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COMPARATIVE KINETIC STUDY OF DECOMPOSITION OF SOME DIAZEPINE DERIVATIVES UNDER ISOTHERMAL AND 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 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.

A kinetic study regarding the diazepam, nitrazepam and oxazepam thermal decomposition was performed, under non-isothermal and isothermal conditions and in a nitrogen atmosphere, for the temperature steps: 483, 498, 523, 538 and 553 K. The TG/DTG data were processed by three methods: isothermal model-fitting, Friedman's isothermal-isoconversional and Nomen-Sempere non-parametric kinetics.

In the model-fitting methods the kinetic triplets ($f(\alpha)$, A and E_a) that defines a single reaction step resulted in being at variance with the multi-step nature of diazepines decomposition. The model-free approach represented by isothermal and non-isothermal isoconversional methods, gave dependences of the activation energies on the extent of conversion.

It is very difficult to obtain an accord with the similar data which resulted under non-isothermal conditions from a previous work.

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.

Keywords: *diazepine, isothermal, kinetic study, non-isothermal, thermal decomposition*

Introduction

The thermal analysis is a routine method to analyze drugs and substances of pharmaceutical interest. The thermal analysis methods are widely used for the study of the stability and decomposition of the substances used in medicine [1–6]. The evaluation of the stability of a drug in solid form is realized especially by analyzing its decomposition in isothermal and non-isothermal conditions. Usually, this takes place by irreversible mass loss. The drugs' decomposition reactions have a theoretical, as well as a practical signification.

The application of thermal methods, especially TG, DTG and DSC is very important when solving pharmaceutical problems, like for example the determination of purity level, qualitative and quantitative analysis of the medicinal compositions, stability tests, kinetic parameters' determination, etc. [7–13].

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 (activation energy, frequency factor and reaction order). These data can provide precious information about the time and the storing conditions. 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 [14–20].

The methods proposed for the kinetic study of thermal decomposition are generally classified in model-fitting and model-free methods. In each case, data from isothermal and/or non-isothermal experiments can be used. The model-free isoconversional methods are considered as also being ones of the most trusted, especially the Friedman–Ozawa method [21, 22], because of its theoretical and experimental advantages.

The thermal analysis has proved its characterization capacity for various pharmaceutical products, especially when coupled with FTIR spectroscopy [9, 23–26]. But the kinetic and mechanism discussions, based upon the data obtained under non-isothermal conditions are often the subject of debates, in comparison with the data obtained under isothermal conditions [18, 27, 28].

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In a previous work, a kinetic study of decomposition of a few diazepine derivatives study was realized under non-isothermal conditions [29]. There was not possible to establish a very clear and secure strategy of experimental data processing.

The purpose of the present work is to obtain kinetic data by thermal decomposition of certain diazepine derivatives under isothermal conditions and to compare them with the data obtained under non-isothermal conditions.

Experimental

The studied derivatives have been pharmaceutical products from the benzodiazepine's class: diazepam, nitrazepam and oxazepam. The molecular formulas are presented in Fig. 1.

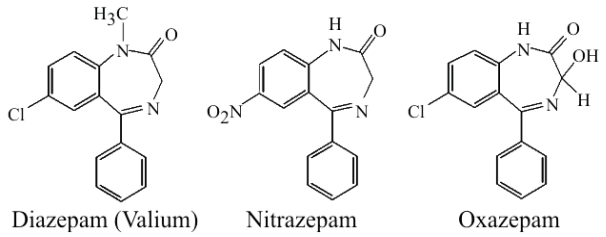

Fig. 1 Structural formula of the diazepine derivatives

The substances were available as pure compounds, able to be used for medical purposes. They were obtained from Terapia S.A./Ranbaxy, Cluj-Napoca, România. Purity of these compounds met requirements of European Pharmacopoeia.

The non-isothermal and isothermal TG/DTG curves 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 of 100 mL min^{-1}. Samples with the mass in the range of 5 to 20 mg were put into aluminium crucibles, at the heating rates of 5, 7, 10 and 15°C min^{-1}.

The isothermal TG curves were measured at 483, 498, 523, 538 and 553 K during 30 min. These curves were recorded by stepwise isothermal heating. The stepwise isothermal approach consists of heating at a constant rate, until a mass change begins and then holding isothermally until the mass change is complete.

This approach has significant advantages over the other techniques in that the reaction onset and completion can be very carefully controlled.

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.

