

Thermal Behaviour of Indomethacin - Active Substance and Tablets

Kinetic Study Under Non-Isothermal Conditions

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Thermal analysis is one of the most widely used methods for studying the solid state of pharmaceutical substances. TG/DTG and DSC curves provide important information regarding the physical properties of the pharmaceutical compounds (stability, compatibility, polymorphism, kinetic analysis, phase transitions etc). The evaluation of thermal stability in the solid state is mostly made by analysing their decomposition under isothermal or non-isothermal conditions. The purpose of a kinetic investigation is to calculate the kinetic parameters and the kinetic model for the studied process. The results are further used to predict the system's behaviour in various circumstances. The present work reports the study of thermal behaviour of indomethacin active substance and tablets, together with a determination of the melting point, respectively the determination of the kinetic parameters under non-isothermal conditions. The kinetic parameters of the decomposition were obtained on TG and DSC curves using the following differential methods: Chang and Friedman isoconversional (Fd), respectively integral methods: Coats-Redfern (CR), Kissinger-Akahira-Sunose (KAS) and Flynn-Wall-Ozawa (FWO). The results obtained show that the indomethacin tablets are thermally more stable than the active substance. The increase in stability was attributed to the presence of excipients in formulation.

Keywords: thermal stability, indomethacin, kinetic study, TG/DTG, DSC, kinetic parameters

The thermal analysis is a generic term used to describe the analytical techniques which study the behaviour of a sample against temperature.

The use of thermal methods is of great importance in solving some pharmaceutical problems such as the determination of purity, the qualitative and quantitative control of drug formulations, the thermal stability and determination of kinetic parameters based on their thermal decomposition [1-3].

The thermal stability is a very important factor since the determination of the temperature range in which a certain medicine substance (drug) is stable regarding its structure as well as its pharmaceutical action is crucial for stocking drugs, for its technological transformations and for the obtaining technology of the right formulas.

Thermal behaviour of the substances of pharmacological interest can also be characterized by the kinetic analysis.

The kinetic studies have become a crucial point regarding the thermal analysis, where the main purpose is to determine the mechanism of decomposition reaction and to calculate the Arrhenius's equation's parameters. These data can provide precious information about the storage conditions, especially the life-time, half-life time and shelf-life time; this usually requires weeks or months [4-7].

The knowledge of such parameters for pure drugs and for their possible associations with other components (excipients) is also meaningful, in order to elucidate the miscibility/compatibility and its effects on thermal stability [1, 7-9].

A series of works, even recent ones, show encouraging results regarding the evaluation of the thermal behaviour of pharmaceuticals products by the kinetic data obtained in non-isothermal conditions [9-10].

Indomethacin is a non-steroidal anti-inflammatory drug with indolic structure. The publications about indomethacin

have studied the drug / excipients compatibility and its photostability [11-12].

Indomethacin's formula is presented in figure 1.

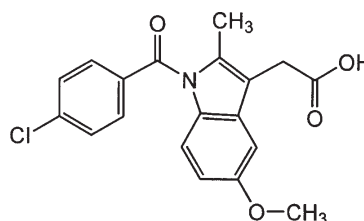


Fig.1. Chemical structure of the indomethacin:

2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]-acetic acid

The purpose of the present paper is to study the thermal decomposition of the indomethacin active substance and tablets, and to estimate its thermal stability in solid state, together with the finding of the melting point through DSC. Also, the kinetic parameters of thermal decomposition under non-isothermal conditions were determined, representing a criterion for the quality control of a product as well as for the estimation of its thermal stability.

Experimental part

The substances examined by thermal analysis were:

- indomethacin " active substance or drug (AS)
- indomethacin " tablets (M)

The active substance (drug) was available as pure compound, able to be used for medical purposes. It was obtained from Terapia S.A. / Ranbaxy, Cluj-Napoca, România as pure compounds. The pharmaceuticals (tablets) were commercial products, containing different excipients, like:

- polyvinylpyrrolidone (PVP), mostly used as a binder, particularly in wet processes;

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- magnesium stearate (MGST), $[\text{CH}_3(\text{CH}_2)_6\text{COO}]_2\text{Mg}$, working as a lubricant during compression;
- microcrystalline cellulose (Avicel) used as a diluent, suspension or viscous medium.

