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Thermal stability of disodium and calcium phosphomycin and the effects of the excipients evaluated by thermal analysis

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Abstract

In the present study, *Thermogravimetry* (TG) and *Differential Scanning Calorimetry* (DSC) are simultaneously applied to determine the thermal properties of two antibiotic salts, disodium and calcium phosphomycin, used either pure or in association with several excipients. This study was carried out kinetically as well by mathematical elaboration of the TG curves performed according to an isothermal procedure applied at different fixed temperatures. Kinetic parameters showing agreement with those produced by the isothermal method were also obtained by means of a non-isothermal method using a dynamic TG curve alone. The main aims of the work were to provide reliable kinetic parameters (kinetic constant k, activation energy E_a and pre-exponential factor A) to evaluate the thermal stability of phosphomycin salts in the presence and absence of the excipients generally contained in the phosphomycin-based pharmaceutical forms available on the market, and to obtain information concerning compatibility towards the active components. These kinetic parameters were then used to extrapolate shelf-life and half-life values at room temperature for pure active components in the solid state and for their pharmaceutical derivatives.

Keywords: Phosphomycin salts; Stability; Kinetic study

1. Introduction

Thermal methods of analysis were used extensively to study important pharmaceutical compounds, such as antibiotics [1,2] and recently to address the solid-state applications of these techniques within the pharmaceutical industry [3]. Some years ago, a study involving the disodium and calcium salt of phosphomycin, an important antibiotic produced by streptomycetes [4,5], was carried out by thermal analysis [6].

In the present research, a thermal analysis study was carried out on the disodium and calcium phosphomycin salts as such as well as in association with several excipients. These excipients in-

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cluded several that are added to the phosphomycin-based antibiotics available on the market.

Thermoanalyser experiments were carried out in an air stream at fixed temperatures (between 483 and 573 K). In elaborating the isothermal thermogravimetric data to give the fraction of compound decomposed α vs. time, three isothermal kinetic methods were presented.

From the slopes and intercepts of the straight lines obtained by applying a linear regression analysis (least-squares method) to the applied kinetic equations, the Arrhenius kinetic parameters (reaction order n, kinetic constant k (s^{-1}), activation energy E_a (kJ mol^{-1}), and pre-exponential factor A (s^{-1})) were calculated. Kinetic parameters were also obtained by means of a non-isothermal method using only a dynamic TG curve.

The effect of the excipients upon the thermal stability of antibiotics was evaluated, also from the kinetic point of view by the mathematical elaboration of each TG curve obtained isothermally at different temperatures.

Lastly, as the stability of the active components of commercial pharmaceutical forms stored at room temperatures is a crucial problem in the pharmaceutical field, it is important to know the shelf-life (the length of time over which a drug's activity is preserved). To this end the kinetic chemical–physical shelf-life and half-life data of disodium and calcium phosphomycin, both pure and in association with commercial excipients, were also evaluated.

2. Experimental

2.1. Materials

Phosphomycin, (1,2-epoxypropyl)phosphonic acid, mono-hydrate calcium salt, (Ca–F) and disodium salt (Na_2–F) (the latter containing moisture only) and the commercial drugs containing them in association with the excipients, i.e., 8.33% (w/w) of Succinic Acid (SA) in the case of Na_2–F (named Na_2–F/SA), and 9.12% of polyethyleneglycol (PEG) and 0.20% of sodiumdioctylsulfosuccinate (SDSS) in the case of Ca–F (denoted as Ca–F/PEG/SDSS) were used as supplied by Crinos S.p.A. All the excipients used were supplied by Merck (analytical grade).

2.2. Instrumental

Thermogravimetry (TG) and Differential scanning calorimetry (DSC) measurements were performed with a Stanton Redcroft 625 simultaneous thermoanalyser connected to an Olivetti 290 computer. Isothermal TG experiments were carried out at fixed temperatures in the range 483–573 K under an air stream of 50 cm^3 min^{-1}. The heating rate of dynamic TG/DSC ranged from 298 to 703 K was 5 K min^{-1} and the furnace atmosphere consisted of air at a flow rate of 50 cm^3 min^{-1}. 5–10 mg samples were used for each TG/DSC experiment.

3. Methods

TG is used to detect any change in sample mass (measured by thermobalance) as a function of temperature or time, when the studied compound is subjected to a controlled temperature program, or when operating at a constant fixed temperature, respectively.

DSC enables one to check any change in the sample enthalpy with respect to that of a reference material, operating at constant pressure.

It was possible to obtain the fraction of compound decomposed as a function of time, $\alpha(t)$, by means of the equation,

$$\alpha(t) = \frac{[(\%m_i - \%m_t)]}{[(\%m_i - \%m_f)]} \quad (1)$$

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 [7].

Of course, for a dynamic TG experiment $\alpha(T)$ (fraction of compound decomposed as a function of temperature) may be defined by the equation

$$\alpha(T) = \frac{[(\%m_i - \%m_T)]}{[(\%m_i - \%m_f)]} \quad (2)$$

where, $\%m_T$ is the percent mass at temperature T.