Kinetic analysis of decomposition process is traditionally expected to produce an adequate kinetic description of the process in terms of the reaction model and the Arrhenius parameters using a single-step kinetic equation:

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t}=k(T)f(\alpha) \qquad (1)$$

where t is the time, T is the temperature and $f(\alpha)$ is the reaction model. The temperature dependence of the rate constant is introduced by replacing $k(T)$ with Arrhenius equation, which gives:

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t}=Ae^{\frac{-\mathrm{E}}{\mathrm{RT}}}f(\alpha) \qquad (2)$$

where E (the activation energy) and A (the pre-exponential factor) are the Arrhenius parameters and R is the gas constant. For non-isothermal conditions $\mathrm{d}\alpha/\mathrm{d}t$ in Eq. (2) is replaced with $\beta\mathrm{d}\alpha/\mathrm{d}t$ where β is the heating rate giving:

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t}=\frac{A}{\beta}e^{\frac{-\mathrm{E}}{\mathrm{RT}}}f(\alpha) \qquad (3)$$

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

For compounds having 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 the temperature and the 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. The use of Eqs (2) and (3) determines reactions model that does not represent multi-step kinetics.

For this reason one cannot justify the establishment of the reaction mechanism from $f(\alpha)$ alone.

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 the effective activation energy as a function of the extent of conversion.

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 but direct comparison between these two methods should not be made because non-isothermal method experiments cover a much wide range of temperatures.

Isothermal model-fitting method

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

$$g(\alpha)=kt \tag{4}$$

where k is the specific constant rate and $g(\alpha)$ is an integral mathematical expression related to a mechanism of solid phase reactions.

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

$$\frac{d\alpha}{dt}=k(T)(1-\alpha)^n \tag{5}$$

where $k(T)$= the rate constant at temperature T; n= the reaction order and $(1-\alpha)^n=f(\alpha)$ – the differential conversion function.

By linearization, it became:

$$\ln\left(\frac{d\alpha}{dt}\right)=\ln k(T)+n\ln(1-\alpha) \tag{6}$$

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

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

In the case where the obtained data indicate a significant variation of the reaction order *vs*. temperature of reaction, and according to Vyazovkin and Sbirrazzouli [30], this denotes the presence of a complex kinetic. Accordingly, another manner of data processing should be attempted.

Friedman's isothermal-isoconversional method

This method is based on the relation:

$$\ln\left(\frac{d\alpha}{dt}\right)=\ln[Af(\alpha)]-\frac{E}{R}\frac{1}{T} \tag{7}$$

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

$$\ln\left(\frac{d\alpha}{dt}\right)=n\ln[A(1-\alpha)]-\frac{E}{R}\frac{1}{T} \tag{8}$$

By plotting the left member *vs*. $1/T$, the activation energy should be obtained at different conversion degrees. A dependence of E *vs*. α is a sign of a complex kinetics.

The kinetic analysis can continue with the question if the decomposition is a simple or a complex process. For this reason we apply the non-parametric kinetics (NPK) method [31–33] in the following manner:

- the experimental data are represented in a 3D space ($d\alpha/dt$, α, T);
- this data are interpolated to generate a continuous surface corresponding to an equation:

$$\left(\frac{d\alpha}{dt}\right)=f(T)g(\alpha) \tag{9}$$

- the continuous surface of the reaction rate is discretised as a *ixj* matrix M:

$$M=\{m_{ij}\}=\{f(T_i)g(\alpha_j)\} \tag{10}$$

- using the singular value decomposition (SVD) algorithm, the matrix M is decomposed according to Eq. (11):

$$M=U(diag.S)V^T \tag{11}$$

and S is the vector of singular value;

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

$$u_1=g(\alpha) \tag{12}$$

respectively, the temperature dependence, i.e.:

$$v_1=f(T) \tag{13}$$

For the kinetic model we suggest the equation of Šesták–Berggren [34]:

$$g(\alpha)=\alpha^m(1-\alpha)^n \tag{14}$$

and for temperature dependence, the classical Arrhenius equation is selected.

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

$$M=M_1+M_2=U_1(diagS_1)V_1^T+U_2(diagS_2)V_2^T \tag{15}$$

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

With these conditions, the following data can be obtained: E, A, m, n.

Results and discussion

Thermoanalytical data

Three representative curves are presented in Fig. 2.

