Thermal Decomposition of Some Benzodiazepines under Non-Isothermal Conditions

Kinetic Study

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Thermal analysis is a routine method for the analysis of drugs and substances of pharmacological interest. Kinetic studies have become a crucial point in thermal analysis, in which the main purpose is to determine the mechanism(s) of decomposition and to calculate the parameters of the Arrhenius equation. The results are further used to predict the system’s behaviour in various circumstances. The diazepam’s, nitrazepam’s and oxazepam’s thermal decomposition kinetics has been studied under non-isothermal conditions, using 5, 7, 10, 12 and 15°C min^{-1} heating rates and a nitrogen dynamic atmosphere. The methods used for TG/DTG data processing have been those of Friedman, Flynn–Wall–Ozawa, Kissinger and respectively Nomen–Sempere. The decomposition process has been relatively complex for a simple and easy correlation of the kinetic data with the molecular structure’s characteristics. The careful treatment of the kinetic parameters obtained in different thermal conditions was confirmed to be necessary, as well as a different strategy of experimental data processing. Only the non–parametric method of Nomen and Sempere was able to provide a less speculative comment.

Keywords: benzodiazepines, kinetic analysis, thermal analysis, non-isothermal, TG/DTG

The thermal analysis methods constitute more and more a distinct method class, which is widely used, especially in fields of growing importance, inclusively in the pharmaceutical field [1–10].

TG/DTG and DSC techniques provide important information regarding the physical properties of the pharmaceutical compounds (stability, compatibility, polymorphism, kinetic analysis, phase transitions, etc) [11–20].

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. This also applies for the isothermal kinetic investigations, as well as for the non-isothermal ones, and the fact that the results of the two types of investigations are the same is accepted as an axiom.

The kinetic parameters, the rate constant (k), the activation energy (E), the pre–exponential factor (A) and the reaction order (n), may be calculated using the different methods that are characteristic to the non–isothermal regime. These data can provide precious information about the time and storing conditions, especially life–time.

A series of works, even recent ones, show encouraging results regarding the evaluation of the thermal behaviour of pharmaceutical products through the kinetic data obtained in non–isothermal conditions [21–30].

The aim of this paper is to realize a kinetic analysis regarding the thermal decomposition, under non–isothermal conditions, of three benzodiazepines (active substances), as for example: diazepam, nitrazepam and oxazepam. This work is in connection with two recent works, regarding the thermal behaviour of the same pharmaceutical products [31], respectively the kinetic study of thermal decomposition under isothermal conditions [32].

Experimental part

The molecular formula of the studied compounds is presented in figure 1.

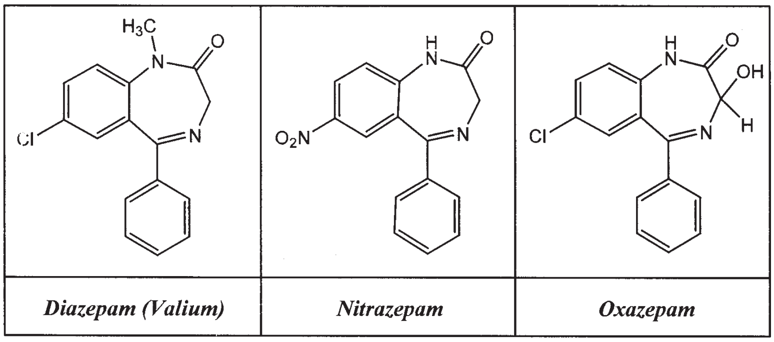

Fig. 1. Structural formula of the benzodiazepines

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The substances studied were:

- diazepam “ active substance or drug (AS);
- nitrazepam “ active substance or drug (AS);
- oxazepam “ active substance or drug (AS).

The substances were available as pure compound, able to be used for medical purposes. These were obtained from Terapia S.A. / Ranbaxy, Cluj-Napoca, România as pure compounds.

TG/DTG experiments were performed with a Perkin-Elmer Diamond thermobalance, in the temperature range of 25–600°C, under a dynamic atmosphere of nitrogen at a flow rate of 100 ml·min^{-1}. Samples with of mass in the range of 5 to 15 mg were put into aluminium crucibles, at a heating rates of 5, 7, 10, 12 and 15°C min^{-1}.

Examples of typical thermoanalytical curves are presented in figure 2.