TG/DTG experiments were performed with a Perkin-Elmer Diamond thermobalance, in the temperature range of 25–500°C, under a dynamic atmosphere of nitrogen at a flow rate of 50 mL min⁻¹. Samples with the mass in the range of 2 to 12 mg were put into platinum crucibles, at a heating rate, β , of 5, 7, 10, 12 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 a heating rate of 10°C min⁻¹, up to a temperature of 600°C.

Results and discussions

Thermal behaviour

Some of the thermal curves of the two substances, obtained under dynamic temperature conditions are presented in figure 2-5.

Thermal decomposition of the indomethacin drug and tablets takes place in one stage and the difference between the temperature ranges corresponding to the decomposition of the two compounds is insignificant.

Thus, the indomethacin drug (AS) decomposes through a unitary process in a temperature range of 236–338°C, with $T_{\text{max}} = 314^\circ\text{C}$ (fig.2.), while in the case of the indomethacin tablets (M) there is a loss of mass between 47 and 137°C, after which the thermal decomposition process takes place between 279 and 359°C, with $T_{\text{max}} = 327^\circ\text{C}$. The small difference between the temperature intervals and between the values of T_{max} corresponding to the thermal decomposition process is more distinguished on DSC curves (figs.4, 5).

According to the DSC curves, it can be distinguished an endothermic transition stage, without loss of mass on the TG curves, which corresponds to the melting process (158.7°C for AS and 157.7°C for M).

The melting point obtained from the DSC curve is similar to the values mentioned in speciality literature (158-162°C) [13–14]. This indicates a high purity of the indomethacin drug and tablets.

Before the melting, the indomethacin AS presents one phase transition at the temperature of 150.9°C, without mass deviation on the TG curve. It is accompanied by endothermic effect and is probably the result of some structural rearrangements (polymorphic transformations). The indomethacin M presents one stage of decomposition with a small loss of mass on the endothermic effect, which correspond to a loss of water or to the decomposition of excipients.

After melting, it takes place the decomposition process, with an endothermal effect for AS, respectively an endothermal effect followed immediately by a strong exothermal effect for indomethacin M.

The process of decomposition is a complex one with competitive reactions. Probably the process begins with the formulation of the decarboxylation product because the UV-irradiation of indomethacin for 72h in the solid-state under nitrogen and air yields 5%, respectively 7.5% of the decarboxylation product [12].

The difference between the values of temperature intervals and those of the endothermal and exothermal peaks are due to the presence of the excipients and to the possible interactions of these ones with the AS, a phenomenon which happens to other drugs too [15–16].

From those presented so far, results a higher thermal stability of the indomethacin tablets as compared to that of the indomethacin drug.

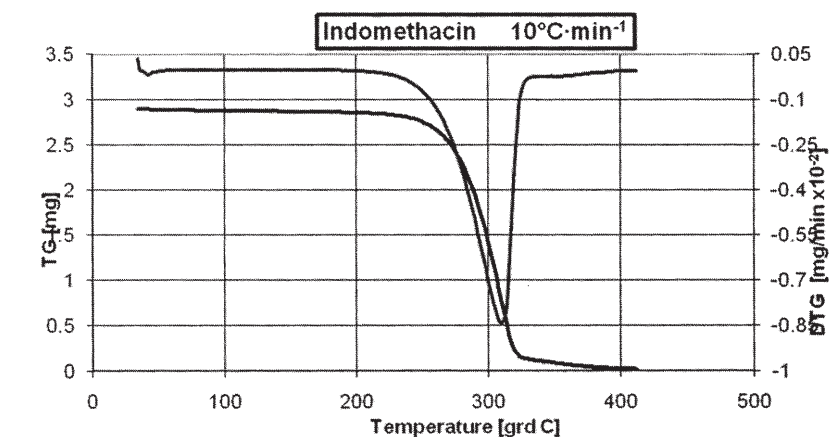


Fig.2. TG and DTG thermal curves of the indomethacin active substance (AS)