Table 1
Values of the reaction order n for the most commonly used solid-state reaction equations [10,11]

Mechanism	$g(\alpha)=kt$	n
D_1	α^2	0.62
D_2	$(1-\alpha)\ \ln(1-\alpha)+\alpha$	0.57
D_3	$[1-(1-\alpha)^{1/3}]^2$	0.54
D_4	$1-(2/3)\ \alpha-(1-\alpha)^{2/3}$	0.57
F_1	$-\ln(1-\alpha)$	1.00
R_2	$1-(1-\alpha)^{1/2}$	1.11
R_3	$1-(1-\alpha)^{1/3}$	1.07
A_2	$[-\ln(1-\alpha)]^{1/2}$	2.00
A_3	$[-\ln(1-\alpha)]^{1/3}$	3.00

Once the values of α have been collected, two alternative methods are recommended in literature to describe the kinetics of solid-state reactions, depending on whether these values are collected as a function of temperature (non-isothermal method) or at a fixed temperature as a function of time (isothermal method) [7–9].

The kinetics of many solid-state reactions can be followed according to the equation

$$g(\alpha)=kt \tag{3}$$

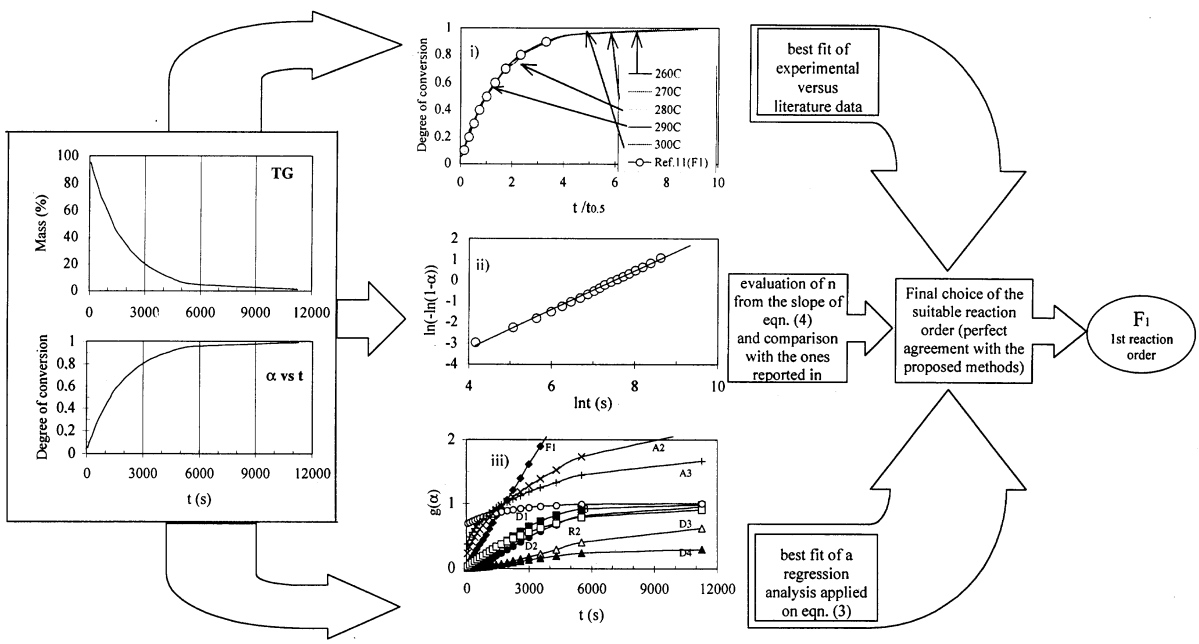
where, $g(\alpha)$ is a mathematical expression which depends on the reaction mechanism and k is the specific rate constant.

The rate-determining step in any solid-phase reaction may be the result of,

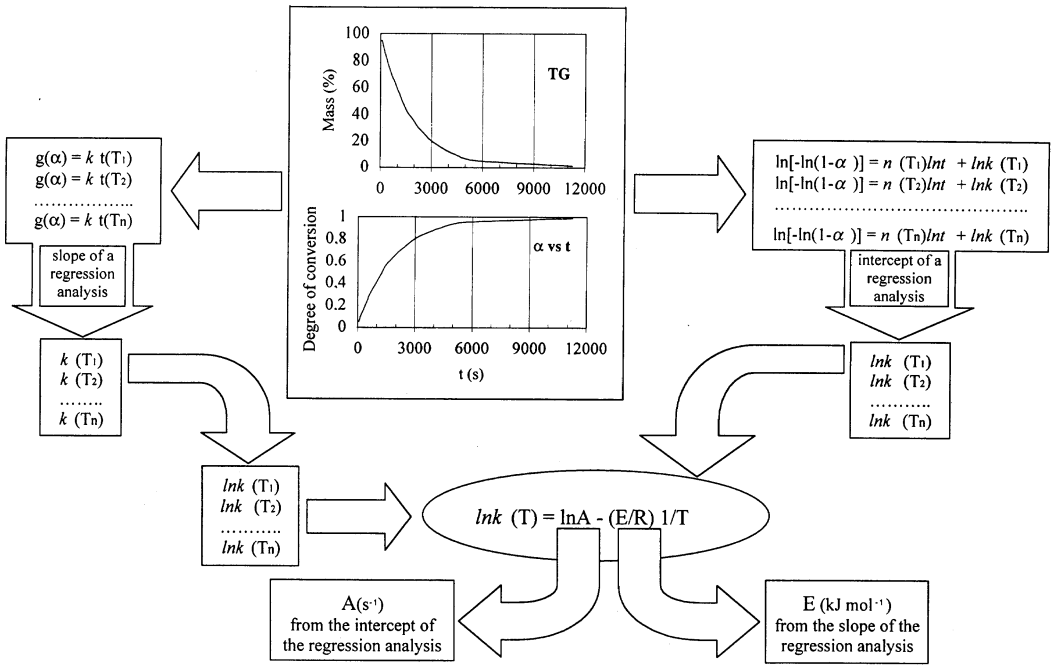
1. diffusion of particles to or from a zone of reaction.
2. a chemical reaction, occurring at a reaction interface, with some bond redistribution steps.
3. a nucleation model in which the initial product formation is identified as active sites and the rate at which these particles grow is considered [10].

