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THERMAL STABILITY OF IBUPROFEN. KINETIC STUDY UNDER NON-ISOTHERMAL CONDITIONS

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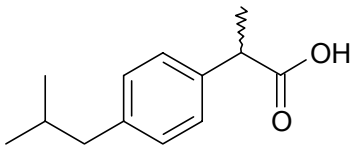
Simultaneous thermogravimetry (TG) and differential scanning calorimetry (DSC) techniques were used for the characterization of the thermal degradation of ibuprofen. TG analysis revealed that the thermal decomposition occurs in single step, in nitrogen atmosphere. DSC curves showed that ibuprofen met before the decomposition and the decomposition products are volatile in nitrogen.
The Chang, Freeman–Carroll (FC) and Friedman isoconversional (Fd) differential methods, respectively integral methods: Flynn–Wall–Ozawa (FWO) and Kissinger–Akahira–Sunose (KAS) were used for the solid–state kinetic analysis of ibuprofen thermal decomposition.

INTRODUCTION

Ibuprofen, (*RS*)–2–(4–(2–methyl–propyl)phenyl) propanoic acid, with the formula:



is a non-steroidal anti-inflammatory drug (NSAID) used for inflammatory and painful diseases of rheumatic and non-rheumatic origin.

The anti-inflammatory activity of NSAID's and most of its other pharmacological effects are related to the inhibition of the conversion of arachidonic acid to prostagladins, which are mediators of the inflammatory process.[1,2] Ibuprofen is a potent inhibitor cyclo-oxygenase (Cox) in vitro and in vivo, thereby decreasing the synthesis of prostaglandins, prostacyclin, and thromboxane products.

Thermal analysis is one of the most frequently used instrumental technique, especially in fields of growing importance, inclusively in the pharmaceutical field.[3,4]

The application of thermal methods, especially TG/DTG and DSC is of great importance in solving pharmaceutical problems such as the determination of purity, the qualitative and quantitative analysis of drug formulation, stability tests, compatibility, kinetic parameters determination etc.[5]

The thermal instability of drugs affects the therapeutic efficiency, toxicity, biodisponibility and the process of obtaining the tablets.[6] Thermal behaviour of the substances of pharmacological interest can also be characterized by the kinetic analysis. The kinetic parameters, the rate constant (k), the activation energy (E), the pre-exponential factor (A), and the reaction order (n), can provide the mechanism and the rate of the decomposition reaction, the storage conditions, especially life-time, half-life time, and shelf-life time etc.[7]

This study is necessary because in the older literature[8] the data were obtained by methods that using a single heating rate, so the value are far from the actual standards in the field and, there isn't an agreement with the ICTAC protocol 2000.[9]

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The kinetic analysis was performed on the process with mass loss of the thermal degradation. For the kinetic analysis a strategy based on different methods was used, all of them in agreement with the ICTAC protocol 2000.[9]

In our previous papers,[10–14] we provided the importance and utility of the kinetic analysis in estimations on the thermal behaviour of different pharmaceuticals.

The purpose of the present paper is to evaluate the thermal behaviour of ibuprofen, together-with the finding of the melting point through DSC, which is a criterion for the quality control. Also, the kinetic parameters of thermal decomposition and non-isothermal condition were determined, representing a criterion for the estimation of its thermal stability.

RESULTS AND DISCUSSION

a) Thermal Behaviour

The thermal curves of this active substance, obtained for the five heating rates under dynamic temperature conditions are presented in figures 1 and 2 (TG/DTG/DSC).

The main observations are summarized in Table 1.

From the thermal curves and thermoanalytical data (Table 1), it is observed that the ibupropen presents a thermal stability relatively reduced, and, at approximately 76–77ºC, this substance is melting.

The melting process is followed by decomposition and evaporation of breakdown products. The decomposition takes place in one step with a single well defined process. The loss of mass is complete.

The melting points obtained from the DSC curves are similar to the values mentioned in speciality literature: 75–78ºC.[15,16] These values together with the accuracy of the melting peaks indicate a high purity of ibuprofen. Melting and decomposition processes are accompanied by endothermic effects.

Based on the analysis of DSC, TG and DTG curves of the examined compound, recorded as a result of an heating rate increase, it was concluded that the heating rate has significant influence on the temperature range and the shape of thermoanalytical curves for the process of decomposition, but non-significant for the process of fusion.