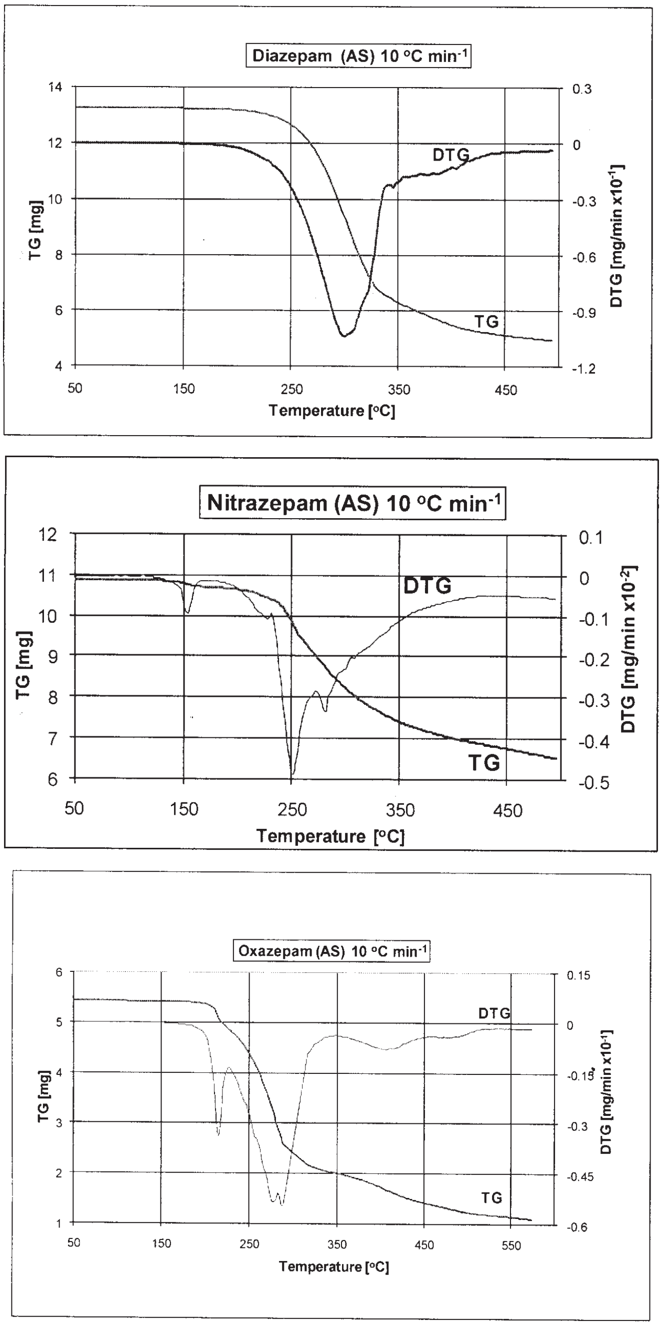


Fig. 2. TG and DTG curves of diazepam, nitrazepam and oxazepam

Results and discussions

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

According to the TG/DTG thermal curves (fig.2), the thermal decomposition occurs by complex processes with successive or competitive reactions:

- a complex process, in a practical single step for diazepam;
- a complex process, in two steps for nitrazepam and oxazepam.

The kinetic analysis of decomposition process can be represented by the equation:

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

where: t is the time, T is the temperature, α is extent of conversion and $f(\alpha)$ is reaction model.

In non-isothermal conditions dα/dt in equation 1 is replaced with $\beta\cdot$ dα/dT, where β is the heating rate, giving:

$$\frac{d\alpha}{dT} = \frac{A\cdot f(\alpha)}{\beta}\cdot \exp(-\frac{E}{R\cdot T}) \quad (2)$$

From the generally accepted equation of the non-isothermal kinetics,(2), the equation corresponding to the Friedman’s isoconversional method [33], was obtained:

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

In order to evaluate more precisely the activation energy one more time, the term ln(d$\Delta\alpha$/dT) was obtained by numerical derivation of the curve $\Delta\alpha$ vs. T with respect to T and subsequent taking logarithms. The curves $d\Delta\alpha/dT$ *vs.* T for the applied heating rates, are given in figure 3.

These curves confirm the existence of complex processes of thermal decomposition with successive or competitive reactions.

For diazepam, the thermal decomposition occurs by a complex process with competitive reactions, as majority, followed by some successive reactions.