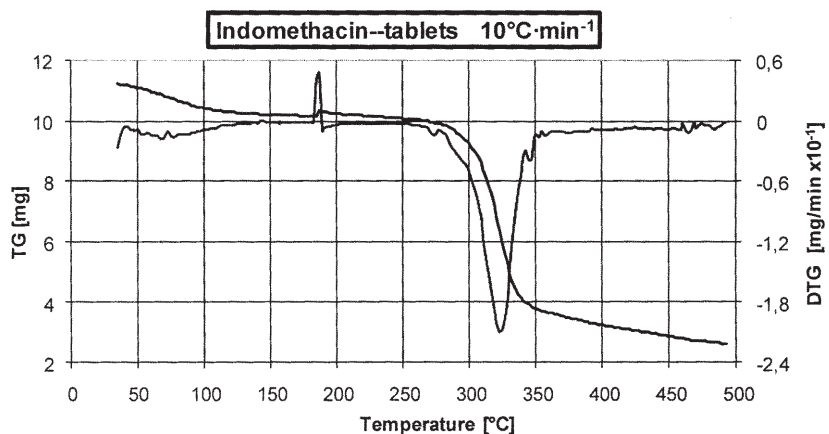


Fig.3. TG and DTG thermal curves of the indomethacin tablets (M)

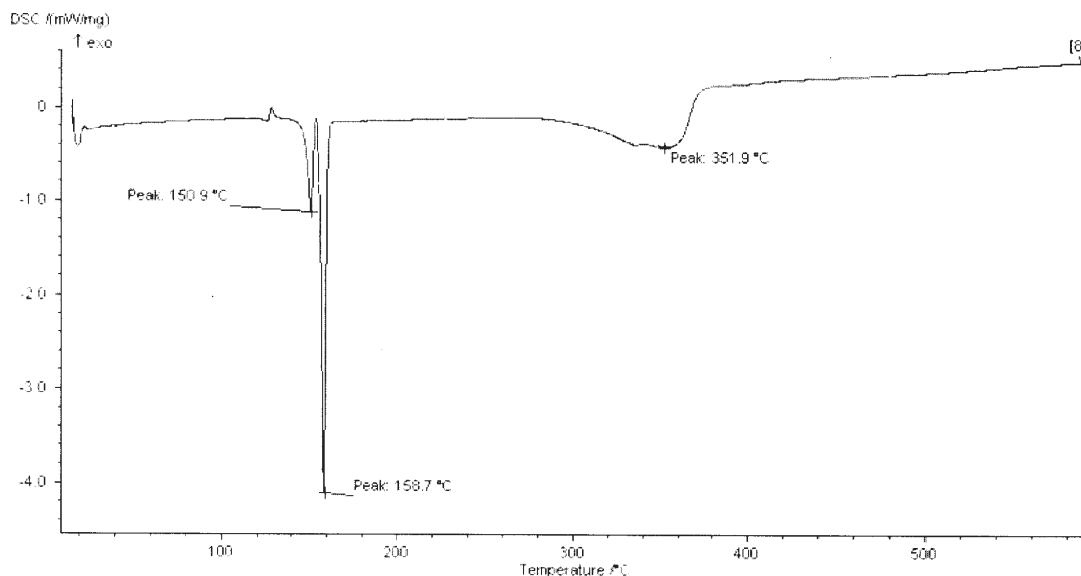


Fig.4. DSC thermal curve of the indomethacin active substance (AS)