The TG/DTG and DSC curves shifted to higher temperatures with increasing rates (Figs. 1–2).

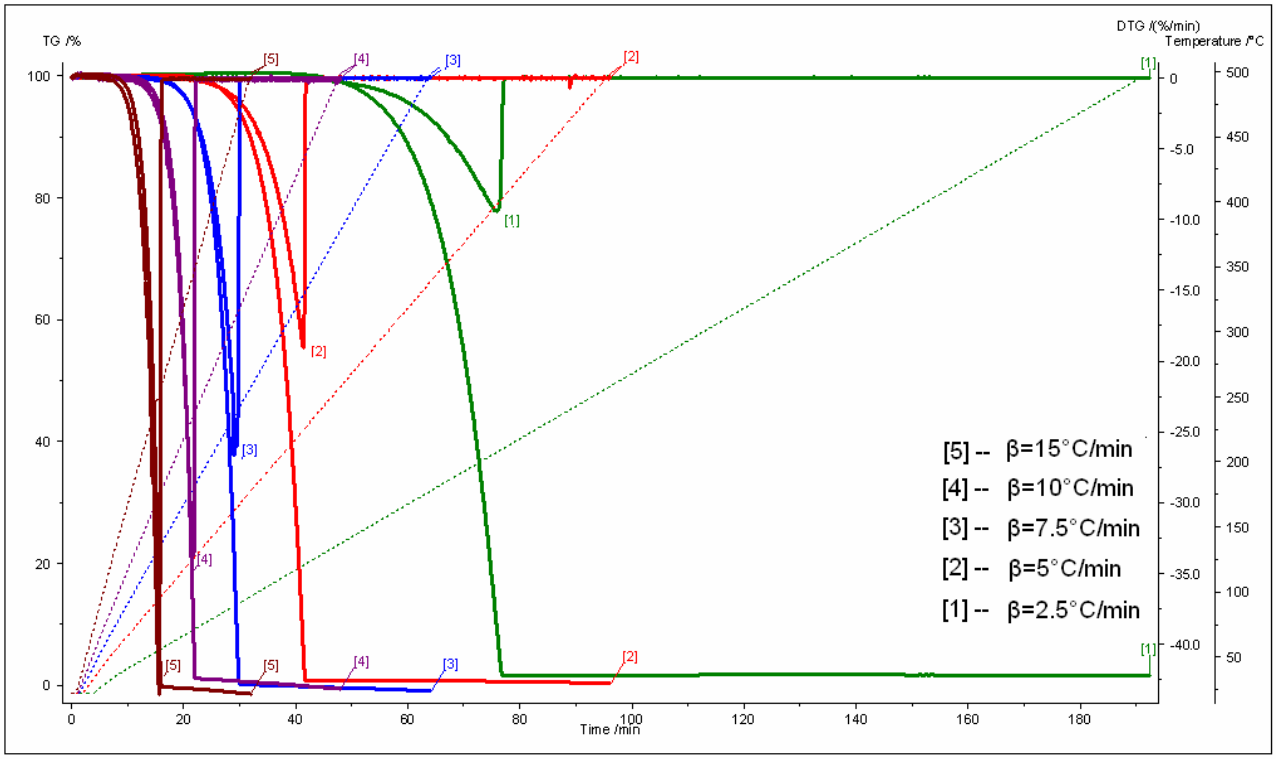

Fig. 1 – The TG/DTG curves of the ibuprofen in nitrogen at different heating rates.

