Kinetic Study of Sodium Diclofenac under Isothermal Conditions

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The application of thermal methods is of great importance regarding the pharmaceutical problems such as the control of raw materials, the determination of purity, the qualitative and quantitative analysis of drug formulation, tests of thermal stability and compatibility, the determination of kinetic parameters etc. The purpose of a kinetic investigation is to calculate the kinetic parameters and kinetic model for the studied process. The results are further used to predict the system behaviour in various circumstances. A kinetic study regarding the sodium diclofenac thermal decomposition was performed under isothermal conditions in a nitrogen atmosphere, the temperature having the following values: 280, 285, 290, 295, 300°C. The TG/DTG data were processed by three methods: isothermal model-fitting, isothermal-isoconversional and Friedman's isothermal-isoconversional. The model-fitting defines a single reaction step, while the model–free approach represented by isothermal-isoconversional methods gave dependences of the activation energy, of the extent of conversion. The obtained results are in good accord with the similar data which resulted in non-isothermal conditions from a previous work. The careful treatment of the kinetic parameters obtained under different thermal conditions was confirmed as necessary, as well as a different strategy of experimental data processing.

Keywords: sodium diclofenac, thermal analysis, TG/DTG/DTA, kinetic study

Diclofenac sodium (DCFNa), which consists of a phenylacetate group, a secondary amino group and a dichlorophenyl ring (fig.1), is a well-known representative of non-steroidal anti-inflammatory drugs (NSAIDs) with strong anti-pyretic, analgesic and anti-inflammatory properties [1,2].

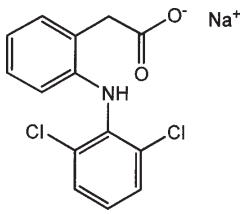

Fig. 1. The chemical structure of the sodium salt of {2-[2,6-(dichlorophenyl)amino]-phenyl}-acetic acid

The anti-pyretic effect is due to a resetting of the hypothalamic temperature-regulating centre, whereas the anti-inflammatory and analgesic effects are due to the inhibition of prostaglandin synthesis [3–5]. Therapeutically, NSAIDs are indicated to control pain and inflammation of rheumatic/ non-rheumatic origin.

The thermal analysis applied to the study of the products of pharmaceutical interest offers different information which can not be obtained by others methods. The main information refers to purity, storage conditions, shelf-life and half-life, and their compatibility in order to keep an adequate bioavailability. Some of this information is obtained by performing a kinetic study [6–11].

The aim of a kinetic investigation is to calculate the kinetic parameters and the kinetic model for the studied process. These results are obtained by isothermal and non-isothermal kinetic investigations, and it is accepted as axiomatic that the kinetic results of the two types of investigations are the same [12–15].

In our previous papers [16–23] we provided the importance and utility of the kinetic analysis in the characterisation of the thermal behaviour of different pharmaceuticals.

Thermogravimetry (TG) is widely used to determine kinetic parameters for pharmaceutical products' decomposition. TG is usually employed to assess thermal stability by determination of the temperature of initial mass loss, which can be viewed as the onset of decomposition. The mass loss steps observed in a TG curve can help to identify components in a sample. In some cases the percentages of the components cannot be determined directly from a TG curve because several decomposition processes occur simultaneously. Isothermal methods and controlled rate thermal analysis can help to separate partially overlapping [7, 24–31].

The methods proposed for the kinetic study of thermal decomposition are commonly classified in model-fitting and model-free methods. The kinetic analysis based on an isoconversional method is frequently referred to as "model-free" because it is possible to obtain the apparent activation energy (E) as a function of the conversion degree (α) which has specific interest when the thermal decomposition occurs in more than one step. By using an isoconversional method one does not obtain directly either the reaction model or pre-exponential factor, but the effective activation energy that tends to vary with the conversion degree [32–37].

The model-free isoconversional methods are considered as the most reliable ones, especially the Friedman method [35], because of its theoretical and experimental advantages. By these methods the overlapping reactions could be detected looking at the dependence of the activation energy on the conversion.

