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Compatibility between active components of a commercial drug

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Abstract

A thermal and a kinetic analysis on the decomposition processes of a commercial drug named diamplicil (AD), obtained by an antibiotic combination of ampicillin (A) and dicloxacillin (D), have been carried out to find their thermal stability. The DSC/TG curves of this commercial drug were compared with those of its active components and an excipient, the magnesium stearate (M). Kinetic study was carried out using both isothermal and dynamic TG curves. Decomposition mechanisms for both active components and commercial drug tested were not found. The kinetic data obtained by the non-isothermal isoconversional method showed that D component causes a decrease of the kinetic stability of the active A component. Additive magnesium stearate does not decrease the stability of the two components. Moreover, storage time values at room temperature were calculated.

Keywords: Active component; Commercial drug; TG/DSC; Kinetic analysis

1. Introduction

Thermal analysis is a routine method for the analysis of drugs and substances of pharmacological interest [1–4]. During the manufacture of commercial drug the active component is mixed with other compounds (the excipients). The last ones sometimes cause variation in the physico-chemical properties of the active component.

The stability of a formulation depends, among others factors, on the compatibility of the active components with the other ingredients. Unless incompatibility is evident (e.g. the formation of an eutectic melting below room temperature) it is necessary to carry out a thermal stability study that usually requires weeks or months.

Thermal analysis has been utilized as a tool for the rapid evaluation of interactions among the active component and the excipients in preformulation stability studies.

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

Indeed this technique (carried out both on pure active components and on some solid mixtures of active component/excipient and active component/component) allows to visualise the interactions among them and to individuate the excipients that are thermally incompatible with the active component.

Kinetics analysis allows to determine the knowledge of the decomposition rate, the suitable mechanism, the activation energy values of pharmacological compounds, thus getting a deeper insight into thermal behaviour.

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

This work aims to study thermodynamic and kinetic properties of the decomposition processes of a drug having a mixture of penicillin salts as active components with and without magnesium stearate as excipient.

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Ampicillin and dicloxacillin are important drugs and are widely used for therapeutic purposes.

Ampicillin is a β-lactam antibiotic [5] widely used for various microbial infections. Dicloxacillin was used for outpatients with acute mild-to-moderate skin and soft-tissue infections.

Ampicillin–dicloxacillin mixture (diamplicil) exhibits synergetic effects on Shigella, Klebisiella and Proteus. The combination of these two components supplies an antibacterial activity significantly higher than that of separated ones against *Staphylococcus aureus*, *Streptococcus faecalis*, *Klebisiella species*, *Aerobacter species* and *Proteus species*.

Magnesium stearate is widely used as powder lubricant in pharmaceutical tablet and capsule formulations, because of its stability in decreasing friction between the surface of tablets and the die wall during the ejection process.

The TG/DSC curves of commercial drug were compared with those of the pure components and the additive M, so that the interactions among them have been studied.

Kinetic study attempts to individuate the decomposition mechanisms for the commercial drugs studied, stressing the reciprocal influence of the active components, of the excipient on them and the consequent variation of the activation energy values.

2. Experimental

The Istituto Biochimico Italiano supplied Ampicillin while Farmitalia supplied dicloxacillin (Table 1). The 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 In, Ga, Pb, Sn, Zn, napthalene 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 the decomposition studies under dynamic and static conditions, samples of 5–6 mg were weighed in aluminium pans placed in an Ar-filled dry box. The TG/DSC equipment was flushed with air or Ar 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 always was 5 K min^{-1} (in non-isothermal experiments) 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.

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

The quantities used to characterise the compounds submitted to non-isothermal measurements were the percentage weight 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, which could provide valuable information for the analytical study of organic compounds. T_p is the temperature at which the process theoretically occurs at 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 [6] 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 [7,8].