According to these assumptions, the kinetic functions $g(\alpha)$ have been classified into three groups: *diffusion* mechanisms (D_1, D_2, D_3, D_4), *chemical reaction* mechanisms (R_2, R_3, F_1), and *nucleation* models (A_2, A_3) (Table 1).

According to the isothermal procedure [10] reported in Scheme 1 the main kinetic aims are to choose the appropriate mechanism (reaction order n) and to calculate the kinetic parameters (kinetic



Scheme 1. Isothermal kinetic procedure to determine the reaction order from isothermal TG measurements according to three different approaches.



Scheme 2. Isothermal kinetic procedure to determine the Arrhenius kinetic parameters E and A from isothermal TG measurements according to two different methods.

constant k, energy of activation E_a and pre-exponent factor A) by means of the Arrhenius equation (Scheme 2).

Following Scheme 1 three different ways of identifying the appropriate function $g(\alpha)$ are presented:

i). the generalized α – time plots (experimental α values vs. normalized $t/t_{0.5}$) were obtained at each fixed temperature. From the best overlapping of these curves with those calculated for the most commonly used solid-state reaction equation reported in reference [11] (Table 1), the most suitable function $g(\alpha)$ is selected.

ii). by evaluating characteristic values of n (reaction order) from the slope of a linear regression analysis (least-squares method) applied to the following equation:

$$\ln[-\ln(1-\alpha)] = n \ln t + \ln k \quad (4)$$

From the comparison between the experimental values of n with those reported in Table 1 for each function $g(\alpha)$ the best mechanism is found.

iii). by including in all $g(\alpha)$ expressions the values of α and the respective time t obtained from the isothermal TG curves carried out at various temperatures. The best linearity was sought using linear regression analysis (least-squares method).

According to Scheme 2 from the slope of the regression straight line $g(\alpha)$ versus time plots (at various temperatures) the kinetic constant values k are obtained as a function of temperature T.

The k values are also obtained from the intercept of the straight line produced by the least-squares method applied to Eq. (4) [10].

The resulting values of k and the respective reciprocal temperature, obtained with the two alternative isothermal methods, are introduced in the following Arrhenius equation,

$$\ln k = \ln A - \left(\frac{E_a}{R}\right) 1/T, \quad (5)$$

and from the slope and the intercept of the regression straight line the kinetic parameters E_a (kJ mol^{-1}) and A (s^{-1}) are obtained respectively.

By combining Eqs. (4) and (5) for first-order reactions ($n = 1$) one can deduce,

$$\ln[-\ln(1-\alpha)] = \ln t + \ln A - (E_a/R)\ 1/T, \qquad (6)$$

and, rearranging,

$$\ln t = \ln[-\ln(1-\alpha)] - \ln A + (E_a/R)\ 1/T, \qquad (7)$$

from which at any given fraction of compound decomposed α it is possible to obtain the activation energy values as a function of α by plotting $\ln t$ against the reciprocal temperature.

Finally a non-isothermal method that enables one to find the kinetic parameters E_a and A by elaborating a single TG curve with rising temperature was examined. A simultaneous dynamic TG and DSC experiment takes only 1 or 2 h and yields precious kinetic data.

The advantage of a non-isothermal kinetic method is that, since it elaborates a single TG curve, it is not a time-consuming technique. The starting equation proposed by McCarty and Green [12] is,

$$d\alpha/dT = \left(\frac{A}{\beta}\right)\exp\left(\frac{-E_a}{RT}\right)(1-\alpha) \qquad (8)$$

where, β is the heating rate and α is the fraction of compound decomposed as a function of temperature ($\alpha(T)$) according to Eq. (2).