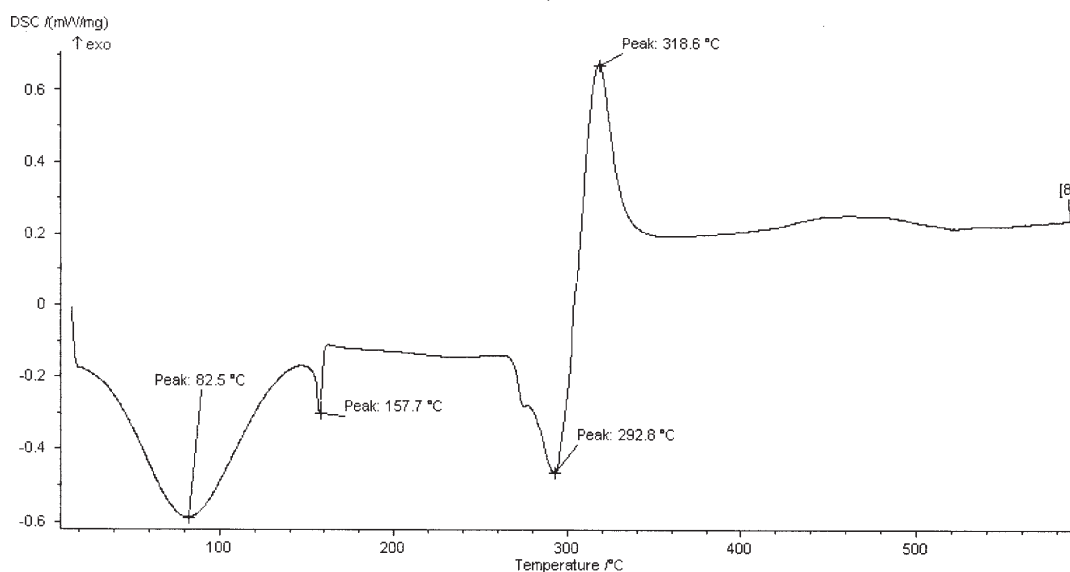


Fig.5. DSC thermal curve of the indomethacin tablets (M)

Function $f(\alpha)$	β ($^{\circ}\text{C}\cdot\text{min}^{-1}$)	Value of r^2 , n and E (kJ/mol)					$(\bar{x} \pm S_x)$
		5	7	10	12	15	
$A_n = n \cdot (1 - \alpha) \cdot [-\ln(1 - \alpha)]^{(n-1)/n}$ (Avrami-Erofeev equation) [23]	r^2	0.9672	0.9594	0.9551	0.9808	0.9765	
	E	5.11	5.23	5.26	5.11	5.20	
	$\ln A$	--	--	--	--	--	
	n	-4.80	-4.40	-4.76	-4.71	-4.29	
$F_n = (1 - \alpha)^n$ (reaction order model)	r^2	0.9998	0.9997	0.9999	0.9993	0.9996	
	E	120.0	119.1	119.4	120.1	119.8	119.7±0.2
	$\ln A$	23.8	23.4	24.4	24.0	23.9	23.9±0.2
	n	0.489	0.487	0.489	0.492	0.491	0.490±0.001
$D_4 = 3/2 \cdot [(1 - \alpha)^{-1/3} - 1]$ (Ginsein-Brouhnstein equation) [23]	r^2	0.8312	0.8405	0.9004	0.8019	0.9091	
	E	1080	1081	1080	1082	1095	
	$\ln A$	1.09	1.12	1.09	1.29	1.01	
	n	-4.80	-4.40	-4.76	-4.71	-4.29	
$P_n = n \cdot \alpha^{(n-1)/n}$ (power law equation) [23]	r^2	0.9916	0.9922	0.9959	0.9901	0.9919	
	E	-3340	-3312	-3345	-3310	-3319	
	$\ln A$	302	302	307	301	307	
	n	12.3	12.9	12.3	12.7	12.2	

Table 1
THE VERIFIED FUNCTIONS OF CONVERSION, THE VALUES OF REGRESSION COEFFICIENT AND ACTIVATION ENERGY

Kinetic analysis

Also, the thermal stability of the two substances 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 rate constant (k), the activation energy (E), the pre - exponential factor (A) and reaction order (n) were determined from the TG/DTG curves, by using the differential methods, *Chang* [17] and *Friedman isoconversional (Fd)* [18], respectively integral

methods, *Coats-Redfern (CR)* [19], *Kissinger-Akahira-Sunrose (KAS)* [20] and *Flynn-Wall-Ozawa (FWO)* [21]. From the equation of reaction rate:

$$\frac{d\alpha}{dt} = A \cdot \exp\left(-\frac{E}{R \cdot T}\right) \cdot f(\alpha) \quad (1)$$

by logarithmation it is obtained the equation corresponding to the *Chang's* method:

$$\ln\left(\frac{d\alpha/dt}{f(\alpha)}\right) = \ln A - \frac{E}{R \cdot T} \quad (2)$$

where:

α is the conversion degree;

t – time;

$f(\alpha)$ – the reaction model;

T – temperature.