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

Name (symbol)	Empirical formula	Molecular weight
Ampicillin (A)	$C_{16}H_{18}N_3NaNO_4S$	371.39
Dicloxacillin (D)	$C_{19}H_{17}C_{l2}N_3NaO_5S$	492.31
Magnesium stearate (M)	$C_{36}H_{70}MgO_4$	590.06

3. Kinetic procedure

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

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

where t is the time, T is the temperature, α 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

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

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

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

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

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

If a process involves several steps with different activation energies, the relative contributions of these steps to the overall reaction rate will vary with both temperature and extent of conversion. This means that the effective activation energy, determined from the analysis of the results, will also be a function of these two variables. Following the model-fitting methods, the $k(T)$ term is determined by the form of the chosen $f(\alpha)$ function. In isothermal kinetics, these terms are separated by the conditions of the experiment ($k(T)$ is constant at constant temperature). The determination of the $f(\alpha)$ is achieved by fitting various reaction models to experimental data. After the $f(\alpha)$ term has been established for a series of temperatures, $k(T)$ can be evaluated. Single non-isothermal experiment provides information on both $k(T)$ and $f(\alpha)$ but not in separate form. For this reason, almost any $f(\alpha)$ can satisfactorily fit data by virtue of drastic variations in the Arrhenius parameters that compensate for the difference between the assumed form of $f(\alpha)$ and the true but unknown kinetic model.

Also for a simple step of decomposition process 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.

However, the application of fitting models to isothermal parameters gives rise to more reliable values of the Arrhenius parameters that, nevertheless, are likely to conceal the kinetic complexity. Indeed 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 process by one set of kinetic parameters.

For this reason the complex nature of a multi-step process can be more easily detected when a broader temperature range in the non-isothermal method is used.

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 E_a on α allows detecting multi-step processes and predicting 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.

3.1. Isothermal methods

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

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

$$g(\alpha) = kt \quad (4)$$

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: (D1, D2, D3, D4), (R2, R3, F1) and (A2, A3, A4) describe, respectively, diffusion, chemical reaction and nucleation mechanisms.

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

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

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 conversion 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 the 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 $t/t_{0.5}$ ($t_{0.5}$ is the experimental time corresponding to $\alpha = 0.5$), have subsequently been constructed.

The $\alpha = f(t/t_{0.5})$ curves were compared with the theoretical ones reported in literature [9,10] 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 $g(\alpha)$ against time (least-square method). These values were subsequently inserted in the Arrhenius equation together with the corresponding temperature values T

$$\ln k = \ln A - E_a/RT \quad (6)$$

supplying activation energy and pre-exponential factor values from the slope and intercept of 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 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 $k = A \times \exp(-E_a/RT)$ in Eq. (4) one obtains

$$g(\alpha) = A \times \exp(-E_a/RT) \times t \quad (7)$$

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):

$$\ln g(a) = \ln A - E_a/RT + \ln t \quad (8)$$

and rearranging it, one obtains

$$\ln t = -\ln A + \ln g(\alpha) + E_a/RT \quad (9)$$

By plotting $\ln t$ versus $1/T$ 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.

3.2. Non-isothermal methods

To avoid this fact non-isothermal model fitting at various heating rates can be applied.

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 [11–14] have carried out a computer program that plots theoretical $d\alpha/dT$ curve by using the Eq. (3) when the hypothesised mechanism $f(\alpha)$ and the suitable values of both A and E are introduced.

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

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

The comparison of these characteristic quantities (half width, α_{max}, T_i, and T_f) for experimental curves with those reported in literature [11–14] 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, the following method can be used.

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

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

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

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

where Doyle's approximation is valid in a temperature range of 100 K [15].

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

$$\ln[(\beta \times d\alpha/dT)/f(\alpha)] \text{ versus } 1/T \quad (12)$$

$$\log[g(\alpha)] \text{ versus } 1/T \quad (13)$$

From the coefficient and the intercept of the regressions straight lines, the E and A parameters can be calculated.

Finally the values of A, E 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.

The values of kinetic triplets obtained in this way can be used in non-isothermal model fitting-method Eq. (10).

To obtain the E values related to the isoconversional non-isothermal method Ozawa–Flynn–Wall equation

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

was applied to non-isothermal TG curves.