Rearranging Eq. (8) and integrating yields,

$$-\ln(1-\alpha) = (AE_a/\beta R)\ p(x), \qquad (9)$$

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

$$p(x) = \frac{(x+3)}{x(x+1)(x+4)e^x}. \qquad (10)$$

On taking natural logarithms of both sides of Eq. (9) one can obtain,

$$\ln[-\ln(1-\alpha)] = \ln\left(\frac{AE_a}{\beta R}\right) + \ln\ p(x) \qquad (11)$$

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

$$\frac{dF(\alpha)}{dx} = \frac{d\ln p(x)}{dx} \qquad (12)$$

Taking into account that $x = E_a/RT$ and therefore $dx = (E_a/R) \times d(1/T)$. Substituting the dx algorithm in Eq. (12) and rearranging, the following may be written,

$$E_a = R\frac{[dF(a)/d(1/T)]}{[d\ln p(x)/dx]} \qquad (13)$$

The data for the construction of this plot are taken from the TG curve. The numerator in Eq. (13) is the slope of a plot of $F(\alpha)$ vs. $1/T$, while the denominator can be estimated from the series,

$$\frac{d\ln p(x)}{dx} = \frac{1}{(x+3)} - \left(\frac{1}{x}\right) - \left[\frac{1}{(x+1)}\right] - \left[\frac{1}{(x+4)}\right] - 1$$

The denominator in Eq. (13) is also a function of E_a and an initial guess of 125.56 kJ mol^{-1} for the activation energy is used [12]. A series of iterative calculations is performed to refine the value of E_a. Once E_a has been determined, the pre-exponential factor A is calculated from Eq. (9). This study considered mass losses that were consistently lower than 10% for the calculation of activation energy. Indeed, it was usually considered [12] that the initial portion of the TG curves could be fitted by a first-order reaction equation. The Arrhenius parameter values (A and E_a) obtained using this integral method are a function of F_1 mechanism (first-order reaction).

Having previously determined a first-order reaction for the solid-state processes studied the results obtained by this dynamic kinetic approach are more reliable.

One important parameter for predicting the stability of a drug at a given temperature is the chemical–physical shelf-life of drugs. Direct measures (long-term tests) of shelf-life require a drug to be kept in a thermostat at about 30–40°C for several months.

The thermal analysis method monitoring the rate of the thermal decomposition of a drug provides a quick estimate of the shelf-life using a rapid low-cost procedure.

The half-life time $t_{0.5}$ (that corresponds to the isothermal decomposition of half the product content) can also be considered, as well as the shelf-life, the onset decomposition temperature and the activation energy values, as interesting qualitative

parameters to evaluate the stability of the pharmaceutical compounds considered.

In the case of samples displaying a first-order reaction, to the extent of 50% conversion, $g(\alpha) = -\ln 0.5$ and the time taken to reach this conversion, $t_{0.5}$, at a given temperature (e.g. room temperature) is calculated by rearranging Eq. (3),

$$t_{0.5} = \frac{-\ln 0.5}{k(T)} \quad (14)$$

while, for any other fraction of compound decomposed α, at a certain temperature T; t_α is obtained from the equation,

$$t_\alpha = \frac{-\ln(1-\alpha)}{k(T)} \quad (15)$$

where, t_α is the time taken to reach a given degree of conversion (generally 1, 2, 3 and 4%) and $k(T)$ is the specific kinetic constant value at temperature T as calculated from Eq. (5).

4. Results

The simultaneous TG and DSC curves of the disodium and calcium phosphomycin antibiotic salts, both pure and in association with the above-mentioned excipients, carried out with rising temperature (5 K min^{-1}) between 298 and 703 K under an air stream, are reported in Figs. 1 and 2, respectively. TG and DSC data referring to each thermal process for all the compounds studied are summarized in Table 2.

Na_2–F shows a first mass loss in the TG curve between 298 and 423 K (Fig. 1a, curve 1) with a corresponding endothermic peak in the DSC curve (Fig. 1b, curve 1) due to water evaporation (17.7% by weight of moisture only) followed by about 20% mass loss with a strong exothermic effect (503–603 K) associated with its complete oxidative decomposition.

The commercial pharmaceutical form containing succinic acid (i.e. Na_2–F/SA) decreases the oxidative decomposition onset temperature by about 9 K with respect to that of pure Na_2–F (Table 2 and Fig. 1b, curve 1 and curve 3).

A decrease in the exothermic effect of the DSC curve between 420 and 520 K is also evident on comparing (Table 2) the relative ΔH values of Na_2–F with those of Na_2–F/SA.

TG and DSC curves of pure SA show its melting point [13] (sharp endothermic peak at about 460 K in Fig. 1b, curve 3) followed by vaporization (broad endothermic peak under 520 K).

The thermal behaviour of Ca–F with rising temperature is described by means of its TG and DSC curves (Fig. 2 a and b). The loss of about one water molecule with a corresponding broad endothermic effect in the range 420–520 K is observed, followed by a very broad and intense exothermic effect (about 20% mass loss in the TG curve) due to its oxidative decomposition.