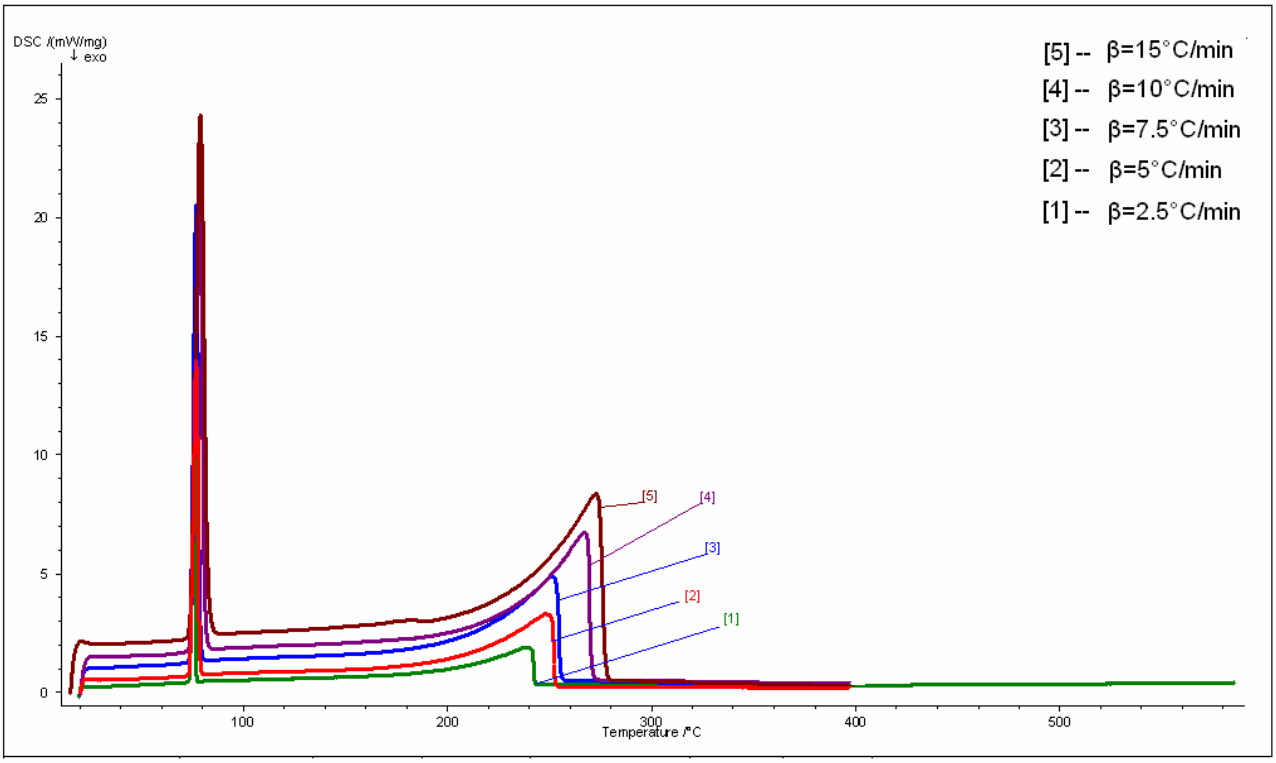

Fig. 2 – The DSC curves of the ibuprofen in nitrogen at different heating rates.

Table 1

Characteristics of the thermal behaviour of ibuprofen

β (°C/min)	T_i (°C)	T_f (°C)	$T_{max\ DTG}$ (°C)	m.p. (°C)	$T_{max\ DSC}$ (°C)	*Δm* (%)
2.5	127.1	213.0	207.6	75.1	238.9	98.4
5	153.8	228.0	224.9	76.1	248.4	99.3
7.5	156.0	237.0	234.7	76.2	251.8	99.9
10	158.0	245.7	243.3	77.7	267.3	99.1
15	160.1	262.1	252.4	78.3	273.3	98.6

b) Kinetic analysis

Also, the **thermal stability** of this substance was characterized by using the **kinetic parameters,** on the basis of the kinetic study performed under non−isothermal conditions, which sustained the present facts.

The kinetic parameters, the activation energy (E), the rate constant (k), the pre−exponential factor (A) and reaction order (n) were determined from the TG/DTG curves, by using the differential methods, Chang,[17] Freeman–Caroll (CR)[18] and Friedman isoconversional (Fd),[19] respectively integral methods, Kissinger–Akahira–Sunrose (KAS)[20] and Flynn–Wall–Ozawa (FWO).[21]

Chang method is a differential one which results directly from equation of reaction rate, from which, by logarithmation it is obtained the equation corresponding to this method:

$$\ln\frac{\beta\cdot\frac{d\alpha}{dT}}{f(\alpha)} = \ln A - \frac{E}{R\cdot T} \qquad (1)$$

For different *f(α),* it was plotting the curve $\ln\frac{\beta\cdot\frac{d\alpha}{dT}}{f(\alpha)} = f(\frac{1}{T})$, considering that the corresponding conversion function for the investigated process is that for which the graphic representation is a straight line (Table 2).

