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Research Article

### STUDY OF KINETIC PARAMETERS OF THERMAL DECOMPOSITION OF CILOSTAZOL UNDER ISOTHERMAL AND NON-ISOTHERMAL CONDITIONS

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**Abstract:**

*Cilostazol is a drug used to treat the symptoms of intermittent claudicating, which is basically leg pain caused by walking. Thermogravimetry/derivative thermogravimetry and differential thermal analysis are useful techniques that have been successfully applied in the pharmaceutical industry to study the thermal degradation and kinetic parameters; activation energy ( $E_a$ ), frequency factor ( $A$ ), and reaction order ( $n$ ), as regarding the physicochemical properties of drugs and excipient molecules, such as polymorphism, stability, purity, formulation compatibility, among others. The kinetic parameters were evaluated by isothermal and non-isothermal conditions including Ozawa's conventional method, Ozawa–Flynn–Wall and Friedman isoconversional methods. The kinetic parameters were determined using the thermogravimetric curves of the decomposition process. The results of TG analysis revealed that the main thermal degradation for the Cilostazol occurs during two temperature ranges of 175–300 and 300–600 °C. The TG/DTA analysis of Cilostazol indicates that this drug melts (at about 160 °C) before it decompose. The results showed that as the heating rate was increased, decomposition temperatures of the compounds were increased. Also, the kinetic parameters such as activation energy values obtained were 162.2 and 163.12 kJ mol<sup>-1</sup> for the isothermal and non-isothermal conditions, respectively. Finally, the values of  $\Delta S^\ddagger$ ,  $\Delta H^\ddagger$ , and  $\Delta G^\ddagger$  of the decomposition reaction were calculated.*

Key words: *Thermal decomposition, Cilostazol, isothermal.***Corresponding author:****Mahmmoud S. Abd-Elmonem,**

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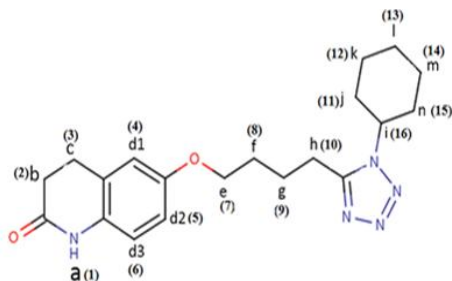


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## INTRODUCTION:

Cilostazol and several of its metabolites are cyclic adenosine monophosphate inhibitors, inhibiting phosphodiesterase activity and suppressing cyclic adenosine monophosphate degradation with a resultant increase in cyclic adenosine monophosphate in platelets and blood vessels, leading to inhibition of platelet aggregation and vasodilatation [1-2].

Molecular structure Cilostazol is given in Fig. (1). Chemical IUPAC Name: 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3, 4 dihydro- 2(1H)-quinolinone



<b>Molecular form</b>	$C_{20}H_{27}N_5O_2$
<b>Molecular weigl</b>	369.4607 g/mo

**Fig. 1: Chemical structure of drugs**

In the case of drugs and medicines, the TG/DTG and DSC techniques allow evaluation and/or comparison of thermal stabilities of pharmaceutical materials, the acquisition of data on drug/excipient compatibility for the pre-formulation studies, and determination of kinetic parameters (activation energies, frequency factor, and reaction order) [3,4]. The application of thermoanalytical methods may provide new information about the temperature and energy associated with events, such as melting, oxidation and reduction reactions, glass transition, boiling, sublimation, decomposition, and crystallization [5–7]. The thermal decomposition of drugs is interesting to predict the degradation rates at temperatures from data collected on accelerated processes that are studied at elevated temperatures. The temperature may increase the chemical reactions, providing sufficient energy (activation energy) required to break chemical bonds and starts the decomposition process [8, 9]. The information from TG/DTG and DSC should be combined to enable optimal characterization of the materials. Although the TG/DTG detect all types of thermal reactions in terms of variations in mass, the DSC also detects reactions which may or may not be associated with loss of mass, such as physical phenomena. For example, a change in physical state (fusion) can be

unequivocally attributed from the DSC curve if losses in mass reactions are not found in the same temperature range on TG/DTG curves. In most cases, interpretation of thermal reactions is difficult without superposition of the TG/DTG and DSC curves obtained under the same experimental conditions. Kinetic parameters is useful in pharmaceutical quality control, development of pharmaceutical products and for evaluation of quality of pharmaceutical products from technologic parameters [10-13] Literature review showed several methods have been reported for the analysis of Cilostazol in pure form, dosage forms, and biological fluids or in combination with other drugs. These methods include gas chromatography [14], high-performance liquid chromatography [15–18], Spectrophotometric methods [19-21], and Electro analysis were also reported [22-23].

## Materials

Cilostazol was kindly supplied by El Delta pharm Pharmaceutical Co, 10th of Ramadan city, Area B4 Egypt

Cilostazol works by improving blood circulation, supplying blood to the legs, dilating the arteries, and decreasing the coagulation of platelets. Clinical studies showed Cilostazol role in increasing fatality rate among patients with congestive heart failure. The same studies showed, however, that the drug does not do same harm to people who do not have the disease.