In a previous work [18], a kinetic study of decomposition of sodium diclofenac was realised under non-isothermal conditions.

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The aim of this work is to determine the kinetic parameters for the thermal decomposition of sodium diclofenac under isothermal conditions and to compare their values with those obtained under non-isothermal conditions.

Experimental part

The sodium diclofenac was available as pure compound, able to be used for medical purposes. It was obtained from Terapia S.A./Ranbaxy, Cluj-Napoca, Romania.

Thermal decomposition was carried out using a TGA/SDTA 851–LF 1100 Mettler apparatus. The samples with mass of about 10 mg were placed in alumina crucible of 70 μL. The experiments were conducted in nitrogen flow of 50 mL . min^{-1}. The temperature range of isothermal heating was between 280 and 300°C, with step of 5°C.

Results and discussions

Experimental data processing strategy

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

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 the temperature and the extent of conversion.

An alternative approach to kinetic analysis is to use 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 E as a function of the conversion degree. The knowledge of the dependence E on α allows detecting multi-step processes and predicting some mechanistic conclusions on the reaction kinetics over a wide temperature range.

The isoconversional methods could also yield similar dependencies of the activation energy on the extent of conversion for isothermal and non-isothermal experiments.

Kinetic analysis

The thermal curves of this substance obtained under non-isothermal conditions are presented in figure 2.

The TG/DTG shows that sodium diclofenac presents two significant mass loss steps. The first mass loss occurs in the temperature range of 42–88°C and corresponds to the loss of absorbed water. The second one takes place in the range 270–390°C and corresponds to the decomposition.

The thermal decomposition of the substance takes place by a single decomposition process, relatively complex and weightily to distinguish on the TG curve. The complexity of the decomposition process is confirmed by the shape of the adequate DTG peak.

The DTG curve is characterized by two endothermic peaks (the second one is complex), the minimum of each peak corresponds to the maximum degradation rate attained in each stage and are centered at temperatures (T_{max}) of 78.5 and 300°C. Both peaks are non-symmetrical. For the peak at lower temperature, the maximum is shifted to the right and while the maximum of the second peak moved to the left.

The second peak is accompanied by one respectively two very small peaks, in the left respectively right part.

There is a big superposition between them because the curves do not achieve the zero level in that interval (270 to 390°C), which indicates that the thermal decomposition occurs by a complex process with simultaneous and/or successive reactions.

The decomposition begins suddenly with the melting of sodium diclofenac. The DSC curve confirms the thermal behavior of the substance and presents three peaks. The first and the third one, of endothermic, respectively exothermic nature, characterize the two processes which take place. Practically, the first is superimposed with the adequate DTG peak and the third has the same shape with adequate DTG peak, but of different nature. The second peak, with T_{max}=280°C corresponds to the melting.

It is difficult to specify the nature of the degradation products because of a possible process of condensation between reacted and non-reacted molecules of the sodium salt, followed by their decomposition.

Mechanisms of the processes in condensed phase are very often unknown or too complicated to be characterized by a simple kinetic model. They tend to occur in multiple steps that have different rates. To describe their kinetics, the methods based on a single step approximation are often used and the kinetic equations of different methods are applied to the overall degradation reaction.

The decomposition of sodium diclofenac in melted state avoid any complication by reactions occurred in solid state. In this case, the kinetic model agrees with a homogenous decomposition of a pure condensed phase with additional transport.

According to mentioned temperature range, there were chosen the following temperatures: 280; 285; 290; 295 and 300°C for the experiments which were effectuated in isothermal conditions.

The kinetic parameters, the rate constant (k), reaction order (n), the activation energy (E) and the pre-experimental factor (A) were determined from TG curves, by using the following methods: isothermal model-fitting, isothermal-isoconversional and Friedman's isothermal-isoconversional.