The curves for nitrazepam confirm the existence of a complex process for the thermal decomposition, through two steps with successive reactions for the second one.

In the case of oxazepam, the curves indicate the same kind of process like the curves TG/DTG. The thermal decomposition occurs through a complex process with the two steps relatively distinct. The second step is characterized by competitive reactions.

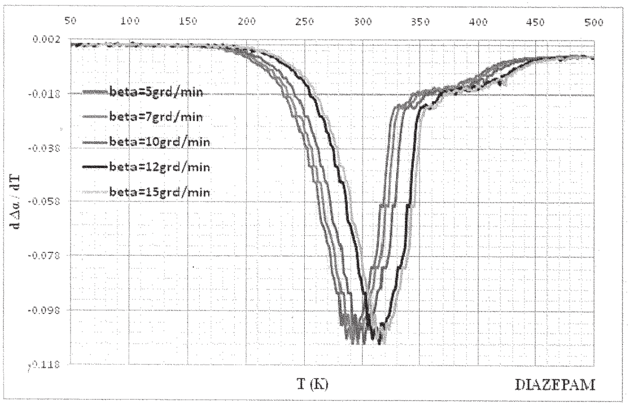
The values of the activation energy as obtained from the slopes of the straight lines ln(d$\Delta\alpha$/dT) *vs.* 1/T are listed in table 1.

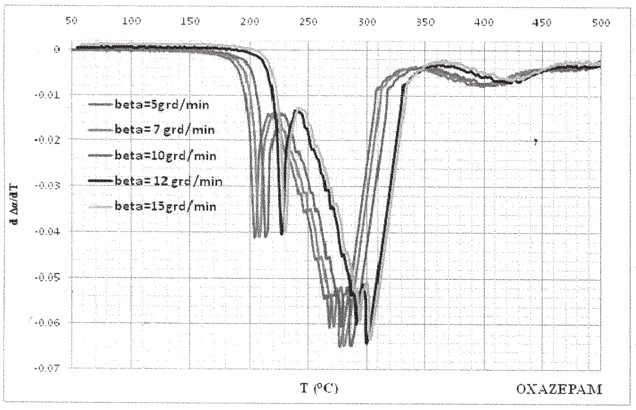
The isoconversional Flynn–Wall–Ozawa method [34–35] is based on the measurement of the adequate temperature to certain values of the conversion α, for experiments effectuated to different rates of heating β. The corresponding equation is the following:

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

Considering isoconversional conditions, for example for the same α_i, the T_i corresponding temperature for different heating rates, the plot of the left member of the equation (1) in connection with $1/T_i$ leads to a straight lines (fig.4.). From these slopes, the activation energy was calculated. The data are systematized in table 1.

The disposal mode of the straight lines confirms the process complexity and the variation way of the reaction rates during thermal decomposition.





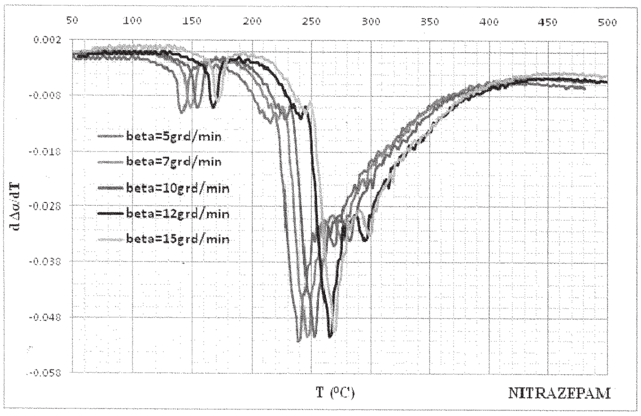
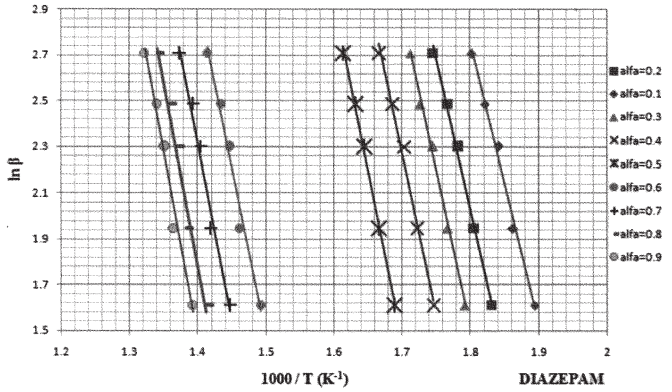
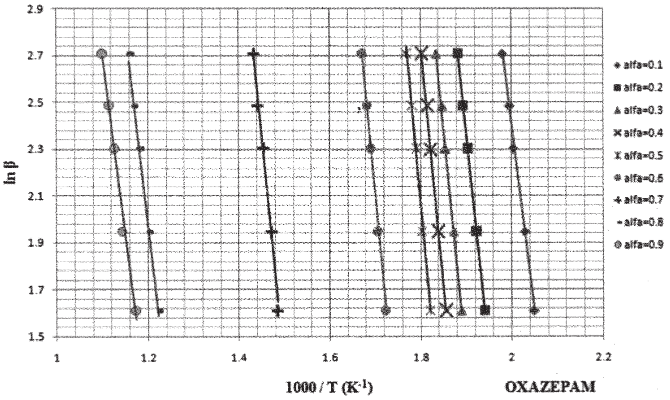