## METHODS:

The weight of samples is ranging from 4 to about 7 mg, using a platinum pan. Measurements were carried out from 600 °C at different heating rates (5, 10, 15, and 20 C min<sup>-1</sup>). The kinetic parameters of decomposition such as, activation energy (E), frequency factor (A), and reaction order (n) were calculated. The kinetic parameter and the order of reaction for Ozawa's method were obtained with TA 60 software. The DSC curves were obtained on a DSC-50 cell (Shimadzu) using aluminum crucibles with about 2 mg of sample, under dynamic N<sub>2</sub> atmosphere (50 mL min<sup>-1</sup>) and heating rate (β) of 10 °C min<sup>-1</sup> between 25 to 200 °C. The DSC cell was calibrated using indium (m.p. 156.6 °C, ΔH<sub>fusion</sub> = 28.54 J g<sup>-1</sup>) and zinc (m.p. 419.6 °C)

Thermogravimetric analysis, derivative thermogravimetry and differential thermal analysis measurements were made by using simultaneous DTA-TGA thermal analyzer apparatus (Shimadzu DTG-

The kinetic parameters and the order of reaction for Ozawa's conventional method [24-25] were obtained with software TA 60 software. Isoconversional method Kinetic methods propose that the isothermal

rate of conversion ( $da/dt$ ) is a linear function and is a function of temperature ( $T$ ) and extent of conversion ( $\alpha$ ), as in Eq. 1 [26].

$$da/dt = k(T) f(\alpha) \dots \dots \dots \text{Eq. 1}$$

Kinetic methods suppose that  $da/dt$  is a linear function of the temperature-dependent rate constant,  $k(T)$ , and a temperature-independent function of conversion,  $f(\alpha)$ , which depends on the mechanism of the reaction [26].

Under non-isothermal conditions, Eq. 1 becomes:

$$da/dt = (A/\beta) e^{-E/RT} \dots \dots \dots \text{Eq. 2}$$

Where,  $\beta = dT/dt$ , is the heating rate,  $A$  is the pre-exponential factor,  $E$  is the activation energy, and  $R$  is the gas constant. Ozawa–Flynn–Wall and Friedman isoconversional methods can be used to calculate  $E$ . These methods consider that for all values of  $\alpha$ ,  $f(\alpha)$  does not change with different heating rates; therefore, measurements of temperature, corresponding to fixed values of  $\alpha$  at different heating rates, are required [27]. Under these conditions Eq. 2 turns into Eqs. 3 and 4:

$$\ln \beta = \ln [A f(\alpha)/dt] - E/RT \dots \dots \dots (3)$$

$$\ln [\beta \cdot da/dt] = \ln [A f(\alpha)] - E/RT \dots \dots \dots (4)$$

The plots of  $\ln \beta$  and  $\ln [\beta \cdot da/dt]$  versus  $1/T$  should give straight lines with slopes of  $-E/R$ .

If the values of  $E$  determined are almost constant for different values of  $\alpha$ , then the decomposition reaction occurs in a single step; on the other hand, a change in  $E$  with increasing degree of conversion is an indication of a complex reaction mechanism. The

results obtained by the isoconversional method may corroborate the results of activation energy using Ozawa's method in the nonisothermal conditions. It is known that the most reliable kinetic methods are the isoconversional ones [27-28]. Arrhenius parameters and the reaction mechanisms were determined through isothermal and non-isothermal kinetic analysis [29-31]. The activation energy can be obtained using several thermogravimetric curves at different heating rates by the non-isothermal method. Melting point measurement was carried out using OptiMelt automated melting point instrument by the American Stanford Research System.

The infrared absorption spectra of the Cilostazol were obtained using model MB102 [A in the region of 4000 to 400  $\text{cm}^{-1}$ . KBr] pellets containing small amount of the samples were prepared.

The studies were done at National Organization for Drug Control and Research,

## RESULTS AND DISCUSSIONS:

The TG/DTG and DSC curves of Cilostazol are shown in Fig. 2. The TG/DTG curves indicated that is thermally stable up to around 159 °C and that the thermal decomposition process occurred in two stages. The first stage occurred rapidly between 175 and 300 °C, with a mass loss of 93.58%. However, the second step occurred slowly between 300 and 600 °C with gradual mass loss of around 7.25 %.

