Non-isothermal Isoconversional Kinetic Study Regarding the Degradation of Albendazole

IONUT LEDETI[1], GABRIELA VLASE[2], TITUS VLASE[2], MARIUS MURARIU[3], CRISTINA TRANDAFIRESCU[4]*, CODRUTA SOICA[4], LENUTA MARIA SUTA[5], CRISTINA DEHELEAN[6], ADRIANA LEDETI[7]

[1] University of Medicine and Pharmacy Victor Babes, Faculty of Pharmacy, Department of Physical Chemistry, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

[2] West University of Timisoara, Research Centre for Thermal Analysis in Environmental Problems, 16 Pestalozzi Str., 300115 Timisoara, Romania

[3] University of Medicine and Pharmacy Victor Babes, Faculty of Medicine, Department of Surgery II, First Surgical Clinic, 2 Eftimie Murgu Sq., 300041, Timisoara, Roamnia

[4] University of Medicine and Pharmacy Victor Babes, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

[5] University of Medicine and Pharmacy Victor Babes, Faculty of Pharmacy, Department of Pharmaceutical Technology, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

[6] University of Medicine and Pharmacy Victor Babes, Faculty of Pharmacy, Department of Toxicology, Eftimie Murgu Sq., 300041, Timisoara, Romania

[7] University of Medicine and Pharmacy Victor Babes, Faculty of Pharmacy, Department of Analytical Chemistry, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

In this paper, we present the results obtained during the study regarding the thermal decomposition of albendazole, by employing kinetic analysis. Three isoconversional methods were used: Friedman, Kissinger-Akahira-Sunose and Flynn-Wall-Ozawa. The mean values for activation energies are in good agreement, independently to differential/integral processing of the data, being around 290 kJ·mol^{-1}. The only difference suggested by isoconversional methods is in the contribution of parallel steps involved in the degradation: the differential method of Friedman suggests the existence of parallel steps, since the variation of E_a vs. α around the mean is outside the 10% limit variation, while the integral methods suggest an independent mechanism of decomposition.

Keywords: albendazole, kinetic study, thermal decomposition, isoconversional methods

The formation of gallstone is a medical problem that nowadays is considered of high impact over the lifestyle of human subject. Generally, a gallstone is a solid concretion that is composed out of bile components, formed during a process of lithogenic development. Cholelithiasis may be associated also with inflammatory processes, due to bile retention but also following infections with microorganisms [1,2].

Since literature data reports also biliary ascariasis located in the common bile duct, in the hepatic abscess cavity but as well in the gallbladder [3], the development of new pharmaceutical formulations is considered a priority in this domain, in correlation with evaluation of physico-chemical properties of the active pharmaceutical ingredients (API) that can influence the stability of these formulations. The treatment should also be correlated with location of infections, and the imagistic diagnosis can be correlated with the possibility of observing morphological variations of the intrahepatic biliary tree or other anatomical parts [4-9].

Albendazole (ABZ), by systematic name being methyl [5-(propylthio)-1*H*-benzoimidazol-2-yl]carbamate or 5-(Propylthio)-2-carbomethoxyaminobenzimidazole, is an effective first-line treatment against ascariasis and giardiasis among other parasitic worm infestations. According to literature [10], ABZ is approved for both human and veterinary use, as prescription product. ABZ is used since 1996, as solid oral formulations in film-coated tablet, with strength of 200 mg API per tablet, by more than 25 international brands [10]. Due to its considerable lower solubility in water (10^{-3} g/L), ABZ is being considered an insoluble compound [11]. Several literature references indicate a melting point for ABZ around 208°C [12,13], which can indicate a high thermal stability. The structural formula of ABZ is presented in figure 1.

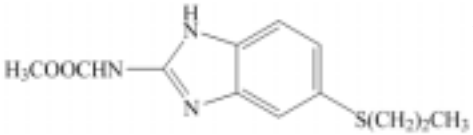

Fig. 1. Structural formula of ABZ

Since kinetic analysis of solid-state degradation of organic molecules is considered one of the most reliable techniques for evaluation of thermal stability under thermal stress [14-18], we set our goal in this paper to evaluate the kinetic parameters regarding the decomposition of ABZ, as to our knowledge it was not previously reported.