In the TG curve of the commercial pharmaceutical form Ca–F/PEG/SDSS three main distinct steps of mass loss are clearly seen. The second with an endothermic effect (see DSC curve 4 in Fig. 2 (b)) due to the loss of water (in the same temperature region of the pure Ca–F mono-hydrate) while in the DSC curve two important exothermic effects correspond to the first and third steps. The former is ascribed to the exother-

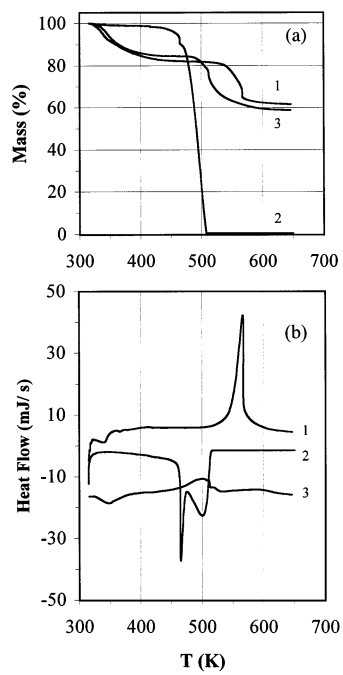


Fig. 1. (a) TG and (b) DSC curves (1) of Na_2–F; (2) SA and (3) Na_2–F/SA.

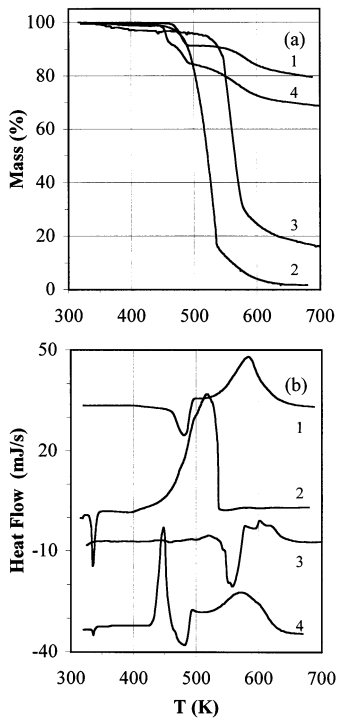


Fig. 2. (a) TG and (b) DSC curves (1) of Ca–F, (2) PEG, (3) SDSS and (4) of Ca–F/PEG/SDSS.

mic decomposition of PEG (the shift to a lower temperature region with respect to that of the pure excipient is evident in Table 2) while the latter represents the oxidative decomposition of Ca–F. The onset TG temperature is 24 K lower than that of the pure Ca–F mono-hydrate compound.

In the DSC curve of Ca–F/PEG/SDSS (Fig. 2b, curve 4) also a slight endothermic effect, without mass loss, occurred around 335 K due to the fusion of PEG (as can clearly be seen from the overlapping of this process with that of the pure PEG in the same temperature region). The measured melting enthalpy is 8.9 kJ g^{-1} (Table 2).

From a comparison of the T_e and ΔH values in Table 2 the following two concluding remarks can be made: the presence of the excipients decreases the oxidative decomposition enthalpy values, as well as the onset decomposition temperatures T_e, of the commercial drugs with respect to that of the pure active principles (Na_2–F, Ca–F). In view of the experimental results described above, the data obtained from kinetic studies of the effects of the excipients on the thermal stability of the two Phosphomycin salts takes on great importance.

The values of the fraction of compound decomposed $\alpha(t)$ obtained from isothermal TG curves under different fixed temperatures were obtained from Eq. (1) and are reported in Fig. 3 as a function of time.

According to the isothermal kinetic procedures listed in Scheme 1 for all the compounds tested a first-reaction order (kinetic function F_1) was found at each fixed temperature using the three different methods described in the previous section.

Following the two different methods represented in Scheme 2 in Table 3 two sets of kinetic constant values k (size order of 10^{-3}–10^{-4} s^{-1}) have been reported at each fixed temperature. At the same temperature, the k values of commercial drugs are always greater than the values of both pure Na_2–F and Ca–F.

The activation energy values as a function of the fraction of compound decomposed α, which are obtained from Eq. (7) by plotting $\ln t$ against the reciprocal temperature, are set out in Fig. 4. The figure shows that the change in activation energy with respect to α, within the range 10–90%, is negligible for all the compounds tested.

By introducing the two sets of k values reported in Table 3 into Eq. (5) and plotting $\ln k$ against reciprocal temperature, the E_a and A kinetic parameters were calculated and presented in Table 4 together with those obtained using the McCarty and Green non-isothermal procedure [12].

The goodness of fit is satisfactory for almost all the compounds tested (the value of correlation coefficient $r^2 \approx 1$). Except for the activation energy values of Ca–F and Ca–F/PEG/SDSS (obtained by using Eq. (4)) the E_a values obtained with the proposed methods (two isothermal and one non-isothermal) agree well enough.

The two sets of kinetic rate constant values reported in Table 3 were also used to extrapolate to the elevated temperature half-life as well as the shelf-life values at room temperature. Both quantities can be determined from Eq. (14) and the

relative values are given in Fig. 5, Table 5 and Table 6, respectively.

The comparison of all the given results shows that the activation energies (Table 4), as well as the onset decomposition temperature (Table 2), of the commercial drugs are always lower than those of the pure phosphomycin salt derivative.