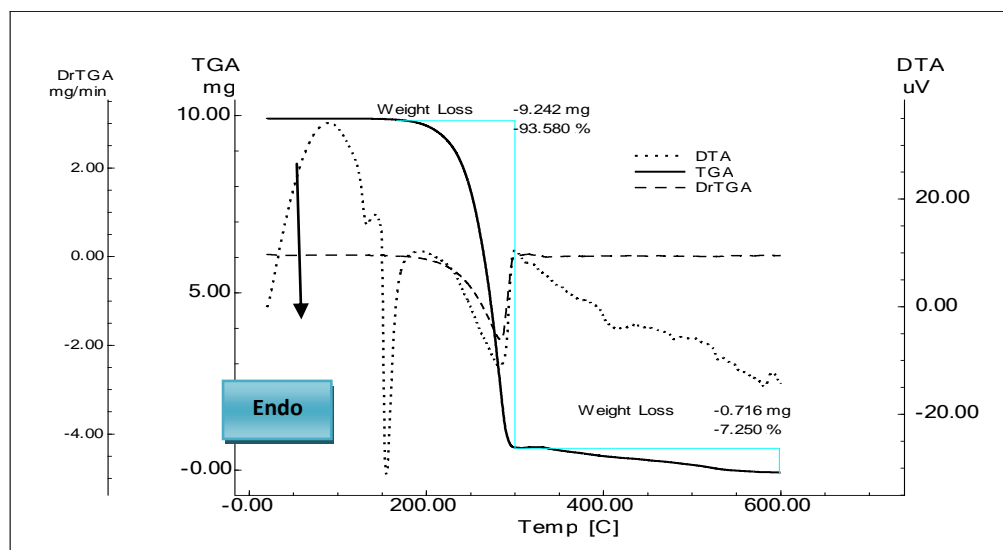


Fig. 2: TG/DTG and DSC curves obtained at 10° C/min for the Cilostazol sample

The FTIR spectra of Cilostazol showed the presence of following peaks: 3317, 3182  $\text{cm}^{-1}$  (N-H stretching); 3056, 3049  $\text{cm}^{-1}$  (Aromatic C-H stretching), 1458, and 1431  $\text{cm}^{-1}$  (C-H bending) 1244, 1195, 1155  $\text{cm}^{-1}$  (C-N stretching) and 1080  $\text{cm}^{-1}$  (C-O stretching). Therefore, Cilostazol is suitable for thermal analysis experiments.

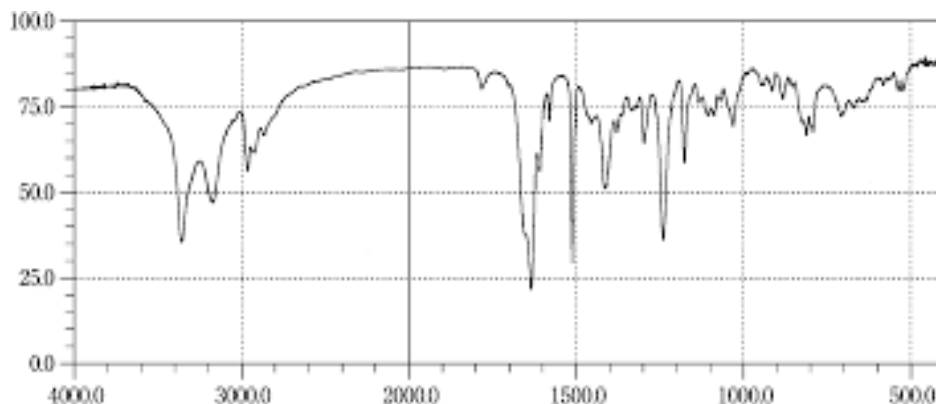


Fig. 3: IR spectra of Cilostazol

### DSC

The DSC thermograms of Cilostazol are shown in Fig. 4. The DSC curves of pure Cilostazol demonstrated the melting points at 161.85°C. The thermal events observed on the DSC curve were endothermic and are according to conversation

evidenced on the TG/DTG curves. The first endothermic reaction was evidenced between 116 and 134 °C ( $T_{peak} = 123$  °C) and the second occurred between 145 and 166 °C ( $T_{peak} = 161.8$  °C