Fig.3. The curves $d\Delta\alpha/dT$ vs. T for the used heating rates





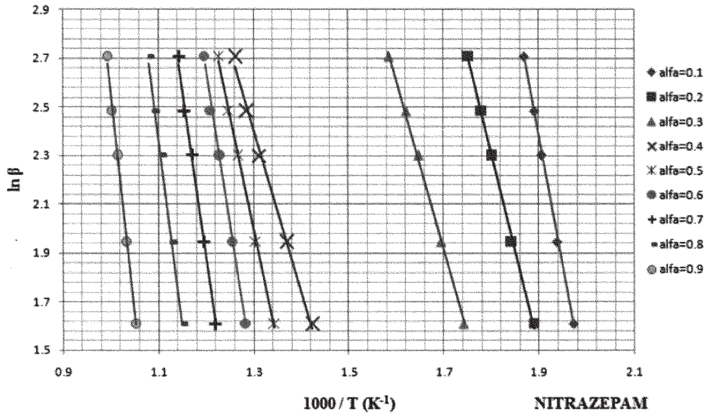


Fig.4. The Flynn–Wall–Ozawa isoconversional diagrams

According to the data in table 1, there appears a variation of *E* values versus α. The percentage of variation (≈20%) confirms the complexity of the thermal decomposition processes, especially in the case of nitrazepam when for the second step occur a series of successive reactions.

The values obtained by the two methods are in fair good agreement.

The Kissinger method [36] is one of the best isoconversional methods and it is based on the equation:

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

This method uses the maxim temperatures of the peaks (T) in experiments effectuated to different rates of heating, β.

From the slope of the straight line obtained by the representation graphic of the $\ln(\beta/T^2)$ vs. (1/T) (fig.5.) was determined the activation energy: (118.6±2.6) kJ/mol for diazepam; (93.4±2.3) kJ/mol for nitrazepam and

Table 1
VALUES OF THE ACTIVATION ENERGY OBTAINED BY USING THE FRIEDMAN AND FLYN-WALL-OZAWA ISOCONVERSIONAL METHODS

Compound	Method	E, (kJ mol^{-1}), for conversion degrees, α									
		0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	Main
Diazepam	Friedman	89.2	90.8	92.1	94	95.3	101.3	108.2	112.4	114	99.7±3.2
	Flynn–Wall–Ozawa	96.1	102.8	108.7	112.8	115.5	116.2	123.4	126.3	129.6	114.6±3.7
Nitrazepam	Friedman	83.2	86.8	87.1	90.5	92.3	96.3	99.2	102.4	107.0	93.9±2.6
	Flynn–Wall–Ozawa	88.7	83.3	78.8	76.6	87.0	100.4	110.6	117.0	123.9	96.3±5.8
Oxazepam	Friedman	117.3	122.9	123.1	125.3	127.9	129.7	132.8	138.4	143.3	129.0±2.7
	Flynn–Wall–Ozawa	126.3	137.8	148.4	152.4	158.4	154.3	143.1	132.5	122.8	141.8±4.2