Finally some importance was given to the parameters determining the stability times at given fraction α and at room temperature of the compounds decomposed were obtained by expression

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

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

If the kinetic triplet ($g(\alpha)$, A and E_a, obtained from the isothermal model-fitting method) fails in the description of kinetic complexity, the values of these quantities extrapolated to room temperature are not acceptable.

4. Results and discussion

4.1. Features of the thermal processes

Trends of thermal behaviour for the examined compounds are shown in Fig. 1. The values of the thermodynamic quantities related to the TG/DSC curves are reported in Tables 2 and 3. 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 AD shows three steps of weight loss (Fig. 1a, curve 3 and Table 2) to which it corresponds one endothermic and three exothermic processes (Fig. 1b, curve 3 and Table 3). The first decomposition process (8.3%) for this compound (Table 2) could be related to the loss of crystallisation water. The exothermic weight losses could be related to a formation of a stable compound or to an oxidative decomposition process.

Table 2
Onset temperatures (T_c) and mass loss percentage obtained from dynamic TG measurements ($\beta = 5$ K min^{-1}) for the decomposition of the antibiotics and the excipient studied

Samples	Dehydration step		Decomposition step	
	T_c (K)	Mass loss (%)	T_c (K)	Mass loss (%)
A	294.2	2.3	502.0	38.2
			572.8	16.3
D	402.5	5.2	487.9	38.6
			648.8	18.3
AD	301.1	8.7	481.7	33.7
			650.3	42.2
M	299.5	2.4	507.7	10.4
			608.9	79.3
ADM	411.6	1.5	517.1	33.1
			653.2	17.7
			789.6	21.3

The ADM shows four decomposition processes (Fig. 1a, curve 4, Table 2) with endothermic and exothermic processes (Fig. 1b, curve 4 and Table 3).

To explain thermal behaviour of these compounds the TG/DSC curves of active components A and D and of the excipient M were carried out.

For ampicillin there are two decomposition steps (Fig. 1a, curve 1) with three exothermic processes (Fig. 1b, curve 1) while a dehydration process occurs at low temperatures (Tables 2 and 3).

Dicloxacillin shows (Table 2, Fig. 1a and curve 2) a dehydration process and two steps of decomposition with endothermic and an exothermic processes in the first and sharp exothermic in the second one (Fig. 1b and Table 3)

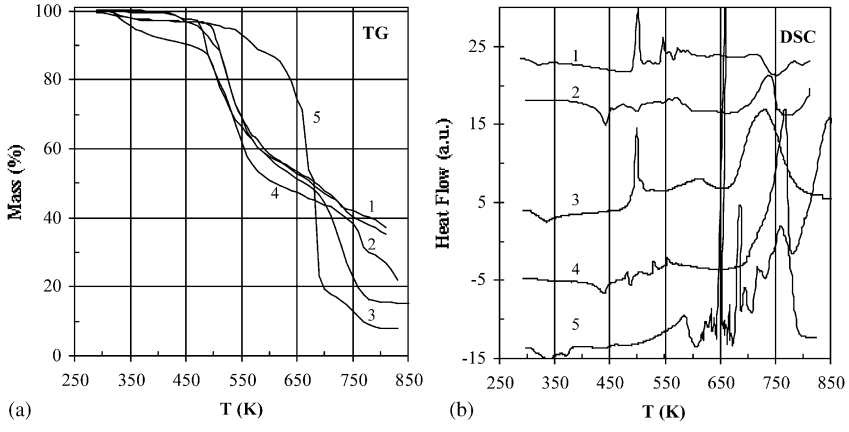

Fig. 1. TG and DSC curves of compounds A (1), D (2), AD (3), ADM (4) and M (5) carried out in air at 5 K min^{-1}.