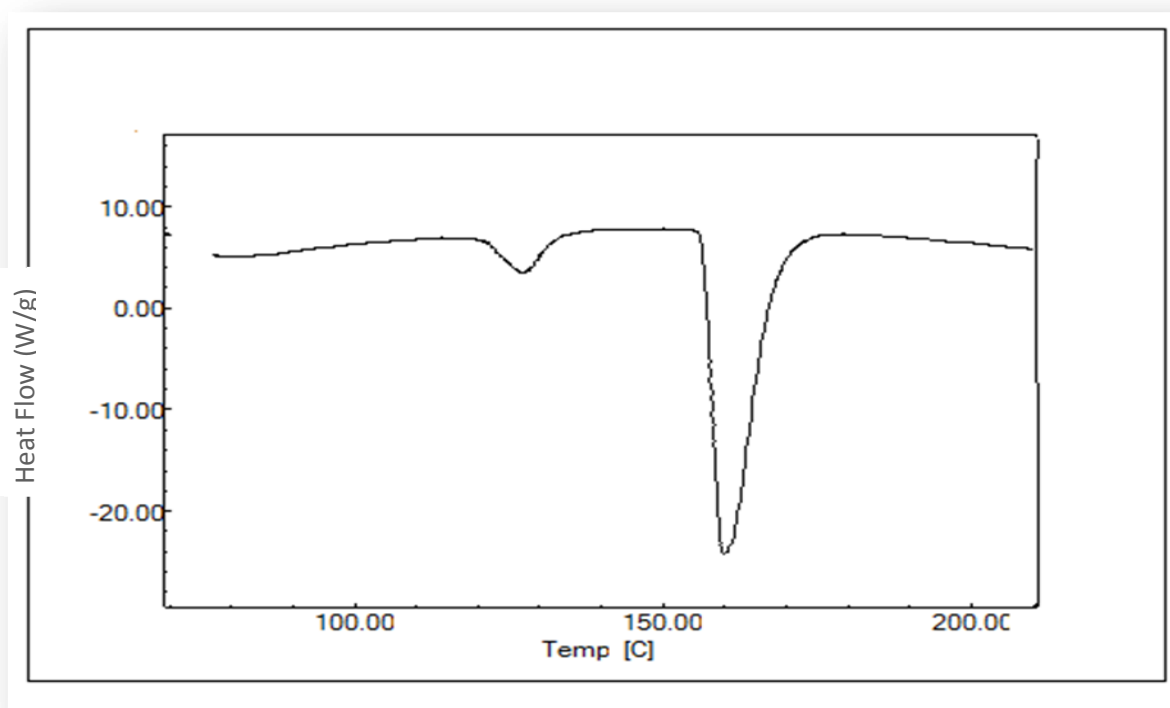
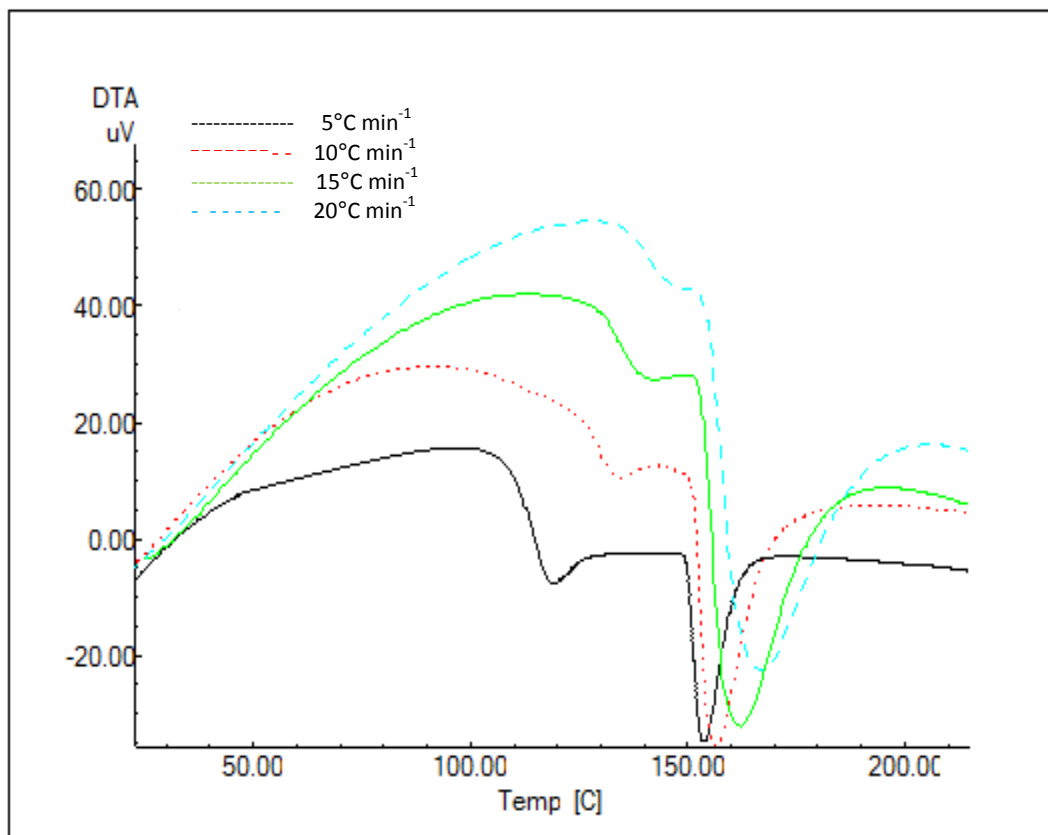


Fig.4: DSC curves obtained at 10 °C /min for the Cilostazol samples

The TG/DTG and DSC curves showed an endothermic event with a heat variation starting at 125 °C ( $T_{peak}=134$  °C), followed by three endothermic events ( $T_{peak}= 160.4$ ; 284.6 and 427.4 °C). The endothermic event which occurred at 160.4 °C ( $T_{peak}$ ) is characteristic of a melting process followed by first decomposition, which in turn is characterized by the endothermic event at 284.6 °C ( $T_{peak}$ ). The thermal decomposition process began with the heat liberated from recrystallization, as indicated on the DSC curve by the temperature peaks at 128.6 and 160.9 °C.

### Effect of heating rate

Fig.5. shows the DTA curves for the decomposition of Cilostazol at several heating rates. It was found that by increasing the heating rate, the melting endothermic peaks of Cilostazol are shifted to higher temperatures.