The different differential functions $f(\alpha)$ were substituted in equation .2 and the relations were linearized therefore obtaining three–parametric linear equations:

$$z = a + b \cdot x + c \cdot y.$$

The use of TableCurve3D Software [22] can determine the kinetic triple (E , $\ln A$, n) through the estimation of the three parameters: a , b , c .

For different $f(\alpha)$, the most probable to describe the kinetic model, it was calculated the regression coefficient. Based on this values and also because of the activation energy's sign (the activation energy must have physical sense), it was chosen the function: $f(\alpha) = (1 - \alpha)^n$, which represents the reaction order model, and $n = 1/2$ (table 1).

From the graphic representation on the experimental data (fig.6.), the values of E , A and n were determined (table 1).

The isoconversional Friedman method is based on the equation:

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

In order to evaluate the activation energy more precisely, the term $\ln(d\alpha/dT)$ was obtained by numerical derivation of the curve α vs. T with respect to T and subsequent taking logarithms.

For $\alpha = \text{constant}$ and using various heating rates (β), the plot $\ln(\beta \cdot d\alpha/dT)$ vs. $(1/T)$ is linear (fig.7). The values of the

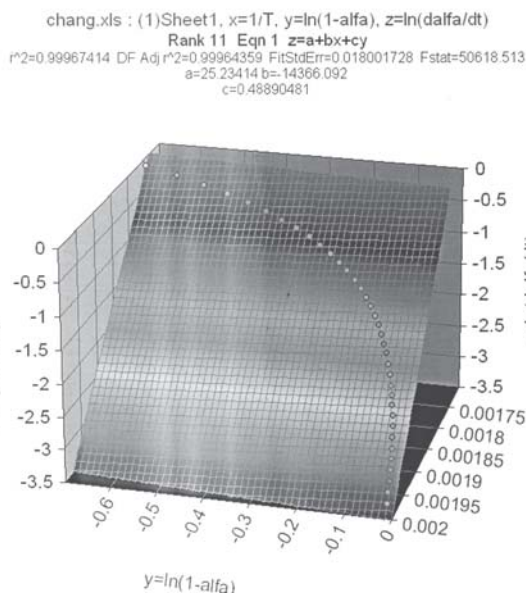


Fig.6. Chang 3D representation for indomethacin - active substance ($\beta = 10^\circ\text{C}\cdot\text{min}^{-1}$)

activation energy as obtained from the slopes of the straight lines are listed in table 2.

The general equation of the reaction rate for non-isothermal conditions at constant heating rate is generally written as:

$$g(\alpha) = \frac{A \cdot E}{R \cdot \beta} \cdot p(x) \quad (4)$$

where:

$g(\alpha)$ – the conversion integral;

$p(x)$ –the temperature integral; $x = E/RT$.

Table 2
VALUES OF THE ACTIVATION ENERGY OBTAINED BY THE FRIEDMAN, FLYNN–WALL–OZAWA AND KISSINGER–AKAHIRA–SUNROSE 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
Friedman	116.3	117.4	118.0	118.9	117.3	119.6	116.2	118.6
Flynn–Wall–Ozawa	120.0	114.6	117.4	116.7	115.8	112.6	118.6	120.6
Kissinger–Akahira–Sunose	122.2	116.1	115.2	112.5	114.5	117.1	117.0	119.1