Table 3
Onset (T_c), peak temperatures (T_p) and enthalpy change values obtained from dynamic DSC measurements ($\beta = 5$ K min^{-1}) for the decomposition of the antibiotics and the excipient studied

Samples	Dehydration step			Decomposition step		
	T_c (K)	T_p (K)	ΔH (J g^{-1})	T_c (K)	T_p (K)	ΔH (J g^{-1})
A	312.0	327.1	21.4	492.0	502.0	−72.4
				537.1	547.1	−43.8
				570.7	572.6	−29.5
				707.2	717.2	−35.1
				772.2	787.0	−23.8
D	419.1	438.7	65.1	479.8	494.6	−17.3
				531.7	558.7	−33.8
					562.5	
				685.8	734.1	−214.1
AD	320.5	334.6	51.9	487.9	500.0	−69.7
				581.0	619.0	−55.2
				694.0	735.8	−1342.7
M	318.2	346.2	79.0	541.2	588.5	−205.9
		376.7		612.6	633.0	−75.5
				639.8	660.8	−21.6
				676.4	684.4	−15.0
				709.3	763.5	−1405.3
ADM	411.8	440.0	54.3	476.5	481.1	−8.4
				482.7	486.3	11.7
				512.1	520.3	13.9
				527.1	528.2	−14.7
				552.5	553.5	9.6
				730.2	767.2	−1101.6
				801.2	849.0	−1380.5

DSC curve of A (Fig. 1b, curve 1) shows that both the first endothermic and exothermic processes of commercial AD drug (Fig. 1b, curve 3) belong to the active component A.

It was also noted that the peak temperature and the enthalpy values of the third exothermic process for this commercial drug (Fig. 1b, curve 3) and of the exothermic process of active component D (Fig. 1b, curve 2) are close. The processes contained in the 450–550 K range of commercial drug ADM (Fig. 1b, curve 4) can be related to the corresponding processes of A (Fig. 1b, curve 1). The exothermic process at 767.2 K is due to the magnesium stearate as it can be seen by its DSC curve (Fig. 1b, curve 5).

Moreover, the peak temperatures related to the dehydration processes for AD and A, as well as for the commercial drug ADM and D, were found to be close.

In the same processes different peak temperature and enthalpy values 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: DSC curve of AD shows a reciprocal obliteration of the exothermic and endothermic processes of A and D (Fig. 1b, curves 1 and 2) with the exception of exothermic processes at 500.0 and 735.8 K. It would be possible to predict the partial incompatibility between the two components.

For ADM exothermic processes of A and D are modified by the presence of stearate to which the peak at 763.5 K belongs. It was clear that M was an inactivating agent with respect the two components. Concluding, thermal analysis shows that there is a reciprocal influence of the two components on the stability but it is not able to show how this occurs. For this purpose, kinetic analysis is an effective tool.

4.2. Kinetics

The $\alpha = f(t)$ isothermal experimental curves of penicillin salts for the two steps of the decomposition processes, chosen at different temperatures (lying in the experimental temperature range), are given in Fig. 2a and b. The t values that in the curves at different temperatures are related to the same α values were divided by the corresponding $t_{0.5}$. This quantity depends on 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 by literature.

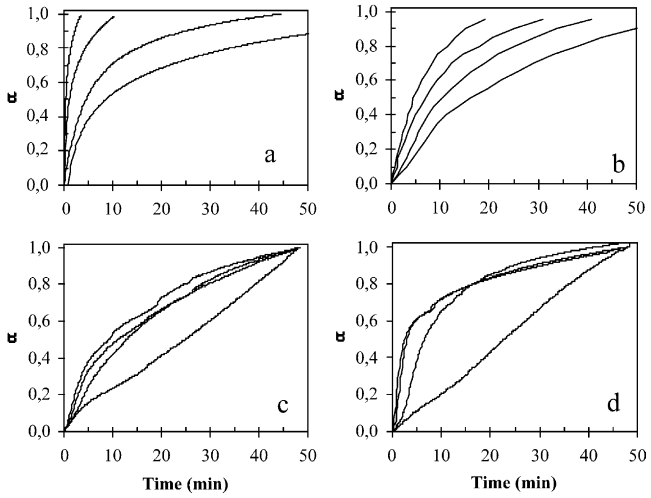

Fig. 2. Isothermal conversion plots for A (a) D (b) AD (c) and ADM (d) at different fixed temperatures.