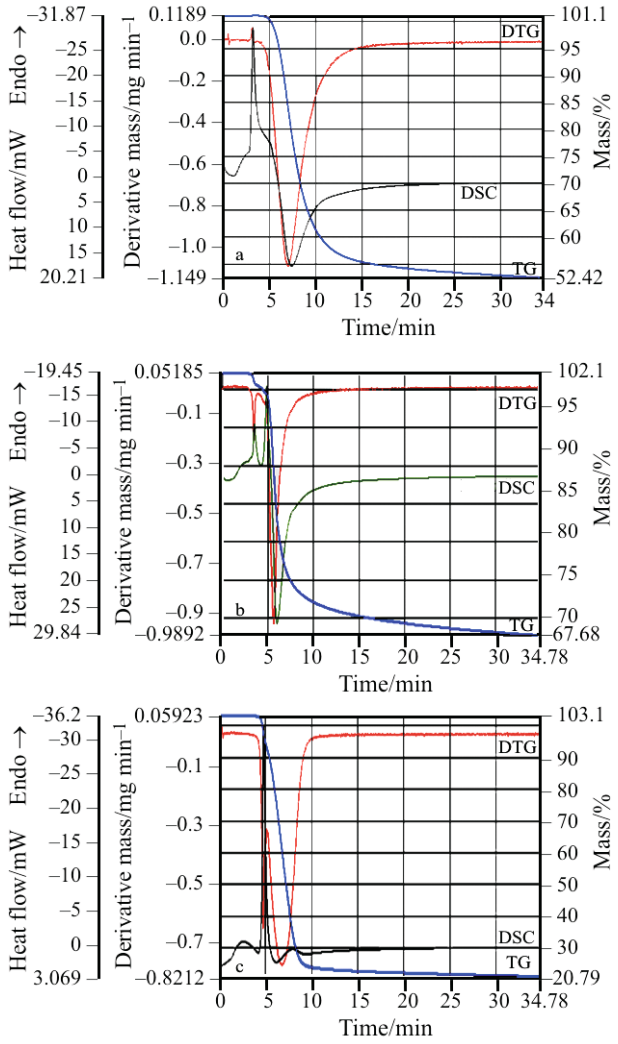

Fig. 2 Isothermal thermoanalytical curves in a dynamic nitrogen atmosphere, during 30 min.; a – Diazepam – 280°C; b – Nitrazepam – 280°C; c – Oxazepam – 280°C

There are great differences regarding the lost mass: 48.7% (52.4% – non-isothermal) diazepam, 34.4% (37.6% – non-isothermal) nitrazepam and respectively 82.3% (79.6% – non-isothermal) oxazepam. Also, the exothermic effect that incurs at the diazepam and nitrazepam decomposition must be noticed, even if the reactions take place in nitrogen. A reasonable explanation could be the existence of a sufficient quantity of oxygen within the molecule to initialize the decomposition process.

Kinetic analysis

The rate of reaction and the reaction order values according to the model-fitting method (Eq. (5)) are presented in Table 1. The variation of the reaction order vs. the temperature of reaction is a sign of a *complex* decomposition process. In these situations, the values for E and A are purely formal, with no real significance whatsoever.

The activation energy values, according to Friedman (Eq. (8)) are comprised in Table 2. A seemingly non-monotonous variation was observed for E *vs*. α, in comparison with the non-isothermal kinetics [29], where a dependence has been established $E=f(\ln(1-\alpha))$. As a result, the Budrugeac–Segal method [35–37], applied to the study under non-isothermal conditions, could not have been also applied for processing the data obtained under isothermal conditions.

The strong dependece of E on α denote that each investigated process is complex. The complexity of each process can be explained by the large differences between E values obtained from isothermal and non-isothermal data.

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

Table 1 Kinetic parameters, according to the Eq. (5)

Compound	Reaction temperature/K										E/kJ mol^{-1}	ln$A$/min^{-1}
	483		498		523		538		553			
	k/s^{-1}	n	k/s^{-1}	n	k/s^{-1}	n	k/s^{-1}	n	k/s^{-1}	n		
Diazepam	0.035	0.02	0.041	0.15	0.432	0.70	0.195	0.90	0.344	1.00	66.9±3.7	13.43±0.62
Nitrazepam	0.113	1.00	0.176	1.25	0.268	1.30	1.064	1.80	0.673	1.70	76.4±4.5	16.71±0.84
Oxazepam	0.107	0.80	0.103	0.60	0.266	1.10	0.255	0.40	0.312	0.25	34.4±2.2	6.29±0.27

Table 2 a) Variation of the activation energy *vs*. conversion by isotherm-isoconversional method

Compound	Activation energy E/kJ mol^{-1}, for α=							
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	Main
Diazepam	61.4	66.4	71.7	66.0	63.7	56.2	44.8	61.5±3.3
Nitrazepam	60.0	58.8	55.8	47.3	46.6	52.2	52.0	53.2±2.0
Oxazepam	51.9	57.2	61.9	63.7	63.8	66.0	64.3	61.3±1.9

Table 2 b) Variation of the activation energy *vs*. conversion by non-isotherm-isoconversional method

Compound	Activation energy E/kJ mol^{-1}, for α=									
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	Main
Diazepam	111.0	114.6	121.2	123.4	127.5	127.4	136.3	127.1	121.1	123.3±2.5
Nitrazepam	79.4	31.5	64.3	111.0	119.8	111.8	121.0	149.2	146.0	103.7±12.9
Oxazepam	167.7	188.2	176.4	160.3	185.9	155.6	87.3	92.6	107.2	146.8±13.4