For the conversion function chosen through Chang method, the Freeman-Carroll[19] method was also applied which led to an average value of the reaction order, **n = 1.046 ± 0.008**, a value that is very close to that determined by Chang's method and that is in accordance with a first-order kinetic. The formula that underpins the Freeman-Carroll method is:

$$\frac{\Delta \ln \beta \cdot \frac{d\alpha}{dT}}{\Delta(\frac{1}{T})} = n \cdot \frac{\Delta \ln(1-\alpha)}{\Delta(\frac{1}{T})} - \frac{E}{R} \qquad (2)$$

The **isoconversional Friedman method** is based on the equation:

$$\ln \beta \cdot \frac{d\alpha}{dT} = \ln[A \cdot f(\alpha)] - \frac{E}{R \cdot T} \qquad (3)$$

For α=constant and using various heating rates (β), the plot $\ln(\beta \cdot d\alpha/dT)$ vs. $(1/T)$ is linear (Fig. 3). The values of the activation energy as obtained from the slopes of the straight lines are listed in Table 3.

Table 2

The verified functions of conversion, the values of regression coefficient and kinetic parameters

Function of conversion **f(α)**		Value of $\mathbf{r^2}$, **n** and **E** (kJ/mol)					
	β (°C·min^{-1})	2.5	5	7	10	15	$(\bar{x} \quad S_{\bar{x}})$
$A_n \quad n \ (1 \quad \alpha) \ [\ ln(1 \quad \alpha)]^{(n \ 1)/n}$ (Avrami–Erofeev equation)	$\mathbf{r^2}$	0.767	0.859	0.855	0.781	0.765	
	E	–33	–31	–31	–63	–39	
	ln A	1.09	1.12	1.09	1.29	1.01	
	n	1.82	1.40	1.16	1.71	1.21	
$F_n = (1-\alpha)^n$ (reaction order model)	$\mathbf{r^2}$	0.944	0.949	0.958	0.953	0.946	
	E	82.1	84.4	79.8	82.3	84.1	82.5±0.8
	ln A	20.99	20.81	21.10	21.23	20.98	21.02±0.07
	n	0.912	0.927	0.981	0.992	0.961	0.955±0.015
	k	1.557	1.524	8.976	7.823	5.624	
$D_4 \quad 3/2 \quad 1 \quad \alpha \quad ^{1/3} \quad 1$ (Ginstein–Brouhnstein equation)	$\mathbf{r^2}$	0.631	0.840	0.600	0.701	0.709	
	E	1.80	1.91	2.08	2.88	2.29	
	ln A	2003	1967	1921	1901	2013	
	n	–9.80	–9.41	–9.72	–9.31	–9.26	
$P_n \quad n \ \alpha^{(n \ 1)/n}$ (power law equation)	$\mathbf{r^2}$	0.996	0.992	0.999	0.991	0.991	
	E	–434	–332	–445	–390	–419	
	ln A	1.22	1.67	1.64	1.61	1.57	
	n	1.3	1.7	1.3	1.7	1.2	