Isothermal model-fitting method [32–34]

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

$$g(\alpha) = k \cdot t \quad (1)$$

where k is the specific constant rate and $g(\alpha)$ is an integral mathematical expression related to a mechanism of solid phase reactions. The choice of the kinetic equation which describes the reaction mechanism is done after the verification of several possible kinetic equations, taking into account that in isothermal conditions, where the rate constant is independent of the reaction time, the graphical representation of $g(\alpha)$ *vs.* time gives a straight line for the correct chosen form of $g(\alpha)$.

According to the squared correlation coefficient values r^2 (table 1), which was calculated for various possible kinetic functions, from plotting, it was revealed that the decomposition process is most likely a first order kinetic (r^2=0.994). The squared correlation coefficient was calculated according to the experimental values from figure 3.

For decomposition processes following first order reaction $g(\alpha)=-\ln(1-\alpha)$; for $n\neq1$ and the $g(\alpha)=-\ln(1-\alpha)^n$ reaction rate is described by:

$$d\alpha/dt = k(T)\cdot(1-\alpha)^n \quad (2)$$

where:

k(T)=the rate constant at temperature T;

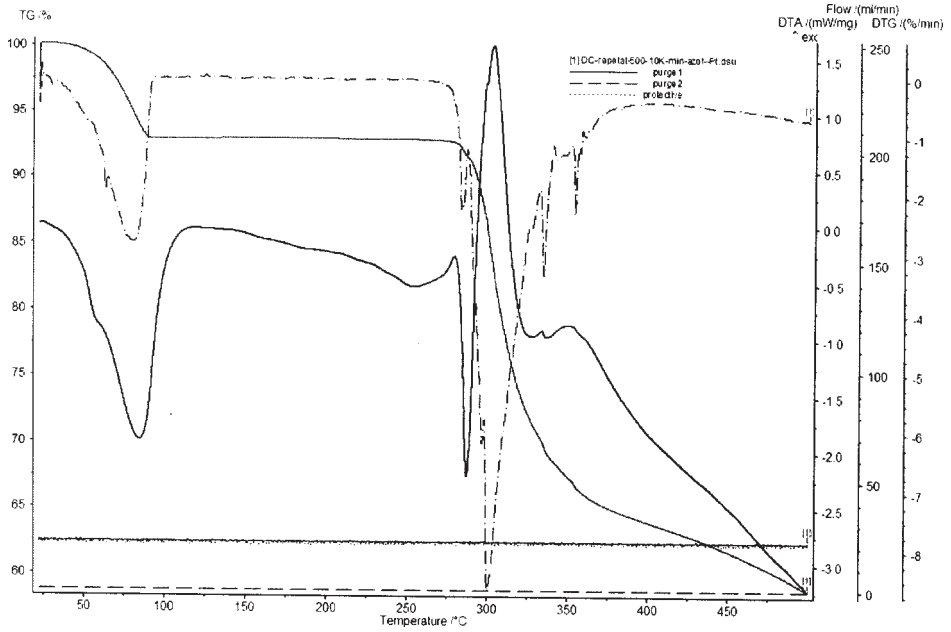

Fig.2. The thermoanalytical curves TG/DTG/DTA obtained at β=10°C·min^{-1} for sodium diclofenac

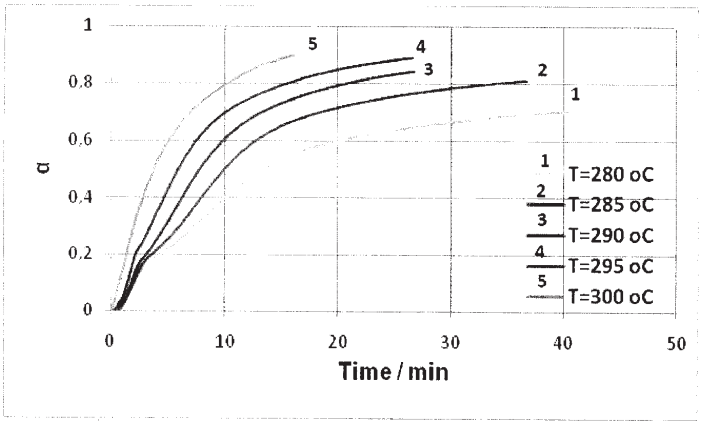

Fig.3. The evolution of conversion degree in time at different isothermal temperatures for diclofenac

