3}$
	563.15	$1.5\cdot10^{2}$	$3.0\cdot10^{2}$	$4.6\cdot10^{2}$	$6.1\cdot10^{2}$	$1.0\cdot10^{3}$
	573.15	$1.2\cdot10^{2}$	$2.5\cdot10^{2}$	$3.7\cdot10^{2}$	$5.0\cdot10^{2}$	$8.5\cdot10^{2}$
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	$3.6\cdot10^{1}$	$7.2\cdot10^{1}$	$1.5\cdot10^{2}$	$1.5\cdot10^{2}$	$7.6\cdot10^{2}$

Conclusions

Commercial drugs having calcium and disodium phosphomycin salts as active components and different excipients show different kinetic and thermal behaviour in their decomposition processes.

Excipients have a lower kinetic stability of active components.

Drugs having Ca–F as active component show a lower kinetic stability with respect to drugs containing Na_2–F.

This fact could be due to the complex interactions system among the components in Fosfocin as it can be seen from the comparison of their TG/DSC curves.

It can be concluded that thermal analysis allows to determine the chemical interactions of the components in a pharmaceutical form and provides a full description of kinetic behaviour in the range of temperatures where these processes occur.

Statistical analysis shows that extrapolation of kinetic parameters at room temperature seems to be unrealistic.

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