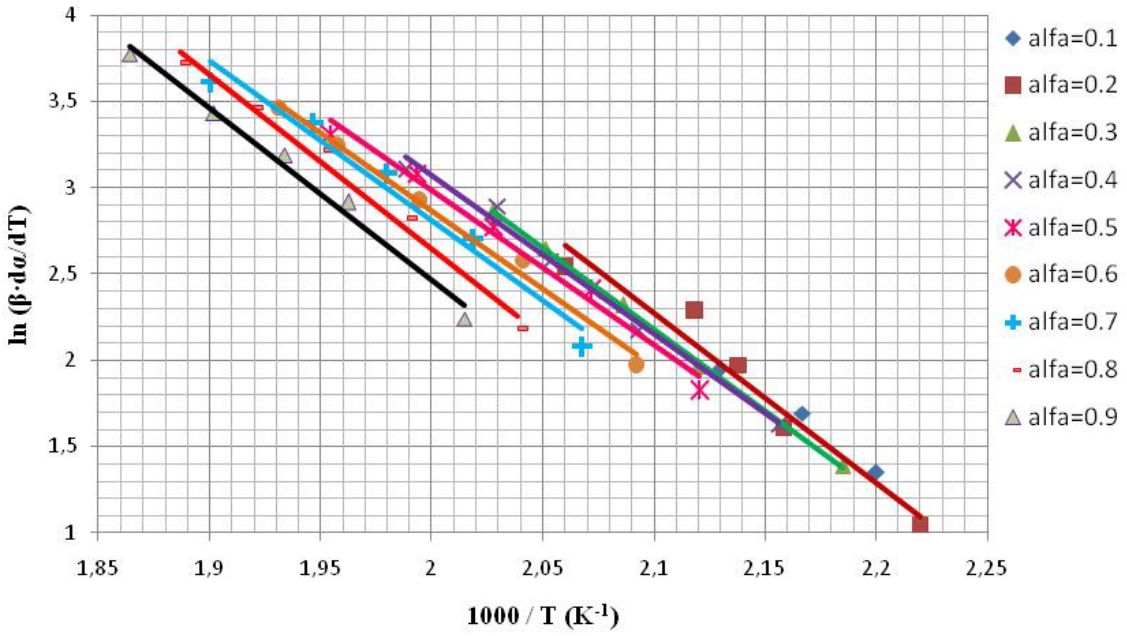

Fig. 3 – Friedman's plot for ibuprofen at different heating rates.

Flynn–Wall–Ozawa's isoconversional method is based on the measurement of the adequate temperature to certain values of the conversion α, for experiments effectuated to different rates of heating β. The equation corresponding to this method is:

$$\ln\beta = \ln\frac{A\cdot E}{R\cdot g(\alpha)} - 5.331 - 1.052\cdot\frac{E}{R\cdot T} \quad (4)$$

The plot *lnβ vs. (1/T)* is linear (Fig. 4) and from the slopes of the straight lines (–E/R), the values of the activation energy (E) were obtained (Table 3).

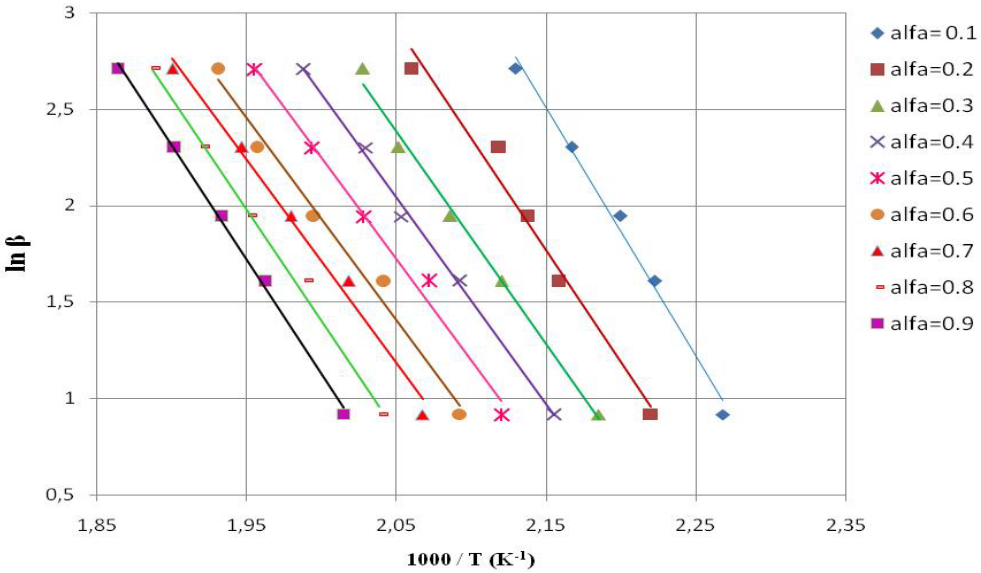

Fig. 4 – The Flynn–Wall–Ozawa isoconversional diagrams.

The **Kissinger–Akahira–Sunose method**, is one of the best isoconversional methods and it is based on the equation:

$$\ln\frac{\beta}{T^2} = \ln\frac{A\cdot R}{E\cdot g(\alpha)} - \frac{E}{R\cdot T} \quad (5)$$

From the slopes of the straight lines obtained by the representation graphic of the $\ln(\beta/T^2)$ *vs.* $(1/T)$ was determined the activation energy (Fig. 5).

According to the values from Table 3, it can observe that there is an insignificant change in the values of the activation energy with conversion degree in any of the three cases where the isoconversional methods have been applied. A smaller difference can be seen between the average values of *E*, values obtained by KAS and FWO method, than one obtained using the FR method. This can be explained by the fact that Friedman method is a differential isoconversional method which analyzes the process "point to point" and KAS and FWO methods are integral methods which analyse the process "overall".