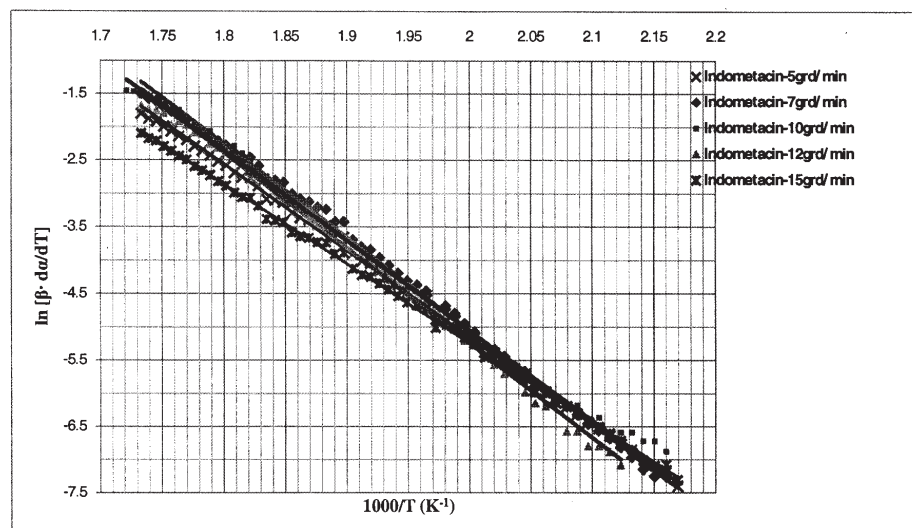


Fig.7. Friedman's plot for indomethacin at different heating rates

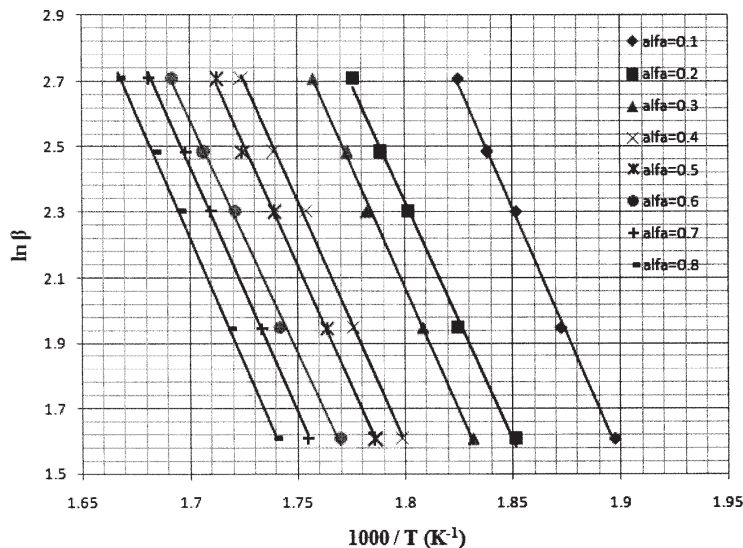


Fig.8. Flynn-Wall-Ozawa isoconversional diagrams

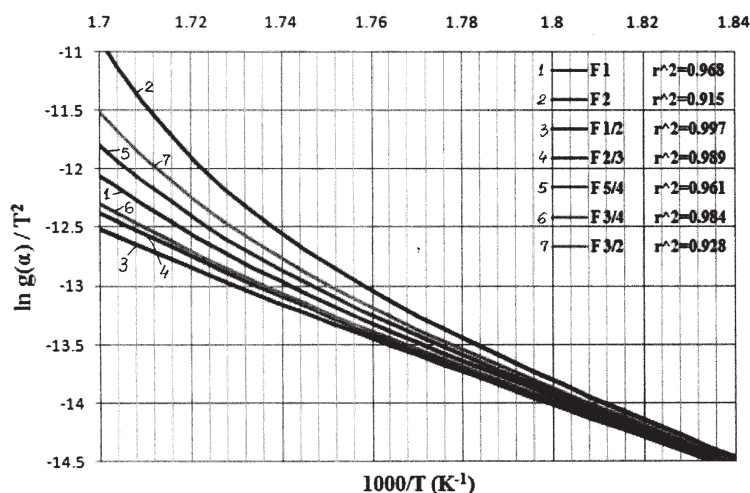


Fig.9. Graphic representation for Coats-Redfern method ($\beta=10 \text{ K}\cdot\text{min}^{-1}$)

From the generally equation (4) using Doyle's approximation [24]:

$$p(x) = \exp(-1.052 \cdot x - 5.331) \quad (5)$$

the equation corresponding to Flynn-Wall-Ozawa's isoconversional method was obtained:

$$\ln \beta = \ln \frac{A \cdot E}{R \cdot g(\alpha)} - 1.052 \cdot \frac{E}{R \cdot T} - 5.331 \quad (6)$$

This 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 plot $\ln \beta$ vs. $(1/T)$ is linear (fig.8.). From the slopes of the straight lines ($-E/R$), the values of the activation energy (E) were obtained (table 2).