Theoretical curves were constructed in the following way: by substituting $k = A\ \exp(-E/RT)$ in the expressions $d\alpha = kf(\alpha)\,dt$ one obtains $d\alpha = A\ \exp(-E/RT)f(\alpha)\,dt$ where the hypothesised mechanism $f(\alpha)$ and the suitable values of both A and E 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 first and second step of decomposition the experimental normalised curves at various temperatures (Fig. 3, curves a and b) for ampicillin and dicloxacillin do not completely overlap with the theoretical ones related to various mechanism. This result allows concluding that a superimposed series of reactions occurs.

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 $g(\alpha)$ against time (least-square method). These values were subsequently inserted in the Arrhenius equation together with the corresponding temperature values T supplying E_a activation energy and pre-exponential factor values from the slope and intercept of regression straight-line (Tables 4 and 5).

The values of activation energies of ampicillin, calculated with isothermal fitting model (Table 4) in the first step of decomposition for all the $g(\alpha)$, are constant (275.5 kJ mol^{-1}) while in the second one (Table 5) vary from 36.5 to 73.0. The activation energies for dicloxacillin, in the first (Table 4) and second (Table 5) steps of decomposition for all the $g(\alpha)$, are nearly constant (about 86 and 160 kJ mol^{-1}, respectively).

In the narrowed temperature range used under isothermal conditions, the differences between the different models are much less visible and, in the first decomposition step of ampicillin and in both the decomposition steps of dicloxacillin, lead to a statistically acceptable description (Tables 4 and 5) of the multi-step process by one set of kinetic parameters.

The Dollimore's computer program used in non-isothermal method cannot be applied to our experimental curves due to the complexity of decomposition process.

The change in E_a values in the isoconversional methods was obtained by using Eqs. (9) and (14).

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

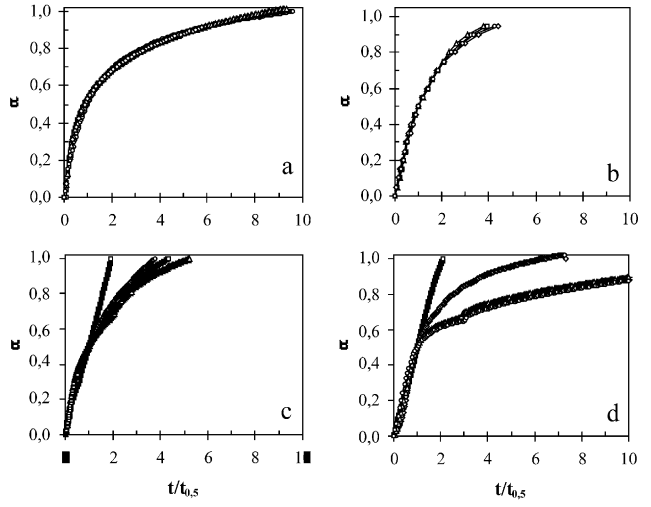

Fig. 3. Reduced time plots for A (a) D (b) AD (c) and ADM (d) at different fixed temperatures.

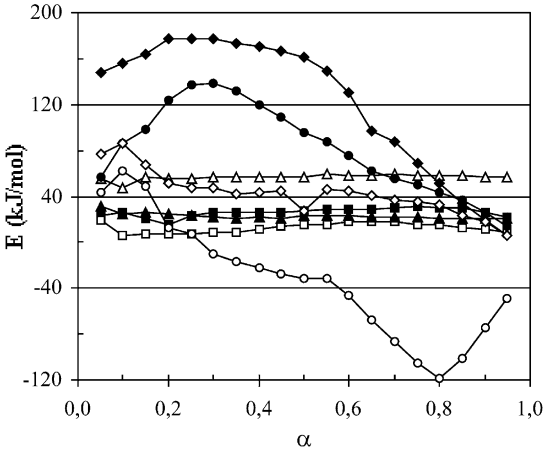

Fig. 4. E values as a function of α obtained by an isothermal isoconversional method for the first (black symbols) and the second (white symbols) decomposition steps: A (squares), D (triangles), AD (circles) and ADM (rhombi).