5. Discussion

The comparison between the TG and the DSC curves and the kinetic data of Na_2–F and Ca–F with those of Na_2–F/SA and Ca–F/PEG/SDSS allows the following remarks to be made: the most important processes shown in the TG and DSC curves of the pure active principles are also evident in those of the commercial pharmaceutical form. Moreover pronounced effects (i.e. the shift of the onset and peak temperature to lower values in the DSC curves) are more evident in the case of the DSC curve of Na_2–F and Na_2–F/SA than in those of the corresponding calcium derivatives.

The effect is also clear in the TG curve: a decrease of about 40 K in the case of Na_2–F/SA with respect to Na_2–F while for Ca–F/PEG/SDSS a decrease of about 23 K is found with respect to that of pure Ca–F mono-hydrate. In addition, a decrease in the decomposition enthalpy values of the pharmaceutical forms Na_2–F/SA and Ca–F/PEG/SDSS with respect to those of both the pure Na_2–F and Ca–F mono-hydrate (Table 2) is also worth noting.

This behaviour is in good agreement with expectations, considering the activation energy values found through the mathematical elaboration of the thermal analysis data carried out in the isothermal and non-isothermal kinetic studies performed.

A decrease of about 50 kJ mol^{-1} of the activation energy values for Na_2–F/SA and of about 10 kJ mol^{-1} for Ca–F/PEG/SDSS with respect to Na_2–F and Ca–F, respectively, is actually observed (Fig. 4).

On the basis of these results the following considerations concerning the thermal stability can be stressed. As previously noted, the presence of the excipients tested (SA in the case of Na_2–F and PEG and SDSS in the case of Ca–F) actually decreases the thermal stability of the active components by about 40 and 20 K, respectively. Moreover, even in the presence of those excipients, the onset decomposition temperatures of the active components are always 150 K higher than room temperature.

Table 2
Thermoanalytical results for the studied compounds as obtained from TG and DSC data[a]

Compounds	Decomposition steps	From TG measurements			From DSC measurements		
		T_e (K)	ΔT (K)	$\%\Delta m$	T_e (K)	T_p (K)	ΔH (kJ g^{-1})
Na_2-F	I (a)	317.3	315–420	17.7	323.7	339.0	46.0
	II (b)	548.4	420–615	19.0	547.1	566.3	−818.7
Na_2–F/SA	I (a′)	321.0	320–420	12.4	329.5	350.0	121.0
	II (b′)	475.0	420–620	26.8	448.5	495.2	−346.1
Ca-F	I (c)	473.6	445–495	8.3	459.5	481.2	204.8
	II (d)	550.1	495–675	10.6	535.7	584.1	−923.0
Ca–F/PEG/SDSS	I	–	–	–	330.7	336.0	8.9
	II	450.6	425–450	6.9	436.8	451.9	−395.5
	III (c′)	475.0	450–490	6.9	465.1	486.1	149.8
	IV (d′)	518.4	490–675	14.9	529.7	575.9	−530.3

[a] T_e (K) and T_p (K) refer to the onset temperature and to the peak temperature respectively while, $\%\Delta m = \%m_f - \%m_i$ represents the percentage mass loss values at any decomposition step. (a) and (a′), (b) and (b′), (c) and (c′) and (d) and (d′) are corresponding steps.

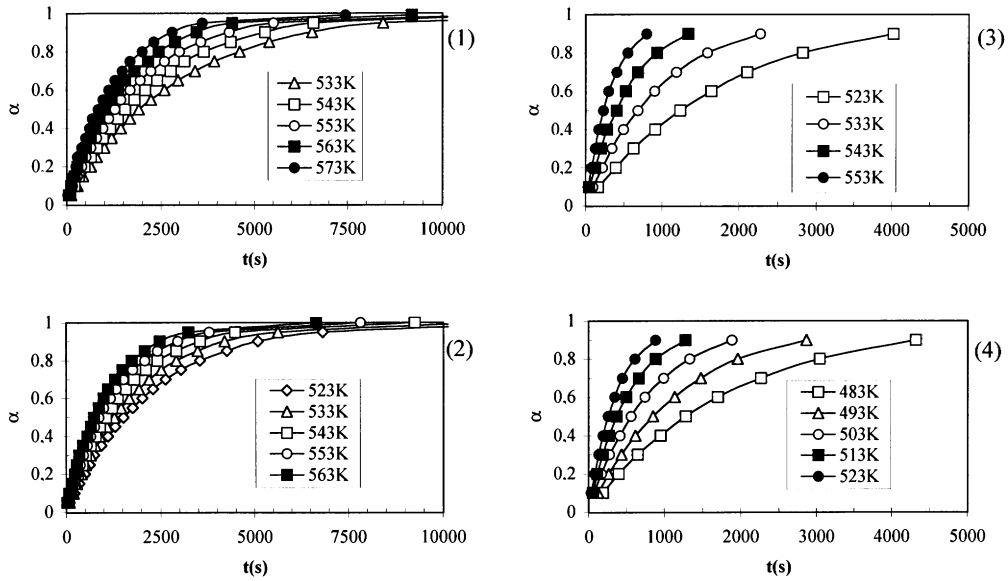


Fig. 3. α vs. time plots for (1) Na_2–F; (2) Na_2–F/SA; (3) Ca–F and (4) Ca–F/PEG/SDSS at different fixed temperature as obtained from isothermal TG curve according to Eq. (1).