Table 1
r^2 VALUES FOR DIFFERENT POSSIBLE KINETIC FUNCTIONS

Notation	The name of kinetic model	$g(\alpha) = k \cdot t$	$f(\alpha)=(1/k)(d\alpha/dt)$	r^2
F1	First order	$-\ln(1-\alpha)$	$(1-\alpha)$	0.994
A2	Avrami–Erofeev equations	$[-\ln(1-\alpha)]^{1/2}$	$2\cdot(1-\alpha)[-\ln(1-\alpha)]^{1/2}$	0.923
A3	(nucleation and growth)	$[-\ln(1-\alpha)]^{1/3}$	$3\cdot(1-\alpha)[-\ln(1-\alpha)]^{2/3}$	0.926
R2	Contracting envelope (2D)	$1-(1-\alpha)^{1/2}$	$2\cdot(1-\alpha)^{1/2}$	0.919
R3	Contracting envelope (3D)	$1-(1-\alpha)^{1/3}$	$3\cdot(1-\alpha)^{2/3}$	0.925
D1	Diffusion control (1D)	α^2	$\frac{1}{2}\alpha$	0.899
D2	Diffusion control (2D)	$(1-\alpha)\ln(1-\alpha)+\alpha$	$[-\ln(1-\alpha)]^{-1}$	0.912
D3	Diffusion control (3D)	$[1-(1-\alpha)1/3]^2$	$3/2\cdot(1-\alpha)^{2/3}\cdot[1-(1-\alpha)^{1/3}]$	0.923

n=the reaction order and $(1-\alpha)^n=f(\alpha)$ the differential conversion function. By linearization, it became:

$$\ln(d\alpha/dt) = \ln k(T) + n\cdot\ln(1-\alpha) \quad (3)$$

and by plotting $\ln(d\alpha/dt)$ *vs.* $\ln(1-\alpha)$ (fig.5), the values of ln*k* and n for each temperature can be obtained (table 2).

Considering the temperature dependence of k to be of Arrhenius type, by plotting ln*k(T) vs.* 1/T (fig.6), the activation energy E and the pre-exponential factor A will be obtained (table 2).

Based to the values presented in table 2, it wasn't observed a significant variation of the reaction order *vs.* temperature of reaction and, according to [38] this denotes the presence of a process which takes place in a single step.

The values of activation energy and pre–exponential factor are in agreement with those obtained under non-isothermal conditions: Coats–Redfern method (E=131.6±1.8, ln A=22.5±0.4), Madhusudanan method (E=130.8±1.6, ln A=22.4±0.4).