The Kissinger-Akahira-Sunrose method, sometimes called the generalized Kissinger method is one of the best isoconversional methods and it is based on the equation:

$$\ln \left(\frac{\beta}{T_\alpha^2} \right) = \ln \frac{A \cdot R}{E \cdot g(\alpha)} - \frac{E}{R \cdot T_\alpha} \quad (7)$$

This method utilises the adequate temperatures (T_α) to certain values of the conversion α for experiments effectuated to different rates of heating, β .

From the slopes of the straight lines obtained by the representation graphic of the $\ln(\beta/T_\alpha^2)$ vs. $(1/T_\alpha)$ was

determined activation energy. The values of kinetic parameters determined by means of the integral methods are presented in table 2.

As shown in table 2, for $0.1 \leq \alpha \leq 0.8$, the activation energy values fluctuate around the average values of: (117.8 ± 0.4) , (117.0 ± 1.0) and respectively (116.7 ± 1.1) $\text{kJ}\cdot\text{mol}^{-1}$, and they are in fair good agreement with the value obtained with the Chang method.

The values obtained by the three methods are in good agreement and the weak variation of E vs. α indicates a single reaction mechanism for the decomposition processes.

For the kinetic model, $f(\alpha) = (1 - \alpha)^n$, mentioned to the Chang method, and frequently met in the decomposition of the drugs, the method Coats - Redfern utilises the following equations:

for $n=1$

$$\log \left[\frac{-\ln(1-\alpha)}{T^2} \right] = \log \frac{A \cdot R}{\beta \cdot E} - \frac{E}{2,303 \cdot R \cdot T} \quad (8)$$

for $n \neq 1$

$$\log \left[\frac{1 - (1-\alpha)^{1-n}}{T^2 \cdot (1-n)} \right] = \log \frac{A \cdot R}{\beta \cdot E} - \frac{E}{2,303 \cdot R \cdot T} \quad (9)$$

The representation graphic of the left side vs. $1/T$, lead to a straight line for $n=1/2$ (fig.9.) and from the obtained slopes and the intercepts of the straight lines, the value of E and A were obtained. The rate constant (k) was calculated by Arrhenius equation.

Table 3
KINETIC PARAMETERS OF INDOMETHACIN OBTAINED BY METHODS OF COATS-REDFERN (CR)

Compound	The kinetic parameters	$\beta / ^\circ\text{C}\cdot\text{min}^{-1}$					
		5	7	10	12	15	Main
Drug	E / kJ mol ⁻¹	123.3	126.1	128.5	127.4	131.6	127.4±1.4
	ln A / min ⁻¹	24.3	24.7	25.8	25.3	26.4	25.3±0.4
	k / s ⁻¹	6.4E-03	5.3E-03	9.8E-03	7.5E-03	9.5E-03	(7.7±0.9)E-03
Tablets	E / kJ mol ⁻¹	145.4	149.1	151.6	148.7	154.2	149.8±1.5
	ln A / min ⁻¹	28.1	28.7	30.1	29.2	30.8	29.4±0.5
	k / s ⁻¹	3.1E-03	2.6E-03	6.4E-03	4.7E-03	7.5E-03	(4.9±0.9)E-03

The values of the kinetic parameters are presented in table 3 are in fair good agreement with the values calculated by the other methods. Also, they show the same kind of the variation of the thermal stability for drugs and tablets, like the thermal behaviour.

Conclusions

There was performed a thermal study (thermal behaviour and kinetic determinations) under non-isothermal conditions for the indomethacin and its pharmaceutical form.

There have been observed insignificant differences between the thermal curves of the pure compound and those of the pharmaceutical product, as well as for the values of the kinetic parameters which were determined by differential and integral methods.

By comparing the thermal curves and the temperature ranges of the two thermal decomposition processes, it is found out a better thermal stability of the indomethacin tablets than of the indomethacin-active substance. This is shown by rather smaller decomposition temperatures in the case of indomethacin AS and by rather larger decomposition ranges. The reason of this behaviour is the possible interaction of the excipients with the active substance, but in a reduced proportion.