**Fig. 5: Melting point peaks at different heating rates**

### Kinetic studies

According to the Ozawa, several methods are proposed for obtaining kinetic parameters from thermogravimetric data. There are a variety of relationships with particular models in differential and integral forms. Specifically, the method described by Ozawa is based on the integral calculations from the equation of Arrhenius.

$$k(T) = A.e^{-E_a/RT} \dots\dots\dots \text{Eq. 4}$$

Where A is the frequency factor, R is the general constant of gases ( $8.314 \text{ J mol}^{-1} \text{ K}^{-1}$ ),  $E_a$  the activation energy and T the absolute temperature. To study the thermal decomposition kinetics for TG of Cilostazol, the Ozawa's method available in the software of the thermal analysis system TA 60-WS (Shimadzu) was applied. For application of this

method the obtainment of at least three TG curves under different heating rates are required.

In this study, four TG curves were obtained at a  $\beta$  of 5, 10, 15 and  $20^\circ\text{C}/\text{min}$  in Fig. 6. Ozawa's method was applied to data obtained from the four TG curves to determine the  $E_a$  at the beginning of the first event of mass loss, corresponding to the process of thermal decomposition that occurs for Cilostazol between 175 and  $300^\circ\text{C}$ , with a mass loss of 93.58%. However, the second step occurred slowly between 300 and  $600^\circ\text{C}$  with gradual mass loss of around 7.25 %.

. Fig.5. correspond to the heating rates logarithm versus the inverse absolute temperature ( $\text{Log } \beta$  vs  $1/T$ ) in Fig.7. , obtained after the processing of data by Ozawa's method, which allowed the kinetic parameters [the activation energy ( $E_a$ ), reaction order (n) and frequency factor (A)] in Fig.8.

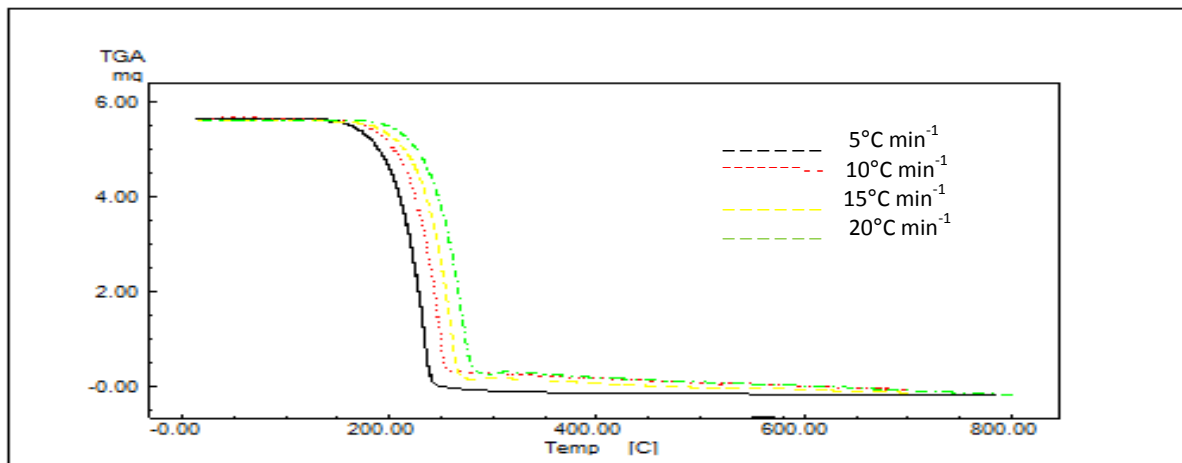


Fig. 6: TG curves of Cilostazol obtained at different heating rates under dynamic nitrogen atmosphere