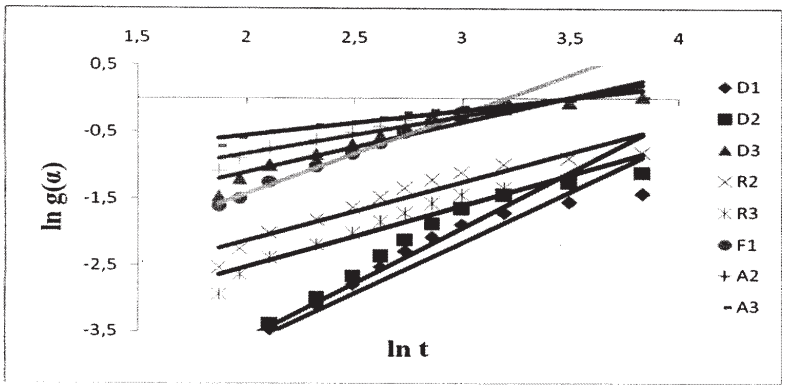

Fig.4. Graphical representation of the ln$g(\alpha)$ with ln$t$

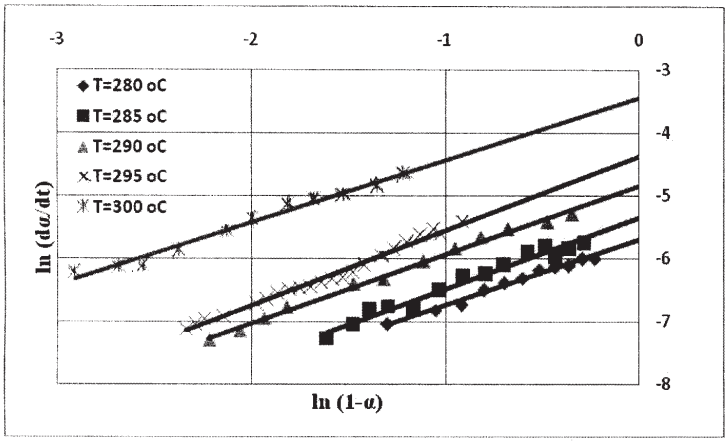

Fig.5. ln(dα/dt) *vs.* ln(1–α) plot to obtain the rate constant and reaction order values

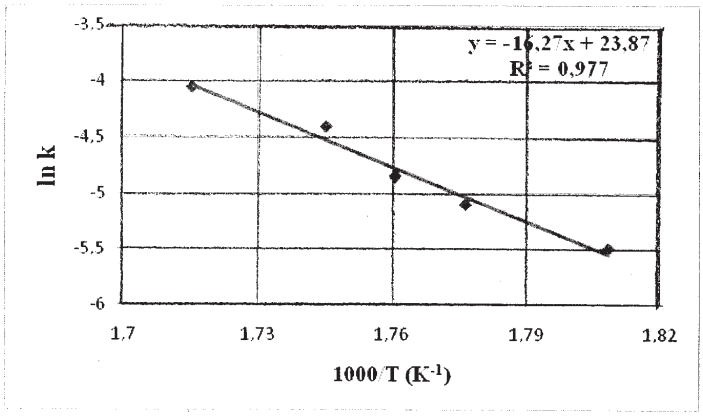

Fig. 6. ln k *vs.* 1/T plots drawn from isothermal experiments

SODIUM DICLOFENAC	Isothemal temperature				
	280°C	285°C	290°C	295°C	300°C
k / s^{-1}	$(4.1\pm0.3)\cdot10^{-3}$	$(6.1\pm0.5)\cdot10^{-3}$	$(7.8\pm0.3)\cdot10^{-3}$	$(12.3\pm0.5)\cdot10^{-3}$	$(17.4\pm0.4)\cdot10^{-3}$
n	1.03±0.04	1.12±0.05	1.09±0.02	1.11±0.04	0.99±0.02
E / kJ·mol^{-1}	135.3±3.4				
ln A	23.9±2.2				

Table 2
KINETIC PARAMETERS FOR SODIUM DICLOFENAC, ACCORDING TO THE EQUATION 3

Isothermal-isoconversional method [32–34]

An alternative procedure, the isothermal isoconversional method, 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 t values were obtained for fixed values of α. Substituting k=A·exp(–E/RT) in equation 1 one obtains:

$$g(\alpha) = A\cdot\exp(-E/RT)\cdot t \quad (4)$$

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 equation 4 it can be written:

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

and rearranging it, one obtains:

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

By plotting ln$t$ *vs.* 1/T according to equation 6 the activation energies were found at any given α value from the slope of a regression straight line (fig.7). The activation energy values are presented in table 3. The variation in a small range of E with α does not reveal a multistage process.

