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THERMAL BEHAVIOR OF SOME PHENITOINE PHARMACEUTICALS

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The topic of the present work is to study the thermal behavior of phenitoine and pharmaceuticals by means of kinetic parameters determined in non-isothermal conditions.

The TG/DTG data were obtained at four heating rates. These data were processed by the following methods: Friedman (FR), Budrugeac–Segal (BS) and the modified non-parametric kinetics (Sempere–Nomen).

The main conclusions of the kinetic study are:

The FR method is versatile, but the values of the kinetic parameters are not certain, especially by multistep processes.

The BS method offer a non-variant part of the activation energy, but the kinetic description is only formal.

The NPK method is able to discriminate between two or more steps of a complex process. In our case, there are a preponderant process (more than 70% of the explained variance).

By the NPK method there is a non-speculative separation of the temperature, respective conversion degree dependence of the reaction rate.

Keywords: *non-isothermal kinetics, phenitoin, thermal stability*

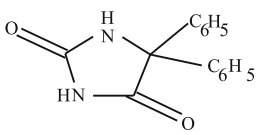
Introduction

The thermal analysis is a current instrumentation technique in assisting the analytical problems of pharmaceuticals [1].

In some recent papers [2–6] we applied different data processing strategies in order to determine the kinetic of the decomposition under non-isothermal conditions. The target was a less speculative interpretation of kinetic data.

The topic of the present paper is to study the thermal behavior of phenitoine (pure substance and pharmaceutical product) by means of kinetic parameters determined under non-isothermal conditions.

Phenitoine, (5,5-diphenyl hydantoine) is the active component of some pharmaceuticals used as anticonvulsive drugs (for example by epilepsy). Also, is utilized in the synthesis of some α-amino acids and derivatives of pyruvic acid.



Experimental

The studied samples were: pure phenitoine **I**, and a pharmaceutical Artmedica.

The thermogravimetric data (TG and DTG) were obtained on Perkin-Elmer TGA7 devices in dynamic air atmosphere (20 mL min^{-1}) and heating rates of 5, 7, 10 and 12°C min^{-1}.

Two representative examples are depicted in Fig. 1 and the data are systematized in Table 1. The only significant difference between the two samples is by the relative mass loss, and this is certain due to the additives of the pharmaceutical product.

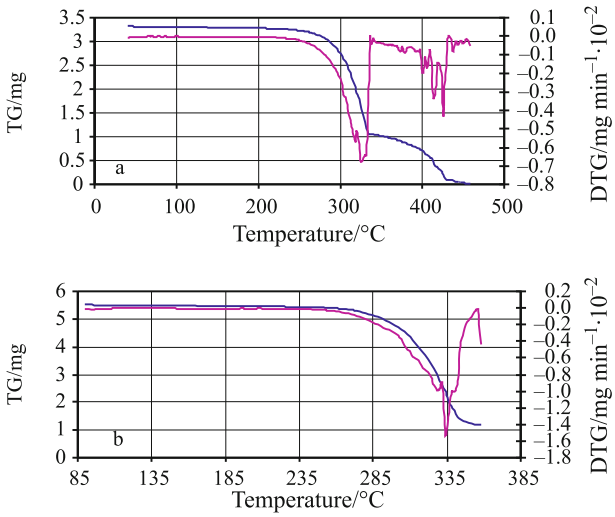


Fig. 1 TG/DTG curves for phenitoin a – phenitoin substance; b – phenitoin drug; heating rated 10°C min^{-1}

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Table 1 Thermogravimetric characteristics

Sample	Beginning of decomposition, T_i/°C	End of decomposition, T_f/°C	Maximum of DTG, T_{max}/°C	Relative mass loss/ %
Pure phenitoine	256	342	324	67.2
Drug	252	356	334	80.0

Data processing

According to the aim of this paper, the strategy of data processing is of relevance, therefore it will be detailed.

The differential-isoconversional method of Friedman [7]

From the generally accepted equation of the non-isothermal kinetics [8]:

$$\beta\frac{d\alpha}{dT}=f(\alpha)A\exp\left(-\frac{E}{RT}\right) \quad (1)$$

(where β is the heating rate and $f(\alpha)$ is the conversion function), considering isoconversional conditions, the equation corresponding to the Friedman's differential-isoconversional method was obtained:

$$\ln\left(\beta\frac{d\alpha}{dT}\right)_\alpha=\ln[Af(\alpha)]-\frac{E}{RT} \quad (2)$$

At a certain conversion, the slope and the intercept of $\ln[\beta/(d\alpha/dT)]_\alpha$ *vs.* $1/T$ give the activation energy and the product $Af(\alpha)$, respectively.