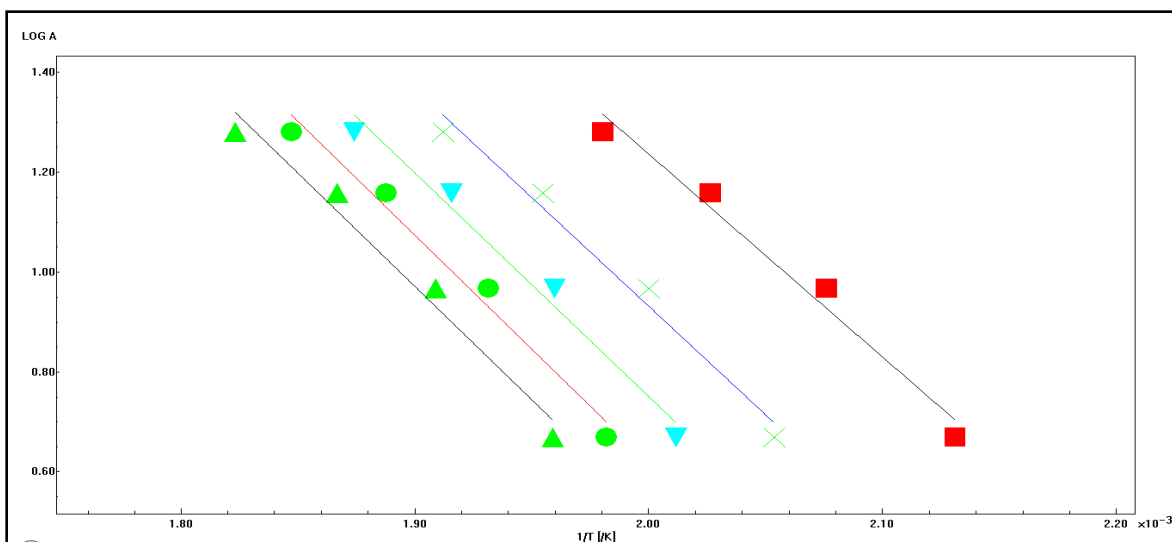


Fig.7: Ozawa curves of Cilostazol plot of log  $\beta$  again  $1/T$

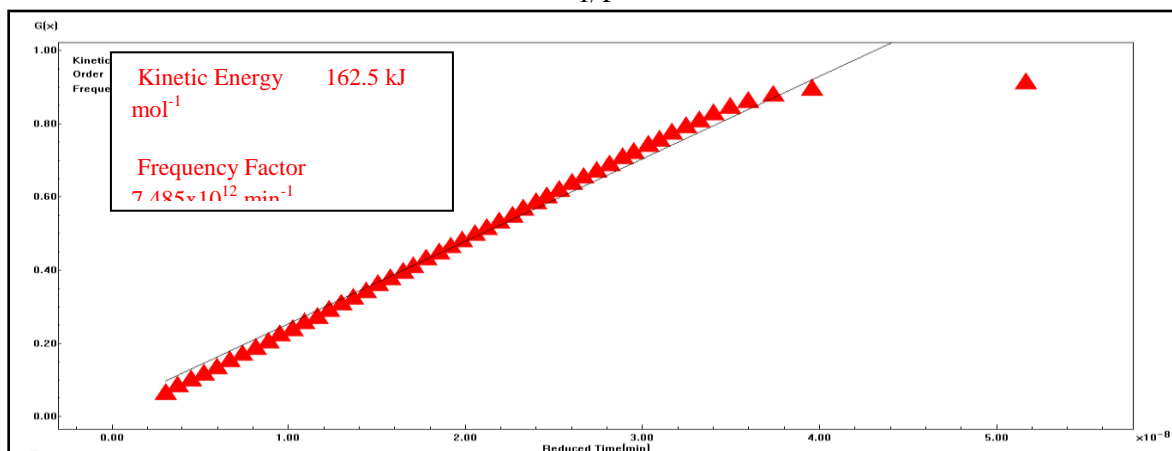


Fig. 8: Integrated form of constant  $G(x)$  and the conversion dependence function,  $f(x)$  of Cilostazol

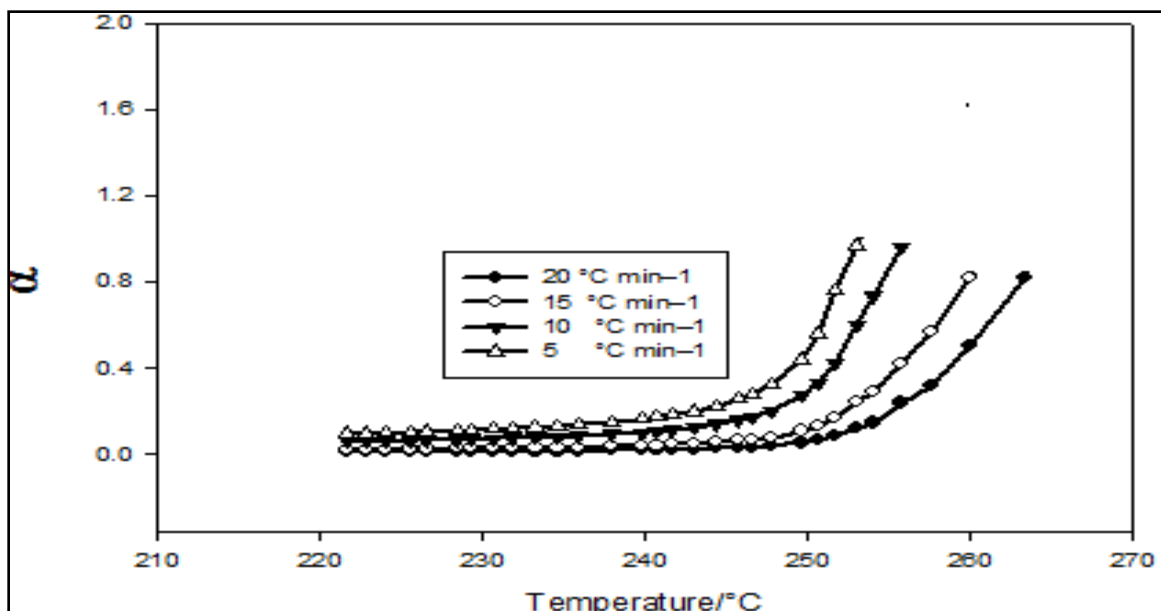


Fig. 9:  $\alpha$ -T curve for the decomposition of Cilostazol at different heating rates

$\alpha$ -T curves for the non-isothermal decomposition of Cilostazol at different heating rates are illustrated in Fig. 9. The values of E according to thermal decomposition of Cilostazol are listed in Table 1. These values were calculated using the Ozawa and

Friedman differential methods by fitting the plots of  $\ln b$  versus  $1/T$  [32] and  $\ln b(d\alpha/dT)$  versus  $1/T$ . The results in Table 1 showed the variations between the values of E obtained using the two isoconversional methods.