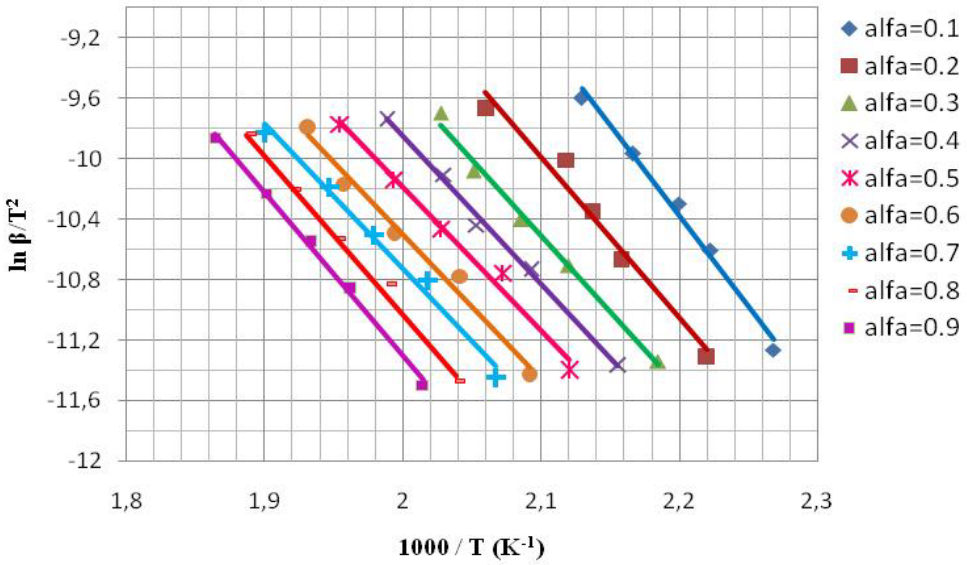

Fig. 5 – The Kissinger–Akahira–Sunose diagrams for ibuprofen at different conversion degrees.

Table 3

Values of the activation energy obtained by the Friedman, Flynn–Wall–Ozawa and Kissinger–Akahira–Sunose methods

Method	E, (kJ mol^{-1}), for conversion degree, α									
	0.1	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**Main value**
FR	82.9± 2.0	80.7± 1.9	80.2± 2.3	80.1± 2.0	79.7± 1.8	79.7± 1.3	83.3± 1.4	82.2± 2.4	81.2± 1.8	81.1± 0.5
FWO	97.3± 0.8	98.3± 0.4	96.8± 0.7	95.4± 2.1	95.4± 1.4	95.1± 2.2	95.2± 1.9	95.2± 1.0	95.9± 1.9	96.0± 0.4
KAS	90.1± 1.1	90.6± 0.9	89.0± 2.2	87.5± 1.2	87.4± 3.7	87.0± 1.9	87.1± 1.8	88.0± 0.9	87.9± 3.7	88.2± 0.5

As shown in Table 3, the values obtained by the three methods are in good agreement with the main value obtained with the Chang method and the weak variation of *E vs. α* indicates that ibuprofen decomposition occurs in a single step, so the process is unitary one.

EXPERIMENTAL

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

TG/DTG experiments were performed with a Netzch thermobalance, model TG–209, in the temperature range of 20–500^{o}C, under a dynamic atmosphere of nitrogen at a flow rate of 50 ml·min^{-1}. Samples with the mass in the range of 5 to 10 mg were put into aluminium crucibles, at a heating rate, β, of 2.5; 5; 7.5; 10 and 15°C·min^{-1}.

DSC curves were recorded with a Netzsch differential scanning calorimeter, model DSC–204, using aluminium crucibles with samples of 2 mg, in a dynamic nitrogen atmosphere, with a constant flow of 50 ml·min^{-1} and heating rates of 2.5; 5; 7.5; 10 and 15°C·min^{-1}, until 500°C.

CONCLUSIONS

There was performed a thermal study (thermal behaviour and kinetic determinations) under non-isothermal conditions for ibuprofen–active substance. The study suggests that the decomposition of ibuprofen occurred, after melting, in a single step in nitrogen atmosphere, in accordance with a first-order kinetic. The values of the kinetic parameters, determined with differential and integral methods, are in fair good agreement and indicate the correctness choice of the conversion function *f(α)*.

It can be concluded that the kinetic study on thermal decomposition can be used for the quality of product, together with the melting point which characterizes their purity.

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