This method is relative simply and independent in respect to the kinetic model, so useful by simple single-step processes with activation energy invariant in respect to conversion degree. A variation of E *vs.* α is clearly a sign of a complex multi-step processes.

The Budrugeac–Segal method [9, 10]

If the E *vs.* α dependence is of the particular form

$$E=E_0+E_1\ln(1-\alpha) \quad (3)$$

then the Friedman's Eq. (2) became

$$\ln\left(\beta\frac{d\alpha}{dT}\right)=\left(a+bE_0-\frac{E_0}{RT}\right)+\left(bE_1-\frac{E_1}{RT}+n\right)\ln(1-\alpha) \quad (4)$$

In obtaining Eq. (4), two supplementary hypotheses were made:

- the existence of a compensation effect, i.e.

$$\ln A=aE+b \quad (5)$$

- a conversion function of reaction order type:

$$f(\alpha)=(1-\alpha)^n \quad (6)$$

The correct value of n will be the one that gives a correlation coefficient closest to 1 for the straight line represented by $\ln(\beta d\alpha/dT)$ *vs.* $\ln(1-\alpha)$. The constants E_0, E_1, a and b are obtained from Eqs (3) and (5).

Despite of some difficulties by interpretation of the significance of E_0 and E_1, Eq. (4) presented a very good simulation capacity, proved in some of our previous papers [3–6, 11, 12].

The non-parametric kinetic (NPK) method by Sempere and Nomen [13–15]

This more sophisticated method rely on the hypothesis that the reaction rate can be expressed as a product of two independent functions

$$r_{ij}=f(T_i)g(\alpha_j) \quad (7)$$

So, the experimental points obtained at different heating rates are represented in a 3D coordinate system (r, T, α) and interpolated as a continuous reaction rate surface.

This surface is discretizated into a square matrix M which is decomposed, using the singular value decomposition algorithm [16], into the product of three matrixes

$$M=U(diagS)V^T \quad (8)$$

A vector u_1 given by the first column of the matrix U is analyzed *vs.* α to determine the conversion function, for example the equation of Šestak and Berggren [17]

$$g(\alpha)=\alpha^m(1-\alpha)^n \quad (9)$$

A similar vector v_1, corresponding to the matrix V is checked for an Arrhenius type temperature dependence.

If the decomposition process is a result of two simultaneous steps, 1 and 2, it means that

$$r=r_1+r_2=f_1(T_i)g_1(\alpha_j)+f_2(T_i)g_2(\alpha_j) \quad (10)$$

respectively the matrix M became

$$M=M_1+M_2 \quad (11)$$

The contribution of each step to the observed process is expressed by the explained variance λ so that $\lambda_1+\lambda_2=100\%$

The data processing strategy of the NPK method allows:

Table 2 Variation of *E vs.* α according to Friedman's method

α	0.2	0.3	0.4	0.5	0.6	0.7	0.8	Main value
E/kJ mol^{-1}	189.0	215.1	204.3	223.8	231.5	224.3	155.5	206.2

- an objective separation of the temperature, respective conversion dependence on the reaction rate;
- a separation of complex processes and discrimination between the contributions of the physical (m) and chemical (n) phenomenons.

Results and discussion

The kinetic study was carried out only on pure phenitoine because kinetics on samples with non-unitary composition (like pharmaceuticals) is purposelessly.

According to the data in Table 2, the *E vs.* α variation is not large. Especially in the range of α=0.3–0.7 this variation is reasonable, therefore a main value was calculated.

With the data of Friedman's method, the kinetic analysis was continued with the BS method. In Figs 2 and 3 the hypotheses according to Eq. (3) respective Eq. (5) was checked and the results of the data processing are systematized in Table 3.

Noticeable is that E_0 value (the invariant part of the activation energy) is very close to the main value obtained by Friedman's method.

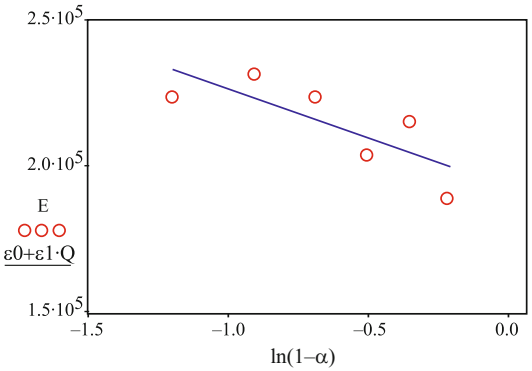

Fig. 2 Variation of *E vs.* ln(1–α)