Table 1: Activation energies for the 5–90 % conversions for the Cilostazol obtained by the Ozawa–Flynn–Wall and Friedman differential methods

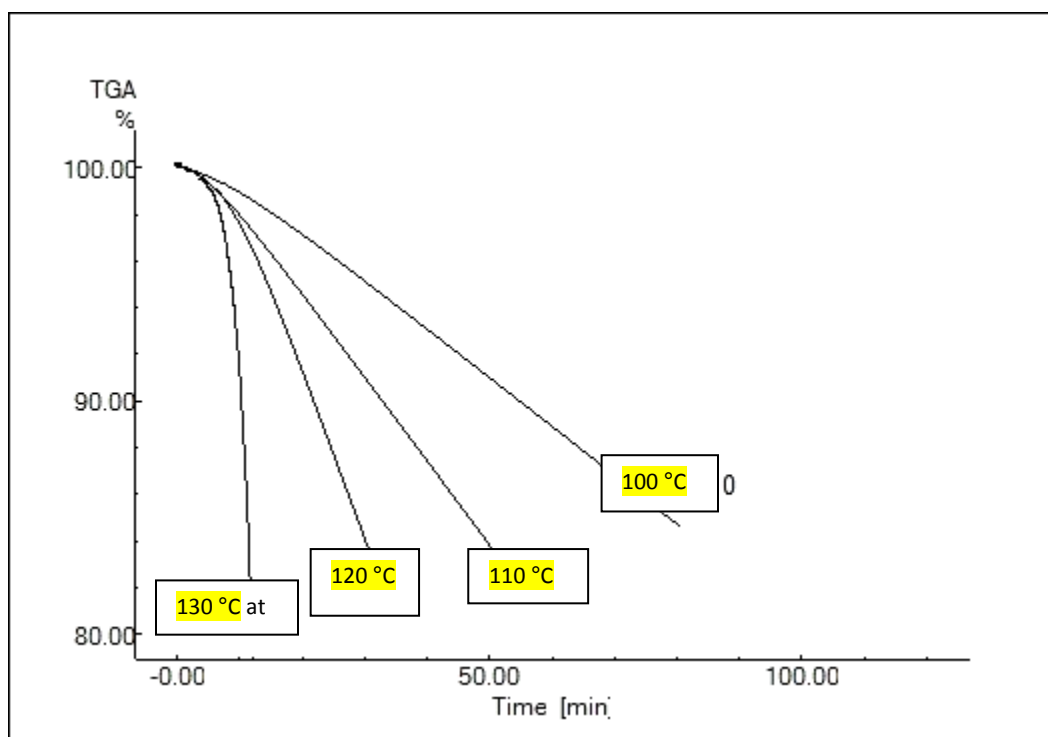
Conversion/%	E/kJ mol <sup>-1</sup>	
	Ozawa–Flynn–Wall method	Friedman differential
5	159.55	159.38
10	159.47	161.84
20	162.48	159.18
30	161.44	163.49
40	158.39	162.82
50	160.04	162.88
60	160.08	163.33
70	159.25	160.96
80	161.48	161.15
90	162.50	162.32

The activation energy values obtained for Cilostazol by Ozawa isoconversional method in the nonisothermal conditions showed practically constant, relative standard deviation of 0.61 %. The results suggest that the reaction occurs in a single step. The kinetic parameters E, A, and n were  $162.5 \text{ kJ mol}^{-1}$  and  $7.485 \times 10^{12} \text{ min}^{-1}$ , and zero -order reaction, respectively.

The isothermal curves obtained are demonstrated in Fig. 10. and show mass loss rate as a function of time. Which obtained by heating the sample at 100, 110, 120, and 130 °C and maintained at isothermal conditions under a dynamic atmosphere of air ( $50 \text{ mL min}^{-1}$ ) for a sufficient time for the mass loss to be at least 10%.for 60, 30, 20 , and 10 min, respectively.

The natural logarithm of time ( $\ln t$ ) corresponding to a certain mass loss ( $\alpha = 5 \%$ ) is linearly dependent on the reciprocal of temperature T. Fig.11. shows the linear relation between  $\ln t$  and  $1/T$ . The equation obtained from this linear regression method was  $y =$

$15.631x - 31.02$  with  $r = 0.9991$ , and it showed that the order of reaction remains constant ( $n = 0$ ) within the temperature and mass loss interval under consideration. The activation energy was calculated from the slope of the line, from linear regression by the product of 15.631 with the molar gas constant ( $R = 8.314 \text{ J K}^{-1} \text{ mol}^{-1}$ ). The activation energy value was  $163.5 \text{ kJ mol}^{-1}$ . The decomposition kinetics for isothermal conditions occurs in constant rate, zero order, and is independent from the concentration of the reactants. Both values of E obtained by Ozawa's conventional method and isothermal and conditions were similar. The combined experiments using isothermal and non-isothermal conditions are the best way to properly determine kinetic parameters. The values of  $\Delta S$ ,  $\Delta H$ , and  $\Delta G$  of decomposition reaction were calculated using isothermal and non-isothermal methods. All data are listed in Table 3. Comparing the results of the application of the two methods, we observe that the calculated values are almost similar.