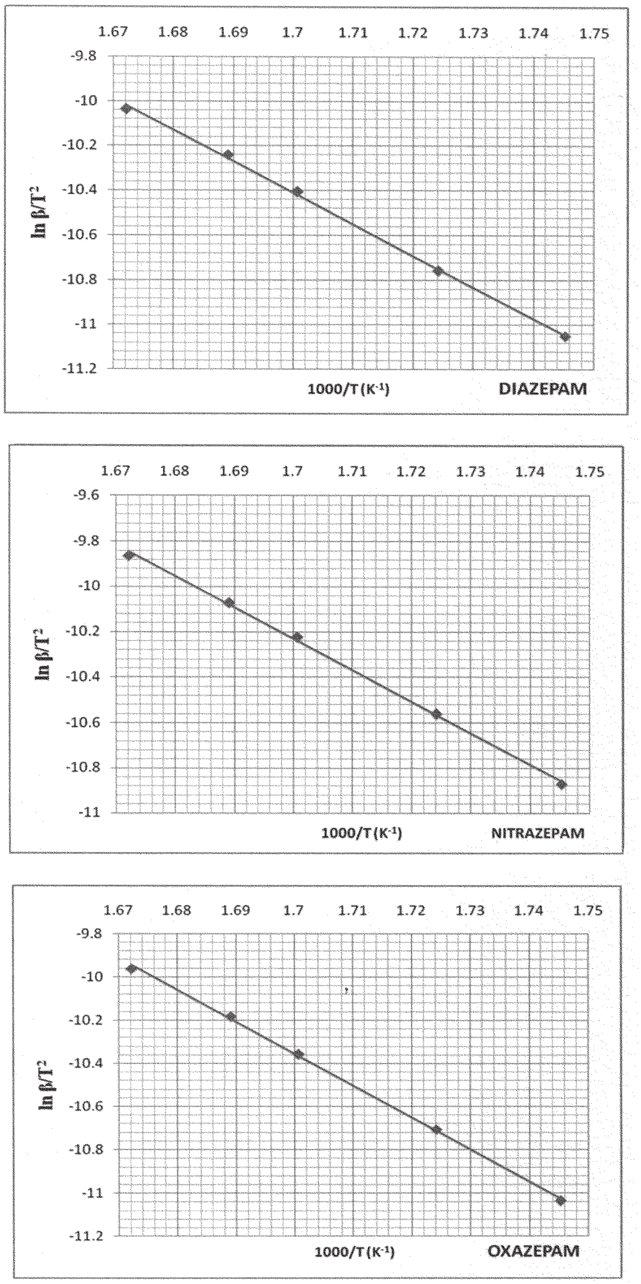


Fig.5. Kissinger plot for decomposition of benzodiazepines

(124.2±2.4) kJ/mol for oxazepam. These values are in fair good agreement with the values determinate by Friedman and Flynn-Wall-Ozawa methods.

Because the variation of *E* vs. α, for calculating the kinetic parameters it is indicated to use *the non-parametric kinetics (NPK)* [37–39] method, a relatively recent well documented method. The main characteristic of this method is its ability to give information about kinetics reaction without presumptions regarding the dependence of the reaction rate on the conversion degree or temperature.

NPK method permits the separation of two or more stages of a complex process, based on the following reasoning:

– the experimental data are represented in a 3D space (dα/dt, α, T);

– this data are interpolated to generate a continuous surface corresponding to an equation:

$$d\alpha/dT = \mathrm{f}(\mathrm{T})\cdot \mathrm{g}(\alpha) \qquad (6)$$

– the continuous surface of the reaction rate is discretized as a *ixj* matrix *M*:

$$\mathrm{M} = \{\mathrm{m_{ij}}\} = \{\mathrm{f}(\mathrm{T_i})\cdot \mathrm{g}(\alpha_j)\} \qquad (7)$$

– using the singular value decomposition (SVD) algorithm, the matrix *M* is decomposed according to equation (8):

$$\mathrm{M} = \mathrm{U}(\mathrm{diagS})\mathrm{V}^{\mathrm{T}} \qquad (8)$$

and the elements of the diagonal of *S* are called “singular values” of M;

– the first columns of *U* and *V* matrix, respectively u_1 and v_1 are analyzed for determining the kinetic model, i.e.:

$$u_1 = g(\alpha) \qquad (9)$$

respectively, the temperature dependence, i.e.:

$$v_1 = f(T) \qquad (10)$$

For temperature dependence, the classical Arrhenius equation is selected and for the kinetic model we suggest the Šesták–Berggren equation of the two–parameter’s model [40]:

$$g(\alpha) = \alpha^m \cdot (1-\alpha)^n \qquad (11)$$

where: *n* is reaction order and *m* is a parameter which together with *n* characterize the mathematical expression of the kinetic model.