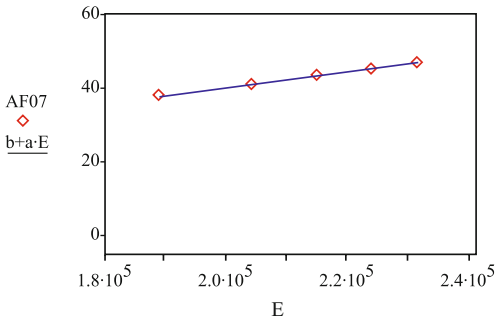

Fig. 3 Compensation effect

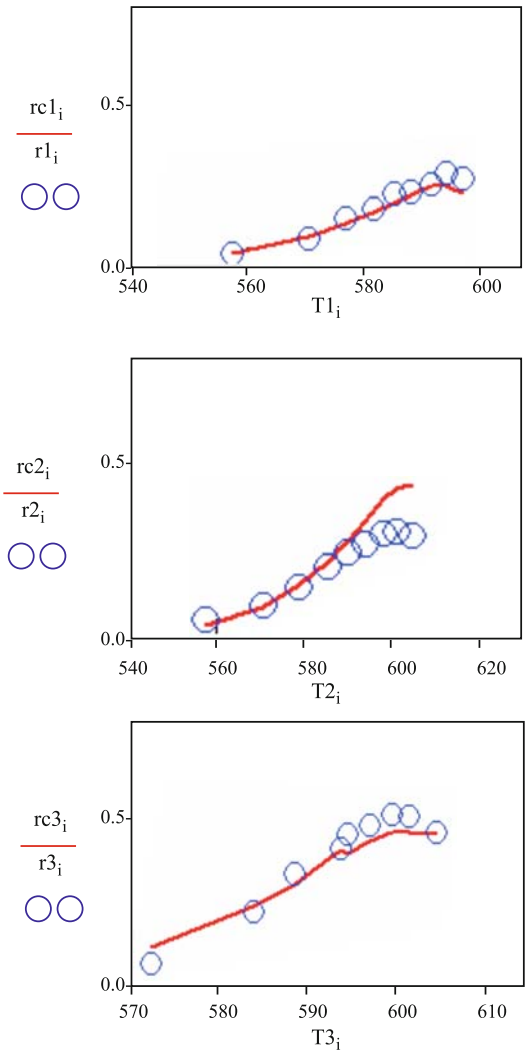

Fig. 4 — – Simulated reaction rates, ○ – respectively experimental reaction rates *vs.* degree of temperature, according to Eq. (4) and Table 3 for heating rates of 5, 7 and 10°C min^{-1}

With the data in Table 3 and using the Eq. (4), the reactions rates were simulated. The data in Fig. 4 demonstrate a rather good description ability.

The results of the kinetic analysis by the NPK method are presented in Table 4.

The decomposition of phenitoine is a complex process with a preponderant step process of a relevance more than 70%. Both the preponderant and the secondary steps are chemically phenomenons, i.e. m=0 and n≠0 by Šestak–Berggren equation. What is remarkable is the value of $\sum\lambda_i E_i$, very close to the

Table 3 The kinetic parameters according to BS method (Eq. (4))

E_0/kJ mol^{-1}	E_1/kJ mol^{-1}	$a\cdot10^4$	b	n	Corr. coeff.
192.7	–33.7	2.09	–1.858	0.7	0.9999

Table 4 Kinetic parameters by the NPK method

Process	Explained variance, λ/%	Activation energy, E/kJ mol^{-1}	Pre-exponential factor, A/min^{-1}	Šestak–Berggren coeff.		$\sum\lambda_i E_i$/ kJ mol^{-1}
				m	n	
Preponderant	72.2	125.2	$1.462\cdot10^{11}$	0	1/5	205.7
Secondary	24.0	480.4	$4.221\cdot10^{42}$	0	2	

values of E_0 (Budrugeac–Segal) respective to the main value by Friedman's method.

The sense of $\sum\lambda_i E_i$ is an adjustment of the contribution of the two processes to the observable temperature dependence of the whole reaction.

Conclusions

- The thermal behavior of phenitoine was estimated by a comparative kinetic study using three data processing strategies.
- The FR method is versatile, but the values of the kinetic parameters are not certain, especially by multistep processes.
- The BS method offer a non-variant part of the activation energy, but the kinetic description is only formal.
- The NPK method is able to discriminate between two or more steps of a complex process. In our case, there are a preponderant process (more than 70% of the explained variance).
- By the NPK method there is a non-speculative separation of the temperature, respective conversion degree dependence of the reaction rate.
- By all the three methods very near values for a parameter considered a main description for the temperature susceptibility of the reaction rate were obtained. Indeed, since E (Friedman), E_0 (BS) and $\sum\lambda_i E_i$ (NPK) have values by 200 kJ mol^{-1}, it is a reasonable conclusion to consider true and real this value as a descriptive parameter similar to an activation energy.

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