Experimental part

Materials and methods

Albendazole (ABZ) with pharmaceutical grade was used as received, without previous purification. The supplier was Biesterfeld Siemgluess (Germany).

* *email; trandafirescu.cristina@umft.ro*

The following abbreviations were used in the kinetic process description: α is the conversion degree, *T* is temperature, f(α) is the differential conversion function, g(α) is the integral conversion function, *R* is the universal gas constant, β is the heating rate $\beta = dT/dt$ (where *t* is time), *A* is the pre-exponential factor and E_a is the activation energy according to Svante Arrhenius.

Thermoanalytical measurements (as TG/DTG/HF data) were obtained using a Perkin-Elmer DIAMOND TG/DTA instrument. The experiments were carried out using about 4 mg of sample, using open aluminum crucibles in a synthetic air atmosphere at a flow rate of 100 mL min^{-1}. The temperature program was selected as follows: non-isothermal heating from 39 °C up to 500°C, linearly at heating rates β = 5, 7, 10, 12 and 15°C·min^{-1}. The kinetic degradation was investigated on 150-215 °C temperature range. Data were processed as in some previous studies, by using three isoconversional methods: the differential method of Friedman and the integral methods of Flynn-Wall-Ozawa and Kissinger-Akahira-Sunose. The estimation of E_a values was realized, for $0.05 \leq \alpha \leq 0.95$, with a variation step for α of 0.05.

Results and discussions

Thermal stability under non-isothermal heating

The thermogravimetric analysis and Heat Flow curve of ABZ pure substance, carried out in air atmosphere at β=7 °C·min^{-1}) are presented in figure 2.

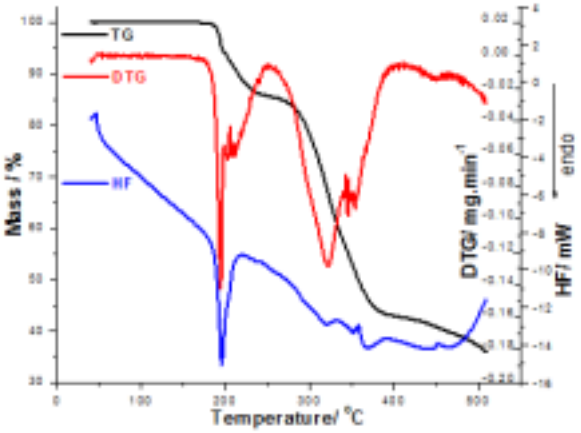

Fig.2. TG/DTG/HF curves obtained for ABZ at heating rate β=7 °C·min^{-1}

The analysis of TG curves demonstrates a gradual decomposition pattern in two steps, as the temperature increases. With the increase of the heating rate, all the parameters (onset temperatures of the TG events, and DTG / HF peaks respectively; maximum of all peaks) increased due to the heat transfer. For β= 7°C . min^{-1}, the decomposition begins at 175.6°C and the mass loss for the first process corresponds to Δm=14.45%. This decomposition step is related to the melting process which takes place with thermal degradation. The narrow endothermic peak is observed on HF curves with maximum at 194.1°C. A shoulder is presented near the melting peak, which sustained the observed mass loss.

Table 1

COLLECTED DATA FOR MELTING AND DECOMPOSITION ONSET OF ABZ AT ANALYZED HEATING RATES

	Heating rate β (°C·min^{-1})				
	5	7	10	12	15
Melting peak (°C)	193.4	195.7	200.0	201.2	202.9
Decomposition onset (°C)	177.2	175.7	178.0	178.9	179.4

The lower value for the observed melting point compared to the literature can be explained by the presence of the two polymorphs in the sample [19]. Second stage of ABZ decomposition is related to the largest mass loss Δm= 49.48 % (T_{onset} = 254 °C) and is connected with a broad peak on DTG curve with T_{max} = 317°C (and a shoulder observed at T=343 °C).

Kinetic study

Since thermal investigation by TG/DTG/HF data determination indicates an increased thermal stability of ABZ, for a better vision over this stability, kinetic study was employed. Some inadvertencies were noticed between our obtained data and the ones reported in literature regarding the melting of ABZ. As previously mentioned, literature indicate a melting point around 208°C [12,13], but without indications regarding the heating rate of the sample. In our experimental condition, the melting takes place at considerable lower temperatures, the processes are accompanied by decomposition, as presented in table 1.