If the decomposition reaction is a two step process, the matrix *M* became:

$$M = M_1 + M_2 = U_1(diagS_1)V_1^T + U_2(diagS_2)V_2^T \qquad (12)$$

and the contribution of each step to the entire process is expressed by the explained variance λ, so that $\lambda_1 + \lambda_2 = 100\%$.

According to these conditions, the following data can be obtained: *E, A, m, n*.

The results obtained by using the NPK method are presented in table 2. The explained variance λ seems the

Table 2
KINETIC PARAMETERS
BY NPK METHOD

Compound	λ (%)	E (kJ mol^{-1})	ln A (min^{-1})	m	n	$\Sigma\lambda\cdot E$
Diazepam	82.2	97.9±6.3	19.6±1.0	0	3/2	80.5
	12.1	44.8±2.7	9.2±0.2	2	0	
Nitrazepam	68.0	42.6±3.0	9.3±0.2	3	0	78.6
	24.7	201.0±11.2	42.7±2.7	0	4	
Oxazepam	74.8	218.6±10.8	47.3±3.2	0	3/2	166.3
	20.6	13.5±1.1	2.9±0.1	0	1/3	

percent from the variation of the experimental data explained by the proposed processes

The utilisation of the NPK method is made on the base that, in the first phase, is eliminated the CO and Cl_2, and after that, the process is continuing.

By inspecting the data in table 2, the first observation is a kinetic which is different for the three compounds, in spite of their similar structure. The differences are not only regarding the kinetic parameter's values, but even in the decomposition process's complexity.

The decomposition of nitrazepam and oxazepam is better described by a two-step process (λ>15%), while the diazepam can be considered having a single-step process. The presupposing second-step is less significant (λ<15%). mal conditions, all the studied compounds show two elementary steps.

The significance of each step for the whole process is different but it is not to be neglected. The value of $m \neq 0$ indicates a contribution of the nucleation process on the kinetic law, followed by the linear increase of the agents of nucleation (inclusive the explosive reactions: $n>1$).

In the last column of table 2 was calculated an average value $\Sigma\lambda\times E$. It is noticed a satisfactory accord for the values of E obtained by the mentioned methods.

Conclusions

There was performed a kinetic study under non-isothermal conditions, regarding the thermal decomposition of three benzodiazepines.

Four different methods were used to process the experimental data. The kinetic parameters obtained by these four methods are in a satisfactory accord.

The variation of the activation energy in an accepted interval shows that the mechanisms of the investigate processes can be more complex that the ones considered to simultaneous or successive reactions.

The information achieved by the NPK method is probably the most credible one because this method uses a larger number of points and a wider range of temperatures comparative with classical methods which use only few points (usually three or four, corresponding to the maximum of the thermoanalytical curves).

Comparing with the classical methods, the NPK method is not restricted to the mathematical equations of the kinetic models.

In spite of the similar structure, the decomposition kinetic of these three studied compounds is quite different, so that a correlation between the kinetic parameters and the molecular "architecture" is risky.