The values of the kinetic parameters, determined with differential and integral methods, are in fair good agreement and the constant difference between their values, which are higher for E and A, respectively lower for k in the case of indomethacin M, indicates a somewhat higher thermal stability of the tablets, as compared to the indomethacin drug.

The concordance of the values for the kinetic parameters determined and the mode of dependence of the activation energy as against the conversion degree show the correctness of the applied methods and the facts that the thermal decomposition process of the indomethacin is indeed an unitary process, but complex.

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

References

1. BARBADILLO, F., FUENTES, A., NAYA, S., MIER, J.L., *J. Therm. Anal. Cal.*, **87**, 2007, p. 223
2. BASU, P., ALEXANDER, K.S., RIGA, A.T., *J. Therm. Anal. Cal.*, **83**, 2006, p. 19
3. LIRA, A.M., ARAUJO, A.A.S., BASILIO, I.D.J., SANTOS, B.L.L., SANTANA, D.P., MACEDO, R.O., *Thermochim. Acta*, **457**, 2007, p. 1.
4. TIȚA, B., FULIAȘ, A., MARIAN, E., TIȚA, D., *Rev.Chim. (București)*, **60**, nr. 4, 2009, p. 419
5. TIȚA, B., FULIAȘ, A., MARIAN, E., TIȚA, D., *Rev.Chim. (București)*, **60**, nr. 5, 2009, p. 522
6. CHENG, Y., *Chinese Journal of Inorganic Chemistry*, **22**, nr. 2, 2006, p. 287
7. FRAGA, F., SOTO, V., BLANCO-MÉNDEZ, J., LUZARDO-ALVAREZ, A., RODRIGUEZ-NÚÑEZ, E., MARTINEZ-AGEITOS, J., PÉREZ, M., *J. Therm. Anal. Cal.*, **87**, 2007, p. 233
8. TIȚA, B., MARIAN, E., TIȚA, D., DOCA, N., VLASE, T., *J. Therm. Anal. Cal.*, **94**, 2008, p. 447
9. KISS, D., ZELRÓ, R., NOVÁK, C., ÉHEN, Z., *J. Therm. Anal. Cal.*, **84**, 2006, p. 447
10. HOWELL, B.A., *J. Therm. Anal. Cal.*, **85**, 2006, p. 165; **93**, 2008, p. 27
11. MARINI, A., BERBENNI, V., MOIOLI, S., BRUNI, G., COFRANCESCO, P., MARGHERITIS, C., VILLA, M., *J. Therm. Anal. Cal.*, **73**, 2003, p. 529.
12. GLASS, D.B., NOVAK, Cs., BROWN, E.M., *J. Therm. Anal. Cal.*, **77**, 2004, p. 1013
13. *** Farmacopeea Română, 10th ed., Ed. Medicală, București, 1993.
14. *** European Pharmacopoeia, 6th ed., Council of Europe, Strasbourg, 2007
15. SILVA, A.A., Jr., SCARPA, M.V., PESTANA, K.C., MERCURI, L.P., de MATOS, J.R., de OLIVEIRA, A.G., *Thermochim. Acta*, **467**, 2008, p. 91.
16. PIJERS, M.F.J., MATHOT, V.B.F., *J. Therm. Anal. Cal.*, **93**, 2008, p. 319
17. CHANG, W.L., *J. Appl. Polym. Sci.* **53**, 1994, p. 1759
18. FRIEDMAN, H.L., *J. Polimer Sci.*, **6C**, 1965, p. 183
19. COATS, A.W., REDFERN, J.P., *Nature*, **201**, 1964, p. 68
20. STARINK, J.M., *Thermochim. Acta*, **404**, 2003, p. 163
21. FLYNN, J.H., WALL, L.A., OZAWA, B.T., *Bull. Chem. Soc. Japan*, **38**, 1965, p. 1881
22. <http://www.sigmaplot.com/products/tablecurve3d/tablecurve3d.php>
23. BROWN, M.E., *Handbook of Thermal Analysis and Calorimetry*, **1**, Principles and Practice, Elsevier, Patrick K. Gallagher, London, 1998, p. 169
24. DOYLE, D.C., *J. Appl. Polym. Sci.*, **6**, 1962, p. 639

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