Table 3 a) Kinetic parameters by NPK method in isothermal conditions

Compound	λ/%	E/kJ mol^{-1}	ln$A$/min^{-1}	M	N	Σλ·E
Diazepam	90.9	45.5±2.8	9.39±0.25	0	0.1	54.9
	5.9	229.5±12.4	50.99±3.52	2	1	
Nitrazepam	95.5	54.3±3.1	11.36±0.53	0	0.02	57.5
	3.8	91.4±6.5	20.26±0.87	2	1	
Oxazepam	86.1	42.3±3.2	8.59±0.22	1	2	51.2
	13.1	111.4±7.2	24.67±1.12	0	0.1	

Table 3 b) Kinetic parameters by NPK method in non-isothermal conditions

Compound	λ/%	E/kJ mol^{-1}	ln$A$/min^{-1}	M	N	Σλ·E
Diazepam	82.2	97.9±6.3	19.55±0.97	0	3/2	80.5
	15.1	44.8±2.7	9.21±0.23	2	0	
Nitrazepam	68.0	42.6±3.0	9.31±0.22	3	0	78.6
	24.7	201.0±11.2	42.67±2.74	0	4	
Oxazepam	74.8	218.6±10.8	47.28±3.18	0	3/2	166.3
	20.6	13.5±1.1	2.86±0.14	0	1/3	

The kinetic data obtained by NPK method are synthesized in Table 3 and the surface of the reaction rate in Fig. 3. The decomposition of oxazepam is better described by a two-step process. Also, rigorously, the diazepam and nitrazepam can be considered having a two-step process, but the last step is less significant. In the last column of Table 3 was calculated an average value ΣλE. It is noticed a satisfactory accord only with the E value for nitrazepam, value also obtained by Friedman's isothermal-isoconversional method (Table 2).

The data obtained by NPK method under isothermal conditions differ significantly from those obtained by the same method, but under non-isothermal conditions (Table 3). The differences are not only regarding the kinetic parameter's values, but even in the decomposition process's complexity: under non-isothermal conditions, all the studied compounds show two elementary steps (λ>15%). That is why a comparison might be risky.

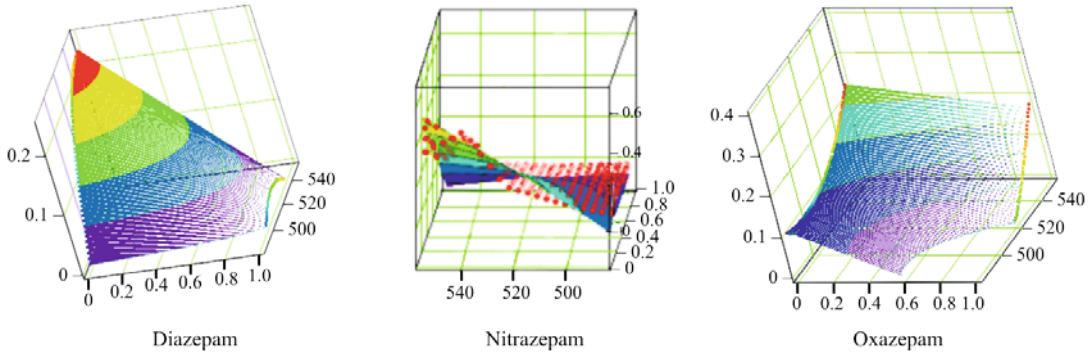

Fig. 3 The reaction surface according to Eq. (12) (Isothermal conditions)

Conclusions

The TG/DTG data obtained for diazepam, nitrazepam and oxazepam's thermal decomposition, under isothermal conditions and in a nitrogen atmosphere, have been processed in three manners: the one of isothermal model-fitting, the Friedman's isothermal-isoconversional model and respectively NPK.

The kinetic parameters obtained by these three methods do not agree very well. The differences between *E* values obtained by isoconversional method and those obtained by NPK method show that the mechanisms of the investigated processes can be more complex that the considered two simultaneous reactions.

Under the conditions of a significant and non-monotonous variation of the activation energy *vs*. conversion, 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 as against with classical methods which uses only few points (usually three or four, corresponding to the maximum of the thermoanalytical curves).

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

Even so the isoconversional methods could also yield similar dependencies of the activation energy on the extent of conversion for isothermal and non-isothermal experiments, a direct comparison between these two methods should not be made because they cover different range of temperatures.

The most surprising results are the two-step process, under non-isothermal conditions, in comparison to the processes that first take place in just a step under isothermal conditions.

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