As regards questions of physico-chemical incompatibility between excipients and active components in TG and DSC curves of commercial products containing excipients, all the most important exothermic and endothermic processes of the corresponding TG and DSC curves of the pure antibiotics are evidently still present. Nevertheless, it has been observed that the onset and peak temperatures as well as the decomposition enthalpy are noticeably modified in the case of pure antibiotics with respect to the pharmaceutical forms, which contain the same compounds as active components.

Conversely, the DSC curves of pure excipients alone are very different from those of the commercial pharmaceutical forms, which contain them in association with the antibiotic salts. The latest observations are evident in the case of the commercial drug containing Na_2-F and SA (Na_2–F/SA) with respect to pure Na_2–F.

The principle of a simple additive superimposition of the drug DSC curves and those of the excipients [14] is not observed for the compounds tested while no new peak appears at a temperature lower than that associated with the first chemical or physical transformation on either component. The opposite finding would instead represent a significant indicator of the effective interaction between active components and excipients [15].

This seems to be the classical case in which the observed deviation from the principle that the thermal properties of a mixture are a simple summation of each single pure component, depends on the dissolution effects of a component in an earlier melt [16]. This situation occurs for instance in the drug containing SA, which melts and then vaporizes.

On the other hand, although the DSC results give an early indication of potential chemical–physical interaction problems between the drugs and the excipients, the occurrence of a physico-chemical interaction under the DSC test conditions cannot be interpreted as a definite incompatibility in the formulated products studied as the DSC technique necessarily requires elevated temperatures that might induce chemical or physical features that do not occur at normal storage temperatures [14].

Table 3
Kinetic constant values at different temperatures obtained from isothermal TG curves according to the procedure listed in Scheme 2

Compounds	Methods	k (s^{-1}) $\times 10^{-4}$									
		483 K	493 K	503 K	513 K	523 K	533 K	543 K	553 K	563 K	573 K
Na_2–F	I[a]	–	–	–	–	5.72	10.08	17.06	28.96	–	–
	II[b]	–	–	–	–	6.86	12.26	26.43	34.77	–	–
Na_2–F/SA	I[a]	5.29	8.05	12.04	17.91	25.74	–	–	–	–	–
	II[b]	6.28	9.07	18.70	21.45	39.33	–	–	–	–	–
Ca–F	I[a]	–	–	–	–	–	3.52	4.43	5.35	6.64	8.14
	II[b]	–	–	–	–	–	4.52	6.38	9.07	13.45	17.90
Ca–F/PEG/SDSS	I[a]	–	–	–	–	4.53	5.53	17.06	7.57	9.16	–
	II[b]	–	–	–	–	6.90	5.74	13.16	15.65	39.61	–

[a] From the slope of a linear regression analysis applied to Eq. (3).
[b] From the intercept of a linear regression analysis applied to Eq. (4).

With regard to the mathematical approach of the kinetic methods used in this study, as already observed in Table 3, both methods using Eqs. (3) and (4) have comparable kinetic constants. This is to be expected as Eq. (3) is known to give reliable kinetic constant values for all possible reaction orders, while Eq. (4) mainly gives reliable kinetic constant values for a first-reaction order process. This was actually found in the case of the decomposition process examined by means of a kinetic elaboration of all three applied methods.

Agreement between the activation energy values calculated by the two isothermal methods and the single non-isothermal method confirms that the methods used to study the decomposition process were chosen wisely and that the agreement between the results obtained with the two different kinetic approaches confirms the reliability of the kinetic data obtained.

As regards the shelf- and half-life values obtained (Table 6 and Fig. 5 respectively) the use of kinetic constant values obtained from isothermal rather than non-isothermal methods (usually employed in literature [17]) is justified by the negligible change in the activation energy values with the fraction of compound decomposed α (Fig. 4).

Finally, it is interesting to observe that the half-life values of both the pure solid-state antibiotic salts and of those of pharmaceutical form containing excipients, at lower temperatures, display negligible variations from each other in the case of Ca–F and Ca–F/PEG/SDSS, while there is a marked difference between those of Na_2–F and Na_2–F/SA (Fig. 5). These results are due to the very fast decomposition reaction rate of the first two (i.e. lower activation energies about 50 and 35 kJ mol^{-1}, respectively) while the last two show appreciably higher activation energies (about 135 and 80 kJ mol^{-1}, respectively), which correspond to a slow decomposition rate process; of course, a marked difference between the activation energies of the last two is also evident (Table 4).

Lastly, from the observation of the storage time data (at a given low fraction of compound decom-

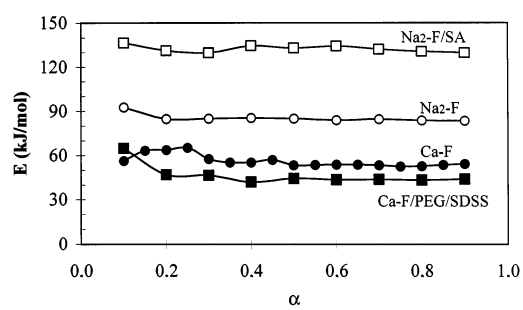


Fig. 4. Activation energy values as a function of fraction of compound decomposed α for the compounds tested obtained using the Eq. (7).