Table 4
Linear aggression [a] and Arrhenius parameters obtained by plotting ln t against reciprocal temperature according to the isothermal model-fitting method for the first decomposition step of each compound studied

Sample	Model	Regression parameters				Arrhenius parameters	
		a	b	r^2	F	E_a (kJ mol^{-1})	ln A (min^{-1})
A	D1	58	−33	0.9985	2585	275	58
	D2	58	−33	0.9984	2457	275	58
	D3	57	−33	0.9982	2235	275	57
	D4	57	−33	0.9983	2383	275	57
	F1	59	−33	0.9983	2300	275	59
	F2	58	−33	0.9984	2489	275	61
	F3	57	−33	0.9985	2602	303	70
	R2	59	−33	0.9983	2408	275	58
	R3	58	−33	0.9984	2427	276	57
D	D1	17	−10	0.9653	111	86	17
	D2	17	−10	0.9680	114	87	17
	D3	16	−11	0.9680	121	89	16
	D4	16	−10	0.9668	116	88	16
	F1	18	−10	0.9675	119	88	18
	F2	16	−10	0.9659	113	92	21
	F3	15	−10	0.9651	110	96	24
	R2	17	−10	0.9664	115	86	17
	R3	17	−10	0.9773	114	85	15
AD	D1	2	−3	0.6621	8	24	2
	D2	3	−3	0.6848	9	29	3
	D3	4	−4	0.7025	9	36	4
	D4	3	−4	0.6920	9	31	3
	F1	4	−3	0.6752	8	29	4
	F2	10	−5	0.7123	10	46	10
	F3	16	−7	0.7222	10	57	16
	R2	1	−2	0.6306	7	21	1
	R3	1	−2	0.5466	5	13	−2
ADM	D1	−3	−0.2	0.6621	8	1	−3
	D2	−2	−0.8	0.6848	9	6	−2
	D3	−1	−1.6	0.7025	9	13	−1
	D4	−3	−1.0	0.6920	9	9	−3
	F1	−1	−0.8	0.6752	8	7	−1
	F2	−5	−2.7	0.7123	10	22	5
	F3	−10	−3.8	0.7222	10	31	10
	R2	−4	0.1	0.6306	7	−1	−4
	R3	−7	1.0	0.5466	5	−9	−7

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

603 K) the activation energy, in the 0.1–1 range, varies from 5 to 18 kJ mol^{-1}.

In the non-isothermal isoconversional method (Fig. 5) the 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.

From these results it can be observed that the complex nature of a multistep process can be more easily detected when using a broader temperature range.

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 method experiments (498–523 K). For dicloxacillin, isoconversional isothermal method related to the first decomposition step shows that the activation energy (Fig. 4) is constant at about 20 kJ mol^{-1}, while in the second decomposition step the activation energy is constant about 60 kJ mol^{-1}.

For non-isothermal isoconversional method, in the range of α 0.1–0.2, the activation energy (Fig. 5) assumes values varying from 20 to 104.82 kJ mol^{-1}.

Subsequently, these values decrease from 104.82 to 70.20 in the range 0.2–0.95.

This behaviour allows to hypothesise that more than one reaction occurs in the decomposition process.