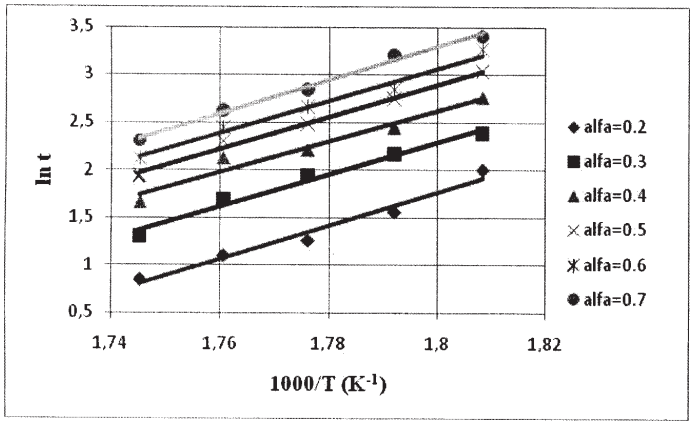

Fig.7. The graphical representation of ln *t vs.* 1/T

Table 3
ACTIVATION ENERGY'S VALUES OBTAINED BY FRIEDMAN ISOCONVERSIONAL ISOTHERMAL METHOD (FR) AND BY ISOCONVERSIONAL ISOTHERMAL METHOD (IIs) FOR SODIUM DICLOFENAC

		Conversion degree, α						
		0.2	0.3	0.4	0.5	0.6	0.7	Mean value
FR method	E_a (kJ/mol)	133.9±4.8	135.3±3.2	139.7±5.1	141.4±2.9	147.2±4.0	146.6±4.0	140.7±2.3
IIs method	E_a (kJ/mol)	138.3±2.1	139.1±3.9	133.8±3.1	138.9±4.3	140.7±5.2	145.8±3.9	139.4±1.6

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.

Friedman's isothermal-isoconversional method [35]

This method is based on the relation:

$$\ln(d\alpha/dt) = \ln[A \cdot f(\alpha)] - E/RT \qquad (7)$$

and for $f(\alpha)=(1-\alpha)^n$, at a constant conversion and with temperature dependence according to Arrhenius equation, the reaction rate is:

$$\ln(d\alpha/dt) = n \cdot \ln[A \cdot (1-\alpha)] - E/RT \qquad (8)$$

By plotting the left member *vs.* 1/T the activation energy should be obtained at different conversion degrees (table 3) and from the variation of E with α, it was show that the process take place in a single decomposition stage.

The activation energy values are in agreement between them, as well as with the values determined in non-isothermal conditions: Friedman (148.4 ± 1.9) and Flynn-Wall-Ozawa (152.4 ± 1.8).

As shown in table 3, the activation energy values fluctuate around the average values presented. A weak variation of E *vs.* α is observed, indicating a single decomposition process, relatively complex [38].

Conclusions

The thermal behaviour of sodium diclofenac – active substance was studied under isothermal conditions and a nitrogen atmosphere. According to the thermal curves, the thermal process of decomposition is one complex, with simultaneous and/or successive reactions.

The experimental data obtained from TG/DTG curves have been processed three methods characteristic of isothermal study, such as: the one of isothermal model fitting, isothermal–isoconversional and Friedman isothermal–isoconversional.

The choice of kinetic equation which describes the reaction mechanism was made after the checking of several equations and calculating the correlation coefficient. Based on its values, it was chosen the reaction model which characterizes a first order kinetic.

Values of the kinetic parameters obtained by the mentioned methods are in very good accord, but the variation of reaction order *vs.* temperature, respectively of the activation energy *vs.* conversion degree shows that the thermal decomposition takes place in a single step.

The kinetic parameter values determined in isothermal conditions are in good agreement with those determined in non-isothermal conditions obtained by applying the mentioned methods.

The activation energy values and the pre-exponential factor, as well as the range of decomposition indicate a relatively high thermal stability of sodium diclofenac. The correlation between the kinetic parameter values determined in different thermal conditions confirms the need to conduct such experiments that also require a different strategy for experimental data processing.

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