Table 4
Kinetic parameters according to Eq. (5)[a]

Compounds	Non-isothermal method			Isothermal methods					
	T_{onset}[b] (K)	E_a (Kj mol^{-1})	ln A (s^{-1})	Data obtained using k values from Eq. (3)			Data obtained using k values from Eq. (4)		
				E_a (kJ mol^{-1})	ln A (s^{-1})	r^2	E_a (kJ mol^{-1})	ln A (s^{-1})	r^2
Na_2–F	546.1	127.4	29.9	129.7	22.4	0.9999	135.9	24.0	0.9751
Na_2–F/SA	480.6	84.9	21.8	83.3	13.2	1.0000	95.2	16.3	0.9985
Ca–F	535.6	54.9	12.6	52.9	4.0	0.9993	89.0	12.3	0.9985
Ca–F/PEG/SDSS	500.5	42.5	10.3	36.1	1.3	0.9965	78.2	11.8	0.8558

[a] Comparison between values obtained using a non-isothermal procedure [12] or two isothermal methods.
[b] Extrapolated from TG measurements.

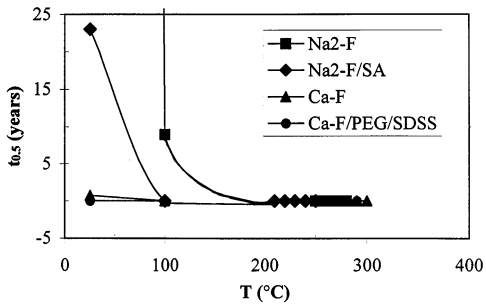


Fig. 5. Half-life values as a function of temperature for the compounds tested according to Eqs. (3) and (5).

Table 6
Storage time values at 25°C for a conversion of 1, 2, 3 or 4% (1 yr $\approx 8.8 \times 10^3$ h)

Compounds	Storage time values			
	$t_{1\%}$ (h)	$t_{2\%}$ (h)	$t_{3\%}$ (h)	$t_{4\%}$ (h)
Na_2–F	2.9×10^7	5.8×10^7	8.7×10^7	1.2×10^8
Na_2–F/SA	2.0×10^3	4.0×10^3	6.0×10^3	8.0×10^3
Ca–F	9.5×10^1	1.9×10^2	2.9×10^2	3.9×10^2
Ca–F/PEG/SDSS	1.6	3.2	4.8	6.5

posed α) reported in Table 6, it is evident that the presence of the excipients contained in the pharmaceutical forms always modifies [17] these values with respect to those of the pure active components. This relationship is more evident in the case of Na_2–F and Na_2–F/SA.

Conversely, perusal of literature reports of similar investigations reveals a paucity of quantitative data from studies on pharmaceutical systems. Most of the reports are semi-quantitative at best [18].

This can largely be accounted for by the fact that the major problems are rarely due to the spontaneous decomposition of the drug but almost invariably involve an external agent, in particular oxygen and/or moisture. These agents are difficult to control within a DSC run using commercially available instruments in their common configuration [18].

For all the above reasons the data reported in Table 6 should be taken in consideration only for

Table 5
Prediction of the storage time/storage temperature for the conversion percentage 1, 2, 3 or 4%[a]

Compounds	Time (h)	Storage temperatures			
		$T_{1\%}$ (°C)	$T_{2\%}$ (°C)	$T_{3\%}$ (°C)	$T_{4\%}$ (°C)
Acetylsalicylic acid	10 000	15.3	25.3	33.1	38.7
	20 000	10.6	20.7	28.7	34.3
	30 000	8.0	18.1	26.1	31.8
Na_2–F	10 000	157.6	166.1	171.3	175.0
	20 000	149.6	157.7	162.6	166.2
	30 000	145.0	152.9	157.8	161.3
Na_2–F/SA	10 000	97.8	107.6	113.6	118.1
	20 000	88.5	97.8	103.6	107.8
	30 000	83.3	92.3	97.9	102.0
Ca–F	10 000	84.1	98.7	107.8	114.6
	20 000	70.7	84.2	92.6	98.9
	30 000	63.3	76.2	84.3	90.3
Ca–F/PEG/SDSS	10 000	14.2	28.1	36.9	43.6
	20 000	1.6	14.3	22.3	28.3
	30 000	−5.3	6.8	14.4	20.1

[a] Comparison between data taken from literature for acetylsalicylic acid [17] with those of the disodium and calcium phosphomycin pure salts or in association with the excipients.

an evaluation of the effects on the stability of a pharmaceutical form due to the presence of an excipient and not for a quantitative prediction of storage times for the considered drug.

6. Conclusion

This study confirms that thermoanalytical methods can be an efficient tool for estimating the thermal stability of commercial pharmaceutical compounds and for evaluating how each excipient can influence the thermal stability of pure compounds.

Moreover, since the necessary experiments take only a few hours, thermal analysis combined with the kinetic approach can be used, although only in the first instance, for a quick estimation of the shelf-life of a solid-state pharmaceutical product. This approach cannot, of course, completely replace the more traditional long-term tests.

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