The experimental normalised curves at various temperatures for AD and ADM (Fig. 3, curves c and d), obtained by the corresponding isothermal experimental curves (Fig. 2, curves c and d), overlap with the

Table 5
Linear aggression [a] and Arrhenius parameters obtained by plotting ln t against reciprocal temperature according to the isothermal model-fitting method for the second decomposition step of each compound studied

Sample	Model	Regression parameters				Arrhenius parameters	
		a	b	r^2	F	E_a (kJ mol^{-1})	ln A (min^{-1})
A	D1	0	−5	0.9992	10^{-5}	38	0
	D2	0	−5	0.9993	10^{-5}	40	0
	D3	0	−5	0.9992	10^{-5}	42	0
	D4	−1	−5	0.9993	10^{-5}	41	−1
	F1	1	−5	0.9991	10^{-5}	41	1
	F2	8	−8	0.9993	10^{-5}	67	8
	F3	12	−9	0.9992	10^{-5}	73	12
	R2	0	−5	0.9993	10^{-5}	38	0
	R3	−2	−4	0.9992	10^{-5}	36	−2
D	D1	26	−20	0.9795	191	165	26
	D2	26	−20	0.9810	207	165	26
	D3	25	−20	0.9831	232	165	25
	D4	17	−15	0.9523	80	122	17
	F1	27	−20	0.9812	208	165	27
	F2	29	−20	0.9856	274	166	29
	F3	33	−21	0.9854	276	173	33
	R2	26	−20	0.9787	184	184	26
	R3	25	−20	0.9765	166	166	25
AD	D1	−16	7	0.8280	19	−59	−16
	D2	−17	7	0.8495	23	−61	−17
	D3	−19	8	0.8791	29	−65	−19
	D4	−19	7	0.8600	25	−62	−19
	F1	−16	8	0.8653	26	−64	−16
	F2	−17	9	0.9197	46	−74	−17
	F3	−16	10	0.9461	70	−83	−16
	R2	−17	7	0.8326	20	−60	−17
	R3	−17	7	0.8039	16	−57	−17
ADM	D1	−3	−0.2	0.0313	0.1	1	−3
	D2	−3	−0.2	0.0524	0.2	2	−3
	D3	−4	−0.3	0.0780	0.3	3	−4
	D4	−4	−0.3	0.0619	0.3	2	−4
	F1	−2	−0.3	0.0584	0.2	2	−2
	F2	0	−0.5	0.1050	0.5	4	0
	F3	4	−0.7	0.1238	0.6	5	4
	R2	−3	0.1	0.0268	0.1	1	−3
	R3	−5	0.0	0.0040	0.0	0	−5

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

theoretical ones related to various mechanisms only as far as $\alpha = 0.6$. This result allows concluding that a superimposed series of reactions occur and it is difficult to make use of these data for a good treatment for the isothermal fitting model.

Indeed, activation energy values of AD for the first step decomposition (Table 4) varied between 57.3 and 13.4 kJ mol^{-1} and for the second one negative unacceptable values were found (Table 5).

For ADM values the first and second steps show very small values (Tables 4 and 5).

As regards AD, for isoconversional isothermal method related to the first decomposition step, the activation energy (Fig. 4) results to be varying from 13 to 138 kJ mol^{-1}, while in the second decomposition step the activation energies show negative values.

The values obtained by the same method for ADM (Fig. 4) varied between 6.27 and 177.83 kJ mol^{-1} for the first step while for the second one value from 6.27 to 86.38 kJ mol^{-1} were found.

For the non-isothermal isoconversional method, AD shows (Fig. 5) activation energies almost constant (36 kJ mol^{-1}) in the range of degree conversion 0.15–0.35. In the range of α 0.4–0.8 the E values varied between 18.50 and 63.11 kJ mol^{-1}while in the range 0.85–0.95 the E values varied between 25.35 and 44.34 kJ mol^{-1}.

For the same method ADM shows constant E values of about 17 kJ mol^{-1} in 0.15–0.35 range of α while in the range 0.40–0.95 the E values varied between 13.5 and 41.0 kJ mol^{-1}.