The obtained results can be due to polymorphic composition of the sample, as previously mentioned, but as well by the influence of the thermobalance furnace atmosphere. However, the study of Moyano et al. [20] reported melting point data that differs from the declared melting point of the substance, and later mentioned by the study of Laura Martinez-Marcos et al. [21]. However, this last study indicated that the melting process starts at 186 °C and the complete melting is observed at 210°C.

The kinetic analysis was carried out according to ICTAC 2000 recommendations. Since the processing of kinetic data, as well the approximations used are different for each isoconversional method, we employed in our study a differential method (Friedman) and two integral – Flynn-Wall-Ozawa (FWO) and Kissinger-Akahira-Sunose (KAS).

The use of isoconversional methods afford superior results in comparison to classical kinetic protocols, since the detection of complex degradative steps, the evaluation of activation energy (E_a) *vs.* conversion degree (α), but as well the estimation of the temperature-dependency of reaction mechanism (i.e. if the reaction order is affected by heating rate).

Friedman [22] proposed a linearized equation for describing the degradation process of samples under non-isothermal conditions (table 2), and after data plotting of $\ln(\beta \frac{d\alpha}{dT})$ vs. (1/*T*), linear correlations were obtained, as presented in figure 3.

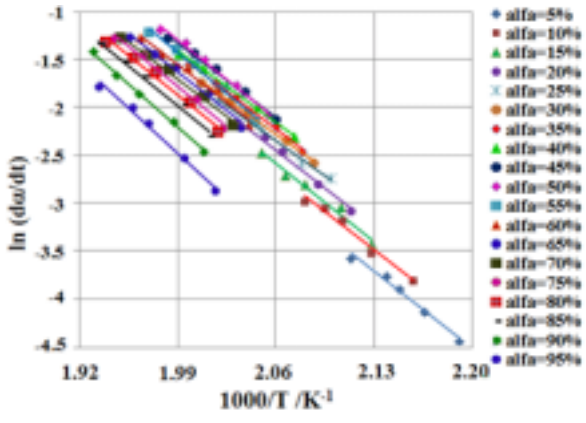

Fig. 3 Friedman's linear plot for ABZ

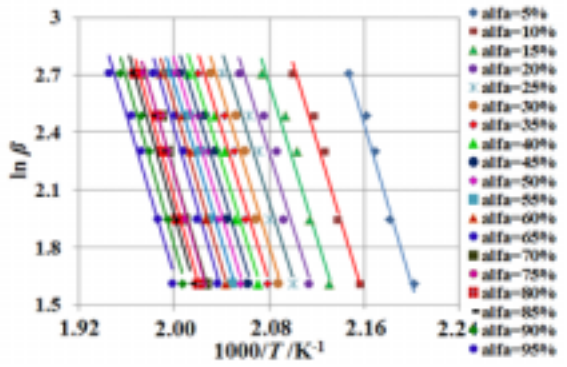

Fig. 4 Ozawa–Flynn–Wall linear plot lnβ vs. 1/*T* for ABZ

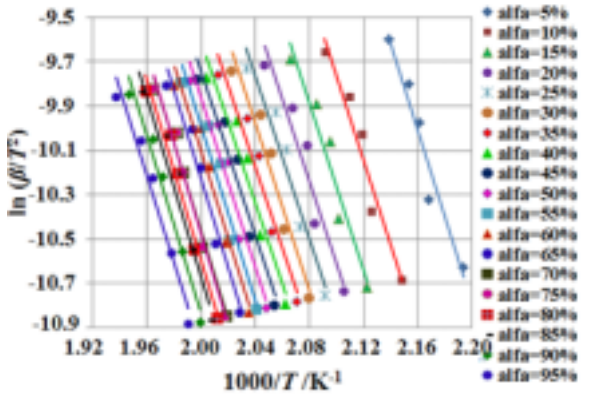

Fig. 5 Kissinger-Akahira-Sunose linear plot lnβ/T^2 vs. 1/*T* for ABZ

Table 2

THE ESTIMATED VALUES FOR E_a *vs.* α for ABZ USING THE SELECTED ISOCONVERSIONAL METHODS

Method and expression	*E_a (* kJ mol^{-1}) for analyzed conversion degree *α*									
FR $\ln(\beta\frac{d\alpha}{dT}) = \ln[A\cdot f(\alpha)] - \frac{E_a}{R\cdot T}$	*0.05*	*0.1*	*0.15*	*0.2*	*0.25*	*0.3*	*0.35*	*0.4*	*0.45*	*0.5*
	320.6	309.6	301.0	299.1	291.7	290.0	292.8	294.5	289.8	282.2
	0.55	*0.6*	*0.65*	*0.7*	*0.75*	*0.8*	*0.85*	*0.9*	*0.95*	$\overline{E_a}$
	286.0	288.7	282.5	278.7	279.1	277.3	288.2	290.7	291.8	**291.3±10.4**
KAS $\ln\frac{\beta}{T^2} = \ln\frac{A\cdot R}{E_a\cdot g(\alpha)} - \frac{E_a}{R\cdot T}$	*0.05*	*0.1*	*0.15*	*0.2*	*0.25*	*0.3*	*0.35*	*0.4*	*0.45*	*0.5*
	294.1	297.7	298.1	296.3	292.8	290.1	295.0	290.3	293.6	288.2
	0.55	*0.6*	*0.65*	*0.7*	*0.75*	*0.8*	*0.85*	*0.9*	*0.95*	$\overline{E_a}$