References

1. 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
2. CHENG, Y., Chin. J. Inorg. Chem., **22**, nr. 2, 2006, p. 287
3. FRAGA, F., SOTO, V., BLANCO-MÉNDEZ, J., LUZARDO-ALVAREZ, A., RODRIGUEZ-NÚNEZ, E., MARTINEZ-AGEITOS, J., PÉREZ, M., J. Therm. Anal. Cal., **87**, 2007, p. 233
4. TOMASETTI, M., CATALANI, A., ROSSI, V., VECHIO, S., J. Pharm. Biomed. Anal., **37**, 2005, p. 949
5. 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
6. XU, F., SUN, L.X., TAN, Z.C., LIANG, J.G., ZHANG, T., J. Thermal. Anal. Cal. **83**, 2006, p. 187
7. CIDES, L.C.S., ARAÚJO, A.A.S., SANTOS-FILHO, M., MATOS, J.R., J. Thermal. Anal. Cal., **84**, 2006, p. 441
8. TERADA, K., MASUDA, T., YOSHIHASHI, Y.E. YONEMACHI, J. Thermal. Anal. Cal., **85,** 2006, p. 675
9. QIANG–GUO, L., XU, L., BIN, D., XU–WU, Y., J. Thermal. Anal. Cal., **85,** 2006, p. 585
10. GIRON, D., MUTZ, M., GARNIER, S., J. Therm. Anal. Cal., **77**, 2004, p. 709
11. MICHALIK, K., DRZAZGA, Z., MICHNIK, A., KASZUBA, M., J. Thermal. Anal. Cal., **84**, 2006, p. 119
12. MICHNIK, A., MICHALIK, K., KLUCZEWSKA, A., DRZAZGA, Z., J. Thermal. Anal. Cal., **84**, 2006, p. 113
13. PIJPERS, M.F.J., MATHOT, V.B.F., J. Therm. Anal. Cal., **93**, 2008, p. 319
14. TOMASETTI, M., CATALANI, A., ROSSI, V., VECHIO, S., J. Pharm. Biomed. Anal., **37**, 2005, p. 949
15. MORA, P.C., CIRRI, M., MURA, P., J. Pharm. Biomed. Anal., **42**, 2006, p. 3
16. BARBADILLO, F. FUENTES, A. NAYA, S. CAO, R. MIER, J.L. ARTIAGA, R., J. Thermal. Anal. Cal., **87**, 2007, p. 223
17. TANAKA, H., BROWN, M.E., J. Thermal. Anal. Cal., **80**, 2005, p. 795.
18. HOWELL, B.A., J. Therm. Anal. Cal., **85,** 2006, p. 165; **93**, 2008, p. 27
19. HOWELL, B.A., RAY, J.A., J. Thermal. Anal. Cal., **83**, 2006, p. 63.
20. YOSHIHASHI, Y., IIJIMA, H., YONEMOCHI E., TERADA, K., J. Thermal. Anal. Cal., **85,** 2006, p. 689
21. TIŢA, B., FULIAŞ, A., MARIAN, E., TIŢA, D., Rev. Chim. (Bucureşti), **60**, nr. 4, 2009, p. 419
22. TIŢA, B., FULIAŞ, A., MARIAN, E., TIŢA, D., Rev. Chim. (Bucureşti), **60**, nr. 5, 2009, p. 522
23. TIŢA, B., FULIAŞ, A., RUSU, G., TIŢA, D., Rev. Chim. (Bucureşti), in press
24. CAI, J., LIU, R., Solid State Sci., **10**, 2008, p.659
25. BIGDA, R., MIANOVSKI, A., J. Thermal. Anal. Cal., **84**, 2006, p. 453
26. FRAGA, F., SOTO, V.H., BLANCO-MÉNDEZ, J., LUZARDO-ALVAREZ, A., RODRIGUEZ-NÚNEZ, E., MARTINEZ-AGEITOS, J.M., PÉREZ, M., J. Thermal. Anal. Cal., **87**, 2007, p. 233
27. ŠIMON, P., J. Therm. Anal. Cal., **79**, 2005, p. 703
28. VYAZOVKIN, S., J. Therm. Anal. Cal., **83**, 2006, p. 45
29. CAVATUR, R., VEMURI, N.M., CHRZAN, Z., J. Thermal. Anal. Cal., **78**, 2004, p. 63
30. KISS, D., ZELRÓ, R., NOVÁK, C., ÉHEN, Z., J. Therm. Anal. Cal., **84**, 2006, p. 447
31. TIŢA, B., FULIAŞ, A., TIŢA, D., FARMACIA, in press
32. TIŢA, B., MARIAN, E., TIŢA, D., VLASE, G., DOCA, N., VLASE, T., J. Therm. Anal. Cal., **94**, 2008, p. 447
33. FRIEDMAN, H.L. J. Polymer. Sci., **6C**, 1965, p. 183
34. FLYNN, I.H., Wall, L.A., Polym. Lett., **4**, 1966, p. 323
35. OZAWA, T., Bull. Chem. Soc. Jpn., **38**, 1965, p. 1881
36. KISSINGER, E.H., Anal. Chem., **29**, 1957, p. 1702
37. SERRA, R., NOMEN, R., SEMPERE, J., J. Therm. Anal. Cal., **52**, 1998, p. 933
38. SERRA, R., SEMPERE, J., NOMEN, R., Thermochim. Acta, **316,** 1998, p. 37
39. SEMPERE, J., NOMEN, R., SERRA, R., J. Therm. Anal. Cal., **56**, 1999, p. 843
40. SESTAK, J., BERGGREN, G., Thermochim. Acta, **3**, 1971, p. 1

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