As it can be observed the various methods supply different values for the same processes. The results

Table 6
Storage time values (years) at 25 °C for degree of conversion values of 0.05, 0.10 and 0.50 (half-life) obtained by the isothermal model-fitting method for some model functions

α	Storage times (years)								
	D1	D2	D3	D4	F1	F2	F3	R2	R3
A [a]									
0.05	7.54	4.35	2.06	3.41	51.71	9.17	164.92	100.04	7042.2
0.10	30.21	17.73	8.50	14.02	106.12	19.36	358.08	202.56	7207.2
0.50	754.30	525.40	305.61	440.77	698.21	174.23	4579.62	1156.52	8580.2
D									
0.05	0.005	0.004	0.003	0.003	0.050	0.417	0.045	0.068	3.623
0.10	0.020	0.015	0.010	0.013	0.103	0.440	0.050	0.137	3.711
0.50	0.511	0.448	0.372	0.424	0.680	0.792	0.162	0.785	4.418
AD [b]									
0.05	0.13	0.17	0.26	0.20	2.06	116.6	45.05	1.05	23.34
0.10	0.53	0.71	1.07	0.83	4.24	123.1	50.19	2.14	23.91
0.50	13.14	21.10	38.39	26.15	27.90	221.5	162.62	12.20	28.46
ADM [b]									
0.05	0.00	0.00	0.01	0.01	0.06	2.25	0.55	0.03	0.80
0.10	0.01	0.02	0.03	0.02	0.12	2.37	0.62	0.07	0.82
0.50	0.37	0.56	0.92	0.68	0.81	4.27	2.00	0.40	0.98

[a] Storage time values $\times 10^{-12}$.
[b] Storage time values $\times 10^{+6}$.

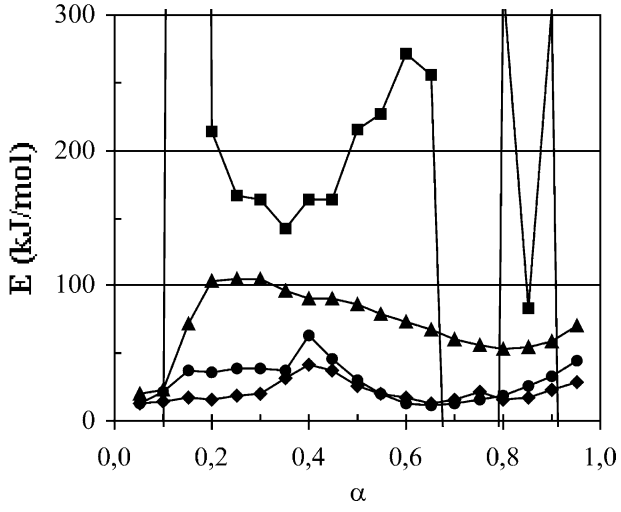

Fig. 5. *E* values as a function of α obtained by a non-isothermal isoconversional method for thermal decomposition processes of A (square), D (triangle), AD (circles) and ADM (rhombi).

obtained by means of the non-isothermal isoconversional method are chosen as more suitable.

By comparing the values obtained by non-isothermal isoconversional method for the pure compounds and the commercial drug it can be observed that the activation energies of AD are shifted towards lower values, because D component lowers the values of the energies of A, thus showing incompatibility between the two components.

The magnesium stearate does not influence, from a kinetic standpoint, the stability of the ADM drug. It can be noted that only the non-isothermal isoconversional method clearly shows that the interaction occurs mostly between the two components.

Finally, storage time values for the drugs examined were calculated by inserting the kinetic triplet values obtained by the isothermal fitting model in Eq. (15) (Table 6). The scattered values displayed by the compounds in the different mechanisms clearly indicate that the failure in the model-fitting method makes unsuitable the values extrapolated at room temperatures.

5. Conclusion

A kinetic and a thermodynamic study on the thermal stability of commercial drugs having ampicillin and dicloxacillin salts as active components and magnesium stearate as additive was carried out.

Thermal analysis shows that there is a reciprocal influence of the two components on the thermal stability of the drug, while kinetic analysis shows, mostly in the non-isothermal isoconversional method, how activation energies of the components interacts each other.

D component lowers the kinetic stability of A (active component), so that the drug having A and D as active components shows less kinetic stability with respect to both the pure A and D components. The excipient M does not influence the kinetic stability of ADM. This fact could be due to the complex interactions system

among the components A and D as it can be seen from the comparison of their TG/DSC curves.

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