	287.8	284.2	289.9	284.1	286.0	284.3	285.1	286.8	288.8	**290.2±4.5**
FWO $\ln\beta = \ln\frac{A\cdot E_a}{R\cdot g(\alpha)} - 5.331 - \frac{1.052\cdot E_a}{R\cdot T}$	*0.05*	*0.1*	*0.15*	*0.2*	*0.25*	*0.3*	*0.35*	*0.4*	*0.45*	*0.5*
	295.2	297.8	299.4	297.5	293.3	291.3	296.9	292.5	294.1	288.5
	0.55	*0.6*	*0.65*	*0.7*	*0.75*	*0.8*	*0.85*	*0.9*	*0.95*	$\overline{E_a}$
	287.9	287.2	291.2	285.1	288.5	285.1	287.5	287.3	289.4	**291.4±4.4**

The integral method of T. Ozawa [23] and J.H. Flynn and L.A. Wall [24] uses the Doyle approximation, and after plotting lnβ *vs.* 1/*T* (fig. 4), the activation energy was estimated (table 2).

Kissinger [25], Akahira and Sunose [26] developed an isoconversional method based on Murray-White approximation. The linear plotting $\ln\frac{\beta}{T^2}$ *vs.* 1/*T* led to the lines presented in figure 6, and the values for E_a are presented in table 2.

The variation of E_a *vs.* α in the case of FR method takes place in the 320-277 kJ/mol range, which may suggest a modification of the reaction mechanism, since the variation is outside the 10% limit, especially at lower conversion degrees. Surprisingly, in the case of integral methods, the variation occurs in narrow intervals, these methods suggest that the modification of the mechanism is not occurring during modification of temperature. The differences obtained between these methods reside mainly in the different processing of kinetic data: differential vs. integral. However, a concrete separation of the parallel steps and the ascertain their existence will be reported after the processing of the kinetic data using the non-parametric kinetic method (NPK), which was previously used by our research group.

Conclusions

It was studied the thermal stability of ABZ, reflected by both thermal analysis (TG/DTG/HF data), and later by kinetic study. The obtained mean values for activation energy falls in the range for molecules with increased thermal stability. This fact was however expected, since the functionalized benzoimidazolic ring is associated with increased stability, due to aromatic structure.

The mean values for activation energies are in good agreement, independently to differential/integral processing of the data, being around 290 kJ·mol^{-1}. The only difference suggested by isoconversional methods is in the contribution to parallel steps involved in the degradation: the differential method of Friedman suggests parallel steps, since the variation of E_a vs. α is outside the 10% limit variation, while the integral methods suggest an independent mechanism of decomposition.

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