**Fig. 10:** Isothermal TG curves of Cilostazol obtained between 100, 110, 120, and 130 °C at 60, 30, 20 , and 10 min, respectively , under a nitrogen atmosphere with a flow rate of  $30 \text{ mL min}^{-1}$

*The data presented in Figures 8 and 9 show the process of obtaining the values of  $E_a$  using the isothermal method for samples of Clistazole.*



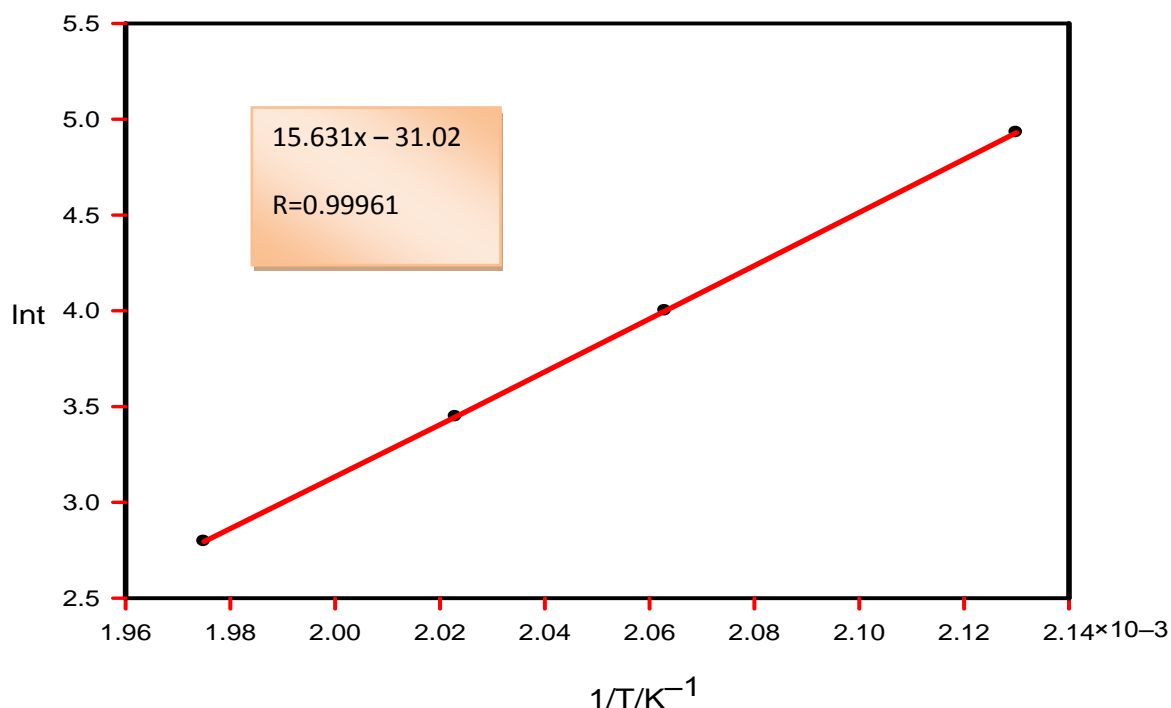


Fig. 11: Plot of  $\ln t$  versus the reciprocal of temperature  $1/T$  from the data obtained in isothermal TG curves

Table 2: Comparison of kinetic parameters of Clistazole obtained by different methods

Method	E/kJ mol <sup>-1</sup>	$\Delta S$ /kJ mol <sup>-1</sup>	$\Delta H$ /kJ mol <sup>-1</sup>	$\Delta G$ /kJ mol <sup>-1</sup>	A/min <sup>-1</sup>
Isothermal	160.7	-178.0	152.06	254.7	4.75x10 <sup>7</sup>
Ozawa's method	162.2	-175.77	153.53	255.31	4.97x10 <sup>7</sup>

### CONCLUSIONS:

The thermal analysis behavior of Cilostazol showed melting point at 160 °C, then it decomposes in liquid medium consisting in pure Cilostazol melted in a single step. The isoconversional methods are used to determine the dependence of E on  $\alpha$ . In these methods, the reaction model is independent of temperature or heating rate and confirms that the decomposition of Cilostazol through a single step. The obtained E values using Ozawa and Friedman isoconversional methods showed variations. The variation of E may be attributed to the temperature integral approximation used in the derivations of the relations of the kinetic methods. The activation energy values for Cilostazol by Ozawa isoconversional method in the

nonisothermal conditions appeared practically constant. Comparing the results of kinetic parameters (E,  $\Delta S$ ,  $\Delta H$ ,  $\Delta G$ , and A) indicates that these values are almost similar using Ozawa's non- isothermal method and isothermal method.

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